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AUGUST 24, 1973

The Effect of Added Salts on the Stereochemistry of Nucleophilic Displacements at Phosphorus in Phosphate Esters and Their Analogs

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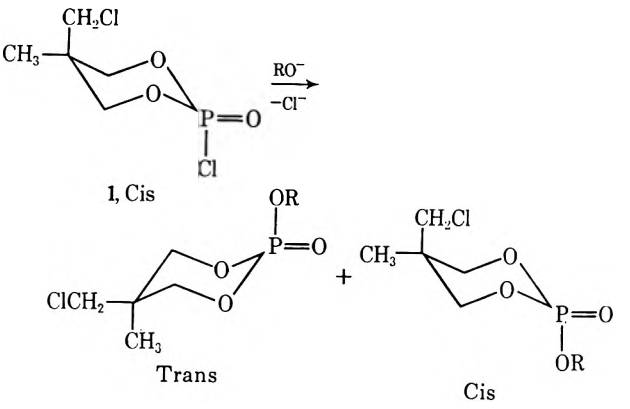
Received February 13, 1973

The stereochemistry of nucleophilic substitutions at phosphorus was studied by means of the 2-substituted 5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan system described previously. It has been observed that added salts dramatically influence the stereochemical outcome. The results are rationalized on the basis of a duality of mechanisms.

The mechanisms by which nucleophiles attack phosphorus leading to substitution have been studied extensively.[1] Both substitution by inversion and retention have been detected and pathways have been advanced to explain results. Because of their importance we are interested in phosphate esters and especially factors which effect the mechanism of substitution at the phosphorus atom. In this paper we report the effect of added cations on the inversion–retention ratio, an effect which may have broad implications not only with respect to phosphate esters and their role in biological systems[2] but with other classes of organophosphorus compounds as well.

In a previous publication[3] we outlined a procedure by which retention and/or inversion could be detected by merely observing the nmr spectra of products. Treatment of *cis*-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (**1**) with a nucleophile gives rise to substitution products whose configurations can be determined simply by observing the chemical shifts of hydrogen contained on groups at the 5 position. The structure of the phosphorochloridate **1** has been well established and the phosphoryl oxygen found to occupy an equatorial position in the cis and trans isomers. The latter was obtained by equilibration of **1**. Single-crystal X-ray analysis performed in our laboratories on the cis and trans phenyl esters (R = C_6H_5) have confirmed their structures.[4] Our data and that accumulated by others[5] gives reliable evidence that, in the case of cyclic phosphorinan esters, the phosphoryl oxygen prefers an equatorial position. The two geometrical isomers show a marked lack of conformational mobility owing to strong preference of groups at phosphorus for axial or equatorial positions. Thus the isomers can be detected *via* nmr, for the hydrogens of an axial chloromethyl group are shifted downfield from those of an equatorial chloromethyl group owing to deshielding by the ring oxygens. Likewise, the methyl hydrogens when axial as in the trans isomers are shifted downfield relative to those of an equatorial methyl group found in the cis isomers.



By means of our diagnostic tool, which eliminates those ambiguities usually associated with optically active substrates, we have followed the course of substitution at phosphorus. Starting with the phosphorochloridate **1**, we find, as outlined in our previous

(1) A. I. Kirby and S. G. Warren, "The Organic Chemistry at Phosphorus," Elsevier, Amsterdam, 1967, Chapter 10; W. E. McEwen, "Topics in Phosphorus Chemistry," Vol. 2, M. Grayson and E. J. Griffith, Ed., Wiley, New York, N. Y., 1965; R. F. Hudson, "Structure and Mechanism in Organo-Phosphorus Chemistry," Academic Press, New York, N. Y., 1965, Chapter 8; M. J. Gallagher and I. D. Jenkins in "Topics in Stereochemistry," Vol. 3, E. L. Eliel and N. L. Allinger, Ed., Wiley, New York, N. Y., 1968.

(2) T. C. Bruice and S. J. Benkovic, "Bioorganic Mechanisms," W. A. Benjamin, New York, N. Y., 1966, Chapter 5.

(3) W. S. Wadsworth, Jr., S. Larsen, and H. L. Horten, *J. Org. Chem.*, **38**, 256 (1973).

(4) R. E. Wagner, W. Jensen, W. S. Wadsworth, Jr., and Q. Johnson, presented at the 8th Midwest Regional Meeting of the American Chemical Society, Columbia, Mo., 1972.

(5) D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc. B*, 1454 (1971).

publication,[3] that the retention–inversion ratio is influenced by the basicity of the nucleophile with retention favored by increased basicity. We have also noted pronounced solvent effects (Table I), and have

TABLE I

PERCENTAGE OF CIS AND TRANS ISOMERS OBTAINED BY TREATING PHOSPHOROCHLORIDATE 1 WITH SODIUM PHENOXIDE IN VARIOUS SOLVENTS[a]

Solvent	Trans (inversion)	Cis (retention)
Benzene	14.3	85.7
Chloroform	14.3	85.7
Dioxane	33.4	66.6
Tetrahydrofuran	50.0	50.0
Acetonitrile	52.0	48.0
Acetone	69.2	30.8
Dimethylformamide	83.4	16.6

[a] All spectra were obtained in $CDCl_3$ by means of a Varian A-60A spectrometer using TMS as an external standard.

now determined that the change in isomer ratio with solvent is a function of the solubility of the salt produced as by-product. The amount of trans isomer increases as the solubility of the salt increases. In all cases the ratio of isomers formed is kinetically controlled, for the individual isomers are stable under the reaction conditions and indeed no isomerization was observed, except where noted, even under drastic conditions.

The influence of salt was determined by carrying out the substitutions in a solvent to which salt was added. Thus in acetonitrile saturated with sodium chloride a change in the ratio was observed with an increase in the product of inversion (Table II). The effect was much

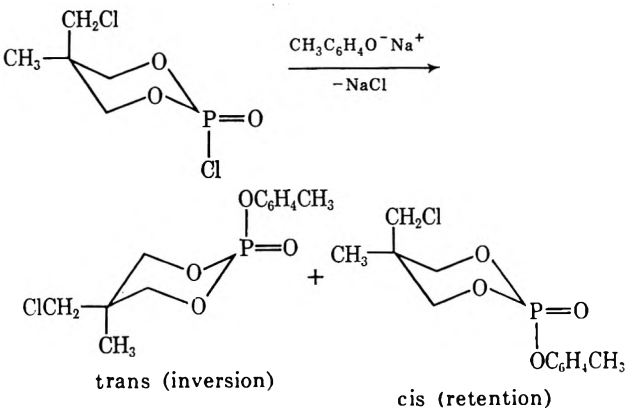
TABLE II

ADDITION OF SODIUM *p*-METHYLPHENOXIDE TO PHOSPHOROCHLORIDATE 1. EFFECT OF ADDED SALTS ON THE INVERSION–RETENTION RATIO

Solvent	% trans (inversion)	% cis (retention)
CH_3CN	46.5	53.5
CH_3CN[a]	55.8	44.2
CH_3CN + saturated NaCl	65.8	34.2
CH_3CN[a] + 1 equiv $(CH_3)_4N^+Cl^-$	88.8	11.2
CH_3CN + 1 equiv $LiClO_4$	12.2	87.8
$HCN(CH_3)_2$[a]	80.2	19.8
$HCN(CH_3)_2$[a] + 1 equiv $(CH_3)_4N^+Cl^-$	95.2	4.8
$HCN(CH_3)_2$[a] + 1 equiv $LiClO_4$	47.4	52.6
Benzene	10.0	90.0

[a] Inverse addition. The phosphorochloridate added to salt solutions.

more pronounced with added tetramethylammonium chloride, for here the added salt and sodium *p*-methylphenoxide precipitated sodium chloride to give acetonitrile-soluble tetramethylammonium *p*-methylphenoxide. Added lithium perchlorate had an effect opposite to that which might be expected. The added perchlorate evidently does not ionize appreciably in acetonitrile and its effect was to reduce the solubility



of the sodium ion, thereby diverting the substitution to predominantly retention. When the order of addition was reversed, the chloridate added to a solution of sodium *p*-methylphenoxide, the amount of inversion increased. The result is not unexpected, for it again reflects the ability of the sodium ion to enhance the inversion mechanism.

Sodium *p*-methylphenoxide was found owing to its better stability and greater ease in product purification to be a more favorable reactant then sodium phenoxide. In all cases lack of solubility of added salts hindered attempts at obtaining meaningful quantitative results. Dimethyl sulfoxide was not a suitable solvent, for it readily reacts with phosphorochloridates.[6]

Solvents, especially those capable of solvating cations, had a pronounced effect on the ability of added salts to divert the substitution to inversion. In ethanol, for example (Table III), in which cations are capable of

TABLE III

ADDITION OF PHOSPHOROCHLORIDATE 1 TO SODIUM *p*-METHYLPHENOXIDE DISSOLVED IN ETHANOL. EFFECT OF ADDED SALT ON ISOMER RATIOS

Solvent	% trans (inversion)	% cis (retention)
CH_3CH_2OH	37.0	63.0
CH_3CH_2OH + saturated NaCl	37.5	62.5
CH_3CH_2OH + 1 equiv $(CH_3)_4N^+Cl^-$	85.2	14.8
CH_3CH_2OH + 1 equiv $LiClO_4$	21.3	78.7
CH_3CH_2OH + 1 equiv LiCl	27.3	72.7

being solvated, inversion is less pronounced than with acetonitrile. The effect of added sodium chloride was much less pronounced even though more soluble in the medium. Again, the addition of tetramethylammonium chloride had a pronounced effect which indicates that the tetramethylammonium ion is particularly effective, owing perhaps to relatively less solvation. In order to reduce the possibility of reaction of the phosphorochloridate with solvent, the chloridate was added to the sodium *p*-methylphenoxide–ethanol mixtures.

The ratio of isomers obtained upon methanolysis of the phosphorochloridate was also effected by added salts. In the absence of added salt the inversion–retention (trans/cis) was 3:2. Addition of 1 equiv of $NaHCO_3$ to the solvent before addition of the phosphorochloridate increased the ratio to 3:1, whereas silver nitrate led to complete inversion. The ratios are

(6) M. A. Ruveda, E. N. Zerba, and E. M. DeMoutier Aldao, *Tetrahedron*, **28**, 5011 (1972).

based on the nmr spectra[3] of distilled products. The methanolysis could also be conveniently followed *via* nmr by using deuterated solvent. By means of this technique, tetramethylammonium ion gave essentially complete inversion with an overall rate approximately twice that without the added salt. The change in isomer ratio and rate is more striking when it is realized that, although a saturated solution of the salt was employed, tetramethylammonium chloride is only sparingly soluble in methanol. Based on the nmr spectrum less than 0.1 equiv of salt was in solution. In comparison to the observed change in stereochemistry, the variation in rate appears to be surprisingly small.

The methanolysis study was complicated not only by lack of solubility of added salt but by a side reaction which is concurrent with solvolysis of the phosphorochloridate. The methyl esters once formed react with methanol especially under acidic conditions to produce by C–O bond scission dimethyl ether and the acid 2-hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (**3**). Unfortunately, the chemical shifts of hydrogen on groups at the 5 position of the acid coincide with those of the starting phosphorochloridate. Equilibration of the initially formed isomer mixtures by acid-catalyzed trans methanolysis also occurs but is extremely slow, requiring over 2 months for the final 2.5:1 cis/trans equilibrium ratio to be reached.

2-Propanolysis of the phosphorochloridate gave only a single isomer, the trans, *via* inversion. Apparently attack by retention is unfavorable owing to steric hindrance. The axial ring hydrogens hinder attack from the side opposite the phosphoryl oxygen (see Discussion section). That steric hindrance is important was evident by comparison of the inversion–retention ratio, 1.26:1, obtained by treatment of the phosphorochloridate with sodium *p*-methylphenoxide, with that obtained under identical conditions with the more bulky sodium 2,6-dimethylphenoxide, 3.55:1.

Data obtained with the phosphorochloridate prompted us to look at substrates with a leaving group other than chloride ion. Owing to its ease of formation, stability, and ease of substitution we selected *trans*-2-*p*-nitrophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan[3] (**2**). As with the phosphorochloridate, the ratio of isomers obtained by treating the *p*-nitrophenyl ester with sodium *p*-methylphenoxide varied with the solvent and was influenced by added salt (Table IV).

The *p*-nitrophenyl ester **2** was of further interest. As with other esters and the phosphorochloridate it gave no indication of isomerization when heated in a variety of polar solvents, *i.e.*, formic acid, nitrobenzene, or acetonitrile. Unlike the phosphorochloridate, which isomerizes readily in dimethylformamide, it also gave no indication of isomerization when a dimethylformamide solution was heated. In the case of phosphorochloridates, dimethylformamide has been found to act as a nucleophile.[7] Evidently the *p*-nitrophenoxide ion is not a good enough leaving group for substitution by the solvent to occur.

Addition of a small amount of sodium *p*-nitrophenoxide to a solution of the ester does, however, owing to ester exchange, cause isomerization with the rate dependent upon the polarity of the medium. Thus in acetonitrile isomerization was incomplete after a solution containing added sodium *p*-nitrophenoxide which was only slightly soluble had stood at room temperature for 4 days. When dimethylformamide was employed an identical mixture of ester and sodium *p*-nitrophenoxide required less than 10 min to reach equilibrium. The large difference in rate may reflect the increased solubility of the sodium *p*-nitrophenoxide in the latter solvent and in turn the greater influence of the sodium ion.

The effect of added salts other than sodium *p*-nitrophenoxide is also striking. Whereas no isomerization of the ester is observed even in refluxing dimethylformamide, it is observed upon warming a dimethylformamide solution containing tetramethylammonium chloride. Upon heating, the solution slowly turns yellow owing to liberated *p*-nitrophenoxide ion with the color fading upon cooling. The added salt appears to increase the electrophilicity of the phosphorus atom, enabling the weak nucleophile, dimethylformamide, to displace the *p*-nitrophenoxide ion which reattacks upon cooling with both inversion and retention to give an equilibrium-controlled ratio of isomers. The other phenyl esters described in this paper, which contain a poorer leaving group, do not equilibrate in dimethyl-

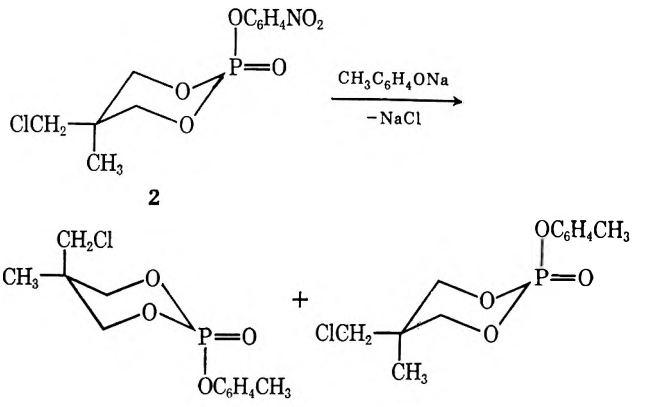
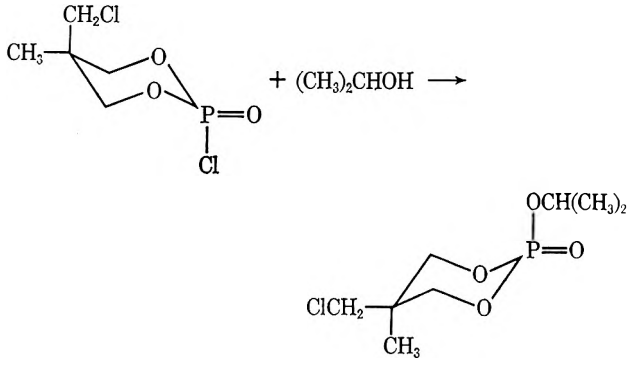


TABLE IV

PERCENTAGE OF CIS AND TRANS ISOMERS OBTAINED BY ADDITION OF *trans*-2-*p*-NITROPHENOXY-5-CHLOROMETHYL-5-METHYL-2-OXO-1,3,2-DIOXAPHOSPHORINAN (**2**) TO SODIUM *p*-METHYLPHENOXIDE. SOLVENT AND SALT EFFECTS

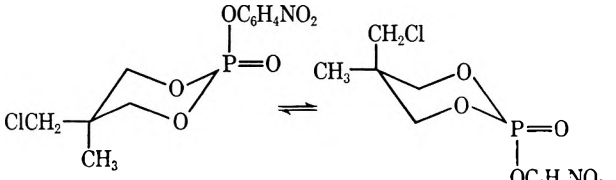
Solvent	% cis (inversion)	% trans (retention)
CH_3CN	44.5	55.5
CH_3CN + 1 equiv $(CH_3)_4N^+Cl^-$	86.0	14.0
$HCN(CH_3)_2$	74.5	25.5



(7) F. Cramer and M. Winter, *Ber.*, **94**, 989 (1961).

formamide upon the addition of a common ion or upon heating solutions containing added tetramethylammonium chloride.

The final equilibrium mixture of isomers obtained upon addition of sodium *p*-nitrophenoxide to the *p*-nitrophenyl ester is thermodynamically controlled and reflects the preference of the chloromethyl group for an axial position possibly owing to dipole interaction between the group and ring oxygens.[8] An identical ratio was obtained upon equilibration of the cis phosphorochloridate **1** by dissolving a sample in dimethylformamide.[3] In the latter case where the solvent acts as a nucleophile equilibrium was reached without added chloride ion or other salts within 15 min. The ability of the trans *p*-nitrophenyl ester in the presence of added *p*-nitrophenoxide ion and cis phosphorochloridate to equilibrate in dimethylformamide may render the isomer ratios obtained upon substitution less valid when this solvent is employed. It should be pointed out, however, that the increased tendency for inversion in dimethylformamide owing to salt solubility is firmly established.



2, trans (1) cis (2.5)

In contrast to dimethylformamide, when dissolved in nonnucleophilic solvents, **1**, **2**, and **4** can be recovered unchanged and under the reaction conditions do not undergo isomerization in the presence of inert salts. Also, when a twofold excess of **2** was added to sodium *p*-methylphenoxide in acetonitrile and the unreacted starting material isolated shortly after substitution was complete (within 15 min), the recovered reactant contained only the starting trans isomer. When inert solvents are employed the starting materials do not undergo isomerization prior to substitution.

Phosphorylation by pyrophosphates has been found to be metal catalyzed.[9,10] It was of interest, therefore, to determine if added cations could have the same influence on the mechanism of substitution with pyrophosphates as substrates as they have with phosphorochloridates and reactive phosphate esters. The pyrophosphate **4** was best prepared by refluxing a chloroform solution of **3** with thionyl chloride. The product was probably a mixture of the three possible isomers which unfortunately defied separation into its components. The two phosphorinan rings of different configurations were not of equal concentration in the mixture. That with the chloromethyl group equatorial predominated over that with the chloromethyl group axial by a 2:1 ratio. We have assumed that, as in the case of the esters, the preference is for the phosphoryl oxygen to be equatorial. Our assumption is based on the ratio of isomeric phosphoramidates obtained by treatment of an acetonitrile solution of the pyrophosphate with piperidine. It has been shown previously[3] that substitution by amines under these conditions proceeds, at least with phosphorochloridates, entirely by inversion. The fact that the combined yield of product was over 90% and that the cis predominated over the trans would indicate our assignment of the configuration at phosphorus to be correct. If the phosphoryl oxygens in the pyrophosphate were axial, the ratio of products should be reversed. The fact that the ratio of cis to trans phosphoramidates is greater than two would indicate that attack by inversion at that phosphorus atom whose phosphorinan ring contains a chloromethyl group equatorial is more facile than attack at that phosphorus atom whose phosphorinan ring has an axial chloromethyl group. By means of X-ray analysis we have shown that the phosphoramidates, unlike the phosphorochloridate and phosphate esters, have the phosphoryl oxygen axial.[11] The reason for the preference of an amido group for an equatorial position, a phenomenon which has also been observed by others,[12] is not certain.

Treatment of the pyrophosphate with sodium *p*-methylphenoxide gave a mixture of the two possible isomers in a ratio which is solvent dependent and which is influenced by added salt (Table V). As the polarity of the medium increases the cis to trans product ratio increases. In benzene, where retention would be expected to predominate, the ratio is unexpectedly large, which may reflect the fact that, while inversion favors attack at that ring containing an equatorial chloromethyl group, attack by retention is favored at that ring having an axial chloromethyl group. It is also possible, of course, that owing to steric hindrance by the relatively large leaving group, inversion is more favorable in this case than with the phosphorochloridate or phosphate esters. At any rate, the trend toward increased inversion with added salt is apparent.

TABLE V

TREATMENT OF PYROPHOSPHATE **4** WITH SODIUM *p*-METHYLPHENOXIDE

Solvent	% cis	% trans
CH_3CN	70.9	29.1
CH_3CN + 1 equiv $(CH_3)_4N^+Cl^-$	83.0	17.0
Benzene	66.6	33.3

The pyrophosphate is completely stable in all solvents studied with the exception of dimethylformamide. In the latter solvent the pyrophosphate slowly equilibrates upon heating to give a new mixture of pyrophosphates in which the ratio of chloromethyl groups axial to equatorial has a final ratio of 2.5:1. The "tail wagging" can easily be followed by nmr and as with the phosphorochloridate must be a consequence of the ability of dimethylformamide to act as a nucleophile. The equilibrium ratio is identical with that obtained with the phosphorochloridate and again reflects the relative thermodynamic stability of the two ring configurations. In the presence of 0.1 equiv of tetramethylammonium chloride the rate of attainment of

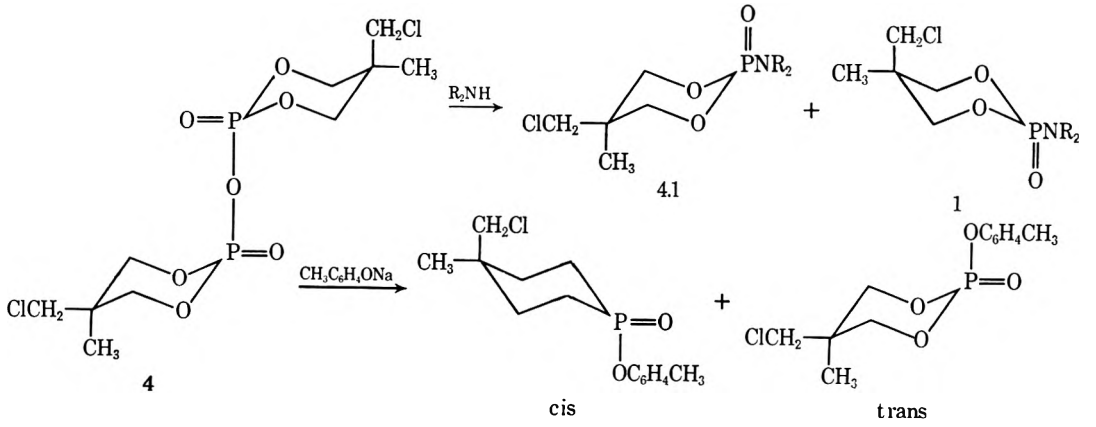
(8) The preference of the chloromethyl group to be axial has been reported for an analogous 2-methoxy phosphite: D. W. White, R. D. Bertrand, G. K. McEwen, and J. G. Verkade, *J. Amer. Chem. Soc.*, **92**, 7125 (1970).

(9) M. Tetas and J. M. Lowenstein, *Biochemistry*, **2**, 350 (1963).

(10) W. P. Jeneks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969, p 112.

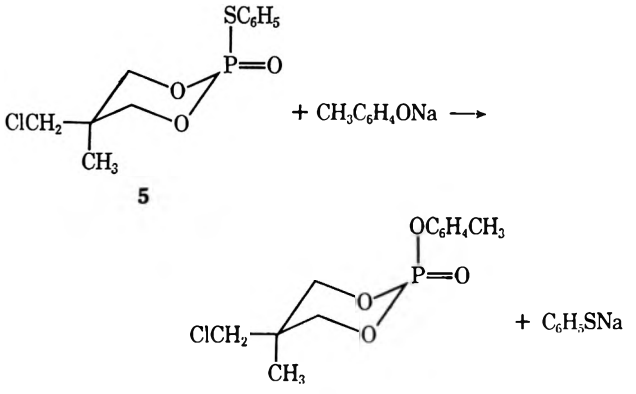
(11) R. E. Wagner, W. Jensen, W. S. Wadsworth, Jr., and Q. Johnson, *Acta Crystallogr.*, in press.

(12) J. A. Mosbo and J. G. Verkade, *J. Amer. Chem. Soc.*, **94**, 8224 (1972).



equilibrium was nearly twice that without the added salt.

In the case of a phosphorothiolate whose configuration is known, substitution of a mercaptide group proceeds entirely by retention. Treatment of *trans*-2-thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (**5**)[3] with either sodium *p*-methyl-



phenoxide or sodium phenoxide gave only the single isomer, the trans. Addition of 1 equiv of $(CH_3)_4N^+Cl^-$ to the reaction mixtures prior to addition of the sodium salt did not change the course of substitution.

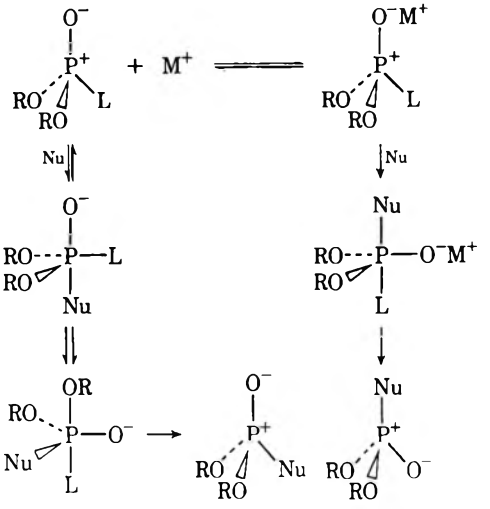
Discussion

In accordance with conclusions drawn by others[13,14] on related systems, there is no evidence that substitutions at phosphorus in phosphates occur by anything but by an associative mechanism. In support of this conclusion, the cis phosphorochloridate does not in the absence of added chloride ion undergo isomerization when dissolved in polar solvents such as nitrobenzene, trifluoroacetic acid, etc., and the solutions were heated. As stated earlier, dimethylformamide and also pyridine are exceptions but here evidence indicates that the solvents are acting as nucleophiles. Methanolysis in the presence of silver ion leads only to the inverted ester, whereas, if a phosphoryl cation were an intermediate, one might expect a mixture with perhaps a 2.5:1 ratio of isomers.[15]

It is probable that cations complex with phosphates through the phosphoryl oxygen.[16] Treatment of the phosphorochloridate **1** with $AlCl_3$ in ether gave a viscous precipitate. The precipitate, when dissolved in acetonitrile and the solution treated with piperidine, gave only a single isomer, the trans phosphoramidate. The latter is also obtained by inversion from the starting phosphorochloridate without added $AlCl_3$. Thus treatment of cis phosphorochloridate with $AlCl_3$ did not cause isomerization, which might have been expected if the $AlCl_3$ had complexed with the chloride ion.

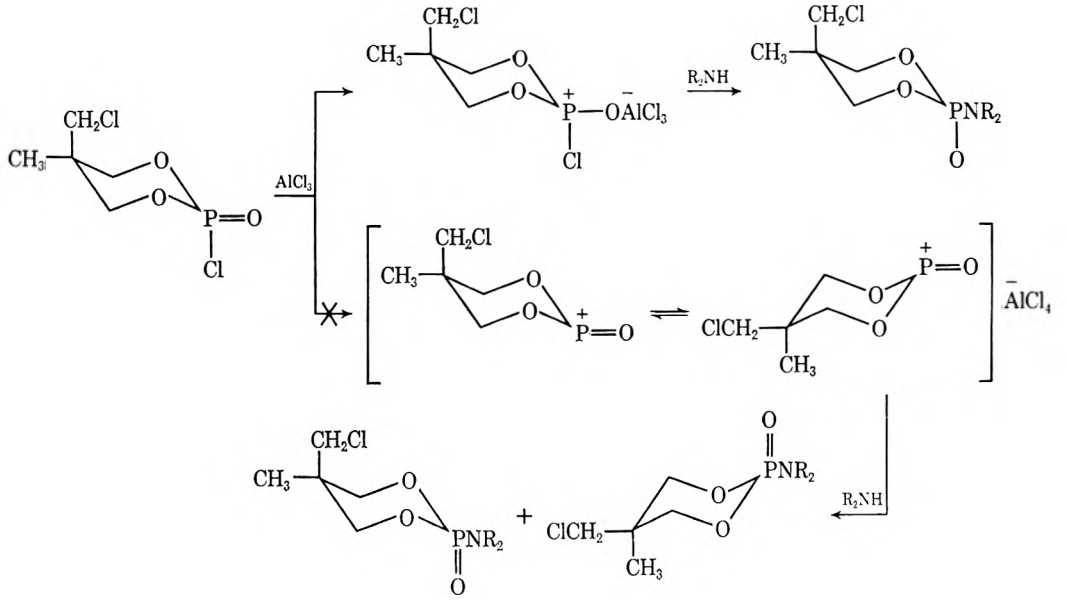
A change in stereochemistry with added salts would suggest two separate mechanisms for substitution, one for retention and one for inversion (Scheme I). If the

SCHEME I



influence of extraneous cations could be completely eliminated, it appears from our data that substitution would perhaps proceed entirely by retention, whereas, if complex formation were complete, substitution might be entirely by inversion. In the presence of a cation an equilibrium may be established which is dependent upon the concentration of the cation and the strength of the complex. The equilibrium will also be influenced by solvation effects. In accordance with the "polarity rule,"[17,18] a charged nucleophile would be expected to attack the uncomplexed phosphate from a side opposite the phosphoryl oxygen, a position of minimum electron density. Pentacoordinated intermediates in the trigonal bipyramid form are well estab-

(13) P. Haake and P. S. Ossip, *J. Amer. Chem. Soc.*, **93**, 6924 (1971).
(14) E. W. Crunden and R. F. Hudson, *J. Chem. Soc.*, 3591 (1962).
(15) Our original assumption that a phosphoryl cation may be involved was based on impure phosphorochloridate and has proven to be false: W. S. Wadsworth, Jr., and H. L. Horten, *J. Amer. Chem. Soc.*, **92**, 3785 (1970).
(16) D. E. C. Corbridge, "Topics in Phosphorus Chemistry," Vol. 3, M. Grayson and E. J. Griffith, Ed., Wiley, New York, N. Y., 1966, p 297.
(17) E. L. Muetterties and R. A. Schunn, *Quart. Rev., Chem. Soc.*, **20**, 245 (1966).
(18) F. Ramirez and I. Ugi in "Advances in Physical Organic Chemistry," Vol. 9, V. Gold, Ed., Academic Press, New York, N. Y., 1971.



lished as intermediates in phosphorus substitutions.[19,20] Nucleophiles are assumed to enter and leaving groups depart from apical positions. The trigonal bipyramid would undergo a pseudorotation which leads to substitution by retention.

As a result of complex formation, the positive charge on phosphorus is increased owing to the reduction in backbonding by oxygen lone-pair electrons with d orbitals of phosphorus. One would, therefore, expect an increase in the rate of substitution as a result of complex formation. Nucleophiles may attack the complex with direct displacement in an Sn2 fashion without the formation of an intermediate, a situation which would lead directly to inversion. There has been some dispute[21-23] as to whether substitutions involve a pentacoordinated intermediate, and it may well be that inversion does not.

With our duality of mechanism scheme, the ability of added cations to shift substitution to the inversion pathway is obvious.[24] The greater ability of more basic nucleophiles to substitute by retention in contrast to less basic ones is also explained. The results merely reflect a difference in rate of attack at the two species in equilibrium. The energy of activation for attack by a weakly basic nucleophile would be greater at the uncomplexed phosphate than at phosphorus in which the phosphoryl oxygen is complexed. With more basic nucleophiles, which form strong bonds to phosphorus, the difference in activation energies would be diminished.

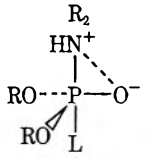
It is apparent that the mode of substitution is also dependent upon the leaving group. This would be expected if the inversion mechanism proceeded by direct displacement. The percentage of inversion should vary with the leaving group, especially if the third step in the retention pathway was not rate determining. Recent kinetic evidence[25] has shown that in the decomposition of suspected pentacoordinated intermediates the departure of the leaving group is rate determining in those cases involving a poor leaving group such as isopropoxide ion, whereas formation of the intermediate becomes the slow step in cases which involve a good leaving group such as phenoxide ion. Under identical conditions the percentage of inversion is greater for the phosphorochloridate than for the *p*-nitrophenyl ester, both of which contain a good leaving group. We believe this to be evidence that inversion proceeds by a one-step mechanism.

Why substitution of a mercaptide ion proceeds only by retention,[26] even in the presence of added salts, is more difficult to rationalize. Certainly, only the mechanism which involves the formation of an intermediate must be operative. Backbonding between sulfur and phosphorus is less than between oxygen and phosphorus and thus the phosphorus atom in phosphorothiolates has more positive character than that in phosphates.[27] In consequence, with respect to phosphorothiolates, backbonding between the phosphoryl oxygen and phosphorus atom might be increased to the extent that complex formation is inhibited.[28]

Unlike charged nucleophiles, neutral nucleophiles such as piperidine and other amines react with the cis phosphorochloridate to give phosphoramidates almost exclusively by inversion. This is the case even under conditions where the effect of the by-product, a quaternary salt, should be at a minimum. Thus, when substitutions are carried out at low temperatures in hexane, only a trace of that phosphoramidate which results from retention is observed. From our previous work both isomers have been obtained in pure form and their spectra are well defined. To account for predominant inversion even without the influence of added salt, one needs to consider the transition state. The charge on the phosphoryl oxygen is partially neutralized as is the charge on nitrogen which would result in a lowering of

(19) F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).
(20) F. Ramirez, *ibid.*, **1**, 168 (1968).
(21) M. Halmann, *J. Chem. Soc.*, 305 (1959).
(22) M. Green and R. F. Hudson, *Proc. Chem. Soc.*, 307 (1962).
(23) J. Michalski, M. Mikolajezyk, A. Halpern, and K. Proszynska, *Tetrahedron Lett.*, 1913 (1966).
(24) We have found that substitutions at phosphorothioates are also influenced by added salts: unpublished work.
(25) R. D. Cook, P. C. Turley, C. E. Diebert, A. H. Fierman, and P. Haake, *J. Amer. Chem. Soc.*, **94**, 9260 (1972).
(26) Displacement of mercaptide ion by complete retention has been reported: G. R. Van den Berg, D. H. J. M. Platenburg, and H. P. Benschop, *Recl. Trav. Chim. Pays-Bas*, 929 (1972); *Chem. Abstr.*, **75**, 125763x (1972).
(27) J. R. Cox, Jr., and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964).
(28) For a different explanation based on the "Polarity Rule" see N. J. Death, K. Ellis, D. J. H. Smith, and S. Trippett, *Chem. Commun.*, 714 (1971).

the energy of activation. If substitution by inversion were a three-step process with a trigonal bipyramid



intermediate, attack could as easily be from two other planes of the starting tetrahedron also with neutralization of charges. Such attack would result in retention. Since inversion is almost exclusive, it would again appear that the leaving group departs as the entering group approaches from the back-side and no intermediate is involved.

Since methanolysis proceeds in the absence of a cation predominantly but not exclusively by inversion, we may assume a transition state similar to that postulated for the amines. Charge stabilization, however, may be less, thereby allowing a greater percentage of retention.

Our results and especially the effect of added salts on the stereochemical pathway serves to point up the complexity of nucleophilic substitutions at phosphorus. The interpretation of our results is not a simple matter and should be accepted only as a starting point for further investigations.

Experimental Section

The nmr spectra and procedures for the preparation of the phosphorochloridate 1, phosphate esters, acid, and amides have been published previously.[3] Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 37921. A typical preparation of a phosphate ester applicable to a study of salt effects is given.

2-*p*-Methylphenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.—Phosphorochloridate 1, 2.18 g (0.01 mol), and tetramethylammonium chloride, 1.09 g (0.01 mol), were added to 20 ml of acetonitrile. Sodium *p*-methylphenoxide, 1.30 g (0.01 mol), was added and the solution was stirred at room temperature for 24 hr. The mixture was diluted with 100 ml of water and filtered. The product, 2.85 g (98.2% yield), was dried and its nmr spectrum was recorded. The product could be recrystallized from hexane without a change in isomer ratio.

Yields were consistently over 95% and no isomerization of isomer mixtures was noted under the procedures of work-up.

For those cases in which a water-immiscible solvent was employed, the solvent was removed under reduced pressure before addition of the water.

Pyrophosphate 4.—2-Hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 5.0 g (0.025 mol), and 10.0 g of thionyl chloride were added to 75 ml of chloroform. The mixture was refluxed for 48 hr and solvent was removed under reduced pressure. The residue was recrystallized from toluene, 4.55 g (95% yield).

Anal. Calcd for $C_{10}H_{18}Cl_2O_7P_2$: C, 31.41; H, 4.71; Cl, 18.32; P, 16.23. Found: C, 31.28; H, 4.69; Cl, 18.59; P, 15.99.

Partial separation of isomers could be accomplished by fractional crystallization from carbon tetrachloride, but pure isomers could not be obtained by this or by chromatographic methods. The mixture of pyrophosphates was equilibrated by heating a dimethylformamide-d_7 solution at 55°. The variation in peak heights was followed by nmr until heating produced no further change.

Phosphoramidates from Pyrophosphate 4.—Piperidine, 0.34 g (0.004 mol), was added to an acetonitrile solution of pyrophosphate, 0.76 g (0.002 mol). The solution was stirred at room temperature for 24 hr, during which time the amine salt of the acid by-product precipitated. The filtrate was diluted with 50 ml of water, the mixture was filtered, and the product was dried to give a mixture of isomeric phosphoramidates, 0.36 g (70% yield). The nmr spectrum of the product was identical with that of an authentic mixture.[3]

The pyrophosphate was treated with sodium *p*-methylphenoxide with and without added salt in a similar fashion to give isomeric mixtures of known esters.

Acknowledgment.—The author is grateful for financial support from the National Science Foundation (Grant No. GP-28947).

Registry No.—**1**, 28097-07-6; **2**, 36912-38-6; **4**, 36914-95-1; sodium phenoxide, 139-02-6; sodium *p*-methylphenoxide, 1121-70-6; *trans*-2-*p*-methylphenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 36912-34-2; *cis*-*p*-methylphenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 36912-33-1.

Aromatic Denitration with Borohydride. Nucleophilic Displacement of Nitrite by Hydride

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Received March 21, 1973

Treatment of certain polysubstituted aromatic nitro compounds with sodium borohydride in dimethyl sulfoxide or alcohol solvent results in nucleophilic substitution of the nitro group by hydride. The reaction requires the presence of bulky substituents adjacent to the nitro group to prevent conjugation with the ring and electron-withdrawing groups to activate the ring toward attack.

The reaction of nitroaromatic compounds with sodium borohydride has been observed to proceed along a variety of paths depending upon the reaction conditions and the type of ring substitution. For instance, in polar aprotic solvents[2a] or ethanol,[2b] most unencumbered nitroaromatics are reduced to azoxybenzenes, azobenzenes, or anilines, depending on the nature of the other groups present on the ring. On the other hand, Bell and coworkers have observed dehalogenation of *o*- or *p*-iodo- or *o*-bromonitrobenzenes in aqueous dimethyl sulfoxide (DMSO) under mild conditions.[2c] With highly electron-deficient nitro compounds, ring attack occurs, resulting in eventual reduction of the nucleus to cyclohexene derivatives by borohydride[3] or the formation of stable hydride–Meisenheimer type adducts when more complex borohydrides are employed.[4]

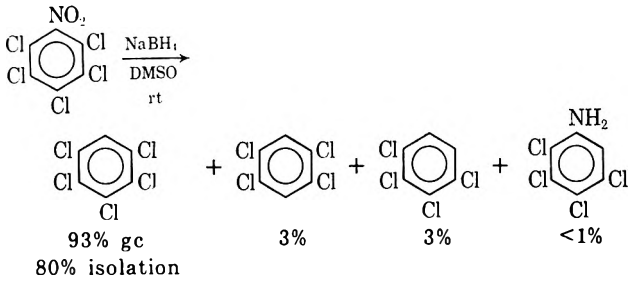
This article describes a further, apparently general, possibility for the reaction of nitroaromatics with borohydride in which the nitro group is displaced by hydride when certain steric and electronic requirements are met.

Results and Discussion

The scope of the denitration reaction is illustrated by the behavior of the substrates contained in Table I. When treated with sodium borohydride in DMSO, pentachloronitrobenzene (Scheme I) and 2,3,5,6-tetrachloronitrobenzene were rapidly denitrated in high yield to pentachlorobenzene and 1,2,4,5-tetrachlorobenzene, respectively (entries 1a and 2a). Chemical tests indicated that nitrite was formed in the reaction.[5]

In the presence of protic solvents, the reaction was somewhat slower than in DMSO alone (entries 1a *vs.* 1e and 1f). Other polychloronitrobenzenes reacted more slowly to give lower yields of denitration products and considerable amounts of side products resulting from reduction of the nitro group and/or removal of chlorines ortho or para to the nitro group. Ortho and meta chlorine substituents appeared to facilitate the reaction (entries 1a *vs.* 6a and 1a *vs.* 3) with para chlorine having less effect (entries 1a *vs.* 2 and 4b *vs.* 5). Thus, the denitration reaction has both steric and electronic requirements. First, the aromatic nucleus evidently must be activated by a suitable amount of electron deficiency induced by withdrawing substituents. Furthermore, substantial steric hindrance apparently must be provided by flanking bulky groups (entries 2a *vs.* 6b). Substrates in which the steric interference was present, but in which the aromatic ring was not sufficiently electron deficient, showed greatly reduced reactivity (entries 11 and 12). Without a significant degree of blockage, reduction of the nitro group competed favorably[2] (entries 8a and 8b).

SCHEME I



To account for the above observations, three types of mechanisms were envisioned as potentially responsible for the occurrence of denitration. The reaction could conceivably involve the formation of a substituted nitrobenzene radical anion followed by fragmentation to afford nitrite anion and a substituted phenyl radical. However, the available evidence concerning radical anions of halonitrobenzenes suggests alternate behavior; for example, 2,3,5,6-tetrachloronitrobenzene radical anion fragments with loss of a chlorine from an ortho position as chloride anion.[6] While this type of mechanism provides one account for the small per cent of dechlorination product obtained from the denitration of pentachloronitrobenzene, it appears not to be involved in the major path of the reaction. A second mechanistic possibility might involve a nucleophilic attack of borohydride on an oxygen atom of the nitro group with concomitant displacement of a substituted phenyl carbanion. Such a unique explanation seemed attractive since the denitration reaction with borohydride anion proceeded more readily and under milder conditions than reactions of other nucleophiles with these same polychloronitrobenzenes (*vide infra*). However, this possibility was ruled out by conducting the reduction in

(1) National Science Foundation Undergraduate Research Participant 1971.

(2) (a) R. O. Hutchins, D. W. Lamson, L. Rua, C. Milewski, and B. Maryanoff, *J. Org. Chem.*, **36**, 803 (1971); G. Otani, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, **16**, 1840 (1968). (b) H. J. Shine and E. Mallory, *J. Org. Chem.*, **27**, 2390 (1962). In addition, sodium borohydride in combination with palladium on carbon gives only the corresponding aniline from aromatic nitro compounds; see T. Neilson, H. Wood, and A. Wylie, *J. Chem. Soc.*, 371 (1962). (c) H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969), and private communication with H. M. Bell.

(3) T. Severin, R. Schmitz, and M. Adam, *Chem. Ber.*, **96**, 3076 (1963).

(4) L. A. Kaplan and A. R. Siedle, *J. Org. Chem.*, **36**, 937 (1971).

(5) F. Feigl, "Spot Tests in Inorganic Analysis," 5th ed, Elsevier, New York, N. Y., 1958, pp 330–332.

(6) A. R. Metcalf and W. A. Waters, *J. Chem. Soc. B*, 918 (1969).

TABLE I

DENITRATION OF AROMATIC NITRO COMPOUNDS WITH SODIUM BOROHYDRIDE

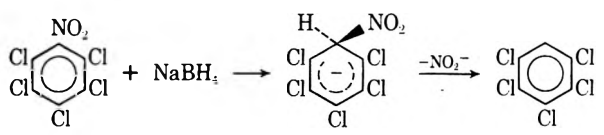
Registry no.	Entry	Substrate: Ar-1-NO_2-	Solvent	$ArNO_2$ concn, M	$NaBH_4$ concn, M	Temp, °C	Time, hr	% Yields[a] de-NO_2 product	% Yields[a] Starting material	% Yields[a] Other
82-68-8	1a	2,3,4,5,6-Cl_5	DMSO	0.10	0.20	Amb[e]	0.5	93	0	3,[b] 3,[c] 1[d]
	1b	2,3,4,5,6-Cl_5	DMSO	0.10	0.15	Amb[e]	0.5	93	0	
	1c	2,3,4,5,6-Cl_5	DMSO	0.10	0.10	Amb[e]	0.5	71	14	
	1d	2,3,4,5,6-Cl_5	DMSO	0.30	0.45	Amb[e]	0.5	80[f]		
	1e	2,3,4,5,6-Cl_5	DMSO-H_2O[h]	0.10	0.20	Amb[e]	20	56[f]		
	1f	2,3,4,5,6-Cl_5	2-Propanol	0.067	0.133	75	1.0	40[g]	23[g]	
117-18-0	2a	2,3,5,6-Cl_4	DMSO	0.10	0.20	Amb[e]	2.0	95	0	
	2b	2,3,5,6-Cl_4	DMSO	0.30	0.45	Amb[e]	2.0	89[f]		
3714-62-3	3	2,3,4,6-Cl_4	DMSO	0.12	0.25	Amb	18	60	0	8,[i] 3[j]
18708-70-8	4a	2,4,6-Cl_3	DMSO	0.07	0.13	Amb	20	2	65	
	4b	2,4,6-Cl_3	DMSO	0.10	0.20	65	44	20	0	8[k]
	4c	2,4,6-Cl_3	DMSO	0.5	1.0	*l*	1.0	27[g]	0	13[g,k]
601-88-7	5	2,6-Cl_2	DMSO	0.08	0.16	60	92	28	13	
879-39-0	6a	2,3,4,5-Cl_4	DMSO	0.05	0.10	19[m]	4.0	33	0	23[d]
	6b	2,3,4,5-Cl_4	DMSO	0.05	0.10	Amb[e]	4.0	56	0	8[d]
	6c	2,3,4,5-Cl_4	DMSO	0.15	0.30	Amb[e]	0.5	45	0	8[d]
89-69-0	7	2,4,5-Cl_3	DMSO	0.125	0.25	Amb[e]	3.0	14	0	19[j]
618-62-2	8a	3,5-Cl_2	DMSO	0.10	0.20	Amb[e]	1.75	0	0	*o*
	8b	3,5-Cl_2	95% ethanol	0.167	0.33	Amb[e]	0.25	0		72[f,p]
40587-63-1	9	2,6-Cl_2-4-CO_2Et	DMSO	0.10	0.20	Amb	1.0	49	0	
40587-64-2	10	2,6-Br_2-4-CO_2Et	DMSO	0.10	0.20	Amb	1.0	23	1	
108-67-8	11	2,4,6-$(CH_3)_3$	DMSO	0.24	0.9[q]	85	190	0	~80	~15
3463-36-3	12	2,3,5,6-$(CH_3)_4$-4-NO_2	DMSO	0.10	0.2	75	92	2[n]	98	

[a] All products were identified by coinjection on gc and most by comparison of ir and mass spectra with those of authentic materials. The per cent yields of products were determined by glpc using internal standards and corrected for detector response. [b] 1,2,4,5-Tetrachlorobenzene. [c] 1,2,3,4-Tetrachlorobenzene. [d] 2,3,4,5-Tetrachloroaniline. [e] Reaction very exothermic; cooling was applied to prevent overflow due to rapid gas evolution. [f] Isolated yield. [g] Product mix isolated, weighed, and analyzed by gc methods. [h] 4:1 v/v DMSO-H_2O. [i] 1,2,4-Trichlorobenzene. [j] 2,4,5-Trichloroaniline. [k] 2,4-Dichloroaniline. [l] After 20-min induction period at 50–60° under application of heat, reaction became extremely exothermic, reaching 135° in 5 min. Water heated in same apparatus at same settings reached only 53° in 1 hr. [m] Temperature maintained by cooling. [n] Thought to be mononitro compound. [o] Only products observed were reductive coupling products. [p] 3,3′,5,5′-Tetrachloroazoxybenzene. [q] 2/3 added initially, 1/3 added after 95 hr.

D_2O–DMSO-d_6. The low degree of deuterium incorporation (*ca.* 15%) in the resulting pentachlorobenzene demonstrated that a significant amount of pentachlorophenyl carbanion was not produced. The small amount of incorporation observed most probably arose *via* base-catalyzed exchange between D_2O and pentachlorobenzene, which was found to occur in the presence of sodium borohydride or sodium deuteroxide in DMSO–D_2O. With sodium borohydride in DMSO-d_6 as solvent, little deuteration occurred during denitration.

The third, and most attractive, mechanistic possibility involves the addition–elimination pathway for aromatic nucleophilic substitution as illustrated for pentachloronitrobenzene in Scheme II. Ostensibly,

SCHEME II



reductive coupling[2a] is minimized by the hindrance introduced by the chlorines adjacent to the nitro group. Borohydride anion, acting as a source of nucleophilic hydride, attacks the most electropositive nitro-attached ring carbon; attacks of this type are not usually hindered by bulky ortho substituents.[7] The formation of the tetrahedral carbon should relieve steric crowding and inductive stabilization of the intermediate anion would be provided by the five chlorine atoms; subsequent loss of nitrite ion furnishes pentachlorobenzene. Furthermore, any addition of hydride to the positions ortho or para to the nitro substituent would not be highly favored, since this group is turned out of planarity with the ring and thus the developing anion is not stabilized by conjugation. The meager amounts of dechlorinated by-products produced could be explained by such attacks, but alternate explanations are equally plausible. As previously mentioned, loss of ortho chlorine may occur from the radical anion to furnish 2,3,4,5-tetrachloronitrobenzene,[6] which can undergo denitration or reduction to 2,3,4,5-tetrachloroaniline (Table I, entry 6). The small amount of 1,2,4,5-tetrachlorobenzene formed may occur from a dechlorination–denitration sequence or by reduction of pentachlorobenzene. This latter compound does slowly furnish 1,2,4,5-tetrachlorobenzene upon treatment with sodium borohydride.

Support for the addition–elimination mechanism for denitration is amply demonstrated by the reactions of other nucleophiles with polychloronitrobenzenes. Nucleophiles which afford products by replacement of the nitro group include azide,[8] fluoride,[9a,b] chloride,[9c]

(7) J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).

(8) P. A. Grieco and J. P. Mason, *J. Chem. Eng. Data*, **12**, 623 (1967).

(9) (a) J. Miller and H. W. Yeung, *Aust. J. Chem.*, **20**, 379 (1967); (b) C. G. Finger and C. W. Kruse, *J. Amer. Chem. Soc.*, **78**, 6034 (1956); (c) P. H. Gore, S. D. Hammond, and D. Morris, *Tetrahedron Lett.*, 2747 (1970).

hydroxide,[10] and methoxide[11] ions, ammonia,[12a,b] and amines.[12b] Indeed the displacement of nitro from even mildly deactivated rings occurs with surprising ease and is documented for a variety of nucleophiles,[12c,13-15] although nucleophilic replacement by hydrogen is relatively rare,[16] apparently because other reactions with hydride reagents, such as reduction, usually, compete effectively.

Experimental Section

Analyses.—Analyses by gas chromatography were performed on a Hewlett-Packard 5250B gas chromatograph (T.C. detector) employing a 6–10 ft × 0.125 in. column of 10% OV-1 on Chromosorb W. Yields were determined using internal standards (1,3,5-trichlorobenzene or *p*-dichlorobenzene) with predetermined detector response factors. The standards were inert to the conditions. All products were identified by glc coinjection techniques and most by comparison of ir and mass spectra with those of authentic samples. Mass spectra were obtained from a Hitachi Perkin-Elmer RMU-6 coupled to a gas chromatograph. Microanalyses were performed by A. Bernhardt, Microanalytical Laboratory, West Germany. Melting points are uncorrected.

Materials.—All organic materials were obtained commercially (except for entries 9 and 10 in Table I) and were used as obtained or recrystallized if not of satisfactory purity. Solvents were commercial reagent grade and used as received. In the deuteration experiments, DMSO-d_6 was 99.5% D grade and D_2O was 99.8% grade.

Ethyl 3,5-dibromo-4-nitrobenzoate was prepared by a method similar to that described for 3,5-dibromo-4-nitrobenzonitrile[17] except that ethyl *p*-aminobenzoate was substituted for *p*-aminobenzonitrile. The light green crystals obtained from ethanol had mp 76.5–77.5°.

Anal. Calcd for $C_9H_7Br_2NO_4$: C, 30.98; H, 2.02. Found: C, 31.23; H, 2.24.

Ethyl 3,5-dichloro-4-nitrobenzoate was prepared by a similar method to that preceding. The colorless crystals from 95% ethanol had mp 77.5–78.5°.

Anal. Calcd for $C_9H_7Cl_2NO_4$: C, 41.57; H, 2.71. Found: C, 41.64; H, 3.12.

General Denitration Procedure.—A solution of the nitroaromatic in the appropriate solvent was prepared in a three-neck flask maintained if necessary at the desired temperature (Table I) and equipped with a magnetic stirrer, condenser, and drying tube. The appropriate amount of sodium borohydride (Table I) was then added directly or as a slurry in the same solvent. Reaction mixtures were worked up by adding about five volumes of water and extracting with ether, chloroform, or carbon tetrachloride. Extracts were dried over anhydrous magnesium sulfate and used for glc analysis and/or concentrated for isolation of products. Progress of the reactions were followed in several cases by removing and working up small aliquots of the reaction mixture for glc analysis as described above. Specific denitration procedures are illustrated below.

Denitration of 2,3,5,6-Tetrachloronitrobenzene. Product Isolation.—To a stirred solution of 2,3,5,6-tetrachloronitrobenzene (7.83 g, 0.03 mol) in 90 ml of DMSO at room temperature was added a mixture of sodium borohydride (1.70 g, 0.045 mol) in 10 ml of DMSO. The reaction mixture was kept at 25–40° by occasional cooling with an ice bath. After 2.5 hr, the mixture was poured into 700 ml of water and extracted with two 50-ml portions of chloroform. The extract was washed with water, dried, and evaporated in a stream of air. The solid residue was recrystallized from 9:1 ethanol–dioxane, giving 5.79 g (89%) of off-white needles, mp 137–139°, mmp with 1,2,4,5-tetrachlorobenzene 137–139°. The ir and mass spectra of the two materials were superimposable.

Denitration of 2,3,5,6-Tetrachloronitrobenzene. Gc Analysis.—Sodium borohydride (0.38 g, 0.01 mol) was added to 2,3,5,6-tetrachloronitrobenzene (1.305 g, 0.005 mol) in 50 ml of a stirred DMSO solution containing 1,3,5-trichlorobenzene (0.907 g, 0.005 mol) as internal standard. At intervals a 1.5-ml aliquot was removed, diluted with 7.5 ml of water, and extracted with 0.5 ml of chloroform, and the extract dried and analyzed by gc. After 2 hr the reaction appeared complete (Table I, entry 2).

Denitration of Pentachloronitrobenzene in Deuterium-Labeled Solvent Mixture.—Sodium borohydride (0.019 g, 0.5 mmol, Ventron Analytical Grade) was added to a stirred solution of pentachloronitrobenzene (0.074 g, 0.25 mmol) in 2 ml of DMSO-d_6 and 0.5 ml of D_2O contained in the usual apparatus and isolated from the atmosphere by a bubble trap. After 1 hr at room temperature, 7.5 ml of D_2O was added and the mixture was extracted with 0.5 ml of carbon tetrachloride. The mass spectrum of the pentachlorobenzene in the extract indicated 15% deuterium incorporation by comparison of the relative peak heights in the parent peak group (248–258) with those of authentic pentachlorobenzene. When the denitration reaction was conducted only in DMSO-d_6 with sodium borohydride, there was little indication of deuterium incorporation.

Dechlorination of Pentachlorobenzene.—A solution of pentachlorobenzene (0.752 g, 3.0 mmol) and sodium borohydride (0.215 g, 5.7 mmol) in 45 ml of DMSO with 1,3,5-trichlorobenzene (0.544 g, 3.0 mmol) as internal standard was stirred at room temperature for 6 days. Glpc analysis showed a 2.5% yield of 1,2,4,5-tetrachlorobenzene (coinjection) with 97% pentachlorobenzene remaining and no observable 1,2,3,4-tetrachlorobenzene or 1,2,3,5-tetrachlorobenzene (coinjection).

Hydrogen–Deuterium Exchange between Pentachlorobenzene and Deuterium Oxide. A. In the Presence of Sodium Deuteroxide.—Sodium (*ca.* 0.05 g, 2–3 mmol) was dissolved in D_2O (2 ml, 110 mmol), and a solution of pentachlorobenzene (0.250 g, 1.0 mmol) in DMSO (13 ml) was added. The stirred solution was protected from atmospheric H_2O by a mineral oil bubble trap. After 20 hr at room temperature, the mixture was worked up with 12 ml of D_2O and extracted with two 10-ml portions of CCl_4. The extracts were dried ($MgSO_4$) and the CCl_4 was evaporated, giving a white crystalline residue which by mass spectral analysis was pentachlorobenzene with 29% D incorporation.

B. In the Presence of Sodium Borohydride.—Sodium borohydride (0.080 g, 2.1 mmol) dissolved in DMSO (5 ml) was added to a solution of pentachlorobenzene (0.250 g, 1 mmol) in DMSO (8 ml), and D_2O (2 ml) was added. After stirring for 20 hr at room temperature in isolation from the atmosphere, the solution was worked up and analyzed as in A, and showed 52% D incorporation in the pentachlorobenzene.

Acknowledgment.—We wish to thank the National Science Foundation for an undergraduate fellowship for Peter Ulrich.

Registry No.—Ethyl *p*-aminobenzoate, 94-09-7; sodium borohydride, 16940-66-2; pentachlorobenzene, 608-93-5.

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(16) (a) Replacement of one or two nitro groups by hydrogen from 1,3,5-trinitro-2,4,6-trichlorobenzene by borohydride has been observed [*cf.* L. A. Kaplan, *J. Amer. Chem. Soc.*, **86**, 740 (1964)] and the absence of chloro displacement was attributed to lack of planarity between the nitro groups and the aromatic ring. (b) A small yield of naphthalene resulted from the reaction of 1-nitronaphthalene with borohydride anion [H. J. Shine and M. Tsai, *J. Org. Chem.*, **28**, 1592 (1958)]. (c) A photoinduced denitration of certain nitro aromatics by borohydride has been observed [W. C. Petersen and R. L. Letsinger, *Tetrahedron Lett.*, 2197 (1971)].

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A Proton Nuclear Magnetic Resonance Study of the Aqueous Chemistry of Acetaldehyde and Ammonia. The Formation of 2,4,6-Trimethylhexahydro-s-triazine[1]

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Proton magnetic resonance techniques were used to study the reaction of ammonia with acetaldehyde. At high pH and 10° significant amounts of ammonia adducts were detected by observing their methyl resonances, which occurred in the region of the acetaldehyde hydrate methyl group (δ 1.65). The adduct which predominates at ammonia/aldehyde ratios of >1 has been identified as the cyclic trimer 2,4,6-trimethylhexahydro-s-triazine, $(CH_3CHNH)_3$. By varying concentrations and pH we have determined the equilibrium constant $K_T = [(CH_3CHNH)_3]/[CH_3CHO]^3[NH_3]^3 = 2.0 \pm 0.6 \times 10^9\ M^{-5}$ at 10°. The pK_a for dissociation of the protonated trimer was 8.36 ± 0.05 at 10°. Two other species were observed and have been tentatively identified as the dimeric compounds $CH_3CH(OH)NHCH(OH)CH_3$ and $CH_3CH(NH_2)NHCH(OH)CH_3$. The trimer was found to be stable in aqueous solution at pH ≥10, but was reversibly dissociated to acetaldehyde and free ammonia by lowering the pH to 7. The methyl resonance of acetaldehyde exhibited a characteristic line broadening which increased linearly with ammonia concentration but decreased with increasing temperature. These effects were analyzed in terms of a three-site chemical exchange problem

$$CH_3CHO + NH_3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CH_3CH(OH)NH_2 \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} CH_3CH{=}NH + H_2O$$

From this analysis the following limits were placed on the rate constants for the addition of ammonia to acetaldehyde at pH 7, 10°: $k_{-1} > 300\ \text{sec}^{-1}$, $k_1 \gtrsim 10^4\ M^{-1}\ \text{sec}^{-1}$, $2 \leq K_1 \leq 17\ M^{-1}$.

In connection with investigations on ethanolamine ammonia lyase, an enzyme that has been postulated to catalyze the conversion of ethanolamine to acetaldehyde and ammonia *via* the intermediate 1-aminoethanol,[3] it became desirable to study the reaction between acetaldehyde and ammonia in aqueous solution. Though there has been little study of this particular reaction, it is a member of an extensively studied class of reactions involving the nucleophilic addition of amines and related compounds to a carbonyl group (eq 1).[4]

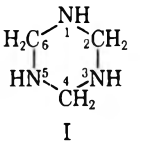
$$R_1R_2C{=}O + RNH_2 \rightleftharpoons R_1R_2C(OH)NHR \qquad (1)$$

The product of eq 1, a tetrahedral adduct termed a carbinolamine, cannot in general be isolated as a stable intermediate,[5] since it readily undergoes dehydration to an imine or similar compound (eq 2).

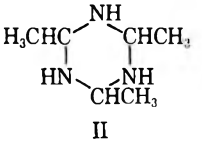
$$R_1R_2C(OH)NHR \rightleftharpoons R_1R_2C{=}NR + H_2O \qquad (2)$$

In a study of semicarbazone and oxime formation, Jencks demonstrated that an intermediate carbinolamine was involved in the two-step mechanism by which these compounds are produced.[6] Later, Cordes and Jencks showed conclusively that the hydrolysis of a Schiff base to a carbonyl compound and an amine involved the formation of the carbinolamine.[7] At neutral or alkaline pH hydration of the imine (eq 2) was rate determining in the hydrolysis, while at lower pH elimination of the amine from the tetrahedral adduct (eq 1) was rate determining. In an extensive series of investigations Hine and coworkers have studied the kinetics and catalysis of the reaction of isobutyraldehyde with various aliphatic primary amines to form imines.[8] Their results concerning mechanism agree with those of Cordes and Jencks.

The reactions between the simpler aldehydes and amines are more difficult to study because of the formation of oligomers. For instance, formaldehyde reacts with ammonia to produce hexamethylenetetramine by way of the trimer, hexahydro-s-triazine (I).[9] With primary amines, such as methylamine and aniline, formaldehyde reacts to form 1,3,5-substituted hexahydro-s-triazines.[4a,10] A similar cyclic trimer, 2,4,6-trimethylhexahydro-s-triazine (II), has been shown to



I



II

be formed by the reaction of ammonia with acetaldehyde in ether solution.[11] A common feature of these polymerizations is that oligomer formation is believed

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(2) (a) Alfred P. Sloan Fellow, 1971–1973. (b) Recipient of a Research Career Development Award from the National Institute of Arthritis and Metabolic Diseases. Address correspondence to New England Medical Center Hospital, 171 Harrison Avenue, Boston, Mass. 02111.

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TABLE I

NMR PARAMETERS FOR THE METHYL GROUPS IN ACETALDEHYDE (A) AND HYDRATE (AOH)[a]

Temp, °C	$\delta_A^{H_2O}$	$\delta_A^{CH_3CN}$	^3J_A	$\Delta\nu^*_A$	δ^A_{AOH}	$^3J_{AOH}$	$\Delta\nu^*_{AOH}$
10	−2.648	0.170	3.04 ± 0.03	0.04	−0.919	5.27 ± 0.02	0.20
25	−2.507	0.168	2.97 ± 0.02	0.04	−0.918	5.22 ± 0.02	0.21
34	−2.414	0.164	2.97 ± 0.01	0.06	−0.914	5.21 ± 0.03	0.23

[a] The chemical shift of species X relative to Y is given in parts per million as δ^Y_X, where downfield shifts are taken as positive; line widths and coupling constants are in Hz. The samples contained 0.40 *M* CH_3CHO, 0.63 *M* CH_3CN, 0.50 *M* NH_4Cl + KCl, and 0.10 *M* phosphate buffer at pH 7.0.

to involve the imine formed from the initial carbinolamine.

Nmr spectroscopy appeared to us to be an appropriate technique for the investigation of the aqueous chemistry of simple aldehydes and amines, since nonchromophoric species could be observed and kinetic information could be obtained from systems at equilibrium. In the present communication we report the results of an investigation of the reaction between acetaldehyde and ammonia as studied by this technique.

Results

All of the proton nmr results presented in this section were obtained at 100 MHz. Details of the techniques used are summarized in the Experimental Section. The general features of nmr spectra of acetaldehyde in aqueous solution are well known; if the H_2O resonance occurs at δ 5.0, then the methyl doublet and methine quartet for acetaldehyde appear at δ 2.55 and 10.0, respectively, while the corresponding resonances for the hydrate of acetaldehyde appear at δ 1.65 and 5.55. Since the H_2O resonance makes the observation of weak resonances in the δ 4–6 region quite difficult, we have examined in detail only the methyl region δ 1–3.

Hydration of Acetaldehyde.—In many of the following experiments, it was necessary to determine the individual concentrations of acetaldehyde and its hydrate in aqueous solution when only one species could be measured. This determination was made from the concentration of the observed species and the equilibrium constant for the reaction acetaldehyde + $H_2O \rightleftharpoons$ hydrate. Preliminary studies were therefore performed on the effect of pH, temperature, and ionic strength on this equilibrium.

The nmr parameters for the methyl group doublets in acetaldehyde and its hydrate are presented in Table I, with chemical shifts and line widths reported for samples containing no ammonia. The line width $\Delta\nu^*$ used throughout this paper is the residual line width (the observed line width minus the line width of the reference peak). This parameter can be used for comparison of line widths obtained under nonidentical conditions of magnetic field homogeneity. The substantial difference in line widths for the aldehyde and hydrate is believed to be the result of a large difference in proton relaxation times. Spin-lattice relaxation times T_1 were measured for the two methyl groups in D_2O at 35° (solutions not degassed) using the conventional Fourier transform inversion–recovery method.[12] The results for acetaldehyde and its hydrate were 11.4 ± 0.4 and 3.25 ± 0.15 sec, respectively.

(12) R. L. Vold, J. S. Waugh, M. P. Klein, and D. E. Phelps, *J. Chem. Phys.*, **48**, 3831 (1968).

Peak area measurements allow the computation of the hydration equilibrium constant.

$$K_h = [CH_3CH(OH)_2]/[CH_3CHO] \quad (3)$$

Table II presents hydration constants obtained in these studies. For comparison, the values of Bell and

TABLE II

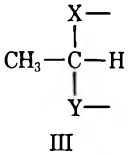
HYDRATION EQUILIBRIUM CONSTANTS

Temp, °C	pH	μ	K_h[a]	K_h[b]
10	4.8–10.5	0.5–1.7	1.92	1.74 ± 0.05
	7.4	0.3		2.11[c]
25	7.0	0.6	1.58	1.19 ± 0.05
34	7.0	0.3	0.93	0.90 ± 0.05
	7.0	0.6		0.84 ± 0.02
	7.4	0.1		1.07[c]
	7.4	0.3		0.91[c]

[a] R. P. Bell and J. C. Clunie, *Trans. Faraday Soc.*, **48**, 439 (1952). [b] Results of this work. [c] Results obtained in D_2O; pD is given.

Clunie obtained by optical methods are included. These authors used 0.02 *M* acetaldehyde and zero ionic strength, while our data are for 0.3–0.4 *M* aldehyde and rather high ionic strengths. Our results are in general agreement with those of previous workers,[13] indicating that K_h is independent of pH over the range of interest but decreases with increasing temperature or ionic strength.

Identity and Properties of the Major Adduct Formed from Acetaldehyde and Ammonia.—Nmr spectra of solutions containing approximately 0.2–0.5 *M* acetaldehyde and NH_4Cl at pH >7 show methyl resonances from species other than acetaldehyde and its hydrate (see Figure 1). The appearance of these additional resonances depended upon both acetaldehyde and NH_3 concentration, indicating that they could not be accounted for by impurities in the reagents. The chemical shifts of these new methyl groups were sensitive to pH but always appeared in the same region as the hydrate methyl (designated H) indicating the structure III, where X and Y are oxygen or nitrogen.



III

Although several compounds were present, at a sufficiently high pH and NH_3 concentration one species (^3J = 6.25 Hz) predominated (designated T in Figure 1).

Similar nmr spectra were obtained for aqueous solutions of commercial "acetaldehyde–ammonia" (com-

(13) L. C. Gruen and and P. T. McTigue, *J. Chem. Soc.*, 5217 (1963).

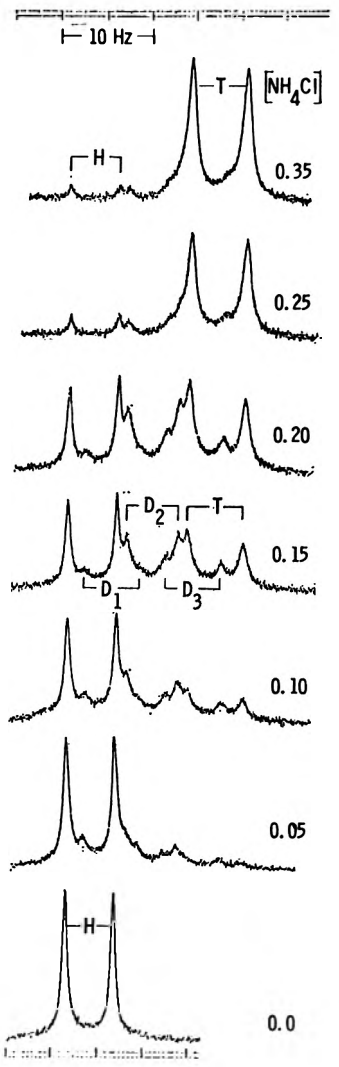


Figure 1.—Nmr spectra of the adduct methyl region for samples containing 0.42 *M* CH_3CHO, 0.067 *M* CH_3CN, 0.50 *M* NH_4Cl + KCl, 0.10 *M* phosphate at pH 10.5 at 10°.

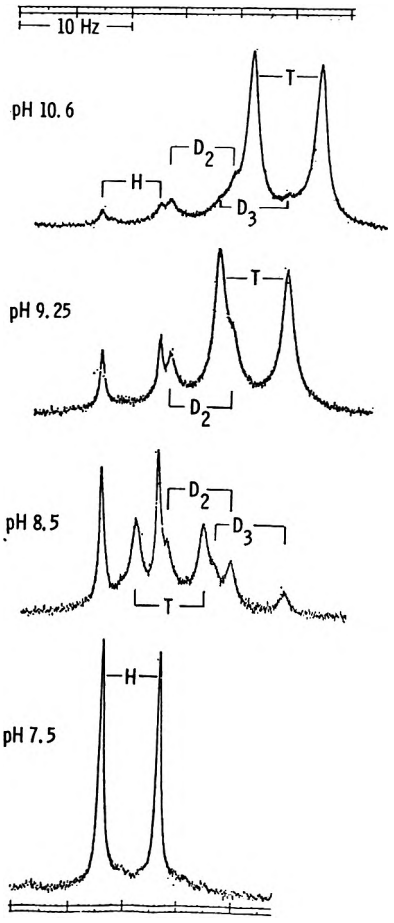


Figure 2.—Nmr spectra of the adduct methyl region for commercial "acetaldehyde–ammonia" (0.16 *M*) in 0.10 *M* phosphate buffer at 10°.

pare the high pH spectrum in Figure 2 with the high ammonia concentration spectrum in Figure 1). [Infrared[14,15] and mass spectroscopy confirmed that the commercial reagent was 2,4,6-trimethylhexahydro-*s*-triazine (II), as had been previously indicated by X-ray studies.[16]]

These nmr spectra, taken in several deuterated solvents at 10 and 35°, showed a single doublet (^3J = 6.05–6.21 Hz) for the trimer methyl groups and a single quartet for the methine protons 2.51–2.61 ppm downfield from the doublet. The ratio of the doublet area to the quartet area was 3.03. A broad peak whose chemical shift varied with solvent and temperature represents the exchangeable protons of –NH– in equilibrium with those of water of hydration. The ratio of this peak area to the methine quartet was 3.0 ± 0.2 in pyridine and acetone at 10 and 35°, consistent with the formula $(CH_3CHNH)_3 \cdot 3H_2O$. A small amount of acetaldehyde was often observed, indicating that some dissociation had occured. The most important feature of these results is that the spectrum of the "acetaldehyde–ammonia" trimer in D_2O shows no significant differences (other than the position of the OH resonance) from those in other solvents, indicating that the trimer can exist in aqueous solution.

The difference in chemical shift of 2.55 ppm between the methyl and methine protons may be compared with corresponding values for acetaldehyde hydrate and paraldehyde of 3.9 and 3.7 ppm, respectively. This characteristic upfield shift of the methine proton for the trimer is consistent with the replacement of oxygens by nitrogens on the methine carbon. The methyl–methine coupling constant of 6.2–6.3 Hz observed in D_2O and H_2O solutions agrees with that obtained by Booth, *et al.*,[17] for the 2,6-methyl doublets of 2,6-dimethyl- and 2,4,6-trimethylpiperidine.

Spectra of completely dry, sublimed "acetaldehyde–ammonia" in acetone-d_6 show no detectable peak for OH, NH or at best a very broad, weak resonance centered near the methyl doublet. The NH proton is expected to have a large line width (short T_2) owing to strong scalar relaxation from quadrupolar relaxed ^{14}N. If intermolecular exchange is slow or hydrogen-bonded dimers are not favored owing to steric interference, then it is not unreasonable to find the NH resonance too broad to detect. This effect has been observed for diisopropylamine.[18]

(14) C. J. Pouchert, "Aldrich Library of Infrared Spectra," 1970, p 154B.
(15) C. W. Hoerr, E. Rapkin, A. E. Brake, K. N. Warner, and H. J. Harwood, *J. Amer. Chem. Soc.*, **78**, 4667 (1956); H. H. Fox, *J. Org. Chem.*, **23**, 468 (1958).
(16) E. W. Lund, *Acta Chem. Scand.*, **5**, 678 (1951); E. W. Lund, *ibid.*, **12**, 1768 (1958).
(17) H. Booth, J. H. Little, and J. Feeney, *Tetrahedron*, **24**, 279 (1968).
(18) R. A. Murphy and J. C. Davis, Jr., *J. Phys. Chem.*, **72**, 3111 (1968).

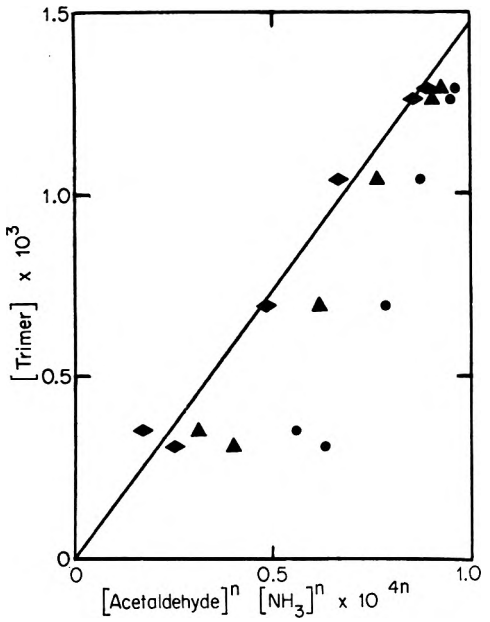


Figure 3.—Plot of the 2,4,6-trimethylhexahydro-*s*-triazine molar concentration *vs.* the concentration term $[\text{acetaldehyde}]^n[\text{NH}_3]^n \times 10^{4n}$ where $n = 1$ (●), $n = 2$ (▲), and $n = 3$ (◆). A least-squares fitted line for the equation $[\text{T}] = K_\text{T}[\text{A}]^3[\text{NH}_3]^3$ is shown with slope $K_\text{T} = 1.47 \times 10^9\ M^{-5}$. Data are from sample set d_2 in Table IV, pH 7.00 at 10°.

Further evidence that the commercial material was in equilibrium with acetaldehyde and ammonia was provided by experiments showing that acidification of aqueous solutions of "acetaldehyde–ammonia" (normally pH ~11) resulted in dissociation of the trimer (Figure 2). At 10° and pH 10.6 about 65% of the methyl resonances can be accounted for as trimer and 5% as aldehyde and hydrate, while at pH 7.5 there is about 80% aldehyde and hydrate.

Comparison of the nmr spectrum of an ammoniacal solution of acetaldehyde (Figure 1) with that of commercial "acetaldehyde–ammonia" (Figure 2) shows that in both cases the major ammonia adduct existing in solution is 2,4,6-trimethylhexahydro-*s*-triazine. The results shown in Figure 2 could also be produced using mixtures of acetaldehyde and ammonia and varying the pH from 7 to 10. Thus, the nmr results demonstrate that in aqueous solution the triazine trimer is in equilibrium with free acetaldehyde and ammonia along with other intermediate species, and that this equilibrium can be shifted from one extreme to the other by varying pH.

The chemical shift of the triazine methyl doublet exhibited a sigmoidal dependence on pH characteristic of species involved in a rapid protonation equilibrium.[19] The observed chemical shift can be expressed as

$$\delta_\text{obsd} = \delta_\text{T}^+ + \left(\frac{K_\text{A}}{K_\text{A} + [\text{H}^+]}\right)(\delta_\text{T} - \delta_\text{T}^+) \qquad (4)$$

where δ_T^+ and δ_T are the chemical shifts of the protonated and unprotonated forms and K_A is the acid dissociation constant for the protonated amine. Using a generalized nonlinear least-squares treatment[20] it was possible to calculate from the δ_obsd *vs.* $[\text{H}^+]$ data that at 10° and ~1.6 *M* ionic strength

$$\delta_\text{T}^{\text{CH}_3\text{CN}} = -0.666 \pm 0.003 \text{ ppm}$$

$$\delta_\text{T}^{+\text{CH}_3\text{CN}} = -0.899 \pm 0.006 \text{ ppm}$$

$$\text{p}K_\text{A} = 8.36 \pm 0.05$$

The difference in the chemical shift of the methyl doublet between the protonated and unprotonated forms is 0.23 ppm, in good agreement with an expected difference of about 0.30 ppm for compounds with the structure CH_3CN.[21] In comparing our $\text{p}K_\text{A}$ with known values, we find that piperidine, piperazine, and hexamethylenetetramine, which are cyclic amines with one, two, and four nitrogens, have $\text{p}K_\text{A}$'s at 25° of 11.2, 9.8, and 6.2, respectively.[22] Thus, our $\text{p}K_\text{A}$ is consistent with the triazine structure.

Further evidence that the trimer is the major ammonia adduct in aqueous solution was the cubic dependence of the concentration of the adduct on the concentrations of acetaldehyde and ammonia. This dependence was established by experiments showing that a plot (Figure 3) of the trimer concentration (T) against the concentration term $[\text{CH}_3\text{CHO}]^n[\text{NH}_3]^n$ gave a straight line passing through the origin only for $n = 3$, consistent with the reaction

$$3\text{CH}_3\text{CHO} + 3\text{NH}_3 \overset{K_T}{\rightleftharpoons} \text{trimer} \qquad (5)$$

The concentrations of the various unprotonated species in solution were calculated from peak area measurements using a $\text{p}K_\text{A}$ for ammonia corrected for the temperature and ionic strength (see Experimental Section) and the measured $\text{p}K_\text{A}$ for the trimer. From the slopes obtained in several experiments, where ammonia concentration, aldehyde concentration, or pH were varied, we have determined a value for K_T, the equilibrium constant for trimer formation, of $2.0 \pm 0.6 \times 10^9\ M^{-5}$ at 10°. This equilibrium constant (as well as all others presented in this report) is expressed in terms of free acetaldehyde concentration, rather than aldehyde plus hydrate.

Other Ammonia Adducts.—Adducts other than the trimer appear consistently in solutions of the trimer and in acetaldehyde and ammonia mixtures. An nmr study of the ammonia concentration dependence of these adducts was conducted at pH 10.5 and 10°. Spectra obtained for the adduct methyl region are shown in Figure 1. Three doublets can be distinguished in addition to those corresponding to hydrate (H) and trimer (T) (see Table III). The relative sizes of the various peaks were found to be a function of NH_3 concentration. At low ammonia con-

TABLE III
ADDUCT METHYL DOUBLETS AT pH 10.5, 10°

Doublet	$\delta^{\text{CH}_3\text{CN}}$, ppm	^3J, Hz
Hydrate	−0.746	5.25
D_1	−0.767	5.7–5.8
D_2	−0.811	5.6–5.7
D_3	−0.858	6.1–6.2
Trimer	−0.882	6.2

(19) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, Chapter 10.

(20) N. Arley and K. R. Buch, "Introduction to the Theory of Probability and Statistics," Wiley, New York, N. Y., 1950; I. S. Sokolnikoff and E. S. Sokolnikoff, "Higher Mathematics for Engineering and Physics," McGraw-Hill, New York, N. Y., 1941.

(21) G. Slomp and J. G. Lindberg, *Anal. Chem.*, **39**, 60 (1967).

(22) A. Albert, "Physical Methods in Heterocyclic Chemistry," Vol. I, A. R. Katritzky, Ed., Academic Press, New York, N. Y., 1963, p 2.

centrations the adduct peaks D_1, D_2, and D_3 were larger than those of the trimer. As ammonia concentration increased, the trimer peaks increased while D_1 decreased; D_2 and D_3 together reached a maximum at 0.20 *M* NH_4Cl but decreased as NH_4Cl was increased to 0.35 *M*. The doublets D_2 and D_3 were also clearly observed in experiments concerned with the pH dependence of solutions of the trimer (Figure 2) and acetaldehyde and ammonia mixtures. These two doublets showed a parallel change in chemical shift toward lower field as pH was decreased below 8, suggesting an amine with $pK_A = 7$–8. These findings suggest that peaks D_2 and D_3 correspond to a single adduct while peak D_1 belongs to a separate species. The possible nature of these additional adducts will be considered in the Discussion.

Line Broadening of Acetaldehyde in the Presence of Ammonia.—Kinetic information on the reaction of acetaldehyde with ammonia was obtained by a study of the line width of the acetaldehyde methyl group as a function of ammonia concentration *at pH 7*. Because of technical problems arising from the exchange of acetaldehyde methyl protons with D_2O solvent when ammonia was present, all of these experiments were carried out in H_2O solution. A series of samples were prepared with an initial acetaldehyde concentration of 0.32–0.40 *M;* the NH_4Cl concentration was varied from zero to 1.6 *M*, maintaining constant ionic strength with KCl. Under these conditions at pH 7 significant line broadening was observed for acetaldehyde while only small amounts of adducts were formed.

There appeared to be no dependence of line width on phosphate or acetaldehyde concentration. However, the line width of the aldehyde methyl doublet increased linearly with increasing NH_4Cl concentration; the line width of the hydrate was unaffected. At NH_4Cl concentrations above 0.40 *M* at 10° we observed the appearance of ammonia adducts described in previous sections. When necessary, the concentration of free NH_4^+ was corrected for these adducts (mostly trimer) by a procedure described in the Experimental Section.

The dependence of line broadening on NH_4^+ and NH_3 concentration can be expressed as follows.

$$\Delta\nu_A^* = S^+[NH_4^+] + C = S[NH_3] + C \quad (6)$$

The concentration of free NH_3 in the sample can be calculated from the usual relation

$$[NH_3] = K_A[NH_4^+]/a_H \quad (7)$$

where a_H is the hydronium ion activity and K_A is the dissociation constant for ammonium ion, corrected for temperature and ionic strength as described in the Experimental Section. A least-squares treatment of the line width *vs.* NH_4^+ and NH_3 concentration data (see Figure 4) gave the values of S^+ and S presented in Table IV.

The values of S^+ are quite reproducible for different experiments at one temperature, whereas the values for S are not nearly so reproducible. This reflects the fact that S depends on a precise knowledge of pH and the pK_A of ammonium ion. However, the fact that S (which contains information concerning the kinetics of the reaction of acetaldehyde with ammonia) *decreases* with increasing temperature is clear and will be considered further in the discussion.

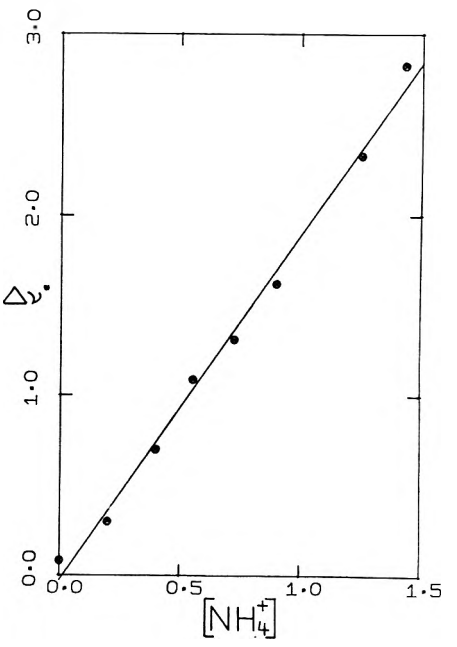


Figure 4.—Plot of residual line width for the acetaldehyde methyl doublet *vs.* ammonium ion concentration. Data are from sample set d_2 in Table IV, pH 7.0 at 10°.

TABLE IV

SLOPE OF ALDEHYDE METHYL LINE WIDTH *vs.* NH_4^+ AND NH_3 CONCENTRATION[a]

Temp, °C	pK_A^0[b]	Samples	S^+	S
10	9.730	d_1	1.87 ± 0.06	1710 ± 90
		d_2	1.91 ± 0.06	1580 ± 40
		c	1.95 ± 0.23	1270 ± 160
25	9.246	e	5.68 ± 0.17	1220 ± 40
34	8.976	c	4.37 ± 0.10	462 ± 8
		e	4.56 ± 0.08	522 ± 5

[a] Slopes are in units of Hz M^{-1} or l. mol^{-1} sec^{-1}. [b] pK_A of NH_4^+ at zero ionic strength (see Experimental Section). [c] 0.35 *M* CH_3CHO, 0.20 *M* NH_4Cl + KCl, 0.10 *M* phosphate, pH 7.00 at 25°. [d] 0.32 *M* CH_3CHO, 0.076 *M* CH_3CN, 1.60 *M* NH_4Cl + KCl, 0.10 *M* phosphate, pH 7.00 at 10°. [e] 0.40 *M* CH_3CHO, 0.063 *M* CH_3CN, 0.50 *M* NH_4Cl + KCl, 0.10 *M* phosphate, pH 7.00 at 10, 25, 34°.

In conjunction with the line broadening of acetaldehyde, we observed an upfield chemical shift of the aldehyde methyl doublet relative to acetonitrile while the hydrate showed no significant change in chemical shift. This change in chemical shift was found to be approximately linear in ammonia concentration, yielding a slope of 380 ± 20 Hz/mol of NH_3 which showed no observable dependence on temperature.

Discussion

Hydration of Acetaldehyde.—In much of the nmr work reported here it was necessary to calculate the concentrations of individual species present in the reaction mixtures. This was complicated by the fact that the adduct methyl resonances generally overlapped the hydrate resonance; hence, we often used the hydration equilibrium constant to calculate the hydrate concentration from that of the aldehyde.

Since kinetics of the addition of ammonia to acetaldehyde was studied by measuring the effect of ammonia on the line width of acetaldehyde, it was important to investigate whether any observed line broadening could

be due to an influence of ammonia on the hydration rate. The line width and hydration constant of acetaldehyde were found to be independent of NH_4^+ concentration at pH 4.8, while at pH 7–10 the aldehyde line width depends on NH_3 concentration. However, the line width of the hydrate is independent of NH_4^+ or NH_3. Thus, the line broadening of acetaldehyde in the presence of ammonia is due to a specific reaction with ammonia and not to a change in the hydration rate. The hydration reaction as an nmr chemical exchange problem has been studied in some detail.[23] Independent measurements of the hydration rate constant indicate that at neutral pH the contribution of exchange to the aldehyde and hydrate line widths would be negligible, in agreement with our observations.

Identity of the Ammonia Adducts.—The experiments which we have described demonstrate that at sufficiently high concentrations of NH_3 the major constituent present in ammoniacal solutions of acetaldehyde is the trimer 2,4,6-trimethylhexahydro-*s*-triazine. The formation of this trimer would be expected to proceed by a sequence of reactions whereby the addition of ammonia (or a primary amine) to the carbonyl group of acetaldehyde is followed by dehydration to form an imine, which undergoes further addition reactions. The detailed mechanism for the addition of RNH_2 to a carbonyl and subsequent imine formation has been demonstrated by several previous studies.[6,7b,24] A representative route to trimer from acetaldehyde and ammonia based on such a sequence is shown in Scheme I, where protonation equilibria have been omitted.

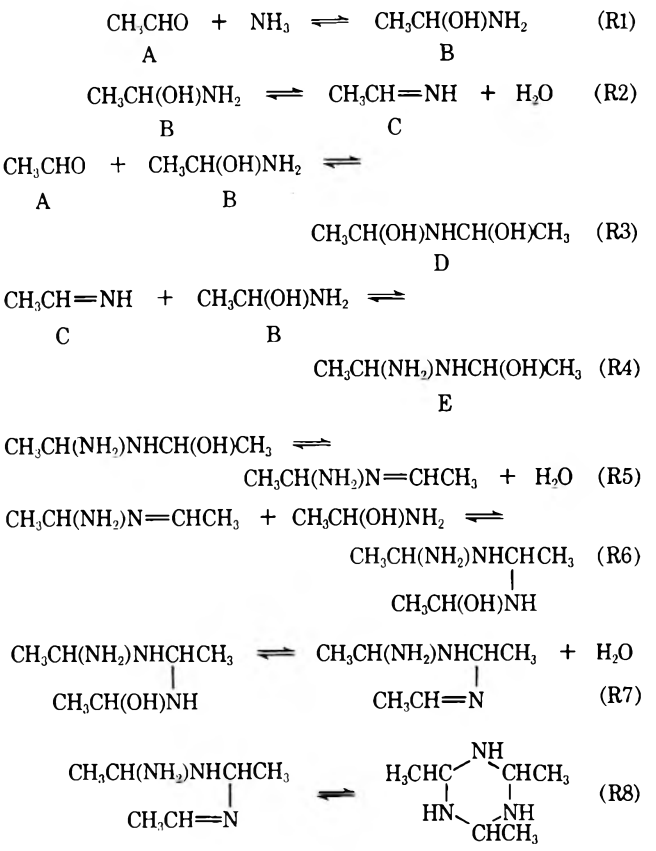
The accumulation of one or more of the intermediates or side products might be expected to occur under the appropriate conditions, and additional resonances were observed in the nmr spectra of aqueous solutions of acetaldehyde and ammonia (Figure 1, Table III). In addition to doublets corresponding to acetaldehyde hydrate and to trimer, three other methyl doublets could be identified when both acetaldehyde and ammonia were present. The doublets D_2 and D_3 were also observed in spectra of the commercial acetaldehyde–ammonia (Figure 2). Thus, these additional resonances represent intermediates involved in the equilibrium between the triazine trimer and free acetaldehyde and ammonia.

The effect of ammonia concentration and pH on the nmr spectra suggest that doublets 2 and 3 represent nonidentical methyl groups on the same molecular species, an amine with a $pK_A < 8$, while doublet 1 belongs to a compound with a single or equivalent methyl groups. The groups corresponding to D_1 and D_2 appear to be attached to a carbon containing one oxygen and one nitrogen as substituents, since the chemical shifts and coupling constants of these peaks are midway between the values for hydrate and trimer. On the other hand, methyl group D_3 would appear to be linked to a carbon bound to two nitrogens, since the coupling constant is the same as observed for the trimer and D_3 appears upfield of D_1 and D_2. We do not expect any

(23) M. L. Ahrens and H. Strehlow, *Discuss. Faraday Soc.*, **39**, 112 (1965); P. G. Evans, G. R. Miller, and M. M. Kreevoy, *J. Phys. Chem.*, **69**, 4325 (1965).

(24) (a) J. Hine, B. C. Menon, J. H. Jensen, and J. Mulders, *J. Amer. Chem. Soc.*, **88**, 3367 (1966); (b) J. Hine and J. Mulders, *J. Org. Chem.*, **32**, 2200 (1967); (c) J. Hine, J. C. Craig, J. C. Underwood II, and F. A. Via, *J. Amer. Chem. Soc.*, **92**, 5194 (1970).

SCHEME I



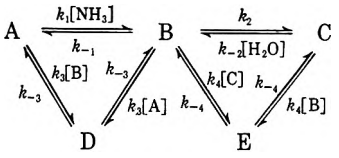
of the observed adducts to represent the carbinolamine 1-aminoethanol (see kinetic discussion to follow), and the various imines are probably too reactive to accumulate in a detectable amount. Furthermore, if these adducts were imines they would have detectable methyl resonances in the region near the aldehyde methyl where no additional peaks were observed. Based on the observed trends in chemical shift and coupling constant, and assuming that when a carbinolamine adds to a C=O or C=N group the nitrogen rather than the oxygen of the carbinolamine is the likely attacking nucleophile, we propose that the resonance D_1 belongs to the equivalent methyl groups of dimer IV (species D, Scheme I) while D_2 and D_3 belong to the two methyl groups of dimer V (species E, Scheme I).

Kinetics of the Addition of Ammonia to Acetaldehyde.—The line broadening of the acetaldehyde methyl resonance in the presence of ammonia is the result of chemical exchange processes which place the methyl group in chemically and magnetically distinguishable environments. Since we have observed that acetaldehyde and the triazine trimer are in equilibrium, the methyl groups are exchanging among all species shown in Scheme I. However, the line broadening shown by the acetaldehyde methyl resonance depends only upon those exchange processes which contribute significantly to the lifetimes in solution of acetaldehyde and of the carbinolamine with which it is in direct equilibrium. We propose that reactions R1–R4 (Scheme I) are the most likely contributors to the lifetime of aldehyde.

The aldehyde–hydrate equilibrium need not be considered, since we have seen that under our experimental conditions this exchange is slow on the nmr time scale, resulting in no measurable line broadening effects. Furthermore, we have observed well-resolved resonances for the triazine trimer in solution, indicating that its decomposition is slow and is not important in determining the lifetime of aldehyde. Protonation equilibria will not be considered, since the rates involved are in the fast exchange-narrowed limit and the nmr resonances observed are the weighted average of the protonated and unprotonated forms.

The chemical exchange problem is summarized in Scheme II.

SCHEME II



Under these conditions the lifetime of species A may be expressed as

$$\frac{1}{\tau_A} = k_1[NH_3] + k_3[B] = (k_1 + k_3K_1[A])[NH_3] \quad (8)$$

where

$$K_1 = k_1/k_{-1} = \frac{[B]}{[A][NH_3]}$$

At this point it is useful to summarize our experimental observations. (1) The resonance corresponding to acetaldehyde (A) has a lorenztian line shape and the line width *increases linearly* with the concentration of NH_3. (2) The rate at which the line width increases (*i.e.*, the slope) *decreases* with increasing temperature from 10 to 35°. (3) The line width is independent of the concentration of acetaldehyde. (4) The chemical shift of acetaldehyde moves upfield linearly with NH_3 concentration. (5) At high NH_3 concentration we observe adducts with possible structures D and E (Scheme I).

If steps R1 and R3 were in the slow exchange limit then the line width of A would be given by

$$\pi\Delta\nu_A = \frac{1}{T_{2A}} + \frac{1}{\tau_A} \quad (9)$$

From eq 8 it is seen that the line width would vary linearly with $[NH_3]$ and also should show a linear dependence on [A]. However, our observations suggest that the term containing [A] does not contribute in a measurable amount to the lifetime of A. This slow exchange result could only show a negative temperature dependence if the term containing K_1 was significant. In the typical slow exchange case the chemical shift of A is expected to remain fixed until line broadening becomes substantial. However, we have observed consistent chemical shifts with line broadening of only 1–3 Hz. Thus, our observations are inconsistent with the slow exchange situation represented by eq 8 and 9.

We have previously described the observation of adducts for which we propose the dimeric structures corresponding to species D and E. Since these species have nearly equal chemical shifts their interconversion must be quite slow (steps 3 and 4), indicating that these species have little effect on the lifetime of the aldehyde. Furthermore, the involvement of D necessitates a dependence of the lifetime of A on the concentration of A, which we did not observe. Therefore, based on the evidence at hand, we reduce the chemical exchange problems to three sites (Scheme III).

SCHEME III

$$A \underset{k_{-1}}{\overset{k_1[NH_3]}{\rightleftharpoons}} B \underset{k_{-2}[H_2O]}{\overset{k_2}{\rightleftharpoons}} C$$

At pH 7 with $[NH_3] \sim 10^{-4}$–10^{-3} M we expect that the concentration of carbinolamine (B) and imine (C) will be much less than the concentration of aldehyde. In the Appendix we present the general solution (originally developed by Swift and Connick[25]) for the three-site exchange problem under these conditions where A is the dominant species.

From eq A2 and A3 (see Appendix) the line width and chemical shift of acetaldehyde are given by

$$\pi\Delta\nu_A = \frac{1}{T_{2A}} + k_1[NH_3]\left[1 - \frac{k_{-1}\tau_B}{1 + \tau_B^2\Delta\omega_{BC}^2}\right] \quad (10)$$

$$\omega_{obsd} - \omega_A = -K_1[NH_3]\left[\frac{k_{-1}^2\tau_B^2}{1 + \tau_B^2\Delta\omega_{BC}^2}\right]\Delta\omega_{BC} \quad (11)$$

where

$$\frac{1}{\tau_B} = \frac{1}{T_{2B}} + k_{-1} + \epsilon k_2 \quad (12)$$

$$\Delta\omega_{BC} = \Delta\omega_b + \gamma\frac{K_2}{[H_2O]}\Delta\omega_c \quad (13)$$

$$\epsilon = \frac{1/T_{2c}^2 + k_{-2}[H_2O]/T_{2c} + \Delta\omega_c^2}{(1/T_{2c} + k_{-2}[H_2O])^2 + \Delta\omega_c^2} \leq 1 \quad (14)$$

$$\gamma = \frac{1}{(1 + 1/T_{2c}k_{-2}[H_2O])^2 + (\Delta\omega_c/k_{-2}[H_2O])^2} \leq 1 \quad (15)$$

The expressions for τ_B and $\Delta\omega_{BC}$ are independent of $[NH_3]$; hence, the line width and chemical shift should vary linearly with ammonia concentration regardless of the rate constants involved.

If the lifetime of the carbinolamine were in a slow exchange limit where $\tau_B^2\Delta\omega_{BC}^2 \gg 1$, then the line width would reduce to

$$\pi\Delta\nu_A = \frac{1}{T_{2A}} + k_1[NH_3] \quad (16)$$

Under these conditions the line width would be expected to increase with increasing temperature owing to an increase in the rate k_1, a situation which is not compatible with our results.

According to eq 10, the line width will decrease with increasing temperature only if the term in brackets (containing τ_B) has a negative temperature dependence which exceeds the positive dependence of k_1. Rearranging eq 10 gives

$$\pi\Delta\nu_A = \frac{1}{T_{2A}} + k_1\left[\frac{\tau_B^2\Delta\omega_{BC}^2 + \dfrac{\epsilon k_2 + 1/T_{2B}}{k_{-1} + \epsilon k_2 + 1/T_{2B}}}{1 + \tau_B^2\Delta\omega_{BC}^2}\right][NH_3] \quad (17)$$

For fast exchange, where $\tau_B^2\Delta\omega_{BC}^2 \ll 1$, the line width will have a negative temperature dependence, since $k_1\tau_B^2$ will have the temperature dependence of τ_B, and k_1 multiplied by the second term in brackets can be shown always to have a negative temperature de-

(25) T. J. Swift and R. E. Connick, *J. Chem. Phys.*, **37**, 307 (1962).

pendence. Thus our results indicate that we are dealing with a fast exchange situation. We therefore cannot observe a distinct resonance for the carbinolamine, since the "aldehyde" resonance is actually the coalesced resonance for both species. Using the fast exchange condition $\tau_B^2\Delta\omega_{BC}^2 \ll 1$ and the fact that $k_{-1} + \epsilon k_2 \gg 1/T_{2B}$ ($1/T_{2B} \sim 1$ sec^{-1}), eq 17 and 11 may be expressed as follows

$$\pi\Delta\nu_A = \frac{1}{T_{2A}} + k_1\left[\tau_B^2\Delta\omega_{BC}^2 + \frac{\epsilon k_2 + 1/T_{2B}}{k_{-1} + \epsilon k_2}\right][NH_3] = \pi(S[NH_3] + C) \quad (18)$$

$$\omega_{obsd} - \omega_A = -K_1\left(\frac{k_{-1}}{k_{-1} + \epsilon k_2}\right)^2\Delta\omega_{BC}[NH_3] \quad (19)$$

where S is the slope of a plot of $\Delta\nu_A$* *vs.* $[NH_3]$ (Table IV).

The term $\Delta\omega_{BC}$ as defined by eq 13 consists of two parts. The quantity $\Delta\omega_b = \omega_{obsd} - \omega_b$ can be estimated as $\sim 2\pi$ (90 Hz) from the fact that the carbinolamine is expected to have a chemical shift very near that of the hydrate. The second term $\gamma\cdot(C/B)\Delta\omega_C$ is more difficult to estimate. However, nmr data for imines suggest that $\Delta\omega_C \lesssim 2$ (20 Hz) and we do not expect $\gamma\cdot(C/B)$ to be large, since $C/B = k_2/k_{-2}[H_2O]$ and if $k_{-2}\cdot[H_2O] < \Delta\omega_C$ then $\gamma \ll 1$. Thus reasonable limits for $\Delta\omega_{BC}$ are

$$550 \leqslant \Delta\omega_{BC} \leqslant 1000 \quad (20)$$

By analogy with data from other systems it is reasonable to assume $\epsilon k_2 \lesssim k_{-1}$. Using this constraint and those described above, limits for the kinetic parameters for carbinolamine formation can be derived. First, the fast exchange condition $\tau_B^2\Delta\omega_{BC}^2 \ll 1$ implies that $k_{-1} + \epsilon k_2 > 550$ or $k_{-1} \gtrsim 300$ sec^{-1}. Next considering eq 18, the term in brackets will be $\gtrsim 1/2$ so that $k_1 \gtrsim 2\pi\cdot S$. From the values of S at 10° (Table IV) $k_1 \gtrsim 10^4\ M^{-1}$ sec^{-1}. Finally we have found that a plot of the aldehyde chemical shift *vs.* $[NH_3]$ has a slope of 380 Hz M^{-1}. From this result and eq 19 and 20, upper and lower bounds for K_1 can be determined. The kinetic parameters are summarized below.

$$k_{-1} > 3 \times 10^2 \text{ sec}^{-1} \qquad k_1 \gtrsim 10^4\ M^{-1}\text{ sec}^{-1}$$
$$2 \lesssim K_1 \lesssim 17\ M^{-1} \quad (21)$$

For comparison, Hine, *et al.*,[24c] have determined the individual rate constants for the reaction of methylamine with isobutyraldehyde. Their values are $k_1 \sim 5 \times 10^5\ M^{-1}$ sec^{-1}, $k_2 \sim 40$ sec^{-1}, and $K_1 = 8.5\ M^{-1}$ at pH 7 and 35°. Hine and Via[8] also found that for a series of alkylamines with polar substitutents K_1 shows a good linear correlation with pK_a and the Taft steric constant E_s. From their relation we calculate a K_1 for ammonia of $\sim 4\ M^{-1}$, a value within the range determined by nmr. (This agreement may be fortuitous, however, since it may be argued that ammonia cannot be treated as a primary amine.) Finally, Hine and Kokesh[26] used nmr to study the addition of trimethylamine to formaldehyde, finding that, at 25°, $k_1 = 1.3 \times 10^7\ M^{-1}$ sec^{-1} and $k_{-1} = 3.4 \times 10^3$ sec^{-1}.

Ogata and Kawasaki[27] studied the kinetics of the addition of ammonia to acetaldehyde by following the decrease in the carbonyl absorption at 278 nm. For calculating rate and equilibrium constants, they assumed that no adducts other than the carbinolamine were formed. However, our results indicate that their experimental conditions of high pH, low temperature, and reactant concentrations of 0.1 M would lead to a substantial amount of other adducts, including the triazine trimer. Furthermore, their rate constants are too low ($k_1 = 26\ M^{-1}$ sec^{-1} at 5°, pH 7) to account for the observed nmr line broadening. We believe that these workers were actually observing the rate-determining step(s) in the slow overall conversion of acetaldehyde to trimer.

Experimental Section

Reagents.—Practical grade acetaldehyde (Matheson Coleman and Bell) was distilled at room temperature immediately prior to use. Nmr observations showed that aqueous solutions of acetaldehyde so purified were free of 1,1′-oxydiethanol,[28] paraldehyde, and acetic acid under all of our experimental conditions. Spectrograde acetonitrile was obtained from Eastman. Analytical reagent grade KCl, NH_4Cl, KH_2PO_4, and K_2HPO_4 were desiccated and used without further purification.

2,4,6-Trimethylhexahydro-*s*-triazine.—Technical grade acetaldehyde–ammonia from Eastman was purified by sublimation at 3 mm, maintaining sample temperature at 40–45° and condensing the sublimate on a cold finger at 5°. Large white crystals of 2,4,6-trimethylhexahydro-*s*-triazine were obtained free from water of hydration (mp 95–96°).

Mass spectra were obtained on an Associated Electrical Industries MS-9 instrument; the parent peak at m/e 129 and extensive fragmentation pattern observed were consistent with the formula $(CH_3CHNH)_3$. Infrared spectra were obtained on a Perkin-Elmer Infracord, and samples were prepared as mulls in Kaydol mineral oil and hexachlorobutadiene.

Sample Preparation.—All samples were prepared fresh and kept cold prior to nmr observations. Aldol condensation was not observed to take place during the course of the experiment, although high pH samples did turn yellow after several hours at room temperature. The sample pH was measured using a Beckman Expandomatic pH meter and 39030 combination electrode; adjustments of pH were made using 6 M HCl or concentrated KOH solutions. A water bath maintained samples within ±2° of the desired temperature throughout the period of measurement and adjustment.

Nmr Spectroscopy.—Proton nmr spectra were obtained at 100 MHz on a Varian HA-100D spectrometer equipped with a variable-temperature probe. A line width and chemical shift reference (acetonitrile) was added to each sample and for aqueous solutions the H_2O resonance was used as a field–frequency lock. Using a flow of nitrogen gas through a Dry Ice–acetone heat exchanger, sample temperatures could be maintained to ±0.2°. Actual temperatures were determined from the chemical shift of the OH resonance in a methanol reference sample using the calibration results of Van Geet.[29]

Spectra were taken using 50-Hz sweep widths and sweep rates of 0.05 or 0.02 Hz/sec. The observed RF power levels were maintained below saturation. Line widths were measured relative to the reference peak whose line width is dominated by field inhomogeneity and is independent of pH or other species present. Chemical shifts were measured with the Hewlett-Packard frequency counter for the HA-100 and are believed accurate to ±0.2 Hz (±0.002 ppm).

Concentration Determination.—Areas under peaks were measured with a Keuffel and Esser Model 620005 polar planimeter, and the individual peak areas were normalized by dividing by the total area for all methyl groups. Concentrations of individual species were calculated by assuming that the total methyl area was equivalent to the initial acetaldehyde concentration. Overlap of the hydrate methyl by other adducts made its measurements difficult; therefore, the concentration of hydrate was usually calculated from the aldehyde peak using the hydration equilibrium constant. The concentration of NH_4^+ plus NH_3 was calculated

(26) J. Hine and F. C. Kokesh, *J. Amer. Chem. Soc.*, **92**, 4383 (1970).

(27) Y. Ogata and A. Kawasaki, *Tetrahedron*, **20**, 855 (1964); Y. Ogata and A. Kawasaki, *ibid.*, 1573 (1964).

(28) G. Socrates, *J. Chem. Soc., Chem. Commun.*, 702 (1969); F. Podo and V. Viti, *Org. Magn. Resonance*, **3**, 259 (1971).

(29) A. L. Van Geet, *Anal. Chem.*, **42**, 679 (1970).

by subtracting from the initial concentration the amount of ammonia incorporated into adduct, assuming one ammonia incorporated per adduct methyl group.

The pK_A of Ammonium Ion.—The pK_A of ammonium ion has been found to satisfy the following equation at 25°.[30]

$$pK_A = pK_A^\circ + 0.132[NH_4Cl] + 0.198[KCl] \quad (22)$$

The value of pK_A° is obtained from the data of Bates and Pinching,[31] who determined pK_A as a function of temperature and extrapolated to zero ionic strength.

$$pK_A^\circ = 2835.75/T - 0.6322 + 0.001225T \quad (23)$$

The variation of mean activity coefficients with temperature over the range of 10–35° has been found to be at most 4% at 2 *m* concentration.[32] Therefore, we have used eq 22 over this temperature range with the appropriate pK_A° determined by eq 23. Any specific effect of the phosphate buffer was not considered.

Appendix

The interpretation of the nmr line broadening results for acetaldehyde in the presence of ammonia depends upon the relationship between chemical exchange and nmr line shapes. From the arguments presented in the text, the system involves exchange among three chemically distinguishable sites.

$$A \underset{1/\tau_{ba}}{\overset{1/\tau_{ab}}{\rightleftharpoons}} B \underset{1/\tau_{cb}}{\overset{1/\tau_{bc}}{\rightleftharpoons}} C \quad (A1)$$

The dependence of nmr line shape on chemical exchange can be analyzed with the standard classical Bloch equations. This treatment is valid in the present system, in which intact methyl groups and methine protons are exchanging among different chemical species.[33] Below are presented the general equations describing the behavior of the chemical shift and line width of the A resonance in the presence of chemical exchange when [A] ≫ [B], [C]. These equations are expressed in the form most useful for the analysis of the system under study.

$$\pi\Delta\nu_A = \frac{1}{T_{2a}} + \frac{1}{\tau_{ab}}\left[1 - \frac{\tau_B/\tau_{ba}}{1 + \tau_B^2\Delta\omega_{BC}^2}\right] \quad (A2)$$

$$\omega_{obsd} - \omega_A = -\frac{[B]}{[A]}\left[\frac{\tau_B^2/\tau_{ba}^2}{1 + \tau_B^2\Delta\omega_{BC}^2}\right]\Delta\omega_{BC} \quad (A3)$$

$$\frac{1}{\tau_B} \equiv \frac{1}{T_{2b}} + \frac{1}{\tau_{ba}} + \frac{\epsilon}{\tau_{bc}} \quad (A4)$$

$$\Delta\omega_{BC} \equiv \Delta\omega_b + \gamma\frac{[C]}{[B]}\Delta\omega_c \quad (A5)$$

$$\epsilon = \frac{1/T_{2c}^2 + 1/T_{2c}\tau_{cb} + \Delta\omega_c^2}{(1/T_{2c} + 1/\tau_{cb})^2 + \Delta\omega_c^2} \leq 1 \quad (A6)$$

$$\gamma = \frac{1}{\left(1 + \frac{\tau_{cb}}{T_{2c}}\right)^2 + \tau_{cb}^2\Delta\omega_c^2} \leq 1 \quad (A7)$$

The line width $\Delta\nu_A$ as usually defined is the full width at half height; ω_i and T_{2i} are the chemical shift (in rad/sec) and the spin–spin relaxation time (in seconds) for the site i in the absence of exchange; ω_{obsd} is the observed chemical shift for site A in the presence of exchange; $\Delta\omega_i = \omega_{RF} - \omega_i \approx \omega_{obsd} - \omega_i$, where ω_{RF} is the frequency of the swept RF field. The terms τ_B, which can be considered a generalized lifetime for site B, and $\Delta\omega_{BC}$, a generalized chemical shift, have been defined to reduce the complexity of the expressions A2 and A3, resulting a in pseudo-two-site formalism.

Registry No.—Acetaldehyde, 75-07-0; ammonia, 7664-41-7; 2,4,6-trimethylhexahydro-s-triazine, 638-14-2; acetaldehyde hydrate, 4433-56-1.

(30) M. T. Emerson, E. Grunwald, and R. A. Kromhout, *J. Chem. Phys.*, **33**, 547 (1960).

(31) R. G. Bates and G. D. Pinching, *J. Amer. Chem. Soc.*, **72**, 1393 (1950).

(32) H. S. Harned and B. B. Owen, "Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, p 727.

(33) H. M. McConnell, *J. Chem. Phys.*, **28**, 430 (1958).

Heterocyclic Studies. 39. Enolic and Bicyclic Isomers of 2,3- and 1,5-Dihydro-1,2-diazepin-4-ones[1]

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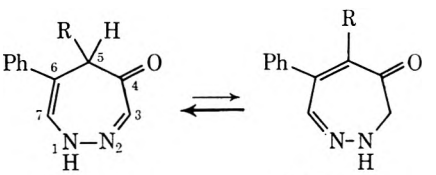
Conditions are described for conversion of the 1,5- and 2,3-dihydrodiazepinones **1** and **2** to *N*-acyl ketones and to *N*-acylenol esters. Enol acylation is much more rapid in the 1,5-dihydro series. Acylation of the 1,5-dihydrodiazepinones under conditions favoring N-2 substitution leads to 2-acyl-2,3-diazabicyclo[3.2.0]-3-heptenones. These bicyclic ketones lose the elements of methylketene or phenylketene on heating, giving 1-acyl-4-phenylpyrazoles.

In an earlier note we reported the formation of the 1,5-dihydrodiazepinone **1a** by base-catalyzed isomerization of the 2,3-dihydro tautomer **2a**.[2] Interconversion of these ketones involves an equilibrium of the respective enolates in which the 1,5-dihydro isomer predominates (**1a**:**2a** ~8). This approach has been applied also to the 2,3-dihydro-5,6-diphenyldiazepinone **2b**,[3] and provided the 1,5-dihydro tautomer **1b** in about 50% yield. The position of the equilibrium could not be measured as was done in the 5-methyl series because of the lack of a distinctive nmr signal, but it clearly favors the 1,5-dihydro tautomer.



1,5-dihydro 2,3-dihydro

1a, R = CH_3 **2a**, R = CH_3
b, R = C_6H_5 **b**, R = C_6H_5

Both of these diazepinone systems contain a multiplicity of nucleophilic centers. In the 2,3-dihydro series, substitutions at N-1, N-2, and C-3 have been observed. Highly reactive electrophiles such as acid chlorides and oxonium reagents attack **2a** at the N-1 position, leading in the former case to the bicyclo-

(1) Supported in part by grants from the National Science Foundation and the Unidel Foundation.

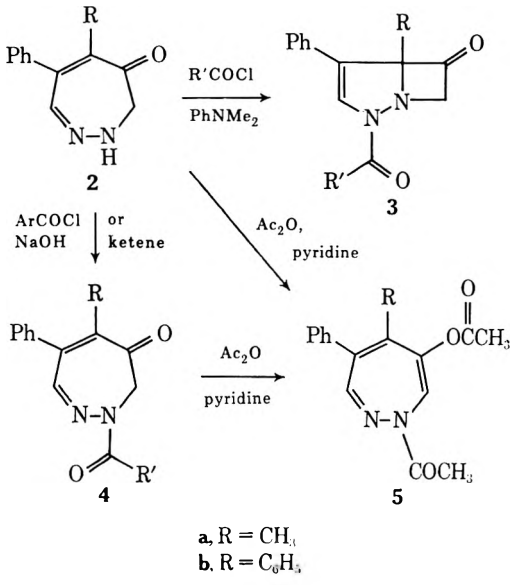
(2) M. G. Pleiss and J. A. Moore, *J. Amer. Chem. Soc.*, **90**, 1369 (1968). Complete details of these base-catalyzed reactions will be found in the Ph.D. Dissertation of M. G. Pleiss, University of Delaware, 1969.

(3) A. Nabeya, F. B. Culp, and J. A. Moore, *J. Org. Chem.*, **35**, 2015 (1970).

[3.2.0] ketones **3** (Chart I).[4] The latter compounds have now been obtained also from **2b**. Alkylation

CHART I

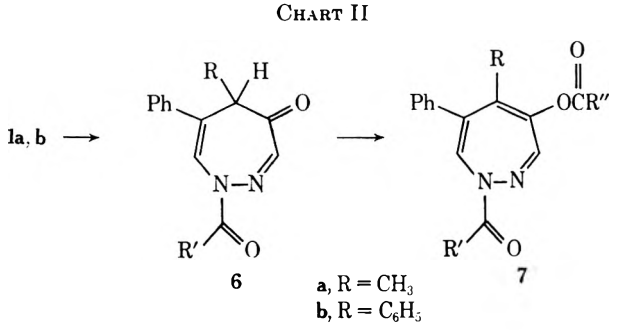
ACYLATION OF 2,3-DIHYDRODIAZEPINONES



of **2a** under basic conditions occurs, presumably *via* the N anion, at N-2.[5]

We have now extended the study of acylation reactions in both diazepinone series. 2-Aroyl derivatives **4** of the 2,3-dihydrodiazepinones are best obtained under Schotten–Baumann conditions, and parallel reactions in the 1,5-dihydro series give the 1-aroyldiazepinones **6** (Chart II). The preferred reagent for the acetyl ketones is ketene.

CHART II



Enol Acylation.—Prolonged treatment of the NH or *N*-acetyl-2,3-dihydrodiazepinones **2** or **4** with acetic anhydride–pyridine at 80° has been found to give crystalline yellow-orange *diacetyl* products. These compounds have ν_{CO} 1755 and 1680 cm^{-1} and are readily hydrolyzed to the parent NH ketones **2**. These properties permit assignment of the acetoxydiazepine structures **5**. Although enolization was clearly implicated by the base-catalyzed deuterium exchange of the C-3 protons of **2**[2] and the equilibration of **2** and **1**, the diazepines **5** are the first enol derivatives to be isolated in this system. Attempts to obtain enol ethers or enamines of **2** have been unsuccessful.

(4) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 34 (1966).

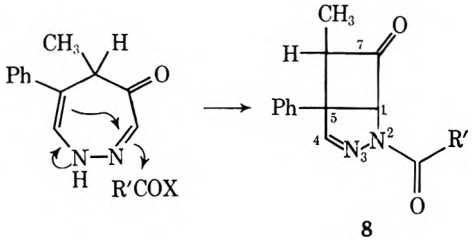
(5) W. J. Theuer and J. A. Moore, *ibid.*, **32**, 1602 (1967).

The 1-acyl-1,5-dihydro ketones **6** were also converted to enol esters **7** by further acylation. These reactions were very much more rapid than those in the 2,3-dihydro series. Solutions of the *N*-acetyl ketones **4a** and **6** (R′ = CH_3) containing 1.6 equiv of Ac_2O and 1.6 equiv of Et_3N were kept at 25° for 36 hr; the formation of enol acetates **5** and **7** was 6 and 90%, respectively (by nmr). The facility of enol acylation in the 1,5-dihydro series permitted the preparation of enol benzoates **7a** (R″ = Bz) as well; the corresponding benzoate esters could not be isolated from the 2,3-dihydrodiazepinones.

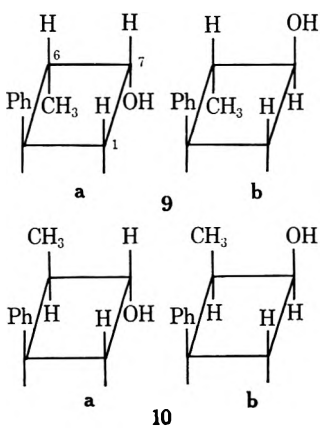
The ease of enol acylation was particularly marked in the 5,6-diphenyl-1,5-dihydro series. Reaction of the NH ketone **1b** with excess acetic anhydride gave the enol acetate **7b** (R′ = R″ = CH_3) plus a colorless isomer (**12**) discussed below. The 1-acetyl ketone **6b** (R′ = CH_3), available by ketene acylation of **1b**, was not detected.

The enol acetates in the two series had very similar spectra, and their structures would not be distinguished except by formation from and hydrolysis to the respective ketones. Studies on the thermal reactions of these diazepines will be reported in a later paper.

2,3-Diazabicycloheptenones.—Reaction of the NH 1,5-dihydrodiazepinone **1a** with acid chlorides and dimethylaniline leads to the bicyclo[3.2.0] ketones **8**. The benzoyl ketone **8** (R′ = C_6H_5, 60% yield) was crystalline; the ir spectrum contained the expected ν_{CO} at 1790 cm^{-1} for a four-membered cyclic C=O group. The nmr spectrum [δ 1.38 (d, 3, J = 7.4 Hz), 4.16 (dq, 1, J = 7.4 and 3.2 Hz), 6.06 (d, 1, J = 3.2 Hz), 6.93 (s, 1), 7.1–7.5 (m, 10)] was consistent with **8**, but did not permit assignment of the steric configuration of the methyl group.



To establish this point, the ketone was reduced with $NaBH_4$. A major carbinol isomer was crystallized in 35% yield; the nmr spectrum of the mother liquor showed peaks due to both isomers. The four possible carbinols are the two pairs **9a** and **9b** and **10a** and **10b**.



The parameters of importance for the stereochemical assignment are the coupling constants $J_{6,7}$ and $J_{1,7}$ for the three methine protons at 1, 6, and 7 in the carbinols. The dd signals for H-1 and H-7 of both isomers were well separated in the spectrum of the mixture, permitting direct measurement of the values given in Table I.

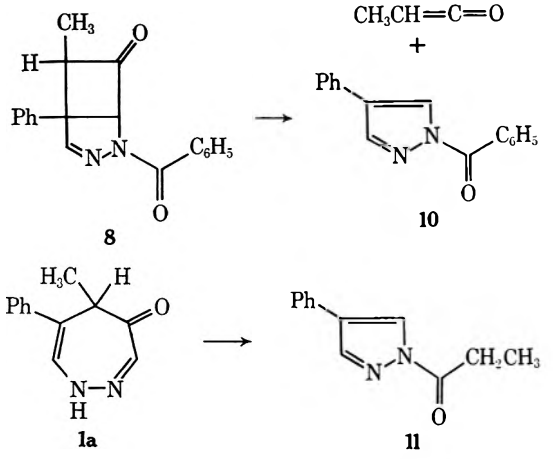
TABLE I
NMR DATA FOR BICYCLIC CARBINOLS 9[a]

	δ, ppm	
	Major isomer	Minor isomer
H-1	5.08	4.86
H-6	3.08	~3.0[b]
H-7	4.48	3.66[c]
6-CH_3	1.17	~1.2[b]
	J, Hz[d]	
1,6	1.2	1.2
1,7	5.3	3.5
6,7	8.6	6.3
CH_3-6	7.2	7

[a] In CCl_4; Perkin-Elmer Model R-12B spectrometer. [b] Obscured by peak of major isomer. [c] Small additional splitting of the dd. [d] Estimated error ±0.3 Hz.

The two isomeric alcohols are **9a** and **9b** or **10a** and **10b**. In **9a** and **9b**, one isomer (**9a**) has the methine protons 1,7 and 6,7 *both* cis, and the other isomer (**9b**) has *both* trans. In the isomeric pair **10**, the isomers have 1,7 cis, 6,7 trans, or vice versa. On the basis that $J_{cis} > J_{trans}$ for vicinal methine protons in cyclobutanes,[6] the data in Table I show that the pair of isomers obtained in the $NaBH_4$ reduction are **9a** and **9b**, since *both* $J_{6,7}$ and $J_{1,7}$ are larger (cis) in one isomer than the corresponding $J_{6,7}$ and $J_{1,7}$ in the other. Thus the ketone **8** must have the endo methyl configuration. It follows that the major crystalline alcohol is the endo alcohol **9a** with the two cis coupling constants. This is clearly predictable, since both the five-membered ring and the endo methyl group act to direct hydride attack from the outer face of the four-membered ring.

In contrast to the complex thermal isomerization of the 1,2-diazabicyclic ketones **3a**,[7] the *N*-benzoyl-2,3-diaza[3.2.0] ketone **8** undergoes cleavage at 100° to methylketene and 1-benzoyl-4-phenylpyrazole (**10**).



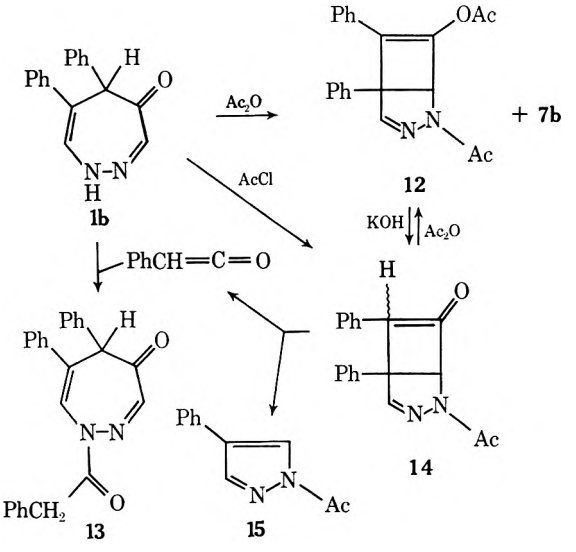
(6) H. Weitkamp and F. Korte, *Tetrahedron, Suppl.*, **7**, 75 (1966).
(7) O. S. Rothenberger and J. A. Moore, *J. Org. Chem.*, **37**, 2796 (1972).

When the pyrolysis was carried out in a heated column with an aniline trap at the exit, propionanilide was isolated in very low yield. In these reactions, a very characteristic sweet odor accompanied the decomposition. The same odor had been noted earlier on heating the parent diazepinone **1a** to its melting point (dec), and we were thus prompted to examine the pyrolysis products of **1a**. Entrainment of the diazepinone in a nitrogen stream through a 300° packed column led to much tar, but 4-phenylpyrazole and 1-propionyl-4-phenylpyrazole (**11**) were isolated in a combined yield of 30%. The latter compound is responsible for the odor, which was also observed with a sample prepared by propionylation of 4-phenylpyrazole.

Pyrolysis of 2,3-dihydrodiazepinone **2a** in the same apparatus gave 4-phenylpyrazole in 10% yield, presumably by prior isomerization to **1**. In view of the severe conditions and the greater stability of **1**, no mechanistic significance can be attached to this result.

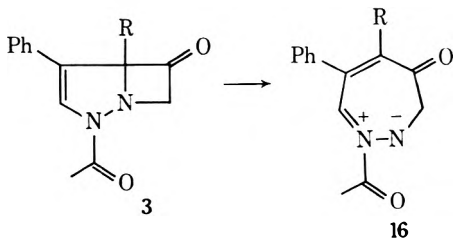
In the diphenyl series, acylation under conditions favoring substitution at N-2 was more complex, and exclusive attack at N-2 was not achieved. Treatment of **1b** with AcCl–pyridine at 20° gave three products which were separated by SiO_2 chromatography and identified as the 1-acetyldiazepinone **6b** (R′ = CH_3), 1-acetyl-4-phenylpyrazole (**15**), and 1-phenylacetyldiazepinone **6b** (R′ = $PhCH_2$). This odd collection of products suggests that the diphenylbicyclic ketone **14** is significantly less stable than **8**, with phenylketene being lost under the reaction conditions and trapped by unreacted diazepinone.

Definite information on this point was gained from the minor diacetyl product of **1b** and acetic anhydride, obtained together with the enol acetate **7b** as mentioned above. This compound had ν_{CO} 1770 and 1680 cm^{-1} and an nmr peak at δ 5.5 ppm. These properties and the source of the compound suggested the bicyclic enol acetate **12**, and this was confirmed by very mild hydrolysis to the ketone **14** (ν 1800 cm^{-1}) which crystallized in slightly impure form. A solution of **14** in $CDCl_3$ decomposed at 25° ($t_{1/2}$ = 24 hr) to **15** and presumably phenylketene.



The difference in the course of the thermal reactions of the bicyclic ketones **3** and **8** is noteworthy. The

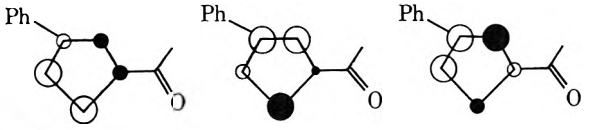
ketones **3** at 80° undergo ring opening to the acyldiazepinium betaines **16**;[7] no scission to pyrazole



3 **16**

and ketene is detected. The reaction **3** → **16** is much slower (for **3**, R = Ph, $t_{1/2}^{80°}$ = 2 hr) than the cleavage of **8** or **14** to pyrazole plus ketene, suggesting that the divergent course of the reactions lies in a lower energy path for the ketene scission with ketones **8** and **14**.

Orbital symmetry considerations for the cycloaddition reactions of ketene with the C-4–C-5 and N-2—C-3 bonds of 1-acyl-4-phenylpyrazole predict an allowed and forbidden $_{\pi}2_a + {}_{\pi}2_s$ path, respectively, if only the highest occupied (HOMO) and lowest unoccupied (LUMO) orbitals of the pyrazole are considered. The pertinent MOs calculated by the HMO method[8] are shown. However, MO ψ_6, separated only by 0.36β from the HOMO and having local



ψ_6 (0.9837β) ψ_7 (0.6243β) HOMO ψ_8 (−0.5346β) LUMO

symmetry opposite to that in the HOMO, may also contribute significantly, making the prediction ambiguous. In fact perturbation treatment[9] including all the MOs indicates no essential difference between the two cycloaddition reactions either for the totally synchronous or for the nonsynchronous path. Moreover, little difference is predicted for the π-complex formation between the carbonyl carbon atom of ketene and the respective π bond of the pyrazole. Thus, the difference observed in the thermal behavior between **3** and **8** cannot be attributed to orbital symmetry control.

Experimental Section

Infrared spectra in KBr pellets were recorded on a Perkin-Elmer Model 137. Ir spectra in $CHCl_3$ were recorded on a Perkin-Elmer Model 180 instrument. Nmr spectra were obtained on a Varian Model A-60A spectrometer.

5,6-Diphenyl-2,3-dihydro-4*H*-1,2-diazepin-4-one (2b).—The following procedure is an improvement over the earlier one,[3] which required evaporation of a relatively large volume of acetic acid; this step causes darkening and formation of oily byproducts.

A solution of 10 g of 3-diazoacetyl-*cis*-3,4-diphenyl-1-pyrazoline in 50 ml of tetrahydrofuran plus 200 ml of MeOH was treated at 0° with 3 ml of 1 *N* methanolic KOH and allowed to stand for 4 hr. Tlc showed nearly complete conversion to the 5-pyrazoline. The solution was then brought to pH 7 by the addition of concentrated HCl and was stirred at 0° for 1 hr (end of gas evolution). The dark orange solution was evaporated *in vacuo* to a thick syrup. On heating this syrup with 200 ml of ether some solid separated and the remainder of the oil dissolved. The solid was filtered and extracted further with ether, and the combined ether solution was evaporated to give a total of 7.1 g (79%) of **2b**, mp 192–196°.

5,6-Diphenyl-1,5-dihydro-1,2-diazepin-4-one (1b).—A solution of 3.8 g of the 2,3-dihydrodiazepinone **2b** in 18 ml of dimethyl sulfoxide was treated with 1.8 ml of 1 *N* NaOH and stirred at 60° under nitrogen for 2 days. The mixture was then poured into 250 ml of water and extracted with ether. The ether solution was washed thoroughly with water to remove DMSO and was then dried and evaporated to give 3.2 g of tan solid. After silicic acid chromatography (twice) and charcoal treatment, recrystallization from benzene–cyclohexane gave 1.7 g of **1b**: mp 133–134°; ν^{KBr} 3400, 1650 cm^{-1}; δ^{CDCl_3} 5.10 (br singlet, actually unresolved m, 1, H-5), 6.94 (dd, J = 4.3, 1.7 Hz, H-3 or H-7), 7.05–7.35 (m, 11, 2Ph + H-3 or H-7).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.85; H, 5.25; N, 10.56.

2-Benzoyl-4,5-diphenyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-one (3b, R′ = C_6H_5).—A solution of 260 mg (1 mmol) of **2b** and 0.5 ml of *N*,*N*-dimethylaniline in 10 ml of CH_2Cl_2 was treated with 0.12 ml (141 mg, 1 mmol) of benzoyl chloride. After 4 hr at 20° the solution was washed with ice water and then dilute HCl and $NaHCO_3$ solution. The solution was dried and evaporated to a solid. Crystallization from ether gave 270 mg of light brown crystals of bicyclic ketone. Further crystallization from benzene–cyclohexane gave nearly colorless crystals: mp 133° dec; ν^{KBr} 1800, 1650 cm^{-1}; δ^{CDCl_3} AB part of ABX (H-7 exo, H-7 endo, and H-3) δ_A 4.57 (dd, 1, J_{AX} = 0.9, J_{AB} = 17 Hz), δ_B 4.77 (dd, 1, J_{AX} = 0.9, J_{AB} = 17 Hz), 7.1–7.6, 7.7–8.0 (m, 11).

Anal. Calcd for $C_{24}H_{18}N_2O_2$: C, 78.67; H, 4.95. Found: C, 78.92; H, 4.85.

The 2-acetyl bicyclic ketone (**3b**, R′ = CH_3) was similarly obtained from 260 mg of **2b** and 0.15 ml of acetyl chloride. The bicyclic ketone crystallized from ether: 151 mg (50%); mp 158–160°; ν^{KBr} 1795, 1665 cm^{-1}; δ^{CDCl_3} 2.26 (s, 3), 4.55 (d, 1, J = 16.8 Hz), 4.90 (d, 1, J = 16.8 Hz), 7.1–7.6 (m, 10), 7.80 (s, 1).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.81; H, 5.29; N, 8.94.

2-Acetyl-5-methyl-6-phenyl-2,3-dihydro-1,2-diazepin-4-one (4a, R′ = CH_3).—A solution of 600 mg (3 mmol) of **2a** in 10 ml of CH_2Cl_2 was treated with 12 mmol of ketene. After 4 days the solution was evaporated and the oil was crystallized on seeding with an earlier sample. Sublimation at 90° (0.3 mm) gave 560 mg (77%) of the acetyl ketone 4a, R′ = CH_3: mp 90–91° (lit.[10] mp 89–90°); ν^{CHCl_3} 1696, 1677 cm^{-1}; δ^{CDCl_3} 1.89 (s, 3), 2.22 (s, 3), 4.55 (s, 2), 7.1–7.5 (m, 5).

1-Acetyl-5,6-diphenyl-1,5-dihydro-4*H*-1,2-diazepin-4-one (6b, R′ = CH_3).—A solution of 262 mg (1 mmol) of **1b** in CH_2Cl_2 was treated with 6 mequiv of ketene. After standing for 12 hr the solution was chromatographed on silicic acid and the resulting yellow oil (280 mg) was dissolved in cyclohexane. After 1 week at 0°, the solution deposited 200 mg of light yellow crystals: mp 105–106°; ν^{KBr} 1725, 1670 cm^{-1}; δ^{CDCl_3} 2.32 (s, 3), 5.16 (m, 1, H-5), 7.1–7.4 (m, 11), 7.85 (d, 1, J = 1.7 Hz, H-3 or H-7).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 75.08; H, 5.29; N, 9.03.

1-Acetyl-5-methyl-6-phenyl-1,5-dihydro-1,2-diazepin-4-one (6a, R′ = CH_3).—A solution of 1.5 g (7.5 mmol) of **1a** in CH_2Cl_2 was treated with 22 mmol of ketene. After 1 day the solution was concentrated and the yellow solid was sublimed at 90–100° (0.2 mm) to give 1.6 g (90%) of **6** (R′ = CH_3) as yellow needles: mp 110–111°; ν^{KBr} 1720, 1655 cm^{-1}; δ^{CDCl_3} 1.18 (d, 3, J = 7 Hz), 2.56 (s, 3), 3.73 (q, 1, J = 7 Hz), 7.19 (s, 6), 7.48 (d, 1, J = 1.5 Hz).

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.25; H, 5.80; N, 10.94.

(8) We are indebted to Dr. Tadamichi Fukunaga, Central Research Department, E. I. du Pont de Nemours and Co., for these calculations and the perturbation analysis.

(9) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, Chapter 6; F. F. Hudson, *Angew. Chem., Int. Ed. Engl.*, **12**, 36 (1973).

(10) J. A. Moore and J. Binkert, *J. Amer. Chem. Soc.*, **81**, 6029 (1959).

1-Benzoyl-5-methyl-6-phenyl-1,5-dihydro-1,2-diazepin-4-one (6a, R′ = C_6H_5).—A solution of 600 mg (3 mmol) of **1a** in 10 ml of CH_2Cl_2 containing 0.35 ml of benzoyl chloride and 15 ml of 10% aqueous KOH was agitated vigorously on a "Super-Mixer" for 15 min. Mixing was repeated with three further 0.35-ml portions of benzoyl chloride. The CH_2Cl_2 layer was washed, dried, and evaporated and the yellow oil was chromatographed on 20 g of silicic acid. Evaporation of the yellow eluent fraction gave 850 mg of yellow solid, mp 123–125°. Crystallization from CH_2Cl_2–ether gave **6** (R′ = C_6H_5) as yellow prisms: mp 127–129°; ν^{KBr} 1720, 1670 cm^{-1}; δ^{CDCl_3} 1.28 (d, 3, J = 7.2 Hz), 3.97 (ddq, 1, J = 7.2, 1.2, and 1.2 Hz), 7.50 (m, 12).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.88; H, 5.48; N, 8.95.

The **p-methoxybenzoyl-1,5-dihydrodiazepinone (6a,** R′ = *p*-$CH_3OC_6H_4$) was obtained by essentially the same procedure from 500 mg of **1** and 850 mg of anisoyl chloride: 591 mg (71%); mp 130–132°; ν^{KBr} 1705, 1670 cm^{-1}; δ^{CDCl_3} 1.29 (d, 3, J = 7.5 Hz), 3.5–4.1 (m, 4 including OCH_3), 6.95 (d, 2, J_{AB} = 8.5 Hz, B of aryl A_2B_2), 7.38 (s, 6), 7.75 (s, 1), 7.82 (d, 2, J_{AB} = 8.5 Hz, A of aryl A_2B_2).

Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.57; H, 5.33; N, 8.16.

The **p-nitrobenzoyl-1,5-dihydrodiazepinone (6a,** R′ = *p*-$NO_2C_6H_4$) was similarly prepared in 78% yield: mp 136–137°; ν 1700, 1655 cm^{-1}; δ^{CDCl_3} 1.32 (d, 3), 3.83 (ddq, 1), 7.26 (s, 1), 7.38 (s, 5), 7.65 (d, 1, J = 1.1 Hz), 8.00 (d, 2, J = 9 Hz, B of aryl A_2B_2), 8.23 (d, 2, J = 9 Hz, A of A_2B_2).

Anal. Calcd for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 65.30; H, 4.38; N, 11.84.

2-Acetyl-4-acetoxy-5-methyl-6-phenyl-2*H*-1,2-diazepine (5a).[11]—One gram of the 2-acetyl ketone **4a** (R′ = CH_3) was dissolved in 4 ml of pyridine and 2 ml of acetic anhydride. After heating 1 hr at 80°, tlc showed the presence of starting **4a** plus a slower moving yellow compound. After heating for 2 hr the two yellow zones were of approximately equal size and a third slower moving colorless compound appeared. After 4 hr the reaction mixture was concentrated at reduced pressure and ether was added. The yellow solid which separated was collected and washed with ether–pentane to give 440 mg of yellow crystals, mp 130°. Recrystallization from ether–pentane gave 370 mg of the enol acetate **5**: mp 135–136°; λ_{max}^{MeOH} 352 nm (ϵ 500), 260 (sh); ν^{CHCl_3} 1760, 1675 cm^{-1}; δ^{CDCl_3} 1.70 (s, 3), 2.22 (s, 3), 2.28 (s, 3), 6.45 (s, 1), 7–7.5 (m, 6).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.76; H, 5.60; N, 9.94.

2-Acetyl-4-acetoxy-5,6-diphenyl-2*H*-1,2-diazepine (5b).—Two grams of **4b** (R′ = CH_3)[3] was acetylated for 4 hr as described above. After concentration of the reaction mixture, addition of ether gave a mixture of **4b** and the enol acetate. After further acetylation for 1 hr, evaporation gave a yellow solid which was washed with ether to give 1.1 g of the enol acetate **5b**, mp 152–154°. The ir and nmr spectra were identical with those of a sample from another source.[12]

1-Acetyl-4-acetoxy-5-methyl-6-phenyl-1*H*-1,2-diazepine (7a, R′ = R″ = CH_3).—A solution of 500 mg of 1-acetyl-5-methyl-1,5-dihydrodiazepinone (**6a**) (R′ = CH_3), 0.6 ml of Ac_2O, and 0.9 ml of Et_3N in 5 ml of CH_2Cl_2 was allowed to stand for 60 hr at 25° and was then washed with HCl, $NaHCO_3$, and H_2O. The dried solution was concentrated. The yellow residue crystallized from ether to give 400 mg (56%) of **7a** as yellow prisms, mp 100–102°. The analytical sample was crystallized from ether: mp 102–103; ν^{CHCl_3} 1762 and 1675 cm^{-1}; δ^{CDCl_3} 1.66 (s, 3), 2.27 (s, 6), 6.45 (s, 1), 7.23 (s, 1), 7.22 (s, 5).

