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4-Methyl-2-pentanone
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2,4-Pentanedione
Phenylacetic Acid
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Propionic Acid

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Benzene-d_6
Benzoyl Chloride
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2-Chloroacetophenone
(phenacyl chloride)
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"sym-Diphenylcarbazone"
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Methanol, 'Baker Instra-Analyzed'
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Ninhydrin
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p-Nitrophenyl Isocyanate
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Phenylhydrazine
Phenyl Isocyanate
4-Phenylsemicarbazide
2-Propanol, 'Baker Instra-Analyzed'
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Trifluoroacetic Acid
4,4,4-Trifluoro-1-(2-thienyl)-1,3-butanedione

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Chlorosulfonic Acid
Cyanogen Bromide
Lithium Aluminum Hydride
Phosphorus Tribromide
Sodium Azide
Sodium Borohydride
Sodium Methoxide
(Methanol, Sodium Derivative)
Thionyl Chloride
Trifluoroacetic Anhydride

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(1-butanol)
Chloroform
Cyclohexane
Decahydronaphthalene
1,2-Dimethoxyethane
Dimethylformamide
Ether
2-Ethoxyethanol
Ethyl Acetate
Heptane
Hexanes
Methanol
2-Methoxyethanol
2-Methylbutane
Methyl Ethyl Ketone
4-Methyl-2-pentanone
Nitromethane
Pentane
Piperidine
Pyridine
Tetrahydrofuran
Toluene
1,1,1-Trichloroethane
Xylenes

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L-Ascorbic Acid
Caffeine
Cinchonine
D-(−)-Fructose
D-(+)-Galactose
L-(+)-Glutamic Acid NAS/NRC
Glycine NAS/NRC
Hematoxylin
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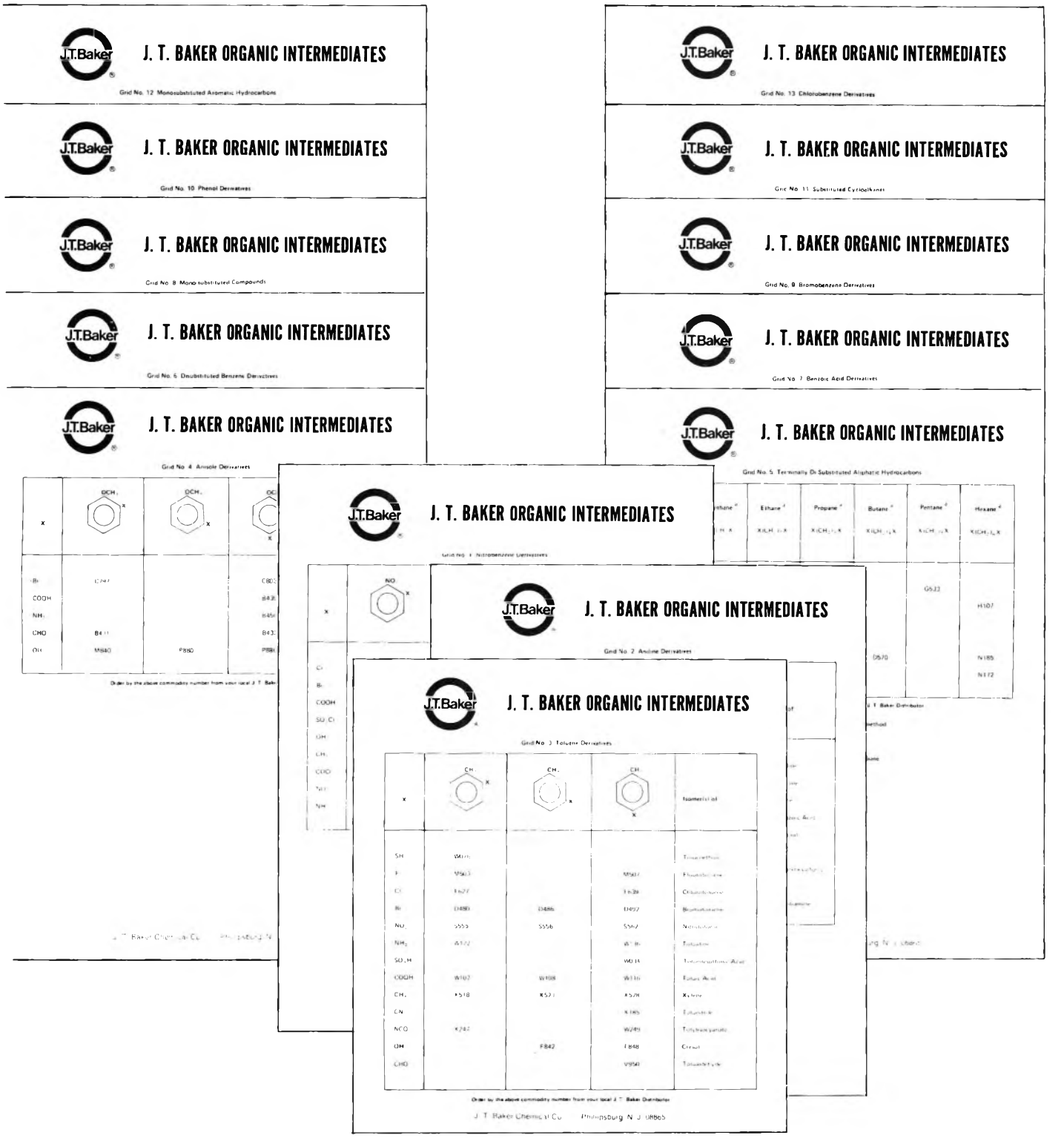

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Aluminum Hydride Reduction of α-Ketols. II. Additional Evidence for Conformational Flexibility in the Transition State

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The stereochemistry of the reduction with four aluminum hydride reagents of five α-ketols and four α-diones has been studied. The results, together with those of a previous study, representing a total of seven substitutional types, are considered in terms of current models of asymmetric induction in α-ketols. The stereoselectivity observed may be correlated by Cram's cyclic model for asymmetric induction in chiral ketones only with a monomeric reagent, triisobutylaluminum. A modification of Cram's model, wherein the intermediate alanate complex exists in a cyclopentanoid half-chair conformation, allows explication of several observed anomalies. A dependence of the stereoselectivity of the reduction upon the bulk of the reagent is accommodated by this model. Two side reactions, Meerwein–Ponndorf–Verley reduction and hydride-catalyzed keto–hydroxyl isomerization, are considered as alternative reaction paths which might affect observed stereoselectivity. While both reactions are noted under specified conditions, the degree to which each occurs (and in the former case, kinetic considerations) suggests that their effect is minimal.

We have recently reported[1] the results of a study of the reduction of several aliphatic α-ketols of the type I and II (Chart I) with the aluminum hydride reagents, triisobutylaluminum (TIBA), diisobutylaluminum hydride (DIBAH), lithium aluminum hydride ($LiAlH_4$), and lithium trimethoxyaluminum hydride (LTMAH). These systems were found to conform to Cram's cyclic model[2] for asymmetric induction in chiral ketones to the extent that, in each case, the predominant isomer formed was the predicted erythro isomer. The degree of stereoselectivity found, however, did not correlate well with α-ketol structure in the presumed cyclic transition state A (Chart II) in which the aluminum-bound ligands are symmetrically disposed on either side of the five-membered chelated ring. To account for the peculiar variations in observed stereoselectivity, and to account for an indicated role of the attacking hydride reagent in determining preferred transition state geometries, we suggested that certain conformations of the chelated ring, *e.g.*, the cyclopentanoid half-chair configurations B and C (Chart II) first proposed by Stocker,[3] provided an improved basis for the rationalization of noted anomalies.

Chart I

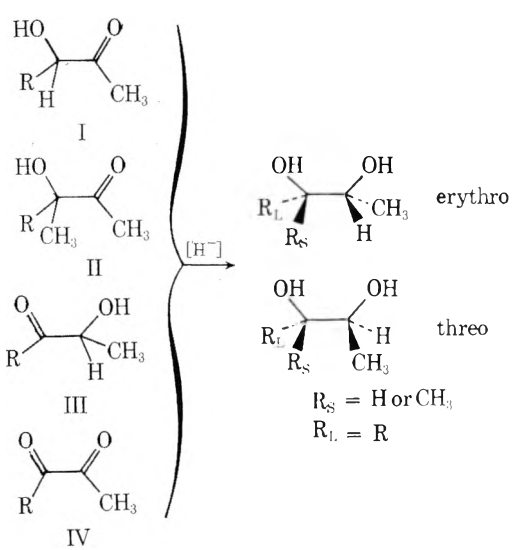
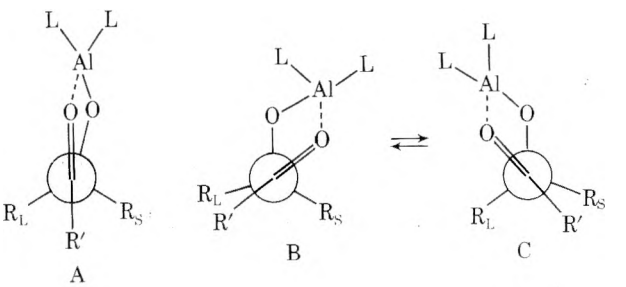
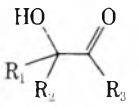


Chart II

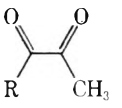


We wish to report the results of studies of the reduction of α-ketols of the type III and the corresponding α-diones IV (Chart I) with the above aluminum hydride reagents. As will be described, the results support our contention that the transition state geometry of the aluminum chelate in the reduction is satisfactorily represented by an equilibrium of the conformers B and C (Chart II).[1] Evidence is also presented that two possible side reactions which might influence observed stereoselectivity, Meerwein–Ponndorf–Verley reduction and hydride-catalyzed keto–hydroxyl isomerization, have only a minimal effect on the steric course of the reaction.

Table I
Yield of Diol Products and Per Cent Erythro Isomer Produced in the Hydride Reduction of Substrates



α-ketols (types I, II, III)



α-diones (type IV)

Registry no.	Compd	Substituents[a] R1	R2	R3	% erythro[b] (diol yield %)[c] TIBA (toluene)	DIBAH (toluene)	$LiAlH_4$ (THF)	$LiAl(OMe)_3H$ (THF)
52279-26-2	1	CH_3	H	n-C_5H_{11}	49 (69)	64 (90)	64 (98)	73 (94)
52279-27-3	2	CH_3	H	i-Pr	71 (71)	55 (83)	58 (78)	46 (98)
52278-28-4	3	CH_3	H	t-Bu	89 (65)	64 (87)	87 (79)	85 (98)
5650-40-8	4	CH_3	H	Ph	66 (83)	60 (94)	87 (92)	85 (98)
90-63-1	5	Ph	H	CH_3	83 (70)	79 (72)	80 (85)	76 (85)
585-25-1	6	n-C_5H_{11}			57 (69)	62 (83)	54 (92)	54 (87)
7493-58-5	7	i-Pr			85 (69)	59 (75)	60 (91)	53 (84)
40898-19-9	8	t-Bu			96 (86)	68 (87)	74 (98)	71 (92)
579-07-7	9	Ph			76 (70)	77 (74)	72 (98)	78 (99)

[a] Substitution as in figures above; in compounds **6–9**, R_1 refers to R in the dione structure. [b] Nmr analysis (see ref 1). [c] Isolated yield of diol, *ca.* 95% pure.

Table II
Stereoselectivity Observed in Reductions of α-Ketols and α-Diones

Compd	Substituents[a] R1	R2	R3	Stereoselectivity[b] (diastereomer ratio)[c] TIBA (toluene)	DIBAH (toluene)	$LiAlH_4$ (THF)	$LiAl(OMe)_3H$ (THF)
			Disubstituted α-Ketols, Type III				
1	CH_3	H	n-C_5H_{11}	−2 (0.96)	28 (1.78)	28 (1.78)	46 (2.70)
2	CH_3	H	i-Pr	42 (2.44)	10 (1.22)	16 (1.38)	−8 (0.85)
3	CH_3	H	t-Bu	78 (8.09)	28 (1.78)	74 (6.69)	70 (5.67)
4	CH_3	H	Ph	32 (1.94)	20 (1.50)	74 (6.69)	70 (5.67)
			Disubstituted α-Ketols, Type I				
d	n-C_5H_{11}	H	CH_3	8 (1.17)	36 (2.13)	40 (2.33)	56 (3.55)
d	i-Pr	H	CH_3	66 (4.88)	24 (1.63)	46 (2.70)	32 (1.94)
d	t-Bu	H	CH_3	>96 (49)	46 (2.70)	50 (3.00)	54 (3.35)
5	Ph	H	CH_3	66 (4.88)	58 (3.76)	60 (4.00)	52 (3.16)
			α-Diones, Type IV				
6	n-C_5H_{11}			14 (1.33)	24 (1.63)	8 (1.17)	8 (1.17)
7	i-Pr			70 (5.67)	18 (1.44)	20 (1.50)	6 (1.13)
8	t-Bu			92 (24.0)	36 (2.13)	48 (2.84)	42 (2.44)
9	Ph			52 (3.16)	54 (3.35)	44 (2.57)	56 (3.55)
			Trisubstituted α-Ketols, Type II				
d	i-Pr	CH_3	CH_3	70 (5.67)	42 (2.45)	−2 (0.96)	20 (1.50)
d	t-Bu	CH_3	CH_3	82 (10.11)	20 (1.50)	28 (1.78)	40 (2.33)
d	Ph	CH_3	CH_3	64 (4.56)	56 (3.55)	34 (2.03)	14 (1.33)

[a] Substitution as in the figures above, Table I; in compounds **6–9**, R_1 refers to R in the dione structure. [b] Stereoselectivity = % erythro − % threo isomer. [c] Diastereomer ratio = % erythro/% threo isomer. [d] Data taken from ref 1.

Results

The substrates **1–9** were reduced in good yields by the aluminum hydride reagents under the same conditions used in our previous study.[1] Quantitation of the erythro isomer in each mixture was accomplished by the nmr technique described; chemical shift data used for these measurements were those previously reported.[1] Stereochemical assignments for the phenyl-substituted systems (**4**, **5**, and **9**), which were not incorporated in our earlier work, were confirmed by comparison to authentic samples of *erythro*- and *threo*-1-phenyl-1,2-propanediol, prepared by trans and cis hydroxylation of isomerically pure *trans*-phenylpropene.

The yields of the product α-diols and the per cent erythro isomer in each mixture are presented in Table I. Stereoselectivity and isomer ratios calculated from these data are presented in Table II, together with the findings of our previous work.[1]

General Observations. Examination of Table II reveals several striking features of the data. Of the reagents, TIBA alone affords the anticipated regular increase of stereoselectivity with increasing bulk of R (Chart I) for all of the

cases studied; $LiAlH_4$ exhibits the same property, albeit to a lesser degree, except in the case of α-ketols of type III (1–4). The results of reduction of phenyl-substituted systems with TIBA are at curious variance with those of other reagents. In the reduction with TIBA, the steric bulk of the phenyl group appears comparable to or smaller than that of the isopropyl group, while with other reagents, the bulk of the phenyl group would seem to be equal to or greater than that of the *tert*-butyl group.

In other respects, the data appear to be poorly correlated. The stereoselectivities of the reduction of trisubstituted systems (final three entries) with DIBAH and LTMAH are badly scattered; for the disubstituted α-ketols and α-diones, however, a recognizable pattern emerges. In many cases the selectivity of the isopropyl-substituted system is less than that of the *n*-pentyl system. Change of R to the *tert*-butyl group reverses this trend, and the stereoselectivity observed is comparable to and usually greater than that of the *n*-pentyl system.

Discussion

Steric Effects Influencing the Stereoselectivity of Reduction. Any model advanced to correlate the data of Table II must include features which allow a role for the attacking hydride reagent in creating preferred transition state geometries, as well as sufficient conformational flexibility of the aluminum chelate to explain the anomolous decrease in stereoselectivity in the reduction of the α-ketols with the medium-sized substituent (R = isopropyl) *vs.* those with the smaller substituent (R = *n*-pentyl). Cram[2] has suggested that a decrease of stereoselectivity noted in reactions with lithium reagents upon change of solvent from ether to pentane is due to the intervention of certain dipolar model[4] transition states, made favorable by increased steric crowding of the cyclic transition state, as well as relief of dipolar repulsions. Under this scheme, however, a regular *decrease* in stereoselectivity relative to the predictions of the cyclic model should be observed in a sterically homologous series with a given reagent; this is clearly not the case.

Our previously postulated[1] model (Chart II) does, however, fulfill the above criteria. While several possible conformational equilibria may be possible, equilibration of conformers of the type B and C allows the simplest rationalization of the results shown in Table II. Thus, increase of R_L from *n*-pentyl to isopropyl would destabilize conformer B with respect to C, due to increased interactions of R_L with the carbonyl-bound stubstituent R′. Observed stereoselectivity would then depend on the relative steric interactions of the approaching hydride reagent with R_L and with the ligands attached to the chelated aluminum. For relatively small ligands and a monomeric reagent (TIBA),[5] attack from the upper right to afford the erythro isomer is favored. In the case of DIBAH, where the chelated species is equivalent to that derived from TIBA, the noted decrease in stereoselectivity may be attributed to the greater interactions between the much bulkier, associated (trimeric)[6] attacking reagent and the chelated aluminum, making attack from the lower left to afford the threo isomer somewhat more favorable. Increase in the bulk of R_L to *tert*-butyl would again favor the conformer C; in this case, however, R_L is sufficiently large to make attack from the lower left unfavorable, and an increase in the stereoselectivity of the reduction (relative to R_L = isopropyl) is noted.

Several additional lines of evidence may be advanced to support our contention of the half-chair conformation equilibrium. In studies of the reactions of trimethylaluminum with substituted cycloalkanones, Ashby[7] has recently formulated an alternative model to the traditional "steric approach control" and "product development control" rationales of the stereochemical course of the reductive alkylation of these systems. From Ashby's analysis emerges a point relevant to the case of the reduction of α-ketols: the effective bulk of the carbonyl is increased by complexation with an organoaluminum species to the extent that severe interactions with groups on adjacent carbons may occur in the transition state.[7] Ashby has dubbed this a "compression" effect, as opposed to eclipsing or torsional effects characteristic of single-bond repulsions. Whether α-ketols are subject to compressive *vs.* torsional effects is academic; the salient feature of the argument is that the increased bulk of the carbonyl, together with the large van der Waals radius of the neighboring alkoxide, ensures that the chelated ring will adopt conformations in which the O—C—C=O unit is not planar, *e.g.*, the half-chair conformations B and C.

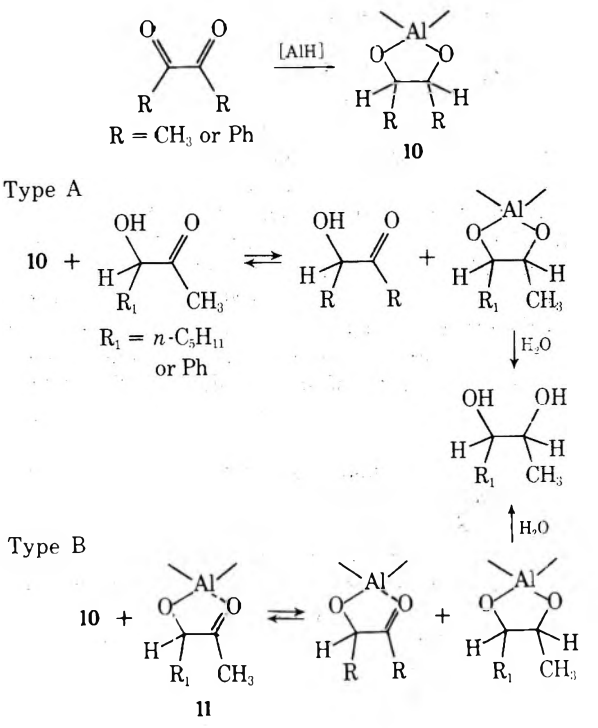
The role of the carbonyl-bound substituent in creating preferred transition state geometries may be inferred from the work of Karabatsos[8] and Felkin[9] with systems following the open-chain[10] model, and is clearly demonstrated by comparison of the stereoselectivity of the reduction of disubstituted α-ketols of types I[1] and III (1–4; Chart I). That the stereoselectivity of the former exceeds that of the latter in 12 of the 16 cases studied is reasonable inasmuch as, in α-ketols of type I, the tetrahedral carbinol carbon allows interaction of R with both the approaching hydride reagent and the carbonyl-bound methyl group to determine a preferred conformation, whereas with α-ketols of type III, interactions of the carbonyl-bound substituent with the β-methyl group alone are those which are anticipated to create a preferred transition state geometry.

Stocker[3] has noted that, in reactions of symmetrically substituted α-diones with organolithium and Grignard reagents, the stereoselectivity observed is the same as that in the reaction of the corresponding trisubstituted α-ketol. The stereoselectivity observed in the reduction of the α-diones **6–9** could, therefore, be the same as that of either the disubstituted α-ketols of types I or III. In any case, the stereoselectivities of the α-ketol reductions, irrespective of their precise transition state geometries, should represent limiting values for the reduction of the corresponding α-dione, as reduction of the latter would presumably be partitioned between the transition states obtained in the α-ketol reductions. Twelve of the sixteen cases studied do indeed conform to this relation.

While the half-chair model provides an adequate rationale to explain many of the unanticipated results in Table II, the behavior of phenyl-substituted systems is clearly outside the predictive domain of the model. The apparent variable effective steric bulk of the phenyl substituent is puzzling, and we have been unable to account for this. For example, an attractive hypothesis which would explain the low stereoselectivity obtained in reductions of substrates possessing the benzoyl moiety with TIBA might be that in these systems the phenyl and carbonyl groups are coplanar, allowing maximum π overlap; in these conformations interactions of the phenyl group with R_L (Chart II) and the attacking hydride reagent would be presumably smaller than in other conformations. The effect is not general, however; in reduction of the same substrates with $LiAlH_4$ and LTMAH, substantially greater stereoselectivities are observed. The effect of the electronic properties of phenyl-substituted systems, as opposed to purely steric factors, is, therefore, a point of continued interest.

Nonsteric Factors Influencing the Stereochemistry of Reduction. Meerwein–Ponndorf–Verley Reduction. Haubenstock and Davidson[11] and Ashby[12] have reported the time-dependent distribution of isomeric cyclohexanols

Chart III



from the reduction of 3,3,5-trimethylcyclohexanone with TIBA as the limiting reagent, and have attributed the observed equilibration to the Meerwein–Ponndorf–Verley reduction—Oppenhauer oxidation scheme. To determine whether the aluminum alkoxides formed in the course of reduction of α-ketols are capable of promoting such reaction, the following experiments were undertaken.

Selected α-ketols were subjected to treatment with aluminum alkoxides analogous to those presumed to be intermediates in the α-ketol reductions (Chart III). The desired alkoxide (**10**) was generated by reduction of benzil (representative of secondary benzylic carbinols) or biacetyl (representative of aliphatic carbinols) with the stoichiometric amount of hydride reagent at room temperature; the substrate was introduced at −78°, and the mixture equilibrated for 24 hr at 25° (type A). Alternatively, addition of the substrate at −78° to solutions of **10** which contained 1 equiv of hydride gave a mixture of substrate as its aluminum derivative (**11**) and **10**, which was equilibrated as above (type B). Separate experiments established that no appreciable reduction of the substrate took place at −78° in this experiment. The use of 1,2-diphenyl-1,2-ethanediol instead of benzil in the generation of the aluminum alkoxide, even at greater than the stoichiometric amount, had no material effect on the observed amount of reduction of the substrate (Table III).

Hydrolysis of the mixtures and analysis of the crude products by glpc gave the results shown in Table III. As opposed to our previous experience with analysis of diol mixtures by glpc,[1] the use of a glass column for these analyses gave highly reproducible results, indicating that decomposition of the diols was minimal. The diastereomeric products were not resolved in the system used, however. While the diol resulting from reduction of the substrate was the only material quantitated, species arising from hydrolysis of the reagent alkoxide (hydrobenzoin or butanediol), oxidation of the reagent alkoxide (benzoin or acetoin) and unreacted substrate were found in each mixture.

The data of Table III correlate in three ways. First, substantially greater reduction is noted in reactions of DIBAH *vs.* $LiAlH_4$. Although there is insufficient information to permit a precise formulation of the alkoxide **10** in these two cases, the more reactive one, derived from DIBAH, is presumed to be neutral and trivalent; the less reactive one, from $LiAlH_4$, anionic and tetravalent (ate complex). Second, reduction is more efficient by secondary benzylic alkoxides than by aliphatic alkoxides; this is thought to represent the difference in the stabilities of the oxidized ligands, the benzylic ketone being stabilized relative to the aliphatic ketone by conjugation with the phenyl ring. Finally, substrates bound to the aluminum species (type B) are reduced more efficiently than the free substrates (type A).

Table III
Meerwein–Ponndorf–Verley-like Reduction of α-Ketols

α-Ketol[a] R_1	Reducing agent[b] (solvent)	Alkoxide[a] R	Ratio[c] (type)	Reduction, %
n-C_5H_{11}	DIBAH (toluene)	CH_3	1:2[d] (A)	16.8
			1:3[e] (B)	35.9
	$LiAlH_4$ (THF)		2:1[d] (A)	3.1
			1.5:1[e] (B)	5.5
Ph	DIBAH (toluene)		1:2 (A)	16.5
			1:3 (B)	24.5
	$LiAlH_4$ (THF)		2:1 (A)	4.7
			1.5:1 (B)	7.0
	DIBAH (toluene)	Ph	1:1.5[f]	(34.6)[g]
			1:2 (A)	32.6 (31.8)
			1:3 (B)	53.3 (54.9)
	$LiAlH_4$ (THF)		2.5:1[f]	(10.5)
			2:1 (A)	10.0 (10.6)
			1.5:1 (B)	18.1 (18.4)

[a] Substitution per Chart III. [b] Reagent from which the aluminum alkoxide was prepared. [c] Mole ratio of starting dione to reducing agent to give **10**. Type A, stoichiometric hydride used in preparation of **10**; type B, 1 equiv of excess hydride used (see Chart III). [d] This ratio represents the case in which the α-ketol is not bound to the aluminum alkoxide at the start of equilibration. [e] This ratio represents the case in which the α-ketol is bound to the aluminum alkoxide at the start of equilibration. [f] This ratio represents an excess of the dione relative to the reducing capacity of the hydride reagent. [g] Numbers in parentheses are the reductions noted when the alanate complex was generated from 1,2-diphenyl-1,2-ethanediol rather than benzil.

While these results are suggestive, it should be noted that the conditions for the reactions from which the data of Table II are derived differ fundamentally from those above in that the hydride reagent is present in excess throughout the reaction. Haubenstock[11] noted that in the reaction of 3,3,5-trimethylcyclohexanone with TIBA, when TIBA was in excess, no measurable amount of ketone was observed. The presence of ketone is, however, necessary for diastereomer equilibration to occur *via* the MPV reduction–Oppenhauer oxidation mechanism. Thus, in order for MPV reduction to significantly alter the ratio of products arising from direct hydride reduction requires that the rates of MPV reduction and direct hydride reduction be of the same order. As most hydride reductions are very rapid, intuition argues that this is not the case. Furthermore, the results of deuterium scrambling studies (*vide infra*) indicate that the contribution of MPV reduction is limited to, at most, a few per cent. In the absence of suitable kinetic measurements, the precise degree of MPV reduction must remain conjectural.

Hydride Catalyzed Keto–Hydroxyl Isomerization. A second possible reaction which might affect observed stereoselectivity is keto–hydroxyl isomerization of disubstituted α-ketols prior to reduction. The isomerization of α-ketols under the influence of base has been well studied.[13] Of particular interest are the findings of Temnikova,[14] who noted

Table IV
Keto–Hydroxyl Isomerization of α-Ketols

Substituents[a]			Isomerization, %	
R_1	R_2	R_3	$LiAlD_4$	$LiAl(OMe)_3D$
n-C_5H_{11}	H	CH_3	1.2 (0.13)[b]	5.3 (0.30)
Ph	H	CH_3	0.0 (0.13)	0.8 (0.35)
CH_3	H	Ph	1.4 (0.47)	7.7 (1.6)

[a] Substituents are as in the α-ketol structure above Table I. [b] Numbers in parentheses are the average deviations of replicate experiments.

that reaction of 1-(4-tolyl)-2-propanon-1-ol with either ethyl or phenyl Grignard gives, in addition to the expected product, a significant amount of material in which the Grignard reagent has added to the carbinol center, and our own observation that reaction of ethyllithium with 2-octanon-3-ol affords both the anticipated 3-methyl-3,4-nonanediol and 3-ethyl-2,3-octanediol.[15] The anomalous products in both studies can arise only by isomerization of the α-ketol prior to addition to the carbonyl, although the mechanism remains to be elucidated.

To determine whether such isomerization may occur in the course of the hydride reduction of α-ketols, the reduction of three substrates with lithium aluminum deuteride and lithium trimethoxyaluminum deuteride was studied. The reductions were carried out under the same conditions as used for the reduction studies involving the protio reagents. After the usual isolation, the product diols were cleaved with sodium metaperiodate in aqueous tetrahydrofuran, and the major aldehyde (corresponding to R_L of the product diol; Chart I) was isolated as its 2,4-dinitrophenylhydrazone derivative. Isotope ratio mass spectrometry was used to measure the amount of deuterium on the aldehyde carbon; from these data the degree of transposition was determined. The results of this experiment appear in Table IV.

While significant amounts of transposition are noted in most cases, the degree of transposition is considerably less than that which would, in itself, account for the anomalies of Table II. Oddly enough, 1-phenyl-1-propanon-2-ol gives substantially more isomerization than does 1-phenyl-2-propanon-1-ol, in direct opposition to expectations based on Temnikova's findings.[14] The reason for this is not known.

The results of these experiments militate against the intervention of MPV reduction considered above. If MPV reduction of α-ketols was operative under these conditions (excess hydride), one would anticipate substantially greater amounts of deuterium scrambling in the present study than is observed.

Conclusions

The results of the studies of this work and our previous report[1] lend support to the contention of the cyclopentanoid half-chair conformations B and C (Chart II) as the simplest models for the transition state of the reduction of α-ketols. While the model suffices to explain retrospectively a number of unanticipated results, its predictive value, in terms of the degree of stereoselectivity observed, is low, due to the several complex interactions giving rise to the observed products.

Of anticipated side reactions which might affect the stereoselectivity of the reduction in the presence of excess hydride, Meerwein–Ponndorf–Verley reduction would not seem to have any measurable effect, although this point remains to be proven unequivocally. Hydride catalyzed keto–hydroxyl isomerization, however, would appear to have some effect, insofar as the starting α-ketol and its transposition product represent distinctly different steric cases in the reduction. This effect is, however, markedly substrate and reagent dependent, and would account for deviations of only some few per cent of stereoselectivity.

Experimental Section

General. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined in $CDCl_3$ solution on Varian A-60A or HR-220 spectrometers; chemical shift data are reported in parts per million downfield from internal tetramethylsilane (δ scale). Isotope ratio mass spectrometry was performed on a Varian-MAT CH-5 spectrometer. Gas–liquid chromatography was performed on a Hewlett-Packard Model 5750B chromatograph equipped with flame ionization detectors, using a 6 ft × 0.125 in. glass 3% Carbowax 20M on 100/120 Gas-Chrom Q column, and nitrogen as carrier gas.

Glassware for reactions involving organometallic reagents was dried for a minimum of 3 hr at 120°; these reactions were carried out in an atmosphere of dry nitrogen. Solutions were dried over magnesium sulfate unless otherwise indicated.

Tetrahydrofuran (THF) solutions of lithium aluminum hydride and lithium trimethoxyaluminum hydride, and toluene solutions of diisobutylaluminum hydride and triisobutylaluminum were prepared as previously described.[1] Lithium aluminum deuteride (99 atom % deuterium) was obtained from E. Merck, Darmstadt; this reagent and lithium trimethoxyaluminum deuteride were used at THF solutions prepared by the method of Brown.[16]

1-Phenyl-1,2-propanedione (**9**) was obtained from Aldrich Chemical Co. and was distilled before use. *trans*-Phenylpropene was obtained from Chemical Samples Co. and was used as supplied. Those α-ketols and authentic specimens of isomerically pure diols whose preparations are not herein reported, were from the collection previously described.[1]

Preparation of α-Ketols. The α-ketols **1–4** were prepared by condensation of the appropriately substituted 2-lithio-1,3-dithiane with acetaldehyde, and hydrolysis of the α-hydroxy dithioketal thus produced as previously described.[1]

3-Octanon-2-ol (1). The compound was prepared from 2-*n*-pentyl-1,3-dithiane[17] in 30% yield: bp 62–65° (0.45 mm); oxime mp 61–62° (petroleum ether) [lit.[18] oxime mp 62–63° (aqueous ethanol)]; nmr δ 4.12 (q, J = 7 Hz, 1 H), 3.65 (s, 1 H), 2.49 (t, 2 H), 1.8–1.1 (m, 6 H), 1.31 (d, J = 7 Hz, 3 H), and 0.91 (t, 3 H).

4-Methyl-3-pentanon-2-ol (2). The compound was prepared from 2-isopropyl-1,3-dithiane[17] in 31% yield: bp 64–66° (22 mm); 2,4-dinitrophenylhydrazone mp 148–151° (aqueous ethanol) [lit.[19] bp 51–53° (11 mm); 2,4-dinitrophenylhydrazone mp 151–152° (aqueous methanol)]; nmr δ 4.37 (q, J = 7 Hz, 1 H), 3.30 (s, 1 H), 2.87 (m, J = 7 Hz, 1 H), 1.31 (d, J = 7 Hz, 3 H), 1.12 (d, J = 7 Hz, 3 H), and 1.10 (d, J = 7 Hz, 3 H).

4,4-Dimethyl-3-pentanon-2-ol (3). The compound was prepared from 2-*tert*-butyl-1,3-dithiane[17] in 43% yield: bp 67–69° (11 mm) [lit.[20] bp 102–103° (100 mm)]; nmr δ 4.48 (q, J = 7 Hz, 1 H), 3.27 (s, 1 H), 1.26 (d, J = 7 Hz, 3 H), and 1.17 (s, 9 H).

1-Phenyl-1-propanon-2-ol (4). The compound was prepared from 2-phenyl-1,3-dithiane[17] in 37% yield: bp 75–77° (0.4 mm) [lit.[19] bp 125–126° (13 mm)]; nmr δ 8.0–7.6 (m, 2 H), 7.6–7.2 (m, 3 H), 5.04 (q, J = 7 Hz, 1 H), 3.63 (s, 1 H), and 1.38 (d, J = 7 Hz, 3 H).

1-Phenyl-2-propanon-1-ol (5). Benzaldehyde (10.6 g, 0.10 mol) was added to a stirred suspension of sodium acetylide[21] (*ca.* 0.1 mol) in 200 ml of refluxing ammonia over a period of 1 hr. The mixture was refluxed for an additional 2 hr before quenching by the cautious addition of 10 g of solid NH_4Cl. The ammonia was allowed to evaporate, and the residue was taken up in brine. Three ether extracts of the brine were washed with two portions of saturated $NaHSO_3$ and once with brine and were dried; the solvent was removed.

The crude propynol was hydrated by reaction with 5% H_2SO_4 in the presence of HgO, as previously described.[1] There was obtained 2.4 g (16%) of material: bp 112–115° (17 mm); 2,4-dinitrophenylhydrazone mp 172–174° (aqueous dimethylformamide) [lit.[19] bp 115–119° (16 mm); lit.[22] 2,4-dinitrophenylhydrazone mp 174° (ethanol)]; nmr δ 7.15 (s, 5 H), 4.86 (s, 1 H), 4.07 (s, 1 H), and 1.94 (s, 3 H).

Preparation of α-Diones. The α-diones used in this study were prepared by oxidation of the corresponding α-ketol with chromium trioxide–bispyridine complex in dichloromethane using the procedure of Radcliffe and Rodehorst[23] without modification.

2,3-Octanedione (6). The compound was prepared from 2-octa-

non-3-ol (1) in 33% yield: bp 65–67° (17 mm); bis-2,4-dinitrophenylhydrazone mp 221–224° (aqueous ethanol) [lit.[24] bp 172–173° (733 mm); lit.[25] bis-2,4-dinitrophenylhydrazone mp 221°]; nmr δ 2.68 (t, J = 7 Hz, 2 H), 2.25 (s, 3 H), 1.7–1.1 (m, 6 H), and 0.91 (t, 3 H).

4-Methyl-2,3-pentanedione (7). The compound was prepared from 4-methyl-2-pentanon-3-ol (2) in 33% yield: bp 113–116° (760 mm) (lit.[26] bp 115–116°); nmr δ 3.33 (m, J = 7 Hz, 1 H), 2.25 (s, 3 H), and 1.07 (d, J = 7 Hz, 6 H).

4,4-Dimethyl-2,3-pentanedione (8). The compound was prepared from 4,4-dimethyl-2-pentanon-3-ol (3) in 61% yield: bp 123–127° (760 mm); bis-2,4-dinitrophenylhydrazone mp 227–229° (aqueous dimethylformamide) [lit.[27] bp 125°; lit.[28] bis-2,4-dinitrophenylhydrazone mp 220.5–221.5° (aqueous dimethylformamide)]; nmr δ 2.28 (s, 3 H) and 1.24 (s, 9 H).

erythro-**1-Phenyl-1,2-propanediol.** The compound was prepared from *trans*-phenylpropene in 54% yield by oxidation with *m*-chloroperbenzoic acid and hydration of the epoxide thus formed by aqueous $HClO_4$ in THF, using the procedure previously reported.[1] The pure compound was isolated as colorless powder: mp 89–91° (benzene–petroleum ether) [lit.[29] mp 91–92.5° (petroleum ether)]; nmr δ 7.27 (s, 5 H), 4.62 (d, J = 4 Hz, 1 H), 3.96 (m, 1 H), 2.80 (s, 2 H), and 1.01 (d, J = 6.2 Hz, 3 H). In a mixture with the threo isomer, the doublet at δ 4.62 was sufficiently well resolved to allow quantitation at 60 MHz.

threo-**1-Phenyl-1,2-propanediol.** The compound was prepared in 22% yield by oxidation of *trans*-phenylpropene with magnesium sulfate–buffered potassium permanganate in aqueous ethanol, by the procedure previously reported.[1] Chromatography of the crude product on silica gel (5% ether in petroleum ether) gave the substantially pure diol which crystallized upon standing in benzene–petroleum ether: mp 51–53° [lit.[29] mp 52–54° (petroleum ether)]; nmr δ 7.27 (s, 5 H), 4.29 (d, J = 7.5 Hz, 1 H), 3.89 (m, 1 H), 3.58 (s, 2 H), 1.00 (d, J = 7 Hz, 3 H).

Hydride Reduction of Substrates. General Procedure. Into a dry, nitrogen-flushed test tube, containing a magnetic spin ball and fitted with a septum cap, was injected 1.5 mmol of hydride solution. After cooling to −78°, the substrate (0.5 mmol in 0.5 ml of the appropriate solvent) was added slowly with stirring. The mixture was stirred for 4 hr at −78°; the cold bath was then removed and stirring was continued at room temperature for 18–20 hr. The reaction was quenched by the cautious addition of 3 ml of water; sufficient 6 N HCl to dissolve the gelatinous precipitate was added, and the mixture was extracted with three 15-ml portions of ether. The combined extracts were dried, and the solvent was removed. The residue was heated briefly at reduced pressure to drive off volatile impurities; the product diol thus obtained was *ca.* 95% pure.

In reactions with protio hydride reagents, the diol was taken up in $CDCl_3$, and the solution was shaken with D_2O to preclude possible interference by the hydroxylic protons, prior to analysis by nmr. In reactions with the deuterated hydride reagents, the diol was subjected to cleavage with sodium metaperiodate, as described below.

Periodate Cleavage of α-Diols. General Procedure. The α-diol (50–75 mg) was dissolved in 5 ml of THF. To the stirred solution, at room temperature, was added sodium metaperiodate (500 mg) and then 3 ml of water. The flask warmed immediately and a voluminous precipitate of sodium iodate was noted within minutes. The flask was tightly stoppered, and the mixture was stirred for 3 hr. The reaction was quenched into saturated $NaHCO_3$, and the solution extracted with three portions of ether. The combined ether extracts were treated with 15 ml of methanolic 2,4-dinitrophenylhydrazine reagent and were set aside while the ether was allowed to evaporate slowly.

After the ether had evaporated, the precipitated 2,4-dinitrophenylhydrazone of hexanal or benzaldehyde was collected. With hexanal, water generally was added to the mixture to ensure quantitative precipitation of the derivative. The crude derivatives were recrystallized and dried *in vacuo* prior to analysis by isotope ratio mass spectrometry.

Meerwein–Ponndorf–Verley Reduction of α-Ketols. Representative Procedure. To a solution of DIBAH (5.0 ml of a 0.4 M toluene solution, 2.0 mmol), stirred at 0° under a nitrogen atomosphere, was added biacetyl (86 mg, 1.0 mmol) in 1.0 ml of toluene. The solution was stirred for 2 hr at room temperature (to allow reduction to the diol) and then was cooled to −78°. 2-Octanon-3-ol (144 mg, 1.0 mmol) dissolved in 1.0 ml of toluene was then added slowly. The cold bath was removed after 30 min and the mixture stirred for 24 hr at room temperature. The reaction was quenched with water; sufficient 1 N HCl was added to dissolve the gelatinous precipitate, and the products were isolated in ether. The ethereal solution of crude products was dried, concentrated to 10.0 ml, and analyzed by glpc at 145°. The per cent conversion was determined by external standardization with authentic diol mixture.

All MPV studies were done using the procedure above and the reagents, solvents and stoichiometries shown in Table III. Reactions with 1-phenyl-2-propanon-1-ol (5) were analyzed at 185°.

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Registry No.—TIBA, 100-99-2; DIBAH, 1191-15-7; $LiAlH_4$, 16853-85-3; $LiAl(OMe)_3H$, 12076-93-6; *erythro*-1-phenyl-1,2-propanediol, 1075-04-3; *threo*-1-phenyl-1,2-propanediol, 1075-05-4.

References and Notes

(1) J. A. Katzenellenbogen and S. B. Bowlus, *J. Org. Chem.*, **38**, 627 (1973).
(2) D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.*, **85**, 1245 (1963), and references cited therein.
(3) J. H. Stocker, P. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *J. Amer. Chem. Soc.*, **82**, 3913 (1960).
(4) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 112 (1959).
(5) E. G. Hoffman, *Justus Liebigs Ann. Chem.*, **629**, 104 (1960); K. Ziegler, W. R. Kroll, W. Larbigand, and O. W. Steudle, *ibid.*, **629**, 53 (1960).
(6) H. W. Schroetter and E. G. Hoffman, *Ber. Bunsenges. Phys. Chem.*, **68**, 627 (1964).
(7) J. Laemmle, E. C. Ashby, and P. V. Roling, *J. Org. Chem.*, **38**, 2527 (1973).
(8) G. J. Karabatsos, *J. Amer. Chem. Soc.*, **89**, 1367 (1967).
(9) M. Cherest, H. Felkin, and N. Pruduct, *Tetrahedron Lett.*, 2201 (1968).
(10) D. J. Cram and F. A. Abd Elhafaz, *J. Amer. Chem. Soc.*, **74**, 5828 (1952).
(11) H. Haubenstock and E. B. Davidson, *J. Org. Chem.*, **28**, 2772 (1963).
(12) G. E. Heinsohn and E. C. Ashby, *J. Org. Chem.*, **38**, 4232 (1973).
(13) T. I. Temnikova and L. A. Petrova, *Z. Obshch. Khim.*, **21**, 677 (1951), and references cited therein; *Chem. Abstr.*, **45**, 9504*h* (1951).
(14) T. I. Temnikova and L. A. Petrova, *Z. Obshch. Khim.*, **21**, 1877 (1951), *Chem. Abstr.*, **46**, 6614*b* (1952).
(15) S. B. Bowlus, unpublished observation.
(16) H. C. Brown and P. M. Weissman, *J. Amer. Chem. Soc.*, **87**, 5614 (1965); H. C. Brown and N. M. Yoon, *ibid.*, **88**, 1464 (1966).
(17) D. Seebach, *Synthesis*, 17 (1969).
(18) S. Samne and P. Freon, *C. R. Acad. Sci., Ser. C.*, **262**, 1013 (1966).
(19) E. M. Kotchergine, *Bull. Soc. Chim. Fr.*, [4], **43**, 573 (1928).
(20) W. Wassilieff, *Bull. Soc. Chim. Fr.*, [4], **43**, 563 (1928).
(21) R. S. Monson, "Advanced Organic Synthesis," Academic Press, New York, N.Y., 1971, p 121 ff.
(22) G. D. Johnson, *J. Amer. Chem. Soc.*, **75**, 2720 (1953).
(23) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).
(24) G. Ponzio and O. Prandi, *J. Prakt. Chem.*, [2], **58**, 401 (1898).
(25) L. A. Jones, C. K. Hancock, and R. B. Seligman, *J. Org. Chem.*, **26**, 228 (1961).
(26) R. Otte and H. V. Pechmann, *Ber.*, **22**, 2115 (1889).
(27) E. B. Reid and R. B. Fortenbaugh, *J. Org. Chem.*, **16**, 33 (1951).
(28) N. J. Leonard, J. C. Little, and A. J. Kresge, *J. Amer. Chem. Soc.*, **79**, 6436 (1957).
(29) M. Stiles, R. R. Winkler, Y.-L. Chang, and L. Traynor, *J. Amer. Chem. Soc.*, **86**, 3337 (1964).

Stereoselectivity of the Rearrangement of Allyl Siloxyvinyl Ethers. A Highly Stereoselective Synthesis of a Diol Found in the Pheromonal Secretion of the Queen Butterfly

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The [3,3] rearrangement of 3-acetoxy-2-methyl-1-nonene (**1b**), derivatized as the trimethylsiloxyvinyl ether, proceeds in moderate yield (*ca.* 53%) but with very high stereoselectivity (>98%) to give the β,γ-unsaturated acid **2a**. Rearrangement of the *tert*-butyldimethylsiloxyvinyl ether derivative proceeds in higher yield (80%), also with very high stereoselectivity. This rearrangement has been used in a stereoselective synthesis of a terpenoid diol (**8**) found in the phermonal secretion of the queen butterfly, in six steps from geraniol.

Several variants of the [3,3]-Claisen-type rearrangements of allylic ethers have been applied over the past few years to the stereoselective synthesis of trisubstituted olefinic systems.[1] Elegant extensions of this reaction to the repetitive 1,5-diene synthesis have been worked out by Faulkner and his associates.[2] More recent has been the description of rearrangements of enolates[3,4] or enolate equivalents[3] of allylic acetates or thioacetate derivatives.[5] A notable feature of these enolate rearrangements, which would be of advantage in certain systems, is that they proceed at moderate temperatures, under basic conditions, while rearrangement of the ethers requires warming in acid media.

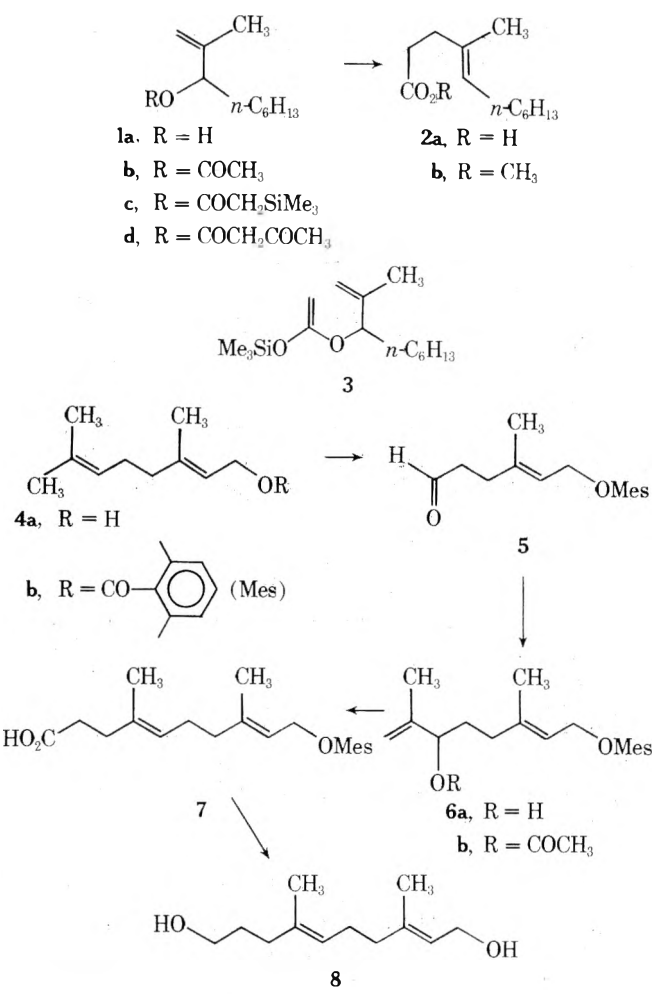
We were intrigued by the report of Ireland[3] that enol silyl ether derivatives of allylic acetates undergo a [3,3]-Claisen-type rearrangement to give β,γ-unsaturated acids under mild conditions. The strategic location of the bulky trimethylsilyl ether function[6] and the mild reaction conditions suggested that this particular rearrangement might proceed with a stereoselectivity[7] greater than the nominal 90–96% generally obtained in such rearrangements. None of the systems detailed by Ireland, however, were of suitable stereochemistry to evaluate this reaction as a method for stereoselective trisubstituted olefin synthesis.

In this report we describe an investigation of this rearrangement in a model system to rigorously establish the minimum reaction temperature and the maximum degree of stereoselectivity. The synthesis of the Queen Butterfly pheromone, using this allyl siloxyvinyl ether rearrangement as the key step, is also described.

Results and Discussion

Rearrangement of 3-Acetoxy-2-methyl-1-nonene (1b). The rearrangement of 3-acetoxy-2-methyl-1-nonene (**1b**), a trisubstituted olefin precursor, was investigated under the conditions described by Ireland.[3] The enol silyl ether was generated using 1.1 equiv of lithium isopropylcyclohexylamide in THF at −78°, followed by 1.05 equiv of trimethylsilyl chloride. Two major products were obtained after the reaction mixture was stirred for 2 hr at 70°. Chromatographic separation on silica gel produced the carboxylic acid (**2a**) and the C-silylated acetate (**1c**). The acid can also be conveniently isolated in 53% yield by extraction into Claisen's alkali[8] causing hydrolysis of **1c** to **1a**. Thus, the yield of rearranged product based on recovered precursors is over 90%. A temperature study showed that the rearrangement was complete within 2 hr at room temperature, but not at 0 or −78°.

We endeavored to improve the yield by increasing the amount of O-silylation relative to C-silylation. Rathke has reported that treatment of lithium enolates derived from acetates with *tert*-butyldimethylsilyl chloride (TBS) in THF–HMPA solutions gave exclusively O-silylated products.[9] Treatment of the lithium enolate of **1b** with TBS and subsequent hydrolysis of the rearranged silyl ester by stirring with acetic acid[10] at room temperature (the trimethylsilyl ester completely hydrolyzes upon washing with 10% HCl) gave **2a** in 80% yield.



Both trimethylsilyl chloride and TBS give rearranged acids with very high stereoselectivity. Nmr analysis of the crude acid shows only one allylic methyl at δ 1.59, consistent with an *E*-type stereochemistry of the trisubstituted olefin (*Z*-type allylic methyl groups generally resonate at 1.67–1.70).[11] Glpc analysis of the methyl ester **2b** (from **2a** with diazomethane) showed it to be identical with the minor component (*E*) of the isomeric esters prepared by the Wittig condensation between levulinic acid and heptylidine triphenylphosphorane. Less than 1% of the *Z* isomer of **2b** was evident upon glpc analysis, indicating a stereoselectivity[7] of greater than 98%.

If the silyl chlorides are omitted from the reaction, a small amount (5–10%) of the rearranged acid is formed; however, the principal products are the allylic alcohol **1a** and the allylic acetoacetate **1d**, resulting from Claisen condensation of the ester enolate. No Claisen condensation product was ever detected under normal conditions (inclusion of the silyl chlorides). In the absence of either silyl chloride the stereoselectivity of the rearrangement of **1b** drops to 85%, which is consistent with predictions of Faulkner and Perrin.[6]

Synthesis of a Queen Butterfly Pheromonal Component. The allyl siloxyvinyl ether rearrangement was utilized in a six-step stereoselective synthesis of a queen butterfly pheromonal component (**8**).[12] The distribution of functionality in this compound makes its synthesis by the Claisen-type rearrangement attractive.

Treatment of geraniol (**4a**) with mesitoyl chloride in pyridine gave geranyl mesitoate **4b** in 80% yield.[13] Ozonolysis of the mesitoate with 1.2 equiv of ozone gave the aldehyde **5** in 30% yield. Since ozonolysis of geranyl acetate under similar conditions produces the related aldehyde in a higher yield (50–60%),[14] it appears that the mesitoate group is less effective in deactivating the allylic double bond toward oxidation. Treatment of the aldehyde **5** with 2 equiv of isopropenylmagnesium bromide at room temperature for 2 hr gave the alcohol **6a**[15] which was generally converted directly to the acetate **6b** (70% overall).

The Claisen-type rearrangement of **6b** using TBS gave the acid **7** in a 70% yield. Treatment of the acid with excess lithium aluminum hydride both reduces the acid function and cleaves the mesitoate, producing the pheromone **8** in 86% after column chromatography.[16] The spectroscopic properties of this material are fully consistent with its assigned structure, and its bis(α-naphthyl)urethane melts at 128–129.5° (lit.[12c] 127–129°).

Conclusion

The high stereoselectivity observed in the rearrangement of allyl siloxyvinyl ethers to β,γ-unsaturated acids follows the stereochemical predictions based on a chair cyclohexane-like transition state.[6] Good yields are obtained under conditions where the enolate can be selectively O-silylated. The particular utility of this rearrangement reaction is that it proceeds under very mild, nonacidic conditions, using stable, conveniently prepared starting materials.

Experimental Section

Tetrahydrofuran (THF) was dried by distillation from sodium naphthalide. Isopropylcyclohexylamine was distilled from calcium hydride and stored under nitrogen. Hexamethylphosphoramide (HMPA) was distilled from sodium hydride and stored over molecular sieves. Geraniol and 2-bromopropene were obtained from Chemical Samples Co. and used without further purification. Levulinic acid was obtained from Eastman Organics and distilled prior to use. Practical grade heptanal was purchased from Matheson Coleman and Bell and used without further purification. Dimethyl sulfide was from Aldrich. Isopropenylmagnesium bromide solutions in THF were prepared from 2-bromopropene and magnesium and were standardized by the method of Gilman.[17] They were stored under nitrogen in flasks capped with rubber septa. Diazomethane was freshly prepared as alcohol-free ethereal solutions from *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald, Aldrich) using preparation II as given. Claisen's alkali was prepared as described by Fieser and Fieser.[8] Ozone was generated in a Welsbach Ozonizer (Model T-816); the rate of ozone production was calibrated before use by iodometric titration. A standard procedure for product isolation was used in all reactions: drying of the organic layer over anhydrous magnesium sulfate, filtration, and evaporation of the solvent under reduced pressure on a rotary evaporator. Nmr spectra were recorded on a Varian A-60 spectrometer, and all chemical shifts are given in parts per million downfield from tetramethylsilane (δ scale). Infrared spectra were run on a Perkin-Elmer Model 521 spectrometer. Mass spectra were recorded on a Varian-MAT CH-5 spectrometer. Elemental analyses were performed by the microanalytical service of the University of Illinois.

Analytical glpc analyses were done on a Hewlett-Packard 5750 instrument fitted with flame ionization detectors using a carrier gas (N_2) flow of 30 ml/min. The column used was a 0.125 in. × 20 ft, 5% SE-30 column on an acid-washed dimethyldichlorosilane-treated 80–100 mesh Chromosorb W support. The preparative glpc separation was done on a Varian Aerograph Model 90-P3 chromatograph with a thermal conductivity detector using a carrier gas (He) flow of 120 ml/min. The column used was a 0.375 in. × 10 ft, 15% SE-30 on a 60–80 mesh Chromosorb W support.

3-Hydroxy-2-methyl-1-nonene (1a). Magnesium (8.85 g, 0.37 g-atom) was added to 70 ml of THF along with a few crystals of iodine. A small amount (<1 ml) of 2-bromopropene was added and the mixture stirred at 25° under nitrogen until Grignard formation had begun. The remaining bromide (29.7 g, 0.24 mol) was added dropwise at such a rate as to maintain gentle reflux. After the mixture was stirred for 1 hr at 25°, heptanal (23.4 g, 0.20 mol) in 30 ml of THF was added dropwise. The reaction was stirred overnight at 25°, and then saturated ammonium chloride added to quench the reaction. The precipitate which formed was filtered and washed with ether, and the combined filtrates were washed with saturated sodium chloride. Product isolation gave 29.7 g of an oil. Distillation produced 23 g (72%) of the alcohol **1a**: bp 68–71° (0.3 mm); ir (CCl_4) 3618 (OH) and 1650 cm^{-1} (C=C); nmr (CCl_4) δ 0.93 (m, 3 H), 1.05–1.65 (br s, 10 H), 1.72 (s, 3 H, allylic coupling barely visible), 2.06 (s, 1 H), 4.01 (t, 1 H), and 4.85 (m, 2 H).

Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.63; H, 12.76.

3-Acetoxy-2-methyl-1-nonene (1b). A solution of alcohol **1a** (7 g, 0.045 mol), acetic anhydride (13.8 g, 0.135 mol), and pyridine (35.5 g, 0.450 mol) was stirred for 40 hr at 25°. The reaction mixture was then poured into ice water, and the aqueous layer was extracted three times with ether. The combined organic extracts were washed with 10% HCl, 10% $NaHCO_3$, water, and saturated sodium chloride. Chromatography on silica gel (16% ether in hexane) gave 8.11 g (92%) of the acetate **1b**: ir (CCl_4) 1745 (C=O), 1650 (C=C), 1460, 1370, 1245 (C—O), and 1020 cm^{-1}; nmr (CCl_4) δ 0.93 (m, 3 H), 1.09–1.61 (m, 10 H), 1.69 (s, 3 H, allylic coupling barely visible), 1.96 (s, 3 H), 4.80 (m, 2 H), and 5.07 (t, J = 6.5 Hz, 1 H).

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.62; H, 11.29.

(*E*)-4-Methyl-4-undecenoic Acid (2a)–Trimethylsilyl Chloride Method. A solution of 10 ml of THF and isopropylcyclohexylamine (1.5 g, 10.6 mmol) was cooled to −78° under nitrogen and was treated with a 1.25 *M* (8.25 ml, 10.6 mmol) solution of *n*-BuLi followed by the addition of **1b** (2 g, 10.1 mmol). The reaction mixture was stirred for 10 min, and trimethylsilyl chloride (1.1 g, 10.3 mmol) was added. After the mixture was warmed to 70° over a 30-min period and stirred for 2 hr (precipitate evident), it was cooled and diluted with ether. The ether was extracted twice with 10% HCl, and the product was isolated to give a yellow oil. Chromatography on silica gel (18% ether in hexane, then 50% ether in hexane) gave 1.05 g (53%) of the acid **2a**.

Treatment of **2a** with diazomethane produced the methyl ester **2b**. The ester was analyzed by glpc (182°), and it was found to contain *ca.* 0.7% of the *Z* isomer. An analytical sample was obtained by preparative tlc on silica gel (16% ether in hexane): ir (CCl_4) 1740 (C=O), 1458, 1438, and 1150 cm^{-1}; nmr (CCl_4) δ 0.93 (m, 3 H), 1.26 (br s, 8 H), 1.59 (s, 3 H), 1.95 (m, 2 H), 2.28 (s, 4 H), 3.59 (s, 3 H), and 5.13 (t, J = 7 Hz, 1 H).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.51; H, 11.39.

***tert*-Butyldimethylsilyl Chloride Method.** A solution of 3 ml of THF and isopropylcyclohexylamine (456 mg, 3.3 mmol) was cooled to −78° under nitrogen and was treated with a 1.9 *M* (1.74 ml, 3.3 mmol) solution of *n*-BuLi followed by the addition of **1b** (594 mg, 3 mmol). After the reaction was stirred for 10 min, HMPA (0.45 ml) and *tert*-butyldimethylsilyl chloride in 0.5 ml of THF (475 mg, 3.15 mmol) were added to it. The reaction was warmed to 70° over a 30-min period and was stirred for 2 hr. Then 15 ml of acetic acid, 5 ml of water, and 2 ml of THF were added and the solution was stirred for 12 hr at 25°. After the reaction mixture was diluted with ether, it was extracted with water and the product was isolated to give 956 mg of a yellow oil. Chromatography on silica gel (20% ether in hexane, then 25% ether in hexane) gave 475 mg (80%) of the acid **2a**. The acid was characterized as its

methyl ester **2b** (CH_2N_2), and it had spectral properties identical with the ester **2b** produced by the trimethylsilyl chloride method above.

***E* and *Z* Isomers of 4-Methyl-4-undecenoic Acid (2a).** To a mixture of heptyl triphenylphosphonium bromide (20 g, 45.4 mmol) and 100 ml of THF at 0° under nitrogen was added a 2.31 *M* (19.7 ml, 45.4 mmol) solution of *n*-BuLi, producing a red solution of ylide which was stirred for 2 hr at 25°. A precipitate appeared upon the addition of levulinic acid (2.63 g, 22.7 mmol), and the mixture was refluxed for 67 hr. The reaction was cooled to 25°, acidified with 10% HCl, and extracted three times with ether. Product isolation from the combined extracts gave 3.8 g of a yellow oil. Chromatography on silica gel (18% ether in hexane, then 50% ether in hexane) produced 922 mg (20%) of a mixture of the *E* and *Z* isomers of 4-methyl-4-undecenoic acid. Analysis of the esterified (CH_2N_2) mixture by glpc (182°) showed the *Z*/*E* ratio as 2/1. The isomers were separated by preparative glpc (150°): nmr (*E* isomer) (CCl_4) δ 0.93 (m, 3 H), 1.26 (br s, 8 H), 1.59 (s, 3 H), 1.95 (m, 2 H), 2.28 (s, 4 H), 3.59 (s, 3 H), and 5.13 (t, *J* = 7 Hz, 1 H); nmr (*Z* isomer) (CCl_4) δ 0.93 (m, 3 H), 1.27 (br s, 8 H), 1.66 (s, 3 H, cisoid allylic coupling barely visible), 1.94 (m, 2 H), 2.25 (s, 4 H), 3.57 (s, 3 H), and 5.08 (t, *J* = 7 Hz, 1 H).

(*E*)-8-Mesitoyloxy-2,6-dimethyl-2,6-octadiene (geranyl mesitoate) (4b) was prepared in 80% yield from geraniol and mesitoyl chloride[18] as previously described.[13]

(*E*)-6-Mesitoyloxy-4-methyl-4-hexenal (5). A solution of geranyl mesitoate (**4b**) (10 g, 33 mmol) and 600 ml of methanol was cooled to −78° and ozone (36.9 mmol) was passed through. After adding excess dimethyl sulfide to the reaction mixture at −78°, it was stirred for 12 hr at 25°. Evaporation of the dimethyl sulfide and methanol left a residue which was diluted with ether, and the ether was washed with water and saturated sodium chloride. Product isolation and chromatography on silica gel (16.6% ether in hexane) gave 2.65 g (30%) of the desired aldehyde **5** and 2.3 g of starting material. An analytical sample was obtained by preparative tlc on silica gel (30% ether in hexane, two developments): ir (CCl_4) 2720 (aldehyde C—H), 1725 (aldehyde and ester C=O), 1615, 1445, 1263, 1169, and 1080 cm^{-1}; nmr (CCl_4) δ 1.77 (s, 3 H), 2.22 (s, 9 H), 2.38 (m, 4 H), 4.73 (d, *J* = 7 Hz, 2 H), 5.45 (t, *J* = 7.5 Hz, 1 H), 6.75 (s, 2 H), and 9.66 (t, *J* = 1 Hz, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 274 (M^+, 2), 164 (12), 148 (13), 147 (M − OR, 100), 146 (31), 119 (M − CO_2R, 19), 110 (M − mesitoic acid, 7), 93 (30), 55 (30), 43 (41), and 31 (69).

Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.31; H, 8.17.

(*E*)-3-Hydroxy-8-mesitoyloxy-2,6-dimethyl-1,6-octadiene (6a). A 1.28 *M* solution (6.25 ml, 8 mmol) of isopropenylmagnesium bromide was treated dropwise at 25° with a solution of **5** (1 g, 3.6 mmol) and 7 ml of THF, and the reaction was stirred under nitrogen for 2 hr. The reaction was quenched with saturated ammonium chloride and extracted twice with ether. Product isolation from the combined organic extracts gave 1.04 g of the crude alcohol **6a**. An analytical sample was obtained by preparative tlc on silica gel (30% ether in hexane, two developments): ir (CCl_4) 3622 (OH), 1722 (C=O), 1612, 1442, 1257, 1162, and 1072 cm^{-1}; nmr ($CDCl_3$) δ 1.53–2.22 (m, 11 H), 2.27 (s, 9 H), 4.05 (t, *J* = 6 Hz, 1 H), 4.75–5.00 (m, 4 H, CH_2=CCH_3 and CH_2OCO), 5.53 (t, *J* = 7.5 Hz, 1 H), and 6.81 (s, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 316 (M^+, 0.18), 298 (M − H_2O, 0.73), 165 (21), 164 (86), 152 (M − mesitoic acid, 37), 151 (16), 148 (28), 147 (100), 146 (67), 119 (42), 93 (28), 81 (27), 55 (26), and 43 (39).

Anal. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92. Found: C, 75.64; H, 8.91.

(*E*)-3-Acetoxy-8-mesitoyloxy-2,6-dimethyl-1,6-octadiene (6b). A dark red solution of crude alcohol **6a** (1.04 g, *ca.* 3.5 mmol) and 10 ml of pyridine was treated with acetic anhydride (1.30 g, 12.7 mmol), and the reaction mixture was stirred for 12 hr at 25°. The reaction mixture was poured into ice water, and the water extracted three times with ether. The combined organic extracts were washed with 10% HCl, 10% $NaHCO_3$, water, and saturated sodium chloride. Product isolation gave 1.2 g of a dark red oil. Chromatography on silica gel (16.6% ether in hexane) gave 900 mg (69% from **5**) of a colorless oil: ir (CCl_4) 1740 and 1727 (C=O), 1612, 1445, 1260 and 1240 (C—O), 1168, and 1078 cm^{-1}; nmr (CCl_4) δ 1.53–1.88 (m, 8 H), 1.89–2.18 (m, 2 H, allylic methylene), 2.06 (s, 3 H, $COCH_3$), 2.27 (s, 9 H), 4.7–5.03 (m, 4 H), 5.18 (t, *J* = 6.5 Hz, 1 H), 5.53 (t, *J* = 7.5 Hz, 1 H), and 6.81 (s, 2 H); mass spectrum (70 eV) *m/e* (rel intensity) 358 (M^+, 0.76), 299 (M − OAc, 8), 195 (6), 148 (11), 147 (100), 146 (18), 135 (11), 134 (11), 119 (21), 93 (14), 55 (18), and 43 (37).

Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.41. Found: C, 73.77; H, 8.51.

(*E,E*)-10-Mesitoyloxy-4,8-dimethyl-4,8-decadienoic Acid (7). A solution of 1 ml of THF and isopropylcyclohexylamine (131 mg, 0.92 mmol) was cooled to −78° under nitrogen and was treated with a 2.06 *M* (0.45 ml, 0.92 mmol) solution of *n*-BuLi. The solution was stirred for 20 min, and **6b** (300 mg, 0.84 mmol) was added producing a red solution. HMPA (0.15 ml) was then added followed by the addition of *tert*-butyldimethylsilyl chloride (132 mg, 0.88 mmol) in 0.5 ml of THF, and the reaction was warmed to 25° over a 30-min period. After stirring the reaction mixture for 3 hr, it was diluted with ether and extracted with 10% HCl and Claisen's alkali. Dropwise acidification at 0° of the alkaline extract with 10% HCl and extraction with ether gave 260 mg of the acid **7** after product isolation. Chromatography on silica gel (40% hexane in ether) gave 210 mg (70%) of pure **7**: nmr ($CDCl_3$) δ 1.63 (s, 3 H), 1.77 (s, 3 H), 2.08 (m, 4 H), 2.28 (s, 9 H), 2.38 (s, 4 H, $HO_2CCH_2CH_2$), 4.81 (d, *J* = 7 Hz, 2 H), 5.20 (m, 1 H), 5.50 (t, *J* = 8 Hz, 1 H), and 6.81 (s, 2 H).

Treatment of **7** with diazomethane gave the corresponding methyl ester. An analytical sample was obtained by preparative tlc on silica gel (30% ether in petroleum ether, two developments): ir (CCl_4) 1744 and 1728 (C=O), 1616, 1438, 1262, 1168, and 1076 cm^{-1}; nmr ($CDCl_3$), identical with **7** except for the addition of δ 3.64 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 372 (M^+, 0.58), 208 (M − mesitoic acid, 11) 164 (12), 148 (13), 147 (100), 146 (23), 121 (17), 119 (23), 81 (35), 80 (35), and 43 (14).

Anal. Calcd for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.24; H, 8.76.

(*E,E*)-3,7-Dimethyl-2,6-decadiene-1,10-diol (8). A 0.67 *M* (5.57 ml, 3.74 mmol) filtered solution of lithium aluminum hydride was treated with a solution of **7** (134 mg, 0.37 mmol) in a small amount of THF, and the reaction mixture was stirred under nitrogen for 40 min at 70°. The reaction was quenched at 0° with ethyl acetate, and it was diluted with saturated ammonium chloride. After the mixture was extracted twice with ether, the product was isolated from the combined ether extracts and was chromatographed on silica gel (50% chloroform in ehter) to give 64 mg (87%) of the diol **8**: nmr ($CDCl_3$) δ 1.5–1.92 (m, 8 H), 1.93–2.36 (m, 8 H, allylic methylenes and OH's), 3.63 (t, *J* = 6.5 Hz, 2 H), 4.15 (d, *J* = 7 Hz, 2 H), 5.18 (m, 1 H), and 5.43 (t, *J* = 7 Hz, 1 H); mass spectrum (10 eV) *m/e* (rel intensity) 198 (M^+, 0.64), 180 (M − H_2O, 5), 167 (M − CH_2OH, 5), 152 (M − H_2O + CH_2=CH_2, 8), 121 (32), 97 (34), 95 (92), 84 (100), 69 (44), and 68 (48).

Treatment of **8** with α-naphthyl isocyanate gave a bis(α-naphthyl)urethane which melts at 128–129.5° (lit.[12c] 127–129°) after recrystallization from hexane–ether.

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Registry No.—**1a**, 52500-37-5; **1b**, 52500-38-6; (*E*)-**2a**, 52500-39-7; (*Z*)-**2a**, 52500-40-0; (*E*)-**2b**, 52500-41-1; (*Z*)-**2b**, 52500-42-2; **4b**, 1674-04-0; **5**, 52500-43-3; **6a**, 52500-44-4; **6b**, 52500-45-5; **7**, 52500-46-6; **7** methyl ester, 52500-47-7; **8**, 24048-35-9; 2-bromopropene, 557-93-7; heptanal, 111-71-7.

References and Notes

(1) For reviews of trisubstituted olefin synthesis, see (a) J. Reucroft and P. G. Sammes, *Quart. Rev., Chem. Soc.*, **25**, 135 (1971); (b) D. J. Faulkner, *Synthesis*, 175 (1971); (c) A. S. Arora and I. K. Ugi, in "Houben-Weyl," 4th ed, V/1b, Thieme Verlag, Stuttgart, Germany, 1972, p 729.
(2) D. J. Faulkner and M. R. Petersen, *J. Amer. Chem. Soc.*, **95**, 553 (1973).
(3) R. E. Ireland and R. H. Mueller, *J. Amer. Chem. Soc.*, **94**, 5897 (1972).
(4) J. E. Baldwin and J. A. Walker, *J. Chem. Soc., Chem. Commun.*, 117 (1973).
(5) H. Takahashi, K. Oshima, H. Yamamoto, and H. Nozaki, *J. Amer. Chem. Soc.*, **95**, 5803 (1973).
(6) C. L. Perrin and D. J. Faulkner, *Tetrahedron Lett.*, 2783 (1969).
(7) Stereoselectivity is defined as (% *E* isomer) − (% *Z* isomer); see J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, p. 10.

(8) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 153.
(9) M. W. Rathke and D. F. Sullivan, *Syn. Commun.*, **3**, 67 (1973).
(10) E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, **94**, 9191 (1972).
(11) Numerous references are given in L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 225.
(12) The diol **8** is secreted together with a pyrrolizidinone (ketone) by brush-like hair pencil glands on the abdomen of males of the queen butterfly (*Donus gilippus berenice*). During mating, the male uses these glands to deposite a dustlike pheromone on the antennae of the female; the ketone appears to act as an aphrodesiac, while the function of the diol appears to be simply that of a glue, securing the attachment of the pheromonal dust to the female antennae. For a description of the biology, see (a) T. E. Pliske and T. Eisner, *Science*, **164**, 1170 (1969), and (b) D. Schneider and U. Seibt, *ibid.*, **164**, 1173 (1969). For chemical studies, see (c) J. Meinwald, Y. C. Meinwald, and P. H. Mazzocchi, *ibid.*, **164**, 1174 (1969), and (d) D. H. Miles, P. Loew, W. S. Johnson, A. F. Kluge, and J. Meinwald, *Tetrahedeon Lett.*, 3019 (1972).
(13) J. A. Katzenellenbogen and R. S. Lenox, *J. Org. Chem.*, **38**, 326 (1973).
(14) E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *J. Amer. Chem. Soc.*, **91**, 4318 (1969).
(15) Attempts to prepare this alcohol directly by the rearrangement of 6,7-oxidogeranyl mesitoate using lithium diisopropylamide or lithium di-*n*-butylamide [see C. L. Kissel and B. Rickborn, *J. Org. Chem.*, **37**, 737 (1972)] were uniformly unsuccessful.
(16) The overall yield from geraniol is 10%.
(17) H. Gilman, E. A. Zoellner, and J. B. Dickey, *J. Amer. Chem. Soc.*, **51**, 1576 (1929).
(18) D. M. Bowen, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 556.

Palladium-Catalyzed Carboalkoxylation of Aryl, Benzyl, and Vinylic Halides

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Aryl and vinylic bromides and iodides and benzyl chloride react with carbon monoxide and an alcohol at 100° or below and atmospheric pressure in the presence of a tertiary amine and a catalytic amount of a palladium–triphenylphosphine complex to form esters. The reaction is tolerant of a variety of functional groups and shows appreciable stereospecificity at 60–80° with cis and trans vinylic halides producing esters with retained configuration.

In previous papers we and others have noted the ready formation of organopalladium complexes by reaction of finely divided palladium metal[1,2] or palladium(0)–organophosphine complexes[3,4] with aryl, benzyl, and vinyl halides.

Since these organopalladium complexes reacted easily with olefins,[1-3] it seemed reasonable to expect that they would also react with carbon monoxide to form acylpalladium derivatives. The last compounds could then possibly reductively eliminate acyl halide or at least react with alcohols to form esters and an unstable metal hydride which could re-form the palladium(0) starting material. Therefore a catalytic synthesis of acyl halides or esters from aryl, benzyl, and vinyl halides and carbon monoxide appeared possible analogous to the known reactions of allylic chlorides.[5,6] A similar reaction is known to occur with bromo-

$$H_2C{=}CHCH_2Cl + CO \xrightarrow{Pd} H_2C{=}CHCH_2COCl$$
$$\xrightarrow[ROH]{Pd} H_2C{=}CHCH_2COOR + HCl$$

π-allylnickel(II) dimer, from allyl bromide and tetracarbonylnickel(0), and carbon monoxide.[7] A related carboalkoxylation of organomercury compounds with palladium salts, carbon monoxide, and an alcohol is known, but generally mixtures of esters, biaryls, and ketones were obtained with only low yields of esters being formed in most instances.[8,9] Tetracarbonylnickel(0) is an excellent reagent for the carboalkoxylation of aryl, benzyl, and vinyl halides particularly in the presence of bases.[10,11] The nickel reaction has two problems which we hoped to overcome by the use of palladium catalysts: (1) tetracarbonylnickel vapor is extremely toxic while the palladium reagents are not volatile and (2) tetracarbonylnickel is either required in stoichiometric quantities or at least in relatively large catalytic amounts while the palladium complexes may react highly catalytically.

Preliminary experiments showed that acyl halides were not formed catalytically from aryl halides at 100° and with 1 atm of carbon monoxide even in the presence of tertiary amines, but in the presence of an alcohol and a tertiary amine a highly catalytic reaction ensued forming esters in good yields.

$$ArX + CO + ROH + R_3'N \xrightarrow{"Pd"} ArCOOR + R_3'NH^+X^-$$

Results

Initial experiments were carried out with aryl iodides adding palladium acetate as catalyst. The palladium(II) acetate was reduced by the carbon monoxide in the reaction mixture. Little carbon monoxide was absorbed at 100° and at 1 atm unless a tertiary amine and an alcohol were added. We used *n*-butyl alcohol as the alcohol and tri-*n*-butylamine as the tertiary amine, since they boiled well above the reaction temperature. Generally, the reactions with 1–2 mol % of catalyst at 100° required 14 hr or more to reach completion and were usually allowed to go longer to be sure the aryl halide had completely reacted. Reactions were carried out in a gasometric apparatus as described previously so that the reaction rate and the amount of gas absorbed could be measured.[12] Products were isolated by ether extraction, acid washing, and distillation. The esters were obtained very pure by this simple procedure. The yields and product properties of representative examples are show in Table I. Nmr data on the products are given in Table III which will appear in the microfilm edition of the journal. See paragraph at the end of paper regarding supplementary material. Substituent effects in the aromatic halide appeared to be less significant than in the reactions of the same halides with olefins.[1,3] Both strongly electron supplying and withdrawing substituents could be present.

The reaction with palladium acetate as catalyst at 100° was limited to aryl iodides; bromides did not react unless they were strongly activated with electron withdrawing substituents. We found, however, that adding 2 equiv of triphenylphosphine would cause unactivated aryl bromides to react at practical rates and produce esters in good yields. Aryl iodides reacted at about the same rates with the phosphine catalysts as they did with the palladium acetate cata-

Table I
Carbobutoxylation of Aryl and Benzyl Halides[a]

Halide	Catalyst	Reaction time, hr	$T_{1/2}$, min	Product (% yield)[b,c]	Bp, °C	Molecular weight Found	Molecular weight Calcd
C_6H_5I (591-50-4)	$Pd(OAc)_2$ (3375-31-3)	20	312	C_6H_5COO-*n*-Bu (70) (136-60-7)	100–110 (10 mm)[i]		
4-$CH_3OCOC_6H_4I$ (619-44-3)	$Pd(OAc)_2$	16		4-$CH_3OCOC_6H_4COO$-*n*-Bu (83) (52392-55-9)	133–134 (0.2 mm)	236.117	236.105
4-$CH_3OC_6H_4I$ (696-62-8)	$Pd(OAc)_2$	16		4-$CH_3OC_6H_4COO$-*n*-Bu (69) (6946-35-6)	114–115 (0.2 mm)[j]	208.107	208.110
2,6-$(CH_3)_2C_6H_3I$ (608-28-6)	$Pd(OAc)_2$	40		2,6-$(CH_3)_2C_6H_3COO$-*n*-Bu (63) (52392-56-0)	78–80 (0.4 mm)	206.122	206.130
C_6H_5I	$PhPdI(PPh_3)_2$ (18115-61-2)	30	467	C_6H_5COO-*n*-Bu (96)[d]		178.104	178.099
C_6H_5Br (108-86-1)	$PhPdBr(PPh_3)_2$ (33381-14-5)	24	718	C_6H_5COO-*n*-Bu (78)[d]			
C_6H_5Br (623-00-7)	$Pd_2Br_4(PPh_3)_2$[e] (M)	24	1376	C_6H_5COO-*n*-Bu			
4-NCC_6H_4Br[f]	$PdBr_2(PPh_3)_2$ (23523-33-3)	14		4-NCC_6H_4COO-*n*-Bu (89) (29240-34-4)	Mp 54–55[k]	203.095	203.095
1-$C_{10}H_7Br$ (90-11-9)	$PdBr_2(PPh_3)_2$	80	1367	1-$C_{10}H_7COO$-*n*-Bu (46)[g] (3007-95-2)	165–170 (19 mm)[l]	228.121	228.115
$C_6H_5CH_2Cl$ (100-44-7)	$PdCl_2(PPh_3)_2$ (13965-03-2)	40	1677	$C_6H_5CH_2COO$-*n*-Bu (45)[h] (122-43-0)	135–142 (22 mm)	192.122	192.115

[a] Reactions were carried out at 100° with 1 atm of CO, 17.2 mmol of halide, 0.25 mmol of catalyst, 21.2 mmol of *n*-butyl alcohol, and 19 mmol of tri-*n*-butylamine. Registry numbers are given in parentheses. [b] Yields are of isolated, pure products except where noted. [c] Products all showed strong ir bands at 1700–1750 cm^{-1} and all had nmr spectra consistent with the proposed structures. [d] Yields determined by glc with diphenyl ether as an internal standard. [e] Only 0.125 mmol of catalyst was used. [f] Reaction was carried out at 60° under 30 psi of CO in a capped bottle. [g] Reaction was only about 81% complete when the product was isolated. [h] Reaction was only about 65% complete when the product was isolated. [i] Reported bp 250°, "Handbook of Chemistry and Physics," 40th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1959, p 846. [j] Reported bp 183° (40 mm), L. G. Radcliffe and W. A. Brindley, *Perfum. Essent. Oil Rec.*, 13, 414 (1922). [k] Reported mp 56–57°, F. E. D. Garigi and H. Gisvold, *J. Chem. Pharm. Ass.*, 38, 154 (1949). [l] Reported bp 151° (0.4 mm), G. B. Arrowsmith, G. H. Jeffery, and A. I. Vogel, *J. Chem. Soc.*, 2072 (1965).

lyst. Examples using the triarylphosphine procedure are also listed in Table I. In most instances purified dihalo- or haloarylbis(triphenylphosphine)palladium(II) complexes were used as catalysts although palladium(II) acetate with 2 equiv of triphenylphosphine produced identical catalysis as near as we could tell.

Table I contains two examples of particular interest. The carbobutoxylation of methyl *p*-iodobenzoate gave an 83% yield of *n*-butyl methyl terephthalate with none of the symmetrical esters being formed. The relatively hindered 2,6-dimethyliodobenzene also reacted normally at about half the rate of iodobenzene to form *n*-butyl 2,6-dimethylbenzoate in 63% yield.

The relative rates of reaction of the differently substituted aryl halides can be estimated from the half lives ($T_{1/2}$) listed in the table. The $T_{1/2}$ was the time required for half of the theoretical amount of CO to be absorbed. Electron withdrawing substituents increased and electron supplying groups decreased the reaction rates. The presence of the phosphine ligands appeared to slow the rate of the reaction of iodobenzene while it must have substantially increased the rate of reaction of bromobenzene since very little or no reaction occurred without the phosphine. With the phosphine catalyst iodobenzene was less than twice as reactive as bromobenzene. This is a remarkably small difference which suggests that oxidative addition may not be rate determining in this reaction. We attempted to measure relative rates of reaction by carrying out competitive reactions of pairs of aryl halides. We found as Cassar did with nickel carbonyl[11] that iodide ion was a very effective inhibitor for the reaction and when mixtures of aryl bromides and iodides were allowed to react the reactions proceeded at about the rates expected for the iodide but that the bromides did not react significantly. Calculating the relative rates of reaction of iodobenzene compared to bromobenzene in the presence of iodide ion (extrapolating back to zero time) from two pairs of relative rates measured where substituents were different gave the result that iodobenzene was 243 times more reactive than bromobenzene. This contrasts with the value of twice as reactive found by comparing half lives. Comparisons by the competitive method should be more meaningful for different aryl halides containing the same halogen. We found for example that 4-bromoanisole was 0.23 times and 4-bromobenzonitrile was 275 times as reactive as bromobenzene by this means. Cassar found the corresponding values for the same halide for his tetracarbonylnickel(0) catalyzed carboxylation were 0.4 and 108, respectively.[11] Apparently the palladium catalyst is more selective than nickel is. Both 1-bromoaphthalene and benzyl chloride were significantly less reactive than was bromobenzene in the carbobutoxylation reaction.

The triphenylphosphine–palladium complexes also catalyzed the carbobutoxylation of vinylic iodides and bromides in the presence of tertiary amines. The compounds studied and the yields of esters obtained from them are listed in Table II. The nmr spectra of the products are given in Table III which will appear in the microfilm edition of this journal. See paragraph at end of paper regarding supplementary material.

Cis- and trans vinylic halides were carbobutoxylated under various conditions to find optimum conditions for retaining the initial stereochemistry in the product. At 100° both *E*- and *Z*-3-iodo-3-hexene give mixtures of three carbobutoxy derivatives. Without triphenylphosphine, palladium acetate produces about equal amounts of the three products while with $PdI_2[P(C_6H_5)_3]_2$ as catalyst the major product was the one formed with retention of stereochemistry. The *E* iodide reacts at 100° about three times more

Table II
Carbobutoxylation of Vinylic Halides[a]

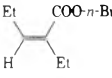
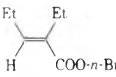
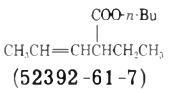
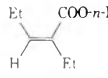
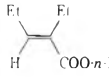
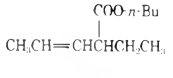
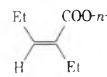
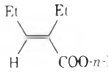
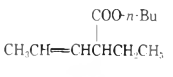
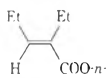
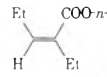
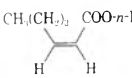
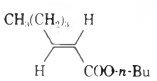
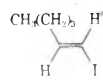
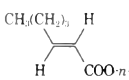
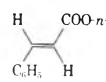
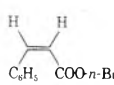
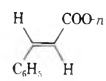
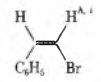
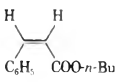
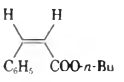
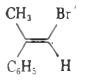
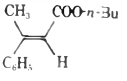
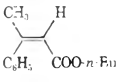
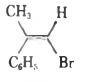
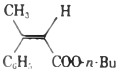
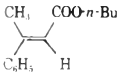
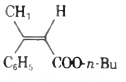
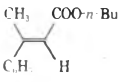
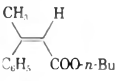
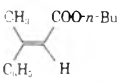
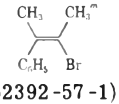
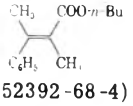
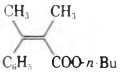
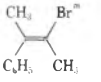
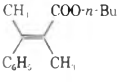
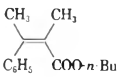
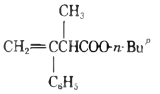
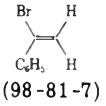
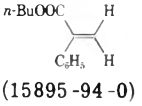
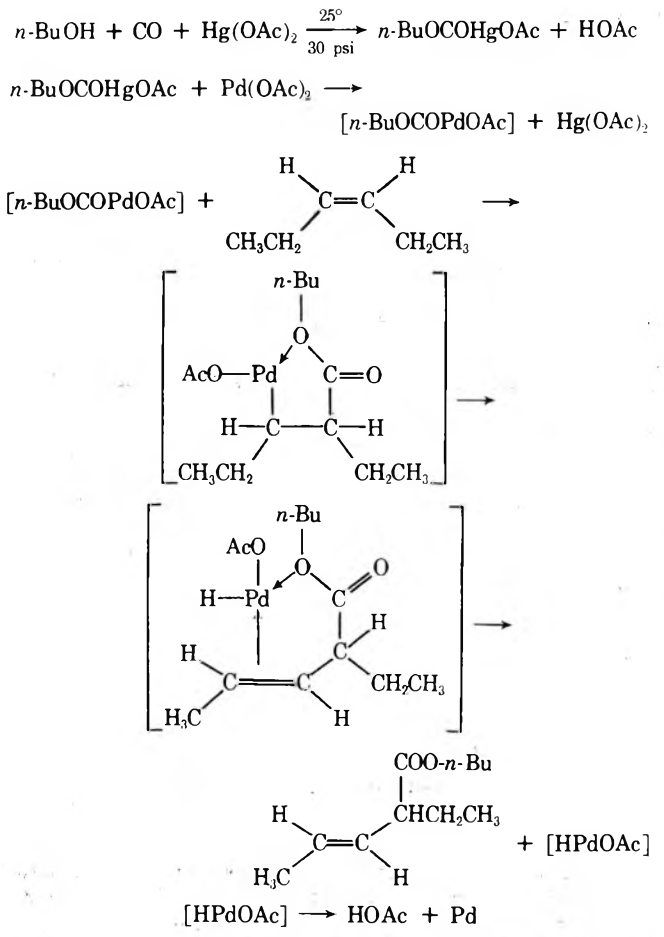
Halide	Catalyst	Temp, °C	Reaction time, hr	$T_{1/2}$, min	Products (% yield)	Bp, °C	Molecular weight Found	Molecular weight Calcd
 (16403-13-7)	$Pd(OAc)_2$	100	17	250	 (52392-59-3) (23)		184.147[b]	184.146
					 (52392-60-6) (29)	50–55 (1.5 mm)	184.147[b]	184.146
					 (52392-61-7) (21)		184.147[b]	184.146
 (23523-32-2)	$PdI_2(PPh_3)_2$	100	4.5	38	 (45)			
					 (13)	60–68 (3 mm)		
					 (24)			
 (16403-09-1)	$PdI_2(PPh_3)_2$	100	4.5	86	 (11)			
					 (69)[b]			
					 (19)[b]			
	$PdI_2(PPh_3)_2$	60	40	575	 (74)			
					 (6)			
 (16538-47-9)	$PdI_2(PPh_3)_2$	80	1.5	34	 (52392-62-8) (79)	66–69 (14 mm)	184.146	184.147
					 (6)			
 (16644-98-7)	$PdI_2(PPh_3)_2$	100	2	35	 (52392-63-9) (83)	74–78 (15 mm)	184[e]	184
 (588-72-7)	$PdBr_2(PPh_3)_2$	100	8	116	 (52392-64-0) (80)	155–165 (13 mm)[f]	204.102	204.115
 (588-73-8)	$PdBr_2(PPh_3)_2$	80	15	350	 (52392-65-1) (52)(53)[g]	90–94 (0.2 mm)	204.104	204.115
					 (30)(33)[g]			

Table II
(Continued)

Halide	Catalyst	Temp, °C	Reaction time, hr	$T_{1/2}$, min	Products (% yield)		Bp, °C	Molecular weight Found	Molecular weight Calcd
	$PdBr_2(PPh_3)_2$	60	43			(68)	96–104 (0.2 mm)		
						(16)			
 (16917-35-4)	$PdBr_2(PPh_3)_2$	125 ± 5			 (52392-66-2)	(83)	108–112 (0.7 mm)		
					 (52392-67-3)	(7)			
 (19647-26-8)	$PdBr_2(PPh_3)_2$	100	44	130		(58)	90–108 (0.4 mm)	218.1295	218.1307
						(33)		218.1297	218.1307
	$PdBr_2(PPh_3)_2$	100	150	3000		(50)			
						(4)			
	$PdBr_2(PPh_3)_2$	100	7			(69)			
						(26)			
 (52392-57-1)	$PdBr_2(PPh_3)_2$	100	168[n]	~1700	 (52392-68-4)	(29)		232.1512	232.1463
					 (52392-69-5)	(38)		232.1519	232.1463
 (52392-58-2)	$PdBr_2(PPh_3)_2$	100	168[o]	~1500		(61)			
						(7)			
						(5)			
 (98-81-7)	$PdBr_2(PPh_3)_2$	100	5	70	 (15895-94-0)	(68)	90–105 (1.5 mm)	204.105	204.115

[a] Carried out with 17.2 mmol of vinylic halide, 0.25 mmol of catalyst, 21.2 mmol of *n*-butyl alcohol, and 19 mmol of tri-*n*-butylamine at 1 atm of CO except where noted. [b] Samples isolated by glc. [c] Data corrected for 18% trans and 8% unknown in cis iodide. [d] Data corrected for 4% cis and 4% unknown in trans bromide. [e] Parent peak was too weak to be used to obtain a more accurate value. [f] Reported bp 162° (12 mm), G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 658 (1948). [g] Yields obtained under 30 psi pressure of carbon monoxide. [h] Reaction carried out at 20–30 psi of carbon monoxide. [i] Data corrected for 7% trans isomer in cis bromide. [j] Carried out under 1025 psig of CO. [k] Carried out with one-half quantities of reagents with an additional 2.5 mmol of triphenylphosphine added. [l] Carried out under an initial 1270 psig of CO with one-half quantities of reagents. [m] Carried out with 4 mmol of vinylic halide, 0.06 mmol of catalyst, 5 mmol of *n*-butyl alcohol, and 4.4 mmol of tri-*n*-butylamine at 1 atm of CO. [n] About 13% of unreacted starting bromide remained at this time. [o] About 15% of unreacted starting bromide remained at this time. [p] Isomeric structure not certain.

rapidly than the *Z* isomer does judging by the half-lives determined. In addition to the *E*- and *Z*-*n*-butyl 3-hexene-3-carboxylates, *n*-butyl 4-hexene-3-carboxylate was formed (probably trans but not definitely established). The identification of the third isomer was made from its nmr spectrum, its molecular weight, and the fact that it is obtained as the major product when "carbobutoxypalladium acetate" is treated with either *Z*- or *E*-3-hexene at 0–25°. The last reaction is similar to one reported previously between "carbomethoxypalladium acetate" and 1-hexene where a mixture of products composed of 42% *E*-methyl 2- and 58% methyl 3-heptenoate was formed.[13] The "carboalkoxypalladium acetates" were prepared by exchange reactions of palladium(II) acetate with carboalkoxymercuric acetates, obtained from alcohols, CO, and mercuric acetate by the method of Schoeller, *et al.*[14] In the 3-hexene reactions the α-substituent appears to be responsible for the formation of the ester as the major product. This result supports the idea that coordination of the palladium atom to the carboalkoxyl group in the alkylpalladium intermediate complex occurs and that this complex undergoes metal hydride elimination exocyclically to give the least strained olefin π-complex. The π-complex then dissociates into unsaturated ester and "hydridopalladium acetate" which itself then decomposes into palladium metal and acetic acid.[15] The α-ethyl group, by an entropy effect, would be expected to relatively favor the chelated form of the complex over the open chain solvated form. The starting olefins



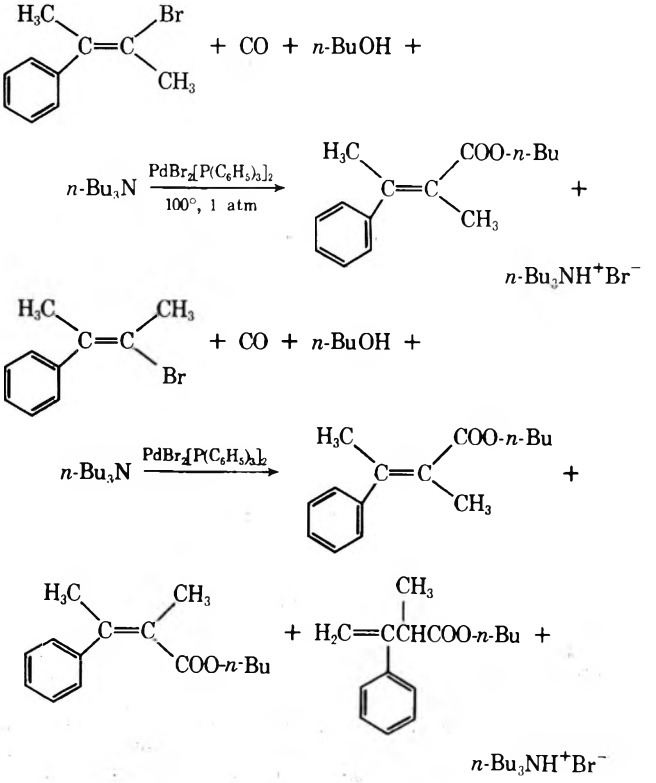
and product esters are stable under the reaction conditions. *Z*-3-Hexene gave 25%, and *E*-3-hexene 44% of *n*-butyl 4-hexene-3-carboxylate. The remainder of the products from *Z*-3-hexene were not the *E*- or *Z*-3-hexene-3-carboxylate but other materials, probably enol and allylic acetates and dicarboxylated products which were not identified. The *E*-3-hexene produced 6% of the *E*-3-hexene-3-carboxylate also but no *Z* ester, as expected by the normal cis addition–cis elimination mechanism believed to operate in the reaction.[13]

The formation of the nonconjugated ester from the carbobutoxylation of the 3-iodo-3-hexenes is quite sensitive to reaction temperature and this product disappears completely when the reactions are carried out at 60° rather than 100°. The relative amount of ester with retained configuration also increased on lowering the reaction temperature. Thus at 60° *E*-3-iodo-3-hexene gives 74% of the *E* carbobutoxylated product, only 6% of the *Z* isomer, and none of the nonconjugated ester compared with 69, 11, and 19%, respectively, at 100°.

The carbobutoxylations of both isomeric 3-iodo-3-hexenes were also carried out in hydroxyl deuterated *n*-butyl alcohol with diiodobistriphenylphosphinepalladium as catalysts in order to gain more information on how these reactions were occurring. In all cases, no mechanistically significant conclusions could be reached since all three isomeric ester products obtained were 50–75% monodeuterated under the reaction conditions. The results are shown in Table IV.

Z-1-Iodo-1-hexene on carbobutoxylation at 80° gave 79% *Z* and 6% *E* ester while the *E* iodide even at 100° gave only the *E* ester, which was isolated in 83% yield. Similarly *E*-2-bromostyrene at 100° gave only *E* *n*-butyl cinnamate, isolated in 80% yield. *Z*-2-Bromostyrene on the other hand at 80° gave 52% *Z* and 30% *E* ester while at 60° the yields were 68 and 16%, respectively. Increasing the CO pressure from atmospheric pressure to 30 psi did not improve the stereochemistry of the *Z*-2-bromostyrene reaction at 80°. Starting materials and products were stable under the reaction conditions.

The *E*- and *Z*-1-bromo-2-phenyl-1-propene isomers were carbobutoxylated with the results that the *E* bromide gave about 83% of the *E* ester (retention) and 7% of the *Z* ester and the *Z* bromide gave a mixture 33% *E* and 58% *Z*



esters. The carbobutoxylation of *Z*-1-bromo-2-phenyl-1-propene in the presence of 20 equiv of triphenylphosphine

per equivalent of $PdBr_2(PPh_3)_2$, on the other hand, led to a substantial improvement in the amount of ester obtained with retained structure, 92% compared with 64% without the excess phosphine under the same conditions. The reaction, however, was much slower with the excess phosphine. The carbobutoxylation under 1270 psig of carbon monoxide was only slightly more sterospecific than at atmospheric pressure (73% retention found *vs.* 64% at atmospheric pressure). Thus lowering reaction temperature or adding excess triarylphosphine are much more effective than increasing CO pressure in improving the stereochemistry of the carbobutoxylation. The *E*- and *Z*-2-bromo-3-phenyl-2-butenes isomers also were carbobutoxylated and the *E*-bromide gave mainly the *E* ester (61%) while the *Z*-bromide gave 38% *Z* and 29% *E* esters. A small amount of a new isomeric ester, presumably *n*-butyl 2-methyl-3-phenyl-3-butenoate was also formed in the *E*-bromide reaction.

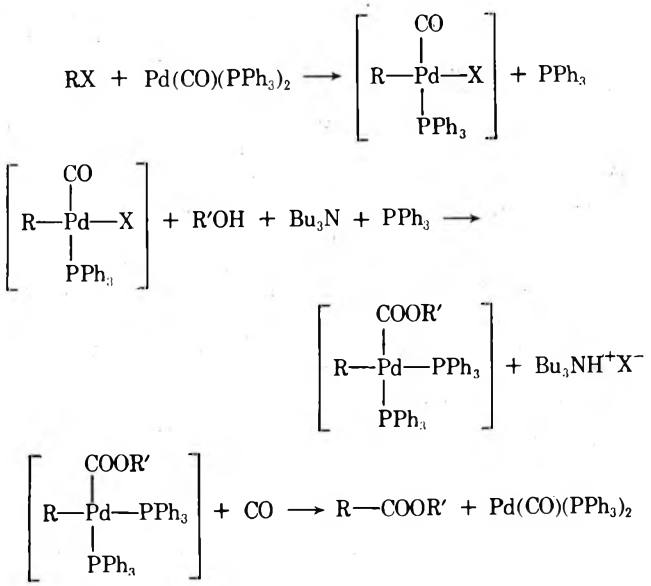
The carbobutoxylation of *E*- and *Z*-1-bromo-2-phenyl-1-propene was also carried out in hydroxyl deuterated *n*-butyl alcohol. In both the *E*- and *Z*-bromide reaction the ester produced with the opposite configuration to the starting bromide contained about 21–28% monodeuterated product while the esters with retained structures contained only about 10–14% monodeuterated product. Results are given in Table IV.

1-Bromostyrene was carbobutoxylated at 100° to give exclusively *n*-butyl 2-phenylacrylate which was isolated in 68% yield.

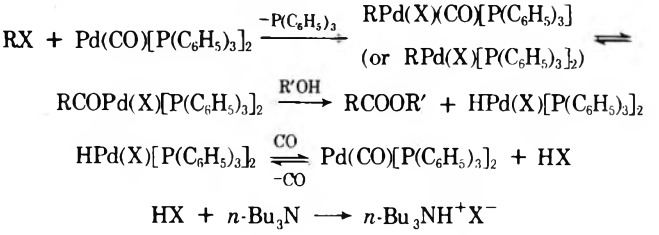
In an attempt to eliminate the toxicity problem encountered with nickel carbonyl in the catalytic halide carboxylation reported by Cassar and Foa[11] we tried the reaction with nonvolatile, dicarbonylbis(triphenylphosphine)nickel(0) as catalyst (5%). At 100° under 1 atm of carbon monoxide with iodobenzene no reaction occurred with only tri-*n*-butylamine present but carbobutoxylation did take place when sodium butoxide was added and *n*-butyl benzoate was formed in 68% yield (isolated) after 30 hr of reaction. This is an alternative method for the carboalkoxylation of halides if the reactants and/or products are not reactive toward sodium alkoxides at 100°. Tricarbonylmonophosphinenickel(0) complexes might be more reactive catalysts but these were not investigated.

Discussion of Results

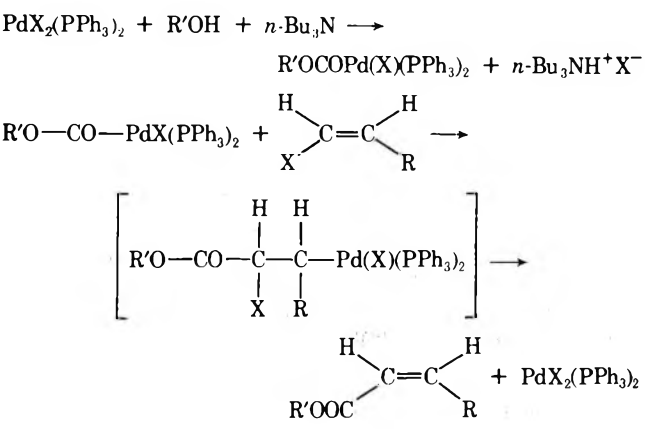
At least two possible mechanisms of carboalkoxylation can be imagined. A reductive elimination of an aryl–carboalkoxypalladium species could be the final step in a mechanism such as the following



Since organopalladium compounds are known to undergo carbon monoxide "insertion reactions" very readily,[16] however, a more likely mechanism involves a CO insertion followed by attack of alcohol upon the acyl group with formation of a hydrido–palladium complex. The hydride then ultimately loses HX and reforms the catalyst.