Anal. Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.58; H, 5.70; N, 9.78.

1-Benzoyl-4-benzoyloxy-5-methyl-6-phenyl-1*H*-1,2-diazepine (7a, R′ = R″ = C_6H_5).—A solution of 380 mg of **6a** (R′ = C_6H_5), 0.43 ml of benzoyl chloride, and 0.5 ml of Et_3N in 3 ml of CH_2Cl_2 stood for 27 hr at 25°. The green solution was washed as above, dried, and evaporated. The residue crystallized from ether to give 249 mg (56%) of enol benzoate **7a** (R′ = R″ = C_6H_5) as yellow crystals: mp 141–143°; ν^{CHCl_3} 1739, 1663 cm^{-1}; δ^{CDCl_3} 1.86 (s, 3), 6.70) (s, 1), 7.49 (m, 12), 7.94 (m, 2).

5,6-Diphenyl-1,5-dihydro-1,2-diazepin-4-one (1b) plus Acetic Anhydride.—A solution of 400 mg of **1b** in 2 ml of pyridine and 2 ml of Ac_2O stood for 16 hr and was then poured into water. The oily precipitate solidified after 20 hr at 0° and was collected and dried (450 mg). Recrystallization from benzene–hexane gave 300 mg of yellow crystals, mp 149–150°. Further recrystallization gave the enol acetate **7b** (R′ = R″ = CH_3): mp 150–151°; ν^{KBr} 1750, 1680 cm^{-1}; δ^{CDCl_3} 2.03 (s, 3), 2.33 (s, 3), 6.07 (s, 1, H-7), 7.1–7.2 (m, 10), 7.40 (s, 1, H-3).

Anal. Calcd for $C_{26}H_{20}N_2O_3$: C, 76.45; H, 4.94; N, 6.86. Found: C, 76.44; H, 4.87; N, 6.86.

Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.83; H, 5.10; N, 7.90.

The mother liquor from crystallization of the enol acetate was concentrated. Slow crystallization from benzene–hexane gave 50 mg of colorless solid. Recrystallization from hexane gave white crystals of the bicyclic enol acetate **12**: mp 156–157°; ν^{KBr} 1770, 1680, 1660 cm^{-1}; δ^{CDCl_3} 2.38 (s, 3), 2.33 (s, 3), 5.33 (s, 1), 7.2–7.4 (m, 11).

Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.84; H, 5.06; N, 8.06.

2-Benzoyl-6-*endo*-methyl-5-phenyl-2,3-diazabicyclo[3.2.0]-3-hepten-7-one (8).—To a solution of 1.0 g of the 1,5-dihydrodiazepinone **1a** in 40 ml of CH_2Cl_2 was added 0.66 ml of *N*,*N*-dimethylaniline and 0.63 ml of benzoyl chloride. After standing for 4 days the solution was washed with aqueous HCl, $NaHCO_3$, and water, dried, and concentrated. The oil was diluted with ether. Crystallization gave 920 mg (60%) of **8** as a pale, cream-colored solid, mp 102–110°. Recrystallization from ether–pentane gave white crystals, mp 107–108°; for spectra, see text.

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.96; H, 5.13.

The 2-acetyl ketone was prepared similarly and obtained as an oil: ν 1790, 1665 cm^{-1}; δ^{CDCl_3} 1.36 (d, 3, J = 8 Hz), 2.30 (s, 3), 4.16 (dq, 1, J = 8 and 3.5 Hz), 5.91 (d, 1, J = 3.5 Hz), 6.95 (s, 1), 7.34 (m, 5).

2-Benzoyl-6-*endo*-methyl-5-phenyl-2,3-diazabicyclo[3.2.0]-3-hepten-7-*endo*-ol (9).—A solution of 304 mg (1 mmol) of ketone **8** in 10 ml of ethanol–water was treated with 200 mg of $NaBH_4$. After 1.5 hr at 26° the solution was acidified with acetic acid, concentrated, and extracted with ether. The oil from the ether solution crystallized to give white prisms of **9**, 106 mg, mp 125–127°; for nmr, see text.

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92. Found: C, 74.39; H, 6.11.

Pyrolysis of 8.—A solution of 305 mg of **8** in toluene was dropped into a vertical helix-filled tube heated to 250° while a stream of nitrogen was passed through the apparatus. The vapors from the column passed first into an empty trap at room temperature and then into a solution of aniline (6 ml) in 50 ml of ether. The toluene solution collected in the first trap was evaporated to yield 107 mg of yellow solid, mp 115–117°. Recrystallization from ether gave white plates of 1-benzoyl-4-phenylpyrazole: mp 128–129°; ν^{KBr} 1690 cm^{-1}; δ^{CDCl_3} 7.18–7.63 (m, 8), 7.92–8.22 (m, 3), 8.61 (s, 1).

Anal. Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 76.94; H, 4.82; N, 11.25.

A comparison sample prepared by benzoylation of 4-phenylpyrazole[13] (C_6H_5COCl, pyridine, 25°) had mp 124–127°; a mixture of the two samples showed no melting point depression.

The ether–aniline solution from the second trap was washed with four portions of 2 *N* HCl and then with Na_2CO_3 and water. The ether solution was evaporated to give 18 mg of brownish solid. Recrystallization from ether gave 6 mg of colorless crystals, mp 106–107°. The infrared spectrum had the same peaks and approximately the same relative intensities as that of an authentic sample of propionanilide (lit. mp 104–105°).

Pyrolysis of 1a.—A 200-mg sample of the diazepinone **1a** was placed in a cool top section of the helix-packed column. The column temperature was set at 300° and a nitrogen flow was begun. The top section was then rapidly heated to melt the diazepinone. A total of 120 mg of yellowish solid was collected in the empty exit trap; tlc of this solid indicated the presence of three compounds. After the column was cooled, 76 mg of dark

(11) This compound was originally prepared by Dr. J.-L. Derocque.

(12) A. Nabeya, K. Kurita, and J. A. Moore, *J. Org. Chem.*, **37**, 2954 (1972).

(13) E. Klingsberg, *J. Amer. Chem. Soc.*, **83**, 2934 (1961). We are indebted to Dr. Klingsberg for a generous gift of 4-phenyl-1,2-dithiolium hydrogen sulfate.

oil was recovered by washing; this material showed eight spots on tlc.

The solid from the trap was triturated with CCl_4 and 32 mg of white solid, mp 232–233°, was collected. The infrared spectrum was identical with that of 4-phenylpyrazole (lit. mp 236–237°). Chromatography of the CCl_4 solution on silicic acid gave 19 mg of solid in the first fractions. Recrystallization gave 9 mg of 1-propionyl-4-phenylpyrazole: mp 101–103°: ν_{CO} 1735 cm^{-1}; mixture melting point with material prepared by propionylation of 4-phenylpyrazole (C_6H_5COCl, Et_3N, 10 min, 80°), 102–103°.

Pyrolysis of 2a.—Treatment of **2a** (310 mg) as described above gave a yellow oil in the first trap. Dilution with ether and seeding gave 24 mg (11%) of 4-phenylpyrazole, mp 230–233°.

5,6-Diphenyl-1,5-dihydro-1,2-diazepin-4-one (1b) plus Acetyl Chloride.—To a solution of 262 mg of diazepinone **1b** in 5 ml of CH_2Cl_2 at 0° was added 0.08 ml (1 equiv) of pyridine followed by 0.07 ml (1 equiv) of acetyl chloride. After 25 min, the solution was poured into ice water and the organic layer was washed twice with water, dried, and evaporated to a yellow oil which was chromatographed in $CHCl_3$ on silicic acid. Three bands separated and were collected in individual cuts which were evaporated to give (1) 100 mg of yellow oil, (2) 40 mg of white solid, (3) 90 mg of yellow oil.

The first fraction was a mixture and was rechromatographed. No bands separated and the eluate was collected in three equal fractions. The first cut was a yellow oil (30 mg) whose nmr spectrum showed one major component and trace impurities. The peaks due to the major component agreed precisely with those in the spectrum of 1-phenylacetyl-1,5-dihydrodiazepinone described below.

The third fraction of the second chromatogram was a yellow oil (20 mg) whose nmr spectrum matched that of the 1-acetyl-1,5-dihydrodiazepinone (**6b**, R′ = CH_3).

The solid from the second fraction of the first chromatogram (of the total product) was recrystallized from petroleum ether (bp 30–60°) to give 30 mg of colorless crystals, mp 80–81°; the ir spectrum (22 peaks) matched that of 1-acetyl-4-phenylpyrazole described below.

1-Phenylacetyl-5,6-diphenyl-1,5-dihydro-1,2-diazepin-4-one (13).—A solution of 130 mg of the diphenyl-1,5-dihydroketone **1b** in 5 ml of CH_2Cl_2 and 2 ml of 10% aqueous NaOH was vigorously stirred in a vibrating mixer and 0.13 ml of phenylacetyl chloride was added. After 10 min the organic layer was separated, washed with acid and water, dried, and evaporated. The resulting yellow oil was chromatographed on silicic acid. The oil obtained was homogeneous by spectral criteria but did not crystallize: ν_{CO} 1730, 1675 cm^{-1}; δ^{CDCl_3} 3.98, 4.06 (calcd δ_A and δ_B of AB dd, J_{AB} = 14.5 Hz, $PhCH_2$), 5.10 (m, H-5), 6.9–7.5 (m, 16), 7.82 (d, 1, J = 1.8 Hz, H-3 or H-7).

1-Acetyl-4-phenylpyrazole (15).—A solution of 50 mg of 4-phenylpyrazole in 0.5 ml of Ac_2O and 0.2 ml of pyridine stood for 2 hr and was then evaporated *in vacuo*. Benzene was added and the solution was again evaporated; this treatment was repeated twice and a trace of anhydride was then removed in a nitrogen stream. The crystalline residue was recrystallized from ether–pentane to give colorless needles of **15**: mp 79–80°; ν_{CO}^{KBr} 1730 cm^{-1}; δ^{CDCl_3} 2.72 (s, 3), 7.2–7.6 (m, 5), 7.95 (s, 1), 8.44 (s, 1).

Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41. Found: C, 70.95; H, 5.23.

2-Acetyl-5,6-diphenyl-2,3-diazabicyclo[3.2.0]-3-hepten-6-one (14).—A suspension of 50 mg of the enol acetate **12** in 1 ml of methanol was treated with 0.3 ml of 1 *N* methanolic KOH at 0°. After the resulting light yellow solution was stirred for 30 min the solution was neutralized with acetic acid, concentrated at 0°, and extracted with $CHCl_3$. The extract was washed, dried, and evaporated to give a solid residue. Recrystallization from $CHCl_3$–methanol gave 33 mg of colorless crystals, mp 105–107°. Recrystallization gave **14**: mp 108–109°; ν^{KBr} 1790, 1675 cm^{-1}; δ^{CDCl_3} 2.39 (s, 3), 5.32 (d, 1, J = 3 Hz), 5.98 (d, 1, J = 3 Hz), 6.73 (s, 1), 7.1–7.5 (m, 10).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30. Found: C, 74.25; H, 5.30.

Reacetylation of **14** (30 mg) with Ac_2O–pyridine gave enol acetate **12** (30 mg), mp 153–156°, ir same as sample from **1b**.

Thermal Decomposition of 14.—The nmr spectrum of a solution of **14** in $CDCl_3$ was recorded at intervals over several days. After a few minutes a peak at δ 2.72 due to **15** was apparent. At 17 hr the ratio of this peak to the CH_3 peak of **14** was 3.5:6.5, and peaks appeared at δ 7.95 and 8.45 due to **15**. In addition, a peak $^2/_3$ of the intensity of the CH_3 peak of **15** was present at δ 3.70. This is attributed to the CH_2 of phenylacetic acid or some other derivative of phenylketene. The reaction was followed to 90% completion. A first-order plot of log [**15**] *vs.* time gave a straight line; $k_1 = 8 \times 10^{-5}$ sec^{-1}.

Registry No.—**1a**, 19971-06-3; **1b**, 40635-76-5; **2a**, 1706-26-9; **2b**, 24301-66-4; **3b** (R′ = C_6H_5), 40711-72-6; **3b** (R′ = CH_3), 5109-45-5; **4a** (R′ = CH_3), 4134-95-6; **4b** (R′ = CH_3), 24301-69-7; **5a**, 40711-76-0; **5b**, 40635-77-6; **6a** (R′ = CH_3), 40711-78-2; **6a** (R′ = C_6H_5), 40711-79-3; **6a** (R′ = *p*-$CH_3OC_6H_4$), 40711-80-6; **6a** (R′ = *p*-$NO_2C_6H_4$), 40711-81-7; **6b** (R′ = CH_3), 40711-82-8; **7a** (R′ = R″ = CH_3), 40711-83-9; **7a** (R′ = R″ = C_6H_5), 40711-84-0; **7b** (R′ = R″ = CH_3), 40711-85-1; **8**, 40704-70-9; **8** 2-acetyl derivative, 40704-71-0; **9a**, 40704-72-1; **9b**, 40704-73-2; **12**, 40711-86-2; **13**, 40711-87-3; **14**, 40711-88-4; **15**, 40711-89-5; 3-diazoacetyl-*cis*-3,4-diphenyl-1-pyrazoline, 40711-90-8; 1-benzoyl-4-phenylpyrazole, 40711-91-9; propionanilide, 620-71-3; 4-phenylpyrazole, 10199-68-5; 1-propionyl-4-phenylpyrazole, 40711-92-0.

Heterocyclic Studies. 40. Formation and Reactions of 1-Acetyl-3-diazoacetylhydroxypyrazolidines. Conversion to a Diazocyclopentanone[1]

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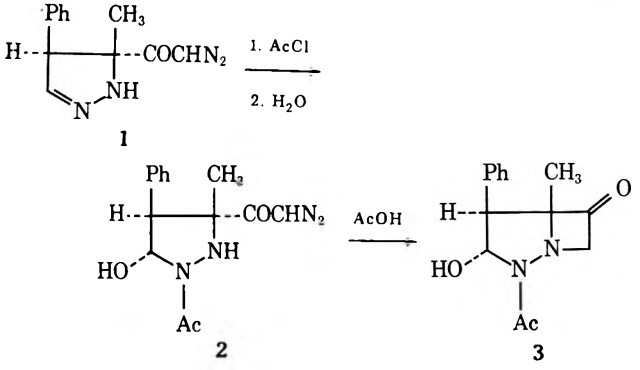
The conversion of two stereoisomeric pairs of 3,4-di-R-3-diazoacetyl-5-pyrazolines to 1-acetyl-5-hydroxy-3,4-di-R-pyrazolidines and subsequent conversion to 2-acetyl-3-*endo*-hydroxy-4,5-di-R-1,2-diazabicyclo[3.2.0]-6-heptanones are described. The reaction of 1-acetyl-3-diazoacetyl-3-methyl-4-phenyl-5-hydroxypyrazolidine with base gives epimers of 2-acethydrazino-2-methyl-3-phenyl-4-hydroxy-5-diazocyclopentanone (18 and 19), which were converted to 3-methyl-4-phenyl-3-cyclopentene-1,3-dione (21) and the 2-diazo derivative 20.

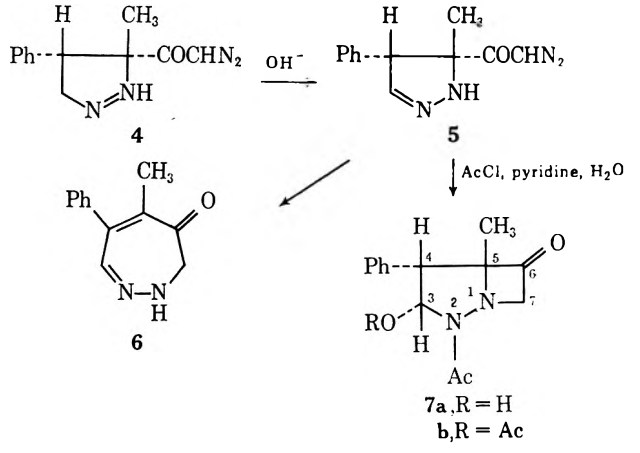
3-Diazoacetyl-Δ^5-pyrazolines undergo cyclization in acid to 1,2-diazabicyclo[3.2.0]heptenones,[2] and are converted by base to pyrazoles.[3] Another reaction of these versatile pyrazolines (*e.g.*, **1**) is the addition



of acetic acid to the C=N bond which occurs on treatment with acetyl chloride followed by water, and leads to 1-acetyl-5-hydroxy derivatives **2**.[4,5] This reaction has now been extended to some additional pyrazolines to provide information on the steric course of the addition, and the chemistry of these acylhydroxypyrazolidines has been studied.

trans-3-Methyl-4-phenyl-Δ^5-pyrazoline **5** was prepared from (*Z*)-α-methylcinnamic acid (α-methyl-*cis*-cinnamic) *via* the mixed anhydride and the Δ^1-pyrazoline **4** (Chart I). The chemistry of **5** paralleled

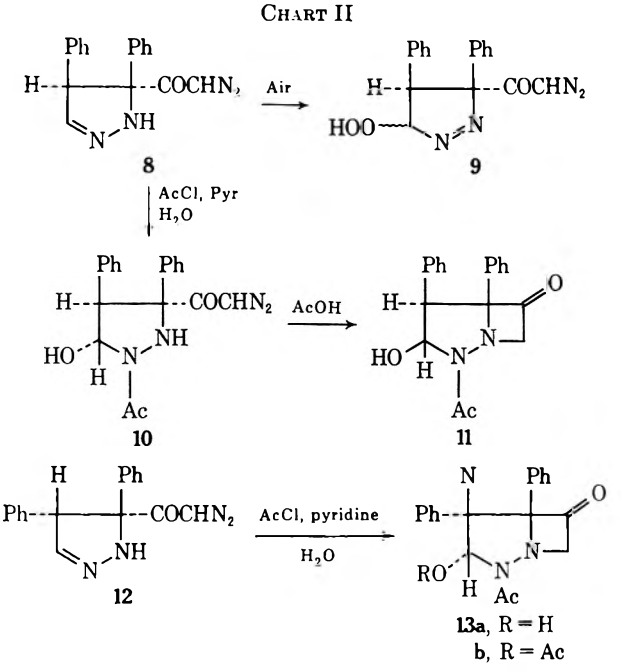
CHART I



that of the isomeric *cis*-pyrazoline **1**; reaction of **4** or **5** with acetic acid gave the diazepinone **6**,[4] and 3-methyl-4-phenylpyrazole was obtained with base.[3] Treatment of the 5-pyrazoline **5** with acetyl chloride–pyridine followed by water gave the 2-acetyl-3-hydroxybicyclic ketone **7a**, which was isolated from the aqueous phase of the reaction mixture. The diazoacetylpyrazolidine analogous to **2** was not detected.

This acylation was also studied with the stereoisomeric diphenylpyrazolines **8** and **12** (Chart II).

CHART II



In repeating the preparation of **8**,[2] the compound was found to undergo rapid air oxidation on recrystallization from ether with formation of a hydroperoxide which is considered to be **9** by analogy to the hydroperoxyazo compounds obtained from hydrazones.[6]

The reactions of the diphenyl-5-pyrazolines **8** and **12** with acetyl chloride and pyridine followed the general pattern seen in the 3-methyl-4-phenyl series. The hydroxyacetylpyrazolidine **10**, analogous to **2**, was isolated in solvated form from **8**. In the reaction of the *trans*-diphenylpyrazoline **12**, the diazoacetylpyrazolidine was observed as an unstable substance which cyclized to **13a** with loss of nitrogen on attempted recrystallization from ether.

(1) Supported in part by the National Science Foundation and the Unidel Foundation.

(2) A. Nabeya, F. B. Culp, and J. A. Moore, *J. Org. Chem.*, **35**, 2015 (1970).

(3) F. B. Culp, A. Nabeya, and J. A. Moore, *ibid.*, **38**, 2949 (1973).

(4) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *ibid.*, **31**, 34 (1966).

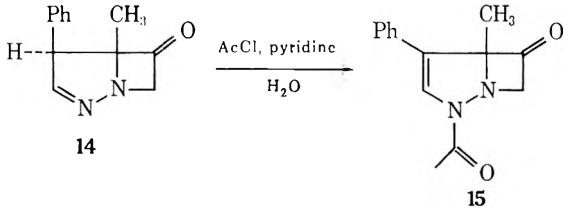
(5) T. Yamauchi and J. A. Moore, *ibid.*, **31**, 42 (1966).

(6) K. N. Pausacker, *J. Chem. Soc.*, 3478 (1950); R. Criegee and G. Lohaus, *Chem. Ber.*, **84**, 219 (1951).

The direct isolation of bicyclic ketones from the trans-3,4-disubstituted pyrazolines **5** and **12** is presumably due to the more rapid cyclization of the intermediate acylhydroxypyrazolidines when the 4-phenyl group is cis to the diazoacetyl chain, perhaps providing orientation for the ring closure. The situation is complex, however, since solubility relationships play a role; pyrazolidines **2** and **10** could be crystallized and extracted, respectively, from the aqueous phase of the reaction mixture, while isolation of products from the other two reaction mixtures required the evaporation of water.

In all of these reactions, the pyrazolidine or bicyclic ketone was obtained as a single stereoisomer. The endo configuration of the hydroxyl group in the *cis*-3-methyl-4-phenylpyrazolidine **2** was assigned on the basis of the nmr spectrum of the derived bicyclic ketone **3**, in which the signals for H-3 and H-4 were broadened singlets ($J_{3,4} \cong$ OHz).[4] The spectra of **7**, **11**, and **13** confirm this stereochemistry and are consistent with an endo hydroxyl in each case. The H-3 and H-4 signals in **7a** and **13a** were doublets, $J_{3,4}$ = 4.2 Hz, appropriate for a cis vicinal coupling, with slightly larger values, 4.7 and 4.5 Hz, for the respective acetates. The corresponding peaks in the spectra of the pyrazolidine **10** and cyclic ketone **11** were singlets. The signals for the 7-CH_2 protons in the hydroxy bicyclic ketones **3** and **7a** are singlets, with the expected equivalence and J_{gem} showing up in the acetates; this relationship is curiously reversed in the endo-phenyl series **13**, with the 7-CH_2 a doublet of doublets in the alcohol and a singlet in the acetate.

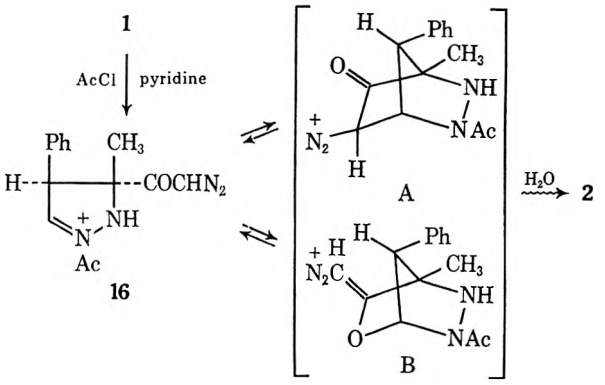
As noted previously,[4] the course of these acylation reactions is unexpected; similar treatment of the unsaturated bicyclic ketone **14** with acetyl chloride and aqueous work-up leads cleanly to the acyl enamine system. The pronounced water solubility of the products during the work-up procedure was attributed to the intermediacy of a pyridinium salt intermediate in the formation of **2**, but this does not account for the absence of products analogous to **15**, nor the consistent formation of endo hydroxy derivatives from both C-4 epimers.



14 **15**

The reaction of **2** with base, described below, suggested that interaction of the diazoacetyl group with C-5 might be responsible for these apparently anomalous acylations. Evidence for participation of the diazo group was found when the reaction of **1** with acetyl chloride was quenched with D_2O; the signal for the CHN_2 proton was absent in the nmr spectrum of the resulting **2**. The reaction of **1** and acetyl chloride was then observed in the nmr spectrometer, and the CHN_2 signal disappeared immediately on addition of acetyl chloride. Hydrolysis with H_2O led to **2** with the CHN_2 signal intact. That these observations were not due to acylation of the $COCHN_2$ group and subsequent hydrolysis of a diazo diketone was established by carrying out the experiment with the 3-diazoacetyl-Δ^1-pyrazoline. The spectrum was unchanged, with no diminution of the CHN_2 peak on addition of acetyl chloride. The nmr spectrum of the reaction mixture of **1** with acetyl chloride underwent a series of changes on standing, but only **2** has been isolated under various work-up times and conditions.

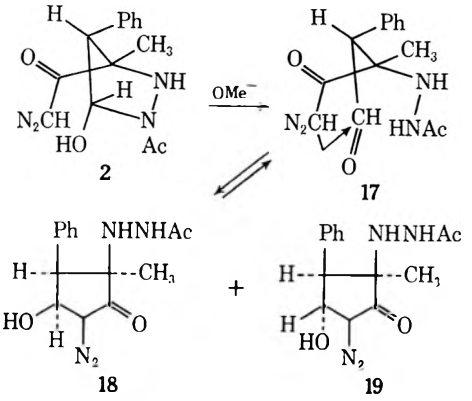
These observations clearly indicate that the $COCHN_2$ group has a role in the acylation of **1** and probably also the other diazoacetylpyrazolines. Interaction of this group with the C=N bond could lead *via* **16**



to the bicyclic intermediates A and/or B. Formation of A would explain loss of diazomethyl proton; hydrolysis of the enol derivative B would lead directly to the observed endo-hydroxy product.[7]

In addition to the extremely facile acid-catalyzed cyclization, the hydroxydiazoacetylpyrazolidines are quite sensitive to base; this reaction was examined in detail with the 3-methyl-4-phenyl compound **2**. On standing in dilute methanolic methoxide, **2** was converted to two products, which were separated by chromatography and found to be isomeric with the starting material. The ir spectra of both compounds showed the presence of a diazocarbonyl system (ν 2080 cm^{-1}) but the nmr spectra contained no signals for diazomethyl protons; peaks were present in both for three exchangeable protons and two mutually coupled methine protons. These data and several chemical transformations establish the structures of these base products as the stereoisomeric hydroxydiazocyclopentanones **18** and **19** (Chart III).

CHART III



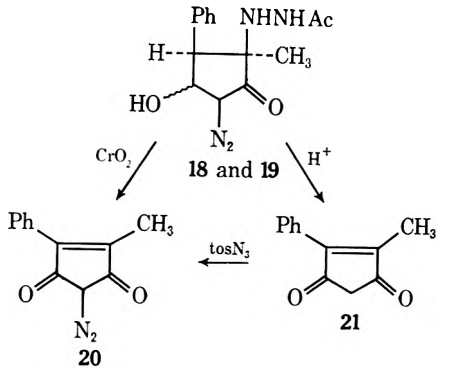
The cyclic diazo ketone structures can be derived readily from the diazoacetylpyrazolidine by ring open-

(7) We are grateful to a reviewer for this suggestion.

ing of the carbinol amide system as in **17** and recyclization by aldol condensation of the diazomethyl group. Comparable condensations have been observed with diazo esters or diazo ketones and aldehydes[8a] or reactive ketones,[8b] and a few intramolecular condensations have also been reported.[9] The steric configuration at C-2 and C-3 in **18** and **19** is based on the known stereochemistry of **2**, the position of the 3-methyl group relative to phenyl ring being inverted in the process.

The hydroxyl configurations in the carbinols are assigned on the basis of the values of $J_{3,4}$ for the two isomers. Epimer **18**, with the OH group cis to the phenyl and acethydrazide groups, was obtained in somewhat larger amount, but the isomers are equilibrated in base, and the product ratio presumably reflects the relative stabilities and not conformational preference in the condensation.

The reactions of **18** and **19** are complicated by the additional sensitive acylhydrazine substituent and the only reaction products that have been fully characterized are compounds in which the elements of acetylhydrazine were eliminated. Oxidation of **18** and **19** with chromic oxide in aqueous pyridine gave in 22% yield a readily crystallized yellow compound which contained a diazo group and in the nmr only phenyl and methyl singlets. The ir diazo band at 2124 cm^{-1} is very similar to that in 2-diazoindandione ($\nu_{N\equiv N}$ 2128 cm^{-1}),[10] and the product is assigned the diazocyclopentenedione structure **20**.



Treatment of the epimeric alcohols with acetic acid in the presence of copper bronze gave a mixture of at least four products. The least polar component was isolated in 5–10% yield by chromatography and sublimation. This compound was a yellow solid, $C_{12}H_{10}O_2$, with nmr showing phenyl and methyl singlets plus a CH_2 peak [δ 3.03 (s, 2)]. These properties suggested the cyclopentene-1,3-dione structure **21**. The compound appeared to be more stable to base than the parent dione reported by DePuy;[11] brief treatment of **21** with NaOD in D_2O caused disappearance of the CH_2 peak without appreciable decomposition. A pK_a of about 12 was indicated spectrophotometrically. Reinforcement of the structure of the 1,3 dione and of the diazo diketone **20** as well was provided by conversion of **21** to **20** by a diazo transfer reaction with tosyl azide.

(8) (a) E. Wenkert and C. A. MacPherson, *J. Amer. Chem. Soc.*, **94**, 8084 (1972); (b) B. Eistert and P. Donath, *Chem. Ber.*, **102**, 1725 (1969).

(9) T. Burkoth, *Tetrahedron Lett.*, 5049 (1969).

(10) M. Regitz and G. Heck, *Chem. Ber.*, **97**, 1482 (1964).

(11) C. H. DePuy and E. F. Zaweski, *J. Amer. Chem. Soc.*, **81**, 4920 (1959); C. H. DePuy and P. R. Wells, *ibid.*, **82**, 2909 (1960).

Experimental Section

(*Z*)-α-Methylcinnamic Acid ("α-Methyl-*cis*-cinnamic").[12,13]—A solution of 10 g of the *E* ("α-methyl-*trans*") acid[17] [δ ($CDCl_3$) 6.85 ppm (d, J = 1 Hz)] in 40 ml of ethanol was irradiated in a quartz tube surrounded by ten 15-W 2537-Å sterilizing lamps. After 24 hr the solution was evaporated to dryness. The mixture of stereoisomeric acids was dissolved in sufficient concentrated aqueous ammonia to produce a clear solution. To this solution was added excess saturated $BaCl_2$ solution. The insoluble barium salt of the *E* (trans) acid was collected and the *E* acid was recovered by acidification.

The filtrate was treated with additional $BaCl_2$ to confirm that precipitation of the *E* salt was complete, and the solution was then cooled and acidified. The resulting precipitate of the *Z* acid ("α-methyl-*cis*") was collected, washed with water, and dried. The nmr spectrum indicated a negligible amount of *E* acid. Recrystallization from $CHCl_3$–petroleum ether (bp 30–60°) gave 1.7 g of the *Z* acid: mp 90–91° (lit.[14] mp 91°); δ^{CDCl_3} 2.06 (d, 3, J = 1 Hz), 6.85 (d, 1, J = 1 Hz), 7.30 (s, 5).

***r*-3-Diazoacetyl-3-methyl-*c*-4-phenyl-1-pyrazoline (4).**—A solution of 6.48 g of (*Z*)-α-methylcinnamic acid and 4.34 g of ethyl chloroformate in 180 ml of anhydrous ether was treated dropwise at 0° with 4.04 g of triethylamine. After stirring for 1 hr the amine hydrochloride was collected by filtration and the solution of the mixed anhydride was concentrated to a thin oil. This oil was added to a solution of diazomethane prepared (with distillation) from 36 g of bis(*N*-methyl-*N*-nitroso)terephthalamide. The solution stood for 2 days at 25° and was then evaporated *in vacuo*. The yellow solid residue was washed with hexane and collected to give 7.21 g (79%) of crude **4**. Recrystallization from ether–petroleum ether gave pale yellow needles: mp 106° dec; ν^{KBr} 2110, 1620 cm^{-1}; δ^{CDCl_3} 1.47 (s, 3), 3.1–3.25 (four lines of X part of ABX, δ_X^{calcd} 3.17, H-4), 4.35–5.25 (eight lines of AB part of ABX, δ_B^{calcd} 4.67, δ_A^{calcd} 5.00, J_{AX} = 2.5, J_{BX} = 7.8, J_{AB} = −18.0 Hz, 5-CH_2), 5.68 (s, 1, CHN_2), 6.7–7.3 (m, C_6H_5).

Anal. Calcd for $C_{12}H_{12}N_4O$: C, 63.14; H, 5.30; N, 24.55. Found: C, 62.77; H, 5.23; N, 24.11.

A solution of 1.5 g of **4** in 15 ml of acetic acid was heated at 85° for 2 hr. Evaporation and crystallization from methanol gave 0.8 g of 2,3-dihydro-5-methyl-6-phenyl-4*H*-1,2-diazepin-4-one (**6**).

***r*-3-Diazoacetyl-3-methyl-*c*-4-phenyl-5-pyrazoline (5).**—To a solution of 2.25 g of the 1-pyrazoline **4** in 60 ml of methanol at 0° was added 1 ml of 1 *N* KOH. After 4 hr, tlc showed **4** to be absent. The solution was treated with solid CO_2 and evaporated to a solid residue which was extracted with ether. Concentration of the ether gave 1.95 g (86%) of pale yellow solid. Recrystallization from ether gave 1.5 g of **5**: mp 102° dec; ν^{KBr} 3400, 3200, 2110, 1620 cm^{-1}; δ^{CDCl_3} 1.54 (s, 3), 3.97 (d, H-4, J = 1.5 Hz), 5.51 (s, 1, CHN_2), 5.67 (br, 1, NH), 6.85 (d, H-5, J = 1.5 Hz), 6.9–7.35 (m, 5).

Anal. Calcd for $C_{12}H_{12}N_4O$: C, 63.14, H, 5.30; N, 24.55. Found: C, 63.36; H, 5.30; N, 24.65.

3-Methyl-4-phenylpyrazole.—A solution of 0.45 g of the 5-pyrazoline **5** in 20 ml of methanol was treated with 2 ml of 1 *N* KOH and was stirred at room temperature for 36 hr; tlc still showed the presence of some **5**. The solution was neutralized with acid and evaporated to a tan solid residue which was washed with water and recrystallized from methanol to give 130 mg of 3-methyl-4-phenylpyrazole, mp 143–145°.

(12) We are greatly indebted to Dr. Aiko Nabeya for carrying out this preparation in the laboratories of the University of Tokyo.

(13) The preparation of this acid ("*allo*-cinnamic acid") by irradiation of the "normal" trans acid (*E*) was described by Stoermer.[14] The *Z* acid was isolated in unspecified yield by a complex fractional crystallization procedure, and was characterized by crystal form and melting point; the structure was confirmed by H_2SO_4-catalyzed cyclization to 2-methylindenone. The acid has subsequently appeared in the literature,[15,16] with ultraviolet data, but the isolation procedure and other physical characterization were not given. The situation is further obscured by the report of three crystalline forms of the *E* acid[17] and the description of two crystalline modifications of the *Z* acid having different melting points and spectra (in solution).[16] To clarify matters we describe the preparation and isolation in detail. It will be noted that the acid with β-H and CO_2H cis (*E*) has a more deshielded β-H and less soluble barium salt than the isomeric *Z* acid, as found with other isomeric α-substituted cinnamic acids.[2]

(14) R. Stoermer and G. Voht, *Justus Liebigs Ann. Chem.*, **409**, 51 (1915).

(15) A. Mangini and F. Montanari, *Gazz. Chim. Ital.*, **88**, 1081 (1958).

(16) Y. Ushibara and M. Hirota, *Nippon Kagaku Zasshi*, **82**, 354 (1961).

(17) J. R. Johnson, *Org. React.*, **1**, 251 (1942).

2-Acetyl-3-*endo*-hydroxy-5-methyl-4-*endo*-phenyl-1,2-diazabicyclo[3.2.0]heptan-6-one (7a).—A solution of 0.84 g of 5-pyrazoline **5** in 10 ml of methylene chloride was treated with 0.6 ml of pyridine and 0.3 ml of acetyl chloride. After stirring at 0° for 20 min, ice water and 0.22 g of Na_2CO_3 were added. The aqueous phase was extracted with CH_2Cl_2 and the combined organic layers were washed twice with water. After drying, the CH_2Cl_2 solution was evaporated to give 0.35 g of tan solid; the ir spectrum of this material had a strong band at 2100 cm^{-1}. No pure compound could be isolated from this fraction; tlc showed the presence of starting **5** and another compound which was not the product **7a**. The aqueous phase (original layer plus washings) was then concentrated at 30° to 20 ml volume; at this point solid began to crystallize. This material (0.60 g) was collected; tlc showed one compound. Recrystallization from ether gave 0.52 g of colorless, granular **7a**: mp 156–158°; ν^{KBr} 3250, 1800, 1630 cm^{-1}; δ ($CDCl_3$) 1.48 (s, 3), 2.18 (s, 3, $COCH_3$), 3.24 (d, J = 4.2 Hz, H-4), 4.77 (s, 2, 7-CH_2), 5.01 (d, J = 3 Hz, 1, in D_2O exchanges), 6.20 (m, 1, H-3, in D_2O → d, J = 4.2 Hz), 7.2–7.4 (m, 5).

Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.70. Found: C, 64.85; H, 6.35; N, 10.69.

For conversion to the acetate **7b**, 0.3 g of alcohol **7a** was treated at 25° with 2 ml of acetic anhydride and 0.8 ml of pyridine. After 12 hr, water was added and the resulting white crystals were collected, dried, and recrystallized from ether to give 0.22 g of **7b**: mp 159–161°; ν^{KBr} 1800, 1755, 1660 cm^{-1}; δ ($CDCl_3$) 1.52 (s, 3, 5-CH_3), 1.87 (s, 3, OAc), 2.25 (s, 3, NAc), 3.53 (d, J = 4.7 Hz, H-4), 4.39–5.06 (four lines AB dd, δ_B^{calcd} 4.82, J_{AB} = 17.8 Hz, 7-CH_2), 7.15–7.45 (m, 6, C_6H_5 + H-3).

Anal. Calcd for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.59; H, 5.97; N, 9.05.

3-Diazoacetyl-*cis*-3,4-diphenyl-5-hydroperoxy-1-pyrazoline (9).—On several occasions attempts to recrystallize the pyrazoline **8** gave a sparingly soluble product. In a typical case, 1.2 g of **8**[2] was dissolved in 100 ml of ether and 400 ml of hexane was added. On standing (exposed to air) overnight, 0.75 g of well-formed needles separated from the solution. Recrystallization from ether–pentane gave colorless needles: mp 119–121° dec; ν^{KBr} 3200, 2100, 1630 cm^{-1}; δ^{DMSO} 4.3 (d, 1, J = 3 Hz), 5.4 (br, 1), 6.00 (s, 1), 7.12–7.24 (m, 10).

Anal. Calcd for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 62.97, 63.18; H, 3.83, 4.37; N, 17.26.

The spectra indicate retention of the CHN_2 and PhCH groups and the presence of an OH group. These data and the incorporation of O_2 led to the assignment of the hydroperoxide structure **9**. Application of the compound to starch–iodide paper moistened with acetic acid caused immediate appearance of a deep violet color. Attempts to obtain transformation products of **9** with acid, base, or reducing agents gave complex mixtures.

1-Acetyl-*r*-3-diazoacetyl-3,*t*-4-diphenyl-*c*-5-hydroxypyrazolidine (10).—To a solution of 0.58 g of the *cis*-diphenylpyrazoline **8** in 10 ml of CH_2Cl_2 at 0° was added 0.4 ml of pyridine and 0.2 ml of acetyl chloride. After 15 min the clear solution was treated with ice water containing 0.15 g of sodium carbonate. The CH_2Cl_2 phase was separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic solution was dried and evaporated; benzene was added and evaporated to remove traces of pyridine. The residual solid was washed with cyclohexane to remove oily material, giving 0.63 g of light yellow solid. Recrystallization from ether gave 0.37 g of **10** as white needles: mp 123–124° dec; ν^{KBr} 3250, 2100, 1640 cm^{-1}; δ (DMSO-d_6) 2.38 (s, 3), 4.44 (s, 1, H-4), 5.50 (br d, in D_2O → br s, H-5), 6.20 (br s, in D_2O exchanges), 6.57 (s, 1, CHN_2), 6.90 (s, in D_2O exchanges), 7.1–7.2 (m, 10). The compound could not be obtained free of solvent despite exhaustive drying.

Anal. Calcd for $C_{19}H_{18}N_4O_3$: C, 65.13; H, 5.18; N, 15.99. Found (dried at 56°, 10 hr, 0.1 mm): C, 64.57; H, 5.55; N, 14.97.

2-Acetyl-3-*endo*-hydroxy-4-*exo*,5-diphenyl-1,2-diazabicyclo[3.2.0]-6-heptanone (11).—A solution of 1.08 g of the pyrazolidine **10** in 10 ml of acetic acid was stirred at 25° for 45 min; visible gas evolution ceased after 30 min. The solution was concentrated *in vacuo* to give 0.83 g of brown solid which was recrystallized from benzene to give 0.43 g of colorless crystals of **11**: mp 165–167°; ν^{KBr} 3200, 1800, 1630 cm^{-1}; δ^{CDCl_3} 2.45 (s, 3), 4.26 (s, 1, H-4), 4.88 (s, 2, 7-CH_2), 5.72 (s, 1 in D_2O exchanges), 6.26 (s, 1, H-3), 7.4–7.66 (m, 10).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.83; H, 5.32; N, 8.51.

2-Acetyl-3-*endo*-hydroxy-4-*endo*,5-diphenyl-1,2-diazabicyclo[3.2.0]-6-heptanone (13a).—A solution of 0.58 g of the *trans*-diphenylpyrazoline **12** in 10 ml of CH_2Cl_2 was treated with 0.6 ml of pyridine and then 0.2 ml of acetyl chloride. A significant amount of white precipitate appeared and then redissolved during 15 min of stirring. Ice water containing Na_2CO_3 was added and, after separation and extraction, the combined CH_2Cl_2 layers were evaporated to give 0.23 g of oily residue which solidified on adding petroleum ether; the ir spectrum of this material showed strong absorption at 2100 cm^{-1}.

The combined aqueous layers from the extraction and washing were concentrated at reduced pressure to 10 ml volume, and 0.36 g of white crystalline solid separated. This material showed strong ir bands at 3200 (br), 2100, and 1630 cm^{-1} (br), and is assumed to be the diazoacetylpyrazolidine. On attempted recrystallization from ether, gas evolution occurred before all of the solid had dissolved; after 20 min of heating, the solution was filtered to remove a trace of solid. Evaporation of the ether and recrystallization of the residue gave 0.3 g of white needles of the bicyclic ketone **13**: mp 185–187° dec; ν^{KBr} 3300, 1800, 1640 cm^{-1}; δ^{CDCl_3} 2.36 (s, 3, NAc), 3.36 (d, J = 4.2 Hz, H-4), 4.57–5.17 (eight lines of 7-CH_2 Ab dd further split by H-3, δ_A^{calcd} 4.77, δ_B^{calcd} 4.97, J_{AB} = 17, J_{3-7A} = 0.7, J_{3-7B} = 0.7 Hz), 6.29 (m, J = 3 Hz, in D_2O → d, J = 4.2 Hz, H-3), 7.25–7.38 (m, 10).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.49; H, 5.60; N, 8.79.

The acetate **13b** was obtained in the usual way (Ac_2O, pyridine): mp 181° dec; ν^{KBr} 1800, 1760, 1670 cm^{-1}; δ ($CDCl_3$) 1.97 (s, 3, OAc), 2.42 (s, 3, NAc), 3.65 (d, J = 4.5 Hz, H-4), 4.83 (s, 2, 7-CH_2), 7.3–7.4 (m, 10), 7.46 (d, J = 4.5 Hz, H-3).

Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.21; H, 5.53; N, 7.69. Found: C, 69.40; H, 5.65; N, 7.60.

5-Diazo-*r*-2-(2-acethydrazido)-*r*- and -*t*-4-hydroxy-2-methyl-*c*-3-phenylcyclopentanone (18 and 19).—A solution of 6.3 g of the acetylpyrazolidine **2** in 125 ml of methanol was flushed with nitrogen and 44 ml of 0.5 *N* sodium methoxide in methanol was added slowly with stirring at 25°. The solution was allowed to stand at room temperature for 1 day and was then neutralized with Dry Ice and concentrated at reduced pressure. The residue was extracted with three 30-ml portions of boiling chloroform. The organic solution was washed with two 15-ml portions of 10% NH_4Cl and once with water and was then dried over $MgSO_4$. Concentration of the solution to a small volume and addition of benzene precipitated a pale yellow powder containing both isomers of the product. The melting point of the isomer mixture varied from 107° to 138°, depending on the composition. Slow recrystallization from CH_2Cl_2–ether gave a mixture (mp 138–142°) containing 80–85% of **19**. Complete separation was achieved by chromatography over a silicic acid column, using 85:15 chloroform–benzene as eluent for **19** and chloroform for **18**. Recrystallization from CH_2Cl_2–ether gave the pure isomers.

Alcohol **18** had mp 165–167°; ν^{KBr} 3130, 2080, 1650 cm^{-1}; δ^{CD_3OD} 1.21 (s, 3), 1.81 (s, 3), 3.13 (d, 1, J = 7.8 Hz, H-3), 5.88 (d, 1, J = 7.8 Hz, H-4), 7.4 ppm (s, 5).

Anal. Calcd for $C_{14}H_{16}O_3N_4$: C, 58.32; H, 5.59; N, 19.44. Found: C, 58.34; H, 5.75.

Alcohol **19** had mp 144–147°; ν^{KBr} 3130, 2080, 1650–1630 cm^{-1}; δ^{CD_3OD} 1.18 (s, 3), 1.87 (s, 3), 3.18 (d, 1, J = 4.6 Hz, H-3), 5.37 (d, 1, J = 4.6 Hz, H-4), 7.1–7.8 ppm (m, 5).

Anal. Found: C, 58.42; H, 5.72; N, 19.18.

The acetate was prepared from 147 mg of **19** with 5 ml of Ac_2O and 0.2 ml of pyridine. The reaction mixture was warmed briefly to dissolve the solid and was then allowed to stand at 26 for 30 min. The solution was poured into iced 1 *N* KOH solution, stirred thoroughly, and extracted with three portions of CH_2Cl_2. After removal of the solvent and addition of a few drops of ether, 92 mg (55%) of yellow solid, mp 143–146°, was obtained. Recrystallization from ether–pentane gave a yellow, chalky solid: mp 144–145°; ν^{KBr} 3200–3100, 2090, 1725, 1690–1640 cm^{-1}; δ^{CDCl_3} 1.24 (s, 3), 1.90 (s, 3), 212 (s, 3), 3.37 (d, 1, J = 5 Hz, H-3), 5.72 (br, 1, in D_2O exchanges), 6.08 (d, 1, J = 5 Hz, H-4), 7.2–7.6 (m, 6).

Anal. Calcd for $C_{16}H_{18}O_4N_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.18; H, 5.48; N, 16.91.

2-Diazo-4-methyl-5-phenyl-4-cyclopentene-1,3-dione (20).—A solution of 0.235 g of chromium trioxide in 1.5 ml of water and 22 ml of pyridine was slowly added to a magnetically stirred solution of 0.507 g (1.75 mmol) of a mixture of **18** and **19** in 30 ml of pyridine. The dark red reaction mixture was stirred at room temperature for 24 hr, treated with 30 ml of water, and extracted with

ether. After drying, the solvent was evaporated to a yellow solid. Recrystallization from ethanol–water gave 64 mg (22%) of yellow needles of **20**: mp 114–115°; ν^{KBr} 2120, 1690, 1378 cm^{-1}; λ_{max}^{MeOH} 238 mμ (ε 25,500), 278 (15,300), 355 (1290); δ^{CDCl_3} 2.20 (s, 3), 7.50 (s, 5).

Anal. Calcd for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.93; H, 3.73; N, 13.03.

Reaction of 18 and 19 in Acetic Acid.—To a solution of 2.0 g of the mixed alcohols **18** and **19** in 50 ml of glacial acetic acid was added about 100 mg of copper powder. The solution was stirred at 45° until gas evolution became very slow (1 hr). The mixture was filtered and the acetic acid was evaporated. The residual greenish-brown syrup was dissolved in CH_2Cl_2 and washed with water to remove copper salts. The organic phase was dried and concentrated and the residue (1.47 g) was chromatographed on 40 g of silicic acid. The first two fractions, eluted with chloroform, gave 190 mg of dark yellow oil which was distilled in short-path apparatus to give 140 mg (10%) of yellow crystals of methylphenylcyclopentene-1,3-dione (**21**): mp 117–118°; ν^{KBr} 1740, 1705, 1385 cm^{-1}; λ_{max}^{MeOH} 224 mμ (ε 10,000), 286 (7800); δ^{CDCl_3} 2.18 (s, 3), 3.03 (s, 2), 7.49 (s, 5).

Anal. Calcd for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.34; H, 5.47.

Conversion of 21 to 20.—To a solution of 61 mg (0.33 mmol) of dione **21** and 71 mg (0.35 mmol) of *p*-toluenesulfonyl azide in 2 ml of acetonitrile was added 0.15 ml of triethylamine. The yellow solution darkened rapidly and tlc examination after 30 min showed no starting material remaining. The orange solution was diluted with 20 ml of ether, washed with water, dried, and concentrated to a dark, noncrystalline residue. Chromatography over a short silicic acid column (85:15 chloroform–benzene eluent) gave 39 mg of an orange oil which crystallized on addition of a few drops of benzene. Recrystallization from benzene–hexane gave 30 mg (43%) of orange needles, mp 112–114°, mixture melting point with **20** prepared by oxidation, 112–114°. The ir spectra of the two samples matched in all peaks.

Registry No.—**2**, 40704-62-9; **4**, 40704-63-0; **5**, 40704-64-1; **6**, 1706-26-9; **7a**, 40704-65-2; **7b**, 40704-66-3; **8**, 24302-15-6; **9**, 40704-14-1; **10**, 40704-68-5; **11**, 40704-69-6; **12**, 24302-17-8; **13a**, 40704-16-3; **13b**, 40704-17-4; **18**, 40704-18-5; **19**, 40704-19-6; **19** acetate, 40704-20-9; **20**, 40674-82-6; **21**, 40704-21-0; (*Z*)-α-methylcinnamic acid, 15250-29-0; diazomethane, 334-88-3; bis(*N*-methyl-*N*-nitroso)terephthalamide, 133-55-1; 3-methyl-4-phenylpyrazole, 13788-84-6.

Heterocyclic Studies. 41. The Conversion of 3-Diazoacetylpyrazolines to Pyrazoles *via* Pyrazolo[1,5-*c*]-*v*-triazines[1]

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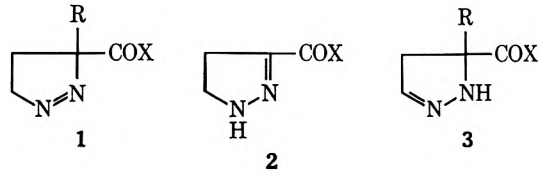
3-Diazoacetyl-4-methoxycarbonyl-3-methyl-1-pyrazoline (**4**) is converted by base to the pyrazolotriazinone **6**. Further reaction of **6** with base leads to the pyrazole **8** and methyl glyoxylate hydrazone (**9**). The hydrazone was also isolated, together with pyrazoles, from the reaction of several related diazoacetylpyrazolines in base, but triazinone intermediates were not detected. *cis*- and *trans*-3,4-di(methoxycarbonyl)-3-methyl-1-pyrazolines (**17** and **18**) were found to epimerize at C-4 on conversion to the 5-pyrazolines, suggesting that the triazinone **6** is isolable because of the rapid isomerization of the double bond in the presumed intermediate **7**.

The 1-pyrazolines **1** (R = H) that are initially formed in the 1,3-dipolar addition of diazomethane to α,β-unsaturated carbonyl systems containing no α substituent are highly labile and rapidly isomerize to the conjugated 2-pyrazoline **2**. With a 3-alkyl or aryl substituent (**1**, R ≠ H) the 1-pyrazolines are more stable, but isomerization with acid or base under mild conditions leads to the 5-pyrazoline **3**.[2] In the preparation of diazabicyclo[3.2.0]heptenones from 3-diazoacetylpyrazolines (**1** X = CHN_2), milder acid conditions can be used for the cyclization if base-catalyzed isomerization to **3** is carried out prior to the



cyclization step.[3] It has been found, however, that longer exposure of a 3-diazoacetyl-5-pyrazoline to base leads to formation of a pyrazole.[2a] The reactions of these compounds with base have now been further examined, and the nature of this unusual elimination reaction has been clarified.

In the attempted tautomerization of the 4-methoxycarbonylpyrazoline **4**[3] with base, an isomer was obtained which was not the diazoacetyl-5-pyrazoline. The ir spectrum contained no diazo band; the nmr spectrum contained peaks for two NH protons and two singlet vinyl protons at δ 6.61 and 6.81 as well as CH_3 signals at δ 1.31 and 3.88 (OCH_3). The uv spectrum had λ_{max} 330 nm (ε 6000). The mass spectrum contained a small parent ion peak at *m/e* 210 and two more intense peaks at *m/e* 141 and 109, corresponding to loss of a C_2HN_2O fragment and further loss of CH_3O. These data, particularly the nmr values, define the bicyclic triazinone structure **6**, resulting from isomerization of the pyrazoline, nucleophilic attack of N-2 at the terminus of the diazocarbonyl group, and tautomerization (Chart I).

A number of reactions have been observed in which the diazo group in $COCHN_2$ and $COCN_2CO$ systems coordinates various nucleophiles, including HSO_3^-, CN^-, amines, phosphines, and hydrazine.[4] In the last case, the intermediate tetrazene breaks down to give an azide.[5] A chain of four contiguous nitrogen atoms has previously been obtained in this type of coupling only with arenediazonium ions and hydrazines or pyrazoles,[6] and with these products the coupling is reversed in acid. The pyrazolotriazinone **6** was relatively stable in acid, and did not give the 1,2-

(1) Supported in part by Grant G.P. 5219 from the National Science Foundation.

(2) (a) J. A. Moore and R. W. Medeiros, *J. Amer. Chem. Soc.*, **81**, 6026 (1959); (b) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 34 (1966).

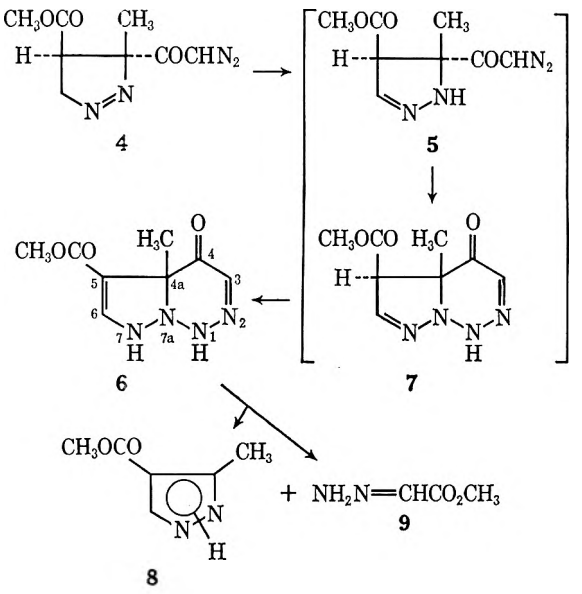
(3) A. Nabeya, F. B. Culp, and J. A. Moore, *ibid.*, **35**, 2015 (1970).

(4) R. Huisgen, *Angew. Chem.*, **67**, 439 (1955).

(5) T. Curtius, A. Darapsky, and A. Bockmuhl, *Ber.*, **41**, 344 (1908).

(6) E. Koenigs and J. Freund, *ibid.*, **80**, 143 (1947).

CHART I

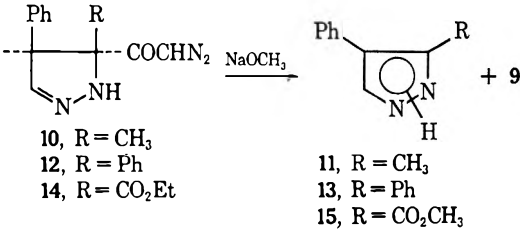


diazepinone which arises[3] from protolysis of the 1-pyrazoline **4**.

The yield of the triazinone **6** in the reaction of **4** with methanolic sodium methoxide was very low because of the rapid further conversion of **6** to the pyrazole **8**. A better procedure for preparing **6** is the reaction of **4** with triethylamine as the base. When solutions of **4** or **6** and a catalytic amount of methoxide stood for several days at 0°, another product was isolated. This material was identified as methyl glyoxylate hydrazone (**9**) by comparison with a sample prepared from α-methoxycarbonyltriphenylphosphazine.[7]

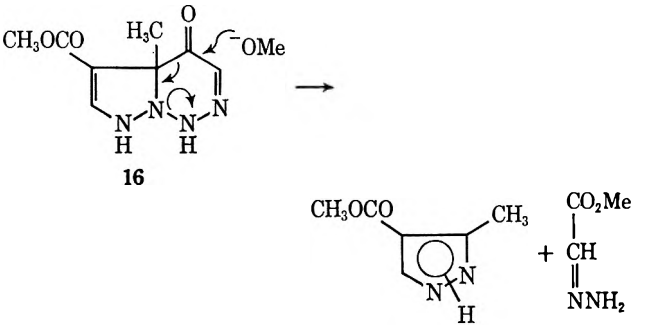
The formation of **8** and **9** from reactions of **4** with base prompted further examination of the products arising from the phenylpyrazoline **10** and also the diphenyl- and 3-ethoxycarbonyl-4-phenylpyrazolines **12** and **14** (Chart II). Conversion of the 3-methyl-4-

CHART II



phenyl-5-pyrazoline **10** (or the Δ^1 isomer) to pyrazole **11** was found to occur under much milder conditions than were previously used,[2] and the hydrazone **9** was isolated under conditions comparable to those used with **4**. Similarly, the *cis*-diphenylpyrazoline **12**[8] and the *c*-4-phenyl-*r*-3-carboxylate **14** were converted to pyrazoles **13** and **15**, respectively; hydrazone **9** was isolated from the same reaction mixture with **13**.

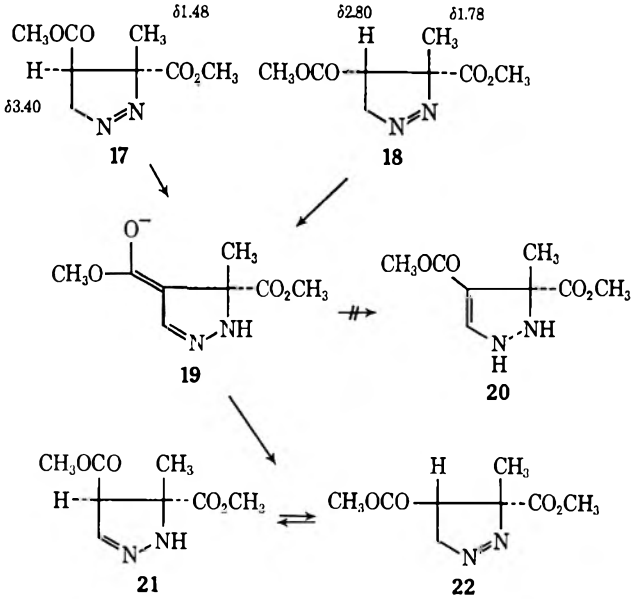
The formation of pyrazole **11** was previously depicted as a β elimination of the $COCHN_2$ group from the pyrazoline **10**.[2] Although this represents the overall reaction, there is no basis for investing the $COCHN_2$ anion with the role of a leaving group. The bicyclic triazine **6** (Chart I) provides a much more satisfactory picture of the process in the case of the 4-methoxycarbonylpyrazoline **1**. The pyrazole and hydrazono ester can arise directly by nucleophilic addition to the carbonyl group and vinylogous elimination as shown in **16**.



Questions remain, however, as to whether a triazinone intermediate is involved in the reactions of the 4-phenylpyrazolines, and why the 5-pyrazoline is not observed in the methoxycarbonyl case. The contrasting behavior of the two series obviously stems from the nature of the C-4 substituent. To probe these points, the pyrazoline diesters **17** and **18** and the 4-phenyl ester **23** were examined as models for the diazo ketones.

The pyrazolines **17** and **18** were described by von Auwers,[9,10] and these preparations were repeated (Chart III). The crude 1-pyrazoline **17** from dimethyl

CHART III



mesaconate was >95% pure by nmr; **18**, from dimethyl citraconate, contained an impurity and was distilled. Treatment of either **17** or **18** with sodium methoxide gave the same mixture of 5-pyrazolines **21** and **22**, in

(7) H. Staudinger and J. Meyer, *Helv. Chim. Acta*, **2**, 619 (1919); H. Staudinger and G. Lüscher, *ibid.*, **5**, 75 (1922).

(8) The reaction of the 3,4-*trans*-diphenylpyrazoline is discussed in the accompanying paper: A. Nabeya, K. Kurita, and J. A. Moore, *J. Org. Chem.*, **38**, 2954 (1973).

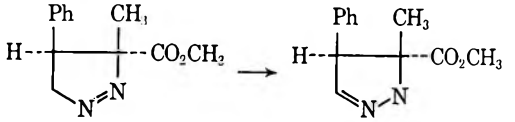
(9) K. von Auwers and E. Cauer, *Justus Liebigs Ann. Chem.*, **470**, 284 (1929).

(10) K. von Auwers and E. Koenig, *ibid.*, **496**, 97 (1932).

a ratio of 1.1:1.0.[11] The reaction of either pyrazoline with anhydrous HCl gave a salt whose nmr spectrum in D_2O showed the same mixture of **21** and **22**, with the H-4 proton signals absent. Isomerization of **17** to **21** and **22** was also observed on heating; after 22 hr at 110°, conversion to the same mixture of **21** and **22** was 60% complete.

The rapid conversion of the Δ^1-pyrazoline esters **17** and **18** to the same mixture of epimeric 5-pyrazolines demonstrates the ease of enolization with the 4-carboxylate substituent (*cf.* **19**). However, the Δ^4-pyrazoline **20** is not present in detectable amounts in the equilibrium mixture. Monocyclic pyrazolines with this tautomeric structure have been observed only when N-1 is substituted, and apparently the conjugated enamino ester system in **20** is insufficient to stabilize this structure. In the diazoacetylpyrazoline, however, cyclization of the side chain (**5** → **7** in Chart I) apparently tips the equilibrium in favor of the conjugated tautomer **6**, perhaps owing to relief of steric repulsion between the ester and bridgehead methyl groups in **7**.

In the 4-phenyl series, the pyrazoline ester **23** was prepared by addition of diazomethane to methyl α-methylcinnamate during a period of several weeks; this reaction had previously been reported to give the α,β-dimethyl ester.[9] Treatment of **23** with base under conditions which led to a mixture of the epimeric diesters **21** and **22** gave the 5-pyrazoline **24**, without



23 **24**

deuterium exchange or epimerization. The diazoacetyl-Δ^5-pyrazoline **10** was unaffected by similar conditions. At a higher base concentration, sufficient to cause conversion to the pyrazole **11**, slow deuterium exchange of H-4 in **10** did occur; when the formation of **11** was 50% complete, the area of the H-4 signal in the remaining **10** indicated approximately 25% exchange.

These qualitative observations suggest the possibility that the pyrazoles may be formed by the same mechanism from both the methoxycarbonyl and phenylpyrazolines, with the contrasting behavior in the two series owing simply to differences in the rates of the several steps. With this in mind, pseudo-first-order rate constants in excess 1.65×10^{-3} *M* methanolic sodium methoxide were determined spectrophotometrically for the 1-pyrazoline and the intermediate in each series. These values are given in Charts IV and V.

In the methoxycarbonyl series (Chart IV) the conversion of **6** to the pyrazole **8** plus hydrazone **9** was followed by the decrease in absorbance of **6** at λ_{max} 330 nm; an isosbestic point (associated with the formation of **9**) occurred at 292 nm. The disappearance of the 1-pyrazoline **4** could not be measured at its absorbance maximum because the further reaction of **6** interfered; the rate constant for **4** was obtained by assuming that **4**, **6**, **8**, and **9** are the only species present and following the change in **4** at 292 nm, the isosbestic point for the reaction of **6**.

CHART IV

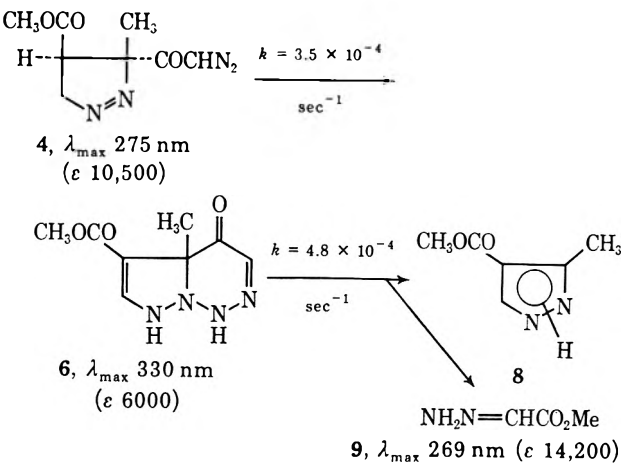
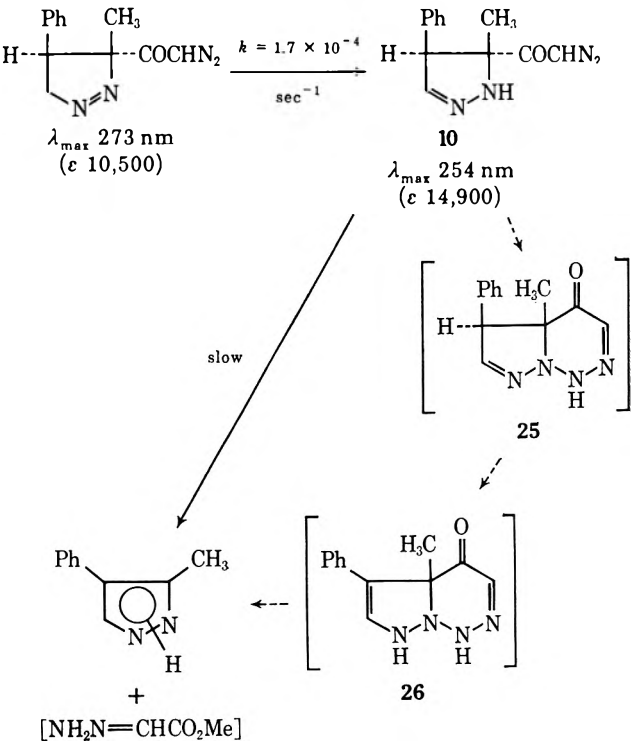


CHART V



In the 4-phenyl series (Chart V) the rate of isomerization of the 1-pyrazoline to the Δ^5 isomer was straightforward. However, the conversion of the 5-pyrazoline **10** to pyrazole plus hydrazone required 10^3-fold stronger base to obtain a comparable rate, and under these conditions the hydrazone **9** undergoes a further reaction which complicated the kinetics and prevented accurate measurement of the rate of reaction of **10**.

These kinetic data establish that the initial isomerization of the 1-pyrazolines in both series occurs at very nearly the same rate. In the methoxycarbonyl case, the conversion of the "missing" 5-pyrazoline

(11) The ratio is based on the nmr spectrum of the mixture of **21** and **22**. Although peaks for the CCH_3 and H-4 protons in each isomer were well resolved, the relative chemical shifts *vis-à-vis* those for the 1-pyrazolines of known configuration did not permit unequivocal assignment of signals to **21** and **22**, and it is not known which was present in the larger amount.

(5, Chart I) to 6 must be a much faster step, as borne out by the very rapid epimerization of the esters 17 and 18, and the fact that the kinetic plots show no detectable intermediate between 4 and the triazinone 6. The rate data show also that conversion of 6 to the pyrazole is actually slightly faster than its rate of formation in NaOMe. If the triazinone 26 is an intermediate in the phenyl series, its fragmentation should occur at a rate similar to that of 6, since this step involves the same six-membered ring in both cases, and a transition state of comparable stability. At the relatively high base concentration required for the reaction of the 5-pyrazoline 10, the triazinone 26 would not be detectable.

A final point is the sequence of enolization and N–N bonding steps in the formation of the triazinones 6, and presumably 26, from the 5-pyrazolines. From circumstantial evidence in related work[8] we are inclined to the sequence indicated in Charts I and V, with initial coupling to give the species 7 and 25, but there is no direct support for these intermediates.

Experimental Section

Methyl 1,4,4a,7-Tetrahydro-4a-methyl-4-oxopyrazolo[1,5-c]-*v*-triazine-5-carboxylate (6).—To an ice-cold solution of 1.05 g (5 mmol) of pyrazoline 4 in 40 ml of methanol was added 0.2 ml (0.4 mequiv) of freshly prepared 5% methanolic sodium methoxide. The yellow color of the solution deepened immediately and a new compound appeared in the tlc. After 2 hr at 0° the solution was neutralized by addition of Dry Ice and was concentrated and then diluted with chloroform. After removal of inorganic salts the resulting oil was chromatographed on silicic acid. Elution with alcohol-free chloroform gave in initial fractions 240 mg of unreacted 4. The second band eluted with chloroform gave 140 ml of yellow solid, mp 136–139°. This material sublimed to a yellow glass on the cold finger; this glass crystallized on rubbing to give cream-colored crystals of the triazinone 6: mp 140–142°; ν^{KBr} 3350, 1160, 1590 cm^{-1}; for nmr and uv, see text.

Anal. Calcd for $C_8H_{10}N_4O_3$: C, 45.71; H, 4.80; N, 26.66. Found: C, 45.96; H, 4.82; N, 26.27.

A more satisfactory preparation of 6 was effected by refluxing a methanolic solution of 206 mg of pyrazoline 4 and 0.5 ml of triethylamine. After 30 min, evaporation and chromatography of the mixture gave 116 mg (70%) of the triazinone 4.

Hydrazone 9 from 6.—A solution of the oxotriazine 6 (750 mg) in 15 ml of methanol containing 0.26 mequiv of sodium methoxide was allowed to stand for 4 days at 0°. After neutralization with Dry Ice the solution was concentrated and the residue was chromatographed on silicic acid. Elution with chloroform gave initially fractions from which 512 mg of unreacted 6 crystallized. Later fractions crystallized to give 21 mg of the hydrazone 9, mp 120–123°, mmp with synthetic material (below), 119–123°.

Methyl 3(5)-Methylpyrazole-4-carboxylate (8).—A cold solution of 2.0 g of the methoxycarbonylpyrazoline 4 in 75 ml of methanol was treated with 50 ml (47 mequiv) of 0.95 *N* methanolic sodium methoxide. After a few minutes, tlc indicated complete disappearance of the starting pyrazoline. The red solution was neutralized with Dry Ice and the solvent was evaporated. The residue was extracted with chloroform; after washing and drying, the chloroform was evaporated to a residue (300 mg) which crystallized on standing, mp 88–95°. Recrystallization from benzene–hexane gave tiny white needles of the pyrazole 8: mp 89–90°; ν^{KBr} 3050, 1722, 1582 cm^{-1}; λ_{max}^{MeOH} 223 nm (ϵ 9700); δ ($CDCl_3$) 12.24 (broad, exchanged in D_2O), 7.98 (s, 1), 3.84 (s, 3), 2.57 (s, 3).[12]

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.32; H, 6.04; N, 20.17.

To obtain an authentic specimen of this pyrazole ester, a sample of dimethyl 3-methyl-1-pyrazoline-3,5-dicarboxylate was prepared by addition of excess diazomethane to 10 g of dimethyl mesaconate. The resulting crude pyrazoline was treated in chloroform with bromine until an orange color persisted and the solution was then concentrated to a brown semisolid residue. This material was then heated for 2 hr with 30 ml of concentrated hydrochloric acid. A small amount of white solid which separated from this solution was removed and discarded, and the dark filtrate was then neutralized with KOH, filtered, and concentrated. The gummy residue was extracted with chloroform to give a solid; recrystallization from ethanol–water gave a white powder, mp 220–230°; further recrystallization from chloroform gave 3(5)-methylpyrazolecarboxylic acid, mp 228° (lit.[13] mp 228–229°).

Treatment of this acid in methanol solution with diazomethane gave a yellow oil which was taken up in benzene. After filtration to remove unreacted acid the solution was evaporated and crystallized by adding hexane. The gray solid was sublimed at 70° to give colorless crystals of methyl ester 8, mp 86–88°; the ir spectrum (16 peaks) corresponded to that of the ester obtained from 4.

3-Methyl-4-phenylpyrazole (11).[2a]—3-Diazoacetyl-c-3-methyl-*r*-4-phenyl-1-pyrazoline[2] (700 mg, 4.4 mmol) was dissolved in 20 ml of methanol. After the solution was flushed with nitrogen, 7 ml (8.8 mequiv) of 1.25 *N* methanolic sodium methoxide was added dropwise and the solution was then stored at 0° for 2 days. The solution was then neutralized with HCl and evaporated to a dark semisolid residue which was extracted with methylene chloride. After washing andd rying, the organic layer was evaporated to give 470 mg of pyrazole 11 as a yellowish solid, mp 140–145°.

Methyl Gloxylate Hydrazone.—A solution of 3 g of the 4-phenyl-1-pyrazoline in 85 ml of methanol was treated with 1.2 ml of 1.3 *N* methanolic sodium methoxide. After standing at 0° for 10 days the solution (two spots by tlc) was neutralized with Dry Ice and concentrated *in vacuo*. Addition of water caused a large crop of the 5-pyrazoline 10[2] to precipitate. After pyrazoline was removed the aqueous residue was evaporated to a red-brown solid which was extracted with hot benzene. Concentration of the benzene solution gave a tan solid which was recrystallized from benzene–hexane to give 40 mg of the hydrazone 9, mp 120–123°. Sublimation gave colorless crystals: mp 124–125°; ν^{KBr} 3350–3150, 1700, 1540 cm^{-1}; δ ($CDCl_3$) 7.07 (s, 1, –CH=N), 6.5 (broad, 2, exchanges with D_2O), 3.83 (s, 3).

Anal. Calcd for $C_3H_6N_2O_2$: C, 35.29; H, 5.92; N, 27.44. Found: C, 35.12; H, 6.02; N, 27.23.

An authentic sample of 9 was synthesized as follows.[7] Methoxycarbonyltriphenylphosphazine was prepared by combining ether solutions of 8.0 g of methyl diazoacetate[14] and 35 g of triphenylphosphine. The solution became warm and, on cooling, a mass of crystals separated which were collected and washed with ether to give 23 g of pale yellow needles of the phosphazine, mp 107–110°. A solution of 10 g of the phosphazine in 40 ml of methanol–water (8:2) was refluxed for 30 min and then concentrated at reduced pressure. The resulting suspension was extracted with benzene to remove triphenylphosphine oxide and the aqueous solution was evaporated to a white solid residue. Sublimation [80° (0.1 mm)] gave 2.05 g of the hydrazone 9, mp 125–126°. The ir spectrum was identical with that of the sample isolated from 6 and from 10.

3,4-Diphenylpyrazole (13) from 12.—To a solution of 890 mg of 12[3] in 15 ml of methanol was added 3 ml of 1 *N* KOH. After 1 hr at room temperature the reaction mixture was neutralized with acetic acid and extracted with ether. After washing and drying, the ether was evaporated to a yellow gum which crystallized on addition of chloroform and petroleum ether (bp 30–60°). This solid, a mixture of hydrazone 9 and pyrazole 13, was placed in a sublimer. At a bath temperature of 100° (0.3 mm), the hydrazone sublimed as white crystals: mp 120°; ir nearly identical with spectra of earlier samples; the nmr spectrum showed a trace of 13.

Sublimation was continued at 150–160°, and 300 mg (45%) of the pyrazole 13 was collected: mp 150°; ν^{KBr} 3300, 3000 (broad), 1600 cm^{-1}; δ ($CDCl_3$) 12.2 (s, 1), 7.58 (s, 1, H-5), 7.4–7.2 (m, 10). Resublimation gave white crystals: mp 152–153°;[15] mass

(12) D. E. McGreer and Y. Y. Wigfield, *Can. J. Chem.*, **47**, 2095 (1969), report for 8 mp 93–94°, δ 7.95 (1), 3.83 (3), 2.54 (3).

(13) H. V. Pechmann and E. Burkard, *Ber.*, **33**, 3597 (1900).

(14) "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 424.

(15) W. E. Parham and W. R. Hasek, *J. Amer. Chem. Soc.*, **76**, 799 (1954), report mp 155° for 3,4-diphenylpyrazole.

spectrum apparent molecular ion m/e 220, base peak (M − 1) m/e 219.0922 (calcd for $C_{15}H_{11}N_2$, 219.0922).

Methyl 4-Phenylpyrazole-3-carboxylate (15).—A solution of 570 mg of ethyl 3-diazoacetyl-*c*-4-phenyl-1-pyrazoline-*r*-3-carboxylate (14)[3] in 10 ml of methanol was treated with 2 ml of 1 *N* KOH. After 1 hr at 30° tlc showed three new components in the reaction. The solution was diluted with water, neutralized with acetic acid, and extracted with methylene chloride. After washing and drying, the organic phase was concentrated to give 60 mg (14%) of crystalline residue, mp 180°. Recrystallization from methanol–water gave white crystals of the pyrazole **15**, mp 185°,[16] identical (mixture, melting point, ir) with authentic **15** prepared by reaction of (*Z*)-α-bromocinnamic acid with diazomethane; after a solution of the crude bromopyrazoline was concentrated, HBr was evolved and the pyrazole was isolated by crystallization from methanol. (Extensive ester exchange occurred in the reaction of the ethyl ester **14** in methanol.)

trans-**3,4-Di(methoxycarbonyl)-3-methyl-1-pyrazoline** (17) was prepared from dimethyl mesaconate (3 g) and about 3 equiv of ethereal diazomethane. After 3 days the solution was evaporated to a nearly colorless oil: δ 1.48 (s, 3), 3.40 (three lines, J = 7.6 Hz, H-4), 3.69 (s, 3), 3.80 (s, 3), 4.90 (d, J = 7.6 Hz, 5-CH_2).

cis-**3,4-Di(methoxycarbonyl)-3-methyl-1-pyrazoline** (18) was similarly prepared from dimethyl citraconate. The crude oil was distilled and **18** was obtained in the first fraction, bp 130–136° (7 mm) (65% yield), as a colorless oil which crystallized at 0°: δ 1.78 (s, 3), 2.80 (three lines, J = 8.2 Hz), 3.68 (s, 3), 3.72 (s, 3), 4.87 (d, J = 8.2 Hz, 5-CH_2).

Isomerization of 1-Pyrazolines 17 and 18.—One gram of the pyrazoline was dissolved in 30 ml of 0.15 *N* methanolic sodium methoxide. After 5 min, tlc showed absence of the starting pyrazoline. The solution was neutralized with Dry Ice and evaporated to a semisolid residue, which was extracted with CH_2Cl_2. After washing, drying, and evaporation the residue was a pale yellow oil. A typical nmr spectrum (from trans isomer **17**) contained the following peaks (δ, neat): two CCH_3 singlets at 1.41 and 1.65 with area ratio 23:21; four $-OCH_3$ singlets at 3.65–3.88, total area 100 (corresponding to two OCH_3 each in **21** and **22** plus H-4 of one isomer); a doublet (J = 1.8 Hz) at 4.38, area 9 (H-4 of one isomer); an exchangeable singlet at 6.29, area 16 (NH of both isomers); multiplet at 6.7, area 15 (C-5 of both isomers).

In a typical acid-catalyzed isomerization, a solution of **18** in ether was treated at 20° with a stream of HCl gas. The resulting white precipitate of hydrochloride was then extracted into water. The aqueous solution was treated with excess Na_2CO_3 and extracted with several portions of CH_2Cl_2, and the solution was dried and evaporated to an oil. The nmr spectrum in $CDCl_3$ closely resembled that described above. In DMSO-d_6 the H-4 signals from both isomers were resolved. The relative peak areas permitted matching the H-4 and CCH_3 peaks of the two isomers, which are designated A and B[11] (A/B = 1.1): δ 1.17 (s, 3-CH_3 of A), 1.43 (s, 3-CH_3 of B), 3.6–3.8 (four s, OCH_3), 4.0 (d, J = 1.8 Hz, H-4 of B), 4.5 (d, J = 1.7 Hz, H-4 of A), 5.3–5.7 (broad, NH), 6.9 (m, C-5 of A and B). In a 100-MHz spectrum ($CDCl_3$), the signal for the H-5 peaks was resolved into two doublets, J = 2 Hz.

r-**3-Methoxycarbonyl-3-methyl-*t*-4-phenyl-1-pyrazoline** (23).—A solution of 3.75 g of freshly distilled methyl α-methylcinnamate in 20 ml of ether–methanol (1:1) was added to 250 ml of 0.3 *M* ethereal diazomethane. After standing for 3 weeks at 25° the pale yellow solution was filtered and evaporated. The resulting oil crystallized at 0°. Recrystallization from ether–pentane gave white crystals: mp 55–56°; δ ($CDCl_3$) 1.21 (s, 3), 3.45–3.8 (m, 1, H-4), 3.80 (s, 3), 4.83–4.98 (m, 2, H-5), 6.8–7.3 (m, 5).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.47; N, 12.84. Found: C, 66.27; H, 6.23; N, 13.03.

A solution of **23** in $CDCl_3$ and CD_3OD containing 0.1 equiv of NaOD was allowed to stand for some time. The nmr spectrum showed only peaks for the Δ^5 isomer **24**: δ 1.03 (s, 3), 3.8 (s, 3), 4.52 (d, J = 1.7 Hz, H-4), 6.8 (d, J = 1.7 Hz, H-5), 7.0–7.4 (m, 5); the areas of the δ 1.03 and 4.52 ppm peaks were in the ratio 3.0:1.0.

Rate Measurements.—The kinetic runs were carried out in a Cary Model 14 spectrophotometer with thermostated cell holders. Temperature was controlled at 25 ± 0.5° with a circulating bath; the cell temperature was monitored with a Model 42SC Telethermometer. Compounds were freshly sublimed or recrystallized and dried *in vacuo* before each series of measurements.

A 2.0-ml portion of the substrate in methanol was placed in a cuvette and equilibrated in the cell compartment for 30 min. One milliliter of standardized methanolic NaOMe was then added, the contents were mixed, and the spectrum was scanned for several half-lives. The reference cell contained 2 ml of methanol and 1 ml of the NaOMe solution. Values of k_1 were obtained from the slope of plots of log A at the appropriate wavelength *vs.* time.

Acknowledgment.—We are particularly grateful to Professor D. L. Dalrymple for helpful discussions and advice on the kinetic determinations.

Registry No.—**4**, 24302-22-5; **6**, 40711-65-7; **8**, 23170-45-8; **8** free acid, 40704-11-8; **9**, 19501-77-0; **10**, 5109-24-0; **11**, 13788-84-6; **12**, 24302-15-6; **13**, 24567-08-6; **14**, 40704-54-9; **15**, 5932-28-5; **17**, 40704-55-0; **18**, 40704-56-1; **23**, 40704-57-2; **24**, 40704-58-3; dimethyl 3-methyl-1-pyrazoline-3,5-dicarboxylate, 40704-10-7; diazomethane, 334-88-3; dimethyl mesaconate, 617-53-8; 3-diazoacetyl-*c*-3-methyl-*r*-4-phenyl-1-pyrazoline, 5109-38-6; 4-phenyl-1-pyrazoline, 40704-12-9; methyl α-methylcinnamate, 21370-57-0.

(16) K. von Auwers and O. Ungemacht, *Chem. Ber.*, **66**, 1205 (1933), report mp 184–187° for **15**.

Heterocyclic Studies. 42. Transformation of a Diazoacetylpyrazoline to a 2,3-Diazabicyclo[4.1.0]-3-hepten-5-one. A New Valence Isomer in the 1,2-Diazepin-4-one System[1]

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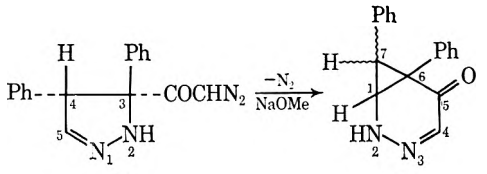
Treatment of diazoacetylpyrazoline 1 with base gives the 2,3-diazabicyclo[4.1.0]heptenone 2. The structure of 2 was established by photoisomerization and substitution reactions leading to derivatives of 2,3-dihydro- and 1,5-dihydro-5,6-diphenyl-1,2-diazepin-4-one. Compound 2 readily undergoes dimerization. The formation of 2 is suggested to occur *via* a tetrazonine intermediate.

The base-catalyzed fragmentation of 3-diazoacetylpyrazolines to pyrazoles plus hydrazonoacetic ester *via* intermediate pyrazolo[1,5-*c*]-*v*-triazines was described in the accompanying papers.[2] This reaction occurs with several pyrazolines having different substituents and steric configurations at C-3–C-4. A striking exception was observed, however, in the reaction of the *trans*-3,4-diphenylpyrazoline **1**. Under the same conditions (1 equiv of NaOMe at 20°), **1** (or the Δ^1-pyrazoline) liberates *nitrogen*, and a product comprising the remainder of the molecule is isolated in 70–80% yield; diphenylpyrazole was not detected. The main product has been shown to be the diazabicyclo[4.1.0]heptenone 2; evidence for the structure and a suggestion concerning the reaction pathway are presented here.

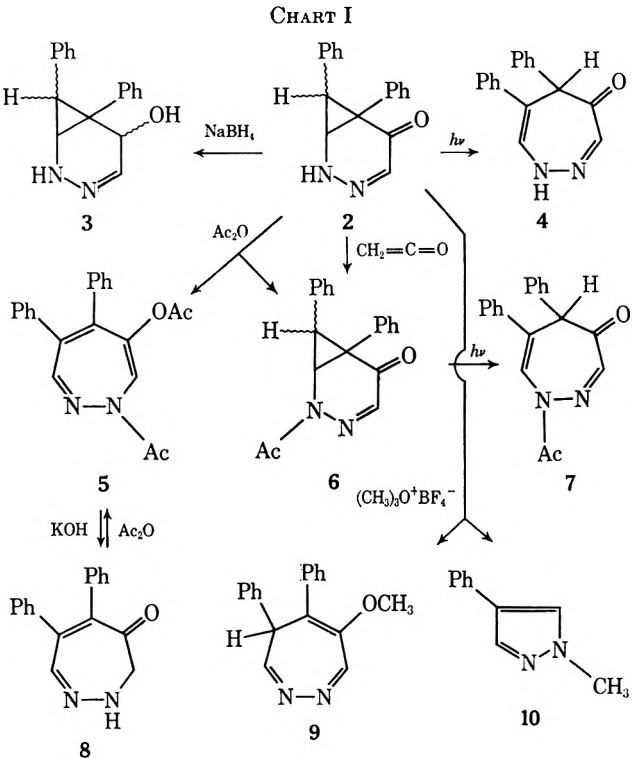


1 **2**

The ir spectrum (ν 3250 and 1630 cm^{-1}) indicates the presence of NH and conjugated carbonyl groups in 2, and the uv spectrum [λ_{max} 327 nm (ϵ 5100)] is consistent with the cyclic –NHN=C–C=O chromophore.[2a] The nmr spectrum contains a doublet of doublets, δ 3.19 and 4.75 (J = 5 Hz), and a singlet at 6.63 ppm. The latter signal is absent in the spectrum of material prepared in CH_3OD, and this proton in 2 thus arises from the CHN_2 in **1**. The presence of a cyclopropane system in 2 was first considered in order to account for the relatively high-field doublets. Chemical shift effects for phenyl and CO_2H substituents in cyclopropane have been derived,[3] and rough application of these values to 2, equating the C-5 CO group to CO_2H and assuming $\Delta\delta$ for *gem*-N as 2.0 and β_c-N as zero,[4] leads to chemical shifts of about δ 3 and 4, respectively, for H-7 and H-1 in 2 (or the endo-phenyl epimer). Neither chemical shift or coupling constant permits conclusions on the configuration at C-7.

For chemical characterization of the functional groups, 2 was reduced with $NaBH_4$ to alcohol **3** (Chart I) ($\delta_{H\text{-}7}$ 3.00, $\delta_{H\text{-}1}$ 3.49, $J_{1,7}$ = 4.5 Hz) and acylated

CHART I



with ketene at 0° to give **6** ($\delta_{H\text{-}7}$ 3.10, $\delta_{H\text{-}1}$ 5.63, $J_{1,7}$ = 5.5 Hz). Acetylation with Ac_2O provided the first correlation of 2 with a known structure. In addition to a small amount of **6**, a yellow diacetyl compound was obtained in 40% yield. This product was recognized as the acetoxydiazepine **5** by hydrolysis to the 2,3-dihydro ketone **8** and reacetylation.[5,6] Compounds **5** and **6** were also obtained from 2 in low yields with acetyl chloride.

A further instructive correlation with the diazepinone system was provided by the irradiation (350 nm) of 2 and the *N*-acetyl derivative **6**, which gave rise to the 1,5-dihydrodiazepinone **4** and the 1-acetyl-1,5-diazepinone **7**, respectively. The structures of these products were confirmed by comparison with samples prepared independently *via* **8**.

(1) Supported in part by the National Science Foundation and the Unidel Foundation.

(2) (a) F. B. Culp, A. Nabeya, and J. A. Moore, *J. Org. Chem.*, **38**, 2949 (1973); (b) F. B. Culp, K. Kurita, and J. A. Moore, *ibid.*, **38**, 2945 (1973).

(3) T. A. Wittstruck and E. N. Trachtenberg, *J. Amer. Chem. Soc.*, **89**, 3810 (1967).

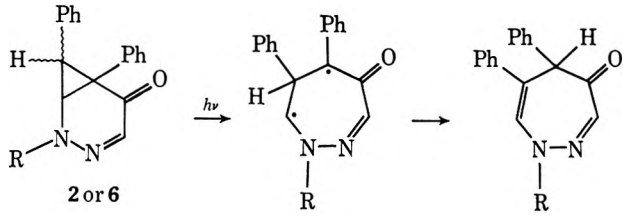
(4) These estimates are based on the spectrum of cyclopropylamine (No. 37 in Varian Associates Spectral Catalog, Palo Alto, Calif., 1962), in which H_α has δ 2.30 and H_β has δ 0.35.

(5) A. Nabeya, F. B. Culp, and J. A. Moore, *J. Org. Chem.*, **35**, 2015 (1970).

(6) J. A. Moore, W. J. Freeman, K. Kurita, and M. G. Pleiss, *ibid.*, **37**, 2939 (1972).

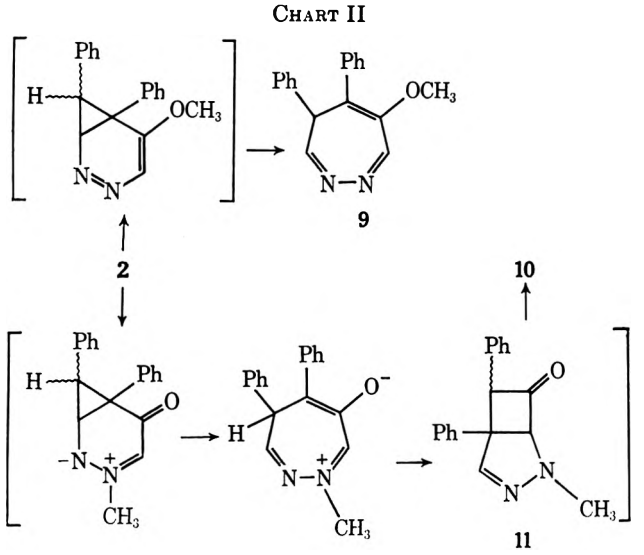
An additional link with the 1,5-dihydrodiazepinone system was established by methylation of **2** with trimethyloxonium fluoroborate. This reaction was complex and erratic, but it was possible to isolate three products on one occasion. One of these was a dimer of **2** with one *N*-methyl group and is related to other dimers mentioned below. The second contained an OCH_3 group and nmr signals at δ 4.09 (d) and 6.81 (d, J = 5 Hz); it is tentatively assigned the 6*H*-methoxydiazepine structure **9**. The third product was identified as 1-methyl-4-phenylpyrazole (**10**). The origin of this compound is clearly analogous to the formation of 1-acylpyrazoles from the bicyclic ketones derived from the 1,5-dihydrodiazepinone **4**.[6]

The conversion of **2** to representatives of the two dihydrodiazepinone tautomers (which are not interconverted under conditions in which either is formed from **2**) requires a structure from which both diazepines can arise by accessible methanisms. All of the products described can be formulated by breaking the 1,6 bond in **2** or its derivatives. The photochemical rearrangements involve hydrogen migration, probably from a diradical.



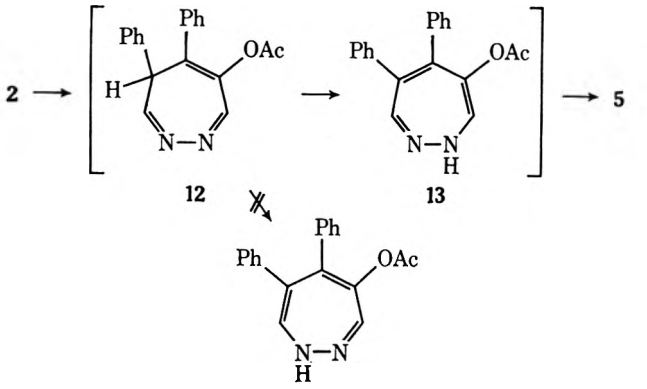
The methylation products **9** and **10** (Chart II) can arise following attack on **2** at the two sites that would

CHART II

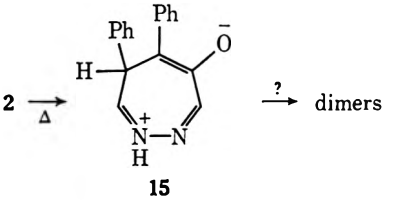


be expected for the trimethyloxonium reagent, namely carbonyl oxygen and N-3, respectively. In the first case, valence isomerization to a diazepine leads directly to **9**. In the second, further rearrangement to the bicyclo[3.2.0]ketone **11** and fragmentation would give **10**. The acyl counterparts of **11** lose phenylketene at room temperature to give 1-acyl-4-phenylpyrazoles.[6]

The acetylation of **2** leading to the 2,3-dihydro enol acetate **5** can be formulated in several ways depending on the sequence of introduction of the acetyl groups. One possibility is initial O-acylation followed by rearrangement to the 2,3-dihydro enol ester **13** and further acetylation. The factors that direct reactions of **2** to the 1,5-dihydro series (**11**) in the methylation and to the 2,3-dihydro series (**5**) in the acetylation cannot be defined.



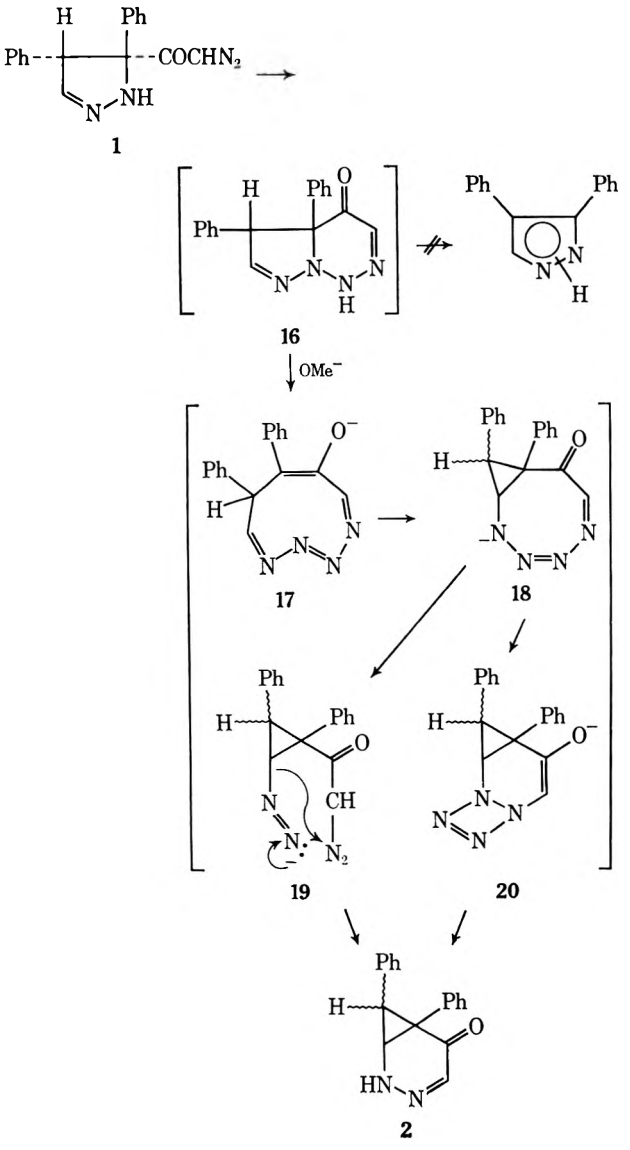
The study of **2** was severely complicated by the formation of a number of dimeric compounds under unpredictable and inexplicable conditions. Thus a dimer of **2** (dimer A) was obtained more or less consistently on heating **2** in methanol, but *not* in ethanol. A different dimer B was obtained from **2** or from dimer A in acetic acid. On heating in toluene, **2** or dimer A gave an anhydro dimer. A monoacetyl dimer was obtained on one occasion from acetylation of **2**; a methyl dimer was noted above. Several of these compounds were partially characterized, but no structural suggestions can be made. We assume that these dimers and derivatives arise from $_4\pi_s + _6\pi_s$ cycloadditions of a valence tautomeric form such as **15** or a derivative (*e.g.*, **9** or **12**), perhaps with a second molecule of **2**. Such additions are well known in the 1*H*-azepine series, and the initial dimers are prone to further rearrangement.[7-9]



Formation of 2.—In considering the pathway by which **2** is formed from the diazoacetylpyrazoline **1** in base, the first step is assumed to be cyclization to the pyrazolo-*v*-triazinone **16**, as postulated for the cis-diphenyl epimer and both isomeric 3-methyl-4-phenyl compounds.[2a,b] To arrive at a precursor of **2** which can lose nitrogen at room temperature, we suggest that **16** undergoes opening at the central bond to a tetrazonine enolate **17**. If **16** has a trans ring fusion,

(7) K. Hafner and A. Mondt, *Angew. Chem., Int. Ed. Engl.*, **5**, 839 (1966).
(8) L. Paquette and J. H. Barrett, *J. Amer. Chem. Soc.*, **88**, 2590 (1966).
(9) A. Johnson and H. E. Simmons, *ibid.*, **89**, 3191 (1967).

this step would lead to the trans N=N double bond in **17**, permitting 8-π-conrotatory cyclization to a *cis*-bicyclo[6.1.0] system (**18**). Subsequent steps could involve opening to a diazoacetyl diazene, loss of nitrogen, and cyclization to **2** or, perhaps more fancifully, cyclization to a fused tetrazete system (**20**) and elimination of nitrogen. These suggestions invoke some unfamiliar species and are, of course, totally speculative.



Experimental Section

6,7-Diphenyl-2,3-diazabicyclo[4.1.0]-3-hepten-5-one (2). A. From 1.—To a solution of 870 mg of the 5-pyrazoline **1** in 15 ml of methanol was added 4 ml of 1 *N* KOH in methanol. The solution was allowed to stand at 20° for 2 hr. (When the reaction was carried out in a sealed system, 1 mol of gas was evolved per mole of **1** in about 1 hr.) Addition of Dry Ice to the solution caused separation of a pale yellow solid which was collected, washed, and dried to give 370 mg (47%) of **2**, mp 175° dec. Crystallization from methanol (note, however, the dimerization in methanol described below!) gave a colorless solid: mp 175° dec; ν^{KBr} 3250, 1630 cm^{-1}; λ_{max}^{MeOH} 327 nm (ϵ 5100); δ^{CDCl_3} 3.19 (d, 1, J = 5 Hz, H-7), 4.75 (d, 1, J = 5 Hz, H-1), 6.63 (s, 1, H-4), 6.8–7.5 (m, 10).

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 78.29; H, 5.64; N, 10.56; *m/e* 262.1106.

B.—A solution of 0.58 g of 3-diazoacetyl-*trans*-3,4-diphenyl-1-pyrazoline in 10 ml of methanol and 10 ml of tetrahydrofuran was treated with 2 ml of 1 *N* methanolic KOH. After standing for 5 hr at 30° the orange solution was treated with Dry Ice and evaporated *in vacuo*. The residual yellow solid was triturated with water and then collected and dried to give 0.51 (94%) of crude powder. Recrystallization from ethanol–water gave 0.40 g (76%) of **2**, ir same as that from A.

6,7-Diphenyl-2,3-diazabicyclo[4.1.0]-3-hepten-5-ol (3).—A solution of 520 mg of **2** in 40 ml of a mixture of EtOH–tetrahydrofuran (1:1) was treated with 100 mg of $NaBH_4$. After 5 hr the reaction mixture was diluted with water, made distinctly basic with NaOH, and extracted with ether. After washing, drying, and evaporation the ether was evaporated and the solid colorless residue was recrystallized from methanol–water to give 240 mg (40%) of **3**, mp 165°. Further recrystallization from ether–pentane gave material with mp 168–170°; ν^{KBr} 3220, 1600, 1496 cm^{-1}; δ^{CDCl_3} 2.6 (s, 1, OH), 3.00 (d, 1, J = 4.5 Hz, H-7), 3.49 (d, 1, J = 4.5 Hz, H-1), 4.18 (br s, 1, –CHOH), 5.95 (s, 1, NH), 6.5–7.3 (m, 11).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 76.98; H, 6.10; N, 10.62.

The 2-acetyl derivative of **3** was obtained by treatment of 211 mg of **3** in CH_2Cl_2 with 2 equiv of acetyl chloride in pyridine. After addition of water, etc., the CH_2Cl_2 was evaporated to give 60 mg of white solid which was recrystallized from $CHCl_3$–pentane: mp 225°; ν^{KBr} 1650, 1605, 3330 cm^{-1}; $\delta^{DMSO\text{-}d}$ 2.31 (s, 3), 2.83 (d, 1, J = 5 Hz, H-7), 4.17 (br s, 1, CHOH), 4.85 (d, 1, J = 5 Hz, H-1), 7.0–7.2 (m, 11).

Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.15. Found: C, 74.30; H, 5.95; N, 8.87.

Excess acetyl chloride gave a noncrystalline diacetyl derivative: δ^{CDCl_3} 2.20 (s, 3), 2.40 (s, 3), 2.87 (d, 1, J = 5.5 Hz, H-7), 5.04 (d, 1, J = 5.5 Hz, H-1), 5.50 (d, 1, J = 1.7 Hz, H-5), 6.78 (d, 1, J = 1.7 Hz, H-4), 7.1 (m, 10).

Reaction of 2 with Acetic Anhydride.—A solution of 0.79 g of **2** in 3 ml of Ac_2O and 5 ml of pyridine was allowed to stand for 4 hr and was then added to water. The mixture was shaken with ether and some white insoluble solid was collected by filtration and dried to give 60 mg (7%) of the 2-acetyl bicyclic compound **6**. Recrystallization from chloroform–hexane gave colorless crystals: mp 245°; ν^{CHCl_3} 1710, 1675 cm^{-1}; δ^{CDCl_3} 2.50 (s, 3), 3.10 (d, 1, J = 5.5 Hz, H-7), 5.63 (d, 1, J = 5.5 Hz, H-1), 6.7–7.3 (m, 11).

Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.49; H, 5.54; N, 9.04.

The ether solution from above was washed, dried, and evaporated to a yellow residue. After the residue was redissolved in ether and the solution was filtered to remove a small amount of **6**, the solution was again concentrated to give 380 mg (37%) of orange solid, mp 150°. Recrystallization from chloroform–hexane gave the enol acetate **5** as yellow needles: mp 152–154; ν^{KBr} 1775, 1690, 1370, 1320, 1210, 1170 cm^{-1} (all strong); δ^{CDCl_3} 1.65 (s, 3), 2.29 (s, 3), 6.62 (s, 1),[10] 6.8–7.3 (m, 10). The ir spectrum matched (positions and relative intensities of 23 peaks) that of a sample prepared by acetylation of the 2,3-dihydrodiazepinone.[5,6]

Anal. Calcd for $C_{21}H_{18}N_2O_3$: C, 72.82; H, 5.24; N, 8.09. Found: C, 72.64; H, 5.34; N, 7.99.

To a solution of 100 mg of the yellow crystals in 3 ml of methanol was added 2 ml of 1 *N* KOH. After 1 hr the solution was diluted with ice water and made acidic with HCl, and the resulting yellow solid was collected, washed, and dried to give 75 mg (88%) of **8**, mp 200° dec; ir identical with that of authentic sample.[5]

5,6-Diphenyl-1,5-dihydro-4*H*-1,2-diazepin-4-one (4) from 2.—A solution of 150 mg of **2** in 140 ml of benzene was irradiated in a Rayonet photochemical reactor with 16 75-W 3500-Å lamps; the solution was cooled to 13° with a circulating water jacket. After 30 min, tlc showed the formation of a yellow, faster moving compound; after 2 hr this appeared to be the major component. After 2.5 hr of irradiation the solution was evaporated *in vacuo* to a solid residue which was chromatographed on silicic acid in $CHCl_3$ solution. The material in the yellow band was treated with charcoal to remove some dark color and was then chromatographed again. Crystallization from benzene–cyclohexane

(10) This signal was absent in the spectrum of a sample prepared by acetylation of **2–4-*d*** obtained from **1** in CH_3OD–NaOD.

gave 30 mg (20%) of bright yellow crystals of **4**, mp 133–134°; the ir spectrum was identical with that of a sample prepared by base-catalyzed isomerization of the 2,3-dihydrodiazepinone.[6]

Photoisomerization of 6.—A solution of 100 mg of the 2-acetyl compound **6** in 100 ml of benzene was irradiated as described above for **2**. After 3 hr the yellow solution was evaporated and the residual oil was chromatographed on silica gel to give 65 mg of yellow oil. The ir spectrum was identical with that of a noncrystalline sample of the 1-acetyl-5,6-diphenyl-1,5-dihydrodiazepinone (**7**) obtained from **4** plus ketene.[5] (Crystalline **7** was obtained subsequent to this photoisomerization experiment.) For further characterization the irradiation product was acetylated with Ac_2O to obtain the crystalline enol acetate, mp 150–151°, identical (ir) with a sample prepared from **4**.[6]

Methylation of 2.—A suspension of 262 mg of **2** in 5 ml of acetone at 0° was treated with 443 mg (3 mequiv) of trimethyloxonium fluoroborate. The solid **2** rapidly dissolved. After 30 min, 0.7 ml of triethylamine was added and acetone was evaporated. The orange oil was dissolved in $CHCl_3$ and the solution was washed with dilute NaOH and then water, dried, and evaporated. The amber oil crystallized from $CHCl_3$–hexane to give 30 mg of white solid: mp 175°; ν^{KBr} 1660, 1610 cm^{-1}; δ^{CDCl_3} 3.55 (s, 3), 3.6–4.3 (m, 3), 4.96 (m, 1), 6.47 (m, 3), 6.9–7.4 (m, 20) (analysis showed retention of $CHCl_3$); mass spectrum *m/e* 538 (dimer of **2** + CH_2) (10),[11] 453 (38), 276 (**2** + CH_2) (80), 219 (100).

The mother liquor from the methyl dimer was chromatographed in $CHCl_3$ on silicic acid. The resulting light amber oil, obtained in one fraction, crystallized from benzene–pentane to give 30 mg of tan solid. Recrystallization from $CHCl_3$–hexane gave 20 mg of white crystals of **9**: mp 192–193°; ν^{KBr} 1640, 1560 cm^{-1} (these are assumed to be C=N stretching); δ^{CDCl_3} 3.66 (s, 3), 4.09 (d, 1, J = 5 Hz), 6.81 (d, 1, J = 5 Hz), 7.0–7.5 (m, 11); λ_{max}^{MeOH} 263 nm (ϵ 9500), 303 (8300), 334 (9000).

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 78.23; H, 5.84; N, 10.14. Found: C, 78.32; H, 5.81; N, 10.19.

The mother liquor from **9** was concentrated and the residual oily solid was sublimed [70° (1 mm)] to give 25 mg of pale yellow solid. Recrystallization from hexane gave white plates of the methylpyrazole **10**: mp 101–102°; δ^{CDCl_3} 3.91 (s, 3), 7.15–7.5 (m, 5), 7.55 (s, 1), 7.75 (s, 1).

Anal. Calcd for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.39, H 6.81; N, 17.61.

An authentic sample of **10** was obtained by treating a suspension of 70 mg of 4-phenylpyrazole in acetone with 220 mg of $(CH_3)_3O\cdot BF_4$ at 9° for 1 hr. After addition of Et_3N, and the usual isolation, the product mixture was chromatographed to remove some unreacted starting material and 35 mg of **10** was obtained, mp 100–101°, ir identical with that of sample described above.

Dimerization of 2 in Methanol (Dimer A).—**2** (600 mg) was warmed with 100 mg of methanol until solution was complete and the solution was then concentrated and allowed to crystallize. A first crop of 150 mg of colorless needles of dimer A was obtained. Addition of water to the mother liquor gave an additional 300 mg of tan crystals. Tlc of the first crop showed one spot, faster moving than **2**; the second crop contained mainly dimer and a small amount of **2**. Recrystallization of the combined material from methanol gave colorless needles: mp 196° dec; ν^{KBr} 3350, 3200, 1720, 1660 cm^{-1}; δ^{CDCl_3} 4.11 (t, 1), 4.7 (d, 1, J = 5 Hz), 4.8 (s, 1), 4.95 (d, 1, J = 5.7 Hz), 5.48 (m, 1, in D_2O → d, J = 5.7 Hz), 6.7 (s, 1), 6.8–7.3 (m, 21), 8.5 (br, in D_2O exchanges).

Anal. Calcd for $C_{34}H_{28}N_4O_2$ (mol wt 524): C, 77.84; H, 5.38; N, 10.68. Found: C, 77.62; H, 5.47; N, 10.33.

Anhydro Derivative of 2.—A solution of 150 mg of **2** in 2 ml of toluene was refluxed for 4 hr. On cooling, 40 mg of tan powder separated. Tlc showed a major component at slightly higher R_f value than **2**. Recrystallization of this solid from methanol gave 20 mg of light tan crystals: mp 209° dec; ν^{KBr} 3350, 1710, 1640, 1560 cm^{-1}; δ^{DMSO} 3.84 (d, 1, J = 7 Hz), 6.0 (dd, 1, J = 3 and 7 Hz), 6.80 (s, 1), 7.0–7.5 (m, 20–23); *m/e* 506 (dimer of **2** − 18) (65),[11] 479 (84), 460 (84), 436 (56), 244 (63), 206 (100).

Anal. Calcd for $C_{34}H_{26}N_4O$ (mol wt 506): C, 80.61; H, 5.17; N, 11.06. Found: C, 80.66; H, 4.89; N, 11.13.

A somewhat higher yield, and more easily purified sample of this compound, was obtained by heating dimer A in toluene for 4 hr.

Dimerization of Acetic Acid.—A solution of 200 mg of **2** (or dimer A) in 10 ml of glacial acetic acid was heated at 60° for 10 hr. After a small amount of undissolved solid was removed the acetic acid was evaporated (benzene added and evaporated) to give a brown powder. Several recrystallizations from methanol gave colorless rods: mp 235° dec; ν^{KBr} 3250, 1730, 1650 cm^{-1}; δ^{DMSO} 4.22 (d, 1, J = 8 Hz), 5.38 (dd, 1, J = 4 and 13 Hz), 5.80 (dd, 2, J = 4 and 8 Hz, in D_2O → d, J = 8 Hz), 6.5 (m, 2), 6.7 (apparent d, J = 6 Hz), 7.2 (br s, 15); *m/e* 524 (4),[11] 505 (7), 496 (6), 478 (24), 467 (20), 451 (17), 437 (18), 436 (18), 363 (20), 334 (21), 308 (23), 262 (40), 247 (42), 235 (100), 234 (55).

Anal. Calcd for $C_{34}H_{28}N_4O_2$ (mol wt 524): C, 77.84; H, 538; N, 10.68. Found: C, 78.06; H, 4.81; N, 10.86.

Registry No.—**1**, 24302-17-8; **2**, 40635-72-1; **3**, 40635-73-2; **3** 2-acetyl derivative, 40635-74-3; **3** diacetyl derivative, 40635-75-4; **4**, 40635-76-5; **5**, 40635-77-6; **6**, 40635-78-7; **8**, 24301-66-4; **9**, 40635-80-1; **10**, 10199-69-6; dimer A, 40633-49-6; 4-phenylpyrazole, 10199-68-5; $(CH_3)_3O\cdot BF_4$, 420-37-1.

(11) Numeral in parentheses is per cent intensity of base peak (100).

Thermally Induced Fragmentation of Some Azidopyrazole Derivatives[1]

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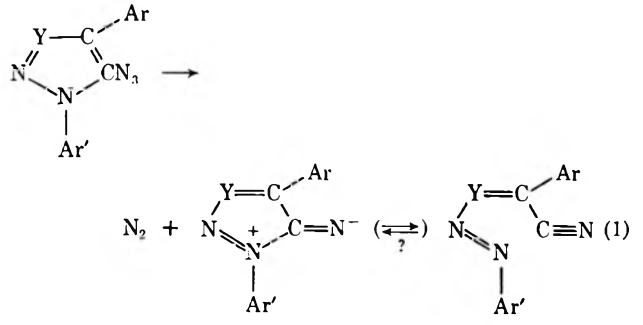
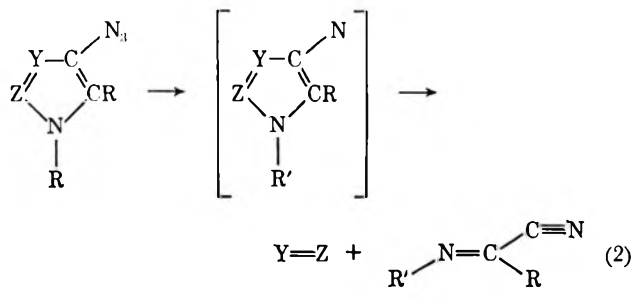
4-Azido-1,5-diphenyl-1,2,3-triazole thermolyzed at 110° into nitrogen and α-phenyliminophenylacetonitrile, as did a series of seven 4-azidopyrazoles bearing methyl and/or phenyl substituents between 40 and 80°, with fragmentation of the ring. The 3 substituent with the attached 3 carbon appeared as a nitrile, R^3CN, and the 1 and 5 substituents together with the 4 and 5 carbons appeared as an α-iminonitrile, $R^5C(CN)=NR^1$. When the 3 and 5 substituents were both phenyl, substantial amounts of the corresponding azopyrazole (formally a dimer of the nitrene) were formed as well. The ratio of dimeric to fragmentation product fell on dilution. Thermolysis of 1-methyl-3,5-diphenyl-4-azidopyrazole in the presence of *p*-anisyl azide gave the same products as in the absence of anisyl azide, and no unsymmetrical azo compound could be detected. Azo compounds are deduced not to arise from either dimerization of nitrene or attack of nitrene on azide. Photolysis of the azides or deoxygenation of the corresponding 4-nitrosopyrazoles gave similar products but in lower yields. 3,5-Dimethyl-4-azidopyrazole formed 4-phenylazo-3,5-dimethylpyrazole when thermolyzed in aniline, apparently through insertion of a pyrazoylylnitrene into an N–H bond. 3-Methyl-4-phenyl-5-azidopyrazole lost nitrogen slowly at 110° and formed the corresponding aminopyrazole (15 to 18%) and α-cyano-β-methylstyrene (38%).

Certain 5-azidopyrazoles and -triazoles have been found to lose nitrogen upon mild thermolysis and to produce a single fragmentation product, a conjugated nitrile, resulting from fission of the ring at the 1,5 bond (eq 1).[2] It is not known whether this is a concerted process, or whether a free nitrene intervenes, although there is some evidence that the conjugated nitriles may equilibrate with a very low concentration of the corresponding heterocyclic nitrene, whose energy content and reactivity are unusually low owing to electronic interaction with the ring.



The positionally isomeric 4-azidoazoles would give rise to a similarly stabilized nitrene (eq 2), but the option of a simple ring opening to form a conjugated nitrene isomeric with the nitrene is not available. If fragmentation occurs, two moieties must be formed, one derived from the 2 and 3 positions of the ring, the other from the 4, 5, and 1 positions. Nitrogen atoms as such are in principle not required at any of the ring positions. We have observed an example of this type of fragmentation in the triazole series: 1,5-diphenyl-4-azido-1,2,3-triazole fragments cleanly into two molecules of nitrogen and a molecule of α-phenyliminophenylacetonitrile when heated (Y = Z = N). Closely related examples in the pyrazole and pyrrole series have been reported: Wright found that 1,5-diphenyl-3-methyl-4-nitrosopyrazole fragments into acetonitrile and α-phenyliminophenylacetonitrile (Y = C, Z = N) when deoxygenated with triethyl phosphite,[3] and Irwin and Wibberley found that 7-nitroso-3,6-diphenylpyrrolo-[1,2-*c*]pyrimidine opens to 4-phenyl-6-(2-phenyl-2-cyano)vinylpyrimidine during catalytic hydrogenation.[4]



4-Azidopyrazoles.—The present work was undertaken to explore the generality of this type of fragmentation and to see if any evidence for an intermediate nitrene could be found. To this end, a group of 4-azidopyrazoles having methyl and/or phenyl substituents was prepared. The conventional route to such compounds would be through reaction of sodium azide with the diazotized amines,[5] which are obtained by reduction of the 4-nitro- or 4-nitrosopyrazoles. However, the general method for introducing nitrogen functionality into the 4 position of the pyrazole ring,[6] reaction of an α-oximino-β-dicarbonyl compound with a hydrazine to form a 4-nitrosopyrazole, gave only traces of 1,3,5-triphenyl-4-nitrosopyrazole and none of the desired product when applied to the synthesis of 1-methyl-3,5-diphenyl-4-nitrosopyrazole, evidently owing to rapid reaction of the desired product with the hydrazine.

Nitration of phenylpyrazoles is known to take place on the benzene ring and was thus not an alternative.[6] Although it has been stated[6] that "direct nitrosation of pyrazoles cannot be accomplished," we were able to effect the nitrosation of 1,3,5-triphenylpyrazole in 50% yield, using dinitrogen tetroxide in methylene chloride in the presence of sodium acetate. 1-Methyl-3,5-diphenyl-4-aminopyrazole was prepared by methylation of the known 3,5-diphenyl-4-aminopyrazole while the amino group was protected with a benzylidene group. 1,3-Diphenyl-4-amino-5-methylpyrazole was prepared from the known 4-carboethoxy compound through the Curtius reaction. Subsequent steps leading from these compounds to the 4-azidopyrazoles were unexceptional.

(1) From the doctoral dissertation of H. Dounchis, 1967.

(2) (a) P. A. S. Smith, W. Resemann, and L. O. Krbechek, *J. Amer. Chem. Soc.*, **86**, 2025 (1964); (b) P. A. S. Smith, G. J. W. Breen, M. K. Hajek, and D. C. V. Awang, *J. Org. Chem.*, **35**, 2215 (1970).

(3) J. B. Wright, *J. Org. Chem.*, **34**, 2474 (1969).

(4) W. J. Irwin and D. G. Wibberley, *Chem. Commun.*, 878 (1968).

(5) G. T. Morgan and I. Ackerman, *J. Chem. Soc.*, **123**, 1311 (1923).

(6) A. N. Kost and I. I. Grandberg, *Advan. Heterocycl. Chem.*, **6**, 347 (1966).

The 4-azidopyrazoles (*cf.* Table I) were obtained in a state of good purity (tlc, ir, nmr), in some instances

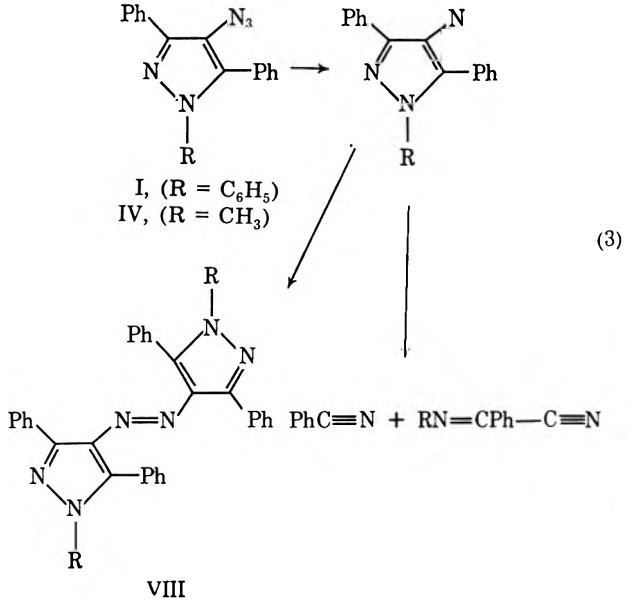
TABLE I
THERMOLYSIS OF 4-AZIDOPYRAZOLES (1-R′, 3-R³, 5-R⁵) IN CYCLOHEXANE SOLUTION

	Substituents			Yields, %[a]		
Compd	1-R¹	3-R³	5-R⁵	R³CN	R¹N=C-(CN)R⁵	Azopyrazole
I	Ph	Ph	Ph	Yes	21	14.5[b]
II	Ph	Ph	CH_3	54	75	None
III	Ph	CH_3	Ph	Yes	100	None
IV	CH_3	Ph	Ph	Yes	Yes	35
V	Ph	CH_3	CH_3	Yes	74	None
VI	CH_3	CH_3	CH_3	Yes	Yes	None
VII	H	CH_3	CH_3	Yes	?	None[c]

[a] Some tar was always formed. [b] 2% of benzanilide also formed. [c] Also formed were ~20% high-melting solid, and 7.5% X ($C_8H_{11}N_5$?): mp 172–174°; ir 3190 (NH), 1675, 1660 (C=N), 1635, 1340 cm^{-1}; nmr δ 1.48 (s, 1), 2.20 (s, 1), 2.23 ppm (s, 1); uv λ_{max} 222 nm (ε 3300), 257 (3400), 272 (3700), 337 (2300); *m/e* 177.

crystalline, but were unusually unstable for aryl azides, and decomposed slowly at ambient temperature and sometimes detonated during combustion, thus precluding meaningful analysis. In dilute solution in cyclohexane, nitrogen evolution was completed in ~30 min at reflux temperature (~80°). Although the products of the generalized fragmentation reaction were detected in each instance, they were usually accompanied by considerable amounts of polymeric material. The simple nitriles (acetonitrile or benzonitrile) were generally not isolated, but were detected by nmr or ir and by glc retention time. The α-iminonitriles bearing one or more phenyl groups were isolated in crystalline form when feasible; α-iminopropionitrile and α-methyliminopropionitrile, however, were too labile and presumably not solid at room temperature. Nmr signals attributable to the latter were obtained, but only presumed transformation products of the former could be detected. The results are collected in Table I.

In addition to the nitrilic fragmentation products, two of the azides, 1,3,5-triphenyl- (I) and 1-methyl-3,5-diphenyl-4-azidopyrazole (IV), produced the corresponding azopyrazoles (VIII, eq 3). Azo compounds



(3)

VIII

could not be detected among the products of the other azides even by thin layer chromatography (the azo compounds were synthesized from the nitroso pyrazoles for comparison). The formation of an azo compound indicates that fragmentation of the azido pyrazole is not a concerted process, but a nitrene is first formed by loss of nitrogen from the azido group in a discrete step. If the lifetime of the nitrene is long enough, reactions other than further fragmentation may compete. The two azidopyrazoles that gave rise to azo compounds are the only ones of those examined that have phenyl groups in the 3 and 5 positions, but it is not clear how such substitution brings about this effect.

The path from nitrenes to azo compounds in general is unlikely to be simple dimerization, although it has often been so represented.[7] Nitrenes are highly reactive intermediates, of unknown but assuredly short lifetimes, and their concentration at any moment in a decomposing azide solution must be very low; the probability that two nitrene molecules would collide before reacting in other ways (intramolecularly or with the medium) would be very small. Extensive kinetic measurements have shown that thermolysis of aryl azides is strictly first order, so that initial dimerization of the azide cannot be involved.[7] The likely alternatives are attack by nitrene on azide (eq 4) or processes involving hydrogenated intermediates, such as dimerization of amino radicals or insertion of nitrene into an N–H bond, followed by dehydrogenation of the resulting hydrazine (eq 5) by nitrene, amino radical, or air. In

$$RN + RN_3 \longrightarrow RN{=}NR + N_2 \qquad (4)$$

$$RN \xrightarrow{[H]} RNH\cdot \longrightarrow RNH_2 \xrightarrow{RN} RNHNHR \xrightarrow{-[H]} RN{=}NR \qquad (5)$$

either case, the proportion of azo compound to unimolecular fragmentation products or primary amine should decrease with dilution.

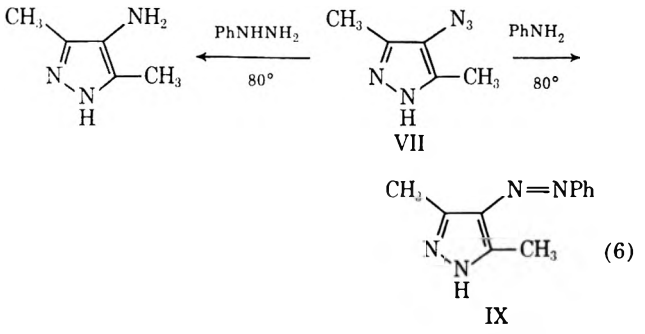
1,3,5-Triphenyl-4-azidopyrazole (I) has a generally low solubility, and thus did not lend itself to experiments over a range of concentrations. 1-Methyl-3,5-diphenyl-4-azidopyrazole (IV) is more soluble, and thermolyses were conducted at the concentrations of 0.40, 0.33, and 0.029 *M* in cyclohexane. The yield of azopyrazole was essentially the same (~35%) at the first two concentrations, but fell by one third (to 23%) at the higher dilution. This result is in qualitative agreement with expectation, but the quantitative significance is uncertain, owing to the extensive formation of intractable gums. Another experiment took advantage of the fact that the decomposition temperature of IV is much lower than that of *p*-anisyl azide, which is known to form *p,p′*-azoanisole on thermolysis. When IV, 0.14 *M* in cyclohexane, was thermolyzed in the presence of excess *p*-anisyl azide, which is stable at the reflux temperature of the solution, azopyrazole VIII was formed in normal yield (25%). No trace of the *p*-anisylazopyrazole which would have resulted from the attack of the pyrazole nitrene on anisyl azide could be detected.

This result is consistent with the observations of Abramovitch, Challand, and Scriven that phenyl azide

(7) P. A. S. Smith, in "Nitrenes," Lwowski, Ed., Wiley-Interscience, New York, N. Y., 1970, Chapter 4.

was unattacked when phenylnitrene was generated in its presence by deoxygenation of nitrobenzene with triethyl phosphite.[8] Such facts imply that eq 4 does not represent the path from azides to azo compounds, and eq 5 is therefore implicated.

There is precedent for insertion of arylnitrenes into N–H bonds to produce hydrazo or azo compounds in several independent reports.[9] Further evidence for this process and for eq 5 was obtained from 3,5-dimethyl-4-azidopyrazole (VII), which alone in benzene or toluene formed no detectable azopyrazole, but in a benzene solution of aniline formed the unsymmetrical azo compound, 3,5-dimethyl-4-phenylazopyrazole (IX), in 5.7% yield. In the presence of phenylhydrazine, a hydrogen donor much superior to benzene or aniline, the principal product was the aminopyrazole (42.6%) instead (eq 6). The formation of primary amine, fragmentation products, azo compounds, etc., would, of course be sensitively determined by influences of the medium and the structure of the azide on the relative rates of the steps in eq 5.



(6)

In the absence of aniline or phenylhydrazine, azide VII gave rise principally to a brown, amorphous material which could not be purified and which appeared to be polymeric. The other products were acetonitrile and, in 7% yield, a colorless, crystalline solid that decomposed slowly; the molecular formula was apparently $C_8H_{11}N_5$ (X). Its nmr spectrum showed three singlets, of equal intensity, corresponding to three methyl groups (the NH hydrogens could not be located, owing to extreme broadening of their signal, but their presence was confirmed in the ir). It corresponds to an adduct of the pyrazolylnitrene with α-iminopropionitrile, the other expected fragmentation product, although it cannot be said if it arose in that way. Its instability, the small quantities accessible, and its uncertain significance recommended that further investigation be deferred.

A sample of azide VII was thermolyzed by adding it in small portions to a boiling solution of maleic anhydride in benzene, in the hope of intercepting α-iminopropionitrile. The only product isolated was an unpurifiable and evidently polymeric solid, whose analysis corresponded roughly to a 1:1 adduct of α-iminopropionitrile with maleic anhydride, in ~85% yield; its poorly resolved ir spectrum showed both carbonyl and N–H stretching bands, but no discernible C≡N absorption.

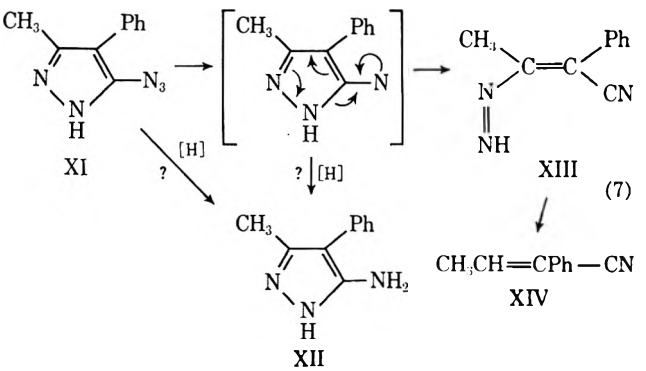
(8) R. A. Abramovitch, S. R. Challand, and E. F. V. Scriven, *J. Amer. Chem. Soc.*, **95**, 1374 (1972).

(9) R. A. Odum and M. Brenner, *J. Amer. Chem. Soc.*, **88**, 2074 (1966); R. Huisgen and K. von Frauenberg, *Tetrahedron Lett.*, 2595 (1969); R. E. Banks and A. Prakash, *ibid.*, 99 (1973); E. F. V. Scriven, H. Suschitzky, and G. V. Garner, *ibid.*, 103 (1973).

One example of a 4-azidopyrazole, IV, was decomposed by photolysis for comparison. The same products, benzonitrile, α-methyliminophenylacetonitrile, and the azopyrazole, were formed, but in lower yield. In addition to these and some tarry materials, an unstable solid photoproduct was isolated. Thin layer chromatography indicated one major and two minor components, but we could not purify them by either chromatography or recrystallization. Nitrile absorption showed in the ir spectrum of the mixture and nmr showed two *N*-methyl singlets and aromatic protons corresponding to a ratio of $CH_3:C_6H_5$ between 1:2 and 2:5. This ratio eliminates the possibility that the substance may have been derived from addition of the azide or nitrene to a fragmentation product, but that is all that can be said at this time.

4-Nitrosopyrazoles.—In two instances, the corresponding 4-nitrosopyrazoles were deoxygenated with triphenylphosphine. 1,5-Diphenyl-3-methyl-4-nitrosopyrazole (corresponding to azide III) gave acetonitrile and α-phenyliminophenylacetonitrile, as Wright obtained[4] by deoxygenation with triethyl phosphite, and as we obtained from the azide, but in lower yield. The yield of iminonitrile was sensitive to concentration, falling from 57% in 0.05 *M* solution to 38% in 0.37 *M* solution. 1,3,5-Triphenyl-4-nitrosopyrazole (corresponding to azide I) gave an intractable mixture on deoxygenation; no azopyrazole and only traces of iminonitrile could be detected by tlc.

5-Azidopyrazoles.—The behavior of the 4-azidopyrazoles, which indicates a role for nitrene intermediates in at least some cases, turned our attention to the possibility that nitrene intermediates might also be detectable from 5-azidopyrazoles. In the examples previously reported,[2b] the conjugated azoacrylonitrile produced according to eq 1 was considerably stabilized by the presence of aryl groups on the unsaturated carbon and nitrogen positions, a circumstance that might accelerate opening of the ring, and thus either bypass the nitrene (concerted fragmentation) or reduce its lifetime (or its equilibrium concentration). We therefore prepared and thermolyzed 3-methyl-4-phenylazidopyrazole (XI), the azoacrylonitrile from which would be stabilized by only one aryl group instead of three, and thus might not form so readily. This azide was considerably more stable than the 4-azidopyrazoles and than 1,3,4-triphenyl-5-azidopyrazole, which thermolyze at temperatures as low as 50°, and it decomposed at a reasonable rate only when heated to 110° (refluxing toluene). The products were the corresponding 5-aminopyrazole (XII, 20%) and α-phenylcrotonitrile (XIV, 38%) (eq 7). The azoacrylonitrile



(7)

derivative XIII was not detected directly, but its formation was inferred from the appearance of XIV and analogy to the behavior of other monosubstituted diazenes.[9]

The formation of an amine, a product of hydrogen abstraction, in substantial quantities distinguishes the behavior of XI from its 1,3,4-triaryl analogs. It is a reaction characteristic of nitrenes and would seem to imply that a nitrene intermediate in this instance has a long enough lifetime for other reactions to compete with the ring-opening path. However, bibenzyl, an expected product if the source of hydrogen were the toluene used as solvent, was detected in only trace amounts, and the same products were obtained when chlorobenzene was used as solvent instead. The most likely alternative source of hydrogen is the diazene XIII [diimide itself is known to be an effective donor of hydrogen, and phenyldiazene (phenyldiimide) is a very active reducing agent].[10]

If XIII is the source of hydrogen, it is more probable that it transfers hydrogen atoms to the azide XI[10] rather than the nitrene, for the latter would be present only at very low concentrations, and the concentration of XIII would also be low, owing to its depletion both by hydrogen transfer and by loss of nitrogen to form XIV. The product of dehydrogenation of XIII, a diazo free radical or the vinyl radical formed from it by loss of N_2, is a likely source of the tarry material formed. The stoichiometry of such a scheme is consistent with the observations, for the 20% yield of amine would require 40% of XIII for its formation, leaving 40% of the reaction mixture to be accounted for as XIV, compared to 38% actually obtained.

Experimental Section[11]

1,3,5-Triphenyl-4-nitrosopyrazole.—A solution of 8.0 g (27 mmol) of 1,3,5-triphenylpyrazole[12] [nmr δ 6.77 (s, 1), 7.3–7.4 (m, 13), 7.85–8.0 ppm (m, 2); ir 1600, 1495, 1365, 1215, 1175, etc., cm^{-1}] in 200 ml of methylene chloride in which 2.2 g of sodium acetate was suspended was cooled in an ice bath and stirred while 10 ml of dinitrogen tetroxide diluted with methylene chloride was added. The mixture was stirred for 6 hr while slowly attaining room temperature and was then washed with water and dried over magnesium sulfate. Evaporation left a green mass, which was recrystallized from 600 ml of ethanol to give 4.35 g (49.6%) of sparkling green crystals of the nitrosopyrazole: mp 184–186°; nmr δ 7.3–7.5 (m, 13), 7.85–8.0 ppm (m, 2); ir (Nujol) 1605, 1595, 1500, 1460 cm^{-1}.

Anal. Calcd for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.65; N, 12.92. Found: C, 77.35; H, 4.76; N, 12.90.

Attempts to increase the yield by use of longer reaction times and excess dinitrogen tetroxide resulted in destruction of the nitroso compound and formation of unidentified orange-yellow substances. 1,3,5-Triphenyl-4-nitrosopyrazole was also prepared from the reaction of 1,3-diphenyl-1,2,3-propanetrione 2-oxime with phenylhydrazine, but in only 1.5% yield.

4-Amino-1,3-diphenyl-5-methylpyrazole.—A suspension of 11.2 g (36.6 mmol) of ethyl 1,3-diphenyl-5-methylpyrazole-4-carboxylate[13] in 24 ml of 95% hydrazine was refluxed with stirring for 5 hr and then poured into ice water. The resulting solid 4-carbohydrazide was washed with water, triturated with a small amount of ethanol, and dried in air: 10.17 g (95.2%); mp 181–183°; ir ($CHCl_3$) 3430, 3325 ($NHNH_2$), 1665–1650 cm^{-1} ($CONHNH_2$); nmr δ 2.53 (s, 3, 5-CH_3), 3.8 (broad, 2, NH_2), 6.9 (broad, 1, NH), 7.45 ppm (s, 10, aryl).

Anal. Calcd for $C_{17}H_{16}H_4O$: C, 69.84; H, 5.52, N, 19.17. Found: C, 69.70; H, 5.62; N, 19.21.

The entire yield of the foregoing hydrazide was quickly dissolved in a cold mixture of 50 ml of glacial acetic acid and 50 ml of 7% hydrochloric acid and treated with 2.4 g of sodium nitrite dissolved in a minimum of water. The gummy acyl azide that precipitated was separated by decantation and taken up in 100 ml of benzene. After one washing with water, the benzene solution was cautiously heated under reflux with 35 ml of concentrated hydrochloric acid. When gas evolution ceased (~1.5 hr), the mixture was filtered, and the aqueous phase was separated, neutralized with sodium bicarbonate, and extracted with chloroform. Attempts at crystallization having failed, the crude amine was converted to its benzylidene derivative by heating for several minutes with an equivalent quantity of benzaldehyde in 20 ml of ethanol; on cooling, 6.85 g (58.3%) of crystalline solid, mp 168–171°, separated. It was hydrolyzed by stirring overnight in a mixture of 50 ml of 5 *M* sulfuric acid and 50 ml of chloroform. The crystalline sulfate salt that separated was washed with chloroform and decomposed with aqueous sodium carbonate to give 2.5 g of 4-amino-1,3-diphenyl-5-methylpyrazole, mp 69–71°. Repeated crystallizations from cyclohexane gave an analytical sample: mp 70–71.5°; ir 3350, 3280, 1600 cm^{-1}; nmr δ 2.16 (s, 3, 5-CH_3), 2.84 (br, 2, NH_2), 7.2–7.5 (m, 8, aryl), 7.7–7.9 ppm (m, 2, *o*-aryl).

Anal. Calcd for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.86. Found: C, 77.03; H, 6.03; N, 17.06.

If the treatment of the acyl hydrazide with sodium nitrite was not done quickly, substantial amounts of *sym*-bis(1,3-diphenyl-5-methyl-4-carbonyl)hydrazine were formed: mp 236–237°; ir 3380, 3186, 1640, 1623 cm^{-1}.

Anal. Calcd for $C_{34}H_{28}N_6O_2$: C, 73.89; H, 5.11; N, 15.21. Found: C, 73.73; H, 5.20; N, 15.25.

4-Amino-3,5-diphenyl-1-methylpyrazole.—4-Amino-3,5-diphenylpyrazole[14] was converted to its pale yellow *N*-benzylidene derivative (mp 225–227°) by heating with an equivalent amount of benzaldehyde in ethanol. A suspension of 11.19 g (36.8 mmol) of the crude product in 200 ml of benzene was refluxed with 5.1 g (10% excess) of methyl sulfate for 16 hr. The cooled mixture was washed with three 100-ml portions of 10% sodium hydroxide solution and then with water and was then dried ($MgSO_4$), filtered, and evaporated. The crude, yellow residue, 9.53 g (77%), mp 130–140°, was recrystallized from ethanol to yield 5.89 g of 4-benzylidenamino-3,5-diphenyl-1-methylpyrazole: mp 145–146°; ir 1635 cm^{-1} (C=N); nmr δ 3.77 (s, 3, *N*-CH_3), 7.2–7.4 (m, 11, aryl), 7.5–7.7 ppm (m, 2, *o*-aryl).

Anal. Calcd for $C_{23}H_{19}N_3$: C, 81.87; H, 5.68. Found: C, 81.72; H, 5.75.

The benzylidene group was removed by stirring a suspension of 2.05 g of the foregoing compound in a mixture of 40 ml of ether and 60 ml of 3 *M* sulfuric acid for ~12 hr. The precipitated salt was decomposed with sodium carbonate solution and the resulting oil was taken up in methylene chloride; crystallization took place slowly upon evaporation, giving 1.30 g (85.5%) of 4-amino-3,5-diphenyl-1-methylpyrazole, mp 83–85°. An analytical sample was obtained by repeated crystallization from cyclohexane: mp 85–86.5°; ir (CCl_4) 3420, 3350, 1610 cm^{-1}; nmr δ 3.02 (s, 2, NH_2), 3.75 (s, 3, *N*-CH_3), 7.3–7.5 (m, 8, aryl), 7.7–7.9 ppm (m, 2, *o*-aryl).

Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.86. Found C, 77.08; H, 6.14; N, 16.90.

Preparation of Azidopyrazoles.—All of the azidopyrazoles were prepared by the reaction of the aminopyrazole with nitrous acid with only small variations according to solubilities. The procedure for 4-azido-1,3-diphenyl-5-methylpyrazole (II) is representative. A solution of 2.0 g (8.03 mmol) of amine in 6 ml of acetic acid and a solution of 0.55 g of sodium nitrite in 5 ml of water were added simultaneously to 10 ml of concentrated hydrochloric acid at 0° with stirring. The resulting solution was added after a few minutes to an ~20% excess of sodium azide dissolved in ice water. After 10 min the precipitated azide was filtered off, washed with water, and dried *in vacuo*: 1.90 g (86.1%); mp

(10) E. M. Kosower, *Accounts Chem. Res.*, **4**, 193 (1971); diimide is implicated in the reported reduction of phenyl azide by hydrazine in the presence of palladium.

(11) Analyses were done by Spang Microanaiytical Laboratories, Ann Arbor, Mich. Ir spectra were taken on a Perkin-Elmer Model 237B instrument; Nujol mulls were used unless otherwise stated. Nmr spectra were taken on a Varian A-60 instrument, using tetramethylsilane as internal reference and deuteriochloroform for solvent, unless otherwise stated. Analyses for C, H, and N within 0.3% of calculated were obtained for all new compounds not explicitly described.

(12) L. Knorr and H. Laubmann, *Ber.*, **21**, 1205 (1888).

(13) L. Knorr and P. Duden, *Ber.*, **26**, 113 (1893).

(14) M. Ruccia, *Ann. Chim. (Rome)*, **49**, 720 (1959).

TABLE II

AMINO- AND AZIDOPYRAZOLES

		Amino				Azido[a]		
Registry no.	Substituents	Source	Registry no.	Yield, %	Mp, °C	No.	Yield, %	Mp, °C
40697-39-0	1,3,5-Ph_3-4-	4-NO	40697-44-7	59[b]	163.5–165.5	I	High	78–80
40697-40-3	1,3-Ph_2-5-Me-4-	4-CO_2Et	7189-04-0	55[c]	70–71.5	II	86	62.5–65
40697-41-4	1,5-Ph_2-3-Me-4-	4-NO[d]	7171-64-4	69	106–107[e]	III	84	Oil
40697-42-5	3,5-Ph_2-1-Me-4-	4-N=CHPh	40697-47-0	85[f]	85–86.5	IV	85	64–66
21683-30-7	1-Ph-3,5-Me_2-4-	4-NO	715-99-1	53	60–63[g]	V	70	34–35
28466-21-9	1,3,5-Me_3-4-	4-NO	7171-70-2	35	99–101[h]	VI	58	36–38
5272-86-6	3,5-Me_2-4-	4-NO_2	14531-55-6	72	204–205[i]	VII	75	80–82[i]
31924-81-9	3-Me-4-Ph-5-	*j*	4468-48-8	35	138–140	XI	88	115–116

[a] Colorless to beige crystalline solids; elemental analyses not performed, owing to instability. Ir and nmr spectra were consistent with those of the corresponding amines; all showed ir absorption near 2120 cm^{-1} (N_3). [b] Reduction with zinc dust in ~1% solution in glacial acetic acid at 0–10°. This amine was also obtained in 53% yield by hydrogenation over platinum oxide in a 1:5:10 mixture of concentrated hydrochloric acid, chloroform, and ethanol. [c] By Curtius degradation. [d] G. Wittig, *Ber.*, 61, 1142 (1928). [e] Reported[14] mp 104°. [f] 57% overall from 3,5-diphenyl-4-aminopyrazole. [g] Monohydrate. [h] Reported[16] mp 100–101°. [i] Reported mp 206° (amine) [reported[5] mp 65 and 81° (azide)]: G. T. Morgan and R. Reilly, *J. Chem. Soc.*, 105, 441 (1914). [j] From 1-cyano-1-phenylacetone; reported[18] mp 140–142°.

62.5–65° with gas evolution; ir (Nujol) 2110 cm^{-1} (N_3); nmr δ 2.33 (s, 3, 5-CH_3), 7.2–7.5 (m, 8, aryl), 7.7–7.8 ppm (m, 2, *o*-aryl). The results are collected in Table II.

Thermolysis of 4-Azidopyrazoles.—The procedures used for the several azides varied somewhat, but principally in the work-up. The following examples are representative. A solution of 1.82 g (8.55 mmol) of 4-azido-1-phenyl-3,5-dimethylpyrazole (V) in 25 ml of cyclohexane was refluxed for 90 min. Monitoring by nmr showed the gradual disappearance of the two methyl singlets of V and the development of new singlets at positions corresponding to acetonitrile and pyruvonitrile anil. The resulting solution showed an ir band at 2220 cm^{-1} (C≡N) and none at 2120 cm^{-1} (N_3). The mixture was evaporated and then distilled, yielding 0.91 g (74%) of pyruvonitrile anil, a pale yellow oil, bp 78–80° (2 mm) [60–61° (0.25)]. On standing, it solidified: mp 44–46°; ir (neat) 3060, 3025, 2220 (C≡N), 1660, 1635 cm^{-1} (C=N); nmr δ 1.88 and 2.18 (s, total 3, ratio 1:3.4), 6.7–7.4 ppm (m, 5, aryl). The two high-field singlets correspond to the syn and anti configurations of the methyl group.

Anal. Calcd for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.43. Found: C, 75.03; H, 5.69; N, 19.33.

A sample of pyruvonitrile anil (0.85 g) was warmed with phenylhydrazine in aqueous ethanol containing 2 ml of concentrated sulfuric acid. After cooling and dilution, the solution deposited 0.25 g (27%) of pyruvonitrile phenylhydrazone: mp 151–153° (reported[15] mp 150–151°); ir 3270 (NH), 2215 (C≡N), 1610 cm^{-1} (C=N); nmr δ 2.07 (s, 3), 7.0–7.4 ppm (5, aryl).

The tarry residue after distillation was examined by tlc on alumina; nothing with a retention time corresponding to authentic[14] 1,1′-diphenyl-3,3′,5,5′-tetramethyl-4,4′-azopyrazole could be detected.

A solution of 1.70 g (6.18 mmol) of 4-azido-1,3-diphenyl-5-methylpyrazole (II) in 16.4 ml of cyclohexane was refluxed for 1.25 hr; ir showed no azide frequency, but a doublet at 2120–2130 cm^{-1} indicated two cyano groups, and glc revealed two volatile components other than solvent. One component was deduced to be benzonitrile by retention time, peak enhancement and nmr (s, δ 7.5 ppm). The solvent was removed and the residue was distilled, bp 66–78° (0.5–1.0 mm). The distillate was collected in three fractions (0.20, 0.77, and 0.05 g). The first two were shown (glc, nmr) to be mixtures of benzonitrile and pyruvonitrile anil, and the last nearly pure pyruvonitrile anil (ir, nmr). Analysis by nmr showed the total distillate to contain 3.33 mmol (53.8%) of benzonitrile and 4.62 mmol (74.6%) of pyruvonitrile anil (the ratio of the *E* and *Z* isomers was 1:4) (some benzonitrile is believed to have been lost during evaporation). The undistilled residue weighed 70 mg (4.5%); tlc showed it to be a complex mixture, of which no single component appeared to be more than 1% of the starting material, thus establishing a maximum limit of azopyrazole, if, indeed, any was formed.

A solution of 4-azido-1,3,5-trimethylpyrazole (VI) in benzene was allowed to decompose at ambient temperature in an nmr tube. The initial peaks at δ 2.15, 2.23, and 3.65 ppm slowly decreased; after 1.5 hr, three new peaks appeared at δ 1.97 (s, CH_3CN), 2.12 (d), and 3.33 ppm (d). After 12 hr, the azide peaks had reached about half their original intensity, and after 6 days were completely gone. The two new doublets (δ 2.12 and 3.33 ppm), presumed to be due to pyruvonitrile methylimine, had increased after 12 hr, but decreased after 6 days in favor of two complex multiplets centered at δ 2.28 and 3.53 ppm. The resonances of 1,1′,3,3′,5,5′-hexamethyl-4,4′-azopyrazole were never seen. Attempts to isolate pyruvonitrile methylimine or the phenylhydrazone derived from it led only to red gums that tlc showed to be complex mixtures.

A solution of 1.65 g (6.0 mmol) of 4-azido-1-methyl-3,5-diphenylpyrazole (IV) in 15 ml of cyclohexane (0.40 *M*) ceased to evolve gas after 30 min at the bp. The solution was decanted from the red-black gum that had deposited; glc showed the presence of benzonitrile (peak enhancement by added authentic material) and a more strongly retained component, in similar amounts. Chromatography of the gum on alumina with benzene as eluant gave 404 mg of dark, amorphous material and 275 mg of 1,1′-dimethyl-3,3′,5,5′-tetraphenyl-4,4′-azopyrazole, mp 183–185°; another 319 mg was obtained by allowing the decantate to cool and stand. Evaporation of the decantate and chromatography yielded 43 mg more; the total yield was 35.8%. The presence of α-methyliminophenylacetonitrile in solution was inferred from the spectra (see below), but it could not be isolated in identifiable form, owing to decomposition.

The foregoing azopyrazole crystallized as a nonstoichiometric hydrate from ethyl acetate: red needles; mp 183–185°; ir 3550, 3345, 1415, 1250, 1200, 1180, 1050, 1030, 980 cm^{-1}.

Anal. Calcd for $C_{32}H_{26}H_6 \cdot H_2O$: C, 74.98; H, 5.51; N, 16.40. Found: C, 75.76; H, 5.62; N, 15.72.

Several recrystallization from cyclohexane gave canary yellow leaflets: mp 183–185°; ir 1415, 1180, 1030, 980 cm^{-1}; nmr δ 3.70 (s, 3), 7.3–7.5 ppm (m, 10).

Anal. Calcd for $C_{32}H_{26}N_6$: C, 77.71; H, 5.30; N, 16.99. Found: C, 77.63; H, 5.23; N, 17.00.

The anhydrous form reverted to the hydrate on exposure to moisture; a mixture showed no melting point depression. Reduction with zinc dust in acetic acid gave 4-amino-1-methyl-3,5-diphenylpyrazole in 95% yield.

A similar experiment in more dilute solution (0.95 g of IV in 118 ml of cyclohexane, 0.029 *M*) was handled similarly, except that the decantate was evaporatively distilled *in vacuo*. A pale yellow liquid (70 mg) was obtained: nmr δ 3.73 (s), 7.30–7.44 (m), 7.50 (s), 7.80–8.0 ppm (m). The 7.50-ppm resonance, identifiable as benzonitrile, had an intensity of <29% of the total of all signals; the other resonances were in the ratio 3:3:2, corresponding to the CH_3, *m*,*p*-C_6H_5, and *o*-C_6H_5 of α-methyliminophenylacetonitrile. The ir spectrum (CCl_4) showed, in addition to bands identifiable with benzonitrile, absorption at 3070, 2960, 2920, 2890, 2770, 2230 (C≡N), 1615 (C=N), 1580, 1405 cm^{-1}.

Chromatography of the original gum and the residue from distillation gave 196 mg (23%) of the azopyrazole.

Photolysis of a solution of 1.60 g of IV in 200 ml of cyclohexane at 5–10° using a Hanovia L-679A-36 immersion lamp with pyrex filter for 2.5 hr resulted in complete disappearance of the ir absorption at 2120 cm^{-1} (N_3). A beige, amorphous solid had precipitated: 0.31 g, mp 120–124° dec. Rapid recrystallization from benzene gave yellow crystals, mp 131–133° dec, but further

(15) G. Favrel, *C. R. Acad. Sci. (Paris)*, 132, 983 (1901).

recrystallization gave a product with a lower, wider melting point range. Tlc indicated one major component and two minor contaminants: ir 2220 (C≡N), 1645, 1615, 1595, 1560 cm^{-1}, etc.; nmr δ 3.76 (s, 3, N-CH_3), 4.25 (s, 3, N-CH_3), 7.32 ppm (24–25, aryl). The filtrate was shown by glc to contain benzonitrile and α-methyliminophenylacetonitrile in about equal amounts; chromatography on alumina (benzene eluent) gave 0.24 g (17.5%) of 1,1′-dimethyl-3,3′,5,5′-tetraphenyl-4,4′-azopyrazole, mp 182–185°.

1,1′,3,3′,5,5′-Hexamethyl-4,4′-azopyrazole.—A solution of 500 mg (3.6 mmol) of 1,3,5-trimethyl-4-nitrosopyrazole[16] in 4 ml of acetic acid containing 150 mg (3.8 mmol) of hydrazine hydrate was heated for 1 hr on a steam bath and then diluted with 2 ml of water. Upon cooling, 120 mg (28%) of the azopyrazole, mp 175–185°, deposited. Sublimation at 150° (0.05 mm) and chromatography on a short column of silica gel ($CHCl_3$ as eluent) gave yellow leaflets: mp 189–192°, raised to 196–197.5° by recrystallization from benzene; ir (Nujol) 1560, 1500, 1420 cm^{-1}; nmr δ 2.43 (s, 3), 2.46 (s, 3), 3.73 ppm (s, 3, N-CH_3).

Anal. Calcd for $C_{12}H_{18}N_6$: C, 58.51; H, 7.37; N, 34.12. Found: C, 58.53; H, 7.30; N, 34.09.

Deoxygenation of 4-Nitroso-3-methyl-1,5-diphenylpyrazole.—Solutions of the nitrosopyrazole in benzene containing a molar equivalent of triphenylphosphine were heated on a steam bath for 30 to 60 min and then chromatographed on alumina. Elution with petroleum ether (bp 30–60°) produced α-phenyliminophenylacetonitrile (38–57%), and elution with chloroform produced triphenylphosphine oxide (~40%) and small amounts of amorphous solid shown by tlc to be a complex mixture, which could not be purified or separated. Reactions conducted at higher dilutions (~0.05 *M*) gave the higher yields.

Thermolysis of 4-Azido-1-methyl-3,5-diphenylpyrazole (IV) in the Presence of *p*-Anisyl Azide.—A solution of 1.20 g (4.36 mmol) of freshly prepared IV in 30 ml of cyclohexane was added with stirring over a 15-min period to a refluxing solution of 3.64 g (23.7 mmol) of *p*-anisyl azide in 20 ml of cyclohexane. One hour after completion of the addition, the dark solution was filtered from some tar. After standing in the cold for several hours, the filtrate deposited a brown, amorphous solid, mp 100–110°, 90 mg, which tlc showed to be a complex mixture. The presence of a substantial quantity of α-methyliminophenylacetonitrile in the solution was detected by glc. Evaporation of the filtrate and trituration of the residue with petroleum ether (bp 30–60°) left 250 mg of red solid, which was chromatographed (alumina, benzene) to give 210 mg of 1,1′-dimethyl-3,3′,5,5′-tetraphenyl-4,4′-azopyrazole, mp 182–185° (mixture melting point undepressed, ir identical). The filtrate was distilled at 70–72° (0.8 mm) to remove *p*-anisyl azide and the residue was chromatographed, to yield an additional 58 mg of azopyrazole, total yield 24.8%. Elution of the column with chloroform removed more strongly retained material in the form of a brown, amorphous solid, which resisted further attempts at purification. Nothing corresponding to 4-*p*-anisylazo-1-methyl-3,5-diphenylpyrazole, which should have been less strongly retained than the symmetrical azopyrazole, could be detected.

Thermolysis of 4-Azido-3,5-dimethylpyrazole (VII) in the Presence of Phenylhydrazine.—The azide VII obtained from 4.0 g (21.7 mmol) of the corresponding amine dihydrochloride (thus ~16.3 mmol) was taken up in 30 ml of benzene and dried ($MgSO_4$); 5 ml of phenylhydrazine was added; and the solution was heated at 60–70° for 4 hr. On cooling, 1.01 g of a reddish solid, mp 198–203°, precipitated. It was identified as the aminopyrazole (ir, nmr, tlc), yield 42.6% based on 21.7 mmol of starting material. Concentration of the filtrate produced more of the same product, but in a less pure state; no other product could be identified. Experiments using lower proportions of phenylhydrazine gave mostly intractable tars. In otherwise identical experiments in the absence of phenylhydrazine, no aminopyrazole could be detected.

Thermolysis of VII in the Presence of Aniline.—A solution of 1.0 g of azide VII (7.5 mmol) in 25 ml of benzene and 15 ml of aniline was heated overnight on a steam bath. The dark mixture was then diluted with 40 ml of benzene and extracted with five portions of 1 *N* HCl. The resulting yellow benzene solution was washed with water, dried ($MgSO_4$), and evaporated. Crystallization of the residue from petroleum ether (bp 60–75°) gave 85 mg (5.7%) of golden needles: mp 138.5–140°, nmr δ 2.66 (s, 6), 7.5–7.7 ppm (m, 5). A recrystallized sample had mp 140–141°, undepressed by an authentic sample of 3,5-dimethyl-4-phenylazopyrazole (reported[17] mp 143°).

Neutralization of the acidic extracts gave only an intractable reddish block gum, which tlc showed to be a complex mixture.

Thermolysis of VII in the Presence of Maleic Anydride.—The damp azide prepared from 11.07 g of amine dihydrochloride (0.06 mol) was dissolved in 125 ml of benzene and dried ($MgSO_4$). The solution was added dropwise to a stirred, refluxing solution of 11.96 g (0.12 mol) of maleic anhydride in 200 ml of benzene over 75 min. After 1 hr more of refluxing, a beige, amorphous powder had precipitated: 8.61 g; mp >305°; insoluble in common solvents; ir 3200–3300 (br), 1600–1800 cm^{-1} (br), poorly resolved.

Anal. Calcd for $(C_6H_7N_2O_3)_x$: C, 50.60; H, 3.64; N, 16.86. Found: C, 50.01; H, 5.22; N, 17.20.

Thermolysis of 5-Azido-3-methyl-4-phenylpyrazole (XI). A. In Toluene.—Azide XI was freshly prepared from the corresponding amine[18] and showed ir 2120 cm^{-1} (N_3) and nmr δ 2.28 (s, 3) and 7.25 ppm (s, 5). A solution of 5.35 g (26.9 mmol) of XI in 200 ml of toluene was refluxed for 3 hr; tlc showed that all azide was gone, and only two significant spots, corresponding to the aminopyrazole and β-methylcinnamonitrile, were present. Glc also detected only small amounts of bibenzyl and showed only one substance of low volatility, with retention time identical with that of an authentic[19] sample of β-methylcinnamonitrile.

The mixture was extracted with three 50-ml portions of 12% hydrochloric acid, and the combined extracts were basified (NaOH) and extracted with methylene chloride. Evaporation of the dried ($MgSO_4$) extract left 1.44 g of solid, shown by tlc to consist mainly of aminopyrazole. Estimation by nmr indicated it to contain 0.92 g (19.7% yield) of amine; recrystallization from benzene gave 0.47 g of pure amine, mp 140–141°. The toluene phase was evaporated and distilled in a kugelrohr at 150–180° (0.5 mm) to give 1.45 g (37.6%) of pale yellow β-methylcinnamonitrile: ir (neat) 3060, 3030, 2975, 2915, 2220 (C≡N), 1625 cm^{-1}; nmr δ 2.18 (d, 3, J = 7 Hz), 6.8 (q, 1, J = 7 Hz), 7.2–7.5 ppm (m, 5).

No other products could be detected by chromatography, and the yields were reproducible within 2% in different experiments.

B. In Chlorobenzene.—In an otherwise similar experiment, using chlorobenzene in place of toluene, the yield of aminopyrazole fell to 15%, with no other significant change.

4-Azido-1,5-diphenyltriazole and Its Fragmentation.[20]—By the general method used for the other azidopyrazoles, 4-amino-1,5-diphenylpyrazole[21] was converted to the azide in 82% yield, mp 95°, ir 2120 cm^{-1} (N_3). An analytical sample recrystallized from chilled petroleum ether had mp 97°.

Anal. Calcd for $C_{14}H_{10}N_6$: C, 64.11; H, 3.84; N, 32.01. Found: C, 64.16; H, 4.00; N, 31.98.

A 0.6-g sample of the foregoing azide dissolved in 30 ml of toluene was refluxed for 8 hr, whereupon the mixture was evaporated to dryness and the residue was recrystallized from petroleum ether (bp 60–80°). Yellow crystals of α-phenyliminophenylacetonitrile deposited, 0.4 g (85%), mp 72° (undepressed by authentic material). The mother liquors appeared to contain only this same substance.

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Registry No.—I, 40697-50-5; II, 40697-51-6; III, 40697-52-7; IV, 40697-53-8; V, 40697-54-9; VI, 40697-55-0; VII, 40697-56-1; XI, 40697-57-2; 1,3,5-triphenylpyrazole, 2183-27-9; 1,3-diphenyl-5-methylpyrazole-4-carbohydrazide, 40697-58-3; 4-amino-3,5-diphenylpyrazole *N*-benzylidene derivatives, 40697-59-4; 4-amino-3,5-diphenylpyrazole, 5272-85-5; pyruvonitrile anil, syn, 40698-05-3; pyruvonitrile anil, anti, 40698-06-4; pyruvonitrile phenylhydrazone, 40697-35-6; 1,1′-dimethyl-3,3′,5,5′-tetraphenyl-4,4′-azopyrazole, 40697-36-7; 1,1′,3,3′,5,5′-hexamethyl-4,4′-azopyrazole, 40697-37-8; VII–maleic anhydride polymer, 40690-47-9; β-methylcinnamonitrile, 14368-40-2.

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(18) W. Kirmse, *Chem. Ber.*, **93**, 2353 (1960).

(19) K. Hoffmann, J. Kerble, and H. J. Schmid, *Helv. Chim. Acta*, **40**, 387 (1957).

(20) We are indebted to Dr. W. Resemann for carrying out this experiment.

(21) O. Dimroth, E. Trisoni, and J. Marshall, *Ber.*, **39**, 3925 (1906).

Tetrafluorohydrazine as Radical Scavenger in the Photoreduction of Benzophenone

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The irradiation of benzophenone dissolved in a hydrocarbon in the presence of tetrafluorohydrazine was found to yield equimolar amounts of difluoraminodiphenylmethanol and the respective difluoramino-substituted hydrocarbon. The hydrocarbons investigated include cyclohexane, 3-methylpentane, toluene, and cumene. The rates of tetrafluorohydrazine consumption were measured.

The mechanism of the photoreduction of benzophenone in solution has been investigated in many laboratories since the pioneering experiments of Ciamician and Silber.[1] There is much supporting evidence that the first excited triplet state of benzophenone is the dehydrogenating species in these systems. The formation of the products isolated was explained by combination and disproportionation reactions of the monoradicals formed in the dehydrogenation step.[2] More recently this mechanism has been modified by postulation of intermediate adducts[3-5] or charge transfer complexes[6] to accommodate conflicting experimental evidence.

Evidence for the existence of the postulated monoradicals by trapping experiments has not been reported to our knowledge. The commonly used scavengers for radicals, such as diphenyl picrylhydrazyl or galvinoxyl, cannot be used because they absorb strongly in the wavelength region utilized for the photoreduction of aromatic ketones.

Superficially, the formation of benzpinacol itself could be considered as such a trapping experiment. However, the initial formation of 1,2-diphenyl-1,2-bis(*p*-chlorophenyl)-1,2-ethanediol during irradiation of *p*-chlorobenzophenone and benzhydrol[7] and the initial formation of unlabeled benzpinacol during the photolysis of benzophenone and benzhydrol (labeled with ^{14}C)[7] in benzene solution indicated that the isolated products do not arise simply by combination reactions of the postulated initial monoradical. Also, the formation of terebic acid during photolysis of benzophenone in isopropyl alcohol in the presence of maleic anhydride[8] has been considered as proof for a trapping reaction of the postulated dimethyl hydroxymethyl radicals. However, no 2,2-diphenylparaconic acid, which should form from the postulated diphenyl hydroxymethyl radicals in an analogous fashion, could be isolated in these experiments.[9] The latter reaction has been shown to occur when diphenyl hydroxymethyl radicals are thermally generated in the presence of maleic anhydride.[9] More recently, *tert*-nitrosobutane has been employed as a radical scavenger. The reported results, however, are inconclusive. Whereas Leaver and Ramsay[10] reported the trapping of dimethyl hydroxymethyl radicals by *tert*-nitrosobutane during the photoreduction of benzophenone in isopropyl alcohol, Perkins and Ward[11] reported the formation of *tert*-butyl nitroxide in the reaction of *tert*-butyl peroxyoxalate and isopropyl alcohol in the presence of *tert*-nitrosobutane. They attribute the formation of *tert*-butyl nitroxide to a hydrogen transfer reaction from the dimethyl hydroxymethyl radical to *tert*-nitrosobutane. Leaver and Ramsay also observed the *tert*-butyl nitroxide; however, they postulate its formation to arise from a hydrogen transfer from the diphenyl hydroxymethyl radical.

It is concluded that trapping experiments in radical reactions are significant evidence for the proposed mechanism only if all postulated radicals are trapped simultaneously and quantitatively.

Tetrafluorohydrazine was expected to be an effective radical scavenger in photochemical dehydrogenation reactions because of its reported properties and reactions. It has been shown to be in equilibrium with difluoroamino radicals at ambient temperature[12] and to react with monoradicals produced by either

$$F_2NNF_2 \rightleftharpoons 2 \cdot NF_2$$

thermal or photochemical[13] decomposition. Undesirable side reactions were not expected, since no ionic addition reactions of tetrafluorohydrazine have been reported and the difluoroamino radicals have been found to abstract hydrogen only at elevated temperatures.[14]

It has been reported in a previous publication[15] that α-difluoramino ethers were formed by irradiation of an ether solution of benzophenone in the presence of tetrafluorohydrazine. This reaction was extended to solutions of benzophenone in hydrocarbons and a detailed investigation of all reaction products was performed.

Results

Difluoraminoalkanes.—Benzophenone dissolved in hydrocarbons was irradiated with a high-pressure mercury lamp while purging with tetrafluorohydrazine from a reservoir. Figure 1 represents a typical plot of gas consumption *vs.* time. The rate of tetrafluorohydrazine uptake slowed down during irradiation

(1) G. Ciamician and P. Silber, *Chem. Ber.*, **33**, 2911 (1900).
(2) G. Weismann, E. Bergmann, and Y. Hirshberg, *J. Amer. Chem. Soc.*, **60**, 1530 (1938).
(3) G. O. Schenck, W. Meder, and M. Pape, "2nd UN Geneva Conference," Pergamon Press, Elmsford, N. Y., 1959, p 352.
(4) J. N. Pitts, R. L. Letsinger, R. P. Taylor, J. M. Patterson, G. Recktenwald, and R. B. Martin, *J. Amer. Chem. Soc.*, **81**, 1068 (1959).
(5) N. Filipescu and F. L. Minn, *J. Amer. Chem. Soc.*, **90**, 1544 (1968).
(6) V. Franzen, *Justus Liebigs Ann. Chem.*, **633**, 1 (1960).
(7) Unpublished results by one of the authors (M. J. Cziesla) in cooperation with M. Pape (BASF, Ludwigshafen, Germany).
(8) G. O. Schenck, H. Koltzenburg, and H. Grossmann, *Angew. Chem.*, **69**, 177 (1957).
(9) G. O. Schenck, G. Mathias, M. Pape, M. Cziesla, and G. Von Buenau, *Justus Liebigs Ann. Chem.*, **719**, 80 (1968).
(10) I. H. Leaver and A. Caird Ramsay, *Tetrahedron*, **25**, 5669 (1969).
(11) M. J. Perkins and P. Ward, *J. Chem. Soc. B*, 395 (1970).
(12) C. B. Colburn and A. Kennedy, *J. Amer. Chem. Soc.*, **80**, 5004 (1958).
(13) R. C. Petry and J. P. Freeman, *J. Amer. Chem. Soc.*, **83**, 3912 (1961).
(14) J. Grzechowick, J. F. Kerr, and A. F. Trotman-Dickenson, *Chem. Commun.*, 109 (1965).
(15) M. J. Cziesla, K. F. Mueller, and O. Jones, *Tetrahedron Lett.*, 813 (1966).

and stopped after an amount of gas approximately equimolar to the starting benzophenone was consumed. During irradiation the solution turned yellow; however, this color was not connected with the decrease in tetrafluorohydrazine consumption. The addition of more benzophenone to the yellow reaction solution again started the photoreaction with tetrafluorohydrazine at the same rate as at the beginning of the experiment.

In Table I, the tetrafluorohydrazine consumption rates for the hydrocarbons investigated are listed.

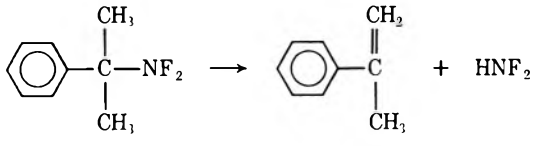
TABLE I
CONSUMPTION OF TETRAFLUOROHYDRAZINE AND RELATIVE QUANTUM YIELDS

Substrate	Consumption, ml/min	Rel ϕ
Cumene	3.58	1.02
Cyclohexane	3.5	1
3-Methylpentane	2.38	0.68
Diethyl ether (15)	3.09	0.88
Dioxane (15)	2.25	0.64
Tetrahydrofuran (15)	1.67	0.48
Diisopropyl ether (15)	0.80	0.23

These values were taken from the initial straight line of plots as in Figure 1.

The hydrocarbon solvents and volatile reaction products were distilled together after irradiation. Vapor phase chromatographic analysis of the distillates indicated one photoproduct in the experiments with toluene and cyclohexane and one major and several minor products in the experiments with 3-methylpentane. The sum of the minor products, however, was less than 5% of the main product. No efforts were undertaken to elucidate the structures of these minor products. The other photoproducts were identified as α-difluoroaminotoluene, difluoroaminocyclohexane, and 3-difluoroamino-3-methylpentane, respectively.

Two products were observed in the distillates of the cumene experiments; infrared analysis indicated the presence of difluoroamino groups (absorption at 885 cm^{-1}). During attempted separation and purification of the two products by distillation, one of them disappeared accompanied by a corresponding increase in the concentration of the other product. The latter showed no absorption at 885 cm^{-1} and was identified as α-methylstyrene, indicating that the product which disappeared was indeed the expected α-difluoraminocumene which lost difluoramine during attempted distillation.



Difluoraminodiphenylmethanol.—Material balance of the reactions indicated that only about one half of the consumed tetrafluorohydrazine could be accounted for in the isolated difluoraminoalkanes. The reaction with cyclohexane was selected for a careful investigation of the distillation residue.

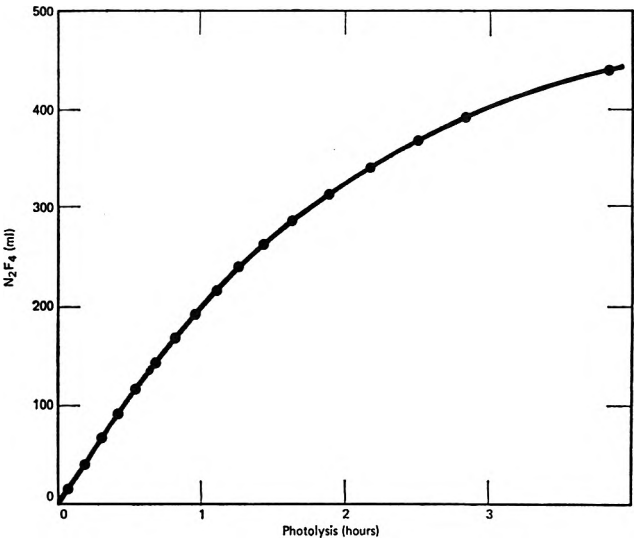
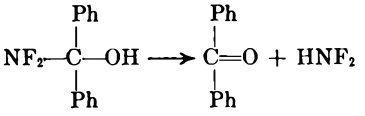


Figure 1.—Photolysis of 4 g of benzophenone in 400 ml of cyclohexane in the presence of tetrafluorohydrazine.

The benzophenone–cyclohexane solution was photolyzed with tetrafluorohydrazine, purging until the gas consumption had ceased; 0.9 mol of tetrafluorohydrazine was consumed for every 1 mol of starting benzophenone. Then the solvent and the volatile reaction product were removed under vacuum at room temperature.

The viscous distillation residue exhibited hydroxyl, difluoramino, and phenyl absorption in the infrared, but only a trace of a carbonyl band could be observed. After hydrolysis of the residue with aqueous acetic acid, over 96% of the original benzophenone could be isolated. Elemental iodine was liberated when the hydrolysis was carried out in the presence of potassium iodide; titration of the iodine gave values of 1.8 molecules of iodine liberated for each molecule of starting benzophenone.

All available data are consistent with the structure of difluoraminodiphenylmethanol for the residue. Compounds containing a difluoramino and a hydroxyl group at the same carbon are known[16] to be easily hydrolyzed to the parent carbonyl compound and difluoramine. Difluoramine itself reacts quantitatively with potassium iodide in acidic solution.[17]



$$HNF_2 + 4HI \longrightarrow 2I_2 + NH_4F + HF$$

Discussion

Mechanism.—The isolation of equimolar amounts of difluoraminocyclohexane and difluoraminodiphenylmethanol constitutes the first example in which both monoradicals, postulated as intermediates in the photo-

(16) (a) J. P. Freeman, W. H. Graham, and C. O. Parker, *J. Amer. Chem. Soc.*, **90**, 121 (1968); (b) S. F. Reed, Jr., *J. Org. Chem.*, **32**, 2894 (1967).
(17) E. A. Lawton and J. Q. Weber, *J. Amer. Chem. Soc.*, **81**, 4755 (1959).

reduction of benzophenone (steps 1 and 2 below), were trapped simultaneously and quantitatively.

$$Ph_2CO \xrightarrow{h\nu} {}^1Ph_2CO \longrightarrow {}^3Ph_2CO \quad (1)$$

$${}^3Ph_2CO + RH \longrightarrow Ph_2\dot{C}OH + R\cdot \quad (2)$$

$$Ph_2\dot{C}OH + \cdot NF_2 \longrightarrow Ph_2C(OH)NF_2 \quad (3)$$

$$R\cdot + \cdot NF_2 \longrightarrow RNF_2 \quad (4)$$

$$Ph_2\dot{C}OH + F_2NNF_2 \longrightarrow Ph_2C(OH)NF_2 + \cdot NF_2 \quad (5)$$

$$R\cdot + F_2NNF_2 \longrightarrow RNF_2 + \cdot NF_2 \quad (6)$$

The reported experiments do not yield conclusive evidence that the monoradicals originating according to reaction 2 form the difluoramino compounds exclusively *via* reactions 3 and 4. Another attractive possibility is their formation through reaction of the monoradicals with undissociated tetrafluorohydrazine according to 5 and 6. The low bond energy of the N–N bond in the tetrafluorohydrazine of 19.9 kcal[18] makes reactions 5 and 6 exothermic by about 50 kcal. Considerations with respect to the concentration of the different radicals in the solution during photolysis further support the possibility of reactions 5 and 6.

High efficiency of the trapping reactions 3–6 was demonstrated by the fact that neither benzpinacol nor mixed radical combination products could be isolated in the experiments carried out in the presence of tetrafluorohydrazine. Benzpinacol would have precipitated during photolysis in the experiments with cyclohexane and 3-methylpentane, since it is practically insoluble in the hydrocarbons.

In the system benzophenone–cyclohexane, 96.3% benzophenone was recovered of the hydrolysis of the distillation residue. Since the theoretical mixed combination product would not yield benzophenone under the reaction conditions, cage combination reactions did occur to less than 4% if at all.

Relative Quantum Yield for Hydrogen Abstraction by Triplet Benzophenone.—The observed rates of tetrafluorohydrazine consumption in the different hydrocarbons should be directly proportional to the quantum yield for hydrogen abstraction by triplet benzophenone providing that the quenching of the excited states of benzophenone by tetrafluorohydrazine is negligible. Whether or not this assumption is correct will be investigated in future experiments. Preliminary data do not indicate a significant quenching. The measured consumption rates of tetrafluorohydrazine are presented in Table I together with values from previous experiments with ethers.[15] The differences in relative quantum yields can be rationalized by a combination of electronic and steric effects.

Selectivity of Triplet Benzophenone.—In the experiments with 3-methylpentane more than 95% of the reaction product resulted from the attack of the triplet benzophenone on the tertiary hydrogen, indicating high selectivity of the excited benzophenone. Similar results were reported in experiments with ethers, where only products could be isolated which resulted from hydrogen abstraction adjacent to the ether oxygen. In Table II relative reactivities per hydrogen are tabulated together with results reported by Walling and Gibian.[19] The values from the experiments with triplet benzophenone are in fair agreement. They show the same high selectivity for the hydrocarbons.

TABLE II
RELATIVE REACTIVITIES PER H ATOM

Substrate	This paper	Ref 19
Cyclohexane	1	1
Cumene	12.2	19.8
3-Methylpentane	8.2	
2,3-Dimethylbutane		6.0
Diethyl ether	2.6	
Dioxane	1.0	
Tetrahydrofuran	1.4	
Diisopropyl ether	1.4	

Conclusion

The results reported in this paper have supported our original postulation[15] that tetrafluorohydrazine can be used as a valuable "reagent" in the investigation of the mechanisms of photochemical reactions and pinpoint the site of attack of excited states.

Experimental Section

General.—Infrared and ultraviolet spectra were obtained with Beckman IR-8 and Bausch & Lomb 505 spectrometers, respectively. The nmr spectra were obtained with a Varian DP 60 spectrometer using deuteriochloroform as the solvent and tetramethylsilane as an internal standard. Reaction mixtures and distillation fractions were monitored on a Perkin-Elmer 154 gas chromatograph and the preparative gas chromatograph work was performed on a Beckman Megachrom equipped with standard Beckman 6 ft × 0.75 in., 20% Paraplex G-25 on 42–60 Chromosorb W columns. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Materials.—Tetrafluorohydrazine (Air Products, 99% pure) was used as received. Toluene (Matheson Coleman and Bell, spectroquality), benzophenone (Fisher, reagent grade), isopropyl alcohol (Fisher, spectrograde), cumene (Baker, Baker grade), and 3-methylpentane (Aldrich, research grade) were used without further purification.

Apparatus and Procedure.—All irradiations were performed in the following manner. Solutions consisting of 4.0 g of benzophenone in 400 ml of the appropriate hydrocarbon solvent were placed in a photoreactor which was equipped with a fritted gas inlet tube at the bottom and gas outlet tube at the top. A jacketed, water-cooled, 100-W Hanovia high-pressure mercury lamp (Type SOL, 608-36A) was immersed in the reactor utilizing a Pyrex 7740 filter to protect the difluoramino radicals and the expected products from the light. Tetrafluorohydrazine was pumped through the solution with a Cole-Parmer Masterflex tubing pump during irradiation and recycled to a reservoir to measure gas consumption. The solutions were thoroughly purged with purified nitrogen both prior to introduction of tetrafluorohydrazine and after completion of irradiation *to avoid potentially hazardous mixtures of organic compounds, tetrafluorohydrazine, and oxygen.* None of the reported photochemical reactions occurred in the absence of ultraviolet light.

The difluoramino compounds and unreacted solvents were separated from the reaction mixture by distillation under vacuum followed by preparative glpc to give the pure difluoramino compounds.

Photolysis of Toluene Solution.—Tetrafluorohydrazine was bubbled through a solution of benzophenone in toluene and irradiated at ambient temperature for 3 hr, yielding only one photoproduct that could be detected by glpc analysis. The unreacted toluene was removed by vacuum distillation (80 mm, 50°). The remaining residue was vacuum distilled at 1 mm and 50° to collect the photoproduct and some toluene. The distillate, containing photoproduct and toluene, was separated by preparative glpc to give the analytically pure sample of α-difluoramino-

(18) J. A. Kerr, *Chem. Rev.*, **66**, 496 (1966).

(19) C. Walling and M. J. Gibian, *J. Amer. Chem. Soc.*, **87**, 3361 (1965).

toluene: ir (neat) 805, 890, and 925 cm^{-1} ($-NF_2$); nmr ($CDCl_3$) δ 4.58 (t, 2, J = 29 Hz, $-CH_2NF_2$) and 7.37 ppm (s, 5, C_6H_5-).

Anal. Calcd for $C_7H_7F_2N$: C, 58.74; H, 4.93; F, 26.54; N, 9.78. Found: C, 58.92; H, 5.19; F, 26.58; N, 9.59.

Photolysis of Cumene Solution.—The above photolysis procedure was repeated substituting cumene for toluene. Two photoproducts were detected by glpc analysis. The unreacted cumene was removed by vacuum distillation (15 mm, 50°) and the remaining residue was distilled at 1 mm and 50°. After the distillate was purified by preparative glpc only one of the original photoproducts could be detected. The photoproduct that decomposed showed difluoramino absorption at 885 cm^{-1} and the remaining photoproduct was passed through the preparative glpc to give an analytical sample of α-methylstyrene.

Anal. Calcd for C_9H_{10}: C, 91.46; H, 8.54. Found: C, 91.38; H, 8.51.

Photolysis of 3-Methylpentane Solution.—The photolysis procedure was repeated using 3-methylpentane as the solvent with an irradiation time of 4 hr. One major and several minor (total <5%) photoproducts were detected by glpc analysis. The major photoproduct was isolated by a similar distillation procedure (450 mm, 50°, then 1 mm, 50°) and purified by preparative glpc to give an analytical sample of 3-methyl-3-difluoraminopentane: ir (neat) 850 and 945 cm^{-1} ($-NF_2$); nmr ($CDCl_3$) δ 0.92 [t, 6, J = 7 Hz, $(CH_3CH_2)_2CCH_3-$], 1.17 [t, 3, J = 2 Hz, $(CH_3CH_2)_2CCH_3-$], and 1.67 ppm [m, 4, $(CH_3CH_2)_2CCH_3-$].

Anal. Calcd for $C_6H_{13}F_2N$: C, 52.54; H, 9.55; F, 27.70; N, 10.21. Found: C, 52.71; H, 9.61; F, 27.64; N, 10.04.

Photolysis of Cyclohexane Solution.—The photolysis procedure was repeated using cyclohexane as the solvent with an irradiation time of 325 min. Only one major and one minor volatile photoproduct were detected by glpc analysis. The photoproducts were concentrated by distillation. Because of the potentially hazardous nature of the products, only a small fraction of the concentrate was passed through the preparation glpc to give an analytical sample of difluoraminocyclohexane for the major product: ir (neat) 840, 910, and 960 cm^{-1} (NF_2); nmr ($CDCl_3$) δ 1.63 (m, 10, $C_6H_{10}NF_2-$) and 3.32 ppm (t, 1, J = 26 Hz).

Anal. Calcd for $C_6H_{11}F_2N$: C, 53.32; H, 8.20; F, 28.19; N, 10.27. Found: C, 53.50; H, 8.20; F, 28.19; N, 10.27.

A sample of the minor product was also isolated; however, the amount was too small for full characterization. This compound did not contain difluoramino groups, since no nitrogen was found by microchemical methods.

In a second experiment (uptake of tetrafluorohydrazine 440 ml, 0.0196 mol) the sequence of distillation was changed to elucidate the composition of the reaction residue. Both photoproduct and unreacted cyclohexane were vacuum distilled (1 mm, 25°) leaving undecomposed residue and trace amounts of cyclohexane and cyclohexane photoproduct. Infrared analysis of the pot residue showed peaks at 3500 (OH) and 885, 855 cm^{-1} (NF_2).

Hydrolysis of the residue was accomplished by adding aqueous acetic acid and excess potassium iodide, liberating iodine. The aqueous solution was extracted with methylene chloride and the resulting aqueous solution was diluted to 2 l. Twenty milliliters of standard arsenous acid (0.099 mol) was needed to titrate a 100-ml aliquot of the stock iodine solution using starch indicator. The total liberated iodine was calculated as 0.0398 mol which corresponds to 0.0199 mol of difluoraminodiphenylmethanol. The methylene chloride extract was evaporated under vacuum (1 mm) leaving 3.85 g (96% recovery) of benzophenone, which was identified by matching the infrared spectrum and melting point with those of an authentic sample.

Proper caution should be taken during distillation of potentially hazardous difluoramino compounds.

Acknowledgment.—This work was supported by the Naval Ordnance Systems Command under Task Assignment ORD-033-101/067-1/F009-06-01.

Registry No.—Tetrafluorohydrazine, 10036-47-2; benzophenone, 119-61-9; toluene, 108-88-3; α-difluoroaminotoluene, 23162-99-4; cumene, 98-82-8; α-methylstyrene, 98-83-9; 3-methylpentane, 96-14-0; 3-methyl-3-difluoraminopentane, 40715-62-6; cyclohexane, 110-82-7; difluoroaminocyclohexane, 14182-78-6.

The Pyrolysis of Alkyl Sulfide Tosylhydrazone Salts. A Search for R_2S-4 Participation in Carbene Reactions. The Pyrolysis of Sodium Toluenesulfinate

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Sodium salts of alkyl sulfide tosylhydrazones **6**, **7**, and **8** have been pyrolyzed at several temperatures to see if sulfur-carbene interaction would lead to intramolecular sulfur ylide formation of the R_2S-4 type. Analysis of the results shows no evidence for sulfur ylide formation but rather α-insertion products typical of singlet carbene reactions producing olefins **9** and **10** and **13** and **15**, respectively. Sodium toluenesulfinate was pyrolyzed at 250 and 320° to establish products resulting from its thermal decomposition at these temperatures.

Recently, evidence for R_2S-4[1] participation in the photolytic reactions of keto sulfides **1**[2] and α-dione sulfides **2**[3] has been reported. Evidence for similar interaction in solvolytic **3**,[4,5] carbonium ion **4**,[6] and radical **5**[7] reactions has also been proposed. We wish to report here our initial search for R_2S-4 participation in sulfur-carbenoid species.[8]

While no exact proximity requirements for sulfur neighboring-group participation have emerged for the different R_2S-4 type transition states, careful solvolysis studies by Ireland[4] and later by Paquette[5] using caged alkyl thiatosylates have shown that sulfur can interact in ground-state reactions by stabilizing a developed reactive species, in these cases carbonium ions. Further, in those systems where conformational mobility is limited and stereochemical requirements are ideal, R_2S-4 effects can accelerate[5,7] the rate of formation of reactive species.

(1) The symbolism R_2S-n is used here to denote the size of a bicyclic ring (n members) ultimately realizable if cyclization were to occur as a result of neighboring group participation. (See ref 5 for other examples of this useful nomenclature.)

(2) P. Y. Johnson and G. A. Berchtold, *J. Org. Chem.*, **35**, 584 (1970).

(3) P. Y. Johnson, *Tetrahedron Lett.*, 1991 (1972).

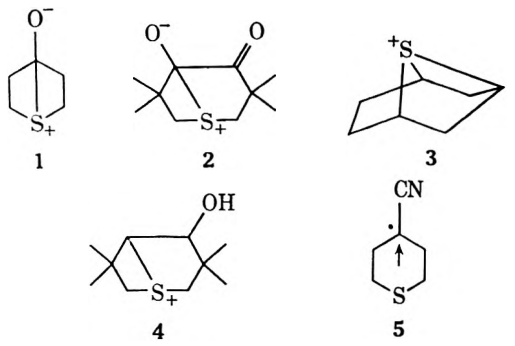
(4) R. E. Ireland and H. A. Smith, *Chem. Ind. (London)*, 1252 (1959).

(5) L. A. Paquette, G. V. Meehan, and L. D. Wise, *J. Amer. Chem. Soc.*, **91**, 3231 (1969).

(6) A. DeGroot, J. A. Boerma, and H. Wynberg, *Tetrahedron Lett.*, 2365 (1968).

(7) A. Ohno and Y. Ohnishi, *Tetrahedron Lett.*, 339 (1972).

(8) For a review on carbene chemistry, see W. Kirmse, "Carbene Chemistry," 2nd ed, Academic Press, New York, N. Y., 1971, and references cited therein.



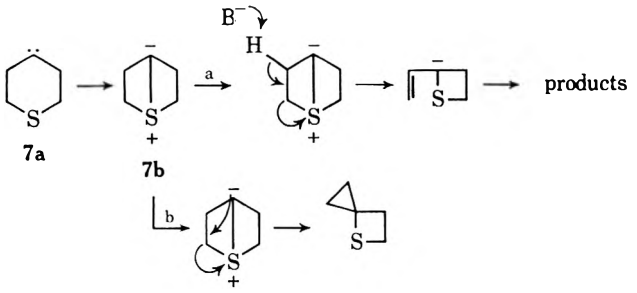
1 2 3 4 5

In photochemical studies[2,3] on a variety of keto sulfides, R_2S-4 transition states appear to be formed *via* charge-transfer mechanisms. In these high-energy excited species the added increment of energy required for formation of the unfavorable "boat" conformation which helps ensure close proximity between sulfur and the carbonyl in the uncaged systems does not seem to be as important a factor as it appears to be in the ground-state reactions. This could be due to the large size of the n,π^* orbitals of the excited carbonyl in the examples cited.

The stereochemical requirements for R_2S-4 sulfur carbene interaction seemed to lie between the fairly rigid solvolyses and less rigid excited-state requirements.

Monomeric products which might result from the decomposition of sulfur ylides[9] formed as a result of R_2S-4 sulfur carbene participation[10] (*e.g.*, ylide **7b** resulting from carbene **7a**) followed by either inter- or intramolecular β elimination (Scheme I, path a) or by a

SCHEME I



concerted or nonconcerted Stevens rearrangement[11] (Scheme I, path b) are shown in Scheme I.

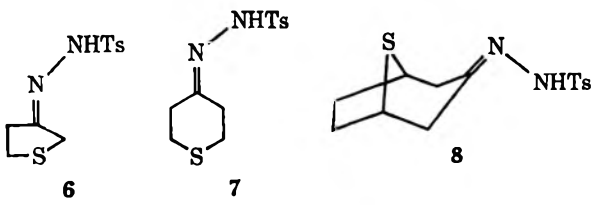
To test this postulate and to examine the potential sulfur carbene interaction as a method of generating a synthesis for thietanes, we have pyrolyzed several alkylthiatosylhydrazone–sodium salts. In this study we have examined the thermal decomposition of dry sodium salts of the tosylhydrazones in order to avoid protic conditions which often lead to carbonium reactions instead of the desired carbene intermediates.[12] The molecules studied were sodium salts of **6**, **7**, and **8**.

(9) Intramolecular sulfur ylides (not of the R_2S-4 type) have been reported. See (a) K. Kondo and I. Ojimo, *Chem. Commun.*, 63 (1972); (b) S. S. Hixson and S. H. Hixson, *J. Org. Chem.*, **37**, 1279 (1972); (c) J. H. Robson and H. Schechter, *J. Amer. Chem. Soc.*, **89**, 7112 (1967).

(10) R_2S-4 carbene interaction in a noncyclic system has been postulated. See K. Kondo and I. Ojimo, *Chem. Commun.*, 62 (1972).

(11) A concerted Stevens rearrangement is symmetry forbidden if it occurs with retention, as would be the case with **7b**. See ref 21a, p 3871.

(12) (a) R. D. Allan and R. J. Wells, *Aust. J. Chem.*, **23**, 1625 (1970); (b) W. Kirmse and B. U. Bulow, *Chem. Ber.*, **96**, 3316 (1963); (c) C. H. DePuy and D. H. Froemsdorf, *J. Amer. Chem. Soc.*, **82**, 634 (1960); (d) J. W. Powell and M. C. Whiting, *Tetrahedron*, **7**, 305 (1959).



6 7 8

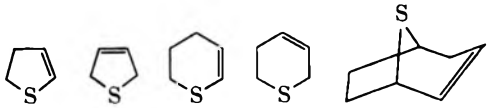
Table I gives the results of these pyrolyses. Analysis of Table I shows that the major products from these

TABLE I

CONDITIONS, PRODUCTS, AND YIELDS FOR PYROLYSIS OF 6, 7, AND 8

Run[a]	Salt (g)	Temp, °C	Recovered, g	Products (ratio of material recovered)
A	6 (1.57)	170-220	0.18	Glyme (39), 9 (39), 10 (11), 11 (trace)
B	7 (1.5)	200	0.39	Glyme (30), 12 (0), 13 (70), 14 (trace)
C	7	270[b]		
D	7 (1.0)	320	0.31	Glyme (19), 13 (63), 12 (0)
				Sodium sulfinate pyrolysis products
E	8 (0.99)	160-200	0.09	15 (75), 16 (25)
F	8	>320		15 + others

[a] In most cases these reactions were run several times with fair repeatibility. [b] Results same as run B.



9 10 12 13 15

pyrolyses are olefins which can best be accounted for by simple insertion of the generated carbene into the adjacent C–H bonds. The glyme found in runs A–D is the result of a 1:1 adduct (nmr) of the salt and glyme, the solvent used in the synthesis of these salts. Attempts to free the salts from the glyme using a high vacuum at 25° failed and heating the adduct at 70° under vacuum led to slow decomposition of the material, yielding a brown substance. The salt–glyme adduct was not observed in the case of **8**, perhaps because of increased steric factors in the bicyclo system.

The lack of observed isomerization of **13** to the conjugated isomer **12** under the reaction conditions (runs B, C, and D) leads us to believe that the 4:1 ratio of **9** to **10** in the pyrolysis of the salt of **6** (run A) is the result of preferential attack of the C–H bond adjacent to sulfur and not due to thermal isomerization of **10** to the conjugated isomer **9**.

While olefinic sulfides **9**,[13] **10**,[13] **12**,[14] and **13**[15] have been reported in the literature, the physical properties given did not enable us to unambiguously assign structures to these isomeric pairs. Hence, these molecules were synthesized, several by unreported routes owing to the availability of appropriate starting materials. Examination of the spectra of these olefins indicated that the best method for distinguishing isomers[16] and establishing purity was by analysis of the vinyl proton absorptions in the nmr spectra (Figure 1). Hence,

(13) S. F. Brich and D. T. McAllan, *J. Chem. Soc.*, 2556 (1951).

(14) R. F. Naylor, *J. Chem. Soc.*, 2749 (1949).

(15) W. E. Parham, L. H. Christensen, S. H. Groen, and R. M. Dodson, *J. Org. Chem.*, **29**, 2211 (1964).

(16) While analysis of the M^+ and $M - 1$ peaks in the mass spectra can be used to establish isomers (see Experimental Section), we found it difficult to establish purity by this method.

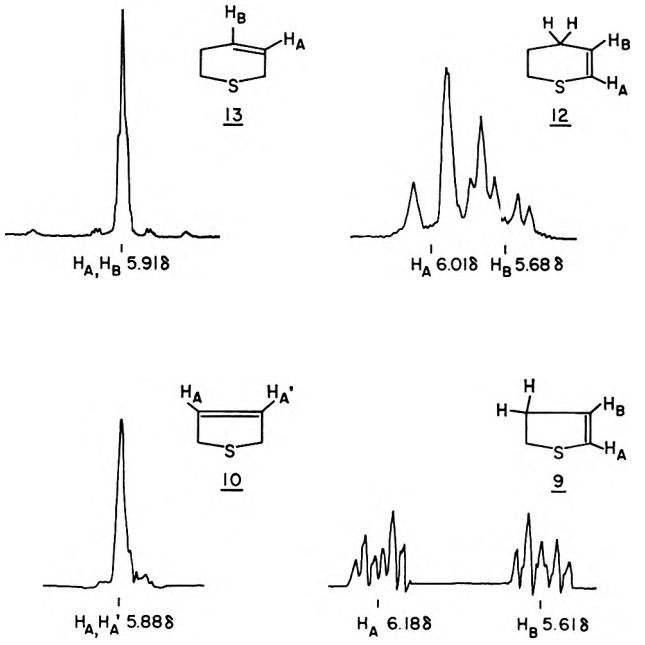
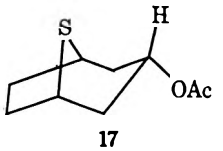


Figure 1.—60-MHz proton nmr absorption in the vinyl region of sulfides 9, 10, 12, and 13, taken in CCl_4 with TMS as internal reference.

integration of the distinctive, nonoverlapping peaks attributable to the vinyl protons of **9** and **10** provided the best method for isomer ratio analysis in the pyrolysis of the salt of **6**. The lack of **12** (runs B, C, and D) was ascertained by the lack of absorption attributable to it in the nmr of the recovered pyrolysis mixture of **7**.

The bicyclo olefinic sulfide **15** was the major product in the pyrolysis of the salt of **8**; however, the yield of recovered material was never high in this reaction. High-temperature pyrolysis (run F) provided shorter contact times and appeared to increase the yield of **15**; however, this procedure also dramatically increased the number of side products, making isolation of **15** impossible and product ratio analysis extremely difficult (see below).

8-Thiabicyclo[3.2.1]oct-2-ene (**15**) is a low-melting solid which decomposed in the presence of air or light but which was stable when stored at 0° in the dark. It was identified by its spectral properties and by comparison to an authentic sample prepared by pyrolysis of acetate **17**.



17

Interestingly, **17**, a single peak by vpc, tlc, and nmr (single $CH_3C{=}O$, δ 1.94), was obtained from a 80:20 mixture (vpc) of epimeric alcohols,[4] by treating them at reflux in acetic acid–acetic anhydride. It seems clear that an R_2S-4 intermediate such as **3** was involved at some stage of this reaction, accounting for its stereoselectivity.[4]

The mass spectrum of **15** shows major ions at *m/e* 126 (M^+, one sulfur indicated by the M + 2 peak) and supporting ions at *m/e* 91 (tropilium ion) and 84 (thiophene ion).

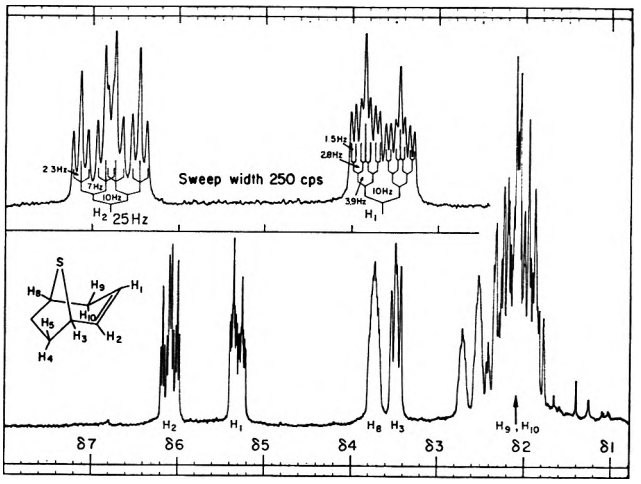


Figure 2.—100-MHz proton nmr spectra of sulfide **15**, taken in CCl_4 with TMS as internal reference.

Since **15** was generated both times by pyrolysis reactions,[17] a 100-megacycle nmr spectrum with 250-cps sweep width expansion of the vinyl absorptions was obtained for this olefin in order to ensure that no thermal rearrangements common to both reactions had occurred. Extensive decoupling experiments allowed complete assignment and interpretation of the downfield absorptions (Figure 2). Important coupling constants obtained from the decoupling experiments are given in Table II and were found to be in excellent agreement

TABLE II

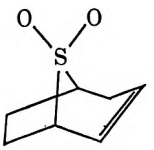
COUPLING CONSTANTS DETERMINED FOR OLEFIN 15[a]

$J_{H_1H_2}$ = 10 Hz[b]	$J_{H_2H_3}$ = 7 Hz
$J_{H_1H_7}$ = 1.5 Hz	$J_{H_2H_9}$ = 2.3 Hz
$J_{H_1H_9}$ = 2.8 Hz	$J_{H_2H_{10}}$ = 2.3 Hz
$J_{H_1H_{10}}$ = 3.9 Hz	$J_{H_3H_4}$ = ~0.0 Hz
	$J_{H_3H_8}$ = 4 Hz

[a] Proton numbers can be found on Figure 2. [b] All values ±0.2 Hz.

with those predicted from studies of models of **15** using the Karplus relationship.[18] Decoupling experiments also showed that allylic protons H_9 and H_{10} were centered at δ 2.1.

Olefin **15** was converted into its sulfone, **15b**, in high yield by treating **15** with hydrogen peroxide in acetic acid, further substantiating its structure.

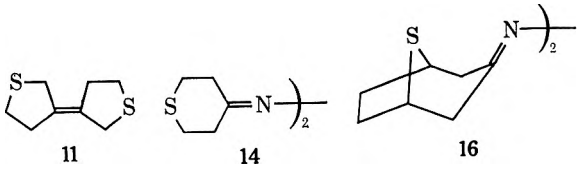


15b

The other products observed in this study were all dimeric in nature. In the pyrolysis of the salt of **6**, the carbene dimer **11** of unknown stereochemistry about the double bond was isolated by vpc and identified by its mass spectrum. In the pyrolysis of salts of **7** and **8** the dimeric products were isolated by vpc and were identi-

(17) Other standard approaches such as reaction of the alcohols with $SOCl_2$ in pyridine failed to give **15** in our hands.

(18) M. K. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

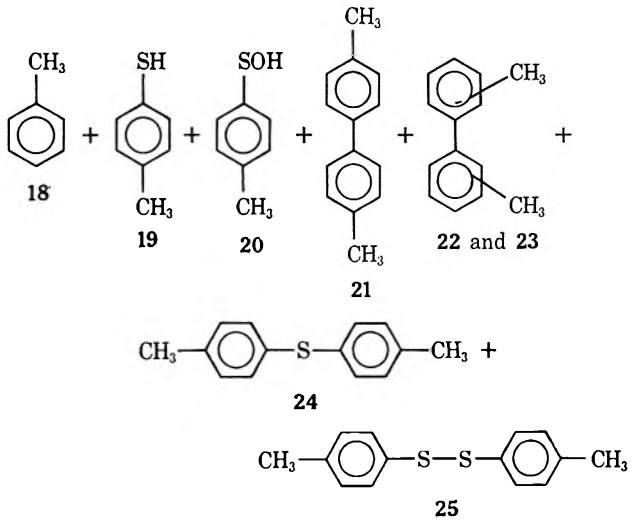


11 14 16

fied as the corresponding azines **14** and **16** by comparison with authentic samples synthesized by reaction of 2 mol of the appropriate ketone with hydrazine. Mechanisms for dimer and azine formation have been discussed.[19] While there is ample precedent for carbene addition to either the sulfur[20] or the olefin[21] part of olefinic sulfides, we found no evidence for dimeric products resulting from ylide–dimer or cyclopropyl–dimer rearrangements.

As noted above (Table I, runs D and F), we found that the bicyclotosylhydrazone salt **8** gave low recovery of material at minimum pyrolysis temperatures, 150–250°. It was decided to use higher temperatures, which would allow shorter contact times, in hopes of increasing the yield of **15**. This goal was partially realized; however, the number of side products increased dramatically as pyrolysis temperatures of 300° were approached. Analysis of some of the products led us to believe that they must have resulted from pyrolysis of the sodium toluenesulfinate at these temperatures.

A search of the literature revealed that, while many authors had noted "extra" products when pyrolyzing tosylhydrazone salts at various temperatures, only toluene was consistently identified. In order to facilitate the interpretation of tosylhydrazone pyrolyses, at higher temperatures in particular, we have identified the products resulting from the pyrolysis of sodium toluenesulfinate[22] below.



18 19 20 21 22 and 23 24 25

We found the products and their yields to be dependent on the temperature, experimental conditions, and time lapse between reaction and analysis.

Toluene (**18**) and toluenethiol (**19**)[23] were the only products observed at pyrolysis temperatures under 300°. If the pyrolysis mixtures was allowed to stand in the presence of air, **19** would dimerize to **25**.

At pyrolysis temperatures of 320–340°, **18**, **19**, **21**, **24**, and **25** became major products.

Sulfenic acid (**20**) was not isolated but was identified from mass spectral data after separation from the reaction mixture by vpc (SE-30 column). This acid disappeared within 30 min after warming the reaction mixture to room temperature.

4,4′-Dimethylbiphenyl (**21**)[24] was identified by comparison to an authentic sample. Biphenyls **22** and **23** were not conclusively identified but are believed to be the 4,3′- and 4,2′-dimethylbiphenyl isomers on the basis of mass spectral similarities to the 4,4′-biphenyl isomer. Several other possibilities, such as 1,2-diphenylethane and benzyl methyl benzenes, were ruled out after comparison of their mass spectra[25] to those of **22** and **23**.

Toluenesulfide **24**[26] and disulfide **25**[27] are white solids easily identifiable by their spectra. The amount of these higher boiling products, which coated the pyrolysis vessel, depended on whether they were "chased" into the collection flask with a low flame or not. We were not able to observe **25** when vpc analysis was performed on a Carbowax column; however, this column gave better separation of the other products.

The identified products can generally be accounted for by intermolecular oxidation–reduction and free-radical processes. The formation of **21**, **22**, and **23** is less clear.

In conclusion, in these pyrolysis studies the main products isolated seem to have resulted from singlet carbene insertion reactions. By contrast, generation of carbene **7a** in ether at 25° using alkyllithiums or by photolysis of the salt **7** appears to give different products, possibly by the desired R_2S-4 pathway. A report on this latter work will be forthcoming.

Experimental Section

Melting points were taken on a calibrated Mel-Temp apparatus. Infrared spectra were taken on a Perkin-Elmer 337 spectrometer; nmr spectra were recorded on Varian A-60 and HA-100 spectrometers using TMS as an internal standard. Mass spectra were obtained on a Hitachi RMU6D mass spectrometer. Vpc analyses were performed using program temperature control on a Hewlett-Packard 5750 gas chromatograph equipped with 8 ft × 0.25 in. 10% Carbowax on Chromosorb P and 8 ft × 0.25 in. 10% SE-30 on Chromosorb P stainless steel columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

General Procedure for Pyrolyses.—The distilling flask of an evacuated (0.05 mm) short-path distillation apparatus containing the tosylhydrazone salt with a plug of glass wool over it was immersed into a preheated oil or sand bath, depending on the temperature required, for 15–30 min. The collection flask was cooled with liquid nitrogen.

Synthesis of Thiacyclohexan-4-one Tosylhydrazone (7).—Thiacyclohexan-4-one[2] (2.3 g) was refluxed with 1 equiv (3.7 g) of toluenesulfonyl hydrazide for 1 hr in 50 ml of ethanol. Benzene, 50 ml, was added and over one half of the total solvent was removed by azeotrope from the reaction flask. The resulting mixture was cooled overnight and the tosylhydrazone crystals that had formed were collected by filtration. Recrystallization from ethanol gave 3.8 g (76%) of **7** as a white solid: mp 151–153°; ir ($CHCl_3$) 3005, 1510, 1430, 1390, 1280, and 1175 cm^{-1};

(19) See ref 8, pp 26–28.

(20) (a) See ref 8, pp 437–442; (b) W. Ando, *et al.*, *J. Org. Chem.*, **37**, 1721 (1972), and references cited therein.

(21) (a) W. Ando, *et al.*, *J. Amer. Chem. Soc.*, **94**, 3870 (1972); (b) W. E. Parham and E. Koncos, *J. Amer. Chem. Soc.*, **83**, 4034 (1961).

(22) "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1944, p 492.

(23) Aldrich Chemical Co.

(24) We wish to thank George Gurria of The Johns Hopkins University for providing us with spectra of this biphenyl.

(25) American Petroleum Institute, Research Project 44, Catalogue of Mass Spectral Data.

(26) Beilstein, "Handbuch der Organische Chemie," **6**,[2] 395.

(27) Reference 26, **6**,[2] 400.

nmr ($CDCl_3$) δ 2.43 (s, 3), 2.66 (m, 8), 7.56 (d, 2), 7.91 (d, 2); mass spectrum (70 eV) *m/e* (rel intensity) 284 (18, M^+), 171 (5), 157 (32), 140 (30), 139 (37), 129 (84, $C_5H_8S{=}NNH^+$), 128 (16), 124 (22), 100 (75), 99 (45), 92 (26), 91 (100), 85 (80).

Anal. Calcd for $C_{12}H_{16}N_2O_2S_2$: C, 50.70; H, 5.63; N, 9.86. Found: C, 50.85; H, 5.49; N, 10.03.

Synthesis of Thiacyclopentan-3-one Tosylhydrazone (6).—Tosylhydrazone 6 was synthesized according to the above procedure from thiacyclopentan-3-one:[28] mp 165° dec;[29] mass spectrum (70 eV) important or major peaks at *m/e* 270 (M^+), 157, 155, 139, 115 ($C_4H_6S{=}NNH^+$), 91

Anal. Calcd for $C_{11}H_{14}N_2O_2S_2$: C, 48.87; H, 5.22; N, 10.36. Found: C, 48.81; H, 5.17; N, 10.33.

Synthesis of 8-Thiabicyclo[3.2.1]octan-3 one Tosylhydrazone (8).—Tosylhydrazone 8 was synthesized according to the above procedure from 8-thiabicyclo[3.2.1]octan-3-one:[2,4] mp 185–186°; mass spectrum (70 eV) important or major peaks at *m/e* 310 (M^+), 155 ($C_7H_8S{=}NNH^+$), 139, 126, 97, 91.

Anal. Calcd for $C_{14}H_{18}N_2O_2S_2$: C, 54.19; H, 5.81; N, 9.03. Found: C, 54.16; H, 5.90; N, 9.03.

General Procedure for the Synthesis of Sodium Salts of 6, 7, and 8.—Salts of 6, 7, and 8 were obtained by adding 1 equiv of NaH to 1 equiv of tosylhydrazone in freshly distilled glyme. After stirring for 24 hr under N_2 the resulting suspensions were filtered, washed with glyme, and dried for 24 hr under high vacuum. The salts, nonhydroscopic white solids, were used without further purification.

Synthesis of Δ^2-Dihydrothiophene (9) and Δ^2-Dihydrothiapyran (12).—These olefins were synthesized in good yields from tetramethylene sulfoxide[30] and pentamethylene sulfoxide[31] using the standard Pummerer[32] reaction (1 hr reflux in acetic anhydride): 9—nmr, see ref 33; mass spectrum (70 eV) *m/e* (rel intensity) *86 (50, M⁺), 85 (100),* 71 (7), 60 (4), 59 (6), 58 (12), 57 (6), 53 (9), 51 (5), 47 (3), 46 (5), 45 (35), 44 (8); 12—nmr, see ref 33; mass spectrum (70 eV) *m/e* (rel intensity) *100 (96, M⁺), 99 (49),* 87 (5), 86 (5), *85 (100),* 74 (4), 73 (6), 72 (76), 71 (37), 53 (7), 47 (6), 46 (8), 45 (37).

Synthesis of Δ^3-Dihydrothiophene (10).—Olefin 10 was obtained in moderate yield by reduction of Δ^3-sulfolene with excess $LiAlH_4$ in ether: nmr, see ref 33; mass spectrum (70 eV) *m/e* (rel intensity) *86 (92, M⁺), 85 (100),* 71 (7), 60 (3), 59 (7), 58 (11), 57 (5), 53 (12), 51 (9), 50 (7), 47 (4), 46 (5), 45 (40), 44 (11).

Synthesis of Δ^3-Dihydrothiapyran (13).—4-Acetoxytetrahydrothiapyran,[34] 1.5 g in 25 ml of hexane, was dripped through an 8-in. glass helix packed column preheated to 500° under N_2. Olefin 13 was isolated in moderate, but varying yields after short-path distillation of the pyrolysis residue: nmr, see ref 33; mass spectrum (70 eV) *m/e* (rel intensity) *100 (100, M⁺). 99 (95),* 97 (5), 87 (3), 86 (4), *85 (47),* 72 (19), 71 (9), 69 (4), 67 (23), 66 (6), 65 (16), 59 (6), 58 (5), 55 (5), 54 (35), 53 (9), 51 (4), 50 (4), 47 (3), 46 (10), 45 (19).

Synthesis of 8-Thiabicyclo[3.2.1]-3-acetoxyoctane (17).—Acetate 17 was obtained from a 80:20 mixture of epimeric alcohols which were obtained from the $NaBH_4$ reduction of 8-thiabicyclo[3.2.1]octan-3-one.[4] The alcohols, 0.76 g, were refluxed in a mixture of 0.5 g of acetic anhydride and 10 ml of acetic acid for 2 hr. The cooled mixture was extracted with ether–water and the ether was washed with aqueous K_2CO_3 until no reaction occurred. Short-path distillation of the residue after evaporation of the ether gave 0.65 g of an oil which appeared to be a single epimer (vpc, tlc, nmr), probably the endo[4,5] acetate: ir (CCl_4) 2950, 2900, 2855, 1758, 1451, 1370, 1262, 1245, 1188, and 1085 cm^{-1}; nmr (CCl_4) δ 1.5–2.5 (m, 8), 1.94 (s, 3), 3.58 (m, 2), 4.97 (m, 1); mass spectrum (70 eV) *m/e* (rel intensity) 186 (22, M^+), 126 (84), 98 (17), 97 (27), 93 (32), 92 (25), 85 (27), 84 (13), 79 (11), 67 (20), 45 (13), 43 (100).

Anal. Calcd for $C_9H_{14}O_2S$: C, 58.00; H, 7.58. Found: C, 58.20; H, 7.73.

Synthesis of 8-Thiabicyclo[3.2.1]oct-2-ene (15)—Pyrolysis of 0.75 g of acetate 17, as noted above in the synthesis of 13, gave 0.3 g (59%) of a yellow oil. Elution of this oil on a silicic acid column with hexane gave, after short-path distillation, 200 mg of 15 as a low-melting solid: nmr, see Figure 2; ir (CCl_4) 3010, 2950, 2880, 2805, 1640, 1420, 1305, 1280, 1240, 1190, 1060, and 1010 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 128 (5), 127 (8), *126 (100, M⁺),* 111 (8), 99 (7), 98 (23), 97 (67), 94 (5), 93 (53), 92 (35), 91 (41), 85 (26), 84 (17), 80 (5), 79 (26), 78 (9), 77 (39), 71 (7), 67 (23), 66 (12), 65 (18), 59 (6), 58 (7), 53 (10), 51 (9).

Anal. Calcd for $C_7H_{10}S$: C, 66.66; H, 7.99. Found: C, 64.67; H, 7.51.

Synthesis of Sulfone 15b.—Sulfide 15 (20 mg) was stirred in 1 ml of acetic acid containing 20 drops of 30% H_2O_2 for 3 days at 25°, at which time 5 ml of H_2O was added. The aqueous layer was extracted with methylene chloride, which was washed well with aqueous K_2CO_3 and H_2O, dried with K_2CO_3, filtered, and evaporated to give 30 mg of crude solid. Recrystallization from hexane with a trace of benzene gave pure sulfone: mp 178–180°; mass spectrum (70 eV) *m/e* (rel intensity) 158 (8, M^+), 94 (38), 93 (21), 91 (11), 79 (100), 77 (24), 66 (19), with a metastable peak at 66.4 ($79^2/94$).

Anal. Calcd for $C_7H_{10}SO_2$: C, 53.17; H, 6.37. Found: C, 52.96; H, 6.31.

Identification of Dimer 11.—Thiatetramethylidene dimer, 11, was identified *via* its mass spectrum (70 eV): *m/e* (rel intensity) 174 (9, M + 2 peak indicates two sulfur atoms per molecule), 173 (10), *172 (100, M⁺),* 144 (17), 139 (12), 138 (16), 126 (10), 125 (39), 124 (22), 112 (25), 111 (47), 105 (10), 99 (12), 98 (10), 97 (36), 93 (19), 65 (12), 61 (10), 58 (10).

Synthesis of Azines 14 and 16.—Azines 14 and 16 were synthesized from the appropriate ketones by the same general procedure given here for 14. Thiacyclohexan-4-one, 2.55 g (2 equiv), and 0.66 g (1 equiv) of 98% hydrazine were refluxed for 6 hr in 50 ml of ethanol. The mixture was allowed to cool and the resulting crystals were collected by vacuum filtration. Recrystallization from ethanol gave 2.8 g (56%) of 14: mp 139–141°; ir ($CHCl_3$) 3000, 2970, 2920, 2840, 1650, 1450, 1350, 1300, 1280, and 1215 cm^{-1}; nmr ($CDCl_3$) δ 2.77 (m, 16); mass spectrum (70 eV) *m/e* (rel intensity) 228 (82, M^+), 116 (32), 115 (13), 114 (49), 113 (100).

Anal. Calcd for $C_{10}H_{16}N_2S_2$: C, 52.57; H, 7.06; N, 12.27. Found: C, 52.85; H, 7.13; N, 12.35.

Azine 16 had mp 188° (yellows), 204–206°; mass spectrum (70 eV) *m/e* (rel intensity) 280 (66, M^+), 247 (29), 142 (28), 141 (25), 140 (36), 139 (61), 106 (19), 99 (100), 98 (19), 97 (33), 85 (47), 81 (20), 79 (25), 77 (10), 71 (28), 69 (24), 67 (36), 65 (43).

Anal. Calcd for $C_{14}H_{20}N_2S_2$: C, 59.94; H, 7.19; N, 10.00. Found: C, 59.96; H, 7.04; N, 9.44.

Toluenesulfenic Acid (20).—Toluenesulfenic acid was identified by its lifetime and mass spectrum (70 eV, rel intensity): *m/e* 140 (5, M^+), 139 (11), 138 (100), 137 (17), 123 (35), 121 (10), 92 (14), 91 (21), 79 (16), 77 (13), 65 (12), 63 (10).

Acknowledgment.—P. Y. Johnson wishes to thank the National Institutes of Health for partial support of this work.

Registry No.—**6**, 1708-23-2; 6 Na salt, 40697-90-3; **7**, 40697-91-4; 7 Na salt, 40697-92-5; **8**, 40697-93-6; 8 Na salt, 40697-94-7; **9**, 1120-59-8; **10**, 1708-32-3; **11**, 40697-97-0; **12**, 13042-80-3; **13**, 40697-99-2; **14**, 40698-00-8; **15**, 40698-01-9; **15b**, 40697-28-7; **16**, 40697-29-8; **17**, 40698-02-0; **20**, 17671-92-0; thiacyclohexan-4-one, 1072-72-6; toluenesulfonylhydrazide, 1576-35-8; thiacyclopentan-3-one, 1003-04-9; 8-thiabicyclo[3.2.1]-octan-3-one, 16892-50-5; Δ^3-sulfolene, 77-79-2; 4-acetoxytetrahydrothiapyran, 40697-32-3; *endo*-8-thiabicyclo[3.2.1]octan-3-ol, 40698-03-1; *exo*-8-thiabicyclo[3.2.1]octan-3-ol, 40698-04-2; hydrazine, 302-01-2; sodium toluenesulfinate, 824-79-3.

(28) M. A. Giantirco, *Tetrahedron*, **20**, 1772 (1964).

(29) No attempt was made to distinguish syn and anti isomers and data is given for the mixture.

(30) D. S. Tarbell and C. Weaver, *J. Amer. Chem. Soc.*, **63**, 2941 (1941).

(31) T. Cairns, G. Eglinton, and D. T. Gibson, *Spectrochim. Acta*, **20**, 31 (1964).

(32) For typical procedure see W. E. Parham and L. D. Edwards, *J. Org. Chem.*, **33**, 4150 (1968).

(33) See Figure 1 for nmr data of **9**, **10**, **12**, and **13**.

(34) S. Olsen and C. Rutland, *Chem. Ber.*, **86**, 361 (1953).

Studies of Acyl and Thioacyl Isocyanates. XIII.[1] The Reactions of Benzoyl and Thiobenzoyl Isocyanates with Hydrazobenzenes and Further Investigation of the Reaction of Thiobenzoyl Isocyanate with Phenylhydrazine

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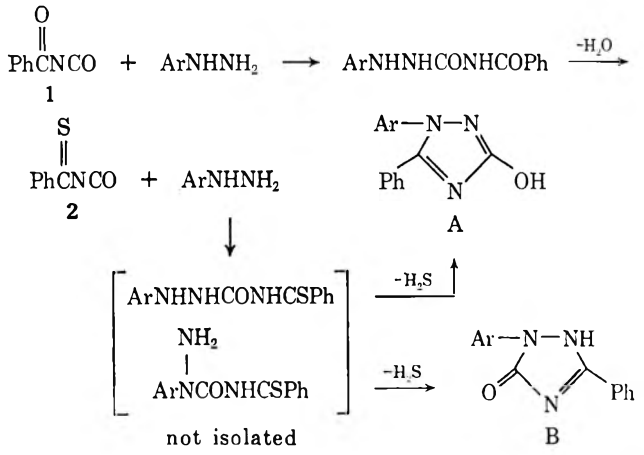
Received March 20, 1973

Benzoyl isocyanate (1) reacts exclusively with the more basic nitrogen atom in hydrazobenzenes (3) to give the corresponding 1,2-diaryl-4-benzoylsemicarbazides (4), which on treatment with hydrochloric acid underwent ring closure to the triazolinones (5) by the loss of water. On the other hand, thiobenzoyl isocyanate (2) attacks both nitrogen atoms to afford a mixture of semicarbazides (6 and 7), which on heating was easily converted into two isomeric triazolinones (5 and 8) with the elimination of hydrogen sulfide. On the basis of the relative amounts of 5 and 8, it is clear that 2 reacts preferentially with the more basic nitrogen atom in 3. In this context, the reaction of 2 with phenylhydrazine (16) has been reinvestigated, and the pathway for the formation of 1,3-diphenyl-Δ^3-1,2,4-triazolin-5-one (19) has been elucidated.

In a previous paper,[2] we reported that benzoyl isocyanate (1) reacted with arylhydrazine to yield the corresponding 1-aryl-4-benzoylsemicarbazide, which on treatment with hydrochloric acid underwent ring closure to 1-aryl-3-hydroxy-5-phenyl-1,2,4-triazole (A), while in the same reaction of thiobenzoyl isocyanate (2) 1-aryl-3-phenyl-Δ^3-1,2,4-triazolin-5-one (B) or A, or both, were obtained. The relative amounts of triazole A and triazolinone B depended on the nature



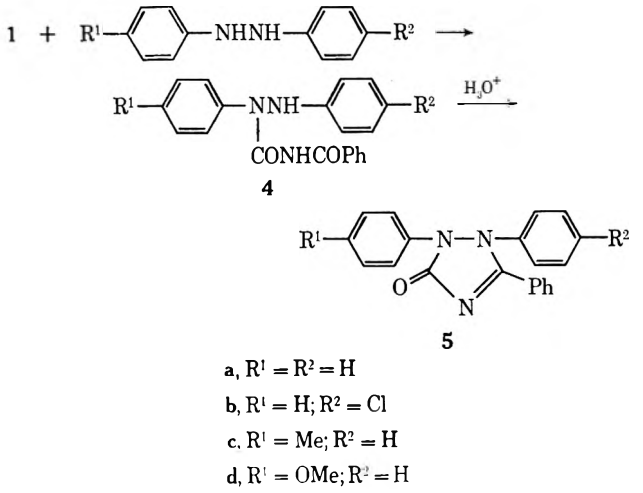
of the substituent of arylhydrazine. These facts seem to indicate that 1 reacts invariably with the β-nitrogen atom, and 2 attacks competitively the α- and β-nitrogen atoms in arylhydrazine.

In order to obtain information on the difference between the reactivity of 1 and 2 toward arylhydrazine, the reactions of 1 and 2 with hydrazobenzenes (3) were studied. In this context, the reaction of 2 with phenylhydrazine was also reinvestigated.

Results and Discussion

Reaction with Hydrazobenzenes.—The reaction of isocyanate 1 with hydrazobenzene (3a) in benzene at room temperature afforded 1,2-diphenyl-4-benzoylsemicarbazide (4a) in an excellent yield. In the reaction of 1 with asymmetrical hydrazobenzenes, 1 would be expected to attack competitively the both nitrogen atoms in the hydrazobenzenes. However, 1 reacted with *p*-chloro- (3b), *p*-methyl- (3c), and *p*-methoxyhydrazobenzene (3d) to give only 1-*p*-chlorophenyl-2-phenyl- (4b), 1-phenyl-2-*p*-tolyl- (4c), and 1-phenyl-2-*p*-anisyl-4-benzoylsemicarbazide (4d) in good yields, respectively (Scheme I): this indicates that 1 attacks exclusively the more basic nitrogen atom in 3.

SCHEME I

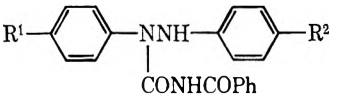


a, $R^1 = R^2 = H$
b, $R^1 = H$; $R^2 = Cl$
c, $R^1 = Me$; $R^2 = H$
d, $R^1 = OMe$; $R^2 = H$

The structures of semicarbazides 4 (Table I) were confirmed by the spectral data as well as by chemical conversions.

TABLE I

1,2-DIARYL-4-BENZOYLSEMICARBAZIDES[a]



Compd[b]	R^1	R^2	Yield, %	Mp, °C[c]	Ir, cm^{-1} ν_{NH}	Ir, cm^{-1} $\nu_{C=O}$
4a	H	H	95	209	3320, 3250	1740, 1720
4b	H	Cl	99	187	3320, 3260	1740, 1730
4c	Me	H	94	201.5–202	3320, 3250	1740, 1730
4d	OMe	H	94	178–179.5	3320, 3240	1740, 1720

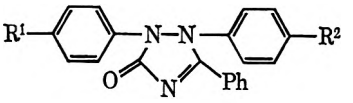
[a] Satisfactory analyses (±0.4% for C, H, and N) were reported for all new compounds listed in the table. [b] All the compounds are colorless prisms. [c] All the compounds melted with decomposition.

(1) Part XII of this series: O. Tsuge, K. Sakai, and M. Tashiro, *Tetrahedron*, in press.

(2) O. Tsuge, S. Kanemasa, and M. Tashiro, *Tetrahedron*, **24**, 5205 (1968).

TABLE II

1,2,3-TRIARYL-Δ^3-1,2,4-TRIAZOLIN-5-ONES[a]



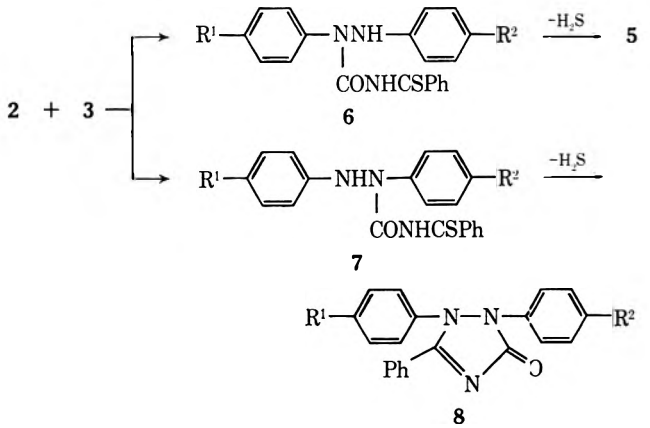
			Reaction conditions						
Compd[b]	R^1	R^2	Acid	Temp, °C	Time, hr	Yield, %	Mp, °C	Ir (C=O), cm^{-1}	Mol wt, *m/e*
5a	H	H	15% HCl	90–95	3	93	233–234	1690	313
5b	H	Cl	15% HCl	90–95	1	84	249–250	1710	347, 349[c]
5c	Me	H	10% HCl	95–100	1	97	222–223	1690, 1680	327[c]
5d	OMe	H	10% HCl	95–100	10 min	74	217.5	1705	343

[a] Satisfactory analyses (±0.4% for C, H, and N) were reported for all new compounds listed in the table. [b] All the compounds are colorless prisms. [c] Compound **5b** showed fragment ions at *m/e* 244, 246 (M^+ − PhCN) (rel intensity 3:1), 216, 218 ($[ClC_6H_4N{=}NPh]\cdot^+$) (3:1), 214, 216 ($ClC_6H_4\overset{+}{N}{\equiv}CPh$) (3:1), and **5c** exhibited fragment ions at *m/e* 224 (M^+ − PhCN), 196 ($[MeC_6H_4N{=}NPh]\cdot^+$) and 180 ($PhN\overset{+}{\equiv}CPh$) in the respective mass spectrum.

Treatment of **4** with hydrochloric acid yields 1-(R^1 substituted phenyl)-2-(R^2 substituted phenyl)-3-phenyl-Δ^3-1,2,4-triazolin-5-ones (**5a–5d**) in good yields (Table II).

In the reaction with **3a** in xylene at room temperature, isocyanate **2** gave 1,2-diphenyl-4-thiobenzoylsemicarbazide (**6a**), which on warming in ethanol or benzene was easily converted into the triazolinone **5a** with the elimination of hydrogen sulfide. However, semicarbazides formed by the reaction of **2** with asymmetrical hydrazobenzenes were rather unstable and converted into the corresponding triazolinones during purification. The reaction of **2** with **3b** or **3c** in xylene at 95° afforded two isomeric triazolinones **5b** and 1-*p*-chlorophenyl-2,3-diphenyl-Δ^3-1,2,4-triazolin-5-one (**8b**), or **5c** and 2-*p*-tolyl-1,3-diphenyl derivative (**8c**), respectively. In the reaction with **3d**, however, **2** gave only the triazolinone **5d**. It is evident that triazolinones **5** and **8** are formed *via* semicarbazides **6** and **7** with the elimination of hydrogen sulfide, respectively (Scheme II). Thus, the stronger

SCHEME II



a, $R^1 = R^2 = H$

b, $R^1 = H; R^2 = Cl$

c, $R^1 = Me; R^2 = H$

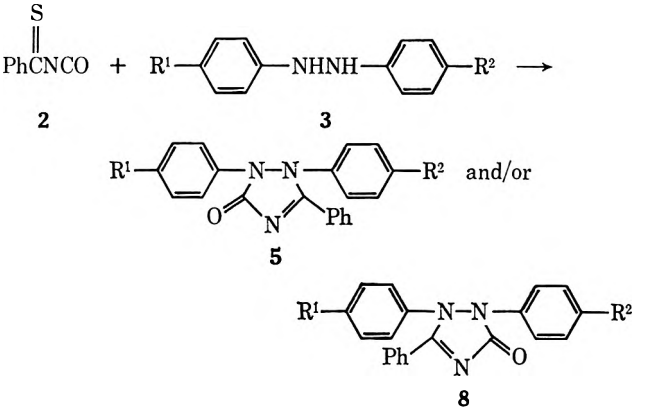
d, $R^1 = OMe; R^2 = H$

the electron-donating property of substituent (R^1) in **3**, the more easily the nitrogen atom having the R^1–C_6H_4 group is attacked.

The structures of isomeric triazolinones **5** and **8** were confirmed by the spectral data shown in Tables II and III as well as by the identification with authentic samples. The ir spectra of **5** were quite similar to

TABLE III

REACTION OF **2** WITH **3**



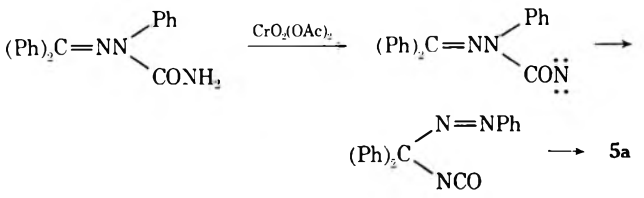
			Yield, %					Ir-(C=O),	
	R^1	R^2	**5**	**8**	Compd[a]	Mp, °C		cm^{-1}	Mol wt, *m/e*
a	H	H	92[b]						
b	H	Cl	52.5	22.5	**8b**	201–202		1700	347, 349[c]
c	Me	H	59	25	**8c**	235.5–236		1705	327[c]
d	OMe	H	90	0					

[a] Satisfactory analyses (±0.4% for C, H, and N) were reported for all new compounds listed in the table. Compounds **8b** and **8c** are colorless prisms. [b] From 1,2-diphenyl-4-thiobenzoylsemicarbazide (**6a**). [c] Compound **8b** showed fragment ions at *m/e* 244, 246 (M^+ − PhCN) (rel intensity 3:1), 216, 218 ($[ClC_6H_4N{=}NPh]\cdot^+$) (3:1) and 180 ($PhC\overset{+}{\equiv}NPh$), and **8c** exhibited fragment ions at *m/e* 224 (M^+ − PhCN), 196 ($[MeC_6H_4N{=}NPh]\cdot^+$), and 194 ($MeC_6H_4\overset{+}{N}{\equiv}CPh$) in the respective spectrum.

those of **8**, and the mass spectra supported the proposed structures for **5** and **8**, respectively.

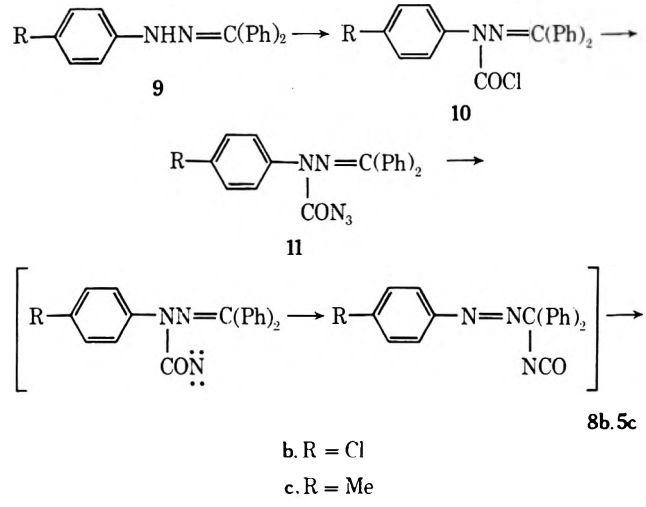
Recently, Schildknecht and Hatzmann[3] found that heating of 1-phenylazo-1,1-diphenylmethyl isocyanate, which was obtained by the oxidation of benzophenone 2-phenylsemicarbazone with chromyl acetate, afforded triazolinone **5a** (reported mp 236–238°) in a good yield. They proposed the following pathway *via* an acylnitrene intermediate.

(3) H. Schildknecht and G. Hatzmann, *Angew. Chem.*, **80**, 287 (1968); *ibid.*, **81**, 469 (1969).



We had success with our attempt to prepare triazolinones **5** and **8** from benzophenone *N*-aryl-*N*-azidocarbonylhydrazones as precursors of acylnitrene intermediates. Benzophenone *N*-*p*-chlorophenyl-*N*-chlorocarbonylhydrazone (**10b**), obtained from benzophenone *N*-*p*-chlorophenylhydrazone (**9b**) and phosgene, reacted with tetramethylguanidium azide to yield benzophenone *N*-*p*-chlorophenyl-*N*-azidocarbonylhydrazone (**11b**).[4] Thermal decomposition of acylazide **11b** in xylene at 135° for 2 hr afforded the expected triazolinone, which was identical with **8b** obtained from **2** and **3b** (Scheme III).

SCHEME III

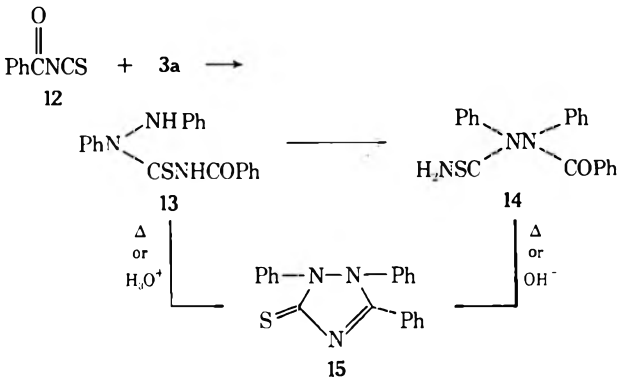


Similarly, benzophenone *N*-*p*-tolyl-*N*-azidocarbonylhydrazone (**11c**) prepared from the corresponding carbamoyl chloride (**10c**) gave triazolinone **5c**. The structures of carbamoyl chlorides **10** and acyl azides **11** were confirmed on the basis of spectral data and microanalyses. The pathway for the formation of triazolinone **5** or **8** from acyl azide **11** can be viewed as *via* acylnitrene and isocyanate intermediates as shown in Scheme III.

Thus, the reaction of **1** or **2** with **3** is a very convenient preparative method for 1,2,3-triaryl-Δ^3-1,2,4-triazolin-5-ones.

We investigated the reaction of benzoyl isothiocyanate (**12**) with hydrazobenzenes (**3**) for comparison of that of acyl isocyanate **1** or **2**. Isothiocyanate **12** easily reacted with **3a** at room temperature to yield a 1:1 adduct **13** as yellow crystals, which on heating in ethanol or benzene transformed into an isomeric 1:1 adduct **14** as colorless prisms. The ir spectrum of **13** exhibited absorption bands due to ν_{NH} and $\nu_{C=O}$ at 3280 and 1700 cm^{-1}, while **14** showed characteristic bands ascribable to ν_{NH} and $\nu_{C=O}$ at 3400, 3240, 3140, and 1680 cm^{-1} in its spectrum, respectively. The nmr spectrum of **14** showed a broad signal (2 H) ascribable to NH_2. On the basis of the above observations and of the inspection of the mass spectra, the structures of **13** and **14** were deduced as 1,2-diphenyl-4-benzoylthiosemicarbazide and 1,2-diphenyl-1-benzoylthiosemicarbazide, respectively (Scheme IV).

SCHEME IV



On heating at 160° or treatment with hydrochloric acid, **13** was converted into 1,2,3-triphenyl-Δ^3-1,2,4-triazoline-5-thione (**15**), which was also obtained from **14** by heating at 220° or action with aqueous sodium hydroxide solution. The structure of **15** was deduced on the basis of its spectral data and microanalysis.

However, a mixture of triazolinethiones of type **15** was obtained in the reaction of **12** with asymmetrical hydrazobenzenes; isolation of pure triazolinethiones was unsuccessful in all cases.

Reaction of Thiobenzoyl Isocyanate (2) with Phenylhydrazine.—Previously,[2] we reported that the reaction of **2** with phenylhydrazine (**16**) gave 1,3-diphenyl-Δ^3-1,2,4-triazolin-5-one (**19**), and suggested that **2** would react with the less basic α-nitrogen atom in **16** to form 2-phenyl-4-thiobenzoylsemicarbazide (**18**) which underwent very rapid ring closure.

To resolve this contradiction, the reaction of **2** with **16** was reinvestigated. Compound **2** reacted with **16** at a low temperature (−5°) to yield an unstable yellow product **17**. When treated with hydrochloric acid or heated at 140–160°, **17** transformed into 3-hydroxy-1,5-diphenyl-1,2,4-triazole (**20**), which was identical with an authentic sample prepared from 1-phenyl-4-benzoylsemicarbazide,[5] with the elimination of hydrogen sulfide. This fact indicates that **17** is 1-phenyl-4-thiobenzoylsemicarbazide formed by the reaction of **2** with the more basic β-nitrogen atom in **16**.

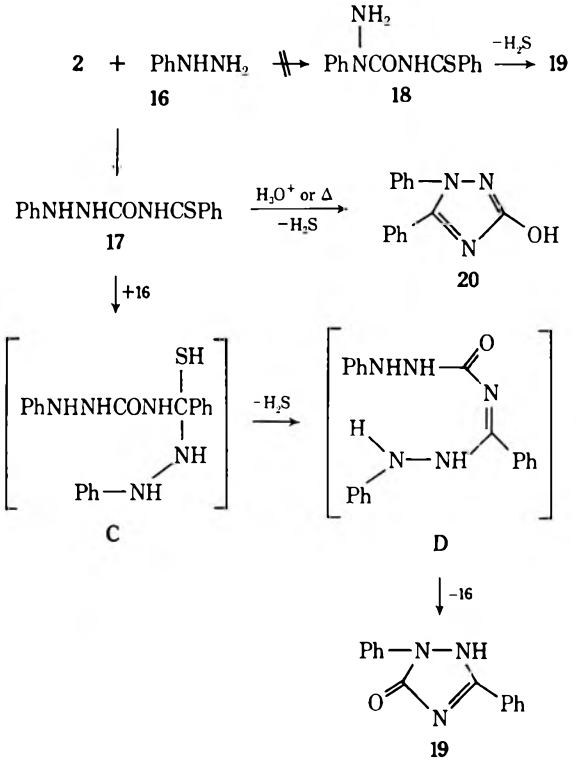
Many experiments were done in order to obtain information on the pathway for the formation of triazolinone **19** from semicarbazide **17**. We found that, when a benzene solution of semicarbazide **17** was refluxed in the presence of small amounts of **16**, the product was not the 3-hydroxy-1,2,4-triazole **20**, but Δ^3-1,2,4-triazolin-5-one **19**. On the basis of the above fact, it is evident that the presence of **16** is indispensable for the formation of triazolinone **19** from semicarbazide **17**. The pathway for the formation of **19** can be viewed as shown in Scheme V.

That is, **16** would react with the carbon atom of thiobenzoyl group of semicarbazide **17** to form an intermediate C, followed by the elimination of hydrogen

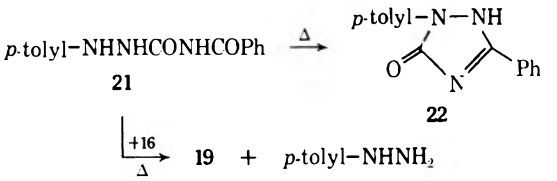
(4) The reaction of carbamoyl chloride **10b** with sodium azide did not give the expected acyl azide **11b**.

(5) O. Tsuge, T. Ito, and S. Kanemasa, *Nippon Kagaku Zasshi*, **89**, 69 (1968).

SCHEME V



sulfide to yield D. The loss of **16** from D would give the triazolinone **19**. This pathway is alsc supported by the following fact. Although heating of 1-*p*-tolyl-4-benzoylsemicarbazide (**21**)[5] at 215–220° gave 1-*p*-tolyl-3-phenyl-Δ^3-1,2,4-triazolin-5-one (**22**) in a good yield, the treatment of **21** with an equimolar amount of **16** under the same conditions afforded the triazolinone **19**.



Previously,[5] we reported that the thermal ring closure of **21** and *p*-chloro derivative gave the corresponding 3-hydroxy-1,2,4-triazole as a main product, respectively. These semicarbazides used previously might be contaminated with arylhydrazine hydrochloride, because the thermal ring closure of the semicarbazides in the presence of trace of arylhydrazine hydrochloride afforded the 3-hydroxy-1,2,4-triazole. We now find that heating of pure semicarbazide gave the triazolinone in a good yield: **21** (255°, 5 min) and *p*-chloro derivative (235°, 3 min) afforded the corresponding triazolinone in 94 and 86% yields, respectively.

Experimental Section[6]

Materials.—Benzoyl isocyanate (**1**) was prepared by the reported method.[7] To prepare thiobenzoyl isocyanate (**2**) a solution of 1.0 g of 2-phenylthiazoline-4,5-dione in 10 ml of xylene was heated at 120°, giving a reddish-violet solution of **2** which was used *in situ*.[8] This solution is referred to as the standard solution of **2**. Benzoyl isothiocyanate (**12**), bp 133–137° (18 mm) [lit.[9] bp 119° (10 mm)], was obtained from benzoyl chloride and lead thiocyanate in boiling benzene.

Hydrazobenzenes (**3**) were prepared by the reported methods, respectively: hydrazobenzene (**3a**), mp 124–125° (lit.[10] mp 126°); *p*-chloro- (**3b**), mp 91–92° (lit.[11] mp 89–90°); *p*-methyl- (**3c**), mp 88° (lit.[12] mp 86–87°); *p*-methoxyhydrazobenzene (**3d**), mp 75° (lit.[13] mp 74–75°).

Reaction of 1 with 3a.—A solution of **3a** (2.8 g) in dry benzene (50 ml) was added dropwise to a solution of **1** (2.25 g) in dry benzene (10 ml) at room temperature; crystals precipitated immediately. Recrystallization from ethanol afforded 1,2-diphenyl-4-benzoylsemicarbazide (**4a**).

Similarly, reactions of **1** with **3b**, **3c**, and **3d** gave the corresponding semicarbazides **4b**, **4c**, and **4d**, respectively. The yields and physical properties of **4** are given in Table I.

Ring Closure of Semicarbazides 4.—A solution of semicarbazide **4a** (0.5 g) in 15% hydrochloric acid (30 ml) was heated at 90–95° for 3 hr. After cooling, the reaction mixture was neutralized with aqueous ammonium hydroxide to give 0.44 g (93%) of colorless crystals. Recrystallization from ethanol afforded 1,2,3-triphenyl-Δ^3-1,2,4-triazolin-5-one (**5a**), mp 233–234°, as colorless prisms.

Similarly, semicarbazides **4b–4d** underwent ring closure to the corresponding triazolinones **5b–5d**. Reaction conditions, yields, and physical properties of **5** are summarized in Table II.

Reaction of 2 with 3. A. With 3a.—To a standard solution of **2** was added 0.97 g of **3a**, and the reaction mixture was then stirred at room temperature for 30 min. Filtration gave 1.6 g (87%) of 1,2-diphenyl-4-thiobenzoylsemicarbazide (**6a**), mp 138° dec, as reddish-orange crystals, which were washed with benzene. The microanalysis of **6a** was submitted without further purification, because **6a** was rather unstable, ir (KBr) 3280 (NH), 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{17}N_3OS$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.08; H, 4.81; N, 11.48.

B. With 3b.—To a standard solution of **2** was added 1.15 g of **3b** at room temperature, and the reaction mixture was heated at 95° for 2 hr, during which time hydrogen sulfide evolved. After cooling, filtration gave 0.95 g (52.5%) of triazolinone **5b**, which was identical with the product obtained from semicarbazide **4b**.

The filtrate was concentrated to leave colorless crystals, which on recrystallization from ethanol gave 0.4 g (22.5%) of 1-*p*-chlorophenyl-2,3-diphenyl-Δ^3-1,2,4-triazolin-5-one (**8b**), mp 201–202°, as colorless prisms.

Similarly, the reaction of **2** with **3c** and **3d** gave the corresponding triazolinones **5** and/or **8**. The results and physical properties of **8** are given in Table III.

Benzophenone *N*-*p*-Chlorophenyl-*N*-chlorocarbonylhydrazone (10b).—To a solution of 15 g of benzophenone *N*-*p*-chlorophenylhydrazone (**9b**) in a mixture of pyridine (8 ml) and benzene (150 ml) was added dropwise 30% phosgene–toluene solution (30 ml) at 0°. The reaction mixture was refluxed for 1.5 hr, and then it was poured into ice–water, which was extracted with benzene. The benzene extract was dried ($CaCl_2$), and evaporated *in vacuo* to leave 14 g (78%) of solid. Recrystallization from petroleum ether (bp 60–80°) gave **10b**, mp 103–104°, as colorless prisms, ir (KBr) 1740 cm^{-1} (C=O).

Anal. Calcd for $C_{20}H_{14}N_2OCl_2$: C, 65.05; H, 3.82; N, 7.59. Found: C, 65.09; H, 3.74; N, 7.64.

Similarly, the reaction of *N*-*p*-tolylhydrazone **9c** (15 g) with phosgene (32 ml of 30% phosgene–toluene solution) in a mixture of pyridine (8 ml) and benzene (150 ml) gave 16.8 g of the corresponding chlorocarbonylhydrazone (**10c**) as liquid, which was used without further purification, ir (neat) 1735 cm^{-1} (C=O).

Benzophenone *N*-*p*-Chlorophenyl-*N*-azidocarbonylhydrazone (11b).—To a solution of tetramethylguanidium azide[14] (1.58 g) in dry chloroform (20 ml), a solution of carbamoyl chloride **10b** (3.69 g) in dry chloroform (20 ml) was added, drop by drop, be-

(6) All melting points are uncorrected. The ir spectra were measured as KBr disks, and nmr spectra were determined at 60 MHz with a Hitachi R-20 nmr spectrometer with TMS as an internal reference. The mass spectra were obtained on a Hitachi RMS-4 mass spectrometer with a direct inlet and an ionization energy of 70 eV.

(7) A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **27**, 4361 (1962); *ibid.*, **28**, 1805 (1963).

(8) J. Goerdeler and H. Schenk, *Chem. Ber.*, **98**, 2954 (1965).

(9) P. A. S. Smith and R. O. Kan, *J. Org. Chem.*, **29**, 2261 (1964).

(10) P. Jacobson and A. Hugershoff, *Chem. Ber.*, **36**, 3841 (1904).

(11) K. Heumann and E. Mentha, *ibid.*, **19**, 1686 (1886).

(12) P. Jacobson, *Justus Liebigs Ann. Chem.*, **303**, 290 (1898).

(13) E. F. Pratt and T. P. McGovern, *J. Org. Chem.*, **29**, 1540 (1964).

(14) A. J. Papa, *J. Org. Chem.*, **31**, 1426 (1966).

low 0° over a period of 30 min. After the reaction mixture was stirred at room temperature for 30 min, it was poured into 50 ml of ice–water containing acetic acid (1 ml). The mixture was extracted with chloroform, and the extract was dried ($MgSO_4$). The extract was evaporated *in vacuo* to leave 3.3 g (88%) of crystals. Recrystallization from petroleum ether (bp 45–70°) afforded **11b**, mp 103° as colorless prisms: ir (KBr) 2180 (N_3), 1680 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 375 (M^+), 305 ($M^+ - CON_3$, base peak).

Anal. Calcd for $C_{20}H_{14}N_5OCl$: C, 63.92; H, 3.76; N, 18.64. Found: C, 64.03; H, 3.48; N, 18.90.

Similarly, the reaction of carbamoyl chloride **10c** with tetramethylguanidium azide in dry chloroform afforded the corresponding acyl azide **11c**, mp 93.5°, as colorless prisms: yield 83%; ir (KBr) 2160 (N_3), 1690 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* 355 (M^+), 285 ($M^+ - CON_3$, base peak).

Anal. Calcd for $C_{21}H_{17}N_5O$: C, 70.96; H, 4.82; N, 19.71. Found: C, 70.87; H, 4.71; N, 19.68.

Thermolysis of Acyl Azide 11b.—A solution of **11b** (0.5 g) in dry xylene (5 ml) was heated at 135° for 2 hr. The reaction mixture was evaporated *in vacuo* to leave an oily substance, which on trituration with a mixture of methanol, acetone, and diethyl ether afforded crystals. Recrystallization from ethanol gave 0.18 g (39%) of triazolinone **8b**, mp 201–202°, as colorless prisms.

Similarly, thermolysis of acyl azide **11c** afforded triazolinone **5c**, mp 222–223°, in 41% yield.

Reaction of Benzoyl Isothiocyanate (12) with 3a.—A solution of **3a** (1.1 g) in dry benzene (20 ml) was added dropwise to a solution of **12** (1.0 g) in dry benzene (10 ml) at room temperature. Filtration afforded 1.85 g (88%) of yellow crystals, which were washed with benzene to give 1,2-diphenyl-4-benzoylthiosemicarbazide (**13**), mp 139.5–140° dec. This compound was submitted to microanalysis without further purification.

Anal. Calcd for $C_{20}H_{17}N_3OS$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.29; H, 4.81; N, 11.73.

1,2-Diphenyl-1-benzoylthiosemicarbazide (14).—A solution of **13** (0.2 g) in ethanol (10 ml) was refluxed for 5 min. The solution was concentrated to give 0.17 g (85%) of colorless crystals. Recrystallization from ethanol afforded **14**, mp 210–211° dec, as colorless prisms: nmr ($CDCl_3$) δ 6.23 (broad, 2, NH_2); mass spectrum (70 eV) *m/e* 347 (M^+).

Anal. Calcd for $C_{20}H_{17}N_3OS$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.38; H, 4.83; N, 12.14.

1,2,3-Triphenyl-Δ^3-1,2,4-triazoline-5-thione (15).—Heating of **13** (0.5 g) at 160° for 10 min or treatment of **13** (0.5 g) with 15% hydrochloric acid (20 ml) at 90–95° for 30 min afforded 0.47 g (99%) or 0.45 g (95%) of **15**, mp 251°, as colorless needles: mass spectrum (70 eV) *m/e* 329 (M^+), 297 ($M^+ - S$), 296 ($M^+ - SH$), 180 ($PhC{\equiv}\overset{+}{N}Ph$).

Anal. Calcd for $C_{20}H_{15}N_3S$: C, 72.93; H, 4.59; N, 12.76. Found: C, 72.71; H, 4.37; N, 12.51.

Reaction of 2 with Phenylhydrazine (16).—A mixture of a standard solution of **2** and **16** (0.56 g) was stirred at −5° for 5 min. Dry diethyl ether was added to the reaction mixture, giving 1.3 g (92%) of 1-phenyl-4-thiobenzoylsemicarbazide (**17**) as yellow crystals. Compound **17** decomposed gradually under the evolution of hydrogen sulfide at room temperature: ir (KBr) 3220, 3150, 3080 (NH), 1680 cm^{-1} (C=O).

Heating of **17** at 140–160° for 5 min or treatment with concentrated hydrochloric acid at room temperature for 30 min afforded 3-hydroxy-1,5-diphenyl-1,2,4-triazole (**20**)[5] in 91 or 86% yield, respectively.

Reaction of 17 with 16.—A solution of **17** (0.2 g) and **16** (0.18 g) in benzene (10 ml) was refluxed for 5 min. After cooling, filtration gave 0.16 g (91%) of 1,3-diphenyl-Δ^2-1,2,4-triazolin-5-one (**19**),[2] mp 230–231° (lit.[15] mp 235°; lit.[16] mp 233°).

Registry No.—**1**, 4461-33-0; **2**, 3553-61-5; **3a**, 122-66-7; **3b**, 949-88-2; **3c**, 621-94-3; **3d**, 953-12-8; **4a**, 40587-77-7; **4b**, 40587-78-8; **4c**, 40587-79-9; **4d**, 40587-80-2; **5a**, 5378-13-2; **5b**, 40587-82-4; **5c**, 40587-83-5; **5d**, 40587-84-6; **6a**, 40587-85-7; **8b**, 40594-85-2; **8c**, 40594-86-3; **9b**, 40594-87-4; **9c**, 40594-88-5; **10b**, 40594-89-6; **10c**, 40594-90-9; **11b**, 40594-91-0; **11c**, 40594-92-1; **12**, 532-55-8; **13**, 40594-93-2; **14**, 40594-94-3; **15**, 40594-95-4; **16**, 100-63-0; **17**, 40594-96-5.

(15) J. Goerdeler and H. Schenk, *Chem. Ber.*, **99**, 782 (1966).
(16) G. Baccar and F. Mathis, *C. R. Acad. Sci.*, **261** (1), 174 (1965).

The Reaction of Aluminum Azide with Cyano Esters. Preparation of Tetrazolo[1,5-*c*]pyrimidin-5(6*H*)-one and Tetrazolo[1,5-*c*]quinazolin-5(6*H*)-one

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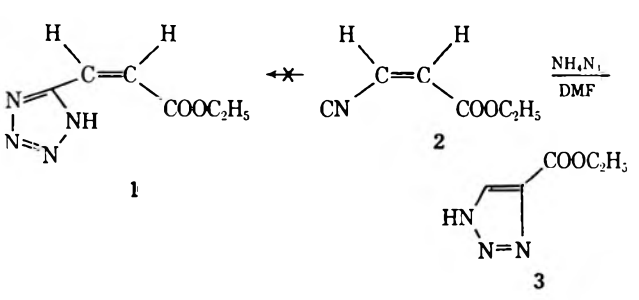
The reaction of aluminum azide and a variety of unsaturated β-cyano esters was studied. Both *cis*- and *trans*-3-cyanoacrylates gave *trans*-3-tetrazole-5-acrylate. *trans*-3-Cyanocrotonate produced *trans*-3-methyltetrazole-5-acrylate, while *cis*-3-cyanocrotonate gave a mixture consisting mainly of 1-(2-cyanopropenyl)tetrazolin-5(4*H*)-one and tetrazolo[1,5-*c*]pyrimidin-5(6*H*)-one. The reaction of aluminum azide and ethyl *o*-cyanobenzoate gave a mixture of four products: tetrazolo[1,5-*c*]quinazolin-5(6*H*)-one, 1-[*o*-(tetrazol-5-yl)phenyl]tetrazolin-5(4*H*)-one, ethyl *o*-(5-tetrazolyl)benzoate, and *o*-(5-oxo-2-tetrazolin-1-yl)benzonitrile. An explanation for the formation of the quinazolinone *via* a Curtius rearrangement is proposed. Alkaline hydrolysis of tetrazolo[1,5-*c*]-quinazolin-5(6*H*)-one produced 5-(*o*-aminophenyl)tetrazole, which could be reconverted to the tetrazolo-[1,5-*c*]quinazolinone by reaction with phosgene.

Because the previously unreported ethyl *cis*-tetrazole-5-acrylate (**1**) was required as a synthetic intermediate, an attempt was made to prepare it from the readily available ethyl *cis*-3-cyanoacrylate (**2**).[2] Several excellent methods are known for converting nitriles to tetrazoles, the most convenient being that of Finnegan, Henry, and Lofquist,[3] which employs ammonium azide in dimethylformamide. This reagent, however, caused elimination of cyanide from the cyanoacrylate



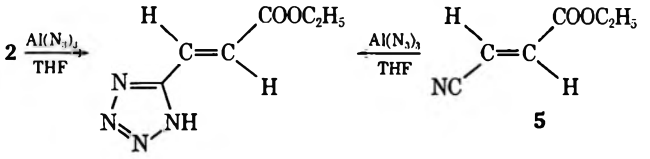
(1) Chemical Biology Research, The Dow Chemical Company, Midland, Mich. 48640.
(2) C. K. Sauers and R. J. Cotter, *J. Org. Chem.*, **26**, 6 (1961).
(3) W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Amer. Chem. Soc.*, **80**, 3908 (1958).

and produced only triazolecarboxylate **3**.[4] The same product was obtained by the reaction of sodium azide with **2** in acetonitrile.

More recently, Arnold and Thatcher[5] have used aluminum azide, prepared *in situ* in anhydrous THF, to obtain 5-vinyltetrazole from acrylonitrile. Unfortunately, this reagent also failed to produce **1** from **2**, but the subsequent study of the reaction of aluminum azide on cyano esters uncovered some novel chemistry that is the subject of this discussion.

Results and Discussion

Cyanoacrylates.—When ethyl *cis*-3-cyanoacrylate was refluxed in THF with an equimolar amount of aluminum azide, a crystalline tetrazoleacrylate **4** was formed in 30% yield. However, in the nmr the coupling constant for the AB quartet of the vinyl protons was now 16.5 cps rather than the original 11.5 cps in **2**, indicating that **4** contained a trans double bond.[6] Treatment of ethyl *trans*-3-cyanoacrylate (**5**)

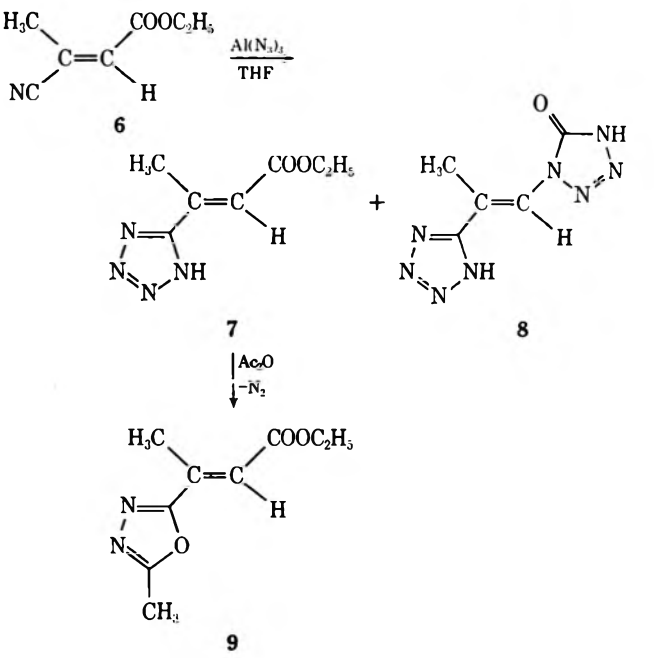


4

with aluminum azide produced a crystalline compound identical with that obtained from the *cis*-acrylate. Aliquots removed at various times from the reaction of the *cis*-cyanoacrylate clearly showed by nmr initial formation of the *trans*-cyanoacrylate from the *cis*-cyanoacrylate followed by conversion to the *trans*-tetrazoleacrylate. No peaks that could be ascribed to the *cis*-tetrazoleacrylate could be detected then or in the product after work-up, indicating that under these conditions the isomerization was preceding the formation of the tetrazole.

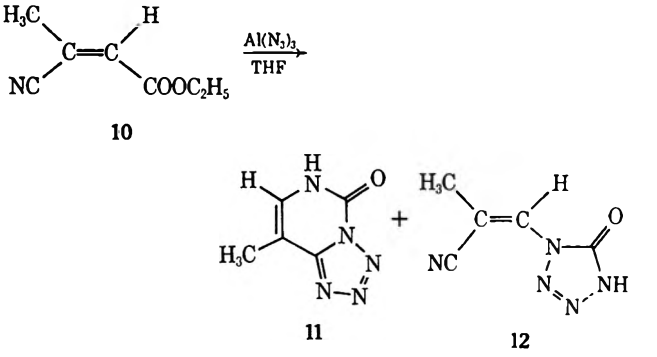
Cyanocrotonates.—In an effort to reduce the rate of isomerization in this system, ethyl *cis*- and *trans*-3-cyanocrotonates[7] were studied. Ethyl *trans*-3-cyanocrotonate (**6**) behaved normally when treated with aluminum azide to produce a 66% yield of ethyl *trans*-3-methyltetrazole-5-acrylate (**7**) and a small amount of **8**, discussed below. The *trans*-tetrazolecrotonate **7** displayed typical tetrazole behavior by forming oxadiazole **9** when treated with refluxing acetic anhydride.[5]

The reaction of aluminum azide with ethyl *cis*-3-cyanocrotonate (**10**), however, produced a completely unexpected result. In this case a mixture of two crystalline products was obtained, but this only amounted to about 14% by weight of the starting material. The remainder was unreacted **10** and polymeric oils which were not characterized. Of the crystalline product,



6 **7** **8** **9**

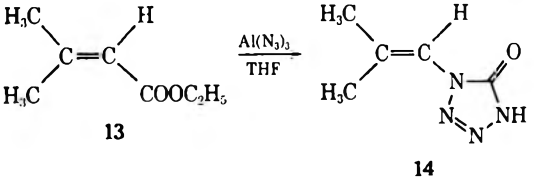
82% was an insoluble $C_5H_5N_5O$ compound **11**, melting at 210–211°. The remaining 18% was an isomeric $C_5H_5N_5O$ material **12** melting at 187–189°. No **7** was



10 **11** **12**

detectable, though it could possibly have been present in the large, noncrystalline fraction.

The structure of **12** was the more readily apparent, since the nmr spectrum showed that the ethyl protons of the ester had been lost while the ir clearly indicated that the cyano group was still present. Apparently the azide ion had attacked the ester instead of the nitrile, forming a new carbonyl function absorbing at 1740 cm^{-1}. Such a reaction has not been previously reported in the literature, but it is given good precedent in the work of Horwitz, *et al.*,[8] who showed that isocyanates, acid chlorides, and α-ketonitriles are transformed by aluminum azide *via* a Curtius rearrangement into 1-substituted tetrazolin-5(4*H*)-ones. Therefore, the low-melting isomer was assigned structure **12**, 1(2-cyanopropenyl)tetrazolin-5(4*H*)-one. To confirm that such a reaction would occur in this system, ethyl β,β-dimethylacrylate (**13**) was treated under the same



13 **14**

(4) Y. Shunichi, M. Tomishige, and A. Akira, *Yakugaku Zasshi*, **77**, 452 (1957); *Chem. Abstr.*, **51**, 14697e (1957).

(5) C. Arnold, Jr., and D. N. Thatcher, *J. Org. Chem.*, **34**, 1141 (1969).

(6) R. H. Bible, "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, p 38.

(7) D. T. Mowry and A. G. Rossow, *J. Amer. Chem. Soc.*, **67**, 926 (1945). Although correct nomenclature would label **6** as the *cis*-crotonate and **10** as the *trans*-crotonate, the opposite terminology is used in this paper as in Mowry's paper so that cis and trans refer to the functional groups of interest, the nitrile and the ester.

(8) J. P. Horwitz, B. E. Fisher, and A. J. Tomasewski, *J. Amer. Chem. Soc.*, **81**, 3076 (1959).

conditions with aluminum azide and formed a 24% yield of 1-(2-methylpropenyl)tetrazolin-5(4*H*)-one (**14**).

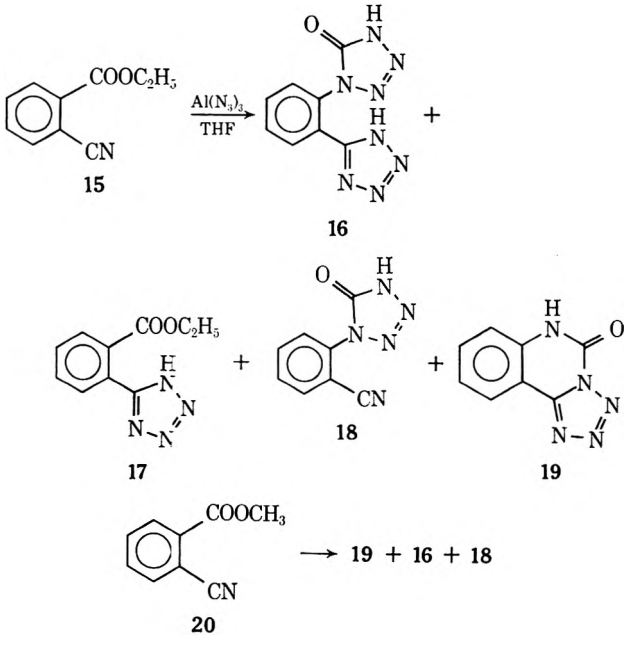
The structure of **8** was assigned by analogy on the basis of its empirical formula and spectral properties to be that of the *trans*-tetrazolypropenyltetrazolinone.

Although the presence of the unchanged nitrile in **12** suggested a possible isomerization to the trans isomer, a nuclear Overhauser effect determination showed a 19% increase in the vinyl proton integral and confirmed the cis form as shown. That **12** was not a precursor of **11** was indicated by the failure of further treatment of **12** with aluminum azide to produce any **11**. The only crystalline product isolated was unchanged **12**.

Compound **11**, though it was not the product of further reaction of the nitrile with the tetrazolinone, nor was it a *cis*-tetrazolylpropenyl tetrazolinone such as **8**, had lost both the original ester and nitrile functions. Its ir spectrum revealed a complex carbonyl region with peaks at 1770, 1730, 1640, and 1550 cm^{-1}. The high-frequency absorption in the 1770-cm^{-1} region was suggestive of 1-acylated tetrazoles.[9] A Curtius rearrangement to an isocyanate resulting from azide attack on the carboethoxy group, followed by cyclization with the adjacent tetrazole, would form 8-methyltetrazole[1,5-*c*]pyrimidin-5(6*H*)-one (**11**). Though not supported by direct degradative evidence, this assignment was corroborated and a better understanding of the rearrangement was obtained by a study of the reaction of aluminum azide on the analogous *o*-cyanobenzoates.

Cyanobenzoates.—Ethyl *o*-cyanobenzoate (**15**) (Scheme I) was treated with aluminum azide in refluxing THF for 42 hr. On work-up, about 50% of the starting ester was recovered unchanged. The remainder had been transformed into a mixture of four crystalline materials, **16, 17, 18,** and **19,** which separated fairly well on tlc, and three of these, **16, 17,** and **19,** could be obtained in a pure state by fractional crystallization.

SCHEME I



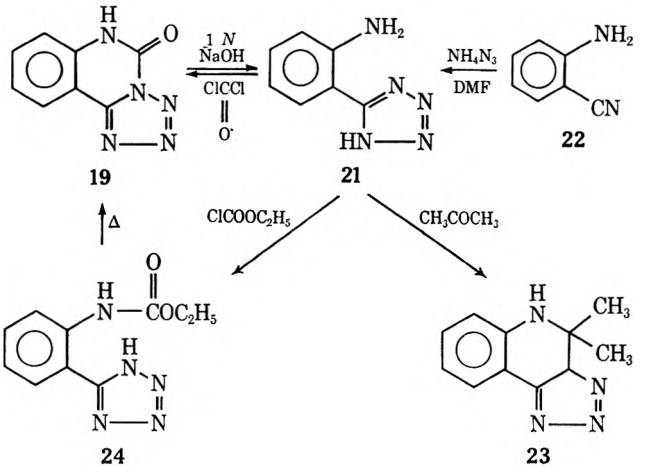
About 25% of the product consisted of the $C_8H_6N_8O$ compound **16**, mp 262–263°, which had a 1690-cm^{-1} carbonyl band in the ir. This data plus a titration with sodium hydroxide, which revealed two acidic protons, indicated that **16** was 1-[*o*-(tetrazol-5-yl)phenyl]-tetrazolin-5(4*H*)-one in which the ester had been converted to the tetrazolinone and the nitrile to the tetrazole.

A second crystalline component comprising 10% of the product was a $C_{10}H_{10}N_4O_2$ material, **17**, mp 142–143°. The nmr spectrum indicated that it had retained the carboethoxy function and the ir showed that it had lost the nitrile. This could therefore be assigned the structure of ethyl (5-tetrazolyl)benzoate (**17**).

Although it could not be isolated pure from this reaction mixture, the alternate compound **18** was also obtained. This $C_8H_5N_5O$ material could be isolated in a pure form from the reaction product of aluminum azide on methyl *o*-cyanobenzoate (**20**). Spectral data showed that the nitrile had been retained and the ester converted to the tetrazolinone, forming 1-(*o*-cyanophenyl)tetrazolin-5(4*H*)-one (**18**).

The largest portion (about 50%) of the crystalline reaction product from ethyl cyanobenzoate consisted of **19** (Scheme II), $C_8H_5N_5O$, mp 273–275°. In the carbonyl region of its ir spectrum, **19** corresponded closely to the compound **11** obtained from the cis crotonate, having in particular a high-frequency carbonyl absorption at 1770 cm^{-1}. The assignment of the tetrazolo[1,5-*c*]quinazolin-5(6*H*)-one structure **19** was, however, made on the basis of the results of alkaline hydrolysis. Being acidic, the compound dissolved readily in 1 *N* aqueous sodium hydroxide, and, after warming on the steam bath for 1 hr and acidification, a new crystalline material precipitated simultaneously with copious evolution of carbon dioxide. Analysis showed this new material to be a $C_7H_7N_5$ compound, having simply lost the carbonyl. Since it was a nitrogeneous material containing no oxygen, yet still retaining its acidic properties, it undoubtedly contained a tetrazole ring. The presence of primary NH_2 absorption at 3450–3400 cm^{-1} in the ir indicated the compound to be 5-(*o*-aminophenyl)tetrazole (**21**). The entire spectrum corresponded closely to that reported

SCHEME II



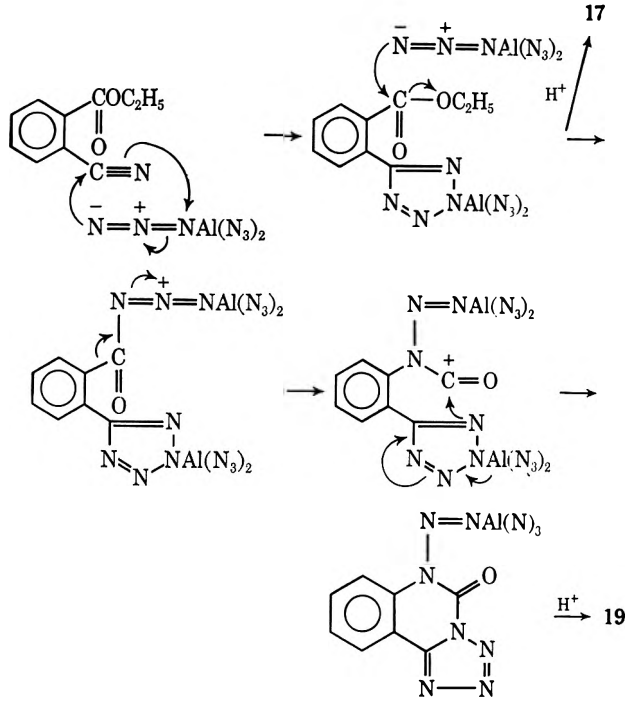
(9) H. W. Thompson and R. J. L. Popplewell, *Z. Electrochem.*, **64**, 746 (1960).

by Postovskii,[10] who prepared it by acid treatment of 5,6-dihydro-5-methyl-5-hydroxytetrazolo[1,5-*c*]quinazoline. Authentic **21** was prepared from anthranilonitrile **22** with ammonium azide in dimethylformamide. It was difficult to obtain this material in pure form and the ir spectrum and melting point seemed to be highly variable depending on the crystallization solvent (solution spectra were identical). Therefore, the acetone condensation products **23** from each source were prepared and were found to have identical ir spectra and showed no depression of the mixture melting point.

On treatment of **21** with phosgene in benzene, a 64% yield of crystalline material identical with **19** was obtained, proving that this compound is tetrazolo[1,5-*c*]quinazolin-5(6*H*)-one. It could also be prepared in about 40% overall yield by treatment of **21** with ethyl chloroformate in ethanol to give **24**, which on pyrolysis at 195–200° produced **19**.

The mechanism of this rearrangement and cyclization probably involves initial 1,3-dipolar addition of azide to the nitrile[11] to form the tetrazole ester **17** in the normal fashion. A second molecule of azide then attacks the ester carbonyl, eliminating ethoxide. A Curtius rearrangement[8] to give the isocyanate intermediate is followed by rapid attack from the adjacent tetrazole nitrogen to give **19**, or **11** in the crotonate case (Scheme III).

SCHEME III

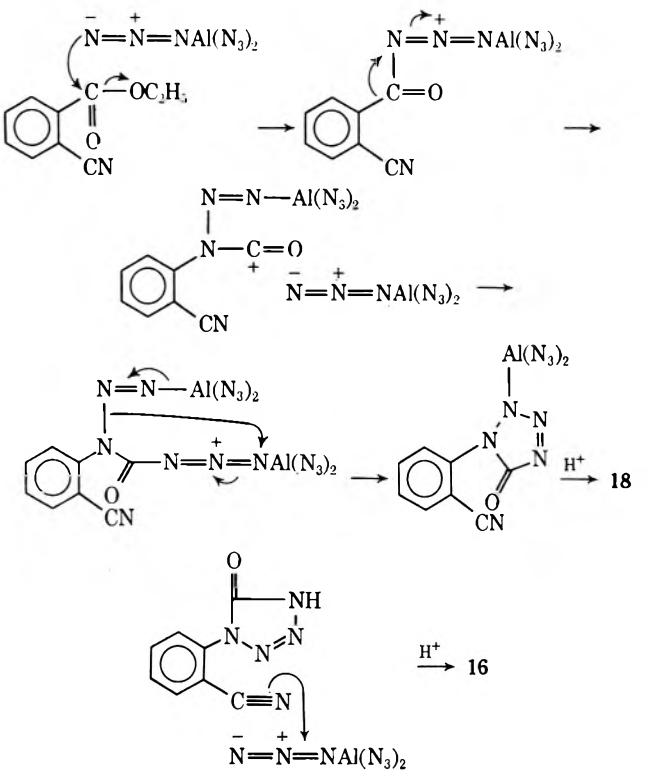


However, in the cases where the ester is the site of the initial azide attack (Scheme IV), the nitrile is not capable of reacting with the intermediate isocyanate which is susceptible to 1,3-dipolar addition of more azide. There is no evidence yet to establish that a free isocyanate is formed in this reaction nor, in fact, has the possibility of the aluminum chloride removing the ethoxide group to form a preliminary carbonium ion intermediate[12] been eliminated.

(10) I. Ya. Postovskii and N. N. Vereshchagina, *Khim. Geterotsikl. Soedin.*, **3**, 944 (1967).

(11) E. Wilberg and H. Michaud, *Z. Naturforsch. B*, **9**, 496 (1954).

SCHEME IV



It is presumably further azide attack on the cyanophenyltetrazolinone **18** that produces the fourth product of the reaction, the tetrazolylphenyltetrazolinone **16**. The high reactivity of the tetrazole in condensation reactions of carbonyl compounds with the ortho amino group in 5-(*o*-aminophenyl)tetrazole would indicate that very little of **16** is formed from **17**.

The relative proportions of the various products are dependent upon the relative rate of primary attack on the ester or the nitrile. Surprisingly, there appears to be little difference, although the nitrile seems to be preferred. A quantitative separation of the components has not been attempted, since their relatively low solubility in common solvents has discouraged quantitative chromatographic separation.

Experimental Section[13]

Ethyl *v*-Triazole-4-carboxylate (3) from Sodium Azide.—To a stirred suspension of 3.35 g of NaN_3 in 100 ml of dry CH_3CN was added, over a 10-min period, a solution of 6.26 g of ethyl *cis*-3-cyanoacrylate[2] (**2**) in 50 ml of CH_3CN. The reaction solution turned pink and after stirring at room temperature for 4 hr was refluxed for 2 days. After cooling, the reaction was filtered and the resulting white solid was washed with CH_3CN. The solid was dissolved in 100 ml of 6 *N* HCl and extracted four times with 50-ml portions of $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to leave 0.8 g of white solid. Recrystallization from CCl_4–$CHCl_3$ mixture gave 0.1 g of colorless crystals of **3**, mp 112–113°.

From Ammonium Azide.—A mixture of 42.3 g of NaN_3, 34.4 g of NH_4Cl, 0.65 g of LiCl, and 56.6 g of **2** in 250 ml of DMF was stirred and heated at 125° for 6 hr. The reaction was filtered hot and the DMF in the filtrate was removed under reduced pressure. The residue was poured into 500 g of ice water and filtered from a

(12) P. A. S. Smith, *J. Amer. Chem. Soc.*, **70**, 320 (1948).

(13) Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Nmr spectra were obtained using a Varian A-60 spectrometer; ir spectra were obtained using a Perkin-Elmer 337 grating infrared spectrophotometer; all melting points were determined using a Thomas-Hoover Uni-melt apparatus and are uncorrected; mass spectral determinations were obtained using a CEC 110B high-resolution mass spectrometer, D. P.

trace of amorphous solid. The resulting dark solution was extracted four times with $CHCl_3$, and the combined extracts were washed twice with H_2O, dried (Na_2SO_4), and evaporated under reduced pressure to leave a dark oil that crystallized on cooling. The crystals were filtered, washed carefully with $CHCl_3$, and dried in air to yield 9.65 g. Recrystallization from $CHCl_3$ after decolorizing with charcoal gave 7.22 g of **3**: mp 112–113° (lit.[4] mp 117–118°); nmr (acetone-d_6) δ 8.0 (s, 1 H, vinyl H) and typical ethyl ester pattern; ir (Nujol) 3170 (NH), 1710 cm^{-1} (C=O). Material was identical with that obtained from sodium azide above.

Anal. Calcd for $C_5H_7N_3O_2$: C, 42.55; H, 5.00; N, 29.77. Found: C, 42.33; H, 4.89; N, 30.03.

Ethyl *trans*-5-Tetrazoleacrylate (4) from Ethyl *cis*-3-Cyanoacrylate (2).—Anhydrous $AlCl_3$ (200 g, 1.5 mol) was added in portions to 3 l. of anhydrous THF stirred and cooled under N_2. To this solution was added 400 g (6.16 mol) of NaN_3 and 187.5 g (1.5 mol) of ethyl *cis*-3-cyanoacrylate and the mixture was warmed to reflux. After refluxing for 19 hr under N_2, the reaction was cooled and 2 l. of 6 *N* HCl was added carefully. The resulting mixture was filtered and the precipitated inorganic solid was washed with THF. The THF was removed under reduced pressure until about 2 l. of a brown solution remained. This was extracted four times with 400-ml portions of $CHCl_3$, and the combined extracts were washed twice with 200-ml portions of saturated NaCl solution, dried (Na_2SO_4), and evaporated to leave a tan solid. This residue was triturated with 900 ml of hot $CHCl_3$, filtered to remove the insoluble amorphous solid, concentrated to 300 ml, and allowed to cool. The total yield of crystalline **4** obtained in three crops was 76 g (30% yield): mp 135–136°; nmr (acetone-d_6) AB quartet centered at δ 7.41 (J = 16.5 cps, 2 H, vinyl H) and typical ethyl ester pattern; ir (Nujol) 3170, 3070 (NH), 1710 (C=O), 1660 (C=C), 1550 cm^{-1}.

Anal. Calcd for $C_6H_8N_4O_2$: C, 42.85; H, 4.80; N, 33.32. Found: C, 42.73; H, 4.86; N, 33.72.

Ethyl *trans*-5-Tetrazoleacrylate (4) from Ethyl *trans*-3-Cyanoacrylate (5).—Ethyl *trans*-3-cyanoacrylate was prepared from ethyl α-chloroacrylate according to the modified method of Sauers and Cotter,[2] but it could not be completely separated from the acetone cyanohydrin also formed. The material used in this reaction was shown by glc to contain 67% of the desired ethyl *trans*-3-cyanoacrylate. A mixture of 19.9 g (0.15 mol) of $AlCl_3$ and 43.2 g (0.665 mol) of NaN_3 in 300 ml of cold, anhydrous THF was treated with 18.7 g of the crude *trans*-cyanoacrylate. After stirring under N_2 at reflux for about 20 hr, the cooled reaction solution was treated with 200 ml of 6 *N* HCl and filtered, and the THF was removed under reduced pressure. The aqueous residue was extracted four times with $CHCl_3$. These extracts were washed twice with saturated NaCl and dried (Na_2SO_4). Evaporation of the solvent left 10.52 g of a viscous orange oil that produced 1.48 g of crystalline **4** when cooled and scratched. This material was identical with that obtained from the *cis*-cyanoacrylate above.