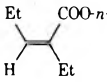
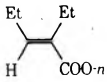
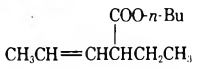
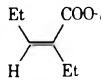
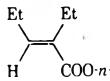
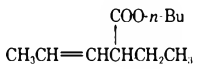
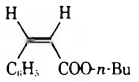
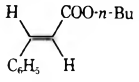
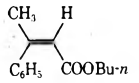
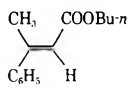


Presumably the vinylic halides and aryl halides react by the same mechanism. However, a possible cis-addition–trans-elimination mechanism with the vinylic halides could be imagined as shown below. This mechanism seems rather unlikely, however, since at least the tri- and tetrasubstituted vinylic halides which undergo this reaction, would not be expected to be very reactive to the addition of organopalladium compounds.[15]

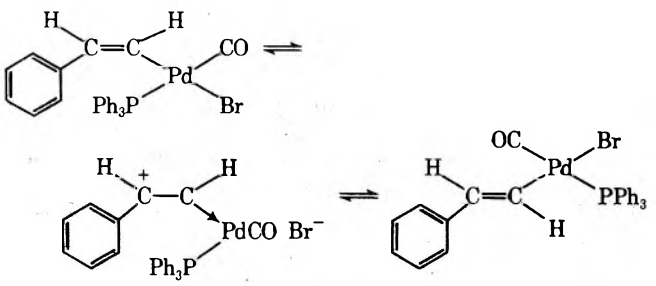


The means by which vinylic isomerization occurs in the carboalkoxylation is also of considerable interest. In all instances where the unsaturated esters produced contained the other geometric isomer than the starting vinylic halide, it was shown that the starting material and the products did not spontaneously isomerize under the reaction conditions. Furthermore, the ratio of isomerized to retained esters remained constant during the reactions. It is also clear that hydrogen groups are not required on the α- or β-vinyl carbon atoms in order for isomerization to take place. In examples where α- and/or β-hydrogens were present, reaction in hydroxyl deuterated *n*-butyl alcohol showed considerable incorporation of deuterium and some of it was at these positions. Clearly, cis–trans isomerization does not occur only by a palladium–hydride (deuteride) addition–elimination mechanism even in these cases. Probably, the isomerization occurs mainly in the σ-vinylic palladium intermediate before the CO insertion and alcoholysis occurs. It is not clear whether or not the CO insertion is reversible under our reaction conditions. A more than doubling of the CO pressure in the carbobutoxylation of *cis*-2-bromostyrene and increasing it by a factor of about 90 in the *Z*-1-bromo-2-phenyl-1-propene case did not greatly change the ratio of cis to trans-esters produced suggesting that the CO insertion is not reversible under our conditions. The loss of configuration at the vinylic palladium bond possibly is by way of an ionic carbene type intermediate such as the following.

Table IV
Carbobutoxylations with n-C_4H_9OD

Organic Halide[a]	Reaction temp, °C	$T_{1/2}$, min	Products (relative % yields)[b]		% Monodeuteration
	100	63		(47)	67
				(26)	55
				(27)	75
	100	105		(8)	67
				(89)	80
				(3)	49
	80	634		(52)	14
				(48)	21
	100	185		(59)	10
				(41)	28

[a] Reactants included 17.2 mmol of organic halide, 0.25 mmol of catalyst, 19 mmol of tri-n-butylamine, and 21.0 mmol of n-C_4H_9OD. [b] Total yields were about the same as in the reactions with undeuterated n-butyl alcohol.



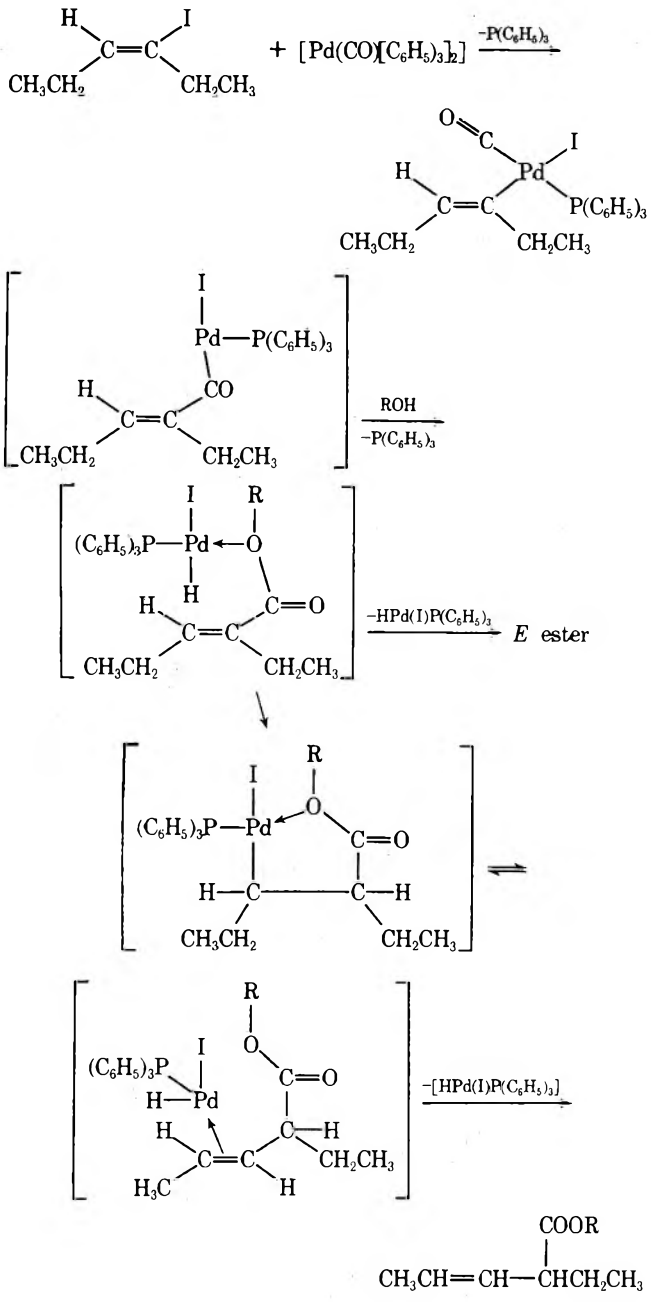
Excess triphenylphosphine may accelerate the CO insertion by forming a five coordinate intermediate and reduce the amount of carbene complex formed.[28]

The formation of β,γ-unsaturated esters in the E- and Z-3-iodo-3-hexene carboalkoxylations may occur by a palladium hydride addition–elimination mechanism although attempts to establish this mechanism by looking for deuterium incorporation in this product when carbobutoxylation was carried out in hydroxyl deuterated n-butyl alcohol did not give conclusive results. As noted above all three of the isomeric esters produced were 50–80% deuterated. The nmr spectra of the glc separated ester products showed the deuterium was not concentrated at the vinylic positions. Presumably it was distributed over several positions, but we could not be certain from the spectra. A reasonable mechanism for formation of some of the β,γ-unsaturated ester can be proposed. In the synthesis of n-butyl 4-hexene-3-carboxylate from 3-hexene and n-carbobutoxypalladium acetate elimination to the β,γ-unsaturated ester was presumed to occur, as noted above, because of chelation of the palladium with the carboalkoxyl group during the elimination. Exactly the same chelated intermediate could be formed in the carbobutoxylation of the 3-iodo-3-hexenes if, after the alcoholysis step, the palladium hydride species formed remained coordinated to the ester group and then the hydride (deuteride) added internally to the existing double bond placing palladium on the β-carbon atom. Elimination of the chelated palladium hydride group exocyclically would form the 4-hexene-3-carboxylate ester.

The palladium hydride addition may occur in both directions and the elimination may produce a new isomer if a different hydride group is lost. In deuterated n-butyl alcohol such an isomerization would lead to deuterium incorporation and could account for the 10–15% excess deuterium found in the isomerized esters compared with the esters with retained configuration in the carbobutoxylations of E- and Z-2-phenyl-1-bromo-1-propenes.

Another mechanism of formation of nonconjugated ester in the 3-iodo-3-hexene carbobutoxylation which needs to be considered is a π-allylic palladium hydride mechanism.[17] A control experiment using a mixture of the E- and Z-butyl 3-hexene-3-carboxylates under the carbobutoxylation conditions, however, failed to show the formation of any nonconjugated ester. Therefore, this ester must be formed directly by the reaction.

The palladium–triphenylphosphine catalyzed carboalkoxylation of aryl, benzylic, and vinylic halides appears to be a general reaction. The reaction with bromides and iodides occurs under mild and convenient conditions and is therefore a useful addition to the list of methods available for the synthesis of carboxylic acid esters.



Experimental Section

Reagents. Tri-*n*-butylamine (Eastman) was distilled from potassium hydroxide and stored over Linde 4A molecular sieves. Iodobenzene (Eastman) and *n*-butyl alcohol (Fisher Scientific) were distilled before use and also kept over molecular sieves. 1-Bromostyrene was prepared by the method of Glaser.[18] *E*-2-bromostyrene was used as obtained from the Aldrich Chemical Co. *Z*-2-Bromostyrene was prepared by the method of Cristol[19] and stored at 0°. *Z*- and *E*-1-bromo-2-phenyl-1-propene were prepared by the procedure of Davis and Roberts.[20] The isomeric mixture of bromides (33% *Z*) was separated by fractional distillation: *Z*-bromide, bp 86° (15 mm), and *E*-bromide, bp 96° (15 mm). *Z*-1-Iodo-1-hexene[21] and *E*-3-iodo-3-hexene[22] were also prepared by literature methods. *Z*-3-Iodo-3-hexene was prepared by refluxing 3-hexyne with constant boiling hydriodic acid for 24 hr, bp 43–44° (10 mm). Other organic halides except *Z*- and *E*-2-bromo-3-phenyl-2-butene (described below) were commercial products and were used without further purification.

Dichloro-, dibromo-, and diiodobis(triphenylphosphine)palladium(II) were prepared by heating potassium tetrachloropalladate with an excess of the potassium halide required and an excess of triphenylphosphine in ethanol solution.[23] The crude products were washed with water, ethanol, and pentane and then recrystallized from hot chloroform. Chlorobis(triphenylphosphine)phenylpalladium(II)[24] was prepared by the addition of the appropriate aryl halide to tetrakis(triphenylphosphine)palladium(0).[25] The bridged complex dibromo-$\mu\mu$-dibromobis(triphenylphosphine)palladium(II) was made by the addition of excess LiBr to equivalent amounts of K_2PdCl_4 and $Pd[C_6H_5)_3P]_2Cl_2$ in ethanol.[26] The bridged complex was then purified by recrystallization from chloroform.

Analysis. Samples were analyzed by gas chromatography on a 10 ft or a 15 ft 20% SE-30 on Chromosorb W column. If known samples were available, sensitivity coefficients were obtained compared with diphenyl ether. The diphenyl ether was then added as an internal standard. High resolution mass spectra were obtained by peak matching using a Du Pont (CED)21-110B double focus mass spectrometer. Infrared spectra were recorded on a Perkin-Elmer Model 337 grating spectrophotometer. Proton nuclear magnetic resonance spectra were measured with a Varian Associates Model A60A spectrometer or a Perkin-Elmer R-12B spectrometer using TMS as an internal standard.

***Z*- and *E*-2-Bromo-3-phenyl-2-butene.** To a stirred solution of 58.0 g (0.80 mol) of 2-butanone in 300 ml of ether at −78° in a 2-l. three-necked flask under argon was added 450 ml of 2.3 *M* phenyllithium in 70:30 hexane–benzene during 1 hr. The reaction mixture was allowed to stir at room temperature overnight. Ice water was then slowly added and the ether layer was separated, dried, and distilled. The crude 2-phenyl-2-butanol, bp 92–97° (11 mm), so obtained was then distilled with 10 g of sodium bisulfate at 11 mm. The crude olefin was redistilled to give a 41% yield of 2-phenyl-2-butene, bp 70–72° (12 mm).

To a stirred solution of 40 g of 2-phenyl-2-butene in 500 ml of chloroform at room temperature was slowly added 50 g of bromine in 200 ml of chloroform. After the addition, the chloroform was distilled from the product and a solution of 75 g of potassium hydroxide dissolved in 1 l. of ethanol was added. The solution was stirred at 55° for 1 hr and then water was added. The product was extracted with ether. The extracts were dried and distilled, bp 60–83° (0.7 mm). The isomeric mixture (38 g, 59%) was separated by fractionation. There was obtained 11.0 g (17%) of the *E*-bromide, bp 95–96° (14 mm) (nmr in $CDCl_3$, τ 2.55–3.10 (m, 5 H), 7.86 (s, 6 H); mol wt 209.9993, calculated 210.0045), and 6.0 g (9%) of the *Z*-bromide, bp 97–98° (14 mm) (nmr in $CDCl_3$, τ 2.80 (s, 5 H), 7.15 (q, 3 H, J = 1.5 Hz), 8.05 (q, 3 H, J = 1.5 Hz); mol wt 210.0015, calculated 210.0045). The structures of the bromides were established by treating each pure bromide with the tetramethylethylenediamine complex of *n*-butyllithium at 0° in ether and carboxylating with solid carbon dioxide. The bicarbonate soluble products were converted into the methyl esters with diazomethane and the samples were identified by comparison of their nmr spectra with those of the known isomeric methyl 2-methyl-3-phenyl-2-butenoates prepared by Jackman.[27]

General Procedure for the Carbonylation of Organic Halides. In a 100-ml jacketed flask containing a magnetic stirring bar was hung a Teflon cup containing 0.25 mmol of the palladium catalyst. The flask was then attached to a thermostated microhydrogenation-type apparatus.[12] The apparatus was flushed several times with carbon monoxide. The reagents, 17.2 mmol of the organic halide, 21.2 mmol of *n*-butyl alcohol, and 19.0 mmol of tri-*n*-butylamine, were injected into the reaction flask by means of a hypodermic syringe through a side arm provided with a stopcock and rubber septum on the end. The reaction vessel was then brought to the proper temperature (steam for 100° and circulating constant temperature bath for all other temperatures) and allowed to come to equilibrium at 1 atm of pressure. The Teflon cup ccntaining the palladium catalyst was then dropped into the reaction mixture by means of a stopcock. Gas volume changes and times were periodically recorded until gas absorption stopped. The theoretical amount of 420 ml at 25° (17.2 mmol) was generally absorbed. The reaction mixture was then dissolved in ether and washed with several portions of 20% hydrochloric acid solution to remove salts and excess amine. The ether layer was washed with a saturated sodium bicarbonate solution followed by distilled water. The ether layer was dried with anhydrous magnesium sulfate, concentrated under reduced pressure, and then distilled *in vacuo* to give the pure esters.

Carbobutoxylations of Organic Halides with *n*-BuOD. Carbobutoxylations with n-C_4H_9OD (Aldrich, 98%) were carried out as described in the general procedure above. Samples for mass spectra were obtained by preparative glc on a 15 ft 20% SE-30 on Chromosorb W column. The ratio of deuterated to undeuterated organic ester was calculated from the intensity of the $(m + 1)/1$ peaks of the deuterated samples (average of three scans) minus the ratio of the intensity of the $(m + 1)/m$ peaks for the undeuterated

samples. The results of the n-C_4H_9OD experiments are shown in Table IV.

***n*-Butyl *p*-Cyanobenzoate.** To a heavy-walled 200-ml Pyrex bottle was added 3.13 g (17.2 mmol) of *p*-bromobenzonitrile, 0.198 g (0.25 mmol) dibromobis(triphenylphosphine)palladium(II), and a magretic stirring bar. The bottle was capped with a rubber-lined metal cap with a small hole in it for injection by a needle and flushed with carbon monoxide several times through a needle and a mixture of 1.57 g (21.2 mmol) of *n*-butyl alcohol and 3.6 g (19.0 mmol) of tri-*n*-butylamine was injected into the bottle. The reaction mixture was placed in a steam bath, pressurized to 20 psi with CO and allowed to stir overnight (14 hr). The reaction mixture was then treated as above except that the product was crystallized from hexane rather than distilled to give 3.11 g (89% yield) of pure cyano ester.

Dicarbonylbis(triphenylphosphine)nickel(0) Catalyzed Carbobutoxylation of Iodobenzene. The same procedure was used as in the palladium catalyzed reaction above except that 5 mol % of dicarbonylbistriphenylphosphinenickel(0) (Alfa Chemical Co.) was used as catalyst and 26 ml of 1.5 *M* sodium *n*-butoxide in *n*-butyl alcohol was used in place of the amine and *n*-butyl alcohol.

Hydrogenation of the Products Obtained from the Carbobutoxylation of *trans*-3-Iodo-3-hexene. In a 45-ml high-pressure reactor was placed 0.75 g of the ester mixture, 7 ml of THF, and 0.25 g of platinum oxide. The reactor was sealed, cooled to −78° and flushed with nitrogen and then with hydrogen. The mixture was stirred magnetically in an oil bath at 60° under 1000 psi of hydrogen for 10 hr. Isolation of the product by dilution with water, extraction, and concentration and analysis by glc showed the reduction was incomplete. A 0.26-g sample of the partially hydrogenated product was rehydrogenated with 0.25 g of catalyst and 5 ml of THF at 100° under 1000 psi of hydrogen for 24 hr. Only a single product was present now which was isolated and identified as *n*-butyl 3-hexanecarboxylate by its nmr spectrum and its molecular weight as determined by mass spectroscopy. The parent ion was too weak to obtain a precise molecular weight but there was clearly a peak at 186 amu.

A new olefinic product was produced when hydrogenation was attempted at 60° under 1000 psi of hydrogen with 5% Pd–C as catalyst. This product judging by its nmr spectrum (from a small sample isolated by vpc) appeared to be *n*-butyl 2-hexene-3-carboxylate.

Carbobutoxymercuric Acetate. This compound was prepared essentially by the method of Schoeller, *et al.*[14] A solution of 6.37 g (20 mmol) of mercuric acetate in 25 ml of *n*-butyl alcohol was prepared in a 200-ml heavy-walled Pyrex bottle. The bottle was capped, flushed with carbon monoxide through a syringe needle through the self-sealing rubber lined cap, and stirred at room temperature under 50 psi of carbon monoxide for 2 days. The resulting mixture was filtered and cooled to 0°. The colorless solid which precipitated was separated by filtration and air-dried. There was obtained 5.51 g (77%) of the product.

Reactions of *Z*- and *E*-3-Hexene with "Carbobutoxypalladium Acetate." A mixture of 1.8 g (5 mmol) of *n*-carbobutoxymercuric acetate, 12 ml of acetonitrile, and 1 ml of the olefin was stirred in a ice bath and 1.15 g (5 mmol) of powdered palladium acetate was added. The mixture was then stirred overnight at room temperature. The products were analyzed by glc on a 15 ft 20% SE 30 on Chromosorb W column at 150° using diphenyl ether as an internal standard. The *Z*-3-hexene gave *n*-butyl 4-hexene-3-carboxylate in 25% yield with no other similar products formed while the *E*-olefin gave 44% of this ester and 6% *E*-*n*-butyl 3-hexene-3-carboxylate along with 14% of an unknown of longer retention time.

Relative Rate Measurements. The same general procedure as described above was employed except that half as much of each of the two halides whose relative rates were being measured was used. An internal standard of diphenyl ether was added. In the cases where two different organic halides were being compared, the catalyst used was half $PdBr_2[P(C_6H_5)_3]_2$ and half $PdI_2[P(C_6H_5)_3]_2$. Small samples (3–5 drops) of the reaction mixtures were withdrawn after about 5, 10, and 15% reaction had occurred judging by the gas absorbed. These samples were diluted with 10–15 drops of ether, washed with 5 drops of 20% hydrochloric acid and 5 drops of distilled water, and dried with anhydrous magnesium sulfate. After analysis by vpc, the data were plotted and linearly extrapolated back to zero time to obtain a more accurate value for the relative rates. The relative rates measured directly were the following: with palladium acetate alone as catalyst, *p*-iodoanisole was 1.1 times as reactive and *p*-bromobenzonitrile was 24 times as reactive as iodobenzene; with $PdX_2[P(C_6H_5)_3]_2$ catalysts, *p*-iodoanisole was 90 times as reactive, *p*-bromoanisole 0.23 times, and *p*-bromobenzonitrile 275 times as reactive as bromobenzene.

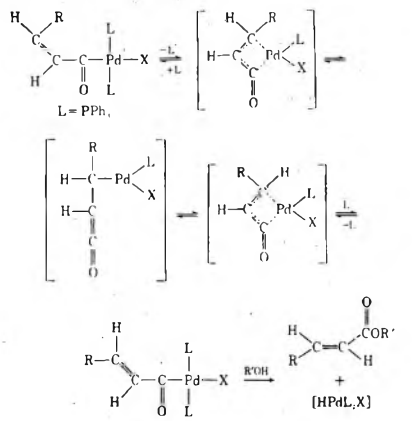
Acknowledgment. Support for this research was provided by the National Science Foundation, Grant No. GP-34492X1. Mass spectra were kindly determined by Dr. Barbara Jelus.

Registry No.—Carbon monoxide, 630-08-0; *n*-butyl alcohol, 71-36-3.

Supplementary Material Available. Full nmr data for the ester products described in this paper will appear in Table III following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3318.

References and Notes

(1) R. F. Heck and J. P. Nolley, ., *J. Org. Chem.*, **37**, 2320 (1972).
(2) T. Mizoroki, K. Mori, and A. Ozaki, *Bull. Chem. Soc. Jap.*, **44**, 581 (1971); **46**, 1505 (1973).
(3) H. A. Dieck and R. F. Heck, *J. Amer. Chem. Soc.*, **96**, 1133 (1974).
(4) P. Fitton and E. A. Rick, *J. Organometal. Chem.*, **28**, 287 (1971).
(5) W. T. Dent, R. Long, and G. H. Whitfield, *J. Chem. Soc.*, 1589, 1852 (1964).
(6) G. P. Chiusoli and L. Cassar, *Angew. Chem., Int. Ed. Engl.*, **1**, 124 (1967).
(7) R. F. Heck, *J. Amer. Chem. Soc.*, **85**, 2013 (1963).
(8) R. F. Heck, *J. Amer. Chem. Soc.*, **90**, 5546 (1968).
(9) P. M. Henry, *Tetrahedron Lett.*, 2285 (1968).
(10) E. J. Corey and L. S. Hegedus, *J. Amer. Chem. Soc.*, **91**, 1233 (1969).
(11) L. Cassar and M. Foa, *J. Organometal. Chem.*, **51**, 381 (1973).
(12) R. F. Heck and D. S. Breslow, *J. Amer. Chem. Soc.*, **83**, 1097 (1961).
(13) R. F. Heck, *J. Amer. Chem. Soc.*, **91**, 6707 (1969).
(14) W. Schoeller, W. Schrauth, and W. Essers, *Chem. Ber.*, **46**, 2864(1913).
(15) R. F. Heck, *Fortschr. Chem. Forsch.*, **16**, 221 (1971).
(16) K. Kudo, M. Sato, M. Hadai, and Y. Uchida, *Bull. Chem. Soc. Jap.*, **46**, 2820 (1973).
(17) R. F. Heck "Organotransition Metal Chemistry," Academic Press, New York, N. Y., 1974, p 80.
(18) C. Glaser, *Ann.*, **154**, 137 (1870).
(19) S. J. Cristol and W. P. Norris, *J. Amer. Chem. Soc.*, **75**, 2645 (1953).
(20) D. R. Davis and J. D. Roberts, *J. Amer. Chem. Soc.*, **84**, 2252 (1962).
(21) G. Zweifel and H. Arzoumanian, *J. Amer. Chem. Soc.*, **89**, 5086 (1967).
(22) G. Zweifel and A. B. Steele, *J. Amer. Chem. Soc.*, **89**, 2573 (1967).
(23) F. R. Hartley, *J. Organometal. Chem. Rev. A*, **6**, 119 (1970).
(24) P. Fitton, M. P. Johnson and J. E. McKeon, *Chem. Commun.*, 6 (1968).
(25) D. R. Coulson, *Inorg. Syn.*, **13**, 121 (1972).
(26) J. Chatt and L. M. Venanzi, *J. Chem. Soc.*, 2351 (1957).
(27) L. M. Jackman and J. W. Lown, *J. Chem. Soc.*, 3776, 3782 (1962).
(28) Another isomerization mechanism can be proposed which also fits the known facts. After CO insertion occurs stereospecifically, a π-acryloylpalladium complex could be formed probably with loss of a ligand. Such a complex could equilibriate isomers through a σ-ketenemethylpalladium form. This form reverts to σ-acryloyl derivatives which ultimately alcoholize to esters.



An isolable π-acryloylcobalt complex has been reported previously [(R. F. Heck and D. S. Breslow, *J. Amer. Chem. Soc.*, **83**, 1097 (1961)] and a σ-ketenemethylcobalt species has been proposed to explain a trans- to cis-α,β-double bond isomerization in the thermal cyclization of tricarbonyltriphenylphospine-2,4-hexadienoylcobalt(I) [(R. F. Heck, *ibid.*, **85**, 3387 (1963)].

Palladium-Catalyzed Amidation of Aryl, Heterocyclic, and Vinylic Halides

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Aryl, heterocyclic, and vinylic halides react with CO and primary or secondary amines with a dihalobistriphenylphosphinepalladium(II) catalyst at 100° or below and 1 atm pressure to form substituted amines in good yields. If the amines are weakly basic, a strongly basic tertiary amine must also be present in stoichiometric amounts. The reaction is highly stereospecific with cis and trans vinylic halides.

The preceding paper reports a new synthesis of esters under mild conditions from aryl, benzyl, or vinylic halides, carbon monoxide, a tertiary amine, an alcohol, and a catalytic amount of various triphenylphosphine–palladium salt complexes.[1] In this paper we report an analogous reaction which produces primary or secondary amides when the above reaction is carried out with a primary or secondary amine in place of the alcohol.

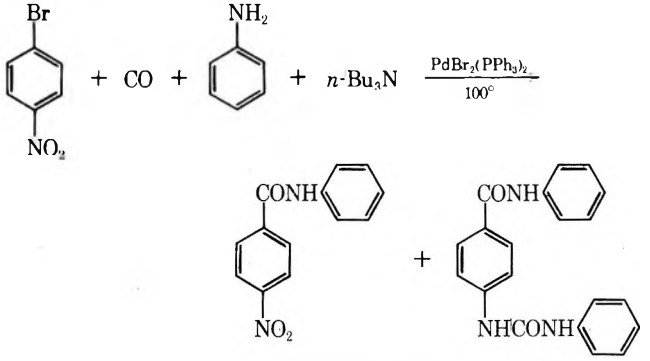
$$RX + CO + R'NH_2 + R_3''N \xrightarrow{PdX_2[P(C_6H_5)_3]_2} RCONHR' + R_3''NH^+X^-$$

Results and Discussion

A variety of aryl, heterocyclic, and vinylic bromides and iodides have been treated with carbon monoxide at atmospheric pressure, a primary or secondary amine, and a tertiary amine in the presence of about 1.5 mol % $PdX_2[P(C_6H_5)_3]_2$ as catalyst at 60–100°. 2-Chloropropene was also allowed to react but under 600 psi pressure. The amides formed in these reactions are listed in Table I along with the yields and reaction conditions. The yields of isolated purified amides ranged from 57 to 94%. The nmr data for the products are given in Table II, which will appear in the microfilm edition of this journal. See paragraph at end of paper regarding supplementary material. The reactions proceeded more rapidly than the related ester synthesis judging by the half-lives ($T_{1/2}$) observed. (The approximate half-lives were the times required for half of the theoretical amount of carbon monoxide to be absorbed). For example, bromobenzene reacts under the above conditions about 17 times faster with benzylamine to form *N*-benzylbenzamide than it does with *n*-butyl alcohol to form *n*-butyl benzoate. The amidation reaction also shows improved stereospecificity over the carboalkoxylation reaction with cis and trans vinylic halides. The reactions proceeded with high specificity producing amides with retained configuration. We were unable to find more than traces of isomerized products in the reaction mixtures. The amides were nicely crystalline compounds in general and were easily purified by recrystallization.

A tertiary amine was generally added with the primary or secondary amine to neutralize the hydrogen halide formed in the reaction. If the primary or secondary amine was a strong enough base the tertiary amine was not required. Aniline for example does not react without the tertiary amine while pyrrolidine does.

The N-phenylamidation of 4-nitrobromobenzene was complicated by the fact that reduction of the nitro group catalyzed by the palladium also occurred forming an *N*-phenylurea group from the nitro group, CO, and aniline. The urea formation may proceed by way of an isocyanate[2] or an amine.[3] In any case, the urea formation is apparently slower than the amidation and by stopping the reaction when approximately the theoretical amount of CO for formation of the amide is absorbed the *N*-phenyl-4-nitrobenzamide was isolated in 57% yield. Allowing the reaction to proceed until 1.57 mol of CO were absorbed, there was isolated 33% of the *N*-phenylamide of 4-carboxydiphenylurea in addition to 10% of the nitroamide. The yield of the urea probably could be improved if more aniline had been used. This reaction is being investigated as a possible method for preparing other unsymmetrical urea derivatives.



cis-2-Bromostyrene was treated with CO and pyrrolidine under the usual conditions but only about half of the theoretical amount of CO was absorbed. In addition to *trans*-*N*-cinnamoylpyrrolidine, isolated in 6% yield (probably formed from the 8% of *trans*-2-bromostyrene present in the starting material), *cis*-1,4-diphenyl-1-buten-3-yne was isolated in 46% yield. The last product is likely produced by a reaction of the intermediate *cis*-styrylpalladium complex with phenylacetylene and then the adduct eliminating metal hydride (a trans elimination is required). The phenylacetylene is probably formed in this reaction and not others because the relatively unhindered, strong base, pyrrolidine causes a trans dehydrobromination of the *cis*-2-bromostyrene. The liquid cis styrylacetylene isomer obtained (J = 12 Hz for the vinylic hydrogens) isomerized slowly on standing in the light at room temperature to the known solid trans isomer, mp 96.5–97° [4] (J = 18 Hz for the vinylic hydrogens). The only other material isolated from the reaction mixture was a viscous oil which by its nmr and ir spectra appeared to be a polymeric mixture of aromatic carbonyl compounds.

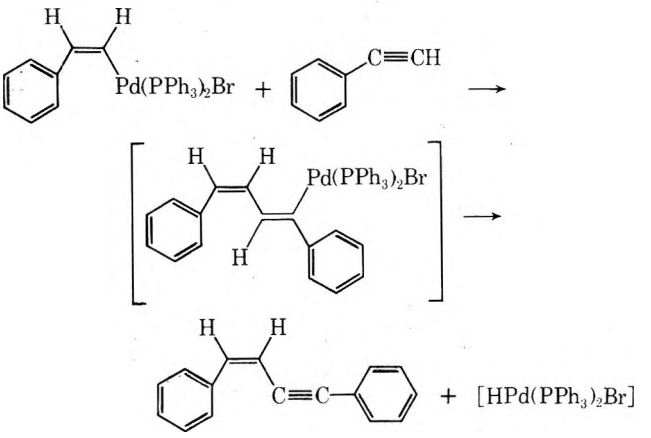
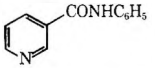
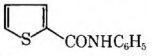
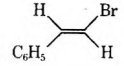
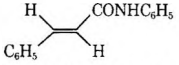
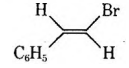
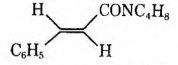
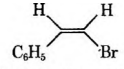
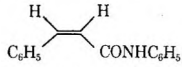
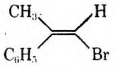
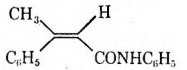
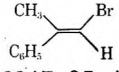
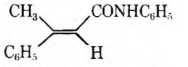


Table I
Amidation of Aryl and Vinylic Halides[a]

Halide	Amine (mm)	Catalyst	Temp, °C	Reaction time, hr ($T_{1/2}$, min)	Product (% yield)	Mp, °C	Molecular weight: Found	Molecular weight: Calcd
C_6H_5Br (108-86-1)	$C_6H_5NH_2$ (38)	$C_6H_5PdBr(PPh_3)_2$ (33381-14-5)	100	3.5 (41)	$C_6H_5CONHC_6H_5$ (94) (93-98-1)	162.5–163[b]	197.086	197.084
C_6H_5Br	$C_6H_5CH_2NH_2$ (25)	$PdBr_2(PPh_3)_2$ (23523-33-3)	100	3 (43)	$C_6H_5CONHCH_2C_6H_5$ (79) (1485-70-7)	105–105.5[c]	211.097	211.100
4-$CH_3OCOC_6H_4Br$ (619-42-1)	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	100	3.5 (47)	4-$CH_3OCOC_6H_4CONHC_6H_5$ (86) (3814-10-6)	192–193[d]	255.090	255.090
4-$CH_3OC_6H_4Br$ (104-92-7)	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	100	10 (85)	4-$CH_3OC_6H_4CONHC_6H_5$ (76) (7465-88-5)	173–174[e]	227.095	227.095
4-$NO_2C_6H_4Br$ (586-78-7)	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	100	3.5 (80)[f]	4-$NO_2C_6H_4CONHC_6H_5$ (57) (619-80-7)	211–212[g]	242.065	242.069
4-$NO_2C_6H_4Br$	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	100	7.5	4-$C_6H_5NHCONHC_6H_4CONHC_6H_5$ (33) (20643-51-8)	235–236	*h*	
				(–)[i]	4-$NO_2C_6H_4CONHC_6H_5$ (10)	211–212		
 (626-55-1)	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	100	5.5 (75)	 (65) (1752-96-1)	118–119[j]	198.0649	198.0793
 (1003-09-4)	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	100	2 (30)	 (63) (6846-13-5)	139–140[k]	203.0514	204.0399
 (588-72-7)	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	60	3 (33)	 (81) (25775-89-7)	147–148[l]	223.097	223.100
	$C_4H_9N^{m,n}$ (50)	$PdBr_2(PPh_3)_2$	60	2.5 (29)	 (91) (52438-21-8)	100–100.5	201.112	201.115
 (588-73-8)	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	60	4 (71)	 (80) (52393-67-6)	101–102	223.102	223.100
 (19647-26-8)	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	100	1 (15)	 (87) (52393-68-7)	94–95[o]	237.1007	237.1154
 (16917-35-4)	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	100	1 (20)	 (88) (21298-82-8)	119–119.5[p]	237.1178	237.1154

(16403-09-1)	$C_6H_5NH_2$ (25)	$PdI_2(PPh_3)_2$ (23523-32-2)	100	1.5 (14)	(52393-69-8) (71)	96–97	203.128	203.130
(16403-13-7)	$C_6H_5NH_2$ (25)	$PdI_2(PPh_3)_2$	100	1 (14)	(52393-70-1) (70)	66.5–67	203.127	203.130
(557-98-2)	$C_6H_5NH_2$ (25)	$PdCl_2(PPh_3)_2$ (13965-03-2)	100	10	(1611-83-2) (74)	84–85[r]	161.0895	161.0841
(40053-01-8)	$C_6H_5NH_2$ (25)	$PdBr_2(PPh_3)_2$	100	1.3 (30)	(52393-83-2) (80)	87–87.5[s]	219.0888	219.0895

[a] Carried out with 17.2 mm of halide, 19.0 mm of tri-*n*-butylamine, and 0.25 mm of catalyst under 1 atm of carbon monoxide. Registry numbers are given in parentheses. [b] Reported mp 160–161°, A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. I, Wiley, New York, N.Y., 1964, p 82. [c] Reported mp 105–106°, E. Beckman, *Ber.*, **37**, 4136 (1904). [d] Reported mp 193°, G. Renckhoff and H. L. Huekmann, U. S. Patent 3,252,977 (1966). [e] Reported mp 171°, A. Rossel, *Justus Liebigs Ann. Chem.*, **151**, 25 (1869). [f] Allowed to react until 17.4 mmol of CO had been absorbed. [g] Reported mp 212°, L. C. Raiford, R. Taft, and H. P. Lankelma, *J. Amer. Chem. Soc.*, **46**, 2051 (1924). [h] Parent ion not observed. Elemental analysis is reported in the Experimental Section. [i] Allowed to react until 27 mmol of CO had been absorbed. [j] Reported mp 124–126°, H. W. Grimmel, A. Guenther, and J. F. Morgan, *J. Amer. Chem. Soc.*, **68**, 539 (1946). [k] Reported mp 140°, "Thiophene and its Derivatives," Interscience, New York, N.Y., 1952, p 376. [l] Reported mp 151°, G. Tsatsas, *Bull. Soc. Chim. Fr.*, 1011 (1947). [m] Reaction carried out without tri-*n*-butylamine. [n] C_4H_9N is pyrrolidine. [o] Reported mp 95°, R. Stoermer, F. Grimm, and E. Lang, *Chem. Ber.*, **50**, 959 (1917). [p] Reported mp 121°, F. Henrich and A. Wirth, *Chem. Ber.*, **37**, 731 (1904). [q] Carried out with 100 mmol of organic halide, 30 mmol of tri-*n*-butylamine, and 0.50 mmol of catalyst at 135° under 600 psig of carbon monoxide. [r] Reported mp 87°, P. Bieber, *C. R. Acad. Sci.*, **231**, 291 (1950). [s] Reported mp 92°, R. Anschütz, *Justus Liebigs Ann. Chem.*, **353**, 139 (1907).

The mechanism of the amidation may involve an attack of the primary or secondary amine upon an acylpalladium intermediate. The reduction of the catalyst probably involves simultaneous formation of a substituted urea. Tris(triphenylphosphine)carbonylpalladium(0) and related carbonyls have been obtained under similar reaction conditions.[5] A possible reaction sequence is shown in Scheme I.

Scheme I

$$PdX_2[P(C_6H_5)_3]_2 + 2CO + R'NH_2 \longrightarrow [Pd(CO)[P(C_6H_5)_3]_2] + R'NHCONHR' + 2HX$$

$$[Pd(CO)[P(C_6H_5)_3]_2] + RX \xrightarrow{-CO}$$

$$RPd(X)[P(C_6H_5)_3]_2 \underset{-CO}{\overset{CO}{\rightleftharpoons}} RCPd(X)[P(C_6H_5)_3]_2 \xrightarrow{R'NH_2} RCNHR' + HPd(X)[P(C_6H_5)_3]_2$$

$$HPd(X)[P(C_6H_5)_3]_2 \xrightarrow{CO} HX + Pd(CO)[P(C_6H_5)_3]_2$$

$$HX + R_3''N \longrightarrow R_3''NH^+X^-$$

The fact that the reaction rates are faster with amines than with alcohols could mean that the rate determining step, at least in the amine reaction, is nucleophilic attack of the amine on an acylpalladium intermediate. The higher stereospecificity could mean that the alkenyl- and acylpalladium species are in equilibrium and that isomerization occurs slowly at the alkenyl stage. Since the amines react with the acyl complexes more rapidly than the alcohols do, there is less time for isomerization to occur. If this were the case, however, increasing the CO pressure probably would have increased the stereoselectivity of the carboalkoxylation, but it apparently did not in the one instance investigated. An alternative explanation could be that amine is coordinated to the palladium during the last stages of the reaction. The function of the tertiary amine in the aniline reaction or the strongly basic amine in other cases may be to remove a proton from the coordinated amine.

A mechanism such as shown in Scheme II could be imagined.

Scheme II

$$RPd(X)[P(C_6H_5)_3]_2 + CO \longrightarrow RCOPd(X)[P(C_6H_5)_3]_2 \overset{C_6H_5NH_2}{\rightleftharpoons} RCOPd(X)P(C_6H_5)_3 + P(C_6H_5)_3$$

$$RCOPd(X)P(C_6H_5)_3 + n\text{-}Bu_3N \rightleftharpoons \begin{bmatrix} RCOPd(X)P(C_6H_5)_3 \\ | \\ C_6H_5NH \end{bmatrix} n\text{-}Bu_3NH^+ \xrightarrow{CO}$$

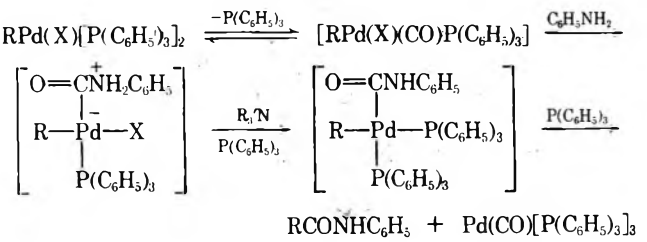
$$RCONHC_6H_5 + [Pd(X)(CO)P(C_6H_5)_3]^-n\text{-}Bu_3NH^+$$

$$[Pd(X)(CO)P(C_6H_5)_3]^-n\text{-}Bu_3NH^+ + P(C_6H_5)_3 \longrightarrow Pd(CO)[P(C_6H_5)_3]_2 + n\text{-}Bu_3NH^+X^-$$

$$Pd(CO)[P(C_6H_5)_3]_2 + RX \xrightarrow{-CO} RPd(X)[P(C_6H_5)_3]_2$$

A third possible mechanism could be attack of the amine on coordinated CO in $RPd(X)(CO)P(C_6H_5)_3$ followed by loss of a proton and X^- from the complex and then reductive elimination as shown in Scheme III.

Scheme III



The amidation reaction of aryl, heterocyclic, and vinylic halides is clearly a very convenient and useful method for producing a variety of substituted amides of aryl, heterocyclic, and α,β-unsaturated acids.

Experimental Section

General. The preparations and sources of the organic halides and catalysts used are given in the preceding paper[1] with one exception. *E*-Methyl 3-bromo-2-methylpropenoate was obtained as described by Canbere.[6] Molecular weights were determined by high resolution mass spectroscopy on a Du Pont (CEC) 21-170B double focus mass spectrometer. Proton nuclear magnetic resonance spectra were measured with a Varian Associates Model A-60A spectrometer or a Perkin-Elmer R-12B spectrometer in DMSO-d_6 or $CDCl_3$ using TMS as an internal standard.

Amidation Procedure. The general procedure used was similar to the one employed in the palladium-catalyzed carbobutoxylation of organic halides previously reported in detail.[1] Usually, 17.2 mmol of the organic halide, 25.0 mmol of the amine, and 19.0 mmol of tri-*n*-butylamine were allowed to react. If the amine being reacted was a strong base, tri-*n*-butylamine was not added and 50.0 mmol of the first amine was used. In the examples where a secondary anine was used, the product was not acid washed because secondary amides are acid soluble.

***N*-Phenylbenzamide.** The carbonylation apparatus containing catalyst suspended in a Teflon cup as described previously,[1] was flushed several times with carbon monoxide. A mixture of 2.7 g of bromobenzene (17.2 mmol) and 3.54 g of aniline (38.0 mmol) was added to the reaction vessel by means of a syringe. After equilibration of 100° (steam), the catalyst, $Pd(PPh_3)_2(Ph)(Br)$ (0.25 mmol), was added by dropping the Teflon cup into the stirred reaction mixture. Since after 1 hr only 12 ml of carbon monoxide had been absorbed, 3.6 g of tri-*n*-butylamine (19.0 mmol) was added and the up-take of carbon monoxide proceeded rapidly. Gas volume changes and times were periodically recorded. After 3.5 hr the absorption stopped (425 ml (17.4 mmol) of CO measured at 25° had been taken up). The reaction mixture was cooled, dissolved in ethyl ether (700 ml), and washed with several portions of 20% hydrochloric acid solution to remove salts and excess amine. The extracts were washed with several portions of distilled water. The ether layer was treated with decolorizing carbon, dried with anhydrous magnesium sulfate and filtered. The solid product formed after concentration of the solution was filtered and air-dried to give 2.89 g (94% yield) of *N*-phenylbenzamide, mp 162.5–163°.

***trans*-*N*-Cinnamoylpyrrolidine.** To the reaction vessel was added 3.12 g of *trans*-β-bromostyrene (17.2 mmol) and 3.56 g of pyrrolidine (50.0 mmol). After the reaction mixture was brought to equilibrium at 60° by means of a circulating constant temperature bath, under 1 atm of carbon monoxide, 0.198 g of $Pd(PPh_3)_2Br_2$ was added. Periodically, gas-volume changes and times were recorded until a total of 423 ml of CO had reacted. The reaction mixture was extracted with ether, and the extracts were washed with several portions of distilled water. The organic layer was concentrated *in vacuo* to remove the ether and excess pyrrolidine. The resulting solid obtained was dissolved in hot heptane, decolorized with charcoal, filtered, and cooled to give 3.15 g (91% yield) of *trans*-*N*-cinnamoylpyrrolidine, mp 100.0–100.5°.

Reaction of *cis*-β-Bromostyrene with CO and Pyrrolidine. *cis*-β-Bromostyrene, 17.2 mmol (92% cis, 8% trans) and pyrrolidine, 50.0 mmol, were treated as above in an attempt to make the *cis*-pyrrolidine amide of cinnamic acid. The CO uptake stopped after 200 ml (about half the theoretical amount) had reacted. The products were extracted with ether. The ether extracts were evaporated, and the oily residue was chromatographed on silica gel, first with pentane, followed by benzene, methylene chloride, and methanol. The pentane fraction was evaporated *in vacuo* to give 1.6 g (46%) of *cis*-1,4-diphenylbutenyne identified by its high resolution mass spectrum and nmr spectrum. Upon standing for several weeks at room temperature in the presence of light the oil crystallized to a solid (mp 93.5–95°) which by nmr was identified as *trans*-1,4-diphenylbutenyne. This cis to trans isomerization in the presence of light has been noted early.[4]

The trans isomer is reported to have a melting point of 96.5–97°. Evaporation of the methylene chloride eluate followed by crystallization from hot hexane gave 0.21 g (6.0%) of the *trans*-pyrrolidine amide of cinnamic acid. The methanol fraction gave 0.95 g of a viscous oil which could not be crystallized. This material contained a strong CO band at 1620 cm^{-1} and the nmr spectrum showed strong aromatic absorption with only weak vinyl absorptions.

N-Phenylamidation of *p*-Bromonitrobenzene. To the reaction vessel was added 3.47 g of *p*-nitrobromobenzene (17.2 mmol), 2.33 g of aniline (25.0 mmol), and 3.6 g of tri-*n*-butylamine (19.0 mmol). The reaction mixture was brought to equilibrium at 100°, with 1 atm of pressure of CO. The catalyst, $Pd(PPh_3)_2Br_2$ (0.25 mmol), was added and CO absorption began. The reaction was allowed to continue until a total of 660 ml of CO had been absorbed. The partially solid reaction mixture was extracted with ether, and the extracts were washed with 20% hydrochloric acid followed by saturated sodium bicarbonate, and then distilled water. The small amount of solid obtained which did not dissolve in the ether was dissolved in methylene chloride and the solution decolorized with charcoal, dried with anhydrous magnesium sulfate, and concentrated on a steam bath and cooled. The solid obtained (0.43 g, 10% of theory) had a melting point of 211–212° which is the same as the reported melting point for *N*-phenyl-*p*-nitrobenzamide.[7] This structure was confirmed by its high resolution mass spectrum and nmr spectrum. The ether soluble fraction was treated with charcoal, dried, filtered, and concentrated on a steam bath to about 100 ml. On cooling, 1.9 g of the *N*-phenylamide of 4-carboxydiphenylurea (33%) was obtained mp 233–235°. Recrystallization from ethanol raised the melting point to 235–236°.

Anal. Calcd for $C_{14}H_{10}O_2N_2$: C, 72.52; H, 5.13; N, 12.68. Found: C, 72.59; H, 5.42; N, 12.78.

Although the parent peak could not be observed in the high resolution mass spectrum, intense peaks were seen at *m/e* 93$^+$ and *m/e* 238$^+$ which indicate the expected decomposition products of the compound, aniline, and 4-*N*-phenylaminocarbonylphenylisocyanate, were being produced.

In order to improve the yield of *N*-phenyl-*p*-nitrobenzamide the above reaction was repeated but the reaction was stopped after 400 ml of CO had been absorbed. This procedure gave 3.44 g of crude amide that was recrystallized from acetone–hexane to give 2.32 g of pure *N*-phenyl-*p*-nitrobenzamide (57% yield).

***N*-Phenylmethacrylamide.** A mixture of 7.64 g (100 mmol) of 2-chloropropene, 2.33 g (25 mmol) of aniline, 5.56 g (30 mmol) of tri-*n*-butylamine, and 0.350 g (0.50 mmol) of $PdCl_2(PPh_3)_2$ was placed in a 45-ml stainless steel high-pressure reactor with a magnetic stirring bar. The container was sealed, flushed with CO, pressured to 600 psig, and heated with stirring at 135° for 24 hr. The pressure dropped from 800 to 475 psi during this time. After cooling to room temperature the pressure was released and the reaction mixture was treated with 6 *N* hydrochloric acid and ether. The solids dissolved and the ether phase was separated, dried with anhydrous magnesium sulfate, filtered, and evaporated. The solid obtained was recrystallized from hexane to give 2.97 g of colorless crystals of product, mp 84–85°.

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Registry No.—Carbon monoxide, 630-08-0; aniline, 62-53-3; benzylamine, 100-46-9; pyrrolidine, 123-75-1; *cis*-1,4-diphenylbutenyne, 13343-78-7; *trans*-1,4-diphenylbutenyne, 13343-79-8.

Supplementary Material Available. Complete nmr spectra data for the compounds prepared will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or

money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3327.

References and Notes

(1) A. Schoenberg, I. Bartoletti, and R. F. Heck, *J. Org. Chem.*, **39**, 3318 (1974).
(2) F. Weigert, *J. Org. Chem.*, **38**, 1316 (1973).
(3) E. W. Stern and M. L. Spector, *J. Org. Chem.*, **31**, 596 (1966).
(4) F. Straus, *Ann.*, **343**, 190 (1905).
(5) M. Hidai, M. Kokura, and Y. Uchida, *J. Organometal. Chem.*, **52**, 431 (1973).
(6) P. Canbere, *Bull. Soc. Chim. Fr.*, **144** (1964).
(7) L. C. Raiford, R. Taft and H. P. Lankelma, *J. Amer. Chem. Soc.*, **46**, 2051 (1924).

Ceric Ammonium Nitrate Promoted Aromatic Substitution with Peroxydicarbonates[1]

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The decomposition of dialkyl peroxydicarbonates in the presence of a two-molar excess of ceric ammonium nitrate (CAN) in toluene led to tolyl alkyl carbonates in yields of 75–90% based on two carbonate moieties from each peroxide molecule. Unlike the previously reported catalytic effect of cupric chloride, where the chain-induced peroxide breakdown by cuprous limited the aryl ester yield to 1 mol/mol of peroxide, the CAN involvement was stoichiometric as both halves of the peroxide substituted onto the aromatic. No peroxide–cerous ion interaction seemed to occur; indeed the overall peroxide decomposition rate was actually retarded relative to that in the absence of metal salts and all the cerium was recovered as cerous nitrate. Based on isomer distributions and relative rates the substituting entity possessed more selectivity than the free carbonate radicals. No polymer production was noted in reactions performed with acrylonitrile, suggesting low oxy radical concentrations. The importance of the hexanitrato cerium(IV) complex as an oxidant in the overall aromatic substitution process was established by studying a variety of other ceric and cerous salts in this reaction.

The decomposition of peroxydicarbonates and diacyl peroxides in the presence of toluene can be modified by the inclusion of suitable redox agents (*e.g.*, $CuCl_2$,[2] $FeCl_3$,[3] I_2,[4] O_2,[5] and various other metal salts[3,6]) which oxidize oxy radical–aromatic adducts to form aryl esters. With most of the metal salts a lower valence inorganic species is produced which then reduces the peroxide, leading to a chain reaction.[2,3] The net stoichiometry is indicated in eq 1 for cupric chloride, which proved to be the most effective metal salt,

$$(RCO_2)_2 + ArH \xrightarrow[CH_3CN]{CuCl_2} RCO_2Ar + RCO_2H \quad (1)$$

$$R = i\text{-PrO or } C_6H_5$$

forming nearly 1 mol of aryl ester/mol of peroxide.[2] With molecular oxygen as a promoter the reaction went by a nonchain mechanism and aryl ester yields somewhat in excess of 1 mol/mol of peroxide were realized.[5] In the absence of added oxidant less than 1% nuclear oxygenation resulted, as the oxy radicals reacted by other pathways.

Recently we found that use of sufficient quantities of ceric ammonium nitrate (CAN) with the same peroxides and toluene led to nearly doubled aromatic oxygenation yields, and we wish to report on the details of this reaction.

Results and Discussion

Reaction Products. The optimum general procedure involved adding a solution of known concentration of diisopropyl peroxydicarbonate (IPP) in toluene to a 2.25 molar excess of CAN, and a 25- to 50-fold molar excess of toluene in acetonitrile at 60°, and allowing the reaction to go for 24 hr. Table I summarizes the organic reaction products.

Apparently, both oxy fragments formed from peroxide homolysis were capable of reacting with the aromatic, as 1.6 mol of oxygenation products (tolyl isopropyl carbonates) were formed from 1 mol of peroxide. This meant that 80% of the potential alkoxycarboxy moieties (2 mol/mol of peroxide) added to the ring, while the remaining 20% decomposed to form carbon dioxide, acetone, and isopropyl alcohol. The material balance based on starting peroxide was excellent in all cases.

Table I
Organic Reaction Products from Diisopropyl Peroxydicarbonate–Toluene–Ceric Ammonium Nitrate System[a]

Product	Yield,[b] %
Tolyl isopropyl carbonates[c]	160
Isopropyl alcohol	26
Acetone	16
Carbon dioxide	47
Benzaldehyde	4
Benzyl alcohol	2
Nitrotoluenes	1
$\sum(CO_2)$[d]	103
$\sum(i\text{-Pr})$[e]	101

[a] Toluene:CAN:peroxide = 25:2.25:1, acetonitrile solvent, 60°, 24 hr (see general procedure). [b] Based on 1 mol of product/mol of peroxide. [c] Isomer distribution, ortho:meta:para = 56.2:11.8:32.0. [d] Material balance based on two CO_2 groups/mol of peroxide. [e] Material balance based on two isopropyl groups/mol of peroxide.

As the reaction proceeded, crystals of cerous nitrate gradually precipitated from the reaction mixture. This and all the other inorganic reaction products were isolated and quantitatively determined (Table II) utilizing total acid, ammonium ion, nitrate ion, and cerium analyses. On the basis of these product studies (Tables I and II), the following stoichiometry was proposed for the reaction (eq 2).

$$(i\text{-PrOCO}_2)_2 + 2(NH_4)_2Ce(NO_3)_6 + 2C_6H_5CH_3 \longrightarrow$$
$$2i\text{-PrOCO}_2C_6H_4CH_3 + 2Ce(NO_3)_3 +$$
$$4NH_4NO_3 + 2HNO_3 \quad (2)$$

Normally, cerous nitrate is soluble in acetonitrile, but apparently it is salted out by ammonium nitrate and nitric

Table II
Inorganic Products from Diisopropyl Peroxydicarbonate–Toluene–Ceric Ammonium Nitrate System[a]

Product	Yield, mol[b] Exptl	Theor	Yield, %
HNO_3[c]	2.10	2.00	105
Ce(III)[d]	2.09	2.00	104
NO_3^- (nonvolatile)[e]	9.60	10.00	96.0
NO_3^- (total)[f]	11.8	12.00	98.3
NH_4^+[g]	3.44	4.00	85.8

[a] Toluene:CAN:peroxide = 25:2:1, acetonitrile solvent, 60°, 24 hr; see Experimental Section. [b] Based on the stoichiometry indicated in eq 6. [c] Determined by potentiometric titration. [d] Determined by ultraviolet spectrophotometry.[8] [e] Determined by phenoldisulfonic acid method.[9] [f] Calculated from HNO_3 and NO_3^- (nonvolatile). [g] Distilled as NH_3 and determined by titration. The low yield is probably the result of sublimation of some ammonium nitrate during vacuum drying of isolated salts.

acid.[7] We were able to verify this common ion effect by adding ammonium nitrate and nitric acid to solutions of cerous nitrate in acetonitrile in the relative quantities present in eq 2, and observing precipitation.

Further checks on the proposed stoichiometry were derived from pH measurements and the analysis of salts from aqueous extracts of the reaction mixture. Aqueous extracts possessed a pH of 1.8, suggesting the presence of a strong acid, and this value agreed closely with the pH 1.7 calculated from the expected yield for nitric acid. The salt yields from duplicate experiments were 100.50 and 99.14% of the value calculated on the basis of the stoichiometry given in eq 2. Failure of this salt to liberate iodine from potassium iodide solution[10] was taken as evidence for the absence of ceric ion in the final mixture. All of these findings lend support to the stoichiometry proposed in eq 2.

The theoretical production of 2 mol of product/mol of peroxide (eq 2) affords a distinct advantage for synthetic purposes over the copper-catalyzed reaction (eq 1), where the theoretical yield is just 1 mol of aryl ester/mol of peroxide.

Reaction Variables. To maximize the efficiency of the CAN-controlled oxygenation reaction and to learn more about the mechanism, a number of reaction variables were studied. Table III summarizes the effect of modifying the catalyst:peroxide ratio on the oxygenation yield for reactions containing toluene:peroxide ratios of 50:1. Unlike the cupric chloride catalyzed system,[2] for which a maximum yield of nuclear oxygenation was obtained using a catalyst:peroxide ratio of just 0.3:1, the amount of ester formed closely paralleled the molar amount of CAN used (Table III). This lends further support to the proposed stoichiometry (eq 2). Although the oxygenation yield leveled off once the stoichiometric amount of CAN was present, a slight improvement in yield was realized when a small excess of the stoichiometric requirement of CAN was used, perhaps because some of the CAN is consumed in side reactions (*e.g.*, benzyl alcohol oxidation[11]).

Under experimental conditions favoring optimum yield, 20–25% of the peroxide was degraded to isopropyl alcohol, acetone, and carbon dioxide. At lower CAN:peroxide ratios, the lesser oxygenation yields were accompanied by correspondingly increased amounts of these by-products, which are the usual products from the thermolytic decomposition of the isopropoxycarboxy radical.[2,12] In like manner benzaldehyde, benzyl alcohol, and bibenzyl, resulting from side-chain abstraction by an alkoxy radical,[2] were found.

Small amounts of nitrotoluenes were also formed in the CAN-promoted systems (Table III), and the yield of these by-products decreased as the concentration of CAN was increased to the stoichiometric amount (eq 2). It is surprising that the greatest nitrotoluene formation occurred with a CAN:peroxide ratio of only 0.5 (Table III), because of those systems containing CAN this one would be expected to contain the lowest concentration of nitric acid (eq 2). It is noteworthy that qualitatively, the meta isomer was the major nitrotoluene product, whereas for straightforward electrophilic substitution by nitric acid, the meta proportion is normally quite small (4%).[13]

With insufficient CAN, considerable intact peroxide would remain to decompose after all of the limited CAN had been consumed in product formation (eq 2). Under these conditions, nitric acid can promote concurrent nitration–oxygenation which results in this unusual isomeric nitrotoluene product pattern.[14] With sufficient CAN present to promote oxygenation little involvement of HNO_3 with the peroxide is noted.

Further evidence for nitric acid involvement can be gleaned from Table III. As the CAN:peroxide ratio was lowered the percentage of *p*-tolyl isopropyl carbonate systematically became larger at the expense of the meta isomer. Extrapolation of each isomer back to zero CAN content leads to an all-around isomer composition of ortho:meta:para = 58:6:36, which is very similar to that found using just nitric acid as the promoter.[14] This value is quite different from that obtained (ortho:meta:para = 57:15:28) with $CuCl_2$ as a catalyst where free oxy radicals are believed to be the substituting entity.[2]

Little effect of temperature on the CAN-promoted oxygenation was noted in the range of 50–70°. Slightly more tolyl isopropyl carbonates with a more selective isomer distribution (ortho:meta:para = 59:10:31) were obtained at 50° but the reaction required more time (48 hr).

Table III
Products as a Function of Ceric Ammonium Nitrate:Peroxide Ratio[a]

CAN:peroxide molar ratio	Products, %[b] Tolyl isopropyl carbonates Yield	Ortho	Meta	Para	Carbon dioxide	Isopropyl alcohol	Acetone	Benzaldehyde	Benzyl alcohol	Nitrotoluenes	Bibenzyl	Σ(*i*-Pr)[c]	Σ(CO_2)[d]
0	1				212	119	55	0	0	0	18	87	106
0.5	38	58.5	7.1	34.4	174	101	44	3	13	3.6[e]	0.05	91	106
1.0	84	58.0	8.3	33.7	116	84	32	1	6	2.5[f]	0[g]	100	100
1.5	121	58.3	9.4	32.3	104	39	17	1	3	1.5	0[g]	90	112
2.0	143	59.1	10.4	30.5	80	28	13	1	1	0.5	0	99	112
2.5	152	58.6	12.3	29.1	66	28	14	2	0.5	0.5	0	97	109

[a] Toluene:diisopropyl peroxydicarbonate = 50:1, 24 hr, 60°, acetonitrile solvent (see general procedure). [b] Yields based on mol product/mol peroxide. [c] Material balance based on two isopropyl groups/mol peroxide. [d] Material balance based on two CO_2 groups/mol peroxide. [e] Ortho:meta:para = 13:78:9. [f] Predominantly meta; not quantitatively determined. [g] Trace of bibenzyl present.

Table IV
Decomposition Rates for Diisopropyl Peroxydicarbonate in Acetonitrile as a Function of Metal Salt[a]

Salt	Temp, °C	$k \times 10^3$, [b] min^{-1}	$t_{1/2}$, min
None[c]	50	6.45	108
$CuCl_2$[c]	50	66	10.4
None	60	13.6	48
CAN[d]	60	4.9	140
CKN[e]	60	5.6	127

[a] Average of duplicates in good agreement. [b] ±10%. [c] Reference 2 (toluene:peroxide:catalyst = 17.3:1:0.3). [d] Toluene:peroxide:CAN = 25:1:2. [e] Toluene:peroxide:CKN = 25:1:2, single determination.

Peroxide Decomposition Rates. The rates of peroxide decomposition in the presence of a number of cerium salts were followed iodometrically. The rate curves plotted nicely as first-order reactions in peroxide with the exception of cerous nitrate (*vide infra*). Previously, first-order kinetics for the thermolysis of diisopropyl peroxydicarbonate in acetonitrile[2] and other solvents[15] had been reported. The rate of formation of aryl carbonate esters was also followed at 50° by glpc, and agreed well with the rate of peroxide decomposition.

Inspection of Table IV shows that the rates of peroxide breakdown at 60° with the ceric salts were slowed in comparison to the rate in the absence of these promoters. The similarity of rates in the presence of ceric ammonium nitrate and ceric potassium nitrate (CKN) indicates both the apparent importance of the hexanitratocerate ion and unimportance of the cationic species in the rate-retarding effect of the ceric salts. This rate-slowing effect stands in marked contrast to the accelerating effect of cupric chloride on the decomposition (50°) of the same peroxide (Table IV). Whereas cupric chloride accelerates the rate of peroxide decomposition by a factor of 10 in relation to the thermolysis rate, CAN and CKN retard the decomposition by a factor of about 3.

With cupric chloride, rate acceleration is attributed to the ability of cuprous ion formed in the radical oxidation step (eq 4) to induce peroxide decomposition (eq 5), leading to a redox chain mechanism. Unlike cuprous ion, cerous ion is oxidized only with very strong oxidizing agents,[16] and is not effective in breaking down the peroxide, explaining the lack of rate enhancement shown by the cerium salts.

$$(i\text{-PrOCO}_2)_2 \longrightarrow 2i\text{-PrOCO}_2\cdot \quad (3)$$

$$i\text{-PrOCO}_2\cdot + \text{ArH} + \text{CuCl}_2 \longrightarrow \text{ArOCO}_2\text{Pr-}i + \text{CuCl} + \text{HCl} \quad (4)$$

$$\text{CuCl} + (i\text{-PrOCO}_2)_2 + \text{HCl} \longrightarrow i\text{-PrOCO}_2\cdot + \text{CuCl}_2 + i\text{-PrOH} + \text{CO}_2 \quad (5)$$

To determine if the rate-retarding effect depends on the relative CAN concentration, additional kinetic studies of peroxide decomposition were made on systems containing CAN:peroxide ratios of 0.5, 1.0, 1.5, and 2.5. The rates in all cases were identical within experimental error, indicating perhaps a medium effect rather than a stoichiometric peroxide–CAN complex.

The actual decrease in the peroxide breakdown rate is not understood at this point, but has been noticed in other peroxide decompositions using metal salts of strong acids.[6]

Other Cerium Salts. Several additional cerium salts were tested for their effectiveness as oxygenation promoters. Table V summarizes the results. Ceric potassium nitrate proved to be nearly as effective as CAN. Of the other salts tested only cerous nitrate and ceric nitrate showed any indication of promoting oxygenation.

Table V
Reaction of Toluene and Diisopropyl Peroxydicarbonate with Other Cerium Promoters[a]

Promoting salt	Tolyl isopropyl carbonates, %[b] Yield	Ortho	Meta	Para	Rate[c] $\times 10^3$, min^{-1}
$K_2Ce(NO_3)_6$	130	60	10	30	5.6
$Ce(NO_3)_3 \cdot 6H_2O$[d,e]	33	59	7	34	7.5[f]
$Ce(NO_3)_3 \cdot 2H_2O$[e]	44	60	6	34	
$Ce(NO_3)_4$[e,g]	14	61	6	33	12.0
HNO_3[h]	11	58	6	36	6.4
$Ce(OH)_4$[i]	1				31.0
$Ce(ClO_4)_3$	1				11.0
$CeCl_3$, $Ce(NH_4)_2(SO_4)_3$, $Ce(acac)_3$, $H_2Ce(SO_4)_2$	1				

[a] Toluene:peroxide:promoter = 25:1:2, unless otherwise stated; acetonitrile solvent, 60°, 24 hr. [b] Yields based on mol product/mol peroxide. [c] ±10%. [d] Other products included acetone (26%), isopropyl alcohol (120%), CO_2 (97%), bibenzyl (2.1%), and small quantities of benzyl alcohol, benzaldehyde, and two unidentified compounds. [e] Initially homogeneous; gradually became heterogenous. [f] Nonlinear curve, approximate value ±15%. [g] Toluene:peroxide:ceric nitrate = 25:1:0.38. Nitrotoluenes (about 10%, mainly meta) were present. [h] HNO_3:peroxide = 6:1. Other products: acetone (28%), isopropyl alcohol (97%), CO_2 (103%), nitrotoluenes (10%, ortho:meta:para = 17:78:5), bibenzyl (2%), benzyl alcohol, benzaldehyde, and an unidentified component; see ref 14. [i] Heterogeneous throughout.

In view of the sluggishness of cerous toward oxidation one might predict that cerous nitrate would not affect the decomposition of the peroxide or promote the oxygenation of aromatics. Experimental results fail to support either prediction. As shown in Table V, cerous nitrate causes a rate-inhibiting effect intermediate between the uncatalyzed and the CAN-promoted reactions, although the curve is more eccentric. This behavior is attributable to precipitation of a ceric oxide hydrate formed as the cerous nitrate hydrolyzed during the reaction. During the stages of ceric oxide precipitation, the rate actually increased owing to $Ce(OH)_4$'s ability to accelerate peroxide decomposition (Table V).

The formation of an appreciable amount of tolyl isopropyl carbonates with $Ce(NO_3)_3$ remains a puzzle. Cerous ion itself is not expected to be a good oxidant, and other potential promoters formed during the reaction can be ruled out, *i.e.*, $Ce(OH)_4$ and nitric acid. The former does not appear to be capable of promoting oxygenation (Table V). Although nitric acid is known to promote oxygenation[14] and does form in appreciable amounts from cerous nitrate during the reaction, the conspicuous absence of nitrotoluenes among the reaction products suggest that it is not involved in promoting aromatic substitution by an oxy species.[14]

The involvement of nitric acid as a promoter seems more plausible (Table V) for the ceric nitrate reactions, since both tolyl ester and nitrotoluene yields and isomer distributions resemble each other. Considering the experimental details, this conclusion can be easily rationalized. Because of unavoidable hydrolysis ceric nitrate does not exist in solid form;[17] rather, it was used as supplied commercially (0.95 *M*) in nitric acid). Very early in the reaction the deep red color of the ceric solution turned yellow and significant amounts of hydrated ceric oxide precipitated. Significant amounts of nitric acid remained in solution to promote oxygenation.[14]

Ceric hydroxide, even though only partially soluble in ac-

Table VI
Toluene Reaction with Peroxide–Ceric Ammonium Nitrate

Peroxide[a]	Temp, °C time, hr	Aromatic substitution product	Yield, %[b]	k_t/k_b
$(i\text{-PrOCO}_2)_2$	60 (24)	$i\text{-PrOCO}_2C_6H_4CH_3$ (58:11:31)[d]	161	6.35
$(sec\text{-BuOCO}_2)_2$	50 (24)	$sec\text{-BuOCO}_2C_6H_4CH_3$ (59:12:29)[d]	181	7.1
$(C_6H_5CO_2)_2$	80 (96)	$C_6H_5CO_2C_6H_4CH_3$[c] (56:14:30)[d]	53	

[a] Toluene:CAN:peroxide = 19–25:2:1, acetonitrile solvent. [b] Based on 1 mol of product/mol of peroxide. [c] Other aromatic substitution products were methylbiphenyls (ortho:meta:para = 68:23:9), 38%, and nitrotoluenes (ortho:meta:para = 60:5:35), 59%. [d] Ortho:meta:para ratio.

etonitrile, caused the greatest acceleration of peroxide decomposition of the cerium salts tested (Table V), even though it did not promote oxygenation.

Of the other cerium salts studied only minor modifying effects on peroxide decomposition were noted, and no candidate was significantly efficient in promoting oxygenation. With cerous chloride, ceric sulfate, and ceric ammonium sulfate very little of the salt appeared to dissolve in acetonitrile, while cerous acetonylacetone was about half in solution. Only with cerous perchlorate was the desired amount of salt able to be utilized.

This work points up the apparent importance of the intact hexanitrato cerium(IV) complex for the efficient promotion of this oxygenation reaction. This complex possesses considerable solvolytic stability,[18] and yet is a vigorous oxidizing agent as expected for a tetrapositive metal.[19] Previously oxygenation had been promoted by another anionic complex, the hexachloroiridate ion ($IrCl_6^{2-}$).[3]

Nature of the Substituting Species. To learn more about the nature of the substituting entity subsequently involved in aromatic substitution, relative rate reactions were carried out. Equimolar quantities of toluene and benzene at a tenfold and again at a 20-fold molar excess relative to peroxide were subjected to the peroxide–CAN mixture, yielding a relative rate value, $k_{C_6H_5CH_3}/k_{C_6H_6} = 6.35$. This value is about twice that attributed to a free isopropoxycarboxy radical ($k_t/k_b = 3.77$),[20] which itself is somewhat electrophilic. The increased selectivity observed in this system is not understood, but may be due to a medium effect or to nitric acid intervention. Other metal salts containing nitrate ligands have given quite similar isomer distributions and relative rates.[6]

Other Peroxides. CAN-promoted reactions of toluene with di-*sec*-butyl peroxydicarbonate and benzoyl peroxide were also looked at. The results are summarized in Table VI along with the diisopropyl peroxydicarbonate reaction. The di-*sec*-butyl peroxydicarbonate reaction gave an even better yield of aryl ester with an isomer distribution and relative rate very much like that from IPP. The aromatic substitution became less effective with benzoyl peroxide, owing largely to the wasting of CAN in nitrating toluene, which occurred at the higher temperature required (80°) for the benzoyl peroxide to undergo thermolysis (Table VI).

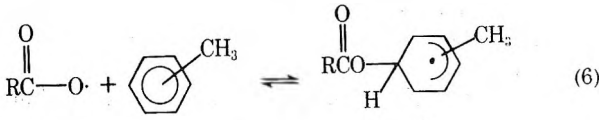
Radical Trapping Studies. Radical trapping experiments were performed with acrylamide and acrylonitrile[21,22] in an effort to determine the extent of involvement of free oxy radicals (Table VII). In a control system containing toluene, acrylonitrile, and peroxydicarbonate, considerable polyacrylonitrile precipitated from the reaction mixture. In a further control, CAN in the absence of peroxide was found to be ineffective as an initiator for polyacrylonitrile formation. When the CAN-promoted oxygenation of toluene was performed with a 15-fold molar excess of acrylonitrile or acrylamide no insoluble polymer was formed nor was the alkyl tolyl carbonate yield lowered appreciably (Table VII). These results suggest either the absence of or a very low concentration of free oxy radicals in the CAN-promoted oxygenation. However, a similar lack of polymerization was noted when the cupric chloride catalyzed oxygenation was subjected to acrylonitrile trapping (Table VII). It appears that in both the CAN and $CuCl_2$–peroxide reactions that oxy radicals are rapidly scavenged by toluene and oxidized to aryl esters, thus keeping the free oxy radical concentration too low to promote polymerization.

Table VII
Radical Trapping Studies[a]

Catalyst	Molar ratio[b]	Trapping agent	Molar ratio[b]	$CH_3C_6H_4OCO_2Pr\text{-}i$ yield[b]
None[c]		None		1[d]
None		$CH_2{=}CHCN$	9	1[e]
CAN	2.25	None		149
CAN	2.25	$CH_2{=}CHCN$	15	127[f]
CAN	2.25	$CH_2{=}CHCONH_2$[g]	15	132
$CuCl_2$[c]	0.3	None		85
$CuCl_2$	0.3	$CH_2{=}CHCN$	9	83[f]

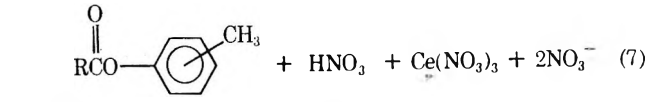
[a] Toluene:peroxide = 20:1, acetonitrile solvent, 60°. [b] Based on mol/mol of peroxide. [c] From ref 2. [d] Bibenzyl, 38%, was the major aromatic product. [e] Solution became heterogeneous as polyacrylonitrile (identified by ir) precipitated; only 1% bibenzyl was formed. [f] No polymer precipitate formed although the solution did darken. [g] Heterogeneous; no polymer precipitate formed, and solution ended up light yellow as was usual for CAN oxygenations.

Mechanism. Based on the experimental results the following mechanism (eq 6) is proposed for the tolyl ester formation following an initial homolytic breakdown of the peroxide (eq 3).



(6)

R = *i*-PrO, *sec*-BuO, C_6H_5 I



(7)

A fast reversible attack on the aromatic by oxy radical or a complexed oxy radical (eq 6) is followed by oxidation of the cyclohexadienyl radical intermediate by Ce^{IV}. The greater selectivity of the attacking entity compared to the free oxy radical[2,20] as indicated by the relative rate and isomer distribution patterns is not understood, but may be due to the increased polarity of the solvent system (nitric acid formation, eq 2),[6] or to complexing of the oxy radical by the cerium species. Alternatively the strong ceric oxidant may be capable of effecting an electron transfer from the oxy radical itself to produce an oxy cation which can then attack the ring. Although such electron transfers are well known for alkyl radicals with ferric,[23] cupric,[24] and ceric[25] ions, the analogous process with oxy radicals is unprecedented and would be expected to be energetically unfavorable.[26] An analogous situation (complexed oxy radical or oxy cation) was considered for the ferric chloride promoted oxygenation of toluene with diisopropyl peroxydicarbonate.[3]

The oxidation step (eq 7) involves Ce^{IV} in a less familiar role of radical oxidant rather than in its well-known function as oxidant of various organic compounds (*e.g.*, alcohols[21,27] and arenes[28]).

Experimental Section

Reagent grade chemicals and metal salts were used directly. The peroxydicarbonates[29] were found to possess >85% theoretical oxygen by iodometry,[30] and were used directly except in those cases involving the study of isopropyl alcohol and acetone yields. Here the peroxide in toluene was thoroughly irrigated with ice water, dried over sodium sulfate, and analyzed iodometrically before usage.

Aryl Alkyl Carbonate Syntheses. Carbonate esters were synthesized using a modification of a literature procedure.[31] Chloroform rather than ethyl ether was used as the solvent for the pyridine-promoted condensation to avoid precipitating the pyridine hydrochloride by-product. The tolyl isopropyl carbonates were shown to be >99.5% pure by gc after work-up and their ir spectra were identical with reference spectra.[32]

Phenyl and the isomeric tolyl *sec*-butyl carbonates were prepared from *sec*-butyl chloroformate (synthesized by a literature method[30]) and phenol or the appropriate cresols in the same manner, and were shown to be greater than 99% pure by gc after work-up and distillation. All gave similar characteristic ir signals at 1750 (C=O) and 1270–1260 and 1230–1210 cm^{-1} (C–O), and the tolyl *sec*-butyl carbonates had nearly identical nmr spectra: 0.95 (3 H, t), 1.25 (3 H, d), 1.50 (2 H, quintet), 2.2 (3 H, s), 4.6 (1 H, sextet), and 6.95 ppm (4 H, broad singlet).

General Procedure for Aromatic Oxygenation. Reactions for the system toluene–peroxide–CAN (25–50:1:2.25) were carried out as follows. CAN (0.0094 mol) was transferred with 80 ml of acetonitrile and 16 ml of toluene to a three-neck flask (250 ml) equipped with stirrer, condenser, and gas-inlet fitting. The assembled flask was immersed in a 60° constant-temperature oil bath, the salt was allowed to dissolve as the mixture was stirred, and the system was allowed to equilibrate for 5 min while being flushed with nitrogen (about 75 ml/min). After the system had been thoroughly purged, a gas train consisting of a Drierite trap leading into an Ascarite trap was attached to the top of the condenser. By momentarily removing the gas-inlet fitting, a toluene solution (4.00 ml) of diisopropyl peroxydicarbonate (1.04 *M*) was quickly pipetted into the stirred flask, and a nitrogen sweep of 10 ml/min was then established using a soap-bubble flow meter temporarily attached to the outlet end of the Ascarite trap. After 24 hr, the flask assembly was removed from the bath and allowed to cool to ambient, and the solution was carefully decanted into a volumetric flask (100 ml). The 3–4 g of salted-out cerous nitrate which remained was rinsed with sufficient 1-ml portions of acetonitrile to bring the volume to the mark.

Separate aliquots were then taken and analyzed directly by gc for product yield and light boilers. In some cases an aliquot was worked up to remove salts and the organic phase was titrated iodometrically to verify the absence of residual peroxide. In still other cases the tolyl isopropyl products were isolated by a procedure given elsewhere,[32] and qualitatively identified by infrared analysis.[32] Although most reactions were stirred and slowly purged with nitrogen, no decrease in product yield was noted when these steps were omitted, but the side-product ratios appeared to be altered somewhat.

Radical trapping studies were made using the general procedure and adding a 9–15 molar excess (to peroxide) of freshly distilled acrylonitrile or solid acrylamide to the system. All reacted solutions were visually examined for insoluble polymer, and after diluting to 100 ml with acetonitrile the solutions were analyzed by gc for aryl esters and by-products.

A slight alteration of the general procedure was employed for relative rate studies. The appropriate amounts of toluene and benzene (10–20 molar excess) were stirred in the assembled flask with the CAN–acetonitrile. A solution of peroxide in acetonitrile was then added, and the reaction was carried out as usual.

The oxygenation reaction was tried in a few other solvents (ethanol, 4-methyl-2-pentanone, and acetone) with discouraging results attributed to the oxidation of these by CAN.[19] Some 3–4% oxygenation was found in ethanol as the solvent, only a trace with acetone, and none with 4-methyl-2-pentanone.

Product yields are the average of duplicate experiments in good agreement, and these yields are based on a stoichiometry of 1 mol of aryl ester products/mol of peroxide. This permits a direct comparison to those from diisopropyl peroxydicarbonate–cupric chloride.[2] Aryl ester and side-product yields were determined by gc.

Identification of Organic Products. Comparisons between the retention times for product components and authentic materials on two or more dissimilar gc columns and noting peak enhancements upon adding authentic compounds to reaction product mixtures comprised the basic approach for product identification. In this way benzaldehyde, benzyl alcohol, isomeric tolyl isopropyl carbonates, tolyl *sec*-butyl carbonates, tolyl benzoates, methyl biphenyls, and nitrobenzenes and bibenzyl were identified (gc columns 1 and 3). Using a similar approach, light-boiling products (acetone and isopropyl alcohol) were characterized (gc column 2).

Identification of Inorganic Products. The inorganic components were extracted from the reaction mixture with water as follows. The solution and precipitate were transferred with acetonitrile and water rinses to a separatory funnel (500 ml) containing toluene (25 ml). This solution was extracted with water (200 ml, 2 × 100 ml, 50 ml), and the combined aqueous phase was then washed once with toluene (10 ml) and made up to 500 ml. The combined toluene phase was diluted to 50 ml and saved for gc analysis. Using suitable aliquots from the aqueous extract (usually 50 ml), appropriate analytical tests were carried out to characterize the various inorganic components. Nitric acid was determined potentiometrically with standard alkali (0.100 *N* NaOH) by titrating duplicate 50-ml aliquots of the aqueous extract. The end points were estimated graphically from the titration curves.

Nonvolatile nitrate was determined spectrophotometrically by modifying a literature procedure.[9] From the 500-ml aqueous extract a 2-ml aliquot was transferred to a 50-ml beaker, and the contents were evaporated to dryness on the steam table. To the dried residue was added 1.0 ml of the phenoldisulfonic acid reagent, and after the salt was dissolved by gentle heating and stirring, the mixture was diluted to 250 ml with water and the absorption of this solution was measured at 407 nm in a 1-cm cell. The nitrate content of this solution was determined by reference to a similarly prepared nitrate calibration curve (0, 0.5, 1.0, and 1.5 μg N/ml).

The nitric acid nitrate and the nonvolatile nitrate were added to obtain the total nitrate in the inorganic reaction products.

Ammonium ion was determined on the vacuum-dried salt (2 hr, 80°) from a 50-ml aliquot of the aqueous extract by dissolving the salt in 0.5 *M* NaOH, distilling the liberated ammonia into standard sulfuric acid (0.050 *N*), and back titrating with standard base.

Cerium was determined on a 5-ml aliquot of the aqueous extract by measuring its ultraviolet absorption peak at 253.6 nm in 1 *N* sulfuric acid following a procedure given in the literature.[8]

Carbon Dioxide Analysis. This analysis was made by flushing the reaction gasses through preweighed Ascarite traps and noting the weight gain.[2] Because of the long reaction times (usually 24 hr) the nitrogen flow had to be restricted to 10–15 ml/min and the condenser temperature maintained below 5° to obtain satisfactory results. The material balance calculations for carbon dioxide yields by this method were 100–112%.

Kinetic Studies. All studies were made at 60° on solutions prepared, sometimes with modifications, as described in the general procedure. In studying the effects of various promoters on the peroxide decomposition rate, an initial toluene/peroxide ratio of 25 was provided in all cases. Aliquots (10 ml) were withdrawn by pipet at predetermined intervals and quickly delivered into separatory funnels (125 ml) containing ice-cold 1.0 *N* sulfuric acid (50 ml). Chilled toluene (10 ml) was added; the solution was gently mixed for 30 sec. After the phases were allowed to separate for 1 min, the aqueous lower phase was discarded and toluene layer was then washed with 10% sodium carbonate (25 ml, 2 × 15 ml) and water (2 × 15 ml). The toluene layer was then delivered with acetone rinses into a titrating flask containing potassium iodide (about 3 g) in acetone (50 ml), and titrated with standard 0.1 *N* sodium thiosulfate. In some cases 5-ml aliquots were withdrawn, in which case 0.05 *N* sodium thiosulfate titrant was used. Reactions without any interfering metal salts were also worked up in this manner before iodometry.

Gas Chromatography Procedures. Gc analyses were made on the following instruments: Hewlett-Packard Models 700 and 5750 B and Varian Models 1400 and 600 D, all equipped with flame ionization detectors and the following columns (all 0.125 in. o.d. stainless steel): column 1, 15 ft 10% Bentone 34–diisodecyl phthalate (50:50) on Diatoport S; column 2, 8 ft 20% Carbowax 400 on Chromosorb W; column 3, 10 ft 20% SE-30 on Chromosorb W; column 4, 12 ft 10% OV-225 on Chromosorb W; column 5, 6 ft Poropak Q.

Product yields for the diisopropyl peroxydicarbonate runs were

determined from duplicate analyses on columns 1 and 3 at 160° after adding an external standard, phenyl isopropyl carbonate, to a reaction aliquot. Isomer distributions were also studied on column 4 in addition to columns 1 and 3. Relative rates were analyzed on column 1 directly using a predetermined response factor. Light-boiling materials (acetone, isopropyl alcohol) were determined on columns 2 and 5 using methyl ethyl ketone in acetonitrile as an external standard.

Products from both benzoyl peroxide and di-*sec*-butyl peroxydicarbonate systems were determined on column 3 using phenyl benzoate and phenyl isopropyl carbonate, respectively, as external standards.

In all cases appropriate detector response factors were determined for the products relative to the marker by running a series of standards.

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Registry No.—Diisopropyl peroxydicarbonate, 105-64-6; toluene, 108-88-3; ceric ammonium nitrate, 16777-21-3; $K_2Ce(NO_3)_6$, 17126-44-2.

References and Notes

(1) Presented at the 28th Annual Southwest Regional Meeting of the American Chemical Society, Baton Rouge, La., Dec 1972. A preliminary account of this work has appeared: M. E. Kurz, E. M. Steele, and R. L. Vecchio, *J. Chem. Soc., Chem. Commun.*, 109 (1973); taken in part from the M.S. Thesis of E.M.S., Illinois State University, 1972.
(2) M. E. Kurz and P. Kovacic, *J. Amer. Chem. Soc.*, **89**, 4960 (1967).
(3) M. E. Kurz and P. Kovacic, *J. Org. Chem.*, 33, 266 (1968).
(4) P. Kovacic, C. G. Reid, and M. J. Brittain, *J. Org. Chem.*, **35**, 2152 (1970).
(5) T. Nakota, K. Tokumaru, and O. Simamura, *Bull. Chem. Soc. Jap.*, **43**, 3590 (1970).
(6) M. E. Kurz and S. S. Schultz, unpublished work.
(7) W. C. Pierce, E. L. Haenisch, and D. T. Sawyer, "Quantitative Analysis," Wiley, New York, N. Y., 1958, Chapter 8.
(8) H. L. Greenhaus, A. M. Feibush, and L. Gordon, *Anal. Chem.*, **29**, 1931 (1957).
(9) "Official Methods of Analysis of the AOAC," 10th ed, 1965, Section 31.005, p 522.
(10) "The Merck Index," 8th ed, P. G. Stecher, Ed., Merck & Co., Rahway, N. Y., 1968, p 224.
(11) W. S. Trahanovsky and J. Cramer, *J. Org. Chem.*, **36**, 1890 (1971).
(12) H. C. McBay and O. Tucker, *J. Org. Chem.*, **19**, 869 (1954); L. M. Terman, *Russ. Chem. Rev.*, **34**, 185 (1965).
(13) G. A. Olah and S. J. Kuhn, "Friedel-Crafts and Related Reactions," Vol. III, G. A. Olah, Ed., Wiley, New York, N. Y., 1964, p 1453; J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, "Nitration and Aromatic Reactivity," Cambridge University Press, New York, N. Y., 1971.
(14) M. E. Kurz, R. Fozdar, and S. S. Schultz, *J. Org. Chem.*, 39, 3336 (1974).
(15) S. G. Cohen and D. B. Sparrow, *J. Amer. Chem. Soc.*, **72**, 611 (1950).
(16) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience, New York, N. Y., 1962, Chapter 31.
(17) F. Ephraim, "Inorganic Chemistry," Chemical Publishing Co., New York, N. Y., 1954, Chapter 15.
(18) G. F. Smith, V. R. Sullivan, and G. Frank, *Ind. Eng. Chem., Anal. Ed.*, **8**, 449 (1936).
(19) W. H. Richardson, "Oxidation in Organic Chemistry," K. B. Wiberg, Ed., Academic Press, New York, N. Y., 1965, Chapter IV, Part A; G. F. Smith, "Cerate Oxidimetry," G. Frederick Smith Chemical Co., Columbus, Ohio, 1942.
(20) M. E. Kurz, P. Kovacic, A. K. Bose, and I. Kugajevsky, *J. Amer. Chem. Soc.*, **90**, 1818 (1968).
(21) P. M. Nave and W. S. Trahanovsky, *J. Amer. Chem. Soc.*, **90**, 4755 (1968); **93**, 4536 (1971).
(22) G. Mino, S. Karzerman, and E. Rasmussen, *J. Amer. Chem. Soc.*, **90**, 4755 (1968).
(23) O. Bamford, A. Jenkins, and R. Johnston, *Proc. Roy. Soc., Ser. A*, **239**, 214 (1957).
(24) J. K. Kochi in "Free Radicals," Vol. I, J. K. Kochi, Ed., Wiley, New York, N. Y., 1973, Chapter 11.
(25) W. S. Trahanovsky and M. D. Robbins, *J. Amer. Chem. Soc.*, **93**, 5256 (1971).
(26) H. E. DeLaMare, J. K. Kochi, and F. F. Rust, *J. Amer. Chem. Soc.*, **85**, 1437 (1963).
(27) W. S. Trahanovsky and L. B. Young, *J. Chem. Soc.*, 5777 (1965); W. S. Trahanovsky, L. B. Young, and G. L. Brown, *J. Org. Chem.*, **32**, 3865 (1967); W. S. Trahanovsky and J. Cramer, *ibid.*, **36**, 1890 (1971).
(28) W. S. Trahanovsky and L. B. Young, *J. Org. Chem.*, **31**, 2033 (1966); W. S. Trahanovsky, M. D. Robbins, and D. Smick, *J. Amer. Chem. Soc.*, **93**, 2086 (1971).
(29) We are grateful to the Pittsburg Plate Glass Co., Barberton, Ohio, and the B. F. Goodrich Co., Henry, Ill., For generous samples of these peroxides.
(30) F. Strain, W. E. Bisslnger, W. R. Dial, H. Rudoff, B. J. DeWitt, H. C. Stevens, and J. H. Langston, *J. Amer. Chem. Soc.*, **72**, 1254 (1950).
(31) D. S. Tarbell and E. J. Longosz, *J. Org. Chem.*, **24**, 774 (1959).
(32) M. E. Kurz, Ph.D. Dissertation, Case Institute of Technology, 1967.

Concurrent Oxygenation–Nitration of Aromatics with Peroxides–Nitric Acid[1]

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Treatment of toluene with peroxydicarbonates or benzoyl peroxide in the presence of nitric acid led to the concurrent production of aryl esters and nitrotoluenes in 10–20% yields. More selectivity was noted in the aryl ester product formation than was previously reported for the free carbonate radical from diisopropyl peroxydicarbonate. Most striking, though, was the nitrotoluene isomer distribution (ortho:meta:para: = 18:77:5) and relative rate (2.66), which contrasted markedly with that for the nitronium ion (ortho:meta:para = 60:5:35; $k_{toluene}/k_{benzene}$ = 20–30). Other aromatics (*e.g.*, chloro- and fluorobenzene) behaved similarly with nitric acid–peroxydicarbonates. Analogous reactions of toluene–nitric acid with a variety of other peroxides indicated that only those capable of forming oxy radicals at a reasonable rate gave rise to the unusual nitration pattern. Nitric acid was shown to inhibit the peroxydicarbonate decomposition rate by a factor of 2. N_2O_4 and N_2O_5 functioned effectively in promoting this concurrent nitration–oxygenation when used instead of nitric acid, indicating the importance of nitrogen dioxide in the reaction scheme. Reactions run with the stable free radical, galvinoxyl, as a trapping agent eliminated the nitration, further implicating nitrogen dioxide as the nitrating species. No evidence for the intermediacy of peroxyacyl nitrates or acyl nitrates was obtained even from peracids treated with various nitrating agents. A mechanism is proposed which involves attack by oxy radicals (or complexed oxy radical) onto the aromatic to form a cyclohexadienyl radical which is trapped by nitrogen dioxide. Under the reaction conditions the resulting dihydroaromatic can either lose HNO_2 to form an aryl ester, or lose RCO_2H to form a nitro aromatic. The result of a $\rho\sigma$ plot using composite partial rate factors tends to support the mechanism proposed.

Previously it had been reported that significant amounts of aryl esters could be produced when peroxydicarbonates and aroyl peroxides were decomposed in toluene in the presence of a variety of promoters.[2] Among the effective promoting species were the metal salts $CuCl_2$,[3] ceric ammonium nitrate,[4] $FeCl_3$,[5] and others,[5,6] molecular oxidants O_2[7] and I_2,[8] and even radicals such as trityl.[9] In most of these cases an oxy radical was felt to be the substituting entity,

Table I
Product Analysis for Toluene–Dialkyl Peroxydicarbonate–Nitric Acid[a,b]

Products	System: HNO_3–SBP	HNO_3–IPP	IPP[c]	HNO_3[d]
$CH_3C_6H_4OCO_2R$	19	17	1	
o-:*m*-:*p*-	59:7:34	65:6:29		
$CH_3C_6H_4NO_2$	17	17		3
o-:*m*-:*p*-	20:76:4	18:77:5		60:5:35
$C_6H_5CH_2NO_2$	13	12[e]		0
$C_6H_5CH_2OCO_2R$	0	0	2	0
$C_6H_5CH_2OH$	6	8	Trace	0
C_6H_5CHO	15	18	2	3
C_6H_5COOH	<1	2[f]	<1	
$(C_6H_5CH_2-)_2$	5	3[f]	36	0
CH_3COCH_3		50	58	
$CH_3CHOHCH_3$		105	130	
$CH_3C_6H_3(NO_2)_2$	<1	2[f]		<1

[a] Peroxide (5 mmol), nitric acid (10 mmol), and toluene (10 ml) in acetonitrile (50–75 ml), 60°, 24 hr. [b] Yields based on moles of peroxide limiting reagent; actual yield of nitration based on nitric acid is one-half the table value. [c] No nitric acid. [d] No peroxide, 72 hr. [e] The average of four widely varying runs. [f] Approximate yields.

and the oxidant served to rearomatize an initially formed cyclohexadienyl radical (eq 1).

$$RCO_2\cdot + ArH \rightleftharpoons Ar(O_2CR)(H) \xrightarrow{[O]} ArO_2CR \qquad (1)$$

Nitrogen dioxide was also utilized to promote this type of reaction in a somewhat different manner characterized by a concomitant production of nitrated aromatics.[10] In connection with our studies on aromatic substitution by oxy species we have had occasion to study peroxide–aromatic combinations in the presence of nitric acid and have observed a similar oxygenation–nitration phenomenon. In light of the fact that peroxyacetyl nitrate (PAN), the best known member of the new class of PAN's produced in photochemical smog,[11] can be made from the reaction of nitric acid and peracetic acid,[12] we became particularly interested in determining the nature of the peroxide–nitric acid–aromatic reaction, and assessing whether or not PAN-type intermediates were involved. We wish to report our findings here.

The standard procedure involved combining peroxide, nitric acid, and toluene in a 1:2:20 molar ratio in excess acetonitrile at 60° for 12–24 hr. The products of the reaction with both diisopropyl peroxydicarbonate (IPP) and di-*sec*-butyl peroxydicarbonate (SBP) are listed in Table I. Control runs containing toluene with IPP alone or with nitric acid alone are also included for comparison.

The formation of significant amounts (17–19%) of tolyl alkyl carbonates shows that the nitric acid apparently can serve as an oxidant in promoting aromatic substitution, especially when compared to the peroxide control. Even more interesting was the fact that a similar amount of nitrotoluenes, comprised predominantly of the meta isomer, was formed in each case, in addition to small amounts of dinitrotoluenes. In contrast, the nitric acid control gave only a small amount of nitrotoluenes with an isomeric pattern which was in agreement with the literature reported values for electrophilic nitration involving nitronium ion.[13,14] Among other major products from IPP–HNO_3–toluene were acetone and 2-propanol, formed by degradation of the peroxide, as described elsewhere.[3] Most of the minor products were produced from side-chain reactions of toluene (*i.e.*, benzaldehyde, benzyl alcohol, α-nitrotoluene, benzoic acid, and bibenzyl). Many of the benzyl radicals were diverted from the dimerization path characteristic of the control run, into side-chain oxidation products typical of toluene nitrations with radicals present.[15]

With IPP a reaction series of different nitric acid to peroxide ratios over the range 0.5–5.0 was run. Both ring oxygenation and nitration increased from 6 to 20%, but the isomeric composition in each case remained essentially the same as in Table I. Side-chain oxidation and nitration also increased somewhat when greater amounts of nitric acid were used.

Other peroxides were decomposed in the presence of nitric acid–toluene to see how general this concurrent production of aryl esters and nitroaromatics was (Table II). The only peroxide other than the peroxydicarbonates which gave significant amounts of both types of aromatic substitution was benzoyl peroxide. In this case tolyl benzoates were produced with an isomer distribution and yield very similar to those of the tolyl carbonate esters while the nitrotoluenes showed a much higher ratio of meta isomer than usual,[14,15] but not as high as with the peroxydicarbonates. This is most likely due to some direct nitration of toluene by nitric acid at this greater reaction temperature and time.

In light of earlier reports[11] potential involvement of PAN's seemed most probable from systems involving peracids (eq 2), and two such candidates (perbenzoic and *m*-chloroperbenzoic acid) were treated with nitric acid and

$$CH_3CO_3H + HNO_3 \longrightarrow CH_3CO_3NO_2 + H_2O \qquad (2)$$

toluene. One can visualize a process analogous to eq 2 leading to peroxybenzoyl nitrate (PBN) from perbenzoic acid. However, under the conditions studied (80° in acetonitrile) little indication of PBN involvement was noted as most of the peracid decomposed to benzoic acid.[16] Small amounts (~1%) of two oxygenation products (cresols and tolyl benzoates) were obtained, suggesting the intermediacy of both the hydroxyl and benzoyloxy radical, respectively (eq 3).

$$C_6H_5CO_3H \longrightarrow C_6H_5CO_2\cdot + HO\cdot \qquad (3)$$

The former was rapidly nitrated, showing up in the final product mixture as nitrocresols and dinitrocresols (in 1% and trace quantities, respectively). Less than 1% of nitrotoluenes (ortho:meta:para = 47:24:29) were formed in this reaction as well as small amounts of methyl biphenyls, benzyl nitrate, and α-nitrotoluene, further substantiating the presence of some radicals (eq 3).

The reaction of *m*-chloroperbenzoic acid–HNO_3–toluene led to small amounts of the same or analogous products except that the nitrotoluene isomers (ortho:meta:para = 58:8:34) more nearly resembled those expected from nitric acid alone.[14]

Two peresters (*tert*-butyl perbenzoate and *tert*-butylperoxy isopropyl carbonate) were studied in like fashion. No oxygenation products were formed with either perester, although nitration did occur. The yields and isomer distribution for all the peroxides studied with nitric acid–toluene are summarized in Table II. Also listed are the relative rates of nitration in each case as obtained by performing toluene–benzene competitions. These intramolecular and intermolecular selectivities are compared to those obtained from nitric acid without any peroxide and to previous literature values for nitrations. For peroxides such as the peroxydicarbonates that decompose quite rapidly at 60° (see the literature values for the peroxide half-lives, Table II) the same high proportion of meta isomer (76–80%) was obtained whereas those peroxides which were reasonably sta-

Table II
Nitration of Toluene with Nitric Acid in the Presence of Peroxides[a]

Registry no.	Peroxide	Temp, °C	Aryl esters, %[b]	Ring nitrotoluenes %yield[b]	o-	m-	p-	k_{tol}/k_{ben}[c]	Temp for 10 hr $t_{1/2}$[d]
105-94-6	$(i\text{-PrOCO}_2)_2$	60	17	17	18	77	5	2.66	34
		80		*e*	17	78	5	3.04	
19910-65-7	$(sec\text{-BuOCO}_2)_2$	60	19	17	20	76	4	*e*	36
		50		*e*	17	80	3	2.33	
94-36-0	$(C_6H_5CO_2)_2$	60	9[f]	10	33	54	13	2.07	72
		80	12[g]	*e*	38	47	15	*e*	
93-59-4	$C_6H_5CO_3H$	60	1[h]	1	47	24	29	*e*	76[i]
937-14-4	$m\text{-ClC}_6H_4CO_3H$	80	1[j]	*e*	58	8	34	*e*	
2372-21-6	$t\text{-BuOOCO}_2\text{Pr-}i$	80	0	3	57	7	36	14.1	97
614-45-9	$t\text{-BuOOCOC}_6H_5$	80	0	14	57	6	37	22.4	105
78-67-1	AIBN[k]	80		5	61	5	34	20.5	
	None	60		3	60	5	35	33.7	
		80		14	60	5	35	29.7	
		30–60[l]			57–61	3–5	37–40	21–27	

[a] Peroxide (5 mmol), HNO_3 (10 mmol), and toluene (10 ml) in acetonitrile (50–75 ml). [b] Based on peroxide limiting reagent; actual yield of nitration based on nitric acid is one-half the table value. [c] Aromatic mixture of benzene (10 ml) and toluene (10 ml) used; value corrected to a 1:1 molar ratio of the two. [d] See ref 17. [e] Not determined. [f] Ortho:meta:para = 73:5:22; methyl biphenyls (3%) also formed. [g] Ortho:meta:para = 69:7:24; methyl biphenyls (25%) also formed. [h] Includes nitrocresols and tolyl benzoates. [i] Approximated from data in ref 16 and 18. [j] Nitrocresols. [k] See ref 13 and 14. [l] Azobisisobutyronitrile.

ble at 60° or even 80° gave isomeric compositions much more compatible with the usual nitronium ion intermediates.[14] Benzoyl peroxide, which was somewhat intermediate in stability of the peroxides studied, gave almost 50% of the meta isomer. Azobisisobutyronitrile, a nonperoxidic radical-producing agent having a similar half-life to that of benzoyl peroxide, failed to appreciably alter the usual pattern of nitric acid–toluene reaction.

The peroxide, IPP, was singled out for further mechanistic studies. Kinetic analyses were performed on the nitric acid promoted IPP decomposition at 60° utilizing both nmr and iodometric techniques. The rates obtained by both methods, 6.09 and 6.53 × 10^{-3} min^{-1}, respectively, were in excellent agreement and indicated roughly a twofold rate hindrance in comparison to that (13.6 × 10^{-3} min^{-1}) for the peroxide decomposition in the absence of nitric acid. The rate of by-product formation (acetone and 2-propanol) was also able to be followed by nmr, and coincided well with that of the peroxide decomposition. Nmr had previously been used to detect PAN formation from peracetic acid through the observance of a new methyl group signal.[19] In our case no sign of any species other than those due to the decomposing peroxide and forming 2-propanol and acetone were spotted by nmr. Attempts to detect an intermediate by uv spectroscopy were also futile. CIDNP effects were not observed while the peroxide–nitric acid decomposition was repeatedly monitored by nmr, even though such effects have been noted for a variety of peroxide systems.[20]

Other nitrogen oxides were studied with both IPP and benzoyl peroxide to see if they could function effectively to promote concurrent nitration and oxygenation of toluene (Table III). N_2O_4 and N_2O_5 served well as oxygenation promoters, as aryl esters were obtained in as good or better yields as in the HNO_3–peroxide reaction. Nitration also occurred in good yield and the preponderance of meta isomer was again evident in the peroxydicarbonate cases. However, with benzoyl peroxide a much greater amount of nitrotoluenes of lower meta content was produced, indicating that direct nitration of toluene with NO_2 was probably competing strongly. In the previous work,[10] where a deficiency of NO_2 relative to peroxide was used, the unusual nitrotoluene composition clearly showed up.

Table III
Product Analyses for Peroxide–Toluene–Nitrogen Oxides System[a]

System	Nitrotoluenes Yield	o-	m-	p-	RCC_2Ar Yield[b]	o-	m-	p-
HNO_3–IPP	17	18	77	5	17	64	5	31
HNO_3	3	60	5	35				
N_2O_4–IPP	18	21	66	13	21	62	10	28
N_2O_4	12	67	5	28				
N_2O_5–IPP[c]	20	33	55	12	48	55	15	30
N_2O_5[c]	19	62	4	34				
HNO_3–$(C_6H_5CO_2)_2$[d]	8	38	47	15	12	72	4	24
N_2O_4–$(C_6H_5CO_2)_2$[d]	33	57	13	30	16	69	9	22
N_2O_4–$(C_6H_5CO_2)_2$[d,e]	5	13	85	2	14	50	16	34

[a] Peroxide (5 mmol), nitrogen oxide (10 mmol), and toluene (100 mmol) in CH_3CN (50 ml) at 60°; see Experimental Section. [b] Based on moles of peroxide limiting reagent; actual yield based on nitric acid is one-half the yield reported. [c] Reference 15. [d] 80°. [e] From ref 10; NO_2:peroxide = 0.53; benzene also present as part of a competition run.

Nitration with N_2O_4 and N_2O_5 alone also led to nitrotoluenes in 18–20% yields, but with isomer values which were in excellent agreement with the literature values[13,14] for nitrations involving nitronium ions.

The similarity in reaction characteristics of the peroxide with the various nitrogen oxides suggests that a common species, most likely nitrogen dioxide, is involved in each case.