Ethyl *trans*-3-Methyltetrazole-5-acrylate (7).—Ethyl *trans*-3-cyanocrotonate (6) was prepared by the method of Mowry and Rossow.[7] The reaction was carried out exactly as with the cyanoacrylates above using 0.4 mol of crotonate, 0.4 mol of $AlCl_3$, and 1.8 mol of NaN_3 in 1 l. of anhydrous THF. After acidification with 600 ml of 6 *N* HCl, the THF was evaporated and the residue was poured into H_2O and extracted with $CHCl_3$. This $CHCl_3$ solution was dried (Na_2SO_4) and filtered. On standing a fine, crystalline solid separated weighing 0.92 g and identical with another 1.67 g of material that slowly separated from the aqueous fraction. It had a melting point of 187–188° after recrystallization from acetone–$CHCl_3$. It is ascribed structure **8** based on its analysis, ir (broad H-bonded NH, carbonyl at 1710, C=C at 1660 cm^{-1}), and nmr, which showed only a vinyl methyl at δ 1.90 (d, 3 H) and a single adjacent vinyl proton at δ 7.05 (m, 1 H).

Anal. Calcd for $C_5H_6N_8O$: C, 30.93; C, 3.11; N, 57.72. Found: C, 30.63; H, 3.11; N, 56.59.

The $CHCl_3$-soluble product from the reaction was isolated by evaporation. The resulting yellow oil crystallized on cooling. It was recrystallized from CCl_4–$CHCl_3$ to produce 48.3 g of **7**, light yellow crystals, mp 83–87°, 66% yield. Recrystallized for analysis from $CHCl_3$, the pure material melted at 88–89°: nmr ($CDCl_3$) δ 1.35 (t, 3 H, ethyl CH_3), 2.80 (d, 3 H, vinyl CH_3), 4.34 (q, 2 H, ethyl CH_2), 7.10 (m, 1 H, vinyl H); ir (Nujol) broad NH, 1740 and 1720 (C=O), 1650 (C=C), 1050 cm^{-1} (tetrazole).

Anal. Calcd for $C_7H_{10}N_4O_2$: C, 46.15; H, 5.53; N, 30.75. Found: C, 45.85; H, 5.18; N, 30.76.

Ethyl *cis*-5-Dimethyl-1,3,4-oxadiazole-2-acrylate (9).—A mixture of 5 g of **7** and 0.29 g of hydroquinone in 100 ml of acetic anhydride was refluxed for 1 hr. The cooled reaction solution was poured into 500 ml of ice water and stirred until a clear solution resulted. The solvents were removed on the rotary evaporator and the residue was extracted into $CHCl_3$. After the extract was dried (Na_2SO_4) and the solvent was removed, a yellow oil remained that crystallized on standing. Recrystallization from EtOH–H_2O produced 3 g of **9**, mp 47–53°. Recrystallized several times for analysis, the pure compound melted at 58–59°: nmr ($CDCl_3$) normal ethyl ester pattern, δ 2.57 (s, 3 H, oxadiazole CH_3), 2.60 (d, 3 H, vinyl CH_3), 6.70 (m, 1 H, vinyl H); ir (Nujol) no NH, 1730 (C=O), 1650 (C=C), 1580 and 1540 cm^{-1} (C=N).

Anal. Calcd for $C_9H_{12}N_2O_3$: C, 55.09; H, 6.16; N, 14.28. Found: C, 55.34; H, 6.06; N, 14.05.

Reaction of Aluminum Azide with Ethyl *cis*-3-Cyanocrotonate.—Ethyl *cis*-3-cyanocrotonate prepared with the trans compound above was treated on a 0.8-mol scale just as was the trans isomer except that it was refluxed for 42 hr. The brown oil that remained after removal of the THF was taken up in 300 ml of H_2O and 300 ml of $CHCl_3$. A crystalline solid separated; so the mixture was filtered and the solid was washed with H_2O and $CHCl_3$. Dried in air, it weighed 13.1 g, mp 202–204°. Recrystallization for analysis from acetone or from EtOH gave 8-methyltetrazolo-[1,5-*c*]pyrimidin-5(6*H*)-one (**11**): mp 210–211°; nmr (DMSO-d_6) δ 2.28 (d, 3 H, vinyl CH_3), 7.55 (m, 1 H, vinyl H); ir (Nujol) 3260–3180 (NH), 1790 (shoulder), 1770, 1730, 1640, 1550 cm^{-1} (C=O, C=C, C=N, N=N); mass spectrum m/e 151 (M^+), 122 [$(M - N_2 - H)^+$], 68 [$(C_3H_4N_2)^+$]; uv (H_2O) max 252 mμ (ϵ 9050), shoulder at 275.

Anal. Calcd for $C_5H_5N_5O$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.40; H, 3.36; N, 46.26.

The two-phase filtrate layers were separated and the aqueous layer was washed twice with $CHCl_3$. The combined $CHCl_3$ layers were dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure. The residue was a brown oil containing fine crystals which after standing several days were collected, washed with $CHCl_3$ and CCl_4, and dried to yield 2.88 g of 1-(2-cyanopropenyl)tetrazolin-5(4*H*)-one (**12**), mp 168–170° dec. A sample recrystallized for analysis from acetone–$CHCl_3$ melted at 186–187°: nmr (acetone-d_6) δ 1.43 (d, 3 H, vinyl CH_3), 6.48 (m, 1 H, vinyl H); ir (Nujol) 3100 (NH), 2220 (C=N), 1740, 1660 cm^{-1} (C=O, C=C).

Anal. Calcd for $C_5H_5N_5O$: C, 39.73; H, 3.33; N, 46.34. Found: C, 39.31; H, 3.36; N, 45.79.

1-(2-Methylpropenyl)tetrazolin-5(4*H*)-one (14).—To a suspension of 66.7 g of $AlCl_3$ and 146 g of NaN_3 in 1 l. of cold anhydrous THF was added 64.1 g of ethyl β,β-dimethylacrylate (**13**) and the resulting mixture was heated to reflux under nitrogen for 43 hr. To the cooled reaction was added 700 ml of 6 *N* HCl and the reaction solution was filtered from the inorganic salt. The THF was removed from the filtrate under reduced pressure and the remaining solution was extracted three times with $CHCl_3$. The combined $CHCl_3$ layers were washed twice with saturated NaCl solution, dried (Na_2SO_4), and evaporated to yield a light yellow oil weighing 51.6 g. Crystals formed on standing and were filtered, washed with hexane, and dried, yield 7.78 g. A second crop weighed 9.1 g. These were combined (24% yield) and recrystallized from 50 ml of $CHCl_3$–hexane to give 15.3 g of 1-(2-methylpropenyl)tetrazolin-5(4*H*)-one (**14**), mp 69–71°. A sample recrystallized for analysis from the same solvents melted at 72–73°: nmr (acetone-d_6) δ 1.82 and 1.88 (each d, 3 H, vinyl CH_3), 6.29 (m, 1 H, vinyl H); ir (Nujol) 3200–3000 (NH), 1740 (C=O), 1700 cm^{-1} (C=C).

Anal. Calcd for $C_5H_8N_4O$: C, 42.85; H, 5.75; N, 39.98. Found: C, 42.79; H, 5.73; N, 40.58.

Reaction of Aluminum Azide with Ethyl *o*-Cyanobenzoate (15).—A mixture of 0.4 mol of ethyl *o*-cyanobenzoate,[2] 0.4 mol of $AlCl_3$, and 1.78 mol of NaN_3 in 1 l. of anhydrous THF was refluxed for 45 hr under N_2 as before. The precipitate formed by addition of 600 ml of 6 *N* HCl was washed with THF and then partially dissolved in 500 ml of H_2O. The residual H_2O-insoluble crystalline solid, 3.7 g, was pure **19**. The THF acid filtrate was evaporated and the solid suspended in the remaining aqueous phase was collected, washed with H_2O and $CHCl_3$, and dried in air to yield 20.0 g of a mixture of **19** and **16** as shown by tlc.[14]

The H_2O layer was extracted twice more with 200-ml portions of

(14) Solvent system used was the top phase of an equilibrated mixture of 4 parts ethyl acetate, 1 part *n*-PrOH, and 2 parts H_2O.

$CHCl_3$ and the combined $CHCl_3$ layers were washed two times with 100 ml of H_2O, dried (Na_2SO_4), and evaporated to leave a solid residue weighing 52.4 g. Acetone (70 ml) was added and on refrigeration, 12.6 g of crystals formed which was a mixture of starting material **15**, **19**, and **17**. The various components were obtained in a pure form, but were not quantitatively isolated by fractional crystallization. The unreacted starting material had the highest solubility in benzene and could be removed by trituration with that solvent. Compound **19** could be recrystallized from large volumes of acetone or EtOH, while compound **16** could be purified by recrystallization from acetone or EtOH after most of the **19** was removed. Compound **17** was obtained by careful fractionation of the mother liquors and could be recrystallized from benzene. Compound **18** could not be obtained in a pure form from this mixture, but was isolated from the product resulting when methyl *o*-cyanobenzoate was used as a substrate.

The following amounts of pure materials were isolated: **19**, 15.8 g; **16**, 7.56 g; and **17**, 0.66 g. Tlc showed larger amounts of starting material and **16**, **17**, **18**, and some **19** present as complex mixtures in the residues which totaled 48 g. Of this 48 g about 35 g was unreacted starting cyanobenzoate.

Tetrazolo[1,5-*c*]quinazolin-5(6*H*)-one (19) had mp 274.5–275.5° dec; nmr (DMSO-d_6) δ 8.3–7.2 (m, 4 H, aromatic H); ir (Nujol) 3300 and 3250 (NH), 1770, 1730 (C=O), 1640, 1600, 1560, 1510 cm^{-1}; mass spectrum *m/e* 187 (M^+), 159 ($M^+ - N_2$), 131 ($M^+ - N_2 - CO$), 104 ($M^+ - C_2HN_3O$); uv (methanol) max 306 mμ (ϵ 4900), max 250 (14,100), max 219 (40,300); uv (alkaline methanol) max 326 mμ (ϵ 4900), max 271 (7500), max 207 (371,100).

Anal. Calcd for $C_8H_5N_5O$: C, 51.34; H, 2.69; N, 37.42. Found: C, 51.28; H, 2.84; N, 37.03.

1-[*o*-(Tetrazol-5-yl)phenyl]tetrazolin-5(4*H*)-one (16) had mp 262–263° dec; nmr (DMSO-d_6) δ 8.2–7.6 (m, 4 H, aromatic H); ir (Nujol) 3100–2700 (NH), 1690 (C=O), 1610, and 1555 cm^{-1}. Titration with NaOH showed two acidic protons and gave mol wt 230.6 compared to the theoretical value of 230.2.

Anal. Calcd for $C_8H_6N_6O$: C, 41.74; H, 2.63; N, 48.68. Found: C, 42.05; H, 2.82; N, 50.01.

Ethyl *o*-(5-tetrazolyl)benzoate (17) had mp 141–142°; nmr (acetone-d_6) δ 1.20 (t, 3 H, ester CH_3), 4.25 (q, 2 H, ester CH_2), 8.1–7.5 (m, 4 H, aromatic); ir (Fluorolub/Nujol) 3000–2600 (NH), 1725 (C=O), 1275 (C=C), 1090, and 1070 cm^{-1} (tetrazole).

Anal. Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.62; N, 25.68. Found: C, 55.09; H, 4.63; N, 26.07.

***o*-(5-Oxo-2-tetrazolin-1-yl)benzonitrile (18)**.—This material was obtained pure from work-up of an exactly identical reaction of methyl *o*-cyanobenzoate with $Al(N_3)_3$. Compounds **19** and **16** were isolated as before with identical work-up, but no material corresponding to the methyl analog of the tetrazole ester **17** could be detected. Pure **18** melted at 146–148°: ir (Nujol) 3200–3000 (NH), 2225 (CN), 1740, 1720, 1700 (C=O), 1610, 1580, 1570, 1540 cm^{-1}.

Anal. Calcd for $C_8H_5N_5O$: C, 51.34; H, 2.69; N, 37.42. Found: C, 51.39; H, 2.70; N, 37.94.

Alkaline Hydrolysis of 19.—A solution of 2 g of **19** dissolved in 40 ml of 1 *N* NaOH was warmed on the steam bath for 1 hr. The resulting yellow solution was cooled and diluted to 60 ml. It was carefully acidified to pH 6 with 6 *N* HCl. A vigorous evolution of CO_2 was observed and near pH 6 the solution turned cloudy and needle-like crystals of **21** began to form. The mixture was filtered and the crystals, washed with water and dried, weighed 0.6 g. Further acidification to pH 3 caused more crystallization and another 0.59 g of **21** was isolated. The combined crystals were recrystallized from $CHCl_3$. The melting point after 2 hr drying under reduced pressure was 143–144° (lit.[10] mp 140–144°); ir (Nujol) 3500–3300 (NH), 1620, 1560 cm^{-1}; mass spectrum *m/e* 161 (M^+). This material proved to be identical with that produced from anthranilonitrile below.

5,6-Dihydro-5,5-dimethyltetrazolo[1,5-*c*]quinazoline (23).—To a mixture of 2 g of **21** in 30 ml of $CHCl_3$ was added 5 ml of acetone and the solution was boiled until crystals formed in the hot solution. Filtered and dried in air, the crystals of **23** weighed 1.48 g, mp 202–204°. Mixture melting point with **23** prepared from **21** obtained from anthranilonitrile was undepressed; nmr (acetone-d_6) δ 1.80 (s, 6 H, CH_3) 8.0–7.0 (m, 4 H, aromatic); ir (Fluorolub/Nujol) 3340 (NH), 1630 (C=N), 1590, 1540, 1500 cm^{-1}; mass spectrum *m/e* 201 (M^+).

Anal. Calcd for $C_{10}H_{11}N_5$: C, 59.69; H, 5.51; N, 34.80. Found: C, 59.85; H, 5.66; N, 34.92.

5-(*o*-Aminophenyl)tetrazole (21) from Anthranilonitrile.—A mixture of 59.1 g (0.5 mol) of anthranilonitrile, 42.3 g (0.65 mol) of NaN_3, 0.65 g (0.65 mol) of NH_4Cl, and 0.65 g of LiCl in 250 ml of DMF was heated and stirred at 125° for 16 hr. The reaction was filtered hot, the solid was washed with a little solvent, and the DMF was removed under reduced pressure. The residue was poured into 750 ml of water, and a yellow oil separated which was extracted into three portions of $CHCl_3$. The aqueous layer was acidified to pH 3–4 and a yellow crystalline solid separated. It was filtered, washed with water, and dried in air and weighed 15 g (**21**). The $CHCl_3$ extracts crystallized on standing, yielding another 18.7 g of **21**. The product could be recrystallized from $CHCl_3$ and proved identical with the **21** isolated from **19**.

Ethyl *o*-Tetrazol-5-ylcarbanilate (24).—To a solution of 10 g of 5-(*o*-aminophenyl)tetrazole (**21**) in 20 ml of absolute EtOH was added about 5 g of K_2CO_3 and then, with stirring, 10 g of ethyl chloroformate. The reaction solution warmed and foamed. When the effervescence ended and no further warming was apparent (5–10 min) the reaction was filtered from the insoluble salt. The filtrate was diluted to 250 ml with H_2O and a white, crystalline precipitate formed. Filtered, washed with H_2O and partially dried, it was redissolved in 75 ml of EtOH. H_2O was added carefully to the point of incipient precipitation and crystals of **24** separated. Filtered, washed with H_2O–EtOH, and dried in air, the crystals weighed 12.5 g, mp 140–141°. Recrystallized for analysis from EtOH–H_2O, the compound lost solvent at 120°, melted at 147–150°, bubbled at 180°, recrystallized at 220°, and remelted at 265°: nmr (DMSO-d_6) δ 1.40 (t, 3 H, ethyl CH_3), 4.28 (q, 2 H, ethyl CH_2), 8.4–7.0 (m, 4 H, aromatic); ir (Nujol) 3200 (NH), 1710 (shoulder), 1700 (C=O), 1620, 1600, 1550 cm^{-1}.

Anal. Calcd for $C_{10}H_{11}N_5O_2$: C, 51.50; H, 4.75; N, 30.03. Found: C, 51.44; H, 4.93; N, 30.02.

Pyrolysis of Carbanilate 24.—Carbanilate **24** (5 g) was heated to 200°, by which time the resulting melt was bubbling and had turned brick red. The heating bath was maintained at 195° for about 15–20 min until the melt suddenly solidified. The reaction was cooled and triturated with 30 ml of EtOH. The insoluble solid was collected on a filter, washed with EtOH, and dried to leave 1.67 g (42%) of a fine yellow solid, mp 271–272°. Recrystallized from 900 ml of hot acetone, filtered, and concentrated to 100 ml, the crystals that formed weighed 0.96 g and were identical with the previously isolated **19** from the aluminum azide reaction in every respect.

Synthesis of 19 *via* the Reaction of Phosgene with 21.—Phosgene was bubbled through a clear solution of 3.2 g of **21** and 4.0 g of Et_3N in 150 ml of CH_2Cl_2 for 5 min. A precipitate formed after 2 min but the reaction was stirred for a total of 20 min, then treated with excess dilute HCl and filtered, and the solid was washed with H_2O. The damp solid was dissolved in 900 ml of hot acetone, concentrated to 300 ml, diluted to 400 ml with H_2O, and allowed to crystallize. The product **19** weighed 2.4 g (64%) after filtration and drying, mp 273–274°, identical with material obtained by other methods above.

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Interaction of Carbonyl Compounds with Organometallic Azides. V. Sorboyl Chloride and Its Conversion to an α-Pyridone[1]

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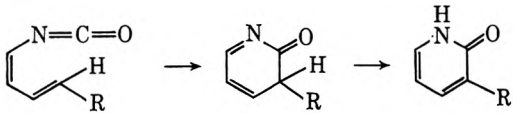
Electrocyclic ring closure of α,β-*cis*-1,3-pentadienyl isocyanate affords 3-methyl-2(1*H*)-pyridone in fair yield. The isocyanate is formed in good yield by treatment of sorboyl chloride with trimethylsilyl azide in refluxing toluene. In refluxing heptane this reaction affords tetrazolinone **6** rather than isocyanate. The sensitive pentadienyl isocyanate is converted to polymer by either pyrolysis or acid treatment.

Intense current interest in electrocyclic reactions[2] has generated novel synthetic routes to numerous ring systems, particularly those accessible by thermally allowed disrotatory six-electron bond reorganizations. The apparent substituent shift shown by Pirkle to obtain in the α-pyrone series is an example,[3] as is the aza-Cope rearrangement leading to dihydroazepinones uncovered by Ohno.[4]

Since the N=C linkage of the isocyanate has been shown to be a willing participant in electrocyclization reactions, we thought that an α,β-cis-diene isocyanate, *e.g.*, **1**, would cyclize to **2** under thermal conditions. A facile 1 → 5 suprafacial hydrogen shift[2] would then convert **2** to the thermally more stable tautomer **3**.



cis-**1** **2** **3**

However, alkenyl isocyanates are particularly sensitive toward hydrolysis to aldehydes *via* the sequence >C=CN=C=O → >C=CNHCO$_2$H → >C=CNH$_2$ → >CHCH=O. *o*-Nitrocinnamic acid gives *o*-nitrophenylacetaldehyde in meager yield upon attempted Schmidt reaction.[5] Pure diene isocyanates are unknown.

The recently reported isocyanate synthesis *via* silyl azides[1,6] offers a route to diene isocyanates under nearly neutral conditions. The ready availability of sorbic acid prompted us to investigate the chemistry of 1,3-pentadienyl isocyanate (**1**). Commercial sorbic acid **4** exists as a single, sharp-melting, all-trans isomer,[7a,b] while the α,β-cis isomer of **4** is required for electrocyclization of the corresponding isocyanate, **1**.

$$\underset{\mathbf{4}}{CH_3CH{=}CHCH{=}CHCO_2H} \xrightarrow[2.\ Me_3SiN_3]{1.\ SOCl_2} \underset{\mathbf{1}}{CH_3CH{=}CHCH{=}CHN{=}C{=}O}$$

This acid is a low-melting, readily polymerizing material,[7c] and its transformation to an acid chloride seemed remote. However, the various isomers of sorbaldehyde are equilibrated by vapor phase thermolysis,[8] and we hoped that the various isomers of **1** would equilibrate, affording some α,β-cis material which could cyclize rather than polymerize.

Results

Refluxing trimethylsilyl azide and sorboyl chloride (which appeared from nmr to contain at least two isomers) in toluene resulted in a 90% yield of nitrogen. Infrared analysis showed the presence of isocyanate, together with a strong band at 1770 cm^{-1}. Distillation gave a lachrymatory liquid which readily resinified. The uv spectrum, intense ir absorption at 2300 cm^{-1}, and the nmr spectrum indicated that it was 1,3-pentadienyl isocyanate (**1**). However, the complexity of the nmr olefinic region resisted attempts to decouple resonances, precluding determining if this sensitive material was a mixture of isomers.

If the above product mixture was heated at reflux in *o*-dichlorobenzene, a decrease in intensity of the 2300- and 1770-cm^{-1} peaks and the gradual growth of a new peak at 1660 cm^{-1} occurred. When the intensity of the new peak was maximized (estimated by quantitative ir analysis to correspond to a yield of 30%), work-up gave a 17% yield (from sorboyl chloride) of 3-methyl-2(1*H*)-pyridone (**3**) whose physical and spectral properties were consistent with literature values. This cyclization is subject to either a solvent or a temperature effect, since the yield in refluxing xylene or mesitylene was less than 5%.

In an effort to improve the yield of the cyclization **1** → **3**, the semisolid product mixture, dissolved in chloroform, was pyrolyzed at 400° in a nitrogen flow system. The pyrolysate contained only traces of **3**, together with unreacted **1** and moderate quantities of carbonaceous material. Under the pyrolysis conditions pyridone **3** was completely stable.

Attempted acid-catalyzed cyclization of **1** with trifluoroacetic acid gave only a brown polymer.

The origin of the 1770-cm^{-1} band in the product ir of the toluene reaction mixture is intriguing. Refluxing heptane solutions of azide and sorboyl chloride gave a white power, $C_{12}H_{14}N_4O_2$, assigned structure **6** on the basis of spectral evidence. Tetrazolinone **6** is apparently formed by cycloaddition of sorboyl azide **5** (initial product of trimethylsilyl azide and sorboyl chloride) with **1**. Similar tetrazolinone-yielding reactions of

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(7) (a) Treatment of **4** with diazomethane gave the methyl ester whose nmr olefinic region was simplified with the use of Eu(FOD)$_3$. The spectra confirms an all-trans stereochemistry for commercial **4**. Full details will be published later. (b) U. Eisner, J. A. Elvidge, and R. P. Linstead, *J. Chem. Soc.*, 1372 (1953). (c) J. A. Elvidge and P. D. Ralph, *J. Chem. Soc. B*, 241 (1966).

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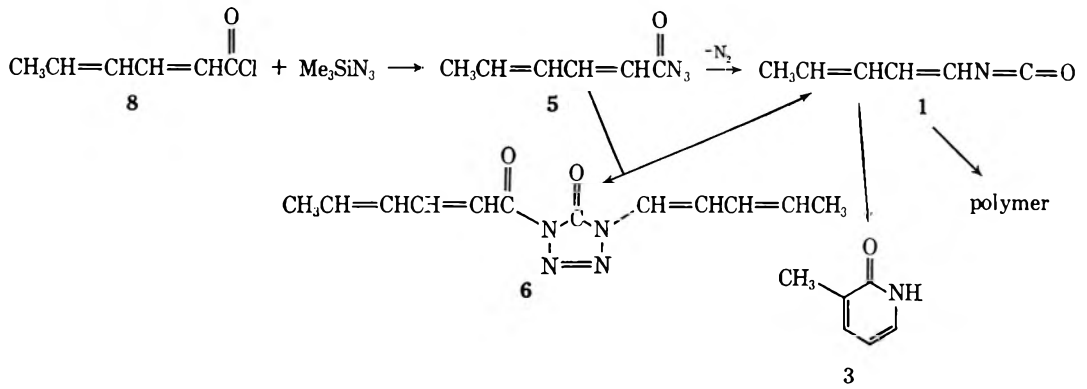
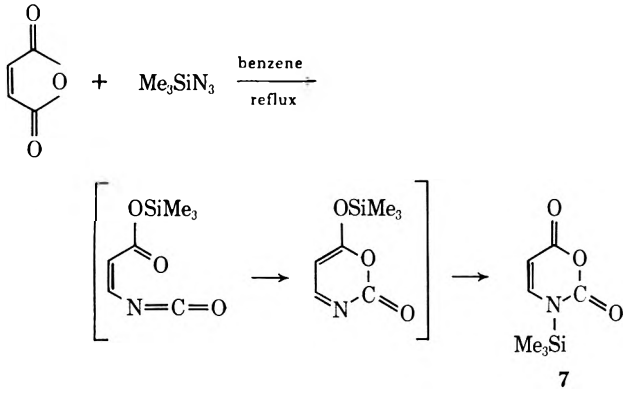


azides with isocyanates bearing electron-withdrawing groups are known.[9]

Heating **6** in refluxing *o*-dichlorobenzene gave only polymeric material, in accord with the known cycloreversion of tetrazolinones.[9a] Cycloreversion of **10** would give two molecules of the readily polymerizing **1**.

Discussion

The **1** → **3** cyclization bears formal analogy to the previously reported synthesis of oxazinedione **7** from



maleic anhydride and trimethylsilyl azide,[6b] which is now seen as an electrocyclic ring closure followed by a suprafacial 1,5 shift of trimethylsilyl. **1** → **3** cyclization requires a higher temperature, in accord with the known acceleration of the Cope rearrangement by –OR substituents.[10]

Although sorboyl chloride is converted to 3-methyl-2(1*H*)-pyridone upon silyl azide treatment, the yield is low and subject to two restraints. At low reaction temperatures, unrearranged sorboyl azide **5** accumulates and diverts isocyanate by cycloaddition to **6**. At higher temperatures, isocyanate polymerizes. In addition, only about 30% of **1** appears to be in the cis form capable of cyclization. Optimum conditions are high dilution at a temperature where Curtius rearrangement of **5** is rapid and sufficient activation energy for the **1** → **3** cyclization is available, but where polymerization of **1** is slow. The toluene reaction apparently maximizes the yield of **1**.

Since the spectroscopic yield of **6** was greater than the observed α,β-cis population (11%) of thermolyzed sorbaldehyde,[8] we postulate that an acid-catalyzed equilibrium is present, resulting in the formation of considerable α,β-cis **1**. At lower temperatures, as in the attempted trifluoroacetic acid isomerization of **1**, the high-energy electrocyclic process yielding pyridone cannot compete with acid-catalyzed polymerization. This postulate is also consistent with the observed low yield of pyridone in the vapor phase reaction and with the low yield in mesitylene and xylene.

Experimental Section

General Comments.—All reactions involving azides were carried out under a blanket of purified nitrogen, behind appropriate shielding. Sorbic acid (Fisher) and trimethylsilyl azide (Petrarch Systems) were used as received. Infrared spectra were determined on a Perkin-Elmer Model 700 or 720 spectrophotometer, ultraviolet spectra on a Cary Model 14 spectrophotometer, and nuclear magnetic resonance spectra on a Varian XL-100-15 spectrometer as dilute solutions in deuteriochloroform or carbon tetrachloride with tetramethylsilane as internal standard. Nmr spectra are reported in δ units, parts per million downfield from tetramethylsilane.

Sorboyl Chloride (8).—Thionyl chloride (13 ml) was added over a 1.5-hr period to a warm (60°) solution of 5.6 g (0.05 mol) of sorbic acid in 160 ml of benzene. After the mixture had been heated at reflux for 16 hr, material boiling up to 81° was removed by distillation. Fractionation of the brown residue gave 5.3 g (81%) of **8**: bp 75° (20 mm); ir 1750, 1620 cm^{-1}; nmr δ 7.30 and 7.70 (total 1 H, multiplets, HC=CCOCl), 5.8–6.6 (3 H, multiplet, olefinic), and 1.9 ppm (total 3 H, two doublets, J = 5 Hz, CH_3CH=).

1,3-Pentadienyl Isocyanate (1).—Trimethylsilyl azide (5.6 g, 0.05 mol) was added to a refluxing solution of 5.0 g (0.038 mol) of **8** in 70 ml of toluene. After heating for 20 hr at reflux, the mixture had evolved 750 ml of N_2. Ir analysis showed intense N=C=O absorption (2300 cm^{-1}) as well as moderate absorption at 2150 ($RCON_3$) and 1770 cm^{-1}. Removal of the toluene by evaporation at reduced pressure gave highly variable quantities (0.1–1.5 g) of **1**, bp 40° (20 mm), together with a polymeric brown residue. Pure **1** rapidly resinified and was handled in dilute $CHCl_3$ or CCl_4 solution: ir (film) 3050 (m), 3020 (m), 2960 (m), 2930 (m), 2300 (vs), 1620 (s), 1490 (m), 1440 (m), 1380 (m), 1320 (m), 1260 (m), 980 (s), 920 (m), and 600 cm^{-1} (m); nmr δ 5.9 (4 H, m) and 1.7 ppm (3 H, d, J = 5 Hz); uv max (heptane) 247 nm (log ϵ 4.4).

3-Methyl-2(1*H*)-pyridone (3).—The reaction described above for preparation of **1** was carrried out up to removal of the toluene. The semisolid was taken up in 190 ml of *o*-dichlorobenzene and heated at reflux. Ir analysis of periodically removed samples showed a steady decrease in absorption at 2300, 2150, and 1770 cm^{-1} together with the growth of a new peak at 1660 cm^{-1}. After 16 hr at reflux the yield of **3** was maximized at 30% (by ir analysis assuming ϵ 500 at 1660 cm^{-1}). Attempts to increase conversion to **3** by adding hydroquinone to inhibit polymerization failed, giving only hydroquinone-contaminated product. The yield of **3** in reactions using xylene or mesitylene as solvent was less than 5% as estimated by ir.

The mixture was cooled and solvent was removed by evaporation at reduced pressure, resulting in loss of some **3** by codistillation (distillate showed absorption at 1660 cm^{-1}). Sublimation (150°, 0.025 mm) of the residue gave 0.7 g (17%) of **3**, mp 130–

(9) (a) J. M. Vandensavel, G. Smets, and G. L'abbé, *J. Org. Chem.*, **38**, 676 (1973); (b) S. S. Washburne and W. R. Peterson, Jr., unpublished results.

(10) J. A. Berson and E. J. Walsh, Jr., *J. Amer. Chem. Soc.*, **90**, 4730 (1968).

140°. Recrystallization from benzene gave white crystals of **3**: mp 140–141° (lit.[11] mp 140–141.5°); picrate mp 158–160° (lit.[11] mp 157.5–159°); ir ($CHCl_3$) 2780, 1660, 1640, 1610, 1570, 1480, 1420, 1380, 1350, 1255, 1230, 1164, 986, 885, 775, 735 cm^{-1} (in complete accord with literature[12] ir); nmr ($CDCl_3$) δ 13.4 (broad s, 1, NH), 7.25 (d, 2, J = 7 Hz), 6.1 ppm (t, 1, J = 7 Hz) (in complete accord with literature[13] nmr).

Anal. Calcd for C_6H_7NO: C, 66.04; H, 6.47; N, 12.84. Found: C, 66.24; H, 6.61; N, 12.88.

Vapor-Phase Pyrolysis of 1,3-Pentadienyl Isocyanate (1).—A 30 × 2.5 cm Pyrex column packed with glass helices and swept with a nitrogen stream was employed. The inlet was a septum cap allowing material to be syringe injected. The semisolid product obtained by the procedure for 1 above was taken up in $CHCl_3$ (20 ml). The oven was heated to 400° in a tube furnace and the material was injected in 1-ml portions with nitrogen sweeping the pyrolysate into a trap at −78°. Considerable carbonization was noticed in the pyrolysis zone. Ir analysis of the pyrolysate showed an intense band at 2300 cm^{-1} (1) but only a faint absorption at 1660 cm^{-1} (3). Peaks at 1770 (6) and 2150 cm^{-1} (5) had totally disappeared. Tlc analysis of the pyrolysate showed a faint spot of R_f corresponding to authentic **3** and an intense spot corresponding to 1 (silica gel, 10% *i*-PrOH in $CHCl_3$).

Pyrolysis of 3.—A solution of 50 mg of **3** in 1 ml of $CHCl_3$ was pyrolyzed in an identical fashion. No carbonization in the tube was observed, and the pyrolysate exhibited an unchanged ir spectrum.

Attempted Acid-Catalyzed Isomerization of 1.—A solution of *ca.* 250 mg of 1 in 5 ml of $CHCl_3$ exhibited an unchanged ir spectrum after being stored for 16 hr with 0.15 ml of trifluoroacetic acid. An additional 0.1 ml of CF_3CO_2H was added and the mixture was heated at reflux for 36 hr. The ir of the brown mixture showed no absorption at 2300 or 1660 cm^{-1}. The tlc showed no spot of R_f corresponding to **3**.

Tetrazolinone 6.—A refluxing solution of 4.9 g (0.037 mol) of **8** in 30 ml of heptane was treated over an 0.5-hr period with 5.8 g (0.05 mol) of trimethylsilyl azide. After 16 hr, 600 ml of N_2 had been evolved and a white powder had separated from the solution. Cooling and filtration gave 2.5 g (55%) of **6**: mp 161–162° (colorless crystals from benzene); ir ($CHCl_3$) 3030 (m), 1770 (s), 1730 (s), 1610 (s), 1600 (s), 1580 (s), 1500 (m), 1400 (m), 1380 (m), 1320 (s), 1250 (m), 1200 (s), 1140 (m), 1090 (m), 980 (m), 960 (s), 910 (m), 840 (m), and 640 cm^{-1} (s); nmr ($CDCl_3$) δ 7.6 (m, 1, HC≡CC=O), 6.0–6.9 (m, 7, olefinic), 1.8 ppm (d of d, 6, J = 5 Hz, CH_3CH=C); uv max (heptane) 285 nm (log ϵ 4.4); uv max (heptane, OH^-) 265 nm (log ϵ 4.5); mass spectrum *m/e* (rel intensity) 247 (4), 246 (27), 152 (7), 137 (6), 109 (22), 95 (100), 81 (20), 80 (19), 67 (34), 54 (22), 41 (42), 39 (35).

Anal. Calcd for $C_{12}H_{14}O_2$: C, 58.53; H, 5.73; N, 22.75. Found: C, 58.01; H, 5.42; N, 22.97.

Thermolysis of 6.—A solution of 50 mg of **6** in 3 ml of *o*-dichlorobenzene was heated at 180° for 16 hr. The solution turned brown and deposited a black polymeric material. Ir analysis showed the absence of absorption at 1770, 1730, and 1660 cm^{-1}, implying that **6** had been consumed but that **3** had not been formed.

Acknowledgments.—This investigation was sponsored under Grant No. CA-13120-01 from the National Cancer Institute. We thank Mr. John Simolike for obtaining the mass spectra.

Registry No.—1, 40711-07-7; **3**, 1003-56-1; **4**, 110-44-1; **6**, 40711-50-0; **8**, 2614-88-2.

(11) G. F. van Rooyen, C. Brink, and P. de Villiers, *Tydskr. Natuurwetensk.*, **4**, 182 (1964); *Chem. Abstr.*, **63**, 13202d (1965).

(12) E. Spinner and J. C. B. White, *J. Chem. Soc. B*, 991 (1966).

(13) C. L. Bell, R. S. Egan, and L. Bauer, *J. Heterocycl. Chem.*, **2**, 420 (1965).

Diaziridines. II. The Addition of Diaziridines to Electrophilic Acetylenes[1]

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Addition of 3,3-dialkyl-, 1,3-dialkyl-, and 1,3,3-trialkyldiaziridines to dibenzoylacetylene, diethyl acetylenedicarboxylate, and ethyl propiolate gives, generally, adducts in which the diaziridine ring is no longer intact. For example, addition of 1,3-dialkyl- and 1,3,3-trialkyldiaziridines to dibenzoylacetylene forms 2-(alkylidenehydrazino)-1,4-diphenyl-2-butene-1,4-diones (**2**). Evidence is presented that it is the alkylated nitrogen of 1-methyl-3,3-pentamethylenediaziridine which adds to the triple bond of dibenzoylacetylene. Stereochemical studies show that diaziridines add to ethyl propiolate to give trans adducts. Hydrolysis of 2-(alkylidenehydrazino)-1,4-diphenyl-2-butene-1,4-diones is shown to be a useful method for the preparation of 1-alkyl-3-phenyl-5-benzoylpyrazoles.

Only a few studies have been reported on the addition of N-unsubstituted or N-monosubstituted diaziridines to alkenes. Miller has found that 3-ethyl-3-methyldiaziridine adds to acrylonitrile and to butenone to form 1-(β-cyanoethyl)-3-ethyl-3-methyldiaziridine and 1-(β-acetylethyl)-3-ethyl-3-methyldiaziridine, respectively.[2] 1,3,3-Trialkyldiaziridines have been shown to react similarly with esters of ethenesulfonic acid.[3] The reaction of 3,3-pentamethylenediaziridine with diphenylcyclopropenone has also been described.[4] Based on the products of reaction it was presumed that the diaziridine added to the carbonyl group rather than the olefinic linkage

No investigations have yet been reported on the addition of diaziridines to electrophilic acetylenes. We have observed that, in contrast to aziridines which have been shown to add to a number of acetylenes to give *N*-vinylaziridines,[5] diaziridines usually react with activated acetylenes to give products in which the diaziridine ring is no longer intact.

Results

Diaziridines **1a–f** react with dibenzoylacetylene in benzene at ambient temperatures to give the 2-(alkylidenehydrazino)-1,4-diphenyl-2-butene-1,4-diones **2a–f** (Table I) (Scheme I).

The nmr spectra of **2a–f** were consistent with the proposed structures. Thus, a singlet (1 H) corresponding to the vinyl proton appeared in the region of δ 5.6–6.4 for all of these compounds. Furthermore, the

(1) For the previous paper in this series, see H. W. Heine, P. G. Williard, and T. R. Hoye, *J. Org. Chem.*, **37**, 2980 (1972).

(2) J. Miller, British Patent 1,081,292 (Aug 30, 1967); *Chem. Abstr.*, **68**, 114071h (1968).

(3) H. Dorn and K. Walter, *Justus Liebigs Ann. Chem.*, **720**, 98 (1968).

(4) J. W. Lown, *J. Chem. Soc. C*, 1338 (1969).

(5) O. C. Dermer and G. E. Ham, "Ethylenimine and Other Aziridines," Academic Press, New York, N. Y., 1969, p 138.

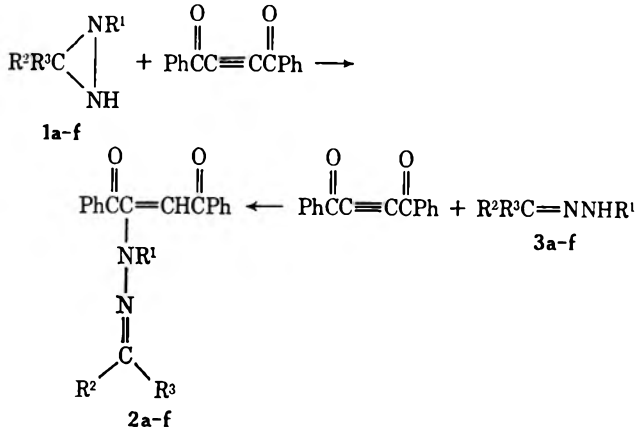
TABLE I

2-(ALKYLIDENEHYDRAZINO)-1,4-DIPHENYL-2-BUTENE-1,4-DIONES FROM THE REACTION OF DIBENZOYLACETYLENE WITH DIAZIRIDINES[a]

	$R^2R^3C{=}NN(R^1)C(COC_6H_5){=}CHCOC_6H_5$				
Compd	R^1	R^2	R^3	Crude yield, %	Mp, °C
2a	H	CH_3	CH_3CH_2	87	97–100
2b	CH_3	CH_3	CH_3	17	143–145
2c	$(CH_3)_2CH$	CH_3	CH_3	47	180–181
2d	CH_3	$CH_2CH_2CH_2CH_2CH_2$		98	114–119
2e	$CH_3CH_2CH_2CH_2$	H	CH_3CH_2	68	142–143
2f	$CH_3CH_2CH_2CH_2$	H	$CH_3CH_2CH_2$	68	86–88

[a] Satisfactory analytical data for C, H, and N were reported for all new compounds listed in the table: Ed.

SCHEME I



1a–f

3a–f

2a–f

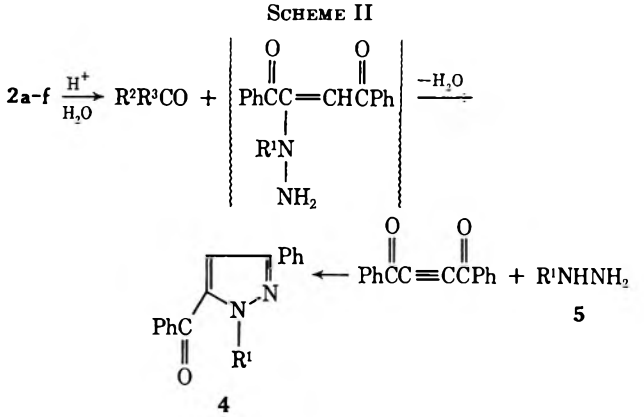
a, $R^1 = H$; $R^2 = CH_3$; $R^3 = CH_3CH_2$
b, $R^1 = R^2 = R^3 = CH_3$
c, $R^1 = (CH_3)_2CH$; $R^2 = R^3 = CH_3$
d, $R^1 = CH_3$; $R^2R^3 = -(CH_2)_5-$
e, $R^1 = CH_3(CH_2)_3$; $R^2 = H$; $R^3 = CH_3CH_2$
f, $R^1 = CH_3(CH_2)_3$; $R^2 = H$; $R^3 = CH_3CH_2CH_2$

nmr spectra of **2e** and **2f** exhibited two triplets centered at approximately δ 3.8 (2 H) and 7.1 (1 H). The downfield triplets in both these cases were assigned to the N=CH protons and the upfield triplets were assigned to the methylene groups bonded to the saturated nitrogen atom.

The structures of **2a–f** were unequivocally established by an alternate synthesis involving the addition of the corresponding hydrazones **3a–f** to dibenzoylacetylene (Scheme I).

Further confirmation for the structures assigned to **2a–f** was obtained by the acid hydrolysis of these substances into 1-alkyl-3-phenyl-5-benzoylpyrazoles (**4**) (Scheme II). These pyrazoles were also prepared by

SCHEME II



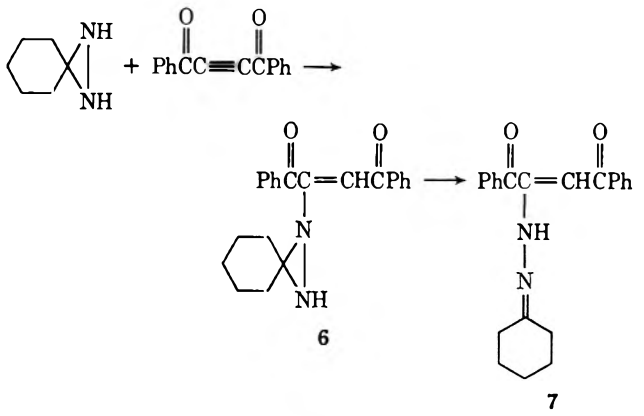
4

5

adding appropriate alkylhydrazines (**5**) to dibenzoylacetylene. The hydrolysis of **2a–f** is a reaction of synthetic importance because the position of the N substituent relative to the other substituents on the pyrazole ring is unequivocal. Some of the methods employed in the past to form N-substituted pyrazoles (such as the alkylation or arylation of unsymmetrically substituted pyrazoles) yield two isomeric products often difficult to separate.[6] The preferred method of preparation of **4**, at least for the present, is the addition of *N*-alkyldiaziridines to dibenzoylacetylene followed by the hydrolysis of the resulting **2**. This method is more convenient than the addition of **5** to dibenzoylacetylene since many of the alkylhydrazines **5** are not readily available except by the hydrolysis of the corresponding diaziridines.

One diaziridine, namely, 3,3-pentamethylenediaziridine, added to dibenzoylacetylene in benzene to form **6**, a product in which the diaziridine ring is still intact (Scheme III). However, with but mild heating

SCHEME III



6

7

in 95% ethanol, **6** rapidly rearranged to **7**. Compound **6** also rearranged into **7** in a nmr tube containing chloroform and 1 drop of deuterium oxide.

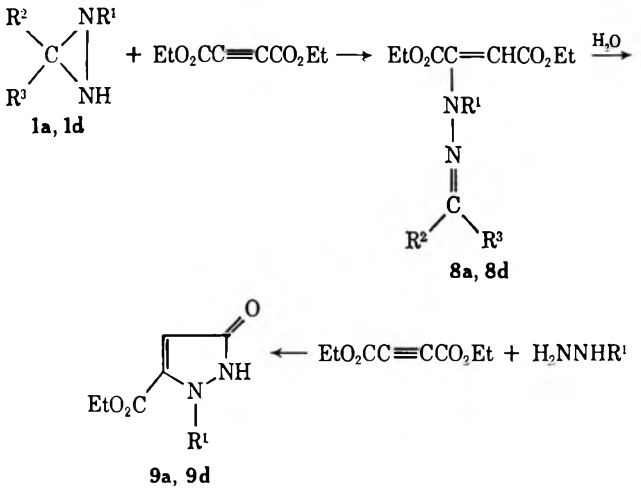
The structures of **6** and **7** were confirmed by nmr spectroscopy. In particular, the splitting pattern of the ring protons of **6** and of 1-methyl-3,3-pentamethylenediaziridine were quite similar. In both compounds the ring protons appear as a broad band with about the same chemical shift of δ 1.2–1.9. On the other hand, the aliphatic protons of **7** appear as two broad multiplets at δ 1.4–1.8 and 2.0–2.6 which is the same pattern observed for the cyclohexylidene moiety in **2d**, cyclohexanone methylhydrazone, and cyclohexanone oxime.

Diaziridines **1a** and **1d** were added to diethyl acetylenedicarboxylate to yield oily products presumed to be

(6) L. C. Bear, R. Fusco, and C. H. Jarboe, "Pyrazoles, Pyrazolines, Pyrazolidines, Indazoles and Condensed Rings," R. H. Wiley, Ed., Interscience, New York, N. Y., 1967, pp 5–8.

8a and **8d**, respectively. The crude oils were characterized by hydrolyzing them to the known 3-carboethoxypyrazolin-5-one (**9a**) and 2-methyl-3-carboethoxy-3-pyrazolin-5-one (**9d**) (Scheme IV). Com-

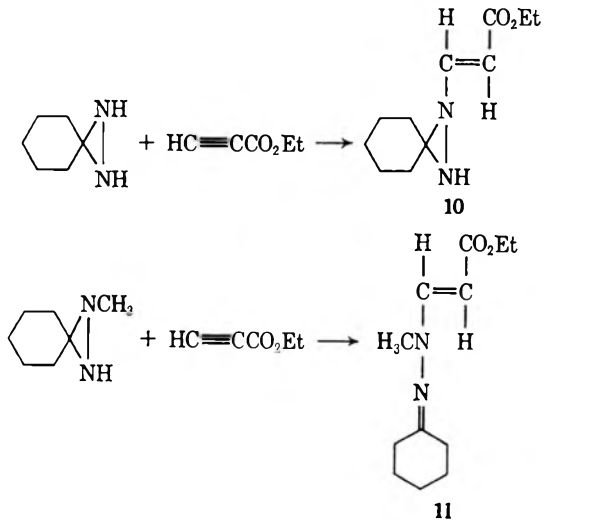
SCHEME IV



pounds **9a** and **9d** were also obtained by the addition of hydrazine and methylhydrazine to diethyl acetylenedicarboxylate.

3,3-Pentamethylenediaziridine and 1-methyl-3,3-pentamethylenediaziridine were also treated with ethyl propiolate in benzene to give **10** and **11**, respectively (Scheme V). Assignment of the trans configura-

SCHEME V



tion to **10** and **11** was made possible by using the results of earlier nmr investigations on adducts obtained from treating aziridine with ethyl propiolate[7] and from treating secondary amines with methyl propiolate.[8]

These studies established that the vinyl protons of ethyl 3-aziridinopropenoates and of methyl 3-dialkylaminopropenoates apear as an AB pattern with coupling constants of 8.0 Hz for the cis adducts and 13.0–13.4 Hz for the trans adducts.[7,8] Both compounds **10** and **11** in $CDCl_3$ gave nmr spectra with the expected AB pattern for the vinylic protons and with coupling constants of 13.0 Hz. However, the nmr spectrum of crude **10** revealed that a small quantity of the cis isomer (~10%) was also present since a second AB pattern was just discernible which had a coupling constant of 8.5 Hz. That compound **10** still had the diaziridine ring intact was deduced from its nmr spectrum (see reasoning employed for assigning the structure of **6**).

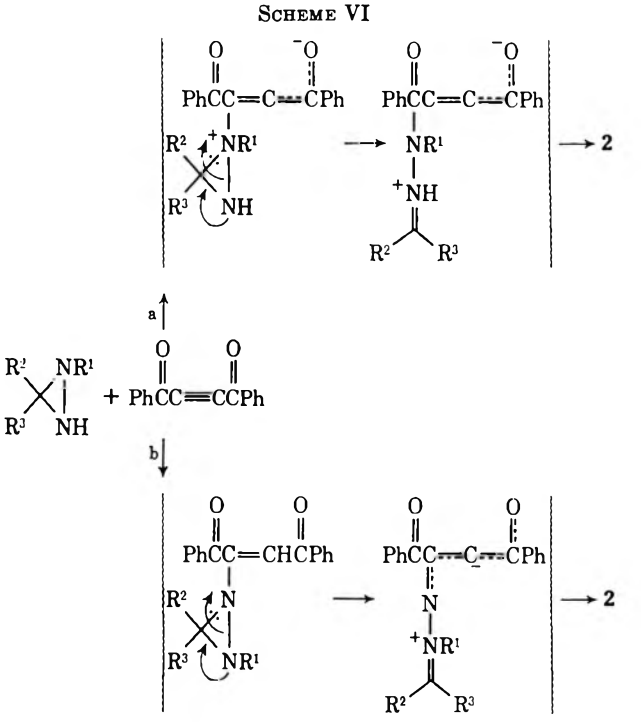
3,3-Pentamethylenediaziridine was also added to hexafluoro-2-butyne to give 1,1,1,4,4,4-hexafluoro-2-cyclohexylidenehydrazino-2-butene (**12**). Compound **12** was distillable and mass spectroscopy confirmed the molecular ion m/e to be 274.

Discussion

A Michael-type addition is undoubtedly involved in the reaction of diaziridines with electrophilic acetylenes. Indeed, in the case of the reaction of the 1,2-unsubstituted diaziridine, 3,3-pentamethylenediaziridine, with dibenzoylacetylene and ethyl propiolate, the addition products **6** and **10** are isolable. The demonstrated penchant of **6** to undergo facile conversion to **7** probably accounts for the Michael adduct not being isolated when the other 1,2-unsubstituted diaziridine used in this investigation, 3-ethyl-3-methyldiaziridine, was treated with dibenzoylacetylene.

The products **2b–f** formed when the 1,3-dialkyldiaziridines and 1,3,3-trialkyldiaziridines **1b–f** reacted with dibenzoylacetylene arise by the addition of the N-alkylated nitrogen (the most nucleophilic nitrogen) of the diaziridine to the alkyne linkage (pathway a, Scheme VI). Another mechanism in which the NH

SCHEME VI

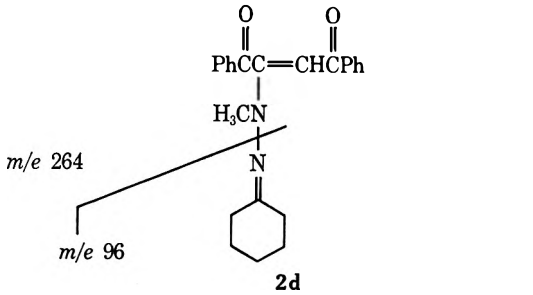


nitrogen of the diaziridine adds to the acetylenic carbon (such as pathway b) was discounted on the basis of the mass spectrum of the product obtained when 1-methyl-2-^{15}N-3,3-pentamethylenediaziridine was added to dibenzoylacetylene.

(7) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).

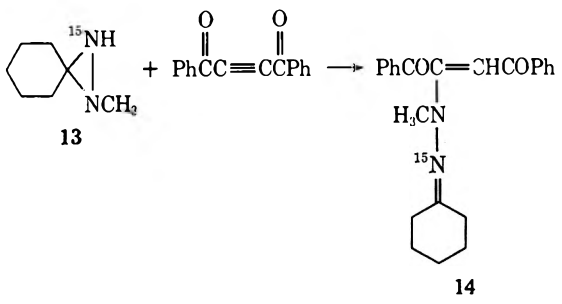
(8) (a) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Ber.*, **99**, 2526 (1966); (b) A. N. Kurtz, W. E. Billups, R. P. Greenlee, H. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965).

The mass spectrum of the adduct **2d** showed cleavage fragments for the ions $(C_6H_{10}N)^+$, *m/e* 96, and $(C_{17}H_{14}NO_2)^+$, *m/e* 264. It is obvious that, if diaziridine **13** (Scheme VII) is added to dibenzoylacetylene, one



2d

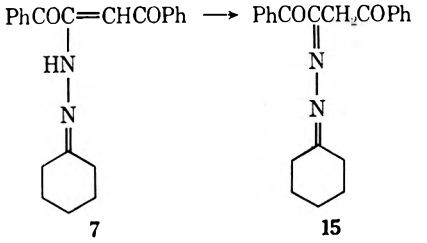
SCHEME VII



13 **14**

of the two cleavage peaks must increase by one mass unit according to which nitrogen of the diaziridine is bonded to the acetylene. Increase in the natural abundance of *m/e* 97 would be evidence for pathway a while increase in the natural abundance of *m/e* 265 would be evidence for pathway b of Scheme VI. Addition of **13** gave only **14** (see Experimental Section) proving unequivocally that the NCH_3 moiety of the diaziridine added to the triple bond directly.

It was observed that the nmr spectrum of **7** taken in $CDCl_3$ slowly changed over several hours. In particular, the vinyl absorption at δ 5.82 and the NH absorption at 13.3 diminished while a new peak at 4.33 appeared. This is most probably due to the isomerization of the enamine **7** into the tautomeric imine **15**.



7 **15**

The isomerization of imine–enamine tautomers obtained from the addition of phenylhydrazine to dimethyl acetylenedicarboxylate has recently been demonstrated.[9]

Experimental Section

Compounds 2a–f (Method A).—To a solution of 2–5 mmol of the known diaziridines (**1a–f**)[10] in 20 ml of dry benzene was added in portions an equivalent quantity of dibenzoylacetylene. The reaction mixture was stirred for 2 hr at room temperature and the solvent was evaporated to give usually a colored oil. In the case of **2a** the oil was dissolved in a minimum of hot 1:1 mixture of dry benzene–petroleum ether (bp 100–115°). After 2 days in the refrigerator, **2a** precipitated and was filtered. In the cases of **2b–f** the oils solidified upon standing in a hood for a day or so. Alternatively, the oils were dissolved in a minimum quantity of warm absolute ethanol. The ethanolic solution was cooled and the crystals of **2b–f** were filtered.

Compound 2a (Method B).—A suspension of 218 mg (2.53 mmol) of butanone hydrazone[11] in dry benzene was added dropwise to a solution of 593 mg (2.53 mmol) of dibenzoylacetylene in 15 ml of dry benzene. The reaction mixture was stirred for 1 hr and the solvent evaporated. A yield of 112 mg (14%) of **2a** was obtained.

Compound 2b (Method B).—A mixture of 169 mg (3.66 mmol) of methylhydrazine and 20 ml of dry acetone was stirred for 1 hr. To this mixture was added portionwise and with stirring 856 mg (3.65 mmol) of dibenzoylacetylene. The solvent was evaporated and a few drops of absolute ethanol was added to the residual oil whereupon **2b** crystallized quantitatively and was filtered.

Compound 2c (Method B).—A mixture of 102 mg (0.5 mmol) of acetone isopropylhydrazone oxalate,[12] 118 mg (0.5 mmol) of dibenzoylacetylene, and 10 ml of dry benzene was refluxed for 4.5 hr. The mixture was filtered and the solvent evaporated to give a red oil which was slurried in a small quantity of absolute ethanol. Crude **2c**, 80 mg (46%), crystallized after a few minutes and was filtered.

Compound 2d (Method B).—To a solution of 937 mg (4.0 mmol) of dibenzoylacetylene in 10 ml of dry benzene was added dropwise 504 mg (4.0 mmol) of cyclohexanone methylhydrazone.[13] The mixture was stirred for 2 hr and the solvent was evaporated. The residual dark oil crystallized upon the addition of a small quantity of ether. The crude **2d** (1070 mg, 74%) was filtered.

Compounds 2e–f (Method B).—A few milliliters of a concentrated sodium hydroxide solution was slowly added to a stirred suspension of 359 mg (2.0 mmol) of *n*-butylhydrazine oxalate in 10 ml of cold ether. The mixture was filtered and the filtrate was saved. The solid residue was washed with two 10-ml portions of ether and all of the ether filtrates were pooled. Five milliliters of propanal was added to the ether filtrates containing the *n*-Bu$NHNH_2$ and the solution was stirred for 1 hr before 314 mg (1.34 mmol) of dibenzoylacetylene was added portionwise. After 0.5 hr the solvent was evaporated to give 237 mg (49%) of crystalline **2e** based on the quantity of dibenzoylacetylene employed. Substitution of 5 ml of butanal gave a 22% yield of **2f**.

Pyrazoles 4 (Method A).—In general **2a–f** were dissolved in 10 ml of 95% ethanol containing 4 drops of concentrated hydrochloric acid. The reaction mixtures were refluxed for 0.5 hr and the solvent was evaporated to give the pyrazoles. Thus, 551 mg (1.72 mmol) of **2a** gave 360 mg (84%) of 3-phenyl-5-benzoylpyrazole,[14] mp 170.5–171°; **2b** (472 mg, 1.47 mmol) gave 200 mg (52%) of 1-methyl-3-phenyl-5-benzoylpyrazole, mp 52–57°; **2c** (680 mg, 1.95 mmol) gave 436 mg (77%) of 1-isopropyl-3-phenyl-5-benzoylpyrazole, mp 124–127°; **2d** (172 mg, 0.48 mmol) gave 76 mg (60%) of 1-methyl-3-phenyl-5-benzoylpyrazole, mp 52–57°; both **2e** (549 mg) and **2f** (487 mg) gave 1-*n*-butyl-3-phenyl-5-benzoylpyrazole as an oil (no yields taken).

3-Phenyl-5-benzoylpyrazole (Method B).—To a solution of 400 mg (1.71 mmol) of dibenzoylacetylene in 10 ml of absolute ethanol was added 55 mg of hydrazine hydrate. The reaction mixture darkened immediately and was stirred for 2 hr. The solvent was evaporated to give a quantitative yield of the pyrazole. Recrystallization from ethanol gave 3-phenyl-5-benzoylpyrazole melting at 170.5–171°.

1-Methyl-3-phenyl-5-benzoylpyrazole (Method B).—Methylhydrazine (46 mg, 1.0 mmol) was added dropwise to a solution of 234 mg (1.0 mmol) of dibenzoylacetylene dissolved in 10 ml of dry benzene. The reaction mixture was stirred for 1.5 hr and the solvent evaporated to give 100 mg (38%) of product. The pyrazole was recrystallized from absolute ethanol to give crystals melting at 52–57°.

Anal. Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.98; H, 5.58; N, 10.44.

(9) N. D. Heindel and P. Kennewell, *J. Org. Chem.*, **35**, 80 (1970).

(10) We recommend the use of freshly prepared hydroxylamine-*O*-sulfonic acid rather than the commercially available product for the preparation of diaziridines.

(11) A. Kinnman, *C. R. Acad. Sci.*, **217**, 148 (1943).

(12) H. L. Lochte, W. A. Noyes, and J. R. Bailey, *J. Amer. Chem. Soc.*, **44**, 2556 (1922).

(13) R. H. Wiley and G. Irick, *J. Org. Chem.*, **24**, 1928 (1959).

(14) D. G. Farnum and P. Yates, *J. Amer. Chem. Soc.*, **84**, 1399 (1962).

1-Isopropyl-3-phenyl-5-benzoylpyrazole (Method B).—To a mixture of 116 mg (0.71 mmol) of isopropylhydrazine oxalate in benzene was added 165 mg (0.71 mmol) of dibenzoylacetylene. The mixture was heated until dissolution occurred. An equivalent quantity of solid potassium hydroxide was added to the reaction mixture, whereupon 122 mg (60%) of the pyrazole precipitated. Four recrystallizations from absolute ethanol gave 1-isopropyl-3-phenyl-5-benzoylpyrazole, mp 125–127°.

Anal. Calcd for $C_{19}H_{18}N_2O$: C, 78.58; H, 6.24; N, 9.64. Found: C, 78.53; H, 6.26; N, 9.78.

1-*n*-Butyl-3-phenyl-5-benzoylpyrazole (Method B).—A solution of 1.97 mmol of *n*-butylhydrazine in ether was prepared from *n*-butylhydrazine oxalate as described previously. To this solution was added an equivalent quantity of dibenzoylacetylene. The reaction mixture darkened immediately and it was stirred for 1 hr. Evaporation of the solvent gave a dark oil which could not be vacuum distilled. The ir and nmr spectra of the oil was identical with the spectra obtained from the hydrolysis of **2e** and **2f**.

Compound 6.—To a solution of 1.49 g (13.3 mmol) of 3,3-pentamethylenediaziridine in 20 ml of dry benzene was added 3.09 g (13.2 mmol) of dibenzoylacetylene. The reaction mixture was stirred for 1 hr and the solvent evaporated. The residual dark oil was dissolved in a small volume of warm, dry 1:1 benzene–petroleum ether (bp 100–115°). The solution after standing at 0° overnight gave 2.68 g (59%) of **6**. After four recrystallizations from the mixed solvent **6** was obtained which melted at 99–101°.

Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.43; H, 6.58; N, 8.18.

Compound 7.—Warming 222 mg of **6** for 2–3 min in 95% ethanol gave 209 mg of **7**, mp 123–125°. A sample of **6** in $CDCl_3$ containing 1 drop of water also rearranged into **7**. Four recrystallizations from absolute ethanol gave **7**, mp 124–125°.

Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.39; H, 6.41; N, 8.21.

3-Carboethoxypyrazolin-5-one (9a).—A mixture of 443 mg (5.14 mmol) of 3-ethyl-3-methyldiaziridine and 875 mg (5.14 mmol) of diethyl acetylenedicarboxylate in 10 ml of dry benzene was refluxed for 0.5 hr. The solvent was evaporated and the residual oil was dissolved in 10 ml of 95% ethanol containing 3 drops of concentrated hydrochloric acid. The mixture was refluxed for 1 hr and the solvent evaporated to give 687 mg (86%) of **9a**. Two recrystallizations from 95% ethanol gave **9a**, mp 184–187° (lit.[15] mp 184–185°).

2-Methyl-3-carbethoxy-3-pyrazolin-5-one (9d).—A mixture of 395 mg (3.14 mmol) of 1-methyl-3,3-pentamethylenediaziridine and 534 mg (3.14 mmol) of diethyl acetylenedicarboxylate in 10 ml of dry benzene was stirred for 0.5 hr. The solvent was evaporated and to the residual oil was added 10 ml of 95% ethanol containing 3 drops of concentrated hydrochloric acid. The mixture was refluxed for 0.5 hr and the solvent was evaporated to give 56 mg (10%) of **9d**. Four recrystallizations from absolute ethanol gave **9d**, mp 151–154°.

Anal. Calcd for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.92; N, 16.47. Found: C, 49.47; H, 5.52; N, 16.40.

***trans*-Ethyl 3 (3,3-Pentamethylenediaziridino)propenoate (10).**—A mixture of 560 mg (5 mmol) of 3,3-pentamethylenediaziridine and 490 mg (5 mmol) of ethyl propiolate in 10 ml of benzene was stirred at room temperature for 48 hr. The solvent was evaporated and the residual oil was placed in a refrigerator. After several days 835 mg (79%) of **10** precipitated (attempts to recrystallize **10** were unsuccessful): molecular ion *m/e* 210; nmr ($CDCl_3$) δ 7.38 (d, 1, J = 13.0 Hz, NCH=), 5.68 (d, 1, J = 13.0 Hz, $CHCO_2$), 4.17 (q, 2, CH_2), 2.2–2.8 (m, 1, NH), 1.62 [s, 10, $(CH_2)_5$], 1.29 (t, 3 H, CH_3).

***trans*-Ethyl 3-(Cyclohexylidenemethylhydrazino)propenoate (11).**—A mixture of 630 mg (5 mmol) of 1-methyl-3,3-pentamethylenediaziridine and 490 mg (5 mmol) of ethyl propiolate in 10 ml of benzene was stirred for 12 hr. Evaporation of the solvent left 1.081 g (97%) of **11** as an undistillable oil: molecular ion *m/e* 224; nmr ($CDCl_3$) δ 7.38 (d, 1, J = 13.0 Hz, NCH), 4.50 (d, 1, J = 13.0 Hz, $CHCO_2$), 4.13 (q, 2, CH_2), 3.10 (s, 3, NCH_3), 2.17–2.60 [m, 4, $CH_2C(=N)CH_2$], 1.68 [s, 6, $CH_2(CH_2)_3CH_2$], 1.25 (t, 3, CH_2CH_3).

(15) S. Ruhemann, *J. Chem. Soc.*, **69**, 1395 (1896).

Compound **11** can also be prepared by mixing equimolar quantities of cyclohexanone methylhydrazone and ethyl propiolate in benzene and working up the reaction mixture as described above.

1,1,1,4,4,4-Hexafluoro-2-cyclohexylidenehydrazino-2-butene (12).—A stream of hexafluoro-2-butyne was slowly passed through a solution of 2.24 g (20 mmol) of 3,3-pentamethylenediaziridine in 9 ml of dry methylene chloride at −70°. After a slight excess of the acetylene was added the reaction mixture was stirred for 2.5 hr. The solvent was evaporated and the residual oil was distilled to give 3.36 g (62%) of **12**, bp 37–38° (0.15 mm), molecular ion *m/e* 274.

Anal. Calcd for $C_{10}H_{12}F_6N_2$: C, 43.80; H, 4.41. Found: C, 43.87; H, 4.58.

Preparation of 13.—A mixture of 0.5 g of hydroxylamine-^{15}N hydrochloride (95 at. % ^{15}N)[16] and 0.5 g of unlabeled hydroxylamine hydrochloride was ground with mortar and pestle and then transferred to a 10-ml beaker. Three milliliters of fuming sulfuric acid (30% SO_3) was added dropwise over a ten minute interval. The reaction mixture was cooled and 5 ml of cold, dry ether was added with stirring. The ^{15}N-enriched hydroxylamine-*O*-sulfonic acid was filtered immediately and washed with cold ether until it took on a fluffy appearance. The dry labeled hydroxylamine-*O*-sulfonic acid was then converted to 1-methyl-3,3-pentamethylenediaziridine according to a published procedure.[17] Specifically 1.4 g of the hydroxylamine-*O*-sulfonic acid enriched with ^{15}N was added to 14 ml of a cooled solution (0°) of 40% aqueous methylamine containing 1.47 g of cyclohexanone, over a time interval of 0.5 hr. The mixture was allowed to stand an additional hour at 0–10° and then extracted four times with 10-ml portions of ether. The extracts were dried over K_2CO_3 and the mixture was filtered. The ether was evaporated and the residue distilled to give 1.15 g of **13** boiling at 34–37° (0.75 mm). Compound **13** was then added to dibenzoylacetylene to yield **14**.

The labeled **14** showed a pair of molecular ion peaks, at *m/e* 360 and 361, in approximately equal abundance. Loss of one benzoyl group yielded fragment ions at *m/e* 255 and 256 for the ^{14}N and ^{15}N species. Cleavage between the two nitrogen atoms occurred most readily with charge retention on the *N*-methyldibenzoylethylene moiety yielding an intense ion (base peak) at *m/e* 264. This ion was not shifted in the mass spectrum of the ^{15}N-labeled product, indicating that the ^{15}N atom was located on the "cyclohexylimide" moiety. Cleavage between the nitrogens with charge retention on this fragment also occurred although the ion produced at *m/e* 96 was not so intense as the ion at *m/e* 264. Approximately equally intense ions at *m/e* 96 and 97 in the ^{15}N-labeled product confirmed the location of the label.

Acknowledgment.—We thank the Camille and Henry Dreyfus Foundation, Inc., and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for financial aid and Professor C. C. Sweeley for the mass spectra and stimulating discussions.

Registry No.—**1a**, 4901-75-1; **1b**, 40711-15-7; **1c**, 17119-93-6; **1d**, 26177-34-4; **1e**, 40711-18-0; **1f**, 40711-19-1; **2a**, 40711-20-4; **2b**, 40711-21-5; **2c**, 40711-22-6; **2d**, 40711-23-7; **2e**, 40711-24-8; **2f**, 40711-25-9; **3a**, 29443-39-8; **3b**, 5771-02-8; **3c**, 7423-01-0; **3d**, 1567-83-5; **3e**, 20607-75-4; **3f**, 38126-74-8; **6**, 40711-31-7; **7**, 40711-32-8; **9a**, 40711-33-9; **9d**, 40711-34-0; **10**, 40711-35-1; **11**, 40711-36-2; **12**, 40711-37-3; **13**, 40711-38-4; **14**, 40711-39-5; dibenzoylacetylene, 1087-09-8; methylhydrazine, 60-34-4; acetone isopropylhydrazone oxalate, 40711-40-8; *n*-butylhydrazine oxalate, 40711-41-9; 3-phenyl-5-benzoylpyrazole, 21111-32-0; 1-methyl-3-phenyl-5-benzoylpyrazole, 40711-43-1; 1-isopropyl-3-phenyl-5-benzoylpyrazole, 40711-44-2; 1-*n*-butyl-3-phenyl-5-benzoylpyrazole, 40711-45-3; hydrazine, 302-01-2; isopropylhydrazine oxalate, 3468-25-5; *n*-butylhydrazine, 3530-11-8; 3,3-pentamethylenediaziridine, 185-79-5; diethyl acetylenedicarboxylate, 762-21-0; ethyl propiolate, 623-47-2; hexafluoro-2-butyne, 692-50-2; hydroxylamine-^{15}N hydrochloride, 40711-48-6.

(16) Isotopic Products, Merck Sharp and Dohme of Canada Ltd, Montreal, Canada.

(17) E. Schmitz, R. Ohme, and R. D. Schmidt, *Ber.*, **95**, 2714 (1962).

The Synthesis of (1R)-[2-^{18}O]-α-Fenchocamphoronequinone. Specific Labeling of One Carbonyl Group in a Norbornane-2,3-dione[1]

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A method has been devised for the preparation of a norbornane-2,3-dione with one of the carbonyl groups enriched specifically in ^{18}O, *viz.*, oxidation of a labeled ketone with selenium dioxide in acetic anhydride. This method has been applied to the oxidation of labeled, optically active α-fenchocamphorone giving specifically labeled α-fenchocamphoronequinone. This diketone, whose optical activity is due only to ^{18}O substitution, showed a small but measureable effect in the CD of both low intensity absorption bands in the region of 250–520 nm.

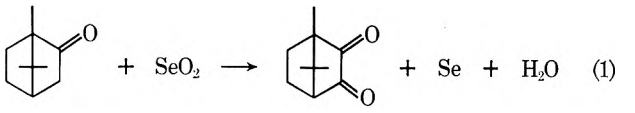
Compounds which derive optical activity from isotopic substitution offer interesting possibilities for studying the origin of vibronic absorption bands if these bands are accessible to CD measurements. Up to now much work has been done to synthesize compounds whose optical activity stems from deuterium substitution.[2] In addition a few examples have been reported where optical activity is due to oxygen isotopes, *viz.*, some ^{16}O–^{18}O sulfones[3,4] and ^{16}O–^{18}O sulfonate esters.[3b] Measurement of the optical activity in these compounds has usually resulted in plain ORD curves.[5]

In view of this situation it seemed worthwhile to start a program for the synthesis of ketones and diketones with optical activity due to isotopic substitution. α diketones were particularly inviting because two low intensity absorption bands in the region of 250–520 nm can be studied by CD provided that the effect is large enough.

One of our efforts was directed toward the synthesis of a specifically labeled ^{16}O–^{18}O α diketone starting from optically active norcamphor or α-fenchocamphorone (**5**). Because of the availability and the price of starting materials ($H_2{}^{18}O$, *e.g.*,) it was decided to try out the various steps in the synthesis with cheaper materials. This resulted in a number of interesting observations which will be discussed first.

Model Experiments.—Initially the synthesis of specifically labeled camphorquinone was attempted from camphor. Water, enriched in ^{18}O (2.095 at. % ^{18}O[6]), was used for labeling the reagents, since an ^{18}O label of 2% is sufficiently high to detect the possible exchange of oxygen between the reagents and the reaction medium by mass spectroscopy.

An α diketone is most conveniently prepared by the oxidation of a ketone with selenium dioxide.[7] Because the water formed in this reaction (eq 1) reacts with selenium dioxide to form selenious acid, which



(1)

might catalyze in unfavorable conditions exchange of oxygen between the carbonyl group and water,[8] a solvent was required in which either selenious acid was insoluble or the water formed could be removed.

In a first experiment labeled camphor was oxidized with selenium dioxide in acetic anhydride[9] (molar ratio of camphor, selenium dioxide, and acetic anhydride, 0.33:0.54:0.53), the intention being to bind the water formed with acetic anhydride. This first experiment was a failure: the camphorquinone prepared from labeled camphor (2.26% ^{18}O) had too low a label (1.62% ^{18}O; retention is 2.45% ^{18}O).

Various possible reasons for this loss of label were systematically investigated. First it was verified that labeled camphor does not lose label[10] when boiled with acetic anhydride for 4 hr.[11,12] Similarly no loss of label occurred when 0.3 g of water was added to a boiling solution of 2.5 g of labeled camphor in 2.5 ml of acetic anhydride[13] (molar ratio of camphor, water, and acetic anhydride, 0.33:0.33:0.53). Apparently under these conditions the reaction between water and acetic anhydride is much faster than the acetic acid catalyzed exchange reaction between water and camphor.

(1) Taken from the thesis of the author, Leiden (1973).

(2) For references on hydrogen–deuterium asymmetry, see D. Arigoni and E. L. Eliel, *Top. Stereochem.*, **4**, 127 (1969); L. Verbit, *Progr. Phys. Org. Chem.*, **7**, 51 (1970).

(3) (a) C. J. M. Stirling, *J. Chem. Soc.*, 5741 (1963); (b) M. A. Sabol and K. K. Andersen, *J. Amer. Chem. Soc.*, **91**, 3603 (1969).

(4) R. Annunziata, M. Cinquini, and C. Colonna, *J. Chem. Soc., Perkin Trans. 1*, 2057 (1972).

(5) Only two exceptions are known (H–D asymmetry). *Cf.* S. Englard, J. S. Britten, and I. Listowsky, *J. Biol. Chem.*, **242**, 2255 (1967); L. Verbit, *J. Amer. Chem. Soc.*, **89**, 167 (1967).

(6) Determined by Miles Laboratories, Inc.

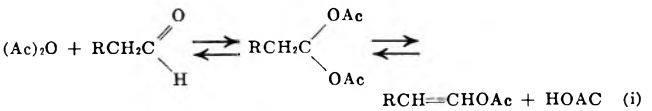
(7) For references to the literature on the application of selenium dioxide in organic chemistry, see the following. L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley-Interscience, New York, N. Y.: Vol. 1, 1967, p 992; Vol. 2, 1969, p 360; Vol. 3, 1972, p 245. C. F. Cullis and A. Fish, "The Chemistry of the Carbonyl Group," S. Patai, Ed., Vol. 1, Interscience, New York, N. Y., 1966, p 159. E. N. Trachtenberg, "Oxidation," R. L. Augustine, Ed., Vol. 1, Marcel Dekker, New York, N. Y., 1969, p 119.

(8) M. Byrn and M. Calvin, *J. Amer. Chem. Soc.*, **88**, 1916 (1966); P. Greenzaid, Z. Luz, and D. Samuel, *Trans. Faraday Soc.*, 2787 (1968).

(9) W. C. Evans, J. M. Ridgion, and J. L. Simonsen, *J. Chem. Soc.*, 137 (1934).

(10) In the low label experiments the maximum absolute error in the determination of ^{18}O labels was ±0.10%. Therefore a statement such as "retention of label was observed" should read "relative loss of label was 5% or less."

(11) Thus the mechanism responsible for the loss of ^{18}O when a labeled aldehyde is treated with acetic anhydride (eq i) does not apply here; *cf.*



(i)

Houben-Weyl, "Methoden der Organischen Chemie," Georg Thieme Verlag, Stuttgart, Bd 7/1, 1954, p 442.

(12) When camphor is treated with trichloroacetic acid anhydride (110–120°) a geminate diester is formed, 2,2-dihydroxycamphane ditrichloroacetate, which decomposes to give after a Wagner–Meerwein rearrangement 1-hydroxycamphene trichloroacetate as the primary product: J. Libman, M. Sprecher, and Y. Mazur, *Tetrahedron*, **25**, 1679 (1969).

(13) This quantity of water (0.3 g) was chosen because it would have been formed when selenium dioxide had been added to the reaction mixture and had oxidized all of the ketone and nothing else.

Reconsidering in the light of these results the oxidation experiment in which loss of label did occur, it was realized that both ketone and solvent[14] were oxidized by selenium dioxide so that toward the end of the reaction hardly any acetic anhydride was left. The lifetime of a water molecule then became long enough to permit oxygen exchange with the carbonyl group.

Indeed it was found that loss of ^{18}O in the oxidation of labeled camphor can be prevented by sufficiently reducing the quantity of selenium dioxide with respect to camphor and acetic anhydride. Although the mass spectra of camphorquinone clearly showed retention of label[10] and that selective label incorporation had been achieved,[15] the possibility of interchange of the two oxygen atoms within one diketone molecule could not be excluded on the basis of these results.[16] On the other hand this process seemed to be very improbable so that continuation of the synthesis with highly labeled materials seemed justified.

Meanwhile two other routes to the desired compounds had been explored. It appeared that the oxidation of labeled camphor with selenium dioxide in toluene[17] proceeds with retention of label, although in poor yield. In this case water is probably removed by the excess of unreacted selenium dioxide.

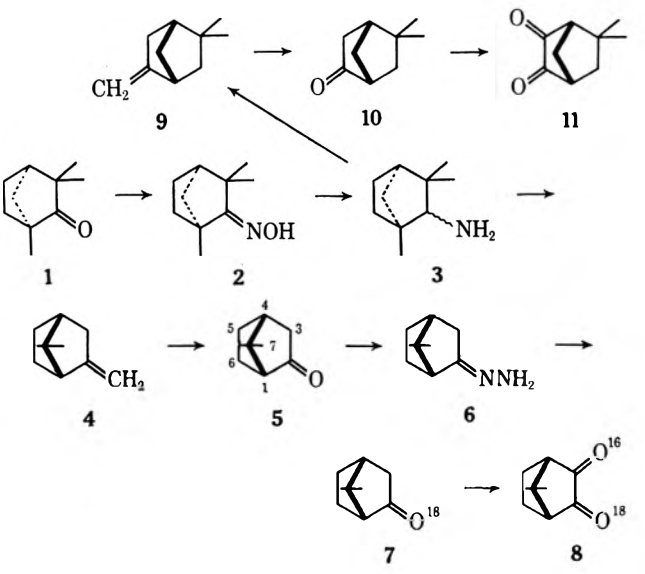
Finally it was tried to devise an oxidation reaction for the preparation of camphorquinone where water could not possibly be a reaction product, so that trouble due to exchange with water could not occur. The oxidation of camphor enol benzoate was attempted with selenium dioxide in benzene. Camphorquinone and benzoic acid were formed in good yield. However, when labeled selenium dioxide[18] was employed, randomly labeled camphorquinone was obtained.

Experiments with High Label Incorporation.—The route followed to (1*R*)-[2-^{18}O]-α-fenchocamphoronequinone (**8**) is indicated in Scheme I (absolute configurations are depicted[19]).

The required α-fenchocamphorone (**5**) was prepared *via* α-fenchene (**4**) from fenchone (**1**); this route was chosen because it was judged to be the one by which α-fenchene (**4**) of the highest chemical purity could be obtained.[20] The α-fenchocamphorone (**5**) thus obtained did not contain the most likely impurity β-fenchocamphorone (**10**), because after selenium dioxide oxidation the diketone obtained was optically inactive (no effect in CD), *i.e.*, the diketone did not contain a measurable quantity of β-fenchocamphoronequinone (**11**) as an impurity.[21]

SCHEME I

THE SYNTHESIS OF THE TITLE COMPOUND FROM (+)-(1*S*)-FENCHONE



α-Fenchocamphorone (**5**) was labeled by regeneration from the hydrazone (**6**) with water enriched in ^{18}O. This labeled ketone contained 62.72% ^{18}O. After oxidation with selenium dioxide in acetic anhydride some unreacted ketone was recovered with a label of 60.19% ^{18}O. Of the diketone prepared 48.05% was specifically labeled with ^{18}O, and 0.08% was doubly labeled. Completely specific labeling had been achieved.[22]

Much less label is missing from the ketone recovered than from the diketone formed. One might suppose that oxygen exchange of the diketone with water formed during the selenium dioxide oxidation is faster than oxygen exchange of the starting monoketone. The results of following two exchange experiments confirmed this hypothesis.

A homogeneous solution of α-fenchocamphorone (0.5754 g), α-fenchocamphoronequinone (0.5063 g), labeled water (1.210 g, 12.062 at. % ^{18}O[6]), and 0.20 *N* acetic acid in dioxane (1.1230 g) was left at room temperature for 96 hr. After work-up it was shown that the ketone had hardly exchanged oxygen (label 0.38% ^{18}O; no label is 0.2% ^{18}O), whereas 14.90% of the diketone was labeled with one ^{18}O.

Labeled α-fenchocamphorone and α-fenchocamphoronequinone were dissolved in acetic anhydride and to the boiling solution the quantity of water calculated to hydrolyze the anhydride was gradually added. Both

(14) J. J. Postowsky and B. P. Lugowkin, *Ber.*, **68**, 854 (1935); L. Rappen, *J. Prakt. Chem.*, *n.F.*, **157**, 196 (1941).

(15) A sample of camphorquinone prepared from labeled camphor[9] had a label of 1.50% ^{18}O and the fragment (M − CO) a label of 0.31% ^{18}O (15-eV spectrum). If both carbonyl groups were equivalent, or if we had a randomly labeled diketone, we should expect the fragment (M − CO) to have a label of 0.75% ^{18}O.

(16) Assuming that the "chain branching rule" (*cf.* F. W. McLafferty, "Interpretation of Mass Spectra," W. A. Benjamin, New York, N. Y., 1967, p 82) can be used to predict that in camphorquinone the bond between C-1 and C-2 is broken preferentially to the bond between C-3 and C-4, we conclude from the labels of footnote 15 that [2-^{18}O]camphorquinone is the main or possibly the only reaction product. If preference for bond rupture should be opposite to the "chain branching rule," then [3-^{18}O]-camphorquinone is the main or the only reaction product, and interchange of oxygen atoms within a molecule has taken place.

(17) J. Vène, *C. R. Acad. Sci.*, **216**, 772 (1943).

(18) Labeled selenium dioxide is commercially available (Miles Laboratories, Inc.).

(19) The absolute configurations follow from the absolute configuration of camphor [M. G. Northolt and J. H. Palm, *Recl. Trav. Chim. Pays-Bas*, **85**, 143 (1966)] and the relative configurations of fenchone (**1**) and camphor [A. Fredga and J. K. Miettinen, *Acta Chem. Scand.*, **1**, 371 (1947)].

(20) For syntheses of α-fenchene (**4**) the reader is referred to (a) J. L. Simonsen, "The Terpenes," Vol. 2, 2nd ed, Cambridge University Press, New York, N. Y., 1949, p 538; (b) E. Gildemeister and Fr. Hoffmann, "Die Aetherischen Oele," Akademie-Verlag, Berlin, 4, Aufl., Bd IIIa, 1960, p 197; (c) V. Mattinen, *Ann. Acad. Sci. Fenn., Ser. AII*, **105**, 22 (1961); *Chem. Abstr.*, **56**, 4798*i* (1962).

(21) Unfortunately the CD of β-fenchocamphoronequinone (**11**) has not been published, but, if we assume that its strongest CD band in the region of 250–520 nm has $\Delta\epsilon$ 0.1, which is a rather low value, then we would have detected **11** by CD if its concentration in α-fenchocamphoronequinone had been >0.35%.

(22) The presence of doubly labeled diketone (0.08%) is due to the natural abundance of ^{18}O in the oxidizing agent.

ketone and diketone lost label, but the diketone much faster than the ketone.[23]

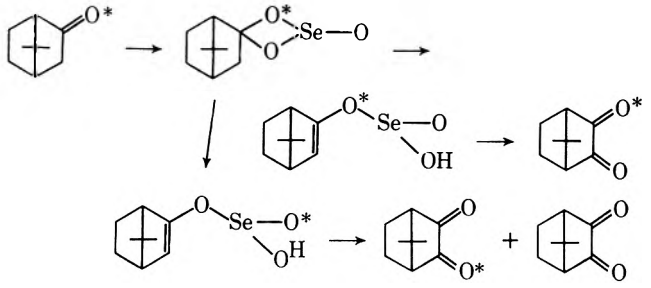
Optical Purity.—Our starting fenchone oxime (2) had $[\alpha]_D$ +41.19° (absolute EtOH); comparison with a reliable value of $[\alpha]_D$ +46.5° (EtOH)[29] indicates an optical purity at 88.6%.

The physical constants recorded by Rassat[30] for (1S)-α-fenchocamphorone (the antipode of **5**), $[\alpha]_D$ −60° (EtOH), $\Delta\epsilon_{max}$ −1.60 (cyclohexane), are not consistent with our best data: $[\alpha]_D$ +67.05° (MeOH),[31] $\Delta\epsilon_{max}$ +2.30 (cyclohexane). Mattinen[20c] recorded $[\alpha]_D$ +73.94° (EtOH); if this is taken as the correct value, then our α-fenchocamphorone has an optical purity of 90.7%.

A discussion of the optical purity of the ^{16}O–^{18}O diketone prepared according to Scheme I must involve the mechanism of the oxidation reaction with selenium dioxide. Corey and Schaefer[32] have postulated a selenite enol ester as a reaction intermediate. If such a species is formed *via* a cycloaddition of selenium dioxide to the ketone, then one would expect (Scheme II) in our case 66.67% racemization and 25%

SCHEME II

A MECHANISM WHICH GIVES RISE TO SPECIFICALLY LABELED DIKETONE, BUT WITH PARTIAL RACEMIZATION



loss of label. This mechanism seems unlikely because labeled camphor can be oxidized with retention of label,[10] and our exchange experiments suggest that during the oxidation of α-fenchocamphorane loss of label is due to exchange with water.

If we assume that oxidation of labeled α-fenchocamphorone with selenium dioxide gives rise to no racemization because of the mechanism of the oxidation reaction,[33] then (1R)-[2-^{18}O]-α-fenchocamphoronequinone (**8**) has an optical purity of 90.7%.

Measurement of the CD of specifically labeled α-fenchocamphoranequinone, although very small, proved to be possible. It is displayed in Figure 1 together with the absorption spectrum. These spectra have been published before.[34,35] The influence of ^{18}O substitution (label 62.72% ^{18}O) on the CD of α-fenchocamphorone was only small. In Figure 2 the ratio of A/B of the values of $\Delta\epsilon$ in the two maxima would be 1% lower if the CD of the labeled ketone was depicted here instead of the CD of the unlabeled ketone. The dotted line in Figure 2 encloses a part of the graph which is different in the case of the labeled ketone. In Figure 3 this detail of the CD curves of both labeled and unlabeled ketone is enlarged. The influence of

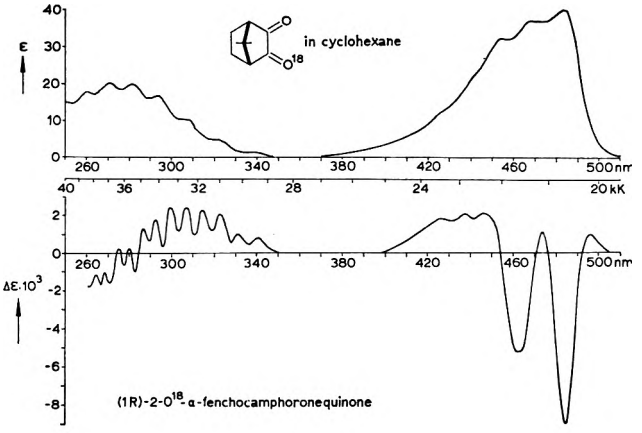
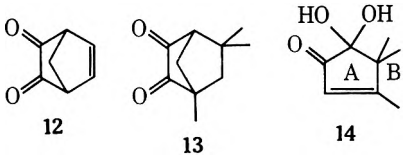


Figure 1.

(23) In this context it may be of interest to mention some data found in the literature. The yellow compound dehydronorcamphorquinone (**12**)



12 **13** **14**

gives a colorless solution in water. A hydrate is postulated.[24] Thus this diketone might undergo uncatalyzed oxygen exchange with water, whereas oxygen exchange between water and a ketone requires catalysis.[25] Rassat[26] states that isofenchonequinone (**13**) is hydrated easily. Some norsteroids with an α-diketone chromophore in the unsaturated A ring (**14**) can be isolated as monohydrates.[27] Cyclobutane-1,2-dione even reacts with water to give α-hydroxycyclopropenecarboxylic acid.[28]

(24) H.-D. Scharf, W. Droste, and R. Liebig, *Angew. Chem.*, **80**, 195 (1968).

(25) This statement does not hold at elevated temperatures; *e.g.*, cyclopentanone recovered after heating in a sealed tube (2 hr; 150°); cyclopentanone (1 ml), THF (1 ml), and labeled water (0.5 g, 12.062 at. % ^{18}O) had a label of 7.36% ^{18}O. For a similar though less convincing experiment, see M. Cohn and H. C. Urey, *J. Amer. Chem. Soc.*, **60**, 679 (1938).

(26) H.-P. Gervais and A. Rassat, *Bull. Soc. Chim. Fr.*, 743 (1961).

(27) T. Kubota and F. Hayashi, *Tetrahedron*, **23**, 999 (1967).

(28) J.-M. Conia and J. M. Denis, *Tetrahedron Lett.*, 2845 (1971).

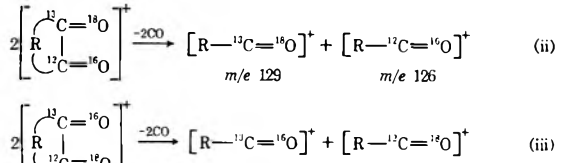
(29) W. Hückel and M. Sachs, *Justus Liebigs Ann. Chem.*, **498**, 166 (1932).

(30) C. Coulombeau and A. Rassat, *Bull. Soc. Chim. Fr.*, 3752 (1966).

(31) The angles of rotation of α-fenchocamphorone in MeOH and EtOH are identical within the experimental error.

(32) E. J. Corey and J. P. Schaefer, *J. Amer. Chem. Soc.*, **82**, 918 (1960); J. P. Schaefer, *ibid.*, **84**, 713, 717 (1962).

(33) It is possible to prove rigorously that oxidation of **7** is not accompanied by racemization. To prove this **7** has to be prepared, enriched in ^{13}C in the 2 or 3 position. This [^{13}C–^{18}O]-**7** has to be oxidized to give **8**. Use has to be made of fragmentation reactions in the mass spectrograph: molecular ions of norcamphorquinones lose CO and OCCO very easily. We can exclude racemization if (1) the fragment (M − 56) is not enriched in ^{13}C, (2) it follows from measurement of M that **8** is labeled specifically, (3) it is proved by measurement of (M − CO) that oxidation of [2-^{13}C–2-^{18}O]-**7**, *e.g.*, gives rise exclusively to [2-^{13}C–2-^{18}O]-**8**. This is possible because scrambling of ^{18}O (equal to inversion of the absolute configuration if the molecule was not enriched in ^{13}C) means formation of [2-^{13}C–3-^{18}O]-**8** which has a structure of the multiplet (M − CO) different from that of [2-^{13}C–2-^{18}O]-**8**; *cf.* eq ii and iii [a fragmentation reaction of **8** labeled with



^{13}C and ^{18}O in the chromophore (R = C_7H_{12})]. 2-^{13}C–2-^{18}O-**8** gives in the fragment (M − CO) a relative increase of intensity of the peak for *m/e* 129 compared with unlabeled **8** (eq ii). 2-^{13}C–3-^{18}O-**8** gives in the fragment (M − CO) a relative increase of intensity of the peaks for *m/e* 127 and 128 compared with unlabeled **8** (eq iii).

(34) W. C. M. C. Kokke and L. J. Oosterhoff, *J. Amer. Chem. Soc.*, **94**, 7583 (1972).

(35) The factor used to correct the observed CD for optical and isotopic impurity was 10000/(48.05 × 90.7); 90.7 stands for the optical purity of the ^{16}O–^{18}O diketone and 48.05 for its isotopic purity, *i.e.*, the percentage of molecules labeled with one ^{18}O.

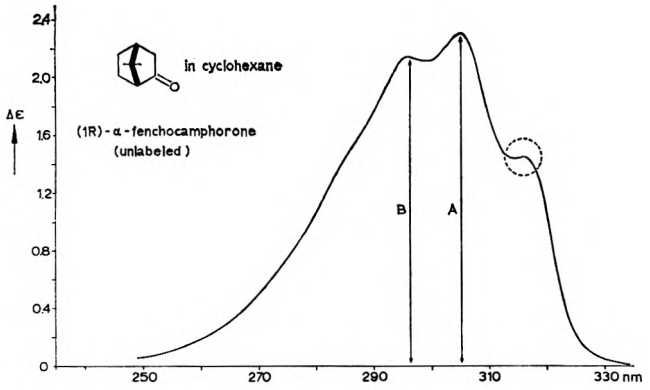


Figure 2.—CD of compound 5.

^{18}O substitution on the absorption spectra of ketone (7) and diketone (8) could not be detected with a Cary 14 or a Cary 15.

Experimental Section

Melting points are not corrected. Angles of rotation were determined with a Bendix-NPL photoelectric polarimeter at room temperature.

Mass spectra.—Labels were calculated from peak intensities in spectra obtained with a MS-9 mass spectrometer. Because of the various methods to calculate percentage labeling from peak intensities, we give a numerical example of the method we have used. In the mass spectrum of a sample of labeled camphorquinone ($C_{10}H_{14}O_2$) peaks due to molecular ions are at M/e 166, 167, and 168 with relative intensities of 100, 11.19, and 2.275. Correction of the peak intensities for M/e 167 and 168 for satellites of M/e 166 due to D and ^{13}C is done by comparison with a mass spectrum of $C_{10}H_{14}$. Relative peak intensities for M/e 134, 135, and 136 in $C_{10}H_{14}$ are 100, 11.03 and 0.55.[36] The ^{18}O label is equal to $[(2.275 - 0.55)/[100 + (11.19 - 11.03) + (2.275 - 0.55)] \times 100\% = 1.67\%$ ^{18}O. Note, the *absolute* ^{18}O content is calculated; no correction for natural abundance is applied.

Camphor Hydrazone[37] was recrystallized from isooctane. Stored at −20° over P_2O_5 it did not liquefy as observed in by Reusch, *et al.*,[37] and after a year the crystals had only turned slightly yellowish.

Camphor enol benzoate, prepared according to Lees,[38] appeared to be very impure (glpc). The composition of the reaction product depends on the reaction time: when camphor is refluxed with benzoyl chloride during 4 hr, the enol ester is the main reaction product, but when refluxed overnight another component of the mixture (probably the benzoate of 1-hydroxycamphene) becomes the main product. The enol ester was purified by column chromatography over silica gel. Elution with carbon tetrachloride then gave pure camphor enol benzoate. The enol ester is a liquid at room temperature. Nmr data (CCl_4) (shifts with respect to TMS) include three methyl groups at δ 0.790, 0.986, 1.042 ppm; a triplet at δ 2.831 ppm [$J = 2 \times 3.50$ Hz; H attached to C_4 (bridgehead proton)]; and a doublet at δ 5.742 ppm [$J = 3.72$ Hz; H attached to C_3 (vinylic proton)].

Labeling of Camphor by Hydrolysis of Camphor Hydrazone.—A mixture of camphor hydrazone (8.3 g), labeled water (4.0 ml, 2.095 at. % ^{18}O[6]), and ethylene chloride (50 ml) was placed in a heavy-walled, long-necked flask at a high vacuum line and degassed, and hydrogen bromide [1.67 l./20° (1 atm)] was then frozen into it. The sealed mixture was left overnight, then heated whilst magnetically stirring for 8 hr at 80°. Normal isolation procedures then gave the labeled camphor which was purified twice by sublimation to give 6.0 g of camphor, label 2.26% ^{18}O.

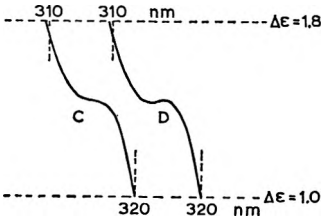


Figure 3.—Detail of the CD of labeled (C) and unlabeled (D) α-fenchocamphorone (in cyclohexane).

Labeling of Selenium Dioxide by Exchange.—Highly labeled selenium dioxide was prepared by exchange between selenium dioxide (4.9 g) and deuterated water (1.0 g, 91.8% ^{18}O; a gift of Professor E. Heilbronner, Basel) (16 hr on a bath at 130°). The water was then removed with a rotatory evaporator until the residue crystallized. Drying was effected in an oven over P_2O_5 *in vacuo*. Label was calculated on the basis of complete exchange 31.25% ^{18}O.

Oxidations of Labeled Camphor. Two Selected Experiments (A and B). A.—A mixture of labeled camphor (3.0 g, 2.19% ^{18}O), selenium dioxide (1.5 g), and acetic anhydride (3 ml) was heated for 3 hr at 145°. After removal of the solvent and sublimation the crude product (1.8 g) was separated by preparative glpc to give camphor (0.8 g) and camphorquinone (0.5 g, label 2.27% ^{18}O). Retention of label was 2.38% ^{18}O.

B.—A mixture of labeled camphor (2.5 g, 2.19% ^{18}O), selenium dioxide (1.85 g), and dry toluene (5 ml) was refluxed for 15.5 hr, then the solvent was removed, and the residue sublimed. Separation of the crude mixture (2.0 g) gave camphor (1.4 g) and camphorquinone (0.1 g) (label 2.32% ^{18}O). Retention of label was 2.38% ^{18}O.

Oxidation of Camphor Enol Benzoate with Labeled Selenium Dioxide.—A stirred mixture of benzene (9 ml), labeled selenium dioxide (3.0 g, 31.25% ^{18}O), and camphor enol benzoate (4.4 g) was heated at 150–160° in an autoclave for 3.3 hr. The reaction can be carried out in xylene as well (4 hr, reflux) but we chose benzene because it can be removed more easily. Methylene chloride was then added to the cooled reaction mixture which was filtered. Benzoic acid was removed by washing with $NaHCO_3$ solution. After sublimation the camphorquinone was purified by recrystallization (twice) from cyclohexane; the mother liquors were worked up by preparative glpc (SE-30 column). The yield was 2.0 g; 30.95% of the molecules was labeled with one ^{18}O; 3.58% was doubly labeled; the fragment (M − CO) had a label of 19.00% ^{18}O (32.5-eV spectrum), 19.07% ^{18}O (15-eV spectrum). These data seem consistent with a diketone, label 19.14% ^{18}O, the ^{18}O randomly distributed over the carbonyl groups; *viz.*, expected for this case were 30.95% of the molecules labeled with one ^{18}O, 3.66% doubly labeled, a fragment (M − CO) with a label of 19.14% ^{18}O. We should expect a random distribution of ^{18}O over the carbonyl groups only if both oxygen atoms of the diketone formed were provided by selenium dioxide, but the label of the diketone is about two-thirds of the value which this mechanism would suggest (19.14% instead of 31.25% ^{18}O); this loss of label might be due to exchange prior to oxidation.

According to our measurements, when optically pure camphor is used for the preparation of the enol benzoate, then oxidation of this enol benzoate gives optically pure camphorquinone.

(+)-Fenchone oxime (2) was prepared from (+)-fenchone (Fluka, purum) according to Wallach[39] in at least 80% yield: $[\alpha]_D$ +41.19° (absolute EtOH), mp 162–164° after recrystallization from heptane and dilute alcohol; lit.[28] $[\alpha]_D$ +46.5° (EtOH), mp 167°.

Fenchylamine (3) was prepared from 2 by reduction[40] with sodium and alcohol. The hydrochloride after two recrystallizations from dioxane had a specific rotation of $[\alpha]_D$ −4.53° (MeOH).

(−)-α-Fenchene (4).—The amine 3 was regenerated from the hydrochloride and treated with nitrous acid.[41] The reaction products were separated by fractional distillation using a Nester-Faust spinning band column (~20 cm). From 1.5 kg of 1 86 g

(36) J. H. Beynon and A. E. Williams, "Mass and Abundance Tables for Use in Mass Spectroscopy," Elsevier, Amsterdam, 1963, p 23.

(37) W. Reusch, M. W. DiCarlo, and L. Traynor, *J. Org. Chem.*, **26**, 1711 (1961).

(38) F. H. Lees, *J. Chem. Soc.*, **83**, 152 (1903).

(39) O. Wallach, *Justus Liebigs Ann. Chem.*, **263**, 136 (1891).

(40) O. Wallach, *Justus Liebigs Ann. Chem.*, **272**, 105 (1893).

(41) W. Hückel, *Ber.*, **80**, 39 (1947).

of α-fenchene fractions was obtained (purity >87.4%) that were used for the preparation of α-fenchocamphorone (5). For the measurements more pure 4 was obtained by careful redistillation (~20 cm, 2 ml/hour) of a forerun. The purest sample (99.54%) had $[\alpha]_D$ −42.62° (ethyl acetate).

(+)-α-**Fenchocamphorone** (5).—Some early terpene chemists[42] have prepared 5 by ozonization of 4, but Matsinen[20c] failed to reproduce their reasonable yields. We prepared 5 by oxidation of 4 with ruthenium tetroxide in methylene chloride in 65.5% yield. A sample of the crude ketone was sublimed; then mp 91–96°, $[\alpha]_D$ +57.93° (MeOH), was found. Another sample was oxidized with selenium dioxide,[9] and after distillation the oxidation product was purified by preparative glpc (SE-30 column) to remove unreacted ketone. After sublimation the α-fenchocamphoronequinone had mp 139.0–139.5°. No effect in CD could be detected. Therefore 5 was not contaminated with β-fenchocamphorone (10), because it would have been possible to detect β-fenchocamphoronequinone (11) by CD.[21]

(−)-α-**Fenchocamphorone hydrazone** (6) was prepared from 5 in the manner of Reusch, *et al.*,[37] in 74.4–82.2% yield. 6 was a liquid at room temperature, but crystallized on storing at −15°. Different angles of rotation were recorded for two preparations: $[\alpha]_D$ −51.27° and −58.32° (MeOH).

Hydrolysis of 6. Introduction of the Label. Labeling Procedure.—Into a degassed mixture of 6, labeled water, and ethylene chloride, attached to a high vacuum line, HBr was introduced. The method used is the same as was pursued for the labeling of camphor by hydrolysis of its hydrazone, but it was found more convenient to introduce HBr in the reaction mixture using a break-seal vessel. A break-seal vessel with two taps and a ground-glass joint (Figure 4) was flushed with HBr, the lower part of the vessel was then immersed in liquid nitrogen, and the calculated quantity of HBr (2 mol of HBr:1 mol of hydrazone) was admitted and condensed. The taps were melted off. Then the vessel was attached to the high vacuum line, the seal broken, the liquid nitrogen removed, and HBr frozen into the reaction mixture. As already described we used 4 g of water for the hydrolysis of 8.3 g of camphor hydrazone, and we obtained 6.0 g of camphor and 2.0 g of residue (azine). It might be expected that further reduction of the quantity of water with respect to the hydrazone would result in an increase of the yield of azine. In the case of 6 azine formation is sterically more easy than in the case of camphor hydrazone. Thus, when 8.3 g of camphor hydrazone was hydrolyzed with 2.0 g of water, 4.4 g of camphor and 3.2 g of residue were obtained, but 6 (7.6 g), hydrolyzed with water (2.0 g) in ethylene chloride (50 ml), gave 4.4 g of residue and 2.65 g of 5, mp 100–105°, $[\alpha]_D$ +65.10° (MeOH).

Labeling.—Water containing 0.31 at. % ^{17}O, 62.38 at. % ^{18}O, and 64.0 at. % D[6] was used. We used deuterated water enriched in ^{18}O, because it is less expensive than water enriched in ^{18}O where the deuterium content has been reduced to natural abundance. Thus 5 will be labeled with ^{18}O and deuterated, but only in the 3 position. Deuteration of norbornanones is well documented.[43] Introduction of D at the exo-3 position is easy, introduction of a second D is more difficult, and deuteration at the 6 position does not take place under our conditions.

6 (7.6 g) was hydrolyzed with labeled water (2.0 g) and HBr; 7 (2.45 g) was obtained and 4.75 g of residue of sublimation. Labels were calculated in the assumption that only monodeuteration had occurred: specific 3 deuteration 3.25%, label 62.72% ^{18}O.

Specifically Labeled α-Fenchocamphoronequinone. High Label Incorporation.—7 (2.40 g, 62.72% ^{18}O) was heated with selenium dioxide (1.53 g) and acetic anhydride (2.2 ml) (4 hr on a bath at 150°). By use of 20 ml of dry methylene chloride the reaction product was separated from selenium; it was washed with a bicarbonate solution until neutral and then with a saturated NaCl solution. The solvent was removed with suction and the residue distilled. Diketone and unreacted monoketone were separated by preparative glpc (SE-30 column): 0.86 g of 7 was recovered, mp 108–110°, specific 3 deuteration 3.44%,

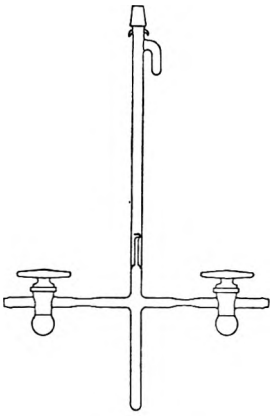


Figure 4.

label 60.19% ^{18}O; 0.55 g of 8 was obtained, 48.05% labeled specifically with ^{18}O, 50.87% unlabeled, and 0.08% doubly labeled with ^{18}O. A solution of 8 showed CD in both absorption bands between 250 and 520 nm. That the observed CD in the visible region was due to isotopic substitution could not be called to question because the precursor 7 does not absorb there, but it happens to be that the second absorption band of 8 at ~300 nm coincides with an absorption band of the precursor 7 and thus it had to be made sure that the observed CD of 8 at ~300 nm was indeed due to 8 and not due to the precursor. The CD band which we observed in this region was shaped like the CD band of 7, but it had a very unusual fine structure. Because of this band shape we suspected that traces of 7 interfered with the CD measurement. Indeed we showed 8 by glpc to be contaminated with 0.1–0.2% of 7. This impurity was removed by preparative glpc to yield 8 (0.4 g), mp 140.0–140.5°. Then CD was measured again; the observed CD curve is displayed in Figure 1.

The Ultimate Proof That the Observed CD of 8 Is Due Only to Isotopic Substitution Is an Exchange Experiment.—First CD and absorption were measured of a spectroscopic solution of 8 (24.2 mg) in heptane (10 ml). Then to this solution was added water (4 g) and acetic acid (1 g). This mixture was magnetically stirred at room temperature for 15.25 hr and neutralized, the layers were separated, and the hydrocarbon layer was used for measurement of CD and absorption. No CD could be detected which may serve as a proof of the purity of 8; the optical density in the visible region decreased by ~50% during this experiment. This might be due to formation of hydrate.[26]

Data of the CD Curve of 8.—The following were obtained: uv bands—$\Delta\epsilon_{max}$ 2.36 × 10^{-3} and peaks at 264.5, 268.3, 275.0, 279.8, 286.7, 292.3, 299.3, 306.6, 314.2, 322.5, 331.0, and 340.7 nm; visible band—$\Delta\epsilon_{min}$ −8.93 × 10^{-3} and peaks at 462.5 and 484.5 nm.

Experiment with Labeled Selenium Dioxide and Unlabeled Ketone.—Attempted preparation of (1S)-2-[^{18}O]-α-fenchocamphoronequinone, the antipode of 8, follows. Using labeled selenium dioxide (31.25% ^{18}O) and 5, and conditions as in the experiment with highly labeled 7, [^{18}O]-α-fenchocamphoronequinone was obtained. Some unreacted ketone (label 0.86% ^{18}O) was recovered. Of the diketone 10.62% was labeled with one ^{18}O and 0.27% was doubly labeled. If no exchange between selenium dioxide and the reaction medium had occurred, we should expect 31.25% of the diketone to be specifically labeled. Because of the low label the effect in CD of this diketone should be weak, but the two highest peaks in the visible band (Figure 1) should have been above noise level. [The maximum pen deflection expected in CD on the basis of the optical density of the solution of the diketone, its low isotopical purity (10.62%), and the observed CD of 8 (Figure 1) was 9 mm; the noise level of the CD apparatus was 3 mm.] However, no CD could be detected. Presumably (partial) racemization had occurred.

Exchange Experiment with 7 and 8 (Both Labeled by Exchange) in Acetic Anhydride.—A solution of 7 (0.4329 g) and 8 (0.4013 g) in acetic anhydride (2.1 g) was heated under reflux. Water was added with a syringe in 5-μl portions at intervals of 3 min. After addition of 30% of the calculated quantity of water (equal to 30% of 0.37 g), a sample of the mixture was taken for the determination of the labels; sampling was also done

(42) G. Komppa and S. V. Hintikka, *Ber.*, **47**, 936 (1914); R. H. Roschier, *Ann. Acad. Sci. Fenn., Ser. A*, **10** (1), 56 (1917).

(43) A. F. Thomas and B. Willhalm, *Tetrahedron Lett.*, **No. 18**, 1309 (1965); J. M. Jerkunica, S. Borcic, and D. E. Sunko, *ibid.*, **No. 49**, 4465 (1965); A. F. Thomas, R. A. Schneider, and J. Meinwald, *J. Amer. Chem. Soc.*, **89**, 68 (1967); T. T. Tidwell, *ibid.*, **92**, 1448 (1970).

when 50, 70, and 90% of the water had been added. The results are shown in the Table I.

TABLE I

Water, added, %	Diketone, labeled with one ^{18}O, %	Ketone, % ^{18}O
0	19.24	30.2
30	13.70	29.4
50	11.25	28.9
70	7.31	27.4
90	5.84	26.3

Acknowledgment.—The author is indebted to the Netherlands Organization for the Advancement of Pure Research (Z.W.O) for the sponsoring of this work. A NATO grant for the purchase of ^{18}O is gratefully acknowledged. It is with pleasure that the author expresses his gratitude to Dr. N. C. Rol (Shell Research N.V., Amsterdam) and Dr. Klebe, Dr. Van Thuyl, and Mr. Van Houte in this laboratory, who spent a great deal of time on the measurement of ^{18}O labels, to Professor W. Parker (Stirling) and to Professor H. Wynberg (Groningen) for their help in improving the presentation of this paper, and to Professor E. Heilbronner (Basel) whose gift of labeled water enabled us to do some experiments with highly labeled selenium dioxide. This work was done in the department of Professor L. J. Oosterhoff.

Registry No.—1, 4695-62-9; 2, 40514-83-8; 3, 21252-46-0; 4, 7378-37-2; 5, 40550-41-2; 6, 40550-42-3; 7, 40550-43-4; 8, 40550-44-5; water-^{18}O, 14314-42-2; selenium dioxide, 7446-08-4.

Chemistry of Cephalosporin Antibiotics. XXVII. 3-Methylenecephams

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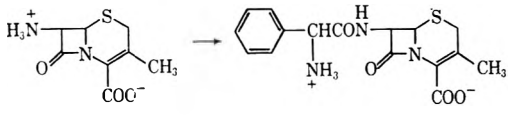
Recovered March 26, 1973

Cephalosporanic acids, in which the acetoxy group is displaced by sulfur nucleophiles, were reduced to 3-methylenecephams. Esterification procedures are described for preparing both 3-methylenecepham and 3-methyl-3-cephem esters. 7-Amino-3-methylenecepham-4-carboxylic acid and its esters were isomerized to 7-ADCA and 7-ADCA esters, respectively.

We have had considerable interest in recent years in developing new synthetic routes to deacetoxycephalosporins. A principal member of this series of antibiotics is cephalexin[1] (1). Syntheses of this orally active compound include acylations of either 7-aminodeacetoxycephalosporanic acid (7-ADCA, 2)[2] obtained by hydrogenolysis of 7-ACA[3] or 7-aminodeacetoxycephalosporanic acid esters (3)[4] produced in the ring expansion of penicillin sulfoxides.[5] This paper reports the preparation of 3-methylenecephams[6] and their conversions to 2 and 3.



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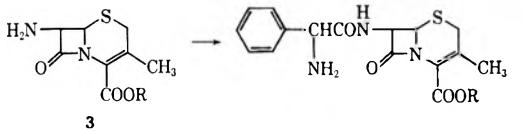


3

We anticipated that a selective desulfurization of cephalosporins in which the acetoxy group at C_3 methylene has been displaced by sulfur nucleophiles (4) would lead to deacetoxycephalosporins (5). While some 3-methyl-3-cephems (5) indeed formed in the treatment of these sulfur-derivatized cephalosporins with Raney nickel, 3-methylenecephams (6) constituted the major products. Other reducing conditions, notably zinc–formic acid–DMF, were also effective in this conversion.

The nmr spectra of 3-methylenecephams show a singlet at τ 4.9 for the C_4 proton and a doublet near τ 4.7 for the *exo*-methylene grouping. The uv chromophore at 268 mμ, characteristic of β-lactam-Δ^3-unsaturation system in cephalosporins, is not seen with 3-methylenecephams. 3-Methylenecepham acids are devoid of antibiotic activity.

Earlier reports of 3-methylenecephams include an isolation of methyl 7-phenoxyacetamido-3-methylenecepham-4-carboxylate as a minor product with 7-phenoxyacetamidodeacetoxycephalosporin methyl ester from ring expansion of penicillin V sulfoxide methyl ester.[6a] More recently Ochiai, *et al.*, published a reductive cleavage of the acetoxy group in cephalosporanic acids using chromium(II) salts that led to 3-methylenecephams in quite respectable yield.[6f]

The starting materials (4) were prepared by known procedures.[7] A variety of cephalosporanic acids were treated with selected nucleophiles (such as thiourea, thiobenzoic acid, potassium ethyl xanthate, and sodium thiosulfate) in neutral, aqueous solutions at 50° for 20 hr. Two separate reductive cleavages of the CH_2–S bond at C-3 in 4 were conducted.

(1) Cephalexin is the generic name for 7-(D-2-amino-2-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid; cephalexin monohydrate, Keflex, Lilly.

(2) C. W. Ryan, R. L. Simon, and E. M. Van Heyningen, *J. Med. Chem.*, **12**, 310 (1969).

(3) R. J. Stedman, K. Severed, and J. R. E. Hoover, *J. Med. Chem.*, **7**, 117 (1964).

(4) R. R. Chauvette, P. A. Pennington, C. W. Ryan, R. D. G. Cooper, F. L. Jose, I. G. Wright, E. M. Van Heyningen, and G. W. Huffman, *J. Org. Chem.*, **36**, 1259 (1971).

(5) R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon, and S. L. Andrews, *J. Amer. Chem. Soc.*, **85**, 1896 (1963); **91**, 1401 (1969).

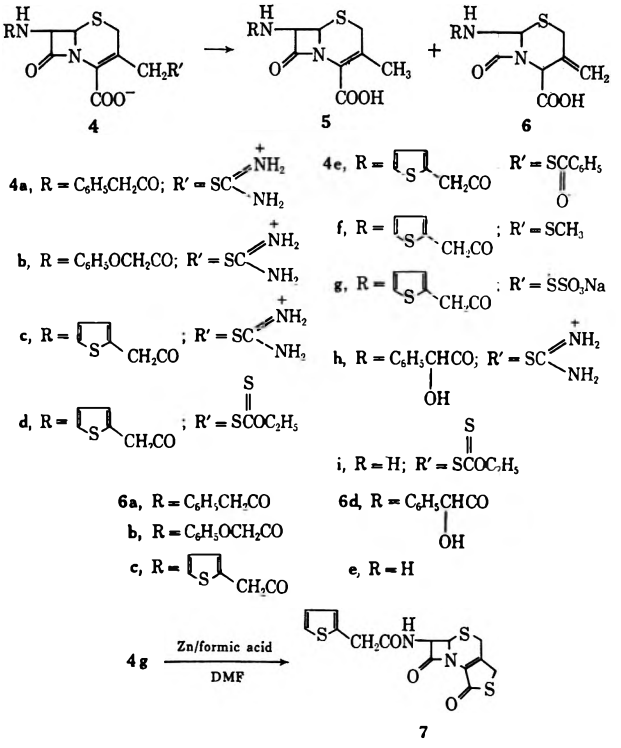
(6) (a) R. B. Morin, private communication, 1962; U. S. Patent 3,275,626 (1966); (b) M. Ochiai, O. Aki, A. Morimoto, T. Okada, K. Shinozaki, and Y. Asaki, *Tetrahedron Lett.*, 2341 (1972); (c) M. Ochiai, O. Aki, A. Morimoto, T. Okada, and T. Kaneko, *ibid.*, 2345 (1972); (d) M. Ochiai, O. Aki, A. Morimoto, and T. Okada, *ibid.*, 3241 (1972); (e) M. Ochiai, E. Mizuto, O. Aki, A. Morimoto, and T. Okada, *ibid.*, 3245 (1972); (f) M. Ochiai, O. Aki, A. Morimoto, T. Okada, and H. Shimadzu, *J. Chem. Soc., Chem. Commun.*, 800 (1972).

(7) (a) J. D. Cocker, B. R. Cowley, J. S. G. Cox, S. Eardley, G. I. Gregory, J. K. Lazenby, A. G. Long, J. C. P. Sly, and G. A. Somerfield, *J. Chem. Soc.*, 5015 (1965); (b) E. M. Van Heyningen and C. N. Brown, *J. Med. Chem.*, **8**, 174 (1965); (c) Netherlands Patent 6,916,634 (1970).

In method A, commercial Raney nickel was used in aqueous ethanol solutions with **4**, under low pressure, room temperature, and overnight hydrogenation conditions.

In method B, zinc dust in tetrahydrofuran–formic acid solutions of **4**, containing catalytic dimethylformamide, were stirred at room temperature overnight. Mixtures of solvents (sometimes including water) were chosen that effectively solubilized the starting material.

The Raney nickel reduction generally gave high yields of 3-methyl-3-cephems (**5**) and 3-methylenecephams (**6**) in a product ratio of 1:4–1:5[8] from iso-

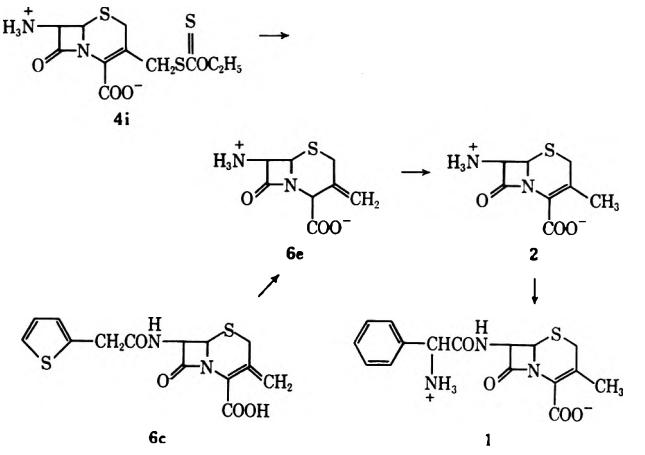


thiouronium (**4a,b,c,h**), xanthate (**4d,i**), and Bunte (**4g**) derivatives but were incomplete (generally about 50–60% conversions) with thiobenzoate (**4e**) and sulfide (**4f**) derivatives.

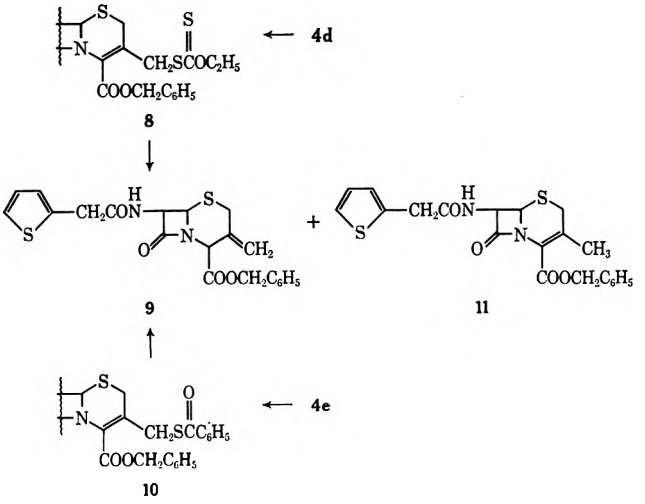
The zinc–formic acid–DMF reduction effectively reduced all starting materials except the Bunte salt (**4g**). The acidic conditions of this reaction converted **4g** largely to thiolactone **7**. Also, the zinc–formic acid–DMF reduction often yielded a nearly 1:1 product distribution[8] of **5** and **6** from thiobenzoates such as compound **4e**.

It should be noted that in contrast to the method of Ochiai, *et al.*,[6] which converts cephalosporanic acids to 3-methylene cephams, neither Raney nickel nor zinc–formic acid–DMF produced more than minor amounts of 3-methylenecephams and deacetoxycephalosporanic acids from cephalosporanic acids.

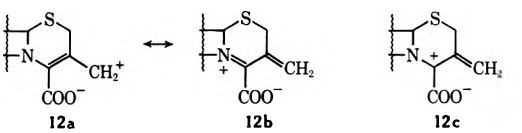
The 3-methylenecepham nucleus (**6e**) was obtained by two different routes. Compound **4i**, prepared by a modification of a reported procedure,[9] was subjected to the Raney nickel reduction conditions. Product **6e** was precipitated from concentrated water solutions at its isoelectric point. Alternatively, the side chain of 3-methylenecepham **6c** was removed in the imino chloride reaction,[10] with silylation[11] and with mixed anhydride[12] protection of the C_4-carboxyl group, to afford **6e**.



An interesting variant of the reduction of these sulfur-derivatized cephalosporins is the reduction of their C_4-esterified analogs. When treated with Raney nickel, the benzyl ester of the xanthate derivative **8** gave a product mixture that was 80% **9** and 20% **11** as determined from the nmr spectrum. Similarly, zinc–formic acid–DMF converted the benzyl ester of the thiobenzoate derivative **10** to a mixture of **9** and **11** in a 2:3 product ratio, as detected in the nmr spectrum.



A carbonium ion (**12a**) stabilized by resonance forms **12b** and **12c** has been suggested as a probable inter-



mediate in the nucleophilic displacement of the acetoxy group of cephalosporanic acids in their free acid form and in aqueous solutions.[7a] The same carbonium ion was invoked as an initial step in the formation of 3-methylenecephams by chromium(II) reductions of

(8) Product ratio was assessed by silica gel tlc (Me_2CO–HOAc, 16:1, and MeCN–H_2O, 7:3) and by nmr analysis of crude reaction products.

(9) U. S. Patent 3,446,803 (1969).

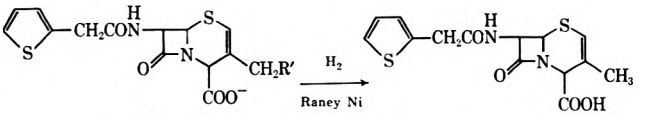
(10) F. M. Huber, R. R. Chauvette, and B. G. Jackson in "Cephalosporins and Penicillins: Chemistry and Biology," E. H. Flynn, Ed., Academic Press, New York, N. Y., 1972, Chapter 2.

(11) B. Fechtig, H. Peter, H. Bickel, and E. Vischer, *Helv. Chim. Acta*, **51**, 1108 (1968).

(12) R. R. Chauvette, H. B. Hayes, G. L. Huff, and P. A. Pennington, *J. Antibiot. (Tokyo)*, **XXV**, 248 (1972).

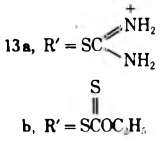
cephalosporins, as free acids and in aqueous media.[6f] Our results with **8** and **10** indicate that, if such a carbonium ion intermediate were involved at all, it does not require the presence of a free carboxyl group at C_4 during C–S bond cleavage at the C_3 CH_2.

As an extension of these reduction studies, we prepared isothiouronium salt **13a** and xanthate **13b** derivatives in the 2-cephem series. The reduction of **13a** and **13b** with Raney nickel gave exclusively the 3-methyl-2-cephem compounds **14**. Zinc–formic acid–DMF reduction of these led to mixtures of **14** and the



13 14

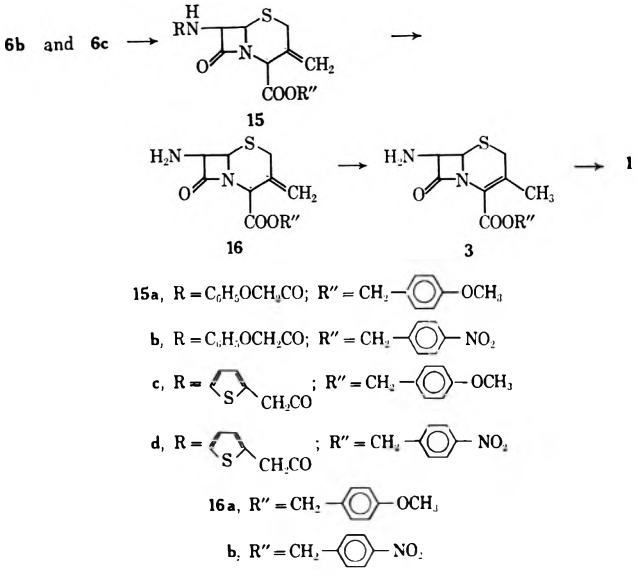
13 $\xrightarrow{\text{Zn/formic acid/DMF}}$ 14 + 6c



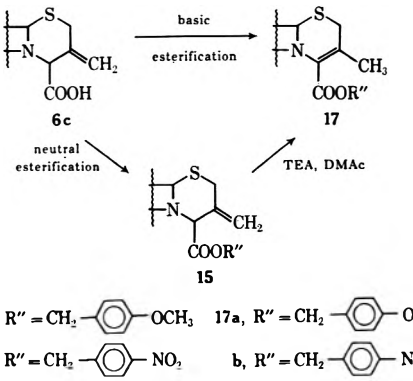
3-methylenecepham **6c** in 6:4–7:3 product ratios as calculated from their nmr spectra.

Both **6b** and **6c**, as *p*-methoxybenzyl (**15a** and **15c**) and *p*-nitrobenzyl (**15b** and **15d**) esters, smoothly underwent side-chain cleavage reactions to their corresponding 7-amino-3-methylenecepham esters **16a** and **16b**.

Esters **15a–d** were prepared using exactly 1 equiv of base in coupling reactions of 3-methylenecepham acids



with benzyl bromides. The same esterification, in the presence of excess base, resulted in double-bond isomerization, giving rise to deacetoxycephalosporin esters **17**. Predictably, 3-methylenecepham esters **15**, dissolved in dimethylacetamide containing a few drops of triethylamine and stored at room temperature overnight, converted to deacetoxycephalosporin esters **17**. Thus, **6c** afforded the *p*-methoxybenzyl ester **17a** and *p*-nitrobenzyl ester **17b** of deacetoxycephalothin either directly or *via* the 3-methylenecepham esters **15** followed by an isomerization step.



This conversion of 3-methylenecephams to 3-methyl-3-cephems effectively provided a new, efficient alternate synthesis of cephalexin. Trimethylsilylation of the 3-methylenecepham nucleus (**6e**), under basic conditions, led to the isolation of **2** in nearly quantitative yield. Its *p*-nitrobenzyl ester (**16b**), as a hydrochloride, was isomerized to **3** in high yield in dimethylacetamide containing triethylamine in excess of 1 equiv.

Alternately, hexamethyldisilazane reacted with 7-(thiophene-2-acetamido)-3-methylenecepham-4-carboxylic acid (**6c**) to simultaneously protect the C_4 carboxyl group and isomerize the double bond by reason of its basicity. The reaction mixture was subjected to the imino chloride side-chain cleavage reaction, leading to the isolation of 7-ADCA (**2**) in 75% overall yield.

Nmr, ir, and uv spectra of both 7-ADCA (**2**) and 7-ADCA ester (**3**) obtained from the reactions just described were identical with those of authentic material. Since both these compounds (**2** and **3**) were integral parts of earlier syntheses,[2,4] this work represents another synthesis of cephalexin from cephalosporanic acids *via* 3-methylenecephams.

Experimental Section[13]

Reduction of Compounds 4a–k, 8, 10, 13a, and 13b. Method A.—3-Amidinothiomethyl-7-(phenoxy-2-acetamido)-3-cephem-4-carboxylic acid inner salt (**4b**), 1 g (2.4 mmol), was dissolved in 50 ml of H_2O and 50 ml of EtOH and hydrogenated at room temperature overnight in a Parr apparatus, using 45 psi of H_2 and 6 g of Raney nickel. The catalyst was filtered and washed with alcohol. The filtrate and wash were combined and concentrated *in vacuo* to remove the alcohol. The aqueous residue was slurried with EtOAc, cooled in ice, and acidified to pH 2.5 with concentrated HCl. The EtOAc solution was separated, washed with H_2O, dried ($MgSO_4$), and concentrated to a smaller volume for crystallization. Yield of 7-(phenoxy-2-acetamido)-3-methylenecepham-4-carboxylic acid (**16b**) was 650 mg (82%).

Method B.—3-Benzoylthiomethyl-7-(thiophene-2-acetamido)-3-cephem-4-carboxylic acid sodium salt (**4e**), 5 g (10 mmol), was dissolved in a mixture of 55 ml of THF, 15 ml of H_2O, 15 ml of formic acid, and 15 ml of DMF. Zinc dust, 6.5 g (100 mmol), was added and the mixture was stirred at room temperature overnight. The spent zinc was filtered and washed with THF. The filtrate and wash were combined and concentrated *in vacuo* to remove lower boiling solvents. The aqueous residue was extracted with EtOAc. The EtOAc solution was washed with HCl to remove DMF and with H_2O and then dried ($MgSO_4$). The EtOAc solution was either concentrated *in vacuo* to about 20 ml and cooled in ice or exchanged for CH_2Cl_2 for fractional crystallization of 7-(thiophene-2-acetamido)-3-

(13) Whenever possible, a single exemplifying experimental description is given as it applies in a general way to numerous compounds. Characterization data for individual products appears in Table I. Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds listed in the table.

TABLE I

Compd	Solvent of crystallization and mp, °C	Characterization data
6a	EtOAc 158–159	Nmr (100 Mc, DMSO-d_6) τ 6.65–6.32 (AB q, s, 4 H, C-2 H_2 and α-CH_2), 4.88 (s, 1 H, C-4 H), 4.80–4.70 (s, d, 3 H, C-3 CH_2 and C-6 H), 4.55 (q, 1 H, C-7 H), 2.73 (s, 5 H, aromatic H), and 0.92 (d, 1 H, C-7 NH).
6b	EtOAc 182–183	Nmr (A60 Mc, DMSO-d_6) τ 6.49 (s, 2 H, C-2 H_2), 5.40 (s, 2 H, α-CH_2), 4.90 (s, 1 H, C-4 H), 4.80–4.40 (m, 4 H, C-3 CH_2, C-6 H, and C-7 H), 3.20–2.60 (m, 5 H, aromatic H), and 0.92 (d, 1 H, C-7 NH).
6c	CH_2Cl_2 178	Nmr (A60 Mc, DMSO-d_6) τ 6.49 (AB q, 2 H, C-2 H_2), 6.24 (s, 2 H), α-CH_2), 4.90 (s, 1 H, C-4 H), 4.80–4.41 (m, 4 H, C-6 H, C-3 CH_2, and C-7 H), 3.12–2.55 (m, 3 H, aromatic H), and 0.98 (d, 1 H, C-7 NH).
6d	EtOAc	Nmr (A60 Mc, D_2O, $NaHCO_3$) τ 6.60 (AB q, 2 H, C-2 H_2), 5.02 (s, 1 H, C-4 H), 4.8–4.5 (m, 5 H, C-3 CH_2, α-CH, C-6 H, and C-7 H), 2.55 (s, 5 H, aromatic H).
6e	H_2O >144° dec	Nmr (A60 Mc, DMSO-d_6) τ 6.52 (AB q, 2 H, C-2 H_2), 5.50 (d, 1 H, C-6 H), 5.11 (s, 1 H, C-4 H), 4.9–4.8 (m, 3 H, C-3 CH_2 and C-7 H), and 4.2 (broad s, washed out by D_2O).
7	EtOAc	Nmr (100 Mc, DMSO-d_6) τ 6.20 (s, 2 H, C-2 H_2), 6.13 (s, 2 H, α-CH_2), 5.67 (s, 2 H, C-3 CH_2), 5.89 (d, 1 H, C-6 H), 4.20 (q, 1 H, C-7 H), 3.1–2.55 (m, 3 H, aromatic H), and 0.83 (d, 1 H, C-7 NH).
15a	$MeCl_2$–Et_2O 108–109	Nmr (T60 Mc, $CDCl_3$) τ 6.66 (AB q, 2 H, C-2 H_2), 6.21 (s, 3 H, p-OCH_3), 5.50 (s, 2 H, α-CH_2), 4.92–4.50 (m, 6 H, C-4 H, C-3 CH_2, ester CH_2, and C-6 H), 4.35 (q, 1 H, C-7 H), and 3.15–2.55 (m, 10 H, aromatic H and C-7 NH).
15b	EtOAc–Et_2O 84–94 dec	Nmr (A60 Mc, $CDCl_3$) τ 6.58 (AB q, 2 H, C-2 H_2), 5.47 (s, 2 H, α-CH_2), 4.80–4.50 (m, 6 H, C-4 H, C-3 CH_2, ester CH_2, and C-6 H), 4.25 (q, 1 H, C-7 H), 3.20–1.65 (m, 10 H, aromatic H and C-7 NH).
15c	EtOAc 114	Nmr (A60 Mc, $CDCl_3$) τ 6.65 (q, 2 H, C-2 H_2), 4.20 (s, 5 H, p-OCH_3 and α-CH_2), 4.95–4.75 (m, 5 H, C-4 H, C-3 CH_2, and ester CH_2), 4.66 (d, 1 H, C-6 H) 4.38 (q, 1 H, C-7 H), and 3.3–2.6 (m, 8 H, aromatic H and C-7 NH).
15d	EtOAc 139–141	Nmr (A60 Mc, DMSO-d_6) τ 6.42 (s, 2 H, C-2 H_2), 6.18 (s, 2 H, α-CH_2), 4.7–4.3 (m, 7 H, C-4 H, ester CH_2, C-3 CH_2, C-6 H, and C-7 H), 3.1–1.6 (m, 7 H, aromatic H), and 0.82 (d, 1 H, C-7 NH).
16a (tosylate)	EtOAc EtOH–Et_2O	Nmr (A60 Mc, DMSO-d_6) τ 7.69 (s, 3 H, p-CH_3), 6.41 (2 d, 2 H, C-2 H_2), 6.23 (s, 3 H, p-OCH_3), 5.0 (d, 1 H, C-6 H), 4.85–4.55 (m, 6, C-4 H, ester CH_2, C-3 CH_2, and C-7 H), and 3.2–2.2 (2 q, 8 H, aromatic H).
16a (HCl)	Me_2Cl_2 EtOH–Et_2O >165 dec	Nmr (T60 Mc, DMSO-d_6) τ 6.47 (s, 2 H, C-2 H_2), 6.23 (s, 3 H, p-OCH_3), 5.12 (d, 1 H, C-6 H), 4.9–4.6 (m, 6 H, C-4 H, ester CH_2, C-3 CH_2, and C-7 H), and 2.86 (q, 4 H, aromatic H).
16b (tosylate)	EtOAc EtOH–Et_2O 145–182 —dec	Nmr (T60 Mc, DMSO-d_6) τ 7.70 (s, 3 H, p-CH_3), 6.39 (s, 2 H, C-2 H_2), 4.98 (d, 1 H, C-6 H), 4.7–4.3 (m, 6 H, C-4 H, ester CH_2, C-3 CH_2, and C-7 H), and 2.95–1.68 (2 q, 8 H, aromatic H).
16b (HCl)	$MeCl_2$ EtOH–Et_2O 160–176 dec	Nmr (A60 Mc, DMSO-d_6) τ 6.34 (AB q, 2 H, C-2 H_2), 4.98 (d, 1 H, C-6 H), 4.7–4.4 (m, 6 H, C-4 H, ester CH_2, C-3 CH_2, and C-7 H), and 2.0 (q, 4 H, aromatic H).
17a	EtOAc 160	Nmr (A60 Mc, $CDCl_3$) τ 7.92 (s, 3 H, C-3 CH_3), 6.75 (AB q, 2 H, C-2 H_2), 6.21 (s, 3 H, p-OCH_3), 6.18 (s, 2 H, α-CH_2), 5.11 (d, 1 H, C-6 H), 4.83 (s, 2 H, ester CH_2), 4.29 (q, 1 H, C-7 H), and 3.21–2.60 (m, 8 H, aromatic H and C-7 NH).
17b	EtOAc 217	Nmr (A60 Mc, DMSO-d_6) τ 7.91 (s, 3 H, C-3 CH_3), 6.47 (AB q, 2 H, C-2 H_2), 6.20 (s, 2 H, α-CH_2), 4.89 (d, 1 H, C-6 H), 4.60 (s, 2 H, ester CH_2), 4.30 (q, 1 H, C-7 H), 3.1–1.65 (m, 7 H, aromatic H), and 0.88 (d, 1 H, C-7 NH).

methylenecepham-4-carboxylic acid (6c) (Table I), 1.2–2.0 g (35–42%).

7-Amino-3-ethoxythionocarbonylthiomethyl-3-cephem-4-carboxylic Acid Sodium Salt (4i).—In a modification of the literature preparation,[9] 80% pure 7-ACA, 6.9 g (20 mmol), was dissolved in 69 ml of H_2O containing sodium bicarbonate, 2.1 g (25 mmol). Ethylxanthic acid potassium salt, 4.0 g (25 mmol), was added and the mixture was heated in an oil bath at 65° for 4 hr. The product crystallized from the cooled reaction mixture, 2.5 g. A second, equal size crop of product was obtained on adjusting the pH to 5.

7-Amino-3-methylenecepham-4-carboxylic Acid (6e). Method A.—7-Amino-3-ethoxythionocarbonylthiomethyl-3-cephem-4-carboxylic acid (4i), 11 g (31 mmol), was dissolved in 260 ml of $NaHCO_3$ solution and 40 ml of EtOH and hydrogenated in the usual way with 66 g of Raney nickel. The catalyst was filtered and washed with H_2O. The combined filtrate and wash were cooled to ice temperature and adjusted to pH 3.5 with concentrated HCl. A 2.2-g precipitate of unreacted starting material was separated. Concentration to near dryness *in vacuo* precipitated the crude product. Recrystallization from H_2O afforded 4.5 g (67%) of 6e.

TABLE II

Compd	Solvent of crystallization and mp, °C	Analysis
6a	EtOAc 158–159	*Anal.* Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.82; H, 4.85; N, 8.43. Found: C, 57.84; H, 5.04; N, 8.31.
6b	EtOAc 182–183	*Anal.* Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.17; H, 4.63; N, 8.04. Found: C, 55.38; H, 4.86; N, 8.09.
6c	CH_2Cl_2 178	*Anal.* Calcd for $C_{14}H_{14}N_2O_4S_2$: C, 49.71; H, 4.17; N, 8.28. Found: C, 49.58; H, 4.36; N, 8.25.
4h	H_2O 189–200 dec	*Anal.* Calcd for $C_{17}H_{18}N_4O_5S_2 \cdot H_2O$: C, 46.35; H, 4.57; N, 12.72. Found: C, 46.54; H, 4.82; N, 12.67.
6d	EtOAc	*Anal.* Calcd for $C_{16}H_{16}N_2O_5S$: C, 55.16; H, 4.63; N, 8.04. Found: C, 55.29; H, 4.91; N, 7.75.
6e	H_2O >144 dec	*Anal.* Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.70; N, 13.08. Found: C, 45.12; H, 4.73; N, 13.11.
7	EtOAc	*Anal.* Calcd for $C_{14}H_{12}N_2O_3S_2$: C, 47.71; H, 3.43; N, 7.94; S, 27.29. Found: C, 47.77; H, 3.60; N, 7.67; S, 27.05.
8	EtOAc–Et_2O 150–152	*Anal.* Calcd for $C_{24}H_{24}N_2O_5S_4 \cdot {}^1/_2Et_2O$: C, 53.30; H, 4.99; N, 4.78. Found: C, 53.80; H, 4.81; N, 4.99.
10	EtOAc 150–151	*Anal.* Calcd for $C_{28}H_{24}N_2O_5S_2$: C, 59.56; H, 4.28; N, 4.96. Found: C, 59.53; H, 4.57; N, 5.12.
13a	H_2O ~194 dec	*Anal.* Calcd for $C_{15}H_{16}N_4O_4S_2$: C, 43.68; H, 3.91; N, 13.58. Found: C, 43.48; H, 3.94; N, 13.32.
13b	H_2O ~154 dec	*Anal.* Calcd for $C_{17}H_{17}N_2O_5S_4Na \cdot H_2O$: C, 40.94; H, 3.84; N, 5.61. Found: C, 41.30; H, 4.30; N, 5.76.
15a	$MeCl_2$–Et_2O 108–109	*Anal.* Calcd for $C_{24}H_{24}N_2O_6S$: C, 61.53; H, 5.16; N, 5.98. Found: C, 61.29; H, 4.94; N, 5.70.
15b	EtOAc–Et_2O 84–94 dec	*Anal.* Calcd for $C_{23}H_{21}N_3O_7S$: C, 57.14; H, 4.38; N, 8.69. Found: C, 56.86; H, 4.32; N, 8.44.
15c	EtOAc 114°	*Anal.* Calcd for $C_{22}H_{22}N_2O_5S_2$: C, 57.64; H, 4.84; N, 6.11. Found: C, 57.76; H, 4.94; N, 6.02.
15d	EtOAc 139–141	*Anal.* Calcd for $C_{21}H_{19}N_3O_6S_2$: C, 53.27; H, 4.04; N, 8.87. Found: C, 52.99; H, 3.98; N, 8.93.
16a tosylate	EtOAc EtOH–Et_2O	*Anal.* Calcd for $C_{23}H_{26}N_2O_7S_2$: C, 54.53; H, 5.17; N, 5.53. Found: C, 54.33; H, 5.05; N, 5.47.
16a (HCl)	Me_2Cl_2 EtOH–Et_2O >165 dec	*Anal.* Calcd for $C_{16}H_{19}N_2O_4SCl$: C, 51.82; H, 5.16; N, 7.55. Found: C, 51.65; H, 5.04; N, 7.72.
16b tosylate	EtOAc EtOH–Et_2O 145–182 dec	*Anal.* Calcd for $C_{22}H_{23}N_3O_8S_2$: C, 50.66; H, 4.45; N, 8.06. Found: C, 50.41; H, 4.51; N, 7.86.
16b (HCl)	$MeCl_2$ EtOH–Et_2O 160–176 dec	*Anal.* Calcd for $C_{15}H_{16}N_3O_5SCl$: C, 46.69; H, 4.18; N, 10.89. Found: C, 46.40; H, 4.20; N, 10.62.
17a	EtOAc 160°	*Anal.* Calcd for $C_{22}H_{22}N_2O_5S_2$: C, 57.64; H, 4.84; N, 6.11. Found: C, 57.39; H, 5.11; N, 5.89.
17b	EtOAc 217°	*Anal.* Calcd for $C_{21}H_{19}N_3O_6S_2$: C, 53.28; H, 4.05; N, 8.88. Found: C, 53.01; H, 4.22; N, 8.94.

Method B.—7-(Thiophene-2-acetamido)-3-methylenecepham-4-carboxylic acid (6c), 1.7 g (5 mmol), was suspended in 40 ml of $MeCl_2$ and treated with diethylaniline, 850 mg (5.7 mmol), acetyl chloride, 430 mg (5.5 mmol), and 4 drops of DMF. The starting material went into solution within 5 min. The mixture was cooled in a carbon tetrachloride–Dry Ice bath for addition of diethylaniline, 1.28 g (8.5 mmol), and phosphorus pentachloride, 1.2 g (5.8 mmol). After 1.5 hr, 12 ml of cold MeOH was added followed by 20 ml of H_2O after another 1.5-hr reaction time. The cooling bath was removed and the aqueous layer was separated, washed with EtOAc, adjusted to pH 3.6, and evaporated to near dryness *in vacuo*. The crystalline residue was triturated with acetone to remove diethylaniline, leaving 700 mg of 6e.

Esterification of 4d, 4e, 6b, and 6c with a Stoichiometric Amount of Base.—7-(Thiophene-2-acetamido)-3-methylenecepham-4-carboxylic acid (6c) sodium salt, 700 mg (2 mmol), was dissolved in 7 ml of dimethylacetamide and treated with anisyl bromide, 600 mg (3 mmol), at room temperature overnight. The mixture was poured into H_2O–EtOAc. The EtOAc layer was separated, washed successively with 5% HCl, 5% $NaHCO_3$ solution, and H_2O, dried ($MgSO_4$), concentrated to a small volume *in vacuo*, and cooled for crystallization. The yield of *p*-methoxybenzyl 7-(thiophene-2-acetamido)-3-methylenecepham-4-carboxylate (15c) was 570 mg (62%).

Esterification of 6c with Excess Base.—7-(Thiophene-2-acetamido)-3-methylenecepham-4-carboxylic acid (6c), 3.4 (10 mmol), was dissolved in 34 ml of DMAc. *p*-Nitrobenzyl bromide, 2.4 g (11 mmol), and triethylamine, 2.2 g (22 mmol), were added and the mixture was stored at room temperature overnight. The precipitated triethylamine hydrobromide was filtered. The filtrate was added to cold H_2O–EtOAc. The EtOAc layer was separated, washed successively with cold 5% HCl, 5% $NaHCO_3$ solution, and water, and dried ($MgSO_4$). The EtOAc solution was concentrated *in vacuo* to a smaller volume for crystallization. Yield of *p*-nitrobenzyl 7-(thiophene-2-acetamido)-3-methyl-3-cephem-4-carboxylate (17b) was 3.0 g (64%).

Side Chain Cleavage of 3-Methylenecepham Esters 15a–d.—*p*-Nitrobenzyl 7-(thiophene-2-acetamido)-3-methylenecepham-4-carboxylate (15d), 12 g (25 mmol), was dissolved in 130 ml of CH_2Cl_2. Dry pyridine, 2.45 g (31 mmol), and phosphorus pentachloride, 6.0 g (25 mmol), were added. The mixture was stirred at room temperature for 2 hr. After the reaction mixture was cooled in an ice–H_2O bath, 12.5 ml of isobutyl alcohol was added. The mixture was stirred in the cold for 2 hr. The product crystallized from the reaction mixture. Filtering and washing the precipitate with CH_2Cl_2 afforded 8.6 g (90%) of *p*-nitrobenzyl 7-amino-3-methylenecepham-4-carboxylate (16b) as a hydrochloride. Alternatively, in the place of cooling the reaction mixture, cold methanol was added and then H_2O. Work-up then consisted in separating the aqueous layer and adjusting the pH to 7 in the presence of EtOAc. The EtOAc layer was separated, washed with H_2O, dried ($MgSO_4$), and treated with slightly more than 1 equiv of *p*-toluenesulfuric acid monohydrate. The product (16b) crystallized in 60% yield as a tosylate salt.

Isomerization of 3-Methylenecephams. 7-Amino-3-methyl-4-carboxylic Acid (2). Method A.—7-Amino-3-methylenecepham-4-carboxylic acid (6e), 215 mg (1 mmol), was suspended in 5 ml of MeCN and treated with an excess of *N*-trimethylsilylacetamide. Three drops of triethylamine was added to the clear solution after 45 min; 1 ml of MeOH was added after 2 hr. Addition of 0.1 *N* HCl to pH 3.6 precipitated 200 mg of product.

Method B.—7-(Thiophene-2-acetamido)-3-methylenecepham-4-carboxylic acid (6c), 2 g (5.9 mmol), was dissolved in 40 ml of MeCN. Hexamethyldisilazane (6 mmol) was added and the solution was stored at room temperature for 4 days. The solvent was exchanged for $MeCl_2$, cooled to −20°, and treated with diethylaniline, 1.46 g (10 mmol), and phosphorus pentachloride,

1.3 g (6.4 mmol). The mixture was stirred for 30 min; 7 ml of MeOH was added, followed after 45 min with 17 ml of H_2O. The aqueous phase was separated, washed with $MeCl_2$, and adjusted to pH 3.6 with saturated $(NH_4)HCO_3$ solution. The precipitated 7-ADCA (2) weighed 900 mg (75% overall yield).

p-Nitrobenzyl 7-Amino-3-methyl-3-cephem-4-carboxylate (3) Hydrochloride Salt.—*p*-Nitrobenzyl 7-amino-3-methylenecepham-4-carboxylate (16b) hydrochloride salt, 386 mg (1 mmol), was dissolved in 5 ml of DMAc containing triethylamine, 198 mg (2 mmol). The mixture was stored at room temperature for 3 hr. The reaction mixture was poured into H_2O–EtOAc. The EtOAc layer was separated, washed with H_2O, dried ($MgSO_4$), and concentrated *in vacuo* to a volume of about 10 ml; 10 ml of 0.1 *N* HCl in EtOAc was added. A crystalline precipitate formed immediately. The product was filtered, washed with EtOAc, and vacuum dried, yield 320 mg (83%).

See Table II for analytical data.

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Polynitroalkyl Ethers[1]

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Polynitroethyl ethers were prepared by nitration of the corresponding oximes. Thus, nitration of (2-fluoro-2,2-dinitroethoxy)acetaldoxime followed by oxidation of the nitroso intermediate yielded 2-fluoro-2,2-dinitroethyl 2,2-dinitroethyl ether (1). Fluorination and chlorination of 1 yielded bis(2-fluoro-2,2-dinitroethyl) and 2-chloro-2,2-dinitroethyl 2-fluoro-2,2-dinitroethyl ether, respectively. Formaldehyde and 1 yielded 3-(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropyl formal. 2-Fluoro-2,2-dinitroethyl glycidyl ether reacted with 2-fluoro-2,2-dinitroethanol to give 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2-propanol, which was oxidized with chromic acid to 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone. Nitration of the oxime of this ketone and oxidation of the nitroso intermediate yielded 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropane. Decomposition of 2-fluoro-2,2-dinitroethanol in alkaline solutions is suppressed by formaldehyde. Under these conditions propargyl bromide gave 2-fluoro-2,2-dinitroethyl propargyl ether. Five 1-(2-fluoro-2,2-dinitroethoxy)-2-propanol derivatives, $FC(NO_2)_2CH_2OCH_2CH(OH)CH_2X$ [X = Cl, Br, I, ONO_2, $OCOC(CH_3)_3$], were synthesized by treating 2-fluoro-2,2-dinitroethyl glycidyl ether with HX. Three of these were oxidized to the corresponding acetone derivatives, $FC(NO_2)_2CH_2OCH_2COCH_2X$ [X = Cl, ONO_2, $OCOC(CH_3)_3$].

Although 2-fluoro-2,2-dinitroethanol can be alkylated in aqueous alkaline solution by reagents such as allyl bromide, methyl sulfate, and simple epoxides to give the corresponding 2-fluoro-2,2-dinitroethyl ethers,[2] alkylating agents with nitro substituents do not yield polynitroalkyl ethers.[3] 2-2-Dinitro alcohols cannot be dehydrated to the corresponding ethers,[4] and bis(2,2-dinitroalkyl) ethers, therefore, must be synthesized indirectly. A recent patent[5] describes the synthesis of bis(2-fluoro-2,2-dinitroethyl) ether in low yield starting with bis(2-iodoethyl) ether. The ether was treated with silver nitrite to give bis(2-nitroethyl) ether. The oxidative nitration of bis(2-nitroethyl) ether with formaldehyde present gave a mixture of methylol derivatives of trinitro- and tetranitrodiethyl ether which was fluorinated to give bis(2-fluoro-2,2-dinitroethyl) ether.

2-Fluoro-2,2-dinitroethyl 2,2-dinitropropyl ether[2] was prepared by nitration of (2-fluoro-2,2-dinitroethoxy)-acetone oxime followed by oxidation of the resulting nitroso intermediate with hydrogen peroxide. The precursor ketone was obtained by oxidation of 2-fluoro-2,2-dinitroethyl 2-hydroxyethyl ether. In the present paper the generality of this route to 2,2-dinitroalkyl ethers is explored.

Although aryldinitromethanes can be readily obtained from aromatic aldoximes[6] by nitration and oxidation, this reaction is not applicable to simple aliphatic aldoximes. It was of interest to determine whether electronegative substituents would facilitate this reaction.

(2,2-Dinitroalkoxy)acetaldehydes have not been described in the literature. A convenient starting material for their synthesis was 3-(2-fluoro-2,2-dinitroethoxy)-1,2-propanediol.[7] (2-Fluoro-2,2-dinitroethoxy)acetaldehyde was obtained by cleaving this diol with either periodic acid or lead tetraacetate. This aldehyde

$$FC(NO_2)_2CH_2OCH_2CH(OH)CH_2OH \xrightarrow[\text{or } Pb(OAc)_4/C_6H_6]{H_5IO_6/H_2O} FC(NO_2)_2CH_2OCH_2CHO + HCHO$$

reacted with hydroxylamine to give (2-fluoro-2,2-dinitroethoxy)acetaldoxime in 90–95% yields. The oxime was nitrated with 90% nitric acid in methylene chloride to give the deep blue nitro–nitroso derivative, which was not isolated. Oxidation of this intermediate

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(7) The diol was prepared by hydrolysis of 2-fluoro-2,2-dinitroethyl glycidyl ether by a procedure of M. B. Frankel (private communication) as modified by H. J. Marcus, Aerojet-General Corp., Technical Report AFATL-TR-69-140, Oct 1969. Available through the Defense Documentation Center, Cameron Station, Alexandria, Va.

with hydrogen peroxide yielded 2-fluoro-2,2-dinitroethyl 2,2-dinitroethyl ether (1). The nitration of (2-

$$FC(NO_2)_2CH_2OCH_2CHO \xrightarrow{NH_2OH} FC(NO_2)_2CH_2OCH_2CH{=}NOH \xrightarrow{HNO_3} FC(NO_2)_2CH_2OCH_2CH(NO)NO_2 \xrightarrow{H_2O_2} FC(NO_2)_2CH_2OCH_2CH(NO_2)_2$$

1

fluoro-2,2-dinitroethoxy)acetaldoxime was found to be very sensitive to reaction conditions, such as the order of addition of reagents, temperature, and reaction time. In experiments where yields of 1 were low, large amounts of (2-fluoro-2,2-dinitroethoxy)acetic acid[2] were obtained. The ether 1 is only moderately stable and decomposes to (2-fluoro-2,2-dinitroethoxy)acetic acid and nitrogen oxides in 2–3 days at ambient temperature.

$$FC(NO_2)_2CH_2OCH_2CH(NO_2) \longrightarrow FC(NO_2)_2CH_2OCH_2CO_2H$$

The sparingly water soluble 1 dissolved in aqueous alkali to give orange-red solutions of the corresponding nitronate salts from which 1 can be recovered on acidification.

$$FC(NO_2)_2CH_2OCH_2CH(NO_2)_2 \underset{H_3O^+}{\overset{OH^-}{\rightleftharpoons}} FC(NO_2)_2CH_2OCH_2C(NO_2)_2^-$$

The anion was found to undergo normal halogenation, formylation, and Michael reactions. Direct fluorination of the aqueous sodium salt of 1, a reaction general for nitronate salts,[8] gave bis(2-fluoro-2,2-dinitroethyl) ether in 50–60% yields, and reaction of 1 with sodium hypochlorite gave 2-chloro-2,2-dinitroethyl 2-fluoro-2,2-dinitroethyl ether.

$$FC(NO_2)_2CH_2OCH_2C(NO_2)_2^-Na^+ + F_2 \xrightarrow{H_2O} [FC(NO_2)_2CH_2]_2O + NaF$$

$$FC(NO_2)_2CH_2OCH_2C(NO_2)_2H + NaOCl \xrightarrow{H_2O} FC(NO_2)_2CH_2OCH_2C(NO_2)_2Cl$$

The reaction of 1 with methyl vinyl ketone was briefly examined and the proton nmr spectrum of the product was consistent with the expected 6-(2-fluoro-2,2-dinitroethoxy)-5,5-dinitro-2-hexanone structure.

$$FC(NO_2)_2CH_2OCH_2C(NO_2)_2H + CH_2{=}CHCOCH_3 \xrightarrow[H_2O]{NaOH} FC(NO_2)_2CH_2OCH_2C(NO_2)_2CH_2CH_2COCH_3$$

Difficulties were encountered with the purification of this ketone and a satisfactory elemental analysis was not obtained.

3-(2-Fluoro-2,2-dinitroethoxy)-2,2-dinitropropanol was obtained in 85–95% yields when 1 was treated with aqueous formaldehyde. This alcohol could be deformylated on treatment with aqueous alkali. The

$$FC(NO_2)_2CH_2OCH_2C(NO_2)_2H + HCHO \underset{OH^-}{\rightleftharpoons} FC(NO_2)_2CH_2OCH_2C(NO_2)_2CH_2OH$$

formylation of 1 provides a practical way to stabilize this compound for storage.

3-(2-Fluoro-2,2-dinitroethoxy)-2,2-dinitropropanol reacted with *s*-trioxane in concentrated sulfuric acid to give bis[3-(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropyl] formal.

$$FC(NO_2)_2CH_2OCH_2C(NO_2)_2CH_2OH + (CH_2O)_3 \xrightarrow{H_2SO_4} [FC(NO_2)_2CH_2OCH_2C(NO_2)_2CH_2O]_2CH_2$$

The nitration method used to synthesize 1 was also applied to the preparation of 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropane (2). The starting material in this reaction scheme, 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2-propanol, was unknown. The rate of reaction of 2-fluoro-2,2-dinitroethanol with 2-fluoro-2,2-dinitroethyl glycidyl ether in aqueous base was so slow that decomposition of the alcohol occurred before a significant amount of addition product could be formed. The decomposition of 2-fluoro-2,2-dinitroethanol, however, was found to be retarded by formaldehyde. In the presence of a base, 2-fluoro-2,2-dinitroethanol is known to be in equilibrium with formaldehyde and fluorodinitromethane anion.[2,9] Excess of formaldehyde shifts this equilibrium to the left and reduces the concentration of this unstable anion.

$$FC(NO_2)_2CH_2OH \underset{}{\overset{OH^-}{\rightleftharpoons}} FC(NO_2)_2CH_2O^- \rightleftharpoons FC(NO_2)_2^- + CH_2O$$

In the presence of a large excess of formaldehyde, 2-fluoro-2,2-dinitroethanol reacted with 2-fluoro-2,2-dinitroethyl glycidyl ether to give 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2-propanol in 40% yield. The alcohol was also obtained in 30–40% yield by treating epichlorohydrin with 2 mol of 2-fluoro-2,2-dinitroethanol for 5 days under similar reaction conditions.

1,3-Bis(2-fluoro-2,2-dinitroethoxy)-2-propanol was oxidized to 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone in 95–100% yields with Jones reagent.[10] This ketone was treated with hydroxylamine to give 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone oxime, an oil which was not analyzed. Its proton nmr spectrum was consistent with the structure. The oxime was nitrated with 90% nitric acid and the blue nitro–nitroso intermediate was ozidized *in situ* with hydrogen peroxide to give compound 2.

$$FC(NO_2)_2CH_2OH + \underset{\diagdown\,\diagup}{O}CH_2CHCH_2OCH_2CF(NO_2)_2 \xrightarrow[HCHO]{NaOH/H_2O} [FC(NO_2)_2CH_2OCH_2]_2CHOH \xrightarrow{CrO_3} [FC(NO_2)_2CH_2OCH_2]_2C{=}O \xrightarrow{NH_2OH} [FC(NO_2)_2CH_2OCH_2]_2C{=}NOH \xrightarrow[2.\ H_2O_2]{1.\ HNO_3}$$

$$[FC(NO_2)_2CH_2OCH_2]_2\!-\!\overset{NO_2}{\underset{NO_2}{C}}$$

2

The above observed formaldehyde effect was exploited in a number of other alkylation reactions of 2-fluoro-2,2-dinitroethanol. Formaldehyde-stabilized solutions allowed higher reaction temperatures and longer reaction times. Higher yields of 2-fluoro-2,2-dinitroethyl ethers by a factor of two or more than previously reported[2] were obtained with allyl bromide (see Experi-

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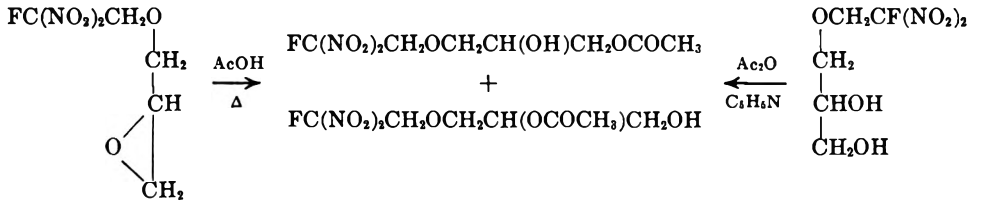

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mental Section), propylene oxide, and epichlorohydrin as alkylating agents.[11] In this way 2-fluoro-2,2-dinitroethanol reacted with propargyl bromide to give 2-fluoro-2,2-dinitroethyl propargyl ether[12] in 55% yield. This ether could not be synthesized without added formaldehyde.

$$FC(NO_2)_2CH_2OH + BrCH_2C{\equiv}CH \xrightarrow[HCHO]{NaOH/H_2O} FC(NO_2)_2CH_2OCH_2C{\equiv}CH$$

Suppression of deformylation of 2-fluoro-2,2-dinitroethanol by formaldehyde was further confirmed by its reactions with α,β-unsaturated carbonyl compounds. While 2-fluoro-2,2-dinitroethanol normally reacts with unsaturated carbonyl compounds in alkaline aqueous solution to give the corresponding Michael reaction adducts of fluorodinitromethane,[13] no reaction takes place when a large excess of formaldehyde is added.

$$FC(NO_2)_2CH_2OH + CH{=}CH_2X \xrightarrow[H_2O]{NaOH} FC(NO_2)_2CH_2CH_2X + HCHO$$

$$\downarrow NaOH/H_2O,\ HCHO$$

no reaction

X = $COCH_3$, $CO_2C_2H_5$, CN

Other 2-fluoro-2,2-dinitroethyl 2-hydroxyalkyl ethers useful in the above reaction schemes were synthesized by the reaction of 2-fluoro-2,2-dinitroethyl glycidyl ether with acids. Thus, dilute hydrochloric, hydrobromic, hydriodic, and nitric acid gave 1-chloro-2-hydroxypropyl, 1-bromo-2-hydroxypropyl, 1-iodo-2-hydroxypropyl, and 1-nitrato-2-hydroxypropyl 2-fluoro-2,2-dinitroethyl ether, respectively, in 80–100% yields.[14]

$$FC(NO_2)_2CH_2OCH_2\underset{O}{\overset{\diagup\diagdown}{CH}}CH_2 + HX \xrightarrow{H_2O} FC(NO_2)_2CH_2OCH_2\underset{OH}{CH}CH_2X$$

X = Cl, Br, I, NO_3

While in the above reaction there was no evidence of the isomeric primary alcohols, a mixture of the two isomeric monoacetates of 3-(2-fluoro-2,2-dinitroethoxy)-1,2-propanediol was obtained when 2-fluoro-2,2-dinitroethyl glycidyl ether was treated with acetic acid or 3-(2-fluoro-2,2-dinitroethoxy)-1,3-propanediol was acylated with 1 mol of acetic anhydride (eq 1). On the other hand, 3-(2-fluoro-2,2-dinitroethoxy)-1,2-propanediol reacted with the more sterically hindered pivaloyl chloride to give only one isomer, 3-(2-fluoro-2,2-dinitroethoxy)-2-hydroxy-1-propyl pivalate.

$$FC(NO_2)_2CH_2OCH_2CH(OH)CH_2OH + (CH_3)_3CCOCl \xrightarrow[C_5H_5N]{CH_2Cl_2} FC(NO_2)_2CH_2OCH_2CH(OH)CH_2OCOC(CH_3)_3$$

Three of these isopropyl alcohol derivatives, 1-(2-fluoro-2,2-dinitroethoxy)-3-chloro-2-propanol, 1-(2-fluoro-2,2-dinitroethoxy)-3-nitrato-2-propanol, and 3-(2-fluoro-2,2-dinitroethoxy)-2-hydroxy-1-propyl pivalate, were oxidized to the corresponding ketones in 85–95% yields with Jones reagent. The preparation of oximes of these ketones was not investigated.

$$FC(NO_2)_2CH_2OCH_2CH(OH)CH_2X \xrightarrow[CH_3COCH_3]{CrO_3/H_2SO_4} FC(NO_2)_2CH_2OCH_2COCH_2X$$

X = Cl, ONO_2, $OCOC(CH_3)_3$

Experimental Section

General.—Explosive properties of the polynitro ethers described below have not been investigated. Adequate safety shielding should be used in all operations. 2-Fluoro-2,2-dinitroethanol is a severe skin irritant and contact should be avoided.

Proton and fluorine nmr spectra were recorded on a Varian T-60 spectrometer using tetramethylsilane and trichlorofluoromethane as the respective internal standards.

(2-Fluoro-2,2-dinitroethoxy)acetaldehyde.—To a stirred solution of 2.0 g (0.0132 mol) of 1-(2-fluoro-2,2-dinitroethoxy)-2,3-propanediol[7] in 10 ml of water was added dropwise over a period of 5 min at 25–28° a solution of 3.0 g (0.0132 mol) of periodic acid (H_5IO_6) in 5 ml of water. The reaction was mildly exothermic and in a few minutes a water-insoluble liquid began to separate. The mixture was stirred for 30 min, saturated with sodium chloride, and extracted with 20 ml of methylene chloride. The methylene chloride extract was distilled to give 2.15 g (83% yield) of (2-fluoro-2,2-dinitroethoxy)acetaldehyde, bp 83–84° (0.1 mm), $n^{25}D$ 1.4365.

Anal. Calcd for $C_4H_5N_2FO_6$: C, 24.5; H, 2.5; N, 14.3; F, 9.7. Found: C, 24.71; H, 2.34; N, 13.74; F, 9.5.

Proton nmr (CCl_4) δ 4.80 (d, J_{HF} = 18.0 Hz, 2 H, $FCCH_2O$–), 4.41 (s, 2 H, $-CH_2CHO$), and 9.78 (s, 1 H, –CHO); ir 5.77 (C=O), 6.29 μ (NO_2).

(2-Fluoro-2,2-dinitroethoxy)acetaldehyde was also obtained in comparable yields by oxidizing the diol with lead tetraacetate in benzene solution at ambient temperatures.

(2-Fluoro-2,2-dinitroethoxy)acetaldoxime.—A mixture of 4.9 g (0.025 mol) of (2-fluoro-2,2-dinitroethoxy)acetaldehyde, 5.75 g (0.0825 mol) of hydroxylamine hydrochloride, and 11.3 g (0.0825 mol) of sodium acetate trihydrate in 70 ml of absolute ethanol was refluxed for 45 min, and then *ca.* 60 ml of ethanol was removed at 25° (25 min). The residue was added to 100 ml of ice water and the product was extracted with 35 ml of methylene chloride. The extract was dried and concentrated to leave 5.2 g of liquid which was distilled in a molecular still

(11) The crude reaction products obtained in alkylation reaction employing excesses of formaldehyde were contaminated with polymethylene oxides introduced by formaldehyde solutions. These impurities presented some problems in the purification of alkylation products.

(12) 2-Fluoro-2,2-dinitroethyl propargyl ether represents a new class of polynitro ethers and some of its reactions were briefly examined. The ether readily added 1 mol of bromine to give 2-fluoro-2,2-dinitroethyl 2,3-dibromoallyl ether.

$$FC(NO_2)_2CH_2OCH_2C{\equiv}CH + Br_2 \longrightarrow FC(NO_2)_2CH_2OCH_2CBr{=}CHBr$$

Concentrated sulfuric acid hydrated the propargyl ether to give (2-fluoro-2,2-dinitroethoxy)acetone.[2]

$$FC(NO_2)_2CH_2OCH_2C{\equiv}CH \xrightarrow{H_2SO_4} FC(NO_2)_2CH_2OCH_2COCH_3$$

See Experimental Section for details.

(13) V. Grakauskas and K. Baum, *J. Org. Chem.*, **34**, 3927 (1969).

(14) 1-Chloro-2-hydroxypropyl and 1-bromo-2-hydroxypropyl 2-fluoro-2,2-dinitroethyl ethers were isolated as by-products in the preparation of 2-fluoro-2,2-dinitroethyl glycidyl ether from aqueous alkaline 2-fluoro-2,2-dinitroethanol and epichlorohydrin and epibromohydrin, respectively. Methanolic potassium hydroxide cyclized these halohydrins to 2-fluoro-2,2-dinitroethyl glycidyl ether (see Experimental Section).

at 100–105° (0.1 mm) to give 4.8 g, 91% yield, of (2-fluoro-2,2-dinitroethoxy)acetaldoxime.

Anal. Calcd for $C_4H_6N_3FO_6$: C, 22.75; H, 2.84; N, 19.90; F, 9.01. Found: C, 22.46; H, 2.58; N, 19.60; F, 9.1.

Proton nmr ($CDCl_3$) δ 8.44 (s, broad, 1 H, =NOH), 7.42 (t, J = 5.8 Hz, *ca.* 60% anti CH=), 6.84 (t, J = 4.0 Hz, *ca.* 40% syn CH=), 4.62 (d, J = 19.1 Hz, $FCCH_2$–, syn isomer), 4.53 (d, J = 19.0 Hz, $FCCH_2$–, anti isomer), 4.50 (d, J = 4.0 Hz, $-OCH_2C$=, syn isomer), and 4.25 (d, J = 5.8 Hz, OCH_2C anti isomer); fluorine nmr φ 110.9 (t, J_{HF} = 18.7 Hz).

2-Fluoro-2,2-dinitroethyl 2,2-Dinitroethyl Ether (1).—To a stirred and cooled solution of 4.2 g (0.02 mol) of (2-fluoro-2,2-dinitroethoxy)acetaldoxime in 60 ml of methylene chloride was added dropwise at 3–5° over a period of 7–8 min 10 g of 90% nitric acid. The mixture became turbid and then turned blue in a moderately exothermic reaction. The deep blue solution was stirred for 20 min and then to it was added dropwise, over a period of 20 min, 6.5 ml of 30% hydrogen peroxide until the blue color was discharged. The mixture was stirred with 90 ml of ice water for a few minutes. The methylene chloride solution was dried over anhydrous sodium sulfate, filtered, and concentrated to leave 3.5 g (65% yield) of crude 1, a colorless liquid. An analytical sample was distilled at 105–110° (50 μ) in a molecular still.

Anal. Calcd for $C_4H_3N_4FO_9$: C, 17.64; H, 1.84; N, 20.59. Found: C, 18.2; H, 1.64; N, 19.2.

Proton nmr ($CDCl_3$) δ 6.51 (t, J = 6.0 Hz, 1 H, CH), 4.94 (d, J_{HF} = 15.8 Hz, 2 H, $FCCH_2$–), and 4.80 (d, J = 6.0 Hz, 2 H, CH_2).

Bis(2-fluoro-2,2-dinitroethyl) Ether.—2-Fluoro-2,2-dinitroethyl 2,2-dinitroethyl ether, 3.5 g (above), was added at 0° to a solution of 1.0 g of sodium hydroxide in 65 ml of water and the resulting orange-red solution was fluorinated with elementary fluorine (diluted fourfold with nitrogen) until the solution became colorless (10 min). The mixture was extracted with 35 ml of methylene chloride to give 2.3 g of bis(2-fluoro-2,2-dinitroethyl) ether, 62% yield, bp 100° (0.4 mm), d 1.629.

Anal. Calcd for $C_4H_4N_4F_2O_9$: C, 16.6; H, 1.4; F, 13.1. Found: C, 16.7; H, 1.3; F, 12.9.

Proton nmr ($CDCl_3$) δ 4.84 (d, J_{HF} = 16.0 Hz); fluorine nmr φ 109.2 (poorly resolved triplet).

2-Chloro-2,2-dinitroethyl 2-Fluoro-2,2-dinitroethyl Ether.—To 20 ml of 5.3% aqueous sodium hypochlorite was added 0.5 g of 1. The mixture was stirred for 10 min and extracted with 20 ml of carbon tetrachloride to give 0.55 g of 2-chloro-2,2-dinitroethyl 2-fluoro-2,2-dinitroethyl ether, a colorless liquid, which was not further purified.

Anal. Calcd for $C_4H_4N_4ClFO_9$: C, 15.66; H, 1.30; F, 6.20. Found: C, 16.1; H, 1.09; F, 6.3.

Proton nmr (CCl_4) δ 5.03 (d, J = 16 Hz, 2 H, $FCCH_2$–) and 4.97 (s, 2 H, CH_2CCl).

Reaction of Methyl Vinyl Ketone with 1.—To a stirred suspension of 0.6 g (2.0 mmol) of 1 and 0.14 g (2.0 mmol) of methyl vinyl ketone in 10 ml of water at 25° was added a few drops of 10% aqueous potassium hydroxide. After 15 min the mixture was extracted with 10 ml of methylene chloride and the extract was evaporated to give 0.5 g of crude product, a viscous oil: proton nmr ($CDCl_3$) δ 4.71 (d, J_{HF} = 18.6 Hz, 2 H, $FCCH_2$), 4.52 (s, 2 H, $-OCH_2C$–), 2.55–2.85 (m, 4 H, $-CH_2CH_2CO$), and 2.20 (s, 3 H, CH_3).

3-(2-Fluoro-2,2-dinitroethoxy)-2,2-dinitropropanol.—To a suspension of 1.0 g of 1 in 10 ml of water was added 1.0 g of 37% aqueous formaldehyde and a few drops of 5% aqueous sodium hydroxide. The mixture was stirred for 20 min at 18–25° and then acidified with a few drops of 10% hydrochloric acid. The mixture was extracted with two 7-ml portions of methylene chloride. The combined methylene chloride extracts were concentrated to leave 0.95 g (86% yield) of 3-(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropanol. An analytical sample was distilled at 120–125° (0.1 mm) in a molecular still.

Anal. Calcd for $C_5H_7N_4FO_{10}$: C, 19.87; H, 2.33; F, 6.28. Found: C, 20.12; H, 2.01; F, 6.1.

Proton nmr ($CDCl_3$) δ 4.70 (d, J_{HF} = 16 Hz, 2 H, $FCCH_2$–), 4.63 (s, 2 H, $-OCH_2CC$–), 4.43 (s, 2 H, CH_2CCH_2OH), and 2.72 (broad s, 1 H, OH).

Bis[3-(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropyl] Formal.—To a stirred solution of 0.6 g (0.002 mol) of 3-(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropanol and 0.03 g (0.001 equiv) of *s*-trioxane in 10 ml of methylene chloride at 5–10° was added 1.0 ml of concentrated sulfuric acid. The mixture was stirred at 22–25° for 2 hr and phases were separated. The sulfuric acid phase was extracted with two 10-ml portions of methylene chloride. The methylene chloride solution was combined with extracts. The solution was washed with 20 ml of water and evaporated to give 0.4 g of a colorless, viscous oil, d 1.641, which was not further purified.

Anal. Calcd for $C_{11}H_{14}N_8F_2O_{20}$: C, 21.47; H, 2.12; F, 6.17. Found: C, 21.28; H, 1.97; F, 6.41.

Proton nmr ($CDCl_3$) δ 4.77 (s, 2 H, formal CH_2), 4.75 (d, J_{HF} = 16 Hz, 4 H, 2 $FCCH_2$–), 4.65 (s, 4 H, 2 $FCCH_2OCH_2$–), and 4.37 (s, 4 H, $-CCH_2OCH_2OCH_2C$–).

1,3-Bis(2-fluoro-2,2-dinitroethoxy)-2-propanol.—To a solution of 4.0 g (0.026 mol) of 2-fluoro-2,2-dinitroethanol in 35 g of 37% aqueous formaldehyde was added 1.32 g (0.02 mol) of 85% potassium hydroxide in 4 ml of water, 4.2 g (0.02 mol) of 2-fluoro-2,2-dinitroethyl glycidyl ether, and 5.0 ml of methanol. The reaction mixture was stirred at 22–25° for 20 hr, diluted with water to 120 ml, and extracted with 50 ml of methylene chloride to give 3.0 g of 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2-propanol. An analytical sample was distilled in a molecular still at 155–160° (0.1 mm).

Anal. Calcd for $C_7H_{10}N_4F_2O_{11}$: C, 23.08; H, 2.76; F, 10.43. Found: C, 23.30; H, 2.61; F, 9.8.

Proton nmr ($CDCl_3$) δ 4.65 (d, J_{HF} = 17.6Hz, 4 H, $FCCH_2$–), 2.52 (broad s, 1 H, OH), and 3.52–4.02 (superimposed multiplets, 5 H, $-CH_2CHCH_2$–); fluorine nmr φ 111.2 (poorly resolved triplet).

1,3-Bis(2-fluoro-2,2-dinitroethoxy)acetone.—To a stirred solution of 13.1 g (0.036 mol) of crude 1,2-bis(2-fluoro-2,2-dinitroethoxy)-2-propanol (above), in 120 ml of acetone at 20–22° was added dropwise, over a period of 45 min, a solution of 10.0 g (0.1 mol) of chromium trioxide and 8.0 g of concentrated sulfuric acid in 10 ml of water (Jones reagent[10]) until chromate color persisted. The unreacted chromate was destroyed with a few drops of isopropyl alcohol. The mixture was filtered and the filtrate was stirred with 10 g of sodium bicarbonate for 10 min. The mixture was filtered again and the filtrate was concentrated to *ca.* 15 ml. The concentrate was added to 200 ml of water and a water-insoluble liquid was extracted with 60 ml of methylene chloride to give 12.8 g (quantitative yield) of 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone, a colorless liquid. An analytical sample was distilled in a molecular still at 140° (0.1 mm).

Anal. Calcd for $C_7H_8N_4F_2O_{11}$: C, 23.21; H, 2.22; F, 10.49. Found: C, 23.43; H, 2.06; F, 10.3.

Proton nmr ($CDCl_3$) δ 4.72 (d, J_{HF} = 16.4 Hz, 4 H, 2 $FCCH_2$–) and 4.43 (s, 4 H, $-CH_2COCH_2$–); fluorine nmr φ 111.2 (poorly resolved triplet).

1,3-Bis(2-fluoro-2,2-dinitroethoxy)acetone Oxime.—To a solution of 10.0 g (*ca.* 0.03 mol) of crude 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone (above) in 70 ml of methanol was added 5.1 g of hydroxylamine hydrochloride and 10 g of sodium acetate trihydrate and the mixture was refluxed for 2 hr. The hot mixture was filtered and the filtrate was concentrated to 20 ml. The concentrated mixture was added to 100 ml of water and water-insoluble oil was extracted with 50 ml of methylene chloride. The methylene chloride solution was concentrated to give 10 g of crude 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone oxime: proton nmr ($CDCl_3$) δ 7.40 (s, broad, 1 H, =NOH), 4.72 (d, J_{HF} = 16.8 Hz, 4 H, 2 $FCCH_2$–), and 4.67 and 4.28 [s, 4 H, $-CH_2C(=NOH)CH_2$–].

1,3-Bis(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropane (2).—To a stirred solution of 2.0 g of crude 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone oxime (above) in 30 ml of methylene chloride at 0.5° was added dropwise, over a period of 10 min, 3.5 g of 90% nitric acid. The reaction mixture first turned turbid and then deep blue. After 20 min, 30% hydrogen peroxide was added dropwise (20 min) until the blue color of the solution was discharged. The mixture was added to 60 ml of ice water and the phases were separated. The methylene chloride solution was stripped to give 1.4 g of crude 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropane. The crude material was purified by passing its $CDCl_3$ solution through a 0.5 × 25 mm column of basic alumina (Biorad, AGlO, 100–200 mesh).

Anal. Calcd for $C_7H_5N_6F_2O_{14}$: C, 19.18; H, 1.84; F, 8.67. Found: C, 20.30; H, 2.01; F, 8.4.

Proton nmr ($CDCl_3$) δ 4.70, (d, J_{HF} = 16 Hz, 4 H, 2 $FCCH_2$–) and 4.55 [s, 4 H, $-CH_2C(NO_2)_2CH_2$–]; fluorine nmr φ 110.8 (poorly resolved triplet).

Allyl 2-Fluoro-2,2-dinitroethyl Ether.—To 35 ml of 37–40% aqueous formaldehyde in 150 ml of water was added 30.8 g (0.2

mol) of 2-fluoro-2,2-dinitroethanol and a solution of 10.8 g (0.26 mol) of sodium hydroxide in 10 ml of water. To the solution was added 36.3 g (0.3 mol) of allyl bromide and the mixture was stirred for 45 hr at 23–25°. The mixture was extracted with 50 ml of methylene chloride to give 25.5 g (66% yield) of allyl 2-fluoro-2,2-dinitroethyl ether, bp 31° (0.2 mm) [lit.[2] bp 31–32° (0.2 mm)].

2-Fluoro-2,2-dinitroethyl Propargyl Ether.—To a mixture of 3.1 g (0.02 mol) of 2-fluoro-2,2-dinitroethanol, 20 ml of 18% aqueous formaldehyde, and 1.0 g (0.025 mol) of sodium hydroxide was added 2.4 g (0.02 mol) of propargyl bromide. The reaction mixture was stirred vigorously at 22–25° for 30 hr and then was extracted with 25 ml of methylene chloride. The methylene chloride extract was distilled to give 2.1 g of 2-fluoro-2,2-dinitroethyl propargyl ether (55% yield), a colorless liquid, bp 35° (0.3 mm).

Anal. Calcd for $C_5H_5N_2FO_5$: C, 31.25; H, 2.62; N, 14.58; F, 9.89. Found: C, 31.56; H, 2.52; N, 14.0; F, 9.4.

Proton nmr (CCl_4) δ 4.59 (d, J_{HF} = 17.8 Hz, 2 H, $FCCH_2$), 4.28 (d, J_{HH} = 3 Hz, 2 H, $OCH_2C{\equiv}$), and 2.56 (t, J_{HH} = 3 Hz, 1 H, $-C{\equiv}CH$); fluorine nmr ϕ 110.7 (poorly resolved triplet).

2-Fluoro-2,2-dinitroethyl 2,3-Dibromoallyl Ether.—To a stirred suspension of 1.92 g (0.01 mol) of 2-fluoro-2,2-dinitroethyl propargyl ether in 25 ml of water was added 1.6 g (0.01 mol) of bromine. The reaction mixture was stirred at 25° for 30 min and then was extracted with 20 ml of methylene chloride. The methylene chloride extract was fractionated to give 2.28 g of 2-fluoro-2,2-dinitroethyl 2,3-dibromoallyl ether, a colorless liquid, bp 80° (0.1 mm).

Anal. Calcd for $C_5H_5N_2FBr_2O_5$: C, 17.05; H, 1.43; F, 5.39. Found: C, 17.41; H, 1.33; F, 5.54.

Proton nmr ($CDCl_3$) δ 6.82 (s, 1 H, $=CHBr$), 4.55 (d, J_{HF} = 17.0 Hz, 2 H, $FCCH_2-$), and 4.57 (s, 2 H, $-CH_2CBr=$); fluorine nmr ϕ 112.0 (poorly resolved triplet).

(2-Fluoro-2,2-dinitroethoxy)acetone.—2-Fluoro-2,2-dinitroethyl propargyl ether, 0.5 g, was added dropwise at 25° to 10 ml of concentrated sulfuric acid. The reaction temperature increased to 30–32° and the mixture darkened. After 5 min, the reaction mixture was added to 50 ml of ice water and extracted with 5 ml of carbon tetrachloride. The proton nmr spectrum of the extract showed that it contained 80% of the starting material and 20% of (2-fluoro-2,2-dinitroethoxy)acetone.[2]

1-Chloro-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol.—A suspension of 2.1 g (0.01 mol) of 2-fluoro-2,2-dinitroethyl glycidyl ether in 30 ml of 8% hydrochloric acid was stirred at 25° for 16 hr. The mixture was extracted with 20 ml of methylene chloride to give 2.45 g (100% yield) of 1-chloro-2-(2-fluoro-2,2-dinitroethoxy)-2-propanol. An analytical sample was distilled at 100° (0.1 mm) in a molecular still.

Anal. Calcd for $C_5H_8N_2ClFO_6$: C, 24.53; H, 3.25; N, 11.36; F, 7.7. Found: C, 24.57; H, 2.91; N, 10.86; F, 7.6.

Proton nmr ($CDCl_3$) δ 4.65 (d, J_{HF} = 17.4 Hz, 2 H, $FCCH_2-$), 2.70 (broad s, 1 H, OH), and superimposed multiplets at 3.47–2.17 (5 H, CH_2CHCH_2); fluorine nmr ϕ 111.0 (poorly resolved triplet).

The compound was also isolated as the side reaction product (incomplete cyclization) in the synthesis of 2-fluoro-2,2-dinitroethyl glycidyl ether from 2-fluoro-2,2-dinitroethanol and epichlorohydrin.

2-Fluoro-2,2-dinitroethyl Glycidyl Ether.—To a stirred solution of 1.23 g (0.05 mol) of 1-chloro-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol in 5 ml of methanol at 22–25° was added, dropwise, a solution of 0.34 g (0.05 mol) of 85% potassium hydroxide in 5 ml of methanol. The mixture was stirred for 15 min, diluted with 50 ml of ice water, and extracted with 25 ml of methylene chloride. The extract was distilled to give 2.0 g (95% yield) of 2-fluoro-2,2-dinitroethyl glycidyl ether, bp 71° (0.1 mm) [lit.[2] bp 70–71° (0.1 mm)].

1-Bromo-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol.—The title compound, a colorless liquid, distilled in a molecular still at 110° (0.1 mm), was obtained in 90% yield by treating 2-fluoro-2,2-dinitroethyl glycidyl ether with 10% hydrobromic acid.

Anal. Calcd for $C_5H_8N_2BrFO_6$: C, 20.62; H, 2.76; N, 9.62; F, 6.52. Found: C, 20.80; H, 2.31; N, 9.50; F, 6.4.

Proton nmr δ 4.65 (d, J_{HF} = 17.2 Hz, 2 H, $FCCH_2-$), 2.58 (d, J_{H-OH} = 3.8 Hz, 1 H, OH), and 3.33–4.13 (superimposed multiplets, 5 H, CH_2CHCH_2); fluorine nmr ϕ 109.5 (poorly resolved triplet, J_{HF} = 17 Hz).

1-Iodo-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol.—The title compound, a colorless liquid, distilled in a molecular still at 115–120° (0.1 mm), was obtained in 92% yield by treating 2-fluoro-2,2-dinitroethyl glycidyl ether with 15% hydroiodic acid following the procedure used for the synthesis of the chloro analog.

Anal. Calcd for $C_5H_8N_2FIO_6$: C, 17.76; H, 2.38; N, 8.28; F, 5.62. Found: C, 18.08; H, 2.31; N, 7.8; F, 5.7.

Proton nmr ($CDCl_3$) δ 4.63 (d, J_{HF} = 17.1 Hz, 2 H, $FCCH_2-$), 2.67 (broad s, 1 H, OH), 3.13–4.05 (superimposed multiplets, 5 H, CH_2CHCH_2); fluorine nmr ϕ 109.6 (t, J_{HF} = 17.0 Hz).

1-(2-Fluoro-2,2-dinitroethoxy)-3-nitrato-2-propanol.—To a stirred solution of 7.0 ml of 70% nitric acid in 14 ml of water at 25° was added 2.1 g (0.01 mol) of 2-fluoro-2,2-dinitroethyl glycidyl ether. After 20 min the solution was extracted with 15 ml of methylene chloride. The extract was concentrated to leave 2.2 g of 1-(2-fluoro-2,2-dinitroethoxy)-3-nitrato-2-propanol (80% yield), a colorless liquid. An analytical sample was distilled in a molecular still at 125° (0.1 mm).

Anal. Calcd for $C_5H_7N_3FO_9$: C, 21.98; H, 2.95; F, 6.95. Found: C, 21.92; H, 2.68; F, 7.1.

Proton nmr ($CDCl_3$) δ 4.67 (d, J_{HF} = 16.0 Hz, 2 H, $FCCH_2-$), 2.80 (broad s, 1 H, OH), and 3.50–4.50 (superimposed multiplets, 5 H, $-CH_2CHCH_2-$); fluorine nmr ϕ 110.7 (poorly resolved triplet).

3-(2-Fluoro-2,2-dinitroethoxy)-2-hydroxy-1-propyl Pivalate.—To a stirred solution of 2.28 g (0.01 mol) of 3-(2-fluoro-2,2-dinitroethoxy)-1,2-propanediol and 0.84 g (0.01 mol) of pyridine in 20 ml of methylene chloride was added at 20–25° dropwise (3 min) a solution of 1.20 g (0.01 mol) of pivaloyl chloride in 5 ml of methylene chloride. The mixture was stirred for 10 min, washed with 50 ml of 3% hydrochloric acid, dried, and concentrated to give 3.05 g (98% yield) of 3-(2-fluoro-2,2-dinitroethoxy)-2-hydroxyl-1-propyl pivalate. An analytical sample was distilled in a molecular still at 135° (0.1 mm).

Anal. Calcd for $C_{10}H_{17}N_2FO_8$: C, 38.46; H, 5.48; N, 8.97; F, 6.08. Found: C, 38.80; H, 5.48; N, 8.69; F, 5.92.

Proton nmr ($CDCl_3$) δ 4.72 (d, J_{JF} = 18.0 Hz, 2 H, $FCCH_2-$), 3.25 (broad s, 1 H, OH), 1.22 [s, 9 H, $-(CCCH_3)_3$], and 3.25–363 (superimposed multiplets, $-CH_2CHCH_2-$); fluorine nmr ϕ 110.0 (t, J_{HF} = 17.8 Hz).

1-Chloro-3-(2-fluoro-2,2-dinitroethoxy)acetone.—To a stirred solution of 4.94 g (0.02 mol) of 1-chloro-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol in 75 ml of acetone was added at 20–23° dropwise over a period of 45 min chromic–sulfuric acid solution (Jones reagent prepared by adding 1.75 ml of concentrated sulfuric acid to a solution of 2.0 g of chromium trioxide in 1 ml of water). The mixture was stirred for 45 min and the excess of chromium trioxide was destroyed with a few drops of isopropyl alcohol. The mixture was filtered and the filter cake was washed with two 5-ml portions of acetone. The combined filtrate and washings were stirred with 5 g of sodium bicarbonate for 10 min, filtered, and concentrated to *ca.* 10 ml. The concentrated solution was diluted with 80 ml of water and extracted with 45 ml of methylene chloride to give 4.6 g (94% yield) of 1-chloro-3-(2-fluoro-2,2-dinitroethoxy) acetone, a colorless liquid. An analytical sample was distilled in a molecular still at 125° (0.1 mm).

Anal. Calcd for $C_5H_6N_2ClFO_6$: C, 24.55; H, 2.45; N, 11.45; F, 7.76. Found: C, 24.69; H, 2.61; N, 11.31; F, 7.98.

Proton nmr (50:50 $CDCl_3$–CCl_4) δ 4.66 (d, J_{HF} = 17.0 Hz, 2 H, $FCCH_2-$), 4.52 (s, 2 H, OCH_2CO), and 4.8 (s, 2 H, $-CH_2Cl$); fluorine nmr ϕ 109.7 (poorly resolved triplet, J_{HF} = 17 Hz).

3-(2-Fluoro-2,2-dinitroethoxy)-2-oxo-1-propyl Pivalate.—The title compound, a colorless oil, was prepared in 85% yield by oxidation of 3-(2-fluoro-2,2-dinitroethoxy)-2-hydroxy-1-propyl pivalate with Jones reagent following the above procedure. An analytical sample was distilled in a molecular still at 145° (0.1 mm).

Anal. Calcd for $C_{10}H_{15}N_2FO_8$: C, 38.71; H, 4.87; N, 9.03; F, 6.12. Found: C, 38.73; H, 5.30; N, 9.18; F, 5.96.

Proton nmr ($CDCl_3$) δ 4.75 (d, J_{HF} = 16.4 Hz, 2 H, $FCCH_2-$), 4.63 (s, 2 H, OCH_2CO), 4.37 (s, 2 H, CH_2), and 1.25 [s, 9 H, $C(CH_3)$]; fluorine nmr ϕ 110.6 (poorly resolved triplet, J_{HF} = 16.5 Hz).

1-(2-Fluoro-2,2-dinitroethoxy)-3-nitratoacetone.—The title compound, a colorless liquid, was prepared in 90% yield by the oxidation of 1-(2-fluoro-2,2-dinitroethoxy)-3-nitrato-2-propanol with Jones reagent following the procedure described above for the 3-chloro analog. An analytical sample was distilled in a molecular still at 125° (0.1 mm).

Anal. Calcd for $C_5H_6N_3FO_9$: C, 22.14; H, 2.23; F, 7.0. Found: C, 21.93; H, 2.03; F, 7.1.

Proton nmr ($CDCl_3$) δ 5.13 (s, 2 H, CH_2ONO_2), 4.75 (d, J_{HF} = 17.0 Hz, 2 H, $FCCH_2$), and 4.48 (s, 2 H, CH_2); fluorine nmr ϕ 109.4 (poorly resolved triplet).

Acknowledgment.—The author wishes to thank Dr. K. Baum for useful discussion.

Registry No.—1, 40695-29-5; 2, 40695-30-8; (2-fluoro-2,2-dinitroethoxy)acetaldehyde, 40696-31-9; 1-(2-fluoro-2,2-dinitroethoxy)-2,3-propanediol, 40696-32-0; periodic acid, 10450-60-9; (2-fluoro-2,2-dinitroethoxy)acetaldoxime, 40696-33-1; hydroxylamine hydrochloride, 5470-11-1; sodium acetate, 127-09-3; bis(2-fluoro-2,2-dinitroethyl) ether, 30290-64-3; 2-chloro-2,2-dinitroethyl 2-fluoro-2,2-dinitroethyl ether, 40696-35-3; methyl vinyl ketone, 78-94-4; 3-(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropanol, 40696-36-4; bis[3-(2-fluoro-2,2-dinitroethoxy)-2,2-dinitropropyl] formal, 40696-37-5; *s*-trioxane, 110-88-3; 1,3-bis(2-fluoro-2,2-dinitroethoxy)-2-propanol, 35323-16-1; 2-fluoro-2,2-dinitroethanol, 17003-75-7; 2-fluoro-2,2-dinitroethyl glycidyl ether, 40696-32-0; 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone, 40696-41-1; 1,3-bis(2-fluoro-2,2-dinitroethoxy)acetone oxime, 40696-42-2; 2-fluoro-2,2-dinitroethyl propargyl ether, 40696-43-3; 2-fluoro-2,2-dinitroethyl-2,3-dibromoallyl ether, 40696-44-4; bromine, 7726-95-6; (2-fluoro-2,2-dinitroethoxy)acetone, 25172-32-1; 1-chloro-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol, 40696-46-6; 1-bromo-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol, 40696-47-7; hydrobromic acid, 10035-10-6; 1-iodo-3-(2-fluoro-2,2-dinitroethoxy)-2-propanol, 40696-48-8; hydriodic acid, 10034-85-2; 1-(2-fluoro-2,2-dinitroethoxy)-3-nitrato-2-propanol, 40696-49-9; nitric acid, 7697-37-2; 3-(2-fluoro-2,2-dinitroethoxy)-2-hydroxy-1-propyl pivalate, 40696-50-2; 3-(2-fluoro-2,2-dinitroethoxy)-1,2-propanediol, 40696-32-0; pyridine, 110-86-1; 1-chloro-3-(2-fluoro-2,2-dinitroethoxy)acetone, 40696-52-4; 3-(2-fluoro-2,2-dinitroethoxy)-2-oxo-1-propyl pivalate, 40696-53-5; 1-(2-fluoro-2,2-dinitroethoxy)-3-nitratoacetone, 40696-54-6.

Synthesis of α-Monosubstituted Indoles

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The preparation of α-monosubstituted indoles by (a) the Madelung reaction, (b) *o*-nitrobenzyl ketone reduction, and (c) *o*,β-dinitrostyrene reduction was explored. The Madelung reaction is limited to use on those toluidides which do not have double bonds or active hydrogens present. Toluidides having tertiary benzylamine groups can be used. *o*-Nitrobenzyl ketone preparations were attempted by the arylation of β-keto esters with *o*-fluoronitrobenzene. This reaction is limited to α-unsubstituted acetoacetic esters. The dinitrostyrene route appears to be useful when the appropriate primary nitro compound is available for condensation with *o*-nitrobenzaldehyde.

Of the many reported syntheses of indole alkaloids, most have used reaction sequences involving either the formation of the disubstituted indole by means of a Fisher indole synthesis or the preparation of an appropriate β-substituted indole followed by a ring closure into the α position of the indole ring.[2] It was thought, however, that it would be advantageous in some cases to first prepare an α-monosubstituted indole and then utilize the higher reactivity of the β position[3] to facilitate the subsequent ring closure.[4] This approach would also avoid the formation of intermediate 3,3-disubstituted 3*H*-indoles, which could rearrange to give a mixture of products.[5]

While a number of methods have been reported for the exclusive preparation of α-substituted indoles,[6] with the exception of the triethylphosphite reduction of *o*-nitrostyrenes[7] and the pyrolysis of *o*-azidostyrenes,[8] little is known about their generality and scope. Thus, the following methods for the preparation of α-monosubstituted indoles were investigated: (1) the Madelung reaction;[9a] (2) *o*-nitrobenzyl ketone reductions;[9b] (3) *o*,β-dinitrostyrene reductions.[9c]

The Madelung reaction,[9a] which involves the heating of an *o*-toluidide with a strong base, has been used successfully for the preparation of a number of α-alkyl-substituted indoles,[10] as well as indoles having alkyl groups on the 5 or 7 positions.[9a] It appears that nitro-[11] or halogen- substituted[12] indoles cannot be prepared by this method. This procedure has been used for the synthesis of 2-(*N*,*N*-dimethylaminomethyl)indole (**1**).[13] In a study of this reaction[13b] it was found that reasonably good yields of **1** were obtained if sodium amide was used as the base but that the use of other bases gave much poorer results. However, in this[13b] and subsequent work[14] utilizing

(1) (a) NSF Graduate Traineeship recipient, summer, 1971; (b) NSF Graduate Traineeship recipient, summer, 1970.

(2) For some examples see (a) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, pp 251–269; (b) J. E. Saxton in "The Alkaloids," Vol. VII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1960, Chapter 10.

(3) R. L. Hinman and E. B. Whipple, *J. Amer. Chem. Soc.*, **84**, 2534 (1962); R. L. Hinman and C. P. Baumann, *J. Org. Chem.*, **29**, 2437 (1964).

(4) See, for example, (a) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *J. Amer. Chem. Soc.*, **76**, 4749 (1954); *Tetrahedron*, **19**, 247 (1963); (b) H. P. Husson, C. Thal, P. Potier, and E. Wenkert, *Chem. Commun.*, 480 (1970); (c) G. Grethe, H. L. Lee, and M. R. Uskokovic, *Syn. Commun.*, **2**, 55 (1972); (d) R. L. Augustine and S. F. Wanat, *ibid.*, **2**, 63 (1972).

(5) A. H. Jackson and A. E. Smith, *Tetrahedron*, **24**, 403 (1968).

(6) (a) Reference 2a, Chapter 3; (b) V. F. Martynov and G. Ol'man, *Zh. Obshch. Khim.*, **25**, 1561 (1955); *Chem. Abstr.*, **50**, 4909 (1956); (c) M. Panunzio, N. Tangari, and A. U. Ronchi, *Chem. Commun.*, 415 (1972); (d) C. D. Jones and T. Saurez, *J. Org. Chem.*, **37**, 3622 (1972); (e) C. D. Jones, *ibid.*, **37**, 3624 (1972); (f) P. G. Gassman and T. J. Van Bergen, *J. Amer. Chem. Soc.*, **95**, 590 (1973).

(7) R. J. Sundberg, *J. Org. Chem.*, **30**, 3604 (1965); **33**, 487 (1968).

(8) R. J. Sundberg, H. F. Russell, W. V. Ligon, Jr., and Long-Su Lin, *J. Org. Chem.*, **37**, 719 (1972).

(9) Reference 2a: (a) p 189; (b) p 176; (c) p 182.

(10) (a) C. F. H. Allen and J. Van Allan, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 597; (b) A. Verley, *Bull. Soc. Chim. Fr.*, **35**, 1039 (1924); **37**, 189 (1925); (c) C. Cardini, F. Piozzi, and G. Casnati, *Gazz. Chim. Ital.*, **85**, 263 (1955); (d) T. Lesiak, *Rocz. Chem.*, **36**, 1097 (1962); *Chem. Abstr.*, **58**, 5615 (1964); (e) F. Piozzi and M. R. Langella, *Gazz. Chim. Ital.*, **93**, 1382 (1963); (f) G. Gasnati, M. R. Langella, F. Piozzi, A. Ricca, and A. Umani-Ronchi, *ibid.*, **94**, 1221 (1964); (g) E. Walton, C. H. Stammer, R. F. Nutt, S. R. Jenkins, and F. W. Holly, *J. Med. Chem.*, **8**, 204 (1965).

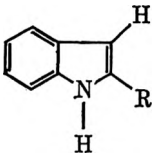
(11) W. E. Noland, L. R. Smith, and K. R. Rush, *J. Org. Chem.*, **30**, 3457 (1965), footnote 15.

(12) W. E. Noland and C. Reich, *J. Org. Chem.*, **32**, 828 (1967).

(13) (a) E. Euler and H. Erdtman, *Justus Liebigs Ann. Chem.*, **520**, 1 (1935); (b) E. C. Kornfeld, *J. Org. Chem.*, **16**, 806 (1951); (c) F. Yoneda, T. Miyamae, and Y. Nitta, *Chem. Pharm. Bull.*, **15**, 8 (1967).

(14) (a) H. R. Snyder and P. L. Cook, *J. Amer. Chem. Soc.*, **78**, 969 (1956); (b) W. Schindler, *Helv. Chim. Acta*, **40**, 1130 (1957).

1 as a synthetic intermediate the method of choice for its preparation was through ethyl indole-2-carboxylate (2).



1, R = $CH_2N(CH_3)_2$
2, R = CO_2Et

In this present work it has also been found that the nature of the base used has a marked influence on the outcome of the reaction. In contrast to the previous report,[13b] however, it was found that the use of potassium *tert*-butoxide gave, by far, the best yields of indoles, especially in those reactions involving toluidides having a nitrogen-containing acyl group. The use of other bases, such as sodium methoxide, sodium ethoxide, sodium amide, lithium amide, or *n*-butyllithium, resulted in either very low yields of cyclized material or extensive decomposition of the product. It is necessary, though, that care be taken to avoid the complete sublimiation of the potassium *tert*-butoxide before cyclization occurred completely. The best results were obtained when the toluidide was refluxed in benzene or *tert*-butyl alcohol for a short time with 4–8 equiv of the base. After removal of the solvent the residue was then placed in a bath prehcated to about 270° and the temperature was raised until the residue melted and frothing was observed. The temperature was held at this level until the frothing subsided and the reaction mixture was analyzed for the presence of toluidide by tlc. If toluidide was present, the mixture was cooled and redissolved, additional base was added, and the procedure was repeated.

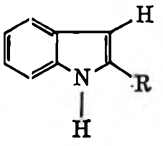
The optimum temperature for cyclization is determined by the nature of the substituent present on the toluidide. If the reaction temperature is too high extensive decomposition can take place. While the best temperature for a given reaction can be found by trial and error, it is generally true that temperatures 5–10° above the melting point of the toluidide salt give satisfactory results in most cases. The superiority of potassium *tert*-butoxide over the sodium- and lithium-containing bases is probably a result of the lower melting points of the potassium toluidide salts as compared to the sodium and lithium analogs. The indoles prepared here by this method and the optimum reaction temperatures are listed in Table I.

As mentioned above, this reaction is quite useful for the preparation of α-alkyl-substituted indoles; even the previously unknown α-cyclopropylindole (**3c**) is obtained in good yield by this procedure. However, if the toluidide contains double bonds (**4c** and **4o**,[15] Table II) or active hydrogens (**4e**), extensive decomposition is observed even at the lowest possible reaction temperature. In agreement with previous work[13] it was found that tertiary amines are stable under these reaction conditions, as shown by the preparation of **3d** and **3g**. However, in neither of these compounds is there available a potential secondary amine which could be utilized in further reactions. The common amine blocking groups such as the amide or the urethane proved to be ineffective, since they are readily cleaved under the reaction conditions and the resulting secondary amine is decomposed on further heating. Tertiary benzylamines are, however, stable and the *N*-benzylpiperidylindoles **3e** and **3f** are obtained in good yields. Secondary amines are potentially available by hydrogenolysis of these benzylamines.[16] The isoquinoline toluidide **4p** did not show any sign of reaction at temperatures below 340°. At higher temperatures a reaction occurred but the product was a nonindolic material which contained no methoxy group as indicated by pmr spectroscopy.

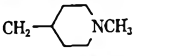
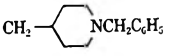
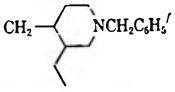
The toluidides used in this reaction are generally prepared by the reaction of *o*-toluidine with an acid chloride or anhydride. They can also be prepared by the reaction of the toluidine anion with an ester (Bourdroux reaction).[17] It has been found that anion generation using alkyllithium reagents rather than Grignard reagents gives much better yields of the toluidide. Some toluidides were also prepared using the modified

TABLE I

α-MONOSUBSTITUTED INDOLES



3

	R	Method of preparation[a]	Reaction temp,[b] °C	Yield, %	Mp, °C
a	CH_3	A	300	86	60–61[c]
		B		96	58–59
		C		42[c]	59-60
b	C_6H_5	A	325	60	186–187[d]
c		A	300	75	58–59[e]
d		A	340	92	137–139[e]
e		A	300	72	112–114[e]
f		A	300	81	195–196[e,g]
g		A	300	66	154–156[h]
h	CH_2CH_3	C		55[i]	40–41[j]
i	$CH_2C_6H_5$	C		43[i]	81–83[k]

[a] A = Madelung reaction, B = nitro ketone reduction, C = dinitrostyrene reduction. [b] For Madelung reaction. [c] Lit. mp 56–57° (ref 10a). [d] Lit. mp 186–188° [R. L. Shriner, W. C. Ashley, and E. Welch, *Org. Syn.*, **22**, 98 (1942)]. [e] All new compounds gave C, H, and N analyses within ±0.3% of theoretical values. [f] Mixture of cis and trans isomers. [g] Melting point of the maleate salt. [h] Lit. mp 155–156° (ref 7b). [i] Overall yield from *o*-nitrobenzaldehyde. [j] Lit. mp 43° [A. Verley and J. Deduwe, *Bull. Soc. Chim. Fr.*, **37**, 190 (1925)]. [k] Lit. mp 86° [P. L. Julian and J. Pikl, *J. Amer. Chem. Soc.*, **55**, 2105 (1933)].

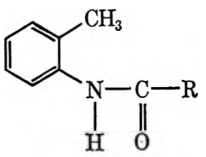
(15) Similar results in the attempted cyclization of **4o** using lithium amide have also been observed: M. R. Uskokovic, private communication.

(16) R. L. Augustine, "Catalytic Hydrogenation," Marcel Dekker, New York, N. Y., 1965, Chapter 6.

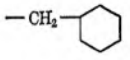
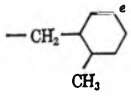
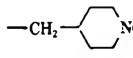
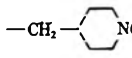
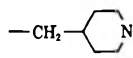
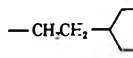
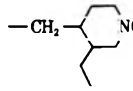
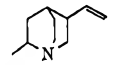
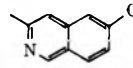
(17) F. Bourdoux, *C. R. Acad. Sci., Ser. C*, **138**, 1427 (1904); **140**, 1108 (1905); **142**, 401 (1906).

TABLE II

o-TOLUIDIDES



4

	R	Method of preparation[a]	Yield, %	Mp, °C
a	CH_3	A	75	110–112[b]
b	C_6H_5	A	90	143–145[c]
c		A	93	154–156[d]
d		A	96	129–131[d]
e	$CH_2C_6H_5$	B	80	161–162[d]
f		C	74	146–148[d]
g		C	81	136–140[d]
h		B	85	63–66[d]
i		C	73	139–140[d]
j		C	83	147–149[d]
k		C	74	143–144[f]
l		C[g]	60	128–129
m		B	79	103–105[d]
n		B	79	113–115[d]
o		B	40	*h*
p		g	75	124–125[d]

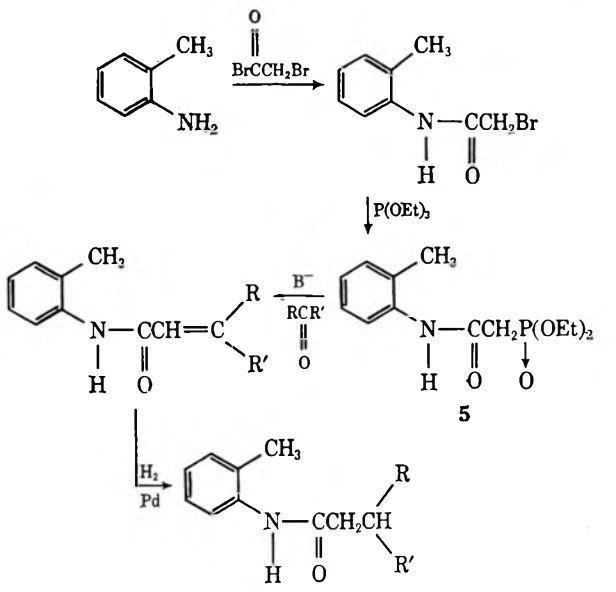
[a] A = from acid chloride or anhydride, B = Bourdroux reaction, C = modified Wittig reaction. [b] Lit. mp 110–111° (ref 10a). [c] Lit. mp 145–146° [P. Jacobson and L. Huber, *Chem. Ber.*, 41, 660 (1908)]. [d] All new compounds gave C, H, and N analyses within ±0.3% of the theoretical values. [e] Mixture of cis and trans isomers. [f] Characterized by conversion to 4e. [g] Modified procedure; details are given in the Experimental Section. [h] Material used without further characterization.

Wittig reaction shown in Scheme I. The toluidides prepared in this work are listed in Table II.

***o*-Nitrobenzyl Ketone Reduction.**[9b]—One of the more common reductive indole ring closure procedures is the Reissert sequence,[18] involving the condensation of *o*-nitrotoluene with ethyl oxalate followed by reduction to give ethyl indole-2-carboxylate (2). This compound

(18) F. T. Tyson, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 479.

SCHEME I



5

is the intermediate commonly used in the preparation of **1**,[13b] indole-2-acetic acid,[19] isotryptophane,[13b,14a,20] and other α-substituted indoles.[14b,21] While this procedure has been used for the preparation of a number of 4-, 5-, 6-, or 7-substituted indoles,[9b] its utility has not been extended to the direct preparation of indoles having an α substituent other than an ester. A number of attempts have been made to condense *o*-nitrotoluene with esters other than oxalates[22] but in no instance was the desired nitro ketone obtained.

The problem in the general utility of this reductive procedure lies mainly in the availability of the required nitro ketones. A partial solution to this problem has been attained with the reported condensations of *o*-nitrophenylacetyl chloride with enamines,[23] malonates,[24] and β-keto esters.[25] The preparation of oxindoles by nucleophilic substitution of malonic acid ester anions on *o*-chloronitrobenzene followed by hydrogenation has been reported.[26] By a similar reaction sequence 4-aza-3-cyanooxindole is prepared from 2-chloro-3-nitropyridine and ethyl cyanoacetate.[27] No mention could be found in the literature of the use of this type of reaction sequence to prepare *o*-nitrobenzyl ketones and of their subsequent reduction of α-substituted indoles.

The reaction between *o*-fluoronitrobenzene (**6a**) and the anion of ethyl acetoacetate occurred readily in hexamethylphosphoric triamide (HMPT) at room temperature. The product aryl β-keto ester **8** (Scheme II) was hydrolyzed and decarboxylated to give the nitro ketone **9**, which was hydrogenated to 2-methyl-

(19) W. Schindler, *Helv. Chim. Acta*, **41**, 1441 (1958).

(20) S. Swaminathan and S. Sulochana, *J. Org. Chem.*, **23**, 90 (1958).

(21) (a) J. R. Johnson, R. B. Hasbrouk, J. D. Dutcher, and W. F. Bruce, *J. Amer. Chem. Soc.*, **67**, 423 (1945); (b) W. J. Brehm, *ibid.*, **71**, 3541 (1949); (c) J. Harley-Mason and E. H. Parvi, *J. Chem. Soc.*, 2565 (1963).

(22) I. C. Pattison, Ph.D. Dissertation, Seton Hall University, South Orange, N. J., 1972.

(23) P. Rosenmund and W. H. Hoase, *Chem. Ber.*, **99**, 2504 (1966).

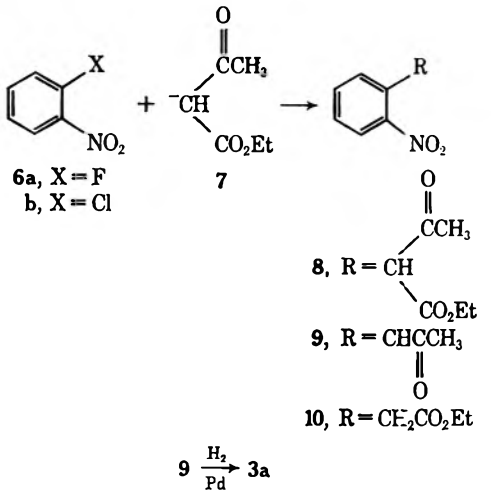
(24) J. R. Piper and F. J. Stevens, *J. Heterocycl. Chem.*, **3**, 95 (1966).

(25) R. Giuliano and M. L. Stein, *Ann. Chim. (Rome)*, **48**, 1284 (1958); *Chem. Abstr.*, **53**, 14084 (1959).

(26) C. A. Grob and O. Weissbach, *Helv. Chim. Acta*, **44**, 422 (1961).

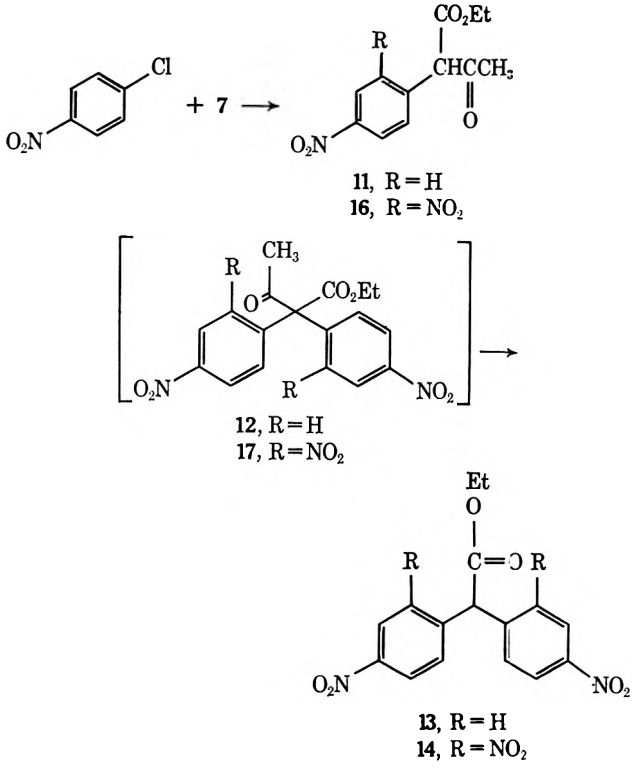
(27) N. Finch, M. M. Robison, and M. P. Valerico, *J. Org. Chem.*, **37**, 51 (1972).

SCHEME II



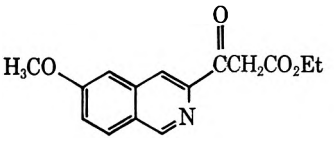
indole (**3a**) in 70% overall yield. As expected, the corresponding reaction on *o*-chloronitrobenzene (**6b**) took place only at the elevated temperatures, with **8** being formed in 65% yield after 4 hr at 110°. After 16 hr at this temperature a quantitative yield of ethyl-*o*-nitrophenylacetate (**10**) was formed. Since it was felt that this deacylation could have been assisted by the nitro group,[28] the reactions were repeated using *p*-chloronitrobenzene (Scheme III). As with the ortho

SCHEME III

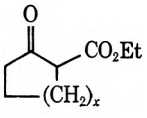


isomer the normal product, **11**, was obtained in 65% yield after 4 hr at 110°. After 20 hr at this temperature the diarylacetic ester, **13**, was formed in nearly quantitative yield. Borsche[29] has reported the formation of a small amount of the corresponding dinitro compound **14** from reaction of 2,4-dinitrochlorobenzene (**15**) with ethyl acetoacetate. He has shown that **14** could be generated by the reaction of **15** with **16** and has suggested that the diaryl β-keto ester **17** thus formed was deacylated by reaction with the solvent. None of the analogous diarylacetic ester was detected in the *o*-chloronitrobenzene reactions discussed above.

The utility of our approach as a general synthesis of α-substituted indoles was shown to be quite limited when it was found that neither the isoquinoline β-keto ester **18** nor the cycloalkanone carboxylic esters **19a** and **19b** would react with **6a** under a variety of



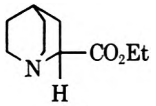
18



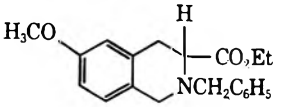
19a, $x = 1$
b, $x = 2$

reaction conditions. Condensation of these β-keto esters with 2,4-dinitrochlorobenzene could be effected but the resulting products resisted all attempts at hydrolysis and decarboxylation.

In conjunction with this phase of the work several attempts were made to prepare β-keto esters from the quinuclidine and tetrahydroisoquinoline esters **20** and **21** by means of mixed Claisen condensations with both



20



21

ethyl and *tert*-butyl acetate. In contrast to a previous report of a successful condensation of **20** with ethyl acetate,[30] only starting amino esters were recovered from our attempts. In order to ascertain the reason for this failure one of the basic reaction mixtures was worked up using deuterioacetic acid, When the recovered amino ester **20** was analyzed by pmr spectroscopy, it was found that the C_2 proton was completely replaced by deuterium. It appears that in these amino esters the α proton is quite acidic and that under the basic reaction conditions relatively facile anion formation at this carbon precludes any condensation.

o,β-Dinitrostyrene Reductions.[9c]—The condensation *o*-nitrobenzaldehyde (**22**) with nitromethane to give the dinitrostyrene **23** (Scheme IV) has been well documented.[31] Reduction of **23** gives indole **24**.[9c,32] While this procedure has been used for the preparation of a number of 4-, 5-, 6-, and 7-substituted indoles[9c] and 2-methylindoles,[33] it does not appear to have been used for the preparation of any other α- or β-substituted indoles.

The primary nitroalkanes **25** required for the extension of this procedure are available by several

(28) J. D. Loudon and G. Tennant, *Quart. Rev., Chem. Soc.*, **18**, 389 (1964).

(29) W. Borsche, *Chem. Ber.*, **42**, 601 (1909).

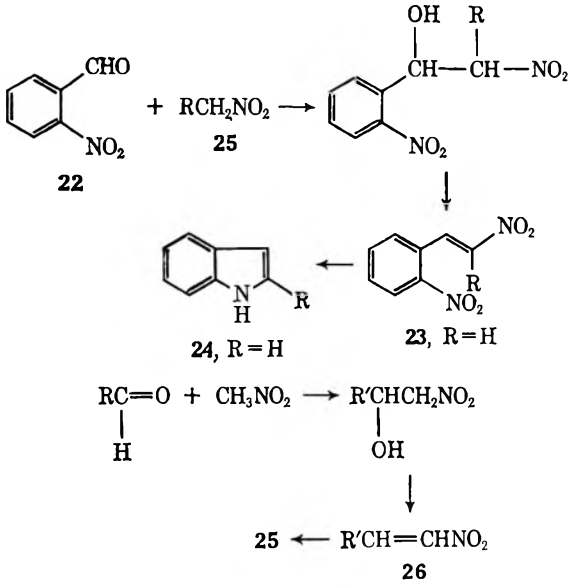
(30) L. N. Yakhontov and M. V. Rubstov, *Zh. Obshch. Khim.*, **27**, 72 (1957); *Chem. Abstr.*, **51**, 12085 (1957).

(31) L. F. Fieser and W. H. Dandt, *J. Amer. Chem. Soc.*, **68**, 2248 (1946).

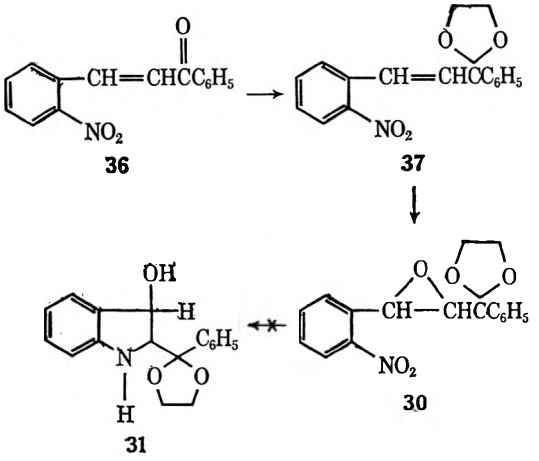
(32) T. van der Lee, *Recl. Trav. Chim. Pays-Bas*, **44**, 1089 (1925).

(33) (a) H. Burton and J. A. Duffield, *J. Chem. Soc.*, 78 (1949); (b) R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *ibid.*, 2029 (1951); (c) R. H. Heacock, O. Hutzinger, B. D. Scott, J. W. Daly, and B. Witkop, *J. Amer. Chem. Soc.*, **85**, 1825 (1963).

SCHEME IV

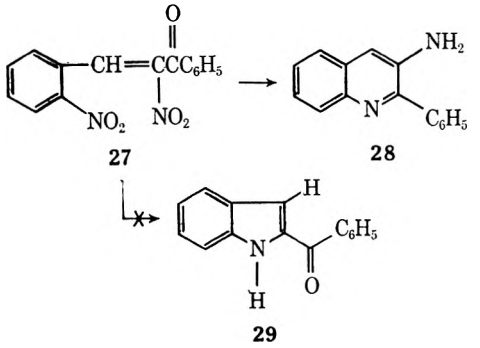


SCHEME V



routes.[34] The method used here involved the condensation of the appropriate aldehyde with nitromethane followed by dehydration of the intermediate alcohol to give the nitro olefin **26**. The double bond in **26** was reduced either with sodium borohydride[35] or by catalytic hydrogenation over $(Ph_3P)_3RhCl$,[36] the latter procedure being effective for aliphatic as well as aromatic nitro olefins. Finally, condensations of these nitroalkanes with **22** occurred readily with sodium acetate in acetic acid. By use of this procedure 2-alkylindoles have been prepared in fairly good overall yields (see Table I).

As an extension of this work, the benzoyldinitrostyrene **27** was hydrogenated to determine whether an indole, **29**, or a quinoline, **28**, would be formed. On



work-up of the reaction mixture only 3-amino-2-phenylquinoline (**28**) was found. All attempts to block the keto group in **27** by ketalization led to either the recovery of starting material or the addition of the alcohol across the double bond.

We also felt that reducing an *o*-nitrostyrene oxide after dehydrating the anticipated hydroxyindoline intermediate, **31**, could lead to the formation of indoles (Scheme V). The ketal epoxide **30** was prepared as shown in Scheme V and hydrogenated under a variety of conditions. In most instances the product mixture was composed of a large number of compounds, none of which gave the characteristic indole test reactions or showed the characteristic β-indole proton resonance in the pmr spectra,[33c] even after acid treatment to attempt dehydration. When palladium on charcoal was used as the catalyst a reasonably pure sample of a single product was obtained. This material still showed the presence of the dioxolane ring by pmr spectroscopy but was found to be polymeric by mass spectral analysis. No further work was done on this material.

Experimental Section[37]

o-Toluidide Formation (Table II). A. From Acid Chlorides.—A dioxane solution of *o*-toluidine was added to a suspension of 1 equiv of sodium hydride in hexane. After gas evolution subsided a dioxane solution of 1 equiv of the acid chloride (or anhydride) was added and the mixture was refluxed for 2–3 hr. The reaction mixture was poured into water and extracted with ether. The extracts were washed with a 2% aqueous sodium carbonate solution, 3 *N* HCl, and water, after which they were dried and evaporated. The solid toluidides were recrystallized from aqueous ethanol or benzene–pentane and were characterized by the presence of infrared absorption bands at 3450–3350 (NH) and 1680–1690 cm^{-1} (C=O) as well as by a three-proton singlet in the nmr spectrum at δ 2.1–2.2 ($ArCH_3$).

B. From Esters.—To 50–75 ml of hexane containing 0.05 mol of *n*-butyllithium was added, slowly and with stirring under nitrogen, 5.4 g (0.05 mol) of freshly distilled o-toluidine in 25 ml of ether. After gas evolution ceased, 0.025 mol of the ester in 25 ml of ether was added and the solution was refluxed for 1–2 hr and then poured over ice water. If a solid formed it was filtered and recrystallized from aqueous ethanol or benzene–pentane. If not, the reaction mixture was extracted with ether. The extracts were washed with water, dried, and evaporated. The excess *o*-toluidine could conveniently be removed by heating at 60° (0.2 mm) overnight.

C. From Ketones. *N*-(Diethylphosphonoacetyl)-*o*-toluidine (5).—To 500 ml of ether containing 54 g of *o*-toluidine and 55 g of triethylamine was added a solution of 125 g of bromoacetyl bromide in 200 ml of ether. After stirring for 1 hr the precipitate was removed and the ether was evaporated from the filtrate under reduced pressure. The residue was treated with 300 ml of pentane and the crystalline *N*-(bromoacetyl)-*o*-toluidine, separated by filtration, was used directly in the following step.

This toluidide (57 g) was added to 83 g of triethyl phosphite and the mixture was heated rapidly to 120°, at which temperature a violent reaction began. When the initial reaction subsided, the mixture was heated further to 150° under reduced pressure until

(34) G. B. Bachman and R. J. Maleski, *J. Org. Chem.*, **37**, 2810 (1972), and references cited therein.

(35) I. Baxter and G. A. Swan, *J. Chem. Soc.*, 468 (1968).

(36) R. E. Harmon, J. L. Parsons, D. W. Cooke, S. K. Gupta, and J. Schoolenberg, *J. Org. Chem.*, **34**, 3684 (1969).

(37) Proton nmr spectra were determined on a Varian A-60A spectrometer. Ir spectra were determined on a Beckman IR-10. Melting points and boiling points are uncorrected. Tlc determinations were performed on Eastman #6060 silica gel thin layer chromatogram sheets using chloroform as the developing solvent.

gas evolution ceased. The cooled residue was dissolved in 400 ml of ether and the resulting solution was poured slowly into 2 l. of petroleum ether (bp 30–60°). The precipitated 5 (32 g, 45%) had mp 76–78° (recrystallization from ether–petroleum ether raised the melting point to 77–78°); ir ($CHCl_3$) 3400, 1684 cm^{-1}; nmr ($CDCl_3$) δ 1.17 (t, 6, $-OCH_2CH_3$), 2.14 (s, 3, $ArCH_3$), 3.00 (d, 2, J = 21 Hz, $PCH_2C{=}O$), 4.06 (m, 4, $-OCH_2CH_3$), and 9.05 (s, 1, NH). *Anal.* Calcd for $C_{13}H_{20}NO_4P$: C, 54.73; H, 7.07; N, 4.41. Found: C, 54.79; H, 7.15; N, 4.90.

A solution of 2.85 g (0.01 mol) of 5 and 1.1 g (0.02 mol) of sodium methoxide in 10 ml of DMF was stirred for 5 min, after which time 0.01 mol of the ketone was added and the slurry was thoroughly mixed. After standing at room temperature for 96 hr the slurry was poured into 50 ml of water and the resulting mixture was extracted with ether. The extracts were dried and evaporated. The residue was dissolved in 100 ml of ethanol and hydrogenated over 50 mg of 5% Pd/C at room temperature and 35 psig. Filtration and evaporation give the toluidide, which was purified by recrystallization from aqueous ethanol or benzene–pentane.

***N*-(1-Benzyl-4-piperidylpropionyl)-*o*-toluidine (41).**—Crude *N*-(4-pyridylpropionyl)-*o*-toluidine (2.15 g, 0.009 mol), prepared from 1.1 g (0.01 mol) of 4-pyridinecarboxaldehyde by method C, was dissolved in 15 ml of ethanol and then treated with 1.4 g (0.11 mol) of benzyl chloride. The solvent was removed by heating on a steam bath and the residue was taken up in a mixture of 30 ml of ethanol and 9 ml of acetic acid. This solution was hydrogenated over 0.5 g of platinum oxide at 35 psig. After 3 equiv of hydrogen was absorbed (about 2 hr) the reaction mixture was filtered and the filtrate was evaporated. The residue was slurried with ether and treated with 15 ml of cold 30% aqueous NaOH. The ether layer was dried and evaporated and the residue was recrystallized from aqueous acetone to give 2 g (60%) of the piperidyl toluidide, 41, mp 128–129°. *Anal.* Calcd for $C_{22}H_{28}N_2O$: C, 78.53; H, 8.39; N, 8.33. Found: C, 78.46; H, 8.56; N, 8.04.

6-Methoxy-3-isoquinolinecarboxo-*o*-toluidide (4p), prepared from 6-methoxy-3-isoquinolinecarboxylic acid[38] by the procedure of Klosa,[39] had mp 124–125°; ir (Nujol) 3320, 1680, 1625, and 1590 cm^{-1}; nmr ($CDCl_3$) δ 2.37 (s, 3, $ArCH_3$), 3.83 (s, 3, $-OCH_3$), 8.43 (s, 1, isoquinoline C_4 H), 8.87 (s, 1, isoquinoline C_1 H), and 10.13 (s, 1, NH). *Anal.* Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.59. Found: C, 74.21; H, 5.58; N, 9.38.

***N*-Benzyl-3-ethyl-4-piperidone (32).**—To a mixture of 30 g (0.27 mol) of potassium *tert*-butoxide, 200 ml of freshly distilled *tert*-butyl alcohol, and 48.3 g (0.31 mol) of ethyl iodide was added all at once 58 g (0.22 mol) of ethyl *N*-benzyl-4-oxo-3-piperidinecarboxylate[40] followed by refluxing, with stirring, for 45 min. The solvent was evaporated under reduced pressure and the residue was taken up in water and extracted with ether. The extracts were dried and evaporated to give 61 g (95% crude yield) of a red oil, nmr ($CDCl_3$) δ 0.85 (t, 3, CCH_2CH_3) 1.20 (t, 3, OCH_2CH_3), 3.57 (s, 2, NCH_2Ph), and 4.01 (q, 2, OCH_2CH_3). This oil was refluxed for 16 hr with 800 ml of 6 *N* HCl. The solution was evaporated nearly to dryness under reduced pressure, the residue was dissolved in 200 ml of water, and the solution was made basic with solid sodium bicarbonate. The mixture was extracted with ether and the extracts were washed with water, dried, and evaporated to give an oil which on distillation gave 22.3 g (49%) of 32: bp 138–139° (1 mm); nmr ($CDCl_3$) δ 0.85 (t, 3, $-CH_2CH_3$), and 3.57 (s, 2, NCH_2Ph). *Anal.* Calcd for $C_{14}H_{19}NO$: C, 77.39; H 8.79; N, 6.45. Found: C, 77.08: H, 8.74; N, 6.41.

Ethyl-*N*-benzyl-3-ethyl-4-piperidyl Acetate (33).—A solution of 50 g (0.22 mol) of triethyl phosphonoacetate in 20 ml of dry benzene was added dropwise with stirring to a suspension of 5.3 g (0.22 mol) of sodium hydride in 300 ml of dry benzene with the temperature of the reaction mixture kept below 40°. After the addition was completed the clear solution was stirred for an additional 15 min, after which time a solution of 46 g (0.21 mol) of 32 in 20 ml of benzene was added dropwise over a period of 1.5 hr. After the addition was finished the reaction mixture was stirred for an additional 1.5 hr and then poured into water. The benzene layer was separated and the aqueous phase was extracted with ether. The combined organic solutions were washed with water, dried, and evaporated to give 45 g of an orange oil which was dissolved in 300 ml of acetic acid and hydrogenated over 1 g of platinum oxide at room temperature and 50 psig. After 1 equiv of hydrogen had been adsorbed the catalyst was removed and the solution was evaporated. The residue was dissolved in water, made basic with sodium bicarbonate, and extracted with ether. The extracts were washed with water, dried, and evaporated to give an oil which was distilled to give 21.3 g (35%) of 33: bp 142–145° (0.3 mm); nmr ($CDCl_3$) δ 0.84 (t, 3, $-CH_2CH_3$), 1.20 (t, 3, $-CH_2CH_3$), 3.46 (2 peaks, 2, NCH_2Ph), and 4.10 (q, 2, $-OCH_2CH_3$). *Anal.* Calcd for $C_{18}H_{27}NO_2$: C, 74.69; H, 9.40; N, 4.84. Found: C, 74.82; H, 9.54; N, 4.97.

Madelung Reaction.—Under a slow nitrogen stream a mixture of 0.5–1.0 g of the *o*-toluidide and 4–8 equiv of potassium *tert*-butoxide was refluxed in 10–20 ml of dry *tert*-butyl alcohol for 30 min. The alcohol was then removed by increasing the nitrogen flow and removing the condenser. When most of the solvent had evaporated the reaction flask was transferred to a Woods metal bath which had been preheated to 200–250°. The temperature was slowly raised until the solid mixture melted with frothing (275–350°) and was held at this level until the reaction was complete. Small samples were withdrawn on a glass rod, quenched in water, and extracted with ether and the extracts were spotted on tlc sheets and developed with chloroform. Detection with iodine vapor followed by spraying with Ehrlich's reagent[41] allowed the reaction to be followed until the starting material (yellow spot) was gone and the indole (pink-violet spot) was at a maximum or until decomposition began. If the presence of starting material persisted, the mixture was cooled, more potassium *tert*-butoxide and *tert*-butyl alcohol were added, and the procedure was repeated. The reaction mixture was then cooled, quenched with water, and extracted with ether. The extracts were washed with water, dried, and evaporated to give the indole, which was readily recrystallized from aqueous ethanol and easily characterized by the β-proton peak in the nmr at δ 6.1–6.2.[33c] A list of compounds prepared in this way, their physical properties, and the optimum reaction temperatures is given in Table I.

When this reaction was attempted on the *N*-carboethoxypiperidyl toluidide 4k, or any material containing a double bond such as the toluidides 4c and 4o, intractable nonindolic product mixtures were obtained. When the reaction on 4k was run at 260° for 5 min a toluidide was obtained which was readily converted by reductive amination with formaldehyde to the *N*-methylpiperidyl toluidide, 4i. Madelung reaction on the methoxyisoquinoline toluidide, 4p, did not take place until the reaction temperature was raised above 340°. The product mixture obtained for this reaction showed no β-indole proton absorption or methoxy methyl absorption in the nmr spectrum.

Ethyl 3-(6-Methoxy-3-isoquinolyl)-3-oxopropionate (18).—To a refluxing solution of 25.5 g (0.11 mol) of ethyl 6-methoxyisoquinoline-3-carboxylate[38] and 13.9 g (0.12 mol) of potassium *tert*-butoxide in 100 ml of toluene was added 10.99 (0.12 mol) of ethyl acetate over a 90-min period. The reaction mixture was refluxed for an additional 15 min, cooled, and filtered. The residue was washed with ether, slurried with water, and neutralized to pH 7 with 1 *N* HCl. The product was extracted into methylene chloride and the extracts were dried and evaporated. Recrystallization of the residue from ether–petroleum ether gave 8.3 g (37%) of the β-keto ester 18: mp 81–82°; ir (Nujol) 1740 and 1690 cm^{-1}; nmr ($CDCl_3$) δ 1.22 (t, 3, OCH_2CH_3), 3.87 (s, 3, $-OCH_3$), 4.17 (q, 2, OCH_2CH_3), and 4.22 (s, 2, CCH_2CO). *Anal.* Calcd for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 66.17; H, 5.50; N, 5.30.

Deuterium Exchange on Ethyl Quinuclidine-2-carboxylate (20).[4d]—A mixture of 90 mg of 20, 500 mg of potassium *tert*-butoxide, and 10 ml of dry benzene was heated at reflux for several hours. The solvent was removed under vacuum and the residue was treated with 0.5 ml of deuterioacetic acid. The resulting solution was neutralized with saturated sodium bicarbonate solution and extracted with ether. The extracts were dried and evaporated. The nmr spectrum of the recovered ester showed no peaks between δ 3.0 and 4.0, in which region the C-2 proton of the starting material absorbed. The rest of the spectrum was essentially the same as that of the starting amino ester.

2-Methylindole from *o*-Fluoronitrobenzene.—To a solution of 1.3 g (0.01 mol) of ethyl acetoacetate in 10 ml of HMPT under nitrogen was added 1.1 g (0.01 mol) of potassium *tert*-butoxide. After 5–10 min all of the base had dissolved and 0.7 g (0.005 mol) of *o*-fluoronitrobenzene was added slowly, giving a dark red solu-

(38) G. A. Swan, *J. Chem. Soc.*, 1534 (1950).

(39) J. Klosa, *J. Prakt. Chem.*, **19**, 45 (1962).

(40) J. R. Thayer and S. M. McElvain, *J. Amer. Chem. Soc.*, **49**, 2862 (1927).

(41) H. W. van Urk, *Pharm. Weekbl.*, **66**, 473 (1929); F. G. Otten, *ibid.*, **74**, 510 (1937).

tion almost immediately. The solution was stirred at 60–70° for 1 hr and then poured into a mixture of 25 ml of 3 *N* HCl and 100 g of ice. This mixture was extracted with ether and the extracts were washed with water, dried, and evaporated. Hydrolysis and decarboxylation were effected by refluxing the residue in 3 *N* HCl. The acid mixture was extracted with ether and the extracts were washed with water, dried, and evaporated to give 0.66 g (74%) of crude nitro ketone. Catalytic hydrogenation of this material over 5% palladium on charcoal in glacial acetic acid at room temperature and 40 psig gave 0.46 g (71% overall) of 2-methylindole, mp 58–59° (Table I). The use of *o*-chloronitrobenzene gave 2-methylindole in only 48% yield. Replacing the ethyl acetoacetate with *tert*-butyl acetoacetate and utilizing benzene and *p*-toluenesulfonic acid for the hydrolysis and decarboxylation gave slightly better yields of indole.

Prolonged Reaction of Ethyl Acetoacetate with *o*-Chloronitrobenzene.—A solution of 26 g (0.2 mol) of ethyl acetoacetate in 50 ml of HMPT was added to a slurry of 7.2 g (0.3 mol) of sodium hydride in 25 ml of HMPT. This mixture was heated to 40° and 31.6 g (0.2 mol) of *o*-chloronitrobenzene was added. The mixture was then heated at 110–120° overnight, cooled, and poured over a mixture of ice and 100 ml of 3 *N* HCl. This suspension was extracted with benzene and the extracts were washed with water, dried, and evaporated, giving a nearly quantitative yield of ethyl *o*-nitrophenylacetate, mp 65–67° (lit.[42] mp 69°), mmp 67–68.5°.

***p*-Nitrophenylacetone.**—A solution of 6.5 g (0.05 mol) of ethyl acetoacetate in 25 ml of HMPT was slowly added to a suspension of 1.8 g (0.07 mol) of sodium hydride in 10 ml of HMPT under a steady nitrogen stream. After gas evolution subsided, 7.5 g (0.05 mol) of *p*-chloronitrobenzene was added and the reaction mixture was heated to 110–120° for 4 hr. The cooled reaction mixture was poured onto ice 3 *N* HCl and extracted with benzene. The extracts were washed with water, dried, and evaporated to give 7.9 g (72%) of crude β-keto ester, which was hydrolyzed and decarboxylated by refluxing with 3 *N* HCl. Extraction with ether gave 3.4 g (53%) of the ketone as an oil: ir (film) 1718 cm^{-1}; nmr ($CDCl_3$) δ 2.22 (s, 3, $OCCH_3$) and 3.85 (s, 2, $ArCH_2CO$). The 2,4-dinitrophenylhydrazone was recrystallized from aqueous ethanol, mp 180–181°. *Anal.* Calcd for $C_{15}H_{13}N_5O_6$: C, 50.14; H, 3.65. Found: C, 50.09; H, 3.62.

Ethyl Bis(*p*-nitrophenyl)acetate (13).—The procedure described above was repeated, only the reaction mixture was heated for 20 hr. On work-up 7.4 g (47%) of the ester **13** was obtained, which after crystallization from aqueous ethanol had mp 128–130°; ir ($CHCl_3$) 1737 (C=O), 1350, and 1522 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 1.25 (t, 3, OCH_2CH_3), 4.25 (q, 2, OCH_2CH_3), and 5.17 (s, 1, $OCCHAr_2$). *Anal.* Calcd for $C_{16}H_{14}N_2O_6$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.24; H, 4.35; N, 8.35.

Ethyl 1-(2,4-Dinitrophenyl)-2-oxocyclopentanecarboxylate (34).—To 11.2 g (0.1 mol) of potassium *tert*-butoxide in 100 ml of HMPT was added 15.6 g (0.1 mol) of ethyl 2-oxocyclopentanecarboxylate. After a few minutes 20.3 g (0.1 mol) of 2,4-dinitrochlorobenzene was added slowly keeping the temperature between 20 and 25°. After the addition was complete the reaction mixture was poured onto ice and the resulting suspension was extracted with ether. The ether extracts were washed with water, dried, and evaporated, giving 16 g (50%) of crude **34**, mp 118–120°. Recrystallization from carbon tetrachloride gave 9.7 g (30%) of pure **34** as bright yellow crystals: mp 119–121°; ir (Nujol) 1755 (ester C=O), 1720 (ketone C=O), and 1500 cm^{-1} (NO_2). *Anal.* Calcd for $C_{14}H_{14}N_2O_7$: C, 52.17; H, 4.38; N, 8.69. Found: C, 52.11; H, 4.28; N, 8.43. Only starting materials were obtained on reaction of ethyl 2-oxocyclopentanecarboxylate with *o*-chloronitrobenzene, *o*-fluoronitrobenzene, or 2,4-dichloronitrobenzene. A similar reaction pattern was observed with ethyl 2-oxocyclohexanecarboxylate and the isoquinoline β-keto ester **18**.

Attempted Hydrolysis of 34.—A 2-g sample of **34** was refluxed overnight in equal parts of acetic acid and concentrated HCl. The solvent was then evaporated and the residue was taken up in ether, washed with water, dried, and evaporated. The infrared spectrum of the residue was identical with that of starting material. The use of 70% sulfuric acid or 20% HCl gave the same results. Ethyl 1-(2,4-dinitrophenyl)-2-oxocyclohexanecarboxylate exhibited similar unreactivity toward these hydrolysis conditions. Hydrolysis of the 2,4-dinitrophenylated β-keto ester **18**, using either 20% HCl or 70% sulfuric acid, gave only 6-methoxyisoquinoline-2-carboxylic acid and recovered starting material.

2-Methylindole from the *o*,β-Dinitrostyrene.—To 25 ml of a 10% anhydrous ammonium acetate solution in glacial acetic acid was added 5 g (0.03 mol) of *o*-nitrobenzaldehyde (**22**) and 10 ml of nitroethane. The resulting mixture was refluxed under nitrogen for 3 hr. After cooling, the reaction mixture was poured into water and extracted with chloroform. The extracts were washed with 10% sodium bicarbonate solution and saturated sodium bisulfite solution, dried, and evaporated to give 4.2 g (63%) of the crude dinitrostyrene **23** (R = Me) as a red oil: ir ($CHCl_3$) 1520 and 1330 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 2.6 (s, 3, $-CH_3$) and 8.1 (s, 1, C=CH). The crude dinitrostyrene was dissolved in a mixture of 10 ml of ethanol, 12 ml of acetic acid, and 80 ml of ethyl acetate and hydrogenated over 1 g of 5% palladium on charcoal at room temperature and 60 psig. After hydrogen uptake ceased the catalyst was removed by filtration and the solution was washed with three 100-ml portions of saturated sodium bicarbonate solution. The organic phase was dried and evaporated to give 1.2 g (42%) of 2-methylindole, mp 59–60° (Table I). 2-Benzylindole (**3i**) was prepared in a similar manner using 2-phenylnitroethane[34] in the condensation with *o*-nitrobenzaldehyde.

2-Ethylindole (3h).—A mixture of 5 g (0.03 mol) of **22** and 0.6 g of anhydrous ammonium acetate was dissolved in 20 ml of 1-nitropropane and the solution was refluxed under nitrogen for 4 hr. After cooling, the reaction mixture was poured onto water and extracted with chloroform. The extracts were washed with saturated sodium bisulfite solution, dried, and evaporated. The residue was chromatographed on silica gel. Elution with 3:1 benzene–hexane gave 4.6 g (66%) of the dinitrostyrene **23** (R = Et) as a light yellow oil: ir ($CHCl_3$) 1515 and 1335 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 1.12 (t, 3, CH_2CH_3), 2.25 (q, 2, $-CH_2CH_3$), and 8.15 (s, 1, C=CH). Hydrogenation under the conditions described above for the preparation of 2-methylindole gave 1.70 g (55%) of 2-ethylindole (**3h**): mp 40–41° (Table I); ir ($CHCl_3$) 3430 cm^{-1}; nmr ($CDCl_3$) δ 1.10 (t, 3, CH_2CH_3), 2.25 (q, 2, $-CH_2CH_3$), and 6.05 (s, 1, β H).

2-Cyclohexylnitroethane.—To a solution of 11 g (0.1 mol) of 1,2,5,6-tetrahydrobenzaldehyde and 6 g (0.1 mol) of nitromethane in 100 ml of methanol was added a solution of 4 g of sodium hydroxide in 20 ml of water over a period of 20 min with cooling and rapid stirring. After 1 hr the reaction mixture was filtered and the residue was washed with cold methanol. The solid was then dissolved in 20 ml of cold water, acidified with 3 *N* HCl, and extracted with chloroform. The extracts were dried and evaporated to give 8.5 g (50%) of crude 2-(3-cyclohexen-1-yl)-2-hydroxynitroethane as a light yellow oil: ir ($CHCl_3$) 3400 (OH), 1550, and 1370 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 4.0–4.6 (m, 3, CHOH and CH_2NO_2) and 5.6 (s, 2, vinyl).

This crude product was stirred overnight with 30 ml of acetyl chloride at room temperature. The solution was evaporated and the residue was treated with petroleum ether to give 10.7 g of the 1-(3-cyclohexen-1-yl)-2-nitroethyl acetate: ir ($CHCl_3$) 1740 (C=O), 1545, and 1370 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 4.5 (d, 2, CH_2NO_2), 5.1–5.5 (m, 1, CHOAc), and 5.6 (s, 2, vinyl). This acetate was dissolved in 100 ml of benzene, 2 g of anhydrous sodium acetate was added, and the mixture was refluxed for 2 hr. The cooled reaction mixture was filtered and evaporated to give 4 g of crude 2-(3-cyclohexen-1-yl)-1-nitroethene: ir ($CHCl_3$) 1540 and 1355 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 5.55 (s, 2, vinyl) and 6.8–7.3 (m, 2, nitrovinyl).

Hydrogenation of this material by the procedure of Harmon[36] gave the crude nitroethane, which on chromatography over neutral alumina with hexane as the eluent gave 3.1 g (20% overall yield) of the product was a light yellow oil: bp 79–80° (1–2 mm); ir ($CHCl_3$) 1530 and 1340 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 4.35 (t, 2, $CH_2CH_2NO_2$). *Anal.* Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.90; H, 9.34; N, 8.90.

ω-Nitroacetophenone (35).—To a solution of 1.13 g (0.16 mol) of sodium ethoxide in 100 ml of absolute ethanol was added simultaneously with cooling and stirring 18 g (0.16 mol) of benzaldehyde and 15 g (0.25 mol) of nitromethane. After being stirred at room temperature overnight the reaction mixture was filtered. The residue was dissolved in a mixture of 75 ml of cold water and 11 g of glacial acetic acid and extracted with ether. The extracts were dried and evaporated to give the crude nitro alcohol, which was dissolved in 60 ml of acetic acid and oxidized with 125 ml of Jones reagent[43] for 1 hr at 10–20°. After the addi-

(42) R. Pshorr and G. Hoppe, *Chem. Ber.*, **43**, 2547 (1910).

(43) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

tion of an excess of sodium bisulfite the mixture was extracted with chloroform and the extracts were washed with water, dried, and evaporated to give 14.2 g (52%) of **35** as a while solid: mp 105–106° (lit.[44] mp 105°); ir ($CHCl_3$) 1710 (C=O), 1570, and 1330 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 5.85 (s, 2, $-COCH_2NO_2$).

α,2-Dinitrochalcone (27).—To a solution of 0.3 g of β-alanine in 6 ml of acetic acid and 60 ml of benzene was added 3.3 g (0.02 mol) of the nitroacetophenone and 3.3 g (0.022 mol) of *o*-nitrobenzaldehyde. The reaction mixture was refluxed through a Dean–Stark trap for 10 hr, cooled, and washed with water and saturated sodium bisulfite solution. The benzene solution was dried and evaporated to give 3.1 g (62%) of **27** which on recrystallization from benzene–hexane had mp 90–92°; ir ($CHCl_3$) 1680 (C=O), 1530, and 1345 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 8.6 (s, 1, nitrovinyl). *Anal.* Calcd for $C_{15}H_{10}N_2O_5$: C, 60.41; H, 3.38; N, 9.39. Found: C, 60.13; H, 3.49; N, 9.34.

Hydrogenation of 27.—A solution of 1 g (0.003 mol) of **27** in a mixture of 2.5 ml of absolute ethanol, 3 ml of acetic acid, and 20 ml of ethyl acetate was hydrogenated over 0.2 g of 5% palladium on carbon at room temperature and 50 psig. After 6 equiv of hydrogen had been absorbed (about 20 min) the catalyst was removed by filtration and the filtrate was washed with a saturated aqueous sodium bicarbonate solution, dried, and evaporated to give 0.9 g of a dark oil which was shown by tlc to be a complex mixture of products. Column chromatography over silica gel using ether as the eluent gave as the only identifiable species 0.2 g of 3-amino-2-phenylquinoline, mp 116–118° (lit.[45] mp 115–116°). No indolic material could be detected.

2-Nitrochalcone (36).—A solution of 4.8 g (0.35 mol) of acetophenone, 6 g (0.04 mol) of *o*-nitrobenazldehyde, and 2 g of ammonium acetate in 20 ml of acetic acid was refluxed under nitrogen for 3 hr. Upon cooling, the light yellow crystals which formed were filtered, washed with cold water, and recrystallized from aqueous ethanol to give 6.5 g (64%) of **36**: mp 117–119° (lit.[46] mp 117–121°); ir ($CHCl_3$) 1675 (C=O), 1540, and 1355 cm^{-1} (NO_2).

2-Nitrochalcone Ethylene Ketal (37).—Following the established[47] procedure, **36** was converted to the ethylene ketal in 81% yield. Recrystallization from 95% ethanol gave **37** as white crystals: mp 73–75°; ir ($CHCl_3$) 1540 and 1355 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 4.0 (m, 4, dioxolane) and 6.15 and 7.15 (d, 2, vinyl). *Anal.* Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.47; H, 5.01; N, 4.72.

2,3-Epoxy-3-(*o*-nitrophenyl)propiophenone Ethylene Ketal (30).—To a solution of 0.75 g (0.0025 mol) of **37** in 20 ml of methylene chloride was added a solution of 1 g (0.006 mol) of *m*-chloroperbenzoic acid in 20 ml of methylene chloride and the resulting solution was stirred at room temperature for 72 hr. The reaction mixture was then washed with a 10% aqueous sodium hydroxide solution, dried, and evaporated to give 0.55 g (57%) of an oil which slowly crystallized: mp 73–76°; ir ($CHCl_3$) 1535 and 1355 cm^{-1} (NO_2); nmr ($CDCl_3$) δ 3.2 (d, 1, C_2H), 3.8–4.4 (m, 4, dioxolane), and 4.6 (d, 1, C_3H). *Anal.* Calcd for $C_{17}H_{15}NO_5$: C, 65.17; H, 4.83; N, 4.47. Found: C, 65.45; H, 4.75; N, 4.33.

Hydrogenation of 30.—A solution of 1.5 g (0.005 mol) of **30** in 90 ml of ethyl acetate was hydrogenated over 0.5 g of 5% palladium on carbon at room temperature and 40 psig. After 24 hr 3 equiv of hydrogen was absorbed. The catalyst was removed and the solution was evaporated to give 1.4 g of a glassy yellow solid which was shown by mass spectrometry to be a polymer having a monomer unit with a molecular weight of 281–285.

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Registry No.—**3a**, 95-20-5; **3b**, 948-65-2; **3c**, 40748-44-5; **3d**, 40748-45-6; **3e**, 40748-46-7; *cis*-**3f** maleate, 40762-74-1; *trans*-**3f** maleate, 40762-75-2; **3g**, 15224-31-4; **3h**, 3484-18-2; **3i**, 3377-72-8; **4a**, 120-66-1; **4b**, 584-70-3; **4c**, 40748-51-4; **4d**, 15924-70-6; **4e**, 40748-53-6; **4f**, 40748-54-7; *cis*-**4g**, 40762-76-3; *trans*-**4g**, 40762-77-4; **4h**, 1752-87-0; **4i**, 40748-56-9; **4j**, 40748-57-0; **4k**, 40748-58-1; **4l**, 40748-59-2; *cis*-**4m**, 40762-78-5; *trans*-**4m**, 40762-79-6; **4n**, 26801-38-7; **4o**, 40790-99-6; **4p**, 40748-61-6; **5**, 40748-62-7; **9**, 1969-72-8; **13**, 40748-64-9; **18**, 40748-65-0; **20**, 39926-11-9; **22**, 552-89-6; **23** (R = Me), 18982-46-2; **23** (R = Et), 40748-68-3; **27**, 40748-69-4; **30**, 40748-70-7; **32**, 40748-71-8; **33**, 40748-72-9; **34**, 40791-00-2; **35**, 614-21-1; **36**, 7473-93-0; **37**, 40748-75-2; *o*-toluidine, 95-53-4; *N*-(bromoacetyl)-*o*-toluidine, 5332-69-4; triethylphosphite, 122-52-1; *N*-(4-pyridylpropionyl)-*o*-toluidine, 40748-77-4; 4-pyridinecarboxaldehyde, 872-85-5; ethyl *N*-benzyl-4-oxo-3-piperidinecarboxylate, 41276-30-6; ethyl 6-methoxyisoquinoline-3-carboxylate, 40748-79-6; *o*-fluoronitrobenzene, 1493-27-2; ethyl acetoacetate, 141-97-9; *o*-chloronitrobenzene, 88-73-3; *p*-nitrophenylacetone, 5332-96-7; *p*-nitrophenylacetone dinitrophenylhydrazone, 40748-81-0; ethyl 2-oxocyclopentanecarboxylate, 611-10-9; 2,4-dinitrochlorobenzene, 97-00-7; *o*-β-dinitrostyrene, 3156-39-6; 1-nitropropane, 108-03-2; 2-cyclohexylnitroethane, 40748-84-3; 1,2,5,6-tetrahydrobenzaldehyde, 100-50-5; nitromethane, 75-52-5; 2-(3-cyclohexen-1-yl)-2-hydroxynitroethane, 40748-85-4; 1-(3-cyclohexen-1-yl)-2-nitroethyl acetate, 40748-86-5; 2-(3-cyclohexen-1-yl)-1-nitroethene, 40748-87-6; benzaldehyde, 100-52-7; nitroethane, 79-24-3.

(44) P. Wieland, *Chem. Ber.*, **36**, 2561 (1903).

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(46) N. H. Cromwell and R. A. Setterquist, *J. Amer. Chem. Soc.*, **76**, 5752 (1954).

(47) A. Marquet, M. Dvolaitsky, H. B. Kagan, L. Manlok, C. Ouannes, and J. Jacques, *Bull. Soc. Chim. Fr.*, 1822 (1961).

Cyclization of 3-(o-Hydroxyphenyl)hexahydroindole 1-Oxides and 4-(o-Hydroxyphenyl)pyrroline 1-Oxides. Preparation of Hydrobenzofuro[3,2-c]indoles and Hydrobenzofuro[2,3-c]pyrroles

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A novel synthesis of the hydrobenzofuro[3,2-c]indole and hydrobenzofuro[2,3-c]pyrrole ring systems is described. Stereochemistry is presented.

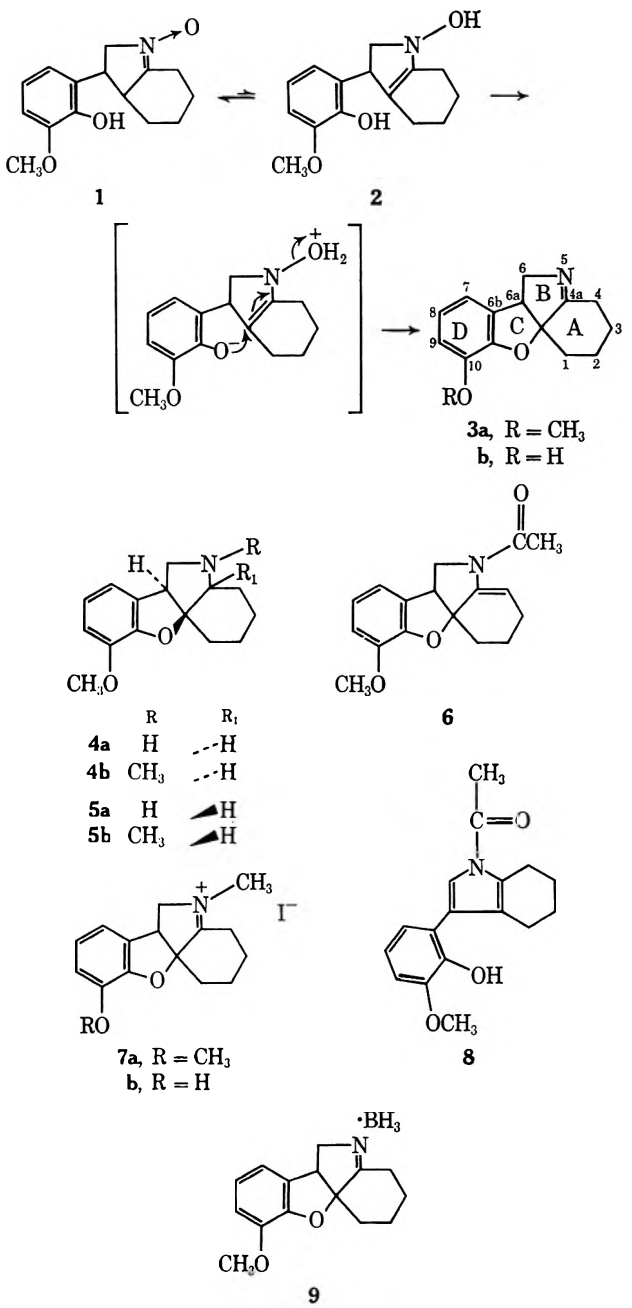
In the accompanying paper we discussed the preparation of various 3-(*o*-hydroxyphenyl)hexahydroindole 1-oxides and 4-(*o*-hydroxyphenyl)pyrroline 1-oxides by the reduction of 4-(nitromethyl)benzodihydropyran derivatives.[1] The present report describes the conversion of these phenolic nitrones to hydrobenzofuro[3,2-*c*]indoles (**3a** and **3b**) and hydrobenzofuro[2,3-*c*]pyrroles (**17**) *via* a novel thermal dehydrative cyclization.

Hydrobenzofuro[3,2-c]indoles.—Heating a xylene solution of the phenolic nitrone **1** at reflux for a brief period resulted in the loss of 1 mol of water and the formation of a nonphenolic compound in 62% yield. The chemical behavior and the spectral properties of the dehydration product were compatible with the hexahydrobenzofuro[3,2-*c*]indole structure **3a**. The ir indicated the presence of a C=N moiety [1660 (base), 1690 cm^{-1} (hydrochloride)] and the lack of an OH group. The nmr spectrum of **3a** as the hydrochloride showed a 1 H quartet at δ 4.9 (H-6), a 2 H multiplet in the δ 4–4.3 region (H-6, $H\text{-}4_{eq}$), a 1 H quartet at δ 3.52 (H-6a), and a 1 H multiplet at δ 2.8 ($H\text{-}4_{ax}$).[2]

To substantiate the structure of **3a** its chemical properties were studied and found to be typical of such a cyclic imine. Treatment with strong acid or base failed to effect any reaction. Catalytic hydrogenation in the presence of acetic acid yielded the expected perhydroindole derivative **4a**. Quaternization of **3a** with methyl iodide gave a quaternary imine **7a** [ir 1695 cm^{-1} (C=N)] which could be catalytically reduced to a tertiary amine **4b**. Demethylation of **3a** gave **3b**. Acetylation of the imine gave the expected ene–acetamide **6**, the ir and nmr spectra of which verified the $CH_3CONC{=}CHR$ grouping. Treatment of the enacetamide with polyphosphoric acid gave the *N*-acetylpyrrole **8** [ir 3330 (OH), 1695 cm^{-1} (–CONC=C–); nmr δ 7.28 (1 H singlet, H-2), 2.98 (4 H multiplet, H-4 and H-7 methylenes)]. The isolation of the pyrrole was important in ruling out any gross structural rearrangements in the formation of **3a**.

The formation of **3a** may be rationalized by consideration of the nitrone **1** in its tautomeric ene–hydroxylamine form **2**. A similar tautomerism between an indolenine 1-oxide and an *N*-hydroxyindole has been observed.[3] Protonation of the hydroxylamine function in **2** by the phenol is followed by an addition–elimination process to give **3a**.[4]

SCHEME I



Stereochemistry of Octahydrobenzofuro[3,2-c]indoles.—The stereochemistry of the octahydrobenzofuro[3,2-*c*]indole ring system concerns only the con-

(1) S. Klutchko, A. Sonntag, M. von Strandtmann, and J. Shavel, Jr., *J. Org. Chem.*, **38**, 3049 (1973).

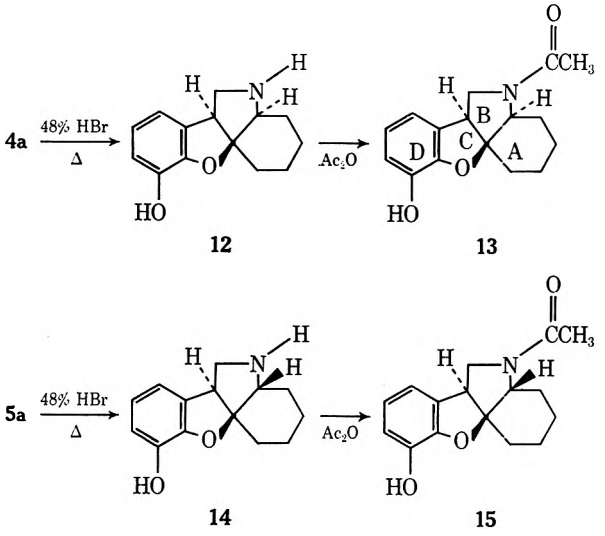
(2) The nmr of **3a** base showed no change in H-6a (δ 3.52) but the H-6 and $H\text{-}4_{eq}$ moved upfield to form a 3 H multiplet in the δ 3.7–4.3 region.

(3) M. Mousseron-Canet and J. P. Boca, *Bull. Soc. Chim. Fr.*, 1296 (1967).

(4) Cyclization of the phenol in **1** to the 2 position of the hydroindole moiety was also considered a possibility if the so-called Behrend rearrangement of the keto nitrone to the aldo nitrone occurred. This rearrangement, however, generally involved strong base catalysis: Behrend, *Justus Liebigs Ann. Chem.*, **265**, 238 (1891); A. Cope and A. Haven, *J. Amer. Chem. Soc.*, **72**, 4896 (1950). Spectral data was inconsistent with any of the benzofuro[2,3-*b*]indole structures that might have arisen from this sort of ring closure.

figuration at the A/B perhydroindole ring juncture, since the 5,5-fused ring system of the furoindole requires a cis fusion. The single product of catalytic reduction of the imine **3a** (Scheme I) was designated as the A/B-trans isomer **4a** on the basis of the expected preferential attack from the opposite side of the ether linkage. The A/B-cis isomer **5a** was isolated when the hydrochloride of **3a** was reduced with borohydride. In the formation of **5a** some of the relatively stable borane complex **9** was isolated. This compound could be converted to **5a** by acid treatment.

To confirm the above configuration assignments, the nmr spectra of the *N*-acetyl derivatives (**13** and **15**) of the demethylation products (**12** and **14**) were compared.[5] The spectrum of **15** displayed proton signals



at δ 4.1, whereas that of the corresponding **13**, except for aromatic resonance, did not exhibit any protons below δ 3.72. Consideration of the structure and models of these compounds indicated that in the case of the A/B-cis isomer (**15**) the proton at C-4a was in the equatorial conformation and in the plane of the amide carbonyl. This proton was therefore expected to resonate at lower field[6] than the corresponding proton of an A/B-trans compound which was limited to an axial conformation and appeared in the spectrum of **13** at δ 2.65.

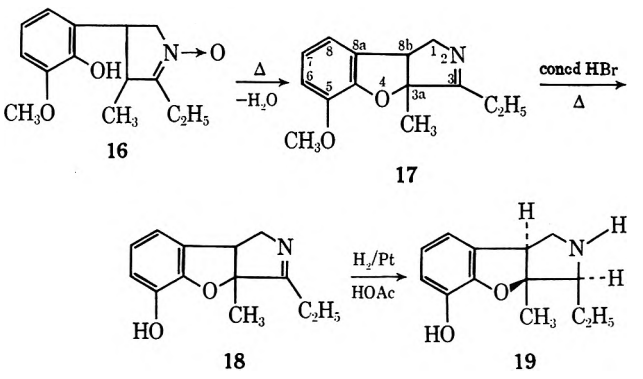
Hydrobenzofuro[2,3-*c*]pyrroles.—The hydrobenzofuropyrroles (**17**, **18**, and **19**) were prepared in a fashion similar to that for the hydrobenzofuroindoles from the 4-(*o*-hydroxyphenyl)pyrroline 1-oxide derivative **16** (Scheme II).

Compound **19** was assigned the trans configuration at positions C-3 and C-3a by analogy to the octahydrobenzofuroindole stereochemistry described above.

(5) The N-acetylation and demethylation were carried out in order to shift the H-4a farther downfield and to remove the masking effect of the methoxy protons.

(6) F. Bohlmann and D. Schumann, *Tetrahedron Lett.*, 2435 (1965), report a chemical-shift difference of 2.4 ppm for the geminal protons at C-6 of 4-oxoquinolizidine. The low-field resonance (4.63 ppm) of the equatorial proton at C-6 is attributed to its position in the plane of the amide carbonyl.

SCHEME II



Experimental Section[7]

1,2,3,4,6,6a-Hexahydro-10-methoxybenzofuro[3,2-*c*]indole Hydrochloride (3a).—A mixture of 60.0 g (0.23 mol) of **1** and 400 ml of xylene was heated with stirring to the boiling point. In a period of 0.5 hr, the theoretical amount of water (4.2 ml) was obtained. The cooled solution was diluted with 300 ml of ether, washed with 200 ml of 2 *M* KOH, dried over anhydrous potassium carbonate, filtered, and treated with HCl gas until complete precipitation of 48 g of the tacky salt. Recrystallization from 200 ml of absolute ethanol gave 40.9 g (62%) of **3a** hydrochloride, mp 224–226°, base mp 94–95°.

Anal. Calcd for $C_{15}H_{17}NO_2 \cdot HCl$: C, 64.40; H, 6.48; N, 5.01. Found: C, 64.31; H, 6.70; N, 5.17.

1,2,3,4,6,6a-Hexahydrobenzofuro[3,2-*c*]indol-10-ol (3b).—A solution of 111.9 g (0.4 mol) of **3a** hydrochloride in 700 ml of 48% HBr was heated at reflux for 20 min. The cooled solution was diluted with 1.5 l. of ice water and concentrated ammonium hydroxide was added until pH 8.5 to precipitate 82 g (90%) of pure **3b**, mp 203–205°.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.46; H, 6.72; N, 6.34.

1,2,3,4,4aα,5,6,6aα-Octahydro-10-methoxybenzofuro[3,2-*c*]-indole Hydrochloride (A/B-trans) (4a).—A mixture of 5.5 g (0.027 mol) of **3a** base, 250 ml of absolute ethanol, 20 ml of glacial acetic acid, and 200 mg of PtO_2 was hydrogenated in a Paar apparatus for 6 hr. After filtration and concentration to remove most of the alcohol, 300 ml of water and then 10 *M* KOH was added to pH 10. The separated viscous oil was extracted into 600 ml of ether, and the solution was dried over K_2CO_3, filtered, and treated with HCl gas to precipitate 6.0 g (94%) of the salt, mp 268–270°. Recrystallization from 2-propanol gave pure **4a** hydrochloride, mp 277–279°.

Anal. Calcd for $C_{15}H_{19}NO_2 \cdot HCl$: C, 63.94; H, 7.15; Cl, 12.58. Found: C, 64.10; H, 7.24; Cl, 12.35.

1,2,3,4,4aα,5,6,6aα-Octahydro-10-methoxy-5-methylbenzofuro[3,2-*c*]indole Hydriodide (A/B-Trans) (4b).—A solution of 6.5 g (0.017 mol) of **7a** in 250 ml of absolute ethanol was hydrogenated in a Paar apparatus for 16 hr using a mixture of 150 mg of PtO_2 and 200 mg of 10% Pd/C as a catalyst. After filtration and concentration to *ca.* 50 ml volume, 200 ml of ether was added to precipitate 6.1 g (93%) of **4b** hydriodide, mp 207–209°. Recrystallization from ethanol–ether gave pure crystals, mp 208–210°.

Anal. Calcd for $C_{16}H_{21}NO_2 \cdot HI$: C, 49.62; H, 5.73; N, 3.62. Found: C, 49.86; H, 5.85; N, 3.47.

1,2,3,4,4aβ,5,6,6aα-Octahydro-10-methoxybenzofuro[3,2-*c*]-indole Hydrochloride (A/B-cis) (5a) and Borane Complex of 3a (9).—Potassium borohydride, 5.4 g (0.1 mol), was added to a stirred solution of 24.3 g (0.1 mol) of **3a**, 100 ml of 1 *N* hydrochloric acid, and 200 g of ice water (containing ice chips). The temperature gradually rose to 25° as a tacky material separated. (Note: This material was shown by tlc to be a mixture of the complex **9** and the product **5a**.) In one run, **9** was isolated and purified from ethyl acetate: mp 165–168°; ir ($CHCl_3$) 2400 (borane complex), 1675 cm^{-1} (C=N).

Anal. Calcd for $C_{15}H_{20}BNO_2$: C, 70.06; H, 7.84; N, 5.45. Found: C, 69.70; H, 7.73; N, 5.14.

(7) Melting points were determined with the Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. Infrared spectra were determined with a Baird Model 455 double beam instrument. Nmr spectra were measured with a Varian A-60 spectrophotometer.

The above tacky mixture was heated on the steam bath with 100 ml of methanol and 110 ml of 1 *N* hydrochloric acid until all material dissolved. Ice water (300 ml) and then excess 10 *M* KOH were added and the separated oil was extracted into ether. Treatment with hydrogen chloride gave 16.6 g (59%) of the salt **5a**, mp 207–209°.

Anal. Calcd for $C_{15}H_{19}NO_2 \cdot HCl$: C, 63.94; H, 7.15; Cl, 12.58. Found: C, 64.12; H, 7.25; Cl, 12.57.

A/B-cis Isomer (5b) (*via* Eschweiler–Clarke Methylation of 5a).—A solution of 4.08 g (0.0167 mol) of **5a** base, 3.24 g (0.04 mol) of 37% formaldehyde, and 40 ml of 98% formic acid was heated on the steam bath for 1 hr, cooled, diluted to 150 ml with ice water, and made strongly alkaline with 10 *M* KOH. The separated base was extracted into ether. The dried (K_2CO_3) solution was treated with HCl gas to precipitate a tacky salt. Dissolution in 2-propanol and addition of ether yielded 4.0 g (81%) of pure crystalline **5b** hydrochloride, mp 208–210°.

Anal. Calcd for $C_{16}H_{21}NO_2 \cdot HCl$: C, 64.97; H, 7.50; N, 4.74. Found: C, 64.72; H, 7.43; N, 4.91.

5-Acetyl-1,2,3,5,6,6a-hexahydro-10-methoxybenzofuro[3,2-*c*]-indole (6).—A quantity of 5.8 g (0.024 mol) of **3a** base was dissolved in 30 ml of acetic anhydride. After 5 min at reflux, 200 ml of water was added and the mixture was stirred for 0.5 hr to precipitate 6.1 g (90%) of **6**, mp 168–170°. Recrystallization from absolute ethanol gave pure crystals: mp 176–178°; ir (Nujol) 1682 (ene–amide C=O), 1650 cm^{-1} (vinyl C=C); nmr ($CDCl_3$) δ 6.72 (m, 3, aromatics), 5.4 (m, 1, H-4), 3.74 (s, 3, OCH_3), 3.3–3.75 (m, 3, H-6 and H-6a), 2.1 (s, 3, CH_3CO), and 1.3–2.4 (m, 6, methylene envelope).

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.51; H, 6.85; N, 5.12.

1,2,3,4,6,6a-Hexahydro-10-methoxy-5-methylbenzofuro[3,2-*c*]indolinium Iodide (7a).—A solution of 4.0 g (0.017 mol) of **3a** base in 25 ml of methyl iodide was maintained at reflux for 1 hr. Most of the methyl iodide was distilled off and 50 ml of ether was added to give 6.0 g (95%) of yellow solid, mp 198–200°. Recrystallization from ethanol–ether gave pure **7a**: mp 200–202°; ir (Nujol) 1695 cm^{-1} (C=N).

Anal. Calcd for $C_{15}H_{17}NO_2 \cdot CH_3I$: C, 49.88; H, 5.23; N 3.64. Found: C, 50.09; H, 5.30; N, 3.77.

1,2,3,4,6,6a-Hexahydro-10-hydroxy-5 methylbenzofuro[3,2-*c*]indolinium Iodide (7b).—Methyl iodide (25 ml) was added to a solution of 4.5 g (0.02 mol) of **3b** in 25 ml of dimethylformamide. After 1.5 hr reaction time, ether (200 ml) was added to precipitate an oil. The supernatant was decanted and the crude product was recrystallized from 50 ml of 2 propanol to give 5.3 g (73%) of **7b**: mp 200–202°; ir (Nujol) 3250 (OH) and 1685 cm^{-1} (C=N).

Anal. Calcd for $C_{14}H_{15}NO_2 \cdot CH_3I$: C, 48.53; H, 4.89; H, 3.77. Found: C, 48.59; H, 4.86; N, 3.52.

1-Acetyl-4,5,6,7-tetrahydro-3-(2-hydroxy-3-methoxyphenyl)-indole (8).—A mixture of 7.3 g (0.0246 mol) of **6** and 60 g of polyphosphoric acid was heated with agitation at 50–60° for 15 min. The resulting reaction solution was poured into 500 ml of cold water to precipitate an orange solid. Recrystallization from 2 propanol gave 3.0 g (41%) of pure **8**, mp 121–123°.

Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.90. Found: C, 71.35; H, 6.90; N, 4.87.

1,2,3,4,4aα,5,6,6aα-Octahydrobenzofuro[3,2-*c*]indol-10-ol (A/B-Trans) (12) (*via* Demethylation of 4a).—A solution of 15.0 g (0.053 mol) of **4a** hydrochloride in 100 ml of 48% hydrobromic acid was maintained at reflux for 1 hr. On cooling 4.5 g (14%) of the HBr salt of **12** separated, mp 286–288°. Recrystallization from methanol–ether gave constant-melting hydrobromide, mp 292–294°. Treatment of an aqueous solution of the salt with ammonium hydroxide gave the pure base, mp 235–237°.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.62; H, 7.42; N, 6.04.

Alternate Preparation of 12 (*via* Catalytic Reduction of 3b).—A solution of 46.0 g (0.3 mol) of **3b** in 150 ml of absolute ethanol and 100 ml of glacial acetic acid was hydrogenated at low pressure using a mixture of 1.0 g of PtO_2 and 1.0 g of 5% Pd/C. The catalyst was filtered, 1 l. of ice water was added to the filtrate, and concentrated ammonium hydroxide was added until complete precipitation of 40 g (87%) of tan solid, mp 220–225°. Recrystallization from absolute ethanol gave pure **12** base, mp 235–237°, hydrochloride mp 301–303°.

1,2,3,4,4aβ,5,6,6aα-Octahydrobenzofuro[3,2-*c*]indol-10-ol (A/B-cis) (14).—A solution of 10.5 g (0.037 mol) of **5a** hydrochloride in 40 ml of concentrated HBr was maintained at reflux for 1 hr and diluted with ice water to 200-ml volume. Concentrated ammonium hydroxide was added to precipitate 7.4 g (80%) of pure base **14**, mp 234–236°.

Anal. Calcd for $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.80; H, 7.40; N, 6.31.

5-Acetyl-1,2,3,4,4aα,5,6,6aα-octahydrobenzofuro[3,2-*c*]indol-10-ol (A/B-trans) (13).—A quantity of 7.2 g (0.031 mol) of **12** was dissolved in 50 ml of acetic anhydride with stirring. After *ca.* 15 min the separated product was filtered, stirred with water for 15 min, and filtered again to give 6.5 g (77%) of **13**, mp 221–224°. Recrystallization from 2-propanol gave **13**, mp 225–227°.

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.23; H, 6.98; N, 5.24.

A/B-cis Isomer (15).—The 5-acetyl cis isomer **15** was prepared from **14** by the same procedure used to prepare **13**, mp 204–205°.

Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.54; H, 7.05; N, 5.33.

3-Ethyl-3a,8b-dihydro-5-methoxy-3a-methyl-1*H*-benzofuro-[2,3-*c*]pyrrole Hydrochloride (17).—A solution of 10.0 g (0.04 mol) of 2-ethyl-4-(2-hydroxy-3-methoxyphenyl)-3-methyl-1-pyrroline 1-oxide (**16**) in 150 ml of xylene was maintained at reflux under nitrogen for 45 min. The calculated amount of water was measured after 15 min. Work-up was similar to that for **3a**, giving 8.2 g (76.7%) of pure **17** hydrochloride, mp 193–195°.

Anal. Calcd for $C_{14}H_{17}NO_2 \cdot HCl$: C, 62.80; H, 6.78; N, 5.23. Found: C, 62.50; H, 6.81; N, 5.09.

3-Ethyl-3a,8b-dihydro-3a-methyl-1*H*-benzofuro[2,3-*c*]pyrrol-5-ol (18).—A solution of 5.0 g (0.019 mol) of **17** hydrochloride in 30 ml of 48% hydrobromic acid was maintained at reflux under nitrogen for 15 min. Ice water (50 ml) was added and the solution was basified with ammonium hydroxide to precipitate 3.9 g (96%) of **18**, mp 171–173°.

Anal. Calcd for $C_{13}H_{15}NO_3$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.15; H, 6.91; N, 6.25.

3-Ethyl-2,3,3a,8b-tetrahydro-3a-methyl-1*H*-benzofuro[2,3-*c*]-pyrrol-5-ol (19).—A solution of 2.0 g (0.009 mol) of **18** in 150 ml of absolute ethanol and 3 ml of glacial acetic acid was hydrogenated in a Paar apparatus with platinum oxide, giving 1.9 g (95%) of pure base, mp 239–241°.

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.38; H, 7.73; N, 6.36.

Acknowledgment.—The authors are indebted to the Analytical and Physical Chemistry Department under the supervision of Mr. A. D. Lewis. In particular, we wish to thank Dr. C. Greenough for the spectral data and Mrs. U. Zeek for analytical determinations. We also wish to thank the Chemical Development Department under the supervision of Dr. A. W. Ruddy for the large-scale preparation of intermediates.

Registry No.—**1**, 40682-18-6; **3a**, 40682-19-7; **3a** HCl, 36860-43-2; **3b**, 36860-37-4; **4a** HCl, 40682-22-2; **4b** HI, 40682-23-3; **5a**, 40682-24-4; **5a** HCl, 40682-25-5; **5b** HCl, 40682-26-6; **6**, 36860-39-6; **7a**, 36860-41-0; **7b**, 36860-36-3; **8**, 40682-30-2; **9**, 40682-31-3; **12**, 40682-32-4; **12** HBr, 40682-33-5; **12** HCl, 40682-34-6; **13**, 40682-35-7; **14**, 40682-36-8; **15**, 40682-37-9; **16**, 40682-38-0; **17** HCl, 40682-39-1; **18**, 40682-40-4; **19**, 40682-41-5.