To determine the extent of free-radical involvement in both the nitration and oxygenation processes, a stable free radical, galvinoxyl,[21] was employed as a radical trapping agent in the IPP–HNO_3–toluene system (Table IV). As more scavenger was added the nitration could be diminished and wiped out, but the oxygenation persisted. It should be pointed out that even when a 1:1 ratio of galvinoxyl to peroxide was utilized, only enough scavenger was available to trap half of the potential oxy radicals; hence oxygenation could still occur. Indeed, when galvinoxyl was

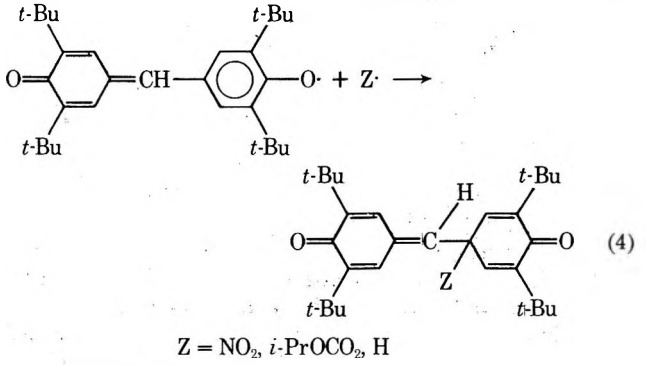
Table IV
Oxygenation–Nitration in the Presence of Galvinoxyl[a]

System	$CH_3C_6H_4NO_2$ Yield	$CH_3C_6H_4NO_2$ o:m:p	$CH_3C_6H_4OCO_2Pr\text{-}i$ Yield	$CH_3C_6H_4OCO_2Pr\text{-}i$ o:m:p
HNO_3–IPP (2:1)	17	18:77:5	17	64:5:31
HNO_3–IPP–galvinoxyl (2:1:0.3)	8[b]	20:77:5	13	60:11:29
HNO_3–IPP–galvinoxyl (2:1:1)	1		12	51:13:36
IPP–galvinoxyl (1:1)[c]			15	56:15:29

[a] Peroxide:HNO_3:toluene = 1:2:20 in excess CH_3CN at 60°; see Experimental Section. [b] Single run only. [c] No nitric acid.

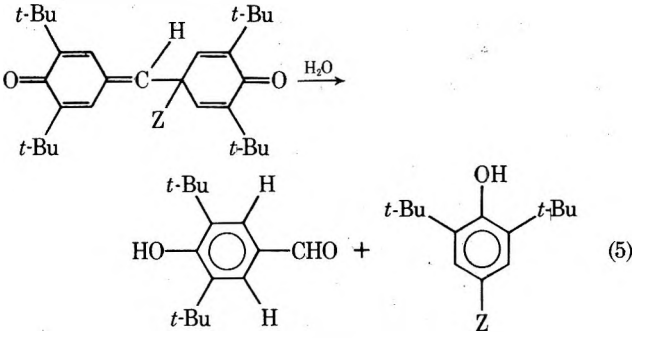
used with the peroxide alone, tolyl esters with an isomer distribution typical of carbonate radical oxygenation[3,24] resulted, which suggests the involvement of galvinoxyl itself as an oxygenation promoter.

Product analyses carried out on the toluene–IPP–HNO_3 reaction with galvinoxyl were quite revealing. Large amounts of 2,6-di-*tert*-butyl-4 nitrophenol and 2,6-dinitrohydroquinone, formed from breakdown of the scavenged products of galvinoxyl with nitrogen dioxide and the isopropyl carbonate radical, respectively (eq 4 and 5), provide



(4)

Z = NO_2, *i*-$PrOCO_2$, H



(5)

good evidence for the involvement of both radicals in the reaction. Furthermore, all of the galvinoxyl is apparently consumed, as evidenced by the disappearance of a product felt to be due to galvinoxyl breakdown on the chromatograph (see paragraph at end of paper regarding supplementary material).

IPP–Nitric Acid–Other Aromatics. The study of the peroxydicarbonate–nitric acid system was extended to other aromatics. In all cases aryl ester formation was accompanied by nitration products (Table V). The nitration pattern observed with the halobenzenes was found to be predominantly meta, in contrast to the usual ortho/para nitration with NO_2^+ (Table V), just as it was with toluene. Relative rate values closer to unity than is typical of nitrations involving NO_2^+ were also obtained for chlorobenzene and fluorobenzene as well as for toluene. Although anisole underwent both substitution reactions the nitration pattern was more typical of straightforward electrophilic nitration,[22] a process which likely competed strongly with this more reactive aromatic under the reaction conditions.

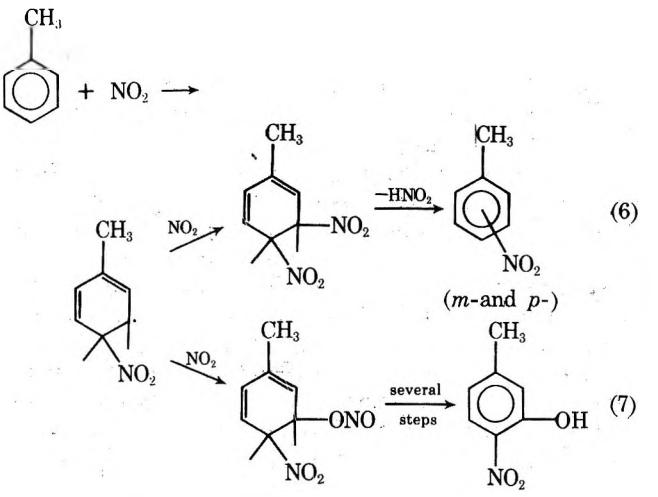
The isomer distributions and relative rates for the oxygenation products differed from those values noted earlier for the isopropyl carbonate radical,[3] except in the case of anisole. (See paragraph at end of paper regarding supplementary material.)

Discussion

Nitric acid effectively promotes aromatic oxygenation with certain peroxides, and in the process nitrates aromatics in an unusual manner. Although a number of mechanistic pathways can be considered for the two aromatic substitutions, most can be discounted.

For example, independent electrophilic substitutions with nitronium ion can be ruled out on the basis of the much different nitration pattern, while the presence of cationic oxygen such as noted previously with peroxydicarbonate–$AlCl_3$[27] seems unlikely, as nitric acid retards peroxide decomposition rather than promoting heterolysis.

Independent radical substitution processes also do not adequately explain the results. Titov[28] has discussed radical nitrations involving substitution by NO_2 and subsequent trapping of the cyclohexadienyl radical as in eq 6 and 7.[29] However, it is unlikely that such a scheme pertains



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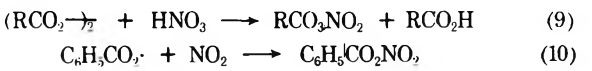
in our case, since we found no evidence for nitrocresols (eq 7) except in the peracid cases and there is no consistent rationale to account for the large preponderance of the meta-nitrated aromatic.

Oxy radical attack followed by subsequent oxidation to the aromatic (eq 1) is not a fully satisfactory mechanism for the oxygenation process either, since one would have anticipated obtaining the same pattern of substitution as noted for $CuCl_2$-,[3] I_2-,[8] and O_2[7]-promoted oxygenations. A complexed oxy radical (eq 8) is a possibility as the oxygenating species and would account for the greater selectivity observed.[5]

(8)

A number of mechanisms involving a common nitrating–oxygenating species can be envisioned.

For example, peroxyacyl nitrates (eq 9) or acyl nitrates (eq 10) could be formed under the reaction conditions but



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(10)

being unstable could conceivably break down in such a manner as to nitrate and oxygenate toluene in the process. There is no prior literature analogy for this type of behav-

Table V
Nitration and Oxygenation of Aromatics with Nitric Acid–Diisopropyl Peroxydicarbonate

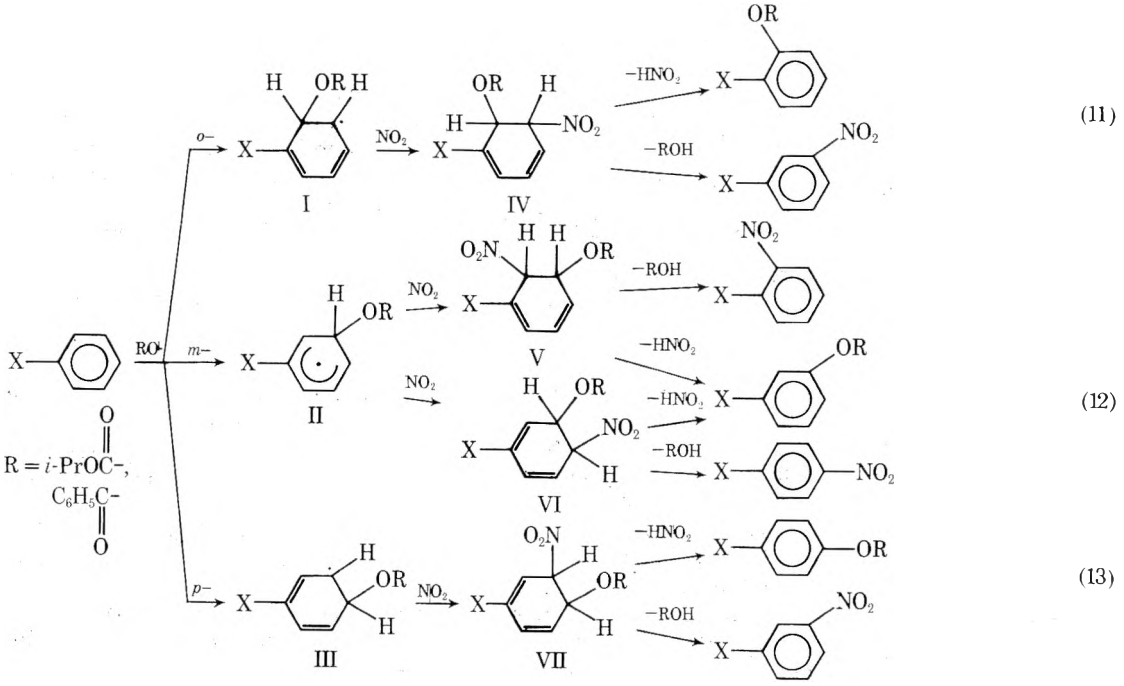
Aromatic	System	$ArNO_2$ Yield[a]	$ArNO_2$ o-:m-:p-	$ArNO_2$ $k_{ArH}/k_{C_6H_6}$	$ArOCO_2Pr$- Yield[a]	$ArOCO_2Pr$- o-:m-:p-	$ArOCO_2Pr$- $k_{ArH}/k_{C_6H_6}$
$C_6H_5CH_3$	HNO_3–IPP[b]	17	18:77:5	2.66	17	64:5:31	12.4
	HNO_3[c]	3	60:5:35	33.7			
	$CuCl_2$–IPP[d]				85	57:15:28	3.77
C_6H_5Cl	HNO_3–IPP[b]	17	10:87:3	0.65	5	64:tr:36	0.85
	HNO_3–H_2SO_4[e]		31:tr:69				
	$CuCl_2$–IPP[f]				29	54:13:33	0.46
C_6H_5F	HNO_3–IPP[b]	16	28:58:16	0.32	7	41:36:23	0.65
	HNO_3–H_2SO_4[e]		20:0:80[g]				
	$CuCl_2$–IPP[f]				30	33:22:45	0.31
$C_6H_5OCH_3$	HNO_3–IPP[b]	31	39:0:61	57.4	16	59:tr:41	19.1
	HNO_3–H_2SO_4[h]		31:2:67				
	$CuCl_2$–IPP[d]				98	63:1:36	24.9

[a] Yield based on mol of products/mol of peroxide. [b] Peroxide (5 mmol), HNO_3 (10 mmol), and aromatic (10 ml) in acetonitrile (50 ml), 60°, 24 hr. [c] Acetonitrile solvent; for other values see ref 14 and 23. [d] See ref 24. [e] HNO_3 (0.05 mol), H_2SO_4 (0.05 mol), and aromatic (20 ml), 60°, 24 hr. [f] See ref 25. [g] Lit. value[26] 12:0:88. [h] See ref 22.

ior for peroxyacyl nitrates, but such a species might be expected to exhibit both peroxide and nitrate reactivity. Previously Fischer and coworkers[30] had demonstrated that protonated acetyl nitrate from acetic anhydride–nitric acid is the common intermediate responsible for both nitrating and acetoxylating aromatics such as toluene and o-xylene. Similar studies[15] of benzoyl nitrate interaction with toluene in the presence of acids did produce some tolyl benzoates, but gave the usual (ortho:meta:para = 60:5:35) nitrotoluene product pattern. However, we obtained no evidence for either type of intermediate, and neither species could suitably explain the predominance of *m*-nitrotoluenes in our system.

The mechanism which appears to be consistent with our experimental observations is analogous to that reported for benzoyl peroxide with nitrogen dioxide[10] and is shown in Scheme I, eq 11–13. It involves the usual reversible attack by the acyloxy radical (or possibly an acid-complexed acyloxy radical) onto the aromatic, giving the three possible cyclohexadienyl radical intermediates (I–III). These in turn are trapped efficiently by small amounts of nitrogen dioxide to produce various dihydroaromatics (IV–VII), which under the reaction conditions tend to rapidly rearomatize losing either nitrous acid or an alkyl hydrogen carbonate (alcohol + carbon dioxide). With toluene at least, the dihydroaromatic tended to partition itself to the aryl ester and nitrotoluene in roughly equal proportions. With the halobenzene, the corresponding intermediates (IV–VII) preferentially formed nitrohalobenzenes (eq 11–13, Table V). Since the oxy radical attacks toluene and the halobenzenes predominantly at ortho and para positions,[3,25] nitroaromatics formed in this manner would be predominantly the meta isomers (eq 11, 13). Only anisole of the aromatics failed to give meta nitration. Perhaps the greater reactivity

Scheme I
Concurrent Oxygenation–Nitration



of anisole toward nitric acid[14] caused the usual electrophilic nitration to occur in that case.

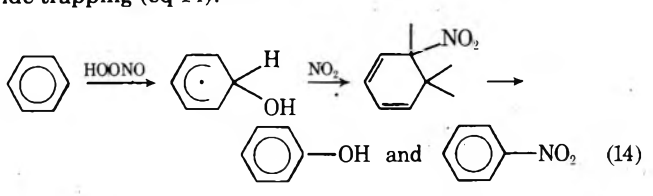
The scheme presented also accounts qualitatively for the unusual "apparent" relative reactivities of toluene and benzene toward both nitration and oxygenation. Since both types of substitution products resulted from initial attack by the oxy radicals onto the aromatic, one can calculate a composite partial rate factor for this process by taking into account the proposed scheme (Scheme I), the apparent partial rate factors for nitration and oxygenation and the molar yields of oxygenation relative to nitration (Table V). Plotting the resulting composite partial rate factors (describing initial oxy radical attack) *vs* the appropriate σ^+ values gave a surprisingly fair correlation with a slope of -1.87 (ρ value) and an average deviation of ± 0.05 (see paragraph at end of paper regarding supplementary material).[31] This value compares quite closely to that obtained (-2.1) by doing a least-squares plot for the same points from isopropyl carbonate radical,[25] providing further evidence for this concurrent nitration–oxygenation scheme.

The fact that N_2O_4 and N_2O_5 also serve efficiently to promote oxygenation is consistent with the mechanism proposed, since both are reasonable sources of nitrogen dioxide.[32] The similarity of these systems to that with nitric acid seems to indicate that NO_2 is the species responsible in nitric acid for promoting aromatic substitution.

The results of the galvinoxyl trapping experiments are also in line with the proposed scheme. Galvinoxyl is known as an efficient scavenger of both carbon and oxygen free radicals, particularly the shorter lived ones such as *tert*-butoxy radical.[21] Despite the fact that potential carbonate radicals exceeded the amount of galvinoxyl used (Table IV), galvinoxyl reacted in ways other than just trapping the longer lived carbonate radicals in this system. It scavenged nitrogen dioxide, present in relatively small amounts in the peroxide–HNO_3 media to wipe out the nitroaromatic production (Table IV) and account for the 2,6-di-*tert*-butyl-4-nitrophenol found. Galvinoxyl also reacted with cyclohexadienyl radicals formed from oxy radical attack on the aromatic to promote aromatic oxygenation by either hydrogen atom abstraction[33] or electron transfer.[34] The small amount of 2,6-di-*tert*-butylphenol (eq 4 and 5) is consistent with hydrogen atom abstraction by galvinoxyl.

The reason for the rate-retarding effect of nitric acid on the peroxydicarbonate is uncertain. It could indicate acid complexing of the peroxide, since the breakdown of complexed peroxides is known to be slowed down.[5,6] A complexed radical formed therefrom could also account for the more selective nature of the oxygenation and essentially the same scheme (Scheme I) for nitration–oxygenation would hold.

There is prior analogy for the mechanism proposed which amounts to a radical addition-elimination mechanism. The reaction of pernitrous acid with aromatics giving nitration and hydroxylation in very low yields was felt to involve hydroxyl radical attack followed by nitrogen dioxide trapping (eq 14).[29,35]



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Analogous addition–elimination mechanisms have been proposed for electrophilic aromatic substitutions, including aminations with trichloroamine–aluminum chloride,[36] concurrent nitration–acetoxylation by protonated acetyl nitrate,[30] and others.[37]

Experimental Section[38]

Reagent-grade solvents and chemicals were used directly, including deuterioacetonitrile (Merck Sharp and Dohme, 99%), which was checked for purity by nmr. The commercial peroxides,[39] checked out to be greater than 95% pure except for 85% *m*-chloroperoxybenzoic acid, were used without purification except for benzoyl peroxide, which was recrystallized from methanol–hexane. Peroxybenzoic acid was synthesized from benzoyl peroxide and hydrogen peroxide by a literature method;[40] the peracid was extracted into toluene, and the toluene stock solution was titrated and used directly in the appropriate reactions.

Tolyl alkyl carbonate authentics (not commercially available) were synthesized from the appropriate phenols and alkyl chloroformates as previously described.[4]

Nitrocresol product mixtures for comparative purposes were made by treating *o*- and *p*-cresol, respectively, with HNO_3 in acetonitrile at 60°. In the former case two major nitration products were found by gc–mass spectrum (*m/e* 153, base peak) and were assumed to be 4-nitro-2-methylphenol and 6-nitro-2-methylphenol. With *p*-cresol just one major nitration product (*m/e* 153), presumably 2-nitro-4-methylphenol, was produced.

Reactions of Aromatics with Nitric Acid–Peroxide. General Procedure. The peroxide (5 mmol) in the appropriate aromatic (10 ml) was mixed with acetonitrile (50 ml) containing the appropriate amount of nitric acid in a lightly stoppered flask, and immersed quickly in a constant-temperature bath for a 24-hr period or longer. At the end of this time, qualitative and quantitative product analysis was carried out on the reaction mixtures. For the competition studies, a mixture of benzene and the appropriate aromatic, both present in at least an 18-fold molar excess, was used with the peroxide and nitric acid. The aromatic:benzene product ratios (both nitration and oxygenation) corrected to equimolar reactant concentrations were used directly as a measure of the relative rates.

Other reactions were carried out with modifications of the general procedure. In the galvinoxyl run additional toluene was required to solubilize the radical trapping agent. Reactions with NO_2 were carried out in special reaction flask containing peroxide–toluene and solvent which was evacuated at liquid nitrogen temperatures. N_2O_4 was weighed out in a separate gas density bulb and then distilled into the reaction vessel. After the appropriate quantity of NO_2 was added, the vessel was sealed, placed in a constant-temperature bath for 24–48 hr at 60°, and then analyzed.

In all cases reactions were carried out in duplicate (unless otherwise indicated) and the yields reported are the average of two or more runs in close agreement.

Kinetic Studies. A. By Iodometry. A method described elsewhere[4] was used. In the runs containing nitric acid, the end point became harder to detect as the decomposition approached midway, owing to the continued development of colored nitrotoluenes. In these cases, titration was carried out to the color of blanks containing the calculated amount of nitrotoluenes.

B. By Nmr. Prior to carrying out a kinetic study by nmr (Perkin-Elmer Hitachi Model R-20), we demonstrated that the signals from the expected products and starting peroxide did not interfere with each other. A control run with HNO_3 in CD_3CN indicated that the nitrile underwent proton exchange but did not interfere with the signals to be followed.

The kinetic run itself was performed on the reaction of diisopropyl peroxydicarbonate with HNO_3 in the absence of aromatic in deuterated acetonitrile. One milliliter of a peroxide solution in CD_3CN (4.5 *M*) was mixed with HNO_3 in an nmr tube to give a peroxide:HNO_3 molar ratio of 1:2. The tube was set into the nmr probe which was thermostatted at a constant temperature of 60 ± 0.5°. The intensities of the following major signals were monitored: isopropyl group doublet from the reactant peroxide (δ 1.28), isopropyl group doublet from 2-propanol (product) (δ 1.04), and methyl group singlet from acetone (product). The changes in integration heights of the signals were followed *vs.* time to obtain changes in concentration of both reactant and products. To take care of any possible error due to instrumental instability, the field homogeneity was checked throughout the experiment. The study was repeated with *p*-dichlorobenzene added as an inert material to the reaction mixture for use as an internal intensity standard. The intensities of the signals could then be adjusted when any fluctuation of the *p*-dichlorobenzene marker occurred. Little correction had to be made and reasonable agreement was noted for the data from the two runs.

Nitration of Halobenzenes. HNO_3 (3.2 ml, 0.05 mol) and

H_2SO_4 (2.65 ml, 0.05 mol) were mixed, cooled, and added to the halobenzenes (fluoro- and chlorobenzene). The mixtures were vigorously shaken at intervals over a 24-hr period at 60°. The products (two) from fluorobenzene was collected by preparatory gc (column A) and analyzed by ir and mass spectrum. The smaller product, ortho, gave an out-of-plane C–H bending signal at 755 cm^{-1}, while the larger para product had the corresponding signal at 840 cm^{-1}. Both had a mass spectrum with *m/e* 141 (molecular ion) and 95 (base peak). The nitrochlorobenzene products were compared to authentics and also analyzed by mass spectrum (*m/e* 157).

Analytical Procedures. A. Product Identification. The product mixture from the reaction of 50 mmol of diisopropyl peroxydicarbonate and 100 mmol of nitric acid with toluene in acetonitrile was concentrated on a rotary evaporator, and the concentrate was separated into a number of components by preparative gc (Varian Model 90-P, thermal conductivity detector, column A, 6 ft × 0.25 in. 3% SE-30 on Chromosorb W). The major product gave an ir consistent with *m*-nitrotoluene contaminated with a small amount of ortho and para isomers. The second largest product was shown by ir to be *o*-tolyl isopropyl carbonate. From other analogous reaction mixtures gc–mass spectral analysis was performed using a Finnegan Model 3000 G.C. peak identifier with a quadrupole mass filter. Mass spectra at 70 eV of the reaction products eluted from three different columns (B, 6 ft × 0.125 in. stainless steel, 3% OV-1 on Chromosorb W: C, 10 ft × 0.125 in. copper, 10% OV-225 on Chromosorb W, AW-DMCS; D, 10 ft × 0.125 in. copper, 20% SE-30 on Chromosorb W, AW-DMCS) indicated the presence of benzaldehyde (*m/e* 106), benzyl alcohol (*m/e* 108), benzoic acid (*m/e* 122), nitrotoluenes (*m/e* 137), tolyl isopropyl carbonates (*m/e* 194, fragments at *m/e* 135, 108, and 43), bibenzyl (*m/e* 182), and traces of dinitrotoluenes (*m/e* 182). Other minor high boilers were detected, but were not identified. Column D programmed at 160–240° was utilized in like manner to separate and identify the nitroanisoles (*m/e* 153) and anisyl isopropyl carbonates from anisole, chloronitrobenzenes (*m/e* 157) and chlorophenyl isopropyl carbonates from chlorobenzene, and fluorophenyl isopropyl carbonates (*m/e* 198) and fluoronitrobenzene (*m/e* 141) from fluorobenzene.

Column D was used with the gc–mass spectrum to identify the benzoyl peroxide reaction products, benzoic acid (*m/e* 122), nitrotoluenes (*m/e* 137), methyl biphenyls (*m/e* 168), phenyl benzoate (*m/e* 198), and tolyl benzoates (*m/e* 212), while both columns C and D were used to identify benzyl nitrate (*m/e* 153), nitrotoluenes (*m/e* 137), benzoic acid (*m/e* 122), nitrocresols (*m/e* 153), methyl biphenyls (*m/e* 168), and tolyl benzoates (*m/e* 212) from the perbenzoic acid runs. Column B was used to pin down the galvinoxyl reaction products. In addition all nitration and oxygenation products were matched with authentic materials by gc retention times on at least two different columns (C and D). Nitrocresol and nitrofluorobenzene isomers were identified by comparison to the product mixtures from the nitrations of *o*- and *p*-cresol and fluorobenzene.

B. Quantitative Analysis. Reaction product yields were determined by adding a known quantity of a marker (usually phenyl isopropyl carbonate) to a one-tenth portion of the reaction mixture and analyzing by gc (Varian Models 1400 and 600D with flame ionization detectors; columns B and C). The appropriate correction factors for detector response were determined from standard mixtures and applied to convert product to marker area ratios to mole ratios.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

Registry No.—Toluene, 108-88-3; nitric acid, 7697-37-2.

Supplementary Material Available. Qualitative and quantitative galvinoxyl product analyses (by gc–mass spectrum), partial rate factors for nitration and oxygenation, and a Hammett $\rho\sigma$ treatment for concurrent nitration–oxygenation will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3336.

References and Notes

(1) Presented at the 166th National Meeting of the American Chemical Society, Chicago, Ill., Aug 1973; abstracted in part from the M.S. Thesis of R.F., Illinois State University, 1973.
(2) For recent summaries see G. Sosnovsky and D. J. Rawlinson in "Organic Peroxides," Vol. 1, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1970, Chapter 9; D. J. Rawlinson and G. Sosnovsky, *Synthesis*, 1 (1972).
(3) M. E. Kurz and P. Kovacic, *J. Amer. Chem. Soc.*, **89**, 4960 (1967); *J. Org. Chem.*, **33**, 1950 (1968).
(4) M. E. Kurz, E. M. Steele, and R. Vecchio, *J. Org. Chem.*, **39**, 3331 (1974); *J. Chem. Soc., Chem. Commun.*, 109 (1973).
(5) M. E. Kurz and P. Kovacic, *J. Org. Chem.*, **33**, 266 (1968).
(6) M. E. Kurz and S. S. Schultz, unpublished work.
(7) T. Nakota, K. Tokumaru, and O. Simamura, *Bull. Chem. Soc. Jap.*, **43**, 3590 (1970); G. E. Gream, J. C. Paice, and C. C. R. Ramsey, *Aust. J. Chem.*, **22**, 1229 (1969).
(8) P. Kovacic, C. G. Reid, and M. J. Brittain, *J. Org. Chem.*, **35**, 2152 (1970); S. Hashimoto, W. Koike, and M. Yammamoto, *Bull Chem. Soc. Jap.*, **42**, 2733 (1969).
(9) T. Suehiro, S. Igeta, O. Kowabara, and N. Hirai, *Tetrahedron*, **26**, 963 (1970).
(10) T. Suehiro, M. Hirai, and T. Kaneko, *Bull Chem. Soc. Jap.*, **44**, 1402 (1971).
(11) E. R. Stephens, *Advan. Environ. Sci.*, **1**, 119 (1969); E. R. Stephens, P. L. Hanst, R. C. Doerr, and W. E. Scott, *Ind. Eng. Chem.*, **48**, 1496 (1956).
(12) W. E. Scott, E. R. Stephens, P. L. Hanst, and R. C. Doerr, *Proc. Amer. Petrol. Inst., Sect. III*, **37**, 171 (1957).
(13) C. K. Ingold, A. Lapworth, E. Rothstein, and D. Ward, *J. Chem. Soc.*, 1959 (1931); H. Cohn, E. D. Hughes, M. H. Jones, and M. G. Peeling, *Nature (London)*, **169**, 291 (1952).
(14) J. G. Hoggett, R. B. Moodie, J. R. Penton, and K. Schofield, "Nitration and Aromatic Reactivity," Cambridge University Press, New York, N. Y., 1971.
(15) M. E. Kurz, L. T. A. Yang, E. P. Zahora, and R. C. Adams, *J. Org. Chem.*, **38**, 2271 (1973).
(16) D. Swern in "Organic Peroxides," Vol. 1, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1970, Chapter 6.
(17) F. Strain, "Isopropyl Percarbonate," PPG Industries Inc., Chemical Division, Pittsburgh, Pa., 1969, p 8.
(18) K. Tokumaru, O. Simamura, and M. Fukuyama, *Bull. Chem. Soc. Jap.*, **35**, 1673, 1678 (1962); **36**, 72, 333 (1963).
(19) S. W. Nicksick, J. Harkinsand, and P. K. Mueller, *Atmos. Environ.*, **1**, 11 (1967).
(20) H. R. Ward in "Free Radicals," Vol. 1, J. K. Kochi, Ed., Wiley-Interscience, New York, N. Y., 1973, Chapter 6.
(21) P. D. Bartlett and T. Funahashi, *J. Amer. Chem. Soc.*, **84**, 2596 (1962).
(22) P. H. Griffiths, W. A. Walkey, and H. B. Watson, *J. Chem. Soc.*, 631 (1934); W. W. Jones and H. Russell, *ibid.*, 921 (1947).
(23) S. Sekiguchi, A. Hirose, S. Kato, and K. Matsui, *Bull. Chem. Soc. Jap.*, **46**, 646 (1973).
(24) M. E. Kurz, P. Kovacic, A. K. Bose, and I. Kugajevsky, *J. Amer. Chem. Soc.*, **90**, 1818 (1968).
(25) P. Kovacic, C. G. Reid, and M. E. Kurz, *J. Org. Chem.*, **34**, 3302 (1969).
(26) G. A Olah and S. J. Kuhn, "Friedel-Crafts and Related Reactions," Vol. 3, G. A. Olah, Ed., Wiley-Interscience, New York, N. Y., 1964, Part 2, Chapter 18.
(27) P. Kovacic and S. T. Morneweck, *J. Amer. Chem. Soc.*, **87**, 1566 (1965); P. Kovacic and M. E. Kurz, *ibid.*, **87**, 4811 (1965).
(28) A. I. Titov, *Tetrahedron*, **19**, 577 (1963).
(29) G. B. Gill and G. H. Williams, *J. Chem. Soc.*, 5756 (1965).
(30) A. J. Fischer, J. Packer, J. Vaughan, and G. J. Wright, *J. Chem. Soc.*, 3687, 3691 (1964).
(31) For a critical examination of use of the Hammett equation for correlating radical reactions, see W. A. Pryor, T. H. Lin, J. P. Stanley, and R. W. Henderson, *J. Amer. Chem. Soc.*, **95**, 6993 (1973).
(32) Y. Rees and G. H. Williams, *Advan. Free-Radical Chem.*, **3**, Chapter 4 (1969).
(33) A. R. Forrester, J. M. Hay, and R. H. Tomson, "Organic Chemistry of Stable Free Radicals," Academic Press, New York, N. Y., 1968, Chapter 7.
(34) E. Muller and K. Ley, *Chem. Ber.*, **87**, 922 (1954).
(35) E. Halfpenny and P. L. Robinson, *J. Chem. Soc.*, 928 (1952).
(36) P. Kovacic, C. T. Goralski, J. J. Hiller, Jr., J. A. Levisky, and R. M. Lange, *J. Amer. Chem. Soc.*, **87**, 1261 (1965); P. Kovacic and J. A. Levisky, *ibid.*, **88**, 1000 (1966); P. Kovacic, M. K. Lowery, and K. W. Field, *Chem. Rev.*, **70**, 639 (1970).
(37) P. C. Myhre, G. S. Owen, and L. J. James, *J. Amer. Chem. Soc.*, **90**, 2115 (1968).
(38) We are grateful to E. M. Steele, R. Vecchio, A. Sparling, and T. Brady for experimental contributions to this study.
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(40) Y. Yogata and Y. Sawaki, *Tetrahedron*, **23**, 3327 (1967).

A Convenient One-Step Conversion of Aromatic Nitro Compounds to Phenols

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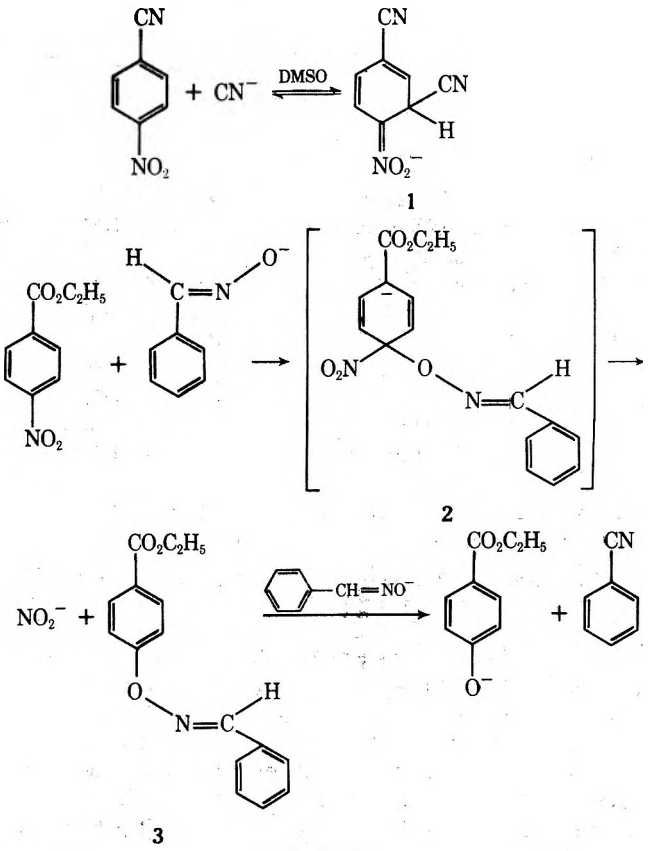
A moderately activated nitro group in a substituted nitrobenzene is displaced by reaction with the anion of an aldoxime in DMSO solution. In the DMSO solution the displacement product, an *O*-arylaldoxime, is rapidly cleaved by a base, yielding the phenol and the nitrile related to the oxime anion. The oxime anion used for the displacement is sufficiently basic to effect the cleavage. Thus, *p*-nitrobenzonitrile is converted to *p*-cyanophenol in excellent yield by reaction with 2 equiv of the salt of benzaldoxime. Similarly, ethyl *p*-nitrobenzoate is converted to ethyl *p*-hydroxybenzoate with little loss resulting from attack at the ester group and subsequent conversion to the nitrobenzoic acid. Displacement of an activated halogen atom followed by *in situ* cleavage of the oxime ether also leads to the phenol. The use of several activating groups in the reactions is reported. Even with the unactivated nitro compound 4-nitrobiphenyl some (~20%) of the phenol has been obtained.

In dipolar aprotic solvents various aromatic nitro compounds undergo the addition of cyanide ion to give adducts, *e.g.*, **1**, similar to Jackson–Meisenheimer complexes, which can be converted to various further transformation products,[1-3] and the anion of 2-nitropropane gives a similar adduct with 9-nitroanthracene.[4] The structural resemblance of the anion of an oxime to that of an aliphatic nitro compound suggests that oximates too might give adducts similar to those observed with cyanide ion. When *p*-nitrobenzonitrile and the sodium salt of benzaldoxime (2 equiv) were brought together in DMSO at ambient temperature the solution rapidly developed an intense purple color, which faded with time, reminiscent of the color changes occurring in reactions of cyanide ion and attributed to the Jackson–Meisenheimer complexes,[4] but when the test was terminated after 48 hr the solution was found to contain an almost quantitative yield of the entirely unexpected product *p*-cyanophenol. Evidently the oximate anion had attacked the aromatic system at the carbon atom bearing the nitro group, displacing it as nitrite ion, rather than adding in the Jackson–Meisenheimer fashion.

The nucleophilic displacement of activated aromatic nitro groups has been studied over many years,[5] but only recently has it found promising application[6] in synthesis. Displacement of a nitro group from a benzene ring carrying only one activating group has been quite rare, and in most such instances the activation has been supplied by a second nitro group. However, very recent studies have shown that a nitro group activated by a single carbalkoxyl, cyano, or carbonyl group, among others, is displaced by a methoxide or a mercaptide anion, sometimes in excellent yield,[6,7] when the reaction is carried out in an aprotic solvent. Cyclization of the diester obtained by the displacement of the nitro group of an ester of 2-nitrobenzoic acid by the anion of methyl mercaptoacetate constitutes a step in a very useful synthesis of methyl 3-hydroxybenzo[*b*]thiophene-2-carboxylates.[6] In the cyanide reactions conducted in this laboratory displacement of an activated nitro group by cyano has been observed only with 9-nitro-10-cyanoanthracene (58% conversion to 9,10-dicyanoanthracene),[1] and none of the displacement product from *p*-nitrobenzonitrile[3] was observed. The nearly complete displacement observed with the anion of benzaldoxime and this nitronitrile suggests that oximate anions may be among the most active displacement agents. Separation of the pure *p*-cyanophenol from the benzaldoxime present at the end of the reaction mentioned above required time-consuming chromatography which could be avoided by the use of the sodium salt of acetaldoxime (2.5 equiv, 45-min reaction time at 30°, 69% yield of pure *p*-cyanophenol isolated by crystallization). The rapid displacement of the nitro group under such very mild conditions suggested the possible successful application of the process to compounds, such as *o*- and *p*-nitrobenzoic esters, in which the activating group is sensitive to attack by base. In a trial with ethyl *p*-nitrobenzoate and the salt of acetaldoxime, reacting for only 20 min at 30°, the yield of ethyl *p*-hydroxybenzoate was 55%, and that of *p*-nitrobenzoic acid was 36% (Table I). Reducing the temperature to 25° increased the yield of the hydroxy ester to 64%, and only 18% nitro acid was obtained. Substantially lower temperatures can be realized with DMF as the solvent (DMSO melts at 18°), but a trial in DMF at 10° gave only 38% hydroxy ester and 45% nitro acid; this solvent evidently favors attack at the ester group rather than at the nucleus. When enough acetonitrile was added to a DMSO solution to permit operation in the liquid state at −3°, the yield of hydroxy ester was also low (31%).



The salt of benzaldoxime reacted more slowly with the

Table I
Ester Activation of Nitro Displacement

Reaction	Ester	Oxime	Solvent	Time	Temp, °C	Yield, % Hydroxy ester	Yield, % Nitro acid
1	*p*-$O_2NC_6H_4CO_2C_2H_5$[a]	CH_3CHNOH[b,c]	DMSO	20 min	30	55	36
2		c	DMSO	10 min	25	64	18
3		c	DMF	20 min	25	46	37
4		c	DMF	2 hr	10	38	45
5		c	$DMSO/CH_3CN$	1.5 hr	−3	31	
6		C_6H_5CHNOH[c,d]	DMSO	5 hr	20	65	5
7		e	DMSO	6.5 hr	20	81	14
8		e	ETOH[f]	8 hr	74	<0.2	64
9	*p*-$O_2NC_6H_4CO_2CH_3$[g]	e	DMSO	7.5 hr	20	63	14
10	*o*-$O_2NC_6H_4CO_2C_2H_5$[h]	e	DMSO	6.5 hr	20	29[i]	37

[a] Registry number, 99-77-4. [b] Registry number, 52540-25-7. [c] Addition of ester to oxime salt. [d] Registry number, 40026-28-6. [e] Addition of oxime salt to ester. [f] Absolute ethanol. [g] Registry number, 619-50-1. [h] Registry number, 610-34-4. [i] Isolated as salicylic acid.

Table II
Replacement of Nitro and Halogen by Hydroxyl

Reaction	Substrate	Registry no.	Solvent	Time	Temp, °C	Product	Registry no.	Yield, %
11	*p*-Dinitrobenzene[a]	100-25-4	DMSO	50 min	30°	*p*-nitrophenol[b]	100-02-7	78
12	*p*-Nitrobenzonitrile[a]	619-72-7	DMSO	46 hr	25	*p*-hydroxybenzonitrile	767-00-0	94
13	*p*-Nitrobenzonitrile[c]		DMSO	45 min	30	*p*-hydroxybenzonitrile		69
14	*o*-Nitrobenzonitrile[a]	619-24-9	DMSO	2 hr	25	*o*-hydroxybenzonitrile	611-20-1	57
15	*p*-Nitrobenzophenone[a]	1144-74-7	DMSO	8 hr	25	*p*-hydroxybenzophenone	1137-42-4	62
16	*p*-Nitroacetophenone[a]	100-19-6	DMSO	12 hr	25	*p*-hydroxyacetophenone	99-93-4	0
17	*p*-Nitrobenzaldehyde[a]	555-16-8	DMSO	1 hr	30	*p*-hydroxybenzaldehyde	123-08-0	0
18	*p*-Nitrobenzamide[c]	619-80-7	DMSO	17 hr	70	*p*-hydroxybenzoic acid[d]	99-96-7	50
19	4-Nitrobiphenyl[a]	92-93-3	DMSO	18 hr	60	4-hydroxybiphenyl	92-69-3	20
20	*p*-Nitrofluorobenzene[a]	350-46-9	DMSO	50 min	30	*p*-nitrophenol[b]	100-02-7	79
21	Ethyl *p*-fluorobenzoate[a]	451-46-7	DMSO	7.5 hr	20	ethyl *p*-hydroxybenzoate[e]	120-47-8	65
22	Ethyl *p*-fluorobenzoate[a]		ETOH[f]	5 hr	74	*p*-fluorobenzoic acid[g]	456-22-4	33
23	2-Chloropyridine[a]	109-9-1	DMSO	15 hr	110	2-pyridone	142-08-5	72

[a] Benzaldoxime. [b] 12% *O*-(*p*-Nitrophenyl)benzaldoxime was also isolated. [c] Acetaldoxime. [d] Hydrolysis of amide occurred under work-up conditions. [e] *p*-Fluorobenzoic acid (2%) was also isolated. [f] Absolute ethanol. [g] Less than 0.5% ethyl *p*-hydroxybenzoate.

nitro ester, but it proved more selective. Thus, a reaction conducted at 20° for 5 hr gave 65% hydroxy ester and only 5% nitro acid. Inverse addition (oximate salt to ester) in a reaction conducted at 20° for 6.5 hr gave 81% hydroxy ester and 14% nitro acid. It might be expected that the methyl ester would be more susceptible to attack at the carboxylate function, but with the inverse addition it gave a good yield (63%) of the hydroxy ester, along with 14% nitro acid (Table I).

The mutual hindrance of the two groups in ethyl *o*-nitrobenzoate evidently is more effective in deterring displacement of the nitro group than of the alkoxy group. Even with the inverse addition of the benzaldoxime salt the ortho ester gave 37% nitro acid; the hydroxy ester also produced was not readily isolated from the mixture and was converted to salicylic acid, obtained in only 29% yield.

Of the other activating groups tested, *p*-nitro, *p*-benzoyl and *p*-carbamyl promoted the nitro displacement (see Table II). Because of the water solubility of the product (*p*-hydroxybenzamide) from *p*-nitrobenzamide it proved convenient to allow it to undergo hydrolysis and to isolate it as the hydroxy acid. Surprisingly, none of the phenol was isolated from a reaction of the benzaldoximate ion with either *p*-nitroacetophenone (25°, 12 hr) or *p*-nitrobenzaldehyde (70°, 1 hr).

The replacement of an activated aromatic nitro group by hydroxyl through reaction with an oximate ion evidently occurs in two steps, displacement of the nitro group to give the *O*-aryl oxime ether (*e.g.*, **3**), and attack of the latter by a second oximate ion acting as a base and converting it to phenoxide ion and benzonitrile. Presumably, an early step in the displacement leads to the intermediate **2**, shown in only one of its resonance forms. Whether the color of the solution is due to such a complex or to a Jackson–Meisenheimer complex similar to **1** but formed reversibly and not leading to products has not been determined. Conversion of the *O*-aryl oxime ethers obtained from 2,4-dinitrochlorobenzene and aldoximes to phenols and nitriles by the action of strong base (KOH) has long been known.[8] In the present work, no attempt to isolate the *O*-(*p*-carbethoxyphenyl)benzaldoxime (**3**) was made, but the benzonitrile shown as arising from its decomposition was isolated in 71% yield. Also, *O*-(*p*-nitrophenyl)benzaldoxime was isolated in quantity sufficient to test its reaction with bases. With refluxing 5% sodium hydroxide it gave a 95% yield of *p*-nitrophenol, along with benzoic acid (75%) and benzamide (5%), formed by hydrolysis of the nitrile, and in DMSO at room temperature the salt of benzaldoxime converted this ether to *p*-nitrophenol in 97% yield at 73% conversion (50 min, room temperature). Thus, in DMSO the oximate ion is able to cleave the ether.

The *O*-aryl oxime ether structure was first proposed by Werner[9] and very recently confirmed by Sheradsky, Salemnick, and Nir,[10] who prepared identical compounds both by

displacement of an activated halogen (as, *e.g.*, in 2,4-dinitrochlorobenzene) by oximate anion and by the reaction of the corresponding *O*-arylhydroxylamine with a carbonyl compound. The *O*-aryl aldoximes reported were assigned the syn configuration,[8,11] but complete spectral data were not presented. In the present work the nmr spectrum of the *O*-(*p*-nitrophenyl)benzaldoxime isolated was found to show only one signal (at δ 8.70, s, 1 H) for the aldoxime proton (CH=NO). Previous work[12] with aldoximes indicates that separate signals would be expected for the syn and anti isomers if both were present. Since the *O*-(*p*-nitrophenyl)benzaldoxime was prepared from the anion of *syn*-benzaldoxime, it seems likely that it too is of the syn configuration.

The powerful directing effect of the aprotic solvent is shown by comparison of the reaction of ethyl *p*-nitrobenzoate and benzaldoxime sodium salt conducted in DMSO with one conducted in ethanol. After 8 hr at room temperature in ethanol there was no indication (tlc) of reaction; so the mixture was heated (74°) for 8 hr. The only product isolated (64%) was *p*-nitrobenzoic acid; if ethyl *p*-hydroxybenzoate was formed vpc tests indicated its yield could not have been more than 0.2%. The response of the oximate ion to the directing effect of the aprotic solvent is shown by comparison of the oximate reaction in DMSO with a sodium hydroxide reaction in the same solvent; only *p*-nitrobenzoic acid (98% yield) was obtained when sodium hydroxide was used.

It would be expected that certain activated aromatic and heterocyclic halogen compounds can also be converted to phenols in a single operation by displacement with oximate in the presence of excess of the reagent. When ethyl *p*-fluorobenzoate was employed with the benzaldoxime salt (7.5 hr, 20°), ethyl *p*-hydroxybenzoate was obtained in 65% yield (Table II). It is interesting that this yield is somewhat lower than that of the same product obtained by nitro displacement. *p*-Nitrofluorobenzene gave *p*-nitrophenol in 79% yield (50 min, 30°), and the intermediate ether, *O*-(*p*-nitrophenyl)benzaldoxime, was also isolated in 12% yield. The yield of the ether was increased to 36% when only 1 equiv of the oximate salt was used. The chlorine atom of 2-chloropyridine was less reactive toward the salt of benzaldoxime, but a reaction at 110° for 15 hr gave 2-pyridone in 72% yield. Although the conditions were among the most vigorous employed in the present study, they are mild compared to some which are used for the same conversion.[13,14]

A trial of the reaction of the benzaldoximate with the unactivated nitro compound 4-nitrobiphenyl resulted in a 20% yield of 4-hydroxybiphenyl after 18 hr at 60°. It seems likely that a more active oximate ion may be found, permitting the useful, direct conversion of an unactivated nitro compound to the phenol.

Experimental Section

Either a Perkin-Elmer 521 or a Beckman IR-12 spectrophotometer was used for ir spectra which were run as KBr disks. Nmr spectra were recorded on a Varian A-60A or A-56/60 spectrometer. Mass spectra were recorded by Mr. J. Wrona and associates on an Atlas CH5 mass spectrometer at 70 eV. Microanalyses were performed by Mr. J. Nemeth and associates. Products were identified by comparison of ir and nmr spectra with those of authentic samples unless otherwise noted. All starting materials were either commercially available reagent grade and were used as received or were prepared in this laboratory by well known synthetic routes. DMSO and DMF were stored over Linde Type 4a Molecular Sieves for 2 weeks prior to use.

***p*-Cyanophenol.** A solution of sodium methylsulfinylmethide was prepared by heating sodium hydride (0.48 g, 20 mmol) in DMSO (25 ml) at 70° until a clear solution resulted (20–30 min). To this solution, benzaldoxime (2.42 g, 20 mmol) in DMSO (10 ml) was slowly added and the resulting mixture was stirred at 70° for 0.5 hr. To the thick paste which formed upon cooling was added 1.48 g of *p*-nitrobenzonitrile (10 mmol) in DMSO (35 ml). The deep purple color, which formed almost immediately, faded after the solution had been stirred for 46 hr at 25°. This light yellow solution was poured into 150 ml of ice water which had been acidified with 8.3 ml of concentrated HCl and the resulting aqueous solution was extracted with ether. Acidification of the 5% NaOH extract of the ether solution resulted in the formation of a yellow oil which was separated. Chromatography of this oil on 30 g of silica gel (benzene elution) resulted in the isolation of 1.12 g (94%) of *p*-cyanophenol, mp 111–112° (lit.[15] mp 112°) after recrystallization from benzene. When acetaldoxime was used the ether extract was dried ($MgSO_4$) and evaporated and the resulting oil was recrystallized from water to give *p*-cyanophenol (69%). The procedure for reactions 14–18 (Table II) was similar.

Ethyl *p*-Hydroxybenzoate. The sodium salt of benzaldoxime (81 mmol) in DMSO (175 ml) was prepared as described above. This salt was slowly added (45 min) to a solution of ethyl *p*-nitrobenzoate (7.8 g, 40 mmol) in DMSO (50 ml). The reaction temperature was maintained at 15° by an ice bath. The reaction mixture was stirred for 1 hr at 15° after addition was complete and then for 5.5 hr at room temperature. The resulting DMSO solution was poured into 500 ml of ice water which had been acidified with 8.3 ml of concentrated HCl. This aqueous mixture was extracted with ether. Acidification of a 5% sodium carbonate extract of the ether solution produced 0.94 g (14%) of *p*-nitrobenzoic acid. Further extraction of the ether solution with 5% NaOH and subsequent acidification produced 5.38 g (81%) of ethyl *p*-hydroxybenzoate, mp 115–116° (lit.[16] mp 116°) after recrystallization from water. The ether solution was then extracted with 10% NaOH until the benzaldoxime was completely removed, washed (H_2O), dried ($MgSO_4$), and evaporated. Distillation of the residue resulted in the isolation of 2.94 g (71%) of benzonitrile. The procedures for reactions 1–10, 21, and 22 were similar, with the differences in conditions noted in Tables I and II.

***O*-(*p*-Nitrophenyl)benzaldoxime.** The sodium salt of benzaldoxime (80 mmol) in DMSO (175 ml) was prepared as described previously. This mixture was slowly added to *p*-fluoronitrobenzene (11.28 g, 80 mmol) in 50 ml of DMSO. The reaction mixture was cooled in an ice bath. After addition was complete, stirring was continued for 0.5 hr at room temperature. The mixture was poured into 500 ml of ice water which had been acidified with 8.3 ml of concentrated HCl. The light tan precipitate which formed was filtered, washed (H_2O), and dried; it weighed 6.95 g (36%). After recrystallization from cyclohexane (Darco) it showed mp 124.5–125.5°; ir (KBr) 1595, 1518, 1485, 1348, 1245, 910, 835, 740, 675 cm^{-1}; nmr ($CDCl_3$) δ 7.55 (d, 2 H), 8.48 (d, 2 H), 8.70 (s, 1 H), 7.6–8.2 (m, 5 H); mass spectrum (rel intensity) *m/e* (I) 242 (14), 104 (100), 77 (90), 51 (16).

Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.13; N, 11.57. Found: C, 64.63; H, 4.13; N, 11.83.

Base Decomposition of *O*-(*p*-Nitrophenyl)benzaldoxime. A. To a solution of 20 ml of 5% NaOH and 20 ml of ethanol was added *O*-(*p*-nitrophenyl)benzaldoxime (300 mg, 1.24 mmol). The mixture was refluxed for 1.5 hr and the ethanol was then removed by distillation. The resulting basic solution was extracted with ether, which upon evaporation produced 7.2 mg (5%) of benzamide (ir identical with that of an authentic sample). Acidification and ether extraction of the aqueous solution resulted in the isolation of 270 mg of a light yellow solid upon evaporation of the ether extract. Nmr comparison with a known mixture showed *p*-nitrophenol and benzoic acid to be present in 95% and 70% yields, respectively.

B. *O*-(*p*-Nitrophenyl)benzaldoxime (600 mg, 2.48 mmol) in DMSO (10 ml) was added to 2.48 mmol of the benzaldoxime salt in 15 ml of DMSO. This mixture was stirred for 50 min at 25° and was then poured into 50 ml of ice water which had been acidified with 0.5 ml of concentrated HCl. Unchanged *O*-(*p*-nitrophenyl)benzaldoxime (163 mg, 27% recovery) was collected by filtration. The ether extract of the filtrate was washed (H_2O), dried ($MgSO_4$), and evaporated. Chromatography of the residue on 10 g of silica gel (benzene elution) resulted in the isolation of 246 mg (97% yield based on unrecovered starting material) of *p*-nitrophenol, mp 112–113° (lit.[17] 114°).

***p*-Nitrophenol.** The sodium salt of benzaldoxime (20 mmol) in DMSO (35 ml) was prepared as usual. *p*-Fluoronitrobenzene (1.41 g, 10 mmol) in DMSO (35 ml) was added; an intense color developed immediately. The dark solution was stirred at 30° for 50 min and then poured into 150 ml of ice water which had been acidified with 2 ml of concentrated HCl. *O*(*p*-Nitrophenylbenzaldoxime (0.28 g, 12%) was separated from the aqueous mixture by filtration.

The ether extract of the filtrate was washed (H_2O), dried ($MgSO_4$), and evaporated. The residue was chromatographed on 30 g of silica gel (benzene elution), yielding 1.09 g (79%) of *p*-nitrophenol, mp 112–113° (lit.[17] 114°) after recrystallization from benzene. Reaction 11 (Table II) was identical.

2-Pyridone. 2-Chloropyridine (1.14 g, 10 mmol) in DMSO (35 ml) was added to 20 mmol of the benzaldoxime salt in 35 ml of DMSO. No color formation was observed after 30 min at room temperature but when the mixture was heated to 110° it became dark red. The solution was stirred at this temperature for 15 hr, cooled, and poured into 150 ml of ice water. The aqueous solution was saturated with carbon dioxide and extracted twice with chloroform. The aqueous layer was evaporated and the residual solid was triturated twice with $CHCl_3$. Filtration and evaporation of the chloroform solution produced 0.69 g (72%) of 2-pyridone, mp 104.5–105.5° (lit.[18] 106°) after recrystallization from xylene.

***p*-Hydroxybiphenyl.** To a mixture of 20 mmol of the benzaldoxime salt in 35 ml of DMSO was added 4-nitrobiphenyl (1.99 g, 10 mmol) in DMSO (35 ml). The mixture was heated for 18 hr at 60°, cooled, and poured into 150 ml of ice-water which had been acidified with 2.5 ml of concentrated HCl. The ether extract of this mixture was washed (H_2O), dried ($MgSO_4$), and evaporated. The residue was tritrated with 10% NaOH. Filtration and acidification of the NaOH solution produced 0.34 g (20%) 4-hydroxybiphenyl, mp 159–60° (lit.[19] 160–2°) after sublimation and recrystallization from ethanol-water.

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Registry No.—*O*-(*p*-Nitrophenylbenzaldoxime, 52540-26-8.

References and Notes

(1) R. G. Landolt and H. R. Snyder, *J. Org. Chem.*, **33**, 403 (1968).
(2) J. H. Gorvin, *Chem. Commun.*, 1120 (1971).
(3) R. B. Chapas, Ph.D. Thesis, University of Illinois, 1972.
(4) R. H. Williams and H. R. Snyder, *J. Org. Chem.*, **36**, 2327 (1971).
(5) See J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).
(6) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972); *ibid.*, **38**, 4086 (1973).
(7) J. H. Gorvin, *Chem. Ind.*, 1525 (1967).
(8) O. L. Brady and R. Truszkowski, *J. Chem. Soc.*, **125** 1087 (1924).
(9) A. Werner, *Ber.*, **27**, 1654 (1894).
(10) T. Sheradsky, G. Salmenick, and Z. Nir, *Tetrahedron*, **28**, 3833 (1972).
(11) Z. Rappoport and T. Sheradsky, *J. Chem. Soc. B*, 898 (1967).
(12) E. Lustig, *J. Phys. Chem.*, **65**, 491 (1961).
(13) J. A. Zoltswicz and A. A. Sale, *J. Org. Chem.*, **36**, 1455 (1971).
(14) J. L. Farmer and E. J. Hawa, *J. Chem. Educ.*, **47**, 41 (1970).
(15) G. W. Wheland, R. M., Brownell and E. C. Mayo, *J. Amer. Chem. Soc.*, **70**, 2492 (1948).
(16) G. W. K. Cavill and J. M. Vincent, *J. Soc. Chem. Ind.*, **66**, 175 (1947).
(17) W. Robertson, *J. Chem. Soc.*, **81**, 1475 (1902).
(18) A. Feer and W. Koenigs, *Ber.*, **19**, 2432 (1886).
(19) J. Kaiser, *Justus Liebigs Ann. Chem.*, **257**, 101 (1890).

Solvolysis of *exo*- and *endo*-2-Bicyclo[3.2.0]hepta-3,6-dienyl *p*-Nitrobenzoates. Possibilities of Antiaromatic Interaction in the Resulting Carbocations

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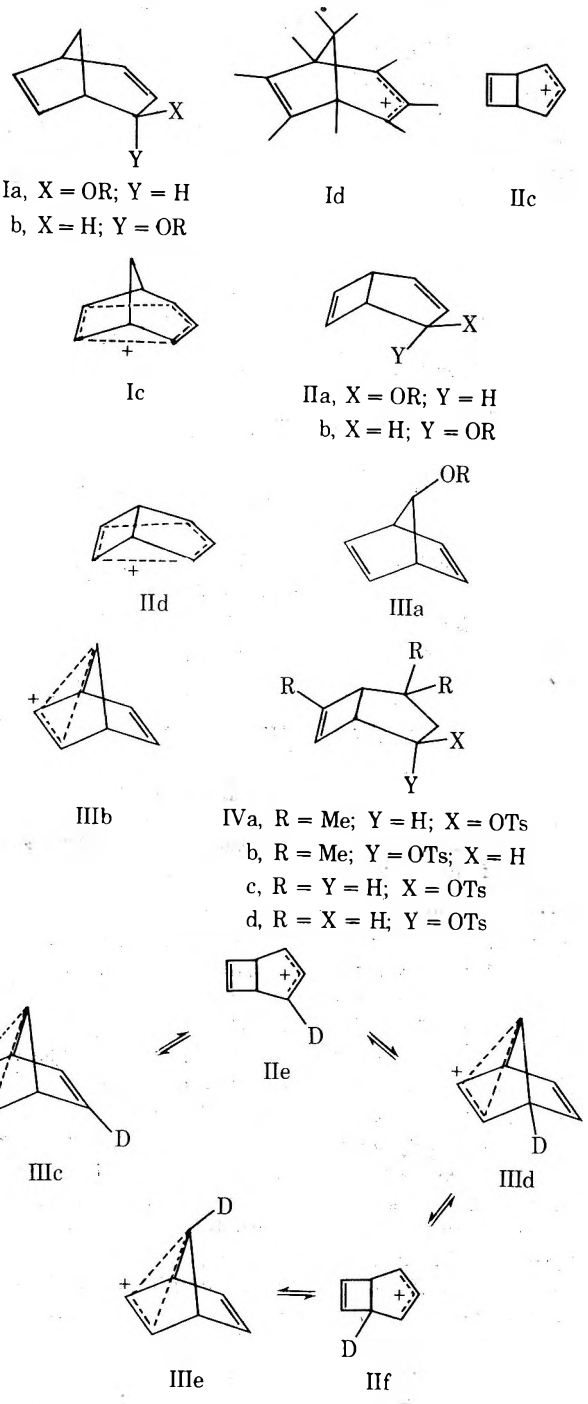
The kinetics and products of the solvolysis of the title compounds (IIa and IIb, R = PNB) were studied. They were found to undergo hydrolysis (80% aqueous acetone) at virtually identical rates, both being slightly more reactive than 7-norbornadienyl *p*-nitrobenzoate (IIIa, R = PNB). Acetolysis and hydrolysis (50% aqueous acetone) of the title compounds were found to yield only mixtures of the unrearranged exo and endo acetates and alcohols, with no ring enlarged 7-norbornadienyl derivatives being detected. The possibility of the intermediacy of an antiaromatic bishomocyclopentadienyl cation (IId) in these solvolyses and in the rearrangement to the 7-norbornadienyl cation (IIIb) observed upon treatment of either exo or endo alcohols (IIa and IIb, R = H) with FSO_3H is discussed.

Reactions involving antiaromatically destabilized intermediates have elicited much interest in the recent literature.[2] Diaz[3] has described the solvolysis of *exo*- and *endo*-2-bicyclo[3.2.1]octa-3,6-dienyl *p*-nitrobenzoates (Ia and Ib, R = PNB), noting an exo/endo rate ratio of virtual unity, and an apparent rate retardation by the double bond at C-6 of a factor of *ca.* 235. The latter observation suggested the involvement of a bishomoantiaromatic cation, Ic. Hart,[4] on the other hand, feels that the nmr data from the nonamethylbicyclo[3.2.0]hepta-3,6-dien-2-yl cation (Id) at −90°[4a] are more consistent with an allylic structure. In a preliminary communication[5] describing the solvolysis of *exo*- and *endo*-2-bicyclo[3.2.0]hepta-3,6-dienyl *p*-nitrobenzoates (IIa and IIb, R = PNB), we noted an exo/endo rate ratio of unity and the observation only of unrearranged products. Winstein,[6] however, noted that treatment of either 7-norbornadienol (IIIa, R = H) or exo and endo alcohols IIa and IIb (R = H) with fluorosulfonic acid (FSO_3H) at −78° results in formation of the 7-norbornadienyl cation (IIIb). Using labeled substrates, he found that the interconversion between 7-norbornadienyl and bicyclo[3.2.0]heptadienyl cations involves stepwise circumambulation of five carbons with respect to the "bound" vinyl group in IIIb (IIIc ⇌ IIe ⇌ IIId ⇌ IIf ⇌ IIIe).[6] Hart[4] noted an analogous degenerate rearrangement in Id at temperatures above −90°, along with other rearrangements detectable only in labeled substrates. We noted, however, that the interconversion between bicyclo[3.2.0]heptadienyl and 7-norbornadienyl cations is quenched in conventional solvolysis media[5] and rationalized our results on the basis of an allylic (IIc), rather than a bishomoantiaromatic (IId) intermediate. We also noted that the allylic double bond at C-2 evidently swamps out homoallylic participation as observed by Whitham[7] in the solvolysis of *exo*-4,4,6-trimethylbicyclo[3.2.0]hept-6-en-2-yl tosylate (IVa). This more detailed description of our results, and their relation to our results from a study of *exo*- and *endo*-bicyclo[3.2.0]hept-6-en-2-yl tosylates (IVc and IVd)[8] shows that allylic cation IIc is probably the solvolytic intermediate, but that the ring enlargement to the 7-norbornadienyl cation probably involves the corresponding bishomocyclopentadienyl cation (IId) as the transition state.



Ia, X = OR; Y = H
b, X = H; Y = OR

Id

IIc

Ic

IIa, X = OR; Y = H
b, X = H; Y = OR

IId

IIIa

IIIb

IVa, R = Me; Y = H; X = OTs
b, R = Me; Y = OTs; X = H
c, R = Y = H; X = OTs
d, R = X = H; Y = OTs

IIe

IIIc

IIId

IIIe

IIf

Experimental Section

Elemental analyses were performed by Midwest Microlabs, Inc. Melting points were determined using a Thomas Hoover capillary melting point apparatus and are uncorrected.

Infrared (ir) spectra were recorded using either a Perkin-Elmer Model 621 or 257 recording infrared spectrophotomer. Nuclear magnetic resonance (nmr) spectra were recorded using a Varian HA-100 spectrometer. Carbon tetrachloride was employed as solvent for all spectral determinations, unless otherwise stated.

Analytical and preparative gas chromatographic (gc) separations were performed using either a Varian A-90-P3, or HiFi-III model recording gas chromatograph. Columns packed with either Carbowax 20M or 1500 on Chromosorb W were used interchangeably for separations described herein.

Samples of *exo*- and *endo*-2-bicyclo[3.2.0]hepta-3,6-dienyl *p*-nitrobenzoates (IIa and IIb, R = PNB) were prepared from the known[9] alcohols in 81 and 89% yields, respectively, by treatment with *p*-nitrobenzoyl chloride in pyridine at 0–5° for 12 hr. After hydrolytic work-up and recrystallization (pentane) the following physical properties were noted: IIa, R = PNB, mp 67–68.5° (*Anal.* Calcd: C, 65.30; H, 4.31; N, 5.44. Found: C, 65.59; H, 4.31; N, 5.54); IIb, R = PNB, mp 75–76°C (C, 65.58; H, 4.46; N, 5.61).

A sample of 7-norbornadienyl *p*-nitrobenzoate (IIIa, R = PNB) was prepared in similar fashion (36% yield), mp 103–104° (lit.[10] 101–102°).

Kinetic Determinations. First-order rate constants for hydrolysis of *p*-nitrobenzoates were determined by least-squares treatment of at least eight data points. Weighed samples of ester were added to volumetric flasks, along with 2.0 ml of distilled water and enough acetone to make the volume up to 10.0 ml. Aliquots of 1.0 ml were transferred to ampoules, which were sealed and thermostated at 100.00 ± 0.05° for measured intervals and analyzed titrimetrically for liberated acid. The following rate constants were obtained (sample size given in parentheses): IIa, R = PNB (128.6 mg, 0.5 mmol), $k = (1.56 \pm 0.02) \times 10^{-5}$ sec^{-1}; IIb, R = PNB (128.6 mg, 0.5 mmol), $k = (1.90 \pm 0.02) \times 10^{-5}$ sec^{-1}; IIIa, R = PNB (343.4 mg, 1.34 mmol), $k = (1.32 \pm 0.01) \times 10^{-5}$ sec^{-1}.

Acetolysis of 2-Bicyclo[3.2.0]hepta-3,6-dienyl *p*-Nitrobenzoates (IIa and IIb, R = PNB). A 150-mg (0.59 mmol) sample of *endo-p*-nitrobenzoate (IIb) was treated with acetic acid (15 ml, 5% in acetic anhydride) in a sealed tube at 101° for 6 hr. After hydrolytic work-up, 64.5 mg (0.428 mmol, 73% yield) of 2-bicyclo[3.2.0]hepta-3,6-dienyl acetates (IIa and IIb, R = Ac) was detected using gc. An analytical sample, collected using preparative scale gc, exhibited the following properties: ir ν_{max} 3040, 1730, 1365, and 1350 cm^{-1}. *Anal.* Calcd: C, 71.98; H, 6.71. Found: C, 72.13; H, 6.71. An authentic sample of *exo*-2-bicyclo[3.2.0]hepta-3,6-dienyl acetate, prepared from a sample of the corresponding alcohol and acetic anhydride in pyridine gave gc and ir spectral data identical with that from the acetolysis product. Treatment of the solvolysis product with lithium aluminum hydride in ether resulted in the formation of an 89:11 mixture of exo and endo alcohols (IIa and IIb, R = H), characterized by gc analysis. A duplicate run was carried out using 0.1 *M* sodium acetate in acetic acid (5% in acetic anhydride) as solvent. A virtually identical acetate mixture was formed. Hydride reduction yielded a 90:10 mixture of exo and endo alcohols.

In a similar fashion, 20 mg (0.08 mmol) of *exo-p*-nitrobenzoate (IIa, R = PNB) was acetolyzed (2 ml) for 5 hr. The crude product contained 8 mg (0.05 mmol, 63% yield) of 2-bicyclo[3.2.0]hepta-3,6-dienyl acetate, characterized by gc and ir analysis. Hydride reduction of the acetate mixture yielded an 88:12 mixture of exo and endo alcohols. A duplicate run using 0.1 *M* sodium acetate in acetic acid yielded an acetate mixture, which upon hydride reduction formed a 91:9 mixture of exo and endo alcohol.

Hydrolysis of IIa and IIb, R = PNB. A 100-mg (0.39 mmol) sample of *endo-p*-nitrobenzoate (IIb, R = PNB) and 10 ml of 50% aqueous acetone were heated at 102° for 6 hr in a sealed tube. After hydrolytic work-up, analysis of the crude product using gc showed the presence of two volatile components in 89:11 proportions, with the minor component eluting first. Subsequent analytical gc injections using weighed protions of 7-norbornadienol as an internal standard, as well as ir analysis of samples of the products obtained from preparative scale gc injections, showed that the volatiles consisted of 17.2 mg (0.16 mmol, 41% yield) of a mixture of *exo*- and *endo*-2-bicyclo[3.2.0]hepta-3,6-dienol (IIa and IIb, R = H). A duplicate run using 50% aqueous acetone 0.1 *M* in sodium bicarbonate as solvent yielded an 89:11 mixture of the same products.

A 30-mg (0.12 mmol) sample of *endo-p*-nitrobenzoate and 3.0 ml of 80% aqueous acetone were sealed in an ampoule, which was thermostated at 102° for 2.5 hr. Isolation and ir analysis of the *p*-nitrobenzoate fraction showed that it consisted of unreacted *exo-p*-nitrobenzoate.

Acid Catalyzed Equilibration of *exo*- and *endo*-2-Bicyclo[3.2.0]hepta-3,6-dienol (IIa and IIb, R = H). A 10-ml ether solution containing 34.9 mg (0.326 mmol) of endo alcohol (IIb, R = H) and 10 ml of 5% aqueous sulfuric acid were mixed and stirred for 7.3 hr. Analysis of the ether layer using gc showed the presence of 29.5 mg (0.276 mmol, 85% yield) of a 94:6 mixture of exo and endo alcohols (IIa and IIb, R = H). A 65-mg (0.61 mmol) sample of exo alcohol (IIa, R = H) was treated in identical fashion. Analysis of the ether layer after 9 hr showed the presence only of unchanged exo alcohol. The material balance was not determined.

Results and Discussion

Samples of the title compounds (IIa and IIb, R = PNB) were found to undergo hydrolysis in 80% aqueous acetone at virtually identical rates, showing essentially the same reactivity as Diaz's[3] 2-bicyclo[3.2.1]octa-3,6-dienyl *p*-nitrobenzoates (Ia and Ib, R = PNB) and 7-norbornadienyl *p*-

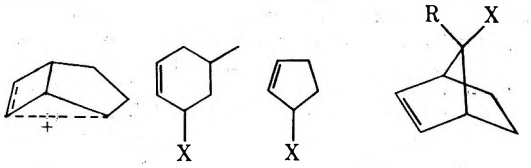
Table I
Kinetics of Hydrolysis of Various *p*-Nitrobenzoate Esters[a]

Substrate	$10^5 k$, sec^{-1}	Ref
Ia, R = PNB	2.76 ± 0.05	3
Ib, R = PNB	2.65 ± 0.03	3
IIa, R = PNB	1.56 ± 0.02	*b*
IIb, R = PNB	1.90 ± 0.02	*b*
IIIa, R = PNB	1.32 ± 0.01	*b*
V, R = PNB	0.339	11
VI, R = PNB	178.0[c]	12

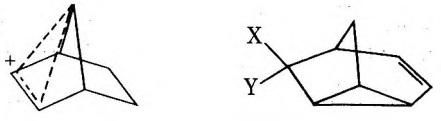
[a] In 80% aqueous acetone at 100.0°. [b] This work. [c] Calculated assuming that the reactivity ratio for ethanolysis for V:VI, X = Cl (1:524 applies to hydrolysis of the corresponding *p*-nitrobenzoates in 80% aqueous acetone at 100.0°).

nitrobenzoate (IIIa, R = PNB). Diaz's data showed that his *exo*- and *endo*-*p*-nitrobenzoates undergo hydrolysis with significant acyl–oxygen cleavage and that the double bond at C-6 retards the rate of hydrolysis by a factor of *ca.* 235, indicating the involvement of a bishomoantiaromatically destabilized species (Ic) in the rate-determining step. The product studies described below show that acyl–oxygen cleavage is not involved in the hydrolysis of *p*-nitrobenzoates IIa and IIb, even though they are slightly less reactive than are Diaz's homologous *p*-nitrobenzoates Ia and Ib. Also, the kinetic data in Table I show that a bishomoantiaromatically destabilized species is probably not involved in the solvolysis of either *exo*- or *endo*-*p*-nitrobenzoates IIa and IIb.

Our exo and endo esters (IIa and IIb, R = PNB) are shown to be *ca.* four–five times more reactive than *cis*-5-methylcyclohex-2-enyl *p*-nitrobenzoate (V, X = OPNB).[11]



IVe V VI VIIa, R = Ar
b, R = CH_2=CH-
c, R = H; X = OTs



VIId VIIIa, X = OH; Y = H
b, X = H; Y = OH

As a control experiment, product studies on the hydrolysis of our substrates were carried out under the conditions of the kinetic determinations, and the unreacted *p*-nitrobenzoate fractions were isolated and characterized. In both cases, only unchanged starting material was observed after 2.5 hr, showing that bulk rearrangement of starting material had not occurred and that the titrimetric rate constants truly represent the solvolytic reactivity of our substrates. Goering[12] found that ethanolysis of 2-cyclopentenyl chloride (VI, X = Cl) proceeds some 524 times faster than does ethanolysis of *cis*-5-methylcyclohex-2-enyl chloride (V, X = Cl). Assuming that this reactivity ratio applies to hydrolysis of the corresponding *p*-nitrobenzoates in 80% aqueous acetone, then *exo*-2-bicyclo[3.2.0]hepta-3,6-dienyl *p*-nitrobenzoate (IIa, R = PNB) is only *ca.* 100 times less reactive than 2-cyclopentenyl *p*-nitrobenzoate (VI, X = OPNB). A rate retardation of this magnitude can be easily explained

Table II
Products from the Solvolysis of Various *p*-Nitrobenzoate Esters at 100°

Substrate	Solvent	Products (% composition)	% total yield	Ref
Ia, R = PNB[a]	60% aq acetone	Ia, R = H(75); Ib, R = H(19); VIIIa(3); VIIIb(3)	83[b]	3
Ib, R = PNB		Ia, R = H(37.5); Ib, R = H(56); VIIIa(3); VIIIb(3)	89[b]	3
IIa, R = PNB[c]	50% aq acetone	IIa, R = H(87); IIb, R = H(13)	54	*d*
IIb, R = PNB[c]		IIa, R = H(89); IIb, R = H(11)	41	*d*
IIa, R = PNB[e]	HOAc	IIa, R = Ac(88); IIb, R = Ac(12)[f]	63	*d*
IIb, R = PNB[e]		IIa, R = Ac(89); IIb, R = Ac(11)[f]	73	*d*

[a] Buffered by 3.0–4.5 × 10^{-3} *M* NaOAc. [b] Other products detected in total yield of 5–8%. [c] Buffered with a threefold excess of $NaHCO_3$. An unbuffered solvolysis yielded a virtually identical product mixture. [d] This work. [e] Buffered by a threefold excess of NaOAc. An unbuffered acetate mixture yielded a virtually identical product mixture. [f] Composition of acetate mixtures determined by $LiAlH_4$ reduction of the acetate mixture, followed by gc analysis of the resulting alcohols.

by inductive withdrawal by the double bond at C-6 and steric hindrance toward solvation of the transition state in the more highly substituted bicyclic substrate. Thus, the kinetic results are adequately explained by the intermediacy of allylic cation IIc.

Gassman[13] found that substitution in the 7-position by electron donating aryl groups, such *p*-anisyl, in *anti*-7-norbornenyl substrates (VIIa, X = OPNB, Ar = *p*-$CH_3OC_6H_4$–) completely levels the 10^{11} solvolytic rate difference observed between *anti*-7-norbornenyl tosylate (VIIc) and its saturated analog.[14] This approach has been used to evaluate anchimeric assistance toward solvolysis in other systems.[15] In our preliminary communication[5] of these results, we noted that the allylic double bond in our esters swamps out homoallylic participation as observed in product studies on the solvolysis of *exo*-4,4,6-trimethylbicyclo[3.2.0]hept-6-en-2-yl tosylate (IVa),[7] but, at that time, there were no rate data available to evaluate the magnitude of this leveling effect. We have completed a study of the solvolysis of *exo*- and *endo*-2-bicyclo[3.2.0]hept-6-enyl tosylates (IVc and IVd)[8] and find an exo/endo rate ratio for SN1 acetolysis at 50.0° of *ca.* 2400. Thus, incorporation of a double bond in the ring system allylic to the reaction center can level solvolytic rate differences of at least 2400. This should be regarded as a lower limit, since Sargent's[16] studies of the solvolysis of 7-vinyl-*anti*-7-norbornenyl 3,5-dinitrobenzoate (VIIb, X = DNB)[16a] and related substrates showed that an exocyclic vinyl group allylic to the reaction center can level solvolytic rate differences as high as 10^8 arising from nonvertical stabilization[16b,c] (*i.e.*, through bridging, rather than hyperconjugation)[17] of the transition state.[18] Studies of other substrates containing allylic double bonds incorporated into the ring system might furnish valuable information concerning anchimeric assistance toward solvolysis in other systems.

Data from the product studies on the solvolysis of our substrates (IIa and IIb, R = PNB) are also adequately ex-

plained by the intermediacy of allylic cation IIc. These results, along with those from product studies on hydrolysis of Diaz's[3] homologous esters (Ia and Ib, R = PNB) are presented in Table II. The product from hydrolysis of both bicyclooctadienyl esters (Ia and Ib, R = PNB) consists mainly of mixtures of the corresponding exo and endo alcohols, along with small amounts of tricyclic alcohols VIIIa and VIIIb. The unrearranged alcohols are thought to arise from acyl–oxygen and alkyl–oxygen cleavage. Diaz[3] calculated that hydrolysis of these substrates in 60% aqueous acetone in the presence of $3.0–4.5 \times 10^{-3}$ *M* sodium acetate as buffer occurs with 60% alkyl–oxygen and 40% acyl–oxygen cleavage, where the alkyl–oxygen cleavage yields 90% unrearranged dienyl alcohols consisting of a 2:1 exo:endo-product mixture (Ia:Ib, R = H). The solvolysis of *exo*- and *endo*-2-bicyclo[3.2.0]hepta-3,6-dienyl *p*-nitrobenzoates (IIa and IIb, R = PNB), on the other hand, yields *ca.* 90:10 mixtures of the corresponding exo and endo derivatives, whether buffered or unbuffered media are used, and for solvents ranging from aqueous acetone to acetic acid. This indicates the absence of acyl–oxygen cleavage, and that the title compounds (IIa and IIb, R = PNB) solvolyze *via* formation of a common intermediate, presumably allylic cation IIc. The difference in product ratio in the unrearranged alcohols from solvolysis of the bicycloheptadienyl and bicyclooctadienyl substrates can be explained on steric grounds. In the latter case, the *syn*-proton in the methylene bridge hinders the exo-side of cation Ic toward nucleophilic attack. This type of interaction is absent in cation IIc.

Consideration of the energetics of the solvolyses of our *exo*- and *endo*-*p*-nitrobenzoates (IIa and IIb, R = PNB), as well as the ring enlargement of the 2-bicyclo[3.2.0]hepta-3,6-dienyl cation (IIc) to the 7-norbornadienyl cation (IIIb) is informative in several respects. Data pertaining to the latter case are presented graphically in Figure 1, along with energy differences and activation paramenters from the hydrolysis of *exo*-*p*-nitrobenzoate (IIa, R = PNB) and 7-norbornadienyl *p*-nitrobenzoate (IIIa, R = PNB). The former case is elaborated as follows.

Acid catalyzed equilibration in diethyl ether–5% sulfuric acid of endo alcohol (IIb, R = H) resulted in a 94:6 mixture of exo and endo alcohols (IIa:IIb, R = H), indicating that, at ambient temperatures, the exo alcohol is the more stable by *ca.* 1.64 kcal/mol. It should be noted in passing that, even under acidic conditions such as these, which should favor rearrangement, no 7-norbornadienol (IIIa, R = PNB) was detected. Calculation directly from the kinetic data yields free energies of activation (ΔG^*) of 30.3 and 30.1 kcal/mol for the hydrolysis of *exo*- and *endo*-*p*-nitrobenzoates (IIa and IIb, R = PNB), respectively. Assuming that the energy difference for the alcohols applies also to the *p*-nitrobenzoates at 100°, then the solvolytic transition states differ in energy by *ca.* 1.44 kcal/mol, with the exo transition state being favored. Calculation directly from the product ratios (ranging from 87:12 to 89:11), which represent the partitioning of allylic cation IIc between exo and endo products (IIa and IIb, R = H or Ac) *via* the solvolytic transition states, yields values of 1.37–1.55 kcal/mol, in excellent agreement for such approximate methods. If bishomoantiaromatic cation IId were involved in the solvolysis of the title compounds, then the transition state for solvolysis of the exo substrate would be somewhat higher than that of the endo substrate. Since the converse is true, the intermediacy of allylic cation IIc, rather than bishomoantiaromatic cation IId, in the solvolysis of *exo*- and *endo*-2-bicyclo[3.2.0]hepta-3,6-dienyl *p*-nitrobenzoates (IIa and IIb, R = PNB) now seems well established. That the bishomoantiaromatic cation is probably involved in the ring enlargement will now be demonstrated.

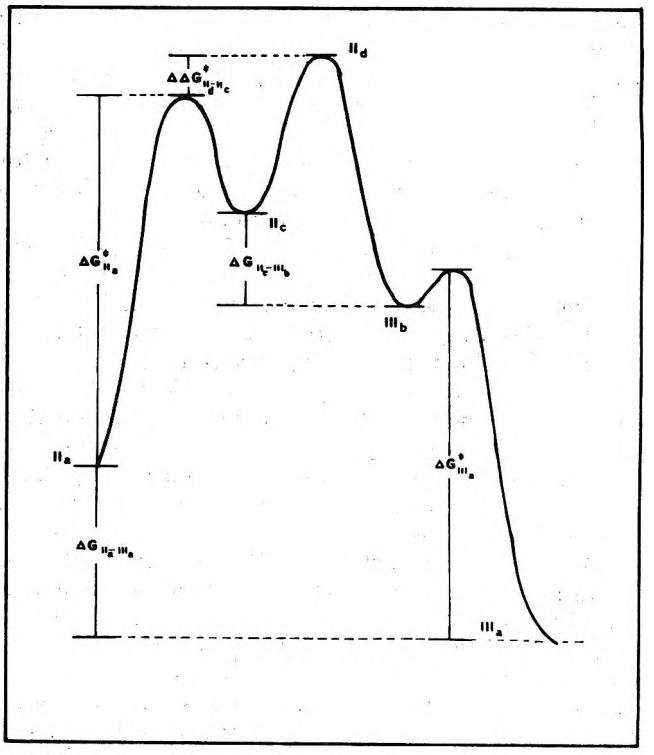
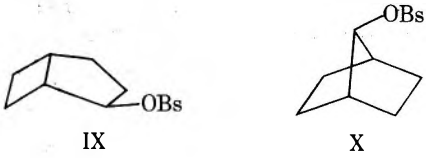


Figure 1. Free energy diagram for solvolysis of *exo*-2-bicyclo-[3.2.0]hepta-3,6-dienyl and 7-norbornadienyl *p*-nitrobenzoates and the resulting cations: $\Delta G_{IIa-IIIa} = 14.4$, $\Delta G^*_{IIIa} = 30.4$, $\Delta G^*_{IIa} = 30.2$, $\Delta G_{IIc-IIIb} \geq 7.5$, $\Delta\Delta G^*_{IId-IIc} > 3.5$ kcal/mol.

The energy diagram in Figure 1 was constructed as follows. The free energy difference between our *exo*-*p*-nitrobenzoate (IIa, R = PNB) and 7-norbornadienyl *p*-nitrobenzoate (IIIa, R = PNB) ($\Delta G_{IIa-IIIa}$) was taken as 14.4 kcal/mol, the difference observed in the corresponding saturated brosylates (IX and X).[20] This value may be somewhat low, since IIa contains double bonds in a cyclobutane, as well as a cyclopentane ring, while the double bonds in IIIa are both contained in less strained cyclopentane rings, but serves as an adequate approximation for this discussion. Calculation directly from the kinetic data described above yielded free energies of activation (ΔG^*_{IIa} and ΔG^*_{IIIa}) of 30.2 and 30.4 kcal/mol for hydrolysis of IIa and IIIa, R = PNB, respectively. Winstein's[6] value for the free energy difference between cation IIc and the 7-norbornadienyl cation (IIIb) ($\Delta G_{IIc-IIIb}$) of 7.5 kcal/mol was used but should be regarded as a lower limit. The published value for the free energy of activation for the ring enlargement (not given in Figure 1), equal to *ca.* 10 kcal/mol in FSO_3H at −120°,[6] appears to be too low by several kilocalories. This discrepancy can be easily explained, since cation IIc (and presumably cation IIIb) is stabilized by solvation in media such as acetic acid or aqueous acetone, thereby lowering its energy relative to the transition state for ring enlargement. Such interaction is, of course, minimal in FSO_3H. A lower limit for the free energy difference between the solvolytic transition state from *exo*-*p*-nitrobenzoate and the transition state for ring enlargement



IX X

(Bs = |*p*-$BrC_6H_4SO_3$)

($\Delta\Delta G^*_{IIc-IId}$) can be fixed with some certainty, however. Assuming that the hydrolysis of *exo*-*p*-nitrobenzoate in 50% aqueous acetone formed, along with the 54% observed yield of unrearranged products, as much as a 0.5% yield of 7-norbornadienol (IIIa, R = H) that escaped detection, then the solvolytic transition state is lower than that for ring enlargement by at least 3.5 kcal/mol. The bridged 2-bicyclo[3.2.0]hept-6-enyl cation (IVe), on the other hand, undergoes ring enlargement to the 7-norbornenyl cation (VIId) at an exceedingly rapid rate, as shown by the fact that solvolysis of *exo*-2-bicyclo[3.2.0]hept-6-enyl tosylate (IVc) yields only products derivable from the 7-norbornenyl cation,[8] even in the presence of strong nucleophiles, such as methoxide, added to trap[21] cation IVe prior to rearrangement. Although no reliable value for the free energy of activation for this ring enlargement can be assigned, it is certainly lower than that for the ring enlargement involving cation IIc by several kilocalories per mole. This difference is explained as follows. the ring enlargement of the 2-bicyclo[3.2.0]hepta-3,6-dienyl cation (IIc) must involve initial interaction between the incipient p orbital at C-4 and either the π-system at C-7, or the σ-bond connecting it to the bridgehead. Although Dewar[22] cautions against the rigorous use of arguments of this type, it seems likely that such interaction would involve the π-system, occupying frontier orbitals,[23] rather than a portion of the lower lying σ-system. This type of interaction would yield bishomocyclopentadienyl cation IId, and is thought to be destabilizing.[2,3,24] This interaction can be minimized by flattening of the concave carbon skeleton in bicyclo[3.2.0]heptadienyl derivatives (II) and is, therefore, unimportant in either the rate-determining or product-forming steps in the solvolysis of the title compounds. Incidentally, such flattening should be less favored in Diaz's[3] homologous bicyclooctadienyl cation (Ic), rendering it a more likely candidate for antiaromatic interaction.

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Registry No.—IIa (R = PNB), 21654-38-6; IIa (R = Ac), 52393-61-0; IIa (R = H), 35826-10-9; IIb (R = PNB), 21654-39-7; IIb (R = Ac), 52438-20-7; IIb (R = H), 35826-09-6; IIIa (R = PNB), 33686-56-5; V (X = OPNB), 52393-62-1; VI (X = OPNB), 21985-86-9; *p*-nitrobenzoyl chloride, 122-04-3.

References and Notes

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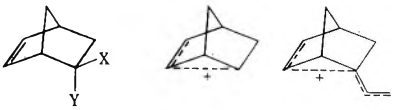
(2) R. Breslow, *Accounts Chem. Res.*, **6**, 393 (1973).
(3) A. F. Diaz, M. Sakai, and S. Winstein, *J. Amer. Chem. Soc.*, **92**, 7477 (1970).
(4) H. Hart and M. Kuzuya, *J. Amer. Chem. Soc.*, **95**, 4096 (1973); M. Kuzuya and H. Hart, *Tetrahedron Lett.*, 3887, 3891 (1973).
(5) P. R. Story and B. J. A. Cooke, *J. Chem. Soc., Chem. Commun.*, 1081 (1968).
(6) R. K. Lustgarten, M. Brookhart, and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 6350 (1967); *ibid.*, **90**, 7364 (1968); M. Brookhart, R. K. Lustgarten, and S. Winstein, *ibid.*, **89**, 6352, 6354 (1967).
(7) S. C. Lewis and G. H. Whitham, *J. Chem. Soc. C*, 274 (1967).
(8) B. J. A. Cooke and P. R. Story, *Tetrahedron Lett.*, 1705 (1974); B. J. A. Cooke and P. R. Story, *J. Org. Chem.*, in preparation.
(9) P. R. Story and S. Fahrenhoitz, *J. Amer. Chem. Soc.*, 87, 1623 (1965).
(10) P. R. Story, *J. Org. Chem.*, **26**, 287 (1961).
(11) H. L. Goering and E. F. Silversmith, *J. Amer. Chem. Soc.*, **77**, 6249 (1955).
(12) H. L. Goering, T. D. Nevitt, and C. F. Silversmith, *J. Amer. Chem. Soc.*, **77**, 5026 (1955).
(13) P. G. Gassman, J. Zeller, and J. T. Lumb, *Chem. Commun.*, 69 (1968); P. G. Gassman and A. F. Fentiman, Jr., *J. Amer. Chem. Soc.*, **91**, 1545 (1969).
(14) S. Winstein and M. Shatavsky, *J. Amer. Chem. Soc.*, **78**, 592 (1956).
(15) P. G. Gassman, and A. F. Fentiman, Jr., *J. Amer. Chem. Soc.*, **92**, 2551 (1970); H. C. Brown, *Accounts Chem. Res.*, **6**, 37 (73), and references cited therein.
(16) (a) G. D. Sargent, J. A. Hall, M. J. Harrison, W. H. Demisch, and M. A. Schwartz, *J. Amer. Chem. Soc.*, **91**, 2379 (1969); (b) T. J. . Mason, M. J. Harrison, J. A. Hall, and G. D. Sargent, *ibid.*, **95**, 1849 (1973); (c) G. D. Sargent and T. J. Mason, *ibid.*, **96**, 1063 (1974).
(17) T. G. Traylor, W. Hanstein, H. J. Berwin, N. A. Clinton, and R. S. Brown, *J. Amer. Chem. Soc.*, **93**, 5715 (1971), and references cited therein.
(18) It should be pointed out that Brown[19] has found that the exo/endo rate ratio from solvolysis of 2-aryl-2-norbornenyl *p*-nitrobenzoates (ia, ib) remains constant (*ca.* 350) for aryl groups of widely differing electron demand. This calls the bridged structure for the 2-norbornenyl cation (ic)



ia, X = OPNB; Y = Ar ic ii
b, X = Ar; Y = OPNB

and the closely related bicyclic cation IVe into serious question and suggests that the high exo:endo rate differences can be explained on steric grounds. Sargent[16] has found some evidence for the intermediacy of cation ii in the product forming step in the solvolysis of 2-(2′ethylidenyl)bicyclo[2.2.1]hept-5-enyl 3,5-dinitrobenzoate, suggesting that, in the 2-norbornenyl system, allylic centers of unsaturation can act cooperatively with homoallylic centers to vertically stabilize[16b,c,17] the cationic center. In any case, the allylic double bond in our substrates (IIa and IIb, R = PNB) acts competitively with the homoallylic double bond, suggesting that IVa, like the 7-norbornenyl cation (VIId), is stabilized by a nonvertical process (*i.e.*, bridging).
(19) E. N. Peters and H. C. Brown, *J. Amer. Chem. Soc.*, **95**, 2398 (1973).
(20) S. Winstein, F. Gadient, E. J. Stafford, and P. E. Kleindinst, *J. Amer. Chem. Soc.*, **80**, 5895 (1958).
(21) H. Tanida, T. Tsuji, and T. Irie, *J. Amer. Chem. Soc.*, **88**, 864 (1966); A. Diaz, M. Brookhart, and S. Winstein, *ibid.*, **88**, 3133 (1966).
(22) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, p 364.
(23) K. Fukui, T. Yonezawa, and H. Shingu, *J. Chem. Phys.*, **20**, 722 (1952); K. Fukui, T. Yonezawa, C. Nagata, and H. Shingu, *ibid.*, **22**, 1433 (1954).
(24) M. J. Goldstein, *J. Amer. Chem. Soc.*, **89**, 6357 (1967); private communication.

The Nitro Enol Ether 4-Nitro-1-cyclohexyl-3-ethoxy-2-oxo-3-pyrroline. Synthesis and Use as a Reagent for Amino Group Protection[1]

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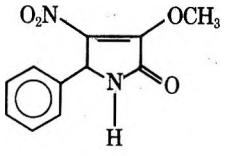
The nitro enol ether 4-nitro-1-cyclohexyl-3-ethoxy-2-oxo-3-pyrroline (IV) was prepared from enolic 4-carbethoxy-1-cyclohexyl-2,3-dioxopyrrolidine by a three-step sequence in which the final reaction was direct nitration of 1-cyclohexyl-3-ethoxy-2-oxo-3-pyrroline-4-carboxylic acid. The enol ether IV served as an active reagent for the attachment of the 4-nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl group (NOPY group) to amino functions, from which it could be removed by the action of ammonia at room temperature. The possibility of using the NOPY group for the protection of amino groups during synthesis was demonstrated in the preparation of two simple dipeptide esters.

It was recently shown that the nitro enol ether 3-methoxy-4-nitro-5-phenyl-2-oxo-3-pyrroline (I) reacts under



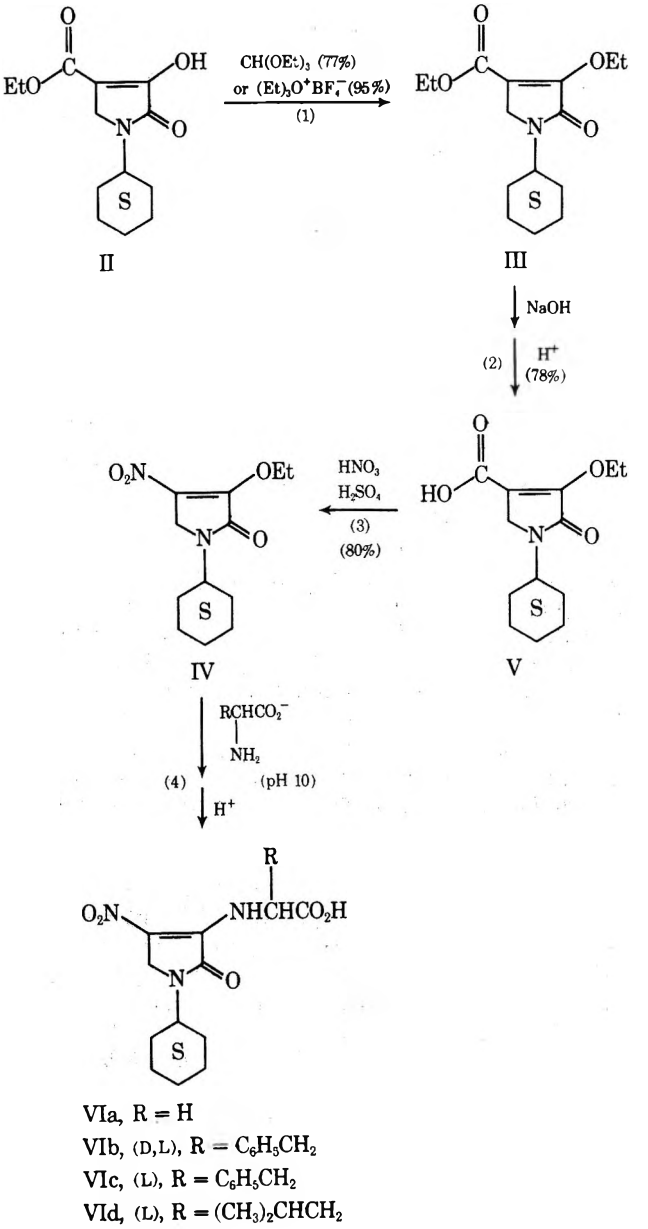
I

mild conditions with ammonia and primary or secondary amines to undergo replacement of the methoxy group by an amino group or substituted amino group.[2] In order to investigate the possible utility of nitro enol ethers in synthetic applications it was desirable to obtain a representative compound of that type which was more easily prepared and which, unlike compound I, did not contain a chiral center to contribute toward unwanted stereochemical complications. The work described here was concerned with the synthesis and reactions of such a compound, 4-nitro-1-cyclohexyl-3-ethoxy-2-oxo-3-pyrroline (IV).

The scheme used for the synthesis of IV is outlined in Chart I. The readily available enol of 1-cyclohexyl-4-carbethoxy-2,3-dioxopyrrolidine (II)[3] was alkylated at the enolic hydroxyl either by use of ethyl orthoformate or triethyloxonium fluoroborate. The resulting ethyl enol ether (III) was then saponified with sodium hydroxide to yield 1-cyclohexyl-3-ethoxyl-2-oxo-3-pyrroline-4-carboxylic acid (V). Direct nitration of the latter compound with a mixture of fuming nitric and concentrated sulfuric acids at 0° resulted in introduction of the nitro group at the 4 position with loss of the carboxyl group through decarboxylation. The yields in the several steps are indicated on the chart; they were good enough to make feasible the preparation of IV in the desired amounts.

In order to test in a preliminary way the possibility that compound IV might be a useful reagent in such applications as protein modification or peptide synthesis, reactions with a number of amino acids were investigated. It was found that the amino group of such compounds reacted readily with compound IV at room temperature in aqueous solutions at pH 10 (borate buffer) to which some acetonitrile was added to increase the solubility of IV. The products were acidic substances which yielded analytical and spectroscopic data completely consistent with assignment of their structures as those of *N*-(4-nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl) derivatives (NOPY derivatives) of the amino acids (VI), formed by replacement of the ethoxyl group as in eq 4. The products of type VI were stable crystalline compounds. Specific rotations of these derivatives were higher than those of the incorporated amino acids in the two instances examined.

Chart I

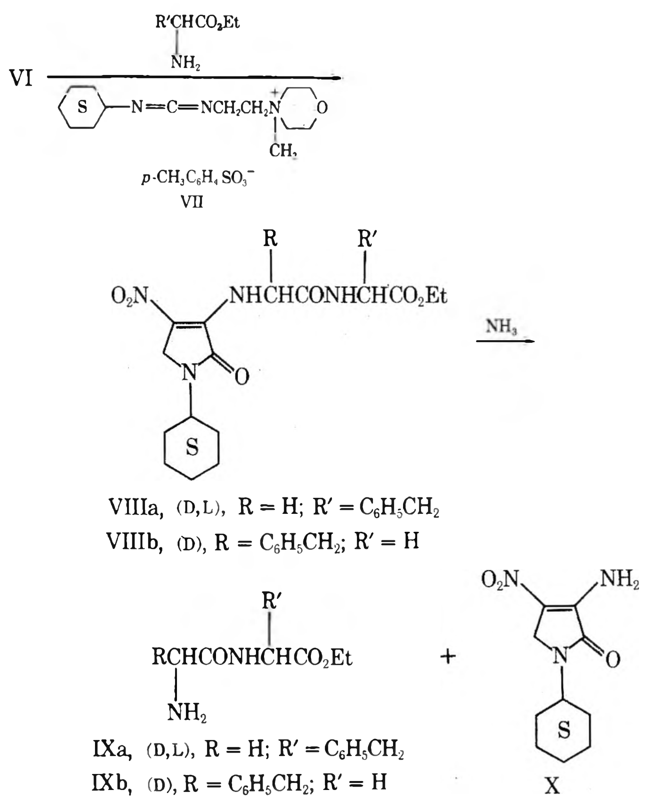


VIa, R = H
VIb, (D,L), R = $C_6H_5CH_2$
VIc, (L), R = $C_6H_5CH_2$
VId, (L), R = $(CH_3)_2CHCH_2$

Two simple examples of dipeptide synthesis were chosen to test the possible utility of the 4-nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl (NOPY) group as a removable protecting group for amino functions. Both ethyl glycyl-D,L-phenylalaninate (IXa) and ethylL-phenylalanylglycinate

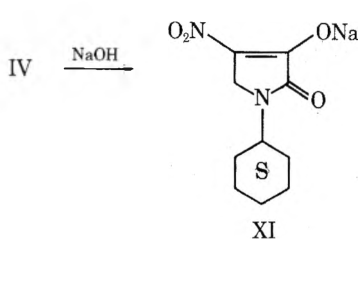
(IXb) were obtained from the appropriate NOPY-protected amino acids (VIa and VIc) by simple procedures in which coupling with an amino acid ester was conducted with 1-cyclohexyl-3-(2-morpholinoethyl)carbodiimide metho-*p*-toluenesulfonate (VII), and removal of the protecting group was accomplished by treatment with ammonia in acetonitrile at room temperature, as indicated in Chart II. The NOPY dipeptides (VIII) were easily sepa-

Chart II



rated from the water-soluble urea derivative formed from VII and were obtained in yields on the order of 75–80%. Cleavage of the NOPY derivatives VIII with ammonia in acetonitrile occurred smoothly and produced the known dipeptide ethyl esters (IXa and IXb) (characterized as hydrobromides). The yield of IXa was 73%; that of IXb was 88%. The other cleavage product was the enamine X. If racemization occurred during coupling of the L-phenylalanine derivative VIc to yield VIIIb or during the cleavage of VIIIb to yield IXb, the extent of it was not sufficient to cause any difficulty in purifying the hydrobromide of IXb to give a specific rotation very close to the value recorded in the literature for that substance. The literature concerning other amino protecting groups removable under basic conditions has been reviewed recently by Carpino and Han.[4] Applications in protein modification for NOPY ethyl ether (IV) may perhaps be foreseen in view of results reported with the somewhat analogous reversible blocking reagent, 2-methoxy-5-nitrotropone.[5]

The nitro enol ether IV underwent hydrolysis readily when treated with aqueous sodium hydroxide to yield a



XI

stable and easily purified sodium salt (XI) of the corresponding nitro enol. The sharply contrasting behavior of enol ethers III and IV toward sodium hydroxide is testimony to the strong electronic effect of the nitro group in this system.

Experimental[6] Section

1-Cyclohexyl-3-ethoxy-2-oxo-3-pyrroline-4-carboxylic Acid (V). A. Ethylation of II with Triethyloxonium Fluoroborate. Triethyloxonium fluoroborate was prepared by the method of Meerwein[7] and stored under anhydrous ethyl ether at 5°. Just prior to use, it was collected by filtration, washed with anhydrous ethyl ether, and dried on the filter under an atmosphere of dry nitrogen. 4-Carbethoxy-1-cyclohexyl-2,3-dioxopyrrolidine (II) was prepared by the method of Southwick, *et al.*,[3] and dried overnight in a vacuum desiccator over Drierite. Triethylamine was distilled and dried over potassium hydroxide pellets. A solution of 48.6 g (0.192 mol) of II and 20.2 g (0.20 mol) of triethylamine in 350 ml of methylene chloride was blanketed with dry nitrogen gas and cooled to −5° in an ice–salt bath. To this solution was added rapidly 76.0 g (0.40 mol) of the white crystalline triethyloxonium fluoroborate. After the pale-yellow solution had been stirred for 45 min at ice-bath temperature, it was extracted with two 75-ml portions of 5% aqueous sodium hydroxide, then with pH 7 phosphate buffer solution until the extracts remained neutral. The methylene chloride solution was dried ($MgSO_4$), filtered, and concentrated in a rotary evaporator over a steam bath. The crude product, 4-carbethoxy-1-cyclohexyl-3-ethoxy-2-oxo-3-pyrroline (III), was obtained in a yield of 51.5 g (95%) as a pale-yellow oil which showed no tendency to crystallize. Spectra: ir (liquid film) 3.33, 3.38, and 3.48 (cyclohexyl C–H), 5.82 (ester C=O), 5.91 (lactam C=O), 6.09 (C=C), 6.89, 7.10, 7.22, 7.40, 8.13 (broad), 9.52 (broad), 11.21, 13.10 μ (broad); nmr ($CDCl_3$) τ 5.14 (q, 2, ethyl $-CH_2-$), 5.33 (q, 2, ethyl $-CH_2-$), 5.50–6.40 (broad, 1, cyclohexyl C–H), 5.89 (s, 2, C-5 $-CH_2-$), 7.90–9.20 (m, broad, 10, cyclohexyl $(CH_2)_5$), 8.58 (t, 3, ethyl CH_3), 8.62 (t, 3, ethyl CH_3).