Peri Effects in the Mass Spectra of Some 8-Substituted 1-Naphthoic Acids and 1-Naphthylcarbinols

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The mass spectra of several 8-substituted 1-naphthoic acids and 1-naphthylcarbinols have been examined to determine if peri interactions are involved in the fragmentation. The substituents at the C_8 position include CH_3O, CH_3, Br, and NO_2. The spectrum of the 8-methoxy acid shows a strong M − CH_3OH ion due to peri interaction whereas its isomeric 2-methoxy acid does not. The loss of water in the spectra of the 8-methyl acid and alcohol and of HBr from the 8-bromo alcohol are indicative of interaction between peri substituents. The expulsion of these neutral molecules from the molecular ion is presumably facilitated by the peri cyclization to form a stable product. The weak molecular ion and facile loss of the 8 substituent in the spectra of the 8-bromo and 8-nitro acids are interpreted as being due to peri interactions. The presence of M − H_2O and M − OH − OH ions in the spectrum of the 8-nitro alcohol also indicates the interaction between the peri substituents.

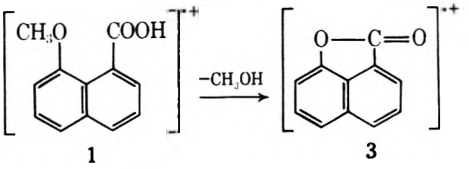
Proximity effects in peri-substituted naphthalenes in solution chemistry have been reported by us in our previous paper[1] and by a number of other workers.[2] From a geometrical consideration peri substituents are much closer to one another than identical ortho substituents. Since ortho effects in the mass spectra of aromatic compounds are very common,[3] one should also observe peri effects in the mass spectra of 1,8-disubstituted naphthalenes. However, there has been considerably less work published on peri effects in mass spectral fragmentations[4-7] than on ortho effects,[3] presumably owing to the fact that the peri-substituted naphthalene derivatives are not so easily available as the ortho-substituted aromatic compounds.

The present study concerns itself with analyses of the mass spectra of several 8-substituted 1-naphthoic acids and 1-naphthylcarbinols to determine whether peri interactions are involved in the electron impact induced fragmentation. Wherever possible, the mass spectra of these peri-substituted naphthalenes are compared with those of corresponding isomers of naphthalene or with appropriate benzene derivatives.

Results and Discussion

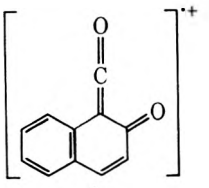
8-Substituted 1-Naphthoic Acids.—The mass spectrum of the unsubstituted parent 1-naphthoic acid obtained by us is similar to that reported by McLafferty and Gohlke[8] and hence will not be reproduced here. Its major fragmentation processes are loss of the hydroxyl radical and subsequent loss of carbon monoxide. These two processes have been substantiated by the observation of an appropriate metastable ion determined by the defocusing technique.[9]

The mass spectrum (Figure 1) of 8-methoxy-1-naphthoic acid (**1**) shows a very strong peak at *m/e* 170 owing to loss of CH_3OH from the molecular ion. The strong loss of methanol as well as the presence of a strong metastable ion for this loss and of a very weak metastable ion for the transition from the *m/e* 185 ion to the *m/e* 170 ion suggest that the methanol loss is primarily, though not exclusively, a one-step loss from the molecular ion. The similar direct methanol loss is absent in the mass spectrum (Figure 1) of the isomeric 2-methoxy-1-naphthoic acid (**2**). A metastable defocusing measurement indicates that the weak *m/e* 170 ion in the 2-methoxy acid **2** is attributed to loss of the methyl radical from the M − OH ion (*m/e* 185). This drastic difference observed in the spectra of isomeric **1** and **2** can be explained by the formation of a stable lactone ion **3** in the former through peri ring closure,[10]



1 **3**

whereas in the latter a similar 1,2 cyclization would lead to the unlikely formation of a very strained four-membered ring compound ion. The fact that a one-step loss of methanol from compound **2** is absent suggests that the methoxy methyl and the carboxyl hydroxy cannot interact to lose methanol even though a stable quinoid ion like **4** could be formed from such an



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(1) D. C. Kleinfelter and P. H. Chen, *J. Org. Chem.*, **34**, 1741 (1969).

(2) For an extensive review of naphthalene peri interactions, see V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

(3) For examples of ortho effects, see H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, pp 197, 200, 220, 279, 516, 636.

(4) (a) J. H. Bowie, P. J. Hoffmann, and P. Y. White, *Tetrahedron*, **26**, 1163 (1970); (b) J. H. Bowie and P. Y. White, *J. Chem. Soc. B*, 89 (1969); (c) B. M. King, D. A. Evans, and K. Biemann, *Org. Mass Spectrom.*, **3**, 1049 (1970).

(5) (a) J. Harley-Mason, T. P. Toube, and D. H. Williams, *J. Chem. Soc. B*, 396 (1966); (b) J. H. Beynon, B. E. Job, and A. E. Williams, *Z. Naturforsch., A*, **21**, 210 (1966).

(6) J. L. Smith, J. L. Beck, and W. J. A. VandenHeuvel, *Org. Mass Spectrom.*, **5**, 473 (1971).

(7) (a) D. L. Fields and T. H. Regan, *J. Org. Chem.*, **36**, 2986 (1971); (b) R. Marchelli, W. D. Jamieson, S. H. Safe, O. Hutzinger, and R. A. Heacock, *Can. J. Chem.*, **49**, 1296 (1971).

(8) F. W. McLafferty and R. S. Gohlke, *Anal. Chem.*, **31**, 2076 (1959).

(9) (a) J. H. Beynon, R. A. Saunders, and A. E. Williams, *Nature (London)*, **204**, 67 (1964); (b) P. Schulze and A. L. Burlingame, *J. Chem. Phys.*, **49**, 483 (1968).

(10) Reference 2, p 593.

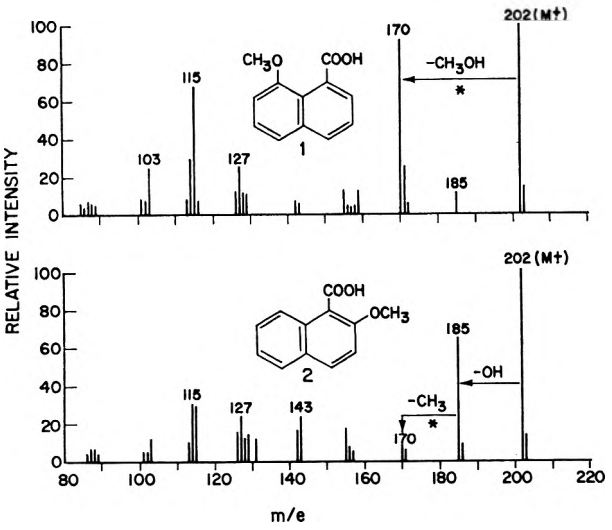


Figure 1.—Mass spectra (70 eV) of 8-methoxy-1-naphthoic acid (1) and 2-methoxy-1-naphthoic acid (2).

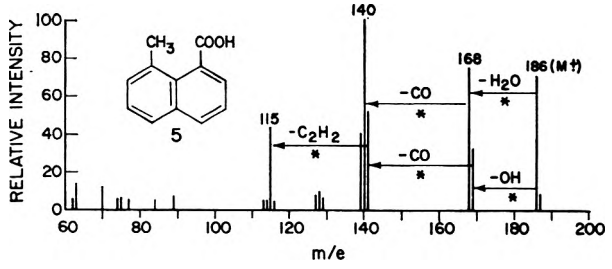
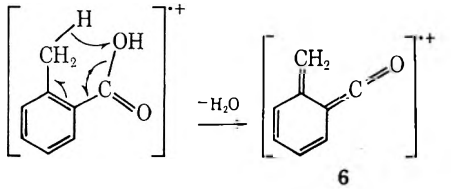


Figure 2.—Mass spectrum (70 eV) of 8-methyl-1-naphthoic acid (5).

interaction (compound 2). This is understandable because such a mechanism for the elimination of methanol would require a transfer of a methyl radical, a process which is much more difficult than a similar transfer of a hydrogen atom.

The mass spectrum (Figure 2) of 8-methyl-1-naphthoic acid (**5**) exhibits a strong M − H_2O peak (*m/e* 168) owing to the interaction of the two peri substituents. The direct loss of water from the molecular ion is substantiated by the presence of an appropriate metastable ion determined by the defocusing technique. This also indicates, at least in part, that the M − H_2O ion is not due to thermal elimination. A comparison of the fragmentation pattern of the 8-methyl acid **5** with its isomeric 2-methyl-1-naphthoic acid is not possible owing to the unavailability of the latter compound. However, a ready comparison can be made with *o*-toluic acid, which also shows strong loss of water from the molecular ion.[8,11] In *o*-toluic acid the water loss is facilitated by the formation of ion **6**,



6

whereas in the 8-methyl acid **5**, the same loss is more than likely facilitated by the formation of the acenaphthenone ion (**7** in Scheme I) through peri ring

(11) T. Aczel and H. E. Lumpkin, *Anal. Chem.*, **33**, 386 (1961).

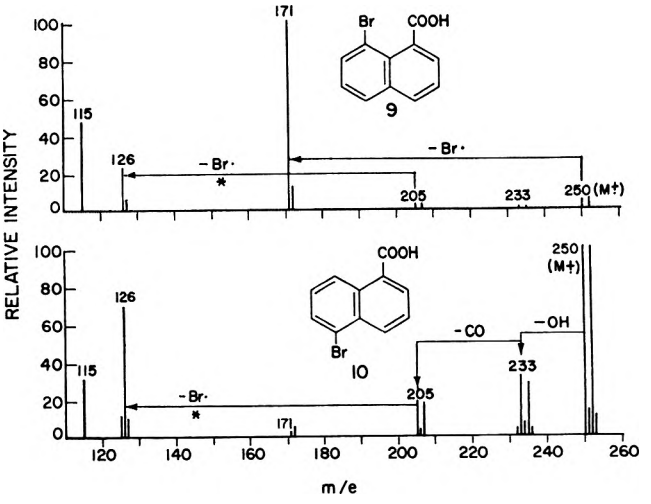
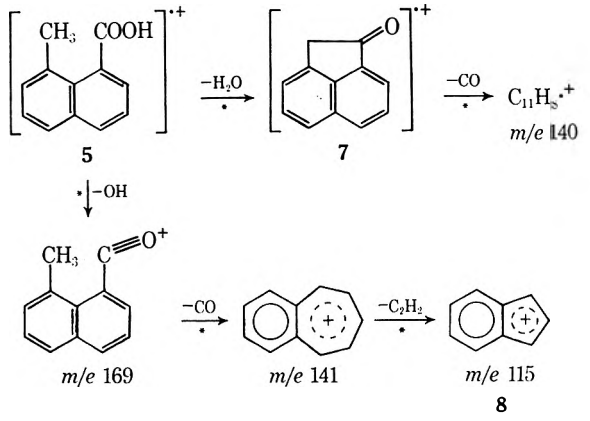


Figure 3.—Mass spectra (70 eV) of 8-bromo-1-naphthoic acid (9) and 5-bromo-1-naphthoic acid (10).

SCHEME I

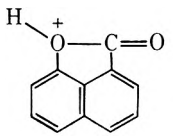


closure, assuming that no ring expansion occurs prior to water loss. The stabilization of the M − H_2O ion in compound **5** by the resonance interaction between substituents is unlikely because peri substituents are separated by three carbon atoms and may therefore be likened to meta substituents. The major fragmentation processes of compound **5** are shown in Scheme I. An asterisk in the scheme indicates the presence of a metastable ion determined by the defocusing technique.[9] The *m/e* 115 ion, which is strong in the spectrum of **5** as well as many of the other peri-substituted naphthalene derivatives, probably has a structure like the indenyl ion (**8**),[12] the ethenyltropylium ion,[13] or the phenylcyclopropenyl cation.[13] The chemical composition of the *m/e* 115 ion has been established to be C_9H_7 by the exact mass measurement.

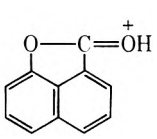
The striking differences between the mass spectra (Figure 3) of 8-bromo-1-naphthoic acid (**9**) and 5-bromo-1-naphthoic acid (**10**) are the following: (1) while the M − Br peak (*m/e* 171) is extremely strong in compound **9**, the corresponding peak is very weak[14] in compound **10**; (2) while the molecular ion peaks are weak in **9**, the corresponding peaks are strong in **10**; (3) the peaks due to the fragmentation of the carboxyl group, *i.e.*, *m/e* 205, 207, 233, and 235, are much more

(12) R. T. Aplin and S. Safe, *Chem. Commun.*, 140 (1967).
(13) H. Schwarz and F. Bohlmann, *Org. Mass Spectrom.*, **7**, 395 (1973).
(14) While the singly charged ion is very weak, the doubly charged ion of M − Br is much more abundant.

prominent in the spectrum of **10** than in that of **9**. The fragmentation behavior of the 8-bromo acid is also different from that of *o*-bromobenzoic acid[15] in that the latter shows very strong molecular ion peaks and a very weak peak corresponding to the loss of bromine from the molecular ion. The facile loss of the bromine atom in the spectrum of the 8-bromo acid **9** is most likely assisted by the presence of the peri carboxyl group. This effect is analogous to that observed in naphthalene solution chemistry, where the presence of a carboxyl group peri to a nitro or halo substituent appears to make the substituents labile and more easily replaced than ones in analogous ortho-substituted compounds.[16] The interactions between the two peri substituents can be attributed to steric effects, electronic effects, and neighboring-group participation. With relation to the steric effect, it has been reported that large steric interactions in the molecule would cause the molecular ion to be less stable and hence to have a greater tendency to decompose to relieve the steric strain.[17] In solution chemistry, in addition to steric effects, direct dipolar field effects have been reported to exert some influence on the pK_a values of the 8-substituted 1-naphthoic acids.[18] It is not known to what extent this field effect would influence the molecular ion intensity. The expulsion of the bromine atom from the molecular ion may not be a simple bond cleavage but may involve a tight transition state where the carboxyl group participates in the elimination, thereby lowering the activation energy.[19] The low activation energy for the process of bromine elimination is supported by the experimental observation that the relative abundance of the M − Br ion remains prominent at low ionizing voltage. The formation of stable protonated lactones like **11a** and/or **11b** may be postulated to follow the loss



11a



11b

of the bromine atom. The metastable defocusing measurement indicates that the *m/e* 126 ion in both **9** and **10** originates from the M − COOH ions (*m/e* 205, 207) by the loss of a bromine atom.

The mass spectra of 8-nitro-1-naphthoic acid (**12**) and its isomeric 5-nitro-1-naphthoic acid (**13**) are shown in Figure 4. The 8-nitro acid **12** has a weak molecular ion and a very strong M − NO_2 ion, whereas the 5-nitro acid **13** has a strong molecular ion and a moderate M − NO_2 ion. The strong molecular ion in the spectrum of **13** is expected because aromatic compounds normally have high molecular ion intensities. The strong molecular ion was also reported for the mass spectrum of *o*-nitrobenzoic acid.[20] The weak molecular ion and the strong M − NO_2 ion in the spectrum of **12** are likely due to some sort of interaction between the two peri substituents. This is in accord with the mass spectral fragmentation behavior of the 8-bromo acid (*vide supra*) and with a report published elsewhere.[21] As shown in Figure 4, the strong *m/e* 115 ion in both **12** and **13** is derived from the *m/e* 171 and 143 ions, presumably by the loss of C_2O_2[20a] and CO, respectively. The ionic formula of the *m/e* 115 ion has been determined to be C_9H_7 by the accurate mass measurement.

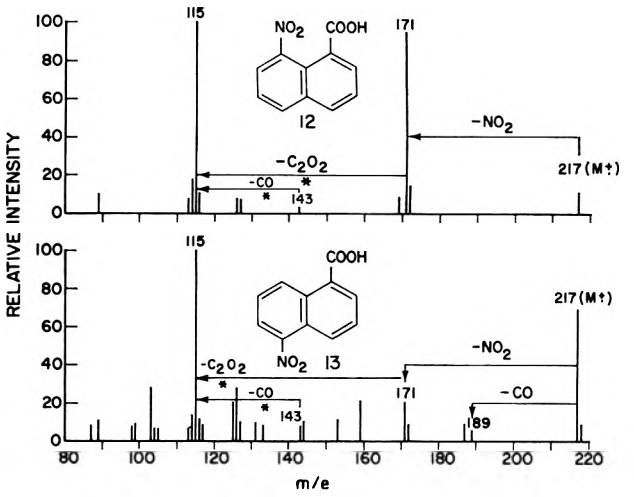


Figure 4.—Mass spectra (70 eV) of 8-nitro-1-naphthoic acid (**12**) and 5-nitro-1-naphthoic acid (**13**).

Williams[5a] and Beynon[5b] reported independently that the loss of CO from the molecular ion was observed in 1-nitronaphthalene but not in nitrobenzene or 2-nitronaphthalene. They both proposed that the peri carbon (C_8) atom was involved in this unique loss of CO. We also observed the loss of CO from the molecular ion of the 5-nitro acid **13** but not from that of the 8-nitro acid (see Figure 4). This is in agreement with Williams and Beynon's observations. However, in the 5-nitro acid, part of the CO loss could come from the carboxyl group.

8-Substituted 1-Naphthylcarbinols.—The mass spectral fragmentation behavior of the unsubstituted 1-naphthylcarbinol (**14**) has been described[22] very recently with the aid of deuterium- and ^{13}C-labeled derivatives. The most prominent fragmentation process is the loss of 29 mass units (CHO) from the molecular ion. This is an important decomposition pathway for most of the naphthylcarbinols examined in this study.

In contrast to the mass spectrum of the 8-methoxy acid **1**, which shows distinguished peri interaction by the loss of methanol from the molecular ion, the spectrum (Figure 5) of 8-methoxy-1-naphthylcarbinol (**15**) shows little or no loss of either CH_3OH or H_2O from interaction of the peri substituents.[23] The metastable defocusing measurement suggests that the weak *m/e*

(15) Mass Spectral Data, No. 2891, Dow Chemical Co., Midland, Mich.

(16) (a) H. G. Rule and A. J. G. Barnett, *J. Chem. Soc.*, 175, 2728 (1932); (b) H. G. Rule and H. M. Turner, *ibid.*, 317 (1935).

(17) (a) K. Biemann and J. Seibl, *J. Amer. Chem. Soc.*, **81**, 3149 (1959); (b) P. Natalis in "Mass Spectrometry," R. I. Reed, Ed., Academic Press, New York, N. Y., 1965, pp 379–399; (c) C. E. Brion, J. S. Haywood-Farmer, R. E. Pincock, and W. B. Stewart, *Org. Mass Spectrom.*, **4**, 587 (1970).

(18) (a) M. Hojo, K. Katsurakawa, and Z. Yoshida, *Tetrahedron Lett.*, 1497 (1968); (b) K. Bowden and D. C. Parkin, *Can. J. Chem.*, **47**, 185 (1969).

(19) For examples of neighboring-group participation reactions in the mass spectral fragmentation, please see (a) R. G. Cooks, N. L. Wolfe, J. R. Curtis, H. E. Petty, and R. N. McDonald, *J. Org. Chem.*, **35**, 4048 (1970); (b) R. H. Shapiro and K. B. Tomer, *Org. Mass Spectrom.*, **3**, 333 (1970); (c) J. M. Pechine, *ibid.*, **5**, 705 (1971).

(20) (a) F. Benoit and J. L. Holmes, *Org. Mass Spectrom.*, **3**, 993 (1970); (b) K. B. Tomer, T. Gebreyesus, and C. Djerassi, *ibid.*, **7**, 383 (1973).

(21) E. F. H. Brittain, C. H. J. Wells, H. M. Paisley, and D. J. Stickley, *J. Chem. Soc. B*, 1714 (1970).

(22) H. Schwarz and F. Bohlmann, *Org. Mass Spectrom.*, **7**, 29 (1973).

(23) While there is little or no peri interaction in the electron impact induced fragmentation, the same 8-methoxy alcohol exhibits a strong intramolecular H bonding in solution chemistry (see ref 1 and P. H. Chen, Ph.D. Thesis, The University of Tennessee, Knoxville, Tenn., 1967).

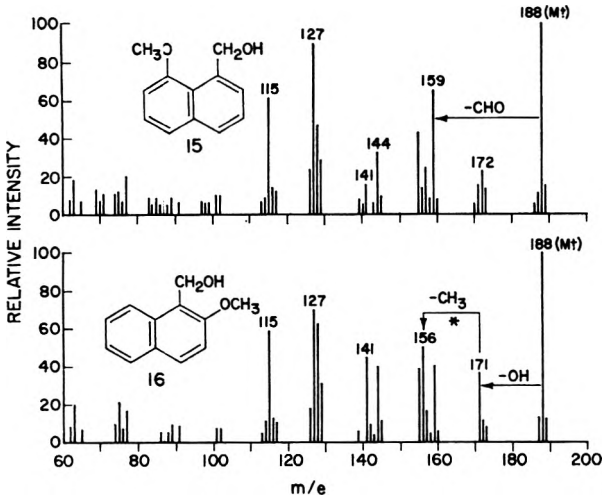


Figure 5.—Mass spectra (70 eV) of 8-methoxy-1-naphthylcarbinol (15) and 2-methoxy-1-naphthylcarbinol (16).

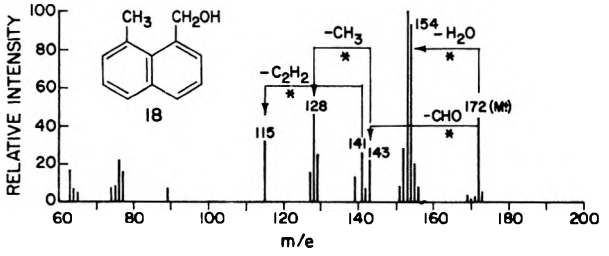
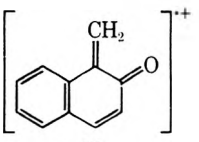


Figure 6.—Mass spectrum (70 eV) of 8-methyl-1-naphthylcarbinol (18).

156 ion is primarily due to two-step elimination from the molecular ion. The absence of significant water loss from the molecular ion is understandable because its formation would require an unfavorable eight-membered cyclic transition state. The reason for little or no direct methanol loss from the 8-methoxy alcohol **15** molecular ion is obscure. It may be related to competing reaction such as the loss of CHO or other fragment(s), or to the possible ring expansion which occurs prior to or during the fragmentation of the molecular ion. Fragmentations are directed by either the hydroxymethyl or methoxy functions. The peaks at *m/e* 115, 126, 127, 128, and 141 are characteristic of naphthalene derivatives. The mass spectrum (Figure 5) of 2-methoxy-1-naphthylcarbinol (**16**) is similar to that of its 8-methoxy isomer **15** except that the M − OH ion (*m/e* 171) and M − OH − CH_3 ion (*m/e* 156) are more prominent for the 2-methoxy isomer **16**. The driving force for the production of the strong *m/e* 156 ion in the spectrum of the 2-methoxy isomer may be due to the formation of a resonance-stabilized structure like **17**.



17

The mass spectrum (Figure 6) of 8-methyl-1-naphthylcarbinol (**18**) exhibits two strong peaks at *m/e* 154 and 153 owing to loss of water and successive

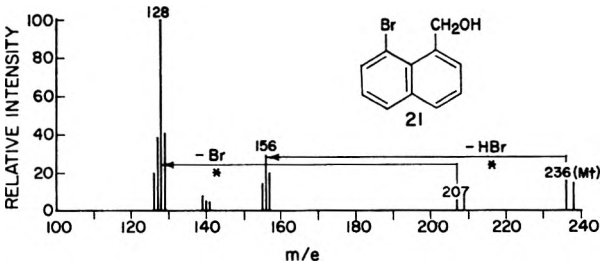
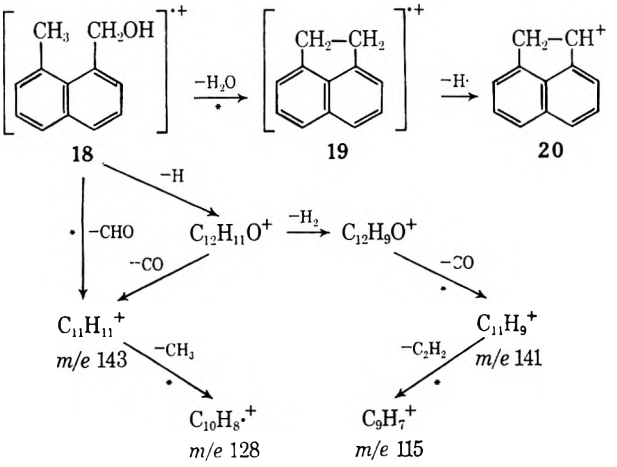


Figure 7.—Mass spectrum (70 eV) of 8-bromo-1-naphthylcarbinol (21).

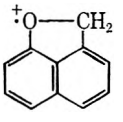
losses of water and the hydrogen radical, respectively. As shown in Scheme II, the M − H_2O ion presumably

SCHEME II



bears the structure of acenaphthene (**19**), which eliminates a hydrogen atom to form an acenaphthenyl ion (**20**). The proposed structures of **19** and **20** are based on the assumption that no ring expansion occurs prior to or during water loss. The other major fragmentation processes are also shown in Scheme II.

Loss of HBr from the molecular ion is also observed in the spectrum (Figure 7) of 8-bromo-1-naphthylcarbinol (**21**), which is indicative of interaction between the two peri substituents. A deuterium-labeling experiment confirms that the hydroxyl hydrogen is lost with the bromine atom in the HBr elimination. The M − HBr ion may have a structure like **22**. The



22

relatively weak molecular ion peaks (*m/e* 236 and 238) are in line with the mass spectra of the 8-bromo and 8-nitro acids (see Figures 3 and 4). The metastable defocusing measurement indicates that the base peak ion (*m/e* 128) originates from the *m/e* 207 and 209 ions by loss of a bromine atom. The ionic formula of the *m/e* 128 ion has been determined to be $C_{10}H_8$ by the accurate mass measurement. Presumably it has the structure of naphthalene.

The mass spectrum (Figure 8) of 8-nitro-1-naphthylcarbinol (**23**) shows a weak molecular ion and strong fragment ions at *m/e* 127, 128, 115, and 141 which are characteristic peaks of naphthalene derivatives. The

weak molecular ion and the presence of the M − H_2O ion (*m/e* 185) and the M − OH − OH ion (*m/e* 169) are indicative of the interaction between the peri substituents. Similar water elimination from the molecular ion has been reported in the mass spectrum of *o*-nitrobenzyl alcohol.[20a] The loss of water and the expulsion of hydroxyl radical from the M − OH ion have been substantiated by the observation of an appropriate metastable ion determined by the defocusing technique. The elimination of water can be postulated by a transfer of a naphthylcarbinyl hydrogen to the neighboring nitro group; the two peri substituents in the rearranged molecular ion (with or without ring expansion) then interact to lose water. Examination of the spectrum of compound **23** with a deuterium replacing the hydroxyl hydrogen revealed that, in addition to a loss of 18 mass units (OD) from the deuterated molecular ion, a loss of 17 mass units (OH) was also observed. Corrections have been made for the hydroxyl loss from the undeuterated molecular ion and also for the ^{13}C contribution. This indicates that either the hydroxyl group formed by a hydrogen transfer to the nitro group is responsible for the OH loss from the deuterated molecular ion or the deuterium in CH_2OD moiety undergoes deuterium–hydrogen exchange prior to hydroxyl loss. The strong *m/e* 141 ion is derived from the *m/e* 169 and 185 ions by the loss of 28 and 44 mass units,[24] respectively. The former loss is presumably due to elimination of CO, which is frequently observed in the mass spectra of aromatic nitro compounds.[25] The *m/e* 141 ion loses a molecule of HCN to the *m/e* 114 ion. The loss of CO and HCN are also observed in the decomposition of *m/e* 155 to *m/e* 127 and of *m/e* 142 to *m/e* 115, respectively.

Experimental Section

Preparation of Naphthoic Acids and Naphthylcarbinols.—Methods or literature references for preparation of most of these compounds have been given in our previous paper[1] except for the compounds described below. The 5-nitro-1-naphthoic acid was prepared by the method of Ekstrand.[26] The 2-methoxy-1-naphthoic acid was prepared by the method of Werner and Seybold,[27] and its corresponding alcohol was synthesized by lithium aluminum hydride reduction of the acid. The 5-bromo-1-naphthoic acid was prepared by the procedure of Short and Wang.[28] The compounds had melting points in agreement with the values reported in the literature.

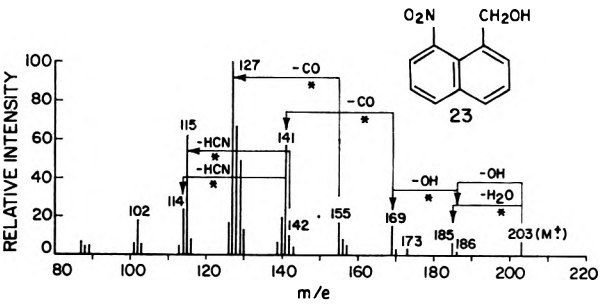


Figure 8.—Mass spectrum (70 eV) of 8-nitro-1-naphthylcarbinol (**23**).

Mass Spectra.—Mass spectra were obtained on a CEC 21-104 mass spectrometer except for the data on the metastable ion and accurate mass measurements. Samples were introduced *via* the direct insertion probe at ambient temperature with a source thermocouple reading of 250°. The metastable ion measurements were obtained with a CEC 21-110B double-focusing mass spectrometer by the defocusing technique similar to the method used by Schulze and Burlingame.[9b] The accurate mass measurements were also done on a CEC 21-110B with a resolution of about 10,000. Deuterium labeling of the hydroxyl hydrogen was done by dissolving the alcohol in chloroform, then adding D_2O, and subsequent evaporating of solvent and D_2O to obtain the deuterated alcohol.

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Registry No.—**1**, 5991-56-0; **2**, 947-62-6; **5**, 19310-98-6; **9**, 1729-99-3; **10**, 16726-67-3; **12**, 2216-13-9; **13**, 1975-44-6; **15**, 19190-42-2; **16**, 40696-22-8; **18**, 10336-29-5; **21**, 14938-58-0; **23**, 19190-46-6.

(24) The assignment of the loss of 44 mass units has some degree of uncertainty because of the presence of a broad flat-topped metastable peak indicating a large kinetic energy release in the fragmentation process.

(25) (a) S. Meyerson, I. Puskas, and E. K. Fields, *J. Amer. Chem. Soc.*, **88**, 4974 (1966); (b) J. H. Beynon, R. A. Saunders, and A. E. Williams, *Ind. Chim. Belg.*, **29**, 311 (1964).

(26) J. Ekstrand, *J. Prakt. Chem.*, **38**, 154 (1888).

(27) A. Werner and W. Seybold, *Chem. Ber.*, **37**, 3661 (1904).

(28) W. F. Short and H. Wang, *J. Chem. Soc.*, 991 (1950).

Arylation of Several Carbanions by the SRN1 Mechanism[1]

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Received February 23, 1973

The carbanions derived from 1,3-pentadiene, 1-(*p*-anisyl)propene, indene, fluorene, 2-butanone, and 3-methyl-2-butanone are phenylated by treating them with bromobenzene and sodium or potassium metal in liquid ammonia. The enolate ions of the two ketones are also phenylated by photostimulated reaction with bromo- or iodobenzene. By either method, 2-butanone is phenylated principally at the 3 position and 3-methyl-2-butanone mainly at the 1 position. In general, the carbanions derived from hydrocarbons give mixtures of mono-, di-, and triphenylated products. These reactions are believed to occur by the SRN1 mechanism.

Nucleophilic displacement of halogen in unactivated aryl halides by the familiar SNAr mechanism[3] tends to occur sluggishly, if at all. On the other hand, substitution reactions involving the very same halobenzenes and nucleophiles often take place with great facility if the novel SRN1 mechanism[4] can be brought into play.

An essential feature of the SRN1 mechanism for substitution at aromatic carbon is the high affinity of aryl radicals for certain strong nucleophiles such as amide ion,[4-6] the cyanomethyl anion,[5,7] and the acetone enolate ion.[8] The mechanism as a whole, depicted in eq 1–4, is initiated by electron transfer to substrate

$$\text{electron donor} + \text{ArX} \longrightarrow [\text{ArX}]\cdot^- + \text{residue} \quad (1)$$

$$[\text{ArX}]\cdot^- \longrightarrow \text{Ar}\cdot + \text{X}^- \quad (2)$$

$$\text{Ar}\cdot + \text{R}:^- \longrightarrow [\text{ArR}]\cdot^- \quad (3)$$

$$[\text{ArR}]\cdot^- + \text{ArX} \longrightarrow \text{ArR} + [\text{ArX}]\cdot^- \quad (4)$$

ArX from a suitable electron donor. The radical anion thus formed then splits (eq 2) to form an aryl radical, releasing the nucleofugic substituent as an anion (if initially neutral). The aryl radical combines (eq 3) with carbanion or other nucleophile to form an adduct, which then must dispose of an excess electron or otherwise react to form a stable product. If the excess electron is transferred to another substrate molecule, as in eq 4, a cycle is completed comprising eq 2, 3, and 4. A more complete description of the system would show termination steps as well as alternative reaction pathways available to some of the intermediates.

The solvated electron in liquid ammonia is very effective for the purpose of getting the mechanism started (eq 1). In other studies, SRN1 reactions stimulated by solvated electrons have afforded high yields of substitution products.[5,6,8] Alternatively, an initiating electron transfer in the sense of eq 1 can be stimulated photochemically.[9]

We now report reactions of bromobenzene with some previously uninvestigated carbanions, induced by sodium or potassium metal in liquid ammonia, as well as photochemical and electron-stimulated reactions of bromo- and iodobenzenes with the enolate ions of 2-butanone and 3-methyl-2-butanone.

Results and Discussion

Phenylation of Carbanions from Hydrocarbons.—Reactions were conducted by (1) preparing KNH_2 in liquid ammonia, (2) adding the hydrocarbon and allowing the carbanion to be formed, (3) adding bromobenzene, (4) adding potassium (or sodium) metal in small pieces until electrons were in excess, and (5) acidifying with NH_4Cl. One set of experiments, summarized in Table I, involved the carbanions derived from 1,3-pentadiene, 1-(*p*-anisyl)propene (also known as anethole), indene, and fluorene.[10]

The carbanion from 1,3-pentadiene did not react with bromobenzene in ammonia at −78°. However, when potassium metal was also added, reaction occurred to form a complex mixture of products (eq 5).

$$\text{CH}_2\text{=CH-CH=CH-CH}_2^- + \text{C}_6\text{H}_5\text{Br} \xrightarrow[\text{NH}_3]{\text{K}} \text{PhCH}_2\text{CH}_2\text{CH}_2\text{CH=CH}_2 + \text{PhCH}_2\text{CH=CHCH}_2\text{CH}_3 + \text{PhCH}_2\text{CH=CHCH=CH}_2 + \text{PhCH=CHCH=CHCH}_3 + \text{other products} \quad (5)$$

A small portion of the mixture was examined by glpc, and several components were isolated. These included 5-phenyl-1-pentene (20%), 1-phenyl-2-pentene (6%), 5-phenyl-1,3-pentadiene (18%), and 1-phenyl-1,3-pentadiene (13%), as well as products representing attachment of two or three phenyl groups to the five-carbon chain. The rest of the mixture was subjected to catalytic hydrogenation, and the resulting melange was found, by glpc, to contain 1-phenylpentane (57% yield), 1,1-diphenylpentane (9%), 1,5-diphenylpentane (7%), and a triphenylpentane fraction (9%). In another run, the yield of 1-phenylpentane after hydrogenation was 74%.

This reaction has both preparative and mechanistic interest. It provides a way of establishing a five-carbon straight chain on a benzene ring in place of a

(1) Research supported in part by the National Science Foundation.

(2) Grateful recipient of a fellowship from the Consejo Nacional de Investigaciones Científicas y Técnicas, Argentina.

(3) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951); J. F. Bunnett, *Quart. Rev., Chem. Soc.*, **12**, 1 (1958).

(4) J. K. Kim and J. F. Bunnett, *J. Amer. Chem. Soc.*, **92**, 7463 (1970).

(5) J. K. Kim and J. F. Bunnett, *ibid.*, **92**, 7464 (1970).

(6) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **37**, 3570 (1972).

(7) J. F. Bunnett and B. F. Gloor, Abstracts, 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, ORGN 45.

(8) R. A. Rossi and J. F. Bunnett, *J. Amer. Chem. Soc.*, **94**, 683 (1972).

(9) R. A. Rossi and J. F. Bunnett, *J. Org. Chem.*, **38**, 1407 (1973).

(10) Inasmuch as the estimated pK_a of ammonia is 35 and those of indene and fluorene are respectively about 20 and 23, KNH_2 clearly will convert these hydrocarbons into their anions. The pK_a of allylic hydrogen in propene is estimated to be 35.5, and conjugation of a vinyl or *p*-anisyl group with the propenide system would cause 1,3-pentadiene or anethole, respectively, to have lower pK_a's. It is therefore expected that KNH_2 will also convert these compounds to their anions. This expectation is supported by our observation of a strong color change (colorless to red) on adding either compound to KNH_2 in ammonia. *Cf.* D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapter I.

TABLE I

REACTIONS OF BROMOBENZENE WITH CARBANIONS AND ALKALI METALS IN LIQUID AMMONIA

Registry no.	Carbanion from	[Carbanion], M	[C_6H_5Br], M	[K],[a] M	Temp, °C	Products (yield, %)[b]	Registry no.
40719-28-6	1,3-Pentadiene	0.28	0.063	Nil	−78	None[c]	
		0.48	0.23	0.25	−78	1-Phenylpentane (57),[d,e] (40)[f]	538-68-1
						1,1-Diphenylpentane (9)[d]	1726-12-1
						1,5-Diphenylpentane (7)[d]	1718-50-9
						Triphenylpentanes (9)[d]	40719-26-4
		0.33	0.063	0.15	−78	1-Phenylpentane (74)[d]	
						Diphenylpentanes (7)[d]	
						Triphenylpentanes (3)[d]	
40719-29-7	Anethole	0.37	0.19	0.28	−78	1-Phenyl-1-(*p*-anisyl)propane (13)[d]	27238-93-3
						3-Phenyl-1-(*p*-anisyl)propane (31)[d]	40715-68-2
						Diphenyl-1-(*p*-anisyl)propanes (37)[d]	40715-69-3
						Triphenyl-1-(*p*-anisyl)propanes (9)[d]	40715-70-6
		0.27	0.14	0.57	−33	1-Phenyl-1-(*p*-anisyl)propane (13)[d]	
						3-Phenyl-1-(*p*-anisyl)propane (36)[d]	
						Diphenyl-1-(*p*-anisyl)propanes (33)[d]	
						Triphenyl-1-(*p*-anisyl)propanes (5)[d]	40715-71-7
40719-30-0	Indene	0.16	0.27	0.28	−78	1-Phenylindan (3)	26461-03-0
						3-Phenylindene (32)	1961-97-3
						Diphenylindenes[g] (11)	40719-27-5
						Triphenylindenes[h] (4)	
		0.31	0.20	0.45	−78	1-Phenylindan (9)	
						3-Phenylindene (32)	
						Diphenylindenes[g] (12)	
						Triphenylindenes[h] (6)	
35782-20-8	Fluorene	0.14	0.14	0.18[i]	−33	9-Phenylfluorene (44)	789-24-2
						9,9-Diphenylfluorene (5)	20302-14-1
		0.037	0.18	0.23	−78	9-Phenylfluorene (57) (40)[f]	
						9,9-Diphenylfluorene (23)	

[a] Concentration if no reaction had occurred. [b] Yields based on reactant in deficiency. [c] Recovered C_6H_5Br, 91%. [d] Product and yield after catalytic hydrogenation of crude product mixture. [e] For products before hydrogenation, see text. [f] Yield of isolated product. [g] Two isomers in approximately equal amounts. [h] Several isomers; composition tentative. [i] Sodium.

halogen atom or, we presume from experience with related reactions,[8] in place of a trimethylammonio, diethyl phosphate, or phenylthio group. The unsaturation in the immediate product would be useful in some syntheses for purposes of further elaboration, but in others hydrogenation to an *n*-pentyl group would be preferable. No doubt similar reactions could be carried out with carbanions from higher 1,3-alkadienes, but some complication would enter from the likelihood that arylation would occur at both the 1 and 5 positions, which in those cases would not be equivalent. It is anticipated that the carbanion from 1,3,5-heptatriene would be arylated at the ends of the seven-carbon chain.

As to mechanism, the immediate consequence of the combination of phenyl radical with pentadienide ion is a radical anion **1** (eq 6). In part, this probably

$$Ph\cdot + CH_2{\cdots}CH{\cdots}CH{\cdots}CH{\cdots}CH_2^- \longrightarrow \underset{\mathbf{1}}{[PhCH_2CH{=}CHCH{=}CH_2]\cdot^-} \quad (6)$$

transfers an electron to a bromobenzene molecule in the sense of eq 4, and the resulting 5-phenyl-1,3-pentadiene is quickly converted to the 1-phenylpentadienide ion in the strongly basic environment. Upon ultimate acidification, protonation occurs at both the 1 and 5 positions, forming the two isomeric phenylpentadienes obtained. However, during the reaction proper the 1-phenylpentadienide ion may be further arylated, apparently to about equal extents at the positions α and ω to the aromatic ring. Similar events may lead to triphenyl and perhaps some more highly phenylated derivatives.

Radical anion **1** is evidently partially reduced in the reacting system, leading ultimately to the phenylpentenes detected as products.

The possibility that radical anion **1** may persist in the reaction mixture needs also to be considered. It ought to be able to couple with phenyl radical as shown in eq 7. The resulting allylic carbanions might

$$\mathbf{1} + Ph\cdot \longrightarrow \underset{\mathbf{2}}{PhCH_2CH{=}CH{=}\bar{C}HCH_2Ph} + \underset{\mathbf{3}}{\begin{matrix} PhCH_2CHCH{=}CH{=}CH_2^- \\ | \\ Ph \end{matrix}} \quad (7)$$

then be further phenylated by phenyl radicals. No product with the carbon skeleton of **3** has been identified, however. If radical anion **1** persisted until quenching with NH_4Cl, disproportionation, protonation, and isomerization might occur during quenching to furnish some of the products that were obtained.

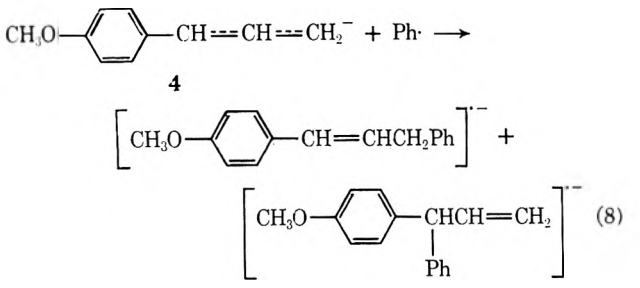
The crude products of phenylation of the carbanion **4** from 1-(*p*-anisyl)propene were catalytically hydrogenated. About three times as much 3-phenyl- as 1-phenyl-1-(*p*-anisyl)propane was obtained, indicating that phenyl radical combines with carbanion **4** preferentially at the allylic position remote from the *p*-anisyl group (eq 8). There were also products of further phenylation.

TABLE II

REACTIONS OF BROMO- AND IODOBENZENES WITH KETONE ENOLATE IONS IN LIQUID AMMONIA AT −33°

Ketone	Method of enolate ion prepn[a]	X of C_6H_5X	Stimulus	Yield, % C_6H_6	Yield, % $PhCR(CH_3)COCH_3$	Yield, % $PhCH_2COCH(R)CH_3$
2-Butanone	K	I	$h\nu$, 12 min	25	41	23
	K	I	K metal	30	31[b]	23[b]
	K	Br	$h\nu$, 20 min	20	43	26
	KNH_2	Br	$h\nu$, 50 min[c]	3	61	19
3-Methyl-2-butanone	K	Br	$h\nu$, 20 min	*d*	5	56
	KNH_2	Br	$h\nu$, 120 min	*d*	9	81
	KNH_2	Br	K metal	*d*	7[b]	55[b]

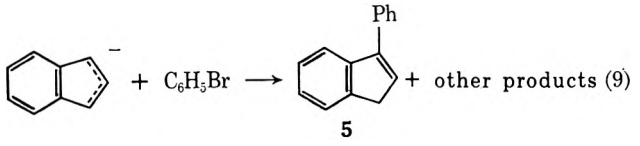
[a] Reaction of ketone with K metal or KNH_2. [b] After oxidation with $K_2Cr_2O_7$ and H_2SO_4. [c] Recovered C_6H_5Br, 7%. [d] Not measured.



4

(8)

The carbanion from indene afforded 3-phenylindene (**5**) in substantial amount. The fact that the yield

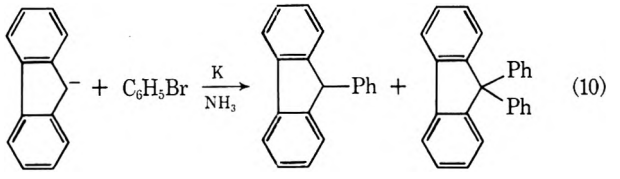


5

(9)

of 1-phenylindan was much lower suggests that electron transfer in the sense of eq 4 occurred to a significant extent. It is noteworthy and surprising that the product distribution in the run with excess bromobenzene was nearly the same as in the run with excess carbanion. Some di- and triphenylindenes were also formed.

One run with the anion from fluorene was conducted with sodium metal and another with potassium metal. Both afforded mainly 9-phenylfluorene together with a lesser amount of 9,9-diphenylfluorene (eq 10). When



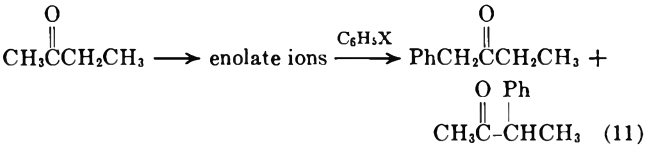
(10)

bromobenzene was used in great excess over the carbanion, the yield of diphenylfluorene was somewhat higher than when those two reactants were employed in equal amounts.

With respect to *application in synthesis*, these reactions require comparison especially with couplings between organocopper reagents and alkyl or aryl halides.[11] We are not aware that any of the products obtained by us have been made by organocopper coupling, but we expect that most could be. We believe also that carbanion arylation *via* aryne intermediates[12] could be performed in many of these cases. Which method is best for a particular synthetic objective depends on many factors, upon which we choose not to dwell.

Phenylation of Ketone Enolate Ions.—Two methods for converting ketones to their enolate ions in liquid ammonia were employed: reaction with KNH_2 and reaction with potassium metal. The latter method also reduces a considerable fraction of a ketone to the corresponding *sec*-alkoxide ion.[9] Most reactions were photochemically stimulated, but one run with each ketone was provoked by potassium metal. Results are summarized in Table II.

In reactions with the enolate ions from 2-butanone, arylation occurred preferentially at the more substituted α carbon, giving about twice as much 3-phenyl-2-butanone as 1-phenyl-2-butanone (eq 11). However, there was some variation in the product ratio between runs, for reasons unclear. A good deal of benzene (20–30%) was formed as a by-product when the enolate ions were generated by the potassium metal method, but the benzene yield was much lower when they were generated by reaction with KNH_2. The higher yields of benzene in the former case are attributed to hydrogen atom abstraction from *sec*-butoxide ions by phenyl radicals. A parallel dependence of benzene yields on the method of enolate ion generation has been observed in reactions with acetone enolate ion.[9]



(11)

Reactions stimulated by potassium metal afford some of the secondary alcohol corresponding to the phenylated ketone, as was previously observed in reactions with acetone enolate ion.[3] For purposes of quantification, the crude product mixtures were treated with $K_2Cr_2O_7$ in acidic medium to oxidize the seondary alcohols to ketones; however, some dehydration to olefins also occurred during chromic acid treatment.

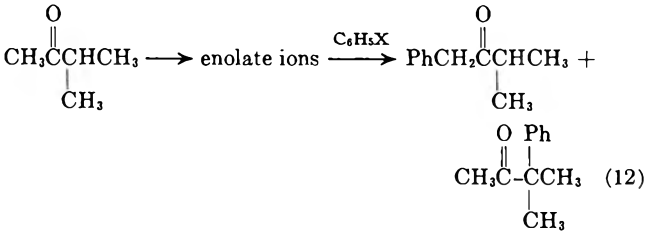
The first and third runs with 2-butanone were substantially the same except that one used iodobenzene and the other bromobenzene as phenyl radical source. They gave similar results. The first and second runs both used iodobenzene, but one was stimulated by photons and the other by solvated electrons. The results were again fairly similar. These observations give assurance that essentially the same phenomena are involved regardless of the identity of the halogen in the halobenzene, the method of stimulation, or

(11) C. E. Castro E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, **31**, 4071 (1966); E. J. Corey and G. H. Posner, *J. Amer. Chem. Soc.*, **89**, 3911 (1967); **90**, 5615 (1968); G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *ibid.*, **91**, 4871 (1969).

(12) J. F. Bunnett, *J. Chem. Educ.*, **38**, 278 (1961).

(except for the competing reaction of hydrogen atom abstraction) the method used to prepare the enolate ions.

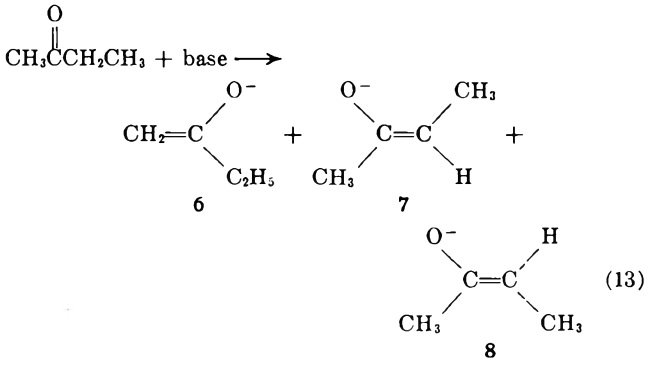
Reactions with the enolate ions from 3-methyl-2-butanone occurred to give predominantly 1-phenyl-3-methyl-2-butanone and relatively little 3-phenyl-3-methyl-2-butanone (eq 12). Thus the less sub-



(12)

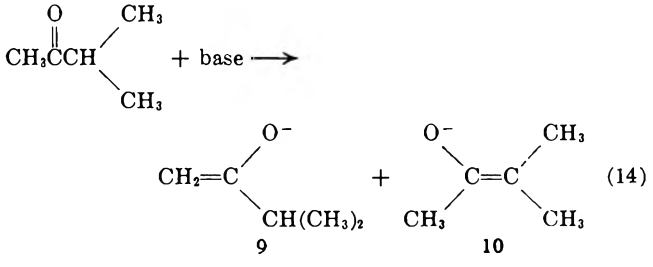
stituted α carbon is preferentially phenylated, in contrast to the situation with 2-butanone. The product ratio was much the same regardless of which method of stimulation or of enolate ion generation was employed.

Interpretation of the shift from predominant phenylation at the 3 position with 2-butanone to predominant phenylation at the 1 position with 3-methyl-2-butanone must take into account several factors. From 2-butanone, three enolate ions can be formed (eq 13)



(13)

and from 3-methyl-2-butanone, two can be formed (eq 14). If the enolate ions from any ketone attain equi-



(14)

librium with the ketone, and therefore with each other, before they are arylated, the relative rates of phenylation at the two α positions will depend on their equilibrium proportions and also on the reactivities of the enolate ions toward phenyl radical. On the other hand, if equilibrium is not established before arylation, the relative rates of formation of the enolate ions will determine their relative populations, but their relative reactivities will also be a factor when the enolate ion are in excess, as in our experiments.

Inasmuch as relative rates of formation of enolate ions from several ketones roughly resemble the proportions of the enolate ions at equilibrium,[13] the outcome should be somewhat the same whether the populations of isomeric enolate ions are kinetically or thermodynamically determined. Moreover, rates of alkylation of enolate ions are not markedly dependent on the number of alkyl substituents on the α carbon,[14] and this is likely to be true also for rates of combination with phenyl radical. Therefore it is not surprising that the proportions of phenylation at the alternative α positions reported in Table II are approximately parallel to the proportions of enolate ion **9** *vs.* **10**, or of **6** *vs.* **7** plus **8**, that one would expect from the data of House and Kramar[13] concerning somewhat analogous ketones.

Photochemically stimulated reactions were slower when enolate ions were generated by the KNH_2 than by the potassium metal method. The analogous phenomenon has been observed for reactions with acetone enolate ion,[9] but the effect is not fully understood.

Comparison is now made with two other methods for the phenylation of ketones. One is reaction of ketone enolate ions with benzyne derived from reaction of bromo- or chlorobenzene with $NaNH_2$ or KNH_2 in liquid ammonia.[15] On the basis of evidence now available, that method and the method explored in the present work are roughly equivalent in yields and in preparative convenience. 2-Butanone was phenylated in 75% yield exclusively at the 3 position by the benzyne method, whereas we observed, in the fourth run of Table II, 61% of phenylation at that position and 19% at the 1 position. On the other hand, acetone afforded only 35% of phenylacetone by the benzyne method, far less than yields as high as 85% in photochemical SRN1 reactions with bromobenzene that we have described elsewhere.[9]

Ketones have also been phenylated through reaction of their enolate ions with diphenyliodonium chloride in *tert*-butyl or *tert*-pentyl alcohol.[16] α-Phenylation of isobutyrophenone in yields as high as 81% and of isovalerophenone in 23% yield were reported. In another study,[17] quite high yields were obtained in the γ-phenylation of dicarbanions from β diketones by diphenyliodonium chloride in liquid ammonia. For these reactions, an electron transfer, radical pair mechanism has been proposed;[18] it resembles the SRN1 mechanism in some respects, but is not a chain mechanism.

For general preparative application, the method investigated in the present work is superior to both of these alternatives. The aryne method is expected to give mixtures of aromatic positional isomers in many cases when substituted halobenzenes are used

(13) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963); H. O. House and B. Trost, *ibid.*, **30**, 1341 (1965).

(14) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 193.

(15) W. W. Leake and R. Levine, *J. Amer. Chem. Soc.*, **81**, 1169 (1959). See also P. Caubere, N. Derozier, and B. Loubinoux, *Bull. Soc. Chim. Fr.*, 302 (1971); P. Caubere and G. Guillaumet, *C. R. Acad. Sci., Ser. C.*, **275**, 463 (1972).

(16) F. M. Beringer, W. J. Daniel, S. A. Galton, and G. Rubin, *J. Org. Chem.*, **31**, 4315 (1966).

(17) K. G. Hampton, T. M. Harris, and C. R. Hauser, *J. Org. Chem.*, **29**, 3511 (1964).

(18) F. M. Beringer, S. A. Galton, and S. J. Huang, *J. Amer. Chem. Soc.*, **84**, 2819 (1962).

as aryne precursors, whereas the present method is not complicated by cine substitution.[8] Arylation by means of diaryliodonium salts suffers from the expense of these reagents or the extra work needed to prepare them.

Attempted Phenylation of Other Nucleophiles.—The potassium metal stimulated reaction of iodobenzene with anilide ion in ammonia affords diphenylamine and 2- and 4-aminobiphenyl, products which represent both N- and C-arylation.[5] Hoping to find analogous behavior, we studied the reaction of potassium metal with bromobenzene in the presence of thiophenoxide or phenoxide ion in ammonia solution. In the former case, we obtained in each of two runs about 0.5% of a product with the same glpc retention time as diphenyl sulfide, as well as benzene and some aniline. No diphenyl ether was obtained as a product from the phenoxide ion reaction, nor were any hydroxybiphenyls found, but benzene and a little aniline were detected.

The immediate product of the combination of phenyl radical with the sulfur atom of thiophenoxide ion would be the radical anion of diphenyl sulfide, a species indicated by other studies to have a propensity to dissociate into phenyl radical and thiophenoxide ion.[8] Our inability to get much diphenyl sulfide as a product is therefore understandable. The reasons for our failure to obtain well-defined products from reaction with phenoxide ion are unclear.

Experimental Section

Reactions Stimulated by Alkali Metals.—A procedure for phenylation of fluorene anion is representative. The reaction was performed in a three-neck, round-bottom flask fitted with a solid CO_2–isopropyl alcohol condenser, stirred by a magnetic stirrer and constantly swept by a slow stream of dry nitrogen. To liquid ammonia (350 ml) from a commercial cylinder, sodium metal (0.060 mol) was added and a little powdered ferric nitrate was added to catalyze formation of $NaNH_2$. After the blue color of the alkali metal had disappeared, 0.050 mol of solid fluorene was added, forming a deep red solution. After 10–15 min, bromobenzene (0.050 mol) was added and then sodium metal (0.065 mol), slowly and in small bits, until the color had changed to deep green. Excess sodium benzoate was added, causing the mixture to turn red. Ammonium chloride was then added in excess, followed by 250 ml of diethyl ether, and the ammonia was allowed to evaporate. An internal standard (anthracene) was added to a portion of the resulting ether solution, and it was analyzed by glpc on a column of 5% silicone rubber SE-30 on Chromosorb W. The ether was evaporated from the rest of the ether layer, and the residue was crystallized from a benzene–pentane mixture. 9-Phenylfluorene, mp 145–146°, was thereby isolated. 9,9-Diphenylfluorene, mp 220.5–221.5°, was isolated by preparative glpc. These products were further characterized by their nmr and mass spectra.

Phenylation of Indene Anion.—By a similar procedure, a product mixture was obtained whose glpc spectrum (on the same column, but with biphenyl as internal standard) showed major peaks for indene, 3-phenylindene, and two isomers of diphenylindene, as well as a minor peak for a phenylindan and a cluster of four small peaks at long retention times presumed to be for triphenylindenes. The compositions of the phenylindan, 3-phenylindene, and each of the two diphenylindenes were determined by the mass spectra of samples isolated by glpc, and the structure of 3-phenylindene was verified by its nmr spectrum.

Phenylation of 1,3-Pentadiene Anion.—By a similar procedure, a product mixture was obtained whose glpc spectrum (on the same column, with biphenyl as internal standard) showed a major phenylpentenes peak, substantial and well-separated peaks for two phenylpentadienes, a group of four small peaks for diphenylpentenes and/or diphenylpentadienes, and a few tiny peaks at long retention times presumed to be for triphenylation products. By distillation and then preparative glpc on a column of 10% silicone rubber SE-54 on Chromosorb P, three fractions were isolated. The nmr and mass spectra of the first were appropriate for a mixture of about 75% of 5-phenyl-1-pentene and 25% of 1-phenyl-2-pentene; attempts to separate these isomers on three different glpc columns were fruitless. The nmr and mass spectra of the second and third fractions indicated 5-phenyl-1,3-pentadiene and 1-phenyl-1,3-pentadiene, respectively.

The combined distillate fractions from distillation of the crude product mixture were hydrogenated (Pd/C, 1 atm) and the product was distilled. 1-Phenylpentane, bp 84–86° (15 Torr), characterized by n_D, nmr, and mass spectra and by the identity of its infrared spectrum with that of an authentic sample, was isolated. The residue from distillation of the crude product mixture was similarly hydrogenated; by preparative glpc on a column of 10% silicone rubber SE-54 on Chromosorb P, three fractions were isolated. The first two fractions had mass spectra appropriate to diphenylpentanes; the major fraction (55%) had an nmr spectrum indicative of 1,1-diphenylpentane and in agreement with that reported by Jung and Brini,[19] and the minor fraction (45%) had an nmr spectrum indicative of 1,5-diphenylpentane. The third fraction had a mass spectrum indicative of triphenylpentanes.

In glpc quantification of the products from fluorene, indene, and 1,3-pentadiene, it was assumed that the response of all hydrocarbons was proportional to molecular mass.

Phenylation of Anethole Anion.—By a similar procedure, with potassium metal being used in excess because of the dark red color of the reaction mixture throughout the reaction, was obtained a mixture of phenylation and/or reduction products. The mixture was hydrogenated (10% Pd/C, 1 atm, 5 hr), and the resulting material was separated into several fractions by distillation and then preparative glpc (column of 10% SE-30 silicone rubber on Chromosorb P). In order of increasing retention time, these were as follows: 1-phenyl-1-(*p*-anisyl)propane, identified by nmr and mass spectrum; 3-phenyl-1-(*p*-anisyl)propane, identified by nmr and mass spectrum; a mixture of 1,3-diphenyl-1-(*p*-anisyl)propane and 3,3-diphenyl-1-(*p*-anisyl)propane, inseparable by glpc and not separately recognizable by nmr, but recognized both to be present by the mass spectrum [*m/e* (rel intensity) 302 (molecular ion, 19), 198 (20), 197 (100), 182 (5), 181 (5), 168 (11), 167 (29), 166 (11), 165 (19), 154 (7), 153 (12), 152 (11), 136 (5), 135 (31), 134 (5), 122 (8), 121 (24), 105 (6), 104 (5), 103 (8), 91 (19) and 77 (12)], of which the peaks at *m/e* 197 (*p*-methoxybenzhydryl cation) and 91 (benzyl cation) are characteristic of the 1,3-diphenyl isomer, those at 167 (benzhydryl cation) and 121 (*p*-methoxybenzyl cation) are characteristic of the 3,3-diphenyl isomer, and the absence of a peak at 273 (*p*-anisyldiphenylmethyl cation) speaks against the possibility of 1,1-diphenyl-1-(*p*-anisyl)propane; and a triphenyl-1-(*p*-anisyl)propane, recognized by its mass spectrum, which indicated it probably to be the 1,3,3-triphenyl isomer.

Phenylation of Ketone Enolate Ions.—Solutions of the enolate ions in liquid ammonia were prepared by techniques described elsewhere.[9] The photochemically stimulated reactions were conducted, in a Rayonet photochemical reactor equipped with 350-nm lamps, as described elsewhere,[9] the progress of the reactions being monitored by withdrawing *ca.* 1-ml samples from time to time by means of a piece of 8-mm glass tubing J-shaped at the bottom, quenching them with water, extracting with ether, and analyzing the extracts by glpc. The potassium metal stimulated reactions were conducted much as described above for reaction with fluorene anion. The enolate ions were about 0.3 *M* and the halobenzene about 0.08 *M* in the reaction mixtures.

To the crude product mixtures, *p*-dichlorobenzene was added as internal standard, and analysis was conducted by glpc, using a column of 20% Carbowax M on Chromosorb P. Then, by preparative glpc on a similar column, phenyl derivatives of the starting ketones were isolated.

3-Phenyl-2-butanone was identified by its infrared, nmr, and mass spectra. 1-Phenyl-2-butanone was identified by its nmr and mass spectra, and by the identity of its infrared spectrum with that of an authentic sample.

3-Phenyl-3-methyl-2-butanone was identified by its infrared and nmr spectra; its mass spectrum did not display a molecular

(19) M. Jung and M. Brini, *Bull. Soc. Chim. Fr.*, **55**, 587 (1965).

ion peak, but rather a prominent peak at *m/e* 119, attributed to the 2-phenyl-2-propyl cation. 1-Phenyl-3-methyl-2-butanone was characterized by its infrared, nmr, and mass spectra; the mass spectrum showed a molecular ion peak at *m/e* 162 but no peak at *m/e* 119.

Registry No.—Bromobenzene, 108-86-1; 5-phenyl-1-pentene, 1075-74-7; 1-phenyl-2-pentene, 27911-12-2; 5-phenyl-1,3-pentadiene, 1007-52-9; 1-phenyl-1,3-pentadiene, 1608-27-1; 3-phenyl-2-butanone, 769-59-5; 1-phenyl-2-butanone, 1007-32-5; 3-phenyl-3-methyl-2-butanone, 770-85-4.

The Preparation of Highly Fluorinated Ethers

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Highly fluorinated ethers are prepared by reducing their corresponding esters in HF at elevated temperature. Under the appropriate conditions the isolated yields of ethers exceed 80%; acyl–oxygen cleavage is negligible. The relative rates of reduction of a series of esters are reported and discussed.

Sulfur tetrafluoride[1] is a useful reagent for converting, among others, carbonyl to difluoromethylene and hydroxyl to fluoro groups. Our interest in this area stems from reports based on the attempted sulfur tetrafluoride reduction of esters to α,α-difluoro ethers. Pioneering investigations[2] dealing with reactions between sulfur tetrafluoride and various functional groups indicate that hydrocarbon aliphatic esters are reduced with predominant concomitance of acyl–oxygen cleavage. A subsequent study,[3] however,

$$RCOR' + SF_4 \longrightarrow [RCF + R'OH] \longrightarrow RCF_3 + R'F$$

demonstrates the conversion of aryl fluoroformates and trifluoroacetates to ethers by treatment with this reagent. Along these lines highly fluorinated ali-

$$XArOCY + SF_4 \longrightarrow XArOCF_2Y$$
$$X = NO_2$$
$$Y = F, CF_3$$

phatic esters conceivably could be reduced to their corresponding ethers, a class of compound that would be difficult to prepare by alternate routes. The sulfur tetrafluoride reductions of this latter and related systems are described in this report.

Results and Discussion

Preparation of Esters and a Carbonate.—Esters of perfluoroalkyl acids were prepared by the reaction between acid chlorides and $C_2F_5CH_2OH$, $(CF_3)_2CHOH$, and $(CF_3)_3COH$. In the presence of DMF, the reaction between acid chlorides and $C_2F_5CH_2OH$ proceeds at 25°; however, higher reaction temperatures (50–60°) were required for esters derived from $(CF_3)_2CHOH$. The yields of the fluorinated propyl esters range from 70 to 90%. A side product, the corresponding acid, is suspected to have resulted from the presence of adventitious moisture which hydrolyzed the ester during distillation.

The reaction between perfluorooctanoyl chloride and perfluoro-*tert*-butyl alcohol afforded the corresponding ester languidly at 50° (17% conversion after 90 hr). However, the addition of a stoichiometric amount of Et_3N[4] effected complete alcohol to ester conversion under mild conditions. When reactions between acid fluorides and $C_2F_5CH_2OH$ or $(CF_3)_2CHOH$ were run in glass vessels, water was inevitably introduced into the reaction. A good yield of ester can be obtained by running acid fluoride esterifications in stainless steel vessels. The esters prepared by the reactions between acid chlorides or fluorides are presented in Table I; yields, reaction conditions, and by-products are included for convenience.

Perfluoro-*tert*-butyl carbonate was prepared by the reaction between sodium perfluoro-*tert*-butoxide (prepared *in situ*) and phosgene.

$$(CF_3)_3COH \xrightarrow[2.\ COCl_2]{1.\ NaH} (CF_3)_3COCOC(CF_3)_3 \quad 35\%$$

The yield obtained is not representative of the reaction. The reaction proceeded smoothly; however, the unexpected physical properties of the carbonate led to losses during work-up.

Reductions of Esters and Related Compounds with SF_4.—The literature[1] indicates that Lewis and Brønsted acids, BF_3 and HF being the most popular, catalyze the SF_4 reduction of carbonyl compounds. However, to the best of our knowledge, there has been no reported comparative study concerning the relative effectiveness of these catalysts on the reduction of carbonyl compounds by SF_4. To this end, preliminary experiments were run under similar conditions using several preselected catalysts. The results are summarized in Table II.

Apparently, HF is the most effective catalyst in this group, and the rate of reduction of the ester is faster when HF is used as solvent rather than in catalytic amounts.

For each ester small-scale experiments were run to determine the temperature and reaction time neces-

(1) For recent reviews on this reagent, see W. C. Smith, *Angew Chem., Int. Ed. Engl.*, **1**, 467 (1962); D. G. Martin, *Ann. N. Y. Acad. Sci.*, **145**, 161 (1967); P. Boissin and M. Carles, *Commis. Energ. At.* [Fr.] *Serv. Doc., Ser. Bibliogr.*, **98**, 29 (1967); J. V. Urenovitch, "Sulfur Tetrafluoride," Technical Bulletin, Air Products and Chemicals, Inc.

(2) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960), and references stated therein.

(3) W. A. Sheppard, *J. Org. Chem.*, **29**, 1 (1964); J. A. Webster, Seventh Quarterly Progress Report, Contract NAS8-21401, "Thermally Resistant Polymers for Fuel Tank Sealants," Oct 1970.

(4) For an alternate preparation of a perfluoro-*tert*-butyl ester, see F. J. Pavlik and P. E. Toren, *J. Org. Chem.*, **35**, 2054 (1970).

TABLE I

SYNTHESIS OF ESTERS

Ester (% yield[a])	Acid (% yield[a])	Reactants (g, mol)	Registry no.	Conditions
$C_7F_{15}CO_2CH_2C_2F_5$ (71)	$C_7F_{15}CO_2H$ (16)	$C_7F_{15}COCl$ (41.5, 0.096) $C_2F_5CH_2OH$ (23.5, 0.156)	335-64-8 422-05-9	1 drop of DMF, reflux 5 hr
$C_7F_{15}CO_2CH(CF_3)_2$ (77)	$C_7F_{15}CO_2H$ (6)	$C_7F_{15}COCl$ (25, 0.058) $(CF_3)_2CHOH$ (12.6, 0.075)	920-66-1	5 drops of DMF, 60°, 24 hr
$C_7F_{15}CO_2C(CF_3)_3$ (17)		$C_7F_{15}COCl$ (20.0, 0.0462) $(CF_3)_3COH$ (14.1, 0.0597)	2378-02-1	DMF (0.5 ml), 50°, 90 hr
$C_7F_{15}CO_2C(CF_3)_3$ (83)				Et_3N (7.0 g, 0.046 mol), −100° → room temperature
$[(CF_3)_2CHO_2CCF_2CF_2]_2$ (92)		$(ClOCCF_2CF_2)_2$ (15.0, 0.046) $(CF_3)_2CHOH$ (20.0, 0.119)	336-06-1	DMF (0.1 ml), 60°, 18 hr
$C_3F_7O(CCF_2O)_2CCO_2CH(CF_3)_2$ (58)	Corresponding acid (20)	$C_3F_7O(CCF_2O)_2CC(=O)F$ (20.5, 0.037) $(CF_3)_2CHOH$ (10.4, 0.062)	27639-98-1	2 drops of DMF, NaF (anhydrous, 5.2 g), 60°, 60 hr[b]
$C_2F_5O(CF_2CF_2O)_2CF_2CO_2CH_2C_2F_5$ (76)	Corresponding acid (13)	$C_2F_5O(CF_2CF_2O)_2CF_2C(=O)F$ (15.0, 0.324) $C_2F_5CH_2OH$ (6.0, 0.040)	13071-66-4	DMF (0.1 ml), 65°, 16 hr[c]
$+C(=O)(CF_2)_3CO_2CH_2(CF_2)_3CH_2O+_n$ (98)		$ClC(=O)(CF_2)_3C(=O)Cl$ (28.9, 0.10) $HOCH_2(CF_2)_3CH_2OH$ (22.4, 0.10)	678-77-3 376-90-9	DMF (0.5 ml), 140°, 5 hr

[a] Yield of isolated product. [b] Reaction run in glass flask. [c] Reaction run in stainless steel autoclave.

TABLE II

CATALYST SCREENING[a]

Catalyst (mol)	Conversion of ester	Selectivity to ether
	<1	
HF (0.01)	25	>98
HF (0.35)	56	>98
BF_3 (0.01)	<1	
SbF_5 (0.01)	<1	
AsF_3 (0.01)	<1	

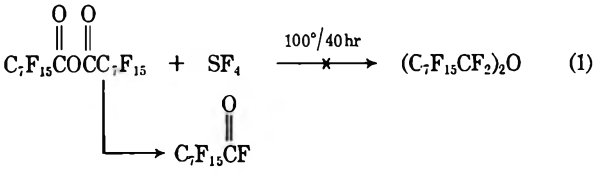
[a] $C_7F_{15}CO_2CH_2C_2F_5$ (1.0 g, 1.83 mmol), Freon E4 standard (0.5 g), and SF_4 (2.16 g, 20.0 mmol) were charged with or without added catalyst into a 30-ml stainless steel autoclave and heated with shaking at 85° for 20 hr.

sary to give the highest conversion of the ester and selectivity to the ether. To minimize a competing cleavage reaction, the lowest reaction temperature was chosen which would afford essentially complete conversion of the ester in a reasonable time interval. Once these conditions were found, the reaction was scaled up roughly by a factor of ten (see Table III). From examination of glc results obtained in these experiments, it was noted that ester to ether conversions were essentially quantitative under the given conditions. The yields of ethers shown in Table III presumably reflect losses due to handling.

In all of the runs, *ca.* a tenfold excess of SF_4 is used along with anhydrous HF as the solvent. No attempts were made to determine the minimum amount of SF_4 needed to effect complete conversion of esters to ethers at a given temperature.

It has been reported[2] that anhydrides can be converted to acid fluorides and under extreme conditions to trifluoromethyl groups. In several instances[2] an ether can be obtained from an anhydride.

Since these reactions were not run in HF solvent, an attempt was made to convert a linear anhydride to the homologous ether with SF_4/HF. The results are shown schematically in eq 1. Under the reaction

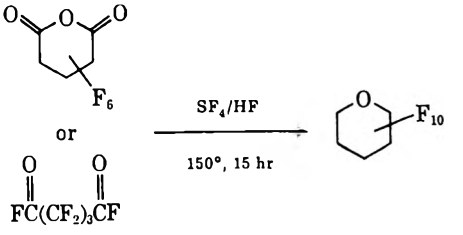


(1)

conditions essentially complete consumption of the anhydride was observed while no other appreciable products were detected in the crude reaction mixture. In another experiment run under milder conditions, the acid fluoride was the only identifiable product with unreacted acid accounting for the remainder of the reaction.

It is interesting that in our SF_4/HF reactions the anhydride, $[C_7F_{15}C(=O)]_2O$, undergoes acyl–oxygen cleavage while the ester, $C_7F_{15}C(=O)OCH_2C_2F_5$, gives carbonyl reduction without cleavage. This could be attributed to the cleavage of the anhydride by HF to an acid fluoride–acid mixture, folowed by the reduction of the acid to the acid fluoride by SF_4. The HF cleavage reaction has previously been reported[5] as a method for the preparation of CF_3COF from $(CF_3CO)_2O$.

However, we have observed that under more severe reaction conditions perfluoro cyclic anhydrides and certain perfluoro diacid fluorides are converted to cyclic ethers by SF_4/HF treatment. In separate experiments perfluoroglutaric anhydride and perfluoro-



(5) G. A. Olah and S. J. Kuhn, *J. Org. Chem.*, **26**, 237 (1961).

TABLE III
REDUCTION OF ESTERS TO ETHERS BY SF_4 IN HF[a]

Ester (mol)	SF_4, mol	Ether, % yield[b]	Reaction conditions, °C, hr	Acid fluoride (yield)[c]
$C_7F_{15}CO_2CH_2C_2F_5$ (0.0183)	0.22	92	150, 15	<1
$C_7F_{15}CO_2CH(CF_3)_2$ (0.0177)	0.21	81	185, 15	<1
$C_7F_{15}CO_2C(CF_3)_3$ (0.0136)	0.29	83	180, 100	1
$(CF_3)_2CHO_2C(CF_2)_4CO_2CH(CF_3)_2$ (0.017)	0.42	89	185, 16	<1
$C_2F_5O(CF_2CF_2O)_2CF_2CO_2CH_2C_2F_5$ (0.0168)	0.252	83	150, 15	<1
$+C(=O)(CF_2)_3CO_2CH_2(CF_2)_3CH_2O+_n$ (0.024)	0.36	89 (polyether)	150, 16	

[a] Reactions run in 300-ml stainless steel autoclave with 50 ml of anhydrous HF. [b] Isolated yield of distilled product. [c] Estimated by glc of the crude reaction mixture.

glutaryl fluoride are converted to perfluoropentamethylene oxide. A common intermediate (possibly a perfluorolactone) is suspected to be involved in these reactions.

Perfluoro di-*tert*-butyl carbonate is unaffected by SF_4/HF treatment at 85° for 20 hr. Similar experiments run at 200° for 24 hr and 250° for 48 hr afforded 7 and 27% conversions, respectively, of the carbonate to a sole product (>95% selectivity). The product was tentatively assigned the structure $[(CF_3)_3CO]_2CF_2$ from glc mass spectra and ^{19}F nmr data.

$$(CF_3)_3OC(=O)OC(CF_3)_3 \xrightarrow[250°/48\ hr]{HF/SF_4} [(CF_3)_3CO]_2CF_2$$
27% conversion
>95% selectivity

To test the applicability of these reactions for polymers, the polyester $+OC(CF_2)_3COOCH_2(CF_2)_3CH_2O+_n$ was prepared from perfluoroglutaryl chloride and hexafluoro-1,5-pentanediol. When the polyester was treated with excess SF_4 in HF at 150° for 16 hr, a polyether was isolated in 89% yield.

$$ClOC(CF_2)_3COCl + HOCH_2(CF_2)_3CH_2OH \xrightarrow[140°]{DMF\ catalyst} +C(=O)(CF_2)_3COCH_2(CF_2)_3CH_2O+_n$$
97.5%

$$+C(=O)(CF_2)_3COCH_2(CF_2)_3CH_2O+_n \xrightarrow[150°,\ 16\ hr]{HF,\ SF_4} +C_{10}H_4F_{16}O_2+_n$$
89%

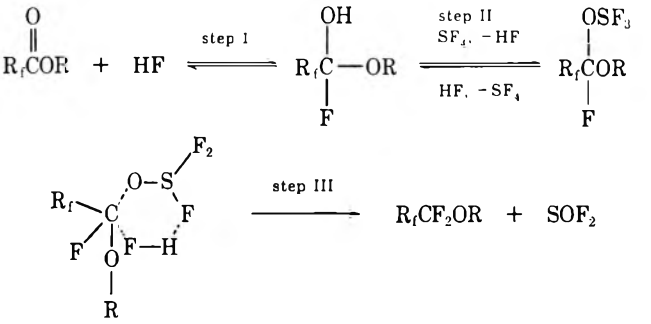
Relative Rate Data.—As a supplement to estimating the ease of reaction of an ester with SF_4 by comparing reaction conditions, semiquantitative data were obtained from a relative rate study. From these and our previously collected data, reasonable predictions could be made as to the feasibility of completely reducing a certain highly fluorinated ester with SF_4.

The relative rates of reaction between four pairs of esters were measured. In these experiments roughly a tenfold excess of SF_4 was employed to approach psuedo-first-order kinetics. The following rate expression was used to calculate the realtive rates.

$$k = \frac{\log A/A_0}{\log B/B_0}$$

The rates were measured at 85 ± 2° (Chart I). The reported values are essentially the rates of consumption of the parent esters.

Mechanistic Implication.—The mechanism proposed[1,6] for the reduction of ketones with SF_4 seems consistent with the data accumulated on the reduction of the fluorinated esters.



The facts that our reactions do not proceed at moderate temperatures in the absence of HF and that the reactions proceed faster when HF is used as a solvent rather than in catalytic amounts suggest the incorporation of HF in the actual rate expression. This is consistent with an equilibrium involving HF in step I or (and) the HF facilitation of step III in the reaction as depicted in the mechanism.[7]

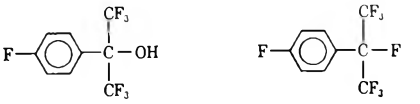
Our relative rate data indicate that steric effects influence the rates of these reactions more than electronic effects. The ester carbonyl absorption occurs at higher energy when a CF_3 is substituted for an H in the alkoxy substituent. This is in keeping with the intuitive expectation that such substitution reduces the electron density at the carbonyl group; *i.e.*, the ester stabilizing contribution[9] a becomes less important

a

(6) W. A. Sheppard and C. M. Sharts, "Organic Fluorine Chemistry," W. A. Benjamin, Inc., New York, N. Y., 1969, p 126.

(7) With regard to the SF_4 reduction of hydrocarbon, carbonyl-containing compounds, the authors in ref 2 make the reasonable suggestion that step I rather than step III is rate determining. However, the paucity of data demonstrating the ease of an SNi or SN2 process at a highly F or R_f substituted, four-coordinate carbon atom limits our assignment of the slow step from the available data. Reactions analogous to step III do not appear to proceed[8] under mild conditions.

(8) For example, the conversion of i to ii is effected by SF_4 at 150°; see W. A. Sheppard, *J. Amer. Chem. Soc.*, **87**, 2410 (1965).



i ii

(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 182.

TABLE IV

PROPERTIES OF ESTERS, ETHERS, AND CARBONATE

Registry no.	Compd	Bp, °C (mm)	Mass spectra
40719-59-3	$C_7F_{15}CO_2CH_2C_2F_5$[a]	81–84 (25)	
40719-60-0	$C_7F_{15}CF_2OCH_2C_2F_5$[a]	75–78 (28)	M − 19, 549
40719-61-7	$C_7F_{15}CO_2CH(CF_3)_2$[a]	73–75 (28)	
40719-62-8	$C_7F_{15}CF_2OCH(CF_3)_2$[a]	82–84 (41)	
40719-63-9	$C_7F_{15}CO_2C(CF_3)_3$[a]	60–62 (1)	M − 19, 613
40691-16-5	$C_7F_{15}CF_2OC(CF_3)_3$[a]	93 (41)	M − 19, 635
40719-64-0	$C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)CO_2CH(CF_3)_2$[a]	103 (27)	
40719-65-1	$C_2F_5O(CF_2CF_2O)_2CF_2CO_2CH_2C_2F_5$[a]	88–91 (41)	
40719-66-2	$C_2F_5O(CF_2CF_2O)_2CF_2CF_2OCH_2C_2F_5$[a]	87–88 (41)	
40719-67-3	$[(CF_3)_2HCO_2CCF_2CF_2]_2$[a]	93–95 (41)	
40719-68-4	$[(CF_3)_2HCOCF_2CF_2CF_2]_2$[a]	99–101 (40)	
355-79-3			M − 19, 247
40719-69-5	$(CF_3)_3COC(=O)OC(CF_3)_3$[a]	(40–42)[b]	
40719-70-8	$(CF_3)_3COCF_2OC(CF_3)_3$		M − 19, 501
26546-05-4	$[C(=O)(CF_2)_3CO_2CH_2(CF_2)_3CH_2O]_n$[a]	(~45)[b]	
40719-25-3 (polymer)	$(C_{10}H_4F_{16}O_2)_n$[a]		

[a] Satisfactory combustion data for C and H (±0.7%) were provided for these compounds: Ed. [b] Melting point.

CHART I

$$k\frac{C_7H_{15}CO_2CH_2C_2F_5}{C_7F_{15}CO_2CH(CF_3)_2} = 1.8$$

$$k\frac{C_7H_{15}CO_2CH_2C_2F_5}{C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)CO_2CH(CF_3)_2} = 21$$

$$k\frac{C_7F_{15}CO_2CH(CF_3)_2}{C_7F_{15}CO_2C(CF_3)_3} = 6.0$$

$$k\frac{C_2F_5O(CF_2CF_2O)_2CF_2CO_2CH_2C_2F_5}{C_7F_{15}CO_2CH_2C_2F_5} = 11$$

Substrate	Relative rate
$C_2F_5O(CF_2CF_2O)_2CF_2CO_2CH_2C_2F_5$	230
$C_7H_{15}CO_2CH_2C_2F_5$	21
$C_7F_{15}CO_2CH(CF_3)_2$	12
$C_7F_{15}CO_2C(CF_3)_3$	2
$C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)CO_2CH(CF_3)_2$	1

as the electron-withdrawing power of the R group increases. Consequently, the rate of step I and from a related argument step III (mechanism) would be expected to increase in the series $R_fCO_2C(R_f)_3 > R_fCO_2CH(R_f)_2 > R_fCO_2CH_2R_f$. Substitution of a CF_3 for an F or an R_fO for an F group α to the carbonyl, *e.g.*, $R_fCF_2CO_2R$, $R_fCF(R_f)CO_2R$, and $R_fOCF_2CO_2R$, does not appreciably change the carbonyl frequency of the esters. In this series F, R_f, and R_fO exert similar electronic effects.[10] Since the data accumulated from the relative rate study is not interpretable from arguments based on the above electronic effects, steric factors must govern the rates of these reactions.

To summarize the rate data, as the bulk of the substituent is increased at sites 1 or 2 (below) of a fluorinated ester, the rate decreases. Rate decline is more pronounced by substitution at site 1 rather than site 2.

$$\underset{}{R_0}\ \underset{1}{CR_2}\ CO_2\ \underset{2}{CR_3}$$

It is notable that $C_2F_5O(CF_2CF_2O)_2CF_2CO_2CH_2C_2F_5$ (TFEO ester) is reduced by an order of magnitude faster than $C_7F_{15}CO_2CH_2C_2F_5$. While most, if not all, of this rate enhancement may be attributed to the smaller steric bulk at site 1 of the ether ester, the possibility of a change in mechanism cannot be dismissed. In the ether ester step III may involve a prior ionization (HF assisted) of the C–OSF_3 bond. The resulting carbocation could be partially stabilized by the neighboring oxygen atoms in the fluorocarbon ether backbone. If this were the case, it might be anticipated that $R_fOCF(CF_3)CF_2OCF(CF_3)CO_2R$ (HFPO ester) would undergo reduction *via* the normal route since substitution of a CF_3 for an F at site 1 would destabilize[11] the incipient carbocation. This could account partially for the difference in the rates of reduction of the TFEO and HFPO esters.

Experimental Section

The highly fluorinated alcohols, acid chlorides, anhydrides, and hexafluoroglutaryl fluoride used in this work are supplied commercially by PCR, Inc. The acid fluorides derived from HFPO[12] and TFEO[13] were prepared by published procedures.

Vapor phase chromatographic analysis was performed on a Hewlett-Packard Model 700 instrument using an 8 ft × 0.25 in. 15 or 35% PFO-XR on Gas-Chrom R 60–80 mesh column. Infrared spectra were recorded on a Perkin-Elmer Infracord spectrometer. ^{19}F nmr spectra were recorded on a Varian XL-100 spectrometer at 94.1 MHz. The mass spectra were recorded on Model 14-107 Bendix time of flight spectrometer.

Preparation of Partially Fluorinated Esters. General Procedure.—The esters were prepared from the appropriate alcohols and acid chlorides or fluorides. The lower boiling component was added to the higher boiling component dropwise at room temperature. Several drops of DMF were added to catalyze the reactions. The esterifications with $C_2F_5CH_2OH$ proceeded at 25°; however, the reactions were run at reflux. It was necessary to heat the reaction mixture to 50–60° to observe appreciable reaction when $(CF_3)_2CHOH$ was used as reactant. Esters were isolated by distilling the crude reaction mixtures. Table I gives the stoichiometries, yields, etc., of these runs. Table IV and V give the properties of these materials.

(10) Similar conclusions can be arrived at from the similarity of the ionization constants of perfluoroalkyl acids; see also W. A. Sheppard, *J. Amer. Chem. Soc.*, **92**, 5419 (1970).

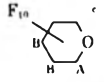
(11) G. A. Olah, R. D. Chambers, and M. B. Comisarow, *J. Amer. Chem. Soc.*, **89**, 1268 (1967); G. A. Olah and C. U. Pittman, Jr., *ibid.*, **88**, 3310 (1966).

(12) C. G. Fritz, E. P. Moore, and S. Selman, U. S. Patent 3,114,778 (1963); *Chem. Abstr.*, **60**, 6750*B* (1964).

(13) J. C. Warnell, U. S. Patent 3,250,806 (1966); *Chem. Abstr.*, **65**, 15230*F* (1966).

TABLE V

$^{19}F^{a}$ AND ^{1}H NMR^{b} DATA

Compd	A	B	C	D	E	F	G	H	I	J	^{1}H nmr
$CF_3CF_2(CF_2)_4CF_2CF_2OCH_2CF_2CF_3$ (A G D F C E B)	3.7 (t, $J \sim 10$)	6.7 (s)	9.1 (br s)	44.6 (br m)	46.6 (t of t)	47.4 (m)	48.6 (m)				3.95 (t, $J = 12$)
$CF_3CF_2(CF_2)_4CF_2CO_2CH(CF_3)_2$ (B E D C A)	−2.7 (d, $J \sim 6$)	5.0 (t of t)	41.4 (t)	45 (br)	49.5 (m)						6.1 (sept, $J = 6$)
$CF_3CF_2(CF_2)_5CF_2OCH(CF_3)_2$ (B E D C A)	−2.1 (d, $J \sim 5$)	5.2 (t, $J \sim 10$)	8.0 (br)	45.2 (m)	48.4 (br)						4.84 (sept, $J = 5.5$)
$CF_3CF_2(CF_2)_4CF_2CO_2C(CF_3)_3$ (B E D C A)	−6.6 (s)	4.9 (t of t)	40.4 (t of t)	45.1 (br)	49.4 (m)						
$CF_3CF_2(CF_2)_4CF_2CF_2OC(CF_3)_3$ (C F D E B A)	−7.0 (t, $J = 9$)	2.9 (br)	5.0 (t, $J \sim 10$)	44.3 (br)	47.2 (br)	48.8 (br)					
$CF_3CF_2CF_2OCCF_2OC(CF_3)CF_2OCF_2CF_2CF_3$ (E H D F C F F F A; J I G J)	−2.9 (m)	1.9 (d, $J \sim 150$)	3.5 (br)	4.7 (br)	5.2 (t, $J = 7$)	5.8 (d, $J \sim 6$)	7.9 (d, $J \sim 150$)	53.0 (s)	54.7 (m)	67.9 (m)	6.0 (sept, $J = 6$)
$+CF_2CF_2CO_2CH(CF_3)_2+_2$ (C B A)	−2.9 (d, $J = 6$)	41.5 (m)	45.2 (m)								5.88 (sept, $J = 6$)
$[CF_2CF_2CF_2OCH(CF_3)_2]_2$ (C or D B A)	−2.3 (q, $J = 5$)	7.9 (m)	45.2 (m)	48.1 (m)							4.88 (sept, $J = 5$)
$CF_3CF_2O(CF_2CF_2O)_2CF_2CO_2CH_2CF_2CF_3$ (B C C C A D C)	0.8 (t, $J = 12$)	8.1 (s)	10.9 (s)	47.6 (t, $J = 12$)							4.76 (t, $J = 12$)
$CF_3CF_2O(CF_2CF_2O)_2CF_2CF_2OCH_2CF_2CF_3$ (A E D D D C F B)	8.3 (s)	11.2 (br s)	11.7 (m)	12.5 (m)	16.5 (s)	48.3 (t of t, $J = 11.5, 2$)					4.34 (t, $J = 12$)
$(CF_3)_3COCOOC(CF_3)_3$ (A)	−6.8 (s)										
$(F_3C)_3COCF_2OC(CF_3)_3$ (B A)	−20.6 (m, $J = 8$)	−6.4 (t, $J = 8$)									
	14.5	60.6									

[a] ^{19}F nmr spectra were recorded on a Varian XL-100 spectrometer at 94.1 MHz. The liquids were run neat with an external lock using a substitute tube of trifluoroacetic acid as reference. The solid samples were run in acetone-d_6 as solvent. Chemical shifts are reported in parts per million from the standard (J in hertz). [b] ^{1}H nmr spectra were run on the same instrument at 100 MHz as neat liquids or in acetone-d_6 using tetramethylsilane as internal standard. Chemical shifts are reported in parts per million from standard (J in hertz). [c] Gas phase.

TABLE VI

RELATIVE RATE DATA

Substrate		Substrate				
A_0, mmol	A, mmol	B_0, mmol	B, mmol	SF_4, g (mmol)	E4, g	Reaction time, hr
$C_7F_{15}CO_2CH_2C_2F_5$		$C_7F_{15}CO_2CH(CF_3)_2$		2.16 (20)	0.4739	15
0.820	0.390	0.886	0.585			
$C_7F_{15}CO_2CH(CF_3)_2$		$C_7F_{15}CO_2C(CF_3)_3$		2.92 (27)	0.503	15
0.604	0.389	1.87	1.74			
$C_7F_{15}CO_2CH_2C_2F_5$		$C_3F_7O[C(CF_3)FCF_2O]_2C(CF_3)FCO_2CH(CF_3)_2$		2.16 (20)	0.5076	15
0.825	0.389	0.905	0.845			
$C_2F_5O(CF_3CF_2O)_2CF_2CO_2CH_2C_2F_5$		$C_7F_{15}CO_2CH_2C_2F_5$		1.73 (16)	0.4954	10
0.421	0.037	0.892	0.702			

Preparation of Perfluoro Di-*tert*-Butyl Carbonate.—Sodium hydride (6.12 g, 0.255 mol, 50% mineral oil dispersion) was added to a flask equipped with an acetone–Dry Ice condenser. This material was slurried with 200 ml of anhydrous THF. Then perfluoro-*tert*-butyl alcohol (20.0 g, 0.085 mol) was added dropwise maintaining 20° in the flask by external cooling. The reaction mixture was allowed to stir overnight at 25°. The vessel was cooled to 5° and then phosgene (4.2 g, 0.0425 mol) was condensed into the flask rapidly. The reaction was exothermic and the temperature rose to 18°. The reaction was stirred at 5° for 1 hr and then at 25° for 24 hr. The solution was filtered under N_2 and the salts were dried with a N_2 flow. The salts were then washed with Freon-113 (2 × 100 ml). Distillation of the THF solution gave an azeotrope which was collected; on cooling, a solid crystallized from the distillate and was filtered cold under N_2 leaving 3.5 g of a white solid, mp 40–42°. Careful fractionation of the Freon wash solution gave a material (bp 84–87°, 3.0 g) which solidified on standing (mp 40–42°). These materials had identical ir spectra (C=O at 5.32 μ) and were found to be the carbonate (7.5 g, theory 21.1 g, 35% yield). Properties are reported in Tables IV and V.

SF_4 Reductions. General Procedure.—The ester was charged into a 300-ml, 316 stainless steel autoclave equipped with a 3000-psi bursting disk. The vessel was cooled to −183° and evacuated, and the appropriate amount of HF, then SF_4, was introduced by vacuum techniques. The autoclave was heated in a rocker for a given period; then the clave was removed, cooled, and vented at atmospheric or slightly reduced pressure through a steel trap packed with NaF. The SF_4 and SOF_2 were collected in a trap cooled at −183°. After the removal of the HF and SF_4 had been effected, the clave was opened and the contents were diluted with Freon-113 and transferred to a flask containing NaF to scavenge residual HF. This solution is referred to in the text as crude product. Concentration of the solution and distillation afforded the product. Yields are reported in Table III, properties in Table IV and V.

Reaction between Perfluorooctanoic Anhydride and SF_4.—Perfluorooctanoic anhydride (10.0 g, 0.0123 mol), HF (50.0 g, 2.5 mol), and SF_4 (70 g, 0.65 mol) were charged to a 300-ml stainless steel autoclave and heated at 100° for 40 hr. The autoclave was vented at 25° (720 mm) through NaF into traps cooled by ice and liquid O_2 consecutively. The autoclave was removed after the vapors were vented. By applying vacuum (0.1 mm) to the NaF and ice trap, $C_7F_{15}C(=O)F$ (6.0 g, >95%) was collected and identified by comparison of glc retention time and ir with those of an authentic sample. The autoclave was opened and Freon-113 (15 ml) was added. Glc of this solution showed that a trace (<1%) of perfluorooctanoic anhydride remained; perfluorooctanoyl fluoride was the only product detected. Distillation afforded 1.5 g of the acid fluoride, bp 105–107° (total 7.5 g, theory 10.2 g, 74%). The bottoms from the distillation (1.7 g) consisted of ~60:40 mixture of $C_7F_{15}C(=O)F$ and $C_7F_{15}C(=O)OH$, respectively, by ir analysis.

The reaction was repeated under milder conditions, *i.e.*, 60° for 24 hr, and gave the same product with perfluorooctanoic acid accounting for ~30% of the mixture. No appreciable amounts of products assignable to a perfluoroether or ester were detected.

Reaction between Perfluoroglutaric Anhydride and SF_4.—Perfluoroglutaric anhydride (5.0 g, 0.0225 mol), SF_4 (48.5 g, 0.45 mol), and HF (50 ml) were charged to a 300-ml stainless steel autoclave and heated at 150° for 15 hr with rocking. The autoclave was cooled and the contents were passed through a steel trap containing NaF to remove the HF. The volatiles were collected at liquid oxygen temperature and weighed 53.2 g. Analysis by glc showed SF_4, SOF_2, and an unknown product in a 50:6:6 ratio, respectively. The unknown product was shown to be perfluoropentamethylene oxide (see Tables IV and V). When the reaction was repeated using perfluoroglutaryl fluoride as starting material, the same results were obtained under analogous reaction conditions.

The SF_4 Reduction of Perfluoro-*tert*-butyl Carbonate.—The carbonate (1.3 g, 2.6 mmol), C_6F_6 (0.6 g, internal standard), HF (5 ml), and SF_4 (5.4 g, 50 mmol) were charged and heated with shaking in a 30-ml stainless steel autoclave at 250° for 48 hr. The contents were cooled and vented through a NaF trap at atmospheric pressure. Then vacuum was applied and the remainder of the material was collected in a trap cooled at −183°. Glc showed a 63:27 ratio of carbonate to product. Tables IV and V recorded the spectral properties of the product.

Competitive Experiments.—Pairs of esters were charged into 30-ml stainless steel autoclaves with 7.0 ml of HF, SF_4, and Freon E4 as a standard. The vessels were heated at 85 ± 2° with shaking for the appropriate time intervals, then cooled to room temperature, and vented. The contents were dissolved in Freon-113 (15 ml), and the resulting solution stored over NaF and then analyzed by glc. The details of these experiments are shown in Table VI.

Acknowledgments.—The author wishes to thank Dr. K. B. Baucom of PCR, Inc., for helpful suggestions as as well as a sample of the polyester. Thanks are due to Drs. W. S. Brey and R. J. Hanrahan of the University of Florida for obtaining and interpreting the nmr and mass spectral data, respectively, reported in this work. This work was sponsored by the Air Force under Contract No. F33615-70-C-1343.

Registry No.—Perfluorooctanoic anhydride, 33496-48-9; perfluorooctanoyl fluoride, 335-66-0; perfluoroglutaric anhydride, 376-68-1; perfluoroglutaryl fluoride, 678-78-4; SF_4, 7783-60-0.

Kinetics of the Condensation of Glycine with Benzaldehyde in Ethanol

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Potassium hydroxide catalyzed condensation of glycine with benzaldehyde in ethanol at 25° to afford phenylserine has been studied kinetically by means of spectrophotometry of remaining benzaldehyde, giving a rate law: $v = k[\text{glycine}][\text{benzaldehyde}]^2([\text{KOH}]_{\text{total}} - [\text{glycine}]_{\text{initial}})$. An ir spectrum of the reaction solution indicates the presence of C=N bond, but the expected intermediate $PhCH{=}NCH_2COOH$ could not be isolated because of its easy decarboxylation. Ethyl glycinate can form the Schiff base with benzaldehyde, but the methylene compounds without primary α-amino group such as acetic acid, methoxyacetic acid or its ester, and *N*-methylglycine of the similar carbon acidity do not react practically with benzaldehyde. These results suggest a mechanism involving an attack of the carbanion of *N*-benzylideneiminoacetic acid on benzaldehyde, implying the activation of the methylene by an electron-withdrawing benzylideneimino group (PhCH=N).

Condensation of glycine with benzaldehyde in ethanolic potassium hydroxide gives the anil of phenylserine in a good yield.[1,2] The base-catalyzed condensations of activated methylenes with carbonyl compounds have been established to involve the carbanions.[3-5] In most cases, two electron-withdrawing groups such as cyano, acyl, carboxy, or amide are favorable to provide sufficient activation of methylene groups for condensation with carbonyl compounds. However, in some cases, a single nitro or carbonyl group is sufficient to effect condensation with carbonyl compounds, when its acidity is fairly high, *e.g.*, $pK_a = 13$ for nitromethane,[6] but a single carboxylate, cyano, or amide group does not seem to be sufficient for the condensation under moderately basic conditions such as in alcoholic potassium hydroxide, *e.g.*, $pK_a = 24$–25 for acetic acid or acetonitrile.[6] α-Amino group may act as a deactivator like α-alkoxy groups which act as deactivators in the carbanion formation.[7] The Schiff base is a possible intermediate in the condensation of glycine with carbonyl compounds, but the example for the activation of the methylene by a N=C group is unknown. The acidity of the methylene in glycine may be increased sufficiently by the complex formation with cobalt ion to effect the condensation with acetaldehyde.[8-10]

To obtain some informations on the mechanism of the condensation and the activation of the methylene by a benzylideneimino group, the potassium hydroxide catalyzed condensation of glycine with benzaldehyde in absolute ethanol at 25° has been studied kinetically by means of uv spectrophotometry.

Results and Discussion

Rate Law.—Glycine exists mainly as a zwitterion in a neutral solution, but in a potassium hydroxide solution it forms the potassium salt; hence excess potassium hydroxide (*i.e.*, $[\text{KOH}]_{\text{excess}} = [\text{KOH}]_{\text{total}} - [\text{NH}_2\text{CH}_2\text{CO}_2\text{H}]_{\text{initial}}$) may be the effective concentration of base. The apparent second-order rate coefficient, k_a, in a rate expression

$$v = k_a[\text{PhCHO}][\text{NH}_2\text{CH}_2\text{CO}_2^-] \quad (1)$$

was found to increase linearly with the initial concentration of benzaldehyde, while the third-order one, k_a', in a rate expression

$$v = k_a'[\text{PhCHO}]^2[\text{NH}_2\text{CH}_2\text{CO}_2^-] \quad (2)$$

was nearly constant, independent of the initial concentration of benzaldehyde, as shown in Table I. The value of k_a' is $(0.76 \pm 0.04) \times 10^{-3}\ M^{-2}\ \text{sec}^{-1}$ at 25°.

Figure 1 indicates the first-order dependence of the third-order coefficient on the concentration of excess potassium hydroxide. Hence, the rate of the reaction in absolute ethanol is expressed as

$$\frac{d[\text{P}]}{dt} = k[\text{KOH}]_{\text{excess}}[\text{PhCHO}]^2[\text{NH}_2\text{CH}_2\text{CO}_2^-] \quad (3)$$

where P denotes phenylserine.

In the reaction of benzaldehyde with ethyl glycinate instead of free glycine, the second-order rate coefficient increases with the initial concentration of benzaldehyde, but it does not show exactly the first-order dependence of the rate on added potassium hydroxide ($[\text{KOH}]_t$), since ethyl glycinate is partly hydrolyzed by potassium hydroxide.

Condensation of the Other Methylene Compounds.—If the carbanions can be produced sufficiently under basic conditions, the condensation with aldehyde should occur. Under the same conditions as for glycine–benzaldehyde condensation, acetic acid, methoxyacetic acid or its ethyl ester, and *N*-methylglycine underwent attempts to condense them with benzaldehyde in ethanolic potassium hydroxide (0.60 *M*); virtually none of them reacted. A little (below 5%) consumption of benzaldehyde in 2.5 hr may be ascribed to the Cannizzaro or the Tischenko reaction, while for the reaction of glycine the conversion to phenylserine was over 70%. Phenylacetonitrile reacted with benzaldehyde in ethanolic potassium hydroxide at 25° to give α-cyanostilbene with second-order rate constant of $2.3 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$ at $[\text{KOH}]_t = 0.30\ M$, which is larger than that for glycine ($k_2 = 0.38 \times 10^{-3}\ M^{-1}\ \text{sec}^{-1}$). Phenylacetic acid did not react with benzaldehyde under the same conditions. The methylene group of phenylacetonitrile appears to be activated sufficiently by the presence of phenyl and cyano groups.

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TABLE I

APPARENT SECOND- AND THIRD-ORDER RATE COEFFICIENTS FOR THE REACTION OF GLYCINE WITH BENZALDEHYDE IN ETHANOL AT 25°[a]

Initial concn						
$[NH_2CH_2CO_2H]$, M	$[PhCHO]$, M	$[KOH]_{added}$, M	$[KOH]_{excess}$, M	10^4k_a, M^{-1} sec^{-1}	$10^3k_a'$, M^{-2} sec^{-1}	$10^4k_a'/[KOH]_{excess}$, M^{-2} sec^{-1}
0.15	0.10	0.30	0.15	0.85	0.82	5.5
0.15	0.20	0.30	0.15	1.4	0.84	5.6
0.15	0.30	0.30	0.15	1.9	0.80	5.3
0.15	0.40	0.30	0.15	2.3	0.64	4.3
0.15	0.51	0.30	0.15	3.0	0.71	4.7
0.15	0.30	0.20	0.05		0.12	2.5
0.15	0.30	0.30	0.15		0.62	4.2
0.15	0.30	0.45	0.30	3.8	1.3	4.5
0.15	0.30	0.60	0.45		2.1	4.6
0.15	0.30	0.75	0.60		3.0	4.9

[a] See eq 1 and 2.

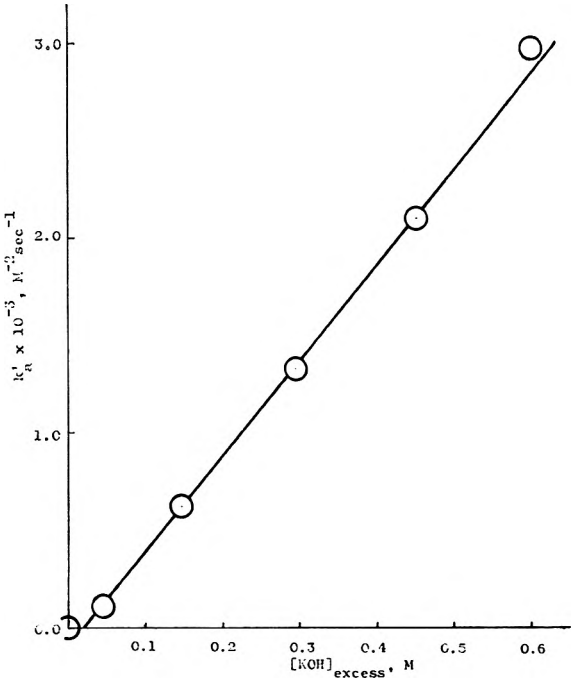


Figure 1.—Effect of excess KOH concentration on the third-order rate constant, k_a', for the condensation of glycine with benzaldehyde in ethanol at 25°: $[NH_2CH_2CO_2H]_{initial} = 0.15\ M$; $[PhCHO]_{initial} = 0.30\ M$.

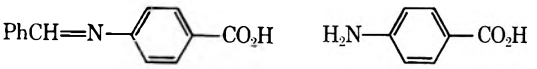
Confirmation of the Schiff Base.—Condensation of ethyl glycinate with benzaldehyde in a benzene solution containing anhydrous magnesium sulfate as a dehydrating agent gives the Schiff base, *N*-benzylideneglycine ethyl ester, almost quantitatively. Reaction of the Schiff base with benzaldehyde in ethanolic potassium hydroxide at 25° gives phenylserine ethyl ester and its hydrolysis product, phenylserine.

On the other hand, we could not isolate the Schiff base, *N*-benzylideneglycine, from the condensation of glycine with benzaldehyde in a benzene or ethanolic solution containing anhydrous magnesium sulfate. The evaporated solution gave *N*-benzylidenemethylamine and *N*-benzylidene-(2-phenyl-2-hydroxylethyl)amine, which are decarboxylation products of *N*-benzylideneglycine and *N*-benzylidenephenylserine, respectively.

Further, an infrared spectrum of the ethanolic mixture of benzaldehyde, glycine, and potassium hydroxide at an early stage of reaction indicates C=N absorption at 1640 cm^{-1}. Hence the formation of the Schiff base is above suspicion.

Mechanism.—Following evidences support the intermediacy of the Schiff base for the condensation of glycine with benzaldehyde. (1) The second-order dependence of the rate on benzaldehyde precludes a simple reaction of one molecule of glycine with one molecule of the aldehyde or a nucleophilic catalysis involving a reaction of glycine with the Schiff base, but is explicable by a reaction between *N*-benzylideneglycine and benzaldehyde. (2) Ethyl *N*-benzylideneglycinate is obtained almost quantitatively from a reaction between ethyl glycinate and benzaldehyde, and its reaction with benzaldehyde gives phenylserine ethyl ester and its hydrolysis product, phenylserine. Though *N*-benzylideneglycine could not be isolated, *N*-benzylidenemethylamine and *N*-benzylidene(2-phenyl-2-hydroxyethyl)amine were obtained, which suggests the formation of *N*-benzylideneglycine. Further, an infrared spectrum of the reaction mixture of glycine with benzaldehyde in ethanolic potassium hydroxide indicates the presence of *N*-benzylideneglycine. (3) Since the electron-releasing α-amino group in glycine suppresses the carbanion formation as the α-methoxy group[7] does, the acidity of glycine as a carbon acid would be slightly lower than that of acetic acid ($pK_a = 24$)[6] and comparable with those of methoxyacetic acid and *N*-methylglycine. Such methylene compounds of similar carbon acidity that cannot form Schiff bases did not condense with benzaldehyde. This fact suggests that the above methylenes cannot dissociate in ethanolic potassium hydroxide sufficiently to effect the condensation and this may be true for the methylene in glycine of similar carbon acidity. However, glycine can easily be converted under the reaction conditions into the Schiff base, *i.e.*, *N*-benzylideneiminoacetate ion, $PhCH{=}NCH_2CO_2^-$ (I), whose methylene may be activated sufficiently by both benzylideneimino and carboxylate groups, though no report on the activation by a $-N{=}CR_2$ group instead of $-CR{=}NR$ group is available. The acidity (pK_a) of *p*-benzylideneiminobenzoic acid (II) as a carboxylic acid is reported to be

almost equal to that of *p*-aminobenzoic acid (III),[11] but the inductive effects of amino and imino substituents

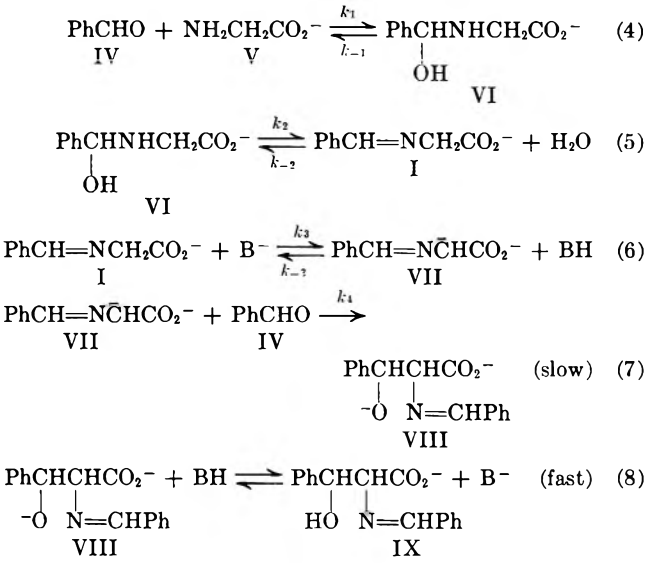


II III

would be small because of the longer distance between the substituent and the acidic proton compared with glycine, and the extent of n–π conjugation in II would be comparable with that in III, since II has a double planar configuration with a dihedral angle of *ca.* 60°.[12,13]

In *N*-benzylideneiminoacetate ion (I), however, a considerable increase of methylene acidity by the adjacent benzylideneimino group is expected. The acidity of I may be close to that of phenylacetonitrile ($pK_a < 24$) in view of the rate constant for the condensation of glycine with benzaldehyde, which is *ca.* $^1/_6$ of that of phenylacetonitrile, while acidity of I is lower than that of acetophenone ($pK_a = 19$),[6] which can easily condense with benzaldehyde.[14] It is higher than that of acetic acid ($pK_a = 24$)[6] which does not condense with benzaldehyde. Hence, the pK_a value of I may be 20–23.

A probable mechanism involving the Schiff base (I) is as follows.



If the concentrations of VI, I, and VII are low, the steady-state approximation leads to the following rate equation, where k and K are rate and equilibrium constants of subscripted steps, respectively.

$$v = \frac{d[IX]}{dt} = k_4[VII][IV] = \frac{k_1k_2k_3k_4[IV]^2[V][B^-]}{(k_{-1} + k_2)k_3k_4[IV][B^-] + (k_{-3}[BH] + k_4[IV])k_{-1}k_{-2}[H_2O]}$$

As an extreme case, if $k_{-1} \gg k_2$ and $k_{-3}[BH] \gg k_4[IV]$, the equation is simplified to

$$v = \frac{K_1k_2K_3k_4\frac{K_{BH}}{[H^+]}}{K_3k_4\frac{K_{BH}}{[H^+]}[IV] + k_{-2}[H_2O]}[IV]^2[V]$$

where $K_1 = k_1/k_{-1}$, $K_3 = k_3/k_{-3}$, and $K_{BH} = [H^+][B^-]/[BH]$. This assumption seems to be rational, since the dehydration (eq 5) is a slower step than the condensation (eq 4) under alkaline conditions in the Schiff base formation,[15] and generally the protonation of carbanion (reverse of eq 6, k_{-3}) is very rapid compared with the carbonyl addition (eq 7).[6]

The dissociation constant or K_3K_{BH} of benzylideneiminoacetate ion may be small ($\lesssim 10^{-20}$), then $K_3k_4(K_{BH}/[H^+])[IV] \ll k_{-2}[H_2O]$; hence the rate equation is expressed as

$$v = K_1K_2K_3k_4\frac{[B^-]}{[BH][H_2O]}[IV]^2[V]$$

Here $K_2 = k_2/k_{-2}$. This is consistent with our observation.[16]

Experimental Section

Materials.—Commercial benzaldehyde was distilled under reduced N_2 flow. Glycine was of commercial guaranteed grade and used without further purification. Methoxyacetic acid[17] and its ethyl ester,[17] *N*-methylglycine,[18] ethyl glycinate,[19] phenylacetonitrile,[20] and phenylacetic acid[20] were prepared according to the literature.

Kinetics.—Absolute ethanol was used as a solvent. Glycine in ethanolic potassium hydroxide and benzaldehyde in ethanol (each 10 ml) were mixed after a thermal equilibrium had been attained. Aliquots were taken out and diluted with a 0.1 *N* HCl solution in 50% (v/v) aqueous methanol to hydrolyze the Schiff base of phenylserine, and the absorbance of benzaldehyde at 248 mμ in the solution was determined. The decrease of absorbance is ascribed to the phenylserine formation. The apparent second-

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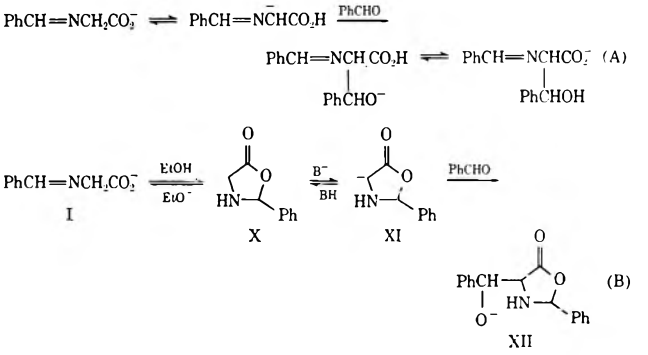
(16) As a referee pointed out, the literature [K. F. Bonhoeffer, K. H. Gerib, and O. Reitz, *J. Chem. Phys.*, **7**, 664 (1939)] shows that the CH_2 group of the acid molecule may ionize 10^4 times as fast as that of the negatively charged acetate ion. However, the observed condensation of glycine or its ester with *p*-nitrobenzaldehyde to *p*-nitrophenylserine without base [E. D. Bergmann, H. Bendas, and W. Taub, *J. Chem. Soc.*, 2673 (1951); G. Ehrhart, *Ber.*, 483 (1953)], in spite of no condensation of unsubstituted acetic acid, should be ascribed to the enhancement of deprotonation by introducing the *p*-$NO_2C_6H_4CH{=}N$ group to acetate ion. Hence, the existence of VII in the presence of base may be probable.

Alternative schemes (A and B) suggested by the referee are considered.



The rate equation derived from scheme A does not show the first-order dependence on the excess concentration of KOH, which is not the case.

Scheme B agrees with the rate equation and is not distinguishable from our mechanism (eq 4–8). However, the methylene in X does not seem to be active enough to effect the condensation, since (1) ethyl methoxyacetate of an acidity similar to that of X did not react with benzaldehyde, and (2) the carbanion formation from X may be suppressed by the neighboring electron-releasing NH group, which is contrasted to the PhCH=N group. No detection of X and also the facile reaction of benzaldehyde with ethyl *N*-benzylideneglycinate, probably in which cyclic X forms with difficulty, are unfavorable to scheme B.

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(20) R. Adams and A. F. Thal, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, pp 107, 436.

order rate coefficient was calculated according to the following stoichiometry.

$$2PhCHO + NH_2CH_2CO_2^- \longrightarrow PhCH(OH)CHCO_2^- + H_2O$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad N{=}CHPh$$

A blank reaction under the reaction conditions without glycine shows a decrease in benzaldehyde below 4% in 2.5 hr which is negligibly small compared with the phenylserine formation (over 70% conversion in 2.5 hr). Phenylserine was isolated from the reaction solution in a yield of 44%: mp 187–189° (lit. mp 192–194°); ν_{max} (KBr) 3500–2500 (NH_3^+, OH), 1630 (CO_2^-), 760 and 710 cm^{-1} (monosubstituted phenyl).

Formation of the Schiff Base.—Condensation of ethyl glycinate with benzaldehyde in benzene containing anhydrous $MgSO_4$ as a dehydrating agent at room temperature gives *N*-benzylideneglycine ethyl ester almost quantitatively. This product was confirmed by ir and nmr: ν_{max} (KBr) 1740 (C=O), 1640 (C=N), 1180 [CC(=O)O)], 750 and 686 cm^{-1} (monosubstituted phenyl); τ (CCl_4) 1.81 (s, CH=N, 1 H), 2.27–2.63 (m, aromatic H, 5 H), 5.73 [s, (C=N)CH_2–, 2 H], 5.85 [q, –CH_2(CH_3)] 2 H], 8.75 (t, CH_3, 3 H).

Condensation of glycine with benzaldehyde in benzene or ethanol containing anhydrous $MgSO_4$ gives *N*-benzylidenemethylamine and *N*-benzylidene(2-phenyl-2-hydroxyethyl)amine, but *N*-benzylideneglycine could not be isolated. The infrared spectrum of the former was consistent with that of the authentic sample and the latter was identified by ir and nmr: mp 106–108°; ν_{max} (KBr) 3350–3000 (NH, OH), 1650 (C=N), 750 and 690 cm^{-1} (monosubstituted phenyl); τ (DMSO) 1.74 (s, CH=N, 1 H), 2.24–2.57 (m, aromatic H, 10 H), 4.59 (b, OH, 1 H), 5.06 (q, CH, 1 H), 6.20 (d, CH_2, 2 H).

The infrared spectrum of the ethanolic mixture of benzaldehyde, glycine, and potassium hydroxide at an early stage of reaction had C=N absorption at 1640 cm^{-1}.

Reaction of Ethyl *N*-Benzylideneglycinate.—To a solution of KOH (5.61 g, 0.1 mol) and ethyl *N*-benzylideneglycinate (9.56 g, 0.05 mol) in absolute ethanol (75 ml), there was added a solution of benzaldehyde (5.31 g, 0.05 mol) in absolute ethanol (25 ml). The mixture was allowed to stand at room temperature. A crystalline product was separated. Ethanol was decanted and the residual crystals were dissolved in a mixture of 2 *N* hydrochloric acid (20 ml) and benzene (20 ml). The solution was concentrated under vacuum until all ethanol was removed. After neutralization with concentrated ammonia, crystalline phenylserine (2.52 g, 27%) was obtained, which was identified by ir and melting point with the authentic specimen. Phenylserine ethyl ester was separated from ethanol solution by means of tlc: ν_{max} (KBr) 3450–3300 (NH_2, OH), 1730 (C=O), 1210–1190 [CC(=O)O], 750 and 700 cm^{-1} (monosubstituted phenyl); τ ($CDCl_3$) 2.70 (m, aromatic H), 4.97 (s, OH, 1 H), 5.35 (d, CH, 1 H), 5.73 (d, CH, 1 H), 6.06 (q, CH_2, 2 H), 7.24 (s, NH_2, 2 H), 9.24 (t, CH_3, 3 H).

Registry No.—Glycine, 56-40-6; benzaldehyde, 100-52-7; phenylserine, 1078-17-7; ethyl glycinate, 459-73-4; *N*-benzylideneglycine ethyl ester, 40682-54-0; *N*-benzylidenemethylamine, 622-29-7; *N*-benzylidene(2-phenyl-2-hydroxyethyl)amine, 25558-12-7; phenylserine ethyl ester, 40682-56-2.

Amino Group Protection in Peptide Synthesis. The 4,5-Diphenyl-4-oxazolin-2-one Group[1]

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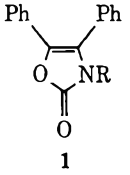
The preparation and properties of 4,5-diphenyl-4-oxazolin-2-one (Ox) derivatives (1) of amino acids are described and these derivatives evaluated as protected intermediates in peptide synthesis. The Ox group—one of the few protecting groups which mask both hydrogens of a primary amino function—is unreactive under the usual conditions used to remove protecting groups, but may be cleaved under mild reductive or oxidative conditions. The use of Ox protection for the ϵ-amino group of lysine is described.

The previously described properties of the 4,5-diphenyl-4-oxazolin-2-ones[2] (1) have indicated the



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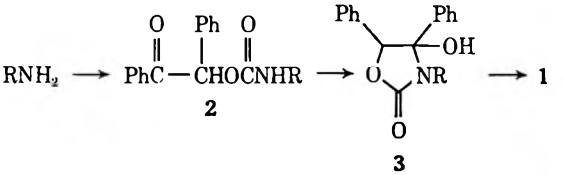
potential of this heterocyclic system[3] as a protecting group for primary amines, one of the few protecting groups which mask both hydrogens of a primary amine function.

Compounds of this type are extremely stable and unreactive under a variety of rigorous conditions. Methods existed for the preparation of this cyclic system through the easily prepared benzoin urethanes. The oxazolinones are highly crystalline, yet reasonably soluble in organic solvents; because of the *cis*-stilbene moiety present in the system, they are also highly fluorescent. Finally, possibilities existed for the removal of the protecting group under mild oxidative or reductive conditions.

The proposed preparation of the 4,5-diphenyl-4-oxazolin-2-one (Ox) derivatives involved a two-step reaction sequence: the preparation of benzoin urethanes, followed by cyclization and simultaneous dehydration of the urethanes to oxazolinones in an acid medium.



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In contrast to the usual methods of preparing urethanes, a novel method is available for the preparation of the benzoin urethanes. Treatment of benzoin with phosgene in the presence of *N*,*N*-dimethylaniline, followed by thermal cyclization of the intermediate, unstable chloroformate affords a cyclic unsaturated carbonate (4) in good yield.[4] Treatment of this

(1) Dedicated to Professor Dr. Theodor Wieland on the occasion of his 60th birthday, June 5, 1973.

(2) J. C. Sheehan and F. Guziec, Jr., *J. Amer. Chem. Soc.*, **94**, 6561 (1972).

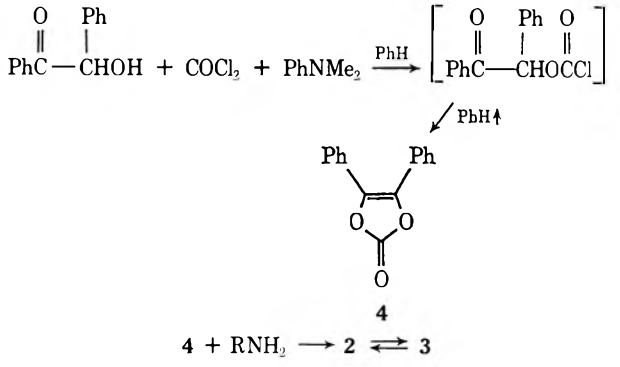
(3) Reviewed by R. Filler, "Advances in Heterocyclic Chemistry," Vol. IV, Academic Press, New York, N. Y., 1965, p 103.

(4) A minor by-product is desyl chloride, formed in a reaction analogous to the thionyl chloride–pyridine chlorination of alcohols. This compound becomes the major product of the reaction unless *N*,*N*-dimethylaniline hydrochloride is removed prior to the chloroformate cyclization.

Table I
Ox Amino Acid Derivatives[a]

Registry no.	Amino acid	Registry no.[g]	Yield,[b] %	Mp,[c] °C	Optical rotation, deg (c, MeOH)
56-40-6	Gly	40691-13-2	79	178–179[d]	
56-41-7	L-Ala	37628-69-2	77	202–204[d] (subl)	$[\alpha]^{26}D$ −31.5 (1.02)
63-91-2	L-Phe	37628-66-3	84	196–197[d] (subl)	$[\alpha]^{25}D$ −176 (1.02)
72-18-4	L-Val	37628-67-4	75	234–236[d] (subl)	$[\alpha]^{24}D$ −69.3 (0.99)
61-90-5	L-Leu	40719-38-8	85	203–204[d]	$[\alpha]^{26}D$ −24.6 (1.02)
73-32-5	L-Ile	40719-39-9	74	225–226[d] (subl)	$[\alpha]^{26}D$ −44.8 (1.08)
60-18-4	L-Tyr	40719-40-2	70	198–202[d] dec	$[\alpha]^{25}D$ −150 (1.00)
63-68-3	L-Met	40719-41-3	82	168–169[d]	$[\alpha]^{25}D$ −51.6 (1.01)
40719-34-4	L-Ser (DCHA salt)	40719-42-4	73	196–198[e] dec	$[\alpha]^{24}D$ −4.3 (0.97)
56-85-9	L-Gln	50719-43-5	67	163.5–165[f]	$[\alpha]^{26}D$ −32.4 (1.04)
40719-35-5	α-Z-L-Lys (DCHA salt)	40719-44-6	82	147–149[e]	$[\alpha]^{26}D$ +4.5 (1.03)

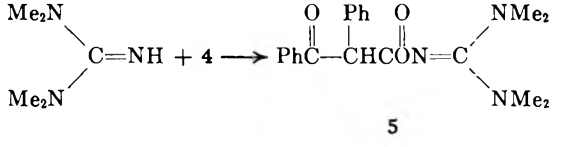
[a] All compounds gave satisfactory elemental analyses. [b] Based on a single recrystallization. [c] All melting points are uncorrected. [d] Recrystallized from ethyl acetate–pentane. [e] Recrystallized from absolute ethanol–ether. [f] Recrystallized from acetone–water. [g] Of Ox derivative.



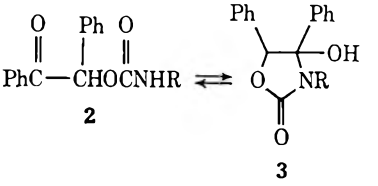
carbonate with a primary amine affords the benzoin urethane in high yield.

Although urethanes of simple primary amines could be prepared without difficulty using the cyclic carbonate in organic solvents, the normal conditions of amino acid acylation in aqueous solvents led to significant hydrolysis of the cyclic carbonate. The catalytic nature of this hydrolysis resulted in poor yields in the acylation reaction. The use of tetramethylammonium or 1,1,3,3-tetramethylguanidine salts of amino acids in anhydrous dimethylformamide, however, offered a reasonable alternative to aqueous systems.

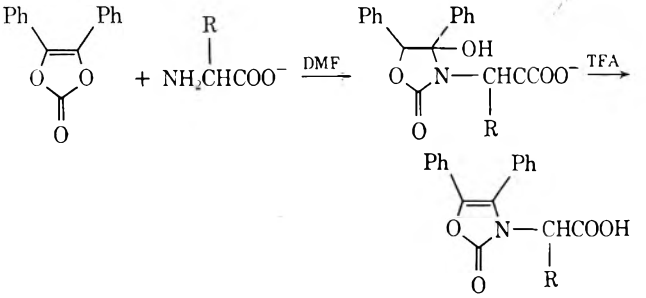
The tetramethylammonium salts of amino acids react with the cyclic carbonate to afford the benzoin urethanes in consistently high yields (70–85%). The use of tetramethylguanidine as a base in the acylation, however, led to high yields of the urethanes only when the amino acid salts were very soluble in dimethylformamide. In those cases where the amino acid salts were only moderately soluble, low yields of the urethanes were obtained due to the acylation of tetramethylguanidine by the cyclic carbonate.



The benzoin urethanes prepared in the acylation reaction were obtained in two major isomeric forms. While the urethanes of glycine, L-alanine, and L-phenylalanine were always obtained as hydroxyoxazolidinone mixtures (3) [ir 1770–1750 cm^{-1}; nmr δ 7.7–7.0 (m, 10 H)], the urethanes of L-valine, L-leucine, L-isoleucine, and L-serine were obtained in either the hydroxyoxazolidinone form, or as the desyl urethanes (2) [ir 1735–1725 cm^{-1}; nmr δ 8.1–7.8 (m, 2H), δ 7.7–6.7



(m, 8 H)], depending on the conditions of the acylation and work-up. Acylation or work-up conditions involving aqueous base led to the predominant formation of the desyl urethanes, while immediate acidification of an anhydrous acylation mixture led to the isolation of the urethane in the hydroxyoxazolidinone form. Because the dehydration of the hydroxyoxazolidinones to oxazolinones occurs under conditions (trifluoroacetic acid, 1–2 hr, quantitative yield) much milder than those required for the cyclization and dehydration of desyl urethanes,[5] the conditions favoring hydroxyoxazolidinone formation were used in a general procedure for the preparation of oxazolinone derivatives of amino acids. The most convenient procedure for the synthesis of 4,5-diphenyl-4-oxazolin-2-one (Ox) derivatives of amino acids therefore involved the treatment of an amino acid tetramethylammonium salt in dimethylformamide at room temperature with 1 equiv of the cyclic carbonate, acidification and isolation of the resulting hydroxyoxazolidinone mixture, and dehydration of this mixture to the desired oxazolinone in trifluoroacetic acid. Pure Ox derivatives of a variety of amino acids could be obtained in consistently high yields using this procedure (Table I). A single recrystallization in each case afforded analytically pure derivatives.

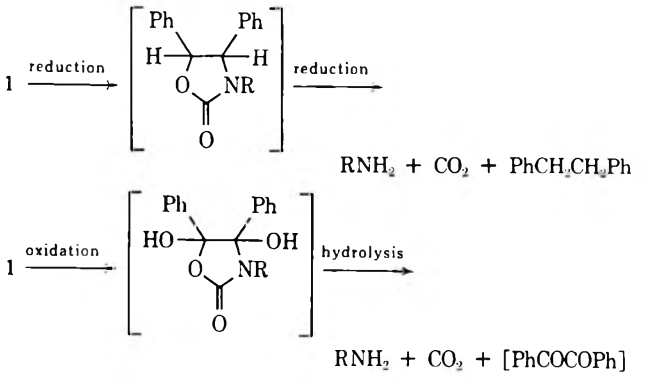


(5) M. Sarttone, *J. Org. Chem.*, **31**, 1959 (1966); K. Auwers and H. Mauss, *Biochem. Z.*, **192**, 200 (1928).

The Ox amino acids are generally high melting crystalline solids. The infrared spectra of Ox derivatives typically exhibit an extremely intense band near 1750 cm^{-1} and a band of moderate intensity near 1370 cm^{-1}, characteristic of the oxazolinone carbonyl.[6a] The nmr spectrum exhibits a characteristic pattern in the aromatic region, a broad singlet or multiplet (5 H) near δ 7.4 and a singlet (5 H) near δ 7.2. The compounds show an intense absorption (ϵ 1.5 × 10^4) in the ultraviolet near 287 nm (EtOH) and are extremely fluorescent upon irradiation with ultraviolet light [excitation (max) 312 nm, emission (max) 395 nm], also characteristic of the 4,5-diphenyl-4-oxazolin-2-ones.[6b]

In an investigation of the stability of Ox derivatives under the normal conditions used in peptide synthesis, Ox-L-Ala was used as a model compound. This derivative was stable to aqueous sodium hydroxide (48 hr at room temperature), hydrazine (2 hr in refluxing ethanol), hydrogen bromide in acetic acid (24 hr at room temperature), trifluoroacetic acid (3 hr at reflux), and anhydrous hydrogen fluoride (3 hr at 20°). In each case recovered yields were greater than 95%, the compounds were homogeneous on thin layer chromatography, and melting point, spectra, and optical rotation remained unchanged.

Although the Ox amino acid derivatives were found to be extremely stable and unreactive under the normal conditions used to remove peptide protecting groups, two possible methods of removal of the Ox protecting group were evident from the oxazolinone structure. The 4,5-diphenyl-4-oxazolin-2-ones could be considered "protected" *N*-carbobenzoxy-*N*-benzylamine derivatives; saturation of the double bond followed by cleavage of the benzyl urethane and benzylamine bonds would free the protected amine. Alternatively, the vinyl oxygen, vinyl nitrogen moieties of the oxazolinone system could be considered as potential carbonyl functions. Oxidation of the oxazolinone to a species equivalent to a dihydroxyoxazolidinone followed by solvolytic cleavage would also remove the protecting group.



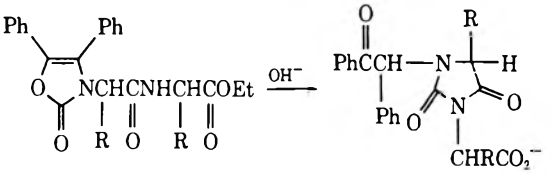
Low-pressure catalytic hydrogenation using 10% palladium-on-charcoal catalyst was found to be the most convenient method of removing the Ox group. Quantitative yields were obtained in the cleavage reaction when the hydrogenations were carried out in ethanol or dimethylformamide containing an equivalent of aqueous acid. In no case could any intermediate hydrogenation product be detected under these conditions, even when the hydrogenation was interrupted prior to completion, suggesting that the slow step in the hydrogenation reaction is the saturation of the oxazolinone double bond. Bibenzyl, the by-product from the reaction, did not interfere with the isolation or characterization of hydrogenation products. When anhydrous solvents were used for the hydrogenation reaction, the cleavage was relatively slow, and small amounts of by-products presumed to be 1,2-diphenylethyl derivatives could be detected by thin layer chromatography during the course of the hydrogenation.

In an alternative reductive procedure the Ox group could be removed from amino acids using sodium in liquid ammonia. Crude products were homogeneous on thin layer chromatography; ion exchange desalting afforded pure amino acids in greater than 70% isolated yield. The main by-product in the reduction was not bibenzyl, but an ether-insoluble material presumed to be a bibenzyl polymer.

Although oxidative removal of amine protecting groups has been limited due to the ready oxidation of a number of amino acids, an amine protecting group removed under very mild oxidative conditions would be very useful in peptide synthesis.[7] Oxidation of the Ox group with 2 equiv of *m*-chloroperbenzoic acid in trifluoroacetic acid cleaves the protecting group in 85% yield. When 1 equiv of the oxidizing agent was used, 52% cleavage of the protecting group was observed along with 40% recovered starting material. Although these oxidative conditions are too vigorous for general use with sensitive amino acids, it is possible that appropriately substituted oxazolinone groups will allow oxidative cleavage under conditions sufficiently mild to be generally useful in peptide synthesis.

Model Ox peptide derivatives could be prepared in good yield using the water-soluble carbodiimide, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride. In contrast to the Ox amino acids which are generally highly crystalline compounds, the Ox peptide derivatives often are difficult to crystallize even when pure. Cleavage of the protecting group followed by hydrolysis afforded pure peptides in good yield. No racemization in peptide couplings could be observed at the 1% level using the "two-spot" chromatographic method for determination of peptide diastereomers.[8]

Alkaline hydrolysis of α-Ox dipeptide esters was hampered by simultaneous hydantoin formation. Although hydantoin formation has been noted in the alkaline hydrolysis of other protected peptide esters,[9] the catalytic nature of the formation of the desyl hydantoin limits the usefulness of Ox protection



(6) (a) R. Gompper and H. Herlinger, *Chem. Ber.*, **89**, 2825 (1956); (b) R. Gompper and H. Herlinger, *ibid.*, **89**, 2816 (1956).

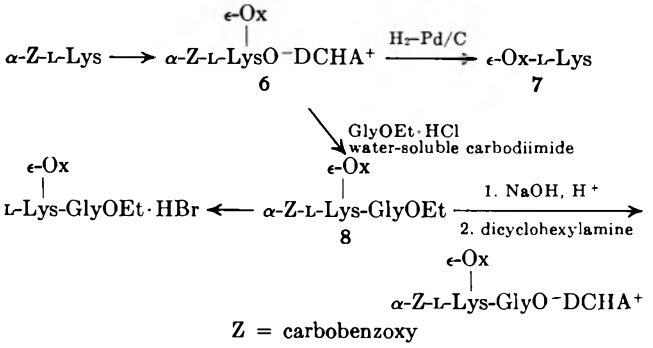
(7) M. Bodanszky and M. Ondetti, "Peptide Synthesis," Interscience, New York, N. Y., 1966, p 32.

(8) E. Taschner, A. Chimiak, J. Biernat, T. Solokowska, Cz. Wasielewski, and B. Rzeszotarksa, "Proceedings of the Fifth European Peptide Symposium, Oxford, 1962," Pergamon Press, Oxford, 1963, p 109.

(9) J. MacLaren, *Aust. J. Chem.*, **11**, 360 (1968).

for α-amino groups in conjunction with protecting groups cleaved with aqueous alkali.

Because the Ox group is extremely stable under conditions used to remove most protecting groups, and because of its fluorescent properties, the protecting group was potentially useful for the protection of the ε-amino function of L-lysine. To investigate this possibility the α-carbobenzoxy-ε-(4,5-diphenyl-4-oxazolin-2-one) derivative of L-lysine (6) was prepared from α-carbobenzoxy-L-lysine in good yield according to the general procedure. This compound could be selectively hydrogenated to ε-(4,5-diphenyl-4-oxazolin-2-one)-L-lysine (7), a potentially useful intermediate for the



preparation of ε-Ox peptide derivatives. The diprotected lysine derivatives could be coupled without difficulty and either the carbobenzoxy or ester groups removed in excellent yield in the presence of Ox protection. Cleavage of the protecting groups under the usual conditions afforded L-lysylglycine hydrochloride in excellent yield.

Experimental Section

General.—Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian T-60 instrument using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as an internal standard. Ultraviolet spectra were determined on a Cary Model 14 spectrophotometer. Optical rotations were measured at 546 and 578 nm on a Zeiss photoelectric precision polarimeter and $[\alpha]_D$ calculated in the usual manner. Elemental analyses were performed by Galbraith Laboratories.

Water-immiscible extracts were washed with saturated NaCl and dried over Na_2SO_4. Benzene was dried over sodium wire. *N,N*-Dimethylaniline was distilled at reduced pressure from a mixture with 2% acetic anhydride, and triethylamine distilled from a mixture with 2% phenyl isocyanate. Thin layer chromatography was performed on fluorescent Baker-Flex silica gel 1B-F plates using the following solvent system: (A) absolute ether; (B) 95% ethanol; (C) 1-butanol–acetic acid–water (3:1:1 v/v); (D) pyridine–1-butanol–water (1:2:2 v/v upper phase). Reduced pressure evaporations were performed on a rotary evaporator. Reactions were run at 25° unless otherwise stated. Typical spectra are reported; all compounds gave satisfactory spectral data.

1,2-Diphenyl-1,2-ethenediol Cyclic Carbonate (4).—Into a cooled (5°) 200-ml three-necked flask, equipped with Dry Ice–acetone condenser, gas-inlet tube, pressure-equalizing dropping funnel, and magnetic stirrer, and charged with a well-stirred suspension of 17.0 g (80 mmol) of benzoin in 100 ml of dry benzene, was distilled 6.4 ml (88 mmol) of liquefied phosgene. To the resulting mixture was added dropwise, over 30 min, 10.2 ml (80 mmol) of distilled *N,N*-dimethylaniline. The mixture slowly was allowed to come to room temperature, stoppered, and stirred in a room temperature water bath overnight. After cooling for a short time in an ice bath, the mixture was filtered from *N,N*-dimethylaniline hydrochloride and the hydrochloride washed with 20 ml of cold benzene. The combined benzene solutions were refluxed 3 hr, cooled to room temperature, consecutively washed with 60 ml 0.5 *N* HCl and 60 ml water, and dried. Removal of solvent under reduced pressure gave a pale yellow oil which crystallized from a minimum of warm 95% ethanol upon scratching. The crude carbonate was recrystallized from ethanol, affording 12.5 g (66%) of the cyclic carbonate: mp 75–76°; ir (CCl_4) 1870, 1840 (sh), 1820 cm^{-1}; nmr (CCl_4) δ 7.45 (m); mass spectrum molecular ion *m/e* 238. A 0.5-mol scale reaction required mechanical stirring; 400 ml of dry benzene was used and *N,N*-dimethylaniline added over 1 hr. The per cent yield was comparable to the small-scale reaction. The pure cyclic carbonate is stable indefinitely at room temperature.

Anal. Calcd. for $C_{15}H_{10}O_3$: C, 75.62; H, 4.23. Found: C, 75.62; H, 4.09.

A small amount of desyl chloride generally contaminates the crude isolated carbonate: mp 66–67° [lit.[10] 66–67°]; ir (CCl_4) 1705, 1690 cm^{-1}; nmr (CCl_4) δ 8.07 (d, 1 H), 7.94 (d, 1 H), 7.61–7.24 (m, 8 H), 6.14 (s, 1 H). This by-product occasionally becomes the main product of the reaction unless *N,N*-dimethylaniline hydrochloride is removed from the mixture prior to refluxing.

4,5-Diphenyl-4-oxazolin-2-one Derivative of L-Phenylalanine,[11] Ox-L-Phe. General Procedure.—A mixture of 3.30 g (20 mmol) of L-phenylalanine and 6.52 g (20 mmol) of tetramethylammonium hydroxide solution (Aldrich, 27.9% in methanol, by titration) was evaporated on a rotary evaporator under reduced pressure. The residual oil was twice taken up in absolute ethanol (20 ml) and solvent removed under reduced pressure, yielding the amino acid tetramethylammonium salt as a colorless solid. The salt was taken up in 20 ml of dimethylformamide and the stirred suspension treated with 4.76 (20 mmol) of 1,2-diphenyl-1,2-ethenediol cyclic carbonate, giving an intense yellow color which rapidly faded. At 30 min the mixture was acidified with 20 ml 2 *N* HCl, diluted with 100 ml of ethyl acetate, washed with water (3 × 75 ml), and dried. Removal of solvent under reduced pressure afforded the hydroxyoxazolidinone as a pale yellow foam.

The foam was taken up in 20 ml of trifluoroacetic acid and allowed to stand 2 hr at room temperature, at which time most of the trifluoroacetic acid was removed at room temperature under reduced pressure. The residue was taken up in 75 ml of methylene chloride, washed with water (3 × 30 ml), and dried. Removal of solvent under reduced pressure afforded a colorless fluorescent solid which was recrystallized from ethyl acetate–pentane, yielding 6.45 g (84%) of the oxazolinone derivative as colorless crystals: mp 196–197° (sublimes); ir (KBr) 1755, 1710, 1380 cm^{-1}; nmr ($CDCl_4$) δ 11.05 (s, 1 H), 7.46–6.59 (m, 15 H), 4.33–3.14 (m, 3 H); $[\alpha]^{25}D$ −176° (*c* 1.02, MeOH); uv (95% EtOH) λ_{max} 286 nm (ε 1.5 × 10); fluorescence spectrum (absolute EtOH) excitation (max) 312 nm, emission (max) 392 nm (at 312 nm).

Anal. Calcd. for $C_{24}H_{19}NO_4$: C, 74.79; H, 4.97; N, 3.63. Found: C, 75.07; H, 5.06; N, 3.40.

α-Phenylphenacyl [Bis(dimethylamino)methylene]carbamate (5).—To a stirred solution of 2.4 g (10 mmol) of 1,2-diphenyl-1,2-ethenediol cyclic carbonate (4) in 30 ml of dimethyl sulfoxide was added 1.2 g (10 mmol) of distilled 1,1,3,3-tetramethylguanidine. After stirring for 1 hr, the reaction mixture was diluted with 70 ml of ethyl acetate, washed with water (3 × 35 ml), and dried. Removal of solvent under reduced pressure and recrystallization of the colorless solid residue from carbon tetrachloride afforded 2.2 g (61%) of **5** as colorless crystals: mp 117–119°; ir (KBr) 1690, 1685 (sh), 1650, 1640 (sh) cm^{-1}; nmr ($CDCl_3$) δ 8.13 (d, 1 H), 8.02 (d, 1 H), 7.72–7.23 (m, 8 H), 6.73 (s, 1 H), 2.84 (s, 12 H). An analytical sample melted at 118–119°. The yield of **5** was 50% using dimethylformamide as a solvent.

Anal. Calcd for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 68.05; H, 6.59; N, 12.00.

4,5-Diphenyl-4-oxazolin-2-one Derivative of 2-Phenethylamine.—To a stirred solution of 6.1 g (50 mmol) of 2-phenethylamine in 40 ml of dimethylformamide was added 11.9 g (50 mmol) of 1,2-diphenyl-1,2-ethenediol cyclic carbonate (4). After 1 hr

(10) A. Ward, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1959, p 159.

(11) Alternatively, *N*-carboxy-*N*-(2-hydroxy-1,2-diphenylvinyl)-L-phenylalanine γ-lactone.

the solution was diluted with 75 ml of ethyl acetate, consecutively washed with 40 ml of 0.5 *N* HCl and 80 ml of distilled water, and dried. After removal of solvent under reduced pressure, the residual yellow oil was taken up in 50 ml of trifluoroacetic acid and allowed to stand 2 hr. After removal of most of the solvent under reduced pressure at room temperature, the residue was taken up in 125 ml of methylene chloride, consecutively washed with water (2 × 50 ml) and 0.5 *N* NaOH (30 ml), and dried. Removal of solvent under reduced pressure and trituration of the residual oil with petroleum ether afforded a slightly yellow solid which was recrystallized from 95% ethanol, affording 13.5 g (79%) of the oxazolinone as colorless plates: mp 121–122°; ir ($CHCl_3$) 1735, 1355 cm^{-1}; nmr ($CDCl_3$) δ 7.55–6.83 (m, 15 H), 3.64 (m, 2 H), 2.78 (m, 2 H); uv (95% EtOH) λ_{max} 288 nm (ϵ 1.5 × 10^4); fluorescence spectrum (absolute EtOH) excitation (max) 316 nm, emission (max) 399 nm (at 316 nm). An analytical sample melted at 123.5–124.5°.

Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.10. Found: C, 81.16; H, 5.61; N, 3.92.

Investigation of the Stability of 4,5-Diphenyl-4-oxazolin-2-one Derivatives. A. In 1 *N* NaOH.—A solution of 618 mg of (2 mmol) Ox-L-Ala was dissolved in 10 ml of 1 *N* NaOH and allowed to stand at room temperature for 48 hr. The mixture was acidified with 8 ml of 2 *N* HCl and extracted with ethyl acetate (3 × 10 ml); the combined extracts were dried. Removal of solvent under reduced pressure afforded 610 mg (99%) of the starting oxazolinone, mp 201–202°, $[\alpha]^{26}D$ −31.6° (*c* 1.03, MeOH). The infrared spectrum was identical with the starting material's, spectrum and a single spot was observed on thin layer chromatography (B, C, D).

B. Upon Treatment with Hydrazine.—A solution of 618 mg (2 mmol) of Ox-L-Ala and 400 mg (8 mmol) of hydrazine hydrate in 20 ml of 95% ethanol was refluxed for 2 hr. The colorless mixture was cooled to room temperature, most of the ethanol removed under reduced pressure, the residue taken up in a mixture of 25 ml of ether and 20 ml of 1 *N* HCl, and the ether layer washed with 20 ml of 0.5 *N* HCl and dried. Removal of the solvent under reduced pressure afforded 589 mg (95%) of the starting oxazolinone as a colorless solid which turned slightly yellow on standing, mp 201–203°, $[\alpha]^{26}D$ −30.0° (*c* 0.88, MeOH). The material was homogeneous on tlc and had an infrared spectrum identical with that of the starting material.

C. Upon Treatment with Mineral Acids.—A solution of 618 mg (2 mmol) of Ox-L-Ala in 15 g of 45% HBr in acetic acid was stirred overnight at room temperature, protected by a calcium chloride drying tube. The mixture was diluted with 150 ml of absolute ether and cooled to 0° for 1 hr. When no cloudiness appeared, the mixture was washed with water (3 × 100 ml) and dried; the solvent was removed under reduced pressure, yielding 583 mg (94%) of the starting oxazolinone as a slightly yellow solid, mp 202–203°, $[\alpha]^{27}D$ −31.9° (*c* 0.97, MeOH), homogeneous on tlc, and with unchanged infrared spectrum.

D. In Refluxing Trifluoroacetic Acid.—A solution of 618 mg (2 mmol) of Ox-L-Ala in 5 ml of trifluoroacetic acid was refluxed 3 hr, protected by a drying tube. The colorless solution was cooled, the solvent removed under reduced pressure, and the residual oil triturated with ethyl acetate–petroleum ether affording 607 mg (98%) of the oxazolinone as colorless crystals, mp 202–203°, $[\alpha]^{26}D$ −31.6° (*c* 0.97, MeOH), homogeneous on tlc, and with unchanged infrared spectrum.

E. In Anhydrous Liquid Hydrogen Fluoride.—A solution of 309 mg (1 mmol) of Ox-L-Ala in 15 ml of liquid hydrogen fluoride was stirred for 2 hr at 20° in a polypropylene reaction vessel, at which time the colorless solution was allowed to evaporate at room temperature, affording colorless crystals of the oxazolinone. This residue was taken up in 20 ml of ether, washed with water (2 × 20 ml), and dried. Removal of the solvent under reduced pressure afforded 294 mg (95%) of the starting oxazolinone, mp 201–203°, $[\alpha]^{26}D$ −31.7° (*c* 0.91, MeOH), homogeneous on tlc, and with unchanged infrared spectrum.

Removal of the 4,5-Diphenyl-4-oxazolin-2-one Group. A. By Hydrogenation.—A mixture of 100 mg of 10% palladium on charcoal moistened with 1.00 ml of 2 *N* HCl and 618 mg (2 mmol) of Ox-L-Ala in 20 ml of absolute ethanol was hydrogenated overnight in a low-pressure hydrogenation apparatus (reaction vessel thoroughly cleaned with warm nitric acid) at 35 psi. When no fluorescent material was noted on thin layer chromatography (B,C,D), the mixture was filtered through Celite, the Celite washed with a small amount of 95% ethanol, and the filtrate evaporated under reduced pressure. The residue was taken up in a minimum of absolute ethanol and absolute ether added to precipitate L-alanine hydrochloride: 238 mg (95%); ir (KBr) 1730 (sh), 1720; nmr (D_2O) δ 4.17 (q, 2 H), 1.58 (d, 3 H). The hydrochloride was converted into the free amino acid either by ion-exchange desalting on a 50W-X8 column or by treating a warm solution of the hydrochloride in absolute ethanol with excess pyridine and cooling. The resulting amino acid was chromatographically pure (B,C,D) and was identical with authentic L-alanine (ir, nmr, optical rotation).

Evaporation of the ethanol–ether filtrate, trituration of the residual oil with a small amount of warm 95% ethanol, and cooling afforded 336 mg (92%) of bibenzyl as colorless crystals: mp 51.5–52° [lit.[12] 52°]; ir ($CHCl_3$) 1600 cm^{-1}; nmr (CCl_4) δ 7.09 (s, 10 H), 2.82 (s, 4 H). Hydrogenations also proceeded without difficulty using purified dimethylformamide with a slight excess of aqueous acid as a solvent.

B. By Sodium in Liquid Ammonia Reduction.—To a solution of 927 mg (3 mmol) of Ox-L-Ala in 100 ml of liquid ammonia (redistilled from sodium) was added, in small portions, metallic sodium (*ca.* 520 mg, 23 mmol) until a distinct blue color persisted for 1 min. The excess sodium was destroyed by addition of solid NH_4Cl, and the ammonia allowed to evaporate at room temperature. The solid residue was taken up in a mixture of 30 ml of ether and 30 ml of 0.5 *N* HCl; a slightly yellow residue remained. The aqueous extract was separated and exhibited a single ninhydrin active spot on tlc (B,C,D). Ion-exchange desalting afforded 201 mg (75%) of L-alanine as a colorless solid, identical with authentic L-alanine (ir, optical rotation, homogeneous on tlc). The yellow residue from the reduction exhibited an intense, very broad, infrared absorption near 1590 cm^{-1} (film deposited with $CHCl_3$).

C. By Oxidation.—To a solution of 1.36 g (4.0 mmol) of the Ox derivative of 2-phenethylamine in a mixture of 1.00 g (8.8 mmol) of trifluoroacetic acid and 10 ml of methylene chloride was added dropwise over 10 min 0.75 g (4.0 mmol) of *m*-chloroperbenzoic acid (92% by titration)[13] in 20 ml of methylene chloride, and the reaction was allowed to proceed overnight. The mixture, negative to KI–starch, was evaporated to dryness under reduced pressure, and the residue taken up in 8 ml of 1 *N* ethanolic HCl. Upon addition of absolute ether a colorless solid separated. Filtration afforded 0.25 g (52%) of phenethylamine hydrochloride, ir (KBr) 1600, 1480 (sh), 1415, 1455 cm^{-1} (identical with the authentic hydrochloride). The filtrate was evaporated to dryness under reduced pressure, the residue taken up in 25 ml of ether, washed with 0.5 *N* $NaHCO_3$, and dried, and the solvent removed under reduced pressure. Crystallization of the residue from ethanol–water with seeding afforded 0.54 g (40%) of the starting oxazolinone, mp 120–122°.

Oxidation of Ox-L-Ala (1.54 g, 5 mmol) with a twofold excess of the peracid in 10 ml of trifluoroacetic acid and similar work-up afforded 0.54 g (85%) of the amino acid, isolated as the hydrochloride.

Attempted oxidations without added trifluoroacetic acid led to mixtures of amine oxidation products.

The Coupling of 4,5-Diphenyl-4-oxazolin-2-one Derivatives of Amino Acids, Ox-L-Ala-Gly-OEt.—To a cooled (0°) stirred mixture of Ox-L-Ala (2.78 g, 10 mmol), glycine ethyl ester hydrochloride (1.40 g, 10 mmol), and purified triethylamine (1.40 g, 10 mmol) in 30 ml of methylene chloride was added 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride[14] (1.92 g, 10 mmol). The mixture was stirred at 0° for 1 hr and allowed to come to room temperature over 2 hr. The solvent was removed under reduced pressure, and the residue taken up in a mixture of 30 ml of ethyl acetate and 30 ml of water. The organic layer was consecutively washed with excess 1 *N* HCl, water, 0.5 *N* $NaHCO_3$, and water, and dried. Removal of solvent under reduced pressure yielded a colorless oil which was crystallized from ethyl acetate–pentane, affording the protected dipeptide as colorless plates: 3.17 g (81%), mp 129.5–130°; ir ($CHCl_3$) 1750, 1735 (sh), 1680, 1385 cm^{-1}; nmr ($CDCl_3$) δ 7.52 (s, 5 H), 7.47 (br s, 1 H), 7.23 (s, 5 H), 4.51–4.02 (m, 5 H), 1.58 (d, 3 H), 1.24 (t, 3 H); $[\alpha]^{26}D$ +3.4° (*c* 0.99, MeOH).

Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 67.16; H, 5.66; N, 6.92.

(12) R. Shriner and R. Fuson, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1964, p 358.

(13) D. Swern, "Organic Peroxides," Vol. 1, Wiley-Interscience, New York, N. Y., 1970, p 498.

(14) J. C. Sheehan and P. Cruickshank, *Org. Syn.*, **48**, 83 (1968).

The following were prepared analogously.

1. **Ox-Val-L-Val-OMe.**—Recrystallization from ether–pentane (seeded with material which spontaneously crystallized) afforded the protected compound as colorless crystals in 75% yield: mp 67–68°; ir (KBr) 1735, 1715 (sh), 1675, 1360 cm^{-1}; the nmr was consistent with the proposed structure.

Anal. Calcd for $C_{26}H_{30}N_2O_5$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.14; H, 6.77; N, 5.97.

2. **Ox-L-Phe-Gly-OEt.**—The compound was obtained as a colorless foam in 82% yield: ir (CCl_4) 1755, 1730 (sh), 1680, 1375, 1365 cm^{-1}; the nmr was consistent with the proposed structure; the compound was homogeneous on tlc (A,B).

3. **Ox-L-Phe-L-Val-OMe.**—The compound was obtained as a colorless foam in 84% yield: ir (CCl_4) 1760, 1740, 1680, 1360 cm^{-1}; the nmr was consistent with the proposed structure; the compound was homogeneous on tlc (A,B).

4. **Ox-L-Ser-L-Ser-OMe.**—The compound was obtained as a colorless oil in 80% yield: ir ($CHCl_3$) 1745, 1725 (sh), 1690, 1370 cm^{-1}; the nmr was consistent with the proposed structure; the compound was homogeneous on tlc (A,B,C).

Alkaline Hydrolysis of Ox Dipeptide Derivatives.—To a solution of 1.97 g (5 mmol) of Ox-L-Ala-Gly-OEt in 25 ml of dioxane (distilled from $LiAlH_4$) was added 5.5 ml of 1.0 *N* NaOH. The solution immediately turned bright yellow. After 1 hr the mixture was diluted with 100 ml of water and extracted with ether (3 × 25 ml); the aqueous solution was acidified to pH 1 with 2 *N* HCl. Extraction with ether (3 × 30 ml), drying, and solvent removal afforded a yellow oil: ir ($CHCl_3$) 1770, 1745, 1720 cm^{-1}; nmr ($CDCl_3$) δ 8.2–7.8 (m, 2 H), 7.6–7.2 (m, 8 H), 6.9 (d, 1 H), 4.7–4.3 (m, 2 H), 1.8–0.7 (m, 3 H); consistent with a desyl hydantoin structure.

Removal of the Protecting Group from Peptide Esters. L-Valyl-L-valine.—A mixture of 1.8 g (4 mmol) of Ox-L-Val-L-Val-OMe in 45 ml of absolute methanol, and 400 mg of 10% palladium on charcoal moistened with 2.0 ml of 2.0 *N* HCl was hydrogenated at 30 psi overnight. The mixture was filtered through Celite, 10 ml of 1 *N* NaOH added, and the solution allowed to stand 30 min at room temperature. Removal of methanol under reduced pressure, extraction with ether (3 × 5 ml), and desalting of the aqueous solution on IRC-50 (NH_4^+) and 50 W-X8 (H^+) columns followed by removal of water under reduced pressure afforded the crude peptide as a colorless solid. Recrystallization from aqueous acetone afforded 0.71 g (82%) of the peptide as colorless crystals: mp 271–274° dec [lit.[15] 250–260°]; $[\alpha]^{25}D$ +14.9° (*c* 0.98, 1 *N* HCl) [lit.[15] $[\alpha]^{20}D$ +15.1° (*c* 1.0, 1 *N* HCl)]; homogeneous on tlc (C,D).

The following were prepared analogously.

1. **L-Alanylglycine.**—Recrystallization from water–ethanol afforded colorless crystals of the peptide in 86% yield mp 230–231° dec [lit.[16] 230–231.5° dec]; $[\alpha]^{24}D$ +50.7° (*c* 2.03, H_2O) [lit.[16] $[\alpha]^{21}D$ +50.9° (*c* 2.0, H_2O)]; homogeneous on tlc (C,D).

2. **L-Phenylalanylglycine.**—Recrystallization from water–acetone afforded slightly yellow crystals of the peptide in 76% yield: mp 259–261° [lit.[15] 258–262°]; $[\alpha]^{26}D$ +99.2° (*c* 2.0, H_2O) [lit.[15] $[\alpha]^{20}D$ +99.8° (*c* 2.0, H_2O)].

3. **L-Phenylalanyl-L-valine.**—Recrystallization from water–acetone afforded colorless crystals of the peptide in 83% yield: mp 260–262° dec [lit.[17] 256–258°]; $[\alpha]^{25}D$ +16.8° (*c* 1.0, 1 *N* HCl) [lit.[17] $[\alpha]^{25}D$ +16.8° (*c* 1.0, 1 *N* HCl)].

Test for Racemization. The "Two-Spot Method."[8]—Two samples of L-phenylalanyl-L-valine, prepared in the usual manner using the water-soluble carbodiimide and either Ox or carbobenzoxy amine protection, and a sample consisting of the LL and DL peptides prepared from DL-carbobenzoxyphenylalanine in the usual manner were chromatographed on Whatman No. 1 chromatography paper using two solvent systems: S_1, ethyl acetate–pyridine–acetic acid–water (5:5:1:3), and S_2, pyridine–water (4:1). The spots were visualized with ninhydrin. The LL-dipeptides gave single spots in each solvent system (S_1, R_f 0.87; S_2, R_f 0.68) even when 100-μg samples were chromatographed (slight tailing). A 2-μg sample of the diastereomeric mixture exhibited a double spot (S_1, R_f 0.87, 0.75; S_2, R_f 0.68, 0.57) suggesting that less than 1% racemization occurred upon coupling of the Ox group using water-soluble carbodiimide.

(15) D. Stevenson and G. Young, *J. Chem. Soc. C*, 2389 (1969).

(16) F. Stewart, *Aust. J. Chem.*, **19**, 1067 (1966).

(17) E. Schnabel, H. Klustermeyer, J. Dahlmans, and H. Zahn, *Justus Liebigs Ann. Chem.*, **707**, 227 (1967).

ε-(4,5-Diphenyl-4-oxazolin-2-one) Derivative of α-Carbobenzoxy-L-lysine Dicyclohexylammonium Salt, ε-Ox-α-Z-L-Lys·DCHA (6).—The compound was prepared according to the general procedure on a 30-mmol scale from α-carbobenzoxy-L-lysine,[18] yielding a colorless oil which could not be crystallized. The oil was taken up in 10 ml of warm absolute ethanol and treated with 5.43 g (30 mmol) of dicyclohexylamine in 20 ml of absolute ether. Absolute ether was added until the solution grew cloudy, and the mixture was scratched until the salt crystallized. Crystallization in two crops afforded 16.7 g (81.6%) as colorless fluorescent rosettes: mp 147–149°; ir (KBr) 1745, 1700, 1625, 1370 cm^{-1}; nmr ($CDCl_3$) δ 7.57 (m, 5 H), 7.40 (s, 5 H), 7.27 (s, 5 H), 5.75 (d, 1 H), 5.13 (s, 2 H), 4.09–3.68 (m, 1 H), 3.58–2.57 (m, 4 H), 2.15–0.76 (m, 28 H); $[\alpha]^{26}D$ +4.5° (*c* 1.08, MeOH). An analytical sample melted at 151–152°, $[\alpha]^{26}D$ +4.5° (*c* 1.03, MeOH).

Anal. Calcd for $C_{41}H_{51}N_2O_6$: C, 75.22; H. 7.54; N, 6.16. Found: C, 72.31; H, 7.60; N, 6.20.

ε-(4,5-Diphenyl-4-oxazolin-2-one) Derivative of L-Lysine Hydrate, ε-Ox-L-Lys·H_2O (7).—A solution of 1.366 g (2 mmol) of ε-Ox-α-Z-L-Lys·DCHA (6) was hydrogenated at atmospheric pressure in 50 ml of 95% ethanol containing 1 ml of acetic acid using 137 mg of 10% palladium-on-charcoal catalyst. At 1.5 hr tlc (B,C) indicated a single fluorescent spot, which was ninhydrin active. The mixture was filtered through Celite (Celite washed with small amount of 95% ethanol) and the solvent removed under reduced pressure yielding a colorless oil which crystallized under trituration with ethanol–water. The solid was dissolved in 20 ml of 2 *N* NH_4OH and extracted with ethyl acetate (3 × 10 ml), the aqueous solution evaporated under reduced pressure, and the colorless residue recrystallized from ethanol–water in two crops, affording 707 mg (92.5%) ε-Ox-L-Lys·H_2O (7): mp 172–174° dec; ir (KBr) 1745, 1730 (sh), 1630 cm^{-1}; nmr (TFA) δ 7.62 (m, 5 H), 7.49 (br s, 5 H), 7.33 (s, 5 H), 4.68–4.21 (m, 1 H), 4.02–3.44 (m, 2 H), 2.46–2.0 (m, 2 H), 2.0–1.36 (m, 4 H); $[\alpha]^{25}D$ +11.8° (*c* 0.96, 1 *N* HCl).

Anal. Calcd for $C_{21}H_{24}N_2O_5$: C, 65.61; H, 6.29; N, 7.29. Found: C, 65.71; H, 6.08; N, 7.14.

α-Carbobenzoxy-ε-(4,5-diphenyl-4-oxazolin-2-one)-L-lysylglycine Ethyl Ester, α-Z-ε-Ox-L-Lys-Gly-OEt (8).—A mixture of finely powdered α-carbobenzoxy-ε-(4,5-diphenyl-4-oxazolin-2-one)-L-lysine dicyclohexylammonium salt (6) (6.82 g, 10 mmol), 30 ml 4 *N* HCl, and 30 ml of ethyl acetate was vigorously shaken in a separatory funnel until homogeneous. The organic phase was dried and evaporated under reduced pressure and the coupling performed as usual using the water-soluble carbodiimide. Recrystallization of the oily residue from ethyl acetate–pentane in two crops afforded 4.7 g (80%) of the protected peptide ester as colorless crystals: mp 112–113°; ir (KBr) 1740, 1725 (sh), 1715 (sh), 1680, 1640 cm^{-1}; nmr ($CDCl_3$) δ 7.44 (m, 5 H), 7.33 (s, 5 H), 7.23 (s, 5 H), 6.82 (t, 1 H), 5.62 (d, 1 H), 5.08 (s, 2 H), 4.35–3.87 (m, 5 H), 3.43 (m, 2 H), 2.00–1.08 (m, 9 H); $[\alpha]^{25}D$ −9.1° (*c* 0.99, MeOH).

Anal. Calcd for $C_{33}H_{35}N_3O_7$: C, 67.68; H, 6.02; N, 7.18. Found: C, 67.48; H, 6.03; N, 7.08.

α-Carbobenzoxy-ε-(4,5-diphenyl-4-oxazolin-2-one)-L-lysylglycine Dicyclohexylammonium Salt.—Hydrolysis of crude 8 in dioxane with 1 *N* NaOH in the usual manner afforded a colorless oil which could not be crystallized. The oil was taken up in a minimum of warm absolute ethanol and treated with 1.6 g of dicyclohexylamine in 20 ml of absolute ether; ether was added until the mixture turned cloudy. The salt crystallized in two crops totaling 2.5 g (68% overall), as colorless crystals: mp 146–148°; ir (KBr) 1745, 1715, 1665 (sh), 1630 cm^{-1}; nmr consistent with proposed structure; $[\alpha]^{25}D$ −8.2° (*c* 1.02, MeOH).

Anal. Calcd for $C_{43}H_{54}N_4O_7$: C, 69.90; H, 7.37; N, 7.58. Found: C, 69.76; H, 7.29; N, 7.42.

ε-Ox-L-Lys-Gly-OEt·HBr.—Treatment of 1.17 g (2 mmol) of 8 with 5 ml of 45% hydrogen bromide in acetic acid over 2 hr followed by addition of absolute ether (60 ml) afforded the crude hydrobromide as a hygroscopic, slightly yellow gum: ir ($CHCl_3$) 1740, 1690, 1375 cm^{-1}; nmr consistent with the proposed structure

L-Lysylglycine Hydrochloride.—Hydrogenation of a crude α-carbobenzoxy-ε-(4,5-diphenyl-4-oxazolin-2-one)-L-lysylglycine

(18) B. Bezas and L. Zervas, *J. Amer. Chem. Soc.*, **83**, 719 (1961).

(551 mg, 1 mmol) in 20 ml of dimethylformamide containing 1.1 ml of 2 *N* HCl over 100 mg of 10% palladium-on-charcoal catalyst, filtration through Celite, and removal of solvent under reduced pressure afforded a colorless solid which was treated with 3 ml of 1 *N* ethanolic HCl, and filtered. The filtrate was immediately treated with 5 ml of pyridine and cooled. The crude peptide hydrochloride separated as an amorphous solid which crystallized from water–methanol in two crops totaling 201 mg (88%): homogeneous on tlc (C,D); $[\alpha]^{25}D$ +69.1° (*c* 1.06, H_2O) [lit.[15] $[\alpha]^{20}D$ +69.5° (*c* 1.0, H_2O)].

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Registry No.—**4**, 21240-34-6; **5**, 40719-46-8; **7**, 40719-47-9; **8**, 40719-48-0; benzoin, 119-53-9; desyl chloride, 447-31-4; tetramethylammonium hydroxide, 75-59-2; 1,1,3,3-tetramethylguanidine, 80-70-6; 2-phenethylamine 4,5-diphenyl-4-oxazolin-2-one derivative, 37628-64-1; 2-phenethylamine, 64-04-0; Ox-L-Ala-Gly-OEt, 37628-68-5; glycine ethyl ester hydrochloride, 623-33-6; 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride, 25952-53-8; Ox-L-Val-L-Val-OMe, 40719-51-5; Ox-L-Phe-Gly-OEt, 40719-52-6; Ox-L-Phe-L-Val-OMe, 40719-53-7; Ox-L-Ser-L-Ser-OMe, 40719-54-8; Ox-L-Ala-Gly-OEt hydrolysis derivative, 40719-55-9; L-valyl-L-valine, 3918-94-3; L-alanylglycine, 687-69-4; L-phenylalanylglycine, 721-90-4; L-phenylalanyl-L-valine, 3918-90-9; α-carbobenzoxy-L-lysine, 2212-75-1; dicyclohexylamine, 101-83-7; α-carbobenzoxy-ε-Ox-L-lysylglycine dicyclohexylammonium salt, 40719-56-0; ε-Ox-L-Lys-Gly-OEt·HBr, 40719-57-1; L-lysylglycine hydrochloride, 40719-58-2.

15-Oxa Steroids

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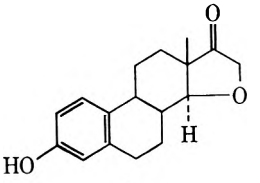
The preparation of the 15-oxa steroid **29** is described, using the half-ester 3β-acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic acid 17-methyl ester (**5b**) as starting material. Treatment of **5b** with lead tetraacetate affords the diacetate **9** which upon hydrolysis and reacetylation gave the acid **26**. Conversion to the diazo ketone **28** followed by treatment with boron trifluoride causes spontaneous ring closure to give 3β-hydroxy-15-oxa-5α-androstan-17-one (**29**). Its conversion to 15-oxaestrone (**1**) is described.

The steroid nucleus has over the past number of years undergone numerous structural modifications in an attempt to bring about an increase in biological activity as well as attempting to control or minimize undesirable side effects. One such modification is the insertion of an oxygen atom in place of a methylene group. This type of transformation has in several cases produced derivatives possessing interesting biological properties.[1] A review of the publications in this field reveals that the introduction of an oxygen atom into the steroid nucleus has produced synthetic modifications which can be generally classified into two main categories. The first of these is the formation of a lactone *via* an oxygen insertion α to a keto group.[2-4] This type of transformation would be expected to alter considerably the chemical nature of the original carbonyl function.

In the second category, the oxa steroid takes the form of a cyclic ether. In this class of compounds the heteroatom takes the place of a carbon atom in a position which is known to effect greatly the biological activity of the parent steroid, *e.g.*, C-11, C-17.[5,6]

The aim therefore of this present work was to prepare an oxa steroid in such a manner so as to (1) not compromise the functionality of the original carbonyl groups, and (2) replace a methylene for an oxygen atom while at the same time not affecting those positions which are known to be essential for biological activity. Such a compound is represented by structure **1**.



1

The starting material in our synthesis was 3β-hydroxy-16,17-seco-16-nor-5α-androstan-15-(2′-indoxyliden)-17-oic acid (**3**) which was obtained from the reaction of 3β-hydroxy-5α-androstan-17-one (**2**) with *o*-nitrobenzaldehyde.[7] Esterification and acetylation of **3** afforded **4b** which has been reported to give 3β-acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic acid 17-methyl ester (**5b**) when oxidized with chromium trioxide in acetic acid[3,8] (Scheme I).

We have found that the chromium trioxide oxidation of **4b** produced an acid whose melting point of 152–158° differed sharply from the reported figure of 204°[3] but was in fact consistent with a second reported value of 158–160°.[8] As a means of verifying structure **4**, and the acid ester obtained from its oxidation with chromium trioxide, a reductive ozonization was carried out which produced the aldehyde **6** in high yield. The nmr confirmed both the secondary nature of the aldehydic group and the axial conformation of the C-14 proton: δ 9.72 (d, 1, J = 3.5 Hz, CHO), 2.58 (d of d, 1, J = 3.5, 11 Hz, C-14 H). Furthermore, chromium trioxide oxidation of the alde-

(1) (a) S. D. Levine, *J. Med. Chem.*, **8**, 537 (1965); (b) R. Pappo and C. J. Jung, *Tetrahedron Lett.*, 365 (1962); (c) H. D. Lennon and F. J. Saunders, *Steroids*, **4** (1964).

(2) R. W. Kierstead and A. Farone, *J. Org. Chem.*, **32**, 704 (1967).

(3) A. K. Banerjee and M. Gut, *J. Org. Chem.*, **34**, 1614 (1969).

(4) C. C. Bolt, *Recl. Trav. Chim. Pays-Bas*, **70**, 940 (1957).

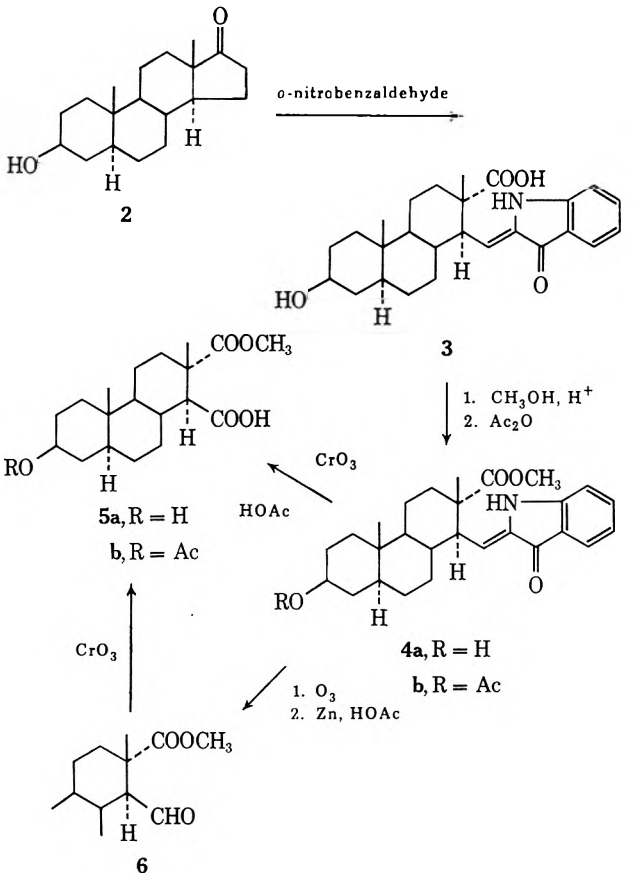
(5) S. Rakhit and M. Gut, *J. Org. Chem.*, **29**, 229 (1964).

(6) Ch. R. Engel and M. V. R. Chowdhury, *Tetrahedron Lett.*, 2107 (1968).

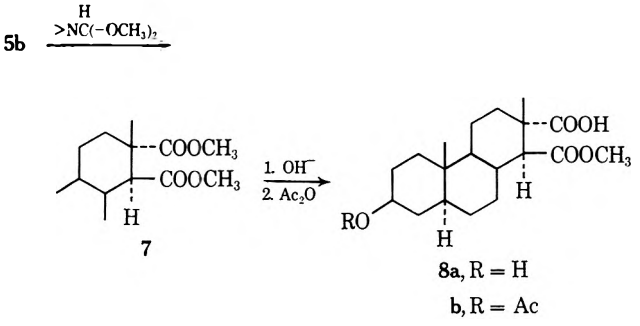
(7) A. Hassner, M. J. Haddadin, and P. Catsoulacos, *J. Org. Chem.*, **31**, 1363 (1966).

(8) M. Fetizon and N. Moreau, *Bull. Soc. Chim. Fr.*, 4385 (1969).

Scheme I

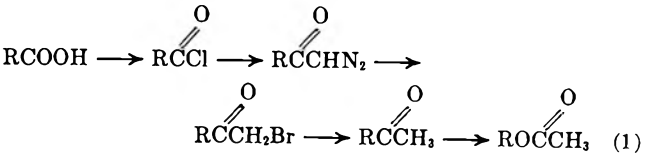


hyde **6** afforded the same acid ester **5b** (mp 160°)[8] which we had obtained directly from the oxidation of **4b**: δ 3.65 (s, 3, $COOCH_3$). Esterification of **5b** with the dimethyl acetal of dimethylformamide produced the dimethyl ester **7** which, after partial hydrolysis and reacetylation of the 3β-hydroxyl group, gave a monoester derivative with a melting point (204°) corresponding to that previously reported[3] for **5b**: δ 3.60 (s, 3, $=COOCH_3$). This material was found to be identical with a sample previously assigned structure **5b**.[9] The nmr spectrum of a mixture of the two acid esters showed two distinct methoxyl peaks: δ 3.59, 3.65. Since it would be generally safe to assume that the hydrolysis of a secondary ester should take place with greater facility than a tertiary ester, the

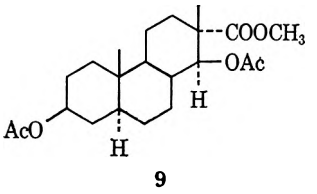


partial hydrolysis of **7** would have been expected to give rise to **5a** rather than the isomeric derivative **8a**.

(9) Kindly supplied by Dr. M. Gut, The Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

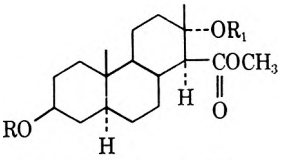


Using a multistep sequence of reactions (1), the degradation of the acid ester (mp 204°) has previously been carried out and reported to give a diacetate represented by formula **9**.[10]



9

This procedure was repeated using the acid ester which we had obtained from the partial hydrolysis of dimethyl ester **7**, and the physical properties of the product obtained were found to be identical with those of a sample previously assigned structure **9**.[9] Inspection of the nmr, however, reveals a broad multiplet at δ 4.8 (1, C-3 H) and a doublet at 2.85 (1, J = 10 Hz, C-14 H). Although the coupling constant is consistent with a C-14 axial hydrogen, the observed chemical shift presumably due to the presence of an acetoxy group at C-14 is much further upfield than one would have anticipated. The nmr would, however, be consistent with the isomeric diacetoxy compound **10a**.



10a, R = R_1 = $COCH_3$
b, R = $COCH_3$; R_1 = H
c, R = R_1 = H

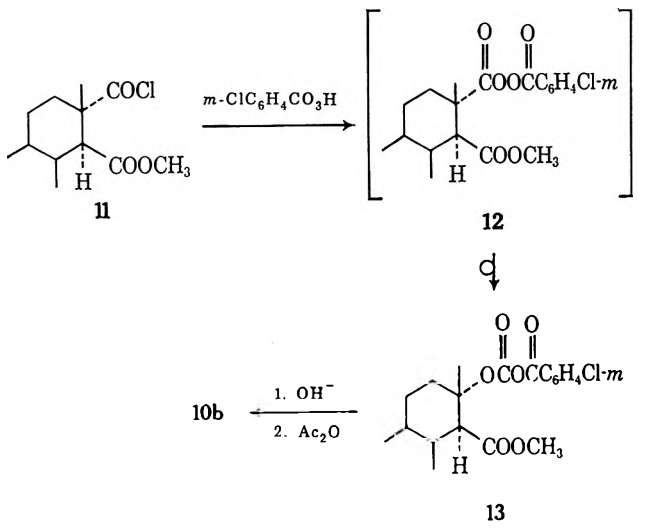
Since the conversion to the diacetate was a multistep process, we attempted to degrade the same acid chloride to the acetate by a carboxy-inversion reaction.[11] It has been found that mixed peroxides derived from *m*-chloroperbenzoic acid rearrange to the mixed carbonate which can then be hydrolyzed to the alcohol.

Using this procedure we were able to obtain (after acetylation) a 55% yield of a monoalcohol whose nmr reveals a broad multiplet at δ 4.66 (1, C-3 H) and a doublet at 2.2 (1, J = 11 Hz, C-14 H). This result would indicate that the structure of the monoalcohol is in fact **10b** and is therefore derived from the acid chloride **11** *via* the peranhydride **12** and the mixed carbonate **13** (Scheme II).

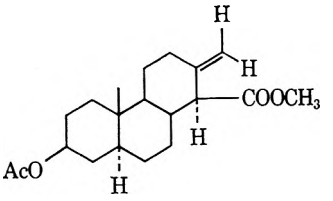
In addition a by-product was obtained which had an observed *m/e* 334 molecular ion peak and an nmr spectrum which reveals a broad multiplet at δ 4.68 and two broad singlets at 4.43 and 4.74. From this data

(10) A. K. Banerjee and M. Gut, *Tetrahedron Lett.*, 51 (1969).
(11) D. B. Denney and N. Sherman, *J. Org. Chem.*, **30**, 3760 (1965).

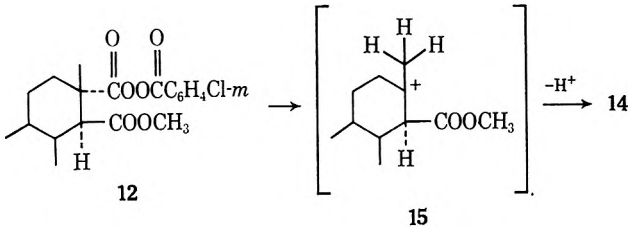
SCHEME II



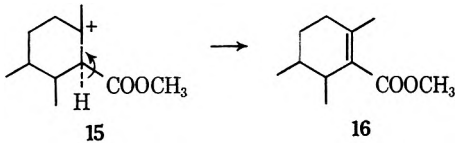
we are able to deduce the structure of this compound to be **14**.



Since the carboxy-inversion reaction is depicted as proceeding through a carbonium-ion-type intermediate,[11] one could simply envisage that the formation of **14** takes place *via* a tertiary carbonium ion **15** derived from the mixed peroxide **12**.

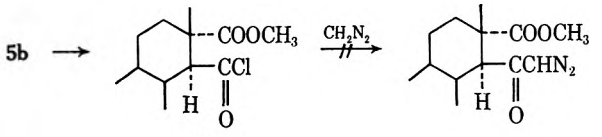


A mechanism which is better identified with a concerted E2 elimination may, however, have greater justification than an E1 intermediate which is depicted by formula **15**. If, in fact, **15** is a true intermediate, it is difficult to see why the product of the reaction is not the tetrasubstituted olefin **16**. An E2-type elimination on **12** would require the loss of a proton from the methyl group since loss of the C-14 H to give **14** would constitute a cis elimination.



The isolation of the methylene derivative **14** together with the previously discussed anomalous nmr data for the diacetoxy and the monoacetoxy compounds clearly suggests that the acid ester (mp 204°) described in the literature[3] was erroneously reported to be compound **5b** and is in fact the isomer **8b**. Furthermore, the diacetoxy compound which was obtained from the degradation of **8b** must have structure **10a** which would be consistent with the observed nmr.

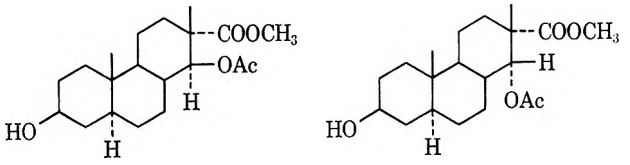
When the conversion of **5b** (mp 163°) to the diacetoxy compound **9** was attempted, it was found that the acid chloride **17** *did not* react with diazomethane to form the diazo ketone **18**.



Since the formation of the diazo ketone must take place by an initial attack at the carbonyl carbon of the acid chloride, the unreactivity of **17** is quite consistent with the result obtained from the partial hydrolysis of **7** to give **8**. Here then is an example of a carbonyl function of a tertiary ester showing a greater degree of reactivity than the carbonyl function of a less substituted secondary ester.[12] Based on these results it was apparent, therefore, that the degradation of **5** to the diacetate **9** could not be accomplished by an initial reaction which would require a reagent addition to the carbonyl carbon of the acid.

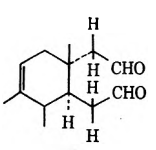
The oxidation of an acid with lead tetraacetate has been shown to give rise to an olefin, an acetoxy compound, or a combination of both. The initial step is an attack at the hydroxyl oxygen atom which derivative **19** then purportedly breaks down to a carbonium-ion intermediate **20**.[13] When this reaction was applied to **5b**, all of the anticipated products which could arise from a carbonium-ion intermediate **20** were indeed found (Scheme III).

The total crude reaction mixture (**9**, **21**, and **22**) was partially hydrolyzed, to give the desired 3β-hydroxy derivate **23** in 60% yield as well as a small amount of its isomer **24**.



Reacetylation of **23** afforded the diacetate **9**. The nmr of **23**, δ 4.98 (d, 1, J = 10 Hz), is consistent with the position of the acetoxy group (C-14) and its equitorial conformation. The nmr of **24**, δ 5.14 (d, 1, J = 2 Hz), clearly indicates the axial conformation of the acetoxy group. Compound **22** (obtained by column chromatography before hydrolysis) is believed to be a 1:1 mixture of the $\Delta^{8(11)}$ and $\Delta^{7(8)}$ olefins.

(12) A similar selectivity has previously been postulated for the dialdehyde **i** [R. B. Woodward, *et al.*, *J. Amer. Chem. Soc.*, **74**, 4223 (1962)]. Based on

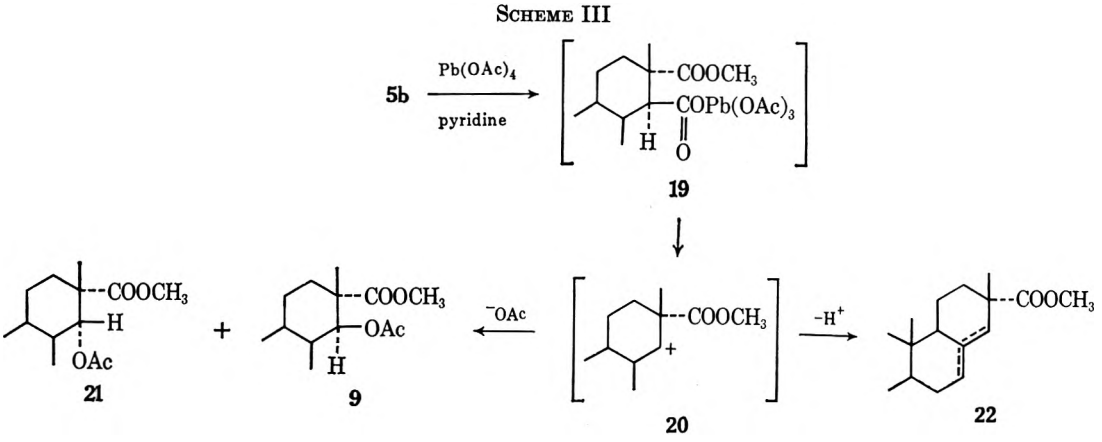


i

model studies, it was concluded that the upper activated methylene group was relatively less crowded compared with the lower.

(13) E. J. Corey and J. Casanova, Jr., *J. Amer. Chem. Soc.*, **85**, 165 (1963).

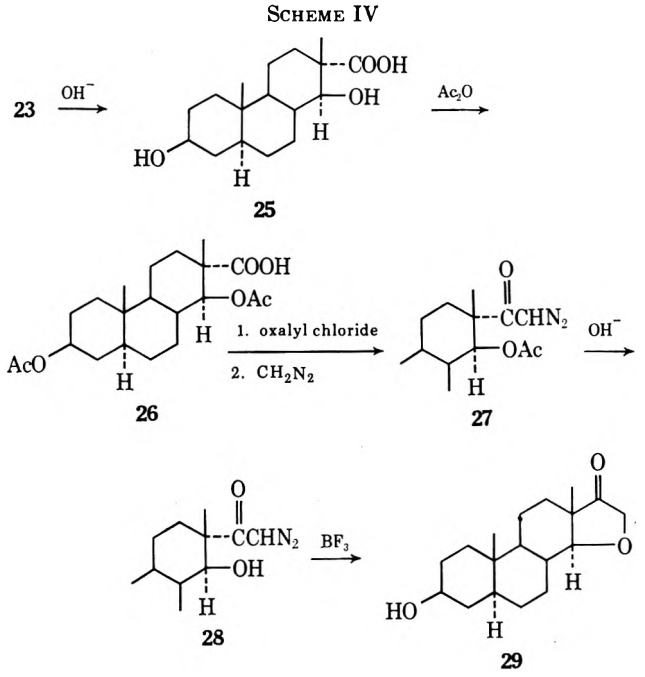
Scheme III



The nmr spectra of **22** reveals two equal singlets for each of the C-10 and C-13 methyl groups as well as weak absorption in the olefinic region.

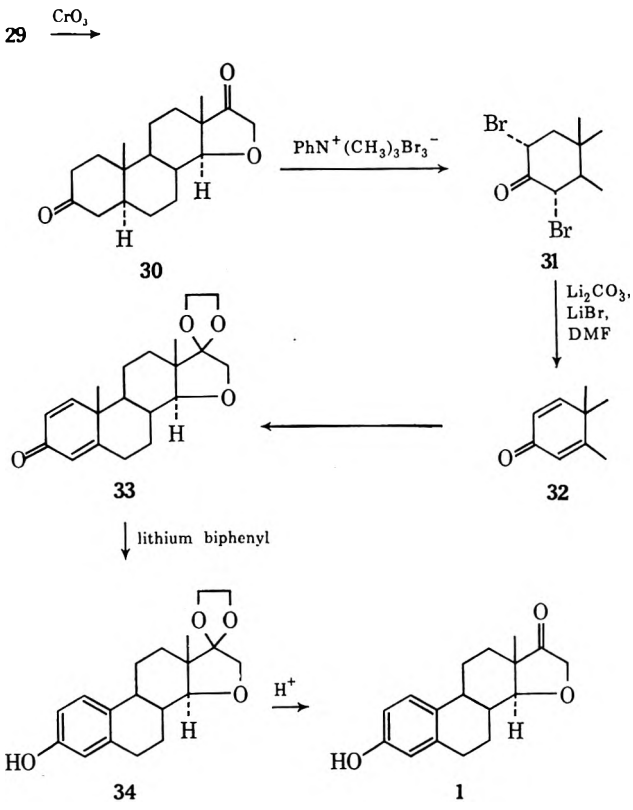
Compound **23** was hydrolyzed to the dihydroxy acid **25** which was reacetylated to give the diacetate **26**.[14] Compound **26** was converted to the diazo ketone **27** *via* the acid chloride and then hydrolyzed to the hydroxy derivative **28** (both **26** and **27** were used as crude intermediates). Treatment of a suspension of **28** in benzene with boron trifluoride etherate afforded **29** in excellent yield[15] (Scheme IV).

Scheme IV



We next turned our attention to the conversion of **29** to the estrone derivative **1**. Oxidation of **29** afforded the diketone **30** which with 2 equiv of phenyltrimethylammonium perbromide gave the diequatorial dibromide **31**. Dehydrobromination afforded the dienone **32** which was then ketalized to give **33**. Aromatization of **33** was accomplished by treatment with lithium biphenyl[16] and the crude estrone derivative **34** was deketalized to give the 15-oxaestrone **1** (Scheme V). The biological activity of **1** and the

Scheme V

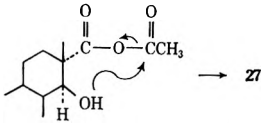


various analogs derived from **1** will be reported elsewhere.

Experimental Section[17]

3β-Hydroxy-16,17-seco-16-nor-5α-androstan-15-(2′-indoxyliden)-17-oic acid (3) was obtained from isoandrosterone as previously described (59%), mp 272–274° (lit.[7] mp 258–260° dec).

(14) The ability to acetylate the highly hindered C-14 hydroxyl group of compound **26** is most likely due to an intramolecular trans-acetylation *via* the mixed anhydride ii.



ii

(15) This reaction is an intramolecular version of the general route to α-alkoxy ketones from diazo ketones and alcohol in the presence of a catalytic amount of boron trifluoride etherate: M. S. Newman and P. F. Beal, *J. Amer. Chem. Soc.*, **72**, 5161 (1952).

(16) H. L. Dryden, Jr., G. M. Webber, and J. J. Wieczorek, *J. Amer. Chem. Soc.*, **86**, 742 (1964).

(17) All melting points were taken in glass capillaries and are corrected. The nmr spectra were determined using a Varian A-60 spectrometer with tetramethylsilane as the internal standard. The high-resolution mass spectra were obtained with a Consolidated Electrodynamics Corporation 21-110 mass spectrometer.

3β-Hydroxy-16,17-seco-16-nor-5α-androstan-15-(2′-indoxyliden)-17-oic Acid 17-Methyl Ester (4a).—To a mixture of 356 g of **3** in 3 l. of methanol was added dropwise 40 ml of acetyl chloride. After the mixture refluxed for 4 hr, the methanol was removed under reduced pressure and 2 l. of water was added to the residue. The resulting precipitate was filtered, washed with water, and dried. The product was then dissolved in a minimum of methylene chloride and treated with Norit and dried ($MgSO_4$). The mixture was filtered and the methylene chloride removed under reduced pressure. Trituration of the residue with ether afforded 325 g (87%) of **4a**, mp 258–261° (lit.[7] mp 263–265°).

3β-Acetoxy-16,17-seco-16-nor-5α-androstan-15-(2′-indoxyliden)-17-oic Acid 17-Methyl Ester (4b).—A solution of 325 g of **4a**, 325 ml of acetic anhydride, and 1300 ml of pyridine was stirred overnight. The mixture was divided into three portions and each then was added to 3 l. of cold (0°) 3 *N* hydrochloric acid. The resulting precipitates were filtered and the combined product was washed with water and dried to give 350 g (93%) of **4b**, mp 260–262° (lit.[7] mp 261–262°).

3β-Acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic Acid 17-Methyl Ester (5b).—To a suspension of 350 g of **4b** in 5 l. of glacial acetic acid was added dropwise 290 ml of a 90% aqueous chromium trioxide solution.[18] Solution soon occurred with the evolution of heat (the temperature was kept below 70° with external cooling). After the solution was stirred overnight, the acetic acid was removed under high vacuum and the residue treated with 4 l. of water. The precipitate was filtered, washed thoroughly with water, and dried. The product was then dissolved in benzene and the solution treated with Norit and anhydrous magnesium sulfate. The mixture was filtered and the benzene removed under reduced pressure. Trituration of the residue with hexane afforded 250 g (98%) of **5b**, mp 152–158° (lit.[8] mp 158–160°).

3β-Acetoxy-15,17-seco-*D*-nor-5α-androstane-15-formyl-17-oic Acid Methyl Ester (6).—A solution of 5 g of **4b** in 500 ml of methylene chloride was cooled to −70° and ozonized until the appearance of a blue-green coloration. The solution was then purged with a nitrogen stream and the resulting yellow solution added dropwise at 0° to a suspension of 12.5 g of zinc in 50 ml of glacial acetic acid. After stirring for 3 hr at 0°, the mixture was filtered and most of the solvent removed under reduced pressure. Water was added to the residue and the mixture extracted with methylene chloride. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. Trituration of the residue with ether gave 3.4 g (92%) of **6**, mp 148–151°. Crystallization from methanol afforded an analytical sample, mp 152–154°, $[\alpha]^{25}D$ +12.49° (*c* 0.9927, $CHCl_3$).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 68.96; H, 8.90.

3β-Acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic Acid Dimethyl Ester (7).—A solution of 500 mg of **5b** and 470 mg of dimethylformamide dimethyl acetal in 5 ml of dry benzene was refluxed for 15 min. The solution was cooled, diluted with ether, and washed successively with 0.1 *N* hydrochloric acid, water, and saturated sodium chloride solution. The ether solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. Crystallization from petroleum ether (30–60°) afforded 400 mg (83%) of **7**, mp 119–121° (lit.[3] mp 120–121°).

3β-Acetoxy-15,17-seco-*D*-nor-5α-androstane-15,17-dioic Acid 15-Methyl Ester (8b).—To a solution of 600 ml of methanol and 600 ml of 6% aqueous potassium hydroxide was added 75 g of **7**. The resulting mixture was refluxed for 4.5 hr, followed by removal of the methanol under reduced pressure. The remaining aqueous solution was then cooled (0°) and acidified (pH ~3) with 1 *N* hydrochloric acid. The product was filtered and air dried to give 64.5 g (99%) of the 3β-hydroxy derivative **8a**, mp 230–232° [lit.[3] (incorrectly assigned as **5a**) mp 234–235°].

To a solution of 97.5 ml of acetic anhydride and 97.5 ml of pyridine was added 64.5 g of the above alcohol **8a**. The mixture was stirred for 6 hr and then diluted at 0° with 130 ml of methanol and 97.5 ml of 2 *N* hydrochloric acid. After stirring for 30 min at 0°, the mixture was then poured into 4 l. of water. The precipitate was filtered, washed thoroughly with water, and dried. Crystallization from ether–hexane afforded three crops of product **8b**: 45.2 g, mp 209–211°; 15.1 g, mp 209–211°; and 4.8 g, mp 208–210°. The total yield of **8b** was 65.1 g (90%) [lit.[3] (incorrectly assigned as **5b**) mp 205–207°].

(18) This solution is prepared by dissolving 90 g of chromium trioxide in 100 ml of water.

Reaction of the Acid Chloride 11 with *m*-Chloroperbenzoic Acid. Formation of 10b, 10c, and 14.—To 1 ml of oxalyl chloride was added 1 g of **8b**. The solution was stirred at room temperature for 4 hr and the excess oxalyl chloride then removed under reduced pressure. Hexane was added to the residue and the solvent again removed under reduced pressure to give 500 mg of the acid chloride **11**, mp 99–101° [lit.[10] (incorrectly assigned as **17**) mp 94°]. The acid chloride was then dissolved in 25 ml of dry ether to which was added at 0° 474 mg of *m*-chloroperbenzoic acid (98% purity) and 0.22 ml of pyridine. After the mixture was stirred overnight at 0°, the precipitated pyridine hydrochloride was filtered off and washed with ether. The combined filtrate was washed with 1 *N* hydrochloric acid followed by 5% sodium bicarbonate solution. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure. The residue was then dissolved in 13 ml of 1 *N* methanolic potassium hydroxide and was stirred at room temperature for 0.5 hr. To the solution was added 50 ml of water and the resulting mixture extracted with methylene chloride and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue triturated with ether to give 370 mg of 3β,13α-dihydroxy-13,15-seco-*D*-bisnor-5α-androstan-15-oic acid methyl ester (**10c**), mp 168–172°, contaminated with a small amount of **14**. Acetylation afforded **10b**, mp 133–134°, $[\alpha]^{25}D$ −29.18° (*c* 1.0966, $CHCl_3$).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.06; H, 8.89.

The solvent from the above mother liquor was removed under reduced pressure and the residue acetylated with 0.45 ml of pyridine and 0.45 ml of acetic anhydride. To the solution was added 10 ml of water and 0.5 ml of 2 *N* hydrochloric acid and the resulting mixture was extracted with ether. The ether solution was washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded 310 mg of material which was chromatographed on 15 g of silica gel. Elution with benzene gave a product which when triturated with pentane afforded 110 mg of 3β-acetoxy-13,15-seco-*D*-bisnor-5α-androst-$\Delta^{13(18)}$-en-15-oic acid methyl ester (**14**), mp 122–125°, $[\alpha]^{25}D$ −16.9° (*c* 0.2120, $CHCl_3$).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.03. Found: C, 71.99; H, 9.17.

Reaction of 5 with Lead Tetraacetate. Preparation of 9, 22, 23, and 24.—A mixture of 255 g of **5b**, 745 g of lead tetraacetate,[19] 108 ml of pyridine, and 3.8 l. of dry benzene was stirred and refluxed for 7 hr. The mixture was cooled and the lead salts were filtered and thoroughly washed with ether. The filtrate was washed with a 10% solution of sodium thiosulfate, 1 *N* hydrochloric acid, and then a saturated sodium chloride solution. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure to give 270 g of crude product. One gram of material was chromatographed on 25 g of silica gel. Elution with benzene afforded a small amount of **22**. The remaining material was then dissolved in a minimum of benzene and washed through 1300 g of neutral alumina (grade I). Elution with 3 l. of benzene followed by 1 l. of a 1% ethyl acetate benzene solution afforded 215 g of crude material. This product was then dissolved in 1.23 l. of 3% methanolic potassium hydroxide and stirred at 0° for 1 hr. The mixture was acidified with 700 ml of 1 *N* hydrochloric acid at 0° and the precipitate filtered and dried to give 108 g of 3β-hydroxy-14β-acetoxy-14,17-seco-*D*-bisnor-5α-androstan-17-oic acid methyl ester (**23**), mp 127–130°. The methanol was removed from the filtrate under reduced pressure, the mixture extracted with methylene chloride, and the resulting solution dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue triturated with methanol to give 2 g of **23**, mp 126–130°. A third crop of 3 g, mp 124–128°, of **23** was obtained by removing a portion of the methanol under reduced pressure. The total yield of **23** was 113 g (49%). Crystallization from methnaol afforded an analytical sample containing 1 mol of methanol, mp 134–136°, $[\alpha]^{25}D$ −164.76° (*c* 1.1113, $CHCl_3$).

Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.59; H, 9.44. Found: C, 65.85; H, 10.09.

Acetylation with pyridine–acetic anhydride afforded the 3β-acetoxy derivative **9**, mp 105–106°, $[\alpha]^{25}D$ −16.23° (*c* 0.7579, $CHCl_3$).

Anal. Calcd for $C_{22}H_{34}O_6$: C, 66.98; H, 8.69. Found: C, 67.11; H, 8.93.

(19) The lead tetraacetate was placed under high vacuum over phosphorus pentoxide for 24 hr prior to use.

The mother liquor obtained from the above trituration was treated with cyclohexane to give 60 g of crude **24** contaminated with **22**. Crystallization from hexane afforded 23 g (10%) of 3β-hydroxy-14α-acetoxy-14,17-seco-*D*-bisnor-5α-androstan-17-oic acid methyl ester (**24**), mp 140–147°.

A second crystallization from cyclohexane afforded an analytical sample, mp 152–153°, $[\alpha]^{25}D$ −22.82° (*c* 0.5390, $CHCl_3$).

Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.45; H, 8.99.

3β,14β-Dihydroxy-14,17-seco-*D*-bisnor-5α-androstan-17-oic Acid (25).—A solution of 86 g of **23** in 2.74 l. of 3% methanolic potassium hydroxide was refluxed for 6 hr. The methanol was removed under reduced pressure and 200 ml of water added to the residue. The solution was cooled to 0° and acidified with concentrated hydrochloric acid. The precipitate was filtered and dried to give 72.2 g (98%) of **25**, mp 285–287°. Crystallization from methanol afforded an analytical sample, mp 285–287°, $[\alpha]^{25}D$ +11.94° (*c* 0.9047, CH_3OH).

Anal. Calcd for $C_{17}H_{28}O_4$: C, 68.88; H, 9.52. Found: C, 69.16; H, 9.71.

3β,14β-Dihydroxy-16-diazo-17-oxo-14,16-seco-*D*-nor-5α-androstane (28).—To a solution of 350 ml of acetic anhydride in 350 ml of pyridine was added 70 g of **25**. The solution was stirred at room temperature overnight and then poured into 6 l. of ice water. The mixture was stirred for 2 hr and then extracted with ether. The ether solution was washed with 1 *N* hydrochloric acid and then water to neutrality. The solution was dried ($MgSO_4$) and the solvent removed under reduced pressure to give 83 g of crude **26** as an oil.

The crude diacetate **26** (83 g) was treated with 90 ml of oxalyl chloride and stirred at room temperature overnight. The excess oxalyl chloride was then removed under reduced pressure, the residue diluted with hexane, and the solvent again removed under reduced pressure to give 85 g of crude acid chloride.

To an ethereal solution of diazomethane prepared from 150 g of *n*-methylnitrosourea was added dropwise with stirring at 0° a solution of 85 g of the crude acid chloride in 200 ml of ether. The solution was stirred at 0° for 2 hr and the solvent and excess diazomethane were then evaporated under a stream of nitrogen. The crude diazo ketone **27** was then added to 790 ml of a 6% methanolic potassium hydroxide solution and stirred at room temperature for 5 hr. The reaction mixture was then cooled to 5° and the precipitate filtered to give 63 g (83%) of **28**, mp 145–150°. Crystallization from ether–methylene chloride afforded an anaytical sample, mp 154–156°, $[\alpha]^{25}D$ −8.46° (*c* 0.9697, $CHCl_3$).

Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81. Found: C, 67.22; H, 8.91.

3β-Hydroxy-15-oxa-5α-androstan-17-one (29).—To a suspension of 63 g of **28** in 1.2 l. of dry benzene was added dropwise with stirring a solution of 15 ml of boron trifluoride etherate in 20 ml of benzene. The evolution of nitrogen began immediately, and after the addition was completed (~15 min) the reaction was stirred for an additional 10 min. The benzene soluton was then washed with 5% sodium bicarbonate solution and the aqueous extracts were back-washed with ether. The organic layers were then combined, dried ($MgSO_4$), heated with Norit, and then filtered. The solvent was removed under reduced pressure and the residue triturated with hexane to give 54.5 g (92%) of **29**, mp 145–150°. Crystallization from ether–methylene chloride afforded an analytical sample, mp 152–154°, $[\alpha]^{25}D$ +54.07° (*c* 0.5049, $CHCl_3$).

Anal. Calcd for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.90; H, 9.82.

Acetylation with pyridine–acetic anhydride followed by crystallization from methanol afforded the 3β-acetoxy derivative, mp 164–167°, $[\alpha]^{25}D$ +45.19° (*c* 0.9249, $CHCl_3$).

Anal. Calcd fof $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.56; H, 8.86.

15-Oxa-5α-androstane-3,17-dione (30).—To a cooled (0°) solution of 10 g of **29** in 100 ml of acetone was added dropwise with stirring 10 ml of Jones reagent. After the addition was complete, the mixture was stirred at 0° for 10 min. The solvent was then removed under reduced pressure and the residue treated with 300 ml of ice water. The precipitate was filtered and washed thoroughly with water and dried. The product was then dissolved in a minimum of methylene chloride and the solution was treated with Norit and filtered. The solvent was removed under reduced pressure to give 9.2 g (93%) of **30**, mp 176–180°. Crystallization from ether–methylene chloride afforded an analytical sample, mp 182–185°, $[\alpha]^{25}D$ +77.39° (*c* 1.1798, $CHCl_3$).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.18; H, 9.01.

2α,4α-Dibromo-15-oxa-5α-androstane-3,17-dione (31).—To a solution of 16.5 g of **30** in 160 ml of dry tetrahydrofuran was added 216 g of phenyltrimethylammonium perbromide. The brominating agent quickly dissolved and after a short time phenyltrimethylammonium bromide began to precipitate. The mixture was stirred for 4.5 hr and the precipitate was filtered and washed with benzene. An additional 100 ml of benzene was added to the filtrate and the resulting solution was then washed with a 5% solution of sodium sulfite and water and then dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue triturated with cold ether to give 14.2 g (55%) of **31**, mp 212–214°. Crystallization from methylene chloride–ether afforded an analytical sample, mp 213–215° dec, $[\alpha]^{25}D$ +18.05° (*c* 0.9861, $CHCl_3$).

Anal. Calcd for $C_{18}H_{24}Br_2O_3$: C, 48.24; H, 5.40. Found: C, 48.20; H, 5.50.

15-Oxaandrosta-1,4-diene-3,17-dione (32).—To a solution of 19.6 g of lithium bromide and 19.6 g of lithium carbonate in 200 ml of dry dimethylformamide at 95° was added dropwise a solution of 14.7 g of **31** in 150 ml of the same solvent. The mixture was stirred and maintained at 95° for 18 hr and most of the dimethylformamide was then removed under high vacuum. To the residue was then added 200 ml of ice water followed by 50 ml of 1 *N* hydrochloric acid. The precipitated semisolid was then extracted with methylene chloride and the organic layer washed thoroughly with water and dried ($MgSO_4$). The solvent was then removed under reduced pressure and the residue was dissolved in a minimum of methylene chloride and passed through 50 g of neutral alumina (grade I). Elution with methylene chloride gave 9.5 g of crude product which when triturated with ether afforded 7 g (74%) of **32**, mp 181–185°. Crystallization from methylene chloride–ether afforded an analytical sample, mp 185–187°, $[\alpha]^{25}D$ +70.50° (*c* 0.9050, $CHCl_3$).

Anal. Calcd for $C_{18}H_{22}O_3$: C, 75.49; H, 7.74. Found: C, 75.77; H, 7.97.

15-Oxaandrosta-1,4-diene-3,17-dione 17-Ethylene Ketal (33).—A mixture of 7 g of **32**, 14 ml of ethylene glycol, 0.28 g of *p*-toluenesulfonic acid, and 350 ml of benzene was placed in a 500-ml flask fitted with a Soxhlet extractor which was charged with Linde 3A Molecular Sieves. After refluxing for 6 hr, the reaction was cooled and washed with a 5% sodium bicarbonate solution and water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue triturated with ether to give 6.5 g (78%) of **33**, mp 147–150°. Crystallization from methylene chloride–ether afforded an analytical sample, mp 147–150°, $[\alpha]^{25}D$ +6.50° (*c* 0.9545, $CHCl_3$).

Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70, H, 7.93. Found: C, 72.76; H, 7.89.

15-Oxaestrone 17-Ethylene Ketal (34).—To a solution of 86.2 g of biphenyl in 1.5 l. of dry tetrahydrofuran was added 4.35 g of lithium wire. The mixture was stirred at room temperature for 4 hr after which time the lithium had completely dissolved. The dark blue solution was then warmed to 50° and a solution of 25.4 g of **33** and 38.8 g of diphenylmethane in 100 ml of tetrahydrofuran was added dropwise over a period of 30 min. The temperature was maintained at 50–52° and the mixture was stirred for an additional hour. The reaction was then cooled to 0° and 45 g of ammonium chloride was added in small portions (color changed from dark green to light brown). Small pieces of ice were then cautiously added causing the reaction to become colorless, followed by the addition of 100 ml of ice water. The resulting two layers were separated and the aqueous solution was extracted with methylene chloride. The organic layers were combined and dried ($MgSO_4$), and the solvent was removed under reduced pressure to give an oily residue. Hexane (800 ml) was added and the mixture stirred until precipitation took place. The crude precipitate (25 g) was dissolved in a minimum of methylene chloride and passed through 250 g of silica gel. Elution with 2 l. of methylene chloride gave 0.9 g of a green-tinted by-product, 4 l. of 1% ethyl acetate–benzene gave 7 g of crude product, and 5 l. of a 5% ethyl acetate–benzene gave an additional 8.5 g of material. The combined product (15.5 g) was triturated with hexane–ether to give 12.5 g (54%) of **34**, mp 212–215°. Crystallization from methylene chloride–ether afforded an analytical sample, mp 214–216°, $[\alpha]^{25}D$ +18.99° (*c* 0.8900, $CHCl_3$).

Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.12; H, 7.65. Found: C, 71.98; H, 7.53.

15-Oxaestrone (1).—A solution of 12 g of **34**, 250 ml of dioxane, and 20 ml of an 8% aqueous sulfuric acid solution was stirred and refluxed for 4 hr. The solution was cooled and poured into 2 l. of ice water, and the precipitate was filtered. The product was washed thoroughly with water and air dried. The crude material was then dissolved in a minimum of 1:1 methylene chloride–tetrahydrofuran solution, dried ($MgSO_4$), and heated with charcoal. The mixture was filtered and the solvent removed under reduced pressure. The resulting residue was triturated with ether to give 9.2 g of crude product. Crystallization from methanol afforded two crops of product: 7.0 g, mp 254–256°; and 1.4 g, mp 252–254°. The total yield of **1** was 8.4 g (81%). Crystallization from methanol of the first crop afforded an analytical sample, mp 255–256°, $[\alpha]^{15}D$ +108.45° (*c* 0.8760, $CHCl_3$).

Anal. Calcd for $C_{17}H_{20}O_2$: C, 74.97; H, 7.40. Found: C, 75.28; H, 7.84.

Acknowledgments.—The authors wish to thank Dr. R. W. Kierstead for his interest and stimulating discussions of this work. We also wish to thank Dr. T. Williams and Dr. W. Benz for the nmr and mass spectra, respectively, as well as Dr. F. Scheidl for the microanalyses.

Registry No.—**1**, 40715-31-9; **3**, 6217-96-5; **4a**, 6217-97-6; **4b**, 6217-98-7; **5b**, 19018-70-3; **6**, 40715-35-3; **7**, 19018-71-4; **8a**, 40715-37-5; **8b**, 26362-62-9; **9**, 21491-12-3; **10b**, 40715-40-0; **10c**, 40715-41-1; **11**, 40715-42-2; **14**, 40715-43-3; **23**, 40715-44-4; **24**, 40715-45-5; **25**, 40715-46-6; **26**, 40715-47-7; **27**, 40715-48-8; **28**, 40715-49-9; **29**, 40830-80-6; **29** 3β-acetoxy derivative, 40715-51-3; **30**, 40715-52-4; **31**, 40715-53-5; **32**, 40715-54-6; **33**, 40715-55-7; **34**, 40715-56-8; *m*-chloroperbenzoic acid, 937-14-4; lead tetraacetate, 546-67-8.

Notes

Purine *N*-Oxides. XLVIII. 1-Hydroxyguanine[1]

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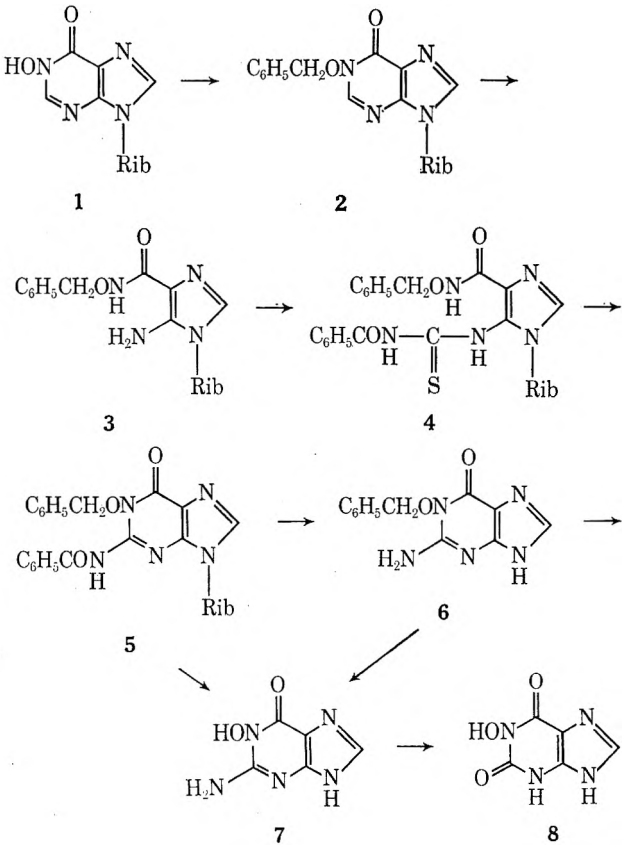
The 1- and 3-*N*-oxide isomers of adenine,[2,3] hypoxanthine,[3,4] and xanthine[5,6] are available, but only the 3 isomer of guanine.[6] By an adaptation of the synthetic route which led *via* substituted imidazoles to a series of 9-hydroxypurines,[7,8] it has now been possible to obtain 1-hydroxyguanine. 1-Hydroxyinosine (**1**), obtained by the nitrosation of adenosine 1-*N*-oxide,[9a] was converted to 1-benzyloxyinosine[9a] (**2**) by reaction with benzyl bromide in DMF in the presence of K_2CO_3. By refluxing **2** in ethanol containing 0.2 volumes of 6 *N* NaOH, the pyrimidine ring was opened to yield 5-amino-1-β-D-ribofuranosylimidazole-4-*N*-benzyloxycarboxamide (**3**). Refluxing **3** with 1 equiv of benzoyl isothiocyanate in acetone yielded 5-(*N'*-benzoylthiocarbamoyl)amino-1-β-D-ribofuranosylimidazole-4-*N*-benzyloxycarboxamide (**4**). Treatment of this with methyl iodide in 0.1 *N* NaOH at room temperature did not give the expected methylmercapto derivative, but the odor of methylmercaptan was observed when the solution was acidified. The white, crystalline product obtained was assigned the structure **5** from its nmr and its subsequent hydrolysis products. In 32% HBr in glacial acetic acid **5** was hydrolyzed to 1-hydroxyguanine (**7**), and was hydrolyzed to 1-benzyloxyguanine (**6**) in refluxing 1 *N* HCl. Debenzylation of **6** with 32% HBr in glacial acetic acid gave 1-hydroxyguanine (Table I). Further proof of the structure of **7** was ob-



(1) This investigation was supported in part by funds from the National Cancer Institute (Grant No. CA 08748).

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(8) A. A. Watson, unpublished work.

(9) (a) J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, **15**, 1334 (1972) (personal communication prior to publication). (b) H. Sigel and H. Britziner, *Helv. Chim. Acta*, **48**, 433 (1965). (c) Pure 1-hydroxyinosine can be obtained by recrystallization from methanol to separate it from some salts, and chromatography over Dowex-50 (H^+) with water to eliminate a fluorescent impurity. F. L. Lam, private communication.

TABLE I
SPECTRAL DATA AND pK VALUES FOR 1-HYDROXYGUANINE[a]

pK_a	λ_{max}, nm	$\epsilon \times 10^{-3}$	pH	Charge
	275	7.20 ± 0.02		
	248	9.8 ± 0.1	1	+1
	208 (sh)	16.1 ± 0.2		
3.49 ± 0.11[b]				
	273	7.29 ± 0.01	5.23	0
	247	9.47 ± 0.02		
6.73 ± 0.07[b]				
	278 (sh)	5.96 ± 0.10		
	257	7.51 ± 0.10	9	−1
	227	30.4 ± 0.5		
11.51 ± 0.07[c]				
	278	7.4 ± 0.1		
	267 (sh)	7.2 ± 0.1	14	−2
	~225	~31.5 ± 0.1		

[a] Comparable pK values for 3-hydroxyguanine are 3.45, 5.97, and 10.67. From the 227-nm absorption band of the mono-anion, it is apparent that the first ionization involves the *N*-hydroxy group, and the second the imidazole. Unlike 3-hydroxyguanine there is only one tautomeric form of the neutral species: J. C. Parham, T. G. Winn, and G. B. Brown, *J. Org. Chem.*, **36**, 2639 (1971). [b] By electrometric titration. [c] Spectrophotometrically, by methods described: A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962; D. D. Perrin, *Aust. J. Chem.*, **16**, 572 (1963).

tained by reduction to guanine in refluxing HI, and also by nitrosation to the known 1-hydroxyxanthine (**8**).

Experimental Section

The uv spectra were determined with a Unicam SP800 spectrophotometer, and the nmr spectra were determined in DMSO-d_6 (TMS) with a Varian A-60 spectrometer. Melting points were taken in a Mel-Temp apparatus. For thin layer chromatograms (tlc) Eastman chromatograph sheets with a silica gel layer containing a fluorescent indicator were used. The microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

1-Hydroxyinosine (**1**).—This was prepared according to the method of Montgomery,[9a] which avoids the requirement of DMF as a solvent.[4,9b] Adenosine 1-*N*-oxide (33.9 g) and $NaNO_2$ (82.8) were added to 1 l. of 29% aqueous acetic acid and the mixture was stirred for 1 or 2 days at room temperature. The acetic acid was removed by repeated extractions (300 ml each) with ether and the aqueous layer was evaporated at a bath temperature below 40°. The pH of the solution was adjusted from 3 to 4 with 1 *N* HCl and the resulting solution was evaporated to dryness. The residue was extracted with 300 ml of water. The product was collected, washed with water, and dried *in vacuo* over P_2O_5 to yield 11–17 g (33–54%) of off-white 1-hydroxyinosine, containing no adenosine 1-*N*-oxide, and of sufficient purity to be used in the next step.[9c]

Synthesis of 1-Benzyloxyinosine (**2**).—1-Hydroxyinosine (4.70 g, 0.013 mol) was stirred with benzyl bromide (3.81 g, 0.025 mol) and finely powdered K_2CO_3 (2.26 g) in 100 ml of dimethylformamide for 20 hr at 75°. The reaction mixture was cooled to room temperature and filtered, and the filtrate was evaporated to a yellow oil. The oil was triturated with 250 ml of hot acetonitrile and filtered to remove unreacted starting material. The filtrate was evaporated and the resulting residue was recrystallized from ethyl acetate and methanol to yield 3.06 g (50%) of colorless crystals, mp 189–191°, of 1-benzyloxyinosine: uv $\lambda_{max}^{pH\ 1}$ sh 244 nm (ϵ 9.74 × 10^3), 251 (10.9 × 10^3), sh 267 (6.08 × 10^3); $\lambda_{max}^{pH\ 13}$ sh 244 nm (ϵ 9.83 × 10^3), 251 (10.7 × 10^3), sh 267 (6.0 × 10^3); nmr δ 8.53 (s, 1, 2-CH), 8.47 (s, 1, 8-CH), 7.52 (m, 5, C_6H_5), 5.95 (d, 1, H-1′), 5.33 (s, 2, $C_6H_5CH_2$), 5.30 (b, 3, OH), 4.3 (m, 3, H-2′, H-3′, H-4′), 3–17 (broad s, 2, CH_2-5′).

Anal. Calcd for $C_{17}H_{18}N_4O_6 \cdot H_2O$: C, 52.19; H, 5.13; N, 14.27. Found: C, 52.19; H, 4.68; N, 14.22.

5-Amino-1-β-D-ribofuranosylimidazole-4-*N*-benzyloxycarboxamide (**3**).—The hydrolysis of 1-benzyloxyinosine was accomplished by refluxing **2** (3.06 g, 0.0082 mol) in 300 ml of ethanol and 75 ml of 6 *N* NaOH for 1.5 hr. The reaction mixture was evaporated at a bath temperature below 40° to 100 ml and carefully acidified to not less than pH 3 with 2 *N* HCl. The solution was cooled and filtered. The crystalline precipitate was washed with 50 ml of hot water and dried to yield 2.1 g (70%) of colorless cubes, mp 180–182°, of **3**: uv $\lambda_{max}^{pH\ 1}$ 275, sh 250 nm; $\lambda_{max}^{pH\ 13}$ 252 nm; nmr δ 10.70 (s, 1, CONH), 7.39 (m, 5, $C_6H_5CH_2$, 1,2-CH), 6.03 (broad s, 2, NH_2), 5.53 (d, H-1′), 5.30 (broad m, 3, OH), 4.90 (s, 2, CH_2), 4.12 (m, 3, H-2′, H-3′, H-4′), 3.63 (broad s, 2, CH_2-5′).

Anal. Calcd for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.37. Found: C, 52.76; H, 5.57; N, 15.22.

5-(*N*′-Benzoylthiocarbamoyl)amino-1-β-D-ribofuranosylimidazole-4-*N*-benzyloxycarboxamide (**4**).—5-Amino-1-β-D-ribofuranosyl-4-*N*-benzyloxycarboxamide (3.64 g, 0.01 mol) was dissolved in 100 ml of boiling acetone; then 100 ml of acetone solution containing 1.1 equiv of benzoyl isothiocyanate[10] was added.[7,11] The mixture was refluxed for ~3 hr, or until tlc run in 4:1 $CHCl_3$–MeOH and development in iodine showed no appreciable change in the reaction mixture.

The reaction mixture was evaporated *in vacuo* to an oil that was chromatographed over silica gel. Eluting with chloroform removed the unreacted benzoyl isothiocyanate and 9:1 $CHCl_3$–EtOH elution removed the starting material. $CHCl_3$–ethanol, 4:1, eluted the benzoylthioureido derivative **4**, which was obtained as a glass after the removal of the solvent: yield 2.16 g (41%); froths between 88 and 93°; uv λ_{max}^{EtOH} 239, sh 277 nm; nmr δ 8.1 (s, 1, 2-CH), 8.01 (m, 2, C_6H_5CO), 7.6 (m, 3, C_6H_5CO), 7.30 (s, 5, $C_6H_5CH_2$), 5.62 (d, 1, H-1′), 4.70 (m, 3, OH), 4.89 (s, 2, $C_6H_5CH_2$), 4.13 (m, 3, H-2′, H-3′, H-4′), 3.69 (broad s, 2, CH_2-5′), 11.21 (1, CONH), 11.99 (d, 2, NHCSNH–).

1-Benzyloxy-2-benzoylguanosine (**5**).—**4** (1.06 g, 0.002 mol) was stirred in 100 ml of 0.1 *N* NaOH until dissolved, then methyl iodide (0.5 ml) was added and stirring was continued for 18 hr. The solution was then acidified with acetic acid and the white precipitate was collected and washed with water. The white solid (**5**) recrystallized as white prisms from acetone–petroleum ether (bp 30–60°): yield 703 mg (71%); mp 174–175°; uv $\lambda_{max}^{pH\ 1}$ sh 235 nm (ϵ 14.0 × 10^3), 263 (11.2 × 10^3), 285 (11.3 × 10^3); $\lambda_{max}^{pH\ 13}$ 248 nm (ϵ 12.7 × 10^3), 263 (13.2 × 10^3), 268 (13.1 × 10^3); nmr δ 8.04 (s, 1, 8-CH), 7.9 (m, 2, C_6H_5CO), 7.6 (m, 3, C_6H_5CO), 7.31 (s, 5, $C_6H_5CH_2$), 5.85 (d, 1, H-1′), 5.30 (b, 3, OH), 5.20 (s, 2, $C_6H_5CH_2$), 4.2 (m, 3, H-2′, H-3′, H-4′), 3.60 (broad, 2, CH_2-5′), 11.00 (s, 1, CONH).

Anal. Calcd for $C_{24}H_{23}N_5O_7 \cdot H_2O$: C, 56.25; H, 5.07; N, 13.67. Found: C, 56.65; H, 4.80; N, 13.34.

1-Benzyloxyguanine (**6**).—**5** (205 mg, 4 × 10^{-4} mol) was refluxed in 20 ml of 1 *N* HCl for 1 hr. The solution was evaporated to dryness *in vacuo*. The residue was dissolved in 2 ml of methanol and chromatographed over Dowex-50. Benzoic acid was eluted with water, then a trace of 1-hydroxyguanine with 1 *N* HCl, and the main fraction with 2 *N* HCl. Recrystallization of the residue from the 2 *N* HCl fraction from methanol afforded white plates of 1-benzyloxyguanine hydrochloride: 95 mg (81%); uv $\lambda_{max}^{pH\ 1}$ 249 nm (ϵ 11.5 × 10^3), 278 (7.33 × 10^3); $\lambda_{max}^{pH\ 13}$ 257 nm (ϵ 7.81 × 10^3), 278 (8.4 × 10^3); nmr δ 9.0 (s, 1, 8-CH), 7.50 (m, 5, $C_6H_5CH_2$), 9.66 (m, 3, NH_3^+), 5.20 (s, 2, $C_6H_5CH_2$).

Anal. Calcd for $C_{12}H_{11}N_5O_2 \cdot HCl$: C, 49.07; H, 4.12; N, 23.84. Found: C, 49.19; H, 4.15; N, 23.73.

1-Hydroxyguanine (**7**). **A.**—1-Benzyloxy-2-benzoylguanosine (205 mg, 4 × 10^{-4} mol) was dissolved in 5 ml of warm glacial acetic acid, and 5 ml of 32% HBr in glacial acetic acid was added. The mixture was heated on a steam bath for 3.5 hr. The reaction mixture was then evaporated *in vacuo* and the residue was dissolved in a few milliliters of very dilute ammonia and chromatographed over Dowex-50. Elution with 1 *N* HCl gave the 1-hydroxyguanine, which was obtained as the hydrochloride on recrystallization from methanol and dried *in vacuo* over P_2O_5 at 78°, 63 mg (77%).

Anal. Calcd for $C_5H_5N_5O_2 \cdot HCl$: C, 29.50; H, 2.97; N, 34.40; Cl, 17.41. Found: C, 29.63; H, 3.14; N, 34.23; Cl, 17.39.

B.—The debenzylation of 6 (50 mg) was carried out as in **A** and the free base **7** was obtained from the hydrobromide salt by dissolving in hot dilute ammonia, treated with charcoal, and

(10) R. L. Frank and P. V. Smith, *Org. Syn.*, **28**, 89 (1948).
(11) A. Yamazaki, I. Kumashiro, and T. Takenishi, *J. Org. Chem.*, **32**, 1825 (1967).

precipitated by the addition of glacial acetic acid. The white crystals were collected, washed with water, and dried *in vacuo* over P_2O_5 at 78°, 30 mg (74%).

1-Hydroxyxanthine.—To a cooled, stirred solution of 1-hydroxyguanine (10 mg) in 5 ml of 2 *N* HCl was added 1 ml of a 2 *M* solution of $NaNO_2$. After 8 hr the solution was evaporated to dryness and the residue was chromatographed over Dowex-50. The uv spectrum of the main fraction, eluted first with 1 *N* HCl, was identical with that of authentic 1-hydroxyxanthine.[6] Traces of 1-hydroxyguanine and an unidentified product were eluted with further 1 *N* HCl.

Guanine.—1-Hydroxyguanine (10 mg) was suspended in 1 ml of concentrated HI, warmed on a steam bath for 1 hr, and evaporated to dryness. The residue was chromatographed over Dowex-50. Elution with 1 *N* HCl removed a trace of unreduced 1-hydroxyguanine, and guanine, identified by its uv spectrum, was eluted with 2 *N* HCl.

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Registry No.—1, 5383-06-2; 2, 40519-34-4; 3, 40519-35-5; 4, 40519-36-6; 5, 40519-37-7; 6, 40550-38-7; 7 hydrochloride, 40429-65-0; adenosine 1-*N*-oxide, 146-92-9; benzyl bromide, 100-39-0; benzoyl isothiocyanate, 4461-33-0.

Reaction of Thiete 1,1-Dioxide with α-Pyrone[1]

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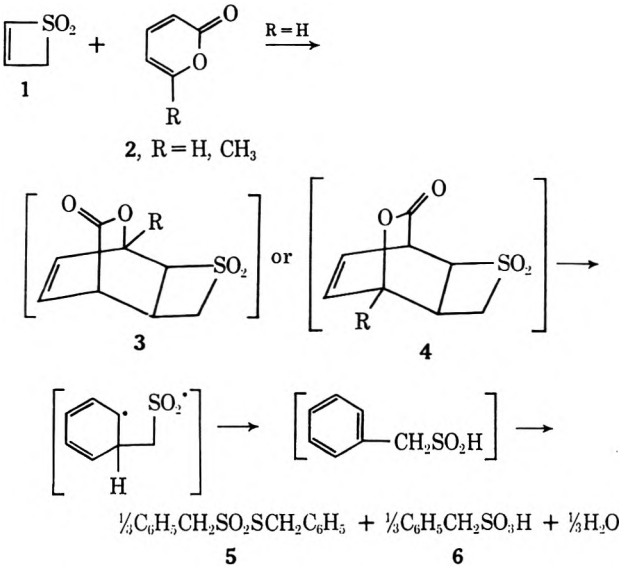
Thiete 1,1-dioxide (thiete sulfone)[2] behaves erratically in cycloaddition reactions. On the one hand it undergoes, in a normal fashion, additions of butadiene,[3] furans,[3,4] anthracene,[5] dienamines,[6] enamines,[6] ynamines,[6] and diazoalkanes.[7] On the other hand, the attempted Diels–Alder cycloaddition of tetraphenylcyclopentadienone to thiete sulfone resulted in evolution of sulfur dioxide and formation of a tetraphenylcycloheptatriene and a bicyclic octadienone in yields of 65 and 15%, respectively.[3]

α-Pyrone[8] is a reactive diene in Diels–Alder reactions and is a useful reagent for introducing the C_4H_4 moiety.[9] Treatment of thiete sulfone, 1 (10 mmol), with α-pyrone, 2 (10 mmol), under nitrogen in refluxing *m*-xylene for 24 hr gave benzyl α-toluenethiosulfonate, **5** (2.59 mmol), and benzylsulfonic acid, **6** (1.05 mmol),



instead of the expected product of the Diels–Alder cycloaddition. The properties of the α-toluene thiosulfonate were identical with those of an authentic sample prepared by oxidation of dibenzyl disulfide with hydrogen peroxide in acetic acid.[10] The benzylsulfonic acid was identified by conversion to benzylsulfonyl chloride, whose properties were identical with those of an authentic sample.[11] No reaction of thiete sulfone and α-pyrone was observed at 50° or 100°.

No reaction was observed between thiete sulfone and 6-methyl-2-pyrone[12] (2, R = CH_3) under the same conditions.

A possible scheme for the formation of benzyl α-toluenethiosulfonate involves the disproportionation of benzylsulfinic acid derived from the Diels–Alder adduct of α-pyrone and thiete sulfone. Although there are conflicting reports in the literature concerning the ease of disproportionation of benzylsulfinic acid, the conditions under which those disproportionation reactions were attempted were different from our conditions.[10,13,14] We have found that both benzyl α-toluenethiosulfonate (65.4%) and benzylsulfonic acid (40.8%) are formed when benzylsulfinic acid is refluxed in *m*-xylene for 30 hr. Disproportionation of sulfinic acids to thiosulfonates and sulfonic acids is well known and the mechanism has been established by Kice and his coworkers.[15] The possible involvement of free radicals in thermolysis of sulfones has been noted previously.[16]

The attempt to distinguish between possible inter-

(1) We are grateful to the National Institutes of Health for support of this work (Grant CA 08250).

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(3) D. C. Dittmer, K. Ikura, J. M. Balquist, and N. Takashina, *ibid.*, **37**, 225 (1972).

(4) D. C. Dittmer and N. Takashina, *Tetrahedron Lett.*, 3809 (1964); L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965); L. A. Paquette and T. R. Phillips, *ibid.*, **30**, 3883 (1965).

(5) D. C. Dittmer and M. E. Christy, *J. Amer. Chem. Soc.*, **84**, 399 (1962).

(6) L. A. Paquette, R. M. Houser, and M. Rosen, *J. Org. Chem.*, **36**, 905 (1970).

(7) D. C. Dittmer and R. Glassman, *ibid.*, **36**, 999 (1970).

(8) H. E. Zimmerman, G. L. Grunwald, and R. M. Paufler, *Org. Syn.*, **46**, 101 (1966).

(9) For examples, see H. E. Zimmerman and R. M. Paufler, *J. Amer. Chem. Soc.*, **82**, 1514 (1960); L. F. Fieser and M. J. Haddadin, *Can. J. Chem.*, **43**, 1599 (1965); A. B. Evnin and D. Seyferth, *J. Amer. Chem. Soc.*, **89**, 952 (1967).

(10) B. G. Boldyrev and L. M. Khovalko, *J. Gen. Chem. USSR*, **31**, 3843 (1961).

(11) T. B. Johnson and J. A. Ambler, *J. Amer. Chem. Soc.*, **36**, 372 (1914).

(12) M. Rey, E. Dunkelblum, R. Allain, and A. S. Dreiding, *Helv. Chim. Acta*, **53**, 2159 (1970); E. Dunkelblum, M. Rey, and A. S. Dreiding, *ibid.*, **54**, 6 (1971).

(13) T. B. Johnson and I. B. Douglass, *J. Amer. Chem. Soc.*, **61**, 2548 (1939).

(14) C. J. M. Stirling, *J. Chem. Soc.*, 3597 (1957).

(15) J. L. Kice and N. E. Pawlowski, *J. Org. Chem.*, **28**, 1162 (1963); J. L. Kice, G. Guaraldi, and C. G. Venier, *ibid.*, **31**, 3561 (1966).

(16) E. M. LaCombe and B. Stewart, *J. Amer. Chem. Soc.*, **83**, 3457 (1961); W. Davies, D. C. Ennis, and Q. N. Porter, *Aust. J. Chem.*, **21**, 1571 (1968); C. L. McIntosh and P. de Mayo, *Chem. Commun.*, 32 (1969); D. C. Dittmer, R. S. Henion, and N. Takashina, *J. Org. Chem.*, **34**, 1310 (1969).

mediates **3** and **4** by use of 6-methyl-2-pyrone was unsuccessful. No reaction was observed with thiete sulfone under the same conditions used with α-pyrone. Although the result was negative, one might, as a consequence, favor the stereochemistry of **3** over **4** because steric hindrance between the methyl group and the oxygens of the sulfone would inhibit reaction. The regiospecificity implied in the formation of **3** also may result from minimization of the opposition of the strong dipoles of the sulfone and carbonyl groups (*i.e.*, they tend to be as far apart as possible). For this reason, an endo configuration of the initial adduct would be expected.

The reaction of α-pyrone with 3-phenyl-2-thiete 1,1-dioxide[17] also failed even after 10 days at 140°. The phenyl group would have blocked aromatization and the adducts corresponding to **3** or **4** perhaps could have been isolated.

Experimental Section[18]

Reaction of α-Pyrone and Thiete Sulfone.—Thiete sulfone[2] (1.04 g, 10 mmol) was added to α-pyrone[8] (0.960 g, 10 mmol, distilled prior to its use) in *m*-xylene (30 ml). The mixture was refluxed and stirred for 24 hr under nitrogen. The *m*-xylene was removed *in vacuo* and the mixture was chromatographed on Florisil (60–100 mesh). Benzyl α-toluenethiosulfonate (0.720 g, 2.59 mmol) was eluted with hexane and with hexane–benzene. The toluene thiosulfonate was recrystallized from ether: mp 106–107.5° (lit.[10] mp 107–108°); ir (KBr) 1320 (s), 1120 cm^{-1} (s); nmr[19] ($CDCl_3$) δ 4.01 (s, 1), 4.21 (s, 1), 7.35 (s, 5); mass spectrum (70 eV) *m/e* 278 (parent), 214 (parent − SO_2), 91 (C_7H_7). A mixture of starting materials (0.420 g) was eluted with ether. Benzylsulfonic acid (0.180 g, 1.05 mmol) was eluted with ether–ethanol (1:2), dissolved in water, and neutralized with 30% sodium hydroxide. Most of the water was removed *in vacuo* and a white solid (0.130 g) was obtained: mp 250°; ir (KBr) 1200 (b, s), 1130 (s), 1050 (s), 1020 cm^{-1} (s). This solid was treated at 70° with phosphorus pentachloride (0.130 g) in 2 ml of phosphorus oxychloride. Benzylsulfonyl chloride (0.084 g) separated when the reaction mixture was added to water: mp 89.5–90.5°, undepressed by admixture with an authentic sample (lit.[20] mp 91–93°); ir (KBr) 1340 (s), 1250 (s), 1190 (s), 1150 (s), 1120 cm^{-1} (s); nmr ($CDCl_3$) δ 4.88 (s, 2), 7.54 (s, 5); mass spectrum (70 eV) *m/e* 192, 190 (parent), 128, 126 (parent − SO_2), 101 ($SO_2{}^{37}Cl$), 99 ($SO_2{}^{35}Cl$), 91 (C_7H_7). Finally, a water-soluble acidic tarry fraction (0.400 g) was eluted with ethanol.

Benzyl α-Toluenethiosulfonate.—Benzyl α-toluenethiosulfonate was prepared in 52% yield by the method of Boldyrev and Khovalko,[10] mp 106–107.5°. The ir, nmr, and mass spectra were identical with those cited above for this compound.

Benzylsulfonyl Chloride.—Benzylsulfonyl chloride was prepared by the method of Johnson and Ambler,[11] mp 89–91° (lit.[11] mp 92–93°). Its nmr, ir, and mass spectra were identical with those given above for this compound.

Disproportionation of Benzylsulfinic Acid.—Benzylsulfinic acid[14] (0.800 g, 5.13 mmol) was dissolved in *m*-xylene (25 ml); the solution was brought to reflux and stirred 30 hr under nitrogen. Benzyl α-toluenethiosulfonate (0.312 g, 1.12 mmol, 65.5%) and benzylsulfonic acid (0.120 g, 0.70 mmol, 40.8%) were isolated and identified as described above for the reaction of thiete sulfone with α-pyrone.

Registry No.—α-Pyrone, 504-31-4; thiete sulfone, 7285-32-7; benzyl α-toluenethiosulfonate, 16601-40-4; benzylsulfonic acid, 100-87-8; phosphorus pentachloride, 10026-13-8; benzylsulfonyl chloride, 1939-99-7.

(17) W. O. Siegl and C. R. Johnson, *J. Org. Chem.*, **35**, 3657 (1970).

(18) Infrared spectra were recorded on a Perkin-Elmer 137 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates A-60 spectrometer. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU 6E spectrometer. Melting points are uncorrected. *m*-Xylene was distilled from calcium hydride just prior to its use.

(19) δ 4.02, 4.19 reported by P. Allen, Jr., P. J. Berner, and E. R. Malinowski, *Chem. Ind. (London)*, 208 (1963).

(20) E. Fromm and J. Palma, *Ber.*, **39**, 3308 (1936).

The Reaction of Enamines with o-Hydroxy-ω-nitrostyrenes. Preparation of Benzodihydropyrans and Hexahydroxanthenes and Their Rearrangement to Pyrroline 1-Oxides and Hexahydroindole 1-Oxides

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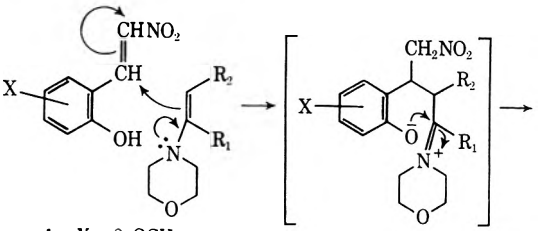
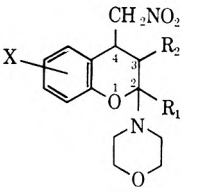
The reaction of enamines with phenolic Mannich bases[1a,b] and *o*-hydroxybenzaldehydes[2] has resulted in the formation of benzodihydropyrans. The present report describes the development of a third method of preparing benzodihydropyrans (**2**) which involves the reaction of enamines with *o*-hydroxy-ω-nitrostyrenes. A useful feature of this approach was the incorporation of a nitromethyl function in the 4 position. The reaction of enamines with nitro olefins has been reported to give good yields of nitrocyclobutanes or nitro ketones.[3,4] In our case the postulated zwitterion intermediate collapsed to a benzodihydropyran **2c** or a hexahydroxanthene **2a,b**, through the intervention of the *o*-hydroxyl, rather than to a nitrocyclobutane or a simple substituted enamine.



1a, X = 3-OCH_3
b, X = 5-OCH_3



2a, R_1 and $R_2 = (CH_2)_4$; X = 8-OCH_3
b, R_1 and $R_2 = (CH_2)_4$; X = 6-OCH_3
c, $R_1 = C_2H_5$; $R_2 = CH_3$; X = 8-OCH_3

Both aliphatic and alicyclic enamines were utilized in this reaction; thus, the morpholine enamine of diethyl ketone yielded a 2-morpholino-4-(nitromethyl)-benzodihydropyran (**2c**) and the morpholine enamine of cyclohexanone gave **4a**-morpholino-9-(nitromethyl)-hexahydroxanthenes (**2a,b**).

In spite of the presence of three asymmetric centers,

(1) (a) M. von Strandtmann, M. P. Cohen, and J. Shavel, Jr., *Tetrahedron Lett.*, 3101 (1965); (b) *J. Heterocycl. Chem.*, **7**, 1311 (1970).

(2) L. A. Paquette, *Tetrahedron Lett.*, 1291 (1965).

(3) M. Kuehne and L. Foley, *J. Org. Chem.*, **30**, 4280 (1965).

(4) A. Risaliti, M. Forchiassin, and E. Valentin [*Tetrahedron*, **24**, 1889 (1968)] have shown that the product of reaction of β-nitrostyrenes and morpholine cyclohexanone enamine has the erythro configuration.

only one compound was generally isolated from the reaction mixture. This is, in part, due to the ability of these cyclic O,N ketals to epimerize[1b] at C-2 and, in part, because of the stereospecificity of the addition reaction which restricts the spatial arrangement at C-3 and C-4 to a cis configuration.[4]

The reactions were effected by heating equimolar amounts of the enamine and nitrostyrene in dioxane at reflux for 1–2 hr, giving generally a 50% yield of the product. The cyclic nature of the compounds was confirmed by the absence of a phenolic OH, C=O, or C=C or C=CN stretching frequency in the ir. The nmr was in agreement with the assigned structures. The spectrum of the xanthene **2a** consisted of a multiplet at δ 6.85 (3 H, phenyl aromatics), octet at 4.8 (2 H, CH_2NO_2), quartet at 4.18 (1 H, benzylic proton), singlet at 3.9 (3, H, OCH_3), 3.62 (4 H, morpholine CH_2O), 2.68 (4, H, morpholine CH_2N) and 1–2.4 (9 H, the methylene envelope). The nmr spectrum of the benzodihydropyran **2c** was analogous.

Reductive Rearrangement of Benzodihydropyrans. The pyrans **2a–c** are formally O,N ketals of γ-nitro ketones. The reduction of γ-nitro ketones has been utilized in the formation of pyrroline and pyrroline 1-oxides.[5] We have now determined that analogous transformations could be achieved with cyclic O,N ketals such as the benzodihydropyran derivatives **2a–c**.

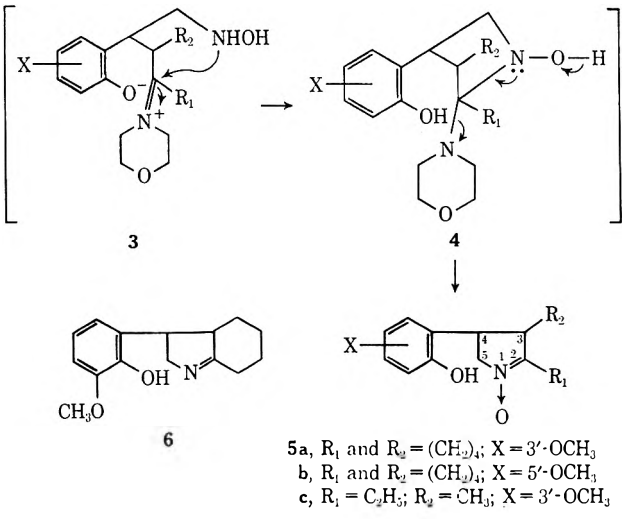
Hydrogenation of **2a** with palladium in ethanol–acetic acid gave the pyrroline 1-oxide derivative **5a**. Assignment of this phenolic nitrone structure rather than the anticipated product of simple reduction, a 4-(aminomethyl)benzodihydropyran, was made on the basis of physical properties, *i.e.*, water solubility, and spectral data: ir (CH_2Cl_2) 3500 (OH), 1620 cm^{-1} (C=N); nmr 2 H multiplet at δ 4.18–4.5 [CH_2N-(O)=C].

The nitrone **5a** could arise through partial reduction of the nitro group to the hydroxylamine followed by cyclization and rearrangement of the hydroxylamine group to the nitrone with elimination of morpholine. The cyclization step probably occurs in the ring-opened form (**3**) (Scheme I), which exists in equilibrium with the closed form.[1b] Consideration of Dreiding models reveals that a direct displacement of morpholine in the presence of the intact pyran ring is unlikely because of severe steric hindrance to the approach of the hydroxylamine moiety. An alternate mechanism would involve hydrolysis of **3** to a ketone with ring closure to **5**.

The configuration at C-3 and C-4, which has been shown above to be cis in **2**, is trans for the two chiral centers in **5**. This change in the spatial arrangement is a consequence of the rotation around the C-4, C-3 axis in the course of the pyrroline ring formation.

A chemical reduction of **2** using aqueous zinc–ammonium chloride[6a,b] also gave **5** in good yield. The pyrroline 1-oxide **5c** was prepared by this method from **2c**. A more complete reduction of **2a** to the 3-(*o*-hydroxyphenyl)hexahydroindole **6** was obtained catalytically with Raney nickel and methanol solvent.

SCHEME I



Experimental Section[7]

1,2,3,4,4a,9a-Hexahydro-5-methoxy-4a-morpholino-9-(nitromethyl)xanthene (2a).—A solution of 145 g (0.74 mol) of 2-hydroxy-3-methoxy-ω-nitrostyrene,[8] 800 ml of dioxane, and 69.6 g (0.8 mol) of cyclohexanone morpholine enamine[9] was heated on the steam bath for 2 hr. About 500 ml of dioxane was removed at reduced pressure and 200 ml of 2-propanol was added to the thick residue. The separated orange crystals were filtered and washed with 2-propanol and then with petroleum ether (bp 30–60°) to give 85 g (32%) of **2a**, mp 198–200°. A total yield of 40–50% of **2a** was isolated by addition of water to the filtrate to precipitate additional crude. Pure material was obtained by recrystallization from tetrahydrofuran–petroleum either, mp 199–201°.

Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.96; H, 7.23; N, 7.73. Found: C, 63.15; H, 7.28; N, 7.48.

7-Methoxy Isomer of 2a (2b).—This compound was prepared from 2-hydroxy-5-methoxy-ω-nitrostyrene by the same procedure used for **2a**: yield 50%; recrystallization from tetrahydrofuran–petroleum ether gave mp 165–167°.

Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 62.96; H, 7.23; N, 7.73. Found: C, 63.00; H, 7.20; N, 7.59.

2-Ethyl-3,4-dihydro-8-methoxy-3-methyl-2-morpholino-4-(nitromethyl)-2*H*-1-benzopyran (2c).—This compound was prepared from 2-hydroxy-3-methoxy-ω-nitrostyrene and the morpholine enamine of diethyl ketone[10] by a procedure similar to that used for **2a**: yield 50%; recrystallization from tetrahydrofuran–petroleum ether gave mp 176–178°.

Anal. Calcd for $C_{18}H_{26}N_2O_5$: C, 61.70; H, 7.48; N, 8.00. Found: C, 61.81; H, 7.46; N, 7.91.

3,3a,4,5,6,7-Hexahydro-3-(2-hydroxy-3-methoxyphenyl)-2*H*-indole 1-Oxide (5a).—A solution of 271.5 g (0.75 mol) of **2a**, 750 ml of glacial acetic acid, and 3 l. of ethanol was hydrogenated for 16 hr at low pressure using 15 g of 10% Pd/C. The catalyst was filtered and the filtrate was concentrated at reduced pressure

(5) J. Hammer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964); F. R. Delpierre and M. Lamchen, *Quart. Rev., Chem. Soc.*, 329 (1965).

(6) The use of aqueous zinc ammonium chloride in the reduction of γ-nitro ketones to Δ¹-pyrroline 1-oxides has been reported: (a) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and A. Todd, *J. Chem. Soc.*, 2094 (1959); (b) M. C. Kloetzel, F. L. Chubb, R. Gobran, and J. L. Pinkus, *J. Amer. Chem. Soc.*, **83**, 1128 (1961).

(7) Melting points were determined with the Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. Infrared spectra were determined with a Baird Model 544 double-beam instrument. Nmr spectra were measured with a Varian A-60 spectrophotometer.

(8) C. B. Gairaud and G. R. Lappin, *J. Org. Chem.*, **18**, 1 (1953).

(9) G. Stork, A. Brizzolava, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).

(10) R. Jacquier, C. Petrus, and F. Petrus, *Bull. Scc. Chim. Fr.*, **9**, 2845 (1966).

to remove most of the solvent. The residue was dissolved in water (750 ml) and enough potassium carbonate was added to neutralize and saturate the solution. The separated material was dissolved in 1.5 l. of methylene chloride and the solution was dried over potassium carbonate, filtered, and concentrated. Ether (300 ml) was added to generate 130 g (66%) of solid **5a**, mp 110–115°. Recrystallization was effected by dissolution in a minimum volume of hot methylene chloride, concentration to about ½ volume, and addition of an equal volume of ethyl acetate: mp 120–122°; nmr δ 6.82 (m, 3, aromatics), 4.18–4.5 (m, 2), 3.9 (s, 3, OCH_3), 2.9–3.7 (m, 3), 1–2.3 (m, 8, methylene envelope).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.69; H, 7.35; N, 5.36.

Alternate Preparation of 5a.—A solution of 0.54 g (0.01 mol) of ammonium chloride in 15 ml of water was added to a solution of 3.6 g (0.01 mol) in **2a** in 75 ml of THF. With vigorous stirring, under nitrogen, zinc powder (7 g) was added over a 2-min period. The mixture was stirred for 45 min and filtered and the filtrate was treated with 50 ml of 1 *N* hydrochloric acid. After 15 min this solution was neutralized with solid potassium carbonate excess and the THF phase was dried further with anhydrous potassium carbonate, filtered, and concentrated. Upon addition of ether to the viscous residue, 2.2 g (85%) of solid **5a** developed, mp 105–110°. Recrystallization was effected as above, mp 118–121°.

2-Hydroxy-5-methoxyphenyl Isomer of 5a (5b).—This compound was prepared from **2b** by the above alternate zinc–NH_4Cl method: yield 78%, mp 180–182°.

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.19; H, 7.44; N, 5.24.

2-Ethyl-4-(2-hydroxy-3-methoxyphenyl)-3-methyl-1-pyrroline 1-Oxide (5c).—A solution of 5.4 g of ammonium chloride in 150 ml of water was added to a warm solution (35°) of 35 g (0.1 mol) of **2c** in 750 mol of tetrahydrofuran. The vigorously stirred mixture was treated with 70 g of zinc powder over the next several minutes. In 15 min, the zinc paste developed into a suspended solid. After ½ hr the reaction was worked up in a fashion similar to that for the alternate preparation of **5a** to give 20.5 g (82.3%) of crude **5c**, mp 101–103°. Recrystallization from EtOAc gave pure nitrone, mp 107–109°.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.30; H, 7.82; N, 5.57.

3,3a,4,5,6,7-Hexahydro-3-(2-hydroxy-3-methoxyphenyl)-2*H*-indole (6).—A mixture of 108.6 g (0.3 mol) of **2a**, 3 l. of methanol, and 30 g of Raney nickel was hydrogenated at low pressure at a temperature of 50° for 16 hr. After filtration of the catalyst, the solution was concentrated to 1-l. volume. A volume of 350 ml of 2 *N* hydrochloric acid was added and the solution was heated on the steam bath for 10 min. Ice water was added to precipitate some red solid. After filtration, concentrated ammonium hydroxide was added to precipitate the tacky base. Recrystallization was effected by dissolution in 200 ml of hot methanol and addition of 100 ml of water to give 25 g (34%) of **6**, mp 135–140°. Recrystallization from absolute ethanol gave pure **6**: mp 140–145°; ir (Nujol) 1655 (C=N), 2500 cm^{-1} (C=NH^+); ir ($CHCl_3$) 1650 (C=N), 3550 cm^{-1} (OH).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.46; H, 7.77; N, 5.89.

Acknowledgment.—The authors are indebted to the Analytical and Physical Chemistry Department under the supervision of Mr. A. D. Lewis. In particular, we wish to thank Dr. C. Greenough for the spectral data and Mrs. U. Zeek for analytical determinations. We also wish to thank the Chemical Development Department under the supervision of Dr. A. W. Ruddy for the large-scale preparation of intermediates.

Registry No.—**2a**, 36848-01-8; **2b**, 40697-22-1; **2c**, 40697-23-2; **5a**, 40697-85-6; **5b**, 40697-86-7; **5c**, 40697-87-8; **6**, 40697-88-9; 2-hydroxy-3-methoxy-ω-nitrostyrene, 1986-06-7; cyclohexanone morpholine enamine, 670-80-4; 2-hydroxy-5-methoxy-ω-nitrostyrene, 35467-98-2; diethyl ketone morpholine enamine, 13654-48-3.

Synthesis of 1,7- and 1,11-Dihydrobenzo[1,2:4,5]dicycloheptene and 1*H*-Benzo[1,2:4,5]dicycloheptenium Tetrafluoroborate(1−)

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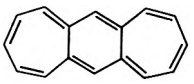
The dihydrobenzo[1,2:4,5]dicycloheptenes (*e.g.*, **3** and **4**) are molecules of considerable synthetic interest, since, in principle, these compounds can act as precursors to a variety of novel conjugated systems. Thus, removal of hydride could provide the monocation **5** and the 14-π-electron dication, proton removal the 18-π-electron dianion, and loss of hydrogen the 16-π-electron hydrocarbon **1**. We now report the synthesis



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of 1,7- (**3**) and 1,11-dihydrobenzo[1,2:4,5]dicycloheptene (**4**), and the conversion of these isomers into 1*H*-benzo[1,2:4,5]dicycloheptenium tetrafluoroborate(1−) (**5**).[1]

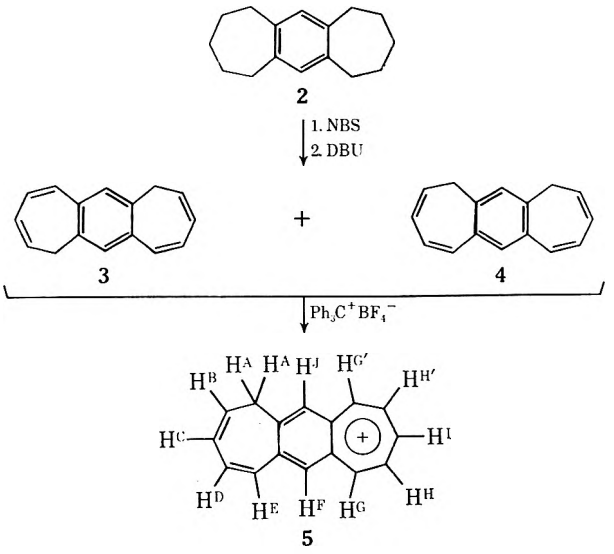
1,2,3,4,5,7,8,9,10,11-Decahydrobenzo[1,2:4,5]dicycloheptene (**2**), prepared by a known route,[2,3] was treated with 4 molar equiv of *N*-bromosuccinimide, and a complex mixture of bromides was formed. The total mixture was dehydrobrominated with 1,5-diazabicyclo[5.4.0]undec-5-ene in dimethylformamide, and the resulting mixture was chromatographed on silica, eluting with petroleum ether (bp 40–60°). A crystalline material was obtained, which on fractional crystallization or chromatography gave mixtures of varying composition of the isomers **3** and **4** (see Experimental Section). Attempts to separate these isomers completely proved unsuccessful, but the mixtures gave satisfactory mass spectral and analytical data. The nmr spectrum of the mixtures showed a singlet in the aromatic region at τ 2.92, assigned to the equivalent aromatic protons of **3**, and singlets at τ 2.75 and 3.06, assigned to the nonidentical aromatic protons of **4**. The allylic protons of **3** and **4** appeared as a doublet (τ 6.97) and the chemical shifts and coupling pattern of the olefinic protons was consistent with structures **3** and **4**.

A mixture (1:2) of the isomers **3** and **4** was treated with trityl fluoroborate in dry acetonitrile under nitrogen, and 1*H*-benzo[1,2:4,5]dicycloheptenium tetrafluoroborate(1−) (**5**) was formed as dark red needles. The nmr spectrum (CD_3CN) was complex [τ 6.49 (H^A, d, $J \approx 6$ Hz), 3.97 (dd, H^B, $J \approx 6$, 10 Hz), 3.68 (H^C, dd, $J \approx 6$, 10 Hz) 3.07 (H^D, dd, $J \approx 6$, 12 Hz), 2.52 (H^E, d, $J \approx 12$ Hz), 1.18–1.46 (H^H, $H^{H'}$, H^F, H^J, m), 0.92 (H^I, dd, $J \approx 10$ Hz), 0.47 (H^G, $H^{G'}$, d, $J \approx 10$

(1) We thank Dr. K. L. Loening, Director of Nomenclature, Chemical Abstracts Service, for helpful discussions concerning the correct name for the cation.

(2) R. Legros and P. Cagniant, *C. R. Acad. Sci.*, **252**, 2733 (1961).

(3) For a second method of preparation, see R. H. Wightman, R. J. Wain, and D. H. Lake, *Can. J. Chem.*, **49**, 1360 (1971).



Hz)] but entirely consistent with the assigned structure. The electronic spectrum [$\lambda_{max}^{CH_3CN}$ 228 nm (ϵ 14,000), 256 (13,700), 261 (12,900), 293 (11,100), 317 (8800), 550 (1800)] resembled that of other annelated tropylium ions.[4]

Attempts to convert **5** into **1** by treatment with trimethylamine according to the method of Dauben and Bertelli[5] gave a complex mixture of products, but no evidence for the production of **1** could be adduced. Reaction of **5** with a second mole of trityl fluoroborate did not lead to the dication, the nmr spectrum remaining virtually unchanged.

Experimental Section

The nmr spectra were run on a Varian HA-100 spectrometer with TMS as internal standard and are reported in τ units. Electronic spectra were recorded on a Unicam SP 800 spectrophotometer. Ir spectra were recorded on a Unicam SP 200 spectrometer. Mass spectra were taken with an AEI MS12 spectrometer at 70 eV.

Preparation of Mixtures of 1,7- (3) and 1,11-Dihydrobenzo[1,2:4,5]dicycloheptene (4).—The hydrocarbon **2** (4.28 g, 20 mmol) and *N*-bromosuccinimide (12.24 g, 80 mmol) were suspended in CCl_4 (300 ml), benzoyl peroxide (20 mg) was added, and the mixture heated under reflux until all of the *N*-bromosuccinimide had reacted (~3 hr). The resulting mixture was filtered to remove the succinimide, and evaporation of the solvent from the filtrate gave a glass (13.4 g). The nmr spectrum (CCl_4) showed signals at τ 2.4–2.6 (m, aromatic), 4.3–4.7 (b, s, benzylic), and 7.2–8.4 (aliphatic). The glass was dissolved in dimethylformamide (40 ml), 1,5-diazabicyclo[5.4.0]undeca-5-ene (10 ml), was added, and the mixture stirred at 80° for 3 hr. The mixture was then poured into water, 50 ml of 5 *N* HCl was added, and the mixture was extracted with ether (3 × 100 ml). The ethereal extracts were washed with water (3 × 50 ml), saturated NaCl solution (1 × 50 ml), and dried (Na_2SO_4). The solvent was removed by evaporation and the resulting dark solid was chromatographed on silica gel (90 g), eluting with petroleum ether. A white crystalline material was obtained (1.75 g) which slowly turned yellow on standing. A number of purification procedures were investigated. Six recrystallizations of the material from ethanol gave white plates (45 mg) which consisted of a 4:1 mixture of **3** and **4**: mass spectra *m/e* 206; ir (KBr) 1500, 1430, 1370, 910, 800, 690 cm^{-1}; nmr ($CDCl_3$) 6.98 (d, $J \approx 7$ Hz), 4.25 (m, $J \approx 7$, 9.5 Hz), 3.96 (dd, $J \approx 5.5$, 9.5 Hz), 3.58 (dd, $J \approx 5.5$, 12 Hz), 3.06 (s), 2.96 (d, $J \approx 12$ Hz), 2.92 (s), 2.15 (s); λ_{max}^{EtOH} 240 nm (ϵ 8000), 311 (14,000).

Anal. Calcd for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 93.09; H, 6.83.

Glc (Carbowax 20M, 256°) of the crystalline material (500 mg) gave a 1:1 mixture (55 mg) of **3** and **4**. Column chromatography on 20% $AgNO_3$-impregnated alumina (80 g)[6] of the crystalline material (800 mg), eluting with ether–benzene, gave a 1:2 mixture (85 mg) of **3** and **4**. A crystalline tetrahydrobenzo[1,2:3,4]dicycloheptene fraction (180 mg) was also isolated in this separation.

Preparation of 1*H*-Benzo[1,2:4,5]dicycloheptenium Tetrafluoroborate(1−) (5).—A mixture (1:2) of the olefins **3** and **4** (25 mg, 0.12 mmol) was added to a solution of trityl fluoroborate (40 mg) in dry acetonitrile (10 ml) under dry N_2. The mixture was stirred until all of the olefin had dissolved (~1 hr), the solvent was removed *in vacuo*, and the residue was washed with dry ether (3 × 5 ml) to give **5** (30 mg, 0.10 mmol, 83%) as dark red needles, which decomposed on attempted mp determination: for nmr see discussion; for electronic spectrum, see discussion; ir (KBr), 1500, 1060, 920, 700 cm^{-1}.

Anal. Calcd for $C_{16}H_{13}BF_4$: C, 65.75; H, 4.78. Found: C, 65.77; H, 4.48.

Registry No.—**2**, 14314-88-6; **3**, 40682-46-0; **4**, 40682-47-1; **5**, 40674-83-7; *N*-bromosuccinimide, 128-08-5; trityl tetrafluoroborate, 340-02-6.

(4) See G. Naville, H. Strauss, and E. Heilbronner, *Helv. Chim. Acta*, **43**, 1221 (1960).

(5) H. J. Dauben and D. J. Bertelli, *J. Amer. Chem. Soc.*, **83**, 4659 (1961).

(6) See R. Wolovsky, *J. Amer. Chem. Soc.*, **87**, 3638 (1965).

Thermally Induced Side Chain to Ring Migrations in Aromatic Systems

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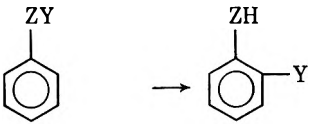
A number of organic molecules undergo rearrangements, by a variety of mechanistic pathways in which a group migrates from a side chain in an aromatic system to a ring position.[1] These migrations may be thermally induced, or acid[1] or base catalyzed.[2]



The purpose of this report is to call attention to the rather general existence of this kind of thermally induced migration which arises during the high-temperature pyrolyses of appropriately substituted aromatic compounds. The recently reported conversion of phenylacetonitrile to *o*-tolunitrile by our laboratories[3] and by Wentrup and Crow[4] is an example of such a migration (see Table I). The relatively high yield of ortho isomer relative to meta and para isomers (tolunitrile) suggests the participation of an intramolecular migration.[1] On the other hand, competitive cleavage also occurs, as shown from the formation of benzene, toluene, and the isomeric cyanophenylacetonitriles.

Many of these side chain to ring migrations are obscured because the initially formed rearrangement

(1) M. J. S. Dewar in "Molecular Rearrangements," Vol. 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, Chapter 5.

(2) W. von E. Doering and R. A. Bragole, *Tetrahedron*, **22**, 385 (1966).

(3) N. F. Haidar, Ph.D. Thesis, University of Kentucky, Lexington, Ky., 1970.

(4) C. Wentrup and W. D. Crow, *Tetrahedron*, **26**, 3965 (1970).

TABLE I

RELATIVE CONCENTRATIONS[a] OF PYROLYSATE COMPONENTS OBTAINED FROM PHENYLACETONITRILE AT 850°

Compd	Concn, %
Benzene	3.1
Benzonitrile	0.6
α-Cyano-*m*-tolunitrile	0.4
α-Cyano-*o*-tolunitrile	1.1
α-Cyano-*p*-tolunitrile	1.1
Diphenylacetonitrile	0.8[b]
Fluorene	0.8[b]
Indole–cinnamonitrile	0.4
Phenanthrene–anthracene	0.1
Phenylacetonitrile	80.4
2-Phenylindole	0.2
p-Phenylphenylacetonitrile	0.3
trans-Stilbene	0.6
Toluene	7.6
o-Tolunitrile	3.0
Wt of pyrolysate, g	8.8
Wt pyrolyzed, g	10.2

[a] Relative concentrations are area per cent as determined by glpc analysis. [b] Unseparated mixture of diphenylacetonitrile and fluorene.

products undergo ring closure. Thus, the results of experiments reported in Tables II and III show that

TABLE II

RELATIVE CONCENTRATIONS[a] OF PYROLYSATE COMPONENTS OBTAINED FROM DIPHENYLMETHANE AND *o*-METHYLBIPHENYL AT 850°

Component	—Substance pyrolyzed— Diphenylmethane	*o*-Methylbiphenyl
Anthracene	0.5	
Benzene	9.7	6.7
Biphenyl	0.4	
Diphenylmethane	64.6	
Fluorene	7.6	45.1
Indene	0.2	
o-Methylbiphenyl		39.6
m-Methylbiphenyl	0.5	0.7
p-Methylbiphenyl	0.7[b]	1.0
Naphthalene	0.1	0.1
trans-Stilbene	1.2[c]	
Styrene	0.1	
Toluene	8.6	3.7
Triphenylmethane	0.7	
Wt of pyrolysate, g	3.80	5.70
Wt of substance pyrolyzed, g	4.02	6.16

[a] Relative concentrations are area per cent as determined by glpc analysis. [b] Fraction also contained acenaphthylene. [c] Identification based upon glpc retention time and uv spectrum.

the formation of fluorene from diphenylmethane[5] and of dibenzofuran from phenyl ether probably arises from the rearrangement products *o*-methylbiphenyl and *o*-hydroxybiphenyl, respectively. Likewise the formation of acridine from *N*-benzylaniline[6] undoubtedly involves the proposed side chain to ring migration. Carbazole formation from diphenylamine[7] and phenanthrene formation from bibenzyl[5] are further examples of the rearrangement.

(5) J. W. Sweeting and J. F. K. Wilshire, *Aust. J. Chem.*, **15**, 89 (1962).
(6) H. Meyer and A. Hofmann, *Monatsh.*, **37**, 698 (1916).
(7) C. Graebe, *Justus Liebigs Ann. Chem.*, **167**, 125 (1873).

TABLE III

RELATIVE CONCENTRATIONS[a] OF PYROLYSATE COMPONENTS OBTAINED FROM *o*-HYDROXYBIPHENYL AND PHENYL ETHER AT 700°

Component	—Substance pyrolyzed— *o*-Hydroxybiphenyl	Phenyl ether
A. Neutral Fraction		
Benzene	4.0	0.4
Biphenyl	4.6	
Dibenzofuran	10.7	2.0
Naphthalene	0.05	0.4
Phenyl ether		96.7
Wt of neutral fraction, g	20.1[b]	5.4
B. Acid Fraction		
o-Hydroxybiphenyl	76.3	
Phenol	4.1	94.0
Wt of acid fraction, g	20.1[b]	0.3
Wt of substance pyrolyzed, g	20.2	6.0

[a] Relative concentrations are area per cent as determined by glpc analysis. [b] Combined weight of acid and neutral fractions.

Experimental Section

Ultraviolet spectra were measured in cyclohexane using a Perkin-Elmer Model 202 spectrophotometer, infrared spectra were measured in chloroform or carbon tetrachloride using a Beckman IR-8 spectrophotometer equipped with a mirror beam condenser, and nmr spectra were measured in deuteriochloroform or carbon tetrachloride (TMS internal standard) using a Varian T-60 spectrometer. Mass spectra were determined on a Hitachi RMU-6E double focusing mass spectrometer using 70 eV ionizing energy with the inlet system at 200°. Glpc analyses and preparative separations of the pyrolysate constituents were carried out on an F & M Model 810 gas chromatograph using a thermal conductivity detector.

Materials.—The substances pyrolyzed were commercially available samples and were used as received. Purities were checked prior to use by glpc analysis.

Pyrolyses.—The pyrolyses were carried out in the apparatus previously described[8] using 20–30 ml of Berl saddles or Vycor beads, and a syringe driven by a Troemer monodrum for the introduction of liquid samples (or a rotating screw device for solid samples) into the pyrolysis tube. Addition rates were *ca.* 4.5 g/hr. Nitrogen gas flow rates were 60 ml/min in the phenylacetonitrile, diphenylmethane, and *o*-methylbiphenyl pyrolyses and 100 ml/min in the *o*-hydroxybiphenyl and phenyl ether pyrolyses. The liquid products were collected in two traps, each of which was cooled in a Dry Ice–chloroform–carbon tetrachloride mixture, and dissolved in ether. The *o*-hydroxybiphenyl pyrolysate was separated into neutral and acidic fractions by extraction with 5% NaOH.

Separation and Identification of Components.—Components of the neutral and acidic fractions were separated by glpc using a 25 ft × 0.375 in. 20% Apiezon L (Anakrom 50/60 U) column heated isothermally at 90° for 8 min and then programmed at 2°/min or 4°/min to 280°.

Identifications of components are based on comparisons of glpc retention times, ultraviolet spectra, and infrared spectra with those obtained from authentic samples with the following exceptions. The identifications of diphenylacetonitrile and *p*-phenylphenylacetonitrile were based upon comparisons of glpc retention times, infrared spectra, mass spectra, and nmr spectra with those obtained from authentic compounds. Biphenyl and dibenzofuran were identified from comparisons of glpc retention times and ultraviolet and nmr spectra. Estimation of relative abundances of constituents are based on area per cent values obtained from glpc analyses. The results are reported in the tables.

Acknowledgment.—This study was carried out under Contract No. 12-14-100-9476-(73) and 12-14-100-9575-

(8) J. M. Patterson, A. Tsamasfyros, and W. T. Smith, Jr., *J. Heterocycl. Chem.*, **5**, 727 (1968).

(73) with the Agricultural Research Service, U. S. Department of Agriculture, administered by the Athens, Ga. Area, Richard B. Russell Agricultural Research Center, Athens, Ga. 30604.

Registry No.—Phenylacetonitrile, 140-29-4; diphenylmethane, 101-81-5; o-methylbiphenyl, 643-58-3; o-hydroxybiphenyl, 90-43-7; phenyl ether, 101-84-8.

Steric Factors in the Solvolysis of Haloallenes

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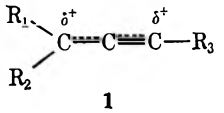
Earlier work[1-3] has established the mechanism of solvolysis of trisubstituted haloallenes in aqueous acetone and aqueous ethanol solutions as a unimolecular C–X bond heterolysis yielding the resonance-stabilized cation, **1**. The solvolysis reaction of the haloallenes



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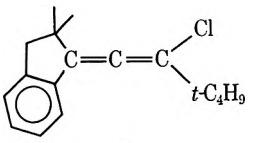
studied parallels the SN1 reaction of saturated systems in every respect. First-order rate laws are obeyed, a large excess of added nucleophile has no effect on the rate of solvolysis, a common ion rate depression is observed, the substituent effects and temperature and solvent dependence of the reaction rate are consistent with a carbonium ion mechanism, and products derived from reaction at each end of **1** are observed.

It was noted, however, that an aromatic ring at C-1 had a much larger effect on the rate of solvolysis than one placed at C-3. For example, 1-chloro-1-phenyl-3-*tert*-butyl-4,4-dimethyl-1,2-pentadiene (R_3 = C_6H_5; R_1 = R_2 = *tert*-butyl) solvolyzes eight times as rapidly as 3-chloro-2,2,6,6-tetramethyl-5-phenyl-3,4-heptadiene (R_1 = R_3 = *tert*-butyl; R_2 = C_6H_5) in 50:50 (v/v) acetone–water at 35°. This is apparently due to the inability of an aromatic ring in the 3 position to achieve the coplanarity necessary for overlap with the developing electron-deficient π MO of the cation. A similar situation obtains in the solvolysis of aralkyl chlorides where 1-chloro-2,2-dimethylindane is reported to solvolyze 10^4 times as fast as 1-chloro-1-phenyl-2,2-dimethylpropane in 80% ethanol at 45°.[4,5]

To test this hypothesis in our system the allenyl halide **2** was prepared. Treatment of the propargyl alcohol obtained upon nucleophilic addition of *tert*-butylethynyllithium to 2,2-dimethylindan-1-one with



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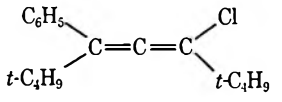
$SOCl_2$ afforded the desired chloroallene. The data in Table I support the conclusion that **2** reacts by a

TABLE I

RATES OF SOLVOLYSIS OF **2** IN AQUEOUS ACETONE SOLVENT

Acetone–water (v/v)	T, °C	10^4k, sec^{-1}
70:30	24.62 ± 0.01	13.0 ± 0.3
80:20	24.62 ± 0.01	2.89 ± 0.03
90:10	24.62 ± 0.01	0.463 ± 0.004
90:10	34.68 ± 0.02	1.68 ± 0.03
90:10	45.30 ± 0.02	4.47 ± 0.03

mechanism identical with that of other trisubstituted haloallenes. A plot of these data *vs.* Y yields m = 0.73. The temperature dependence of the rate constant yields $\Delta H^{\pm}$ = 20.0 kcal/mol and $\Delta S^{\pm}$ = −11.0 eu at 25°. These data also point up the remarkable rate enhancement over the structurally similar compound **3** (R_1 = R_3 = *tert*-butyl; R_2 = C_6H_5). The



3

indanyl derivative, **2**, reacts 6800 times as fast as the open-chain analog, **3**, in 90:10 acetone–water at 35°.

It is likely that some of this rate acceleration is due to the presence of an ortho alkyl substituent in the fused-ring compound which is not present in the open-chain compound. However, for this rate acceleration to be accounted for solely by the substituent effect, ρ must equal −12, a value at least twice as large as that observed for any other solvolysis reaction. Furthermore, since no hybridization changes occur at C-3, any strain introduced by the five-membered ring remains the same in the ground state and transition state. Thus, no change in rate due to the introduction of strain in the ground state is to be expected. It seems likely therefore that a major portion of the rate enhancement is associated with the constrained coplanarity of the aromatic ring and vacant π MO and the attendant stabilization of **1**. We have attempted unsuccessfully thus far to prepare analogs of **2** and **3** having substituents in the aromatic ring in an attempt to assess the magnitude of substituent effects on this system.

Experimental Section

All melting points and boiling points are uncorrected. Ir spectra were obtained using a Perkin-Elmer Model 457 spectrophotometer or a Bausch and Lomb Model 250 spectrophotometer. Nmr spectra were obtained using a Perkin-Elmer Model R-20B spectrometer. Microanalyses were performed by Atlantic Microlabs, Atlanta, Ga.

2,2-Dimethyl-1-indanone was prepared by dialkylation of 1-indanone with methyl iodide and potassium *tert*-butoxide in *tert*-butyl alcohol according to Woodward, *et al.*[6] Distillation at reduced pressure (80–81° at 0.7 mm) afforded the ketone in

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(2) M. D. Schiavelli, S. C. Hixon, H. W. Moran, and C. J. Boswell, *J. Amer. Chem. Soc.*, **93**, 6989 (1971).
(3) M. D. Schiavelli, R. P. Gilbert, W. A. Boynton, and C. J. Boswell, *J. Amer. Chem. Soc.*, **94**, 5061 (1972).
(4) G. Baddeley and J. Chadwick, *J. Chem. Soc.*, 368 (1951).
(5) G. Baddeley, J. W. Rasburn, and R. Rose, *J. Chem. Soc.*, 3168 (1958).
(6) R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1131 (1957).

55% yield: mp 42–43° (lit.[6] mp 42–43°); ir (CCl_4) 1710 cm^{-1} (C=O); nmr (CCl_4) δ 1.15 (s, 6), 2.9 (s, 2), 7.3 (m, 4).

1-*tert*-Butylethynyl-2,2-dimethylindan-1-ol was prepared as described earlier[2] for the general synthesis of tertiary propargyl alcohols by addition of *tert*-butylethynyllithium to 2,2-dimethyl-1-indanone. Distillation afforded the alcohol in 82% yield (99–100° at 0.5 mm): ir (neat) 3460 cm^{-1} (O—H), 2250 cm^{-1} (C≡C); nmr (CCl_4) δ 1.0 (s, 3), 1.15 (s, 3), 1.23 (s, 9), 2.02 (s, 1), 2.55 (s, 1), 2.78 (s, 1), 7.05 (m, 4).

1-(*tert*-Butylchlorovinylidene)-2,2-dimethylindan (2) was prepared according to the general procedure for the preparation of chloroallenes by Jacobs and Fenton.[7] After three successive distillations from a small amount of sodium borohydride to remove unreacted alcohol, the desired chloroallene was obtained in 23% yield: bp 96–100° at 0.3 mm; ir (neat) 1945 cm^{-1} (C=C=C); nmr (CCl_4) δ 1.22 (s, 9), 1.29 (s, 6), 2.86 (s, 2), 7.08 (m, 4).

Anal. Calcd for $C_{17}H_{21}Cl$: C, 78.31; H, 8.06; Cl, 13.63. Found: C, 78.40; H, 8.12; Cl, 13.46.

Kinetic Procedure.—The rate of appearance of HCl was measured conductometrically as described earlier.[2,3] All rates are the average of triplicate determinations. Acetone was purified according to Denoon.[8] Kinetic solvent solutions exhibited initial measured conductances of less than 2 μmho.

Acknowledgments.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. The senior author acknowledges the support of the College of William and Mary Faculty Research Fellowship Program.

Registry No.—2, 40548-49-0; 2,2-dimethyl-1-indanone, 10489-28-8; 1-*tert*-butylethynyl-2,2-dimethylindanol, 40548-50-3; *tert*-butylethynyllithium, 37892-71-0.

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A New Synthesis of Benzocyclobutene[1]

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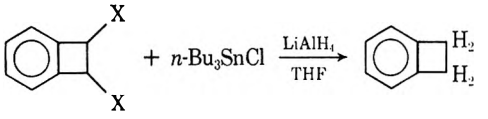
Received March 7, 1973

In connection with current studies of transition metal complexes of strained cyclic olefins, we required a supply of benzocyclobutene. The preparations of benzocyclobutene (2) previously reported in the literature are inconvenient for large-scale synthesis. Hydrogenation of 1,2-diiodobenzocyclobutene with palladium on carbon[3] requires a specially aged sodium ethoxide catalyst and involves lengthy purifications. High temperature pyrolyses *in vacuo* (without or with uv irradiation) of 1,3-dihydroisothianaphthene 2,2-dioxide[4,5] require special apparatus. A recent synthetic route to 2 involves the dissolving metal reduction of benzocyclobutenyl acetate[6] which is prepared by the cycloaddition of vinyl acetate to benzenediazonium-2-carboxylate, an explosive benzyne[7] precursor requiring special handling.

We devised a convenient reduction of the mixture of 1,2-dibromo- and 1,2-diiodobenzocyclobutene[3b] (1) which is readily prepared in 90% yields from the commercially available α,α,α′,α′-tetrabromo-*o*-xylene (Columbia Organic Chemicals, Co., Inc.). Reduction of 1 with lithium aluminum hydride in refluxing tetrahydrofuran gave 2 in 20% yields. This method was inconvenient since large quantities of lithium aluminum hydride were required and much polymeric material was formed, thus making purification tedious. A more expedious method involved the reduction of 1 with tri(*n*-butyl)tin hydride generated *in situ* from tri(*n*-butyl)tin chloride with lithium aluminum hydride. Since the reduction of 1 with the hydride gives



1, X = Br or I 2

2 and tri(*n*-butyl)tin halide (which can be reduced to the hydride), only a limited amount of tri(*n*-butyl)-tin chloride is needed. Thus this route is convenient for a large-scale synthesis since the reaction is carried out in one reaction vessel with no special apparatus required, the course of the reaction is readily monitored by nmr spectroscopy, and the purification procedures are straightforward. Assuming the reactants to be pure 1,2-dibromobenzocyclobutene, yields of >50% of 2 have been realized.