B. Ethylation of II with Ethyl Orthoformate. Compound II (126.7 g, 0.50 mol) with dissolved in 106 ml (94.5 g, 0.64 mol) of triethyl orthoformate and 70 ml of dimethylformamide containing a few crystals of *p*-toluenesulfonic acid. The mixture was heated and stirred for 16 hr in a distillation apparatus having a 12-in. column packed with steel helixes. During the reaction period heat input was adjusted so that ethyl orthoformate refluxing from the mixture condensed just within a Claisen distillation head fitted above the column while ethyl formate and ethanol distilled. The mixture was then concentrated under reduced pressure (aspirator) in a rotary evaporator over a steam bath, and the residue (136.4 g) was distilled. The product (yield 109 g (77.6%)) was a straw-colored oil which distilled between 170 and 175° at *ca.* 7 mm of pressure.

C. Saponification of III. A solution in 250 ml of absolute ethanol of 32 g (0.114 mol) of the ethylation product III from either procedure A or B was concentrated to a total volume of 125 ml by distillation under a nitrogen atmosphere in order to remove dissolved oxygen. In a similar manner, a 10% solution of sodium hydroxide in 80 ml of water was concentrated under nitrogen to one-half the original volume. The deoxygenated solutions were combined and stirred overnight at room temperature while blanketed with a nitrogen atmosphere. The deep-red reaction mixture which resulted was diluted to 800 ml with water and extracted twice with 75-ml portions of methylene chloride. The aqueous solution was treated with activated carbon (Norit) and filtered through a Celite filter cake. The gold-colored filtrate was made strongly acidic with 20% aqueous hydrochloric acid to precipitate the product. The suspension was stored at 5° until the precipitate had settled. The solid was collected by filtration and recrystallized from 95% ethanol to yield 22.8 g (79%) of V; mp 154–156°. A second recrystallization from 95% ethanol provided V as white prisms; mp 155–156°. Spectra: ir (Nujol) 5.81 (carboxyl C=O), 5.97 (lactam C=O), 6.11 (C=C), 6.75, 7.24, 8.04, 8.38, 8.65, 9.02, 9.36, 12.98, 13.10, 14.24 μ; nmr ($CDCl_3$) τ 6.05 (q, 2, ethyl $-CH_2-$), 5.60–6.10 (broad, 1, cyclohexyl C–H), 5.84 (s, 2, C-5 $-CH_2-$), 7.80–9.20 (m, broad, 10, cyclohexyl $(CH_2)_5$), 8.54 (t, 3, ethyl CH_3); uv (95% EtOH) 246 nm (ϵ 10,900).

Anal. Calcd for $C_{13}H_{19}O_4N$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.53; H, 7.62; N, 5.35.

4-Nitro-1-cyclohexyl-3-ethoxy-2-oxo-3-pyrroline (IV). A solution of 12.0 g (0.048 mol) of 1-cyclohexyl-3-ethoxy-2-oxo-3-pyrroline-4-carboxylic acid (V) in 150 ml of concentrated sulfuric

acid was cooled to −5° in an ice–salt bath. A solution of 10 ml of white fuming nitric acid (90%) and 10 ml of concentrated sulfuric acid was added from a dropping funnel to the reaction mixture at a rate such that the temperature did not exceed 0°. The clear, yellow-colored solution was stirred for 4 hr at −5°. After 15 min gas evolution from the stirred solution became evident. The rate of evolution gradually increased to a maximum after *ca.* 1 hr and then slowly subsided to a virtual halt by the end of the 4-hr reaction period. The solution was slowly poured into 2 l. of ice–water with vigorous stirring. The suspension which resulted was stored overnight at 5° to allow the precipitate to settle. The pale-yellow solid was collected by filtration, washed with water to remove acid, and dried on the filter. Recrystallization from 95% ethanol yielded 9.60 g (80%) of IV as yellow needles; mp 88–90°. An analytical sample of IV, mp 89–90°, was prepared by a second recrystallization from 95% ethanol. Spectra: ir (Nujol) 5.92 (lactam C=O), 6.17 (C=C), 6.70 (conj NO_2), 7.13, 7.25, 7.35, 7.72, 8.01, 8.29, 8.40, 11.31 μ; nmr ($CDCl_3$) τ 4.83 (q, 2, ethyl $-CH_2-$), 5.57 (s, 2, C-5 $-CH_2-$), 5.65–6.10 (broad, 1, cyclohexyl C–H), 7.50–9.00 (m, 10, cyclohexyl $(CH_2)_5$), 8.47 (t, 3, ethyl CH_3); uv (95% EtOH) 297 nm (ϵ 8800).

Anal. Calcd for $C_{12}H_{18}O_4N_2$: C, 56.68; H, 7.14; N, 11.02. Found: C, 56.85; H, 7.02; N, 11.05.

Sodium 4-Nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-oxide (XI). A suspension of 1.00 g (3.9 mmol) of IV in 20 ml of 20% aqueous sodium hydroxide solution was stirred at room temperature overnight. The starting material slowly dissolved to give a bright yellow solution and then the product began to precipitate as a fluffy tan solid. The suspension was filtered to collect the precipitate, which was dried on the filter and recrystallized from water to give 0.84 g (86%) of XI as pale-yellow plates. Two additional recrystallizations from water provided an analytical sample of XI; mp 163° (softens to give a gel). The product gave a weak ferric chloride test (brown) in aqueous solution. Spectra: ir (Nujol) 5.85 (lactam C=O), 6.04 (C=C), 7.10 (conj NO_2), 7.60, 7.90, 8.40, 9.56, 10.00, 10.63 μ; nmr (DMSO-d_6) τ 5.92 (s, 2, C-5 $-CH_2-$), 5.80–6.35 (broad, 1, cyclohexyl C–H), 8.00–9.30 (m, 10, cyclohexyl $(CH_2)_5$); uv (H_2O) 363 nm (ϵ 17,300).

Anal. Calcd for $C_{10}H_{13}O_4N_2Na$: C, 48.41; H, 5.24; N, 11.29. Found: C, 48.59; H, 5.48; N, 11.09.

***N*-(4-Nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-amino Acid Derivatives (VI). General Procedure.** To a solution of 6.0 mmol of the amino acid in 40 ml of a pH 10.0 borate buffer solution (VWR Scientific) was added 1.02 g (4.0 mmol) of the nitro enol ether IV and 8 ml of acetronitrile. The suspension was stirred at room temperature until the starting material had dissolved to give a clear bright-yellow solution (*ca.* 30 min usually sufficed). An aliquot was then withdrawn from the solution, diluted with 95% ethanol, and its uv spectrum recorded. Completion of the reaction was indicated by the appearance of an absorption maximum at *ca.* 380 nm and the disappearance of that at 290 nm (due to unchanged IV). After a total period of 1 hr at room temperature, the reaction mixture was diluted to 100 ml with water. The aqueous solution was made strongly acidic (pH <2) with 20% aqueous hydrochloric acid, the resulting suspension was stirred vigorously at room temperature until the precipitated material solidified, and the mixture was then stored at 5° until the solid had settled. The precipitate was collected by filtration, recrystallized, and characterized as indicated for the following individual examples.

***N*-(4-Nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-glycine (VIa).** The crude product obtained from the reaction of glycine with 1.02 g (4.0 mmol) of IV was recrystallized from 95% ethanol to give 1.07 g (94%) of VIa as fine pale-yellow needles, mp 180–183°. A second recrystallization from 95% ethanol provided an analytical sample of VIa, mp 185–186° dec. Spectra: ir (Nujol) 2.98 (enamine N–H), 5.69 (acid C=O), 5.90 (lactam C=O), 6.01 (C=C), 6.80 (conj NO_2), 7.22 (broad), 7.79, 7.92, 8.03, 8.30 (broad), 8.97, 13.24 μ; nmr ($CDCl_3/CF_3CO_2H$) τ 1.20–1.80 (broad, 1, enamine N–H), 5.21 (d, J = 7 Hz, 2, glycine $-CH_2-$), 5.68 (s, 2, C-5 $-CH_2-$), 5.70–6.35 (broad, 1, cyclohexyl C–H), 8.75–9.05 (m, 10, cyclohexyl $(CH_2)_5$); uv (95% EtOH) 370 nm (ϵ 16,600).

Anal. Calcd for $C_{12}H_{17}O_5N_3$: C, 50.88; H, 6.05; N, 14.83. Found: C, 50.60; H, 5.99; N, 14.79.

***N*-(4-Nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-D,L-phenylalanine (VIb).** Recrystallization of the crude product from an ethanol–water mixture yielded 1.42 g (95%) of VIb as pale-yellow, very fine needles; mp 147–149°. An analytical sample, mp 148–149.5° dec, was obtained by two additional recrystallizations from ethanol–water. Spectra: ir (Nujol) 2.75, 2.89 (enamine N–H and acid O–H), 5.76 (acid C=O), 5.84 (lactam C=O), 6.01 (C=C), 6.86 (conj NO_2), 7.13, 7.39, 7.50, 7.80 (broad), 7.90, 8.44, 9.11, 13.26, 13.80 (broad), 14.13 μ (broad); nmr ($CDCl_3/CF_3CO_2H$) τ 1.36–1.82 (d, broad, 1, enamine N–H), 2.44 (s, 5, C_6H_5), 3.65–4.20 (m, broad, 1, phenylalanine C–H), 5.67 (s, 2, C-5 $-CH_2-$), 5.50–6.20 (broad, 1, cyclohexyl C–H), 6.40–7.00 (m, 2, phenylalanine $-CH_2-$), 7.76–9.30 (m, 10, cyclohexyl $(CH_2)_5$); uv (95% EtOH) 373 nm (ϵ 15,600).

Anal. Calcd for $C_{19}H_{23}O_5N_3$: C, 61.11; H, 6.21; N, 11.25. Found: C, 60.99; H, 5.98; N, 11.16.

***N*-(4-Nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-L-phenylalanine (VIc).** The crude product from the reaction of 2.04 g (8 mmol) of IV with L-phenylalanine was recrystallized from carbon tetrachloride to yield 2.65 g (89%) of VIc as clusters of very fine, pale-yellow needles: mp 153–156°. A second recrystallization from carbon tetrachloride provided an analytical sample of VIc; mp 155–156° dec. Spectra: ir (Nujol) 3.00, 3.27 (broad) (enamine N–H and acid O–H), 5.71 (acid C=O), 5.90 (lactam C=O), 6.03 (C=C), 6.90 (conj NO_2), 7.15 (broad), 7.44, 7.84, 7.93, 8.39, 9.10, 13.29, 14.42 μ (broad); nmr ($CDCl_3$) τ 0.95 (broad, 1, OH), 1.50–2.00 (d, broad, 1, enamine N–H), 2.70 (s, 5, C_6H_5), 3.75–4.30 (m, broad, 1, phenylalanine C–H), 5.88 (s, 2, C-5 $-CH_2-$), 5.70–6.30 (broad, 1, cyclohexyl C–H), 6.40–7.00 (m, 2, phenylalanine $-CH_2-$), 7.60–9.10 (m, 10, cyclohexyl $(CH_2)_5$); uv (95% EtOH) 373 nm (ϵ 15,800); $[\alpha]^{25}D$ −164° (c 2, 95% EtOH).

Anal. Calcd for $C_{19}H_{23}O_5N_3$: C, 61.11; H, 6.21; N, 11.25. Found: C, 60.88; H, 6.35; N, 10.98.

***N*-(4-Nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-L-leucine (VId).** Recrystallization of the crude product from 95% ethanol yielded 1.44 g (93%) of VId as bright green-yellow needles; mp 81–86°. A second recrystallization gave an analytical sample; mp 86–87°. The nmr and analysis both showed the presence of ethanol of crystallization in a ratio of 1 mol of ethanol per mol of VId. Spectra: ir (Nujol) 2.97 (broad) (enamine N–H and acid O–H), 5.81 (acid C=O), 5.91 (lactam C=O), 6.02 (C=C), 6.90 (broad) (conj NO_2), 7.18, 7.22, 7.73, 8.07, 8.25 μ; nmr ($CDCl_3$) τ 1.25–1.86 (d, broad, 1, enamine N–H), 1.95 (s, 2, OH's), 3.83–4.50 (m, broad, leucine C–H), 5.61 (s, 2, C-5 $-CH_2-$), 5.40–6.31 (broad, 1, cyclohexyl C–H), 6.16 (q, 2, ethanol $-CH_2-$), 7.30–9.35 (m, 22, cyclohexyl $(CH_2)_5$, leucine $CH_2-CH(-CH_3)_2$, and ethanol CH_3); uv (95% EtOH) 272 nm (ϵ 7200), 372 nm (ϵ 17,100); $[\alpha]^{25}D$ +22.4° (c 2, 95% EtOH) (based upon molecular weight without ethanol of crystallization).

Anal. Calcd for $C_{16}H_{25}O_5H_3 \cdot C_2H_5OH$: C, 56.09; H, 8.11; N, 10.90. Found: C, 56.00; H, 7.98; N, 11.08.

Ethyl *N*-(4-Nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-glycyl-D,L-phenylalaninate (VIIIa). To a suspension of 1.12 g (4.0 mmol) of *N*-(4-nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-glycine (VIa) in 40 ml of methylene chloride was added 0.76 g (4.0 mmol) of ethyl D,L-phenylalaninate.[8] The starting materials dissolved to give a clear yellow solution. The solution was cooled to 0° in an ice bath and 1.70 g (4.0 mmol) of 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-*p*-toluenesulfonate (VII)[9] was added. The mixture was stirred at 0° for 40 min while the by-product urea began to precipitate. The reaction mixture was then allowed to warm slowly to room temperature and stirred overnight. After 18 hr at room temperature the reaction mixture was filtered, and the filtrate was extracted with two 10-ml portions of 1% aqueous hydrochloric acid and two 25-ml portions of water to remove the urea by-product. The methylene chloride solution was dried ($MgSO_4$), filtered, and concentrated in a rotary evaporator over a steam cone. The evaporation was continued at room temperature until the residue solidified. The solid was recrystallized from 95% ethanol to yield 1.38 g (76%) of VIIIa as pale-yellow, very fine crystals; mp 123–128°. A second recrystallization from 95% ethanol provided an analytical sample of VIIIa; mp 129–130°. Spectra: ir (Nujol) 2.99 (NH), 5.77 (ester C=O), 5.86 and 5.99 (amide C=O), 6.03 (C=C), 6.50 (amide), 6.91 (conj NO_2), 7.17, 7.71, 7.90, 8.28, 8.89, 9.12, 9.65, 10.34, 13.22, 14.30 μ; nmr ($CDCl_3$) τ 0.80–1.35 (broad, 1, enamine N–H), 2.45 (s, 5, C_6H_5), 2.50–3.00 (m, 1, amide N–H), 4.60–5.10 (m, 1, phenylalanine C–H), 5.13 (d, J = 7 Hz, 2, glycine $-CH_2-$), 5.34–6.10 (m, 5, C-5 $-CH_2-$, ethyl ester $-CH_2-$, and cyclohexyl C–H), 6.72 (d, J = 6 Hz, 2, phenylalanine $-CH_2-$), 7.40–8.90 (m, 10, cyclohexyl $(CH_2)_5$), 8.70 (t, 3, ethyl ester CH_3); uv (95% EtOH) 370 nm (ϵ 17,000).

Anal. Calcd for $C_{23}H_{30}N_4O_6$: C, 60.25; H, 6.60; N, 12.22. Found: C, 60.01; H, 6.63; N, 12.10.

Ethyl *N*-(4-Nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-L-phenylalanylglycinate (VIIIb). To a solution of 1.49 g (4.0 mmol) of *N*-(4-nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-L-phenylalanine in 40 ml of methylene chloride, maintained at 0° by cooling in an ice bath, was added 0.44 g (4.2 mmol) of ethyl glycinate.[8] A bulky precipitate (probably the carboxylate salt) formed

almost immediately. To the cold suspension was added 1.70 g (4.0 mmol) of 1-cyclohexyl-3-(2-morpholinoethyl)-carbodiimide metho-*p*-toluenesulfonate. The starting materials first dissolved and then the by-product urea began to precipitate. The reaction mixture was stirred overnight while allowing it to warm slowly to room temperature. After a total period of 20 hr the suspension was filtered and extracted with three 100-ml portions of water. The methylene chloride solution was dried ($MgSO_4$), filtered, and concentrated in a rotary evaporator over a steam cone. The evaporation was continued at room temperature until the residue solidified. The residue was recrystallized from carbon tetrachloride to give 1.49 g (82%) of VIIIb; mp 61–65° (softens to a gel). Two additional recrystallizations from carbon tetrachloride provided an analytical sample of VIIIb; mp 62–63° (softens). Spectra: ir (Nujol) 2.99 (NH), 5.70 (ester C=O), 5.95 (amide C=O), 6.04 (C=C), 6.47 (amide), 6.85 (broad) (conj NO_2), 7.25 7.62, 7.82 (broad, 8.30 (broad), 9.65 μ (broad); nmr ($CDCl_3$) τ 1.40–1.85 (broad, 1, enamine N–H), 2.74 (s, 5, C_6H_5), 2.95–3.35 (broad, 1, amide N–H), 3.80–4.40 (m, 1, phenylalanine C–H), 5.52–6.30 (m, 7, glycine $-CH_2CH-$, C-5 $-CH_2-$, ethyl ester $-CH_2-$, and cyclohexyl C–H), 6.50–7.00 (m, 2, phenylalanine $-CH_2-$), 7.60–9.00 (m, 10, cyclohexyl $CH_2)_5$), 8.73 (t, 3, ethyl ester CH_3); uv (95% EtOH) 373 nm (ϵ 15,900); $[\alpha]^{25}D$ − 164° (c 2, 95% EtOHz.

Anal. Calcd for $C_{23}H_{30}O_6N_4$: C, 60.25; H, 6.60; N, 12.22. Found: C, 60.04; H, 6.46; N, 12.06.

Ammonia Cleavage of Ethyl *N*-(4-Nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-glycyl-D,L-phenylalaninate (VIIIa). Preparation of Ethyl Glycyl-D,L-phenylalaninate Hydrobromide (IXa). Anhydrous ammonia gas was bubbled slowly with stirring into a solution of 0.92 g (2.0 mmol) of ethyl *N*-(4-nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-glycyl-D,L-phenylalaninate (VIIIa) in 20 ml of acetonitrile. After 2 hr, the addition of ammonia was discontinued, the reaction flask was stoppered loosely, and the solution was stirred at room temperature. The progress of the reaction was monitored by withdrawing aliquots of the solution periodically and determining the wavelength of maximum absorptivity in the uv. Over a 24-hr period the absorption maximum gradually shifted from 370 nm (due to the starting material VIIIa) to 352 nm (due to the by-product 4-nitro-1-cyclohexyl-3-amino-2-oxo-3-pyrroline (X)). After 24 hr the acetonitrile solution was poured slowly into 200 ml of dilute hydrochloric acid and crushed ice to give an acidic suspension (pH *ca.* 2) from which most of the by-product X precipitated. The solid was removed by filtration in a yield of 0.41 g (91%) of crude 4-nitro-1-cyclohexyl-3-amino-2-oxo-3-pyrroline (X); mp 181–190° (*vide infra*). After the precipitated X had been filtered out, the acidic aqueous filtrate was extracted with three 30-ml portions of methylene chloride to remove the last traces of X. The pH of the aqueous solution was adjusted successively to pH 7–8, 8–9, and 9–12 by the stepwise addition of portions of 3% aqueous sodium hydroxide. Following the addition of each increment of sodium hydroxide, the aqueous solution was extracted with two 20-ml portions of methylene chloride. The combined methylene chloride extracts were dried ($MgSO_4$), filtered, and concentrated in a rotary evaporator over a steam bath to give ethyl glycyl-D,L-phenylalaninate (IXa) as a pale-yellow oil. The identification of this product as IXa was supported by its nmr spectrum. Spectra: nmr ($CDCl_3$) τ 1.80–2.20 (d, broad, 1, amide N–H), 2.58 (s, 5, C_6H_5), 4.80–5.30 (m, 1, phenylalanine C–H), 5.75 (q, 2, ethyl ester $-CH_2-$), 6.50–7.10 (m, 4, glycine $-CH_2-$ and phenylalanine $-CH_2-$), 8.00–8.50 (broad, 2, amine NH_2), 8.80 (t, 3, ethyl ester CH_3).

The oil IXa which was isolated from the methylene chloride extractions was immediately dissolved in 20 ml of anhydrous ethyl ether and anhydrous hydrogen bromide was slowly bubbled with stirring into the solution at room temperature. A bulky white precipitate formed immediately. After 5 min, the addition of hydrogen bromide was discontinued, and the reaction mixture was cooled overnight to 5° in a stoppered flask. The solid was collected by filtration, washed with anhydrous ethyl ether, and recrystallized from a mixture of acetic acid and ethyl ether to yield 0.48 g (73%) of the white crystalline hydrobromide salt of IXa; mp 152–154°. A second recrystallization from acetic acid and ethyl ether raised the mp to 154–155° (lit.[10] mp 154–155°).

4-Nitro-1-cyclohexyl-3-amino-2-oxo-3-pyrroline (X). The crude by-product which precipitated upon dilution of the ammonia-cleavage reaction mixture from VIIIa with aqueous acid was recrystallized twice from 95% ethanol to give X as pale tan prisms; mp 191–192°. Spectra: ir (Nujol) 2.90, 3.06 (NH_2), 5.80 (lactam C=O), 5.96 (C=C), 6.95 (conj NO_2), 7.25, 7.60, 7.84, 8.31, 8.43, 10.15, 13.45 (broad), 15.20 μ (broad); nmr ($CDCl_3/CF_3CO_2H$) τ 1.90–2.90 (broad, 2, NH_2), 5.50 (s, 2, C-5 $-CH_2-$), 5.20–6.30 (broad, 1, cyclohexyl C–H), 7.50–9.20 (m, 10, cyclohexyl $(CH_2)_5$); uv (95% EtOH) 353 nm (ϵ 14,700).

Anal. Calcd for $C_{10}H_{15}O_3N_3$: C, 53.32; H, 6.71; N, 18.66. Found: C, 53.30; H, 6.71; N, 18.56.

Ammonia Cleavage of *N*-(4-Nitro-1-cyclohexyl-2-oxo-3-pyrrolin-3-yl)-L-phenylalanylglycinate (VIIIb). Preparation of Ethyl L-Phenylalanylglycinate Hydrobromide (IXb). The procedure employed was essentially identical with that for the conversion of VIIIa to IXa. The hydrobromide of the crude dipeptide ester IXb was collected by filtration, washed with anhydrous ethyl ether, and recrystallized from acetonitrile to yield 0.58 g (88%) of the white crystalline salt IXb; mp 131–136°. The salt was recrystallized a second time from acetonitrile to provide a sharper melting sample; mp 132–134° (lit. mp[11] 134–137°); $[\alpha]^{25}D$ +39.1° (*c*, 2, H_2O) (lit.[11] $[\alpha]^{25}D$ +39.2° (*c*, 2, H_2O)).

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Registry No.—II, 4563-90-0; III, 52555-21-2; IV, 52555-22-3; V, 52555-23-4; VIa, 52555-24-5; VIb, 52555-25-6; VIc, 52555-26-7; VId, 52555-27-8; VII, 2491-17-0; VIIIa, 52555-28-9; VIIIb, 52555-29-0; IXa, 52555-30-3; IXa HBr, 52555-31-4; IXb HBr, 5399-16-2; X, 52555-32-5; XI, 52555-33-6; triethyloxonium fluoroborate, 368-39-8; triethyl orthoformate, 122-51-0; glycine, 56-40-6; D,L-phenylalanine, 150-30-1; L-phenylalanine, 63-91-2; L-leucine, 61-90-5; ethyl D,L-phenylalaninate, 1795-96-6; ethyl glycinate, 459-73-4.

References and Notes

(1) Taken from the Ph.D. Theses of R. F. Dufresne, 1972, and J. C. Lindsey, 1973, Carnegie-Mellon University.
(2) P. L. Southwick, J. A. Fitzgerald, R. Madhav, and D. A. Welsh, *J. Org. Chem.*, **34**, 3279 (1969).
(3) P. L. Southwick, E. P. Previc, J. Casanova, Jr., and E. H. Carlson, *J. Org. Chem.*, **21**, 1087 (1956).
(4) L. A. Carpino and G. Y. Han, *J. Org. Chem.*, **22**, 3404 (1972).
(5) H. Tamaoki, Y. Murase, S. Minato, and K. Nakanishi, *J. Biochem. (Tokyo)*, **62**, 7 (1967).
(6) Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were recorded from Nujol mulls or potassium bromide pellets employing either the Perkin-Elmer Infracord or Perkin-Elmer Model 237-B spectrophotometers. Major peaks at wavelengths from 2.5 to 7.0 μ are reported with assignments where possible; additional absorption maxima of intensity greater than 0.15 absorbance are reported for wavelengths between 7.0 and 16.0 μ. Nuclear magnetic resonance spectra were obtained with a Hitachi Perkin-Elmer Model R-20, 60-MHz instrument. Chemical shifts are reported as τ values. For well resolved, symmetric, doublets, triplets, or quartets, the reported chemical shifts refer to the midpoints of those multiplets. A range of values is given for the chemical shifts of more complex multiplets or of broad unresolved signals. The following abbreviations have been used in reference to nmr data: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Ultraviolet spectra were run as *ca.* 1×10^{-4} *M* solutions using a Perkin-Elmer Model 202 spectrophotometer. The wavelength in nanometers and molar absorptivity have been reported for all intense absorption maxima at wavelengths greater than 205 nm. Less intense features, such as shoulders (sh), are also indicated where relevant. Optical rotations were determined with a Rudolph Model 80 polarimeter at the sodium D line. Elemental microanalyses were performed by H-H-W Laboratories, Garden City, Mich.
(7) H. Meerwein in "Organic Syntheses," Collect. Vol. V, H. E. Baumgarten, Ed., Wiley, New York, N.Y., 1973, p 1097.
(8) Obtained from the hydrochloride (T. Curtins and E. Muller, *Chem. Ber.*, **37**, 1261 (1904)) by adjustment of a concentrated aqueous solution to pH 10 with 1% sodium hydroxide and extraction into methylene chloride.
(9) Pierce Chemical Co.
(10) G. W. Anderson and F. M. Callahan, *J. Amer. Chem. Soc.*, **82**, 3359 (1960).
(11) S. Lande, *J. Org. Chem.*, **27**, 4558 (1962).

Decomposition of a β,γ-Unsaturated Diazo Ketone. Evidence for the Intermediacy of a Bicyclopentanone[1]

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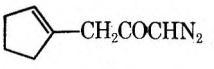
Decomposition of the β,γ-unsaturated diazo ketone **1** was carried out by photolysis, silver oxide catalysis, and thermal reaction at 150–180° in benzyl alcohol and *N,N*-diethylaniline. Thermal reactions yielded both the normal Wolff rearrangement product **5** and abnormal product **9** in which there has been an apparent allylic shift of an acetic acid residue. This compound could be made the exclusive product in the presence of small amounts of a copper salt. Its formation is rationalized in terms of an intramolecular addition to form tricyclo[3.3.0.0^{1,4}]octan-3-one, which opens to a ketene from which **9** is derived. A deuterium labeling experiment is in accord with this pathway.

The copper-catalyzed decomposition of unsaturated diazo ketones is a well-known and useful reaction leading to an intramolecular carbenoid addition to the double bond to form cyclopropyl ketones.[2] Such reactions are not common, however, for α,β- or β,γ-unsaturated diazo ketones.

The investigation of β,γ-unsaturated diazo ketones should be of interest, since an intramolecular addition here would lead to a highly strained bicyclopentanone. Of the diazo ketones of this type that have been prepared, **1**, for example, is reported to undergo normal Wolff rearrangement.[3] There are other examples, however, run under a variety of conditions, in which the double bond does participate.[4–6] In one of these cases,[5] an addition product actually survives the reaction conditions. In the other two cases,[4,6] abnormal products were isolated from attempted Wolff rearrangements. These are attributed by Wilds[4] to steric crowding in the reactive portion of the molecules.

We have had occasion to investigate the decomposition of **1** under a variety of conditions, and present here evidence that, in some cases, carbenoid interaction with the double bond does occur, with the possible intermediacy of the tricyclic ketone **2**. The diazo ketone **1** is a pale yellow



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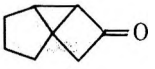
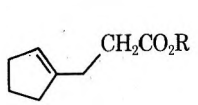
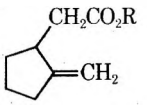


2

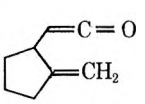
liquid, which can be crystallized from hexane at low temperatures or distilled (usually with some decomposition). Because the few impurities in the crude material were shown not to affect the later reactions, the compound was used in most of our experiments in crude form. The Wolff rearrangement of this compound either using silver oxide as catalyst or by photolysis (253.7 nm) in a dioxane–water solution led to **3** as the only acidic product in 20 and 70% yield, respectively, while nearly quantitative yields of the ester **4** could be achieved by photolysis in methanol.



3, R = H
4, R = CH_3
5, R = $CH_2C_6H_5$



6, R = H
7, R = CH_3
8, R = C_2H_5
9, R = $CH_2C_6H_5$

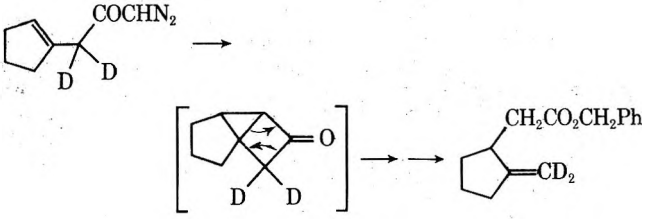


10

An attempt, however, to rearrange **1** using Wilds' conditions[4] (heating in a mixture of benzyl alcohol and diethylaniline[7]) yielded a mixture, nearly 1:1, of two benzyl esters, identified as **5** and **9**. The identity of **5** was established by saponification to the known acid **3**, that of **9** by direct comparison of the corresponding methyl ester **7** with material prepared by an independent route as described in the Experimental Section. The product ratio observed in the thermal reaction proved to be somewhat unreproducible, and the fraction of **5** in the ester product on later attempts varied from 5 to 95%. The total ester yield (gas chromatographic analysis), however, was always nearly quantitative, based on diazo ketone.

The variability in product ratio was traced to minute traces of copper ions, whose source was a copper steam heating coil in a large container used to soak glassware in a detergent solution. Inadequate rinsing of glassware in which the diazo ketone was handled was at fault, and increased quantities of **9** could be achieved either by deliberately using poorly rinsed flasks to handle the diazo ketone or, better, by adding traces of copper(II) acetylacetonate (**11**) to the reaction mixtures. The quantity of copper necessary to make a substantial difference in the product ratio was extremely small. A mixture of 20 mg of **1** in 300 ml of solvent, to which a few milligrams of **11** were added before heating, produced only **9** with no **5** detectable. In the absence of any copper, the ratio was reproducibly 5% **9** and 95% **5**. It was determined that other potential contaminants, including water, acid, and certain impurities separated from the diazo ketone, had no consistent effect when deliberately added to reaction mixtures.

In order to clarify the structural change in the formation of **9**, a deuterium labeling experiment was performed. A sample of cyclopent-1-enylacetic acid was treated with sodium deuterioxide in D_2O, and after equilibration contained 1.5 atoms of D per molecule (nmr analysis), all in the α position. Conversion of this to the diazo ketone **1**-d_2 was accomplished without loss of label. Thermal reaction of this under conditions conducive to formation of **9** led to material still containing the same amount of deuterium, all of it in the vinyl positions. This is consistent with a process going through an intermediate such as **2**.

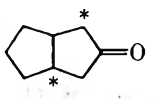


Several attempts were made to generate and isolate the intermediates involved in the pathway by which **9** was formed, without success. These involved reactions of **1** with suspensions of copper sulfate or solutions of **11** in dry cyclohexane, but neither **2** nor **10** was observed, nor was there

evidence for volatile monomeric products of any kind. It is suspected that **2**, if formed, goes rapidly, even at room temperature, to **10** and that **10** reacts with unreacted diazo ketone[8] to form more complex products.

While the major route to **6** or its derivatives is the copper-catalyzed reaction, there appears to be another pathway, as well. In the thermal reactions run after the clarification of the role of adventitious copper, there was always at least 5–15% of **9** formed along with the major product **5**. This suggests that some intermediate in the uncatalyzed reaction, perhaps a ketocarbene, can add to the double bond to form **2** at least transiently.

In addition to the pathway we are suggesting for the formation of **9** (**1** → **2** → **10** → **9**) one can write at least two others. One of these involves an intermediate, **12** (either biradical or dipolar), in which only one new bond is yet formed (**1** → **12** → **10** → **9**). The other[9] would invoke a di-



12 (*,* = +,−, or ·,·)

rect electrocyclic pathway from a carbenoid to **10** with simultaneous bond breakage and formation. In the absence of firm evidence for **2**, we prefer to consider it an intermediate for two reasons. The first is analogy to the products in larger unsaturated systems;[2] the second is the known chemistry of bicyclopentanones.

There have been several photochemical studies on cyclopentenones, in which bicyclopentanones are products or presumed intermediates.[10] In two of these cases, bicyclopentanones which are sterically protected by bulky *tert*-butyl groups have been isolated at room temperature, but in the two unprotected cases, examined by Zimmerman and Agosta, only ring-opened products have been isolated from room temperature irradiations. In Zimmerman's case, the bicyclopentanone could be observed in a low-temperature irradiation, and on further irradiation it opened to a ketene in a manner analogous to the transformation of **2** to **10** in the present case. In the case of **2**, indeed, the added strain from the additional fused five-membered ring should increase the facility of ring opening and might account for our failure to isolate the compound.[17]

In summary, rearrangement of this β,γ-unsaturated diazo ketone proceeds normally under most conditions. It is possible, though, for participation of the double bond to occur, particularly in the presence of a copper catalyst. In such cases, the strained tricyclic ketone **2** is a likely intermediate, and the final product is related to the normal Wolff rearrangement product by an apparent allylic shift of an acetic acid residue. This reaction, which proceeds in high yield, may be of synthetic use.

Experimental Section

All melting points were determined on a Thomas Hoover apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer Model 337 grating spectrometer, nmr spectra on Varian A-60A or Perkin-Elmer R12-B instruments at 60 MHz, using deuteriochloroform as solvent and tetramethylsilane as internal reference, and uv spectra on a Cary 14 uv–visible recording spectrophotometer. Gas chromatographic analyses were performed on an F & M Model 609 instrument with flame ionization detector, and small-scale preparative gc was done on a Varian Aerograph 90-P3 instrument with a thermal conductivity detector. Columns used were ¼ in. × 10 ft copper columns packed with 10% SE-30 silicone oil on 60/80 Chromosorb W. Relative amounts of esters in the rearrangement reactions were determined by area measurements on the chromatograms and corrected for results on mixtures of known composition. Microanalysis was done by the Galbraith Laboratories, Inc., Knoxville, Tenn. The mass spectra were run on a Hewlett-Packard 5930A quadrupole spectrometer operating at 70 V.[11]

Preparation of (Cyclopenten-1-ylacetyl)diazomethane (1). Ethyl cyclopentylidineacetate was prepared in 81% yield according to the procedure[12] reported for the analogous six-membered case. The product was distilled at 96–104° (17–19 mm): nmr δ 5.84 (m, 1 H), 4.18 (q, 2 H), 1.45 (t, 3 H), 1.5–3.0 (4 H); ir (neat) 1705, 1650 cm^{-1}. A small amount of the unconjugated isomer was also present (ir 1730 cm^{-1}).

This ester was, without further purification, refluxed for 15 hr with 200 ml of 20% KOH. From the cooled, acidified solution was isolated cyclopent-1-enylacetic acid (**13**) which was recrystallized from petroleum ether (36–50°). The yield of solid (mp 51–52°, lit.[13] 52°) was 21.2 g (63%): nmr δ 11.4 (s, 1 H), 5.61 (s br, 1 H), 3.18 (s br, 2 H), 1.6–2.6 (6 H); ir ($CHCl_3$) 1710 cm^{-1}.

A solution of **13** (16.55 g, 0.131 mol) in 50 ml of CH_2Cl_2 was cooled to 0°. Oxalyl chloride (20 ml, 29.7 g, 0.23 mol) was slowly added to this stirred solution. The mixture was allowed to warm to room temperature over a 3-hr period, and the solvent was removed at reduced pressure. The product cyclopent-1-enylacetyl chloride (**14**) was distilled at 76–77° (25 mm) to yield 17.84 g (94%) of colorless liquid: nmr δ 5.73 (m, 1 H), 3.68 (s br, 2 H), 1.7–2.6 (6 H); ir (neat) 1795 cm^{-1}.

A solution of **14** (5.13 g, 0.036 mol) in 55 ml of anhydrous ether was added dropwise to an ice-cold, dry solution of approximately 6 g of CH_2N_2 in 500 ml of ether. The resulting solution was allowed to come to room temperature overnight and then was filtered and evaporated. The residual yellow oil was taken up in petroleum ether, dried over $MgSO_4$, and evaporated to yield 5.11 g (95%) of **1** as a light yellow oil: nmr δ 5.61 (m, 1 H), 5.37 (s, 1 H, CHN_2), 3.15 (s br, 2 H), 1.6–2.6 (6 H); ir (neat) 2100, 1630, 1360 cm^{-1}.

Decomposition of 1. A. Photolysis. A solution of crude **1** (19.2 g, 0.13 mol) in 300 ml of purified dioxane and 250 ml of H_2O was irradiated in a quartz vessel with low-pressure Hg lamps (253.7-nm maximum output) at room temperature in a Rayonet[14] photochemical reactor for 20.5 hr. The reaction was followed by observing the disappearance of diazo ketone absorbance at 250 nm in aliquots. The solution was made basic with 7.2 g of KOH (0.13 mol) and concentrated to 200 ml on a rotary evaporator. It was washed with ether, acidified, and extracted with ether. The ether layer was separated, dried ($MgSO_4$), and evaporated to provide 12.19 g (68%) of 3-(cyclopenten-1-yl)propanoic acid (**3**), mp 63.5–64.5° from petroleum ether (36–50°) (lit.[3] 64°).

B. Thermal Reactions. In general, especially for reactions in which only the product ratio of normal to abnormal products was being investigated, the procedure involved dissolving 20 μl of **1** in a mixture of 150 μl of purified[15] benzyl alcohol (BA) and 150 μl of *N,N*-diethylaniline (DEA) in a 10 × 75 mm test tube. This was immersed in a pre-heated oil bath (150–180°) for 2 min and the product ratio determined by gas chromatography of the reaction mixture.

A larger scale reaction leading to **3** was run under similar conditions. A solution of 1.56 g (10.4 mmol) of **1** in 10 ml each of BA and DEA was prepared in a 50-ml round-bottom flask fitted with a reflux condenser. This was immersed for 8 min in an oil bath heated to 180°. The cooled mixture was diluted with ether, washed with 10% HCl to remove DEA, and then dried and evaporated. The residue was stirred at reflux in 10 ml of CH_3OH, 4.5 g of KOH, and 6.5 ml of H_2O for 3 hr. The methanol was removed by evaporation. The aqueous residue was diluted with water, washed with ether, and then cooled and acidified with 10% HCl. The dark solid that separated was taken up in ether, washed with 10% HCl and then saturated NaCl, dried, and evaporated to yield 0.837 g (57%) of crude **3**.

A separate reaction in which both **3** and **6** were formed was worked up as above, and then the mixture of acids, in ether, was treated at room temperature with an excess of CH_2N_2 in ether. After reaction was complete, the solution of methyl esters was dried and evaporated to yield 46% (based on crude **1**) of a mixture of methyl (2-methylenecyclopent-1-yl)acetate (**7**) and methyl 3-(cyclopenten-1-yl)propanoate (**4**). The esters were separated and isolated by gc at 150°. The shorter retention time isomer was **7**: nmr δ 4.85 (m, 2 H), 3.70 (s, 3 H), 1.1–3.1 (9 H); ir (neat) 1745, 1655, and 883 cm^{-1}; mass spectrum molecular ion at m/e = 154, base peak 94. The longer retention time product was **4**: nmr δ 5.40 (m, 1 H), 3.70 (s, 3 H), 1.7–2.5 (10 H); ir (neat) 1740 cm^{-1}; mass spectrum molecular ion 154, base peak 79.

Synthesis of 7. In a 500-ml round-bottom flask equipped with N_2 inlet, reflux condenser, addition funnel, and stirrer was placed a solution of 33.95 g (0.25 mol) of the pyrrolidine enamine of cyclopentanone[16] [bp 103° (25 mm)] in 200 ml of acetonitrile. Ethyl

bromoacetate (24 ml, 36.4 g, 0.218 mol) was added dropwise to this stirred solution. The mixture was then heated at reflux for 17 hr. When the deep red solution cooled, most of the solvent was removed at reduced pressure and replaced with 130 ml of H_2O, and the mixture was refluxed again for 45 min. The ethyl (2-oxocyclopentyl)acetate (**15**) was extracted from the cooled mixture with ether and isolated by fractional distillation: 13.3 g (36%); bp 133–135° (23 mm); ir (neat) 1730 cm^{-1}.

A 250-ml three-neck flask equipped with N_2 inlet and reflux condenser and containing 0.72 g (0.03 mol) of NaH and 25 ml of dimethyl sulfoxide (DMSO) was heated at 70–75° under N_2 for 45 min. To the cooled solution was added a solution of 10.7 g (0.03 mol) of $CH_3P(C_6H_5)_3Br$ in 33 ml of DMSO. After an additional 10-min stirring, 5.0 g (0.03 mol) of **15** in 3 ml of DMSO was added, and stirring continued at room temperature for 1.5 hr. After 40 ml of H_2O was added, the mixture was extracted with 350 ml of petroleum ether in three portions and with 50 ml of ether. The combined extracts were dried and evaporated carefully to 25 ml. Distillation in a short-path apparatus yielded approximately 1 ml of a fraction boiling 110–140° (22 mm). This was dissolved in petroleum ether and rapidly chromatographed on a silica gel column. A total of 250 mg (5%) of ethyl (2-methylenecyclopent-1-yl)acetate (**8**) was recovered. No further attempts to optimize the yield were made. Purification for analysis was accomplished by preparative gc at 230°. *Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.39; H 9.59. Found: C, 71.18; H, 9.37. Spectral data: nmr δ 4.85 (m, 2 H), 4.15 (q, 2 H), 1.27 (t, 3 H), 1.1–3.1 (9 H); ir ($CHCl_3$) 1730, 1655, 887 cm^{-1}. This was converted into **7**, identical with that derived from **1**, by treatment with $NaOCH_3$ in CH_3OH and isolation by gc.

Deuteration of 13. A sample of 2.50 g of **13** was refluxed for 2 hr in 10 ml of 8% NaOD in D_2O. The solution was cooled and acidified with 2.5 ml of concentrated H_3PO_4. The deuterated acid was isolated by filtration and dried, recovery 1.70 g. This was converted into the acid chloride as above, and nmr analysis indicated that 74% of the α-hydrogens were replaced by D. Conversion into 1 and then **9** was accomplished, and that benzyl ester isolated by gc. The vinyl protons (δ 4.85) exhibited 28% of the intensity expected by comparison with the intensity of the methylene protons of the benzyl group (δ 5.17). The nmr spectrum was otherwise identical with that of undeuterated material.

Registry No.—**1**, 5261-30-3; **3**, 2910-67-0; **4**, 52358-08-4; **7**, 52358-09-5; **8**, 52358-10-8; **13**, 21622-08-2; **14**, 2910-65-8; **15**, 20826-94-2; cyclopentanone pyrrolidine enamine, 52358-11-9; ethyl bromoacetate, 105-36-2; ethyl cyclopentylidineacetate, 1903-22-6.

References and Notes

(1) (a) This work has been supported by Lawrence University, The Research Corp., and the National Science Foundation (Grant. No. GY-7663); (b) Department of Chemistry, University of Wisconsin—Milwaukee.
(2) (a) G. Stork and J. Ficini, *J. Amer. Chem. Soc.*, **83**, 4678 (1961); (b) C. J. V. Scanio and D. L. Lickei, *Tetrahedron Lett.*, 1363 (1972), and references therein.
(3) M. Julia and F. Le Goffic, *C. R. Acad. Sci.*, **255**, 714 (1962).
(4) (a) A. L. Wilds, J. Van Der Berghe, C. H. Winestock, R. L. Von Trebra, and N. F. Woolsey, *J. Amer. Chem. Soc.*, **84**, 1503 (1962); (b) A. L. Wilds, N. F. Woolsey, J. Van Der Berghe, and C. H. Winestock, *Tetrahedron Lett.*, 4841 (1965); (c) A. L. Wilds, R. L. Von Trebra, and N. F. Woolsey, *J. Org. Chem.*, **34**, 2401 (1969).
(5) W. von E. Doering and M. Pomerantz, *Tetrahedron Lett.*, 961 (1964); S. Masamune, *J. Amer. Chem. Soc.*, **86**, 735 (1964).
(6) G. Eglinton, J. C. Nevenzel, M. S. Newman, and A. I. Scott, *J. Amer. Chem. Soc.*, **78**, 2331 (1956); see also ref 4a.
(7) A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).
(8) P. Yates and T. J. Clark, *Tetrahedron Lett.*, 435 (1961).
(9) We thank a referee for urging the inclusion of this alternative.
(10) T. Matsuura and K. Ogura, *J. Amer. Chem. Soc.*, **89**, 3850 (1967); D. A. Plank and J. C. Floyd, *Tetrahedron Lett.*, 4811 (1971); S. Wolff and W. C. Agosta, *J. Chem. Soc., Chem. Commun.*, 226 (1972); H. E. Zimmerman and R. D. Little, *ibid.*, 698 (1972).
(11) These spectra were kindly obtained by Dr. M. L. Druelinger of the Chemistry Department, Indiana State University.
(12) W. S. Wadsworth, Jr., and William D. Emmons, "Organic Syntheses," Collect. Vol. V, Wiley, New York, N.Y., 1973, p 547.
(13) G. A. R. Kon and R. P. Linstead, *J. Chem. Soc.*, **127**, 620 (1925).
(14) New England Ultraviolet Co., Middletown, Conn.
(15) Benzyl alcohol was washed successively with saturated $NaHSO_3$, 45% KOH, and saturated NaCl, dried, and distilled at reduced pressure.
(16) G. Stork, A Brizzolara, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(17) Since the initial submission of this paper, a report has appeared presenting evidence for the detection of an intermediate analogous to **2** arising in a copper-catalyzed decomposition of another β,γ-unsaturated diazo ketone; H. E. Zimmerman and R. D. Little, *J. Amer. Chem. Soc.*, **96**, 4623 (1974).

Chlorocyclophosphazene–Epoxide Reactions. Catalysis by Lithium Halides

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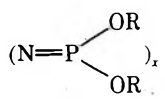
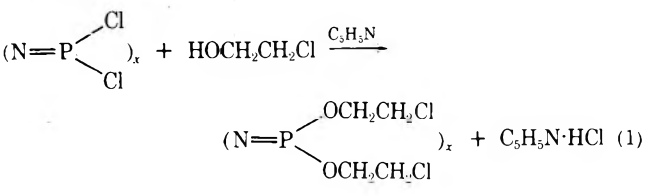
The reactions of chlorocyclophosphazenes with epoxides catalyzed by soluble salts were investigated. Lithium halide catalysts were found to be most effective for the preparation of fully substituted β-chloroethyl phosphazene esters from $(NPCl_2)_4$ and ethylene oxide. Tetraalkylammonium halides, lithium perchlorate, or cesium fluoride–hexamethylphosphoramide gave significantly lower oxirane incorporations. All reactions were extremely slow. The relative effectiveness of lithium halide catalysts is believed to be due to their ability to cleave an oxirane ring; promotion of reaction through a salt effect is also possible. Rearrangement of β-chloroethoxyphosphazene to *N*-(β-chloroethyl)oxophosphazanes appears to be a facile process.

Although the alkoxyphosphazene esters **1** are fairly well known as a general class of compounds,[1] studies of phosphazene esters which contain haloalkyl substituents other than fluoroalkyl have been limited in number and scope. The first reported haloalkyl ester was prepared by the bromination of an allyloxycyclotriphosphazene ester.[2] More recently, β-chloroethoxy- and 2,3-dichloropropoxy esters were prepared by reactions of the chlorophosphazene oligomers with the corresponding alcohols in pyridine,[3] *e.g.*, reaction 1.

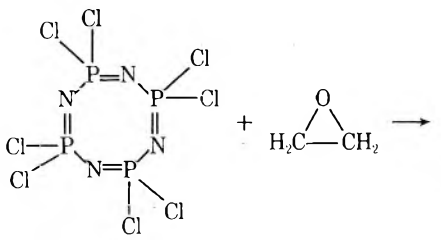


1, R = alkyl, aryl; $x = 3, 4, \ldots n$

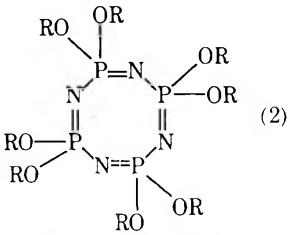


$x = 3, 4$

An appealingly direct route to chloroalkoxy phosphazene esters, *e.g.*, **3**, is through the reaction of chlorophosphazenes with epoxides, (reaction 2). The analogous prep-



2



3, R = $ClCH_2CH_2$

(2)

aration of β-haloalkyl phosphate esters from oxiranes and phosphoryl halides is a facile process. The synthesis of bis(2,3-dichloropropoxy)phosphazene octamer has been reported, using $(NPCl_2)_8$ and epichlorohydrin with $TiCl_4$ catalyst.[4] However, the same reaction repeated with chlorophosphazene cyclic tetramer, $(NPCl_2)_4$, **2**, gave only poly(epichlorohydrin). We thus investigated other potential catalysts for the chlorophosphazene–epoxide reaction. The work reported here is a study of the effect of soluble salt catalysts in several chlorophosphazene-epoxide reactions, as well as a brief examination of the products and their thermal behavior.

Results and Discussion

The uncatalyzed reactions of $(NPCl_2)_3$ or $(NPCl_2)_4$ with ethylene oxide are extremely slow. The maximum incorporation obtained in a reaction of this type after five days was 29% (THF solvent, closed vessel, 50°, tetramer **2**) and no fully substituted esters were isolated. Little nmr evidence for POCH could be found. Uncatalyzed reactions at elevated temperatures and pressures in a Carius tube afforded no improvement, although some decomposition of the partially formed products was noted at temperatures of 100 to 180°.

Whereas conductance measurements showed that phosphonitrilic chlorides autoionize at temperatures in excess of 200 to 230°,[5] radiotracer experiments indicated that chloride ion exchanged readily in the presence of tetraalkylammonium chloride in acetonitrile at room temperature.[6] Since it seemed reasonable that salts of this type might also promote chlorophosphazene–epoxide reactions by inducing ionization of the P–Cl bond, reactions of $(NPCl_2)_4$ with ethylene oxide in the presence of (a) tetraalkylammonium halides, (b) lithium halides, (c) lithium perchlorate, or (d) cesium fluoride were examined. Results of these experiments are summarized in Table I.

Tetraalkylammonium Halides. An improvement in net epoxide incorporation over uncatalyzed conditions was found with several tetraalkylammonium salts (experiments 2 and 3). The products resulting from these reactions were unstable, viscous oils which rapidly decolorized and fumed, liberating HCl on standing.[7] No incorporation of ethylene oxide greater than 45–50% was achieved using either tetraethylammonium bromide or tetra-*n*-butylammonium chloride. The product mixtures had ir and ^1H nmr spectra which were similar to those of authentic octakis(2-chloroethoxy)cyclotetraphosphazene[8] (**3**), although ir absorptions at 1081 and 1031 cm^{-1} were weak, and nmr bands were both broadened and shifted 0.2 ppm downfield from those of **3**.

Table I
Effect of Catalyst on the Reaction of $(NPCl_2)_4$ with Ethylene Oxide[a]

Expt	Catalyst	Catalyst concn, mol/l.	Reaction time, hr	% oxirane incorpd[b]
1	None		120	29
2	$(C_2H_5)_4N^+Br^-$	0.05	84	37
3	$(C_4H_9)_4N^+Cl^-$	0.05	96	45
4	LiCl	0.058	96	100[c]
5	LiBr	0.058	96	90
6	LiBr	0.058	108	100
7	LiBr	0.058	24	50
8	LiBr	0.001	96	47
9	$LiClO_4$	0.058	72	40–50[d]
10	CsF·HMPA[e]	0.025	120	30–35

[a] Reaction procedure described in Experimental Section: THF solvent, sealed vessel, 50°, 1.74 equiv of $(NPCl_2)_4$, 3.4 equiv of ethylene oxide, 100-ml liquid volume. [b] Calculated from weight increase in product when concentrated under vacuum. [c] Dark red, discolored product. [d] Yield estimated by nmr; significant amounts of polyether also present. [e] Hexamethylphosphoramide added (1:1) in attempt to dissolve CsF.

Lithium Halides. When lithium chloride catalyst was employed (Table I, experiment 4), the yield of **3** was essentially quantitative after 96 hr. Both ir and ^1H nmr spectra of the product were identical with those of **3** prepared by reaction 1, although the product was deep red in color.

The use of lithium bromide catalyst (Table I, experiments 5 and 6) gave a quantitative yield of **3** after 108 hr. The product had ir spectra identical with those of the product of reaction 1. Only a 50% incorporation of epoxide was observed after 24 hr, the crude product mixture closely resembling those obtained using tetraalkylammonium halides (Table I, experiment 7). Extent of epoxide incorporation was also dependent on catalyst concentration (experiment 8).

Lithium Perchlorate. Maximum epoxide incorporations of 40–50% were obtained after 72 hr with lithium perchlorate catalyst (Table I, experiment 9). The partially formed products were unstable. Substantial quantities of polyethers from both ethylene oxide and solvent (THF) were also obtained.

Cesium Fluoride. It was necessary to add hexamethylphosphoramide (HMPA) in a 1:1 ratio with cesium fluoride, since the salt alone was insoluble in THF. Inclusion of HMPA did not dissolve the salt completely, as evidenced by a cloudy reaction mixture. Reaction products again resembled those from other incomplete reactions.

Reactions with Epichlorohydrin. Epichlorohydrin was found to be much less reactive than ethylene oxide toward $(NPCl_2)_4$; however, incorporations of up to 70% of theoretical were obtained when the reactions were catalyzed by lithium bromide. The results of several reactions of $(NPCl_2)_4$ with epichlorohydrin are listed in Table II. Lithium perchlorate, in contrast to lithium bromide, showed no evidence for catalysis of the chlorophosphazene–epoxide reaction, and tetra-*n*-butylammonium bromide showed very little effect. However, polymerization of epichlorohydrin was observed with lithium perchlorate.

Mechanism. Since all of the salts investigated showed some catalytic effect in the $(NPCl_2)_4$–ethylene oxide reaction, a general mechanism involving salt effects is likely. However, the greater effectiveness of lithium bromide evidenced in both ethylene oxide and epichlorohydrin reactions suggests that lithium halides perform an added catalytic function, perhaps through a cleavage of the epoxide ring to give a lithium halohydrin salt, similar to those pos-

Table II
Effect of Catalyst on the Reaction of $(NPCl_2)_4$ with Epichlorohydrin[a]

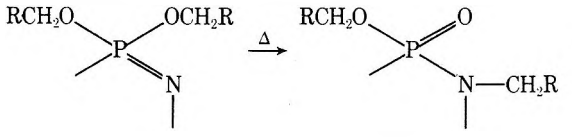
Expt	Catalyst	Catalyst concn (mol/l.)	Reaction time, hr	% oxirane incorpd[b]
1	LiBr	0.058	36	50[c]
2	LiBr	0.058	108	70[d]
3	$LiClO_4$	0.058	108	0[e]
4	$(C_4H_9)_4N^+Cl^-$	0.05	96	7

[a] Reaction conditions described in Experimental Section: THF solvent, sealed vessel, 50°, 1.74 equiv of $(NPCl_2)_4$, 1.74 equiv of epichlorohydrin, 100-ml of liquid. [b] Calculated from weight increase, product concentrated under vacuum. [c] ^1H nmr showed a >6:1 ratio of 1,3-dichloro-2-propoxy- to 2,3-dichloro-1-propoxy substituents. [d] ^1H nmr showed a 4:1 ratio of 1,3-dichloro-2-propoxy- to 2,3-dichloro-1-propoxy substituents. [e] Weight increase was observed owing to formation of poly(epichlorohydrin); no evidence for POCH by ^1H nmr.

tulated for the rearrangement of epoxides.[9] Such a mechanism might also explain the relative ineffectiveness of the poorer nucleophile, lithium perchlorate.

Products and Thermal Behavior. Product **3**, prepared from ethylene oxide and **2**, was typically a straw-colored oil. Small quantities of solids could be obtained from the oil after repeated extractions with petroleum ether and cooling to −50°. In some cases, solid **3** formed in the purified oil on standing and was recovered by filtration, being pressed dry on filter paper. This yielded 60–70% by weight of a colorless, waxy solid, mp 49–50°, whose spectra and analyses are described below. Isolation of solid **3** from the oils was not consistently achieved.

Although the chloroethoxyphosphazenes are stable for extended periods at ambient conditions, when heated to 100–120° as under vacuum distillation,[3] the oils are known to fume (HCl detected), discolor, and resinify. Since Shaw and coworkers have shown that alkoxyphosphazene esters readily undergo thermal alkoxyphosphazene–oxophosphazane rearrangement[10] (eq 3), facile phosphazane forma-



(3)

tion may contribute to thermal instability of **3**, with the added complication of HCl elimination.

Careful examination of the ir spectrum of unheated **3** revealed a small shoulder at 1250 cm^{-1}, corresponding to P=O stretch (Table III), but no evidence for phosphazane NCH was found by nmr. Treatment with refluxing 1,2-dichloroethane[11] caused the disappearance of the strong 1325-cm^{-1} band (P=N stretch) and enhancement of the 1250-cm^{-1} shoulder; a broad band was also found at 1285 cm^{-1}. A noticeable change in the position and width of the POCH nmr absorption was observed. The ir spectrum of residue from attempted vacuum distillation was very similar to that of halide-rearranged **3**, the main difference being relative intensities of strong bands and location of weak bands. Both the product oils and the isolated solids exhibited the same thermal behavior.

It appears that some rearrangement to phosphazane accompanies the formation of β-chloroethoxy ester at temperatures ≤50°, which may account for their oily nature. Phosphazane predominates after treatment with dichloroethane and also appears to form in thermal decomposition at higher temperatures. Other processes, including evolution of HCl and cross-linking, also accompany rearrangement during thermal decomposition.

Table III
Ir and Nmr Data for Octakis(2-chloroethoxy)cyclotetraphosphazene, 3

Identity	ν^a (neat), cm^{-1}	$\delta(CHCl_3\text{-}d)$
3	1325, 1295 (sh, 1250), 1081, 1031, 712	3.74 (t, J = 5.5 Hz, w^b = 14 Hz); 4.25 (m, w = 16 Hz)
3, refluxed for 16 hr in $(CH_2Cl)_2$	1285 (str sh, 1250), 1081, 1031	3.74 (t, J = 5.6 Hz, w = 15 Hz); 4.38 (m, w = 35 Hz)
3, after attempted vacuum distillation, 130–150°, 0.5 Torr	1290 (str sh, 1250), 1085, 1030	Insoluble

[a] Wavenumbers of strong bands only are listed. [b] w, peak width at half height.

It has been observed that the tendency of alkoxyphosphazenes to undergo rearrangement to phosphazanes is related to the presence of electron-withdrawing substituents on the alkyl group. This has been interpreted as reduction of basicity of the ring nitrogen through electron withdrawal.[10] On this basis the predicted stability of β-chloroethoxyphosphazenes would be intermediate between that of ethoxy and trifluoroethoxy analogs. The very facile rearrangement observed is probably a result of intra- and intermolecular catalysis by the β-chloroethoxy groups which are susceptible to nucleophilic reactions, as well as by HCl formed in thermal dehydrochlorination.

Experimental Section[12]

Hexachlorocyclotriphosphazene (phosphonitrilic chloride trimer), mp 115°, was separated from a mixture of cyclic oligomers by fractional vacuum distillation. Octachlorocyclotetraphosphazene **2** (phosphonitrilic chloride cyclic tetramer), mp 124°, was purified by repeated fractional sublimation under vacuum of the resulting distillation residue. Reactions were carried out by the following method. A dry 300-ml glass vessel was charged with 10.0 g of purified phosphonitrilic chloride, 100 ml of freshly distilled anhydrous tetrahydrofuran, and 0.25–0.50 g of catalyst. The bottle was closed and cooled, and 15–20 ml of liquid epoxide was added quickly. The bottle was sealed and placed in a rotating bath at 50°. After reaction the bottle was cooled and opened, and the solvent was removed under vacuum. If the product was stable, catalyst was then removed by dissolving the product in chloroform, washing with water, drying ($MgSO_4$), and concentrating under vacuum.

Incorporation of epoxide was determined from weight gain and estimated purity from ^1H nmr. Partially esterified products were analyzed by nmr and weight gain immediately after initial concentration. In several cases, yields determined from weight gain were checked in the following manner. Concentrated product was treated with an excess of sodium 2,2,2-trifluoroethoxide in THF at 65° and worked up as a fully substituted ester; comparison by ^1H nmr of the absorptions at δ ~4.6 and 4.2–4.3 showed agreement to within 5% of the incorporations calculated by weight gain.

Fully substituted octakis(2-chloroethoxy)cyclotetraphosphazene (**3**) as either the solid or oils from LiBr-catalyzed reactions gave carbon, hydrogen, and chlorine analyses consistent with the expected formula (Calcd for $C_{16}H_{32}N_4O_8P_4Cl_8$: C, 23.55; H, 3.95; Cl, 34.76. Found (solid): C, 23.66; H, 4.00; Cl, 34.80. Found (oil): C, 23.62; H, 3.97; Cl, 34.90).[13] No molecular ion was observable in the mass spectrum of **3**, but m/e 740 ($M^+ - 72$, loss of 2HCl) with six chlorines was detected. The ir spectrum was identical with that for **3** prepared from 2-chloroethanol by reaction 1 (see below).

Elemental and mass spectral analyses do not distinguish between isomeric phosphazene and phosphazane structures, and the only evidence for phosphazane in the oils was found in the shoulder at 1250 cm^{-1} in the ir spectrum of **3**. Purification by distillation or gas chromatography was unsuccessful owing to the high molecular weight and thermal instability of the esters. Chromatography of the oily product **3** on silica gel or alumina columns using various ratios of chloroform–hexane or chloroform–benzene gave a single eluent band identical with that of unchromatographed **3**. In

view of facile O → N rearrangement, the oils may contain small amounts of *N*-alkylphosphazanes.

The $TiCl_4$-catalyzed reaction of octachlorocyclotetraphosphazene and epichlorohydrin was attempted by adding $TiCl_4$ slowly to a mixture of the other reactants at 85°, followed by heating and work-up similar to that described above.

Octakis(2-chloroethoxy)cyclotetraphosphazene, 3, by reaction 1.[3] A 2-l., 3-neck round-bottom flask containing 700 ml of anhydrous pyridine and 87 g (1.5 equiv) of **2** was cooled to 15°, and 121 g (1.5 equiv) of 2-chloroethanol was added dropwise over 1 hr. After the mixture was stirred at room temperature for 20 hr, solvent was removed under vacuum below 50°. The residue was then poured into 600 g of ice–water, and the oil layer taken up with chloroform. The chloroform extract was washed with 5% HCl, 5% Na_2CO_3, and water, dried ($MgSO_4$), and concentrated on a rotary evaporator. The residual oil was concentrated further at room temperature and 0.1 Torr for 16 hr. The product was a viscous yellow oil, weight 145.2 g, 95% of theoretical yield, characterized by ir spectrum (see following paragraph on supplementary material).

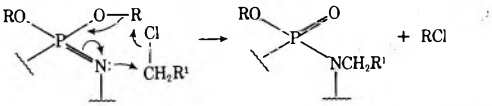
Acknowledgments. The author is grateful to personnel of the Analytical Services Division, Firestone Central Research Laboratories, for technical assistance, and to The Firestone Tire and Rubber Company for permission to publish this work.

Supplementary Material Available. Nmr spectrum of compound **3** and ir spectra of **3** prepared by reactions 1 and 2 will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3357.

Registry No.—**2**, 2950-45-0; **3**, 52539-64-7; $(C_2H_5)_4N^+Br^-$, 71-91-0; $(C_4H_9)_4N^+Cl^-$, 1112-67-0; LiCl, 7447-41-8; LiBr, 7550-35-8; $LiClO_4$, 7791-03-9; CsF, 13400-13-0; ethylene oxide, 75-21-8; epichlorohydrin, 106-89-8; hexachlorocyclotriphosphazene, 940-71-6.

References and Notes

(1) (a) H. R. Allcock, "Heteroatom Ring Systems and Polymers," Academic Press, New York, N.Y., 1967. (b). H. R. Allcock, "Phosphorus–Nitrogen Compounds," Academic Press, New York, N.Y., 1972.
(2) C. Hamaleinen and J. D. Guthrie, *Textile Res. J.* **26**, 141 (1956); C. Hamaleinen, W. A. Reeves, and J. D. Guthrie, *ibid.*, **26**, 145 (1956).
(3) L. A. Godfrey and J. W. Schappel, *Ind. Eng. Chem. Prod. Res. Devel.*, **9**, 426 (1970); (b) L. A. Godfrey and N. J. Pennington, German Offen. 2,016,153 (1970).
(4) P. M. Zavlin, M. A. Sokolovskii, and I. V. Yurenko, U.S.S.F. Patent 176,402 (1965).
(5) H. R. Allcock and R. I. Best, *Can. J. Chem.*, 42, 447 (1964).
(6) D. B. Sowerby, *J. Chem. Soc., London*, 1396 (1965).
(7) Considering degree of substitution and stereochemistry, 32 partially substituted products are possible from **2**. No attempt was made to identify the components of incomplete reaction mixtures.
(8) Prepared by the method of ref 3b.
(9) B. Rickborn and R. M. Gerkin, *J. Amer. Chem. Soc.*, **93**, 1963 (1971); also F. Johnson, "Friedel–Crafts and Related Reactions," Vol. IV, G. A. Olah, Ed., 1965, pp 32–41.
(10) B. W. Fitzsimmons, C. Hewlett, and R. A. Shaw, *J. Chem. Soc., London*, 4459 (1964).
(11) Alkyl halides were shown to catalyze O → N migration,[10] *via*



(12) Melting points were determined in capillary tubes and are uncorrected. Chlorine analysis was by Schöniger flask combustion and Volhard titration. Carbon, hydrogen analyses performed by Galbraith Laboratories, Inc.
(13) C, H, and N microanalyses using an F&M Model 185 analyzer gave varying high results for **3**. *Anal.* (typical). Calcd: C, 23.5; H, 3.9; N, 6.9. Found: C, 25.5; H, 4.1; N, 7.4. Such results are presumably due to premature loss of HCl during analysis.

Reactions of Cyclopropanols with Halogenating Agents and Other Electrophiles

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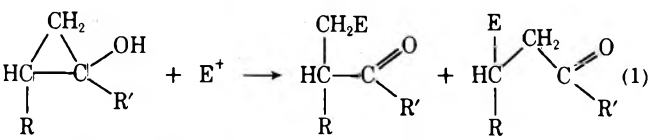
A study has been made of the reactions of *cis*- and *trans*-2-phenyl-1-methylcyclopropanol and their methyl ethers, *cis*- and *trans*-2-methyl-1-phenylcyclopropanol, and *cis*- and *trans*-1,2-diphenylcyclopropanol with various electrophiles, including mercuric acetate, acid, and various sources of positive halogen. The direction of ring opening is found not to depend upon the stereochemistry of the starting material. The free-radical opening of optically active *trans*-2-phenyl-1-methylcyclopropanol by $FeCl_3$ is shown to give racemic chloro ketone. The results are compared with those from related systems.

For some time we have been interested in the mechanism and stereochemistry by which cyclopropanols and their derivatives react with electrophiles.[1] In previous studies we have reported that *trans*-2-phenyl-1-methylcyclopropanol undergoes electrophilic ring opening with retention of configuration when treated with D^+ [2] and that the various cis–trans isomers of 2,3-dimethyl-1-phenylcyclopropanol ring open with inversion of configuration upon reaction with mercuric acetate[3] or various brominating agents.[4] In the course of these and other studies[1] we have also had occasion to measure the effect of a ring substituent on the direction of ring opening upon attack by an electrophilic reagent (eq 1). In the work reported in this paper we have attempted to make a more systematic study of cyclopropanol ring openings as a function of the nature and stereochemistry of the substituents R and R′, particularly as they apply to halogenation, but also for protonation and mercuration.



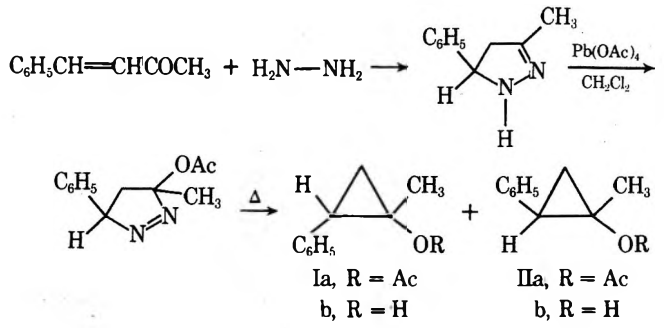
(1)

Results

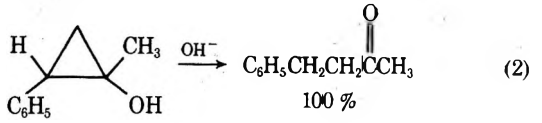
***cis*-2-Phenyl-1-methylcyclopropanol (Ib).** The first system chosen for study in this investigation was *cis*-2-phenylcyclopropanol (Ib) since we had previously determined the product composition on ring opening of the trans isomer.[2] We were interested in determining if simple cis–trans isomerization would have any effect on the direc-

tion of opening. Unfortunately the method we had used for the preparation of the trans isomer[2] was not applicable to the cis isomer, and we had to prepare and separate a cis–trans mixture of cyclopropyl acetates (Ia and IIa) prepared by a modification of Freeman's method[5] (Scheme I). The isomers were difficult to separate, but we were finally able to obtain small quantities of pure Ia by careful column chromatography. The pure crystalline cis alcohol, Ib, was obtained from Ia by reaction with methyllithium and work-up under carefully controlled pH conditions. Once pure, it, like the trans isomer, was indefinitely stable when stored in a polyethylene bottle in the cold. Its spectral properties were in full accord with its assigned structure.

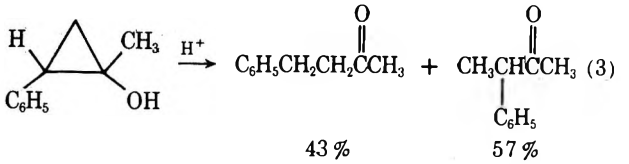
Scheme I



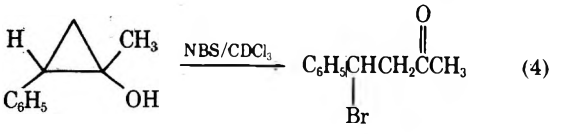
Base-catalyzed cleavage of Ib (eq 2) at 85–90° in 50:50 (v/v) 0.2 *N* NaOH–dioxane yielded a single product which



(2)



(3)



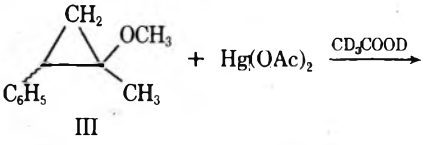
(4)

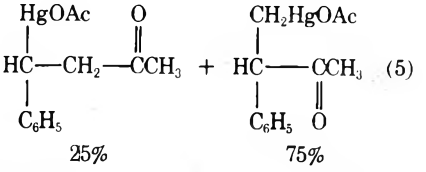
was identified as 4-phenyl-2-butanone by comparison of its nmr spectrum and gpc retention time with those of an authentic sample. Acid-catalyzed cleavage of Ib (eq 3) was carried out under conditions similar to those reported earlier[2] for the trans isomer by heating at 90–95° in 50:50 (v/v) 2 *N* HCl–dioxane. Ring opening occurred in >97% yield to give 4-phenyl-2-butanone (43%) and 3-phenyl-2-butanone (57%) in essentially the same ratio as that found for the trans isomer (40%:60%).[2] Finally, Ib was treated with *N*-bromosuccinimide in $CDCl_3$ in the dark. Reaction occurred immediately. The nmr spectrum of the product was consistent with the formation of 4-bromo-4-phenyl-2-butanone as the sole product (eq 4), just as was found previously to be the case for the trans isomer (IIb).[4] Thus the change in stereochemistry at C-2 has no effect on the direction of ring opening.

2-Phenyl-1-methylcyclopropanol Methyl Ether (III). To determine if the direction of ring opening would change if the free hydroxyl group were masked, the methyl ether was prepared. This was accomplished in 76% yield when a 1:3 mixture of *cis*- and *trans*-2-phenyl-1-methylcyclopropanol in ether was treated with diazomethane and aluminum chloride.[6] This method proved much superior to several others tried, including alkylation with methyl iodide, trimethyloxonium tetrafluoroborate, or diazomethane and boron trifluoride.

These cyclopropanol methyl ethers (III) are significantly less reactive toward cleavage with acid than the corresponding alcohols. However, upon heating at 95–105° in 60:40 dioxane–sulfuric acid (8.3 *N*), ring opening is complete within 26 hr. The products are 62% 3-phenyl-2-butanone and 38% 4-phenyl-2-butanone, a mixture which is not significantly different from that found for the corresponding alcohols. The reaction was monitored by gpc from the beginning, and at no time were there more than three components present, the starting ether mixture (III) and the two ketonic products. Moreover the ratio of ketones did not change during the course of the reaction. It thus seems very unlikely that any rearrangement of products or incursion of alternate methods of ring opening (for instance carbon–oxygen cleavage followed by rearrangement to an allylic cation) could be occurring.

Reaction of the ether mixture (III) with an equivalent of mercuric acetate was carried out in acetic acid-d_4 and the results monitored by nmr spectroscopy. The reaction was complete within less than 10 min at room temperature and the product mixture (eq 5) was identical with that found for the corresponding alcohol.[3]





(5)

In contrast to the results for protonation and mercuration, where ring opening occurred identically for the ether and the alcohol, although somewhat more slowly on the former, the cyclopropanol methyl ethers (III) could not be induced to react with *tert*-butyl hypochlorite even after several days. Yet the alcohols react immediately, almost explosively, even at ice-bath temperatures. The ether mixture does react slowly with *N*-bromosuccinimide, as compared to an almost instantaneous reaction of the alcohols, but a complex mixture of reaction products is obtained and the products anticipated for simple brominative ring opening could not be detected. These results are in accord with previous observations that cyclopropanols are almost unique in their ability to react readily with halogenating agents.[4]

Stereochemistry of Halogenation of *trans*-2-Phenyl-1-methylcyclopropanol (IV). We have previously shown that 2,3-dimethyl-1-phenylcyclopropanols and their acetates brominate stereospecifically with inversion of configuration, while the alcohols react with chlorinating agents in a nonstereospecific manner and the acetates do not react at all.[4] To account for the lack of stereospecificity upon chlorination, we proposed an oxidative attack on the OH bond leading to ring opening *via* a radical mechanism since cyclopropanols are known to be easily oxidized. Indeed the threo:erythro product ratio obtained upon chlorination is the same as that obtained by ferric chloride oxidation[4] (eq 6), a process which has been shown to occur by way of radical intermediates.[7] One reasonable explanation for our results with the 2-phenyl compounds might be that the phenyl group greatly accelerates this oxidative pathway so that the reaction occurs exclusively on the O–H bond. To test

EXPERIMENTAL SECTION

All boiling and melting points are uncorrected. Melting points were taken on a Fischer-Johns melting point apparatus. Glc analyses were performed on an Aerograph Model 202 or an F&M scientific Corporation Model 700 gas chromatograph. The columns used are listed as follows and are referred to by letter with the temperature used specified for each individual analysis: A 10' x 3/8" aluminum column containing 5% SE-30 on 60:80 Chromosorb W; B 5' x 1/4" stainless steel column containing 20% Carbowax 20M on 60:80 Chromosorb W; C 5' x 1/4" stainless steel column containing 15% Apiezon L on 60:80 Chromosorb W; D 5' x 1/4" stainless steel column containing 10% Apiezon L on 60:80 Chromosorb W.

Infrared spectra were obtained on a Beckman IR-10 or a Perkin-Elmer Model 457 spectrophotometer calibrated with the 1604 cm^{-1} band of polystyrene. Solution spectra were obtained using solvent-matched sodium chloride cells of 0.05 mm or 0.10 mm thickness. Nmr spectra were obtained on Varian Associates A-60 or A-60-A spectrometers at 60 megacycles and the symbols s, d, dd, t, and m refer to singlet, doublet, doublet of doublets, triplet, and multiplet. Spin decoupling experiments were done on a Varian Associates HA-100 spectrometer at 100 megacycles. All mass spectra were obtained using a Varian M-66, Varian MAT CH-7, or Consolidated Electrodynamics Corporation Type 21-103C (modified) spectrometer.

Synthesis of 2-Phenyl-1-methylcyclopropyl Acetates (Ia and IIa).--The acetate mixture was prepared according to the following procedure patterned after that of Freeman[5] with some modifications.

Benzalacetone[15] (50 g, 0.34 mole) and 200 ml of absolute ethanol were placed in a 500-ml three-neck round-bottom flask. Hydrazine (15 g, 0.45 mole) was added to the stirred solution over a period of 5--10 min with some evolution of heat. The reaction mixture was heated at reflux for 3 hr, then cooled, and the ethanol-water removed on a rotary evaporator at 70-75° to yield 55 g (100%) of a yellow oil which had properties consistent with those expected for 3-methyl-5-phenyl-2-pyrazoline: nmr ($CDCl_3$) τ = 8.05 (s, 3, CH_3), 7.21 (m, 2, CH_2), 5.30 (t, 1, CH), 5.07 (broad s, 1, N-H), 2.71 (s, 5, C_6H_5); ir (CCl_4) 3370 (N-H) and 1630 cm^{-1} (C=N). This crude 2-pyrazoline was used in the next step without further purification.

A flame-dried two-liter three-neck round-bottom flask was charged with 216 g (0.49 mole) of lead tetraacetate and 600 ml of dry CH_2Cl_2 while nitrogen was passed through the flask. The pyrazoline (55 g) in 200 ml of dry CH_2Cl_2 was added to the well-stirred slurry over a period of 1--5 hr, maintaining the temperature at 10-20°. The mixture was then heated at reflux for 1 hr, stirred for 6.5 hr at room temperature and 400 ml of water was added to the reaction mixture. After the aqueous layer was extracted with 250 ml of CH_2Cl_2, the combined CH_2Cl_2 extracts were extracted repeatedly with saturated $NaHCO_3$ solution and water over a period of at least 1 hr or until the solution remained neutral after standing for a period of 30 min. After drying ($MgSO_4$), the solvent was removed on a rotary evaporator to yield 74.8 g of a brown oil which had properties consistent with those expected for the 3-acetoxypyrazoline: nmr ($CDCl_3$) τ = 8.22 (s, CH_3), 7.94 (s, acetate CH_3), 8.37, 7.45 (m, CH_2), 4.03 (dd, CH), 2.65 (m, C_6H_5), ir (CCl_4) 1755 (C=O), 1567 cm^{-1} (cis azo).

The brown oil was heated in a distillation apparatus. At 130-140° a vigorous evolution of nitrogen occurred. After the initial reaction had subsided, heating at 170-190° for 20 min resulted in no further evolution of nitrogen. The brown oil was distilled and a fraction (bp 80-83°/0.5 mm, lit. bp 70°/0.35 mm[5]) was the expected acetates (27.15 g or 42%, cis:trans ~ 1:3).

Separation of cis- and trans-2-Phenyl-1-methylcyclopropyl Acetates (Ia and IIa).--A sample of the acetate mixture (10.5 g) was separated on a 38 mm x 90 cm silica gel column (260 g Baker powder) eluting with Skellysolve B-benzene mixtures. After combining appropriate fractions 6 g of the trans acetate (IIa), 3.6 g of a mixture of acetates, and 0.3 g of the cis acetate (Ia) was obtained. cis-Enriched acetate mixtures from several of the above chromatographies were combined to yield 7 g of the acetates (61% cis, 39% trans). Separation of this mixture on a large silica gel column (38 mm x 90 cm -250 g of Baker powdered silica gel) with Skellysolve B-benzene mixtures as eluents yielded 1.4 g of the trans acetate (IIa), 2.10 g of a mixture of acetates, and 2.3 g of the cis acetate (Ia). Spectral data supported the assignment of the cis and trans acetates: trans acetate (IIa): nmr ($CDCl_3$) τ = 8.82 (m, 5, CH_3 and cyclopropane CH_2), 8.02 (s, 3, acetate CH_3), 7.68 (dd, 1, cyclopropane CH), 2.77 (s, 5, C_6H_5); ir ($CHCl_3$) 1745 cm^{-1} (C=O); cis acetate (Ia): nmr ($CDCl_3$) τ = 8.83 (m, 2, cyclopropane CH_2) 8.38 (s, 6, CH_3 and acetate CH_3), 7.93 (dd, 1, cyclopropane CH), 2.89 (s, 5, C_6H_5); ir (CCl_4) 1755 cm^{-1} (C=O).

Synthesis of cis-2-Phenyl-1-methylcyclopropanol (Ib).--The procedure was patterned after that of DePuy et al.[16] In a dry 250-ml three-neck round-bottom flask was placed 50 ml of anhydrous ether and 2 g (0.01 mole) of the cis acetate (Ia). To the stirred solution, under nitrogen, 12 ml of 2.1 M methyllithium in ether was added dropwise over a period of 10 min. The resulting mixture was stirred for 2 hr, and rapidly added to a suspension of 25 g of boric acid in 50 ml of distilled water. Beyond this point, all glassware, etc., coming into contact with the cyclopropanol was washed with a 5% HF solution, tap water, distilled water, and then dried. The mixture was filtered, the solid washed with ether, the layers separated, and the ether layer washed with three 50-ml portions of distilled water. Pentane (100 ml) was added to the ether and a final extraction was made with 50 ml of water. After drying, the ether-pentane was removed on a rotary evaporator to yield 1.7 g of a yellow oil. Recrystallization of the crude alcohol several times from pentane-ether at Dry Ice temperatures yielded 0.6 g (42%) of a white crystalline solid which was dried under vacuum: nmr ($CDCl_3$) τ = 8.85 (m, 2, cyclopropane CH_2), 8.44 (s, 4, CH_3 and OH), 8.01 (dd, 1, cyclopropane CH), 2.74 (s, 5, C_6H_5); mass spectrum m/e (rel intensity) 148(46.6), 133(17.9), 105(83), 91(40), 77(22.9), 43(100); mp 61-63°.

Reactions of cis-2-Phenyl-1-methylcyclopropanol (Ib). A. with N-Bromosuccinimide: N-bromosuccinimide (0.13 g, 0.0006 mole) and 1 ml of $CDCl_3$ were placed in an aluminum foil-covered 50-ml erlenmeyer flask. The system was flushed with nitrogen and cooled in an ice bath. With stirring, 0.08 g (0.0006 mole) of the cis alcohol (Ib) in 1 ml of $CDCl_3$ was added in portions. After stirring 5 min, a sample of the reaction mixture was transferred to an nmr tube and nmr spectrum was recorded. In addition to singlets due to N-bromosuccinimide (τ = 7.07) and succinimide (τ = 7.27), the nmr spectrum was consistent with 4-bromo-4-phenyl-2-butanone as the sole product: τ = 7.93 (s, 3, CH_3), 6.61 (t, 2, CH_2), 4.54 (dd, 1, CH), 2.63 (m, 5, C_6H_5).[4]

B. with Base.--The procedure used was patterned after that of DePuy et al.[2] The cis alcohol (Ib) (0.1 g, 0.0007 mole) was added in portions to a 25-ml round-bottom flask containing 8 ml of 0.2 M aqueous NaOH and 8 ml of spectral grade dioxane (MCB). The system was flushed with argon, sealed, and heated at 85-90° for 61 hr. After cooling, the contents of the flask were neutralized with 3 M HCl and extracted 6 times with 20 ml of ether. The dioxane-ether was dried and removed by distillation to yield a brown oil. Analysis of the oil by gpc (Column B at 96°) indicated the presence of a single component. Comparison of the nmr spectrum of the oil with the nmr spectrum of an authentic sample proved the compound to be 4-phenyl-2-butanone.

C. with Acid.--The procedure used was patterned after that of DePuy et al.[2] A sample of the cis alcohol (Ib) (0.15 g, 0.001 mole), 6 ml of 2 M HCl, and 6 ml of dioxane were placed in a 25-ml round-bottom flask. The system was flushed with argon, sealed, and heated to 90-95° for 72 hr. The solution was cooled and neutralized with 1 N NaOH and worked up as above. Analysis of the resulting oil by nmr spectroscopy and gpc indicated the presence of 44% 4-phenyl-2-butanone and 56% 3-phenyl-2-butanone.

Synthesis of 2-Phenyl-1-methylcyclopropanol Methyl Ether (III). Crude 2-phenyl-1-methylcyclopropanol [from 13 g (0.07 mole) of 2-phenyl-1-methylcyclopropyl-acetate, cis:trans ~ 1:3] was dissolved in 200 ml of anhydrous ether in a one-liter suction flask equipped with a drying tube. The solution was cooled with an ice bath and two spatulas of aluminum chloride (anhydrous reagent) were added. The diazomethane solution was added dropwise (from a burette equipped with a drying tube) with stirring. Whenever the reaction of the diazomethane subsided as evidenced by a lack of nitrogen evolution, a spatula of fresh aluminum chloride was added. After the addition of diazomethane was complete, the solution was allowed to stir overnight while warming to room temperature. To decompose any remaining diazomethane, 50 ml of 3 N HCl was added slowly to the reaction mixture. The layers were separated and the ether layer was extracted with water until the pH of the water extract was about 5. The solution was dried ($MgSO_4$) and the ether removed with a rotary evaporator to yield a yellow oil which nmr and ir spectra indicated was cyclopropanol methyl ether (III) with little starting alcohol present. Distillation gave 8.5 g (76%) of a colorless oil (bp 51-65°/1.5 mm). The oil was chromatographed (150 g of Baker powdered silica gel) with Skellysolve-B as the eluting solvent. In general, all attempts to separate the mixture of cis and trans ethers by gpc with various columns, failed. The column chromatography, early fractions collected were always enriched in the cis ether and late fractions were enriched in the trans ether. Analysis of the ether mixture from column chromatography by gpc (Column A at 116°) yielded a single peak. The 2-phenyl-1-methylcyclopropanol methyl ether mixture (III) had the following properties: bp 46-49°/0.6 mm; ir ($CHCl_3$) 2838 (C-H of OCH_3), 1060-1090, 1230 cm^{-1} (C-O-C); nmr ($CDCl_3$) τ = 8.89 (trans CH_3 and cyclopropane CH_2), 8.52 (cis CH_3), 8.08 (cis cyclopropane CH), 7.66 (trans cyclopropane CH), 6.94 (cis OCH_3), 6.63 (trans OCH_3), 2.76 (C_6H_5); mass spectrum m/e (rel intensity) 162(15.7), 147(46.4), 130(10.2), 129(14.4), 115(27.1), 91(21.3), 77(12.1), 51(10.7), 43(100).

Reactions of 2-Phenyl-1-methylcyclopropanol Methyl Ether (III). A. with Acid at 95-105°.--A sample of the ether mixture (III) (0.4 g, 0.0025 mole) was dissolved in 40 ml of 60:40 dioxane--8.3 N aqueous H_2SO_4 in a round-bottom flask. The system was flushed with nitrogen, sealed, and heated at 95-105°. The reaction was monitored by gpc analysis (Column A at 125°). After 24 hr, the reaction was complete and the ether peak in the gas chromatogram was replaced by two peaks with relative areas of 40% and 60%. The reaction mixture was neutralized and worked up in the usual manner. The resulting brown oil was a mixture of 62% 3-phenyl-2-butanone and 38% 4-phenyl-2-butanone identified by ir and nmr spectroscopy as well as gpc.

B. with Mercuric Acetate.--The ether mixture (III) (0.2 g, 0.001 mole) was placed in an nmr tube with 0.25 ml of CD_3COOD. An nmr spectrum indicated the ether was stable in this solvent. To the solution, 0.4 g (0.0013 mole) of mercuric acetate (MCB reagent) in 0.5 ml of CD_3COOD was added as a slurry. The reaction was monitored by nmr spectroscopy. All of the ether had reacted within 10 minutes. The solvent was removed on a rotary evaporator, the residue taken up in $CHCl_3$ and filtered to remove unreacted mercuric acetate. After removing the solvent, the resulting oil (0.367 g) gave an nmr spectrum identical to that obtained by A. DeBoer for the products of the reaction of trans-2-phenyl-1-methylcyclopropanol (IIb) with mercuric acetate.[3] On this basis the products of the reaction were assigned as 75% 3-phenyl-4-acetoxymercuri-2-butanone and 25% 4-phenyl-4-acetoxymercuri-2-butanone.

C. with tert-Butylhypochlorite.--A sample of the ether mixture (III) (0.06 g, 0.0004 mole) was placed in an aluminum foil-covered 50-ml erlenmeyer flask with 1.5 ml of CCl_4. The system was flushed with nitrogen and, with cooling (ice bath), 0.08 g (0.0008 mole) of tert-butylhypochlorite prepared according to the method of Walling[17] was introduced. After 1.5 hr of stirring, a sample was removed and an nmr spectrum recorded. The only resonance in the nmr spectrum in addition to starting ether was at τ = 8.69 (tert-butylhypochlorite). After 24 hr at room temperature, there was still no evidence of reaction. The reaction was also carried out in $CDCl_3$ with no evidence of reaction after 2 days.

Reaction of trans-2-Phenyl-1-Methylcyclopropanol (IIb) with Ferric Chloride. A. Racemic Alcohol (IIb).--The alcohol (IIb) was made by methyl lithium reduction of trans-2-phenyl-1-methylcyclopropylacetate (IIa).[16] A sample of the alcohol (IIb) (0.1 g, 0.0008 mole) and 10 ml of anhydrous ether were placed in a 25-ml three-neck round-bottom flask. The solution was cooled to 0.5°, and with stirring 0.18 g (0.0011 mole) of anhydrous ferric chloride (MCB reagent) in 15 ml of ether was slowly added. Stirring was continued at 5° for 0.5 hr. The mixture was then warmed to room temperature, filtered, extracted twice with 10 ml of water, and dried ($MgSO_4$). Removal of the solvent followed by nmr analysis indicated the presence of some unreacted alcohol. The reaction was rerun in the same manner as above using an additional 0.14 g (0.0009 mole) of ferric chloride. The sole product was 4-chloro-4-phenyl-2-butanone: nmr ($CDCl_3$) τ = 7.82 (s, 3, CH_3), 6.78 (5, 2, $-CH_2CO-$), 4.58 (dd, 1, CH), 2.60 (s, C_6H_5); ir ($CHCl_3$) 1725 cm^{-1} (C=O).[4]

B. (+)-Alcohol (IV).--The (+)-alcohol (IV) was provided by D. Gibson and was made according to the procedure of DePuy et al.[2] A Rudolph Model 70 No. 709 Polarimeter with a sodium light source was used to determine optical rotations. The (+)-alcohol (IV) gave optical rotations, $[\alpha]_D$, of +39.11 ± 1° in ethanol and +39.44 ± 3.5° in $CHCl_3$. The maximum reading given for the (+)-alcohol (IV) is +41.9° (EtOH), indicating the optical purity of this alcohol was 93%. The (+)-alcohol (IV) (0.026 g, 0.0018 mole) was treated with 0.6 g (0.004 mole) of ferric chloride as described in part A. An nmr spectrum of the resulting oil indicated the presence of the chloroketone along with a small amount (~ 10%) of benzalacetone. A solution of 0.12 g of this oil in 1 ml of $CHCl_3$ gave an observed rotation of -0.25° or $[\alpha]_D$ = -1.97 ± 0.6°. An ir spectrum was taken of the solution from the polarimeter tube. A 1725 cm^{-1} (C=O) band indicated the chloroketone was still present. This solution was stirred with 1 N KOH in ethanol for 1 hr. Work-up gave a yellow oil, the nmr and ir of which, were identical to those of an authentic sample of benzalacetone.[15]

Preparation and Separation of cis- and trans-1,2-Diphenylcyclopropyl Acetates.--The acetate mixture was prepared according to the procedure of Freeman[5] and DePuy[9] with the modifications already described for the synthesis of 2-phenyl-1-methylcyclopropylacetates. Chalcone (75 g, 0.360 mole), prepared from condensation of acetophenone and benzaldehyde,[18] and 12.5 g (0.39 mole) of 97% hydrazine were condensed to give 3,5-diphenyl-2-pyrazaline in nearly quantitative yield. The 2-pyrazoline was treated with 230 g (0.5 mole) of lead tetraacetate to yield 98 g of the 3-acetoxypyrazoline which upon pyrolysis gave a mixture of 73% trans and 27% cis acetates. The acetates were separated and purified by a combination of spinning band distillation and recrystallization.[9] cis-1,2-Diphenylcyclopropyl acetate: mp 73.5-75° (lit. mp 74.5-75°).[9]

Synthesis of trans-1,2-Diphenylcyclopropanol (Vb).--A sample of the trans acetate (3 g, 0.01 mole) was cleaved with 13 ml (0.03 mole) of methyllithium in ether. Work-up yielded 2.6 g of a white solid. Recrystallization from Skellysolve B-ether gave 1.4 g (53%) of the pure alcohol (Vb): mp 96.5-99° (the value of the melting point varied considerably with various fractions, lit. mp 75-76.5°);[9] nmr ($CDCl_3$) τ = 2.82, 2.97 (s + m, 10, C_6H_5's), 7.23 (dd, 1, cyclopropane CH), 7.47 (s, 1, OH), 8.35 (m, 2, cyclopropane CH_2); ir ($CHCl_3$) 3610, 3430 cm^{-1} (OH).

Synthesis of cis-1,2-Diphenylcyclopropanol (Va).--A sample of the cis acetate (3.5 g, 0.014 mole) was cleaved with 14 ml (0.03 mole) of 2.3 M methyllithium to yield 3.3 g of a white solid which was recrystallized from hexane-ether mixtures at freezer or Dry Ice temperatures. The alcohol (Va) had the following properties: mp 79-82.5° (lit. mp 67-69°);[9] ir ($CHCl_3$) 3600, 3450 cm^{-1} (OH); nmr ($CDCl_3$) τ = 2.67 (d, 10, C_6H_5's), 7.51 (dd, 1, cyclopropane CH), 7.79 (s, 1, OH- which disappeared on shaking with D_2O), 8.35 (m, 2, cyclopropane CH_2).

Reactions of trans-1,2-Diphenylcyclopropanol (Vb).--A. with N-Bromosuccinimide: The trans alcohol (Vb) (0.17 g, 0.0008 mole) in 2 ml of $CDCl_3$ was added to a stirred slurry of 0.16 g (0.0009 mole) of N-bromosuccinimide (MCB) in 2 ml of $CDCl_3$ in a 50-ml erlenmeyer flask covered with aluminum foil. Immediately an aliquot was removed and nmr analysis within 5 min of mixing indicated the reaction was complete. The nmr sample was transferred back to the reaction mixture and the solvent was removed. The residual solid-oil was taken up in $CDCl_3$. In addition to singlets at τ = 7.08 and 7.28 for N-bromosuccinimide and succinimide, the nmr spectrum was consistent with β-bromo-β-phenylpropiophenone as the sole reaction product: τ = 2.12, 2.43 (m, 10, C_6H_5's), 4.30 (t, 1, Br-C-H); 6.05.[2] Passage of the reaction mixture through a small silica gel column with CH_2Cl_2 removed the N-bromosuccinimide and succinimide. An ir spectrum of the resulting oil showed a carbonyl absorption at 1690 cm^{-1}. The N-bromosuccinimide reaction product (0.2 g) was taken up in 4 ml of dioxane, 3 ml of 1 N K_2CO_3 in dioxane-water was added, and the resulting yellow solution was stirred for 40 hr at room temperature. Methylene chloride (20 ml) was added and the solution was extracted twice with 10 ml of 5% $NaHCO_3$, and several times with water. Drying ($MgSO_4$) and removal of solvent on a rotary evaporator, yielded 0.0726 g of an oil. An nmr spectrum indicated the presence of chalcone (compared to an authentic sample)[18] and dioxane. Further water extraction removed the dioxane and yielded 0.03 g of a yellow oil which had properties identical to an authentic sample of chalcone.[18]

B. with tert-Butylhypochlorite: A 50-ml aluminum foil-covered erlenmeyer flask was charged with 0.14 g (0.0007 mole) of the trans alcohol (Vb) and 1.5 ml of $CDCl_3$. tert-Butylhypochlorite[17] (0.1 g, 0.001 mole) in 0.5 ml $CDCl_3$ was added to the stirred solution. An nmr spectrum obtained within 5 min of mixing indicated that the alcohol had been completely consumed. The reaction mixture was taken up in CH_2Cl_2 and extracted several times with water to remove the tert-butanol. After drying ($MgSO_4$) and removal of solvent, 0.1133 g of a solid was obtained. An nmr spectrum ($CDCl_3$) indicated the product was exclusively β-chloro-β-phenylpropiophenone. The chloroketone was treated with 1 N K_2CO_3 as described in part A. The resulting product was exclusively chalcone as identified by nmr and ir spectroscopy, and gpc analysis. Reaction of the alcohol (Vb) with tert-butylhypochlorite in carbon tetrachloride was also rapid yielding the

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chloroketone. Elimination with DABCO (Aldrich), gave greater than 95% chalcone identified by nmr and ir spectroscopy, and gpc analysis versus an authentic sample.[18]

C. with Mercuric Acetate: The trans alcohol (Vb) (0.4 g, 0.002 mole) was dissolved in 15 ml of glacial acetic acid in a 50-ml erlenmeyer flask. Mercuric acetate (0.6 g, 0.002 mole, MCB reagent) was added to the stirred solution in portions. After stirring 1 hr, the solvent was removed on a rotary evaporator at 45°. The resulting cloudy oil was taken up in CH_2Cl_2 and filtered to remove some of the unreacted mercuric acetate. Removal of the solvent yielded 1.0 g of an orange semi-solid: nmr ($CDCl_3$) τ = 2.10, 2.78 (m's, C_6H_5's), 6.22 (m, CH_2 and possibly $CHHgOAc$), 8.02 (s, acetate CH_3). Further rotary evaporation removed traces of CH_2Cl_2 and HOAc to yield 0.9344 g of an orange semi-solid.

The crude organomercurial acetate from above was placed in a 125-ml erlenmeyer flask with 50 ml of MeOH to form a slurry. Sodium borohydride (0.3 g, 0.008 mole) was added in portions with cooling (ice bath) and stirring. The reaction was exothermic and mercury precipitated. After 0.5 hr of stirring, 25 ml of saturated NH_4Cl solution was added to the reaction mixture. This solution was extracted 5 times with 30 ml of CH_2Cl_2. The combined CH_2Cl_2 was extracted with saturated NH_4Cl and water. After drying ($MgSO_4$) and removing the solvent on a rotary evaporator, 0.3 g of an oil was obtained. An ir spectrum indicated both alcohol and ketone to be present. Oxidation of the mixture with a dichromate solution, yielded 0.0563 g of an oil: ir ($CHCl_3$) 1685 cm^{-1} (C=O). Analysis by gpc (Column D at 181°) yielded two peaks of 87.5% and 12.5% which had the same retention times as authentic samples of β-phenylpropiophenone and α-phenylpropiophenone respectively. These two peaks accounted for greater than 80% of the gas chromatogram. There was a small amount of material (~ 10%) with a retention time identical to chalcone. These results were supported by nmr and ir data.

Reactions of cis-1,2-Diphenylcyclopropanol (Va). A. with N-Bromosuccinimide: The cis alcohol (Va) was allowed to react with N-bromosuccinimide in $CHCl_3$ according to the procedure given for the trans alcohol (Vb) above. The reaction was rapid yielding β-bromo-β-phenylpropiophenone as the sole product identified by

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nmr and ir spectroscopy. Elimination of the bromoketone yielded exclusively chalcone identified by nmr and ir spectroscopy as well as gpc analysis.

B. with tert-Butylhypochlorite: The cis alcohol (Va) was allowed to react with tert-butylhypochlorite[17] in $CHCl_3$ according to the procedure given for the trans alcohol (Vb) above. The reaction was rapid, yielding β-chloro-β-phenylpropiophenone identified by nmr and ir spectra.

C. with Mercuric Acetate: The cis alcohol (Va) was allowed to react with mercuric acetate in HOAc according to the procedure given for the trans alcohol (Vb). Reduction of the organomercurial with sodium borohydride and oxidation with dichromate solution yielded an oil. The absence of α-phenylpropiophenone was indicated by gpc analysis (Column D at 185°). There were two major peaks with retention times identical to β-phenylpropiophenone (68%) and chalcone (32%). Spectral data (nmr and ir) indicated the presence of these two components.

β-Phenylpropiophenone: An authentic sample showed: mp 70-71° (lit. mp 72-73°).[20]

α-Phenylpropiophenone: Phenylmagnesium bromide was prepared in the usual manner from 4 g (0.16 g at.) of magnesium turnings (MCB) and 16.5 ml (25 g or 0.16 mole) of phenyl bromide. 2-Phenylpropionaldehyde (20 g, 0.150 mole, Aldrich) in 25 ml of ether was added to the Grignard over a 25-min period. After stirring for 2 hr, saturated NH_4Cl was added to the mixture until salts precipitated. The ether was decanted and the solids were washed several times with ether. The combined ether extracts were extracted twice with 100 ml of water. After drying ($MgSO_4$), the ether was removed on a rotary evaporator to yield 15 g (50%) of a yellow oil: ir ($CHCl_3$) 3620, 3480 cm^{-1} (O-H); nmr ($CDCl_3$) τ = 2.64, 2.73 (m, 10, C_6H_5's), 5.18 (d, 1, H-C-OH), 6.88 (m, 1, CH), 8.06 (s, 1, OH), 8.69, 8.91 (d, 3, CH_3's).

The alcohol (12 g, 0.06 mole) was oxidized with a dichromate solution according to the procedure used for the synthesis of isobutyrophenone. Work-up yielded 11 g of a yellow oil. Recrystallization from ethanol-Skellysolve B gave a pure sample: mp 48.5-50° (lit. mp 49-51°).[21]

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Synthesis of 2-Methyl-1-Phenylcyclopropanol (VI).--A mixture of cis- and trans-2-methyl-1-phenylcyclopropyl acetates was prepared by the method of Freeman[5] (cis:trans ~ 1.8:1). The acetate mixture (10 g, 0.05 mole) was cleaved with 56 ml of 2.3 N methyllithium[16] and worked up to give a yellow oil. The material was distilled and 7 g (88%) of a colorless oil (VI) was collected, bp 65-75°/0.8 mm): ir ($CHCl_3$) 3600, 3430 (OH); nmr ($CDCl_3$) τ = 8.7-9.4 (m, 6, cyclopropane CH_2, CH, and CH_3), 7.52 (s, 1, OH), 7.64, 7.73 (s, 5, C_6H_5).