Experimental Section

Benzocyclobutene (2).—To a 1000-ml round-bottom flask fitted with a magnetic stirrer, heating mantle, and reflux condenser was added tetrahydrofuran (200 ml), tri(*n*-butyl)tin chloride (70 g, 0.22 mol), and 100 g of a mixture of 1,2-dibromo- and 1,2-diiodobenzocyclobutene.[3b] Lithium aluminum hydride (10 g, 0.26 mol) was added in 0.5-g portions over a period of 6 hr. while a gentle reflux was maintained. The mixture was allowed to cool to room temperature, transferred to a 1000-ml erlenmeyer flask, treated sequentially with 10 ml of H_2O, 10 ml of 15% NaOH, and 30 ml of H_2O, and shaken after each addition. The resulting mixture was filtered through a large sintered-glass filter, and the residue was washed with two 50-ml portions of THF. The filtrate was rapidly distilled under reduced pressure (12 mm) into a trap cooled in liquid nitrogen until 202 ml of volatile material had been collected and the pot temperature reached 60°. While at 60°, the residue was placed under high vacuum (10^{-2} mm) and an additional 6 ml of volatile material collected. The nmr spectrum of the residue showed no remaining benzocyclobutene. The volatile fractions were combined (208 ml) and poured into 1250 ml of water in a large separatory funnel. The lighter organic layer was separated from the aqueous layer and then extracted three times with 50-ml portions of water, dried over $MgSO_4$, and filtered through a sintered-glass funnel. The remaining solvent was removed by distillation through a 25-cm Vigreux column until the head temperature reached 80°. The product (2) was collected *via* short-path distillation of the residue: 20 g, ~50% yield; bp 143°; uv max (95% EtOH) 260, 265.5, 271.5 nm; nmr (CCl_4) τ 6.88 (s, 4), 3.03 (m, 4).

Registry No.—1 (X = Br), 22250-72-2; 1 (X = I), 6639-21-0; 2, 694-87-1; tri(*n*-butyl)tin chloride, 1461-22-9.

(1) We gratefully acknowledge support from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Graduate School of Boston University.

(2) An EPDA, Part E Fellowship from the Office of Education is gratefully acknowledged.

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The Reaction Product of 3,3-Dichloro-2-methylpropenal and Piperidine

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Contribution No. 4652 from the Arthur Amos Noyes Laboratory of Chemical Physics, California Institute of Technology, Pasadena, California 91109

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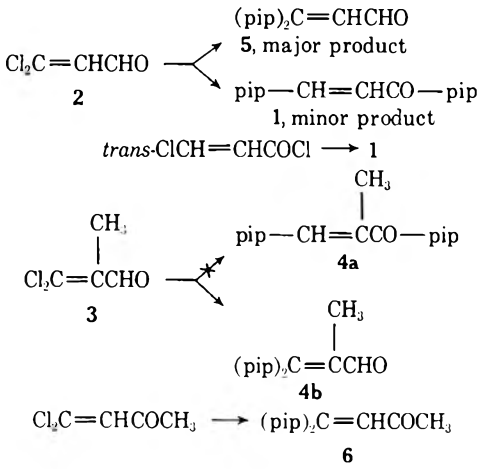
We recently attempted to prepare the vinylogous urea **1** (Chart I) by reaction of 3,3-dichloropropenal

CHART I

SUMMARY OF REACTIONS[a]



[a] pip = $C_5H_{10}N$.

(2) with piperidine. Our hope for success lay in the claim by Kundiger and Morris,[1] later mentioned in passing somewhat less definitely,[2] that 3,3-dichloro-2-methylpropenal (**3**) gives the 2-methyl homolog (**4a**) of **1** with piperidine. The authors[1] suggested initial attack of the amine on the carbonyl group as a mechanism. Since the aldehyde **2** is less hindered at the carbonyl than its homolog **3**, we anticipated the formation of the desired urea **1**.

We found that reaction of **2** gave a mixture of two olefins (nmr) in 70–80% crude yield. The first, **5**, 85–90% of the mixture, had absorptions at δ 4.18 (d, J = 7 Hz) and 9.03 (d, J = 7 Hz). The other, 10–15% of the mixture, absorbed at δ 4.91 (d, J = 13 Hz) and 7.14 (d, J = 13 Hz). Only the absorptions of the minor product are consistent with those of **1**. An authentic sample of **1** prepared from *trans*-3-chloropropenoyl chloride has the same absorptions (confirmed by peak enhancement) and coupling constant, and two distinct envelopes for the α-piperidino protons centered at δ 3.10 and 3.37.

The spectrum of the major product **5** is consistent with that expected for the formyl ketenaminal 3,3-bis(piperidino)propenal. The δ values and coupling constant are reasonable for =CHCHO in this compound. The α-piperidino protons are in a single envelope for this compound.[3]

We therefore duplicated the preparation of Kundiger and Morris.[1] To avoid possible loss of a minor or more soluble isomer, we initially assayed the crude material. There was no absorption near δ 7 but a singlet at δ 9.0 and one envelope for the α-piperidino protons, centered at δ 3.12. Work-up gave ~40% yield of a bright yellow solid with the properties reported by the above workers. The nmr spectrum of this purified material was the same as that of the crude, allowing for medium differences and minor impurities. Comparison of this spectrum with those of the aminal **5** and the vinylogous urea **1** strongly suggests that compound **4** is the formyl ketenaminal **4b** rather than the vinylogous urea **4a**.

Support for our structure assignment for **4** is found in the nmr spectrum of the isomeric acetyl ketenaminal **6**. This aminal **6** has α-piperidino proton absorptions in a single envelope, like **4** and **5** and unlike **1**.

We conclude therefore that the title product is in fact 3,3-bis(piperidino)-2-methylpropenal (**4b**). None of the evidence cited by the original workers[1] excludes this structure. Thus, **4b** as a *vinylidenolog*[4] of a formamide can base hydrolyze to give 2 equiv of piperidine; the other hydrolysis product, 2-formylpropionic acid, would be the same from **4a** or **4b**. The low carbonyl stretching frequency is consistent with either structure; our comparative data in dilute CCl_4 give bands at 1616 cm^{-1} for **4b**, 1627 cm^{-1} for the isomeric acetyl ketenaminal **6**, and 1640 cm^{-1} for **1**.

The small amount of **1** formed from **2** may be from initial attack at the carbonyl[1] or by the rearrangement of the possible intermediate 3-chloro-3-(piperidino)-propenal to 1-(3-chloropropenoyl)piperidine[5] and aminolysis of this vinylogous carbamyl chloride.

Experimental Section

Caution.—β-Chlorovinyl carbonyl compounds exhibit mustard gas-like vesicatory action. The aldehyde **2** and 4,4-dichloro-3-buten-2-one are cleaved by concentrated aqueous alkali to explosive chloroacetylene. All the dihalides can be safely destroyed by slow addition to excess aqueous ammonia.

General Synthetic Procedure.—Essentially the procedure of Kundiger and Morris was followed.[1] The dihalides were added dropwise with stirring at 0–5° to 6–8 molar equiv of piperidine in ether or benzene and stirred at room temperature for 1–2 days. The piperidine hydrochloride was filtered off and washed thoroughly with ether (90–100% yield), and the ether solution was stripped on a rotary evaporator [50–60° (13 mm)]. If any solid appeared and then redissolved (piperidine hydrochloride) or an amine odor remained, the material was taken up in hot methylcyclohexane, filtered, and restripped.

(1) D. G. Kundiger and G. F. Morris, *J. Amer. Chem. Soc.*, **80**, 5988 (1958). A referee has pointed out that the structure assignment for the title product **4** was corrected in the Ph.D. Thesis of G. F. Morris [Kansas State University, 1961; *Diss. Abstr.*, **21**, 3273 (1961)]. Examination of the thesis shows that Morris also prepared authentic **4a** and proved it different from the title reaction product **4b**. However, the result first alleged by Kundiger and Morris is not in general incorrect. The *tri*halopropenals reportedly give 2,3-dihalopropenamides with piperidine [C. Raulet and E. Levas, *Bull. Soc. Chim. Fr.*, 2139 (1963)].

(2) R. L. Soulen, D. G. Kundiger, S. Searles, Jr., and R. A. Sanchez, *J. Org. Chem.*, **32**, 2661 (1967).

(3) Acyl ketenaminals typically have low barriers to rotation about the carbon–carbon double bond and have their α-amino proton absorption isosynchronous or nearly so: J. Sandström and I. Wennerbeck, *Chem. Commun.*, 1088 (1971), and E. Ericsson, J. Sandström, and I. Wennerbeck, *Acta Chem. Scand.*, **24**, 3102 (1970), and references cited therein. We have found 4,4-bis(dimethylamino)-3-buten-2-one to have a single sharp absorption for all four *N*-methyls at 38° with only slight broadening at −70° in ether.

(4) Name adopted to describe the relationship between, *e.g.*, RCOX and RCOC=CX_2, as does *vinylog* for RCOC=CX, and *ethynylog* for RCOC≡CX [latter due to K. Hafner and M. Neuenschwander, *Angew. Chem., Int. Ed. Engl.*, **7**, 459 (1968)]. A referee has noted that *vinylidenolog* does not distinguish XCH=C(CHO)$_2$ from X_2C=CHCHO.

(5) M. Neuenschwander and A. Niederhauser, *Chimia*, **25**, 122 (1971).

When stored in sealed vials, compounds **1**, **4b**, and **6** discolor slowly. However, decomposition was very slow when these compounds were stored in *open* vessels over KOH|H_2SO_4| paraffin shavings in a desiccator protected from light at room temperature.

Reaction of 3,3-Dichloropropenal (2).—The starting material was prepared as reported.[6]

Following the general procedure, 2.50 g (20 mmol) of **2** in 50 ml of ether was allowed to react with 15 ml (~150 mmol) of piperidine in 100 ml of ether. Work-up afforded 3.37 g (76%) of an orange oil, which was a ~7:1 mixture of **5** and **1**: nmr (CCl_4) δ 1.62 (broad and unresolved, all 12 β- and γ-piperidino H's in both products), ~3.18 (broad and distorted multiplet, all eight α-piperidino H's in both products), 4.18 (d, J = 7 Hz, α-vinyl H in **5**), 4.91 (d, J = 13 Hz, α-vinyl H in **1**), 7.14 (d, J = 13 Hz, β-vinyl H in **1**), 9.03 (d, J = 7 Hz, formyl H in **5**). The absorptions at δ 4.91 and 7.14 were enhanced on addition of authentic **1** to the mixture.

1-[3-(Piperidino)propenoyl]piperidine (1).—Distillation of 48.0 g (450 mmol) of *trans*-3-chloropropenoic acid[7a] with 82 ml (710 mmol) of benzoyl chloride through a 30-cm Vigreux column keeping the head temperature below 116°[7b] afforded 32.6 g (58%) of *trans*-3-chloropropenoyl chloride: bp 107–116° (748 mm) [lit.[7a] bp 115–115.5° (1 atm)]; nmr (neat) δ 6.22 (d, 1, J = 13 Hz, α-H), 7.32 (d, 1, J = 13 Hz, β-H). This material contained some dissolved HCl and a little benzoyl chloride but was not further purified.

Following the general procedure, 12.5 g (100 mmol) of the acid chloride in 30 ml of ether was allowed to react with 60 ml (600 mmol) of piperidine in 350 ml of ether. Work-up gave 19.3 g (87%) of crude yellow product. Two recrystallizations from ethyl acetate afforded slightly stained material, mp 98.5–99.5°. Two further recrystallizations gave near-white needles: mp 99–100°; ir (CCl_4) 1640 (s, C=O), 1572 cm^{-1} (s, C=C); nmr (CCl_4) δ 1.57 (broad, 12, β- and γ-piperidino H's), 3.10 and 3.37 (two distorted multiplets cleanly separated, 4 each, α-piperidino H's), 4.89 (d, 1, J = 13 Hz, α-vinyl H), 7.11 (d, 1, J = 13 Hz, β-vinyl H).

Anal. Calcd for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60. Found: C, 70.06; H, 10.01; N, 12.44.

3,3-Bis(piperidino)-2-methylpropenal (4b).—In 40 ml of ether 7.0 g (50 mmol) of the aldehyde **3**[1] was allowed to react with 35 ml (350 mmol) of piperidine in 200 ml of ether in the usual way to give 8.71 g (74%) of crude yellow-orange solid. The reported work-up[1] and repeated recrystallization from ethyl acetate and cyclohexane gave yellow needles of **4b**: mp 127–129° (lit.[1] mp 129–131°); nmr (CCl_4) δ 1.47 (s, CH_3), 1.59 (broad, β- and γ-piperidino H's, base overlaps δ 1.47, total both 15), 3.12 (distorted poorly resolved multiplet but one envelope, 8, α-piperidino H's), 8.97 (s, 1, CHO); ir (CCl_4) 2853 (m), 2819 (m, sh), 2727 (w, sh) (possibly formyl CH),[8] 1616 (s, C=O), 1541 cm^{-1} (vs, C=C); ir (Nujol) 1604, 1535–1520 cm^{-1} (lit., 1608, 1527 cm^{-1}).

4,4-Bis(piperidino)-3-buten-2-one (6).—4,4-Dichloro-3-buten-2-one was prepared as previously described (Darzens–Friedel–Crafts acetylation of 1,1-dichloroethene)[9a,b] except that substitution of dichloromethane for carbon tetrachloride as solvent facilitates stirring.

The general procedure, using 13.9 g (100 mmol) of the dichlorovinyl ketone in 25 ml of benzene and 65 ml (650 mmol) of amine in 180 ml of the same solvent, gave 21.8 g (92%) of crude yellowish product.[10] Two recrystallizations from ethyl acetate gave 14.5 g (61%) of near-white crystals: mp 79.5–80.5° (lit.[11] mp 80–81°) [rework of the mother liquors ultimately gave a total of 19.3 g (82%) of material of mp >78°]; ir (CCl_4) 1627 (s, C=O), 1501 cm^{-1} (s, C=C); ir (Nujol) 1617, 1508 cm^{-1} (lit.[11] 1623, 1517 cm^{-1}); nmr (CCl_4) δ 1.56 (broad, 12, β- and γ-piperidino H's), 1.80 (s, 3, methyl), 3.07 (broad and distorted but one envelope, 8, α-piperidino H's), 4.23 (s, 1, vinyl H); nmr ($CDCl_3$) δ 1.60, 1.96, 3.17, 4.40 (lit.[11] δ 1.60, 1.98, 3.19, 4.41). This compound has an anise odor not abolished when stored for several months as described above.

Acknowledgment.—This research was supported by the National Science Foundation.

Registry No.—**1**, 6162-62-5; **2**, 2648-51-3; **3**, 1561-34-8; **4b**, 40428-93-1; **5**, 40428-94-2; **6**, 10099-09-9; piperidine, 110-89-4; *trans*-3-chloropropenoic acid, 2345-61-1; *trans*-3-chloropropenoyl chloride, 3721-36-6; 4,4-dichloro-3-buten-2-one, 5780-61-0.

(6) M. Levas, *Ann. Chim. (Paris)*, [12] **7**, 719 (1952).

(7) (a) E. Gryszkiewicz-Trochimowski, W. Schmidt, and O. Gryszckewicz-Trochimowski, *Bull. Soc. Chim. Fr.* 593 (1948); (b) H. C. Brown, *J. Amer. Chem. Soc.*, **60**, 1325 (1938). This method was chosen for its convenience rather than yield.

(8) L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958, p 157.

(9) (a) S. Searles, Jr., R. A. Sanchez, R. L. Soulen, and D. G. Kundiger, *J. Org. Chem.*, **32**, 2655 (1967); (b) J. B. Ellern and H. B. Gray, *J. Org. Chem.*, **37**, 4485 (1972).

(10) The acetylene, 4-(piperidino)-3-butyn-2-one is an intermediate (ir). Use of too little piperidine permits this intermediate to decompose to red-brown polymeric material. If diethylamine is substituted for piperidine, addition of excess amine to the corresponding acetylene is so slow that it can be isolated in >75% yield. These results will be presented in detail in a future article.

(11) W. E. Truce, D. J. Abraham, and P. Son, *J. Org. Chem.*, **32**, 990 (1967).

Synthesis of DL-3-(3,4-Dihydroxyphenyl)alanine Methyl Ester and Related Compounds

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Successful results with L-3-(3,4-dihydroxyphenyl)-alanine (L-dopa) in the treatment of Parkinson's disease[2] have stimulated efforts in both the synthesis and resolution of DL-dopa. Ring-hydroxylated α-amino acids have usually been prepared[3] by condensation of an appropriate aromatic aldehyde with an active methylene compound, such as an azlactone in the Erlenmeyer synthesis. Low to moderate yields (30–60%) of DL-dopa have been reported by these methods.

We wish to report the synthesis of DL-3-(3,4-dihydroxyphenyl)alanine methyl ester, which was carried out *via* a single-vessel process in 83% yield. Methyl isocyanoacetate[4] (**1**), a material known[5] to undergo a wide variety of carbanion condensation reactions, was used as a starting material.[6] The isocyano group, in addition to activating the α-carbon atom for proton abstraction, affords an ideal protective group for a primary amine easily regenerated by acid hydrolysis. Condensation of **1** with 3,4-dibenzyldioxybenzaldehyde (**2**) in methyl alcohol with potassium *tert*-butoxide as the catalyst yielded the alkoxide

(1) Summer Research Associate, Procter & Gamble.

(2) A. Barbeau, *Can. Med. Ass. J.*, **101** (13), 59 (1959); D. B. Calne and M. Sandler, *Nature (London)*, **226**, 21 (1970); J. D. Parkes, K. J. Zilka, D. M. Calver, and R. P. Knill-Jones, *Lancet*, **1**, 259 (1970).

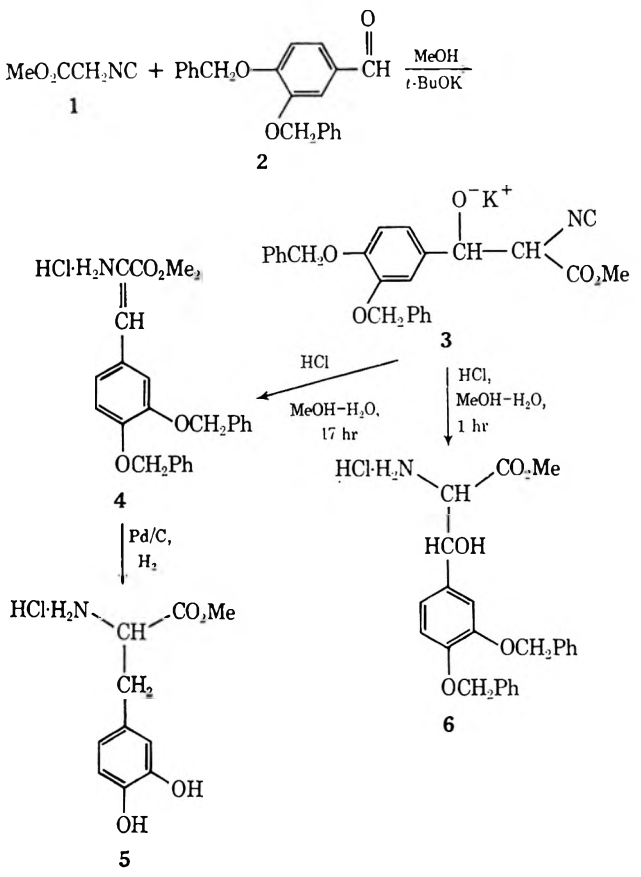
(3) J. P. Greenstein and M. Winitz, Ed., "Chemistry of the Amino Acids," Wiley, New York, N. Y., 1961, pp 2713–2723.

(4) We have used methyl isocyanoacetate to prepare several amino acids; U. S. patent application filed December 19, 1969, serial no. 886,748.

(5) U. Schoellkopf, *Angew. Chem., Int. Ed. Engl.*, **9**, 763 (1970), and references cited therein.

(6) Recently, Schoellkopf and coworkers and Suzuki, *et al.*, have used isocyano and isocyanopropionic esters to prepare alkyl amino acids and α-methyl-dopa by alkylation of the isocyano ester carbanions: U. Schoellkopf, D. Hoppe, and R. Jentsch, *Angew. Chem., Int. Ed. Engl.*, **10**, 331 (1971); M. Suzuki, K. Matsumoto, T. Iwasaki, and K. Okumura, *Chem. Ind. (London)*, 687 (1972).

3. Hydrochloric acid was added and the solution was heated at reflux for 17 hr to give the amine hydrochloride 4. Catalytic hydrogenation of the mixture with 5% Pd/C at 50 psi reduced the olefinic linkage of 4. It was critical at this step to keep the solution acidic. Neutralization of 4 before hydrogenation caused loss of the amino and ester groups, probably through condensation reactions. Vacuum evaporation of the solvent and recrystallization of the product from methanol–ether gave an 83% yield of the hydrochloride of methyl 3-(3,4-dihydroxyphenyl)alanate (5). Acid hydrolysis of 5 produced DL-dopa in essentially quantitative yield.



If the acidic hydrolysis of 3 is carried out for 1 hr instead of 17 hr the alcohol 6 is the predominant product. This intermediate may prove valuable for the synthesis of norepinephrine or dopamine derivatives.

The synthesis also works smoothly for other aromatic aldehydes. For example, 3,4-methylenedioxybenzaldehyde and 3,4-dimethoxybenzaldehyde were converted to 5; however, an additional hydrolysis using boron tribromide in methylene chloride[7] was needed to remove the methylene or methyl ether groups.

Experimental Section

Methyl Isocyanoacetate (1).—The phosgene method of Ugi[8] was used for the synthesis of 1. Methyl *N*-formylglycinate (41 g, 0.31 mol) was dissolved in a mixture of 600 ml of methylene chloride and freshly distilled triethylamine (79.2 g, 0.78 mol). Phosgene mixed with argon was then slowly bubbled through the mixture for 1–1.2 hr to maintain a temperature of 40°. The triethylamine hydrochloride was filtered and the methylene chloride was evaporated. The residue was treated with benzene and refiltered. Methyl isocyanoacetate (18 g, 0.18 mol, 58% yield) was obtained after distillation at 77.0–79.0° (2.5 mm).

Reaction of Methyl Isocyanoacetate (1) with 3,4-Dibenzyldioxybenzaldehyde (2).—Potassium *tert*-butoxide (2.5 g, 0.022 mol) was added to a methanolic solution of 1 (2 g, 0.02 mol) and the mixture was heated to 60°, at which time 3,4-dibenzyldioxybenzaldehyde (6.36 g, 0.02 mol) was added. The resulting solution was heated for 3 hr and cooled to room temperature and 10 ml of concentrated hydrochloric acid and 10 ml of water were added. This solution was refluxed for 17 hr, cooled to room temperature, and hydrogenated at 50 psi (Parr apparatus) for 4 hr with palladium on charcoal (5%) as a catalyst. Evaporation of the solution to dryness yielded a tan solid which on recrystallization from methanol–ether gave 4.1 g (0.017 mol, 83% yield) of the methyl ester hydrochloride of dopa (5). A proton nmr spectrum of 5 in DMSO-d_6 showed signals at δ 6.66 (m, 3, HAr), 4.08 [t, 1, $HC(NH_2 \cdot HCl)CO_2CH_3$], 3.70 (s, 3, H_3CCO_2–), 3.00 (d, 2, CH_2Ar). This nmr spectrum and an ir spectrum of 5 are identical with spectra of an authentic sample prepared by refluxing dopa with a methanolic solution of hydrochloric acid for 1 hr. Compound 5 can be hydrolyzed to dopa by refluxing in 6 *N* hydrochloric acid for 4 hr.

Reaction of Methyl Isocyanoacetate with 3,4-Methylenedioxybenzaldehyde.—A similar procedure was used with 3,4-methylenedioxybenzaldehyde (3.0 g, 0.02 mol) except that hydrolysis was carried out for 1 hr. The solvent was evaporated under vacuum and the residue was washed with ether to remove residual piperonal. The benzylic alcohol (type 6) was the major product as evidenced by its infrared spectrum (plates), ~3500 (OH), 1725 cm^{-1} ($-CO_2CH_3$), and nmr spectrum (DMSO-d_6), δ 4.45 (HCOH). This material was hydrolyzed further with HCl–H_2O–MeOH and evaporated to give 4.5 g (81%) of olefinic material (type 4): ir (KBr) 1695 cm^{-1} (ester C=O); nmr (DMSO-d_6) δ 7.12 (m, 3, HAr), 6.42 (s, 1, HC=C), 6.01 (s, 2, OCH_2O), 3.80 (s, 3, CO_2CH_3). This material was hydrogenated using platinum oxide in acetic acid to give 4.1 g (0.016 mol, 80% yield) of 3,4-methylenedioxyphenylalanine methyl ester after recrystallization from methanol–ether: mp 276–279° (lit.[9] mp 278–280°); nmr (DMSO-d_6) δ 6.90 (m, 3, HAr), 6.00 (s, 2, OCH_2O), 4.14 [t, 1, $HC(NH_2 \cdot HCl)CO_2CH_3$], 3.65 (s, 3, CO_2CH_3), 2.85 (d, 2, CH_2Ar). The product was further identified by conversion to its *N*-acetyl derivative, mp 107–108° (lit.[10] mp 107–108°). The 3,4-methylenedioxyphenylalanine methyl ester was converted to 5 by boron tribromide using the method of McOmie, *et al.*[7] To 1 g of this product was added 4 ml of boron tribromide in 50 ml of methylene chloride and the reaction mixture was refluxed for 6 hr. At the end of this period excess acetic anhydride was added and the reaction mixture was stirred for 1 hr, at which time the mixture was poured into water and hydrolyzed for 0.5 hr. The mixture was evaporated and then treated with MeOH–HCl–H_2O at reflux for 2 hr. After evaporation and recrystallization from methanol–ether, 0.3 g (35% yield) of 5 was obtained.

These experiments to produce type 4 can also be efficiently accomplished in a single-vessel process in 80% yield.

Reaction of Methyl Isocyanoacetate with 3,4-Dimethoxybenzaldehyde.—When a procedure identical with reaction of 1 with 3,4-methylenedioxybenzaldehyde was used with 3,4-dimethoxybenzaldehyde (3.3 g, 0.02 mol), methyl 3,4-dimethoxyphenylalanate hydrochloride (4.4 g, 0.016 mol, 80% yield) was obtained. Treatment of this product with excess boron tribromide in methylene chloride and acidification with hydrochloric acid in methanol gave 3.9 g (78% yield) of 5 after recrystallization from methanol–ether.

Registry No.—1, 39687-95-1; 2, 5447-02-9; 4, 40635-70-9; 5, 40611-00-5; 6, 40635-71-0; 3,4-methylenedioxybenzaldehyde, 120-57-0; 3,4-dimethoxybenzaldehyde, 120-14-9.

(7) J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron*, **24**, 2289 (1968).

(8) I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, *Angew. Chem., Int. Ed. Engl.*, **4**, 472 (1965).

(9) K. S. Narang, N. Ray, and T. D. Sachdeva, *J. Indian Chem. Soc.*, **13**, 260 (1936).

(10) M. Ohraa, *J. Pharm. Soc. Japan*, **72**, 145 (1952).

The Formation of *cis*- and *trans*-1,2-Dimethoxyethylene in the Potassium *tert*-Butoxide Initiated Elimination on Substrate 1,1,2-Trimethoxyethane

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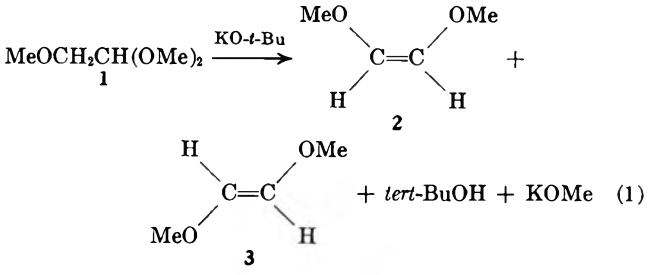
There is very little information in the literature on alkoxide initiated eliminations on substrates bearing poor leaving groups, such as RO^- where R = Me, Et, etc.[1] We report here on the potassium *tert*-butoxide initiated elimination on 1,1,2-trimethoxyethane (**1**) as substrate to produce *cis*- and *trans*-1,2-dimethoxyethylene (**2** and **3**, respectively), *tert*-butyl alcohol, and potassium methoxide (eq 1). Com-

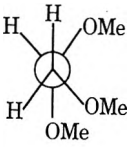


$$\underset{\mathbf{1}}{MeOCH_2CH(OMe)_2} \xrightarrow{KO\text{-}t\text{-}Bu} \underset{\mathbf{2}}{\overset{MeO}{\underset{H}{}}\!\!>\!C\!=\!C\!<\!\overset{OMe}{\underset{H}{}}} + \underset{\mathbf{3}}{\overset{H}{\underset{MeO}{}}\!\!>\!C\!=\!C\!<\!\overset{OMe}{\underset{H}{}}} + \textit{tert}\text{-BuOH} + KOMe \quad (1)$$

pounds **2** and **3** have been previously obtained by the dechlorination of 1,2-dimethoxy-1,2-dichloroethane.[2,3] Earlier attempts to prepare **2** and **3** *via* the dehydrochlorination of 1-chloro-1,2-dimethoxyethane have been reported by Scheibler[4] and Baganz, but in the present authors opinion these compounds were not unambiguously identified. Similarly McElvain and Stammer[5] failed to duplicate the olefin preparation as described by Scheibler.

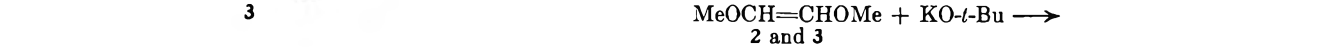
Results and Discussion

The results from two elimination runs performed in a bomb reactor at 165 ± 5° are shown in Table I. These data were obtained after a number of runs were made to determine the optimum conditions for carrying out the eliminations. The reaction was much too slow at 126° (the boiling point of **1**) and at 200° extensive amounts of dark-colored products were formed. Since the cis:trans ratio was ~2:1, the cis formation probably proceeds by a lower energy mechanism with one conformation of the substrate (**1**) reacting preferentially over the other. The eliminations could also proceed by a cis-syn departure of the leaving group and the β hydrogen, but our results cannot distinguish this possibility. Evidence in the literature for many E2 eliminations favors the anti elimination for the present case.[6-9] More recent investigations[10-12] on the "syn–anti dichotomy" reveal an intriguing pattern of results in which cis olefins are formed by anti elimination, but trans olefins by syn elimination. In support of the high cis:trans ratio found for reaction 1, anti elimination on conformer **1a** seems reasonable. In addition, the dealcoholation of **1** by a continuous pyrolysis over alumina yields the cis olefin (**2**) almost exclusively with no evidence for extensive side reactions.[13]



1a

The formation of methyl *tert*-butyl ether (**4**) as a reaction product (Table I) indicates that nucleophilic substitution was also taking place. In the reaction of diglyme with potassium *tert*-butoxide, no evidence for substitution was found.[1] Compound **4** can be produced by attack of the *tert*-butoxide on the starting substrate **1** and on the dimethoxyethylenes **2** and **3**. However, the most likely route to **4** was *via* the reaction of **2** and **3** with potassium *tert*-butoxide since the electron-delocalized enolate ion (**5**) of methoxyacetaldehyde would be the leaving group in this case (eq 2). Since the total number of moles of **2**, **3**, and **4** produced almost equals the amount of *tert*-butyl alcohol formed (Table I), substitution *via* the olefins **2** and **3** appears reasonable.



$$\underset{\mathbf{2}\text{ and }\mathbf{3}}{MeOCH{=}CHOMe} + KO\text{-}t\text{-}Bu \longrightarrow \underset{\mathbf{4}}{MeO\text{-}t\text{-}Bu} + \underset{\mathbf{5}}{MeOCH{=}CH{-}OK} \quad (2)$$

An independent experiment was carried out similar to reaction 2. The major product from the reaction of the olefins with potassium *tert*-butoxide was methyl *tert*-butyl ether (**4**). Compound **4** was observed in a 41% yield. If the total amount of both cis and trans olefins **2** and **3** that formed in reaction 1 equalled the amount of *tert*-butyl alcohol produced exclusively, a conversion of 44% (SN2 substitution of potassium *tert*-butoxide on products **2** and **3**) would give the amount of **4** that formed (Table I). This appears to be confirming evidence for assigning the substrate undergoing substitution to the cis and trans olefins **2** and **3** and not methoxy acetal **1**. The product **5** was not isolated. The above reaction was carried out at 120° and not 165° to control the extent of reaction 2. Higher temperature would have led to too rapid reaction with the alcohol-free *tert*-butoxide that we employed.[14]

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TABLE I

POTASSIUM *tert*-BUTOXIDE INITIATED ELIMINATION ON 1,1,2-TRIMETHOXYETHANE (1)

		Reactants, mmol		Products, mmol					
Run[a]	Time, hr	KO-*t*-Bu	1	*t*-BuOH	2	3	4	1[b]	X_A,%[c]
1	30	63.5	196	14.8	4.39	2.09	5.90	179	19.6
2	33	64.3	209	15.6	4.83	2.34	6.39	189	21.1

[a] The reaction was carried out in a Parr bomb reactor at 165 ± 5°. The products were separated on a 10-ft, 0.25-in. column containing 20% Carbowax 20M on Chromosorb W. The recovery of solid and liquid products was 96% in both runs. [b] Unreacted. [c] The conversion of limiting reactant, potassium *tert*-butoxide, to form products **2**, **3**, and **4**.

Although the presence of ketene dimethyl acetal (**6**) was never observed in reaction 1, it could be argued that 6 was formed as in shown reaction 3 and under-

$$1 + \text{KO-}t\text{-Bu} \longrightarrow CH_2{=}C(OMe)_2 + t\text{-BuOH} + KOCH_3 \quad (3)$$

went substitution with potassium *tert*-butoxide yielding methyl *tert*-butyl ether (**4**). If that were the case, **6** (a reaction intermediate) would not be observed. The fact that we observe **1** → **2** + **3** and not **6** is probably due to the decrease in acidity of the proton bound to the carbon atom bearing the two methoxy groups[15-17] in compound **1**.

To support this argument **6** was prepared *in situ* in a bomb reactor (reaction 4) and allowed to be in

$$\underset{\mathbf{7}}{BrCH_2CH(OMe)_2} + \text{KO-}t\text{-Bu} \longrightarrow \mathbf{6} + t\text{-BuOH} + KBr \quad (4)$$

the presence of excess potassium *tert*-butoxide at 120° for 8 hr. No methyl *tert*-butyl ether (**4**) was observed. This was confirmed by gas chromatography using an authentic sample of **4**. McElvain, *et al.*, has used this procedure to produce a series of ketene acetals.[16,18,19] He also observed that ketene dimethyl acetal remains unaffected if heated alone for 6 hr at 200°.[20] The above results are reasonable in light of the work[19] that was done recycling **6** through a strong base, $NaOC(CH_3)_2Ph$, at 175–185°. No substitution or elimination products were observed.

Elementary analysis, ir absorption (see Experimental Section) and nmr spectroscopy are in accord with the assigned structures **2** and **3**. The τ values (CCl_4) relative to TMS for **2** and **3** (**3** values in parenthesis) are 4.28 (3.85) for the vinyl protons and 6.48 (6.60) for the methoxy protons. The absorptions appeared as sharp singlets and the peak areas were in the expected ratio of 1:3.

Details on the thermodynamics of cis–trans isomerization of the 1,2-dimethoxyethylenes are being reported elsewhere.[21]

Experimental Section

Methoxyacetaldehyde Dimethyl Acetal (1).—Methoxy acetal **1** was prepared from bromoacetaldehyde dimethyl acetal (**7**) and sodium methoxide *via* a Williamson ether synthesis employing a modification of that used by McElvain[5] for the ethoxy derivative. Compound **7** was either prepared by the addition of bromine to vinyl acetate in methanol[22,23] or purchased from Columbia Organic Inc.

Potassium *tert*-Butoxide.—This base was prepared by cleavage of di-*tert*-butyl peroxide with potassium metal in 1,2-dimethoxyethane solvent.[24] The solvent was removed under vacuum in a rotary evaporating apparatus. All transfers were made under purified nitrogen. The purity of KO-*t*-Bu was established as better than 98% by titration with standard HCl.

Elimination Reactions on Methoxy Acetal 1.—A number of exploratory runs were made with solid potassium *tert*-butoxide both at atmospheric and elevated pressures to determine the optimum conditions necessary for reaction to occur. The reactions under atmospheric pressure were much too slow and no appreciable amounts of products were formed at the boiling point of the acetal (126°) for periods of up to 48 hr. A number of runs were then made in a closed bomb reactor at 150–200°. It was found that reasonable reaction rates could be obtained at 165°. A typical quantitative run at 165 ± 5° was carried out as follows. Solid KO-*tert*-Bu (7.10 g, 0.0635 mol) and 23.5 g (0.196 mol) of **1** was weighed into the monel bomb reactor under a dry N_2 atmosphere. The bomb was sealed and immersed in an oil bath at 165 ± 5° for 30 hr. Final pressure at this temperature was 200 psig. The bomb was removed from the bath and cooled to room temperature. After cooling to 0°, the contents were transferred quantitatively to a small standard taper flask under N_2. The liquid (23.4 g) was removed under vacuum in a rotary evaporating apparatus and collected in a cooled receiver (−40°). A 0.6991-g sample of the solid residue (6.00 g) was titrated with 1.007 *N* H_2SO_4 (5.65 ml) to pH 7 (Beckman Zeromatic pH meter). Thus, the solid residue contained 48.4 mequiv of base.

The liquid products were subjected to analytical and preparative gas chromatography (vpc) on Carbowax 20M on Chromosorb W. Five peaks were found which were in order of increasing retention time: *tert*-butyl methyl ether (**4**), *tert*-butyl alcohol, *trans*-1,2-dimethoxyethylene (**3**), *cis*-1,2-dimethoxyethylene (**2**), and methoxy acetal **1**. The peaks were collected, identified by their ir absorption, and compared with authentic samples, except for **2** and **3**. The reaction mixture was analyzed by quantitative gas chromatography using a synthetic mixture of reaction products prepared gravimetrically. The results for two runs are shown in Table I. The ratio of cis:trans isomer (**2**:**3**) for both runs was 2.1:1.0. After removal of most of the methyl *tert*-butyl ether and some of the *tert*-butyl alcohol on a Todd distillation column, preparative vpc on the pot residue gave sufficient quantities of **2** and **3** for running elementary analyses and for determining the nmr spectra.

Anal. for **2**. Calcd for $C_4H_8O_2$: C, 54.00; H, 9.10. Found: C, 53.97; H, 9.10.

Anal. for **3**. Calcd for $C_4H_8O_2$: Same as above. Found: C, 54.08; H, 9.46.

The average ir vibrational frequencies found (5% in CCl_4) for **2** and **3** (**3** values in parenthesis) were vinyl C–H stretching at 3031 (3084), double-bond stretching at 1693 (1661), C–O stretching at 1116 (1084), and C–H out of-plane bending at 718 (960) cm^{-1}. Nmr absorption relative to tetramethylsilane (TMS) is covered in the main section.

Reaction of *cis*-1,2-Dimethoxyethylene (2) with Potassium *tert*-Butoxide.—A small Parr bomb reaction, fitted with a pressure gauge, was charged with 1.5032 g (0.01342 mol) of potassium *tert*-butoxide and 5.0325 g (0.05188 mol) of **2**. The reaction was placed in a 120 ± 0.1° constant-temperature oil bath for 8 hr. The final pressure was 100 psig. The reactor was cooled to room

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temperature and vented. The reaction mixture was transferred to a 25-ml flask and the liquid portion transferred on a high vacuum system. The total recovery of solids and liquids was 95% (6.2096 g). The liquid portion was analyzed by quantitative gas chromatography. Methyl *tert*-butyl ether (4) was observed in 41% yield. The solid products (1.7989 g) were dissolved in water and titrated with standard HCl (14.5 ml of 1.00 *N* HCl). This represented 14.5 mequiv of base from the solid products.

Reaction of Bromo Acetal 7 with Potassium *tert*-Butoxide.—A Parr reaction bomb was charged with 1.1256 g (0.0101 mol) of potassium *tert*-butoxide, 6.4422 g (0.0871 mol) of *tert*-butyl alcohol, and 0.8623 g (0.0051 mol) of 7. The reactor was heated at 120 ± 0.1° for 8 hr. The final pressure reading was 30 psig. The reactor was cooled to room temperature and vented. The product mixture was transferred on a high vacuum system and the liquid products were collected in a cooled (−60°) receiver at 0.1 mm pressures. The liquid portion was analyzed by quantitative gas chromatography. The yield of ketene dimethyl acetal (6) was 52%. The total recovery of solid and liquid was 8.1359 g (97% recovery). No 4 was observed.

Registry No.—1, 24332-20-5; 2, 7062-96-6; 3, 7062-97-7; 4, 1634-04-4; 6, 922-69-0; 7, 7252-83-7; potassium *tert*-butoxide, 865-47-4; *tert*-butyl alcohol, 75-65-0.

A Convenient Synthesis of Adamantylideneadamantane[1]

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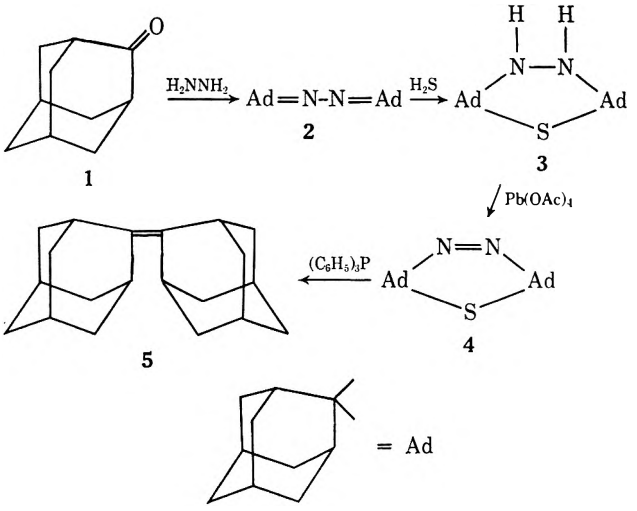
Recent investigations in this laboratory of the photooxidation of adamantylideneadamantane (5) in pinacolone solvent have provided the first direct evidence for the intermediacy of perepoxides in the addition of singlet oxygen to alkenes to form 1,2-dioxetanes.[2] Adamantylideneadamantane (5) has also been the subject of considerable interest because of the unusual stability of the 1,2-dioxetane[3] and the bromonium ion[4] obtained from this alkene.

We have found the synthesis of 5[5] *via* the carbenoid dimerization with *gem*-dibromoadamantane and zinc–copper couple to be very sensitive to the surface area and activity of the Zn–Cu couple. Reduction of the dibromide to adamantane is often the predominant reaction. We are therefore prompted to report a convenient, high-yield synthesis of 5 based on the extrusion of nitrogen and sulfur from an azo sulfide 4.[6]

Condensation of adamantanone (1) with hydrazine hydrate gives the azine 2. Addition of hydrogen sulfide to 2 yields the thiadiazolidine 3. Oxidation of 3 with lead tetraacetate affords the thiadiazine 4. Adamantylideneadamantane (5) is obtained by heating a melt of 4 and triphenylphosphine at 125°. The overall yield of 5 from 1 is 65%.



Experimental Section

Methods.—Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared spectra were measured on a Perkin-Elmer Model 257 grating infrared spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model T-60 spectrometer with tetramethylsilane as internal standard. Microanalyses were performed by Midwest Microlabs, Inc., Indianapolis, Ind.

Adamantanone Azine (2).—A solution of hydrazine hydrate (98%, 1.30 g, 26 mmol) in 15 ml of *tert*-butyl alcohol was added dropwise under nitrogen over a period of 45 min to a stirred refluxing solution of adamantanone (5.22 g, 35 mmol) in 60 ml of *tert*-butyl alcohol. After the addition was complete, the solution was refluxed for an additional 12 hr and subsequently allowed to stand at ambient temperature for 24 hr. The solvent was removed on a rotary evaporator to give an off-white crystalline mass to which was added 200 ml of water. The aqueous mixture was extracted with ether (4 × 100 ml). The combined ether extracts were washed with brine, dried ($MgSO_4$), and concentrated to give following recrystallization from hexane 5.10 g (98%) of 2: mp 313–315°; ir (KBr) 2885, 1622, and 1430 cm^{-1}; nmr ($CDCl_3$) δ 3.28 (m, 1 H), 2.62 (m, 1 H) and 1.93 (m, 12 H).

Anal. Calcd for $C_{20}H_{28}N_2$: C, 81.03; H, 9.52; N, 9.54. Found: C, 80.86; H, 9.51; N, 9.30.

Adamantanespiro-2′-(1′,3′,4′-thiadiazolidine)-5′-spiroadamantane (3).—Hydrogen sulfide was bubbled through a solution of the azine 2 (12.2 g, 41.1 mmol), and 5 mg of *p*-toluenesulfonic acid in 300 ml of 1:3 acetone–benzene at ambient temperature. Thin layer chromatography (silica gel, ethyl ether) indicated complete consumption of 2 after 12 hr. The solvent was removed on a rotary evaporator to give 12.8 g (95%) of the thiadiazolidine 3. This material was used in the subsequent step without further purification. Recrystallization from hexane afforded colorless crystals of 3: mp 300–307° dec; ir (KBr) 2880, 1705, and 1620 cm^{-1}; nmr ($CDCl_3$) δ 3.62 (br, 1 H) and 2.25–1.26 (m, 14 H).

2′,5′-Dihydroadamantanespiro-2′-(1′,3′,4′-thiadiazine)-5′-spiroadamantane (4).—To a suspension of $CaCO_3$ (20.7 g, 0.21 mol) in 300 ml of benzene at 0° was added in several portions lead tetraacetate (20.7 g, 46.7 mmol); the mixture was stirred for 20 min. A mixture of thiadiazolidine 3 (11.85 g, 35.9 mmol) and 300 ml of benzene was added dropwise with stirring over a period of 1.5 hr. After the addition was complete, the mixture was stirred at ambient temperature for 8 hr. Thin layer chromatography (silica gel, ether) indicated complete consumption of 3. Upon addition of 400 ml of water, a brown precipitate formed which was removed by filtration. The aqueous layer was separated, saturated with NaCl, and extracted with ether. The organic portions were combined, washed with brine, dried ($MgSO_4$), and concentrated to give 10.94 g (94%) of a yellow residue 4, mp 140–145°. This material was used in the subsequent step

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without further purification. Column chromatography over silica gel with 70:30 ether–hexane afforded colorless crystals of **4**: mp 145–146° dec; ir (KBr) 2870, 1710, 1570, and 1440 cm^{-1}; nmr ($CDCl_3$) δ 2.98 (m, 1 H), 2.78 (m, 1 H), and 1.95 (m, 12 H).

Anal. Calcd for $C_{20}H_{28}N_2S$: C, 73.12; H, 8.59. Found: C, 73.06; H, 8.98.

Adamantylideneadamantane (5).—An intimate mixture of thiadiazine **4** (1.092 g, 3.32 mmol) and triphenylphosphine (2.04 g, 7.79 mmol) was heated at 125–130° for 12 hr under an atmosphere of nitrogen. Column chromatography of the residue over silica gel with hexane gave 0.668 g (74%) of **5**, mp 184–185° (lit.[5] mp 184–187°).

Registry No.—**1**, 700-58-3; **2**, 39555-34-5; **3**, 40682-51-7; **4**, 40682-52-8; **5**, 30541-56-1; hydrazine, 302-01-2.

Reduction of *meso*-1,2-Dibromo-1,2-diphenylethane to 1,2-Diphenylethane by Hydrazine

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Many reagents dehalogenate vicinal dihalides to yield alkenes:[1] I^-, SH^-, ArS^-, $ArSO_2^-$, AlH_4^-, $RCHCOR^-$, $ArNH_2$, $ArNHNH_2$, C_5H_5N, Ar_2Hg, $(CH_3O)_3P$, Ar_3P, Zn, Mg, Cr(II), Bu_3SnH, Cl^-, Br^-, $Ph_2CCH_3^-$, Ph_2CH^-, $C_{10}H_8\cdot^-$, $RCHCO_2CH_3^-$, $(CH_3O)_3BH^-$, $2\text{-}C_{10}H_7OH$, $(Me_3Si)_2Hg$, $(C_2H_5O)_3P$, Cu, Cu(I), Sn(II), Co(II), Fe(II), and Ti(III). These reactions all involve attack on halogen, leading either to an E2 transition state or a halonium ion intermediate (two-electron reductants) or to radical intermediates (one-electron reductants).[1k,l]

On the other hand only a single, inadvertent instance (below) of reduction to the *alkane* has been reported in systems of this type.[2] (The reduction of vicinal dibromide to alkane by $NaBH_4$ is apparently a pair of independent displacements by hydride.[3])

We have found that hydrazine reduces *meso*-stilbene dibromide ($STBr_2$) to bibenzyl (BB).

Results and Discussion

The Reaction with Hydrazine Alone.—Variable quantities of *cis*-1-bromo-1,2-diphenylethene are produced (Table I). The anti stereochemistry and the increasing proportion of this product (Table II) accompanying increasing concentration of N_2H_4 (a good base, $pK_a^{BH^+}$ 8.11) are consistent with straightforward E2 dehydrobromination of $STBr_2$ (eq 1). The

$$\underset{\text{meso}}{\text{PhCHBrCHBrPh}} + N_2H_4 \longrightarrow \underset{\text{cis}}{\text{PhCH=CBrPh}} + N_2H_5^+Br^- \quad (1)$$

more basic solvents also dehydrobrominate $STBr_2$ in parallel with N_2H_4 (Table I).

trans-Stilbene (ST) formation (Table I) results from stereospecific anti dehalogenation, implying nucleophilic attack on bromine by a two-electron donor,[1l] either N_2H_4, the Br^- present as a result of reaction 1, or solvent. The production of BB as well as ST can then be rationalized by paths 2–4 or 5–7. Both paths involve the potentially interceptible intermediate diimide, NH=NH. We demonstrated the presence of NH=NH by the reduction of cyclohexene added to the $STBr_2$–N_2H_4 reaction; cyclohexane is formed at the expense of BB (Table III).

$$N_2H_4 + >CBrCBr< = >C=C< + \overset{+}{N}H_2\overset{+}{N}H_2Br\ Br^- \quad (2)$$

$$\overset{+}{N}H_2\overset{+}{N}H_2Br\ Br^- + 2N_2H_4 = NH=NH + 2\overset{+}{N}H_2\overset{+}{N}H_3\ Br^- \quad (3)$$

$$NH=NH + >C=C< = >CHCH< + N_2 \quad (4)$$

$$Br^- \text{ (or S)} + >CBrCBr< = >C=C< + Br_2 \text{ (or } BrS^+ + Br^-) \quad (5)$$

$$Br_2 \text{ (or } BrS^+ + Br^-) + 3N_2H_4 = NH=NH + 2N_2H_5^+Br^- \quad (6)$$

$$NH=NH + >C=C< = >CHCH< + N_2 \quad (7)$$

Table I

Products[a] from *meso*-Stilbene Dibromide[b] and Hydrazine[c]

Solvent	Temp, °C	% BB	% ST	% *cis*-stilbene	% *cis*-α-Bromostilbene
$(CH_2OH)_2$	110	33	24		24
CH_3OH	65	39	27	Trace	28
$(CH_3)_2CHOH$	83	38	22	Trace	25
CH_3COOH	120	18	22		
$(CH_3)_2SO$	110	18	7		66
$HCON(CH_3)_2$	110	Trace	4		56
CH_3CN	80	6	10		79
1,4-Dioxane	101	7	8		87
Pyridine	116	4	6		85

[a] Time, 24 hr. [b] 0.2 *M*. [c] 4.2 *M*.

Table II

Product Dependence on Hydrazine Concentration[a]

N_2H_4 molarity	Mol N_2H_4 / mol $STBr_2$	% BB	% ST	% *cis*-α-Bromostilbene
21	105	8 ± 1	26 ± 1	72 ± 1
4.2	21	38 ± 2	22 ± 2	25 ± 2
0.84	4.1	56 ± 2	26 ± 1	4 ± 1

[a] In refluxing 2-propanol under N_2; $STBr_2$ concentration, 0.2 *M*. Results are mean values for 2–3 runs.

Table III

Effect of Added Cyclohexene[a]

Additive	% BB	% ST	% *cis*-α-Bromostilbene	% C_6H_{12}
None	38 ± 2	22 ± 2	25 ± 2	
C_6H_{10}	17 ± 1	39 ± 1	43 ± 1	17 ± 1

[a] Equimolar C_6H_{10} and $STBr_2$ in refluxing 2-propanol; mol of N_2H_4:mol of $STBr_2$ = 21; time, 24 hr.

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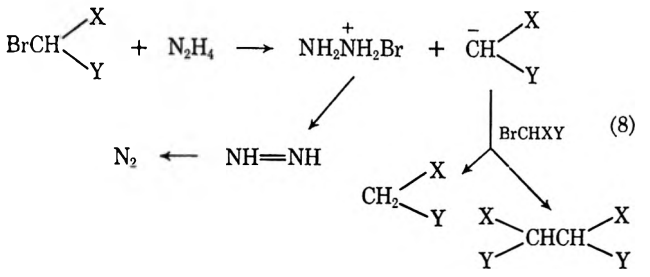
Consider the choice between paths 2–4 and 5–7. Analogies for the former path are provided by nucleophilic displacements by N_2H_4 on bromine in the systems BrCHXY (X, Y = COOR, COR, CN, NO_2) according to eq 8,[4] by the demonstrated intermediacy



(8)

of diimide in the oxidation of hydrazine by CCl_4[5] and by the protodebromination of hexabromobenzene.[6] With respect to the second path, debromination by Br^- (eq 5) is known (at least in aprotic solvents; see below); the oxidation of N_2H_4 by halogen (eq 6) is rapid,[7] and by analogy with oxidation by *N*-chloramines is expected to give diimide;[8] the reduction of alkenes by diimide (eq 11) is well known. Thus both paths appear plausible and several tests can be designed to distinguish between them. If N_2H_4 is the nucleophile (as well as the dehydrohalogenating base in eq 1) then the ratio (BB + ST):α-bromostilbene should be independent of the hydrazine concentration. If Br^- or solvent is the nucleophile this ratio should decrease with increasing N_2H_4 concentration. Table II shows that a 25-fold increase in N_2H_4 concentration produces a *ca.* 44-fold depression, favoring path 5–7. Addition of Br^- increases (BB + ST) at the expense of dehydrobromination (below) in a 2-propanol solvent, which further implies that eq 5 is operative. The more nucleophilic solvents may dominate Br^- in eq 5, however. The above indications of dehalogenation by Br^- in 2-propanol contrast with the report that Br^-, though reactive in DMF, is unreactive toward $STBr_2$ in methanol (conditions unspecified).[9] The explanation may be that the unreactivity derives from an unfavorable equilibrium position and is overcome in the present system by the reduction of product Br_2 (eq 6).

An excess of diimide is generally employed in alkene reductions in order to achieve good yields in the face of competitive disproportionation of diimide. Based on the behavior of similar systems, the 1:1 NH=NH/ST ratio characteristic of the present system should result in a *ca.* 25% yield of BB.[8] Reduction of ST with 1.0 molar equiv of $I_2 + N_2H_4$ gives in fact only 4% of BB. In contrast, the $STBr_2$–N_2H_4 reaction gives reduction yields [100 BB/(BB + ST)] as high as 84%. That the increased efficiency is not due to consumption of NH=NH in the original solvent cage is shown by two pieces of evidence. (1) Added cyclohexene is able to compete for the diimide. (2) The BB/ST ratio increases from *ca.* 0.2 to 2 during the reaction, *i.e.*, the efficiency of ST reduction increases with increasing ST concentration, implying that NH=NH survives long enough to encounter ST diffusing up from bulk solution. The efficient BB formation thus appears to result from generation of NH=NH at high dilution, favoring reduction of alkene over second-order disproportionation of diimide.

The Effect of Added Nucleophiles.—An added nucleophile, X^-, which is more reactive in dehalogenation than Br^- or N_2H_4 should increase (BB + ST) at the expense of α-bromostilbene. If the oxidized form, XBr, is also capable of oxidizing N_2H_4 rapidly, BB formation should be maintained, though perhaps in altered proportions. Table IV contains results for several nucleophiles.

TABLE IV

PRODUCTS FROM *meso*-STILBENE DIBROMIDE, HYDRAZINE, AND ADDITIVES[a]

Additive[b]	Mol N_2H_4 / mol $STBr_2$	% BB	% ST	% *cis*-α-Bromostilbene
None	4.2	56	26	4
None[c]	21.0	39	27	28
KI	4.2	70	13	Trace
KI[c]	21.0	55	29	9
KBr	21.0	Trace	70	Trace
KBr[c]	21.0	37	42	16
NaSCN	4.2	57	24	9
NaSCN	6.0	65	25	5
$C_2H_5SO_2Na$	4.2	27	17	20
$C_2H_5SO_2Na$	6.0	30	20	21
C_6H_5SK[d]	4.2	24	67	0
C_6H_5SK[d]	6.0	21	68	0
KNCO[d]	4.2	19	14	38
KNCO[d]	6.0	22	16	50
KCN	4.2	6	7	28
KCN	6.0	4	9	29
$NaOCH_3$	4.2	10	18	80
$NaOCH_3$	6.0	10	21	67
Zn[e]	21	13	81	0
Ag[e,g]	21	32	64	0
None[f]	21	5	13	71
Cu(I)[f,g]	21	9	83	0

[a] Solvent 2-propanol, except as noted. Reaction time 24 hr, at reflux in nitrogen atmosphere. [b] 0.2 *M*. [c] In CH_3OH. [d] Additional, unidentified peak in gas chromatogram. [e] From $AgNO_3$ in the presence of excess N_2H_4. [f] In CH_3CN. [g] From $CuCl_2$ in the presence of excess N_2H_4.

I^-, which is known to be a superior dehalogenating nucleophile, when added at low N_2H_4 concentration eliminates dehydrohalogenation altogether. The reaction is visualized as eq 9 + 10 + 11 = 12.[10] The

$$>CBrCBr< + 2I^- = >C{=}C< + I_2 + 2Br^- \quad (9)$$

$$I_2 + 3N_2H_4 = NH{=}NH + 2N_2H_5{}^+I^- \quad (10)$$

$$NH{=}NH + >C{=}C< = >CHCH< + N_2 \quad (11)$$

$$>CBrCBr< + 3N_2H_4 = >CHCH< + 2N_2H_5{}^+Br^- + N_2 \quad (12)$$

BB/ST ratio is also increased. The other highly polarizable nucleophiles (SCN^- and PhS^-) increase

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(10) The possible involvement of PhCHI–CHBrPh is apparently eliminated by evidence that I^- attacks $STBr_2$ more rapidly at Br than at C, both in methanol and DMF.[11,12]

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(BB + ST) and depress α-bromostilbene strongly, as expected for attack on bromine.[13] In the case of PhS^- the BB/ST ratio is also depressed, apparently owing to reaction 13 (known[14] to accompany dehalogenation by PhS^-) which competes with oxidation of N_2H_4.

$$PhSBr + PhS^- \longrightarrow PhSSPh + Br^- \quad (13)$$

The more basic nucleophiles attack H, and the proportion of α-bromostilbene increases.

The remaining dehalogenating agents [Zn, Ag, and Cu(I)] are efficient at suppressing dehydrobromination and generally depress the BB/ST ratio as expected for one-electron reductants, since their oxidized states do not oxidize hydrazine to diimide.[15]

Davis and Ansari,[2] attempting to dehydrobrominate RCHBrCHBrPh with NH_2^- in liquid ammonia, observed the formation of RCH=CHPh and RCH_2CH_2Ph (*ca.* 2:1), which they attribute to eq 14–17.[16]

$$RCHBrCHBrPh + NH_2^- \longrightarrow RCH{=}CHPh + NH_2Br + Br^- \quad (14)$$

$$NH_2Br + 2NH_2^- \longrightarrow NH_2NH^- + NH_3 + Br^- \quad (15)$$

$$NH_2NH^- + RCH{=}CHPh + NH_3 \longrightarrow NH_2NHCHRCH_2Ph + NH_2^- \quad (16)$$

$$NH_2NHCHRCH_2Ph \longrightarrow RCH_2CH_2Ph + {}^1/_2N_2 + {}^1/_2N_2H_4 \quad (17)$$

Our results open the possibility that diimide is also an intermediate in this reaction, production of hydrazine in eq 15 being followed by either reactions 2–4 or 5–7.

Other Substrates.—In preliminary experiments we failed to observe reduction of 1,2-dibromoheptane, *trans*-1,2-dibromocyclohexane, or 2,3-dibromopropanol by N_2H_4 under the conditions applied to $STBr_2$. This is consistent with the reported formation of only products of nucleophilic displacement on carbon in the reaction of 1,2-dihaloethanes with hydrazine.[17]

Experimental Section

General.—*cis*-1-Bromo-1,2-diphenylethene was prepared by the method of Wislicenus and Seeler[18] and purified by trapping a center cut from the gas chromatographic peak. The ^1H nmr spectrum (CCl_4) displayed a broad singlet (δ 7.4 ppm) due to one phenyl group and the α proton, and a multiplet (δ 7.0 ppm) due to the other phenyl group, with area ratio 6:5.

Anal. Calcd for $C_{14}H_{11}Br$: C, 64.89; H, 4.28; Br, 30.83. Found: C, 64.68; H, 4.30; Br, 31.09.

meso-1,2-Dibromo-1,2-diphenylethane (Aldrich) was recrystallized from xylene: mp 237–238° (lit.[19] mp 240–241°). Bibenzyl (Distillation Products Industries) was recrystallized from ethanol: mp 51.4° (lit.[20] mp 51.8°). All other chemicals were the highest quality commercial materials, used without purification.

Nmr spectra were obtained with a Varian A-60 instrument. Melting points were measured by hot-stage microscopy, and are corrected. Analyses were performed by Galbraith Laboratories, Inc.

Analytical Procedure.—Product solutions (containing 100 mg of diphenylacetylene per 25 ml as an internal standard) were gas chromatographed at 150° through 5-ft columns of 3% SE-30 on Varapost 30, 100/120 mesh, using a Varian Aerograph 600-D chromatograph with flame ionization detection. The sample size was 0.4–0.6 μl; the carrier gas was N_2. For those runs to which cyclohexene was added the stationary phase was 12% Carbowax 1500 on Chromosorb W, 60/80 mesh, at 50°, and ethylbenzene was the internal standard. Response coefficients were determined on standard solutions and peak areas were measured by planimetry. Analyses were carried out in duplicate; precision *ca.* 3%. The precision of typical duplicate runs (standard deviation) is shown in Table II.

Reaction of Hydrazine with *meso*-Stilbene Dibromide.—340 mg (1.0 mmol) of $STBr_2$ and 4.0 ml of solvent were placed in a one-piece glass apparatus consisting of round-bottom flask, condenser, and port with Teflon stopcock (this apparatus served as a separatory funnel for the work-up, avoiding transfer of the contents). The condenser was capped with a mercury bubbler and oxygen was purged with a stream of nitrogen while the solution was heated to reflux (or 105° for solvents with bp >105°) for 5 min. The hydrazine and any additives were added through the condenser and the mixture was heated with magnetic stirring under nitrogen, usually for 24 hr. To the cooled mixture were added 7 ml of $CHCl_3$ and at least 25 ml of water. The aqueous layer was extracted twice more with 6–7 ml of $CHCl_3$ and the combined extracts were made up to 25.0 ml. This solution was dried by adding a few pieces of molecular sieve. In the runs to which cyclohexene was added toluene was used as extracting solvent.

The identity of bibenzyl was confirmed by isolation. We experienced difficulty with the liquid chromatographic separation of bibenzyl and *trans*-stilbene and resorted to destruction of the latter by aqueous permanganate. The product of a 1.0-mmol run in presence of KI, so treated, gave on elution from silicic acid with benzene–hexane (1:2) 0.128 g (0.70 mmol, 70%) of colorless crystals, melting point and mixture melting point identical with those of bibenzyl.

Extent of Reduction of Stilbene Due to Adventitious Oxidation of Hydrazine.—A solution of 180 mg (1.00 mmol) of *trans*-stilbene, 0.7 ml (21 mmol) of hydrazine, and 119 mg (1.00 mmol) of KBr in 4.0 ml of 2-propanol was refluxed for 24 hr under N_2. Work-up and analysis as above gave the following results for duplicate runs: bibenzyl, 3 and <1%; *trans*-stilbene, 100 and 97.8%.

Reduction of *trans*-Stilbene by Diimide Generated from N_2H_4 and I_2.—To a refluxing solution of 180 mg (1.00 mmol) of *trans*-stilbene and 0.35 ml (10 mmol) of hydrazine in 7 ml of methanol was added 254 mg (1.00 mmol) of iodine in 10 ml of methanol and the solution was refluxed for 35 min. Work-up and analysis as above revealed the presence of 0.038 mmol (3.8%) of bibenzyl and 0.930 mmol (93%) of *trans*-stilbene.

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Registry No.—*meso*-1,2-Dibromo-1,2-diphenylethane, 13440-24-9; 1,2-diphenylethane, 103-29-7; hydrazine, 302-01-2; *cis*-1-bromo-1,2-diphenylethene, 15022-93-2.

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Di(phenyl-d_5)cyclopropenone[1]

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In the young chemistry of the triafulvenes,[2] a leading role has been played by diphenylcyclopropenone

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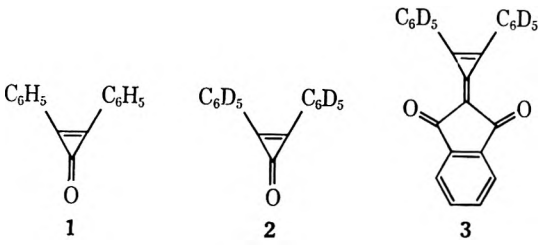
(1),[3,4] the readily available prototype of the "aromatic" [3]annulenone series. During a study of the electron impact behavior of triafulvenes derived from 1,[5] it was deemed necessary to prepare di(phenyl-d_5)-cyclopropenone (2). We wish to report a straightforward synthesis of 2 and its application in the preparation of a deuterated triapentafulvalenequinone and di(phenyl-d_5)acetylene.

Of the numerous methods available for the synthesis of 1, the electrophilic substitution of aromatic



1 2 3

$C_6D_5C{\equiv}CC_6D_5$

4

substrates by trichlorocyclopropenium salts (the method of Tobey and West[6]) seemed promising. Indeed, treatment of trichlorocyclopropenium tetrachloroaluminate with benzene-d_6 in carbon disulfide solution[7] afforded the desired 2 in 70% yield. The structure of 2 was established by the elemental analysis and spectroscopic observations. The infrared spectrum of 2 showed characteristic cyclopropenone frequencies at 1840 and 1615 cm^{-1},[8] a C–D stretching absorption at 2240 cm^{-1}, and C–D out-of-plane bending bands at 560 and 540 cm^{-1} (five adjacent phenyl deuterium atoms). No absorption appeared in the pmr spectrum. The strongest signal in the mass spectrum of 2 (rel intensity 100%) was due to $[C_{14}D_{10}]\cdot^+$ ($[M - CO]\cdot^+$, m/e 188), while the intensity of the molecular ion at m/e 216 was only 0.4%. No signals appeared at m/e 178 and 206, ruling out the presence of 1 as a significant impurity. The relatively high abundance (6.1%) of the $[M - CO]^{2+}$ signal (at m/e 99) is noteworthy.

The use of 2 as a starting material for the synthesis of deuterated 1,2-diphenyltriafulvenes may be illustrated in the preparation of 1,2-di(phenyl-d_5)-4,5-benzotriapentafulvalene-3,6-quinone (3). Condensation of 2 with 1,3-indandione in boiling acetic anhydride in the presence of boron trifluoride etherate[9] gave 3 in 64% yield. The properties of 3 closely resemble those of its undeuterated analog.[10] The infrared spectrum of 3 shows a C–D stretching absorption at 2040 cm^{-1}, characteristic triafulvene frequencies at 1840 and 1485 cm^{-1}, a carbonyl stretching absorption at 1655 cm^{-1}, and a C–H and C–D out-of-plane bending band at 730 and 550 cm^{-1}, respectively. The pmr spectrum of 3 (in $CDBr_3$) exhibited only the symmetrical AA'BB' pattern of the indandione protons centered at 7.85 (2 H, ortho to CO) and 7.65 ppm (2 H, meta to CO). The structure of 3 was confirmed by the molecular ion at m/e 344 in the mass spectrum and the absence of any signal in the region m/e 334–340.[5]

Finally, the photolytic decarbonylation of 2 in 2-propanol solution proceeded smoothly, providing a simple and efficient synthesis of di(phenyl-d_5)acetylene (4).[11,12] The molecular ion at m/e 188 was the strongest signal in the mass spectrum of 4, while the signals due to undeuterated and partially deuterated diphenylacetylene at the m/e 176–182 region were completely absent. The facile synthesis of 4 may lead to practical syntheses of deuterated compounds derived from 4, *e. g.*, phenanthrene-d_{10}.

Experimental Section

Melting points were taken on a Unimelt Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 457 spectrophotometer in Nujol and in KBr disks. Ultraviolet spectra were recorded on a Unicam Model SP800 spectrophotometer. Nmr spectra were taken on a Varian HA-100 spectrometer (TMS as internal standard). Mass spectra were measured on a Varian MAT CH-5 instrument operating at 70 eV, employing the direct insertion technique. Tetrachlorocyclopropene was obtained from Aldrich Chemical Co., Inc.

Di(phenyl-d_5)cyclopropenone (2).—A solution of 2.0 g (11 mmol) of tetrachlorocyclopropene in 2.5 ml of carbon disulfide was added dropwise, at 5°, under anhydrous conditions to a magnetically stirred suspension of 2.80 g (21 mmol) of anhydrous aluminum chloride in 6 ml of carbon disulfide and left for 15 min at room temperature. The resulting mixture containing trichlorocyclopropenium tetrachloroaluminate was treated dropwise with a solution of 5 ml of benzene-d_6 in 5 ml of carbon disulfide. After 16 hr at room temperature, the dark red complex was diluted with 200 ml of methylene chloride, cooled to 0°, and poured into 200 ml of hydrochloric acid (2 *N*). The organic fraction was washed with water, dried over magnesium sulfate, and evaporated to dryness under vacuum. Recrystallization of the remaining solid from cyclohexane gave 1.44 g (70% yield) of 2 as colorless needles: mp 119–120°; uv max (cyclohexane) 222 nm (log ϵ 4.24), 229 (4.23), 284 s (4.20), 291 (4.27), 300 (4.32), 316 (4.10), and 363 (3.00).

Anal. Calcd for $C_{15}D_{10}O$: C, 83.3; D, 9.3. Found: C, 83.2; D, 9.4.

1,2-Di(phenyl-d_5)-4,5-benzotriapentafulvalene-3,6-quinone (3).—A solution of 1.08 g (5 mmol) of 2 and 0.73 g (5 mmol) of 1,3-indandione in 30 ml of freshly distilled acetic anhydride containing 1 drop of boron trifluoride etherate was refluxed with magnetic stirring under anhydrous conditions for 2.5 hr and left at room temperature for 16 hr. The slightly red crystalline precipitate was filtered off and washed with methanol to give 1.1 g (64%) of crude 3. Recrystallization from benzene afforded 3 as pale yellowish needles: mp 226°; uv max (CH_3CN) 232 nm (log ϵ 4.64), 250 s (4.46), 265 s (4.20), 287 (4.02), 297 (4.28), and 342 (4.66).

Anal. Calcd for $C_{24}D_{10}H_4O_2$: C, 83.7; D + H, 7.0. Found: C, 83.9; D + H, 7.1.

Di(phenyl-d_5)acetylene (4).—A solution of 0.108 g (0.5 mmol) of 2 in 200 ml of 2-propanol was irradiated for 2 hr at room temperature under argon with a 70-W uv lamp. Removal of the solvent *in vacuo* yielded 4, mp 57° (0.085 g, 90%). Sublimation at 45–65° (0.6 mm) afforded 4 as colorless crystals, mp 59°.

Anal. Calcd for $C_{14}D_{10}$: C, 89.4; D, 10.6. Found: C, 89.5; D, 11.0.

Registry No.—2, 40736-43-4; 3, 40682-48-2; 4, 19339-46-9; tetrachlorocyclopropene, 6262-42-6; benzene-d_6, 1076-43-3; 1,3-indandione, 606-23-5.

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A Simple Fraction Collector for Gas Chromatography. Compatibility with Infrared, Ultraviolet, Nuclear Magnetic Resonance, and Mass Spectral Identification Techniques

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Isolation of the individual components of a reaction mixture in pure form by gas chromatography prior to examination by ir, uv, nmr, and mass spectroscopy is an important and recurring problem for organic chemists. The fraction collection techniques presently available are not so convenient as might be desired. The most popular devices are cold traps.[1-4] These, however, require coolants and some means of preventing aerosol formation, which lowers the collection efficiency. Other fraction collectors have been proposed in which a sample is sorbed on an inert support[5-8] or is partitioned on a chromatographic liquid phase.[9-11]

Some of these devices require relatively complicated equipment, which makes the technique inconvenient. Many require heat and/or vacuum equipment to transfer a sample from the collection device, and some cause chemical transformation of the collected components. This report will describe a simple procedure which circumvents these difficulties and is easily adaptable for use in uv, ir, nmr, and mass spectral analyses of the separated components.

A supply of collection tubes is made by loosely packing 4–12 mg of 80–100 mesh Rohm and Haas XAD-4 resin into 1.6–1.8 × 70 mm borosilicate glass capillary tubes. The resin is held in the tubes with small plugs of clean glass wool on either side. The ends of the tubes are lightly fire polished and the tubes are stored in a sealed container until ready for use.

The method of attaching the tubes to the exhaust port of the gas chromatograph will depend on the instrument used. When a Varian Autoprep A700 chromatograph is used, this is accomplished by drilling a $^1/_{16}$-in. hole, tapered on one side, into a 9 mm diameter × 3 mm thick Teflon disk. The disk is placed, taper out, inside the nut on the exhaust port of the chromatograph. The nut is tightened so that the Teflon disk holds the capillary collection tube snugly in place but loose enough that the tube can be easily inserted or removed. With other chromatographs, similar designs can be easily adapted.

For fraction collection, a packed tube is inserted into the modified exhaust port at the beginning of the gas chromatographic run and the instrument recorder zeroed. At the onset of the desired fraction, as indicated by the recording of a peak, this tube is removed and a new collection tube inserted. When the gc peak has returned to base line, the collection tube is removed and another tube is inserted to collect the next fraction. There is generally only a slight deflection of the recorder pen as one tube is removed and another tube is inserted. The time required to change tubes is less than 1 sec, so that multiple collections across a single gc peak are possible.

The efficiency of sample collection for several model compounds was tested. Typical recoveries, based on repeating the chromatography of the collected material, were between 60 and 95% for α-methylstyrene, *n*-hexyl alcohol, *n*-pentyl alcohol, benzyl chloride, benzaldehyde, toluene, anisole, and acetophenone. In view of the simplicity of the device and the ease of fraction collection and transfer, these recoveries are considered satisfactory for auxilary instrumental qualitative analysis, such as ir, uv nmr, and mass spectroscopy.

Infrared Spectra.—For infrared analyses, the sample component is eluted directly from the collection tube into the ir cell using a suitable solvent such as carbon tetrachloride. The plunger and needle are removed from a 1-ml disposable syringe which is fitted into the opening on one end of the ir cell. With the other opening of the ir cell plugged, the collection tube is eluted into the syringe until the syringe barrel contains ~0.1 ml of a carbon tetrachloride solution. The plug is then removed from the ir cell allowing the solution to fill the cell. Using this technique, well-resolved and easily interpretable ir spectra were obtained using a Beckman IR-33 for ~1.0 mg of each of the following compounds: α-methylstyrene, acetophenone, aniline, *n*-hexyl alcohol, toluene, and hexyl acetate.

Nmr Spectra.—For nmr analyses, the sample component is transferred from the collection tube directly into an nmr tube by elution with ~1.0 ml of carbon tetrachloride. Good quality nmr spectra were obtained using a Hitachi R20-B, 60-MHz instrument for ~4 mg of each of the following compounds: *n*-hexyl acetate, 2-methylcyclohexanol, α-methylstyrene, and toluene.

Uv Spectra.—For uv analyses, the sample component is eluted from the resin with ~0.2 ml of an appropriate solvent such as hexane or 95% ethanol. The eluate is then diluted to 25 ml and an aliquot of this solution is transferred to the uv cell. With this technique, quality uv spectra were obtained using a Cary Model 14 spectrophotometer for 0.5-mg fraction-collected samples of α-methylstyrene, toluene, acetophenone, benzaldehyde, and anisole.

Mass Spectra.—It is unnecessary to transfer the sample by elution from the collection tube to obtain a mass spectrum. The resin containing the sorbed sample is simply transferred to the direct insertion probe of the mass spectrometer for mass spectral analysis. This technique is particularly convenient for a Du Pont 21-490 series mass spectrometer, since the

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(7) F. W. Karasek and R. J. Smythe, *Anal. Chem.*, **43**, 2008 (1971).
(8) D. M. Kane and F. W. Karasek, *J. Chromatogr. Sci.*, **10**, 501 (1972).
(9) J. W. Amy, E. M. Chait, W. E. Baitinger, and F. W. McLafferty, *Anal. Chem.*, **37**, 1265 (1965).
(10) M. D. D. Howlett and D. Welti, *Analyst*, **91**, 291 (1966).
(11) B. A. Bierl, M. Beroza, and R. M. Ruth, *J. Chromatogr. Sci.*, **6**, 286 (1968).

borosilicate 1.6 × 1.8 mm collection tubes are easily converted into direct insertion sample containers. After fraction collection, one end of the collection tube is sealed and the resin containing the sorbed sample is pushed to the sealed end. The unsealed end is then cut off, leaving an 18–20 mm long sample container which is identical with those supplied by Du Pont. Using this technique high-quality mass spectra were obtained for samples as volatile as toluene as well as for benzaldehyde, *o*-xylene, benzyl chloride, 1-methylnaphthalene, acenaphthylene, α-methylstyrene, 2-ethyl-1-hexanol, acetophenone, and methyl octanoate, with quantities as low as 10^{-8} g. The background spectra caused by the XAD-4 resin as it is received is significantly reduced by vacuum degassing the resin used in preparing the collection tubes at 10^{-6} Torr and ~200° for 1 hr.

Acknowledgment.—This work was supported by a grant from the National Science Foundation under Contract No. GP-33526X.

Bisdiazo Insertion in Cycloheptanone

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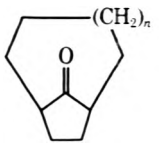
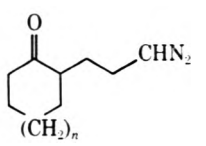
In connection with an investigation into steric effects on the McLafferty rearrangement,[2] we were interested in obtaining a sample of bicyclo[6.2.1]undecan-11-one (**1**). This compound has not previously been prepared, but both bicyclo[5.2.1]decan-10-one (**2**) and bicyclo[4.2.1]nonan-9-one (**3**) have been obtained by reaction of 1,4-bisdiazobutane (**4**) with cyclopentanone and cyclohexanone respectively,[3] and also by intramolecular diazoinsertion of the side chain diazoalkyl ketones **6** and **7**, respectively.[4] In the original report describing the reactions of **4**, it was stated that reaction with cycloheptanone (**8**), which would have been expected to yield the desired ketone **1**, yielded complex mixtures, and it was inferred from a study of the vapor phase chromatographic behavior of these mixtures that the bridged ring ketones could be no more than minor constituents.[3] No information was available on the alternate route to **1** *via* the side chain diazoalkyl ketone



1, $n = 3$
2, $n = 2$
3, $n = 1$



5, $n = 3$
6, $n = 2$
7, $n = 1$

5, but a recent paper by Wiseman and Chan showed that the structures of the two major product ketones produced by reaction of 1,3-bisdiazopropane with cyclohexanone differed from those previously assigned on the assumption of double expansion of the six-membered ring.[5] It thus seemed likely that the reaction of **4** with cycloheptanone would not prove to be a good synthetic route to the ketone **1**.

In spite of this discouraging situation, we decided to investigate the reaction of **4** with **8** in order to determine whether any of the desired product at all was produced. Since our need was for only a small quantity of **1**, it was believed that sufficient material could be obtained even from a low-yield reaction. Reaction of bis-*N*,*N*′-dinitroso-1,4-butanediamine with cycloheptanone by the method of Gutsche and Smith yielded a mixture of six major products, as detected by vapor phase chromatography (vpc). In contradistinction to the findings of Gutsche and Smith, however, one of these products (and only one), representing about 20% of the total product mixture, had a vpc retention time in the region expected for the desired ketone **1**. Examination of this product by high-resolution mass spectrometry showed that it had the composition $C_{11}H_{18}O$. The presence of a cyclopentanone ring was confirmed by its infrared absorption maximum of 1731 cm^{-1}, and the bicyclic nature of the material was shown by the absence of low-field resonances in the nmr spectrum due to vinyl protons.

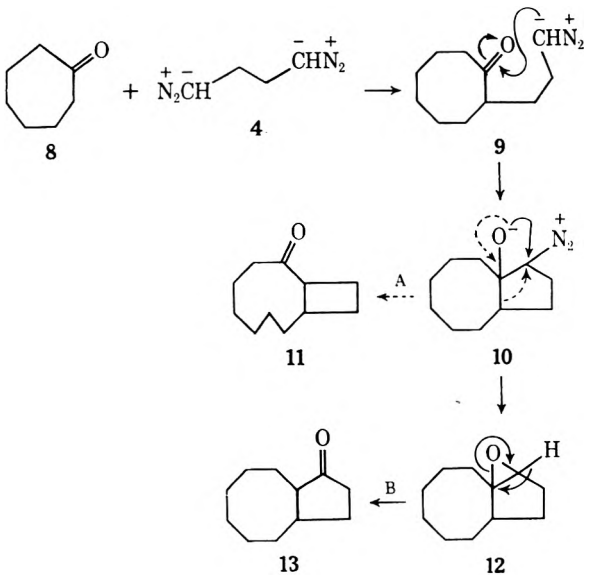
In spite of the similarity of the isolated product to the ketone **1**, there were some features in its mass spectrum which were not consistent with its formulation as **1**; in particular, the compound showed a moderately intense ion at m/e 148 $[M - H_2O]\cdot^+$ which was absent in the spectra of compounds **2** and **3**. The location of the carbonyl group in the compound was deduced by deuteration followed by mass spectral analysis of deuterium incorporation. This showed clearly that it possessed three exchangeable hydrogens, and it must, therefore, have the bicyclic structure of bicyclo[6.3.0]undecan-2-one (**13**). Other structures are incompatible with the requirement of a cyclopentanone ring in the product, the nature of the starting materials, and the absence of olefinic protons in the nmr spectrum.

A plausible rationalization for the formation of **13** from the reagents used is given in Scheme I.

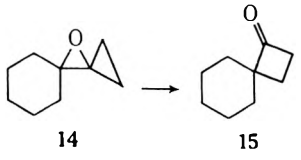
Monodiazo insertion into cycloheptanone would yield the intermediate **9**, which could react to form the intermediate **10**. Rearrangement of **10** by the pinacol route (pathway A) would yield the cyclononanone **11**, while rearrangement *via* the epoxide **12** (pathway B) would yield the observed product **13**. The structure **11** is, of course, excluded for the product by the observed infrared adsorption of the latter; presumably, the angular strain in the transition state leading to a cyclobutane is sufficient to make pathway A energetically unfavorable as compared with pathway B. The latter pathway must also be favored over the bis insertion to give **1**, presumably also because of conformational restrictions when forming a medium-ring ketone by ring expansion.[6] It is well known that the formation of medium-ring alicyclic ketones by ring expansion of the lower homologs with diazomethane is

(1) Author to whom inquiries should be directed: Virginia Polytechnic Institute and State University.
(2) J. D. Henion and D. G. I. Kingston, unpublished work.
(3) C. D. Gutsche and T. D. Smith, *J. Amer. Chem. Soc.*, **82**, 4067 (1960).
(4) C. D. Gutsche and D. M. Bailey, *J. Org. Chem.*, **28**, 607 (1963).
(5) J. R. Wiseman and H. F. Chan, *J. Amer. Chem. Soc.*, **92**, 4749 (1970).
(6) C. D. Gutsche, *Org. React.*, **8**, 364 (1954).

SCHEME I

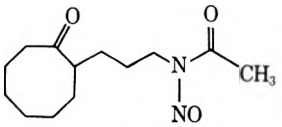


difficult unless Lewis acid catalysts are used.[7] Formation of the epoxide is an important side reaction of diazomethane ring expansions,[6] and collapse of the epoxide to give **13** is analogous to the formation of spiro[3.5]nonan-1-one (**15**) from 10-oxadispiro[2.0.5.1]-



decane (**14**).[5] In this connection, it should be noted that the ketone **13** may be an artifact of the work-up procedure, with the epoxide **12** being the initial product rather than a reaction intermediate. Wiseman and Chan showed that the epoxide **14** was, indeed, the initial product of the reaction of cyclohexanone and 1,3-bisdiazopropane and that rearrangement of **15** occurred on injection into the vpc.[5] It did not prove practicable to separate our crude reaction mixture without recourse to vpc, however; so it was not possible to confirm this point.

Many attempts under a variety of conditions were made to prepare the desired ketone **1** by the bisdiazo insertion route, but all such attempts were uniformly unsuccessful. Similarly, attempts to prepare **1** by the alternate route of Gutsche and Bailey[4] were also unsuccessful. Base-catalyzed decomposition of *N*-nitroso-*N*-acetyl-3-(2′-ketocyclooctyl) propylamine (**16**)



yielded a similar mixture to that obtained from **4** and **8**, and the ketone **13** was again isolated as the only product having a retention time close to that expected for **1**. This formation of **13** from the diazo ketone **9** generated from **16** lends support to the mechanistic pathway outlined in the scheme.

(7) H. O. House, E. J. Grubbs, and G. F. Gannon, *J. Amer. Chem. Soc.*, **82**, 4099 (1960); E. Muller, B. Zeeh, R. Heischkeil, F. Fricke, and H. Suhr, *Justus Liebigs Ann. Chem.*, **662**, 38 (1963).

Experimental Section[8]

Bicyclo[6.3.0]undecan-2-one (13). Method A.—A 25-ml three necked round-bottomed flask equipped with a magnetic stirrer, thermometer, addition funnel, and gas bubbler was flame dried in a stream of dry nitrogen and charged with a solution of cycloheptanone (1 g, 8.9 mol), anhydrous (3A molecular sieve) methanol (3.2 ml), and anhydrous pulverized potassium carbonate (1.2 g, 8.9 mol).[9] This mixture was cooled to 5° in an ice bath and a solution of bis-*N*,*N*′-dicarbethoxy-*N*,*N*′-dinitroso-1,4-butanediamine[10] (2.6 g, 8.9 mol) in 6.4 ml of reagent chloroform added dropwise with stirring at a rate slow enough to keep the temperature below 10°. The resulting yellow reaction mixture was stirred for an additional hour at 5° and then allowed to warm to room temperature. The crude product was diluted with 20 ml of chloroform, filtered, and concentrated *in vacuo*. Preparative gas chromatography (inlet temperature 250°; column temperature 175°) yielded **13** (20% yield estimated from peak area): mp 49–50°; ν_{max} 1731 cm^{-1}; nmr 1.17–2.26 ppm (multiplet); parent ion at *m/e* 166.1357 (calcd for $C_{11}H_{18}O$: 166.1358); mass spectrum major peaks observed at *m/e* (rel intensity) 166 (80), 148 (12), 139 (11), 123 (22), 112 (36), 109 (40), 97 (80), 84 (100), 67 (60), 55 (64), 41 (62).

Method B.—A 10-ml, one-necked flask fitted with an addition funnel and magnetic stirrer was charged with anhydrous methanol and cooled to 5° in an ice bath. A solution of *N*-nitroso-*N*-acetyl-3-(2′-ketocyclooctyl)propylamine[4] (0.5 g, 2.1 mmol) in methylene chloride was added dropwise over a 45-min period to produce a yellow reaction mixture which was stirred for 1 hr at 5° and then allowed to warm to room temperature.

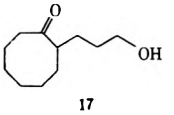
The crude product was steam distilled to give an aqueous distillate which was extracted with ether, dried over anhydrous magnesium sulfate, and concentrated by careful fractionation. The pleasant-smelling yellow pot residue on purification by preparative gas chromatography yielded a product identical in all respects with that obtained by method A.

Deuterium Exchange.—Deuterium exchange of **13** was carried out most efficiently by a modification of the on-column exchange procedure of Burlingame.[11] An 8 ft × 0.25 in. stainless steel column was packed with 5% phosphoric acid and 10% Apiezon L on 60–80 mesh Chromosorb W. Immediately prior to use, the column was equilibrated by injection of several hundred microliters of 99.7% deuterium oxide, followed by injection of the sample to be exchanged. The exchanged sample was collected, the column was reequilibrated with deuterium oxide, and the cycle was repeated twice. It was found that these conditions gave good deuterium incorporations even in some cases where base-catalyzed exchange in solution gave poor results. Application of this procedure to **13** yielded a compound having parent ion peak *m/e* 169.

Registry No.—**13**, 40696-12-6; cycloheptanone, 502-42-1; bis-*N*,*N*′-dicarbethoxy-*N*,*N*′-dinitroso-1,4-butanediamine, 19935-89-8; *N*-nitroso-*N*-acetyl-3-(2′-ketocyclooctyl)propylamine, 40752-89-4.

(8) Melting points are uncorrected. Infrared spectra were taken in carbon tetrachloride solution, nmr spectra were determined in deuteriochloroform using tetramethylsilane as internal standard, and mass spectra were obtained on an A. E. I. MS-902 mass spectrometer using a heated inlet system. Exact mass measurements were made at a resolution of one part in 10,000, using heptacosafluorotri-*n*-butylamine as internal standard. Vapor phase chromatograms were run on a Hewlett-Packard Model 5750 gas chromatograph equipped with a thermal conductivity detector, using a 6 ft × 0.125 in. 10% Carbowax 20M on 60–80 mesh Chromosorb W column for analytical studies and a 6 ft × 0.25 in. column packed with the same material for preparative work.

(9) The second insertion step appears to be quite slow, and in the presence of traces of water the intermediate diazo ketone **9** appears to be intercepted to form a keto alcohol such as **17**.



(10) C. M. Samour and J. P. Mason, *J. Amer. Chem. Soc.*, **76**, 441 (1954).

(11) M. Senn, W. J. Richter, and A. L. Burlingame, *J. Amer. Chem. Soc.*, **87**, 680 (1965).

Reactions of Phosphorus Compounds. 34. Preparation of Pyrazol-3-yl Ketones and Ethyl Ester from Vinyltriphenylphosphonium Bromide, Substituted Diazoacetophenones, and Ethyl Diazoacetate

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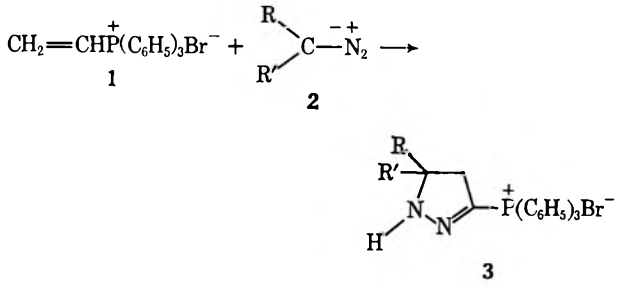
In previous papers[1,2] the preparation and reactions of 5-aryl- and 5-alkyl-substituted 2-pyrazolin-3-yltriphenylphosphonium salts (**3**) from vinyltriphenylphosphonium bromide (**1**) and substituted diazomethanes (**2**) were reported.

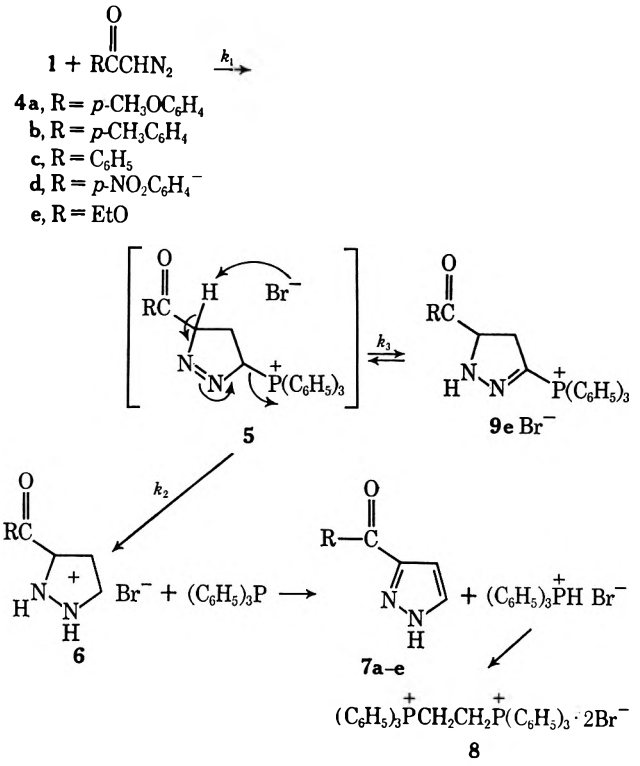


Spontaneous decomposition was observed[1] only where the 2-pyrazolinyl structure could not be formed owing to substitution α to the phosphonium moiety. The 1-pyrazolinyl species obtained from isopropenyltriphenylphosphonium bromide and diazomethane, or diphenyldiazomethane, decomposed to give 3-methylpyrazole hydrobromide and 3,3-diphenyl-1-methylallyltriphenylphosphonium bromide, respectively.[1]

In the present work, we wish to report that attempted preparation of 5-carbonyl-substituted 2-pyrazolinyltriphenylphosphonium bromides (**9**) from **1** and substituted diazoacetophenones, **4a–d**, using identical conditions with those previously reported,[1] only resulted in the isolation of pyrazol-3-yl ketones **7** and disalt **8**. The yields of **7a–e** were improved using 2 mol of vinyl salt **1** to 1 mol of **4a–e**.

The greater acidity of the 5 proton of compounds **5** compared to that of compounds **3** (where R = H, R′ = aromatic, alkyl, or H) evidently makes the rate $k_2 \gg k_3$ and none of **9** was observed. Support for this proposition is found in the fact that the lowering of the acidity of the 5 proton in compound **5e** obtained by treating ethyl diazoacetate (**4e**) with **1** allows for the conversion of **5e** to the 5-carbethoxy-2-pyrazolinyltriphenylphosphonium bromide (**9e**) in 90% yield.

Attempts to phosphonioethylate **9e**, under more vigorous conditions as described previously[2] for compounds **3**, proved to be unsuccessful, yielding only the corresponding pyrazole **7e** and disalt **8**. It has been shown[2] that phosphonioethylation of 5-substituted pyrazolines **3** is accomplished only under forcing conditions which must be greater than the conditions needed to decompose **9e** to **6e** (and thence to **7e**). Decomposition of **9e**, by heating in the absence of **1**, also gave the expected[2] 3-carbethoxypyrazole hydrobromide **6e**.



The relative rates of addition of the substituted benzoyldiazomethanes **4a–d** to the vinyl salt **1** were followed by observing the disappearance of the diazo peak (2100 cm^{-1}) in the ir. The relative rates were found by measuring the slope of the curve obtained by plotting $(absorbance)^{-1}$ *vs.* time. The relative rates (k_1) for the addition were *p*-MeO > *p*-CH_3 > H > *p*-NO_2 (see Table I), *i.e.*, inversely proportional to the expected stabilities of the carbanion of the 1,3 dipole. As **5d** would be expected to decompose faster than **5a**, because of the greater acidity of the α proton, the rate-determining step must be the initial formation of the 1-pyrazoline **5** from **1** and **4a–d** (k_1).

In the decomposition of the intermediate **5**, it is proposed that the bromide ion, acting as a base, removes the proton α to the carbonyl and triphenylphosphine is eliminated forming the pyrazole and triphenylphosphine hydrobromide. The triphenylphosphine hydrobromide then reacts with vinyl salt **1** to form 1,2-ethylenebis(triphenylphosphonium bromide) (**8**).[3]

Thus, it was shown that the nature of the substituent on the diazomethane dipolarophile has a profound influence on the course of the reaction.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 137 spectrophotometer. Pmr spectra were taken on a Varian A-60A and a Perkin-Elmer R12B. The para-substituted diazoacetophenones (**4a–d**) were made by adding the appropriate acid chloride to an ether solution of diazomethane. Ethyl diazoacetate was purchased from Aldrich Chemical Co. All melting points are uncorrected.

Preparation of 3-Substituted Pyrazoles (7).—In a 100-ml flask fitted with a drying tube were placed 0.02 mol of vinyl salt, 0.01

(1) E. E. Schweizer and C. S. Kim, *J. Org. Chem.*, **36**, 4033 (1971).
(2) E. E. Schweizer and C.S. Kim, *J.Org. Chem.*, **36**, 4041 (1971).
(3) E. E. Schweizer and R. Bach, *J. Org. Chem.*, **29**, 1746 (1964).

TABLE I

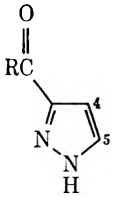
PREPARATION OF 3-SUBSTITUTED PYRAZOLES (7a-e) FROM VINYL SALT 1 AND SUBSTITUTED DIAZOMETHANES

Product	Ratio of 1:4	Time, days	Yield, %	Yield of 8, %	Anal. sample 7, mp, °C		Analysis, % C	Analysis, % H	Rel rate
7a	2:1	2	56		93–94	Calcd	65.34	4.98	50
7a	1:1	2	34			Found	64.94	5.00	
7b	2:1	2	67		130–132	Calcd	70.95	5.41	47
						Found	70.85	5.41	
7c	2:1	3	64	96	94–95[a]				26
7c	1:1	3	24	54					
7d	2:1	4	58	85	190–191	Calcd	55.30	3.25	1
						Found	55.24	3.18	
7e	2:1	1 (15)	20 (51)	55	155–157[b]				
9e	1:1	0.5	90[c]		*c*				

[a] Lit. mp 95–96°: J. Elguero and R. Jaquier, *Bull. Soc. Chim. Fr.*, 2832 (1966). [b] Lit. mp 155–157°: J. Elguero, G. Guirand, and R. Jaquier, *ibid.*, 619 (1966). [c] See Experimental Section.

TABLE II

SPECTRA OF PYRAZOLES



Product	Nmr C-4	Nmr C-5	Nmr Phenyl	Nmr Other	Ir NH	Ir C=O	Ir C=N
7a	6.85 (d) J = 2.4 Hz	7.65	6.95 (d), 8.15 (d) J = 8.5 Hz		3200	1630	1600
7b	6.92 (d) J = 2.7 Hz	7.91	7.26 (d), 7.84 (d) J = 9.5 Hz	CH_3O, 2.40 (s)	3150	1640	1600
7d	7.26 (d) J = 2.3 Hz		8.0–8.65 (m)		3250	1660	1600

mol of the diazo compound, and 10 ml of dried chloroform. The reaction mixture was stirred for the required amount of time at room temperature, concentrated to half volume, filtered to remove 1,2-ethylenebis(triphenylphosphonium bromide), mp 285–290° (lit.[3] in A mp 297–300°), and further concentrated to an oil. This material was placed on a Florisil column (4 × 25 cm) and eluted with ethyl acetate. The first fraction (200 ml) was concentrated, petroleum ether (bp 30–60°) was added to precipitate the product, and the pyrazole was filtered and collected. The product was recrystallized from benzene–petroleum ether. The physical data are given in Tables I and II. The results of experiments run with equimolar quantities of the species 1 and 4 are also listed in Table I. Examination of the crude reaction mixture from the equimolar experiments, by nmr, shows none of the expected peaks for the intermediate 9. The nmr shows only pyrazole 7, disalt 8, and some starting material 4.

5-Carbethoxy-2-pyrazolin-3-yltriphenylphosphonium Bromide (9e).—In a three-necked 100-ml flask with a drying tube and addition funnel was placed ethyl diazoacetate (0.57 g, 0.005 mol) in 5 ml of methylene chloride. Vinyl salt (1.85 g, 0.005 mol) in 5 ml of methylene chloride was added slowly over a 12-hr period and the solution was allowed to stir for an additional 2 hr. The reaction mixture was poured into ethyl acetate and the residue was recovered by filtration. The salt was recrystallized from methylene chloride–ethyl acetate at room temperature. An analytical sample could not be obtained owing to ready decomposition. The nmr was consistent with the assigned structure: nmr ($CDCl_3$) δ 1.25 (t, 3, CH_3, J = 7 Hz), 3.25 (2 d, 2, C-4, J = 9, 12 Hz), 4.15 (q, 2, OCH_2, J = 7.0 Hz), 5.1 (dd, 1, C-5, J = 9, 12 Hz), 7.6–8.1 ppm (m, 15, phenyl).

Attempted Phosphonioethylation of 5-Carbethoxy-2-pyrazolin-3-yltriphenylphosphonium Bromide (9e).—Vinyltriphenylphosphonium bromide (0.001 mol), **9e** (0.001 mol), and 10 ml of chloroform were refluxed for 24 hr, concentrated to half volume, and filtered. The white solid collected was disalt **8** in a 73% yield. There was no phosphonioethylated product found.

Kinetic Data.—The sample for the kinetics was obtained from the reaction mixture as soon as the chloroform had been added and the mixture was homogeneous. The sample was placed in a liquid cell and the change in absorbance of the diazo peak was followed with time on a Perkin-Elmer 421 spectrophotometer. A plot of the reciprocal of the absorbance *vs.* time in minutes gave the straight-line plot. The relative rates reported are the slopes of these plots.

Pyrolysis of 5-Carbethoxy-2-pyrazolin-3-yltriphenylphosphonium Bromide (9e).—In an nmr tube some of **9e** was heated to a melt for 5 min. $CDCl_3$ was added and an nmr was taken. The pyrazole hydrobromide could not be isolated pure but the nmr was consistent with that of a sample prepared from **7e** (Table I): nmr ($CDCl_3$) δ 1.35 (t, 3, CH_3, J = 7 Hz), 4.4 (q, 2, DCH_3 J = 7 Hz), 6.95 (d, 1, C-4, J = 2.8 Hz), 8.05 (d, 1, C-3, J = 2.8 Hz), 10 ppm (s, 2, NH solvent dependent, exchanges with D_2O).

Acknowledgment.—This work was supported by a U. S. Public Health Service Grant (CA 11000) for which we are most grateful.

Registry No.—**1**, 5044-52-0; **4a**, 6832-17-3; **4b**, 4250-01-5; **4c**, 3282-32-4; **4d**, 4203-31-0; **4e**, 623-73-4; **7a**, 19854-93-4; **7b**, 40711-94-2; **7c**, 19854-92-3; **7d**, 40711-96-4; **7e**, 5932-27-4; **8**, 1519-45-5; **9e**, 40711-97-5.

Kinetic Evidence for the Existence of a 1,4 Dipole

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Received December 27, 1972

Recently we presented experimental evidence for the rearrangement of a proposed 1,4 dipole (**1**), gen-

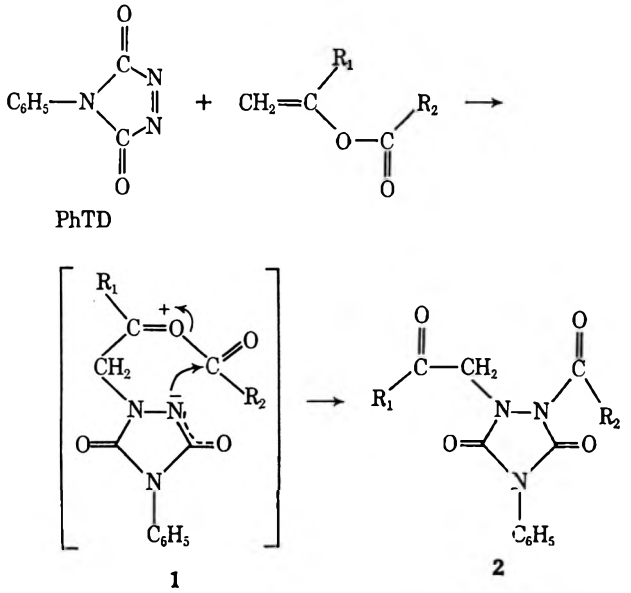
TABLE I

Registry no.	Vinyl ester	R_1	R_2	k, l./mol sec	ΔE_{act}, kcal/mol (c of c)[a]
108-22-5	Isopropenyl acetate	CH_3	CH_3	2.7×10^{-1}	7.4 (0.977)
108-05-4	Vinyl acetate	H	CH_3	4.2×10^{-2}	12
2424-98-8	Vinyl isobutyrate	H	$CH(CH_3)_2$	5.9×10^{-2}	12 (0.997)
3377-92-2	Vinyl pivalate	H	$C(CH_3)_3$	4.0×10^{-2}	12
2549-51-1	Vinyl chloroacetate	H	CH_2Cl	8.1×10^{-4} [b]	14 (0.997)
769-78-8	Vinyl benzoate	H	C_6H_5	4.3×10^{-2} [b]	11 (0.988)

[a] c of c refers to the coefficient of correlation, calculated for each set of data, reflecting the accuracy of the results. The closer the value is to unity, the better the straight-line fit. If no value is shown in the table, the c of c is 0.999 or better. [b] These values were obtained from an Arrhenius plot of second-order rate constants measured at four other temperatures.

erated by reaction of 4-phenyl-1,2,4-triazoline-3,5-dione (PhTD) and vinyl esters (Scheme I), and suggested that the apparent rate of reaction was a function of the vinyl ester employed.[1] These reactions have been studied spectroscopically[2] and the results lend additional support for the existence of the 1,4 dipole.

SCHEME I



Assuming irreversibility, the reactions have been found to be second order overall—first order in each reactant—as might be expected in the formation of an adduct. Table I lists the second-order rate constants at 60° along with the energies of activation for each vinyl ester.

The size of R_2 has no effect on the energy of activation, as shown by the R_2 = alkyl series. This is indicative of an intermediate being formed, followed by nucleophilic attack by the dipole effecting rearrangement. Since the relative yield of 2 decreases as the size of R_2 increases,[1] the product ratios must be determined by the activation energies in the second step. This is exemplified in the energy diagram (Figure 1) for the vinyl isobutyrate reaction, which has a product ratio of 10:2:1 for 1-formylmethyl-2-(2-methylpropionyl)-4-phenyl-1,2,4-triazoline-3,5-dione:copolymer:3-phenyl-6-(2-methylpropionyloxy)-1,3,5-triazabicyclo[3.2.0]hepta-2,4-dione.[1] The possibility of product formation occurring from other than a common intermediate was considered, *i.e.*, formation of rearranged product and polymer *via* ring opening of the corresponding 1,3,5-triazabicyclo[3.2.0]hepta-2,4-dione. This pathway was eliminated by heating to 60° a solution of the three products resulting from the vinyl pivalate reaction for 16 hr to determine if the product ratio would change. No change was observed.

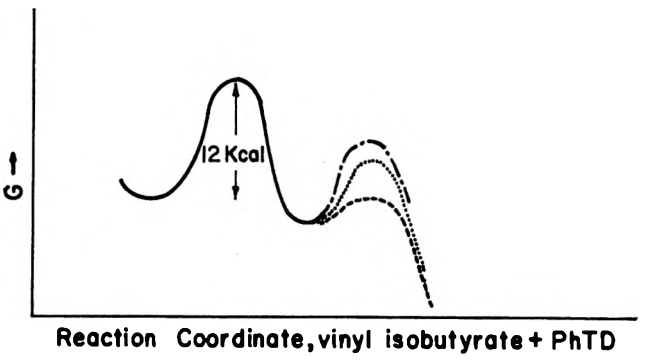


Figure 1.—Probable energy pathways: -------, 1-formylmethyl-2-(2-methylpropionyl)-4-phenyl-1,2,4-triazoline-3,5-dione (2 in Scheme I); ·····, copolymer; —·—·—, 3-phenyl-6-(2-methylpropionyloxy)-1,3,5-triazabicyclo[3.2.0]hepta-2,4-dione. The second step is not necessarily lower in energy than the first step.

The stability of the 1,4 dipole is directly affected by the inductive effects of R_1 and R_2. Changing R_1 from methyl to hydrogen increases the activation energy *ca.* 4.5 kcal/mol, demonstrating the importance of cation stabilization. The dipole is destabilized further by placing a chloromethyl group at R_2, a phenomenon analogous in the opposite sense to the increase of the acidity of chloroacetic over acetic acid. The activation energy for the vinyl benzoate reaction is slightly lower than for the R_2 = alkyl series, possibly owing to conjugation of the ester carbonyl with the aromatic ring allowing increased lone-pair sharing by the ester oxygen.

Experimental Section

Kinetics Procedure.—Portions (1 ml) of equimolar solutions of vinyl ester and PhTD in 1,1,2,2-tetrachloroethane were pipetted into a pressure-resistant uv cell. Visible spectra were recorded and the PhTD absorbance at 545 nm was measured *vs.* time. A minimum of seven readings were taken during each run. The reaction was determined to be second order overall by fitting the data in the second-order rate expression (eq 1), which assumes formation of the 1,4 dipole to be irreversible.

$$\frac{1}{A_t} = \frac{k}{a}t + \frac{1}{A_0} \qquad (1)$$

(1) K. B. Wagener, S. R. Turner, and G. B. Butler, *J. Org. Chem.*, **37**, 1454 (1972).

(2) Visible spectra were recorded on a Beckman DK-2A Ratio recording spectrophotometer. All straight-line slopes were calculated by the least squares method.

TABLE II[a]

Vinyl ester	Temp, °C	k, l./mol sec (c of c)[b]	ΔE_{act}, kcal/mol
Isopropenyl acetate	34.8	1.0×10^{-1}	7.44
	40.6	1.5×10^{-1}	
	48.1	2.0×10^{-1}	
Vinyl acetate	44.5	1.7×10^{-2} (0.998)	11.9
	68.3	6.1×10^{-2}	
	74.9	9.1×10^{-2}	
Vinyl isobutyrate	69.7	9.9×10^{-2}	11.6
	78.8	1.8×10^{-1}	
	90.0	2.5×10^{-1} (0.998)	
Vinyl pivalate	51.1	2.6×10^{-2}	12.1
	73.1	8.5×10^{-2}	
	80.2	1.2×10^{-1}	
Vinyl chloroacetate	71.3	1.8×10^{-2}	13.6
	78.3	2.7×10^{-2}	
	90.0	5.0×10^{-2}	
	101.5	9.0×10^{-2}	
Vinyl benzoate	62.5	3.8×10^{-2}	10.7
	69.0	5.7×10^{-2}	
	75.7	7.2×10^{-2}	
	80.0	8.4×10^{-2}	

[a] Since the third decimal place in the absorbance readings was estimated, these values are accurate to two decimal places only, as reported in Table I. [b] Coefficient of correlation, as in Table I.

In eq 1, A_t = absorbance at time t, a = PhTD absorptivity coefficient × cell path length, k = second-order rate constant, and A_0 = initial absorbance.

The reaction was determined to be first order in each reactant by first noting a tenfold increase in rate when using a 10:1 molar ratio of vinyl ester:PhTD, indicating the reaction to be first order in vinyl ester. The results were double checked by fitting the 10:1 molar ratio data in the first-order rate expression (eq 2),

$$\ln \frac{A_t}{a} = kt + A_0 \qquad (2)$$

demonstrating the reaction to be pseudo first order in PhTD under these conditions.

Energies of activation, calculated by the Arrhenius method, are listed to three significant figures in Table II. Second-order rate constants measured at temperatures other than 60° are reported also.

Check of Triazabicycloheptadiene Stability.—A sample of the solid resulting from reaction of 4-phenyl-1,2,4-triazoline-3,5-dione and vinyl pivalate was dissolved in chloroform-d_1 and its nmr taken. The nmr appeared as a superimposition of the nmr spectra of the three pure products. Of special note was the ratio (1:2) of the *tert*-butyl singlets of the monomeric products, one at δ 1.37 corresponding to the *tert*-butyl group of the rearranged product, the other at δ 1.20 caused by the *tert*-butyl of the triazabicycloheptadione. The nmr tube was heated to 60° for 16 hr, followed by nmr analysis. No change in the *tert*-butyl ratio occurred, and there was no noticeable increase in polymer; thus, the triazabicycloheptadiene did not ring open.

Acknowledgment.—The authors would like to thank Dr. W. Brey, Dr. T. Hogen Esch, and Mr. J. Wrobel, all of the University of Florida, for helpful discussions and Dr. M. Vala, also of the University of Florida, for the use of the Wang 700 Advanced Programming Calculator.

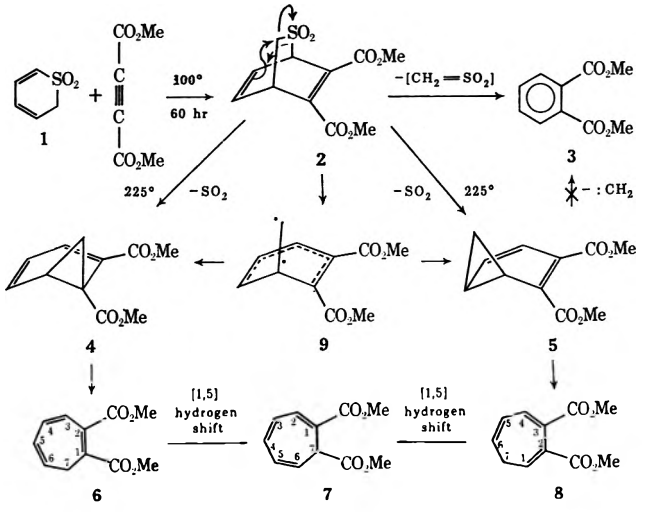
Registry No.—PhTD, 4233-33-4.

See Editorial, *J. Org. Chem.*, 37, No. 19, 4A (1972).

Cycloheptatriene Derivatives from a 2,2-Dioxido-2-thiabicyclo[2.2.2]-octa-5,7-diene

Summary: Thermolysis of dimethyl 2,2-dioxido-2-thiabicyclo[2.2.2]octa-5,7-diene-5,6-dicarboxylate at 220° provides in a sulfur dioxide extrusion–rearrangement reaction a mixture of dimethyl cycloheptatriene-1,2-, -2,3-, -1,7-dicarboxylates and, in a retro Diels–Alder reaction under the loss of sulfene, dimethyl phthalate.

Sir: The generation of sulfene ($CH_2{=}SO_2$) by dehydrohalogenation of methanesulfonyl chloride with tertiary amines has the disadvantage that, in the absence of reactive partners such as strongly nucleophilic olefins[1,2] or diazoalkanes,[1,3,4] the components form sulfonyl chloride–amine adducts[5,6] or sulfene–trialkylamine adducts.[7] We considered as a possible route for the formation of a nonstabilized sulfene thermolysis of dimethyl 2,2-dioxido-2-thiabicyclo[2.2.2]octa-5,7-diene-5,6-dicarboxylate (2) which in a retro Diels-Alder reaction was expected to liberate sulfene and dimethyl phthalate as the only coproduct.



Recently, King and Lewars[8] reported the thermolysis of the 4-phenyl derivative of 2 to give dimethyl biphenyl-2,3-dicarboxylate and sulfene which was detected by trapping experiments with an enamine and amine. Thermolysis of the bicyclic sulfone without a reaction partner also gave high yields of dimethyl biphenyl-2,3-dicarboxylate and sulfur dioxide. The authors discussed as a possible route initial formation of sulfene and subsequent reactions leading to sulfur dioxide and unidentified methylene fragments. The present communication describes preliminary results on the thermolysis of sulfone 2 which undergoes a sulfur dioxide extrusion–rearrangement. The reaction represents a useful extension of the thermal rearrangement of allylic sulfones[9] to bicyclic analogs.

Heating of α-thiopyran 1,1-dioxide (1)[10] with dimethyl acetylenedicarboxylate at 100° for 60 hr gave 60% 2: mp 108–110°; λ_{max}^{MeOH} 239 nm (ϵ 3.86 × 10^3); *m/e* 272 (M^+), 149 (base peak); ν_{max}^{KBr} 1755, 1652, 1656, 1305, 1155 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.76 (m, 2 H, CH_2SO_2), 3.85 (s, 6 H, CO_2Me), 4.32 (br dq, 1 H, J = 3.0, 5.5 Hz, $CHCH_2SO_2$), 5.06 (dd, 1 H, J = 2.0, 5.5 Hz, $CHSO_2$), 6.67 (m, 2 H, CH=CH). Thermolysis of 2 at 230° for 10 min with 1-morpholinocyclohexene gave <5% sulfene cycloaddition product,[1,8] Thermolysis of 2, neat or in THF, for 10 min at 220–225° resulted in a mixture of several compounds. Samples from the gas phase of the thermolysis tube showed on gas chromatographic–mass spectral (gc–ms) analysis (8-ft Porapak S column) only one component with major peaks at *m/e* (rel intensity) 66 (4.9), 64, (100), 48 (49), and 38 (11); the mass spectrum was identical with that of sulfur dioxide. The gc–ms analysis of the crude oil on a 12-ft SE-30 column isothermal at 200° gave one well-resolved peak followed by a minor and a major broad peak. The mass spectrum (70 eV) [*m/e* (rel intensity) 194 (10), 77 (100)] of the first eluted component was identical with that of dimethyl phthalate (3). The other two gc bands exhibited highly similar mass spectral patterns showing parent peaks at *m/e* 208 ($C_{11}H_{12}O_4^+$) and intense peaks at *m/e* 149 (base peak) and 91. The mass spectral fragments at *m/e* 149 and 91 indicated methyltropylium carboxylate ions ($C_9H_9O_2^+$) and tropylium ions ($C_7H_7^+$), respectively.

Column chromatography (silica gel–benzene) of the crude mixture resulted in a partial separation and an enrichment of the different components. Purified samples[11] which were essentially free of 3 showed uv absorptions at λ_{max}^{MeOH} 211 and 275 nm and ir bands at 2945 (m), 1725 (s), 1620 (m), 1440 (s), 1260 (s), 1125 (s), and 1060 (s) cm^{-1}. The above uv and ir spectral parameters are in good agreement with data reported in the literature[12,13] for cycloheptatrienecarboxylates, strongly suggesting dimethyl cycloheptatrienedicarboxylates in the thermolysis mixture obtained from 2.

(1) G. Opitz, *Angew. Chem.*, **79**, 161 (1967); *Angew., Chem., Int. Ed. Engl.*, **6**, 107 (1967).
(2) G. Opitz and H. Adolph, *Angew. Chem.*, **74**, 77 (1962); *Angew Chem. Int. Ed. Engl.*, **1**, 113 (1962).
(3) G. Opitz and K. Fischer, *Angew. Chem.*, **77**, 41 (1965); *Angew. Chem. Int. Ed. Engl.*, **4**, 70 (1965).
(4) N. H. Fischer, *Synthesis*, 393 (1970).
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(6) G. Opitz and K. Fischer, *Z. Naturforsch. B*, **186**, 775 (1963).
(7) G. Opitz, M. Kleemann, D. Bücher, G. Walz, and K. Rieth, *Angew. Chem.*, **78**, 604 (1966); *Angew. Chem. Int. Ed. Engl.*, **5**, 594 (1966).
(8) J. F. King and E. G. Lewars, *J. Chem. Soc., Chem. Commun.*, 700 (1972).
(9) E. M. LaCombe and B. Stewart, *J. Amer. Chem. Soc.* **83**, 3457 (1961).
(10) E. Molenaar and J. Strating, *Recl. Trav. Chim. Pays-Bas.*, **86**, 1047 (1967).
(11) A mixture of 6, 7, and 8 gave elemental analyses satisfactory for $C_{11}H_{12}O_4$.
(12) H. Prinzbach and R. Schwesinger, *Angew. Chem. Int. Ed. Engl.*, **11**, 940 (1972).
(13) R. Darm, T. Threlfall, M. Pesaro, and A. Eschenmoser, *Helv. Chim. Acta*, **46**, 2893 (1963).

Structural assignments and compositional analyses of the components were made by inspection of increasing and decreasing nmr signals in spectra obtained from different column chromatography fractions. The nmr structural assignments[14] were verified by double irradiation experiments. Initial fractions contained a mixture of dimethyl phthalate (**3**) and dimethyl cycloheptatriene-1,2-dicarboxylate (**6**): $\delta_{TMS}^{CDCl_3}$ 2.52 (d, 2 H, J = 7.0 Hz, C-7 protons), 3.79 (s, 3 H, CO_2Me), 3.81 (s, 3 H, CO_2Me), 5.48 (dt, 1 H, J = 8.8, 7.0 Hz, C-6 proton), 6.33 (dt, 1 H, J = 8.8, 3.0 Hz, C-5 proton), 6.82 (br d, 2 H, J = 3.0 Hz, C-3 and C-4 protons). Subsequent fractions provided increasing amounts of dimethyl cycloheptatriene-1,7-dicarboxylate (**7**) [$\delta_{TMS}^{CDCl_3}$ 3.61 (s, 3 H, CO_2Me), 3.81 (s, 3 H, COOMe), 4.18 (d, 1 H, J = 8.0 Hz, C-7 proton), 5.91 (br dd, 1 H, J = 8.0, 10 Hz, C-6 proton), 6.42 (br dd, 1 H, J = 10, 6 Hz, C-5 proton), 6.64 (br dd, 1 H, J = 10, 6.0 Hz, C-3 proton), 6.84 (dd, 1 H, J = 10, 6 Hz, C-4 proton), 7.38 (br d, 1 H, J = 6.0 Hz, C-2 proton)] and dimethyl cycloheptatriene-2,3-dicarboxylate (**8**) [$\delta_{TMS}^{CDCl_3}$ 2.45 (dd, 2 H, J = 6.5, 7.5 Hz, C-7 protons), 3.74 (s, 3 H, CO_2Me), 3.82 (s, 3 H, CO_2Me), 5.86 (dt, 1 H, J = 9.5, 7 Hz, C-6 proton), 6.35 (dd, 1 H, J = 9.5, 5.5 Hz, C-5 proton), 6.52 (t, 1 H, J = 7.5 Hz, C-1 proton), 7.65 (d, 1 H, J = 5.5 Hz, C-4 proton)]. The fourth possible isomer, dimethyl cycloheptatriene-3,4-dicarboxylate,[12] was not detected. Integration of the carbomethoxy region in the nmr spectrum of the crude thermolysis mixture of **2** showed the following composition: **3** (24%), **6** (18%), **7** (27%), and **8** (31%). Thermolysis of a mixture of **3** (28%), **6** (33%), **7** (29%), and **8** (10%) at 220–225° for 1 hr resulted in an increase of **8** (33%) at the expense of compound **6** (7%) whereas the amount of **7** (30%) and **3** (30%) remained practically constant. Heating of a mixture of **3** (11%), **6** (19%), **7** (29%), and **8** (44%) gave a similar relative ratio of cycloheptatriene derivatives as in the previous reaction, indicating that the **6**, **7**, and **8** readily interconvert at 220°. In all cases, equilibrium was already established after 20 min at 220°.

The formation of compounds **3**, **6**, **7**, and **8** from **2** is of considerable mechanistic interest. A possible formation of the cycloheptatriene derivatives **6**–**8** from **2** could proceed under extrustion of sulfur dioxide to give first diradical **9** followed by a collapse to the norcaradiene derivatives **4** and **5**. The reaction could also involve initial formation of dimethyl norborna-2,5-diene-2,3-dicarboxylate. When the latter was thermolyzed under the same conditions as described for **2**, the starting material was recovered exclusively, thus excluding dimethyl norborna-2,5-diene-2,3-dicarboxylate as an intermediate in the formation of compounds **6** to **8**. Another attractive mechanism would be a linear [$_\pi 2_s + {}_\sigma 2_a + {}_\sigma 2_s$] or nonlinear [$_\pi 2_s + {}_\sigma 2_a + {}_\sigma 2_a$] cheletropic sulfur dioxide extrusion–rearrangement reaction (shown for conversion of **2** to **5**) also leading to the norcaradiene intermediates **4** and **5**. From the latter, cycloheptatriene derivatives **6** and **8** would be derived by skeletal rearrangements followed by [1,5]-hydrogen shifts to give **7**.

The formation of **3** may be formulated either as a sulfene extrusion reaction from **2** or possibly as a carbene extrusion reaction of intermediates **4** and **5**. Examples for the loss of carbene from cycloheptatriene derivatives *via* norcaradienes have been described in the literature.[15] Thermolysis of **2** in the presence of cyclododecene as a carbene acceptor as well as prolonged heating of a mixture of **3**, **6**, **7**, and **8** did not result in an increase of **3**. Thus, formation of **3** from intermediates **4** and **5** by a carbene transfer reaction seems to be an unlikely route. The experimental data indicate that in the thermolysis of **2** two independent processes are competing: sulfur dioxide extrusion leading to cycloheptatrienes **6**, **7**, and **8** represents the predominant route, whereas retro Diels–Alder reaction which liberates sulfene from **2** is energetically less favored at 220°. The presence of a phenyl group at C-4 in the thermolysis of the bicyclic sulfone can essentially suppress norcaradiene formation and force the reaction to proceed *via* the sulfene route exclusively.[8] The fate of methylene fragments, possibly derived from sulfene, is not clear. Minor nmr signals typical for cyclopropane ring protons at about δ 0.5 were observed in a short-time thermolysis of **2** at 220°, but were not detected in the 10-min reactions. These signals could be due to thermally labile, sulfene-derived, methylene transfer products. Present investigations are oriented toward the study of the electronic and/or steric influence of different substituents on the two competing processes as well as synthetic aspects of the previously described sulfur dioxide extrustion–rearrangement reaction.

Acknowledgment.—We wish to thank Dr. J. Strating for valuable information on the synthesis of α-thiopyran 1,1-dioxide.[16] We are also grateful for helpful discussions with Dr. K. N. Houk, G. R. Newkome, and J. G. Traynham.

(14) The chemical shifts for compounds **7** and **8** which were determined in $CDCl_3$ differ by 0.05 to 0.15 ppm from the reported parameters[12] which were obtained in CCl_4.

(15) A. P. Ter Borg, E. Razenberg, and H. Kloosterziel, *Recl. Trav. Chim. Pays-Bas.*, **85**, 774 (1966).

(16) Detailed experimental data on the synthesis of α-thiopyran 1,1-dioxide will be described in a coauthored full paper.

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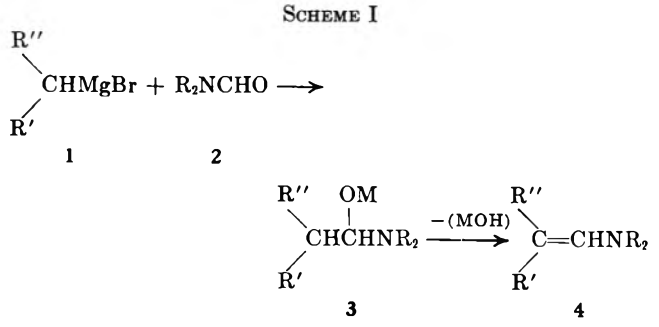
The Preparation of Enamines by Addition of Grignard Reagents to *N*,*N*-Dialkylformamides

Summary: The reaction of *N*,*N*-dialkylformamides with alkylmagnesium bromides, unlike the corresponding reaction with lithium alkyls, gives a primary addition product which undergoes spontaneous elimination forming an enamine in preparatively useful yield.

Sir: We have found that the reaction of Grignard reagents with readily available *N*,*N*-dialkylformamides affords a method of wide applicability for the preparation of aldehyde enamines (Scheme I). The reaction is particularly suited for the preparation of enamines **4** where R′ = alkyl, R″ = H, and R is a bulky substituent such as secondary alkyl. Enamines of this

SCHEME I



type may be of value as synthetic intermediates, as indicated by promising alkylations of enamines prepared from *N*-butylisobutylamine,[1] but they are not readily synthesized by direct condensation of aldehydes with hindered secondary amines.[2,3] A similar addition of Grignard reagents to N-alkylated five- and six-ring lactams has previously been used to prepare heterocyclic enamines.[4]

When primary alkylmagnesium bromides (ether solution) are added to tertiary formamides in tetrahydrofuran (THF) at −15° and the mixture is allowed to reach room temperature, the reaction solution soon shows the characteristic downfield vinyl proton signal (δ 5.5–6.5 ppm) of an enamine. No spectral evidence was found for the accumulation in significant quantities of α-amino alcoholates of type **3** which are presumed to be intermediates in the Bouveault and similar aldehyde syntheses. Pure enamines can be isolated by precipitating inorganic material with hexane and distilling the supernatant (Table I). These sterically

TABLE I

ENAMINES (4) FROM TERTIARY FORMAMIDES (2, 1.3 MOL) AND GRIGNARD REAGENTS (1, 1.0 MOL) IN THF–Et_2O[a]

R′	R″	R	Yield, %[b]
Me	H	*sec*-Bu	63
1-Pr	H	*sec*-Bu	62
1-Pentyl	H	*sec*-Bu	63
1-$C_{11}H_{23}$	H	*sec*-Bu	52
Ph	H	*sec*-Bu	59
CH_2=CH	H	*sec*-Bu	30
1-Pr	H	*n*-Bu	80
1-Pr	H	*i*-Bu	62
1-Pentyl	H	*sec*-Bu	55[c]
1-Pentyl	H	Me	81[c]
Cyclohexyl		Me	66
Cyclohexyl		*sec*-Bu	22[d]

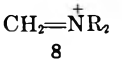
[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed unless otherwise stated. [b] Distilled product. Yields were based upon 1. [c] Solvent: pure Et_2O. [d] See footnote *b*, Scheme II.

hindered enamines may be alkylated, *e.g.*, with ethyl iodide in acetonitrile, in high yield without prior isolation of the enamine.

Preliminary experiments had indicated that yields were generally better and the work-up more convenient using THF–Et_2O as solvent instead of pure Et_2O, which is less basic (see Table I). It was found essential to employ a moderate excess of the formamide but the mode of addition and the reaction temperature were less critical. Inverse addition of the Grignard reagent at a low temperature was found to be favorable. It is of interest in this connection that the yield of aldehyde in the related Bouveault syntheses has very recently been reported to be significantly improved when the reaction is run in an ether–hexamethylphosphoric triamide solvent.[5]

Not unexpectedly, reactions with secondary alkyl Grignard reagents were quite sensitive to the steric bulk of the formamide component, particularly in the addition step. With increasing bulk the yields of enamines were lower and the side reactions more pronounced. The reaction of cyclohexylmagnesium bromide with *N*,*N*-dimethylformamide (DMF) and *N*,*N*-di-*sec*-butylformamide was investigated in some detail to obtain information about the major side reactions (Scheme II). After adding the Grignard reagent as before, the temperature was allowed to rise to 25° over ~4 hr and held there for the remainder of the experiment. The reaction was monitored by nmr spectra, vpc, and vpc–ms of the reaction mixture and of samples quenched with water. With R = Me, the by-products cyclohexane and cyclohexene were formed at about the same rate during the first phase of the reaction. After 4 hr their concentrations were constant (quenched samples) indicating that all Grignard reagent had been consumed. Enamine formation progressed much more slowly with secondary Grignard reagents than with primary and was complete only after ~120 hr. No nitrogenous products which could be associated with hydrocarbon formation were identified.

Cyclohexylmagnesium bromide and **2** (R = *sec*-butyl) gave cyclohexane and cyclohexene as before, but in larger quantities (Scheme II). Consumption of the Grignard reagent was complete only after ~40 hr when the enamine signals (δ 5.5 ppm) had just begun to appear. Enamine formation was complete after a further 120 hr, but the yield was low. Our present results indicate that cyclohexene and **6** (R = *sec*-Bu) are formed mainly in a reduction of the formamide **2** by the Grignard reagent with subsequent elimination to form an electrophile, such as **8**, which then adds



8

Grignard reagent. (Similar reductions of carboxamides[6] and immonium salts[7] have been observed before.) Cyclohexane and the glyoxylic amide **7** (R = *sec*-Bu) are presumably formed by abstraction of a proton from the formamide **2** by the Grignard reagent. The resulting carbamoylmagnesium intermediate either adds to a second molecule of **2** or dimerizes like a carbene. No evolution of carbon monoxide could be

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(5) J. Fauvarque, J. Ducom, and J. F. Fauvarque, *C. R. Acad. Sci., Ser. C*, **275**, 511 (1972).
(6) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, N. Y., 1954, p 872.
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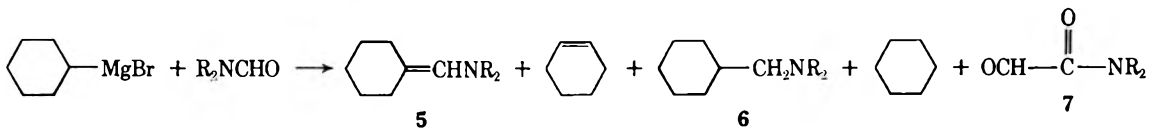
SCHEME II[a]



	5		6		7
R = Me	66%	5%[c]	Not found	7%[c]	Not found
R = *sec*-Bu	22%[b]	28%[c]	27%[b]	24%[c]	10% (2,4-DNP)

[a] Yields were based on cyclohexylmagnesium bromide. [b] 5 and 6 (R = *sec*-Bu) were isolated by distillation as a mixture and analyzed by vapor phase chromatography (vpc)–mass spectrometry (ms). Hydrolysis afforded pure 6 and cyclohexanecarboxaldehyde. [c] By vpc of the reaction mixture.

detected by vpc. Analogous cases have been reported.[8,9]

When alkyllithium reagents in hexane were added to *N*,*N*-dialkylformamides, the amino alcoholates **3** (M = Li) formed rapidly but did not undergo spontaneous elimination to form enamines. The product **3** (M = Li; R = methyl; R′ = *n*-propyl; R″ = H) was isolated in an amorphous but reasonably pure state by stripping the solvent (30° at 0.3 mm). It was surprisingly soluble in nonpolar solvents but gave consistent ^1H ($CDCl_3$) and ^{13}C (C_6D_6) nmr spectra. Elimination forming an enamine occurred readily when the amino alcoholate **3** was treated *in situ* with Lewis acids ($MgBr_2$, BF_3, and $AlCl_3$) or with alkylating or acylating reagents (MeI, Ac_2O, and also Me_3SiCl). However, the overall yields were lower (40–50%) than with the procedure employing Grignard reagents.

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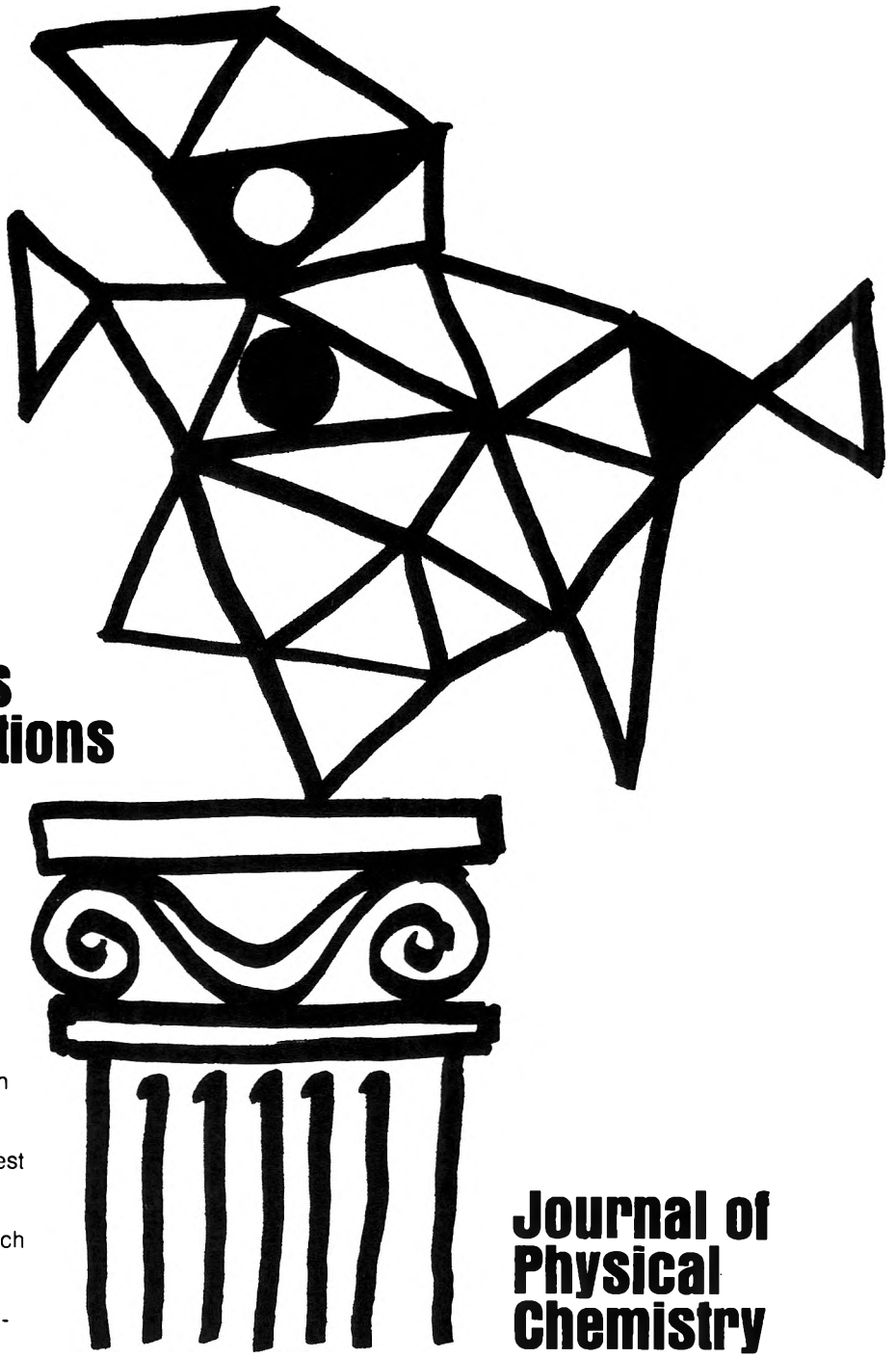

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Ketone	Alcohol epimer	Selectrides		$NaBH_4$	$LiAlH_4$	$LiAlH(O/Bu)_3$
		I	K			
2-Methylcyclohexanone	cis	99.3%	99+%	31%	24%	30%
3-Methylcyclohexanone	trans	85		17	16	10
4-Methylcyclohexanone	cis	80.5	88	18	17	17
4-*tert*-Butylcyclohexanone	cis	96.5		20	11	10
3,3,5-Trimethylcyclohexanone	trans	99.8		86	82	88

The Selectrides (lithium and potassium tri-*sec*-butylborohydride) quantitatively reduce ketones to alcohols in excellent stereochemical purity.[1,2]

The bulky trialkyl groups of these reagents control the stereochemistry of the reduction so effectively that the selectivity of L-Selectride has been compared to that of an enzyme. Enzymatic reduction of 4-*tert*-butylcyclohexanone gives 95% *cis*-4-*tert*-butylcyclohexanol, whereas, L-Selectride gives 96.5% *cis* alcohol.

The Selectrides and other bulky trialkylborohydrides have been used in the synthesis of prostaglandins where other known reducing agents failed.[3,4] Selectride cleanly reduced the 15-keto group to an 89/11 ratio of 15S/15R alcohols.

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LITERATURE AVAILABLE

Send for a comprehensive data sheet covering all of our trialkylborohydrides. An extensive review of the synthetic applications of borane complexes and organoboranes is available: C. F. Lane, *Aldrichimica Acta*, **6**, 21 (1973).

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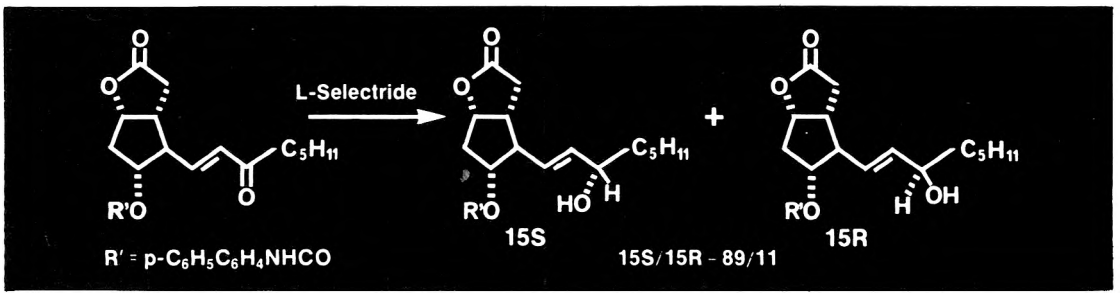

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