Reactions of 2-Methyl-1-Phenylcyclopropanol (VI) with Halogenating Agents. A. with N-Bromosuccinimide: N-bromosuccinimide (0.3 g, 0.002 mole, MCB) and 5 ml of $CHCl_3$ were placed in an aluminum foil-covered 50-ml erlenmeyer flask to form a slurry. The alcohol (VI) (0.2 g, 0.001 mole) in 5 ml of $CHCl_3$ was added to the stirring slurry over a few moments. The solution initially turned orange and it was stirred for 30 min. The solvent was removed on a rotary evaporator to yield 0.5 g of a solid-oil mixture which was taken up in CCl_4 and filtered to remove some of the succinimide. Removal of the CCl_4 yielded 0.3 g of an oil. An nmr spectrum ($CDCl_3$) showed phenyl absorptions at τ = 2.12 and 2.43 in the ratio of 1:1.7 assigned the ortho and meta-para protons; a series of complex absorptions in the region τ = 5.9 to 6.9 assigned to $BrCH_2$, CH-CH_3, and CH_2CO-; a weak absorption at τ = 5.29 assigned to CH-Br; and doublets at τ = 8.20 and 8.73 in the ratio of ~ 1:8 assigned to the CH_3 of β-bromo-β-methylpropiophenone and to the CH_3 of β-bromo-α-methylpropiophenone respectively. Traces of N-bromosuccinimide and succinimide were removed by silica gel chromatography with CH_2Cl_2 as the eluting solvent. An ir spectrum ($CHCl_3$) showed a carbonyl absorption at 1685 cm^{-1}. The oil was treated with K_2CO_3 for 24 hr as previously described. Pentane (50 ml) was added to the reaction mixture. The layers were separated and the pentane was extracted with 20 ml of 10% HCl, twice with 20 ml of 5% $NaHCO_3$, and twice with 20 ml of water. The pentane solution was dried ($MgSO_4$) and the solvent removed on a rotary evaporator to yield 0.0535 g of an oil. Based on comparison with nmr spectra of authentic samples, an nmr spectrum ($CDCl_3$) indicated the presence of isopropenyl phenyl ketone (VIII) and propenyl phenyl ketone (VII) with the former

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predominating. An ir spectrum showed a carbonyl absorption at 1665 cm^{-1}. Analysis by gpc (Column A at 167°) indicated the presence of two components in the amounts of 86% and 14% with retention times corresponding to authentic samples of isopropenyl phenyl ketone (VIII) and propenyl phenyl ketone (VII) respectively.

B. with Ferric Chloride: The alcohol (VI) (0.2 g, 0.002 mole) was allowed to react with 0.6 g (0.004 mole) of ferric chloride (MCB reagent) according to previously described procedures. After stirring for 30 min at 0-5°, the mixture was stirred for 2 hr at room temperature. Work-up yielded 0.2 g of a yellow oil: ir ($CHCl_3$) 1690 cm^{-1} (C=O). An nmr spectrum ($CDCl_3$) was consistent with β-chloro-β-methylpropiophenone as the sole product: τ = 8.36 (d, 3, CH_3), 6.58 (AB portion of ABX spectrum 2, CH_2), 5.32 (sextet, 1, CH), 2.01, 2.42 (m, 5, C_6H_5). These nmr assignments were confirmed by nmr spin decoupling experiments. The chloroketone was treated with 1 N K_2CO_3 as described in part A. The resulting oil had nmr, ir, and gpc properties consistent with those of an authentic sample of propenyl phenyl ketone (VII). Only a trace of the other isomer, isopropenyl phenyl ketone (VIII), was present as indicated by gpc (Column A at 167°).

C. with tert-Butylhypochlorite. No Inhibitor: The alcohol (VI) (0.2 g, 0.002 mole) was allowed to react with 0.2 g (0.002 mole) of tert-butylhypochlorite in $CHCl_3$ according to previously described procedures. After stirring 45 min, the solvent was removed on a rotary evaporator yielding 0.3 g of a colorless oil. The oil was taken up in CH_2Cl_2 and extracted several times with water. After drying ($MgSO_4$) and solvent removal, another nmr spectrum indicated the presence of β-chloro-β-methylpropiophenone. In addition a doublet at τ = 8.73 and a complex multiplet in the region τ = 5.8 to 6.5 indicated the presence of β-chloro-α-methylpropiophenone in lesser amount. An ir spectrum ($CHCl_3$) showed a carbonyl absorption at 1690 cm^{-1}. The chloroketones were treated with 1 N K_2CO_3 as described in part A. After work-up, an nmr spectrum indicated the presence of 35% isopropenyl phenyl ketone (VIII) and 65% propenyl phenyl ketone (VII). An ir spectrum ($CHCl_3$) showed carbonyl absorptions at 1655 and 1629 cm^{-1}. Analysis by gpc (Column A at 167°) indicated the presence of 42% isopropenyl phenyl ketone and 58% propenyl phenyl ketone compared with retention times of authentic samples.

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Preparation of Propenyl Phenyl Ketone (VII).--The ketone was prepared by Friedel-Crafts acylation of benzene with crotonyl chloride (Aldrich) and $AlCl_3$ according to published procedures.[22] The propenyl phenyl ketone had the following properties: bp 69-73°/0.8 mm (lit. bp 135-140°/20 mm);[23] ir ($CHCl_3$) 1660 (C=O), 1627 cm^{-1} (C=C); nmr ($CDCl_3$) τ = 8.10 (d, 3, CH_3), 2.14, 2.54, 3.04 (m, 7, C_6H_5, CH=CH); mass spectrum m/e (rel intensity) 146(54.4), 105(100), 77(82.1), 69(56.1), 51(45.8). Analysis by gpc (Column A at 167°) indicated the olefin was greater than 90% pure.

Preparation of Isopropenyl Phenyl Ketone (or Methacrylophenone) (VIII). A. Preparation of Isopropylphenylcarbinol: Phenyl magnesium bromide was prepared in the usual manner from 34 g (1.4 g at.) of magnesium turnings (MCB) and 218 g (1.4 mole) of bromobenzene (MCB). Isobutyraldehyde (100 g, 1.4 mole, MCB) in 250 ml of anhydrous ether was added dropwise to the Grignard over a period of 2 hr. The mixture was then stirred under reflux for 0.5 hr. Saturated aqueous NH_4Cl was then added until a precipitate formed. The ether was decanted and the precipitate washed with ether. The combined ether was extracted with water and dried. Removal of the ether by distillation yielded a liquid which upon distillation gave 174.2 g (91%) of isopropylphenylcarbinol: bp 61-67°/-0.7 -1mm (lit. bp 101-104°/7 mm).[23]

B. Preparation of Isobutyrophenone: In a 500-ml three-neck round-bottom flask was placed 50 g (0.3 mole) of the above alcohol and 100 ml of ether. To this stirred solution was added 150 ml of dichromate solution (prepared from 55 g of sodium dichromate dihydrate and 41.5 ml of concentrated H_2SO_4 diluted to 225 ml with water) over a 70-min period at room temperature. Some cooling with an ice bath was necessary. The mixture was then stirred for 16 hr. The ether and green chromate layers were separated and the chromate layer was extracted with ether. The combined ether was extracted with 50 ml of 5% $NaHCO_3$, 50 ml of water, and dried ($MgSO_4$). Removal of the ether and distillation yielded 47.0 g (94%) of isobutyrophenone: bp 60-65°/1.6 mm (lit. bp 120°/20 mm).[24]

C. Preparation of α-Bromo-α-Methylpropiophenone: The procedure followed was patterned after that for the preparation of α-bromoacetophenone from acetophenone.[25] A 250-ml three-neck

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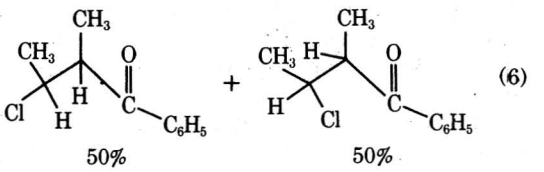
round-bottom flask was charged with 10 g (0.07 mole) of isobutyrophenone and 50 ml of anhydrous ether. This mixture was cooled with an ice bath and about 0.1 g of aluminum chloride (MCB reagent) was added. Bromine (3.3 ml, 10.3 g, 0.07 mole, MCB reagent) was added dropwise to the cold solution with stirring over a 5-min period. No reaction seemed to occur, so two spatulas of aluminum chloride were added and the ice bath was removed. After stirring 30 min the reaction was complete as evidenced by the disappearance of the bromine color. The solvent was removed on a rotary evaporator to leave an orange oil which was taken up in ether and extracted twice with 25 ml of water. The water layer was extracted with ether. The ether solutions were combined and dried ($MgSO_4$). The ether was removed on a rotary evaporator to yield 14 g (89%) of a yellow oil. Treatment of a few drops of the oil with silver nitrate-ethanol produced a yellow precipitate (AgBr). Spectral properties were consistent with those expected for α-bromo-α-methylpropiophenone: nmr ($CDCl_3$) τ = 1.93 (m, 2, ortho protons), 2.48 (m, 3, meta and para protons), 7.96 (s, 6, CH_3's); ir ($CHCl_3$) 1680 cm^{-1} (C=O).

D. Preparation of Isopropenyl Phenyl Ketone (or Methacrylophenone VIII): Heating of α-bromo-α-methylpropiophenone with an equivalent of DABCO (Air Products or Aldrich) in dioxane at 100-100° for 12 hr resulted in the formation of a precipitate (DABCO·HBr) which was filtered and washed with CH_2Cl_2. The dioxane-CH_2Cl_2 was extracted with water several times. The solution was dried ($MgSO_4$) and the solvent removed on a rotary evaporator to yield an oil which an nmr spectrum indicated was fairly pure isopropenyl phenyl ketone (VIII). The oil was taken up in pentane and extracted with 20 ml of 2 N HCl, 20 ml of 5% $NaHCO_3$, and twice with 20 ml of water. After drying ($MgSO_4$) and removal of solvent, the resulting oil was distilled and a fraction (bp 49-51°/1 mm, lit. bp 60°/3 mm)[26] was collected. It had spectral properties consistent with those expected for isopropenyl phenyl ketone (VIII): ir ($CHCl_3$) 1660 (C=O), 1630 cm^{-1} (C=C); nmr ($CDCl_3$) τ = 2.31 (m, 2, ortho protons), 2.45 (m, 3, meta and para protons), 4.10, 4.38 (m's, 2, CH_2=C), 7.90 (s, 3, CH_3); mass spectrum m/e (rel intensity) 146(40), 105(100), 77(65.8), 58(16.3), 51(28.6), 43(57.3), 41(12.1), 39(16.1), 32(16.4). Analysis by gpc (Column A at 167°) indicated the olefin was pure.

this hypothesis optically active *trans*-2-phenyl-1-methylcyclopropanol (IV)[2] was allowed to react with NBS, *tert*-butyl hypochlorite, and $FeCl_3$. Cleavage with NBS and *tert*-butyl hypochlorite in $CDCl_3$ proceeds with predominant or exclusive inversion at the benzylic carbon yielding optically active 4-halo-4-phenyl-2-butanone (eq 7).[8] In contrast, cleavage with $FeCl_3$ in ether yields racemic 4-chloro-4-phenyl-2-butanone.



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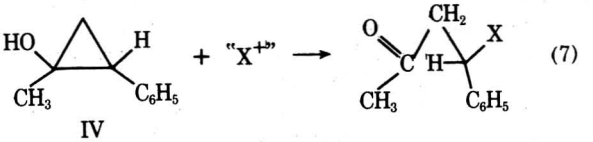

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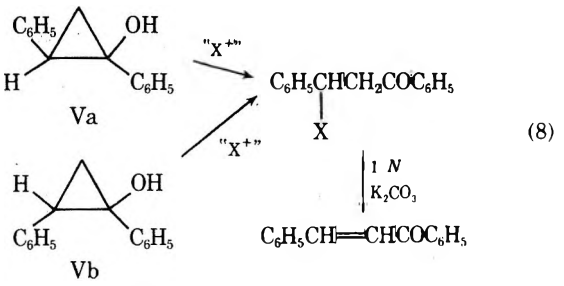
"X^+" = NBS, *t*-BuOCl

X = Br, Cl

cis- and *trans*-1,2-Diphenylcyclopropanol (Va and Vb). A mixture of *cis*- and *trans*-1,2-diphenylcyclopropylacetates was prepared and separated according to the method of Freeman[5] and DePuy.[9] Cleavage with methyllithium produces the corresponding alcohols Va and Vb. These alcohols melt over a relatively wide range even after numerous recrystallizations even when it appeared by nmr and ir spectroscopy that they were pure. Perhaps they melt with some ring opening induced by air or glass.

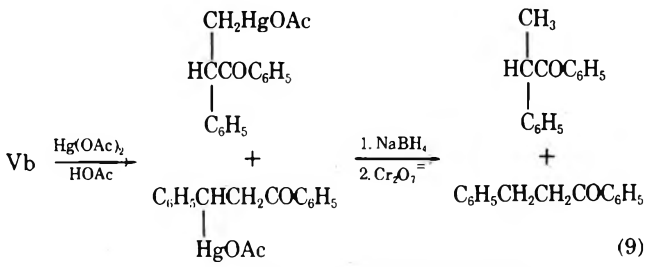
Both of these alcohols react rapidly with NBS or *tert*-butyl hypochlorite in CCl_4 solution to yield a single halo ketone whose nmr spectrum is consistent with the struc-



"X^+" = NBS, *t*-BuOCl

ture of β-halo-β-phenylpropiophenone (eq 8). This structure was confirmed when it was found that stirring with 1 *N* potassium carbonate solution converted the product exclusively to chalcone.

When either Va or Vb is stirred with an equivalent of mercuric acetate in acetic acid at room temperature, ring cleavage occurs within an hour, giving rise to a mixture of organomercurials (eq 9). To determine the relative amount



(9)

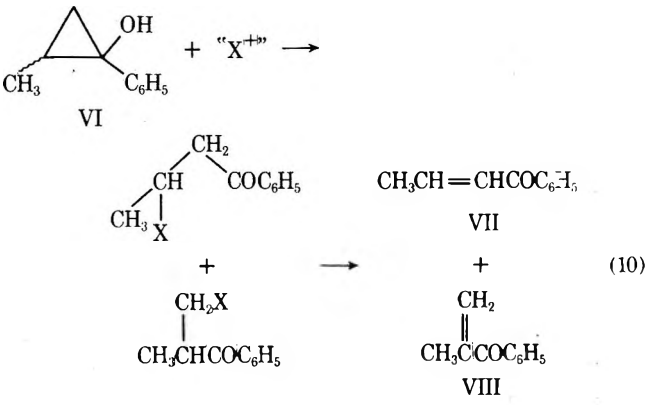
of C_1–C_2 compared to C_1–C_3 bond cleavage, the carbon–mercury bond was reduced with sodium borohydride and the resulting mixture of alcohols was reoxidized to a mixture of α- and β-phenylpropiophenone. Analysis of the mixture of ketones was made by gpc and comparison was made with authentic samples which were synthesized by standard methods (see Experimental Section). Both the cis and trans isomers gave mainly or exclusively C_1–C_2 cleavage; from the former no α-phenylpropiophenone was formed, the ketone fraction being 68% β-phenylpropiophenone and 32% chalcone while the latter gave 88% β-phenyl- and 12% α-phenylpropiophenone together with chalcone. The chalcone must have arisen by elimination of the highly reactive benzylic organomercurial either by solvolysis or during reduction.[10] In any event it could only have arisen from the products of C_1–C_2 cleavage so that cleavage in this direction occurs to the extent of 90–100%. We have also shown that cleavage of these isomers by H^+ leads to 93–95% C_1–C_2 cleavage.[9] These results confirm scattered literature results which indicate that in a 1,2-diphenylcyclopropane the ring bond between two phenyl groups is cleaved preferentially. Levina[11] reported that cleavage of 1,2-diphenylcyclopropanes occurs between the two phenyls upon reaction with bromine at −7°. LaLonde[12] also found exclusive C_1–C_2 cleavage of the 1,2-diphenylcyclopropanes with bromine in CCl_4 at −20°. Young[13] has noted a similar direction of cleavage for 1,2-diphenylcyclopropanes with ceric ammonium nitrate.

2-Methyl-1-phenylcyclopropanol (VI). In previous work we had determined that this compound undergoes 99% C_1–C_3 cleavage with mercuric acetate, 53% C_1–C_3 cleavage with H^+, and 83% C_1–C_3 cleavage with OH^-.[3] To complete our comparison with the 1,2-diphenyl and 2-phenyl-1-methyl systems, we wished to determine the product composition upon ring opening with halogenating compounds (eq 10). Brominations were carried out with NBS in chloroform and chlorinations with *tert*-butyl hypochlorite in chloroform and ferric chloride in ether. The results are given in Table I.

Table I
Product Distributions from Cleavage of 2-Methyl-1-phenylcyclopropanol (VI) with Halogenating Agents[a]

Reagent/solvent	% C_1–C_2 cleavage	% C_1–C_3 cleavage
$NBS/CHCl_3$	14	86
t-BuOCl/$CHCl_3$	58	42
$FeCl_3$/ether	100	0

[a] Based on elimination of the β-halo ketones to isopropenyl phenyl ketone (VIII) and propenylphenyl ketone (VII).



"X^+" = NBS, *t*-BuOCl

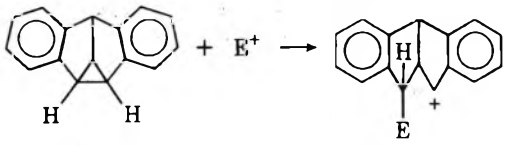
These results for NBS and $FeCl_3$ are those expected on the basis of earlier studies. For example, bromination of 1,2,2-trimethylcyclopropanol gives 100% C_1–C_3 bond cleavage, by attack of the electrophile on the least substituted carbon, while $FeCl_3$ oxidation gives 100% C_1–C_2 opening with the generation of the most stable radical.[4] The reaction products with *tert*-butyl hypochlorite are difficult to account for. When the reaction was carried out in the presence of hydroquinone or *p*-cresol, the product mixture did not change. These inhibitors did not interrupt any radical chain reaction.

Discussion

The results reported in this paper complement and reinforce those reported earlier[1,3,4,9] without affording final answers to several striking aspects of the reactions of cyclopropanols with electrophiles. The most puzzling anomalies lie in ring opening with various halogenating agents. We might take 1,2,2-trimethylcyclopropanol as a "well behaved" compound. This molecule reacts rapidly with NBS or *tert*-butyl hypochlorite giving quantitative yields of products resulting from attack on the methylene ring carbon.[4] 2-Phenyl-1-methylcyclopropanols reacts equally rapidly, but exclusively at the benzylic carbon, and completely, or nearly so, with inversion of configuration at C_2. This high stereospecificity would seem to rule out any radical-chain mechanism, especially so since $FeCl_3$ oxidation leads to nearly racemic chloride, and, while ionic chain mechanisms are conceivable, they do not give any clear-cut explanation for the differences found on halogenation of 2-methyl-1-phenylcyclopropanols nor for the differing stereochemical results reported earlier for the 2,3-dimethyl-1-phenylcyclopropanols and cyclopropyl acetates.[4] Further work will be needed to clear up these differences in behavior which are especially interesting because cyclopropanes in general are not reactive toward halogenating agents, cyclopropanols being a notable exception.

Our results also confirm that 1,2-diphenylcyclopropanes are especially susceptible to cleavage of the ring bond between the phenyl groups, no matter what the electrophile.

The effect is observed whether the two aromatic rings are cis to one another or trans, and thus cannot be due to a steric relief of strain. We do not have any stereochemical results in a diphenyl system, so we cannot say whether the electrophile is entering with retention or inversion, but in the system studied by Cristol and coworkers[14] ring opening always occurred on the bond between the aromatic rings and with retention (eq 11). It will be interesting to see if this stereochemistry will hold for simple cyclopropanes.



(11)

The independence of product composition with cyclopropane stereochemistry is also clearly shown by the reactions of *cis*- and *trans*-2-phenyl-1-methylcyclopropanols, and the product composition is also unchanged when the much less reactive methyl ethers are used in place of the alcohols. Additional work is now in progress which may shed light on some of these puzzling observations.

Acknowledgment. The authors wish to thank the National Science Foundation for support of this research by Grant GP 13783X.

Registry No.—Ia, 52306-22-6; Ib, 52438-83-2; IIa, 52306-23-7; IIb, 10606-71-0; *cis*-III, 52306-24-8; *trans*-III, 52306-25-9; (+)-IV, 52306-26-0; Va, 43187-69-5; Vb, 43187-79-7; *cis*-VI, 52374-29-5; *trans*-VI, 52306-27-1; VII, 495-41-0; VIII, 769-60-8; benzalacetone, 122-57-6; hydrazine, 302-01-2; 3-methyl-5-phenyl-2-pyrazoline, 939-03-7; 3-acetoxy-3-methyl-5-phenyl-1-pyrazoline, 52306-28-2; *N*-bromosuccinimide, 128-08-5; mercuric acetate, 1600-27-7; *tert*-butyl hypochlorite, 507-40-4; ferric chloride, 7705-08-0; 4-chloro-4-phenyl-2-butanone, 52306-29-3; 4-bromo-4-phenyl-2-butanone, 52306-30-6; *cis*-1,2-diphenylcyclopropyl acetate, 43187-69-5; *trans*-1,2-diphenylcyclopropyl acetate, 43187-79-7; β-bromo-β-phenylpropiophenone, 52306-31-7; α-phenylpropiophenone, 2042-85-5; 2-phenylpropionaldehyde, 93-53-8; 1,2-diphenyl-1-propanol, 28795-94-0; β-chloro-β-methylpropiophenone, 34880-85-8; isobutyraldehyde, 78-84-2; isopropylphenylcarbinol, 611-69-8; isobutyrophenone, 611-70-1; α-bromo-α-methylpropiophenone, 10409-54-8.

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References and Notes

(1) C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).
(2) C. H. DePuy, F. W. Breitbeil, and K. R. DeBruin, *J. Amer. Chem. Soc.*, **88**, 3347 (1966).
(3) A. DeBoer and C. H. DePuy, *J. Amer. Chem. Soc.*, **92**, 4008 (1970).
(4) C. H. DePuy, W. C. Arney, Jr., and D. H. Gibson, *J. Amer. Chem. Soc.*, **90**, 1830 (1968).
(5) J. P. Freeman, *J. Org. Chem.*, **28**, 885 (1963); **29**, 1379 (1964).
(6) E. Müller, R. Heischkeil, and M. Bauer, *Justus Liebigs Ann. Chem.*, 677, 55 (1964). We are grateful to Professor Th. DeBoer for bringing this method to our attention.
(7) S. E. Schaafsma, H. Steinberg, and Th. J. DeBoer, *Recl. Trav. Chim. Pays-Bas*, **85**, 70 (1966).
(8) W. C. Arney, Jr., unpublished results.
(9) C. H. DePuy, R. A. Klein, and J. P. Clark, *J. Org. Chem.*, **39**, 483 (1974).
(10) F. G. Bordwell and M. L. Douglass, *J. Amer. Chem. Soc.*, **88**, 993 (1966).
(11) R. Y. Levina, P. A. Gembitskii, V. N. Kostin, S. M. Shostakovskii, and E. G. Treshova, *J. Gen. Chem. USSR*, **33**, 358 (1963).
(12) R. T. LaLonde, P. B. Ferrara, and A. D. Debboli, Jr., *J. Org. Chem.*, **37**, 1094 (1972).
(13) L. B. Young, *Tetrahedron Lett.*, 5105 (1968).
(14) S. J. Cristol, W. Y. Lim, and A. R. Dahl, *J. Amer. Chem. Soc.*, 92, 4013 (1970).
(15) N. L. Drake and P. Allen, Jr., "Organic Syntheses," Collect Vol. I, A. H. Blatt, Ed., Wiley, New York, N. Y., 1932, p 77.
(16) C. H. DePuy, G. M. Dappen, K. L. Eilers, and R. A. Klein, *J. Org. Chem.*, **29**, 2813 (1964).
(17) C. Walling, private communication; see ref 4.
(18) E. P. Kohler and H. M. Chadwell, ref 15, p 78.
(19) T. T. Tidwell and T. G. Traylor, *J. Org. Chem.*, 33, 2614 (1968).
(20) Roger Adams, J. W. Kern, and R. L. Shriner, ref 15, p 101.
(21) A. McKenzie and R. Roger, *J. Chem. Soc.*, 844 (1924).
(22) E. P. Kohler, *Amer. Chem. J.*, **42**, 375 (1909).
(23) J. B. Conant and A. H. Blatt, *J. Amer. Chem. Soc.*, **50**, 551 (1928).
(24) H. Christol, A. Laurent, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 2313 (1961).
(25) R. M. Cowper and L. H. Davidson, "Organic Syntheses," Collect Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 480.
(26) J. Burckhalter and R. C. Fuson, *J. Amer. Chem. Soc.*, **70**, 4184 (1948).

Activation of Dimethyl Sulfoxide by Electrophiles and Use of the Reactive Intermediates in the Preparation of Iminosulfuranes[1a]

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Dimethyl sulfoxide (DMSO) reacts at oxygen with SO_3, P_4O_{10}, BF_3, and H_2SO_4 at or below room temperature. With the first two electrophiles, intermediates are obtained that generally react readily with sulfonamides, amides, and aromatic amines to give iminosulfuranes in good to excellent yields (60–90%). Although intermediate complex formation is necessary for the formation of iminosulfuranes, it is not a sufficient condition for successful reaction, as a good leaving species must also be provided to facilitate cleavage of the S–O bond of DMSO. Acetic anhydride does not form significant quantities of "activated" intermediate with DMSO at room temperature but does at elevated temperatures and, if sulfonamides or carboxamides are present, iminosulfuranes are obtained. The activation of DMSO with SO_3 has received detailed study; SO_3 is especially useful in the preparation of iminosulfuranes from DMSO and aromatic amines; and it can also be used with the other nitrogen compounds. Salts have been prepared from selected iminosulfuranes and hydrogen chloride. Mechanistic considerations are also discussed.

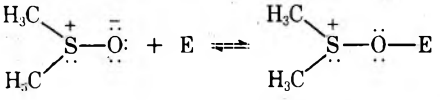
In this paper we are reporting (a) the "activation" of DMSO by liquid SO_3 and, for comparison, P_4O_{10}, acetic anhydride, concentrated sulfuric acid, and boron trifluoride; (b) the scope and limitations of the reaction of "activated" DMSO with a variety of nitrogen compounds (sulfonamides, amides, and aryl amines) to prepare iminosulfuranes with a wide range of structures ($R_2S^+-N^--R'$); (c) certain mechanistic aspects of the iminosulfurane preparative reaction; and (d) some spectral and other miscellaneous characteristics of iminosulfuranes. As a corollary of (a),

we were also interested in knowing if complex formation between DMSO and any electrophile followed by reaction with an appropriate nitrogen compound as the nucleophile is a sufficient condition to ensure iminosulfurane formation.

Various electrophiles have been used to "activate" DMSO;[2] these include, among others, dicyclohexylcarbodiimide + acid,[3] acetic anhydride,[4] acetyl chloride,[5] phosphorus pentoxide,[6] polyphosphoric acid,[7] sulfur trioxide–pyridine,[8] and diphenylketene-*p*-tolylimine + acid.[9] In most instances, alcohols have been the nucleophiles,[2-4] but in a limited number of cases phenols,[10] enols,[11] oximes,[12] and amines[6,13] have also been used.

Results and Discussion

A. "Activation" of DMSO by Electrophiles. Nuclear magnetic resonance spectroscopy is an excellent microtechnique for *in situ* observation of complex formation between DMSO and electrophiles without the need to isolate and handle extremely labile and hygroscopic intermediates. DMSO shows a sharp singlet at *ca.* δ 2.6 (TMS 0), but upon the addition of certain electrophiles, usually with cooling, a new downfield singlet appears immediately at *ca.* δ 3.0. A downfield shift would be expected if a DMSO–electrophile complex (1) had formed owing to the greater deshielding of the $S(CH_3)_2$ protons as a result of the development of a full positive charge on sulfur. Such a downfield shift is observed upon addition to DMSO of BF_3, P_4O_{10}, SO_3, or concentrated sulfuric acid but not acetic anhydride at room temperature.



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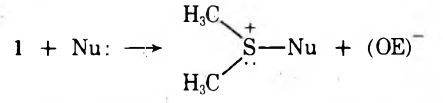
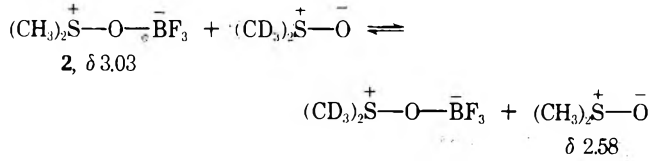


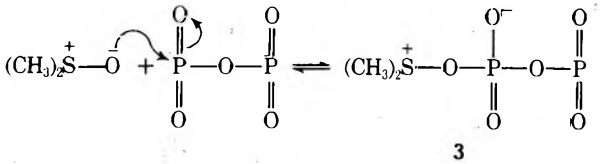
To be certain that the new signal was, in fact, derived from the complex (1) and was not an artifact, we isolated the intermediates in some cases and examined their nmr spectra. The nmr spectrum of the isolated (very hygroscopic) DMSO–BF_3 complex (2), mp 51° (lit.[14a] mp 53°), in acetone-d_6 shows a sharp singlet at δ 3.08; in DMSO-d_6, in which the complex is more soluble, two sharp singlets are observed at δ 3.03 and 2.58 suggesting that the following equilibrium exists.



2, δ 3.03

δ 2.58

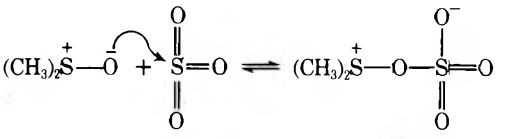
Interaction of DMSO with P_4O_{10} in chloroform at room temperature immediately yields an extremely hygroscopic white precipitate whose nmr spectrum in acetone-d_6 shows only one sharp singlet at δ 2.96. We visualize the formation and structure of the complex (3) as follows (P_2O_5 is used



3

for convenience in the equation). As with the DMSO–BF_3 complex, 3 also shows two sharp singlets at δ 2.87 and 2.61 in DMSO-d_6 suggesting an equilibrium exchange process.

A solid DMSO–SO_3 complex having the formula 4, where x ranges from 1 to 3, has been reported recently by Pettit.[15] We find that reaction of DMSO with liquid SO_3 yields an immediate white precipitate (5) but we have been unable to isolate it without decomposition as it is extremely sensitive to moisture. A DMSO solution of this complex, however, shows the anticipated sharp singlets at δ 3.06 and 2.6.



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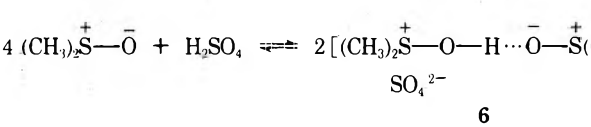
5

In contrast, no changes are observed in the nmr spectrum of a solution of DMSO and acetic anhydride at room temperature over several hours; two singlets are seen at δ 2.51 and 2.2 corresponding to the methyl protons of DMSO and acetic anhydride, respectively, with no peaks farther downfield. DMSO reacts slowly with acetic anhydride at room temperature,[16] a result that is not surprising, as bond breaking is first required. Upon heating the solution, however, the Pummerer rearrangement occurs rapidly and is easily observed by nmr.

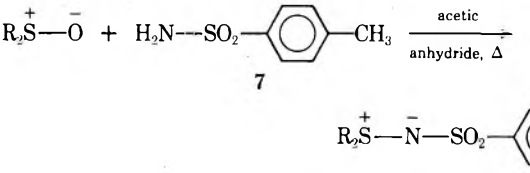
A solution of DMSO in concentrated sulfuric acid (4:1 molar ratio) exhibits two singlets at *ca.* δ 3.2 and 11.32. Since no DMSO signal is observed at δ 2.6 it is assumed that all of the DMSO is bound as a rapidly equilibrating hydrogen-bonded complex 6. The proposed structure is



6

similar to that of the complexes of DMSO with methanesulfonic acid[17] and 2,4,6-trinitrobenzenesulfonic acid.[18]

B. "Activated" DMSO Reaction with *p*-Toluenesulfonamide. We next directed our attention to the question of whether complex formation between DMSO and the electrophiles is a sufficient condition to ensure iminosulfurane formation on reaction of the complexes with an appropriate nitrogen compound as the nucleophile. We chose *p*-toluenesulfonamide (7) as the standard nucleophile because Tarbell and Weaver[19] had shown that certain sulfoxides condense with 7 on heating a chloroform solution in the presence of acetic anhydride or phosphorus pentoxide to give low to modest yields of crystalline iminosulfuranes (dimethyl sulfoxide was not studied by Tarbell and Weaver). The condensation was apparently viewed as a simple dehydration reaction with the P_4O_{10} or acetic anhydride functioning as the dehydrating agent; no suggestion of complex formation was offered.[19]



7

As a control, DMSO and *p*-toluenesulfonamide (7) were shown to be unreactive at room temperature for 72 hr (nmr, tlc). In contrast, reaction of 7 with excess DMSO containing sulfur trioxide or phosphorus pentoxide at room

Table I
N-Sulfonyliminosulfuranes from "Activated" DMSO and Sulfonamides

Sulfonamide	Registry no.	Activator	Reaction conditions: Temp, °C	Time, hr	Product	Yield,[a] %	Mp,[a] °C	Lit. mp, °C	Ref
p-Toluenesulfonamide 7	70-55-3	SO_3	15–25	10	*p*-H_3C—$C_6H_4SO_2\bar{N}$—$\dot{S}(CH_3)_2$	60–80	156–158	158–159	20
		P_4O_{10}	15–25	1.5	8	60–75	156–158		
		Ac_2O	85–90	1.5		60–75	156–158		
Benzenesulfonamide 9	98-10-2	SO_3	15–25	20	$C_6H_5SO_2\bar{N}$—$\dot{S}(CH_3)_2$	65	128–130.5	131	21
		Ac_2O	90	4	10	60–75	124–126		
p-Nitrobenzenesulfonamide 11	6325-93-5	SO_3	15–25	27	*p*-O_2N—$C_6H_4SO_2\bar{N}$—$\dot{S}(CH_3)_2$	>75	183–185	186	22
		Ac_2O	95	2.5	12	>90	183–185		
p-Chlorobenzenesulfonamide 13	98-64-6	SO_3	15–25	5	*p*-Cl—$C_6H_4SO_2\bar{N}$—$\dot{S}(CH_3)_2$ 14[c]	70–90	110–113	116–117[b]	
Methanesulfonamide 15	3144-09-0	Ac_2O	85–90	4	$CH_3SO_2\bar{N}$—$\dot{S}(CH_3)_2$ 16	30–40	111–117	122–123	23

[a] Crude reaction product. [b] New compound purified by crystallization successively from methylene chloride and then acetone. *Anal.* Calcd for $C_8H_{10}NO_2S_2Cl$: C, 38.16; H, 4.00; N, 5.56; S, 25.47; Cl, 14.08. Found: C, 38.45; H, 4.03; N, 5.68; S, 25.26; Cl, 14.30. [c] Registry no., 52259-84-4.

temperature for 10 or 1.5 hr, respectively, followed by dilution of the reaction mixture with 10% aqueous sodium hydroxide gave 60–80% yields of the iminosulfurane, *S,S*-dimethyl-*N*-*p*-toluenesulfonyliminosulfurane (**8**). Dilution of the reaction mixture with water rather than with base gave substantially lower yields of **8** contaminated with adhering sulfuric or phosphoric acids. Solvents, such as chloroform used by Tarbell and Weaver,[19] are undesirable as lower yields are obtained.

Although we had shown earlier that complex formation could not be detected after several hours (by nmr) between DMSO and acetic anhydride at room temperature, if **7** (1 mol) is dissolved in a DMSO–acetic anhydride solution (5:1.02 molar ratio) for 28 hr at room temperature, nmr shows that some reaction has taken place but most of the amide (**7**) is unchanged. On work-up, an approximately 20% yield of iminosulfurane **8** is isolated and almost 60% of the starting material **7** is recovered. We conclude that the initial reaction at room temperature between DMSO and acetic anhydride is an equilibrium process which highly favors reactants and the small quantity of complex present cannot be detected by ordinary nmr monitoring. In the presence of **7**, however, the intermediate complex is drained off, the equilibrium is reestablished, and some iminosulfurane **8** (20%) is slowly formed. If a solution of **7** in DMSO–acetic

$$(CH_3)_2\overset{+}{S}\text{—}\overset{-}{O} + (CH_3CO)_2O \underset{\text{room temperature}}{\longleftrightarrow}$$

$$(CH_3)_2\overset{+}{S}\text{—}O\text{—}\overset{O}{\overset{\|}{C}}\text{—}CH_3 + CH_3CO_2^- \xrightarrow{7}$$

$$(CH_3)_2\overset{+}{S}\text{—}\overset{-}{N}\text{—}SO_2\text{—}C_6H_4\text{—}CH_3$$

8

anhydride is heated at about 85° for 1.5 hr all the amide **7** reacts and a 75% yield of **8** is obtained. In the absence of **7**, heating a solution of DMSO–acetic anhydride yields Pummerer rearrangement product.

Although "activation" of DMSO by electrophilic reagents is essential for iminosulfurane formation, certain complexes do not yield iminosulfuranes on reaction with *p*-toluenesulfonamide (**7**). Thus, DMSO forms complexes with boron trifluoride and concentrated sulfuric acid but no reaction is observed between those complexes and **7** for up to 72 hr (80–85% of **7** is recovered). In the sulfuric acid case, reaction temperatures up to 85° were studied.

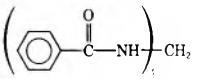
C. Scope of the Reaction of "Activated" DMSO with Nitrogen Compounds. *N*-Sulfonyliminosulfuranes. Table I lists sulfonyliminosulfuranes (**8, 10, 12, 14, 16**) prepared from sulfonamides (**7, 9, 11, 13, 15**) (1 mol), DMSO (5 mol), and the three electrophilic activating agents (1.1 mol) that had proven to be successful in the earlier control studies. The sulfonyliminosulfuranes are white solids with the exception of ylide **12** [from *p*-nitrobenzenesulfonamide (**11**)] which is pale yellow. They are nonhygroscopic compounds, stable at room temperature without special precautions.

***N*-Acyliminosulfuranes.** In view of the uncertainty and sparsity of the earlier work, we next examined the reaction of DMSO with a series of amides. Table II summarizes the results. With the exception of **22** which is pale yellow, all the other *N*-acyliminosulfuranes, including those previously reported by us,[28] are white, crystalline, nonhygroscopic, stable solids at room temperature.

***N*-Aryliminosulfuranes.** When this study was initiated, *N*-aryliminosulfuranes had not yet been described in the literature. The first preparation was reported by Claus and Vycudilik[6] from aromatic amines and DMSO in chloroform solution for 2–24 hr in the presence of phosphorus pentoxide–triethylamine. If triethylamine is omitted, bismethylene derivatives of the amine or polymers are obtained.[13] Subsequently, Lerch and Moffatt[13] obtained *N*-aryliminosulfuranes in 75–85% yields only from *m*- and *p*-nitro- and 3,5-dinitroaniline on reaction with DMSO, dicyclohexylcarbodiimide, and anhydrous phosphoric acid; 2,4-dinitroaniline did not react and was recovered. Acetic anhydride acetylates the amines and thus is not a suitable activator. Our study of the preparation of *N*-aryliminosulfuranes, therefore, focussed exclusively on sulfur trioxide activation; results are summarized in Table III.

The *N*-aryliminosulfuranes with a powerful electron-withdrawing group (CN or NO_2) on the ring (**40, 42, 48, 50, 52, 58**) are fairly stable; they have been stored for 1–12 months at room temperature with no observable change, and appear to be stable indefinitely at −20°. In contrast, the iminosulfuranes obtained from the haloanilines (**28, 30, 32, 34, 36, 38, 44**) are hygroscopic and decompose within a few days to a few weeks at room temperature but they can be stored for at least 1 month at 0° and up to 6 months at −30°. The least stable iminosulfurane (**54**), prepared from

Table II
***N*-Acyliminosulfuranes from "Activated" DMSO and Amides**

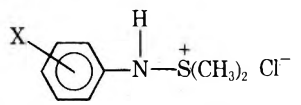
Amide	Registry no.	Activator	Reaction conditions: Temp, °C	Time, hr	Product	Yield,[a] %	Mp,[b] °C	Lit. mp, °C	Ref
Dichloroacetamide **17**	683-72-7	SO_3	15–25	46	$Cl_2CH-C(=O)-\bar{N}-\overset{+}{S}(CH_3)_2$ **18**	25–35	84–89		
		Ac_2O	80–95	9.5		25–30	(101–102)	101–102	24
							95–98		
							(101–102)		
Trichloroacetamide **19**	594-65-0	Ac_2O	90	3	$Cl_3C-C(=O)-\bar{N}-\overset{+}{S}(CH_3)_2$ **20**	4	86–87	78–79	25
							(91–92)		
p-Nitrobenzamide **21**	619-80-7	SO_3	15–25	24	*p*-$O_2N-C_6H_4-C(=O)-\bar{N}-\overset{+}{S}(CH_3)_2$ **22**[f]	80–85	202–206		
		P_4O_{10}	15–25	24		70–75	184–200	220–222[d]	
		Ac_2O	95–100	3.5		0[c]			
Benzamide **23**	55-21-0	SO_3	15–25	45	 **24**	22–26[e]	216 (219)	219	26
$NCNH_2$ **25**	420-04-2	Ac_2O	25	44	$NC-\bar{N}-\overset{+}{S}(CH_3)_2$ **26**	28	63–70	82–83	27
		SO_3	<25	4		0	(74–78)		

[a] Crude reaction product. [b] Crude (pure). [c] **21** (85%) was recovered. [d] New compound. *Anal.* Calcd for $C_9H_{10}N_2O_3S$: C, 47.78; H, 4.46; N, 12.38; S, 14.17. Found: C, 48.06; H, 4.56; N, 12.44; S, 13.96. [e] **23** (58%) was recovered. [f] Registry no., 52259-85-5.

p-toluidine, turns black within several days at room temperature but it can be stored at −30°.

In the reaction of aromatic amines and amides with DMSO–SO_3 two points are noteworthy: (1) some amines react rapidly and quite exothermically, and require careful temperature control, whereas sulfonamides and carboxamides react slowly and only slightly exothermically; and (2) in the reaction of sulfonamides, a portion of the iminosulfurane precipitates during the reaction but the best yields are obtained only if the reaction mixture is diluted with aqueous base. With the amines, dilution of the reaction mixture with water gives no precipitate of iminosulfurane (water-insoluble), suggesting that the reaction product is a (bisulfate?) salt; base is required to obtain the ylide from the salt and solvent extraction of the aqueous DMSO solution is often needed to obtain the best yields (up to 90%).

D. Salts of Iminosulfuranes with Hydrogen Chloride. Iminosulfuranes are basic and form salts with hydrogen chloride but, in the cases studied, the salts were unstable and hygroscopic and lost hydrogen chloride readily, thereby precluding correct elemental analyses. The salts are easily precipitated by treating a cold ether solution of iminosulfurane with a hydrogen chloride–ether solution. Rapid work-up and solvent evaporation permits isolation of salts that are fairly pure as shown by titrimetric analysis. The following salts were prepared.



X=3-Cl, 4-Cl, 3-Br, 4-NO_2, 4-CN

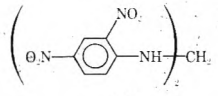
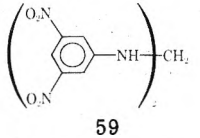
All salts have strong ir absorptions at 3500–3000 cm^{-1} (NH). The salts in which X = 4-NO_2 and 4-Cl have been reported by Vilsmaier and Sprügel,[31] but in the latter case we obtain mp 113–114° dec (lit. mp 103–104°).

E. Mechanistic Considerations. "Activation" of DMSO by an electrophilic reagent which converts it to an intermediate with a good leaving group is an essential condition for successful preparation of iminosulfuranes from DMSO and the nitrogen compounds discussed in this paper. In the initial stages of our study, when we had examined only a few sulfonamides, carboxamides, and aromatic amines, and based also on the literature,[6,19,32] we tentatively concluded that the acidity of the N–H proton was the most important structural feature for the successful preparation of iminosulfuranes from "activated" DMSO.[33] That conclusion was based on the higher yields obtained when the amino compounds contained a good electron-withdrawing group either on the aromatic ring (*p*-nitroaniline and *p*-nitrobenzamide, for example) or attached to the nitrogen function (*p*-toluenesulfonamide, for example). With improved monitoring and work-up techniques and better handling of liquid sulfur trioxide to prevent the entry of water, it was shown that proton acidity is not the crucial factor in the yields obtained. The acidity of the N–H proton of the nitrogen component, however, is important in facilitating the removal of the second proton from the intermediate iminosulfonium salt. The nucleophilicity of the nitrogen component is important in controlling the time required for reaction, although the effects have not been quantitated nor are they very large.

Aromatic amines fall into three groups: (a) those with electron-donor or weak electron-withdrawing groups on the ring are usually completely consumed after addition to the reaction mixture is complete (very exothermic reaction); (b) those with one powerful electron-withdrawing group require 1.5–2 hr (slight exothermicity); and (c) those with more than one electron-withdrawing group require up to 5 hr. The reaction rates do not differ by the orders of magnitude that might be expected in comparing *p*-toluidine, for example, with *p*-nitroaniline (rate ratio approximately 5:1). We believe that the relatively small rate differences among the amines are due to a "leveling" effect caused by the facile departure of an effective leaving group from the DMSO–SO_3 intermediate. In transition-state terms, bond breaking in the highly polar DMSO medium is expected to be an energetically favorable process and should be farther advanced than bond making. The reaction may thus be viewed as a solvolytically assisted nucleophilic displacement reaction.

Although we have not attempted a systematic study of

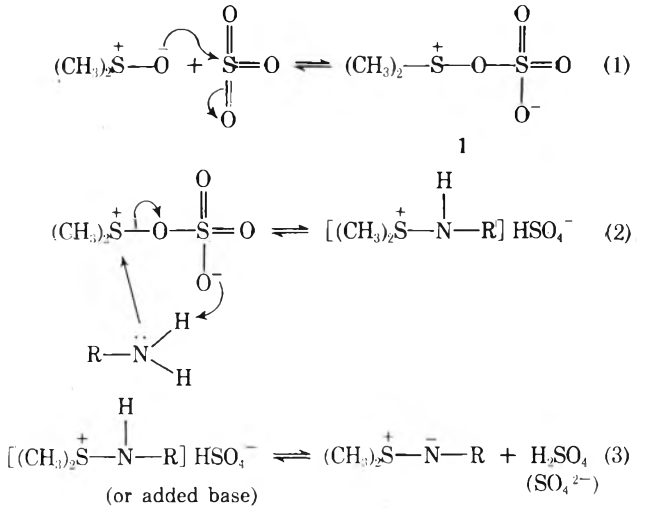
Table III
***N*-Aryliminosulfuranes from Aromatic Amines and DMSO "Activated" by SO_3[a]**

Aromatic amine	Registry no.	Reaction time, min	Product[b]	Yield,[c] %	Mp,[d,e] °C	Lit. mp, °C	Ref
o-Chloroaniline **27**	95-51-2	15	*o*-Cl—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **28**	70	73–75 (74–75)	58–60	6b
m-Chloroaniline **29**	108-42-9	10	*m*-Cl—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **30**	75–100	53–55 (55.5–56.5)	50–52	6b
p-Chloroaniline **31**	106-47-8	40	*p*-Cl—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **32**	50–75	65–66 (66.5–67.5)	64–66 66–67	6b 30
o-Bromoaniline **33**	615-36-1	90	*o*-Br—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **34**	60–70	61.5–62.5 (62–63)		
m-Bromoaniline **35**	591-19-5	10–15	*m*-Br—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **36**	60–90	55–58 (58.5–59.5)		
p-Bromoaniline **37**	106-40-1	10–15	*p*-Br—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **38**	50–70	73.5–74.5 (74–75)	72–74	6b
o-Cyanoaniline **39**	1885-29-6	100	*o*-NC—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **40**	80–90	94–95.5 (95–96)		
p-Cyanoaniline **41**	873-74-5	90	*p*-NC—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **42**	70–85	104–108 (111–112)	108–112	30
p-Fluoroaniline **43**	371-40-4	45	*p*-F—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **44**	50–85	106–108 (109–110)		
2,4,6-Tribromoaniline **45**	147-82-0	300	2,4,6-$Br_3C_6H_2$—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **46**	65–75	76–79 (79–81)	78–80	6b
m-Nitroaniline **47**	99-09-2	180	*m*-O_2N—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **48**	60–75	96–98 (97.5–99)	100–101	13
p-Nitroaniline **49**	100-01-6	165	*p*-O_2N—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **50**	70–90	169–170 (172–174)	148–151 163–165	6b 13
2-Methyl-5-nitroaniline **51**	99-55-8	120	2-CH_3—5—O_2N—C_6H_3—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **52**	85	92–95 (100.5–101.5)		
p-Toluidine **53**	106-49-0	30	*p*-H_3C—C_6H_4—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **54**		49–52 (55–56)	45 40–45	6b 30
2,4-Dinitroaniline **55**	97-02-9	1560	 **56**	>90	277–279 (286–286.5)	275–277	13
3,5-Dinitroaniline **57**	618-87-1	270	2,3-$(O_2N)_2C_6H_3$—$\bar{N}$—$\overset{+}{S}(CH_3)_2$ **58**	65–70	166–168 (169–170)	168–170	13
			 **59**	25–35	197–200 (253–254)		

[a] Mole ratios of DMSO:SO_3:amine were approximately 5:1.2:1 in most cases (consult Experimental Section for variations); reaction temperature 10–20°; reaction time determined by disappearance of amine (tlc). [b] Registry no.: **28**, 20094-93-3; **34**, 52259-86-6; **36**, 52259-87-7; **40**, 52259-88-8; **44**, 52259-89-9; **50**, 27691-52-7; **52**, 52259-90-2; **54**, 27691-50-5; **56**, 31896-61-4; **59**, 52259-91-3. [c] Crude reaction product. [d] Crude (pure). [e] Satisfactory analytical data (±0.3% for C, H, N, S, and halogen when present) were reported for **28**, **34**, **36**, **40**, **44**, **50**, **52**, **54**, **56**, and **59**: Ed.

steric effects on iminosulfurane formation, a large ortho substitutent in the aromatic amines seems to slow down the reaction markedly (Table III).

A reaction pathway which accounts for all the facts is shown below, using SO_3 as the activating agent for illustrative purposes as it is the most generally useful of the electrophiles studied taking into account not merely overall reaction times but ease of handling as well.



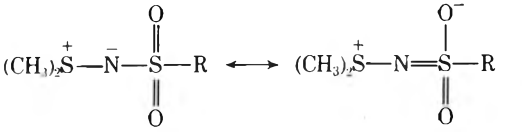
The first step is the formation by the equilibrium process shown of the DMSO–SO_3 intermediate (**1**, E = SO_3) which undergoes nucleophilic attack by amine (sulfonamide or carboxamide). Step 2 is rapid with amines and slow with sulfonamides and carboxamides (the role of electron-withdrawing substituents in reducing the overall reaction rate has already been noted). The equilibrium in step 3 is disfavored (far to the left) with aromatic amines owing to the lower acidity of the remaining N–H proton but the forward reaction is favored with sulfonamides and *p*-nitrobenzamide. With amines, no iminosulfurane can be detected until strong base is added, which forces step 3 to the right. With sulfonamides and *p*-nitrobenzamide the higher acidity of the remaining N–H proton permits its facile removal either by the excess DMSO present or even to some extent by HSO_4^-. Iminosulfurane is present in substantial amounts in these cases even before strong aqueous base is added and it precipitates upon addition of water or spontaneously.

The formation of bis(amino)- [or bis(amido)-] methanes in the DMSO–SO_3 reactions is a side reaction that occurs only when the longest reaction times are required. In the case of 2,4-dinitroaniline, the bis(amino)methane is the major (sole?) product. In the one case studied, we have shown that the bis(amino)methane (**59**, Table III) can be formed from preformed iminosulfurane, *S,S*-dimethyl-*N*-3,5-dinitrophenyliminosulfurane (**58**), by dissolving it in DMSO–SO_3 reaction mixture overnight. This experiment leads us to believe that iminosulfuranes or their bisulfate salts may be the precursors of the bis(amino)methanes, but whether that is the exclusive pathway is uncertain.

F. Spectral Characteristics of Iminosulfuranes.[34-37] Nmr spectra show no unexpected features and are readily interpreted by first-order analysis. The singlet observed for the $S^+(CH_3)_2$ protons indicates that (a) resonance contribution to the ylide structure of the S=N form (3d–2p overlap) is minor or (b) if cis–trans isomerism does exist interconversion of isomers is rapid on the nmr time scale.

Ir spectra of iminosulfuranes are considerably more complex than those of the starting amines or amides. No characteristic absorptions are observed between 3600–3100 and 2900–1620 cm^{-1} in the iminosulfuranes. They show weak to medium absorptions in the 3100–2900-cm^{-1} region assigned to the C–H stretching frequency of the SCH_3 group, and strong absorptions in the 1100–770-cm^{-1} region assigned to the N–S stretch.

The SO_2 stretching frequencies of the *N*-sulfonyliminosulfuranes (**8, 10, 12, 14, 16**) are significantly lower than those of the sulfonamides (**7, 9, 11, 13, 15**) from which they are derived. The ν_{SO_2} (unsym) is shifted by about 40–70 cm^{-1} and the ν_{SO_2} (sym) by 30–60 cm^{-1}. This shift suggests that there is substantial delocalization of the negative charge on nitrogen into the SO_2 group as shown.



N-Acyliminosulfuranes (**18, 20, 22**) show strong absorption bands in the region of 770–840 and 945–1000 cm^{-1}, not present in the amide starting materials (**17, 19, 21**). In *N*-acyliminosulfuranes, carbonyl stretching absorptions (1550–1600 cm^{-1}) are also strong and shifted to lower frequencies (*ca.* 90–130 cm^{-1}) than those of the amides from which they are derived. The shift to lower frequencies is attributed to extensive charge delocalization from nitrogen to oxygen. A similar shift to lower frequency (110 cm^{-1}) is observed in the C=N group of *S,S*-dimethyl-*N*-cyanoiminosulfurane (**26**) compared to that of cyanamide (**25**).

N-Aryliminosulfuranes (**28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 58**) show weak to moderate absorption around 1020 cm^{-1} and several moderate to strong bands between 990 and 890 cm^{-1}.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer Model 137B or Pye Unicam SP-1000. Nmr spectra were obtained on Varian Models A-60A or XL-100, with TMS as internal standard. Melting points (uncorrected) were obtained using a Thomas-Hoover capillary apparatus. Tlc was conducted on Eastman silica gel chromagrams with fluorescent indicator; visualization was conducted either with uv light or by development in a chamber containing iodine crystals. All reagents were the purest obtainable; in all cases purity exceeded 97%. Solvents were the best commercial grades and were used as received. DMSO was distilled under reduced pressure from calcium hydride and stored in a nitrogen atmosphere over Linde molecular sieve, Type 4A. Sulfan (stabilized SO_3) and phosphorus pentoxide were obtained from Allied Chemical Co. Elemental analyses were done by Micro-Analysis, Inc., Wilmington, Del.

"Activation" of DMSO by Electrophiles. DMSO–BF_3 Complex (2).[14a] Boron fluoride–diethyl ether complex (27.2 g, 0.192 mol) was placed in a 100-ml three-neck flask equipped with a magnetic stirrer, thermometer, addition funnel, and drying tube. The contents of the flask were cooled to 20° and DMSO (15.0 g, 0.192 mol) was added dropwise with stirring and cooling over 20–35 min. The reaction was strongly exothermic and a white precipitate formed. It was filtered, washed with dry ether, and dried under vacuum; the yield of **2** (very hygroscopic) was 81% (23.5 g, mp 50–51°) (lit.[14a] mp 53°). Compound **2** is insoluble in chloroform but slightly soluble in acetone: nmr (acetone-d_6) δ 3.08 (s); nmr (DMSO-d_6) δ 3.30 (s) and 2.58 (s).

DMSO–P_4O_{10} Complex (3). As described above, DMSO (1.4 g, 0.018 mol) was added to a stirred suspension of phosphorus pentoxide (2.5 g, 0.018 mol) in dry chloroform. The white precipitate was filtered, washed with dry ether, and dried under vacuum. The product was exceedingly hygroscopic and quickly liquefied: nmr (acetone-d_6) δ 2.96 (s); nmr (DMSO-d_6) δ 2.87 (s) and 2.61 (s).

DMSO–SO_3 Complex (5). Although **5** was prepared by the method of Pettit,[15] we were unable to isolate it without decomposition as it is extremely moisture sensitive: nmr (DMSO) δ 3.06 (s) and 2.6 (s). Reaction of SO_3 with DMSO is exothermic.

Reaction of *p*-Toluenesulfonamide (7) with DMSO. A. SO_3 Activation. DMSO (34.0 g, 0.436 mol) was cooled to 20° in a 100-ml three-neck flask fitted with a thermometer, stirrer, addition

funnel, and drying tube. Sulfur trioxide (7.1 g, 0.089 mol) was slowly added (40 min) while maintaining the temperature of the well-stirred DMSO below 20°. Compound 7 (15.0 g, 0.088 mol) was added in one portion with stirring; a precipitate began to form within a few minutes at 15–25°. Tlc monitoring showed that all of 7 had been consumed after about 10 hr. Addition of water (80 ml) followed by 10% aqueous NaOH (80 ml) to pH 12 precipitated the product, *S,S*-dimethyl-*N*-*p*-toluenesulfonyliminosulfurane (8), 14.2 g, mp 156–158.5° (lit.[25] mp 158–159°). The aqueous filtrate was extracted with methylene chloride (3 × 200 ml), washed with water, and dried to yield additional 8 (2.0 g, mp 156–158°) after solvent evaporation. The ir spectra of the two portions of 8 were identical, as were their nmr spectra, and consistent with the proposed structure. The total yield of 8 in a replicate experiment was 60–80%. Analytically pure 8 (recrystallized from methylene chloride) had mp 158.5–159.5°.

B. P_4O_{10} Activation. As described in A above but using P_4O_{10} instead of SO_3, 7 was consumed in less than 2 hr and a 70% yield of 8, mp 157–158.5°, was obtained; its ir and nmr spectra were identical with those of 8 prepared as in A.

C. Acetic Anhydride Activation. Acetic anhydride (2.75 g, 0.027 mol) was added to DMSO (10.3 g, 0.132 mol) followed by *p*-toluenesulfonamide (4.5 g, 0.026 mol). The solution was heated on the steam bath (85–90°) for 1.5 hr, at which time tlc showed that all of 7 had disappeared. The cooled reaction mixture was then diluted with cold water (200 ml) and made basic to pH 12 with 10% aqueous sodium hydroxide (30 ml). The precipitate was filtered, washed with water until free of base, and dried (yield 1.1 g, mp 156–158°). The aqueous filtrate was extracted with methylene chloride (3 × 200 ml) and the combined extracts were washed with aqueous sodium hydroxide (60 ml) and then with water (2 × 100 ml) and dried. Solvent evaporation yielded additional 8 (3.4 g, mp 156–158°). The ir spectra of both precipitates were identical, as were their nmr spectra, and identical with the corresponding spectra of authentic 8. The total yield of 8 in replicate experiments was 60–75%.

Repetition of this experiment at room temperature for 28 hr with tlc monitoring showed a small spot due to 8 but most of 7 remained unreacted. Nmr also suggested the presence of 8. Dilution with cold water (120 ml) caused unreacted 7, mp 136–138°, to precipitate (56% recovery). The filtrate was made basic (pH 12) with 10% sodium hydroxide; no precipitation occurred. The basic solution was extracted with methylene chloride (3 × 100 ml) and the combined extracts were dried and then evaporated under vacuum. The white solid residue (1.0 g, 19% yield, mp 156–158°) had the same ir and nmr spectra as authentic 8.

D. BF_3 Activation. *p*-Toluenesulfonamide (7, 3.2 g, 0.019 mol) was added to a stirred solution of DMSO (8.8 g, 0.11 mol) and boron fluoride–diethyl ether complex (2.9 g, 0.02 mol); the reaction system was monitored by nmr and tlc. Nmr showed the formation of the DMSO–BF_3 complex but no other spectral changes were observed over 3 days at room temperature (except for disappearance of the ether signals). Tlc showed no diminution in 7 nor the appearance of any new spots. Dilution with water yielded unreacted 7 (2.0 g, mp 136–138°) whose melting point and ir were identical with those of authentic 7. Extraction of the aqueous filtrate with methylene chloride (3 × 200 ml) yielded additional 7 but no 8.

E. H_2SO_4 Activation. Similarly, 65–82% of 7 was recovered from a reaction system consisting of concentrated H_2SO_4 (1.2 g, 0.013 mol), DMSO (4.4 g, 0.056 mol), and 7 (1.7 g, 0.01 mol) held at room temperature for 48 hr or at 85° for 3 hr.

Preparation of Iminosulfuranes. *N*-Sulfonyliminosulfuranes (Table I). A. SO_3 Activation. The procedure described above for the reaction of *p*-toluenesulfonamide (7) with DMSO–SO_3 was used with minor modifications. Reaction time was determined by tlc. If the sulfonyliminosulfurane did not precipitate (10) when the reaction mixture was made basic it was extracted with methylene chloride. If the sulfonyliminosulfurane was particularly insoluble on basification (12), the alkaline aqueous filtrate was discarded. When methylene chloride was not suitable as the extraction solvent (14), benzene was used. About 50% of 14 precipitated from the reaction mixture before addition of aqueous base and the remainder was isolated by benzene extraction of the aqueous phase.

B. Acetic Anhydride Activation. The procedure described above for the reaction of 7 with DMSO–acetic anhydride was used with minor modifications as mentioned in A. Compound 12 precipitated almost completely from the reaction mixture (>90% yield) but an additional quantity (*ca.* 1.5%) could be obtained by the usual work-up of the aqueous alkaline filtrate. In the reaction of methanesulfonamide (15), excess DMSO and acetic anhydride were largely removed by distillation under reduced pressure (maximum temperature *ca.* 60°). The yellow oily residue (16 + DMSO) was washed with cold ether and the white precipitate (crude 16) was filtered and dried (4.2 g, mp 111–117°, 25%). The oily residue from the filtrate was dissolved in a minimum quantity of acetone and hexane was added until the solution was turbid. Upon cooling to 0°, white crystals of pure 16 were obtained (2.9 g, mp 122–123°, 18%). Both the crude and pure 16 had identical ir spectra and nmr spectra.

***N*-Acyliminosulfuranes (Table II). *S,S*-Dimethyl-*N*-*p*-nitrobenzoyliminosulfurane (22). A. SO_3 Activation.** *p*-Nitrobenzamide (21, 7.0 g, 0.042 mol) was added to a stirred solution of DMSO (11.3 g, 0.145 mol) and SO_3 (4.1 g, 0.051 mol). After 24 hr at room temperature, tlc showed that all of the 21 had disappeared. The reaction mixture was diluted with water (100 ml), precipitating 22 in 75% yield (7.2 g, mp 202–206°); its ir and nmr spectra were consistent with its structure. Recrystallization from methanol gave analytically pure 22, mp 220–222°. The original aqueous filtrate was made basic to pH 12 with 10% aqueous sodium hydroxide (80 ml) when an additional quantity of 22 precipitated (0.7 g, 8% yield, mp 218–219°); its spectra were identical with those of analytically pure 22.

B. P_4O_{10} Activation. Compound 22 was prepared from 21 (4.6 g, 0.028 mol), DMSO (22.2 g, 0.29 mol), and P_4O_{10} (4.3 g, 0.03 mol); the reaction time was 24 hr. Dilution of the reaction mixture with water yielded crude 22 (4.3 g, 70%, mp 184–200°); it consisted largely of 22 contaminated with a small quantity of 21.

C. Acetic Anhydride Activation. Compound 21 was recovered in 85% yield upon dilution of the reaction mixture. No 22 could be detected during the reaction nor could any be isolated from the aqueous filtrate upon basification to pH 12.

***S,S*-Dimethyl-*N*-dichloroacetyliminosulfurane (18). A. SO_3 Activation.** After 46 hr, the reaction mixture of DMSO (27.4 g, 0.35 mol), SO_3 (5.5 g, 0.069 mol), and dichloroacetamide (17, 8.7 g, 0.068 mol) still showed unreacted 17. Dilution with water (50 ml) followed by addition of 10% aqueous sodium hydroxide (50 ml) to pH 12 gave a turbid solution which was extracted with methylene chloride (3 × 150 ml) and washed with water. Evaporation of the dried methylene chloride solution yielded a white solid which was moderately pure 18 (4.2 g, 34%, mp 84–89°) contaminated with a trace of DMSO (ir and nmr). Recrystallization from methylene chloride yielded analytically pure 18 (3.2 g, 28%, mp 101–102°) which showed no depression in melting point on admixture with authentic 18.[24] A reported[25] melting point of 46–47° for 18 appears to be in error.

B. Acetic Anhydride Activation. Similar results were obtained upon heating a solution of DMSO (17.1 g, 0.22 mol), acetic anhydride (16.8 g, 0.165 mol), and 17 (13.8 g, 0.108 mol) for 9.5 hr followed by evaporation of volatiles at 65° under high vacuum. The brown solid residue was washed with ether (25 ml) which removed the color and residual DMSO; the residue was moderately good quality 18 (5.6 g, 28% yield, mp 95–98°). Recrystallization from methylene chloride yielded pure 18, mp 101–102° (mixture melting point with authentic 18 was undepressed).

***N*-Ariyliminosulfuranes (Table III).** For the highest yields and purity of crude reaction products in the shortest reaction times, the molar ratio of DMSO:SO_3:aromatic amine was 4–6:1:0.6–0.9. A DMSO:SO_3 ratio as low as 2–3:1 was sometimes used but those ratios were atypical and are not recommended. For convenience, high-melting amines were sometimes added in solution in a portion of the total DMSO. In some cases, the crude reaction products precipitated when the reaction solution was made basic but extraction with benzene or methylene chloride was usually required.

Typical Procedures. *S,S*-Dimethyl-*N*-2-chlorophenyliminosulfurane (28). DMSO (14.5 g, 0.19 mol) was cooled to 20° and SO_3 (4.0 g, 0.05 mol) was added with stirring while maintaining the reaction temperature between 15–20°. When addition was complete the reaction mixture was cooled to 10° and *o*-chloroaniline (27, 3.0 g, 0.024 mol) was added; 15 min after addition was complete tlc showed that all of the 27 had been consumed. The reaction mixture was diluted with ice-cold water (80 ml) and then made basic with 10% aqueous sodium hydroxide (45 ml), followed by multiple extraction with benzene (3 × 150 ml) or ether. The combined extracts were evaporated to dryness and the brown oily residue (4.0 g) was dissolved in ether. Hexane was added to the ether solution until it was turbid and the mixture was cooled to 0°. Compound 28 was obtained as a white, crystalline solid (3.1 g, 71% yield, mp 73–75°). The sample for analysis, mp 74–75°, was ob-

tained by recrystallization from ether–hexane. (The melting point reported[6b] for **28** is 58–60°).

S,S-**Dimethyl-*N*-4-nitrophenyliminosulfurane (50).** This was prepared from DMSO (10.2 g, 0.13 mol), SO_3 (2.1 g, 0.026 mol), and *p*-nitroaniline (**49**, 2.6 g, 0.019 mol); reaction time 165 min. Crude **50** (3.3 g, 90%, mp 169–170°) precipitated cleanly from the diluted alkaline reaction mixture and was virtually pure upon drying. The sample for analysis, mp 172–174[c] (yellow needles), was obtained by recrystallization from benzene (literature melting points reported for **50** are 163–165[13] and 148–151°.[6b]): uv spectrum λ_{max} (CH_3OH) 386 mμ (ε 17,900), 234 (6700), 201 (16,500) (c 1.06 × 10^{-4} mol/l.) [lit.[13] λ_{max} (CH_3OH) 386 mμ (16,700), 234 (6200)]. In a duplicate experiment, base was not added to the diluted reaction mixture, which was extracted directly with CH_2Cl_2 (2 × 125 ml). The product obtained (0.3 g) had ir and nmr spectral characteristics suggestive of a mixture of **50** and its bisulfate salt; it was not studied further. When the aqueous layer was made basic to pH 12 with 10% sodium hydroxide, **50** (3.0 g, 67%, mp 168–170°) precipitated; its ir and nmr spectra were identical with those of pure **50**.

S,S-**Dimethyl-*N*-3,5-dinitrophenyliminosulfurane (58) and Bis(3,5-dinitrophenylamino)methane (59).** To the stirred DMSO (10.4 g, 0.13 mol)–SO_3 (4.2 g, 0.053 mol) mixture, a solution of 3,5-dinitroaniline (**57**, 4.8 g, 0.026 mol) dissolved in DMSO (14.9 g, 0.19 mol) was added. After 30 min, a yellow precipitate began to form. After 4.5 hr, all of the **57** had been consumed (tlc). The yellow precipitate (1.6 g, 33%, mp 195–197°) was filtered, washed with water until free of acid and adhering DMSO, and dried. Three crystallizations from pyridine yielded pure **59**: mp 253–254°; ir (KBr) 3500–3350 (s), 3150 (w), 2350 (w), 1620 (m), 1520 (vs), 1343 (vs), 1270 (s), 1120 (s), 1080 (w), 1050 (w), 980 (w), 920 (m), 875 (m), 808 (m), and 728 cm^{-1} (vs).

The DMSO filtrate after filtration of **59** was diluted with cold water, and 10% aqueous sodium hydroxide (45 ml) was added to pH 12. An orange precipitate formed; it was filtered, washed with water until free of base, and dried (4.3 g, 67%, mp 164–165°). It was virtually pure **58**. Recrystallization from methylene chloride gave orange needles, mp 169–170° (lit.[13] mp 168–170°).

Bis(2,4-dinitrophenylamino)methane (56). In the reaction of DMSO (15.2 g, 0.19 mol), SO_3 (3.4 g, 0.0425 mol), and 2,4-dinitroaniline (**55**), a yellow precipitate started to form after about 3 hr but it required 26 hr for all of the **55** to be consumed (tlc). The reaction mixture was filtered and the yellow solid precipitate was washed several times with water and dried (4.9 g, 92%, mp 277–279°). Two crystallizations from pyridine yielded pure **56**: mp 285–286° (lit.[13] mp 275–277°); ir (KBr) 3450–3300 (m), 1600 (s), 1510 (m), 1420 (w), 1340 (m), 1320 (m), 1160 (w), 1140 (w), 1085 (m), 1030 (w), 920 (w), 830 (m), 740 (m), and 700 cm^{-1} (w).

S,S-**Dimethyl-*N*-2,4-dinitrophenyliminosulfurane** was prepared by a modification of the method of Yamamoto, *et al.*[29,32]

Hydrochlorides of *N*-Aryliminosulfuranes. It is important to work up the salts promptly and analyze them immediately owing to their instability and hygroscopicity.

Typical Procedure. *S,S*-Dimethyl-*N*-*p*-chlorophenyliminosulfurane (**32**, 1.0 g, 0.0053 mol) was dissolved in dry ether (15 ml) and the solution was cooled to 0°. A 0.5 *N* solution of anhydrous HCl in ether (11 ml) was added dropwise and the precipitated salt was filtered under dry nitrogen, washed with ether, and dried under vacuum, 0.9 g (75%), mp 113–114° dec (lit.[30] mp 103–104°), calcd neut equiv 224, found 227. The salt is very hygroscopic: ir (KBr) 3100 (s), 2900–2800 (s), 1595 (m), 1480 (s), 1420–1395 (m), 1292 (w), 1263 (m), 1200 (s), 1175 (w), 1112 (w), 1095 (m), 1020 (w), 995 (s), 965 (w), 930 (w), 905 (m), 847 (w), 825 (s), 805 (m), and 725 cm^{-1} (m).

The *m*-chlorophenyl, *m*-bromophenyl, *p*-nitrophenyl, and *p*-cyanophenyl analogs, obtained in 65–75% yields, had the following melting points respectively: 115–120, 95–102, 115–116, and 202–203°.

Acknowledgment. The authors thank the National Cancer Institute of the U. S. Public Health Service (CA-07803 and 122273) and the Samuel S. Fels Fund for partial support of this research.

Registry No.—**30** HCl, 52259-92-4; **32** HCl, 52259-93-5; **36** HCl, 52259-94-6; **42** HCl, 52259-95-7; **50** HCl, 52259-96-8; DMSO, 67-68-5.

Supplementary Material Available. Full ir and nmr data will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3365.

References and Notes

(1) (a) Iminosulfuranes. XIV. Part XIII: *Tetrahedron Lett.*, 1071 (1974). The present paper was presented in part at the Sixth Middle Atlantic Regional Meeting of the American Chemical Society, Baltimore, Md., Feb 1971. (b) In partial fulfillment of the requirements for the Ph.D. degree, Temple University, 1973.
(2) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, **67**, 247 (1967); T. Durst, *Advan. Org. Chem.*, **6**, 285 (1969); J. G. Moffatt, "Oxidations," Vol. 2, R. L. Augustine and D. J. Trecker, Ed., Marcel Dekker, New York, N.Y., 1971, p 1.
(3) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965).
(4) J. D. Albright and L. Goldman, *J. Org. Chem.*, **20**, 1107 (1965); *J. Amer. Chem. Soc.*, **87**, 4214 (1965); **89**, 2416 (1967).
(5) K. Anzari and S. Suzuki, *Bull. Chem. Soc. Jap.*, **40**, 2854 (1967).
(6) (a) P. Claus and W. Vycudilik, *Tetrahedron Lett.*, 3607 (1968); (b) *Monatsh. Chem.*, **101**, 396 (1970).
(7) T. Sato, A. Takatsa, Y. Saito, T. Tohyama, and K. Hata, *Bull. Chem. Soc. Jap.*, **41**, 221 (1968).
(8) J. R. Parikh and W. von E. Doering, *J. Amer. Chem. Soc.*, **89**, 5505 (1967).
(9) R. E. Harmon, C. V. Zenarosa, and S. K. Gupta, *Chem. Commun.*, 327 (1969); *Tetrahedron Lett.*, 3781 (1969).
(10) P. Claus, *Montash. Chem.*, **99**, 1034 (1968); M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **89**, 4725 (1967).
(11) A. F. Cook and J. G. Moffatt, *J. Amer. Chem. Soc.*, **90**, 740 (1968).
(12) D. A. Kerr and D. A. Wilson, *Tetrahedron Lett.* 2885 (1968); A. H. Fenselau, E. H. Hamammura, and J. G. Moffatt, *J. Org. Chem.*, **35**, 3546 (1970).
(13) U. Lerch and J. G. Moffatt, *J. Org. Chem.*, **36**, 3861 (1971).
(14) (a) F. A. Cotton and R. Francis, *J. Amer. Chem. Soc.*, **82**, 2986 (1960); (b) R. Francis and F. A. Cotton, *J. Chem. Soc.*, 2078 (1961).
(15) D. J. Pettitt, U. S. Patent 3,527,810 (1970).
(16) L. Horner and P. Kaiser, *Justus Liebigs Ann. Chem.*, **626**, 19 (1959), obtained good yields of the Pummerer rearrangement product from DMSO–acetic anhydride after 3 days at 25°.
(17) J. M. Williams and M. Kreevoy, *J. Amer. Chem. Soc.*, **89**, 5499 (1967).
(18) M. A. Khuddus and D. Swern, *J. Amer. Chem. Soc.*, **95**, 8393 (1973); M. A. Khuddus, Ph.D. Dissertation, Temple University, Philadelphia, Pa., 1972.
(19) D. S. Tarbell and C. Weaver, *J. Amer. Chem. Soc.*, **63**, 2939 (1941).
(20) L. Horner and A. Christmann, *Chem. Ber.*, **96**, 388 (1963).
(21) M. V. Likhosherstov, *Zh. Obshch. Khim.*, **17**, 1478 (1947).
(22) U. Lerch and J. G. Moffatt, *J. Org. Chem.*, **36**, 3686 (1971).
(23) R. Appel and H. Rittersbacher, *Chem. Ber.*, **97**, 852 (1964).
(24) D. Swern, I. Ikeda, and G. F. Whitfield, *Tetrahedron Lett.*, 2635 (1972).
(25) R. Niedlein and E. Heukelbach, *Arch. Pharm. (Weinheim)*, **299**, 64 (1966).
(26) G. Pulvermacher, *Ber.*, **25**, 310 (1892).
(27) F. D. Marsh, U. S. Patent 3,505,401 (1970).
(28) H. Kise, G. F. Whitfield, and D. Swern, *J. Org. Chem.*, **37**, 112 (1972).
(29) T. Yamamoto, Y. Harigaja, and M. Okawara, *Chem. Lett.*, **1**, 1009 (1972).
(30) P. Claus and W. Rieder, *Monatsh. Chem.*, **103**, 1163 (1972).
(31) E. Vilsmaier and W. Sprügel, *Tetrahedron Lett.*, 625 (1972).
(32) D. Martin and H. J. Niclas, *Chem. Ber.*, **102**, 23, 31 (1969).
(33) T. E. Varkey, G. F. Whitfield and D. Swern, *Int. J. Sulfur Chem., Part A*, **1**, 126 (1973).
(34) P. Claus and W. Vycudilik, *Monatsh. Chem.*, **101**, 405 (1970).
(35) K. Tsujihara, N. Furukawa, and S. Oae, *Bull. Chem. Soc. Jap.*, **43**, 2153 (1970).
(36) A. Kucsman, F. Ruff, I. Kapovits, and T. G. Fischer, *Tetrahedron*, **22**, 1843 (1966); A. Kucsman, I. Kapovits, and F. Ruff, *Acta Chim. Acad. Sci. Hung.*, **54**, 153 (1967).
(37) See paragraph at end of paper regarding supplementary material.

Synthesis and Reactions of N,N′-Dichlorodiiminosuccinonitrile

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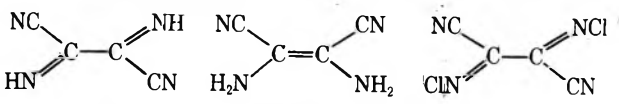
N,N′-Dichlorodiiminosuccinonitrile (Cl_2DISN) has been prepared from diaminomaleonitrile (DAMN) by an improved method in an excellent yield. Namely, Cl_2DISN reacts with thiols affording *N,N′*-disulfenyl compounds, whereas it is reduced into diiminosuccinonitrile (DISN) by diphenyl sulfide or *N*-benzyl-1,4-dihydronicotinamide. Olefins react with Cl_2DISN to yield pyrazine derivatives by simultaneous dehydrochlorination.

Oligomers of hydrogen cyanide have received intensive attention because of their relationship to chemical evolution[1,2] and the versatility of their reactions.[3] Diiminosuccinonitrile (DISN) and diaminomaleonitrile (DAMN) have been extensively studied,[4-6] and DAMN is now commercially available.[7,8] In the course of our current study to extend the reactions of DAMN,[9] we have found an improved synthesis of *N,N′*-dichlorodiiminosuccinonitrile (Cl_2DISN), which will be described in this paper together with some representative reactions of Cl_2DISN.

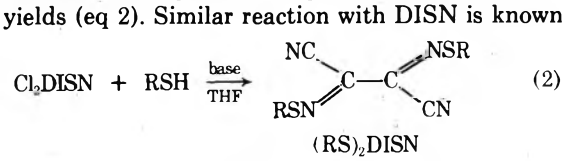


Results and Discussion

Synthesis of Cl_2DISN. The formation of Cl_2DISN from DAMN (50% yield) or DISN (quantitative) by chlorination in acetonitrile has been reported.[5] The reactions, however, required low temperature (between −40 and −20°) because liquid chlorine was employed and both DAMN and DISN are susceptible to decomposition by acids, especially in solvents contaminated with moisture. To avoid these difficulties, the reaction was carried out in carbon tetrachloride or chloroform at 0°, using *tert*-butyl hypochlorite instead of liquid chlorine (eq 1). The results are summarized in Table I. DAMN is soluble in acetonitrile, sparingly soluble in chloroform, and insoluble in carbon tetrachloride or benzene, but all of these solvents readily dissolve Cl_2DISN. The data in Table I suggest that the effect of solvent rather than temperature is the most important factor increasing the yield of Cl_2DISN.

$$\text{DAMN} + 3\,t\text{-BuOCl} \longrightarrow Cl_2DISN + 3\,t\text{-BuOH} + HCl \quad (1)$$

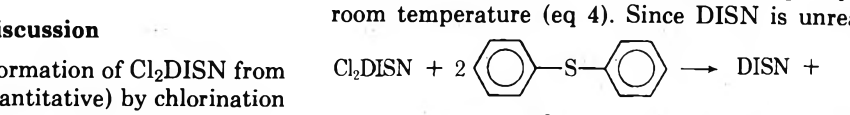
Reaction of Cl_2DISN. When Cl_2DISN in tetrahydrofuran (THF) was treated with thiols in the presence of pyridine or triethylamine, the corresponding *N,N′*-disulfenyldiiminosuccinonitriles [$(RS)_2DISN$] were obtained in excellent yields (eq 2). Similar reaction with DISN is known to afford DAMN.[5] Since chlorimine is a potential halogenating agent,[10] the reaction may proceed *via* sulfenyl chloride and DISN (eq 3) analogously to the reaction of DISN with sulfur dichloride.[6] However, the present reaction is advantageous over the reactions requiring DISN and sulfenyl chlorides in that the starting materials are easily available and a stable thiol can be used in place of an unstable sulfenyl chloride.



$$Cl_2DISN + 2RSH \longrightarrow [DISN + 2RSCl] \longrightarrow (RS)_2DISN \quad (3)$$

A solution of Cl_2DISN in dimethyl sulfoxide (DMSO) spontaneously underwent reaction to provide $(MeS)_2DISN$ (37%) and dimethyl sulfone (43%).

DISN and *N*-chlorodiiminosuccinonitrile (ClDISN)[5] can be obtained by treating Cl_2DISN with diphenyl sulfide at room temperature (eq 4). Since DISN is unreactive with sulfides, excess diphenyl sulfide may be used and the present reaction constitutes a novel and convenient route to DISN. The reaction with thioanisole, however, is too fast to be controlled even at relatively lower temperatures, whereas that with anisole does not proceed even at elevated temperatures. It should be noted that normal electrophilic aromatic substitution proceeds faster with anisole than thioanisole, for which initial formation of a sulfonium ion has been proposed.[11] The observed reactivity of the sulfides, then, may be accounted for by the initial formation of a charge-transfer complex, **1** (*vide infra*). DISN is also obtained in the reaction of Cl_2DISN with *N*-benzyl-1,4-dihydronicotinamide (BNAH) at −20°. Since DISN is itself reduced (although more slowly) by BNAH into DAMN, exactly 2 molar equiv of BNAH should be used in this preparation of DISN from Cl_2DISN (eq 5). On the other



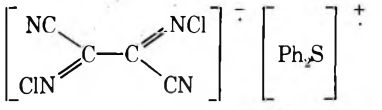
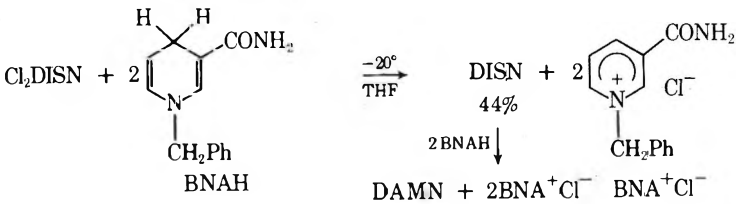


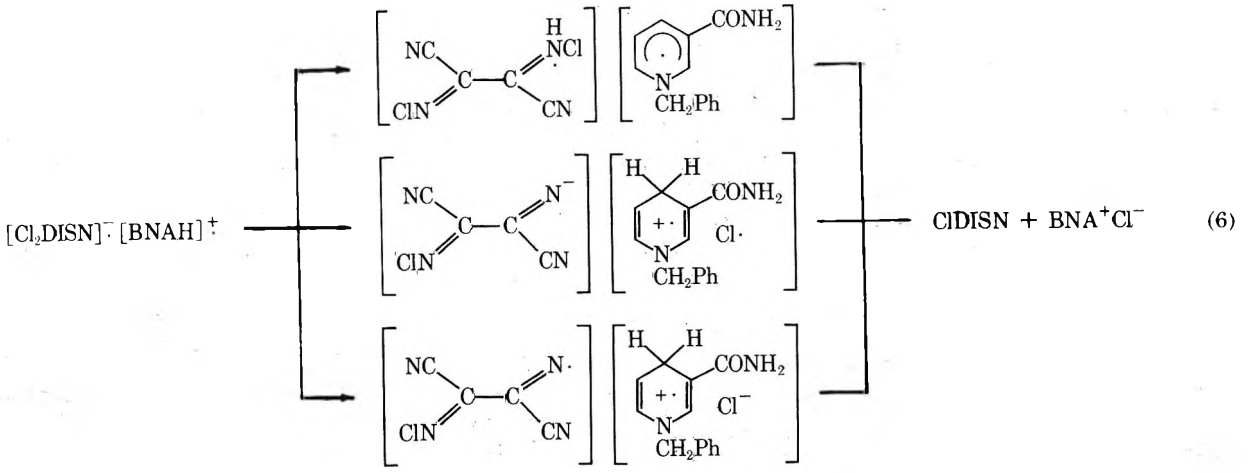
Table I
Reaction of Diaminomaleonitrile with *tert*-Butyl Hypochlorite

t-BuOCl, mmol	DAMN, mmol	Na_2CO_3, mmol	Solvent (ml)	Reaction temp, °C (time, hr)	Convn of DAMN, %	Yield of Cl_2DISN, % Crude	Isolated[a]
15.05	5.02	15.02	CCl_4 (90)	29 (1.5)	93.2	90.3	85.7
15.02	5.02	15.03	$CHCl_3$ (90)	29 (1.5)	97.8	83.2	66.1
15.09	5.01	15.42	Benzene (90)	9 (1.5)	99.3	88.7	79.8
15.09	5.02	15.00	CCl_4 (90)	3 (1.5) and −20 (15)	97.6	94.0	89.1
15.02	5.00		CCl_4 (90)	3 (1.5) and −20 (15)	97.3	76.9	73.8

[a] Purified by sublimation at 85° (1 Torr).



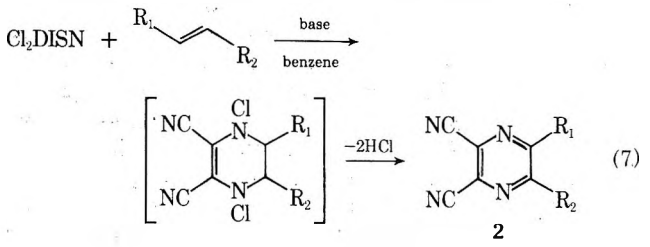
(5)



(6)

hand, sodium borohydride does not react with Cl_2DISN. This fact suggests that the mechanism of the reduction by BNAH is not a simple SN2-type hydride attack.[12] Recently, we reported that reductions by BNAH involve an electron–proton–electron transfer process.[13] We consider the present reaction to proceed with a similar mechanism (eq 6), but a detailed discussion will be deferred until the necessary data are accumulated.

Cl_2DISN reacts with some olefins to provide pyrazine derivatives, **2** (eq 7). DISN itself also reacts with olefins.[14]



(7)

2

2a, R_1 = Ph; R_2 = H (63%)
b, R_1 = Ph; R_2 = CH_3 (35%)
c, R_1, R_2 = $-OCH_2CH_2CH_2-$ (26%)

However, products from DISN are aziridines and/or dihydropyrazines, depending on the nature of the olefin: the more electron rich the double bond, the higher the yield of dihydropyrazine. A charge-transfer complex, or zwitterionic structure, has been proposed for the transition state of this reaction.[14] Although we did not try to optimize the yields, the fact that styrene gave the highest yield[15] and 2,3-dihydropyran gave the lowest, as well as the fact that chlorine is more electronegative than hydrogen, seems to suggest that [2 + 4] cycloaddition is more plausible than the two-step addition at least for the reaction of Cl_2DISN. Since dehydrochlorination occurs spontaneously, the use of Cl_2DISN is superior to DISN when pyrazines are desired.

Experimental Section

Preparation of Cl_2DISN. Into a mixture of DAMN (0.54 g), $NaCO_3$ (1.59 g), and CCl_4 (60 ml), a solution of *tert*-butyl hypochlorite (1.64 g) in CCl_4 (30 ml) was added dropwise at room temperature or at a temperature of ice–water (3°). The reaction mixture was stirred for 1.5 hr; then precipitates were filtered off and washed by CCl_4. The combined solution of CCl_4 was concentrated by means of a rotary evaporator, yielding 0.805 g (94% yield) of crude Cl_2DISN, which was sublimed at 80° (1 Torr), affording pure crystals of Cl_2DISN: mp 160–161° (lit.[5] mp 164.5–165.5°).

Table II
Yield and Melting Point of $(RS)_2DISN$

R in $(RS)_2DISN$	Yield, %	Mp, °C	Registry no.
i-Pr	86.6	91–92	52109-62-3
$PhCH_2$	90.8	144–145	52109-63-4
Ph	91.4	205–207	52147-69-0
p-$CH_3OC_6H_4$	94.1	243–244	52109-64-5
p-ClC_6H_4	89.9	298–300	52109-65-6

Reaction of Cl_2DISN with Thiols. Into an ice-cooled solution of Cl_2DISN (0.35 g) and pyridine (0.16 g) or triethylamine (0.20 g) in 25 ml of anhydrous THF was added dropwise a solution of ethanethiol (0.26 g) in 10 ml of anhydrous THF. The reaction mixture was stirred for 30 min at 3°, then for an additional 30 min at room temperature (22°). Precipitates were filtered off and the solvent was evaporated from the filtrate under a reduced pressure. The solidified material thus obtained was recrystallized from ethanol, yielding *N,N'*-diethylthiodiiminosuccinonitrile [$(EtS)_2DISN$] in 80% yield: mp 114–115°; ir (KBr) 2950, 2925, 2920, 2860, 2225, 1520, 1460, 1430, 1390, 1258, 1053, 1000, 985, 965, 769, 725, and 653 cm^{-1}; mass spectrum (100°, 70 eV) *m/e* 226 ($M\cdot^+$, 37.3%), 197 ($M\cdot^+ - Et\cdot$, 26.8%), 169, 137, and 61 (EtS^+, 100%). *Anal.* Calcd for $C_8H_{10}N_4S_2$: C, 42.48; H, 4.46; N, 24.77; S, 28.29. Found: C, 42.22; H, 4.21; N, 24.52; S, 28.22.

Other thiols were reacted similarly. The yields and melting points of the products are listed in Table II.

Reaction of Cl_2DISN with Dimethyl Sulfoxide. Cl_2DISN (0.50 g) was dissolved into 1 ml of DMSO and the solution was stirred for 1 hr at 10–15°. An exothermic reaction took place at this moment. The reaction mixture was subjected to column chromatography on silica gel with benzene as an eluent. Yellow crystals thus obtained were recrystallized from cyclohexane, affording 0.22 g (37% yield) of *N,N'*-dimethylthiodiiminosuccinonitrile [$(MeS)_2DISN$]: mp 191–192°; ir (KBr) 2915, 2230, 1510, 1435, 1325, 990, 974, 940, 720, and 695 cm^{-1}; mass spectrum (100°, 70 eV) *m/e* 198 ($M\cdot^+$, 100%), 183 ($M\cdot^+ - Me\cdot$, 93.6%), 169, 151, 137, 99, and 47 (MeS^+, 66%). *Anal.* Calcd for $C_6H_6N_4S_2$: C, 36.37; H, 3.05; N, 28.28; S, 32.30. Found: C, 36.23; H, 3.14; N, 28.19; S, 32.30.

Elution with benzene–ethyl acetate (1:1) gave 0.25 g (43% yield) of dimethyl sulfone.

Reaction of Cl_2DISN with Diphenyl Sulfide. Cl_2DISN (0.35 g) and diphenyl sulfide (0.76 g) were dissolved into 20 ml of acetonitrile and the solution was stirred for 12 hr at room temperature

(22°). After evaporation of the solvent *in vacuo*, the residue was treated with benzene. The gray solid, which is insoluble to benzene, was found to be sufficiently pure DISN (68 mg): mp 163–165° dec (lit.[4] mp 165–166°).

Materials soluble to benzene were subjected to silica gel column chromatography. *p*-Chlorophenyl phenyl sulfide (0.60 g, 68% yield), which was contaminated by a small amount of *p,p'*-dichlorodiphenyl sulfide, and ClDISN (50 mg, 18% yield) were isolated from fractions eluted with benzene–*n*-hexane (3:2). Diphenyl sulfoxide (0.25 g, 30% yield) was obtained from fractions eluted with benzene–ethyl acetate (3:2). Furthermore, elution with benzene–ethyl acetate (1:1) gave additional 13 mg of DISN (38% total yield).

Reaction of Cl_2DISN with *N*-Benzyl-1,4-dihydronicotinamide. A solution of Cl_2DISN (0.35 g) in THF (10 ml) was cooled to −20° by a Dry Ice–CCl_4 bath. To this solution was added a solution of BNAH (0.86 g) in THF (30 ml). The solution was stirred for 30 min at −20° and crystals of BNA^+Cl^- (0.93 g, 94% yield) were filtered off. The solvent was evaporated *in vacuo* from the filtrate and the residue was purified by a column of silica gel. Elution with benzene–ethyl acetate (4:1) gave 94 mg of DISN (44% yield).

Reaction of Cl_2DISN with Sodium Borohydride. A mixture of Cl_2DISN (0.35 g) and $NaBH_4$ (0.16 g) in THF (30 ml) was stirred for 15 hr at room temperature. After usual work-up, 81% of Cl_2DISN used was recovered and no indication was obtained for the formation of DISN.

Reaction of Cl_2DISN with Olefins. A mixture of Cl_2DISN (0.35 g), Na_2CO_3 (0.42 g), and styrene (1.0 g) in benzene (10 ml) was kept at room temperature in a dark for 5 days. The residue remained after evaporation of the solvent *in vacuo* was subjected to column chromatography on silica gel, yielding 0.10 g of Cl_2DISN and pale yellow crystals, which was sublimed at 110° (1 Torr), giving white needles of 2,3-dicyano-5-phenylpyrazine (0.18 g, 63% yield): mp 164–165°; ir (Kbr) 3050, 2240, 1560, 1540, 1520, 1460, 1430, 1120, 794, 770, 693, and 510 cm^{-1}. *Anal.* Calcd for $C_{12}H_6N_4$: C, 69.89; H, 2.93; N, 27.17. Found: C, 69.84; H, 2.66; N, 27.00.

Similar reactions with β-methylstyrene and 2,3-dihydropyran gave **2b** and **2c** in 35 and 26% yields, respectively, after similar work-up described above.

Registry No.—**2a,** 52109-66-7; **2b,** 52109-67-8; **2c,** 52109-68-9; DAMN, 1187-42-4; DISN, 28321-79-1; Cl_2DISN, 33420-44-9; $(EtS)_2$DISN, 52109-69-0; $(MeS)_2$DISN, 52109-70-3; *tert*-butyl hypochlorite, 5923-22-8; ethanethiol, 75-08-1; 2-propanethiol, 75-33-2; benzenemethanethiol, 100-53-8; benzenethiol, 108-98-5; *p*-methoxybenzenethiol, 696-63-9; *p*-chlorobenzenethiol, 106-54-7; dimethyl sulfoxide, 67-68-5; diphenyl sulfide, 139-66-2; *N*-benzyl-1,4-dihydronicotinamide, 952-92-1; sodium borohydride, 16940-66-2; styrene, 100-42-5; β-methylstyrene, 637-50-3; 2,3-dihydropyran, 110-87-2.

Supplementary Material Available. Full ir, mass spectral, and elemental analyses data for compounds **2b, 2c,** and those listed in Table II as well as melting points of **2b** and **2c** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3373.

References and Notes

(1) R. A. Sanchez, J. P. Ferris, and L. E. Orgel, *J. Mol. Biol.*, **30,** 223 (1967); *Science* **153,** 72 (1963).
(2) R. M. Lemmon, *Chem. Rev.*, **70,** 95 (1970).
(3) E. Ciganek, W. J. Linn, and O. W. Webster, "Cyano Carbon and Polycyano Compounds," in "The Chemistry of the Cyano Group," Z. Rappoport, Ed., Interscience, New York, N.Y., 1970, Chapter 9.
(4) R. W. Begland, A. Cairncross, D. S. Donald, D. R. Hartter, W. A. Sheppard, and O. W. Webster, *J. Amer. Chem. Soc.*, **93,** 4953 (1971).
(5) O. W. Webster, D. R. Hartter, R. W. Begland, W. A. Sheppard, and A. Cairncross, *J. Org. Chem.*, **37,** 4133 (1972).
(6) R. W. Begland and D. R. Hartter, *J. Org. Chem.*, **37,** 4136 (1972).
(7) N. Asai and T. Okada, Japanese Patent 7,205,925 (1972); *Chem. Abstr.*, **76,** 112743v (1972).
(8) Manufacturers are Nippon Soda Co., Ltd., and Kyowa Gas Chemical Industry Co., Ltd.
(9) Prior studies of the chemistry of DAMN are reported by (a) J. P. Ferris, S. B. Donner, and W. Lotz, *J. Amer. Chem. Soc.*, **94,** 6968 (1972); (b) H. Bredereck and G. Schmötzer, *Justus Liebigs Ann. Chem.*, **600,** 95 (1956); (c) L. E. Hinkel, G. O. Richards, and O. Thomas, *J. Chem. Soc.*, 1432 (1937); (d) R. P. Linstead, E. G. Noble, and J. M. Wright, *ibid.*, 911 (1937); (e) G. J. Janz and A. G. Keenan, *Can. J. Res.*, **25B,** 272 (1947).
(10) D. Y. Curtin and C. G. McCarty, *J. Org. Chem.*, **32,** 223 (1967).
(11) S. Oae, A. Ohno, and W. Tagaki, *Bull. Chem. Soc. Jap.*, **35,** 681 (1962), and references cited therein.
(12) R. H. Abeles, R. F. Hutton, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **79,** 712 (1957).
(13) A. Ohno and N. Kito, *Chem. Lett.*, 369 (1972).
(14) T. Fukunaga, *J. Amer. Chem. Soc.*, **94,** 3242 (1972).
(15) Only an azirine compound was formed by the reaction of styrene with DISN.[14]

Synthesis of α-Cyanoglycine *N*-Carboxyanhydride and α-Cyanoglycine[1]

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α-Cyanoglycine *N*-carboxyanhydride (4), a new, monomeric precursor of poly-α-cyanoglycine (2) required for chemical evolution studies, was synthesized from ethyl α-cyanoglycine (**6a**) by the following sequence of reactions, rather than by standard procedures from the highly labile amino acid, α-cyanoglycine (**5**). Compound **6a** was converted to its *N*-benzyloxycarbonyl (CBZ) derivative by treatment with benzyl chloroformate in refluxing ethyl acetate and then was selectively hydrolyzed with aqueous KOH to *N*-CBZ-α-cyanoglycine (**7b**). A slight change in the reaction conditions to KOH in 50% acetone–water brought about hydrolysis of both the ester and the nitrile groups and yielded *N*-CBZ-aminomalonic acid. Compound **7a** reacted with trifluoroacetic anhydride to produce α-cyanoglycine *N*-carboxyanhydride (4), which with a large excess of water gave α-cyanoglycine (**5**).

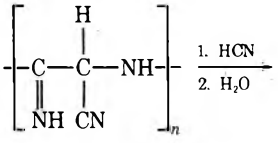
During the past 2 decades, extensive research on the origin of life[3] has led to the widespread belief that the prebiological formation of primitive proteins occurred in two stages, α-amino acid synthesis initiated by the action of high energy from natural sources on the components of a reducing atmosphere followed by polycondensation of the accumulated monomers in the oceans or on land. A critical examination of the evidence for the second step suggests, however, that the inherent thermodynamic barrier to spontaneous polymerization of α-amino acids has been overcome only when specific environments have been invoked (anhydrous locales, high-temperature milieu, or acidic bodies of water, for example) that are not characteristic of a young, developing planet. This objection does not apply to an alternative route for protein abiogenesis that has been proposed[4] for the direct synthesis of heteropolypeptides from hydrogen cyanide and water without the intervening formation of α-amino acids.

Table I
Nmr Spectra of *N*-CBZ-α-cyanoglycine Derivatives[a,b]

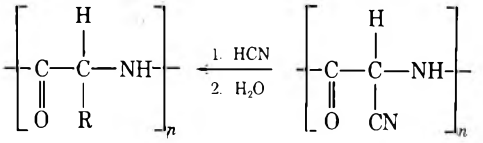
Positions of hydrogens	Compounds 7a	7b	7c	8
COOH		13.53 s		
>NH	8.65 bd[c] (J = 8.0 Hz)	8.65 bd (J = 8.0 Hz)	*e*	8.03 bd (J = 8.0 Hz)
C_6H_5	7.38 s	7.37 s	7.40 s	7.37 s
NH_2				6.62 bs[d]
>CH	5.72 d (J = 8.0 Hz)	5.62 d (J = 8.0 Hz)	4.70 d (J = 6.5 Hz)	5.62 d (J = 8.0 Hz)
CH_2	5.15 s	5.20 s	5.15 s	5.20 s
CH_2CH_3	4.23 qt 1.12 tr			

[a] In dimethyl-d_6 sulfoxide. [b] All chemical shifts in ppm from tetramethylsilane. [c] Broadened doublet. [d] Broadened singlet. [e] No peak observed.

According to this hypothesis a low-energy pathway exists for the spontaneous polymerization of hydrogen cyanide to polyaminomalononitrile (**1**). Successive reactions of hydrogen cyanide with the activated nitrile groups of **1** then yield heteropolyamidines that become converted by water to heteropolypeptides (**2**) possessing side chains of today's proteins. To demonstrate the feasibility of the postulated

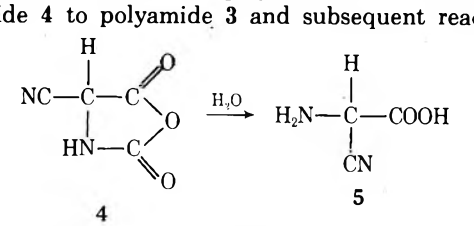


1



2 **3**

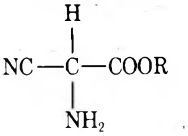
conversion of homopolymer **1** to heteropolymer **2** one would like to synthesize polymer **1** unambiguously and then show that it can be modified to polymer **2** by treatment with hydrogen cyanide and water. On the other hand, using the tools of amine acid chemistry, one can synthesize poly-α-cyanoglycine (**3**),[4c,e] a polyamide analog of polyamidine **1** that should be readily obtainable in a pure state by controlled polymerization of α-cyanoglycine *N*-carboxyanhydride (**4**). We report here the first synthesis of **4** and its hydrolysis to α-cyanoglycine (**5**), a highly reactive amino acid hitherto[5] obtained only by enzymatic deacylation of acetoamidocyanoacetic acid. Future papers will report the second part of this work (polymerization of *N*-carboxyanhydride **4** to polyamide **3** and subsequent reaction of



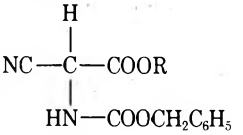
4 **5**

compound **3** with hydrogen cyanide and water to yield heteropolypeptides).[4c,e]

A key intermediate in the synthesis of α-cyanoglycine (**5**) was ethyl aminocyanoacetate (**6a**), readily prepared by nitrosation[6] of ethyl cyanoacetate followed by reduction with mercury amalgam.[7] Methyl aminocyanoacetate (**6b**) was prepared by the same route from methyl cyanoacetate. Both cyanoacetates **6a** and **6b** form stable salts with *p*-toluenesulfonic acid[7b] but not with hydrogen chloride.



6a, R = C_2H_5
b, R = CH_3



7a, R = CH_2CH_3
b, R = H
c, R = K

All attempts to synthesize α-cyanoglycine in one step by hydrolysis of ethyl ester **6a** or methyl ester **6b** were unsuccessful; only black, intractable polymer was obtained. This result prompted the development of a synthesis of α-cyanoglycine-NCA (**4**) and of α-cyanoglycine (**5**) by the following series of reactions: (a) conversion of compound **6a** to its *N*-benzyloxycarbonyl (*N*-CBZ) derivative **7a**, (b) hydrolysis of ester **7a** to acid **7b**, (c) conversion of acid **7b** to *N*-carboxyanhydride **4**, and (d) conversion of anhydride **4** to α-cyanoglycine (**5**). The lability of compounds **6a**, **7a**, and **7b** to base and to nucleophilic reagents (*e.g.*, chloride ion) brought about the development of new methods for carrying out these synthetic steps.

Ethyl *N*-CBZ-α-Cyanoglycine (7a). Use of standard Schotten-Bauman procedures[8] (base + acid chloride + amino acid) to acylate ethyl ester **6a** with benzyl chloroformate gave very poor yields (less than 5%) of *N*-CBZ derivative **7a**. However, a direct acylation of **6a** with benzyl chloroformate in refluxing ethyl acetate produced the desired compound in better than 80% yield.[9]

***N*-CBZ-α-Cyanoglycine (7b).** The selectivity of the hydrolysis of ethyl ester **7a** was controlled by the solvent. With aqueous 0.25 *N* KOH **7a** was converted to **7b** in better than 90% yield. With the same concentration of KOH in 50% (v/v) acetone–water the ester and the nitrile functions were both hydrolyzed and *N*-CBZ-aminomalonamic acid (**8**) was obtained in 85% yield. Malonamic acid **8**, on the other hand, was converted back to nitrile **7b** by treatment with dicyclohexylcarbodiimide in dimethylformamide.[10] The nmr spectra of compounds **7a**, **7b**, **7c**, and **8** are presented in Table I.

The selectivity of the hydrolysis reaction appears to be related to the solubility of ester **7a** in the two hydrolysis solvent systems. Ethyl ester **7a** is soluble in acetone–water and insoluble in water. Addition of KOH to the water causes **7a** to dissolve, and nmr analysis of the solution (0.25 *N*

KOD in D_2O) shows that the methine and imine protons on ester **7a** have exchanged with deuterium. Thus ionization of **7a**, concomitant with its dissolution in water, appears to account for the selectivity of the reaction.

α-Cyanoglycine-NCA. The conversion of *N*-CBZ-α-amino acids to α-amino acid *N*-carboxyanhydrides (Leuchs' anhydrides, NCAs) is a well-worked out process.[11] The general method is to convert the CBZ-α-amino acid to its acid chloride or bromide, which then cyclizes either spontaneously or with gentle heating. However, all attempts to convert compound **7b** to α-cyanoglycine-NCA by the acid chloride route were unsuccessful, since *N*-CBZ acid **7b** formed an acid chloride that, while stable at room temperature, slowly polymerized at 45° in anhydrous methyl acetate. One possible reason for this result is that chloride ion was reacting with α-cyanoglycine-NCA to produce polymer. At any rate, this concept suggested the use of trifluoroacetic anhydride (TFAA) as the condensing reagent, since the literature provides evidence that mixed anhydrides formed from TFAA are more reactive than corresponding acid chlorides[12] and that the trifluoroacetate leaving group is a poorer nucleophile than chloride ion.[13]

Addition of trifluoroacetic anhydride to a suspension of *N*-CBZ amino acid **7b** in benzene produced the desired result. The amino acid immediately went into solution, and 30 sec later α-cyanoglycine-NCA appeared in better than 90% yield as a white precipitate with spectral (nmr, ir) and elemental analysis consistent with the structure of α-cyanoglycine-NCA. Benzyl trifluoroacetate, the by-product of the reaction, was isolated and identified by comparison of its glpc retention time and ir spectrum with those of an authentic sample.

Reaction of α-cyanoglycine-NCA with methanolic HCl followed by reaction with trifluoroacetic anhydride produced a volatile *N*-trifluoroacetyl methyl ester derivative (**9**) of α-cyanoglycine. This compound was identical (same retention time on two different glpc columns) with that obtained by trifluoroacetylation of the *p*-toluenesulfonate salt of methyl ester **6b**.

α-Cyanoglycine (5). Reaction of α-cyanoglycine-NCA with a large excess of water followed by lyophilization of the resulting clear solution gave a white powder, with elemental analysis and ir spectrum consistent with structure **5**. A chemical proof of structure was provided by conversion of **5** to its *N*-trifluoroacetyl methyl ester derivative by treatment first with trifluoroacetic anhydride to form a mixed anhydride followed by addition of methanol to form the methyl ester. This derivative had the same retention time on two different glpc columns as the compound obtained by trifluoroacetylation of the *p*-toluenesulfonate salt of methyl ester **6b**.

Experimental Section

General. Melting points are uncorrected; nmr spectra were obtained with a Varian A60; infrared spectra were obtained with a Beckman IR4; microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn. A Varian Aerograph 2100 dual-column gas chromatograph equipped with flame ionization detectors was used in the single column made for gas chromatographic analyses. The signal from the chromatograph was fed to an Infotronics CRS-104 digital integrator and then to a Varian Aerograph Model 30 recorder. The chromatograph was fitted with two 1.9 m × 2 mm i.d. glass U columns, one packed with OV 17 (1%) on 80–100 mesh HP Chromosorb G (OV 17 column) and the other with ethylene glycol adipate on 80–100 mesh acid-washed, heat-treated Chromosorb W (EGA column). EGA packing was purchased from Regis Chemical Co. (Code No. 201033). General gas chromatographic conditions were as follows: nitrogen carrier gas flow, 20 ml/min; H_2 flow, 30 ml/min; air flow, 350 ml/min; detector temperature, 230°; injector temperature, 170°. Derivatization reactions were carried out in 16 × 75 mm screw-capped test tubes fitted with Teflon-lined caps (Corning 9826, A. H. Thomas Co.). A Lab-Line Temp-Blok (A. H. Thomas Co.), which was heated with a Thermolyne, Model HP-A1G15B hot plate (Fisher Scientific Co.), was used to heat the derivatization tubes.

Ethyl (6a) and Methyl Aminocyanoacetate (6b). Methyl and ethyl cyanoacetate were converted to oximino derivatives by the method of Parker[6] and then reduced to amines by the method of Ferris and Orgel.[7a,b] Overall yields for each compound ranged from 48 to 55%. Both amines rapidly polymerized at room temperature but were stable at −70°.

The reduction of ethyloximinocyanoacetate by aluminum amalgam was conveniently followed by gas chromatography. The reaction mixture (3 ml) was filtered through a sintered glass filter. Trifluoroacetic anhydride, 0.5 ml, and 1.0 ml of the filtrate were placed into a derivatization tube and heated to 65° for 5 min. This solution (1 μl) was injected onto the OV 17 column: column oven temperature, 50 to 200° at 40/min; retention times ethyloximinocyanoacetate, 6.9 min; ethyl aminocyanoacetate (**6a**), 12.5 min.

Methyl aminocyanoacetate–*p*-toluenesulfonate salt was prepared by the method of Ferris and Orgel[7a,b] in 50% yield: mp 174–176° (dec); ir (KBr) 2875, 2240 (weak), 1775, and 1195 cm^{-1}; nmr (DMSO-d_6) δ 8.77 (broad singlet, 3, NH_3^+), 7.28 (quartet, 4, CH_3–C_6H_4–SO_2^-), 5.96 (s, 1, CH–CN), 3.88 (s, 3, $COOCH_3$), 2.32 (s, 3, CH_3–CH_6H_4–).

Anal. Calcd for $C_{11}H_{14}N_2O_5S$: C, 46.15; H, 4.93; N, 9.78; O, 29.94. Found: C, 45.97; H, 5.00; N, 9.64; O, 28.07.

Ethyl *N*-Benzyloxycarbonyl-α-cyanoglycine (7a). Ethyl aminocyanoacetate (**6a**, 13.6 g, 0.106 mol) was added to 100 ml of ethyl acetate which contained 21.1 g (0.124 mol) of benzyl chloroformate. The reaction mixture was stirred for 10 min at room temperature and then refluxed for 2.5 hr. Norit-A (1 g) was added to the reaction mixture, which was then filtered, and the solvent was stripped off *in vacuo*. The resulting yellow residue, washed with 100 ml of ether and recrystallized from benzene, gave 23.5 g (85% yield) of **7a**, mp 113–114.5°.

***N*-Benzyloxycarbonyl-α-cyanoglycine (7b).** Ethyl *N*-benzyloxycarbonyl-α-cyanoglycine (**7a**, 13 g, 50 mmol) was stirred with 210 ml of 0.25 *N* KOH for 2.5 hr. The resulting yellow solution was acidified with 116 ml of 2 *N* H_2SO_4 and then extracted with four 100-ml portions of ether. The ether extracts were dried over $MgSO_4$ and then concentrated under reduced pressure to an oil, which was diluted with 50 ml of methylene chloride and stripped to dryness again. The resulting white residue was recrystallized from methylene chloride to yield 10.7 g (45.7 mmol, 91% yield) of **7b**. An analytical sample was prepared by a further recrystallization from methylene chloride, mp 103–105° (dec).

Anal. Calcd for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.30; N, 11.95. Found: C, 56.44; H, 4.25; N, 11.76.

***N*-Benzyloxycarbonylaminomalonamic Acid (8).** Ethyl *N*-CBZ-α-cyanoglycine (**7b**, 5.2 g, 20 mmol) was dissolved in 50 ml of acetone and added to 50 ml of 0.50 *M* KOH. The solution was stirred for 3 hr at room temperature, and the acetone was stripped off *in vacuo*. The aqueous portion of the solution was extracted with two 20-ml portions of methylene chloride, acidified to pH 1.0 with sulfuric acid, and extracted with five 20-ml portions of ether. The ether extract was dried over magnesium sulfate and the ether was then stripped off to give a yellow residue, which was washed with pentane and finally methylene chloride to yield 4.3 g (85%) of a white powder, mp 85–87° (dec). The nmr spectrum is presented in Table I.

Anal. Calcd for $C_{11}H_{12}N_2O_5$: C, 52.38; H, 4.80; N, 11.1. Found: C, 52.10; H, 4.86; N, 10.90.

α-Cyanoglycine *N*-Carboxyanhydride (4). All procedures were carried out in an N_2-filled drybox. Benzene and pentane were dried over molecular sieves (Linde 4A). All glassware was heated to 130° for 1 hr prior to use. To a rapidly stirred suspension of *N*-benzyloxycarbonyl-α-cyanoglycine (**7b**, 7.17 g, 30.7 mmol) in 250 ml of benzene was added 7.7 g (37 mmol) of trifluoroacetic anhydride. The resulting mixture was stirred at room temperature (21°) for 30 min, during which time **7b** went into solution and a white precipitate appeared. The reaction mixture was diluted with 200 ml of pentane and filtered through a fritted glass filter; the precipitate was washed with 25 ml of chloroform and 25 ml of pentane: yield, 3.41 g (27.5 mmol, 90%); mp 110–114° (dec); ir (KBr) 2340 cm^{-1} (–C≡N), 1870 and 1790 cm^{-1} (–C(=O)–O–C(=O)–); nmr (acetone-d_6) δ 8.9 (broad singlet, 1, HN<), 6.05 (d, 1, J = 1.75 Hz, HC–CN).

Anal. Calcd for $C_4H_2N_2O_3$: C, 38.10; H, 1.60; N, 22.22; O, 38.07. Found: C, 38.32; H, 1.71; N, 22.38; O, 38.85.

α-Cyanoglycine (5). α-Cyanoglycine *N*-carboxyanhydride (**4**,

1.24 g, 10 mmol) was dissolved into 50 ml of dioxane which had been distilled from lithium aluminum hydride. This solution was placed into an addition funnel and added dropwise to 180 ml of vigorously stirred water. During the addition process a slow stream of nitrogen was passed through the addition funnel to prevent premature reaction of the anhydride with water vapor. After addition was complete the material was stirred for an additional 1 hr and freeze-dried to yield 746 mg (75% yield) of a white powder, mp 101–103° (dec).

Anal. Calcd for $C_3H_4N_2O_2$: C, 36.01; N, 4.03; N, 27.99. Found: C, 36.03; H, 3.99; N, 27.73.

Recrystallization was carried out by dissolution of 500 mg of the freeze-dried residue in 10 ml of H_2O. The aqueous solution was acidified to pH 2 with HCl, treated with charcoal at room temperature for ~2 min, filtered, and cooled in an ice bath, and 30 ml of absolute ethanol was added to initiate crystallization. The crystals were washed with ethanol and then ether; 210 mg (47% yield) of material were obtained: mp 126.5° (dec) (lit.[5,6] mp 121.5°); ir (KBr) 2980 cm^{-1} (NH_3^+), 2264 (CN), 2020 (NH_3^+), 1660 (COO^-), 1620 (NH_3^+), 1590 (NH_3^+), 1360 (COO^-), 485 (NH_3^+).

Anal. Calcd for $C_3H_4N_2O_2$: C, 36.01; H, 4.03; N, 27.99. Found: C, 35.34; H, 4.19; N, 27.27.

Elemental analyses suggest that recrystallization increases and sharpens the melting point (possibly by removing traces of aminoacetonitrile, which could otherwise initiate base-catalyzed decomposition of the molecule) but does not increase the purity of the material.

Chemical Proof of Structure of α-Cyanoglycine (5) and α-Cyanoglycine-NCA (4). (a) Formation of *N*-Trifluoroacetyl Methyl Ester Derivatives. Methyl aminocyanoacetate–*p*-toluene sulfonate salt (20 mg) was added to 1 ml of 25% (v/v) trifluoroacetic anhydride in methylene chloride in a 16 × 75 mm screw-capped test tube and heated at 45° for 30 min.

α-Cyanoglycine-NCA (4), 20 mg, and 12.5 *N* methanolic HCl (1.0 ml) were placed into a 16 × 75 mm screw-capped test tube and heated to 45° for 5 min. Volatile reagents were stripped off with a stream of nitrogen, 1 ml of 25% (v/v) trifluoroacetic anhydride was added to the residue, and the mixture was heated to 45° for 30 min.

α-Cyanoglycine (5), 10 mg (0.1 mmol), was added to 2 ml of 25% trifluoroacetic anhydride (1.7 *M*) in a screw-capped test tube. The material was heated to 40° for 30 min and cooled to room temperature. Methyl alcohol (140 μl, 3.34 mmol) was cautiously added to the reaction mixture.

(b) Gas chromatographic Procedure. Samples (1 μl) of each solution and a 1-μl sample of a mixture of all three samples were injected onto the OV 17 and the EGA columns. Only one peak (better than 90% of total peak area) was observed on the EGA column. On the OV 17 column peak for *p*-toluenesulfonyl trifluoroacetate and a peak for methyl *N*-trifluoroacetyl-α-cyanoglycine were observed. Conditions for the EGA column were as follows: column oven, 90 to 210° at 4°/min; retention time methyl *N*-TFA-α-CN-Gly, 13.0 min; conditions for the OV 17 column: column oven, 80 to 220° at 4°/min; retention time *p*-toluenesulfonyl trifluoroacetate, 2.0 min; methyl *N*-TFA-α-CN-Gly, 4.2 min.

Registry No.—**4**, 52486-66-5; **5**, 6232-21-9; **7a**, 3878-13-5; **7b**, 52486-67-6; **7c**, 52486-68-7; **8**, 52486-69-8; methyl aminocyanoacetate–*p*-toluenesulfonate salt, 52486-71-2.

References and Notes

(1) Presented at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 29, 1971.
(2) Address all correspondence to C. B. Warren at the Monsanto Co., St. Louis, Mo. 63166.
(3) Recent monographs and reviews on chemical evolution and the origin of proteins include (a) S. W. Fox and K. Dose, "Molecular Evolution and the Origin of Life," W. H. Freeman, San Francisco, Calif., 1972; (b) C. Ponnamperuma, Ed., "Exobiology," American Elsevier, New York, N.Y., 1972; (c) R. M. Lemmon, *Chem. Rev.*, **70**, 95 (1970); (d) D. H. Kenyon and G. Steinman, "Biochemical Predestination," McGraw-Hill, New York, N.Y., 1969; (e) M. Calvin, "Chemical Evolution," Oxford University Press, New York, N.Y., 1969.
(4) (a) C. N. Matthews and R. E. Moser, *Proc. Natl. Acad. Sci. U. S.*, **56**, 1087 (1966); (b) C. N. Matthews and R. E. Moser, *Nature (London)*, **215**, 1230 (1967); (c) C. N. Matthews in "Chemical Evolution and the Origin of Life," R. Buvet and C. Ponnamperuma, Ed., North Holland Publishing Co., Amsterdam, 1971, pp 231–235; (d) W. Yang, R. D. Minard, and C. N. Matthews, *J. Chem. Soc., Chem. Commun.*, 435 (1973); (e) R. D. Minard, W. Yang, and C. N. Matthews, presented at the 161st National meeting of the American Chemical Society, Chicago, Ill., 1973, Abstract ORGN 117; (f) C. N. Matthews, "Origins of Life," Vol. 6, in press.
(5) (a) C. Ressler and D. V. Kashelikar, *J. Amer. Chem. Soc.*, **88**, 2025 (1966); (b) C. Ressler, G. R. Nagarajan, M. Kirisawa, and D. V. Kashelikar, *J. Org. Chem.*, **36**, 3960 (1971).
(6) C. D. Parker, *Tetrahedron*, **17**, 109 (1962).
(7) (a) J. P. Ferris and L. E. Orgel, *J. Amer. Chem. Soc.*, **88**, 3829 (1966); (b) J. P. Ferris, R. A. Sanchez, and R. W. Mancuso, *Org. Syn.*, **48**, 1 (1968); (c) J. W. Cornforth in "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N.J., 1949, p 725; (d) I. Heilbron, *J. Chem. Soc.*, 2099 (1949).
(8) J. P. Greenstein and M. Winitz, "The Chemistry of the Amino Acids," Vol. II, Wiley, New York, N.Y., 1971, p 890.
(9) (a) E. Ronwin, *J. Org. Chem.*, **18**, 127 (1953); (b) E. Ronwin and C. B. Warren, *ibid.*, **29**, 2276 (1964).
(10) D. V. Kashelikar and C. Ressler, *J. Amer. Chem. Soc.*, **86**, 2476 (1964), report an analogous reaction in which *N*-CBZ-L-asparagine was converted to *N*-CBZ-β-cyano-L-alanine.
(11) (a) C. H. Bamford, A. Elliot, and W. E. Hanby, "Synthetic Polypeptides," Academic Press, New York, N.Y., 1965, pp 29–32, 53–58; (b) E. Katchalski, *Advan. Protein Chem.*, 6, 123 (1951); (c) E. Katchalski and M. Sela, *ibid.*, **13**, 243 (1958); (d) V. V. Korshak, S. V. Rogozhin, V. A. Davankov, Yu. A. Davidovich, and T. A. Makarova, *Russ. Chem. Rev.*, **34**, 329 (1965); (e) G. D. Fasman, N. Tooney, and Y. Shalitin in "Encyclopedia of Polymer Science and Technology," Vol. 2, H. F. Marks, H. G. Gaylord, and N. M. Bikales, Ed., Interscience, New York, N.Y., 1965, pp 837–59; (f) M. Szwarc, *Advan. Polym. Sci.*, **4**, 1 (1965).
(12) R. C. Parish and L. M. Stock, *J. Org. Chem.*, **30**, 927 (1965).
(13) P. E. Peterson, R. J. Bopp, and M. M. Ajo, *J. Amer. Chem. Soc.*, **92**, 2834 (1970).

A Synthetic Approach to the Skeleton of Histrionicotoxin[1]

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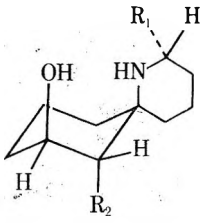
An approach to the ring skeleton of histrionicotoxin and dihydrohistrionicotoxin, involving the intramolecular oxidative cyclization of a nitrone moiety with an activated olefin, is described. The regiochemistry of the adduct is considered.

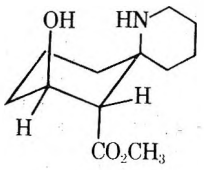
Histrionicotoxin and dihydrohistrionicotoxin (1 and 2, respectively), venoms isolated from the skins of certain Colombian frogs, are anticholinergic agents.[2a,b] These alkaloids are structurally intriguing in that they possess a spiro structure and may be the first examples of acetylenic and allenic moieties appearing in animal kingdom derived natural products.[2c] That the biological activity is not intimately associated with the unsaturated linkages is evidenced by the fact that perhydrohistrionicotoxin (3) retains activity.[2b]

It is clear that these alkaloids provide an unusual synthetic challenge. Our initial efforts have been directed



1, $R_1 = CH_2C{\equiv}CC{\equiv}CH$; $R_2 = C{=}CC{\equiv}CH$ (H, H)
2, $R_1 = CH_2CH_2CH{=}C{=}CH_2$; $R_2 = C{=}CC{\equiv}CH$ (H, H)
3, $R_1 = n\text{-}C_5H_{11}$; $R_2 = n\text{-}C_4H_9$
4, $R_1 = H$; $R_2 = CO_2CH_3$
5, $R_1 = H$; $R_2 = H$

toward the synthesis of spiro ester **7**, which offers promise as a key intermediate in the synthesis of the natural toxins. Compound **4** embodies the desired spiro skeletal system,



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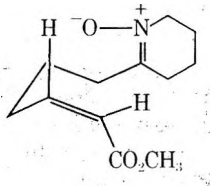
the proper stereochemical relationship between the hydroxyl and amine functions, and incorporates a functional group (*i.e.*, the ester moiety) of requisite stereochemistry capable, in principle, of chemical manipulation into the desired unsaturated side chain of the parent alkaloid. The introduction of the second side chain (*i.e.*, R_1 in **1**–**3**) appears conceivable as well.

Method of Attack. The use of nitrones in ring formation is well documented.[3,4] Moreover, it has been demonstrated recently that various alkaloidal systems can be approached by nitrone-induced cyclizations.[5,6] Thus, the cyclization of the nitrone ester **6** offers promise of producing the desired ring system **7** spontaneously. Hydrogenolysis of the nitro-



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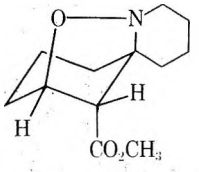

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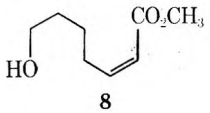
gen–oxygen bond of the isoxazolidine **7** would afford **4** directly. It is to be noted that the cis geometry about the double bond is essential to the introduction of an axial carbomethoxyl group. With these concepts in mind, we embarked on a synthesis of nitrone ester **6**.

The synthesis of the nitrone ester may be separated into three parts: (a) the preparation of the *cis*-α,β-unsaturated ester **8**; (b) the further elaboration of **8** into the keto ester **9**, and (c) the transformation of the hydroxyl group into the nitro functionality in **10**, the immediate presursor of nitrone **6**.



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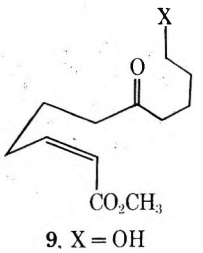
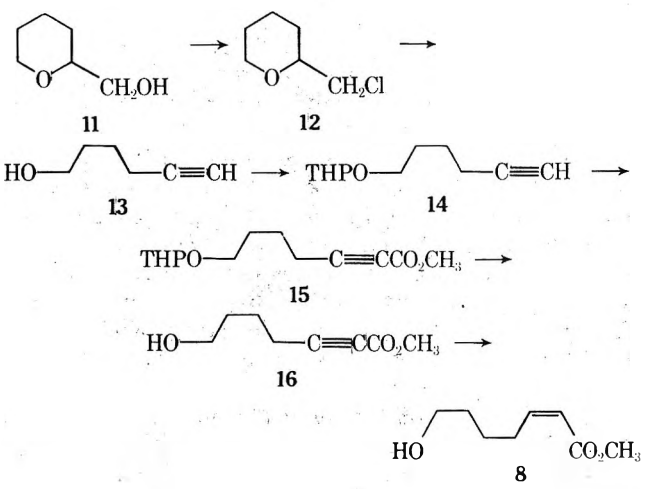


9, X = OH
10, X = NO_2

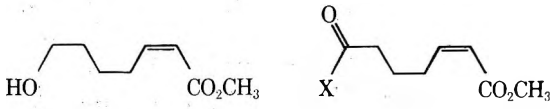
Methyl 7-Hydroxy-cis-2-heptenoate (8). Chlorination of 2-hydroxymethyltetrahydropyran (**11**) with thionyl chloride in pyridine[7] gave 2-hydroxymethyltetrahydropyran (**12**, Scheme I). Sodium amide in liquid ammonia[8] induced ring opening, and dehydrohalogenation afforded 5-hexyn-1-ol (**13**). The tetrahydropyranyl ether of **13** was acylated with methyl chloroformate, using *n*-butyllithium as base. The blocking group of the resulting ester, **15**, was removed with *p*-toluenesulfonic acid in anhydrous methanol. Reduction of **16** with Lindlar catalyst,[9] containing a small amount of quinoline, afforded methyl 7-hydroxy-*cis*-2-heptenoate (**8**) in 51% overall yield from **11**. This completed the first stage of our synthetic plan.

Scheme I



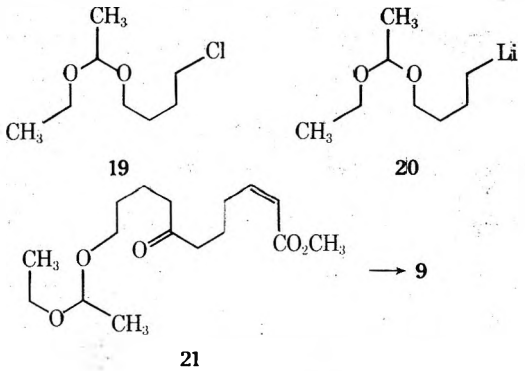
11 **12** **13** **14** **15** **16** **8**

Methyl 11-Nitro-7-keto-*cis*-undec-2-enoate (10). The second phase of the plan requires the conversion of the primary alcohol **8** into the acid chloride **18**, followed by the addition of a four-carbon segment by means of a lithium organocuprate.



8 **17**, X = OH; **18**, X = Cl

The organocopper reagent necessary for the chain extension was prepared from ethyl 4-chlorobutylacetaldehyde acetal (**19**) using the method of Eaton and coworkers,[10] followed by conversion of **19** into the organolithium reagent

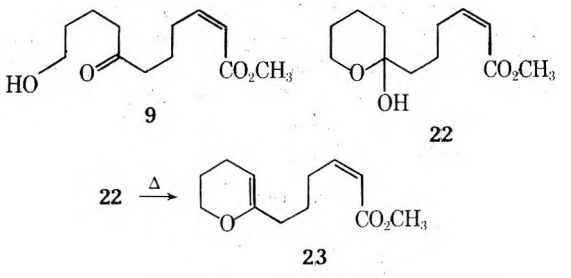


19 **20** **21** → **9**

20, using lithium wire containing 1% sodium. The organocopper reagent was then prepared by treatment of **20** with the copper complex derived from cuprous iodide and hexamethylphosphorus triamide in ether.[11] Addition of a precooled ether solution of the acid chloride **18**, prepared by stirring a benzene solution of the acid **17** with oxalyl chlo-

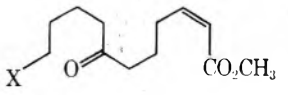
ride overnight at room temperature, to an ether solution of the organocopper reagent,[12] which was cooled to −78°, afforded the chain extended acetal **21**. The production of the keto alcohol **9** was accomplished by hydrolysis of the acetal using dilute hydrochloric acid in tetrahydrofuran.

Upon standing at room temperature, the keto ester **9** undergoes cyclization to the hemiketal **22**. This transformation was followed by the reduction in the intensity of the carbonyl absorption in the infrared region and a decrease in the intensity of the signal due to the methylene protons adjacent to the ketone function at δ 2.4 ppm in the nmr spectrum. Attempts to distill the keto ester resulted in dehydration to the dihydropyran **23**. Since the acyclic keto ester was required for our synthetic purposes, the mixture of isomers (*i.e.*, **9**, **22**, and **23**) was stirred in dilute aqueous acid for 30 min prior to further chemical transformation. The product was then extracted into methylene chloride, dried over anhydrous magnesium sulfate, and used directly.



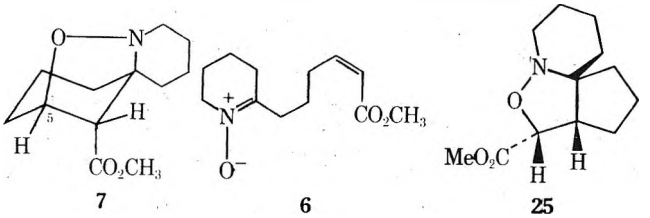
9 **22** **23**

The transformation of **9** into the nitro ketone **10** was straightforward. Treatment of **9** with triethylamine and methanesulfonyl chloride[13] in methylene chloride at 0° gave the corresponding methanesulfonate, **24a**. The bromide **24b** was obtained from **24a** using lithium bromide in acetone. Finally reaction of the bromide with sodium nitrite in dimethyl sulfoxide[14] gave **10**, and this completes the synthesis of the desired nitrone precursor.



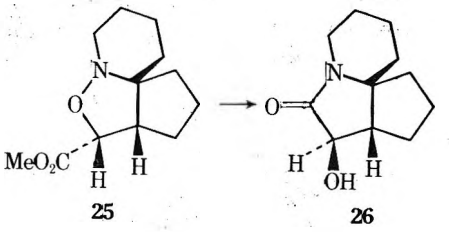
24a, X = OMs
b, X = Br
10, X = NO_2

Nitrone Cyclization. It was suspected that the nitrone **6**, produced by reductive cyclization of the nitro ketone **10**, would spontaneously add to the intramolecularly situated α,β-unsaturated ester moiety, a good dipolarophilic unit.[3] Indeed, treatment of a solution of **10** in aqueous methanol with zinc and ammonium chloride gave no detectable sign of the nitrone **6**. The reaction did produce a basic product, however, which exhibited no olefinic proton signals between 5.8 and 6.2 ppm, clearly suggesting that the nitrone had spontaneously cyclized as expected. Significantly, the pmr spectrum exhibited a doublet (J = 8.5 Hz) at 4.72 ppm. This signal is ascribed to the proton on the oxygen-bearing carbon of the isoxazolidine ring. The observed multiplicity would appear to rule out **7** as the major product of the reaction. Clearly, the proton on the 5 carbon of the isoxazolidine ring of **7** would be expected to be coupled to three other protons. Thus, the major product of the nitrone cyclization must be assigned the structure **25**.



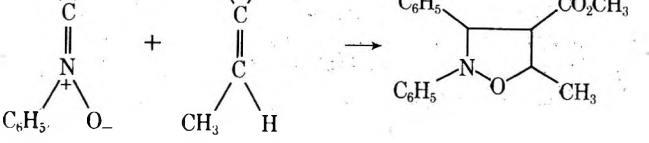
7 **6** **25**

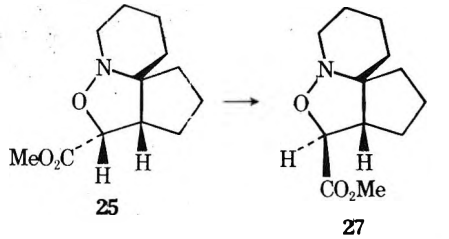
Chemical evidence for the structure **25** was obtained by cleavage of the nitrogen–oxygen bond with zinc and acetic acid.[4] Such treatment afforded a white solid which exhibits a carbonyl stretch at 5.95 μ and a hydroxyl band at 3.0 μ in the infrared spectrum. Further evidence for the hydroxy lactam structure **26** was obtained by examination of its pmr spectrum. The proton doublet due to the proton at the 5 position of the isoxazolidine ring shifted upfield from 4.72 (*i.e.*, in **25**) to 4.1 ppm. The smaller magnitude of the coupling (J = 5 Hz) indicates a trans coupling to a single proton, an expected consequence of the transformation. Mass spectral examination of adduct **25** and hydroxy lactam **26** indicates molecular ions at *m/e* 225 and 195, respectively.



25 **26**

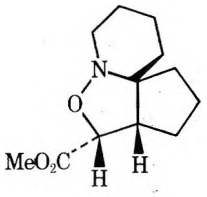
Since it now is apparent that the intramolecular cycloaddition did not proceed in the desired sense, one must reexamine the foundation upon which our initial expectations were based. A body of evidence[15–18] has accumulated which suggests that nitrones add to β-substituted α, β-unsaturated esters to give β-oxido ester adducts (*e.g.*, *vide infra* [16a]). This mode of addition would have produced the desired regioisomer **7** in the case in question. An explanation for the unexpected regiochemistry centers about the possibility that our initially derived adduct, **25**, is the product of kinetic control. Indeed, this adduct was formed spontaneously under very mild conditions (*vide supra*). There are examples where isoxazolidines, formed under kinetic conditions, can be converted to their thermodynamically favored counterparts;[15] however, refluxing a 1% solution of adduct **25** in toluene for 7 hr gave only a quantitative recovery of starting material. When adduct **25** was exposed to refluxing xylene for 30 hr, a new doublet appeared in the pmr spectrum at δ 4.18 ppm. The expected pattern for the proton at the 5 position of the isoxazolidine ring in **7** is a multiplet. Comparison of the coupling constant associated with the doublet at δ 4.72 ppm (J = 8.5 Hz) in adduct **25** with the doublet at δ 4.18 ppm (J = 6 Hz) in the thermally generated compound led to the conclusion that epimerization of the carbomethoxy group in **25** had occurred to give the isomeric adduct **27**, possibly *via* a base-catalyzed pathway. The marked similarity of the mass spectra of the adducts **25** and **27** is supportive of the structural assignment.





25 **27**

The predominant formation of **25**, and not **7**, from the nitrone cyclization might derive from the inherent relative stabilities of the ring systems involved. Examination of **25** and **7** suggests a piperidine ring common to both. If one focuses on the skeletal differences between the systems, it is clear that **25** possesses a *cis*-bicyclo[3.3.0]octyl skeleton, while **7** contains a bicyclo[3.2.1]octyl moiety. Clearly, if the



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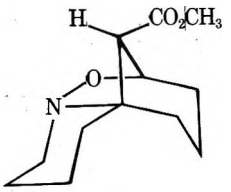

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cis-bicyclo[3.3.0]octyl system is thermodynamically preferred, a reasonable rationale for the observed mode of cyclization would be available; however, Allinger and coworkers[19] have calculated an additional strain energy of *ca.* 4.7 kcal/mol in bicyclo[3.3.0]octane. This figure might be somewhat high[19] but does suggest that the [3.2.1] system should be at least somewhat more stable than its [3.3.0] counterpart. In addition, Schleyer and coworkers[20] have studied the thermodynamic properties of bicyclo[2.2.2]octane (**28**), bicyclo[3.3.0]octane (**29**), and bicyclo[3.2.1]octane (**30**). The isomers were equilibrated at temperatures

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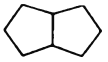

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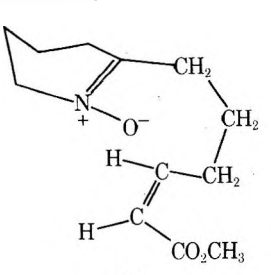
30

ranging from 23 to 72° and the product ratios determined. As the temperature increased, the amount of **29** increased at the expense of **28** and **30**, but even at 72°, the amount of **30** still predominated. Since thermodynamic considerations, albeit simplified, imply that appreciable amounts of **7** should be formed in the nitrone cyclization, the predominant formation of adduct **25** suggests the operation of some other factor.

It is quite possible that functionality and skeletal features not considered above may alter the relative adduct stabilities significantly; however, since the adducts are formed under conditions of apparent kinetic control, an examination of the relative transition state energies was undertaken using molecular models.

The transition states leading to the bicyclo[3.3.0]octyl system **25** and the bicyclo[3.2.1]octyl system **7** are depicted. An examination of the interactions apparent in these transition states discloses apparently serious steric interactions, indicated by the doubleheaded arrows in **32**, between the



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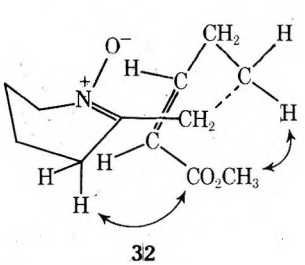

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carbomethoxy group and both C-3 of the nitrone and one of the side-chain methylene groups in the transition state leading to **7**. These interactions are absent in **31**. Thus, these steric interactions might outweigh an inherent preference for closure to the [3.2.1] system (*i.e.*, **7**).

We are testing this hypothesis by studying the cyclization of the olefin in which the ester group has been replaced by a hydrogen. Hopefully, such cyclization, where steric repulsions are minimized, would give **5** after hydrogenolysis.

Experimental Section

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5a spectrophotometer and calibrated using the 6.238-μ band of polystyrene. Proton magnetic resonance spectra were obtained using a Jeol MH-100 or a Varian A-60 spectrometer using tetramethyl silane as the internal standard. Notations s, d, t, q, m, and b designate singlet, doublet, triplet, quartet, multiplet, and broad, respectively. Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6 spectrometer.

2-(Chloromethyl)tetrahydropyran (12). An adaptation of the procedure used by Brooks[7a] to prepare tetrahydrofurfuryl chloride was used to prepare **12**. To a mixture of 103 g (0.888 mol) of tetrahydropyran-2-methanol (**11**) and 150 ml (1.09 mol) of freshly distilled pyridine was added 76.0 ml (1.06 mol) of freshly distilled thionyl chloride at a rate to maintain a reaction temperature of 40–45°. When the addition was complete, the mixture was heated for 8 hr at 45° by means of an oil bath. The resulting heavy brown oil was washed with ether (6 × 150 ml) and each time the ether was decanted. The combined ether solution was washed with water (4 × 75 ml), saturated aqueous sodium bicarbonate (3 × 75 ml), and saturated aqueous sodium chloride (2 × 75 ml). The ether solution was dried over anhydrous magnesium sulfate, and ether was removed at reduced pressure. Distillation of the residue gave 79 g (66% yield) of the chloride **12** as a colorless liquid: bp 55.0–55.5° (6 mm) [lit.[7b] 53–54° (12 mm)].

5-Hexyn-1-ol (13). An adaptation of the procedure used by Whiting[8] to prepare 4-pentyn-1-ol was used to prepared 5-hexyn-1-ol (**13**). Sodium amide was prepared by the addition of 35.9 g (1.52 mol) of freshly cut sodium to 600 ml of anhydrous liquid ammonia, containing 0.3 g of ferric nitrate nonahydrate. When the addition was complete, stirring was continued for 30 min. To the gray suspension of sodium amide was added dropwise 48.1 g (0.360 mol) of 2-(chloromethyl)tetrahydropyran (**12**). When the addition was complete, stirring was continued for 3 hr. Gradually, 80 g (1.5 mol) of ammonium chloride was added at a rate to allow a controllable neutralization of the base. The ammonia was allowed to evaporate overnight. The residual oily solid was extracted with a Soxhlet extractor with ether for 24 hr. The ether solution was dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure. Distillation of the residue gave 30.3 g (86% yield) of the alcohol **13** as a colorless liquid: bp 53° (1.2 mm) [lit.[21] bp 82° (20 mm)].

Tetrahydropyranyl Ether of 5-Hexyn-1-ol (14). To a mixture of 39.5 g (0.402 mol) of 5-hexyn-1-ol (**13**) and 1 ml of concentrated hydrochloric acid, cooled in an ice bath, was added 40.0 g (0.476 mol) of dihydropyran. When the addition was complete, stirring was continued at room temperature overnight. The solution was poured into 200 ml of saturated aqueous sodium bicarbonate, and the organic layer was separated. The aqueous layer was extracted with ether (3 × 100 ml). The combined extracts were dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure. Distillation of the residue gave 72.2 g (98% yield) of the tetrahydropyranyl ether **14** as a colorless liquid: bp 60–65° (0.2 mm); ir (neat) 8.95 (s), 9.3 (s), and 9.65 μ (s); nmr ($CDCl_3$) δ 1.3–2.0 (m, 10), 1.95 (t, 1, J = 2.5 Hz), 2.2 (m, 2), 3.5 (m, 2), 3.8 (m, 2), and 4.6 ppm (broad singlet, 1).

Methyl 7-Hydroxy-2-heptynoate (16). To a solution of 70.5 g (0.387 mol) of the tetrahydropyranyl ether **14** in 500 ml of freshly distilled tetrahydrofuran which was cooled to −78° was added 176 ml (0.412 mol) of a 2.34 M hexane solution of n-butyllithium. When the addition was complete, stirring was continued at −78° for 30 min. By means of a Dry Ice cooled addition funnel, the tetrahydrofuran solution, just prepared, was added over 4 hr to a solution of 62 ml (0.80 mol) of freshly distilled methyl chloroformate, in 500 ml of tetrahydrofuran which was cooled to −78°. When the addition was complete, the resulting mixture was stirred at −78° for 1 hr. The tetrahydrofuran solution, without warming, was siphoned into 1.6 l. of saturated aqueous sodium bicarbonate. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 100 ml). The combined organic extracts were dried over anhydrous magnesium sulfate, and the solvent was removed at reduced pressure, to give the crude ester **15**.

To a solution of the crude ester **15**, in 500 ml of anhydrous methanol, was added 0.5 g of *p*-toluenesulfonic acid, and the resulting mixture was stirred overnight at room temperature. The acid was neutralized by the addition of 2 ml of triethylamine, and the methanol was removed at reduced pressure. The residue was taken up in 300 ml of methylene chloride and washed with 2% aqueous hydrochloric acid (2 × 100 ml) and saturated aqueous sodium bicarbonate (2 × 100 ml). The methlene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure. Distillation of the residual oil gave 56.4 g (93% yield) of ester **16** as a light yellow oil: bp 90–95° (0.15 mm); ir (neat) 2.95 (m), 4.45 (s), 4.83 (s), 7.95 (s), and 9.3 μ (m); nmr ($CDCl_3$) δ 1.68 (m, 4), 2.4 (m, 2), 3.2 (broad singlet, 1) 3.65 (m, 2), and 3.75 ppm (s, 3); mass spectrum (M+) *m/e* 156.

Methyl 7-Hydroxy-*cis*-hept-2-enoate (8). A mixture of 54.0 g (0.346 mol) of methyl 7-hydroxy-2-heptynoate (**16**), 200 ml of absolute methanol, 0.4 g of Lindlar catalyst,[9] and 12 drops of quinoline was hydrogenated in a Parr apparatus at 14 psi until the hydrogen up-take ceased. The catalyst was removed by filtration, and the methanol was removed at reduced pressure. The residue was dissolved in 300 ml of methylene chloride and washed with cold 5% aqueous hydrochloric acid (1 × 30 ml) and saturated aqueous sodium bicarbonate (1 × 50 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure. Distillation of the residue gave 45.8 g (84% yield) of the ester **8** as a colorless oil: bp 74–78° (0.15 mm); ir (neat) 2.9 (s), 5.8 (s), 6.1 (m), 7.8 (s), 8.35 (s), 9.4 (s), 9.75 (s), and 12.2 μ (m); nmr ($CDCl_3$) δ 1.6 (m, 4), 2.7 (m, 2), 2.9 (broad singlet, 1), 3.7 (m, 2), 3.75 (s, 3), 5.8 (d, 1, J = 12 Hz), and 6.3 (doublet of triplets, 1, J = 8, 12 Hz); mass spectrum (M − H_2O *m/e* 140.

Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.29; H, 8.78.

4-Chloro-1-butanol. Using the procedure of Starr and Hixon,[22] 4-chloro-1-butanol was prepared in 26% yield as a clear liquid: bp 58–60° (2 mm) [lit.[22] 70–71° (7 mm)].

Ethyl-4-chlorobutylacetaldehyde Acetal (19). Modification of Eaton's procedure[10] was necessary to prepare ethyl-4-chlorobutylacetaldehyde acetal (**19**). To a mixture of 70 g (0.65 mol) of 4-chloro-1-butanol, which had been washed with saturated aqueous sodium bicarbonate and dried over anhydrous potassium carbonate, and 250 ml (2.6 mol) of ethyl vinyl ether was added 1.5 ml of trifluoroacetic acid. The resulting solution was stirred in an ice bath for 4 hr and stored in a refrigerator overnight. The trifluoroacetic acid was neutralized by the addition of 7 ml of triethylamine, and the excess ethyl vinyl ether was removed at reduced pressure. The residue was dissolved in 150 ml of ether and washed with water (1 × 100 ml). The ether solution was dried over anyhdrous magnesium sulfate, and the ether was removed at reduced pressure. Distillation of the residue gave 101 g (86% yield) of acetal **19** as a colorless liquid: bp 37–39° (0.1 mm); ir (neat) 8.8 (s), 9.15 (s), 9.4 (s), and 15.5 μ (m); nmr ($CDCl_3$) δ 1.18 (t, 3, J = 6 Hz), 1.38 (d, 3, J = 6 Hz), 1.8 (m, 4), 3.55 (m, 4), and 4.7 ppm (q, 1, J = 6 Hz).

Ethyl-4-lithiobutylacetaldehyde Acetal (20). To a vigorously stirred suspension of 215 cm (1.33 mol) of freshly washed lithium 1% sodium alloy wire cut into 0.5 cm lengths, in 600 ml of anhydrous ether, was added 2 ml of 1,2-dibromoethane, to clean the surface of the lithium metal. The suspension was cooled to −18° and 98 g (0.4 mol) of ethyl-4-chlorobutylacetaldehyde acetal (**19**) was added dropwise over 2 hr. When the addition was complete, stirring was continued at −18° for 2 hr. The precipitate was allowed to settle for 20 min, and the ether solution was filtered through a sintered glass disk by a positive pressure of argon. The solution was stored at −30° in a freezer. Immediately before use, the concentration of the organolithium was determined using the procedure of Watson and Eastham.[3]

A 2.0-ml aliquot of the ether solution was added to water. The aqueous solution was saturated with sodium chloride and extracted with ether (4 × 25 ml). The combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure to give a colorless liquid characterized as the ethylbutylacetaldehyde acetal: nmr ($CDCl_3$) δ 0.9 (t, 3, J = 6 Hz), 1.2 (t, 3, J = 6 Hz), 1.25 (d, 3, J = 6 Hz), 1.5 (m, 4), 3.5 (m, 4), and 4.7 ppm (q, 1, , J = 6 Hz).

Methyl 6-Carboxy-*cis*-hex-2-enoate (17). To a solution of 45.3 g (286 mmol) of methyl 7-hydroxy-*cis*-hept-2-enoate (**8**), in 473 ml of acetone, was added 400 ml of an aqueous solution of 65 g (650 mmol) of chromium trioxide and 49 ml of concentrated sulfuric acid, prepared by the procedure of Meinwald[24] over 1.5 hr. When the addition was complete, stirring was continued at room temperature for 1.5 hr. The excess chromic acid was destroyed by the addition of a saturated aqueous solution of sodium bisulfite, until the orange color was discharged. The organic layer was separated, and the aqueous layer was extracted with ether (3 × 150 ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (3 × 150 ml). The aqueous solution was acidified with concentrated hydrochloric acid and extracted with ether. The ether extracts were dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure, to give 33.8 g (69% yield) of the acid **17** as a light yellow oil; ir (neat) 3.0 (s), 5.85 (s), 6.1 (m), 8.4 (s), and 12.2 μ (w); nmr ($CDCl_3$) δ 1.78 (m, 2), 2.4 (t, 2, J = 8 Hz), 2.7 (m, 2), 3.6 (s, 3), 5.9 (d, 1, J = 12 Hz), 6.15 (doublet of triplets, 1, J = 8 and 12 Hz), and 11.2 ppm (broad singlet, 1).

Methyl 7-Chloro-7-keto-*cis*-hept-2-enoate (18). To a solution of 33.7 g (0.196 mol) of methyl 6-carboxy-*cis*-hex-2-enoate (**17**), in 400 ml of dry benzene, was added 27.0 ml (0.305 mol) of freshly distilled oxalyl chloride. The resulting solution was stirred overnight at room temperature. The benzene was removed at reduced pressure (40 mm). Two 50-ml protions of dry benzene were added then removed at reduced pressure to ensure that no traces of oxalyl chloride remained. Without further purification, the acid chloride **18** was used in the next step: ir (neat) 5.55 (s), 5.85 (s), 61. (w), 8.3 (s), and 12.25 μ (w).

To a small sample of the acid chloride **18** was added methanol. The methanol was removed at reduced pressure to give a light yellow diester: nmr ($CDCl_3$) δ 1.7 (quintet, 2, J = 7 Hz), 21. (m, 2), 2.5 (m, 2), 3.05 (s, 3), 3.10 (s, 3), 5.5 (d, 1, J = 12 Hz), and 5.9 ppm (doublet of triplets, 1, J = 8, 12 Hz).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.96; H, 7.90.

Methyl 11-Hydroxy-7-keto-*cis*-undec-2-enoate (9). An adaptation of the Posner[12] procedure was used to prepare ketone **9**. To a suspension of 40 g (0.21 mol) of purified cuprous iodide[25] and 350 ml of anhydrous ether was added 78.0 ml (0.425 mmol) of hexamethylphosphorus triamide.[26] The resulting solution was stirred at room temperature for 30 min and was then cooled to −78°. To the cooled solution was added 450 ml (0.42 mol) of a 0.92 *M* ether solution of the organolithium reagent **20**. The resulting yellow solution was warmed to −50° and stirred for 2 hr. The solution was recooled to −78° and, by means of a Dry Ice cooled dropping funnel, was added to an ether solution of acid chloride **18**, which had just been prepared from 0.190 mol of **17**. When the addition was complete, stirring was continued at −78° for 30 min. The excess copper reagent was quenched by the addition of 45 ml of anhydrous methanol, warming to −30°, and siphoning the ether solution into 1.0 l. of saturated aqueous ammonium chloride. The ether layer was separated and added to 1.0 l. of cold 2% aqueous sulfuric acid. This produced a fluffy white precipitate. The solid was filtered through Celite, and the ether layer was separated from the filtrate. The ether solution was washed with saturated aqueous sodium bicarbonate (2 × 150 ml). The ether solution was dried over anhydrous magnesium sulfate, and the ether was removed at reduced pressure, to give crude ketone **21** as a yellow oil.

Water was added to a solution of the crude ketone **21** in 300 ml of tetrahydrofuran until the first sign of turbidity, then 6 drops of concentrated hydrochloric acid were introduced. The solution was stirred at room temperature for 4 hr. The tetrahydrofuran was removed at reduced pressure, and the hydrochloric acid was neutralized with solid sodium bicarbonate. The aqueous solution was extracted with methylene chloride (1 × 300 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure, to give 36.3 g of keto alcohol **9** in an 83.5% yield from acid **17**: ir (neat) 2.9 (m), 5.8 (s), 6.1 (w), 8.3 (s), 8.5 (s), and 12.2 μ (w); nmr ($CDCl_3$) δ 1.6 (m, 6), 2.4 (m, 4), 2.6 (m, 2), 3.2 (broad singlet, 1), 3.6 (m, 2), 3.7 (s, 3), 4.7 (d, 1, J = 12 Hz), and 6.1 ppm (doublet of triplets, 1, J = 8, 12 Hz); mass spectrum (M − H_2O) *m/e* 210.

A sample of **9** was collected from a gas chromatograph, using a 2 ft, 0.5 in. diameter column, packed with 15% silicone rubber on 60–80 mesh Chromasorb W, and heated to 180°, for elemental analysis. The results of the elemental analysis were far from being accurate. By nmr spectroscopy the predominant component of the collected material was the dihydropyran **23**: nmr ($CDCl_3$) δ 1.4–2.2 (m, 8), 2.7 (m, 2), 3.7 (s, 3), 4.0 (t, 1, J = 5 Hz), 4.55 (t, 1, J = 4 Hz), 5.8 (d, 1, J = 12 Hz), and 6.2 ppm (doublet of triplets, 1, J = 8, 12 Hz).

Methyl 11-Hydroxy-7-keto-*cis*-undec-2-enoate Methanesulfonate (24a). Using the procedure of Crossland[13] the methane-

sulfonate **24a** was prepared. To a solution of 35.8 g (0.157 mol) of the alcohol **9** and 40 ml (0.29 mol) of freshly distilled triethylamine, in 500 ml of methylene chloride which was cooled to −15°, was added dropwise 14.5 ml (0.191 mole) of freshly distilled methanesulfonyl chloride. When the addition was complete, stirring was continued at −15° for 30 min. The methylene chloride solution was washed with cold water (2 × 150 ml), saturated aqueous sodium bicarbonate (2 × 150 ml), and saturated aqueous sodium chloride (2 × 150 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure, to give 41.6 g (87% yield) of the methanesulfonate **24a** as a red oil: ir (neat) 5.8 (s), 6.1 (w), 7.4 (m), 8.35 (s), 8.5 (s), and 12.2 μ (w); nmr ($CDCl_3$) δ 1.3–2.0 (m, 6), 2.3–2.8 (m, 6), 3.05 (s, 3), 3.7 (s, 3), 4.3 (t, 2, J = 6 Hz), 4.9 (d, 1, J = 12 Hz), and 6.3 ppm (doublet of triplets, 1, J = 8, 12 Hz).

Methyl 11-Bromo-7-keto-*cis*-undec-2-enoate (24b). A mixture of 41.0 g (134 mmol) of the methanesulfonate **24a** and 60 g (690 mol) of -anhydrous lithium bromide, in 500 ml of acetone, was refluxed overnight. The solid was removed by filtration, and the acetone was removed at reduced pressure. The residue was taken up in 250 ml of methylene chloride and washed with water (2 × 150 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure to give 37.7 g (97% yield) of the bromide **24b** as an orange oil: ir (neat) 5.8 (s), 6.1 (w), 8.3 (s), 8.5 (s), and 12.2 μ (w); nmr ($CDCl_3$) δ 1.4–2.0 (m, 6), 2.2–2.8 (m, 6), 3.4 (t, 2, J = 6 Hz), 3.7 (s, 3), 5.8 (d, 1, J = 12 Hz), and 6.2 ppm (doublet of triplets, 1, J = 8, 12 Hz).

Methyl 11-Nitro-7-keto-*cis*-undec-2-enoate (10). Using the procedure of Kornblum,[14] the nitro compound **24c** was prepared. To a solution of 31 g (0.52 mol) of dry urea and 27 g (0.39 mol) of dry sodium nitrite, in 170 ml of freshly distilled dimethyl sulfoxide, was added dropwise 37.0 g (0.127 mol) of bromide **24b.** When the addition was complete, stirring was continued for 4 hr. The dimethyl sulfoxide solution was poured into 2 l. of ice–water and continuously extracted with ether for 24 hr. The ether solution was washed with water (2 × 100 ml) and dried over anhydrous magensium sulfate, and the ether was removed at reduced pressure. The residue contained a mixture of the nitrite ester of alcohol **9,** the methyl ester of acid **17,** and the nitro compound **24c** which was determined by its nmr spectrum. Heating the mixture to 60° (0.03 mm) for 12 hr removed all of the nitrite ester and most of the methyl ester. The resulting orange oil (25.6 g) contained 85% of the nitro compound and 15% of the methyl ester of the acid **17,** which was determined by the integration of the methyl ester singlet at δ 3.6 ppm relative to the triplet at δ 4.4 ppm, characterized as the methylene protons adjacent to the nitro group in **10:** ir (neat) 5.8 (s), 6.1 (w), 6.4 (s), 8.3 (s), 8.5 (s), and 12.2 δ (w); nmr ($CDCl_3$) δ 1.2–2.0 (m, 6), 2.1–2.7 (m, 6), 3.7 (s, 3), 4.4 (t, 2, J = 6 Hz), 5.9 (d, 1, J = 12 Hz), and 6.3 ppm (doublet of triplets, 1, J = 8, 12 Hz).

Attempted separation of a small portion of the mixture for elemental analysis by preparative layer chromatography, using silic gel as absorbent, and a 75:25 mixture of methylene chloride and hexane as elutents, failed.

Methyl Octahydro-1*H*-cyclopent[3,4]isoxazolo[2,3-*a*]pyridine-*endo*-4-carboxylate (25). To a solution of 1.23 g (4.76 mmol) of the nitro compound (**10**) obtained in the previous experiment, in 70 ml of 25% aqueous methanol containing 0.38 g (7.1 mmol) of ammonium chloride, was added 2.0 g of freshly activated zinc dust. The suspension was stirred at room temperature for 4.5 hr. The zinc salts were removed by filtration and washed with hot 50% aqueous methanol (2 × 50 ml). The methanol was removed at reduced pressure. The aqueous solution was saturated with solid sodium chloride and extracted with methylene chloride (5 × 50 ml). The methylene chloride solution was washed with 10% aqueous hydrochloric acid (3 × 20 ml) and dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure, to give 0.357 g of a neutral yellow oil. The aqueous solution was basified with solid sodium bicarbonate, saturated with solid sodium chloride, and extracted with methylene chloride (5 × 30 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure, to give 0.62 g (51% yield) of adduct **25** as a light yellow oil: ir (neat) 5.7 (s), 6.95 (m), 8.35 (s), and 9.4 μ (m); nmr spectrum ($CDCl_3$) 1.1–2.1 (m, 12), 2.7–3.4 (m, 3), 3.72 (s, 3), 4.72 ppm (d, 1, J = 8.5 Hz); mass spectrum (70 ev) m/e (rel intensity) 225 (24), 182 (6), 167 (12), 166 (100), 138 (27), 124 (28), 113 (53), 97 (11).

The methiodide of adduct **25** was prepared by the addition of 1.0 ml (16 mmol) of methyl iodide to a small amount of the adduct **25.** The resulting solid was recrystallized from ethanol–ether to give a hydroscopic white solid, mp 167–168°. Even though a small sample of the methiodide was dried at 80° (0.05 mm) for 12 hr, the results of the elemental analysis suggested that the white solid contained water.

Octahydro-7-hydrocyclopent[*i*]indolizin-6(7*H*)-one (26). To a solution of 0.306 g (1.36 mmol) of adduct **25,** in 5 ml of 50% aqueous acetic acid, was added 1.0 g (15 mmol) of zinc dust. The mixture was heated at 70° for 24 hr. The remaining zinc metal was removed by filtration and washed with hot water (*ca.* 70°). The filtrate was basified with solid sodium carbonate, saturated with solid sodium chloride, and continuously extracted with methylene chloride for 24 hr. The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure. Recrystallization of the resulting solid from hexane–ether gave 0.207 g (78% yield) of a white solid: mp 99–100°; ir (KBr) 3.0 (s), 5.95 (s), and 6.9 μ (s); nmr ($CDCl_3$) 1.2–D.1 (m, 12), 2.00 (m, 1), 2.74 (bt, 2, J = 7 Hz), 4.1 (d, 1, J = 5 Hz), 5.3 ppm (bs, 1); mass spectrum (70 ev) m/e (rel intensity) 195 (51), 167 (13), 166 (75), 153 (87), 152 (100), 138 (30), 125 (32), 124 (14).

Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17. Found: C, 67.38; H, 8.77; N, 7.07.

Attempted Isomerization of Methyl Octahydro-1*H*-cyclopent[3,4]isoxazolo[2,3-*a*]pyridine-*endo*-4-carboxylate (25). Trial A. A solution of 184 mg (0.815 mmol) of the adduct **25,** in 50 ml of toluene, was refluxed under a constant stream of argon for 7 hr. The toluene solution was cooled and extracted with cold 10% aqueous hydrochloric acid (3 × 25 ml). The aqueous solution was basified with solid sodium bicarbonate, saturated with solid sodium chloride, and extracted with methylene chloride (4 × 25 ml). The methylene chloride solution was dried over anhydrous magnesium sulfate, and the methylene chloride was removed at reduced pressure to give 134 mg of a light yellow oil whose nmr spectrum was identical with that of the starting material **25.**

Trial B. A solution of 0.30 g (1.3 mmol) of adduct **25,** in 60 ml of xylene, was refluxed under a constant stream of argon for 8 hr. The reaction product was isolated as in trial A to give 0.28 g of a yellow oil. The nmr spectrum of the yellow oil appeared identical with the starting material except for a small shoulder on the methyl ester singlet at δ 3.75 ppm.

Trial C. A solution of 0.265 g (1.18 mmol) of the adduct **25,** in 70 ml of xylene, was refluxed under a constant stream of argon for 30 hr. The reaction product was isolated as in trial A to give 0.222 g of a brown oil. The nmr spectrum of the brown oil showed the appearance of a distinguishable doublet at δ 4.1 ppm. The mixture was separated by preparative layer chromatography, using silica gel as the adsorbent and a 50:50 mixture of hexane and methylene chloride as elutents, to give two fractions. The major component gave 126 mg of a light yellow oil whose nmr and ir spectra were identical with those of starting material **25.** The minor component gave 30 mg of a light yellow oil which was assigned the structure methyl octahydro-1*H*-cyclopent[3,4]isoxazolo[2,3-*a*]pyridine-*exo*-4-carboxylate (**27**): ir (neat) 5.7 (s), 6.95 (m), 7.9 (m), and 8.15 μ (s); nmr ($CDCl_3$) 1.1–2.0 (m, 12), 2.70 (m, 1), 3.17 (m, 2), 3.89 (s, 3), 4.18 (d, 1, J = 6 Hz); mass spectrum (70 ev) m/e (rel intensity) 225 (14), 187 (18), 166 (34), 138 (21), 124 (100), 113 (42), 97 (9).

Registry No.—**8,** 52500-23-9; **9,** 52571-11-6; **10,** 52500-24-0; **11,** 100-72-1; **12,** 18420-41-2; **13,** 928-90-5; **14,** 1720-37-2; **15,** 52500-25-1; **16,** 52500-26-2; **17,** 52500-27-3; **18,** 52500-28-4; **19,** 52500-29-5; **20,** 52500-30-8; **21,** 52500-31-9; **24a,** 52500-32-0; **24b,** 52500-33-1; **25,** 52611-61-7; **25** methiodide, 52555-45-0; **26,** 52500-34-2; **27,** 52500-35-3; 4-chloro-1-butanol, 928-51-8; methyl 6-carbomethoxy-*cis*-hex-2-enoate, 52500-36-4.

References and Notes

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(2) (a) J. W. Daly, I. L. Karle, C. W. Meyers, T.Tokuyama, J. A. Waters, and B. Witkop, *Proc. Nat. Acad. Sci. U.S.*, **68,** 1870 (1971); (b) E. X. Albuquerque, E. A. Barnard, T. H. Chiu, A. J. Lapa, J. O. Dolly, S. E. Jansson, J. Daly, and B. Witkop, *ibid.*, **70,** 949 (1973); (c) I. L. Karle, *J. Amer. Chem. Soc.*, **95,** 4036 (1973).

(3) (a) R. Huisgen, *Angew. Chem., Int. Ed. Engl.*, **2,** 565, 633 (1963); (b) J. Hamer and A. Macaluso, *Chem. Rev.*, **64,** 473 (1964); (c) L. I. Smith, *ibid.*, **23,** 193 (1938); G. R. Delpierre and M. Lamchen, *Quart. Rev., Chem. Soc.*, 329 (1965).

(4) N. A. LeBel, N. D. Ojha, J. R. Menke, and R. J. Newland, *J. Org. Chem.*, **37,** 2896 (1972), and references cited therein.

(5) J. J. Tufariello and J. P. Tette, *Chem. Commun.*, 469 (1971).

(6) (a) J. B. Bapat, D. St. C. Black, R. F. C. Brown, and C. Ichlor, *Aust. J. Chem.*, **25**, 2445 (1972); (b) J. J. Tufariello and E. J. Trybulski, *Chem. Commun.*, 720 (1973).
(7) (a) L. A. Brooks and H. R. Snyder, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N.Y., 1953, p 689; (b) M. A. Dmitriev, *Zh. Obshch. Khim.*, 931 (1964); *Chem. Abstr.*, **61**, 5501b (1962).
(8) E. R. Jones, E. Eglington, and W. C. Whiting, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N.Y. 1963, p 755.
(9) H. Lindlar, *Helv. Chim. Acta*, **35**, 466 (1952).
(10) P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37**, 1947 (1972).
(11) L. J. Loeffler, S. F. Britcher, and W. Baumgarten, *J. Med. Chem.*, 13, 926 (1970).
(12) G. H. Posner, C. E. Whitten, and P. E. McFarland, *J. Amer. Chem. Soc.*, **94**, 5106 (1972).
(13) R. K. Crossland and K. L. Sevis, *J. Org. Chem.*, **35**, *3195 (1970)*.
(14) N. Kornblum, H. C. Larson, R. K. Blackwood, D. D. Mooberry, E. P. Oliveto, and E. E. Graham, *J. Amer. Chem. Soc.*, **78**, 1497 (1956).
(15) G. R. Delpierre and M. Lamchem, *J. Chem. Soc.*, 386 (1960).
(16) (a) R. Huisgen, H. Houk, R. Grashley, and H. Seidl, *Chem. Ber.*, **101**, 2568 (1968); (b) R. Huisgen, H. Seidl, and I. Bruning, *ibid.*, **102**, 1102 (1969).
(17) B. G. Murray and A. F. Turner, *J. Chem. Soc. C*, 1338 (1966).
(18) J. J. Tufariello, J. P. Tette, and E. J. Trybulski, unpublished results.
(19) N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, **93**, 1637 (1971).
(20) P. v. R. Schleyer, K. R. Blanchard, and C. P. Woody, *J. Amer. Chem. Soc.*, **85**, 1358 (1963).
(21) L. I. Zakharkin, V. I. Stanko, and V. A. Brattsev, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 931 (1964); *Chem. Abstr.*, **61**, 5501b (1964).
(22) D. Starr and R. M. Hixon, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N.Y., 1943, p 571.
(23) S. Watson and J. Eastham, *J. Organometal. Chem.*, **9**, 165 (1969).
(24) J. Meinwald, J. Crandall, and W. E. Hymans, *Org. Syn.*, **45**, 77 (1965).
(25) G. B. Kauffman and L. A. Terer, *Inorg. Syn.*, **7**, 9 (1963).
(26) E. J. Corey and D. Beames, *J. Amer. Chem. Soc.*, **94**, 7210 (1972).

Total Synthesis of β-Lactam Antibiotics. VI. 3-Arylcephalosporins[1]

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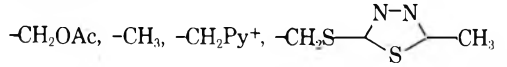
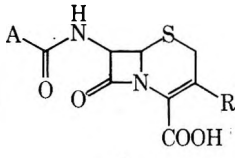
The total synthesis of *dl*-3-phenyl-, 3-*p*-carbomethoxyphenyl-, and 3-(4-thiazolyl)-7β-(2-thienyl)acetamidodecephalosporanic acids **12a–c** is described.

Cephalosporins **1** are a class of semisynthetic antibiotics that are being increasingly used because of their breadth of spectrum, potency, acid stability, and high degree of tolerance by man. In recent years an intensive worldwide effort has been made to obtain modified cephalosporins with improved properties.[2] Variations at the 3 position have been particularly fruitful, resulting in clinically useful drugs having such diverse substituents R as



Many other modifications have also been reported, the vast majority of which have $-CH_2X$ as the 3 substituent,[2,3] although R = H has also been reported.[4]



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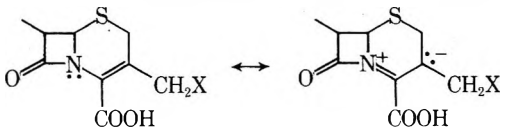
It is believed that resonance of type **2** plays a role in the bioactivity of cephalosporins, since electronegative groups X increase potency, and Δ^2-cephalosporins are inactive.[2]



2

However, the activity of 3-methylcephems such as cephalexin (X = H) shows that X^- does not have to depart during the bioactive event. Furthermore, a theoretical study also concluded that during thiolation of cephalosporins at the β-lactam carbonyl, negative charge tends to accumulate at C-3 but that the CH_2–X bond does not break.[5]

For these reasons it seemed worthwhile to prepare cephems bearing aromatic rings directly attached to C-3. At the inception of this project, there was no known way to do this by partial synthesis.[6] However, the total synthesis recently developed in these laboratories[7] has the capability of great variation in the 3 substituent, and this route (Scheme I) was therefore chosen for the preparation of 3-aryl cephems.

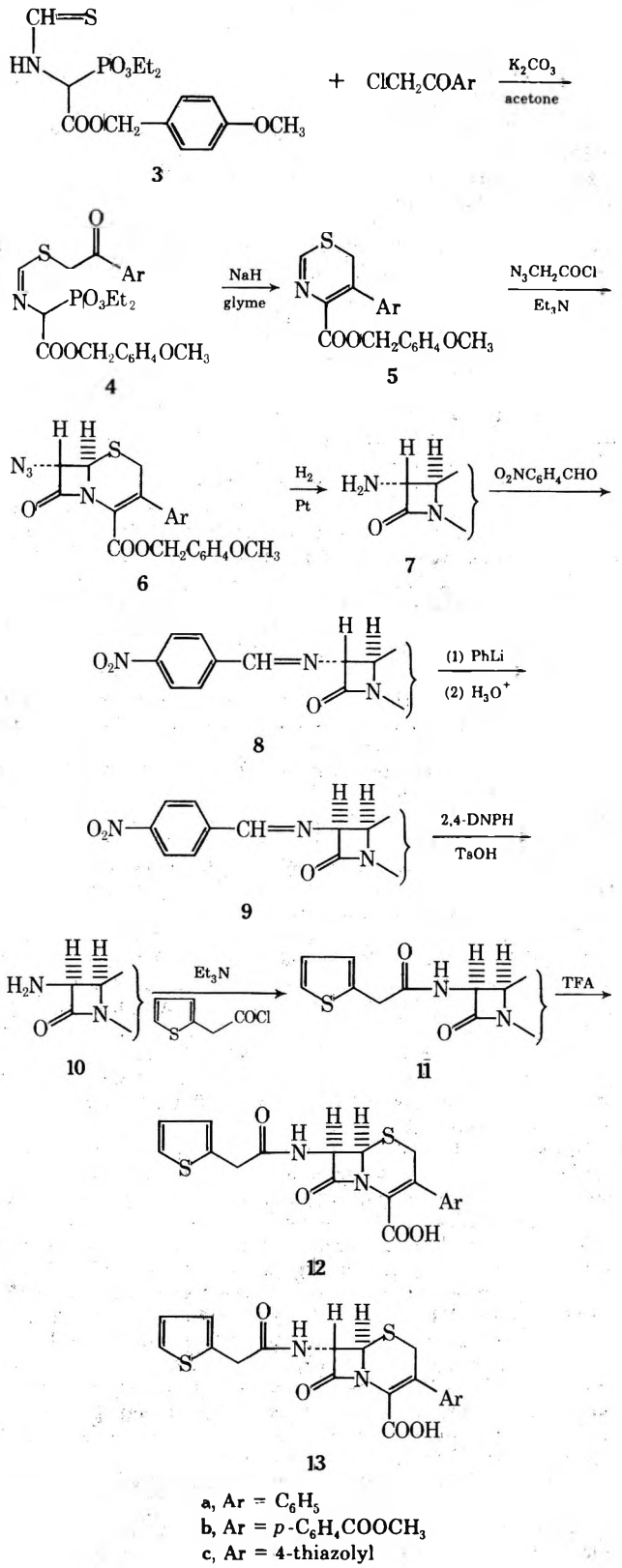
The alkylation of thioamide **3**[7] with phenacyl chloride and cyclization of **4a** to the thiazine **5a** were best done sequentially, with isolation of **4a.** When more than 1 equiv of K_2CO_3 was used with phenacyl chloride as had previously been done with 1-chloro-3-acetoxy-2-propanone,[7] extensive decomposition occurred. Phenacyl bromide could be used in place of the chloride, but in addition to **4a** it gave an isomer, presumably trans. Both isomers were stable to interconversion in refluxing $CDCl_3$.

Many conditions were tried for the cyclization of **4a** to **5a,** including K_2CO_3–acetone,[7] $KHCO_3$–acetone, Et_3N–$CHCl_3$, PhLi–THF, NaH–THF, LDA–THF, and NaH–glyme. Of these, the latter gave the cleanest product and was used in all subsequent work.

Cycloaddition of azidoacetyl chloride to **5a** gave cephem **6a,** sometimes containing the Δ^2 isomer, which was formed from **6a** with catalysis by triethylamine. The isomers were separable by chromatography, but with care the problem was avoidable altogether.

The stereochemistry of **6a** was established as trans by the coupling constant of 1.5 Hz for H-6 and H-7, in accord with previous observations[7] as well as our own subsequent examples. Since all naturally occurring cephalosporins and penicillins have cis stereochemistry, and trans compounds are inactive, it was necessary to epimerize the 7 substituent. This could not be done by simple equilibration because the trans isomers are generally the more stable ones, and so our procedure based upon steric approach control was used.[8] Azidocephem **6a** was reduced to amine **7a,** which was converted to its Schiff base **8a** with *p*-nitrobenzaldehyde. Formation of the 7 anion with phenyllithium, activation with DMF, and then acidification under kinetically controlled conditions, which occurs preferentially from the less hindered side, provided the cis Schiff base **9a** with the natural configuration at C-7, along with recovered **8a,** in a 2:1 ratio.

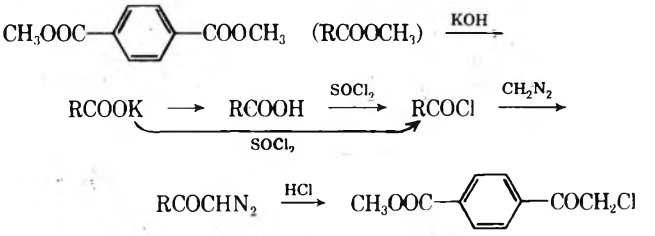
Scheme I



a, Ar = C_6H_5
b, Ar = p-$C_6H_4COOCH_3$
c, Ar = 4-thiazolyl

The steps **9a** → **12a** were done in the usual manner,[7,8] providing totally synthetic *dl*-3-phenyl cephem **12a**. It contained some 7-epi isomer **13a** carried through from the epimerization and some Δ^2 formed during thienylacetylation, but these, being inactive, did not interfere with the bioassay.[9]

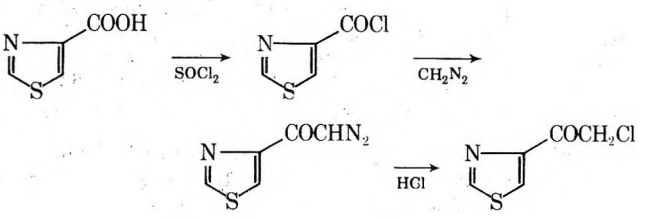
With the expectation that an additional electron-withdrawing group would increase bioactivity, the p-carbomethoxyphenyl cephem **12b** was also synthesized. The required p-carbomethoxyphenacyl chloride was prepared by the sequence below.



Our mp for the acid chloride, 50–55°, was different from that reported,[10] 130°; so we prepared it by an alternate route to be secure.

The sequence of Scheme I was repeated, starting with **3** and p-carbomethoxyphenacyl chloride. The reactivity of the latter was much greater than that of phenacyl chloride, forming **4b** in minutes instead of hours. The epimerization of **8b** gave a normal:epi ratio (**9b:8b**) of only about 1:1, not separable at the **11b** stage, so that the final product *dl*-**12b** contained also **13b** in about a 1:1 ratio.[9] Isomerization to Δ^2 was less than in the phenyl series, and in other respects the sequence was done in the same way as before.

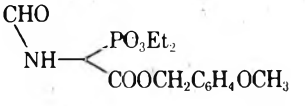
To provide an example of a 3-heteroaryl cephem, the 4-thiazolyl analog **12c** was made by the same route. The required chloromethyl 4-thiazolyl ketone was prepared from the acid as before.



The pathway of Scheme I was again followed, furnishing *dl*-**12c**[9] which was free of both Δ^2 isomer and **13c**.

In all three syntheses, the yields of thiazines **5a–c** were critically dependent on the purity of **3**, which must be carefully chromatographed even though this does not change the ir or nmr spectra. We believe that crude **3**, which is made from the amino compound by thioformylation in liquid H_2S, contains some form of active sulfur because sulfides of the type $(ArCOCH_2)_2S$ (**14**) have been obtained from poor preparations of **5**.

An unexpected transformation occurred on compounds **4a** and **4c**. On several days' standing, they were transformed into the formamide **15**. We do not know the path-



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way of this reaction, or the fate of the other fragment of the molecule.

A final point of interest concerns the conformation of the 3-aryl substituents. The phenyl and p-carbomethoxyphenyl groups have hydrogen atoms on both carbons adjacent to the point of attachment, which project in the plane of the ring and prevent it from becoming planar with the thiazine ring, in all compounds from **5a,b** to **12a,b**. On the other hand, the thiazole ring has only one such hydrogen, which is apparently not sufficient to prevent it from enjoying planarity, and thus conjugation, with the thiazine ring in **5c–12c**. We infer this from the nmr spectra on these grounds. In the **a** and **b** series relative to the **c** series, SCH_2, OCH_2Ar, and the two hydrogens in $CH_2C_6H_4OCH_3$ ortho

to CH_2 appear *ca.* 0.2 ppm upfield. In the thiazolyl series, the latter two chemical shifts are about the same as those of the corresponding 3-alkyl compounds, showing that the protons in question are in the shielding cone of the phenyl rings in the **a** and **b** series.

The preparation of other totally synthetic β-lactam antibiotics will be reported in due course.

Experimental Section

Nmr spectra were taken on a Varian T-60; ir spectra were taken on a Perkin-Elmer Infracord.

Preparation of 4a–c. A mixture of 77 mg (0.2 mmol) of **3,** 32 mg of phenacyl chloride (0.2 mmol), 29 mg of ground K_2CO_3, and 2 ml of acetone was stirred 18 hr at 25° under N_2, filtered, and evaporated, affording 111 mg of crude **4a,** suitable for further reactions: 112% wt yield; ir (film) 5.72 (ester), 5.93 (COPh), 6.20, 6.28 μ (Ar, C=N); nmr ($CDCl_3$) δ 1.20 (t, J = 7 Hz, CH_2CH_3), 3.79 (s, OCH_3), 4.08 (d of q, J_{HP} = 8 Hz and J = 7 Hz, CH_2CH_3), 4.56 (s, SCH_2), 4.69 (d, J_{HP} = 21 Hz, CHP), 5.16 (s, OCH_2Ar), 6.9 (d, J = 9 Hz), 7.3 (d, J = 9 Hz, C_6H_4), 7.5, 8.0 (m, C_6H_5), 8.49 (d, J_{HP} = 4 Hz, CH=N). When this reaction was done using 53 mg of phenacyl bromide, 37 mg of K_2CO_3, 100 mg of **3,** and 2 ml of acetone (0.267 mmol scale), nmr showed two products. From plc on silica gel with 4:1 $CHCl_3$–EtOAc was obtained 35 mg of **4a** and 34 mg of an isomer, ir similar to **4a,** nmr similar except for CH=N at δ 9.06 (d, J_{HP} = 4 Hz), mass spectrum 493. The nmr spectra of **4a** and its isomer did not change after brief boiling in $CDCl_3$.

Compound **4b** was prepared by the same procedure but with only 25 min reaction time. The ir was similar to that of **4a** with an added $COOCH_3$ at 5.78 μ, and the nmr was also similar, with an added $COOCH_3$ at δ 3.98.

Compound **4c** was best prepared by a slightly modified procedure, using a threefold excess of K_2CO_3 and stirring 1 hr. After filtering, evaporating, and flushing with benzene, the crude **4c** was ready for the next step. The ir and nmr spectra resembled those of **4a,** lacking the C_6H_5 bands and with additional ones at δ 8.31 and 8.85 (m, thiazolyl).

Cyclization of 4a–c to 5a–c. Crude **4a,** prepared as above from 77 mg of **3,** was dissolved three times in glyme and evaporated and then treated 5 min in 1 ml of glyme with 1 equiv of NaH (10 mg of 50% NaH in oil, washed twice with hexane to remove oil) suspended in 1 ml of glyme. The reaction mixture was diluted with 10 ml of benzene, washed with water, dried with $MgSO_4$, filtered, and evaporated. Weight yields of crude **5a** generally ran >100%. Purification by chromatography was not successful, but crude **5a** was suitable for cycloaddition. The ir showed only ester carbonyl at 5.78 μ: nmr ($CDCl_3$) δ 3.58 (s, SCH_2), 3.76 (s, OCH_3), 4.93 (s, OCH_2), 6.71 (d, J = 9 Hz), 6.80 (d, J = 9 Hz, C_6H_4), 7.25 (s, C_6H_5), 8.30 (s, CH=N); mass spectrum 339.

Compound **5b** was made as above: ir 5.80 μ; nmr ($CDCl_3$) δ 3.60 (s, SCH_2), 3.81 (s, OCH_3), 3.97 (s, $COOCH_3$), 4.98 (s, OCH_2), 6.78 (d, J = 9 Hz), 6.96 (d, J = 9 Hz, $C_6H_4OCH_3$), 7.27 (d, J = 8 Hz, $C_6H_4COOCH_3$), 8.40 (s, CH=N); mass spectrum 397. Crude yield >100%, 30% of crystalline **5b,** mp 144–6° from 1:1 benzene–cyclohexane.

Compound **5c** was prepared similarly, ~100% crude yield, 39% crystalline, mp 134° from benzene–cyclohexane: ir 5.79 μ; nmr ($CDCl_3$) δ 3.84 (s, OCH_3), 5.22 (s, OCH_2), 6.91 (d, J = 9 Hz), 7.27 (d, J = 9 Hz, C_6H_4), 8.43 (s, CH=N), 7.3 (d, J = 2 Hz), 8.75 (d, J = 2 Hz, thiazolyl); mass spectrum 346.

Cycloaddition of Azidoacetyl Chloride[12] to 5a–c Forming 6a–c. Crude **5a** prepared from 0.25 mmol of **3,** in 2 ml of CH_2Cl_2, was treated with 0.139 ml (1 mmol) of Et_3N. Then, under N_2, 0.033 ml of azidoacetyl chloride (0.37 mmol) in 2 ml of CH_2Cl_2 was added at 0° over 30 min. The mixture was allowed to warm to 25°, diluted with 30 ml of benzene, washed successively with pH 3 aqueous phosphate, water, and aqueous K_2HPO_3, dried with $MgSO_4$, filtered, and evaporated, leaving 106 mg of crude cephem **6a.** This was chromatographed on 5 g of silica gel (E. Merck's) with 10:1 $CHCl_3$–EtOAc, providing 28.5 mg (27%) of pure **6a:** ir (film) 4.73 (azide), 5.61 (β-lactam), 5.79 μ (ester); nmr ($CDCl_3$) δ 3.66 (s, SCH_2), 4.59, 4.70 (d's, J = 1.5 Hz, H-6 and -7), other peaks correct; mass spectrum 422, 394.

Crystalline **5b** was similarly treated with 4 equiv of Et_3N and 2 equiv of azidoacetyl chloride, affording 130 mg of crude (83%) and 29 mg of crystalline cephem **6b.** Chromatography of the crude gave 33 mg more **6b,** 40% total: ir like **6a;** mass spectra 480, 452; nmr ($CDCl_3$) δ 3.63 (s, SCH_2), 4.62, 4.70 (d's, J = 1.5 Hz, H-6 and -7), other peaks correct.

Crystalline **5c** similarly gave, after chromatography, 28% of **6c:** ir like **6a,b;** mass spectrum 429, 401; nmr ($CDCl_3$) δ 3.81 (s, SCH_2 and OCH_3), 4.67, 4.73 (d's, J = 1.5 Hz, H-6 and -7), other peaks correct.

Caution! Vigorous explosions have been reported[13] during the preparation of azidoacetyl chloride. Using a modified procedure[14] we have had no trouble, but we urge the greatest caution in making and handling this compound.

Hydrogenation of 6a–c to 7a–c. Azidocephem **6a,** 170 mg, was hydrogenated in 25 ml of benzene with 170 mg of PtO_2 for 45 min at 40 psi, filtered through a bed of Supercel and evaporated, affording 101 mg of **7a,** 63%: ir (film) 5.66, 5.78 μ; nmr ($CDCl_3$) δ 2.0 (m, NH_2), 3.59 (s, SCH_2), 4.16, 4.52 (d's, J = 1.5 Hz, H-6 and -7), other peaks correct. Also present was the Δ^2 isomer, nmr ($CDCl_3$) δ 4.26 (d, J = 1 Hz, H-7), 5.51 (m, H-6), 6.45 (d, J = 1.5 Hz, SCH=).

Likewise **6b** was reduced to **7b,** 67%: ir (film) 2.9, 5.65, 5.78 μ; mass spectrum 454; nmr ($CDCl_3$) δ 2.3 (m, NH_2), 3.60 (s, SCH_2). 4.24, 4.58 (d's, J = 2 Hz, H-6 and -7), other peaks correct.

Similarly **6c** gave 56% **7c:** ir (film) 2.9, 5.64, 5.77 μ; mass spectrum 403; nmr ($CDCl_3$) δ 2.25 (m, NH_2), 3.80 (s, SCH_2), 4.30, 4.60 (d's, J = 2 Hz, H-6 and -7), other peaks correct.

Preparation and Epimerization of Schiff Bases 8a–c to 9a–c. Compounds **7a–c,** *ca.* 2.5% in CH_2Cl_2, were treated 2 hr with 1 equiv of *p*-nitrobenzaldehyde in the presence of $MgSO_4$, filtered, and evaporated, providing 7α-Schiff bases **8a–c.** Excess of $MgSO_4$ should be avoided. Epimerization was done by the published procedure,[8] giving mixtures of **8a–c** and the 7β-Schiff bases **9a–c** in these ratios: **9a:8a,** 2:1; **9b:8b,** 1:1; **9c:8c,** 1:1. Epimerization was gauged by comparing in the nmr the CH=N peaks, δ 8.55 for 7α and δ 8.75 for 7β.

9a–c → 10a–c → 11a–c. Deblocking of epimerized Schiff bases **9a–c** and thienylacetylation of amines **10a–c** were done as before.[8] The crude amines were checked by ir only (similar to **7a–c**) and carried forward without purification. Esters **11a–c** were isolated by chromatography on silica gel (E. Merck, 70–230 mesh) in weight ratios of about 30:1, 40:1, and 50:1 respectively, eluting with 10:1 chloroform–ethyl acetate, and the single-spot products had R_f's of about 0.3, 0.2, and 0.3, respectively, on tlc in the same system. Compound **11a** had ir (film) 3.06 (NH), 5.62 (β-lactam), 5.77 (ester), 5.97 μ (amide); nmr ($CDCl_3$) δ 3.59 (s, SCH_2), 3.79 (s, OCH_3), 3.82 (s, CH_2C=O), 4.90 (s, OCH_2), 4.97 (d, J = 4 Hz, H-6), 5.87 (d of d, J = 4, 8 Hz, H-7), other peaks correct; mass spectrum 520, 340. Compound **11b** had ir (film) 3.0, 5.61, 5.79, 5.95 μ; nmr ($CDCl_3$) δ 3.58 (s), 3.78 (s), 3.84 (s), 3.93 (s, $COOCH_3$), 4.92 (s), 4.99 (d, J = 4 Hz), 5.86 (d of d, J = 4, 8 Hz), *et al.;* mass spectrum 578, 397. Compound **11c** had ir (film) 3.04, 5.62, 5.80, 5.98 μ; nmr ($CDCl_3$) δ 3.72 (s, SCH_2), 3.81 (s, OCH_3), 3.88 (s, CH_2C=O), 5.07 (d, J = 4 Hz, H-6), 5.14 (s, OCH_2), 5.89 (d of d, J = 4, 8 Hz, H-7), *et al.;* mass spectrum 527, 347.

De-esterification of 11a–c to 12a–c. Samples of 20–25 mg of **11a–c** were taken up in 0.5 ml of anisole, cooled to 0°, and treated with 2.5 ml of trifluoroacetic acid for 4–5 min. Vacuum of <1 Torr was then applied while the sample warmed gradually to 30°; this removes first TFA, then anisole. Another 2.5 ml of anisole was added and pumped off to assure quantitative removal of TFA. The residue was taken up in a few ml of water containing excess $NaHCO_3$, washed 3 times with CH_2Cl_2, acidified with pH 2 phosphate, and extracted 3 times with AcOH-free EtOAc. The EtOAc was sometimes dried with $MgSO_4$, filtered, and evaporated to obtain the free acids **12,** or else re-extracted directly with water containing the calculated amount of $NaHCO_3$ and lyophilized to obtain **12a–c** as sodium salts. Samples of **12a–c** were treated with CH_2N_2 and sent for mass spectrum without purification.

Our general de-esterification procedure more recently is to treat one part ester with 2 parts anisole and 10 parts TFA for 2.0 min at 0° and work up as above. Sometimes good sodium salts are obtained simply by treating the residue with water containing the calculated amount of $NaHCO_3$, washing with CH_2Cl_2, and lyophilizing. Yields vary from 60 to 95%.

Compound **12a** had ir (film) 2.9–3.7, 5.60, 5.8, 6.0 μ; nmr (Na salt, D_2O) δ 3.70, (s, SCH_2), 3.92 (s, CH_2C=O), 4.63 (HDO), 5.15 (d, J = 4 Hz, H-6), 5.67 (d, J = 4 Hz, H-7), *et al.;* also δ 6.50 (broad s, SCH= of Δ^2 isomer). High resolution mass spectrum of Me ester, 414.0713; calcd for $C_{20}H_{18}N_2O_4S_2$, 414.0707. Compound **12b** had nmr (Na salt, D_2O) δ 3.68 (s), 3.88 (s, $COOCH_3$ and CH_2C=O), 4.68 (HDO), 5.16 and 5.67 (d's, J = 5 Hz), *et al.;* also δ 6.65 (m, SCH= of Δ^2 isomer). High resolution mass spectrum of Me ester, 472.0714; calcd for $C_{22}H_{20}N_2O_6S_2$ 472.076. Compound **12c's** Me ester had mass spectrum 421, 241, 208, 181.

***p*-Carbomethoxybenzoyl Chloride.** Following the published

procedure,[10] dimethyl terephthalate was saponified to the monopotassium salt monoester and converted to the monoacid chloride monoester with $SOCl_2$. The crystalline product had good ir and nmr spectra, but melted at *ca.* 50° instead of the reported 130°. Therefore another method was also used. To a solution of 21.4 g (0.11 mol) of dimethyl terephthalate in 100 ml of MeOH and 100 ml of ether was slowly added a solution of 5.6 g (0.1 mol) of KOH in 100 ml of MeOH and 5 ml of H_2O. After being stirred for 18 hr the mixture had pH 7 and a white precipitate which was filtered, dissolved in H_2O, filtered to clarify, and acidified to pH 2 with HCl. A white precipitate of monomethyl terephthalate appeared which was filtered, washed, and dried, 11.4 g, mp 218–220° (reported[15] 230°). One gram was refluxed 2 hr with 1.5 ml of $SOCl_2$ and evaporated, leaving a white powder, mp 50–55°, identical with the sample made by the first method: ir (Nujol) 5.63, 5.76 μ; nmr ($CDCl_3$) δ 3.98 (s, OCH_3), 8.15 (s, C_6H_4).

***p*-Carbomethoxydiazoacetophenone.** Diazomethane was made by adding 27.2 g of Diazald in 165 ml of ether to 6.34 g of KOH in 10 ml of H_2O and 31.5 ml of EtOH. Over 1 hr, the CH_2N_2 solution was added to 6 g of *p*-carbomethoxybenzoyl chloride in 200 ml of ether at 0°. The volume was reduced to *ca.* 150 ml and the crystalline product was filtered and dried, 4.3 g, mp 98–101°: ir ($CDCl_3$) 4.74, 5.79, 6.16 μ; nmr ($CDCl_3$) δ 3.95 (s, $COOCH_3$), 5.93 (s, CHN_2), 7.81, 8.09 (d's, J = 8 Hz, C_6H_4).

***p*-Carbomethoxyphenacyl Chloride.** The diazo compound, 4 g, was dissolved in 40 ml of AcOH and 4 ml of concentrated HCl. When effervescence ceased, 200 ml of H_2O was added, precipitating the product which was filtered, washed with water, and dried, 3.8 g, mp 144–7°: ir ($CDCl_3$) 5.79, 5.9 μ (sh); nmr ($CDCl_3$) δ 3.95 (s, $COOCH_3$), 4.70 (s, $COCH_2Cl$), 8.02, 8.07 (d's, J = 8 Hz, C_6H_4).

Thiazole-4-carbonyl Chloride. Thiazole-4-carboxylic acid, 0.97 g (0.01 mol), was refluxed with 10 ml of $SOCl_2$ for 90 min. The solution was evaporated and the residue flushed with benzene and recrystallized from 50 ml of hexane: mp 85–86.5°; ir ($CDCl_3$) 5.64 μ; nmr ($CDCl_3$) δ 8.59, 9.01 (d's, J = 2 Hz).

4-Diazoacetylthiazole. The acid chloride, 4.01 g (0.027 mol), was added to 680 ml of 0.1 *N* CH_2N_2 in ether (0.068 mol) at 0°. The reaction took *ca.* 5 min and was stirred 30 min at 0° and 30 min at 25°. The solution was partly concentrated, filtered to clarify, and evaporated to dryness, leaving 4.4 g of yellow solid which was washed with petroleum ether; mp 80–82°. It was recrystallized from ether–petroleum ether and then from ether, giving 1.8 g of pure product: ir ($CDCl_3$) 4.72, 6.17 μ; nmr ($CDCl_3$) δ 6.48 (s, $COCHN_2$), 8.27, 8.84 (d's, J = 2 Hz, thiazolyl).

4-Chloroacetylthiazole. The diazo compound, 3 g, was added at 0° to 50 ml of EtOH saturated with HCl. The mixture was stirred 5 min and evaporated to dryness. The solid was washed with a little ether, then stirred with pH 8 aqueous phosphate, and extracted 4 times with ether. The ether solution was dried with $MgSO_4$, filtered and evaporated, leaving 2.62 g of yellow solid, 83%; ir ($CDCl_3$) 5.85 μ; nmr ($CDCl_3$) δ 4.95 (s, $COCH_2Cl$), 8.40, 8.94 (m's, thiazolyl).

Sulfides 14a–c. From chromatography of cephems **6a–c** and crystallization of thiazines **5b,c** were obtained variable yields of **14a–c**, depending on the quality of 3. Compound **14a** had ir (film) 5.92 (sh), 5.97 μ; mass spectrum 302 [$(C_6H_5COCH_2)_2S_2$], 270, 237, 165, 152, 119, 105, 77. Compound **14b** had ir ($CHCl_3$) 5.80, 5.92, 5.97 μ; nmr ($CDCl_3$) δ 3.94 (s, $COOCH_3$), 3.97 (s, SCH_2), 7.98, 8.10 (d's, J = 8 Hz, C_6H_4); mass spectrum 386, 355, 353, 223, 178, 163, 135. Compound **14c**, in mixtures with cephem **6c**, had ir 5.93, 5.98 μ and a sample purified by tlc had mass spectrum 284, 158, 126, 112, 84.

Formamide 15. On standing for several days, **4a** and (more rapidly) **4c** were transformed into **15**: ir (film) 3.1–3.2, 5.74, 5.96 μ; nmr ($CDCl_3$) δ 5.30 (d of d, J_{HP} = 22 Hz and J = 8 Hz, CHP), 8.20 (s, CH=O), *et al.*; mass spectrum 359, 331, 210, 195, 166, 138, 121.

Registry No.—**3,** 50917-87-8; **4a,** 52539-73-8; **4b,** 52539-74-9; **4c,** 52539-75-0; **5a,** 52539-76-1; **5b,** 52539-77-2; **5c,** 52539-78-3; **6a,** 52539-82-9; **6b,** 52539-83-0; **6c,** 52539-84-1; **7a,** 52539-85-2; **7a** Δ^2 isomer, 52539-79-4; **7b,** 52539-86-3; **7c,** 52539-87-4; **8a,** 52539-88-5; **8b,** 52539-89-6; **8c,** 52539-90-9; **9a,** 52539-91-0; **9b,** 52539-92-1; **9c,** 52539-93-2; **10a,** 52539-94-3; **10b,** 52539-95-4; **10c,** 52585-05-4; **11a,** 52539-96-5; **11b,** 52539-97-6; **11c,** 52539-98-7; **12a,** 52539-99-8; **12a** Na salt, 52540-00-8; **12a** Δ^2 isomer Na salt, 52539-80-7; **12a** Me ester, 52540-01-9; **12b,** 52540-02-0; **12b** Na salt, 52540-03-1; **12b** Δ^2 isomer Na salt, 52539-81-8; **12b** Me ester, 52540-04-2; **12c,** 52540-05-3; **12c** Na salt, 52540-06-4; **12c** Me ester, 52540-07-5; **14a,** 2461-80-5; **14b,** 52540-19-9; **14c,** 52540-20-2; **15,** 52540-21-3; phenacyl chloride, 532-27-4; *p*-carbomethoxyphenacyl chloride, 52540-22-4; thiazole-4-carbonyl chloride, 52540-23-5; azedoacetyl chloride, 30426-58-5; *p*-carbomethoxybenzayl chloride, 7377-26-6; *p*-carbomethoxydiazoacetophenone, 22744-13-4; thiazole-4-carboxylic acid, 3973-08-8; 4-diazoacetylthiazole, 52540-24-6; 4-chloroacetylthiazole, 52540-23-5.

References and Notes

(1) Paper V: N. G. Steinberg, R. W. Ratcliffe, and B. G. Christensen, *Tetrahedron Lett.*, in press.
(2) E. H. Flynn, Ed., "Cephalosporins and Penicillins," Academic Press, New York, N.Y., 1972.
(3) J. H. C. Nayler, M. J. Pearson, and R. Southgate, *Chem. Commun.*, 58 (1973).
(4) R. Scartazzini and H. Bickel, *Helv. Chim. Acta*, **55**, 423 (1972).
(5) W. C. Topp and B. G. Christensen, *J. Med. Chem.*, **17**, 342 (1974).
(6) Since that time we have prepared 3-heteroaryl cephems by partial synthesis but the method is not suitable for phenyl or substituted phenyl: J. L. Fahey, R. A. Firestone, N. S. Maciejewicz, and B. G. Christensen, manuscript in preparation.
(7) R. W. Ratcliffe and B. G. Christensen, *Tetrahedron Lett.*, 4645, 4649, 4653 (1973).
(8) R. A. Firestone, N. S. Maciejewicz, R. W. Ratcliffe, and B. G. Christensen, *J. Org. Chem.*, **39**, 437 (1974).
(9) The bioactivities of these and other analogs prepared by total synthesis will be reported elsewhere.
(10) B. W. Hotten, *Ind. Eng. Chem.*, **49**, 1691 (1957).
(11) We thank Dr. B. A. Arison for his invaluable assistance in the interpretation of nmr spectra.
(12) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967).
(13) Personal communication from Dr. J. L. Fahey.
(14) J. L. Fahey and R. W. Ratcliffe, manuscript in preparation.
(15) A. Baeyer, *Justus Liebigs Ann. Chem.*, **245**, 103 (1888).

Synthesis of the A_{14-21} Sequence of Ovine Insulin by the Solid-Phase Technique[1]

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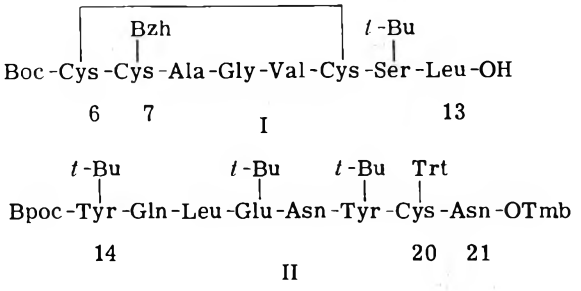
An improved synthesis of the *tert*-alkyloxycarbonylhydrazide resin (IX) is given. The resin has been used as the support in the solid-phase synthesis of an N-protected hexapeptide hydrazide (XIX) comprising the A_{14-19} fragment of insulin. Incorporation of the subsequent amino acid residues as their *N*-2-(*p*-biphenylyl)isopropyloxycarbonyl derivatives enabled us to determine the incorporation percentage in each coupling step and to find optimum conditions for the condensation reactions. Dicyclohexylcarbodiimide-*N*-hydroxybenzotriazole was used as the condensing agent for the coupling of asparagine and glutamine residues. Residual free amino groups were blocked by formylation. The N-terminal amino group was temporarily protected by the newly developed 2-(methylsulfonyl)ethyloxycarbonyl group. After cleavage from the resin the product has been coupled with *S*-trityl-L-cysteinyl-L-asparagine by the azide method, resulting in the formation of an *S*-trityl derivative of the C-terminal A_{14-21} sequence of insulin.

Although several useful laboratory syntheses of the A and B chains of insulin have been described,[2] the problem of the specific introduction of the four disulfide bonds has not yet been solved. An approach to overcome this problem has been described by Hiskey,[3] who demonstrated that selective bridging of *S*-trityl thioethers in the presence of an *S*-benzhydryl thioether is possible with thiocyanogen as the oxidizing agent. This method has been used[4] in the synthesis of a suitably protected octapeptide (I) comprising the A_{6-13} sequence of ovine insulin, in which the cysteinyl residue at A_7 is present as its *S*-benzhydryl derivative.



This technique can be applied to the ultimate bridging of the complete A and B chains of insulin. The peptide I has then to be incorporated in an A chain containing *S*-trityl-cysteine at A_{20}. The synthesis of a proper A_{14-21} fragment (II), suitable for the desired extension of I at the C-terminal end, has already been described.[5]

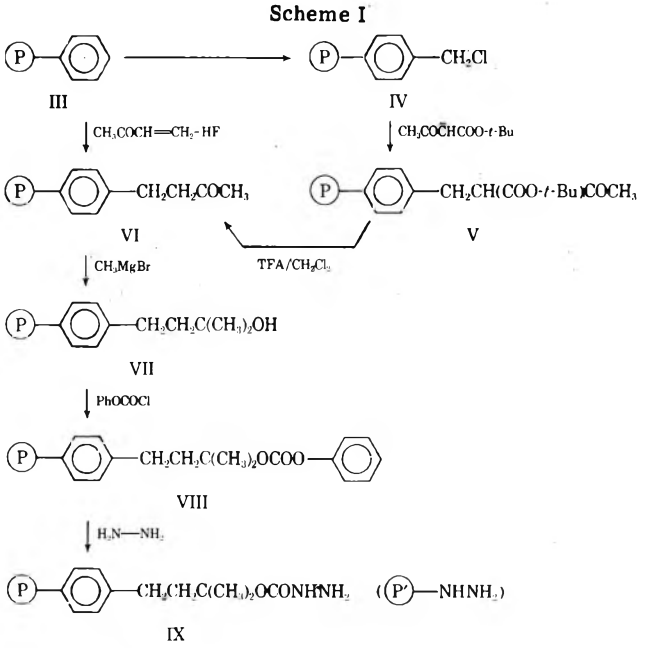
In view of this promising progress toward a useful synthesis of the complete insulin molecule we started investigations on the *solid-phase* synthesis of fragments of the A chain, fitting into the given overall strategy. The present paper concerns the development of a new synthesis of the A_{14-21} fragment which has largely been done on a solid support.

Since it was found in orienting experiments that acylation of free amine functions in solid-phase synthesis with *S*-trityl cysteine derivatives is always far from quantitative,[6] the synthesis of the desired octapeptide was conducted in two stages: a solid-phase synthesis of the hydrazide of an N-protected A_{14-19} sequence, followed by a condensation of the corresponding azide with *S*-tritylcysteinylasparagine in solution.

The obvious support for this investigation was the *tert*-alkyloxycarbonylhydrazide resin (IX), introduced by Merrifield and Wang.[7] The mild conditions needed to cleave a peptide from this resin facilitate isolation of a partly protected peptide hydrazide, suitable for further fragment condensations.

A. Synthesis of the *tert*-Alkyloxycarbonylhydrazide Resin. An attempted preparation[7] of the resin was unsuccessful. Direct substitution of copolystyrene–divinylbenzene (III) with methyl vinyl ketone did not occur when the recommended HF was used, nor when other Friedel–Crafts catalysts ($AlCl_3$, $SnCl_4$, $BF_3 \cdot OEt_2$, H_2SO_4) were applied. This may have been due to the particular batch of the copolymer used. The resin VI could, however, be readily obtained by the substitution of an acetoacetate residue for chlorine in the chloromethyl resin (IV), followed by acid hydrolysis and decarboxylation with 50% TFA–CH_2Cl_2 (Scheme I). The intermediate V was completely free from chlorine and could be well characterized by ir spectroscopy. The product VI had an ir spectrum identical with that given by Merrifield.[7]

Scheme I



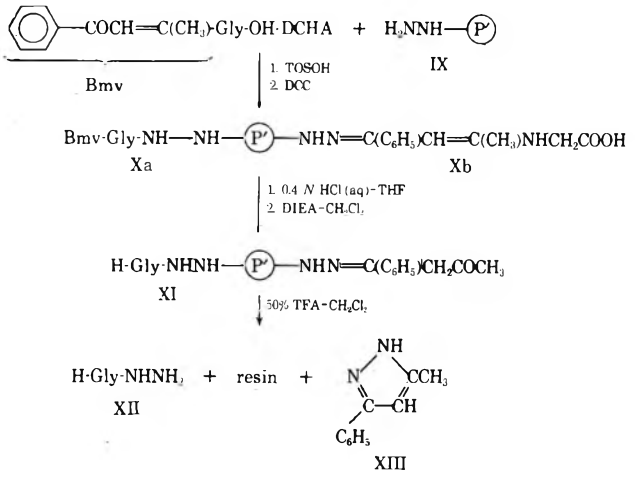
The further synthesis of IX proceeded smoothly as described in the literature and reproduced in Scheme I. From the nitrogen content it was calculated that the overall yield over five reaction steps was 71%.

The new route includes two important improvements: the percentage of anchoring side chains in the hydrazide resin can be controlled by the extent of chloromethylation in the synthesis of IV, and the use of the hazardous HF can be avoided.

B. Synthesis of the Hydrazide of an N-Protected A_{14-19} Fragment. Peptide syntheses on the resin IX can only be done with amino acid derivatives containing N_α-protecting groups which are more acid labile than the tertiary carbazate link between the peptide and the resin. Possible N-protecting functions seemed to be the Bpoc group[8] and the Bmv group[9] because of their high acid lability. Use of either group also permits measurement of the effectiveness of each coupling step. Cleavage of the Bpoc group with 0.5% TFA–CH_2Cl_2 proceeds quantitatively, yielding apart from carbon dioxide 2-(*p*-biphenylyl)propene and a trace of 2-(*p*-biphenylyl)propanol-2. Removal of the Bmv group under acidic conditions (0.4 *N* HCl in aqueous THF) gives benzoylacetone quantitatively. In both cases the amount of the cleavage products can be determined by uv spectrophotometry.

The Bmv group cannot be used, however, in the coupling of the first amino acid with IX. In a preliminary experiment with Bmv-glycine (Scheme II) it appeared that the Bmv amino acid is not only bound *via* the carboxyl group as a hydrazide (Xa) but also as a hydrazone by condensation of the hydrazide groups on the resin with the carbonyl function in the Bmv group (Xb). Subsequent cleavage of the Bmv group and liberation of the amino acid from the resin yielded apart from the expected glycylhydrazide (XII) substantial amounts of a side product which appeared to be 5-methyl-3-phenylpyrazole (XIII) by comparison with an authentic sample.

Scheme II



The Bpoc group appeared very attractive for N_α protection. It is stable under the experimental conditions of the synthetic procedures, and the conditions for its removal are milder than for the cleavage of Bmv residues.

Before cleavage of the A_{14-19} fragment from the resin the N-terminal Bpoc group was exchanged for the Msc group[10] which remains during this cleavage procedure. The Msc group could be removed at the octapeptide stage with dilute base and without interference with the *S*-trityl function at A_{20}.

For side-chain protection of the tyrosyl residues (A_{14} and A_{19}) and the glutamyl residue (A_{17}) *tert*-butyl groups were used. They are completely stable under the cleavage conditions for the Bpoc group but are eliminated during removal of the peptide from the resin, which was done with 50% TFA in CH_2Cl_2. The absence of side-chain protecting groups in the final product improves its solubility, which is of advantage in the subsequent azide coupling with the A_{20-21} fragment. The same is true when the resulting A_{14-21} fragment is to be extended at the N-terminal side *via* the mixed anhydride method or *via* an azide coupling.

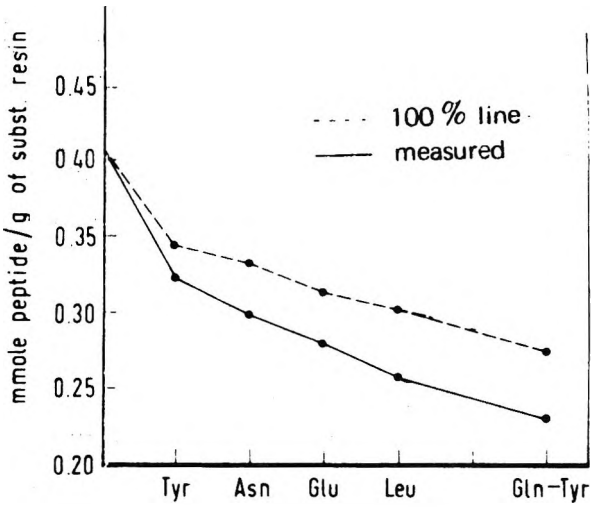


Figure 1. Relative incorporation of the subsequent amino acid residues in the solid-phase synthesis of the A_{14-19} fragment of insulin.

The introduction of asparagine (A_{18}) and glutamine (A_{15}) required special attention because condensing agents such as DCC can cause dehydration of amides to nitriles. Recent investigations[11] have revealed that *p*-nitrophenyl ester couplings proceed rather slowly in solid-phase syntheses, giving incomplete acylations even after prolonged reaction times. An attempt to use Mitin's method, previously applied to the incorporation of amide-containing amino acid residues,[12] had to be abandoned because it also led to incomplete condensations. Finally, a clean and rapid introduction of these amino acids appeared to be possible by condensation with DCC–HOBt, as was found by König and Geiger[13] in syntheses in solution and was recently applied to a solid-phase synthesis.[14] In preliminary experiments thin layer chromatograms of asparagine-containing peptides obtained thus showed that no appreciable formation of the corresponding β-cyanoalanyl derivative had occurred, and the complete absence of dehydration products could be deduced from the absence of any nitrile absorption at 2260 cm^{-1} in the ir spectra of the products.

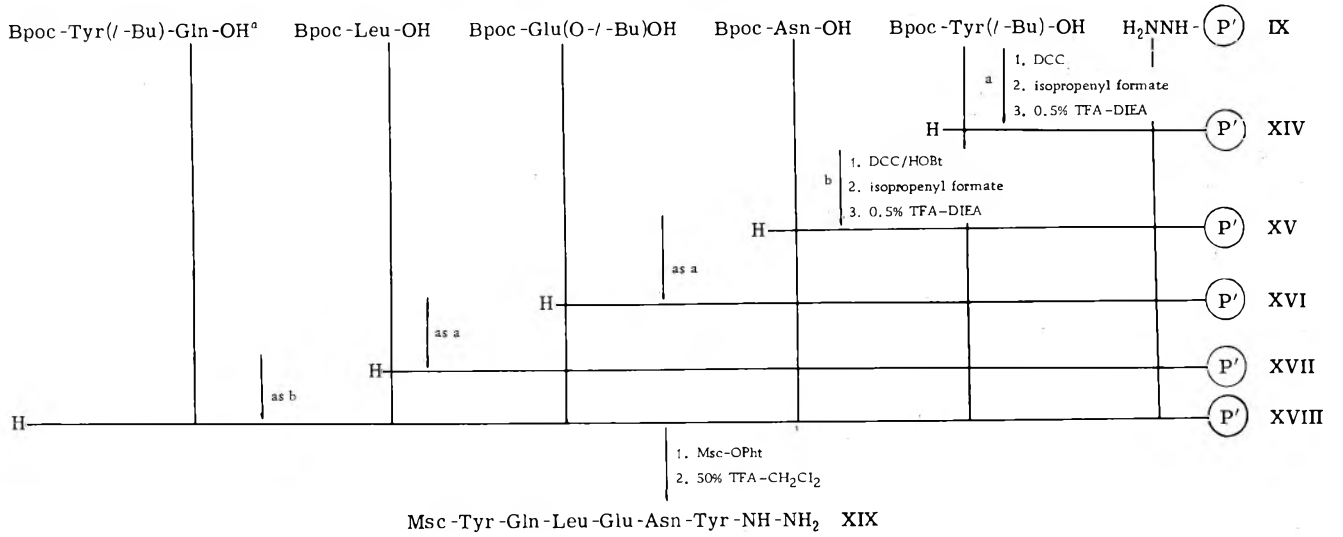
On account of these results DCC–HOBt was selected as the condensing reagent in the coupling of the asparagine and glutamine derivatives, and DCC alone in all other coupling steps. After each coupling residual free amino groups were formylated by treatment of the peptide resin with isopropenyl formate.[15] Omission of this treatment in a parallel synthesis led to an impure product difficult to purify.

To estimate the yields of the subsequent coupling steps the number of millimoles of the peptide present in 1 g of the resin was determined after each coupling by spectrophotometric determination of 2-(*p*-biphenylyl)propene, formed by removal of the terminal Bpoc group. The number was compared with that calculated for quantitative incorporation of the relevant amino acid residue (Figure 1).

The overall synthetic procedure is given in Scheme III. The synthesis was performed with a Schwarz Bio Research peptide synthesizer. After cleavage from the resin the Msc-hexapeptide hydrazide (XIX) was dissolved in DMF and precipitated with ethanol–ether. It was obtained in 62% yield, based on the Bpoc content at the hexapeptide level. It was chromatographically pure in a number of solvent systems and gave a correct elemental analysis.

C. Synthesis of the *S*-Trityl A_{14-21} Sequence. The A_{14-19} fragment (XIX) was coupled with a slight excess of *S*-trityl-L-cysteinyl-L-asparagine *via* the azide method (Scheme IV). The remaining dipeptide was removed from the reaction mixture by filtration through an AG1-X2 ion

Scheme III
Synthesis of the Protected A_{14-19} Peptide Derivative



[a] In the automated synthesis coupling with a dipeptide was chosen in this stage because tlc of a pentapeptide derivative obtained from XVII and Bpoc-Gln-OH showed in addition to the ninhydrin-positive pentapeptide hydrazide a small spot which was Reindel–Hoppe positive but ninhydrin negative. This might have been a pyroglutamyl derivative. When the synthesis was completed *via* this pentapeptide stage by a coupling with Msc-Try(*t*-Bu)-OH the hexapeptide hydrazide (XIX) was, however, obtained in the same yield and as pure as *via* the given scheme.

Scheme IV

XIX + H-Cys(Trt)-Asn-OH $\xrightarrow{\text{azide coupling}}$

Msc-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys(Trt)-Asn-OH (XX)

$\downarrow OH^-$

H-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys(Trt)-Asn-OH (XXI)

exchange column, which proved to be very useful for the selective separation of peptides differing in net negative charge. The N,S-protected octapeptide (XX) was obtained in 58% yield. Cleavage of the Msc group was done with dilute base in 1-butanol–methanol–water. The *S*-trityl substituted A_{14-21} fragment was isolated in 90.5% yield. It was homogeneous without purification and analyzed correctly.

Experimental Section

Melting points are uncorrected. Optical rotations were measured with a Zeiss 366343 polarimeter. Infrared spectra were taken on a Perkin-Elmer 257 infrared spectrophotometer with KBr pellets. For the automated solid-phase synthesis a Schwarz Bio Research instrument was used.

Thin layer chromatography was performed on precoated silica gel GF_{254} plates (Merck). The following solvent systems were used: heptane–*tert*-butyl alcohol–acetic acid–water–pyridine, 25:70:6:24:20 (system A); 1-butanol–acetic acid–water–pyridine, 4:1:2:1 (system B); chloroform–methanol, 3:1 (system C); *n*-heptane–1-butanol–acetic acid, 3:1:1 (system D); 1-butanol–acetic acid–water, 4:1:1 (system E); benzene–acetone, 1:1 (system F); 1-butanol–acetic acid–water–pyridine, 30:6:24:20 (system G).

For column chromatography AG1-X2 (chloride form, 200–400 mesh, Bio-Rad Laboratories) was washed twice with 2 *N* KOH, then with water until neutral, twice with 10% acetic acid, and again with water until neutral. Columns were equilibrated with the appropriate solvent before use.

Samples for elemental analysis were dried *in vacuo* over P_2O_5 at 50–60°.

***tert*-Butyl Acetoacetate Adduct of Chloromethylated Polystyrene (V).** *tert*-Butyl acetoacetate (18.5 ml, 0.113 mol) was added to a freshly prepared solution of 2.6 g (0.113 mol) of sodium in 60 ml of ethanol, and the mixture was supplied with more of the solvent to a total volume of 100 ml. Chloromethylated polystyrene (20.0 g, 2.26% Cl) was added to 40 ml of the solution and the solvent was evaporated *in vacuo*. DMF (15 ml) was then added and the mixture was concentrated *in vacuo* to a small volume. Another 25 ml of DMF was added and the reaction was allowed to proceed for 2 hr at 70° under stirring. The resin was filtered and washed several times with DMF, dioxane, dioxane–water, dioxane, CH_2Cl_2, and ethanol. An ir spectrum showed characteristic absorptions at 1735, 1715, and 1255 cm^{-1}. A Beilstein test for chlorine appeared to be negative.

3-Oxobutyl Resin (VI). The β-keto acid ester resin (V, 20 g) was suspended in 50 ml of 50% TFA–CH_2Cl_2, and the suspension was stirred for 1 hr. The resin was then filtered and thoroughly washed with CH_2Cl_2, 10% DIEA in CH_2Cl_2, CH_2Cl_2, and ethanol. The ir spectrum showed a strong absorption at 1715 cm^{-1} (keto C=O), but no absorptions at 1735 (ester C=O) and 1255 cm^{-1} (ester CO).

***tert*-Alkyloxycarbonyl Hydrazide Resin (IX).** The resin was prepared from VI as described by Wang and Merrifield.[7] The product contained 1.21% nitrogen, indicating 0.43 mmol of hydrazide/g of resin. The overall yield was therefore 71%, based on the chlorine content of the starting chloromethyl resin (2.26%).

Measurement of the Incorporation of Bpoc Amino Acid Residues. An accurately weighed sample of the dried *N*-Bpoc-peptide resin (4–7 mg) was suspended in 50 ml of a 0.5% TFA solution in CH_2Cl_2. After 10 min the optical density of the solution below the floating particles was measured at 274 nm. From the molar extinction of 2-(*p*-biphenylyl)propene in the solvent used (ε 20,400) the incorporation was calcualted as follows: milliequivalents of Bpoc residues/gram of substituted resin = 2.45 d/x, when d = optical density measured and x = milligrams of resin used.[16] The incorporation expressed in milliequivalents per gram of unsubstituted resin (C) can then be found from $C = x/[(1 - x) \cdot M \cdot 10^{-3}]$ in which M = equivalent weight of the newly introduced residue. Bpoc determinations carried out in duplicate never varied by more than 2–3%.

Methylsulfonylethyl Phthalimidocarbonate (Msc-OPht). 2-Methylmercaptoethanol was oxidized by treatment with the calculated amount of 30% hydrogen peroxide in a sodium tungstate catalyzed reaction. After evaporation of the reaction mixture with ethanol the remaining methylsulfonylethanol was crystallized from isopropyl alcohol (mp 29°). It was dissolved in a cooled tetrahydrofuran solution containing a twofold excess of phosgene, and the reaction flask was left for some hours at room temperature. The solution was then concentrated *in vacuo*, whereupon the residue crystallized as large crystals. The methylsulfonylethyl chloroformate was purified by crystallization from tetrahydrofuran–ether (mp 49.0–49.5°).

A solution of 2.44 g (13.1 mmol) of Msc chloride in 5 ml of acetone was added dropwise to a cooled solution (0°) of 2.14 g (13.1 mmol) of *N*-hydroxyphthalimide and 1.83 ml (13.1 mmol) of triethylamine in 10 ml of acetone. The addition was stopped as soon as the red color disappeared. Water was then added, and the pre-

Table I
DCC Mediated Coupling of Bpoc Amino Acids

Step	Reagent	Vol, ml	Time, min
1	4 equiv of Bpoc amino acid in CH_2Cl_2 or CH_2Cl_2–DMF[a]	10	2
2	4 equiv of DCC in CH_2Cl_2	9	90
3, 4, 5	CH_2Cl_2 (washing)	25	5, 2, 2
6, 7, 8	DMF (washing)	25	5, 2, 2
9, 10, 11	EtOH (washing)	25	5, 2, 2[b]
12, 13, 14	CH_2Cl_2 (washing)	25	5, 2, 2
15	10% isopropenyl formate solution in CH_2Cl_2	18	60
16, 17, 18, 19	CH_2Cl_2 (washing)	25	5, 2, 2, 2[c]

[a] In the couplings with Bpoc-Asn-OH and Bpoc-Tyr-(*t*-Bu)-Gln-OH 1 equiv of HOBt dissolved in DMF was added. [b] At this stage samples were taken for qualitative analysis; samples were treated with 50% TFA–CH_2Cl_2 to cleave the peptide from the resin. After filtration the solvent was evaporated, and DMF was added to get a 1% peptide solution which was applied to tlc plates. [c] At this stage samples were taken for measurement of the incorporation yield by the procedure given above.

cipitate was collected and washed with water, yielding 3.84 g (93%) of the carbonate, mp 160–163°.

Anal. Calcd for $C_{12}H_{11}NO_7S$: C, 46.01; H, 3.54; N, 4.47. Found: C, 46.2; H, 3.6; N, 4.4.

***N*-Methylsulfonylethyloxycarbonyl-*O*-*tert*-butyltyrosine.** *p*-Nitrophenyl chloroformate was dissolved in dry pyridine (2 ml/g) containing a slight excess of methylsulfonylethanol, with stirring at 0°. After 4 hr at room temperature the reaction mixture was concentrated to a thick sirup and poured into a hydrochloric acid solution (1 *N*). Msc-ONp separated as an oil which rapidly solidified. The tan-colored crystals were recrystallized from ethyl acetate–methanol, yield 73%, mp 102°.

Equimolecular amounts of this product and of *O*-*tert*-butyltyrosine were stirred together in 80% aqueous acetonitrile (10 ml/g of tyrosine) at room temperature. An equivalent amount of triethylamine was then added. After 1 hr the reaction mixture was concentrated, acidified to pH 5, and extracted with ether. The ether extracts were discarded. Acidification of the water phase with potassium hydrogen sulfate (2 *N*) yielded an oil which was extracted into ethyl acetate. Evaporation of the dried extract gave a foam which crystallized rapidly on trituration with ether, giving 2.9 g (75%) of the product, mp 130°, $[\alpha]^{24}D$ +4.0° (*c* 1.05, MeOH), $[\alpha]^{25}D$ +10.3° (*c* 1.01, 90% AcOH).

Anal. Calcd for $C_{17}H_{25}NO_7S$: C, 52.70; H, 6.50; N, 3.62; S, 8.28. Found: C, 52.8; H, 6.5; N, 3.6; S, 8.3.

***N*-2-(*p*-Biphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-L-glutamine.** Bpoc-Tyr(*t*-Bu)-ONSu[5] (mp 139–141°, 2.9 g, 5 mmol) was dissolved in 15 ml of dimethoxyethane, and the solution was added to a solution of 0.73 g (5 mmol) of glutamine and 0.84 g (10 mmol) of sodium bicarbonate in 15 ml of water. To obtain a clear solution 10 ml of dimethylethane was added. After 4 hr the organic solvent was evaporated and a 10% citric acid solution was added at 0°. The precipitate was extracted into ethyl acetate, and the extract was washed with water, dried, and concentrated to a small volume. By addition of ether and diisopropylether 2.34 g (78%) of the product precipitated, mp 132–134°, $[\alpha]^{23}D$ +13.5° (*c* 1, DMF), homogeneous (system G).

Anal. Calcd for $C_{34}H_{41}N_3O_7 \cdot 0.25H_2O$: C, 67.14; H, 6.88; N, 6.91. Found: C, 67.2; H, 7.0; N, 6.85.

***N*-Methylsulfonylethyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-L-glutaminyl-L-leucyl-γ-*tert*-butyl-L-glutamyl-L-asparaginyl-*O*-*tert*-butyl-L-tyrosyl Hydrazide Resin (XVIII).** The necessary Bpoc amino acid derivatives were prepared according to Schnabel[17] by treatment of 2-(*p*-biphenylyl)isopropyl *p*-biphenylyl carbonate with a solution of the Triton B salt of the appropriate amino acid derivative. The compounds were isolated as DCHA salts. Bpoc amino acid solutions were prepared just before use. The acids were liberated from their salts with 2 *N* $KHSO_4$ at 0°.

The alternating coupling and deprotection steps given in Scheme III were performed with samples (1.5 g) of the resin (0.6–0.9 mmol) according to standard procedures which are given in Tables I and II. After the final deprotection step the N-terminal amino groups were protected by treatment of the peptide resin with a tenfold excess of Msc-OPht, dissolved in DMF–CH_2Cl_2 for 16 hr at 20°.

Table II
Cleavage of Bpoc Groups

Step	Reagent	Vol, ml	Time, min
1, 2	0.5% TFA–CH_2Cl_2	44	2, 10
3, 4, 5	CH_2Cl_2 (washing)	22	2, 2, 2
6	10% DIEA–CH_2Cl_2	25	2
7, 8, 9	CH_2Cl_2 (washing)	25	2, 2, 2
10, 11, 12	EtOH (washing)	25	2, 2, 2
13, 14, 15	CH_2Cl_2 (washing)	25	2, 2, 2
16	10% DIEA–CH_2Cl_2	25	10
17, 18, 19, 20	CH_2Cl_2 (washing)	25	2, 2, 2, 2

***N*-Methylsulfonylethyloxycarbonyl-L-tyrosyl-L-glutaminyl-L-leucyl-L-glutamyl-L-asparaginyl-L-tyrosyl Hydrazide (XIX).** The peptide resin XVIII (1.2 g) was treated with 25 ml of 50% TFA–CH_2Cl_2 for 30 min at 20°. The remaining polymer was filtered and washed twice with 5 ml of CH_2Cl_2. From the absence of carbonyl absorptions in the ir spectrum of the resin it appeared that the peptide as well as the formyl residues had been completely cleaved from the resin.

The filtrate was evaporated, and the oily residue was dissolved in 12.5 ml of DMF. By addition of 50 ml of ethanol and 40 ml of ether a precipitate was formed, which was collected and dried over KOH. Tlc (solvents A and B) showed it to be homogeneous: yield 62% (based on the last Bpoc content measured); mp 225–227°; $[\alpha]^{23}D$ −28.3° (c 1, DMF).

Anal. Calcd for $C_{42}H_{60}N_{10}O_{16}S$: C, 50.80; H, 6.09; N, 14.10. Found: C, 50.7; H, 6.0; N, 14.1.

***N*-*tert*-Butyloxycarbonyl-*S*-trityl-L-cysteinyl-L-asparagine.** DCC (2.45 g, 11.8 mmol) was added to a stirred solution of 5.45 g (11.8 mmol) of *S*-tritylcysteine[18] and 1.36 g (11.8 mmol) of *N*-hydroxysuccinimide in 15 ml of 1,2-dimethoxyethane at −10°. Stirring was continued for 2 hr at 0° and 1 hr at 20°. The mixture was filtered, and the precipitate was washed with two 7.5-ml portions of dimethoxyethane. The combined filtrates were then added to a solution of 1.74 g (11.8 mmol) of asparagine hydrate and 1.63 g (11.8 mmol) of potassium carbonate in 20 ml of water. To obtain a clear solution 20 ml of dimethoxyethane was added. After 90 min this solvent was evaporated, and the residue was acidified with a $KHSO_4$ solution. The separated oil was extracted into ethyl acetate–ether (2:1), the extract was washed with water, and the oil was extracted again with a 10% *N*-methylmorpholine solution in water. The combined extracts were acidified with a 2 *N* H_2SO_4 solution and then extracted with ethyl acetate. Finally the organic layer was washed with water until neutral, dried, and evaporated, giving a foam which solidified on addition of petroleum ether. Tlc (systems C and D) showed that the N,S-protected dipeptide (5.97 g, 88%) was still contaminated with some impurities. Therefore, 0.9 g of the product was dissolved in 100 ml of 1-butanol–methanol–water (1:1:1) and applied to an AG1-X2 column (12 × 1.5 cm) which was washed and equilibrated previously with the same solvent system. On elution with 1-butanol–methanol–1.5% acetic acid (1:1:1) the chromatographically homogeneous fractions containing the protected dipeptide were collected and evaporated. Trituration of the residue with petroleum ether yielded 660 mg of a pure product, $[\alpha]^{22}D$ +29.0° (c 1, MeOH).

Anal. Calcd for $C_{31}H_{35}N_3O_6S$: C, 64.45; H, 6.11; N, 7.27. Found: C, 64.4; H, 5.9; N, 7.2.

***S*-Trityl-L-cysteinyl-L-asparagine.** Boron trifluoride etherate (0.26 ml, 1.8 mmol) was added to a stirred solution of 355 mg (0.615 mmol) of Boc-Cys(Trt)-Asn-OH in 5 ml of acetic acid. After 30 min the solution was poured into a solution of sodium acetate. The separated oil was extracted into 1-butanol, previously saturated with water, and the extract was washed with the corresponding water phase. The solvent was evaporated, and the oily residue was triturated with ether, yielding 285 mg (97.5%) of the product, homogeneous on tlc (system E), $[\alpha]^{23}D$ +27.7° (*c* 1, DMF).

Anal. Calcd for $C_{26}H_{27}N_3O_4S \cdot 0.5\ H_2O$: C, 64.18; H, 5.80; N, 8.64. Found: C, 63.9; H, 5.6; N, 8.55.

***N*-Methylsulfonylethyloxycarbonyl-L-tyrosyl-L-glutaminyl-L-leucyl-L-glutamyl-L-asparaginyl-L-tyrosyl-*S*-trityl-L-cysteinyl-L-asparagine (XX).** A solution of XIX)286 mg, 0.288 mmol) in 8 ml of DMF and 1 ml of DMSO was cooled to −20° and

treated with 0.105 ml of a 7.5 *N* HCl solution in dimethoxyethane (0.79 mmol) and 0.043 ml (0.375 mmol) of *tert*-butyl nitrite. The mixture was stirred at −15° for 20 min, then cooled to −30° and treated with 0.11 ml (0.79 mmol) of triethylamine.

A cooled solution of 167 mg (0.35 mmol) of H-Cys(Trt)-Asn-OH in 3 ml of DMF was added to this azide solution. The pH was adjusted to 7 with 10% Et_3N–DMF, and the solution was left for 3 days at 4°. The mixture was then diluted with 200 ml of 1-butanol–methanol–water (1:1:1) and added to an AG1-X2 column (1.6 × 22 cm). The column was eluted with 1-butanol–methanol–dilute acetic acid (1:1:1) mixtures in which the concentration of the acetic acid used was gradually raised: 0% (100 ml), 0.3% (300 ml), 1% (100 ml), 3% (200 ml), 15% (400 ml). Absorbancy measurements (254 nm) and tlc revealed that the excess of dipeptide was eluted with the 0.3% acetic acid mixture, while the desired product was located in the 15% acetic acid eluate.

Fractions containing the product were collected and evaporated. The residue was dissolved in 5 ml of DMF and precipitated with methanol–water, yielding 242 mg (58%) of XX, mp 253° dec, $[\alpha]^{23}D$ −20.2° (*c* 1, DMF), homogeneous (systems B and F).

Anal. Calcd for $C_{68}H_{83}N_{11}O_{20}S_2 \cdot H_2O$: C, 56.07; H, 5.88; N, 10.58. Found: C, 55.9; H, 5.8; N, 10.5.

Amino acid ratios in acid hydrolysate (in the presence of phenol): Asp, 1.9; Glu, 2.0; Leu, 1.1; Tyr, 1.95.

L-Tyrosyl-L-glutaminyl-L-leucyl-L-glutamyl-L-asparaginyl-L-tyrosyl-*S*-trityl-L-cysteinylasparagine (XXI). A suspension of 105 mg (0.073 mmol) of XX in water was treated with 0.35 ml (0.14 mmol) of 4 *N* NaOH. After 4 min the clear solution was acidified with a few drops of 2 *N* $KHSO_4$ solution and water was added. The precipitate was filtered, washed with water, and dried, yielding 85 mg (90.5%) of XXI, mp ~300° dec, $[\alpha]^{23}D$ −15.0° (*c* 1, DMF), homogeneous (system B).

Anal. Calcd for $C_{64}H_{77}N_{11}O_{16}S \cdot 2H_2O$: C, 58.04; H, 6.16; N, 11.63. Found: C, 57.9; H, 5.9; N, 11.5.

Amino acid analysis in acid hydrolysate, oxidized with performic acid: Asp, 2.0; Cys(SO_3H), 1.0; Glu, 1.9; Leu, 1.0; Tyr, 1.5.

Registry No.—XIX, 52278-85-0; XX, 52278-86-1; XXI, 52278-87-2; methylsulfonylethyl phthalimidocarbonate, 52278-88-3; 2-methylmercaptoethanol 5271-38-5; *N*-methylsulfonylethyloxycarbonyl-*O*-*tert*-butyltyrosine, 52278-89-4; *p*-nitrophenyl chloroformate, 7693-46-1; *N*-2-(*p*-biphenylyl)isopropyloxycarbonyl-*O*-*tert*-butyl-L-tyrosyl-L-glutamine, 52278-90-7; Bpoc-Tyr(*t*-Bu)-ONSu, 33527-03-6; *N*-*tert*-butyloxycarbonyl-*S*-trityl-L-cysteinyl-L-asparagine, 52278-91-8; *S*-trityl-L-cysteinyl-L-asparagine, 52278-92-9.

References and Notes

(1) The following abbreviations have been employed in the text: DCC = *N,N*-dicyclohexylcarbodiimide; HOBt = *N*-hydroxybenzotriazole; TFA = trifluoroacetic acid; THF = tetrahydrofuran; DCHA = dicyclohexylamine; TOSOH = *p*-toluenesulfonic acid; DIEA = *N*-ethyldiisopropylamine; Im = imidazole; DMF = *N,N*-dimethylformamide; DMSO = dimethy sulfoxide; BOC = *tert*-butyloxycarbonyl; Bzh = benzhydryl; *t*-Bu = *tert*-butyl; Bpoc = 2-(*p*-biphenylyl)isopropyloxycarbonyl; Trt = triphenylmethyl; Tmb = 2,4,6-trimethylbenzyl; Bmv = 2-benzoyl-1-methylvinyl; Msc = 2-(methylsulfonyl)ethyloxycarbonyl; Pht = phthalimido; NSu = succinimido.
(2) P. G. Katsoyannis, A. M. Tometsko, J. Z. Ginos, C. Zalut, and M. A. Tilak, *J. Amer. Chem. Soc.*, **88**, 164, 166 (1966); A. Marglin and R. B. Merrifield, *ibid.*, **88**, 5051 (1966); H. Zahn, T. Okuda, and Y. Shimonishi, *Angew. Chem.*, **79**, 424 (1967).
(3) R. G. Hiskey, T. Mizoguchi, and E. L. Smithwick, *J. Org. Chem.*, **32**, 97 (1967).
(4) R. G. Hiskey, L. M. Beacham, III, and V. G. Matl, *J. Org. Chem.*, **37**, 2472 (1972).
(5) R. G. Hiskey, E. T. Wolters, G. Ülhü, and V. R. Rao, *J. Org. Chem.*, **37**, 2478 (1972).
(6) E. Th. M. Wolters, Thesis (Nijmegen), 1973, p 46.
(7) S. S. Wang and R. B. Merrifield, *J. Amer. Chem. Soc.*, **91**, 6488 (1969).
(8) P. Sieber and B. Iselin, *Helv. Chim. Acta*, **51**, 622 (1968).
(9) G. L. Southard, G. S. Brooke, and J. M. Pettee, *Tetrahedron Lett.*, 3505 (1969).
(10) G. I. Tesser, I. Balvert-Geers, and E. Th. M. Wolters, in preparation.
(11) G. Losse and R. Ulrich, *Tetrahedron*, **28**, 5823 (1972).
(12) Y. V. Mitin and O. V. Glinskaya, *Tetrahedron Lett.*, 5267 (1969).
(13) W. König and R. Geiger, *Chem. Ber.*, **104**, 2427 (1971).
(14) V. J. Hruby, F. Muscio, C. M. Groginsky, P. M. Gitu, D. Saba, and W. Y. Chan, *J. Med. Chem.*, **16**, 624 (1973).
(15) J. E. W. van Melick and E. Th. M. Wolters, *Syn. Commun.*, **2**, 83 (1972).
(16) Incorporation of Bmv amino acids (*Y*) can be measured in a similar way by suspending a sample in 25 ml of 0.4 *N* HCl (aqueous)–THF, and measuring the optical density at 307 nm after 30 min. From the molar extinction of benzoylacetone it can be derived that $Y = 1.67\ d/x$ (milliequivalents of Bmv residues per gram of substituted resin).
(17) E. Schnabel, G. Schmidt, and E. Klanke, *Justus Liebigs Ann. Chem.*, **743**, 69 (1971).
(18) L. Photaki, J. Taylor-Papadimitriou, C. Sakarellos, P. Mazarakis, and L. Zervas, *J. Chem. Soc., C*, 2683 (1970).

Isolation and Structure Determination of One of the Toxic Constituents from *Tetradymia glabrata*

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Tetradymol (I) isolated from *Tetradymia glabrata*, has been shown to be 4β,5β-dimethyl-10β-hydroxyfuranoermophilane. The combined results and relationships of chemical, nmr, and X-ray analyses of I are discussed. The mercuric chloride derivative of tetradymol crystallized in a space group $P2_12_12_1$ with cell dimensions a = 7.371 (5) Å, b = 10.304 (9) Å, c = 19.759 (17) Å with Z = 4. Counter data were refined by full-matrix least-squares to a residual of 5.4%. Tetradymol has been shown to effect hepatodysfunction and has an LD_{50} (mice) of 250 mg/kg.

Investigations reported in the literature on the components of *Tetradymia glabrata* are both long-standing and limited. The presented paper deals with the isolation of one of its toxic components, tetradymol (I),[2] and proof of its stereochemical structure.

Because of the work of Fleming,[3] Clawson and Huffman[4] prior to 1937, this plant was known to contain toxic components fatal to sheep and was further suspected to contain a component causing the maladay "bighead" in the same animal. These investigators suspected that at least two toxic compounds were present, one apparently effecting heptodysfunction, and the other effecting cardiac failure. We have not been successful in repeating the conditions necessary for the development of the "bighead" symptom,[5] and have found that the plant extract fraction reportedly containing the cardiac toxin actually contains another hepatotoxin which will be reported later. Tetradymol (I) has been shown to be a moderate hepatotoxin in several animals including sheep, mice, rats, rabbits, guinea pigs, and gerbils [oral LD_{50} (mice) is 250 mg/kg].

Results and Discussion

Isolation of Tetradymol. During the isolation procedure (Figure 1) we concluded that the toxin was located near the surface of the plant as we obtained similar amounts of I from either ground or unground plant. To

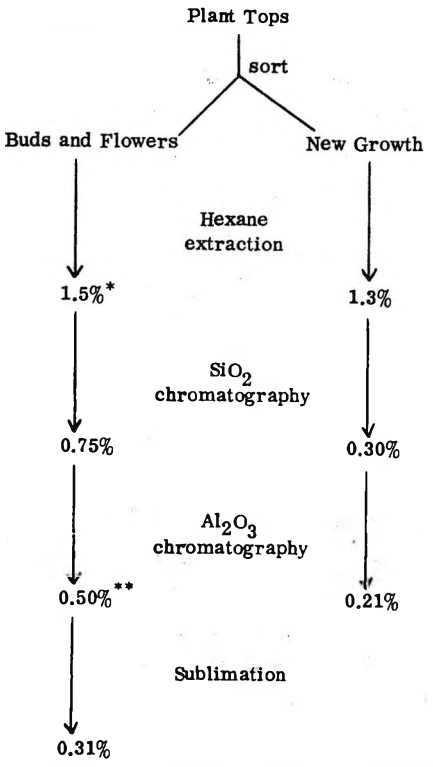


Figure 1. * Percentages based on isolated material at each step relative to the whole green plant material. ** A base extract was needed at this point for correct analyses.

monitor the isolation procedure, mice were used as the assay.[6]

Tetradymol was obtained from the extract of new growth stems and flower buds as colorless crystals, $C_{15}H_{22}O_2$, mp 92–92.5°, $[\alpha]^{25}D$ + 56°. From its uv [λ_{max} (MeOH) 222 nm (log ϵ 3.83)] and from its positive Ehrlich's color test, tetradymol (I) was assumed to contain a furan ring.

Presence of the furan ring was further confirmed by spectra and chemical data. The nmr spectrum of I (Figure 2) shows a single furan proton resonance at 7.00[7] which is coupled to a three-proton resonance (doublet J = 1.1 Hz) at 1.9 which was assigned to a furan methyl group. Such assignments are consistent with the following methyl furano compounds.

Compd	Furan methyl	Furan proton	J, Hz
Euryopsol[8]	7.12	2.04	1
Petasalbiene[9]	7.05	2.03	1.1
Menthofuran[10]	6.84	1.85	1.0

Tetradymol readily reacted with buffered mercury(II) chloride to form the 2-chloromercury derivative, mp 205–205.5°. Treatment of this derivative with H_2S regenerated tetradymol.

Hydrogenation Studies. Inspection of the formula for I ($C_{15}H_{22}O_2$) revealed that any structure proposed should incorporate five unsaturations and two oxygens. The furan ring described three unsaturations, and, from ir evidence, the second oxygen was assigned to a hydroxyl group (3400 cm^{-1}). The two remaining unsaturations were sorted out by catalytic hydrogenation (*vide infra*).

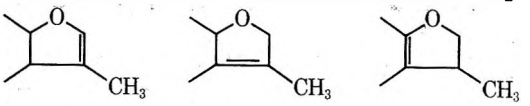
Catalytic hydrogenation of I resulted in several products, the relative concentrations of which were contingent upon the catalytic conditions (Table I). Products having incorporated 1, 2, and 3 mol of hydrogen were found (Figure 3). Structure IV is in fact a mixture of at least six components all having parent ions in the mass spectrum of 222, consistent with loss of H_2O and the addition of 3 mol of hydrogen. Ir spectra confirmed the loss of H_2O. New nmr resonances occurred in the fully hydrogenated products at 3.5 and 4.5 accounting for three protons adjacent to the ether linkage of the newly formed tetrahydrofuran moiety. Concluding that 3 mol of H_2 saturated the system of I, further characterization of constituents was terminated.

Table I

Product[a]	Catalyst: Rh on alumina in MeOH	Catalyst: Pd on charcoal in EtOH
IV	6	18
IIA	22	52
IIB	52	18
III	19	12

[a] Yields were based on isolated products.

Compound III ($C_{15}H_{24}O_2$, mp 145–146°, M^+ 236 m/e) was of interest because addition of one mole of H_2 could

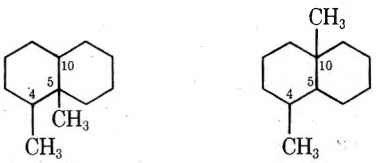


IIIa IIIb IIIc

yield three different structures, IIIa–c. The nmr spectrum of III showed three new proton resonances in the 4.7–5.5 region which is consistent with IIIb in which these protons are allylic to an olefin and adjacent to an ether oxygen. Further, the furan methyl did not move into the saturated methyl region which excluded structure IIIc. Structure IIIa was also eliminated as a possibility by the nmr spectrum since there is no single olefinic proton resonance, coupled to the furan methyl. An interesting fact is that further hydrogenation of IIIb yields only one of the tetrahydro compounds, IIB.

The two major products, IIA and IIB, analyzed correctly for $C_{15}H_{26}O_2$ with m/e 238. Ir data indicated that the hydroxyl group (3400 cm^{-1}) was still intact. In the nmr spectra, both IIA (mp 75–77°) and IIB (mp 104–105°) showed the loss of furan proton resonance and new resonances at 3.0–4.1, consistent with protons adjacent to an ether function. Other than the possibility that these two compounds are two of six possible tetrahydrotetradymol isomers, further speculation on their stereochemical structure shall be deferred until additional data are obtained. The conclusion reached from these hydrogenation data is that 2 mol of H_2 saturated I, indicating that the furan ring accounted for all the olefins.

Proof of Ring System and Hydroxyl Position. Several sesquiterpene ring systems can be envisioned, but usually either a furanoeremophilane or a furanoeudesmone skeleton can be postulated. To distinguish between these two choices, additional interpretation of the nmr spectrum of I was necessary. The tentative assignments from Figure 2 are given in Table II and discussed below.



eremophilane A eudesmane B

Hydroxyl groups are usually found at positions 1,[12] 3,[13] and 6.[8,11] Euryopsol[8] is the only compound exhibiting this group at C-10. Based upon the fact that I would not esterify under a variety of conditions, that I eliminated H_2O under hydrogenation, and that the nmr spectrum of I

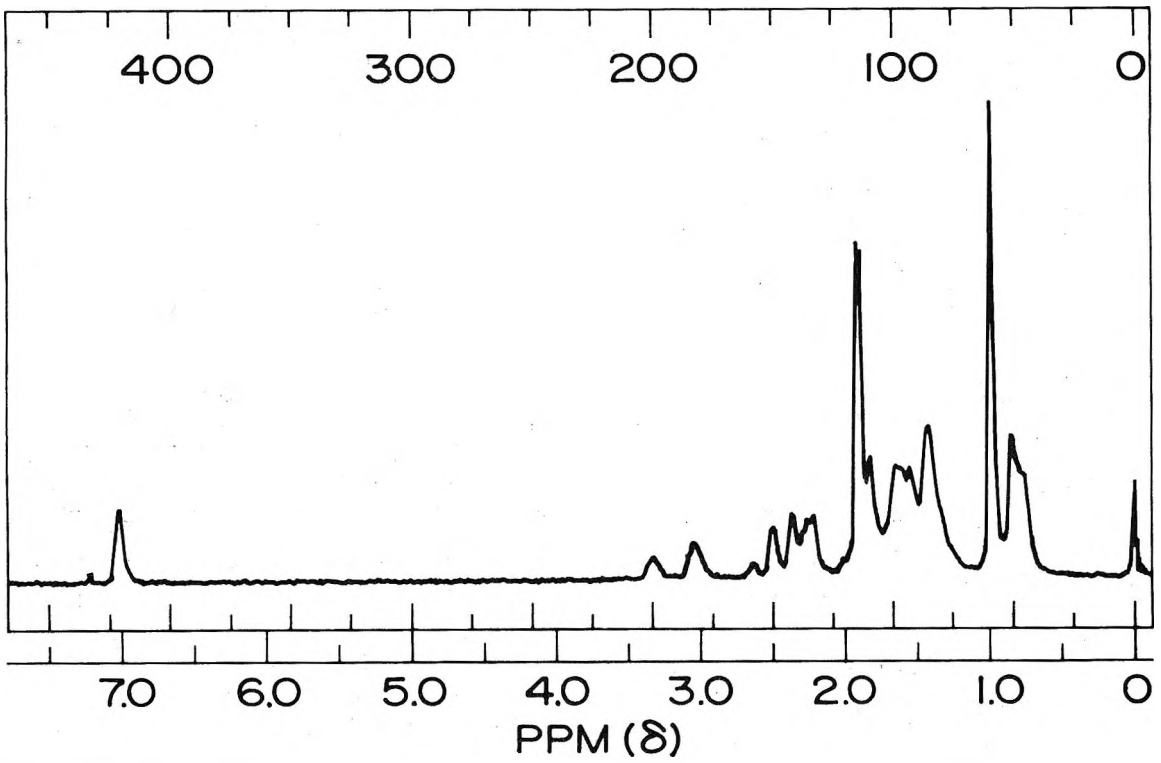


Figure 2. Nmr of I ($CDCl_3$).

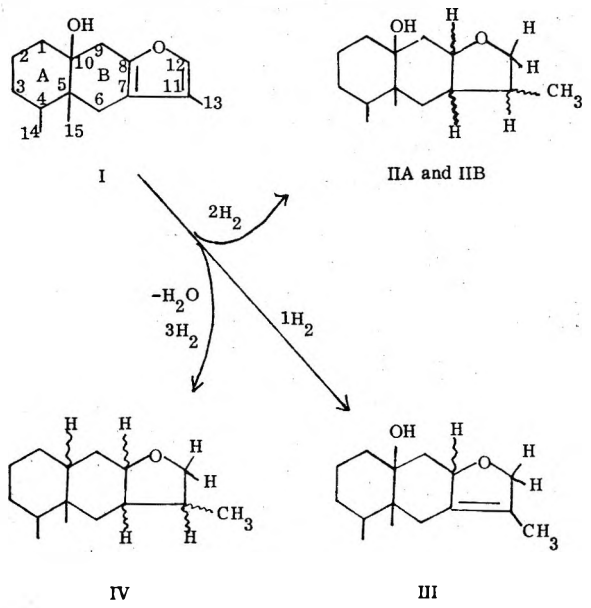
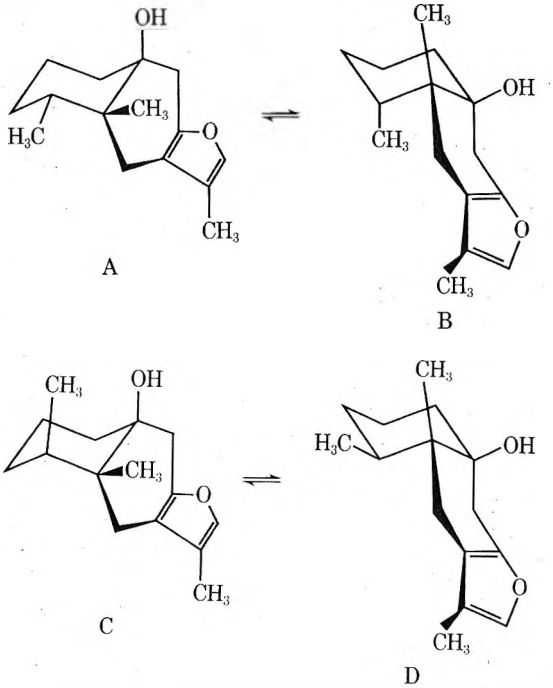


Figure 3.

showed no peaks assignable to a proton on a carbon bearing a hydroxyl, we concluded that the OH group was at a tertiary position and most likely at C-10 in A or at C-5 in B. The only other tertiary position would have been at C-4, but the methyl already assigned to that position would have been seen as a singlet rather than a doublet in the nmr spectrum.

It was extremely fortuitous to have the OH in such unique positions as it was properly disposed to yield a great deal of structural evidence when coupled with solvent-induced chemical shifts[14] from nmr spectroscopy: $\Delta_{C_5H_5N}$ ($CDCl_3$) −0.18 ppm for the tertiary methyl of tetradymol, −0.22 ppm for the tertiary methyl of the 2-chloromercury derivative, −0.03 ppm for the secondary methyl of tetradymol. As a result of these data, tetradymol was assumed to have the eremophilane skeleton with the hydroxyl at position 10. Further the dihedral angle between the 10-OH and the tertiary methyl was estimated to be 60°. Additional data on the position of the C-4 secondary methyl and the confirmation of the cyclohexane ring was obtained from the mass spectrum.

If the C-4, or secondary CH_3 is cis and axial to the hydroxyl at C-10, a six-membered-ring transition state can be envisioned for the facile loss of H_2O during mass spectral analysis. In fact, the parent ion is 23% of the base peak which suggests that a route for facile loss of H_2O is not present. Of the four possibilities shown below only C could be eliminated from these data. The stereochemistry of the C-4 CH_3 will be clarified later in this paper.



Proof of the Furan Position. Except for the C-4 methyl group stereochemistry, the remaining step in the structure proof was the proper placement of the furano ring on the perhydronaphthalene skeleton. Two general models were

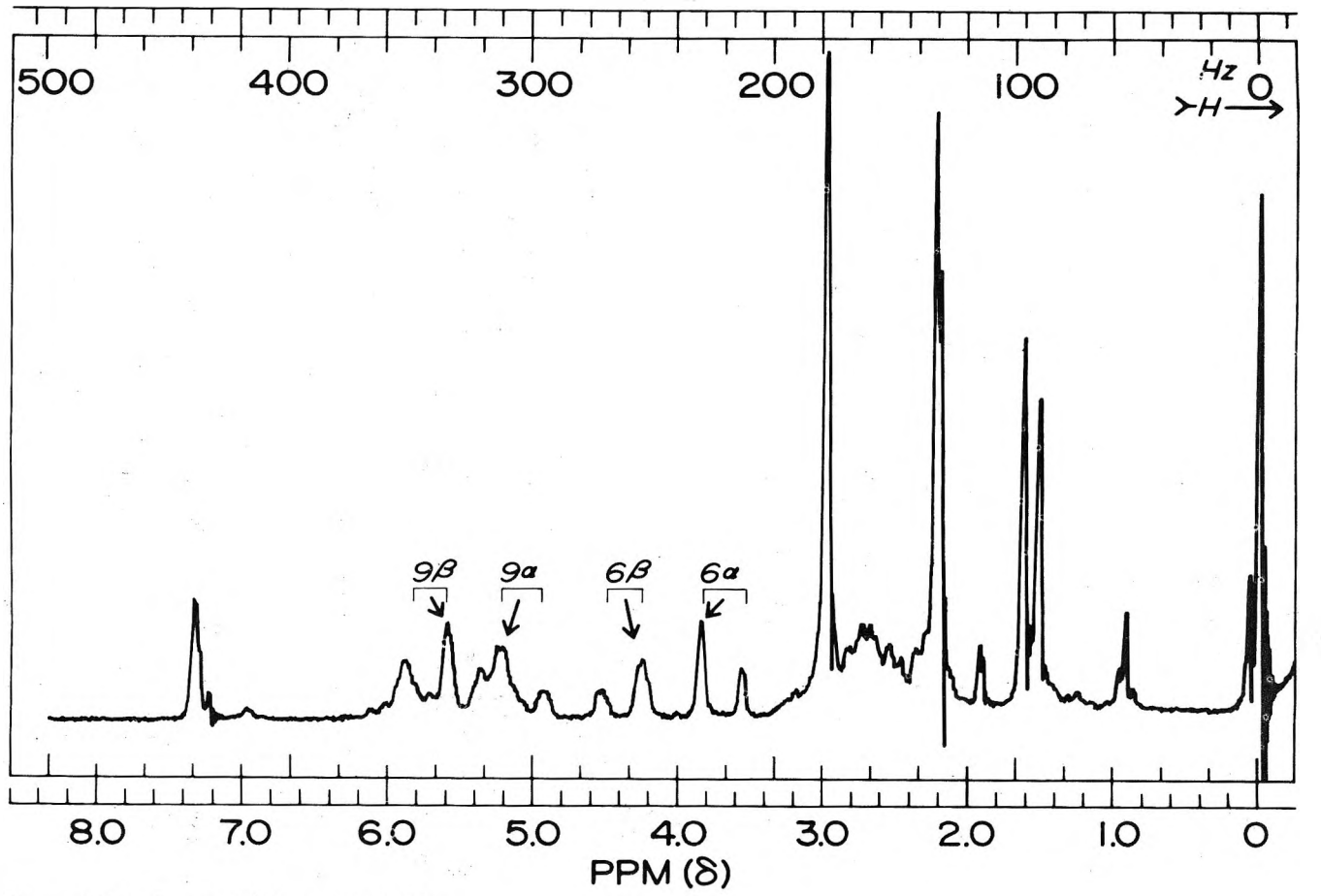
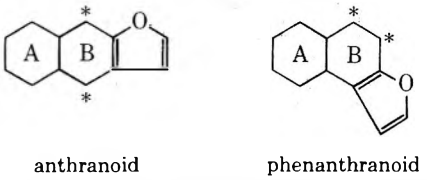


Figure 4. Tetradymol with 60 mg of $Eu(THD)_3$.

Table II

Proton	Shift (J in Hz)
4-Me	0.80 (7), "filled-in" doublet, secondary
5-Me	0.95, tertiary
1,2,3-CH_2	1.1–1.75
10-OH	1.81
13-Me	1.88 (1.1)
6,9-CH_2	2.1–3.5
12-H	7.04 (1.1)

postulated: anthranoid and phenanthranoid. These two skeletons could be easily distinguished if resonance peaks



anthranoid phenanthranoid

for the methylenes (starred) in ring B were properly sorted out in the nmr spectrum. These protons were previously assigned (Table II) to the area of 2.1–3.5 ppm in Figure 2. To sort out these peaks, their resolution was improved by using a paramagnetic shift reagent (Figure 4). $Eu(thd)_3$ was chosen rather than $Eu(fod)_3$ as the latter is known to be a stronger acid and hence might complex with both the hydroxy and the furan oxygens.[15] As will be shown, $Eu(thd)_3$ complexes solely with the hydroxyl oxygen.

Following the movement of the methylene resonances through the spectral series of increasing concentrations of shift reagent, one observes finally, in Figure 4, a clear indication of two AB or AX quartets. Decoupling experiments revealed that each quartet was independent of the other indicating that the two methylene groups were not cross-coupled as would be the case in the phenantroid skeleton. Thus it was concluded that tetradymol should be assigned the anthranoid skeleton. The AB or AX quartet arises from the fact that the β protons are in different environments than the α protons, probably owing to inflexibility of the ring system. We have tentatively[16] assigned the narrower quartet with peaks at 2.63, 2.35, 2.30, and 2.02 (J = 16.5 Hz) to the 6α and β protons. Graphical presentation of how a few of the protons of I shift *vs.* shift reagent and substrate concentrations is shown in Figure 5. Since the furan methyl and proton resonances shift only slightly and did not show any upward curvature at high concentrations of $Eu(thd)_3$, we have concluded that the reagent complexes exclusively with the hydroxyl oxygen.

Table III

Position	Portion of quartet	$\Delta_{C_5H_5N(CDCl_3)}$
9α	Downfield	−0.05
9β	Upfield	−0.25
6α	Downfield	−0.09
6β	Upfield	−0.20

One additional feature of interest in the europium work deals with the fact that the upper half of each methylene quartet shifts downfield faster than the lower half (Figure 5). This suggests that the upper portion of each quartet can be assigned predominantly to a β proton cis to the hydroxyl group. This is further corroborated by the solvent induced chemical shift data shown in Table III.

Except for the stereochemistry of the C-4 methyl group,

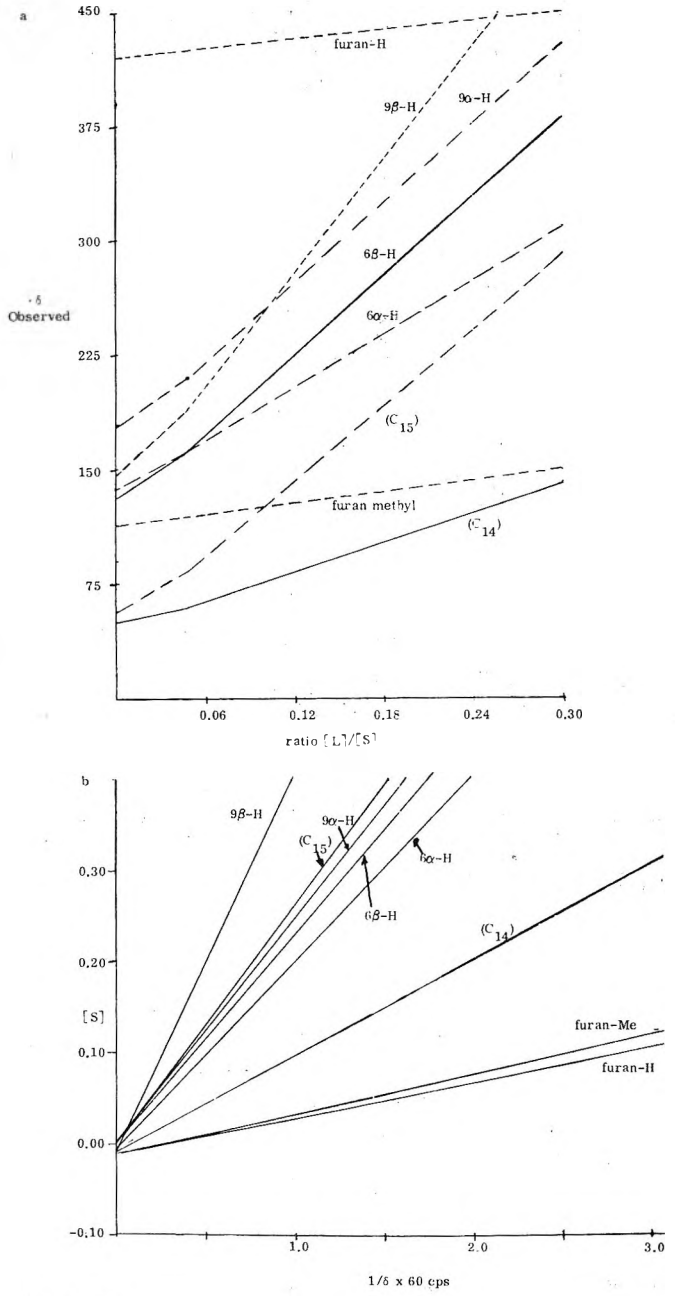


Figure 5.

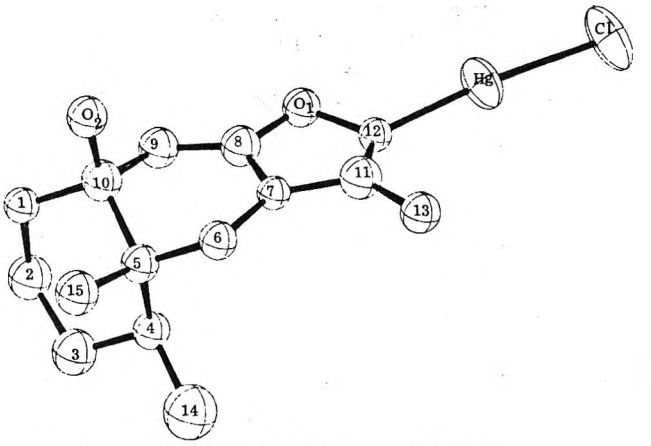


Figure 6. ORTEP drawing of tetradymol · HgCl.

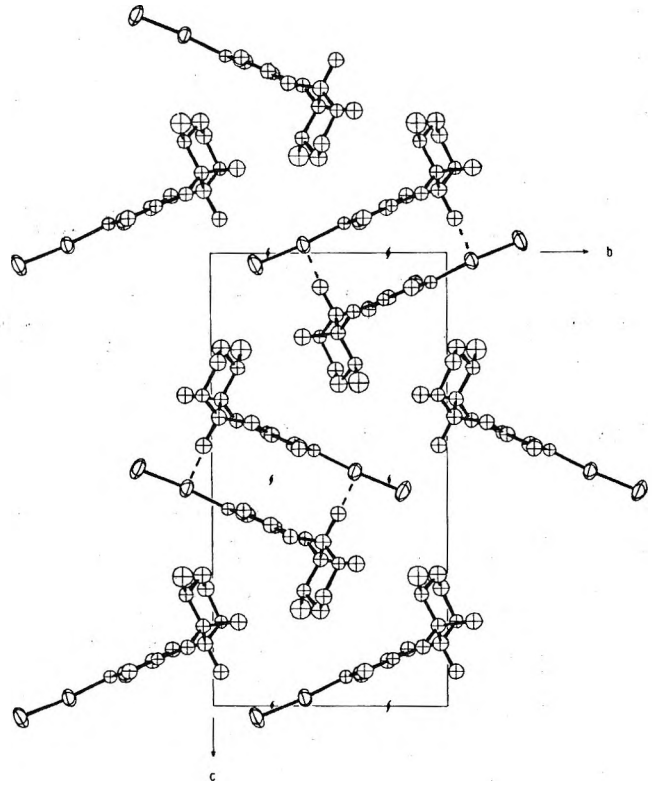


Figure 7.

the structure of tetradymol was complete. Because we could not sort this difficulty out and because there had never been an unambiguous structure proof for the furanoeremophilane system, a single-crystal X-ray analysis was performed on the 2-chloromercury derivative. The previous spectral and chemical evidence might ordinarily be regarded as penultimate to a X-ray study, but it is felt that the corroboration and correlation of these techniques may help other structural problems in this area if a single crystal X-ray facility is not available.

Discussion of X-Ray Analysis. Results of the single crystal X-ray study on the 2-chloromercury derivative of tetradymol (I) are depicted in an ORTEP drawing (Figure 6). The C(4) methyl group is equatorial in ring A and is in fact cis to both the C(5) methyl and the C(10) hydroxyl groups. Also the dihedral angle between the C(10) hydroxyl and the C(5) methyl is 57.3° which is very close to that predicted by the solvent-induced shift work. Similarity between the crystal structure and the solution structure is thus evident and would be consistent with the mass spectral data cited earlier.

Table IV

equation of plane[a] 0.0016X − 0.36276Y + 0.93188Z − 6.453 = 0

Atom	Distance to plane
Hg	0.16
Cl	0.20
C(13)	0.14
C(6)	−0.03
C(9)	−0.18

[a] The orthogonal coordinate system from which this plane is derived is defined by X along *a*, Y along *b*, and Z along *c*. The sum of the squares of the deviations of the atom from the least-squares plane is 0.005 Å².

The furan ring is nearly planar, the average deviation of the five atoms in the ring being 0.03 Å. Carbon 12 has the largest deviation of −0.05 Å. Table IV shows the distances of other atoms to the least-squares plane of the furan ring which substantiates the assumption that C(6) and C(9) are

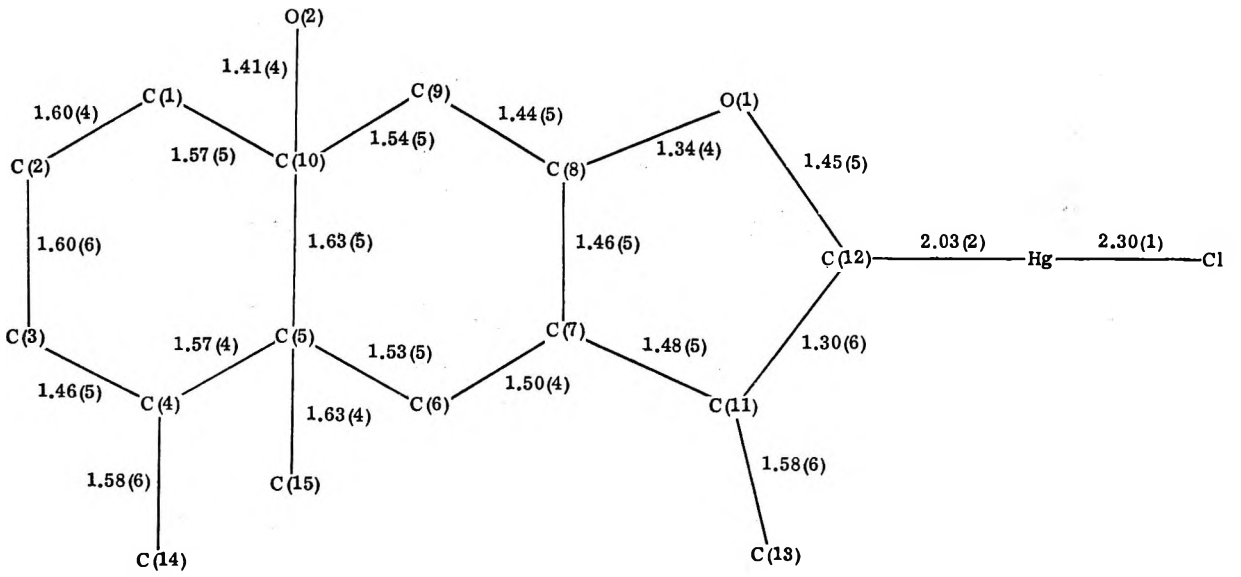


Figure 8. Bond distances.

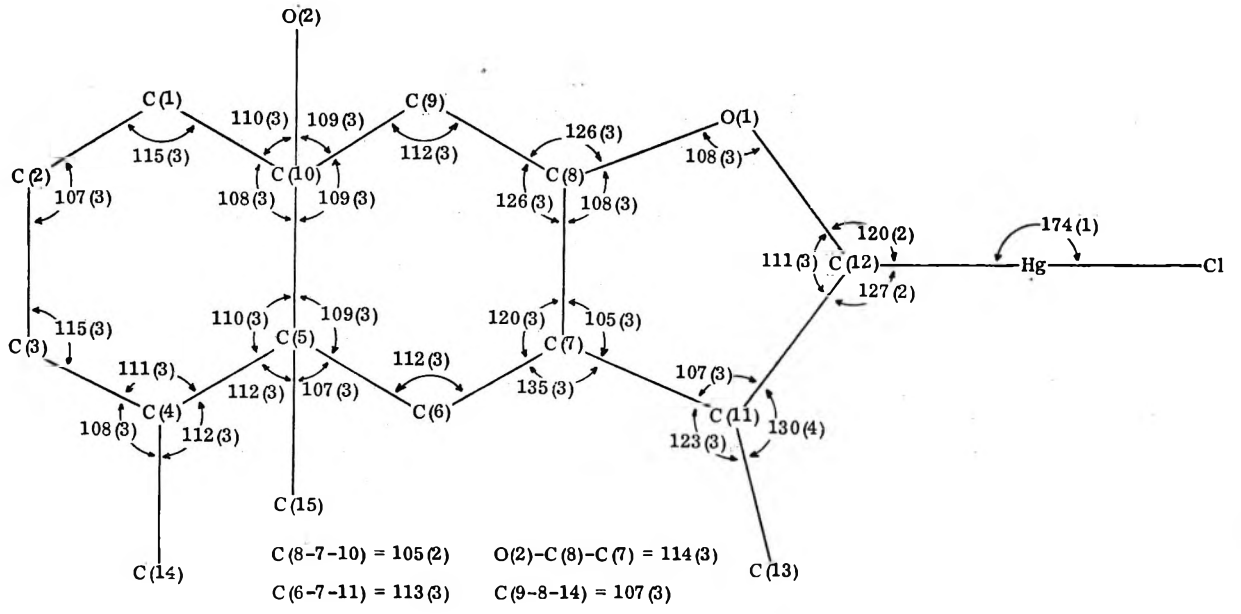


Figure 9. Bond angles.

fixed and flat resulting in the AB or AX quartet for the hydrogens.

It appears from the arrangement of the molecules within the crystal (Figure 7) that a hydrogen bond exists between the hydroxyl group, O(2), and the mercury atom, since the distance of 2.80 Å is 0.1 Å shorter than the sum of the van der Waals radii of mercury and oxygen. In fact, pairs of symmetry related molecules are hydrogen bonded by two such intermolecular interactions as shown by dotted lines in the figure. The next closest intermolecular distance was found to be 3.34 Å, between O(2) and C(13).

The bond distances and angles (Figures 8 and 9) of the light atoms differ somewhat from accepted values, but these differences are probably due primarily to small, systematic errors in the data caused by decomposition of the crystal in the X-ray beam, absorption, and the unusually large contribution of the heavy atom. The mercury–carbon and mercury–chlorine bond distances agree well with the published values.

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Registry No.—I, 52279-13-7; I HgCl, 52279-14-8; II, 52279-15-9; III, 52279-16-0; IV, 52340-24-6.

Supplementary Material Available. The Experimental Section and a listing of calculated and observed structure factors in electrons and a table of positional and thermal parameters will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $4.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3392.

References and Notes

(1) Abstracted in part from the Ph.D. Theses of S.K.R., 1971, Montana State University, and J.C.H., 1972, Montana State University.
(2) 4β,5β-Dimethyl-10β-hydroxyfuranoeremophilane.
(3) (a) C. E. Fleming, "Range Plants Poisonous to Sheep and Cattle in Nevada," Report 95, Agricultural Experiment Station, The University of Nevada (1918); (b) C. E. Fleming, M. R. Miller and L. R. Vawter, *Univ. Nevada Agr. Expt. Station Bull.*, No. 95 (1922).
(4) (a) A. B. Clawson and W. T. Huffman, *Nat. Wool Grower*, 18 (Jan 1935). (b) A. B. Clawson and W. T. Huffman, *ibid.*, 14 (March 1937). (c) A. B. Clawson and W. T. Huffman, *ibid.*, 20 (Jan 1936).

(5) There appears to be a certain sequence of events including *Tetradymia*, time, water, and possibly another plant which leads to the bighead syndrome.
(6) There may be some danger in characterizing a sheep toxin with mice, but symptoms and morphological slides were identical.
(7) When expanded this resonance is a quartet with J = 1.1 Hz. All nmr values are in δ (parts per million).
(8) G. A. Eagle, D. E. A. Rivett, D. H. Williams, and R. G. Wilson, *Tetrahedron*, **25**, 5227 (1969).
(9) H. Ishii, T. Tozyo, and H. Minato, *Tetrahedron*, **21**, 2605 (1965).
(10) L. H. Zalkow, J. W. Ellis, and Sister M. Roger Brennen, *J. Org. Chem.*, **28**, 1705 (1963).
(11) L. Novotny, Z. Samek, J. Harmatha, and F. Šorm, *Collect. Czech. Chem. Commun.*, **34**, 1739 (1969).
(12) (a) A. Stoll, R. Morf, A. Rheiner, and J. Renz, *Experentia*, **12**, 360 (1956); (b) see ref 8.
(13) T. Kubota in "Cyclopentanoid Terpene Derivatives," W. I. Taylor and A. R. Battersby, Ed., Marcel Dekker, New York, N. Y., 1969, pp 279–356.
(14) P. V. Demarco, E. Farkas, D. Doddrell, B. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).
(15) R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971).
(16) Since these quartets, especially the narrower one, are AB quartets, each doublet is not strictly one proton.

Sterol Metabolism. XXXII. Radiation-Induced Oxidation of Isomeric Cholesten-3β-ols[1]

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The air oxidation induced by ^{60}Co γ radiation of cholest-4-en-3β-ol, 5α-cholest-6-en-3β-ol, and 5α-cholest-7-en-3β-ol yielded allylic hydroperoxides and other oxidized derivatives. The Δ^4-sterol gave cholest-4-en-3-one, 6β-hydroperoxycholest-4-en-3-one, 3β-hydroxycholest-4-ene 6α-hydroperoxide, and cholest-4-ene-3β,6α-diol. The Δ^6-sterol gave cholesterol 7α- and 7β-hydroperoxides, the epimeric cholest-5-ene-3β,7-diols, 3β-hydroxycholest-5-en-7-one, and 5α-cholest-6-ene-3β,5-diol but no 3β-hydroxy-5α-cholest-6-ene 5-hydroperoxide. The Δ^7-sterol gave the epimeric 3β-hydroxy-5α-cholest-7-ene 6-hydroperoxides, the epimeric 5α-cholest-7-ene-3β,6-diols, 3β-hydroxy-5α-cholest-7-en-6-one, and cholesta-5,7-dien-3β-ol. Pyrolysis of either Δ^7-6-hydroperoxide gave the corresponding 5α-cholest-7-ene-3β,6-diol, 3β-hydroxy-5α-cholest-7-en-6-one, and cholesta-5,7-dien-3β-ol. Reaction pathways for oxidations by radiation-induced processes of the isomeric Δ^4-, Δ^5-, Δ^6-, and Δ^7-sterols and for their photosensitized oxidations in which singlet molecular oxygen is implicated were compared.

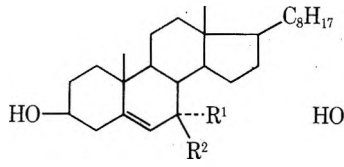
We have recently demonstrated that radiation-induced oxidation of the Δ^5-sterol cholesterol (**1a**) by air afforded the epimeric 7-hydroperoxides **1b** and **1c**,[3] with the quasi-equatorial[4] 7β-hydroperoxide **1c** predominating. In contrast oxidation of cholesterol by excited-stage (singlet) molecular oxygen yielded the 5α-hydroperoxide **3b** as major product, with small amounts of the epimeric 3β-hydroxycholest-4-ene 6-hydroperoxides **2b** and **2c** but with neither 7-hydroperoxide **1b** nor **1c** formed.[5] This distinction in major products formed provides a means of differentiation between participation of ground-state or of singlet molecular oxygen in chemical and enzymic[6] reactions.

Although the mechanism of attack of singlet molecular oxygen on steroid olefins has been extensively studied, free-radical oxidations by ground-state molecular oxygen have not received systematic attention. In order to determine whether additional distinctions between free-radical and singlet molecular oxygen oxidations of sterol olefins existed, as well as to provide additional substrates for use as probes in reactions in which cholesterol was unsuited, we examined the oxidation of cholest-4-en-3β-ol (**2a**), 5α-cholest-6-en-3β-ol (**3a**), and 5α-cholest-7-en-3β-ol (**4a**) induced by γ radiation of ^{60}Co for comparison with their previously reported behavior toward singlet molecular oxygen.

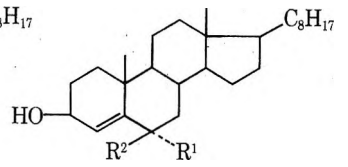
Oxidation of the Δ^4-3β-alcohol **2a** yielded cholest-4-en-3-one (**5a**) as major product, with 6β-hydroperoxycholest-4-en-3-one (**5b**) as the major hydroperoxide product. Small amounts of the 6α-hydroperoxide **2b** were also formed. The Δ^4-3-ketone **5a** was stable to ^{60}Co γ radiation, but irradiation of the pure Δ^4-6β-hydroperoxide **2c** yielded **5b** along with previously recognized thermal decomposition products cholest-4-ene-3β,6β-diol (**2e**) and 3β-hydroxycholest-4-en-6-one (**6**).[5] Accordingly, the 6β-hydroperoxide **5b** did not derive from **5a** but must have derived from **2c**. Inadequate amounts of the 6α-hydroperoxide **2b** precluded study of its radiation stability.

Formation of the 6-ketone **6** as a thermal decomposition product from **2c** was previously supported by detection of its pyrolysis products cholest-4-ene-3,6-dione (**7**) and 5α-cholestane-3,6-dione (**8**) among pyrolysis products from **2c**.[5] Direct observation of **6** following irradiation of **2c** now clearly establishes this reaction pathway of the 6β-hydroperoxide **2c**. However, pyrolysis of the 6β-hydroperoxide **5b** also gave the 3,6-diketones **7** and **8** as prominent products, a point previously suggested but not examined.[5] Derivation from **5b** of the saturated 3,6-diketone **8** must involve intermediate formation of 6β-hydroxycholest-4-en-3-one (**5c**) which then rearranges to **8**. Formation from **2c** of the Δ^4-3,6-diketone **7** may occur by three pathways— **2c** to **5b** to **7**, **2c** to **5b** to **5c** to **7**, or **2c** to **6** to **7**—whereas that of the saturated 3,6-diketone **8** may be by two pathways—**2c** to **5b** to **5c** to **8** and **2c** to **6** to **8**.

Oxidation of the Δ^6-3β-alcohol **3a** gave unexpectedly the epimeric cholesterol 7-hydroperoxides **1b** and **1c** as major products, the 7β-hydroperoxide **1c** predominating. The secondary oxidation products cholest-5-ene-3β,7α-diol (**1d**), cholest-5-ene-3β,7β-diol (**1e**), 5α-cholest-6-ene-3β,5-diol (**3c**), and 3β-hydroxycholest-5-en-7-one (**9**) were also formed. However, no 5α-hydroperoxide **3b** was detected. The 5α-hydroperoxide **3b** was fairly stable to ^{60}Co γ radiation in air, with less than 10% being converted to a mixture of **1b**, **1c**, **1d**, **1e**, and **3c**. Accordingly, were **3b** formed from **3a** initially, **3b** would have survived and been detected. Thus, initial formation of **3b** with complete allylic rearrangement to **1b**, epimerization of **1b**, and thermal decomposition of **1b**, **1c**, and **3b** cannot account for the presence of **1b**, **1c**, **1d**, **1e**, and **3c** as products from **3a**. Residual parent sterol **3a** recovered after ^{60}Co irradiation was not contaminated with detectable amounts of cholesterol, so the product 7-hydroperoxides **1b** and **1c** did not derive by initial isomerization of the Δ^6-double bond to the Δ^5 position, followed by oxidation of cholesterol thereby formed. Rath-



1a, $R^1 = R^2 = H$
b, $R^1 = OOH$; $R^2 = H$
c, $R^1 = H$; $R^2 = OOH$
d, $R^1 = OH$; $R^2 = H$
e, $R^1 = H$; $R^2 = OH$



2a, $R^1 = R^2 = H$
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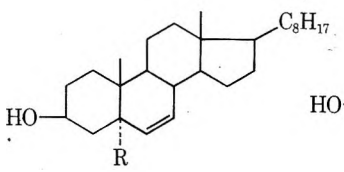
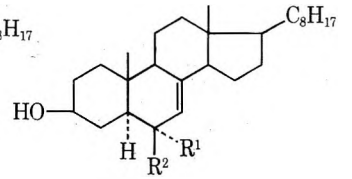
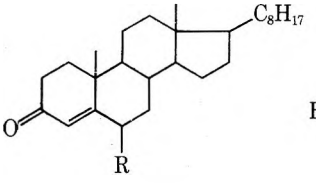
e, $R^1 = H$; $R^2 = OH$



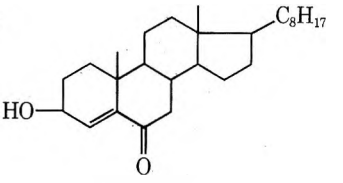
3a, R = H
b, R = OOH
c, R = OH



4a, $R^1 = R^2 = H$
b, $R^1 = OOH$; $R^2 = H$
c, $R^1 = H$; $R^2 = OOH$
d, $R^1 = OH$; $R^2 = H$
e, $R^1 = H$; $R^2 = OH$



5a, R = H
b, R = OOH
c, R = OH



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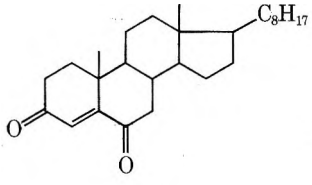

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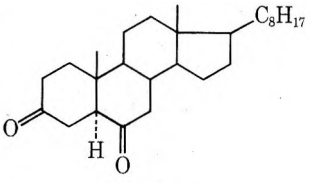

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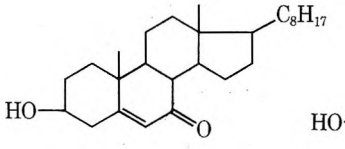

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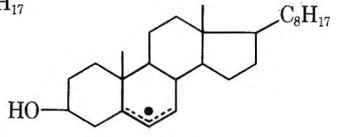

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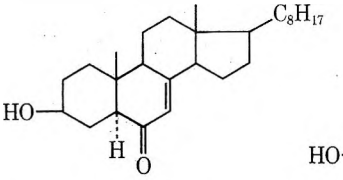
er, initial generation from **3a** of a mesomeric free-radical species **10** from which the Δ^5-7-hydroperoxides **1b** and **1c** were derived appears to be the case. The quasiequatorial 7β-hydroperoxide **1c** predominated, as it does in the radiation-induced oxidation of **1a**.[3] The secondary products **1d**, **1e**, and **9** are clearly accounted for as thermal decomposition products of the initially formed 7-hydroperoxides **1b** and **1c**.[3,4,7] The 3β,5α-diol **3c** must derive by allylic rearrangement of the Δ^5-7α-alcohol **1d** in that the parent 5α-hydroperoxide **3b** was not implicated.

Oxidation of the Δ^7-sterol **4a** yielded a complex mixture of products including four peroxides, two of which were prominent and which could be recovered. The major hydroperoxide was 3β-hydroxy-5α-cholest-7-ene 6β-hydroperoxide (**4c**); the other was the epimeric 6α-hydroperoxide (**4b**). The 6β-hydroperoxide **4c** was also found in commercial samples of **4a** which had been stored for some time in the laboratory.[8] Identity of the Δ^7-6-hydroperoxides was established by sodium borohydride reduction to the corresponding alcohols, thus **4b** to **4d** and **4c** to **4e**.

Other products formed from **4a** were the epimeric Δ^7-3β,6-diols **4d** and **4e**, the Δ^7-6-ketone **11**, and cholesta-5,7-dien-3β-ol (**12**), all recognized as thermal decomposition



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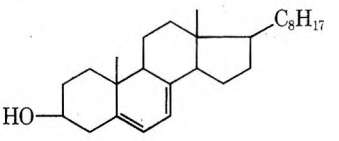

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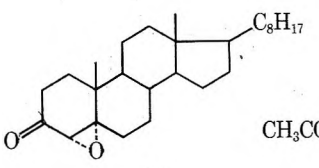

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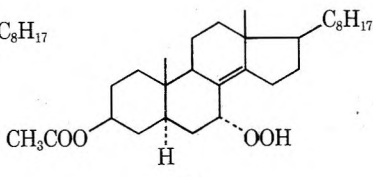

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products of the parent 6-hydroperoxides **4b** and **4c**. Pyrolysis of the 6α-hydroperoxide **4b** gave the corresponding 6α-alcohol **4d**, the 6-ketone **11**, and the 5,7-diene **12** as major product. Pyrolysis of the epimeric 6β-hydroperoxide **4c** gave likewise the 6β-alcohol **4e**, the 6-ketone **11**, and the 5,7-diene **12**, also as major product.

The Δ^7-3β,6-diols **4d** and **4e** both survived pyrolysis in part, but both were dehydrated to the 5,7-diene **12** as chief product. The 3β,6β-diol **4e** additionally was epimerized to **4d**, dehydrogenated to the 6-ketone **11**, and dehydrated to a nonpolar derivative, presumably cholesta-2,4,6-triene or cholesta-3,5,7-triene. Thermal epimerization of the 6β-alcohol **4e** but not of the epimeric 6α-alcohol **4b** taken with the greater number of pyrolysis products from **4e** infers the less stable quasiaxial conformation for the 6β-hydroxy group. However, in distinction to the Δ^5-7α-oxygenated sterols **1b** and **1d**,[4,7a] neither the Δ^7-6-alcohols **4d** and **4e** nor the Δ^7-6-hydroperoxides **4b** and **4c** were epimerized in acetone solutions.

The 5,7-diene **12** detected as the major pyrolysis product from **4b**, **4c**, **4d**, and **4e** was present as a minor component among the oxidation products from **4a**. The instability of **12** in air is notorious, and irradiation of **12** yielded a very complex mixture of oxidized products including sterol peroxides, some of which had chromatographic properties similar to uncharacterized sterol peroxide derivatives derived by irradiation of **4a**. The two unidentified peroxides from **4a** may include the theoretically possible 9α- or 14α-hydroperoxides of **4a** or the Δ^6-5α,8α-epidioxide derivative of the 5,7-diene **12**.

The facile thermal elimination reactions of **4b**, **4c**, **4d**, and **4e** yielding the 5,7-diene **12** provoke recollection of the conversion of the Δ^7-sterol **4a** to **12** by liver microsomal enzymes, which conversion requires molecular oxygen.[9] An enzyme–molecular oxygen complex has been suggested[10] which moderates cis elimination of the 5α- and 6α-hydrogens,[11] the 6α-hydrogen being removed as a proton and not as hydride ion.[12] Although the Δ^7-6-alcohols **4d** and **4e** are converted by liver microsomal enzymes to cholesterol, presumably *via* the 5,7-diene **12**, they do not appear to be natural intermediates,[10a,13] and speculations regarding involvement of sterol peroxides or hydroperoxides have been made.[14] In view of experimental evidence for the participation of cholesterol 20α-hydroperoxide in the biosynthesis of 3β-hydroxypregn-5-en-20-one from cholesterol in the adrenal cortex,[15] the possibility that the Δ^7-6α-hydroperoxide **4b** serves as an intermediate in the bioconversion of **4a** to **12** should not be overlooked.

The radiation-induced oxidations of **2a, 3a,** and **4a** thus took different courses from one another, and only the oxidation of the Δ^7-3-alcohol **4a** followed the same direct course of abstraction of the allylic methylene hydrogens and formation of both epimeric allylic hydroperoxides without double bond migration, as found for cholesterol.[3] The marked preference for formation of the quasiequatorial 7β-hydroperoxide **1c** from cholesterol was not seen in the case of the isomeric sterols **2a, 3a,** and **4a.** Rather, more nearly equal amounts of epimeric hydroperoxides were formed. For **2a** the product ratio (**2b** + **2d**):**5b** was 1:1; for **3a** the ratio **1b**:**1c** was approximately 1:2; for **4a** the ratio (**4b** + **4d**):(**4c** + **4e**) was 3:5.

Radiation-induced oxidations of **2a, 3a,** and **4a** take different courses from their previously reported oxidations by singlet molecular oxygen. Reaction of the Δ^4-sterol **2a** with singlet molecular oxygen is complex,[16] with the Δ^4-3-ketone **5a** and 4α,5-epoxy-5α-cholestan-3-one (**13**) as major products.[16a] However, the variable amounts of **5a** found relative to the epoxy ketone **13**[16c-e] and our present demonstration of the ease with which **5a** is formed from **2a** by radiation-induced free-radical attack of molecular oxygen suggest that **5a** also arises from **2a** in photosensitized oxidations by hydrogen atom abstraction and free-radical attack of molecular oxygen and not by attack of singlet molecular oxygen.[17] Formation of the epoxy ketone **13** from singlet molecular oxygen attack on **2a** *via* the putative intermediate 3-hydroxy-5α-cholest-3-ene 5-hydroperoxide[16a,c] would then be the likely event.

Attack of singlet molecular oxygen on the Δ^6-sterol **3a** and on the 3β-acetate of **3a** yielded the expected Δ^5-7α-hydroperoxide **1b** and the 3β-acetate of **1b,** respectively, as major product.[19] Small amounts of epimeric 7β-hydroperoxide **1c** were also apparently formed but not noticed.[19] By contrast free-radical oxidation of **3a** gave the same epimeric Δ^5-7-hydroperoxides **1b** and **1c** but with the quasiequatorial 7β-hydroperoxide **1c** predominating.

Singlet molecular oxygen attack on the 3β-acetate of the Δ^7-sterol **4a** proceeded by abstraction of the 14α-hydrogen and formation of 3β-acetoxy-5α-cholest-8(14)-ene 7α-hydroperoxide (**14**) as initial product, which itself was oxidized by singlet molecular oxygen to yield 3β-acetoxy-5α-cholest-14-ene 7α,8α- and 7α,8β-dihydroperoxides.[16c] The Δ^7-sterol **4a** also consumed two molecules of oxygen in photosensitized oxidations, but products were not isolated. It would seem likely that the same course of oxidation be taken for both **4a** and its 3β-acetate however. The point of attack and the sensitivity to further oxidation of the initially formed hydroperoxide are thus in total distinction to the behavior of **4a** in radiation-induced free-radical oxidations.

These results establish that the Δ^7-sterol **4a** as well as cholesterol, but not the Δ^4- and Δ^6-sterols **2a** and **3a,** may serve as probes in test of the electronic excitation state of molecular oxygen involved in chemical and enzymic reactions.

Experimental Section[20]

Irradiation Conditions. Pure crystalline samples of the parent sterols **2a, 3a,** and **4a** were irradiated in glass beakers open to the air for 16–20 hr (2.7×10^5 rads/hr) with ^{60}Co γ radiation from a Gammacell 200 (Atomic Energy of Canada Ltd., Ottawa), after which time the samples were recrystallized from methanol–diethyl ether. Recovered parent sterol free from detectable oxidation products was again irradiated and recrystallized. Irradiation and recrystallization were repeated several times to provide adequate amounts of oxidation products. Mother liquors containing oxidation products were evaporated under vacuum, and the combined residues were chromatographed on 1.0-mm thick chromatoplates using benzene–ethyl acetate (1:1) with triple development. Sterol components were detected and characterized by their thin-layer chromatographic mobility factors R (*vs.* the indicated parent sterol **2a, 3a,** or **4a** as unit mobility), color response to sulfuric acid spray, sterol peroxide test, and ultraviolet light absorption. Each resolved component was excised from the chromatoplate and eluted with acetone for further purification and for identification.

Pyrolysis Conditions. Analytical gas chromatography of **2b, 4b, 4c, 4d, 4e, 5b,** and **12** was conducted in the usual manner[7a,b,22] to obtain characteristic patterns of pyrolysis products. Gas chromatography of 1-mg samples, dissolved in 200 μl of acetone, was conducted for collection of all pyrolysis products in a single glass capillary.[21] The pyrolysis products were then chromatographed on a chromatoplate using benzene–ethyl acetate (1:1) with triple development and visualization in the same manner described for irradiation products. Pyrolysis products were eluted with acetone and recovered by evaporation of the solvent under vacuum for further purification and for identification.

Oxidation of Cholest-4-en-3β-ol (2a). From 75.3 mg of **2a,** mp 132–133°, irradiated and recrystallized, there was recovered 58.1 mg of pure **2a,** mp 131–133° (lit. mp 128–132°[23a]). Chromatography of the mother liquors resolved five components characterized and identified as follows: (a) R 1.13, yellow color, ultraviolet light absorbing, **5a;** (b) R 1.06, yellow color, positive peroxide test, ultraviolet light absorbing, **5b;** (c) R 1.00, pink color, **2a;** (d) R 0.72, tan color, positive peroxide test, **2b;** (e) R 0.56, tan color, positive peroxide test; and (f) R 0.32, tan color **2d.**

Cholest-4-en-3-one (5a). Fraction a derived from irradiation of **2a** was recovered and crystallized from methanol, yielding 2.1 mg of **5a,** mp 79–81° (lit. mp 76–82°[23a]); t_R 2.33; identical with authentic **5a** by uv, ir, tlc, and gc comparisons.

Irradiation of pure **5a** for 24 hr with ^{60}Co radiation did not afford chromatographically detectable alteration products.

6β-Hydroperoxycholest-4-en-3-one (5b). Fraction b derived from **2a** recovered from the acetone eluate yielded 1.0 mg of **5b,** homogeneous by thin-layer chromatography, identified by its characteristic pyrolysis pattern with components at t_R 0.38, 1.48, 1.98 (**2e**), 6.65 (**8**), and 7.14 (**7**). Identity of **5b** was further established by reductions to **2e** and to **5c.**

Irradiation of 0.2 mg of **2c** for 18 hr yielded a mixture of products, chief among which were **2e, 6,** and **5b,** all identified by their thin-layer chromatographic properties.

Cholest-4-ene-3β,6β-diol (2e). A small amount of **5b** (derived from **2a**) in methanol was reduced with an excess of sodium borohydride, yielding the 3β,6β-diol **2e,** R 0.31 in benzene–ethyl acetate (1:1); steel blue color with 50% sulfuric acid; pyrolysis pattern t_R 0.44, 0.81. and 2.00; identical in these properties with those of an authentic sample of **2e.**[5]

6β-Hydroxycholest-4-en-3-one (5c). A small sample of **5b** (derived from **2a**) was reduced with sodium iodide and acetic acid, yielding **5c,** R 0.62 in benzene–ethyl acetate (1:1); yellow color with 50% sulfuric acid; pyrolysis pattern t_R 6.65 (**8**) and 7.14 (**7**); identical in these properties with those of an authentic reference sample of **5c.**

3β-Hydroxycholest-4-ene 6α-Hydroperoxide (2b). Fraction d derived from **2a** yielded 0.7 mg of **2b,** homogeneous by thin-layer chromatography, identified as such by its characteristic pyrolysis pattern on gas chromatography: t_R 1.48, 1.98 (**2d**), 6.66 (**8**), and 7.14 (**7**), and by reduction to **2d.**

Cholest-4-ene-3β,6α-diol (2d). (A) From 2a. Fraction f from irradiated **2a** yielded 0.3 mg of **2d,** identified as such by its chromatographic properties R 0.32 in benzene–ethyl acetate (1:1); tan color with 50% sulfuric acid; pyrolysis pattern t_R 0.44, 0.80, and 2.04; identical in these properties with those of an authentic reference sample of **2d.**[5]

(B) From 2b. A small sample of **2b** derived from irradiation of **2a** was reduced with an excess of sodium borohydride in methanol, yielding the 3β,6α-diol **2d,** R 0.32 in benzene–ethyl acetate (1:1); tan color with 50% sulfuric acid; pyrolysis pattern t_R 0.44, 0.81, and 2.04; identical in these properties with those of an authentic reference sample of **2d.**[5]

Fraction e derived from **2a** was recovered on evaporation of the acetone eluates, yielding 0.2 mg of an unidentified sterol peroxide characterized by a characteristic pyrolysis pattern t_R 0.37, 1.92, and 2.66. From fraction c 5.3 mg of unaltered parent sterol **2a,** mp 130–133°, was recovered.

Oxidation of 5α-Cholest-6-en-3β-ol (3a). Irradiation of a 3.2-mg pure crystalline sample of **3a** (free from **1a** and other detectable sterols) was conducted for 20 hr. Direct thin-layer chromatography of the entire irradiated sample without prior recrystallization to recover **3a** resolved six zones: (a) R 1.00, orange-red color, **3a;** (b) R 0.74, instant blue color, positive peroxide test, **1b** and **1c;**

(c) *R* 0.62, no color, ultraviolet light absorbing, **9**; (d) *R* 0.53, instant blue color, **3c** (trace only); (e) *R* 0.42, instant blue color, **1e**; (f) *R* 0.35, instant blue color, **1d**.

3β-Hydroxycholest-5-ene 7-Hydroperoxides (1b and 1c). Fraction b derived from **3a** recognized to contain **1b** and **1c** by thin-layer chromatography was reduced with sodium borohydride in methanol, and the product 3β,7-diols **1d** and **1e** were identified as such by additional thin-layer and gas chromatographic analyses. Based on relative intensity of color response of the 3β,7-diols **1d** and **1e** to 50% sulfuric acid spray the 7β-hydroperoxide **1e** was present in approximately twice the amount as **1d**. No **3c** indicative of the presence of **3b** among the hydroperoxide products from **3a** was detected despite a careful search.

Identity of fractions c, d, e, and f from **3a** containing **9**, **3c**, **1e**, and **1d**, respectively, was achieved by additional thin-layer and gas chromatographic analyses. Behavior identical with that of authentic reference sterols was obtained in each case. Identity of recovered **3a** was carefully checked by thin-layer chromatography using benzene–ethyl acetate (7:3) with triple ascending development, which technique resolved **3a** (*R* 0.93) from **1a** (*R* 1.00). No **1a** was detected in **3a** recovered from fraction a.

A 2.1-mg sample of **3b** was irradiated for 20 hr. Analysis of the sample indicated that approximately 90% of the 5α-hydroperoxide **3b** was unaltered and that only approximately a 10% conversion of **3b** to a mixture of **1b** and **1c** had occurred. Traces of the epimeric 3β,7-diols **1d** and **1e** and of the 3β,5α-diol **3c** were also detected.

Oxidation of 5α-Cholest-7-en-3β-ol (4a). From 715 mg of pure **4a**, mp 120–122°, free from **12**, irradiated, a total of 215 mg of **4a**, mp 119–121° (lit. mp 118–127°[23d]), was recovered by recrystallization. The combined mother liquors were complex, but nine discrete zones were resolved for characterization and recovery work, as follows: (a) *R* 1.25, purple color, containing several components, not examined further; (b) *R* 1.00, tan turning purple color, **4a**;[24] (c) *R* 0.85, tan color, positive peroxide test, **4c**;[24] (d) *R* 0.81, tan color, positive peroxide test, **4b**;[24] (e) *R* 0.77, yellow color, ultraviolet light absorbing, **11**; (f) *R* 0.60, tan color, positive peroxide test, not examined further; (g) *R* 0.50, tan color, positive peroxide test, not examined further; (h) *R* 0.35, tan color turning purple, **4e**; (i) *R* 0.30, tan color turning purple, **4d**.

3β-Hydroxy-5α-cholest-7-ene 6α-Hydroperoxide (4b). Fraction d derived from **4a** was rechromatographed several times using benzene–ethyl acetate (1:1) with triple development. Elution of the *R* 0.81 component with acetone yielded 6:8 mg of **4b**, homogeneous by thin-layer chromatography but which could not be crystallized. The 6α-hydroperoxide **4b** was characterized by thin-layer chromatographic mobility, *R* 0.81, in benzene–ethyl acetate (1:1) and by a characteristic pyrolysis pattern which included major components at t_R 1.21, 3.08, 4.07, 5.68, 6.17, and 7.18.

3β-Hydroxy-5α-cholest-7-ene 6β-Hydroperoxide (4c). From fraction c crude **4c** was recovered which was rechromatographed several times on both 0.25 and 1.0 mm thick chromatoplates using the system benzene–ethyl acetate (1:1) with triple development, yielding 13.4 mg of pure **4c**. Recrystallization of the sterol from methanol gave the analytical sample of **4c**, mp 145–149°: $\bar{\nu}_{max}$ (KBr) 3375, 3150, 1650, and 1055 cm^{-1}; pyrolysis pattern t_R 1.20, 3.00, 4.06, 5.69, 6.16, 7.17.

Anal. Calcd for $C_{27}H_{46}O_3$: C, 77.46; H, 11.08. Found: C, 77.74; H, 10.89.

A commercially obtained sample of **4a** stored as received for some months in the laboratory was recrystallized from methanol–diethyl ether, and the mother liquors were chromatographed on thin-layer chromatoplates using benzene–ethyl acetate (1:3) with double development. The parent sterol **4a** was recovered from a zone at R_f 0.71. The major peroxide zone at R_f 0.64 was identified as **4c** by additional thin-layer and gas chromatography. A third component at R_f 0.57 was identified as the Δ^7-6-ketone **11** by thin-layer and gas chromatography.

5α-Cholest-7-ene-3β,6α-diol (4d). (A) From 4a. Fraction i from irradiation of **4a** was eluted and the sterol recrystallized from methanol, yielding 8.5 mg of pure **4d**, mp 186–188° (lit. mp 192°;[25a] mp 178–179° and 185–186°;[13b] mp 114°[25b]); pyrolysis pattern t_R 1.20, 1.49, 2.88, and 3.08; identical with authentic **4d** prepared by hydroboration of **12**[25a] by ir, tlc, and gc comparisons.

(B) From 4b. A solution of 3.5 mg of **4b** in methanol was treated with an excess of sodium borohydride and the product recovered, yielding 2.7 mg of **4d** as colorless crystals, mp 184–188°; identical in spectral and chromatographic properties with an authentic reference sample of **4d**.

(C) From Pyrolysis. Pyrolysis of **4b**, **4c**, **4d**, and **4e** yielded a component recognized as **4d** by thin-layer chromatography. Elution and thin-layer chromatography confirmed the presence of **4d**, further recognized by its characteristic pyrolysis pattern which included components at t_R 1.20 (**12**), 1.49, 2.88, and 3.08 (**4d**).

5α-Cholest-7-ene-3β,6β-diol (4e). (A) From 4a. Fraction h from irradiation of **4a** was eluted and recrystallized from methanol, yielding 11.3 mg of **4e**, mp 204–207° (lit. mp 207–209°;[13a] mp 204–207°[13b]); pyrolysis pattern t_R 1.19, 1.48, and 3.00; identical with authentic **4e** prepared by sodium borohydride reduction of **11**[13b] by ir, tlc, and gc comparisons.

(B) From 4c. A solution of 3.4 mg of **4c** in methanol was reduced with an excess of sodium borohydride and the product recovered, yielding 2.3 mg of pure **4e**, mp 205–207°; identical in spectral and chromatographic properties with those of an authentic reference sample of **4e**.

(C) From Pyrolysis. Pyrolysis of **4c** and **4e** yielded a component recognized as **4e**. Elution from the chromatoplate and additional thin-layer chromatography confirmed identity as **4e**, further recognized by its characteristic pyrolysis pattern which included components at t_R 1.19 (**12**), 1.48, and 3.00 (**4e**).

3β-Hydroxy-5α-cholest-7-en-6-one (11). (A) From Irradiation of 4a. Fraction e obtained by irradiation of **4a** was rechromatographed on 1.0 mm thick chromatoplates using chloroform–acetone (23:2) with triple ascending development. The ultraviolet light absorbing zone was eluted with acetone, yielding 28.5 mg of **11**, mp 195–197° (lit. mp 196–197°;[26] mp 162–164°[13b]); t_R 4.07, 5.69, 6.17, and 7.16; identical with authentic **11** by uv, ir, tlc, and gc comparisons.

(B) From Pyrolysis of 4b, 4c, and 4e. Pyrolysis of **4b**, **4c**, and **4e** gave in each case a component with thin-layer chromatographic properties of **11**. Elution of the component gave chromatographically homogeneous **11**, identified by comparison of spectral and chromatographic properties with those of an authentic reference sample of **11**.

Cholesta-5,7-dien-3β-ol (12). (A) From Pyrolysis of 4b, 4c, 4d, and 4e. The major pyrolysis product from **4b**, **4c**, **4d**, and **4e** was eluted from the thin-layer chromatoplate with acetone and crystallized from methanol, yielding **12**, typically characterized by mp 148–150° (lit. mp 142–150°[23a]); t_R 1.20; identical with authentic **12** by uv, ir, tlc, and gc comparisons.

(B) From Irradiation of 4a. Fraction b obtained by irradiation of **4a** was eluted with acetone and crystallized from methanol, yielding 228 mg of **4a**, mp 119–122° (lit. mp 118–127°[23a]), recognized as containing the 5,7-diene **12** as contaminant by chromatographic and spectral data. Thin-layer chromatography of the recovered **4a** using benzene–ethyl acetate (6:1) with triple development resolved **4a** at R_f 0.66 (tan color turning purple with 50% sulfuric acid) and **12** at R_f 0.70 (steel blue color). Absorption of the recovered **4a** fraction exhibited λ_{max}(EtOH) 271.5, 282, and 293 nm characteristic of **12**. From the absorbance of the 282-nm band approximately 0.3% of **12** in the recovered **4a** sample was indicated.

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Registry No.—**1b**, 2846-29-9; **1c**, 36871-91-7; **2a**, 517-10-2; **2b**, 41-209-89-6; **2d**, 15013-60-2; **2e**, 570-88-7; **3a**, 22420-06-0; **4a**, 80-99-9; **4b**, 52718-87-3; **4c**, 52555-46-1; **4d**, 2259-91-8; **4e**, 2259-90-7; **5a**, 601-57-0; **5b**, 2207-76-3; **5c**, 570-89-8; **11**, 14858-06-1; **12**, 434-16-2.

References and Notes

(1) Paper XXXI of the series: Y. Y. Lin and L. L. Smith, *J. Label. Compounds*, in press. Financial support of these studies was kindly provided by the Robert A. Welch Foundation, Houston, Tex.
(2) Robert A. Welch Foundation Postdoctoral Fellow, 1972–1974.
(3) L. L. Smith, J. I. Teng, M. J. Kulig, and F. L. Hill, *J. Org. Chem.*, **38**, 1763 (1973).
(4) J. I. Teng, M. J. Kulig, L. L. Smith, G. Kan, and J. E. van Lier, *J. Org. Chem.*, **38**, 119 (1973).
(5) M. J. Kulig and L. L. Smith, *J. Org. Chem.*, **38**, 3639 (1973).
(6) (a) J. I. Teng and L. L. Smith, *J. Amer. Chem. Soc.*, **95**, 4060 (1973); (b) L. L. Smith and J. I. Teng, *ibid.*, **96**, 2640 (1974).
(7) (a) J. I. Teng, M. J. Kulig, and L. L. Smith, *J. Chromatogr.*, **75**, 108 (1973); (b) L. L. Smith, M. J. Kulig, and J. I. Teng, *Steroids*, **22**, 627 (1973).
(8) L. L. Smith and F. L. Hill, *J. Chromatogr.*, **66**, 101 (1972).
(9) (a) G. J. Schroepfer and I. D. Frantz, *J. Biol. Chem.*, **236**, 3137 (1961);

(b) M. E. Dempsey, J. D. Seaton, G. J. Schroepfer, and R. W. Trockman, *ibid.*, **239**, 1381 (1964); (c) M. E. Dempsey, ibid., **240**, 4176 (1965).
(10) (a) S. M. Dewhurst and M. Akhtar, *Biochem. J.*, **105**, 1187 (1967); (b) M. Akhtar and M. A. Parvez, *ibid.*, **108**, 527 (1968).
(11) (a) A. M. Paliokas and G. J. Schroepfer, *Biochem. Biophys. Res. Commun.*, **26**, 736 (1967); (b) A. M. Paliokas and G. J. Schroepfer, *J. Biol. Chem.*, **243**, 453 (1968); (c) M. Akhtar and S. Marsh, *Biochem. J.*, **102**, 462 (1967).
(12) D. J. Aberhart and E. Caspi, *J. Biol. Chem.*, **246**, 1387 (1971).
(13) (a) W. E. Harvey and K. Bloch, *Chem. Ind. (London)*, 595 (1961); (b) M. Slaytor and K. Bloch, *J. Biol. Chem.*, **240**, 4598 (1965).
(14) (a) A. M. Paliokas and G. J. Schroepfer, *Biochim. Biophys. Acta*, **144**, 167 (1967); (b) A. Fiecci, M. Galli Kienle, A. Scala, G. Galli, R. Paoletti, and E. Grossi Paoletti, *J. Biol. Chem.*, **247**, 5898 (1972).
(15) (a) J. E. van Lier and L. L. Smith, *Biochim. Biophys. Acta*, **210**, 153 (1970); **218**, 320 (1970); (b) J. E. van Lier and L. L. Smith, *Biochem. Biophys. Res. Commun.*, **40**, 516 (1970).
(16) (a) A. Nickon and W. L. Mendelson, *J. Org. Chem.*, **85**, 1894 (1963); **87**, 3921 (1965); (b) E. J. Corey and W. C. Taylor, *J. Amer. Chem. Soc.*, **86**, 3881 (1964); (c) W. Eisfeld, Dissertation, Göttingen, 1965, p 63; (d) D. R. Kearns, R. A. Hollins, A. U. Khan, R. W. Chambers, and P. Radlick, *J. Amer. Chem. Soc.*, **89**, 5455 (1967); (e) D. R. Kearns, R. A. Hollins, A. U. Khan, and P. Radlick, *ibid.*, **89**, 5456 (1967); (f) R. W. Murray and M. L. Kaplan, *ibid.*, **91**, 5358 (1969).
(17) Formation of **5a** from **2a** suggested as arising from participation of the $^1\Sigma_g^+$ excited state of molecular oxygen rather than the first $^1\Delta_g$ excited state[16d,e] has since been qualified.[18] Although hydrogen atom abstraction by excited dye molecules had previously not been thought likely,[16e] free-radical oxidation initiated by the $^3(n,\pi^*)$ sensitizer has recently been posited.[18a]
(18) (a) K. Gollnick, T. Franken, G. Schade, and G. Dörhöfer, *Ann. N. Y. Acad. Sci.*, **171**, 89 (1970); (b) C. S. Foote, *ibid.*, **171**, 105 (1970); (c) D. R. Kearns, *ibid.*, **171**, 106 (1970).
(19) A. Nickon and J. F. Bagli, *J. Amer. Chem. Soc.*, **81**, 6330 (1959); **83**, 1498 (1961).
(20) Melting points were taken on a calibrated Kofler block under microscopic magnification. Infrared absorption spectra were recorded over the range 400–4000 cm^{-1} on 1.5 mm diameter KBr disks incorporating the sample using a Perkin-Elmer Model 337 spectrophotometer equipped with a beam condenser lens. Ultraviolet light absorption spectra were recorded on 95% ethanol solutions using a Cary Model 14 spectrophotometer. Thin-layer chromatography was conducted with 20 × 20 cm chromatoplates of silica gel HF_{254} (E. Merck GmbH., Darmstadt), 0.25 and 1.0 mm thick, using specified solvent systems. Thin-layer mobility factors *R* for products derived from parent sterols **2a**, **3a**, or **4a** were measured using the appropriate parent sterol as unit mobility. Sterols were detected by viewing under 254-nm light, followed by spraying with *N,N*-dimethyl-*p*-phenylenediamine for peroxides,[8] and finally by spraying with 50% aqueous sulfuric acid and heating for full color display. Gas chromatography was conducted on 1.83 m long × 4 mm diameter silanized glass U-tubes packed with 3% SP-2401 on 100–120 mesh Supelcoport (Supelco Inc., Bellafonte, Pa.) using a Hlewlett-Packard F&M Model 402 gas chromatograph equipped with a hydrogen flame ionization detector. Injection temperature was 250°; column temperature was 230°; detector temperature was 250°. Nitrogen was used as carrier gas at a flow rate of 20 ml/min. Retention time data (t_R) are expressed in terms of cholesterol as unit retention time in all cases. Preparative gas chromatography was achieved by collection of effluxing components in glass capillaries as previously described.[21]
(21) J. E. van Lier and L. L. Smith, *J. Chromatogr.*, **36**, 7 (1968).
(22) J. E. van Lier and L. L. Smith, *Steroids*, **15**, 485 (1970).
(23) Literature melting point and ultraviolet light absorption data for the common steroids were obtained, respectively, from (a) J. Jacques, H. Kagan, and G. Ourisson, "Tables of Constants and Numerical Data," Vol. 14, Pergamon Press, Oxford, 1965; (b) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953).
(24) Chromatographic resolution and differentiation by color display of the parent sterols **1a** and **4a** as well as of their major hydroperoxides formed by radiation-induced oxidation are achieved using benzene–ethyl acetate (18:7), as follows: **1a**, red color, *R* 1.00; **4a**, orange-red color, *R* 0.91; **1b**, instant blue color, *R* 0.52; **1c**, instant blue color, *R* 0.57; **4b**, tan color, *R* ~0.37; **4c**, tan color, *R* 0.39. The chief product **3a** of singlet molecular oxygen attack on **1a** is not resolved from **1b** but the corresponding 3β,5α-diol **3c** is readily resolved from **1d** and from **1e** in a variety of solvent systems. The putative initial product of singlet molecular oxygen attack on **4a** as well as the secondary dihydroperoxides formed is resolved from **4b** and **4c** using multiple irrigation with benzene–ethyl acetate (18:7).
(25) (a) L. Caglioti, G. Cainelli, and G. Maina, *Tetrahedron*, **19**, 1057 (1963); (b) D. J. Aberhart, J. G. Lloyd-Jones, and E. Caspi, *Phytochemistry*, **12**, 1065 (1973).
(26) L. Tökés, G. Jones, and C. Djerassi, *J. Amer. Chem. Soc.*, **90**, 5465 (1968).

A Reexamination of the Origin of Regioselectivity in the Dimerization of Acrolein. A Frontier Orbital Approach

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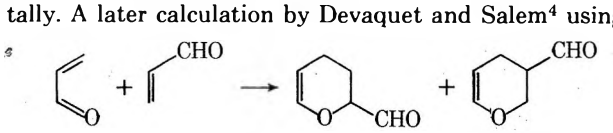
The relative frontier orbital coefficient magnitudes of acrolein were determined from *ab initio* SCF molecular orbitals. These frontier orbital coefficients favor the experimentally observed regioisomer in the dimerization of acrolein. Various all valence electron semiempirical SCF MO methods agree with the *ab initio* calculations on the origin of regioselectivity in the reaction. First-order charge interactions were not useful in predicting the regioselectivity of the reaction. Generalized rules for the prediction of the regioselectivity in cycloadditions involving three terminal carbon atoms and one terminal oxygen atom are given.

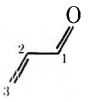
The regioselectivity in the dimerization of acrolein has been of theoretical interest [1-5] over the last several years. Salem[3] found that Hückel orbital interactions favored regioisomer II whereas only regioisomer I occurs experimentally. A later calculation by Devaquet and Salem[4] using π



I II

SCF MO's and including first-order charge interactions as well as overlap was found to be in agreement with the experimental results. However, the major contribution (60–70%) to the stabilization of I relative to II arose from the electrostatic term. This is confusing because consideration of the π charge densities of acrolein would lead to the wrong prediction.[1] There is also some question about the reliability of the overlap energy term in this calculation because it predicts that the exo approach is more stable than the endo for regioisomer II. This prediction is contrary to orbital symmetry considerations[6,7] and experimental evidence,[8] which indicate that the endo configuration is more stsble than the exo. Later, Eisenstein, *et al.*,[1] was successful in predicting the observed regioisomer I using a frontier orbital approach based on Hückel orbitals. However, Houk[2] has recently found that various molecular orbital methods disagree on the relative coefficient magnitudes of the HOMO of acrolein. Consequently, the origin of the regioselectivity in the dimerization of acrolein is presently unclear. In this paper, we have reexamined this reaction

Table I
Eigenvectors of the Highest Occupied Molecular Orbital and the Lowest Unoccupied Molecular Orbital of Acrolein



Molecular orbital method	Conformational isomer	HOMO 0	HOMO C-1	HOMO C-2	HOMO C-3	LUMO 0	LUMO C-1	LUMO C-2	LUMO C-3
INDO	Cisoid	−0.578	−0.266	0.503	0.584	−0.499	0.483	0.386	−0.607
INDO	Transoid	0.578	0.273	−0.499	−0.586	−0.500	0.479	0.393	−0.605
CNDO/2	Cisoid	0.578	0.284	−0.494	−0.584	0.504	−0.468	−0.397	0.608
CNDO/2	Transoid	0.578	0.291	−0.489	−0.585	−0.504	0.464	0.404	−0.601
CNDO/S	Cisoid	0.391	0.052	−0.655	−0.644	0.367	−0.426	−0.479	0.675
CNDO/S	Transoid	0.391	0.063	−0.638	−0.661	−0.367	0.420	0.502	−0.662
Iterative extended Hückel	Cisoid	0.559	0.188	−0.461	−0.557	−0.675	0.576	0.225	−0.619
Iterative extended Hückel	Transoid	0.557	0.180	−0.465	−0.556	−0.680	0.577	0.213	−0.621
MINDO/2	Cisoid	−0.464	−0.175	0.598	0.630	0.428	−0.423	−0.471	0.645
MINDO/2	Transoid	−0.464	−0.187	0.584	0.639	0.425	−0.418	−0.490	0.635
Ab initio[a]	Transoid	0.415	0.223	−0.546	−0.595	0.574	−0.459	−0.464	0.653
Ab initio[b]	Transoid	0.391	0.227	−0.559	−0.583	0.565	−0.414	−0.490	0.683

[a] Reference 9. [b] Reference 10.

through *ab initio* and the various semiempirical molecular orbital methods to determine the origin of its regioselectivity.

Results and Discussion

Since the various semiempirical molecular orbital methods (CNDO/2, INDO, Hückel, extended Hückel, MINDO/2) disagree on the relative coefficient magnitudes of the frontier orbitals of acrolein,[2] we have determined the relative coefficient magnitudes from *ab initio* SCF calculations. We feel that the eigenvectors of the *ab initio* calculations should be more reliable than the semiempirical methods. One good STO minimal basis *ab initio* SCF calculation was available[9] in the literature and we have also carried out a minimal gaussian (4G) basis set calculation[10] using Clementi single ζ's.[11] Even though the two *ab initio* calculations use slightly different orbital screening constants, they agree well for the relative coefficient magnitudes of the frontier orbitals (Table I). Both methods predict that the highest occupied molecular orbital (HOMO) is a π molecular orbital and that the nonbonding molecular orbital is of lower energy. The lowest unoccupied molecular orbital (LUMO) is a π molecular orbital in both methods. The relative *ab initio* coefficient magnitudes of the frontier orbitals of *trans*-acrolein are given in Figure 1.

Since *ab initio* calculations require considerable amounts of computer time, it is advantageous to carry out such molecular orbital investigations with semiempirical methods. Therefore, the agreement of the various all-valence electron semiempirical methods with the *ab initio* calculations was determined.[12] The CNDO/S[14] and MINDO/2[15] methods predict similar frontier orbital coefficients for *trans*-acrolein (Table I). The relative coefficient magnitudes of these methods agree well with the *ab initio* calculations. The only disagreement is in the magnitude of the LUMO coefficient of the oxygen, which the semiempirical methods predict to be smaller in magnitude than the LUMO coefficient of the C-2 position. The INDO and CNDO/2[16] methods have several disagreements with the *ab initio* calculations on the frontier orbital coefficients. They predict a reversal in the relative LUMO coefficient magnitudes of the C-1 and C-2 positions and an oxygen HOMO coefficient of equal magnitude with the C-3 position. Finally, the iterative extended Hückel[17] method has the most disagreement with the *ab initio* calculations. Its disagreements are an oxygen HOMO coefficient of equal magnitude with the C-3 position, a reversal in the relative LUMO coefficients magnitudes of the C-1 and C-2 positions, and an oxygen LUMO coefficient that is larger than the C-3 coefficient.

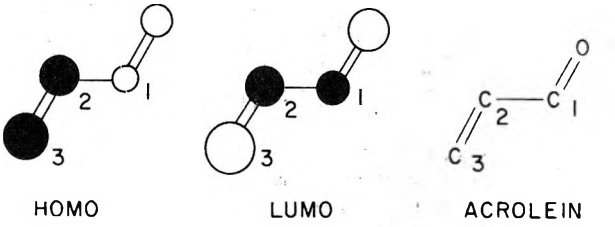


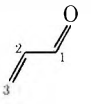
Figure 1. Relative coefficient magnitudes of the frontier orbitals of *trans*-acrolein from *ab initio* calculations.

When *trans*-acrolein is rigidly rotated to *cis*-acrolein, the only change in the relative coefficient magnitudes of the semiempirical frontier orbitals was that the HOMO C-2 coefficient became larger than the HOMO C-3 coefficient in the CNDO/S method (Table I). Even if this change in the relative CNDO/S coefficient magnitudes of HOMO is real, it will not affect the conclusions drawn from the frontier orbital coefficients concerning regioselectivity. Therefore, the relative *ab initio* coefficient magnitudes of the frontier orbital of *trans*-acrolein will be used for *cis*-acrolein.

It has been shown[1,2,7] that the regioselectivity of a concerted cycloaddition process can be predicted from perturbation molecular orbital theory. The expression for the energy change which accompanies the orbital overlap of two molecules involved in a cycloaddition process is as follows.[5]

$$\Delta E = 2\left(\sum_{R}^{occ}\sum_{S}^{unocc} - \sum_{R}^{unocc}\sum_{S}^{occ}\right)\frac{\left(\sum_{ab} c_a c_b \gamma_{ab}\right)^2}{E_R - E_S} \quad (1)$$

Table II
Net π Charges of Acrolein



Molecular orbital method	Conformational isomer	O	C-1	C-2	C-3
INDO	Cisoid	−0.228	+0.180	−0.023	+0.055
INDO	Transoid	−0.221	+0.175	−0.014	+0.060
CNDO/2	Cisoid	−0.200	+0.157	−0.019	+0.062
CNDO/2	Transoid	−0.193	+0.153	−0.011	+0.051
CNDO/S	Cisoid	−0.396	+0.341	−0.050	+0.105
CNDO/S	Transoid	−0.389	+0.340	−0.006	+0.055
Iterative extended Hückel	Cisoid	−0.127	−0.009	+0.030	+0.106
Iterative extended Hückel	Transoid	−0.123	−0.020	+0.029	+0.115
MINDO/2	Cisoid	−0.254	+0.217	−0.033	+0.070
MINDO/2	Transoid	−0.247	+0.215	−0.002	+0.035
Hückel[a]	Transoid	−0.529	+0.333	−0.034	+0.228

[a] Reference 1.

In this expression γ_{ab} is the atomic orbital transition state resonance integral for atomic orbitals a and b in MO's R and S, and c_a is the atomic orbital coefficient at atom a in the molecular orbital R. The theory predicts[2] that the principal stabilization of the transition state will arise from the HOMO–LUMO pair of addend frontier orbitals which are closest in energy, and that the larger terminal coefficients on each addend will become bonded preferentially in the transition state.[18] In the dimerization of acrolein, the four terminal atoms are not the same type. Thus, the resonance integral, γ_{ab}, will not be a constant in eq 1 and consideration must be taken of its magnitude. The γ_{CC} and γ_{CO} for a $2p\sigma$, $2p\sigma$ overlap as a function of distance are available in the literature.[19] The γ_{CC} is significantly larger than γ_{CO} at interatomic distances of 3.0–1.75 Å; thus, the carbon–carbon orbital interactions will have the greater effect on the stability of the transition state. Consequently, only the carbon–carbon orbital interactions will be considered in predicting the regioselectivity in the dimerization of acrolein.

In this cycloaddition reaction both frontier orbital interactions, HOMO diene–LUMO dienophile and LUMO diene–HOMO dienophile, have the same energy separation and will equally affect the regioselectivity of the reaction.[20] Using the relative terminal coefficient magnitudes of acrolein in Figure 1, the theory predicts that both frontier orbital interactions favor the observed regioisomer I. The approach which yields regioisomer I allows bond formation between the C-3 positions of the reactants where the terminal coefficients of HOMO and LUMO are the largest (Figure 2). The other possible regioisomer II is not favored by either frontier orbital interactions because the largest coefficients of HOMO and LUMO do not become bonded (Figure 3). Thus, the frontier orbital approach accounts for the high degree of regioselectivity observed in the dimerization of acrolein.

When the terminal coefficients of the semiempirical methods are used in this approach, they also predict that both frontier orbital interactions favor regioisomer I. Even if we assume that γ_{CC} and γ_{CO} are equal in magnitude, thereby considering carbon–oxygen and carbon–carbon orbital interactions, all the SCF molecular orbital methods except the iterative extended Hückel favor regioisomer I.

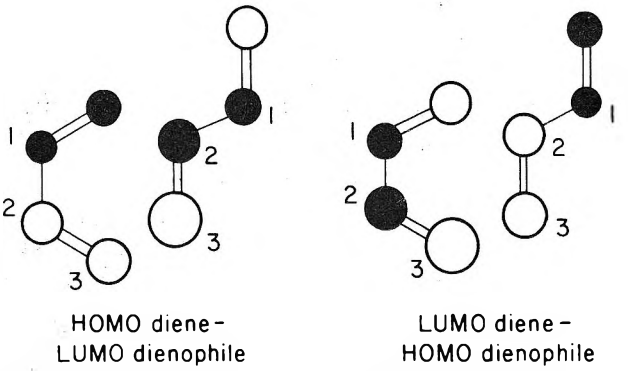


Figure 2. Frontier orbital interactions yielding regioisomer I.

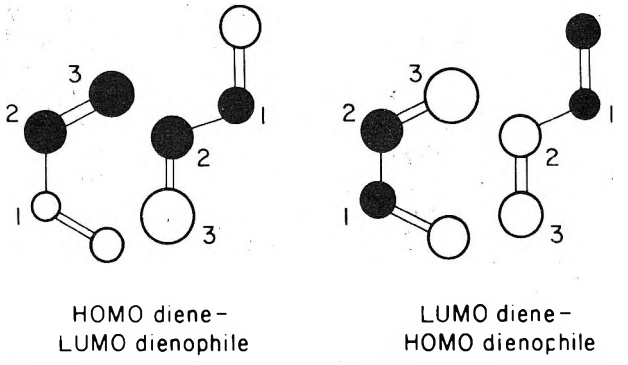


Figure 3. Frontier orbital interactions yielding regioisomer II.

Consideration was also given to the effect of secondary orbital interactions between the C-1 position of the dienophile (*trans*-acrolein) and the C-1 and C-2 positions of the diene (*cis*-acrolein) on the regioselectivity of the reaction (Figures 2 and 3). We found that the C-2 coefficient of the HOMO and the LUMO of the diene was larger than the corresponding C-1 diene coefficient. Thus, the stabilization of the endo transition state is greater when C-1 of the dienophile is near C-2 of the diene, thereby favoring the unobserved regioisomer II. Consequently, the secondary orbital interactions make a minor contribution to the stabilization of the regioisomers.

Earlier we stated that Devaquet and Salem[4] had indicat-

Table III
Change in Energy[a] Due to First-Order π Charge Interactions for the Dimerization of Acrolein

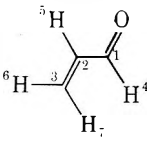
Molecular orbital method	Regioisomer I (exo)	II (exo)	I (endo)	II (endo)
INDO	0.337	−0.368	0.411	−0.279
CNDO/2	0.310	−0.269	0.367	−0.202
CNDO/S	0.764	−0.725	1.187	−0.327
MINDO/2	0.316	−0.299	0.482	−0.141
Hückel	3.951	−3.412	3.826	−3.312

[a] In kilocalories per mole.

The iterative extended Hückel and minimal gaussian *ab initio* methods were not used in the above calculations because of the unrealistic atomic charge densities predicted by these methods. For example, the iterative extended Hückel predicts that all the atoms of acrolein except oxygen are positively charged (Table IV). This electron distribution appears to be another example of the method's overemphasis of ionic contributions. Also, the *ab initio* charge densities appear to be more characteristic of the basis set than a true effect.[23] For example, the method predicts that the C-2 and C-3 carbons have more electron density than the oxygen (Table IV).

The origin of the regioselectivity predicted from the

Table IV
Net Atomic Charges of Acrolein



Molecular orbital method	Conformational isomer	Net atomic charges 0	C-1	C-2	C-3	H-4	H-5	H-6	H-7
INDO	Cisoid	−0.286	+0.338	−0.042	+0.056	−0.078	+0.002	−0.002	+0.011
INDO	Transoid	−0.283	+0.334	−0.041	+0.045	−0.073	+0.015	0.0	+0.003
CNDO/2	Cisoid	−0.231	+0.244	−0.039	+0.009	−0.042	+0.014	+0.017	+0.029
CNDO/2	Transoid	−0.228	+0.239	−0.039	−0.001	−0.037	+0.027	+0.021	+0.018
CNDO/S	Cisoid	−0.468	+0.398	−0.073	−0.019	+0.017	+0.030	+0.048	+0.066
CNDO/S	Transoid	−0.462	+0.397	−0.044	−0.073	+0.020	+0.051	+0.057	+0.053
Iterative extended Hückel	Cisoid	−0.386	+0.136	+0.038	+0.028	+0.063	+0.041	+0.041	+0.040
Iterative extended Hückel	Transoid	−0.388	+0.137	+0.030	+0.019	+0.037	−0.039	+0.046	+0.073
MINDO/2	Cisoid	−0.353	+0.359	−0.019	−0.062	−0.004	−0.043	+0.056	+0.070
MINDO/2	Transoid	−0.346	+0.354	−0.090	−0.095	−0.003	−0.062	+0.066	+0.052
Ab initio[a]	Transoid	−0.215	+0.034	−0.272	−0.344	+0.176	−0.218	+0.205	+0.199

[a] Reference 10.

ed that first-order charge interactions were the major contributor (60–70%) to the stabilization of regioisomer I relative to regioisomer II. The expression for the change in energy due to first-order charge interactions is as follows.[4]

$$\Delta E = \sum_a \sum_b Q_a Q_b \frac{1}{R_{ab}}$$

In this expression Q_a is the total initial charge on atom a and R_{ab} is the distance between atoms a and b. If first-order charge interactions are the major contributor to the stability of the transition state, one should be able to predict the preferred regioisomer of the reaction from the net changes.[21] However, we find that the net π charges favor the unobserved regioisomer II for all the SCF molecular orbital methods investigated (Tables II and III). When all valence electrons are included, the net atomic charges of all the MO methods still favor the unobserved regioisomer II (Tables IV and V). Of the molecular orbital methods investigated, we feel that the CNDO/2 net charges are the more realistic because Hehre and Pople[22] have observed that CNDO/2 determined atomic populations of oxygen-containing compounds parallel quite closely those obtained from *ab initio* calculations. Thus, first-order charge interactions cannot be the origin of the regioselectivity observed in the dimerization of acrolein and are not the major contributor to the stabilization of regioisomer I relative to regioisomer II.

Table V
Change in Energy[a] Due to First-Order Atomic Charge Interactions for the Dimerization of Acrolein

Molecular orbital method	Regioisomer I (exo)	II (exo)	I (endo)	II (endo)
INDO	0.390	−0.168	0.591	−0.054
CNDO/2	0.301	−0.195	0.357	−0.166
CNDO/S	1.018	−0.944	1.388	−0.483
MINDO/2	0.447	−0.400	0.458	−0.244

[a] In kilocalories per mole.

first-order charge interactions in our calculations and those of Devaquet and Salem[4] does not have a simple interpretation because charge–charge interactions between many pairs of atoms play an important role. Consequently, the exact cause of Devaquet's and Salem's incorrect conclusion is impossible to determine without the atomic charge densities used in their calculations. However, the energy difference between the exo regioisomers calculated from the Hückel net π charges was 7.36 kcal/mol, while the less approximate CNDO/2 method predicts a difference of 0.579 kcal/mol from net π charges and 0.496 kcal/mol from the net atomic charges (Tables III and V). It appears that the use of π charge densities from π SCF molecular orbital methods can overemphasize the role of the first-order

charge interactions, and this could lead to incorrect conclusions concerning regioselectivity. Thus, we feel that the origin of their incorrect conclusion probably lies with the π charge densities of the π molecular orbital method that they used.

Eisenstein, *et al.*,[1] was correct in analysis of the first-order charge interactions because of the Hückel π charge densities used, which allow a simple interpretation of these interactions. Their conclusion originated from the large negative charge on the oxygen and the large positive charge on the C-3 carbon whose interaction favors the unobserved regioisomer II. This electronic distribution causes the Hückel method to overemphasize the effect of first-order charge interaction in the dimerization of acrolein.

Conclusions

The dimerization of acrolein is under overlap control and there is no evidence that first-order charge interactions have a dominant role in determining its regioselectivity. Also, it appears that the atomic charge densities from the π SCF MO methods are too crude to be used in determining the energy change due to first-order charge interactions.

The frontier orbital approach used in analyzing the regioselectivity of the dimerization of acrolein can be applied to all cycloaddition reactions which involve terminal orbital interactions of three carbon atoms and one oxygen atom. The generalized rules are as follows.

(1) The principal stabilization of the transition state will arise from the HOMO-LUMO pair of addend frontier orbitals which are closest in energy.

(2) The larger carbon terminal coefficients on each addend will become bonded preferentially in the transition state.

(3) If the terminal carbon coefficients of either addend are equal in magnitude, the regioselectivity can be predicted from secondary orbital interactions.[7]

Finally, the relative coefficient magnitudes in Figure 1 and the above generalized rules can be used to predict the preferred regioisomer of any cycloaddition reaction involving acrolein. They correctly predict the preferred regioisomer in the cycloaddition of acrolein with styrene, acrylonitrile, and methyl acrylate.[24]

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Registry No.—Acrolein, 107-02-8.

References and Notes

(1) O. Eisenstein, J.-M. Lefour, and N. T. Anh, *Chem. Commun.*, 969 (1971).
(2) K. N. Houk, *J. Amer. Chem. Soc.*, **95,** 4092 (1973).
(3) L. Salem, *J. Amer. Chem. Soc.*, **90,** 553 (1968).
(4) A. Devaquet and L. Salem, *J. Amer. Chem. Soc.*, **91,** 3793 (1969).
(5) W. C. Herndon, *Chem. Rev.*, **72,** 157 (1972), and references cited therein.
(6) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8,** 781 (1969).
(7) P. V. Alston, R. M. Ottenbrite, and D. D. Shillady, *J. Org. Chem.*, **38,** 4075 (1973).
(8) K. N. Houk, *Tetrahedron Lett.*, 2621 (1970).
(9) A. Devaquet, *J. Amer. Chem. Soc.*, **94,** 5160 (1972).
(10) D. D. Shillady and C. Trindle, *Int. J. Quantum Chem., Symp.*, No. 7, 269 (1973).
(11) E. Clementi and D. L. Raimondi, *J. Chem. Phys.*, **38,** 2686 (1963).
(12) The geometry of *trans*-acrolein used in the molecular orbital calculations was obtained from the very accurate microwave spectrum by Wagner, *et al.*[13] The geometry of *cis*-acrolein was determined by rigid rotation from *trans*-acrolein. We found that the interpretations from the semiempirical HOMO–LUMO eigenvectors and atomic charge densities were independent of small changes in bond angles and bond lengths. Thus, there was no justification of the use of computer time for an extensive optimization of the conformational isomers of acrolein with each method. Furthermore, the iterative extended Hückel method does not take into account repulsion and can not be used to obtain equilibrium geometries. Also, the parameters of the CNDO/S method are optimized for excited-state properties and would not give a reliable equilibrium geometry. Small variations in the geometry of Wagner, *et al.*, for both conformational isomers of acrolein were carried out in the CNDO/2, INDO, and MINDO/2 methods. These variations indicated that the geometry of Wagner, *et al.*, is very close to the predicted equilibrium geometry for both *cis*-and *trans*-acrolein.
(13) R. Wagner, J. Fine, J. W. Simmons, and J. H. Goldstein, *J. Chem. Phys.*, **26,** 634 (1957).
(14) G. Keuhnlenz and H. H. Jaffe, *J. Chem. Phys.*, **58,** 2258 (1973). Available from Quantum Chemistry Program Exchange, Indiana University, Bloomington, Ind. 47401, Program No. 174. In our version we used 0.529167 Å/atomic unit, 27.21 eV/atomic unit, and double precision to be compatible with Pople's CNDO/2 program.
(15) J. A. Hashmall and S. Raynor, *J. Chem. Phys.*, **58,** 5464 (1973), and references cited therein.
(16) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, N. Y., 1970. Available from Quantum Chemistry Program Exchange, Indiana University, Bloomington, Ind. 47401, Program No. 141.
(17) R. Rein, N. Fukuda, H. Win, G. A. Clarke, and F. E. Harris, *J. Chem. Phys.*, **45,** 4743 (1966). The VOIP for carbon, oxygen, and hydrogen were obtained from B. J. Duke, *Theor. Chim. Acta*, **9,** 260 (1968). Calculations were carried to a self-consistency of 0.005 electron in charge.
(18) When the terminal coefficients are of equal magnitudes, the preferred regioisomer can be predicted from secondary orbital interactions.[7]
(19) K. N. Houk, J. Sims, C. R. Watts, and L. J. Luskus, *J. Amer. Chem. Soc.*, **95,** 7301 (1973).
(20) Molecular orbital calculations predict that the differences in the frontier orbital energies of *cis*-acrolein and *trans*-acrolein are less than 0.2 eV.
(21) In the calculations of the change in energy due to first-order charge interactions, the parallel planes of the interacting acrolein molecules were separated by a distance of 3 Å. The terminal atoms of the *cis*-acrolein molecule were symmetrically below the carbon–carbon double bond of the *trans*-acrolein molecule. Asymmetry in the approach of the molecules did not change the interpretations from atomic charge densities.
(22) W. J. Hehre and J. A. Pople, *J. Amer. Chem. Soc.*, **92,** 2191 (1970).
(23) J. A. Kroll and D. D. Shillady, *J. Amer. Chem. Soc.*, **95,** 1422 (1973).
(24) The coefficient magnitudes of the dienophiles were determined from CNDO/2 calculations.

1,3-Bridged Aromatic Systems. XII. Hydrogen–Deuterium Exchange Reactions in 1-Substituted 12,13-Benzo-16-chloro[10](2,4)pyridinophanes [1]

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Deuterium exchange reactions have been studied with a variety of *syn*- and *anti*-pyridinophanes of type **1** and **2**, both in acetic acid-d_4 and in alcohol with added alkoxide or hydroxide. Deuterium exchange at the methine carbon in acetic acid-d_4 is highly specific for syn and anti acetates (**1a** and **2a**) and for syn bromide **1b** with retention of configuration; epimerization was observed for the anti bromide **2b**. Exchange reactions in more basic media at the methine carbon are also stereospecific, with retention of configuration, with the exception of the anti bromide **2b** which leads to some epimerization. Reaction of syn alcohol **1b**, but not anti alcohol **2b**, with ethoxide in ethanol results in appreciable dechlorination of aryl halide.

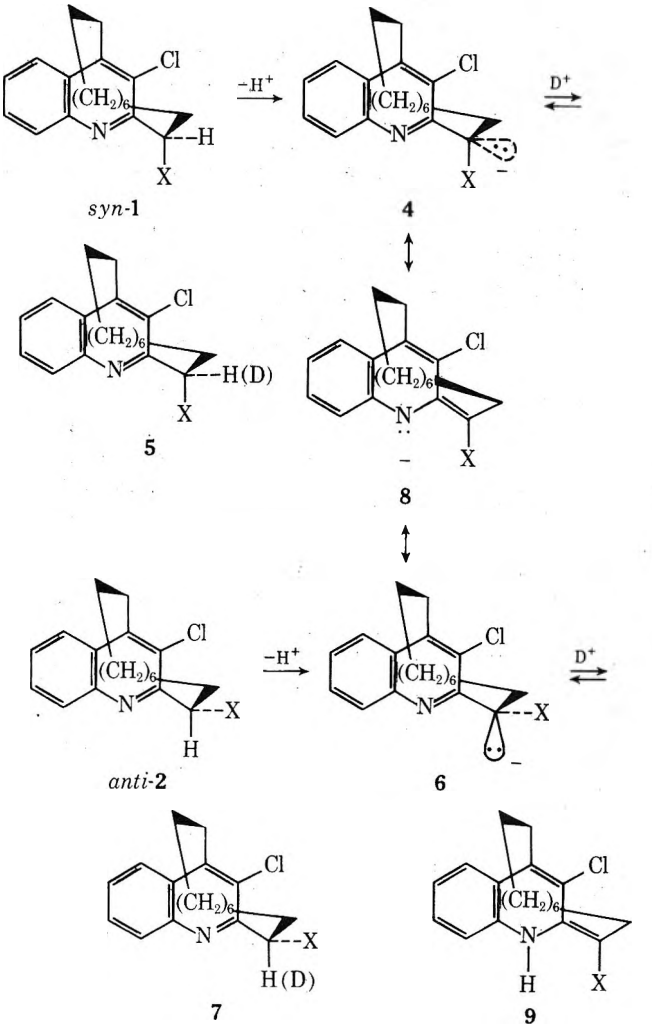
Since it is known that 2- and 4-alkylpyridines undergo H–D exchange in the presence of base[2] or by action of hot acetic acid,[3,4] we have examined such exchange with *syn*- and *anti*-pyridinophanes[5] of type **1** and **2** in order to gain insight into the stereochemical consequence of such exchange (Scheme I). It is known[6] that syn and anti diastereomers **1** and **2** do not interconvert by rotation of the methylene bridge to the other face of the aromatic ring; consequently, one would expect exchange with retention of syn or anti configuration if intermediates of type **4** and **6** resist rehybridization to **8**, due possibly to steric constraint.[5] Nonstereospecific exchange would be expected (syn ⇄ anti interconversion) if intermediates **4** and **6** either invert configuration at the α carbon or if they rehybridize to intermediate **8**. In cases involving exchange in acetic acid medium, and perhaps even in alcohol under base catalysis, it is assumed[3,4] that **4** and **6** would exist as the corresponding zwitterions (N-protonated), and that **8** would exist as the anhydro base **9**.

I. Exchange Reactions in Acetic Acid-d_4. It was shown that syn and antiacetates **1a** and **2a** do not interconvert (epimerize) in hot (118°, 48 hr) acetic acid.[6] Significantly, both *syn*-**1a** and *anti*-**2a** undergo exchange of benzylic hydrogen by deuterium in hot acetic acid-d_4 (118°, 48 hr), and in neither case was any interconversion (epimerization) detected by liquid chromatography (less than 1% interconversion). Thus, *syn*-**1a** gave recovered syn acetate **5a** which contained 71% deuterium at the methine position and 28% deuterium at the benzylic methylene position; no anti acetate was detected. Similarly, *anti*-**2a** gave recovered anti acetate **7a** which contained 29% deuterium at the methine position and 20% deuterium at the benzylic methylene position.

These results conclusively establish that an intermediate such as **8** [X = OC(=O)CH_3], or more likely the corresponding anhydro base **9** (X = $OCOCH_3$), is not an intermediate in these exchange reactions.[7] Retention of configuration in exchanges observed for **1a** and **2a** suggest that exchange is more rapid from **4** or **6** (or the corresponding N-protonated zwitterions) than rehybridization to an intermediate **8** (or **9**).

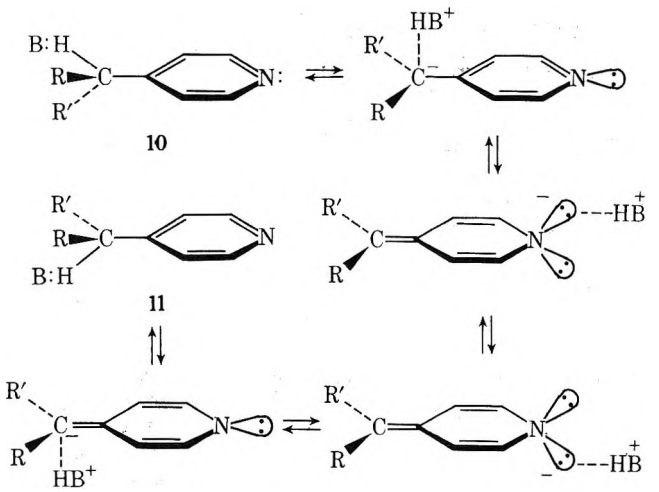
Base-catalyzed exchange in asymmetric carbon atoms has been studied in great detail[8,9] and can occur with retention of configuration, racemization, inversion of configuration, isoracemization, or a combination of these processes depending on structure and polarity of solvent. Exchange with racemization or isoracemization is usually observed[9] for those derived anions which can be stabilized (resonance) by an electronegative group. The only prior case studied which involves stereochemistry of exchange in alkylpyridines was carried out by Cram (Scheme II). In this

Scheme I



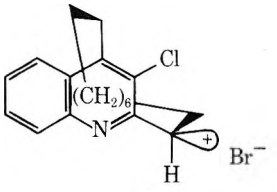
a, X = $OCOCH_3$
b, X = Br
c, X = OSO_2Ar
d, X = OH
e, X = OC_2H_5

Scheme II



case it was observed[8] that exchange in **10** occurred, accompanied by a "conducted tour mechanism" to give **10** and **11** with both racemization and inversion.

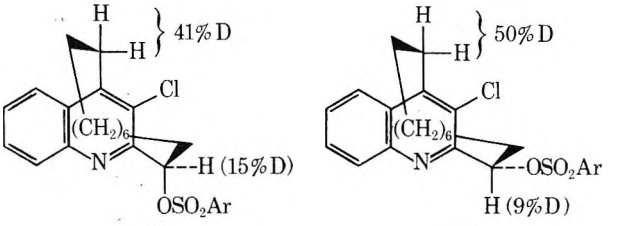
Exchange reactions in the syn and anti bromides **1b** and **2b** are of interest, but gave less definitive stereochemical results. Reaction of **1b** and **2b** with acetic acid-d_4 were carried out under identical conditions (118°, 48 hr) and recovered bromides (>70% in each case) were separated by high pressure liquid chromatography; deuterium exchange was determined by pmr.[10] Bromide recovered from *syn*-**1b** contained only a trace (detected only by lc) of anti bromide **7b;** recovered pure *syn*-**5b** (80% recovery) showed complete deuterium incorporation at the methine carbon atom and 35% deuterium incorporation at the benzylic methylene position. Bromide recovered from anti bromide **2b** was a mixture of syn bromide **5b** (18%) and anti bromide **7b** (52%); recovered *syn*-**5b** was essentially completely deuterated at the methine carbon and contained 17% deuterium at the benzylic methylene position while recovered anti bromide **7b** showed essentially no deuterium incorporation at the methine carbon but ~30% deuterium at the benzylic methylene position. Obviously syn bromide (anti H) undergoes more rapid deuterium exchange at the methine position than does the anti bromide (syn H). These results do not unequivocally differentiate epimerization and subsequent exchange through an anhydro base **9** (X = Br) which protonates (or adds D^+) to give the more stable[6] syn bromide, or through an ion pair of type **12,** which epimerizes to the



12

more stable syn bromide which subsequently undergoes exchange. The comparative inertness to solvolysis or replacement of the anti bromide relative to syn bromide has been previously noted.[6]

II. Exchange Reactions in Basic Media. Although syn and anti tosylates **1c** and **2c** undergo slow hydrolysis, by O–S bond cleavage, to syn and anti alcohols (**1d** and **2d,** respectively) by action of KOH in methanol, we have reconfirmed the observation[6] that there is no epimerization either in recovered starting material or in the derived alcohols when either **1c** or **2c** is treated in this manner. Both *syn*-**1c** and anti-**2c** were treated under identical conditions (20 hr, reflux) with KOD in methanol-*O*-*D;* recovered tosylate in each case was separated from the corresponding alcohol by tlc, and deuterium label was determined by pmr. The results are summarized in **13** and **14.** It was observed



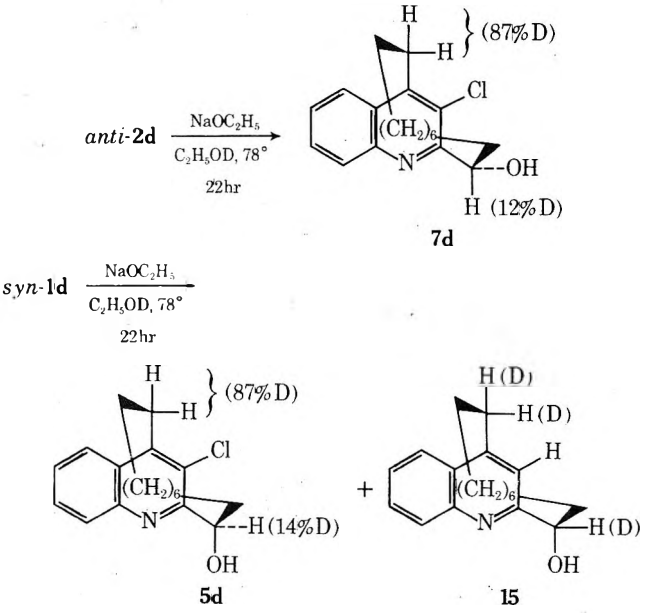
13 **14**

that (1) in both cases exchange occurred at the methine position without epimerization, (2) exchange is much more rapid at the benzylic methylene position,[2b] (3) exchange is somewhat more rapid at the methine hydrogen of syn tosylate **13** than at the methine hydrogen of anti tosylate **14.**

These results are interpreted by arguments essentially identical with those presented above for exchange with acetic acid-d_4. It is clear that base-catalyzed exchange at the methine position occurs with retention of configuration under these conditions.

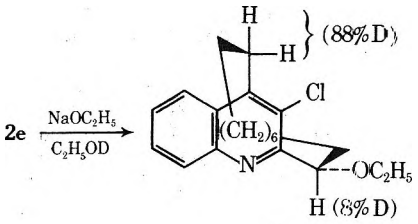
Similar results were obtained with other cyclophanes; however, in some cases results are less definitive because of side reactions.

Reaction of anti alcohol **2d** with sodium ethoxide in hot ethanol-*O*-*D* gave recovered anti alcohol **7d** (83%) labeled as shown in **7d,** below; there was no evidence for formation of epimeric syn alcohol **5d.** Reaction of syn alcohol under



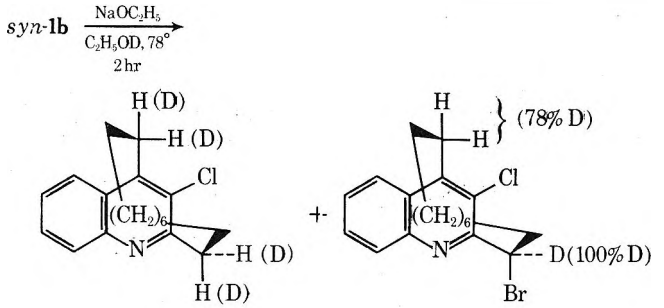
identical conditions gave *syn*-**5d,** labeled as shown in the accompanying formula, together with a dechlorinated alcohol (~45% yield, completely deuterated at methine and benzylic methylene positions) to which structure **15** is assigned. Repetition of the reaction with **1d** with unlabeled solvent gave unlabeled **15** (~60% yield) and its structure was assigned by composition and spectra (pmr and mass spectrum).

Reaction of anti ether **2e** with sodium ethoxide in ethanol-*O*-*D* (48 hr, reflux) gave 70% recovery of anti ether labeled as shown in **7e.** Examination of the mother liquor from which **7e** was obtained by tlc showed a possible trace of syn ether **5e.**



7e

Finally, examination of exchange of syn and anti bromides **1b** and **2b**, respectively, was examined in hot ethanol-*O*-*D* with ethoxide (2 hr, reflux). The reaction was complicated by debromination, a reaction previously reported,[6] to give **16**. Reaction of **1b** under these conditions gave **16** (~49% yield, which was not further examined as to label) and recovered syn bromide **5d** labeled as shown in **17**; there was no evidence for formation of anti bromide **7d**.



16 17

Reaction of the anti bromide **2b** under these same conditions gave a complex mixture which was not resolved; however, tlc analysis showed reduced pyridinophane **16**, anti bromide **7b**, epimeric **5b** (appreciable, but considerably less than **7b**).

In summary it is concluded that (1) in basic media the anti-substituted pyridinophanes **1** (syn H) undergo exchange somewhat less readily at the methine position than the *syn*-pyridinophanes (anti H), and (2) in all cases studied except the anti bromide **2b**, exchange is highly specific with retention of configuration.

Our data on these exchange reactions[3] suggest that the reactivity ratio of 2- and 4-alkyl hydrogens of pyridines (k_2/k_4) is generally ≥ 1 for acid-catalyzed exchange, whereas k_2/k_4 is generally <1 for base-catalyzed exchange. While $k_2/k_4 < 1$ for basic exchange is in agreement with the literature,[2b] $k_2/k_4 \geq 1$ has no precedent of which we are aware.

Experimental Section

Starting Materials. Syn and anti acetates **1a** and **2a** were prepared from the corresponding pure alcohols[11] by conversion into the lithium salt (in THF by titration with 2 *M* butyllithium in hexane) with subsequent treatment of the derived salts with acetyl chloride (77% yield of **1a**, mp 118–119°, lit.[12] 116–118°; 50% yield of **2a**, mp 149.5–150°, lit.[12] 144–146°). Alternatively, the mixed acetates[11] were separated by high pressure liquid chromatography [8 ft × 2.2 mm i.d., Porasil A, eluted with chloroform–petroleum ether[13] (1:1) at 0.75 ml/min]. The retention times of **1a** and **2a** under these conditions are 16 and 22.5 min, respectively.

Syn[11] and anti[6] bromides **1b** and **2b** can be separated by tlc (silica gel, multiple developments with petroleum ether[13]–ether); however, they are more efficiently purified by high pressure liquid chromatography (8 ft × 2.2 mm i.d., Porasil A, eluted with 5% chloroform–petroleum ether[13] at 2.7 ml/min). The retention times of **1b** and **2b** under these conditions are 3.8 and 5.7 min, respectively.

All materials used in exchange studies contained no trace of epimeric impurities as judged by characteristic pmr resonances of methine hydrogens.[5,6,11]

Exchange Reactions in Acetic Acid-d_4. A mixture of syn acetate (**1a**, 144.5 mg, 0.402 mmol) and acetic acid-d_4 (4.94 g, 77.2 mmol, Stohler Isotopic Chemicals, Inc.) was heated at the reflux temperature for 48 hr under an atmosphere of dry nitrogen. After most of the acetic acid was removed by distillation, the residue was dissolved in chloroform which was subsequently extracted with aqueous sodium bicarbonate and dried ($MgSO_4$). Analysis of the oil (143 mg) obtained from the chloroform by high pressure liquid chromatography (see starting materials) showed the absence of anti acetate **7a**. Preparative tlc separation of the mixture (silica gel developed twice with 15% ether in petroleum ether[3]) gave recovered syn acetate **5a** as an oil (93 mg, 64.4% recovery; mp 114–116°[12] from petroleum ether[14]), and syn alcohol **5d** (39.6 mg, 31%, mp 154–155°, mixture melting point with sample mp 160° was 155–157°; pmr identical with authentic sample except for decreased intensity of methine resonance due to deuterium incorporation) which was not further examined. Deuterium analysis of recovered syn acetate[10] showed 71% deuterium incorporation at the benzylic methine position at δ 6.55 and 28% deuterium incorporation at the benzylic methylene position (δ 3.8–3.0).

The anti acetate 2a was treated as described above. Analysis of the crude product, as described above, showed no syn acetate **5a** to be present; recovered anti acetate [78% recovery, mp 138–140°, from chloroform–petroleum ether,[14] mp 149.5–150° (pure) by high pressure liquid chromatography]. The pmr spectrum showed[10] 29% deuterium incorporation at the methine position (δ 6.08) and 20% deuterium incorporation at the benzylic methylene position (δ 3.8–3.3)

Syn Bromide[11] **1b** (70.8 mg) was treated with acetic acid-d_4 as described above. Analysis of the crude yellow solid by high pressure liquid chromatography (see starting materials) showed syn bromide **5b** and a trace (less that 2% assuming equal extinction coefficients of **1b** and **2b** at 254 nm) of anti bromide **7b**. Recovered syn bromide (**5b**, mp and mmp 145–145.5°, lit. 149–151°,[11] obtained by recrystallization of the crude bromide from petroleum ether,[14] 80% recovery) showed ~100% deuterium incorporation at the benzylic methine position (no resonance at δ 6.05)[11] and 35% deuterium incorporation at the benzylic methylene position (1.29 H at δ 3.7–3.3).[11]

Anti Bromide 2b.[6] Analysis of the crude product (83.1 mg, 80%, mp 130–135°), obtained by treatment of pure **2b** (103.9 mg) with acetic acid-d_4 as described above, by high pressure liquid chromatography (see starting materials, except 2% chloroform in petroleum ether[13] was employed) showed the presence of syn bromide **5b** (retention time 7.7 min) and anti bromide **7b** (retention time 13 min). Preparative separation by high pressure liquid chromatography (conditions as described above for analysis) gave syn bromide **5b** (16.6% yield, mp 143–145°, mmp 142–144°, lit.[11] 149.5–151°) and anti bromide **7b** (52.7% recovery, mp 149–151°, mmp 148–149°, lit.[6] 152–153°). The syn bromide showed[10] 90–100% deuterium incorporation at the benzylic methine carbon (integration of the small signal at δ 6.05 did not permit a more accurate estimate) and 17% deuterium at the benzylic methylene position (δ 3.7–3.3). The anti bromide **7b** showed[10] essentially no deuterium exchange at the benzylic methine position (0.97 H at δ 5.50) and 30% deuterium incorporation at the benzylic methylene position (δ 3.8–3.0).

Exchange Reactions with Syn and Anti Tosylates (1c and 2c). Syn Tosylate 1c.[5] Potassium hydroxide (0.36 g) was dissolved in deuterium oxide (5.71 g, 99.8% D, Aldrich) and D_2O was removed by distillation; the exchange process was repeated with 3.31 g of additional D_2O. The resulting potassium deuterioxide was dissolved in methanol-*O*-*D* (9.7 g, Stohler Isotope Chemicals, Inc.), syn tosylate **1c** (200 mg) was added, and the mixture was heated for 20 hr at the reflux temperature protected from atmospheric moisture. The methanol was removed by distillation and the residue was treated with aqueous ammonium chloride and was then extracted with chloroform. The oil, obtained from the dried ($MgSO_4$) chloroform, showed (pmr) the presence of syn tosylate (δ 6.46) and syn alcohol (δ 5.35) and the absence of anti tosylate (δ 5.72) and anti alcohol and was purified by preparative tlc [silica gel; eluent petroleum ether[3] (3:1)] to give, in order of increasing R_f, (1) recovered syn tosylate **5c** (123 mg, 61.5% recovery, mp 120–121° from ether; lit.[5] 105–107° from chloroform–petroleum ether,[13] 120–121°[12b] from ether) showing[10] 15% deuterium incorporation at the benzylic methine position (δ 6.46) and 41% deuterium incorporation at the benzylic methylene position (δ 3.6–3.2); and (2) syn alcohol **5d** (44.3 mg, 33% yield, slightly impure, mp 152–153°, lit.[11] mp 160–162°). This material was not examined further.

Anti tosylate 2c was treated as described above for **1c**. The

crude oil showed the presence of anti tosylate **7c**, anti alcohol **7d**, and the absence of syn tosylate **5c** and syn alcohol **5d**. The oil was recrystallized from chloroform–petroleum ether[14] to give recovered **7c** (mp 119–121°, lit. 121–123°, 93% recovery) which showed[10] 9% deuterium incorporation at the methine position (δ 5.72) and ~50% incorporation at the benzylic methylene position (δ 3.7–2.5).

Preparation of 15. Syn alcohol **1d**[11] (100 mg, 0.314 mmol) was treated with sodium ethoxide (from 0.18 g, 7.85 mg-atoms of sodium) in absolute ethanol (25 ml) at the reflux temperature (90 hr) under a dry nitrogen atmosphere. Excess ethanol was removed *in vacuo*, and saturated aqueous NH_4Cl was added to the cold residue. The product was extracted with chloroform and the oil (97.3 mg) obtained from the dried ($MgSO_4$) extract was separated into two components by preparative tlc [silica gel with petroleum ether[13]–ether (3:1) as eluent].

(1) Crude **15**, 64% by wt, mp 136–138°, was recovered from carbon tetrachloride–petroleum ether.[14] The solid was further purified by multiple injections into a high pressure liquid chromatograph (8 ft × 2.2 mm i.d., Porasil A, eluted with 40% chloroform–petroleum ether[14] at a flow rate of 2.7 ml/min), mp 139–140°. The mass spectrum of **15** showed *m/e* (relative intensity) 283 (91), 254 (56.5), 185 (100), 172 (56.5) [the M^+ is consistent with **15** (no chlorine)]; pmr ($CDCl_3$) δ 8.2–7.4 (m, 4, aromatic H), 7.26 (s, 1, isolated aromatic H), 5.00 (q, 1, methine H, X portion of ABX system $J_{AX} + J_{BX}$ = 10 Hz), 3.40 (octet, 1, benzylic H), 2.78 (octet, 1, benzylic H), 2.2–0.4 (m, ~16, bridge CH_2); ir (KBr disk) ν_{OH} 3225 cm^{-1} (broad).

Anal. Calcd for $C_{19}H_{25}NO$: C, 80.57; H, 8.89; N, 4.94. Found: C, 80.81; H, 8.74; N, 4.79.

(2) Impure syn alcohol **1d** (35 mg, 35% recovery, pmr methine at δ 5.35[11]) was recovered but was not processed further.

Exchange Reactions of Syn and Anti Alcohols (1d and 2d). Anti Alcohol 2d.[11] The anti alcohol **2d** (109.9 mg) was treated in a manner similar to that described for the preparation of **15**; however, anhydrous ethanol-*O-D* (3.45 g, Stohler Isotope Chemicals) was employed (26-hr reflux). Tituration of the residue (121.7 mg) with methanol gave 90.6 mg (83% recovery) of **7d** (mp and mmp 203–205°, lit.[11] 205.5–207°); the product[10] contained 12% deuterium at the methine position (δ 5.05) and 87% deuterium at the benzylic methylene position.

Examination of the mother liquor by tlc [silica gel with petroleum ether–petroleum ether[13] (3:1)] showed no detectable amounts of epimeric alcohol **5d** although there were some other minor byproducts formed.

Syn Alcohol 1d. Reaction of *syn*-**1d**[11] (103.5 mg) with sodium ethoxide in ethanol-*O-D* was carried out as described for **2d**. Examination of the product by tlc (as described for **2d**) showed no detectable quantity of anti alcohol **7d**, but rather two major components listed in order of increasing R_f: (1) ~45% by wt of impure **15** (completely deuterated at benzylic positions[10]) and (2) slightly impure recovered syn alcohol **5d** (mp 153–154°, pmr methine at 5.34, lit.[11] mp 160–162°, 32 mg, 32% recovery). The pmr analysis[10] of this slightly impure sample of **5d** showed 14% deuterium incorporation at the methine position (δ 5.35) and 74% deuterium incorporation at the benzylic methylene position (δ 3.6–3.2).

Reaction of Anti Ether 2e with Sodium Ethoxide in Ethanol-*O-D*. A sample of **2e** (108.5 mg, 0.314 mmol) was treated essentially as described for **1d** and **2d** (48-hr reflux) to give 110.3 mg of crude crystalline product. Recrystallization of this product from absolute ethanol gave 75.9 mg (70%) of recovered **7e** (mp 107–108°, mmp 106–107°, lit.[15] 107.5–110°); analysis for deuterium by pmr[10] showed 8% deuterium incorporation at the methine position (δ 4.76) and ~88% deuterium incorporation at the benzylic methylene position. (δ 3.8–3.2, under CH_2 resonance of ethyl group).

Examination of the mother liquor by tlc showed principally additional **7e**; however, six trace materials were detected, one of which had an R_f corresponding to syn ether **5e**.[15]

Exchange of Syn and Anti Bromides 1b and 2b with Sodium Ethoxide in Ethanol-*O-D*. These reactions were conducted essentially as described for **1d** and **2d**.

From syn bromide 1b[11] (131.3 mg) there was obtained 104.4 mg of crude product. Preparative tlc [silica gel, petroleum ether[13]–ether (3:1)] showed no detectable quantities of anti bromide **7b**, but two major products listed in order of increasing R_f: (1) reduced pyridinophane[6,11] **16** (51.2 mg, 49% yield, mp 77–78° from petroleum ether,[4] lit. 81.2–82.5°), and (2) recovered syn bromide **5b** [21 mg, 16% yield, mp 140–141°; mp 147° from petroleum ether,[14] lit. 149.5–151°; nmr ($CDCl_3$) methine H at δ 6.05] showed[10] 100% deuterium incorporation at the methine position and 78% incorporation at the benzylic methylene position (δ 3.6–3.0).

From anti bromide 2b (106.5 mg, 0.28 mmol) there was obtained 82.7 mg of a solid product. Analysis of this material by high pressure liquid chromatography [8 ft × 2.2 mm i.d., Porasil A, chloroform–petroleum ether[13] as eluent (9:1) at 2.7 ml/min] showed it to be a complex mixture containing at least six components; syn and anti bromides **5b** (major) and **7b** were shown to be present by injection (lc) of authentic samples. Attempts to resolve the mixture by tlc [silica gel with petroleum ether[13]–ether (9:1) as eluent] were not successful; reduced pyridinophane **16** was shown to be present.

Registry No.—**1a**, 51933-62-1; **1b**, 25859-37-4; **1c**, 37781-25-2; **1d**, 25866-36-8; **2a**, 52078-88-3; **2b**, 42880-45-5; **2c**, 37781-31-0; **2d**, 25907-82-8; **2e**, 34844-97-8; **5a**, 52437-22-6; **5b**, 52437-23-7; **5c**, 52437-24-8; **5d**, 52437-25-9; **7a**, 52151-91-4; **7b**, 52437-26-0; **7c**, 52437-27-1; **7d**, 52079-43-3; **7e**, 52437-28-2; **15**, 52438-79-6.

References and Notes

(1) Supported in part by National Science Foundation Grant No. 35429.
(2) (a) J. A. Zoltewicz and P. E. Kandetzki, *J. Amer. Chem. Soc.*, **93**, 6562 (1971), and references cited therein; (b) "Heteroaromatic Nitrogen Compounds: Pyrroles and Pyridines," K. Schofield, Ed., Butterworths, London, 1967, pp 325–327, and references cited therein.
(3) W. E. Parham and P. E. Olson, *Tetrahedron Lett.*, **48**, 4783 (1973).
(4) 2- and 4-alkylpyridines also undergo exchange in HCl–ethanol-*O-D* and deuterium oxide: *cf.* ref 2a, and A. I. Shatenshtien, "Isotopic Exchange and the Replacement of Hydrogen in Organic Compounds," translated by C. N. Turton and T. I. Turton, Consultants Bureau, New York, N. Y., 1962, pp 33–37.
(5) W. E. Parham, K. B. Sloan, K. R. Reddy, and P. E. Olson, *J. Org. Chem.*, **38**, 927 (1973).
(6) W. E. Parham, P. E. Olson, K. R. Reddy, and K. B. Sloan, *J. Org. Chem.*, **39**, 172 (1974).
(7) While it is clear that intermediates **8** or **9** cannot be involved as such in these exchange reactions, some contribution from structures implied by **8** and **9** is possible. Resonance stabilization of this type does not require coplanarity but is a function of the cosine of the angle and is rather at a maximum when the atoms involved are coplanar.
(8) D. A. Jaeger, M. D. Broadhurst, and D. J. Cram, *J. Amer. Chem. Soc.*, **95**, 7525 (1973), and references cited in footnotes 2 and 4 of that communication.
(9) D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N.Y., 1965, pp 85–114, and references cited therein.
(10) Deuterium isotope analyses performed by pmr were calculated by comparison of the integral of aromatic hydrogens, which were assigned the theoretical value, *vs.* the integral of benzyl methylene hydrogen and/or benzyl methine hydrogen. In no case where an additional standard was used (methylene chloride) was there any observed aromatic hydrogen–deuterium exchange.
(11) W. E. Parham, R. W. Davenport, and J. B. Biasotti, *J. Org. Chem.*, **35**, 3775 (1970).
(12) (a) K. R. Reddy, Ph.D. Thesis, University of Minnesota, Minneapolis, Minn., 1972; (b) W. E. Parham and P. E. Olson, *J. Org. Chem.*, in press.
(13) Bp 30–60°.
(14) Bp 60–90°.
(15) W. E. Parham and K. B. Sloan, and J. B. Biasotti, *Tetrahedron Lett.*, **27**, 5767 (1971).

1,3-Bridged Aromatic Systems. XIII. Reactions of Hindered Grignard Reagents with Oxygen[1]

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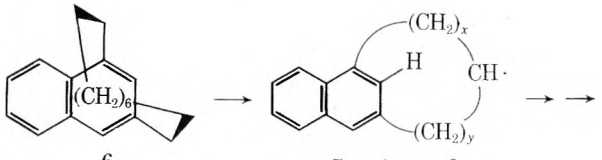
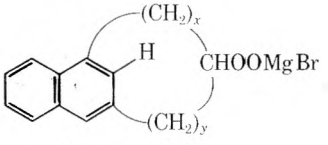
While there has been some controversy[2-4] as to whether the initiation step in the reactions of Grignard reagents with oxygen is ionic or involves radical intermediates, the reaction is now considered[5-9] to occur as shown in eq 1. The

$$\begin{aligned} RMgX + O_2 &\longrightarrow R\cdot + \cdot OOMgX \\ R\cdot + O_2 &\longrightarrow ROO\cdot \\ RMgX + ROO\cdot &\longrightarrow R\cdot + ROOMgX \end{aligned} \qquad (1)$$

previous report[10] that the reaction of **2** with oxygen (Scheme I) gives the transannular alcohols **5** is consistent with rapid radical transfer[12,13] as shown in eq 2; however,



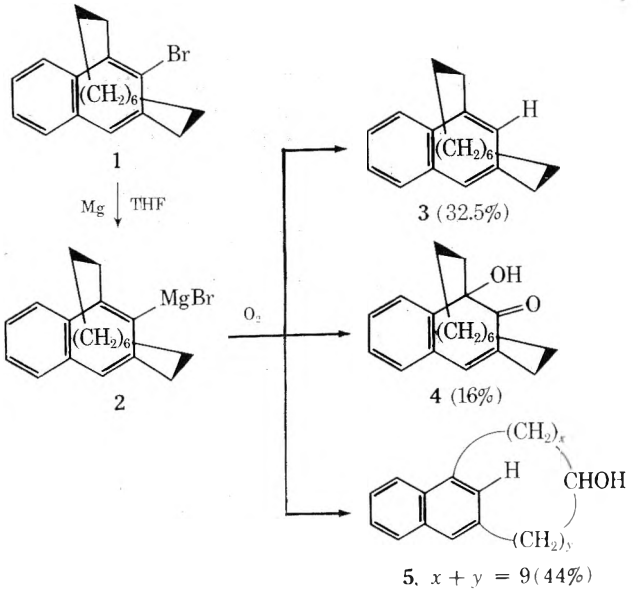
6 → **7**, $x + y = 9$



8, $x + y = 9$ (2)

the reaction sequence leading to **3** and **4** has not been established. We have reinvestigated the process outlined in Scheme I with the following observations.

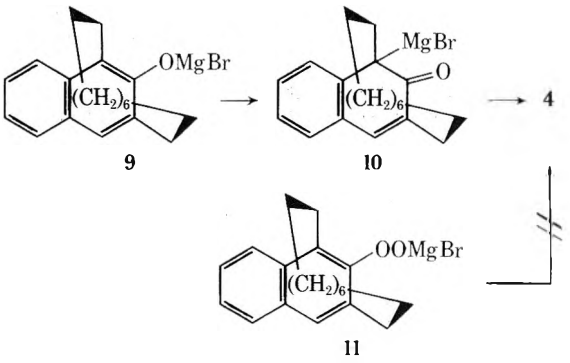
Scheme I[11]



1 → (Mg, THF) → **2** → (O_2) → **3** (32.5%), **4** (16%), **5**, $x + y = 9$ (44%)

(1) The expected[9] phenol **9** is not detected in the products of the reaction, but is the probable precursor to the keto alcohol **4** as shown in Scheme II; we had originally considered that **4** may be derived from the hydroperoxide **11**.

Scheme II



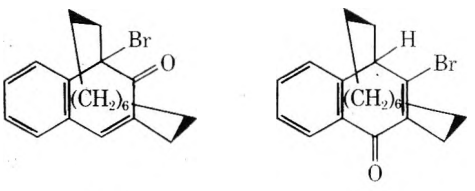
9 → **10** → **4**; **11**

Reaction of **2** with the bromomagnesium salt of *tert*-butyl hydroperoxide, a process that should give **9** by an ionic process,[8] gave **4** in high yield. These results were obtained in the presence of excess **2**; consequently, the intermediate **9** is oxidized more rapidly by hydroperoxide salt to **4** than is the Grignard reagent **2** to **9**. That the phenolate ion **9** would rearrange to **10** is reasonable since such rehybridization within the aryl ring would reduce strain in the cyclophane system;[14] tertiary C–MgX bonds are known[3,15] to react with hydroperoxide to give alcohols.

(2) Reduced cyclophane **3** is not derived to any appreciable extent from unreacted Grignard reagent **2** since decomposition of the reaction product with D_2O gave **3** which contained only 7.3% of the d_1 species (mass spectrum).

(3) Reduced cyclophane **3** (and the aryl H in **5**) is not derived to any appreciable extent by reaction of either **6** or **7** with solvent. When the reaction of **2** with oxygen was carried out in pure perdeuteriotetrahydrofuran as solvent, the reduced cyclophane **3** contained only 9% of the d_1 species (mass spectrum); the principal ketone[2] obtained by oxidation of **5** showed essentially no (0.4%) d_1 species.

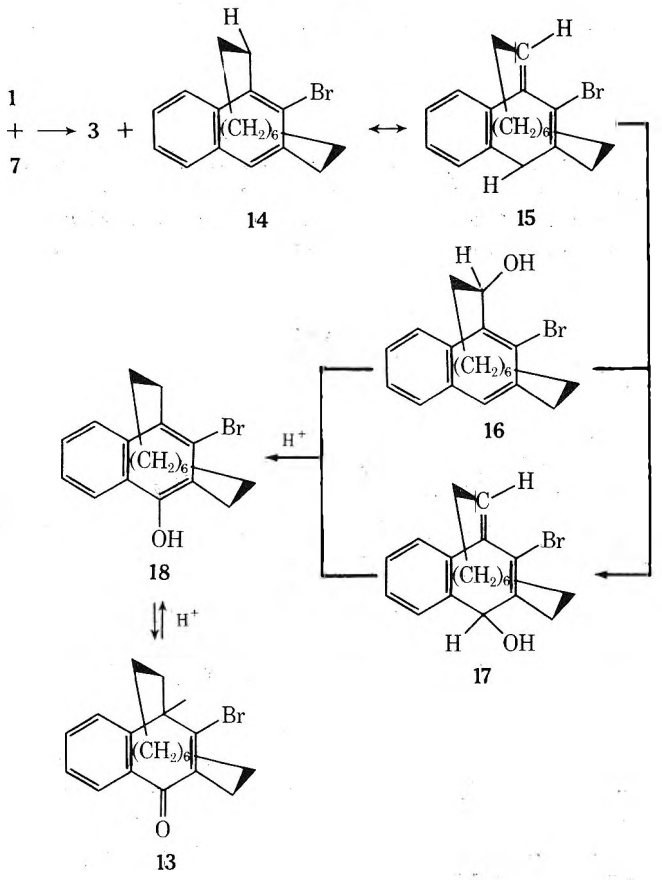
(4) A new, relatively unstable, bromine-containing product was isolated from the reaction mixture (ir shows ν at 1660 cm^{-1}, characteristic[16] of conjugated phenone; pmr shows peri-H at δ 7.7, one benzylic proton at δ 3.0 and two allylic protons at δ 2.6) for which structures **12** and **13** were



12 **13**

considered. Compound **12** could form by elimination of magnesium oxide from **11**. The single benzylic proton at δ 3.0, however, suggests structure **13**. The isolation of **13** suggests that unconverted **1**, which is generally recovered from such reactions, is the source of hydrogen leading to **3**, as shown in Scheme III. The proposed intermediate alco-

Scheme III



hols **16** and/or **17** could be formed[17] by a normal sequence of reactions from **14** or **15**; the conjugated ketone **13** is assumed to result by prototropic rearrangement of **16** and/or **17** upon acid work-up. That **13** would exist in the keto form rather than the phenolic enol form **18** is interesting and is attributed to relief of strain in the cyclophane system.[14]

Experimental Section

Reaction of 2 with Oxygen. The crude product obtained from **1** (0.75 g)[10] was separated into four bands by preparative chromatography as previously described[10] which were removed with 15% methanol in chloroform to give: (1) leading band, mixture of **1** and **3** (0.240 g); pure **3** (0.107 g, mp 39–40° from ethanol[10]) obtained from trailing edge after rechromatography;[18] (2) yellow oil (0.063 g), mostly **13**; (3) nearly pure **4** (0.101 g; 0.086 g by sublimation, mp 140–142°[10]); (4) alcohols **5** (0.248 g). The yields of **3**, **13**, **4**, and **5** based on consumed **1** were 32.5, 9, 16, and 44%, respectively.

Compound **13**: mp 110–112° from diethyl ether, 0.042 g, yellow solid; high-resolution mass spectral parent ion 360.1089 ($C_{20}H_{25}BrO$); ν 1660 cm^{-1}; pmr δ 7.7 (m, aromatic H, 1.0), 7.6–7.1 (m, aromatic H, 3.0), 3.0 (broad m, ArCH, 1.0), 2.6 (broad m, $=CCH_2$, 2.0), 2.3–0.5 (m, CH_2, 17.5).

Anal. Calcd for $C_{20}H_{25}BrO$: C, 66.48; H, 6.97; Br, 22.12. Found: C, 66.36; H, 7.17; Br, 21.72.

Perdeuteriotetrahydrofuran (98.5% d, E. Merck, Darmstadt) was distilled from $LiAlD_4$ prior to use. Calculations of protio to d_1 species were calculated from mass spectral data as described by Biemann.[19]

Reaction of 2 with *tert*-Butyl Hydroperoxide. A solution of *tert*-butyl hydroperoxide[20] (0.13 g, 1.45 mmol, 99.2% solution[21,22]) in dry (from $LiAlH_4$) tetrahydrofuran (5 ml) was added slowly to a solution of **2** (from **1**,[10] 1.00 g, 2.90 mmol) in dry tetrahydrofuran (15 ml) packed in ice,[15] and the resulting solution was stirred, under nitrogen, for 16 hr while warming to room temperature. The mixture was cooled and 50 ml of 5% aqueous hydrochloric acid was added; the organic material was extracted with ether which was subsequently dried ($MgSO_4$) and concentrated. Chromatography of the oil (0.513 g) obtained from the ether as described above [petroleum ether (bp 60–90°) followed by petroleum ether (bp 30–60°)–5% ether] gave: (1) **3** (1.93 mmol), mp 40–41°,[10] and (2) crude **4** (0.213 g, 98.4% yield; 0.119 g from acetone, 55% yield, mp 138–140°[10]).

Registry No.—**1**, 25097-45-4; **3**, 25097-46-5; **4**, 25097-53-5; **5**, 52358-29-9; **13**, 52358-30-2; *tert*-butyl hydroperoxide, 75-91-2.

References and Notes

(1) Supported by the National Science Foundation GP-35429.
(2) C. W. Porter and C. S. Steele, *J. Amer. Chem. Soc.*, **42**, 2650 (1920).
(3) C. Walling and S. A. Buckler, *J. Amer. Chem. Soc.*, **77**, 6032 (1955).
(4) C. Walling, "Free Radicals in Solution," Wiley, New York, N.Y., 1957.
(5) G. A. Russell, *J. Amer. Chem. Soc.*, **76**, 1595 (1954).
(6) M. E. H. Howden, H. Maercker, J. Burdon, and J. D. Roberts, *J. Amer. Chem. Soc.*, **88**, 1732 (1966).
(7) R. C. Lamb, P. W. Ayers, M. K. Tooney, and J. F. Garst, *J. Amer. Chem. Soc.*, **88**, 4261 (1966).
(8) C. Walling and A. Cioffari, *J. Amer. Chem. Soc.*, **92**, 6609 (1970).
(9) J. F. Garst, C. D. Smith, and A. C. Farrar, *J. Amer. Chem. Soc.*, **94**, 7707 (1972).
(10) W. E. Parham, R. W. Davenport, and J. K. Rinehart, *J. Org. Chem.*, **35**, 2662 (1970).
(11) The yields of products are based on **1** consumed.
(12) G. A. Russell and R. F. Bridger, *J. Amer. Chem. Soc.*, **85**, 3765 (1963).
(13) While aryl radicals react with oxygen 10^3 faster than hydrogen abstraction,[11] models show that four bridge hydrogen atoms are in close proximity to the radical site in **6**, and thus are in high concentration relative to molecular oxygen.
(14) W. E. Parham, D. C. Egberg, and W. C. Montgomery, *J. Org. Chem.*, **38**, 1207 (1973).
(15) S. O. Lawesson and N. C. Yang, *J. Amer. Chem. Soc.*, **81**, 4230 (1959).
(16) N. B. Colthup, L. H. Daly, and S. E. Wiberly, "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N.Y., 1964, p 244.
(17) Product **13** could form by related reactions involving abstraction of hydrogen from the other benzylic methylene group.
(18) Leading edge contained 52% of **1** and 48% of **2**; liquid chromatographic analysis [8 ft × ⅛ in. Porasil A, petroleum ether (bp 30–60°); 1 ml/min, six recycles].
(19) K. Biemann, "Mass Spectrometry: Organic Chemical Applications," McGraw-Hill, New York, N.Y., 1962, Chapter 5.
(20) Kindly supplied as 90% solution by Lucidol Chemical Division, Pennwalt Corp.
(21) Concentrated by azeotropic distillation: *cf.* P. D. Bartlett and H. Minato, *J. Amer. Chem. Soc.*, **85**, 1858 (1963).
(22) P. D. Bartlett, E. P. Benzing, and R. E. Pincock, *J. Amer. Chem. Soc.*, **82**, 1762 (1960).

Reactions of *N*-Sulfinylamides with Sulfoxides Bearing Electronegative Substituents

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It has been reported that *N*-sulfinylsulfonamides react with sulfoxides to give sulfimides.[1a,b] In an attempt to get various types of sulfimides for investigation of reactivities, we used sulfoxides containing electron-withdrawing groups on the α carbon. The reaction did not afford the expected substituted sulfimides **7** but led to the rearranged derivatives **3** and their thermal decomposition products **4**.

Reaction of *N*-sulfinyl-*p*-toluenesulfonamide (**1a**) with 2-(methylsulfinyl)acetophenone (**2a**) in refluxing benzene gave 2-(methylthio)-2-(*p*-toluenesulfonamido)acetophenone (**3a**), 2,2-bis(*p*-toluenesulfonamido)acetophenone (**4a**), and 2-methylthioacetophenone (**5a**) in 5, 71, and 11% yields, respectively. The reaction in refluxing ether, however, necessitated prolonged heating and resulted in the formation of **3a** (61%) and **4a** (15%). The structure of **3a**

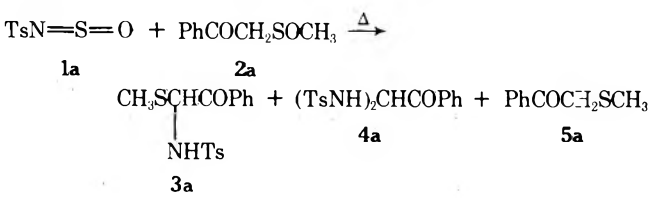


Table I
Reactions of *N*-Sulfinylamides 1a–c with Sulfoxides 2a–f

R^1 in 1	R^2 in 2	Solvent[a]	Temp, °C	Time, hr	Products (yields, %) 3	4	5	6
p-$MeC_6H_4SO_2$	PhCO	B	80	1.5	3a (5)	4a (71)	5a (11)	
p-$MeC_6H_4SO_2$	PhCO	E	35	14.0	3a (61)	4a (15)		
p-$MeC_6H_4SO_2$	*p*-$MeOC_6H_4CO$	B	80	7.0	3b (32)	4b (23)		
p-$MeC_6H_4SO_2$	*p*-$MeOC_6H_4CO$	E	35	14.0	3b (54)			
p-$MeC_6H_4SO_2$	MeOCO	B	80	7.5	3c (3)	4c (66)		
p-$MeC_6H_4SO_2$	*n*-$C_5H_{11}CO$	B	80	5.0		4d (58)		
p-$MeC_6H_4SO_2$	CN	B	80	6.5		4e (61)	5e (4)	6e (53)
p-$MeC_6H_4SO_2$	$C_6H_{11}CO$	B	80	1.5	3f (29)			
$MeSO_2$	PhCO	B	80	9.0	3g (15)	4g (50)		
PhCO	PhCO	B	45–50	5.5	3h (21)		5a (19)	
PhCO	*p*-$MeOC_6H_4CO$	B	40–45	8.0	3i (49)			

[a] B, benzene; E, ether.

was established as follows. The ir spectrum of **3a** shows N–H and carbonyl absorption bands at 3320 and 1665 cm^{-1}. The frequency of the carbonyl group suggests that **3a** is not phenacylidene (*p*-toluenesulfonamido)methylsulfurane, since the carbonyl group of known phenacylidenemethylphenylsulfurane appears at 1505–1470 cm^{-1} [2] The nmr spectrum (DMSO-d_6) displays S–CH_3 (s, 3 H), *p*-CH_3 (s, 3 H), methine (d, J = 9.5 Hz, 1 H), phenyl protons (m, 9 H), and N–H (d, J = 9.5 Hz, 1 H) at δ 1.82, 2.35, 6.12, 7.15–8.15, and 8.82, respectively. Reduction of **3a** by Raney Ni in refluxing ethanol yielded a mixture of 2-(*p*-toluenesulfonamido)acetophenone (**9**, 10%) and **4a** (29%).

$$CH_3SCHCOPh \xrightarrow[\text{ethanol}]{\text{Raney Ni}} TsNHCH_2COPh$$
NHTs
3a 9

This chemical property and physical data are consistent with the structure **3a**. Structural assignment of **4a** was based on ir data (NH and C=O absorptions at 3250 and 1690 cm^{-1}), nmr data [absorptions for *p*-CH_3 (s, 6 H), methine (t, J = 8.3 Hz, 1 H), aromatic protons (m, 13 H), and NH (d, J = 8.3 Hz, 2 H) at δ 2.32, 6.16, 7.00–8.00, and 8.75], and elemental analysis.

The reactions of **1a** with 2-(methylsulfinyl)-4′-methoxyacetophenone (**2b**), methyl methylsulfinylacetate (**2c**), and (methylsulfinyl)methyl cyclohexyl ketone (**2f**) in refluxing benzene gave the corresponding N-substituted *p*-toluenesulfonamides **3b,c,f** and bisamides **4b,c**, respectively.

The reactions with 1-(methylsulfinyl)-2-heptanone (**2d**) and cyanomethyl methyl sulfoxide (**2e**) led only to the bisamides **4d** and **4e** along with di(methylthio)acetamide (**6e**).

The reactions using *N*-sulfinylmethanesulfonamide (**1b**) and *N*-sulfinylbenzamide (**1c**) gave similar results. These results are summarized in Table I.

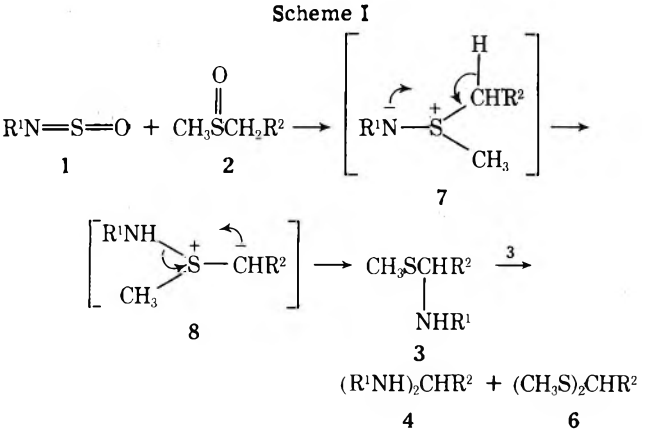
Possible mechanisms for formation of **3** and **4** are shown in Scheme I. Similar results in pyrolysis of *N*-acetyldialkylsulfimides have been reported by Swern, *et al.*[3] In the above reactions, our failure to isolate the expected sulfimides **7** may be due to the methylene group being activated by the electron-withdrawing groups such as the carbonyl (including ester) and cyano groups.

Irradiation of a methanol solution of **3i** with a 500-W

$$CH_3SCHCOC_6H_4\text{-}p\text{-}OCH_3 \xrightarrow{h\nu} PhCONHCHCOC_6H_4\text{-}p\text{-}OCH_3$$
NHCOPh
3i

$$PhCONHCHCOC_6H_4\text{-}p\text{-}OCH_3$$
10

Scheme I



high-pressure arc afforded 1,2-di-*p*-anisyl-1,2-dibenzamidoethane (**10**), structural assignment to which could be made with confidence on the basis of its analysis and spectroscopic properties (see Experimental Section), in 27% yield.

Experimental Section[4]

General Procedure. The reactions were run under dry N_2. The temperature was held at the boiling points of benzene or ether until the evolution of sulfur dioxide ceased.

Materials. *N*-Sulfinyl-*p*-toluenesulfonamide,[5] *N*-sulfinylmethanesulfonamide,[5] *N*-sulfinylbenzamide,[6] 2-(methylsulfinyl) acetophenone,[7] 2-(methylsulfinyl)-4′-methoxyacetophenone,[7] 1-(methylsulfinyl)-2-heptanone,[7] (methylsulfinyl)methyl cyclohexyl ketone,[7] and cyanomethyl methyl sulfoxide[8] were prepared according to the established procedures. Methyl methylsulfinylacetate was synthesized by oxidation of methyl methylthioacetate [bp 162–163° (760 mm)], which was prepared from methyl chloroacetate and methyl mercaptan sodium salt, with hydrogen peroxide in 72% yield: bp 103–104° (2.5 mm); $n^{21.5}D$ 1.4840; ir (neat) 1730 (C=O) and 1045 cm^{-1} (SO); nmr (CCl_4) δ 2.77 (s, 3 H, CH_3S=O), 3.73 (s, 2 H, $-CH_2-$), and 3.80 (s, 3 H, $-OCH_3$).

Reaction of *N*-Sulfinyl-*p*-toluenesulfonamide (1a) with 2-(Methylsulfinyl)acetophenone (2a). A solution of **1a** (6.00 g, 27.6 mmol) and **2a** (5.00 g, 27.4 mmol) in 50 ml of dry benzene was refluxed for 1.5 hr. After the solution was allowed to stand at ambient temperature overnight, the resulting crystals (4.0 g) were filtered. The crystals were recrystallized from ethanol to give pure **2,2-bis(*p*-toluenesulfonamido)acetophenone (4a)**: nmr (DMSO-d_6) δ 2.32 (s, 6 H, *p*-CH_3), 6.16 (t, J = 8.3 Hz, 1 H, >CH–), 7.00–8.00 (m, 13 H, aromatic protons), and 8.75 (d, J = 8.3 Hz, 2 H, NH); mass spectrum (70 eV) no molecular ion, *m/e* 212 ($M^+ - TsNH_2 - Ph$), 171 ($TsNH_2$), and 105 ($PhCO^+$).

The filtrate was concentrated to afford a mixture of **4a** and **2-(methylthio)-2-(*p*-toluenesulfonamido)acetophenone (3a)**. Pure samples of individual **4a** (0.50 g) and **3a** (0.50 g, 5%) were isolated by repeated recrystallization of the mixture from ethanol.

Table II
(Methylthio)(substituted amido) methanes 3
$(CH_3S)(R^1NH)CHR^2$

Compd	R^1	R^2	Mp, °C	Ir (Nujol), cm^{-1} ν NH	Ir (Nujol), cm^{-1} ν C=O	Empirical formula[a]
3a	p-$MeC_6H_4SO_2$	PhCO	162–166	3320	1665	$C_{16}H_{17}NO_3S_2$
3b	p-$MeC_6H_4SO_2$	p-$MeOC_6H_4CO$	149–151	3330	1655	$C_{17}H_{19}NO_4S_2$
3c	p-$MeC_6H_4SO_2$	MeOCO	89–90	3240	1725	$C_{11}H_{15}NO_4S_2$
3f	p-$MeC_6H_4SO_2$	$C_6H_{11}CO$	144–145	3270	1665	$C_{16}H_{23}NO_3S_2$
3g	$MeSO_2$	PhCO	135–140	3280	1670	$C_{10}H_{13}NO_3S_2$
3h	PhCO	PhCO	141–142	3360	1670, 1635	$C_{16}H_{15}NO_2S$
3i	PhCO	p-$MeOC_6H_4CO$	155–156	3360	1660, 1635	$C_{17}H_{17}NO_3S$

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds in the table.

Table III
***N,N'*-Substituted Methylene Bis(substituted amides) 4**
$(R^1NH)_2CHR^2$

Compd	R^1	R^2	Mp, °C	Ir (Nujol), cm^{-1} ν NH	Ir (Nujol), cm^{-1} ν C=O	Empirical formula[a]
4a	p-$MeC_6H_4SO_2$	PhCO	206–208	3250	1690	$C_{22}H_{22}N_2O_5S_2$
4b	p-$MeC_6H_4SO_2$	p-$MeOC_6H_4CO$	176–178	3270	1675	$C_{23}H_{24}N_2O_6S_2$
4c	p-$MeC_6H_4SO_2$	MeOCO	189–190	3270	1745	$C_{17}H_{20}N_2O_6S_2$
4d	p-$MeC_6H_4SO_2$	n-$C_5H_{11}CO$	160–165	3250	1725	$C_{21}H_{28}N_2O_5S_2$
4e	p-$MeC_6H_4SO_2$	CN	156–158	3240		$C_{16}H_{17}N_3O_4S_2$
4f	$MeSO_2$	PhCO	200–205	3200	1680	$C_{10}H_{14}N_2O_5S_2$

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds in the table.

The combined yield of **4a** was 4.50 g (71%). **3a** showed the following physical properties: nmr (DMSO-d_6) δ 1.82 (s, 3 H, $-SCH_3$), 2.35 (s, 3 H, p-CH_3), 6.12 (d, J = 9.5 Hz, 1 H, >CH–), 7.15–8.15 (m, 9 H, phenyl protons), and 8.82 (d, J = 9.5 Hz, 1 H, NH); mass spectrum (70 eV) no molecular ion, m/e 288 ($TsNHCHCOPh^+$), 230 ($M^+ - PhCO$), and 212 ($TsNHCHCO^+$).

The filtrate was combined, concentrated, and chromatographed on alumina using benzene as eluent to give 0.51 g (11%) of 2-(methylthio)acetophenone (**5a**), which was identical with an authentic sample[9] by comparison of ir spectra and the retention time of glpc.

In the reaction using ether as solvent at the refluxing temperature for 14 hr, **3a** and **4a** were obtained in 61 and 15% yields.

Reaction of *N*-Sulfinyl-*p*-toluenesulfonamide (1a) with Cyanomethyl Methyl Sulfoxide (2e). The reaction was carried out at 80° for 6.5 hr using **1a** (6.50 g, 0.03 mol) and **2e** (3.10 g, 0.03 mol) in dry benzene (60 ml). After similar treatment, **2,2-bis(*p*-toluenesulfonamido)acetonitrile (4e)**, cyanomethyl methyl sulfide (**5e**), and **dimethylthioacetamide (6e)** were isolated in 3.50 (61%), 0.20 (4%), and 1.21 g (53%) yields, respectively. The crude product **4e** was recrystallized from benzene–ethanol to give a pure sample: mp 156–158°; nmr (DMSO-d_6) δ 2.36 (s, 6 H, p-CH_3), (t, J = 9 Hz, 1 H, >CH–), 7.15–7.80 (m, 8 H, phenyl protons), and 9.50 (d, J = 9 Hz, 2 H, NH); mass spectrum (70 eV) no molecular ion, m/e 287 ($M^+ - PhCH_3$), 261 ($M^+ - PhCH_3 - CN$), and 224 ($M^+ - Ts$). The structure **5e** was determined by comparison of the ir spectrum and glpc behavior with those of an authentic sample.[8]

The crude product **6e** was recrystallized from benzene to give a pure sample: mp 148.5–149°; ir (Nujol) 3340 and 3230 (NH) and 1645 cm^{-1} (C=O); nmr (DMSO-d_6) δ 2.13 (s, 6 H, SCH_3), 4.39 (s, 1 H, >CH–), 7.00–7.30 (broad, 1 H, NH), and 7.30–7.60 (broad, 1 H, NH); mass spectrum (70 eV) m/e 151 (M^+), 107 ($M^+ - CONH_2$), and 105 ($M^+ - CH_3S + H$).

Anal. Calcd for $C_4H_9NOS_2$: C, 31.79; H, 6.00; N, 9.27. Found: C, 31.89; H, 5.91; N, 9.27.

Reactions of *N*-Sulfinylamides 1a–c with Sulfoxides 2a–f. The reactions were carried out in a similar manner. After similar treatments, the products,[10] **3b,c,f–i** and **4b–d,f**, were obtained by recrystallization. The results are summarized in Table I. Melting points and NH and carbonyl absorptions in the ir spectra of **3** and **4** are shown in Tables II and III.

Reduction of 3a. A solution of 0.50 g (1.5 mmol) of **3a** in 100 ml of ethanol containing 1 g of Raney Ni was allowed to stir under reflux for 4 hr. The organic layer was separated and allowed to stand overnight. The resulting crystals were filtered, followed by recrystallization from benzene–ethanol to give 40 mg (10%) of pure **2-(*p*-toluenesulfonamido)acetophenone (9)**: mp 195–197°; ir (Nujol) 3200 (NH), 1670 (C=O), 1345 (SO_2), and 1165 cm^{-1} (SO_2); nmr ($CDCl_3$) δ 2.30 (s, 3 H, p-CH_3), 5.08 (d, J = 7.0 Hz, 1 H, $>CH_aH_b$), 5.70 (d, J = 7.0 Hz, 1 H, $>CH_aH_b$), 7.08 (d, J = 7.0 Hz, 1 H, NH), and 7.30–7.70 (m, 9 H, phenyl protons); mass spectrum (70 eV) m/e 288 ($M^+ - H$), 171 ($TsNH_2^+$), and 105 ($PhCO^+$).

Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.28; H, 5.19; N, 4.84. Found: C, 62.27; H, 5.07; N, 4.92.

The filtrate was concentrated and the resulting crystals were recrystallized from benzene to give pure **4a** (0.20 g, 29%).

Irradiation of 3i. A solution of **3i** (0.55 g, 1.75 mmol) in 20 ml of methanol was irradiated for 20 hr with a 500-W high-pressure mercury arc under nitrogen at room temperature. The resulting precipitate was filtered and recrystallized from benzene–ethanol to give 0.128 g (27%) of **1,2-di-*p*-anisoyl-1,2-dibenzamidoethane (10)**: mp 209–211°; ir (Nujol) 3280 (NH), 1670 (C=O), and 1630 cm^{-1} (C=O); nmr (DMSO-d_6) δ 3.84 (s, 6 H, OCH_3), 6.10–6.35 (broad, 2 H, >CH–), 6.90–8.15 (m, 18 H, phenyl protons), and 8.90–9.20 (broad, 2 H, NH); mass spectrum (70 eV) m/e 536 (M^+), 415 ($M^+ - PhCONH_2$), 401 ($M^+ - MeOC_6H_4CO$), and 280 ($M^+ - PhCONH_2 - MeOC_6H_4CO$).

Anal. Calcd for $C_{32}H_{28}N_2O_6$: C, 71.63; H, 5.26; N, 5.22. Found: C, 71.28; H, 5.09; N, 5.17.

Registry No.—**1a,** 4104-47-6; **1b,** 40866-96-4; **1c,** 20043-21-4; **2a,** 2813-22-1; **2b,** 2813-23-2; **2c,** 52147-67-8; **2d,** 2863-47-0; **2e,** 52109-49-6; **2f,** 2863-48-1; **3a,** 52109-50-9; **3b,** 52109-51-0; **3c,** 52109-52-1; **3f,** 52147-68-9; **3g,** 52109-53-2; **3h,** 52109-54-3; **3i,** 52109-55-4; **4a,** 52109-56-5; **4b,** 52109-57-6; **4c,** 52109-58-7; **4d,** 52109-59-8; **4e,** 52109-60-1; **4f,** 52109-61-2; **6e,** 5311-18-2; **9,** 30057-92-2; **10,** 1183-24-0; methyl methylthioacetate, 16630-66-3.

Supplementary Material Available. Nmr and mass spectral data of **3b,c,f–i** and **4b–d,f** will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3412.

References and Notes

(1) (a) G. Schultz and G. Kresze. *Angew. Chem.*, **75**, 1022 (1963). (b) D. J. Cram, J. Day, D. R. Rayner, D. M. Schriltz, D. J. Duchamp, and D. C. Garwood, *J. Amer. Chem. Soc.*, **92**, 7369 (1970).
(2) H. Nozaki, K. Kondo, and M. Takaku, *Tetrahedron Lett.*, 251 (1965).
(3) H. Kise, G. F. Whitefield, and D. Swern, *J. Org. Chem.*, **37**, 1125 (1972).
(4) All melting points of products were determined with a Yanagimoto micromelting apparatus and are uncorrected. The nmr spectra were obtained on a JEOL LNM-3H-60 spectrometer with tetramethylsilane as an internal standard. The ir spectra were recorded with a Jasco IR-E spectrometer. The mass spectra were taken with a Hitachi RMU-6E spectrometer.
(5) G. Kresze and W. Wucherpfennig, *Angew. Chem.*, **79**, 109 (1967).
(6) O. Tsuge and S. Mataka, *Bull. Chem. Soc. Jap.*, **44**, 2836 (1971).
(7) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).
(8) S. Hünig and O. Boes, *Justus Liebigs Ann. Chem.*, **579**, 23 (1953).
(9) K. Griesbaum, A. A. Oswald, and B. E. Hudson, Jr., *J. Amer. Chem. Soc.*, **85**, 1969 (1963).
(10) See paragraph at end of paper regarding supplementary material.

Sulfonation of Unsaturated Compounds. I. Sulfonation of Branched-Chain Ketones with Sulfur Trioxide. A One-Step Synthesis of Tetramethylene Sulfate through a Retro Pinacol-Type Rearrangement

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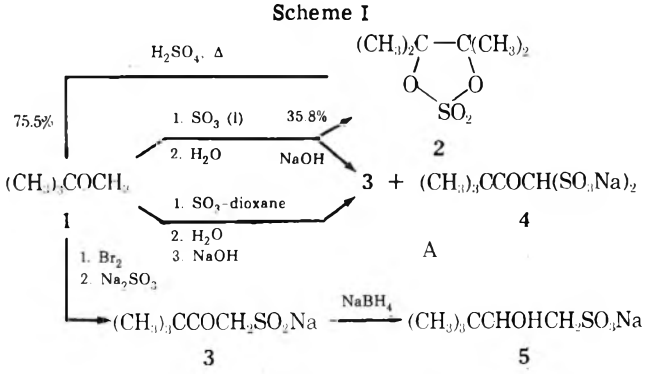
The sulfonation of aldehydes,[1] ketones,[1,2] and carboxylic acids[3] with sulfur trioxide and its adducts[4] is a facile process[4] leading to the corresponding sulfonic acids in which the sulfo group is attached α to the carboxylic function.[1-4] The products are isolated ordinarily as the corresponding salts after neutralization of the acidic sulfonation mixture. Consequently, the nature of possible intermediates has not been established and the presence of some by-products may have been overlooked. Moreover, the purity of the isolated products is questionable in many cases, since disulfonates may accompany the desired monosulfonates, and the separation between the two might prove to be very difficult.

It has been established[1,3] that carbonyl compounds which contain no α-hydrogen atoms are inert toward sulfur trioxide. It has also been shown that sulfonation of γ-branched olefins[5] is accompanied by the migration of either methyl or hydrogen to the incipient adjacent positive center.

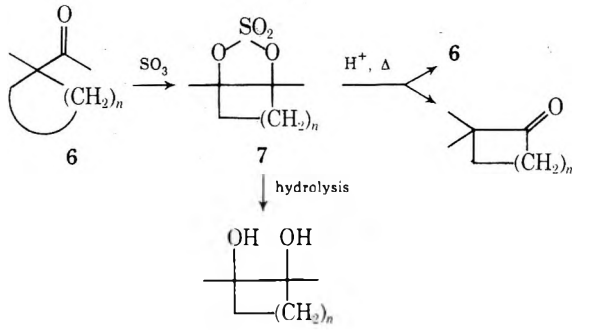
This note presents results of a study of sulfur trioxide sulfonation of pinacolone as a model compound (Scheme I).

Scheme I

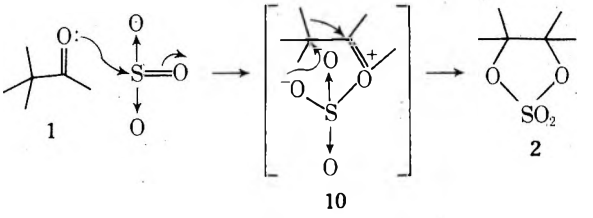


Direct sulfonation of pinacolone with liquid sulfur trioxide afforded a 36% yield of the cyclic tetramethylene sulfate **2**. The isolation of **2** is interesting both synthetically and mechanistically. First, **2** is required for the preparation of highly C-methylated compounds.[6] Alternative methods of preparation are laborious and result in overall low yields.[6] Secondly, other cyclic sulfates may be prepared using the same method. An extension of our findings would be the development of useful methods for initial ring expansion followed by formation of either ketones or glycols according to Scheme II.

Scheme II



In accord with the suggested mechanisms for the sulfonations of ketones,[1] and for the anhydrous acid-catalyzed epoxide–ketone[7] rearrangement the following mechanism for the formation of **2** is proposed.



The yield of sulfate **2** shows that migration of a methyl group from the adjacent quarternary carbon, to form a stable tertiary carbonium ion, successfully competes with the abstraction of available hydrogen from the α position. Rearranged products obtained in the sulfonation of γ-branched olefins[5] presumably arise from an analogous zwitterionic species.

We have found that heating of **2** under aqueous acidic conditions resulted in a rapid pinacol-type rearrangement to give back the starting pinacolone in good yield. This appears to be the first example of a direct transformation from a cyclic sulfate to a ketone.

The monoketosulfonate[8] **3** was not the only sulfonate obtained by direct sulfonation of pinacolone. The nmr spectrum of the initial product (after extractions and crystallizations) always revealed two types of *t*-butyl groups[9] and both methylene and methine protons. This and the finally separated disulfonate **4** after numerous crystallizations clearly showed the main product **3** to contain an appreciable amount of the disulfonate **4**. Disulfonate **4** was formed regardless of whether sulfur trioxide itself or the dioxane complex[4] was used. The alternative route *via* bromination followed by the Strecker reaction[10] proved to be the way of choice for obtaining pure **3** (Scheme I). Selective reduction of **3** with sodium borohydride afforded **5** in high yield. This suggests a convenient method of obtaining hydroxysulfonic acids from ketosulfonates.

Experimental Section

Tetramethylethylene sulfate (2). Sulfur trioxide (20.5 g, 0.256 mol) was distilled out of Sulfan (stabilized liquid sulfur trioxide, Allied Chemicals) into a cooled (0–5°) stirred solution of 1,2-dichloroethane (100 ml). Pinacolone **1** (25.65 g, 0.256 mol) in 45 ml of 1,2-dichloroethane was added over a period of 25 min. The exothermic reaction caused the temperature of the reaction mixture to reach 11°. Stirring was continued for 20 min, allowing the temper-

ature to reach 15°. Water (200 ml) was added with stirring for an additional 30 min at room temperature. The two layers were separated; the organic layer was washed with water, 5% sodium bicarbonate, and again with water and dried (Na_2SO_4). The solvent was removed under reduced pressure to give 16.5 g (35.8%) of the cyclic sulfate **2**. Recrystallization from ethanol–water or ether–petroleum ether yielded colorless crystals: mp 129–131° (dec), lit.[10] mp 131° (dec); ir [(KBr) 2993, 1469, 1405, 1352, 1214, 1201, 961 883 cm^{-1}] and nmr [δ 1.7 (s)] are consistent with this structure.

Anal. Calcd for $C_6H_{12}O_4S$: C, 40.00; H, 6.67; S, 17.78. Found: C, 40.12; H, 6.56; S, 18.03.

The aqueous layer was neutralized with 20% aqueous sodium hydroxide and evaporated under reduced pressure to yield 25.5 g of a crude mixture of sulfonic acids A (Scheme I). Crystallization of A from 60% aqueous alcohol afforded a mixture of **3** and **4** containing very little inorganic sulfate. Nmr of the mixture (D_2O) reveals peaks at δ 5.75 and 1.16 (**4**) and at δ 4.13 and 1.08 (**3**).

Several recrystallizations from 60% alcohol afforded relatively pure **4**, the assigned structure of which is based on its nmr and ir spectra [(KBr) 3550, 3410, 2980, 1690, 1275, 1240, 1043, 690 cm^{-1}].

Anal. Calcd for $C_6H_{10}Na_2O_7S_2$: C, 23.69; H, 3.32; Na, 15.11; S, 21.07. Found: C, 23.55; H, 4.07; Na, 15.36; S, 21.55.

Sulfonation of Pinacolone with Dioxane–Sulfur Trioxide Complex. To the dioxane–sulfur trioxide complex prepared in the usual manner[11] from sulfur trioxide (23.45 g, 0.293 mol), dioxane (25.8 g, 0.293 mol), and dry 1,2-dichloroethane (125 ml) was added dropwise with stirring 29.3 g (0.293 mol) of pinacolone over a period of 40 min, followed by additional stirring for 60 min at room temperature. Water (200 ml) was added and the organic layer separated. The aqueous layer was neutralized with 15% aqueous sodium hydroxide, and the neutralized solution was evaporated to dryness to yield about 60 g of a crude mixture of sulfonic acids A (Scheme I), containing inorganic sulfate.

Nmr integration of mixture A showed the molar ratio of monosulfonate **3** to disulfonate **4** to be within the range of 1.8–2.5:1. The ratio of **3**:**4** in the mixture is changed with every recrystallization from aqueous alcohol.

Rearrangement of 2. A dispersion of **2** (0.518 g, 2.875 mmol) in 3 ml of 20% sulfuric acid was refluxed for 15 min, followed by addition of 5 ml of water. Extraction with methylene chloride, drying (Na_2SO_4), filtration, and removal of the solvent under reduced pressure gave 0.217 g (75.5%) of pinacolone (**1**) identical with an authentic sample.

Sodium 2-Keto-3,3-dimethylbutanesulfonate (3). Bromination of pinacolone according to the procedure of Boyer and Siraw[12] gave the α-bromination product in 82.3% yield, which was converted to **3** according to the method of Parkes and Tinsley.[13] Recrystallization from 60% aqueous ethanol yielded **3** as colorless plates: mp 216.5–218°; ir (KBr) 3580, 3520, 2970, 2935, 1710, 1645, 1392, 1245, 1215, 1203, 1161, 1056, 745 cm^{-1}; nmr (DMSO-d_6) δ 3.75 (s, 2, CH_2), 1.1 (s, 9, CH_3).

Anal. Calcd for $C_6H_{11}NaO_4S$: C, 35.64; H, 5.48; Na, 11.37; S, 15.84. Found: C, 35.55; H, 5.61; Na, 11.47; S, 15.98.

Sodium 2-Hydroxy-3,3-dimethylbutanesulfonate (5). To a solution of **3** (3.5 g, 17.3 mmol) in 20 ml of distilled water was added sodium borohydride (0.4 g, 10.57 mmol) in 3.5 ml of water dropwise over a period of 20 min, followed by stirring of the reaction mixture for an additional 3.5 hr. Acidification with 2% aqueous sulfuric acid (about 28 ml) was followed by the addition of methanol to make the solution 60% methanolic (v/v). The hydroxysulfonic salt **5** crystallized on cooling. The total amount of two crops was 3.45 g (97.5%): mp 272–276°; ir (KBr) 3385, 2958, 2870, 1630, 1364, 1238, 1168, 1050, 810 cm^{-1}; nmr (D_2O) δ 3.78 (m, 1, CH), 3.03 (m, 2, CH_2), 0.92 (s, 9, CH_3).

Anal. Calcd for $C_6H_{13}NaO_4S$: C, 35.32; H, 6.42; Na, 11.27; S, 15.69. Found: C, 35.73; H, 6.37; Na, 11.49; S, 15.25.

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Registry No.—**1**, 75-97-8; **2**, 52393-63-2; **3**, 52393-64-3; **4**, 52393-65-4; **5**, 52393-66-5; SO_3, 7446-11-9

References and Notes

(1) W. E. Truce and C. C. Alfieri, *J. Amer. Chem. Soc.*, **72**, 2740 (1950).
(2) W. E. Truce and C. W. Vriesen, *J. Amer. Chem. Soc.*, **75**, 2525 (1953).
(3) A. J. Stirton, *J. Amer. Oil. Chem. Soc.*, **39**, 490 (1962).
(4) E. E. Gilbert, "Sulfonation and Related Reactions," Interscience, New York, N.Y., 1965.
(5) F. G. Bordwell, R. D. Chapman, and C. E. Osborne, *J. Amer. Chem. Soc.*, **81**, 2002 (1959).
(6) W. Baker and B. F. Burrows, *J. Chem. Soc.*, 2257 (1961).
(7) P. de Mayo, Ed., "Molecular Rearrangements," Interscience, New York, N.Y., 1963, p 20.
(8) Truce and Alfieri[1] reported the preparation of sulfonate **3** (sulfonation with the sulfur trioxide–dioxane complex) characterized as the corresponding *S*-benzylthiuronium salt, but failed to report complete elemental analysis or any supporting physical or spectral data.
(9) The relative ratio was shown to be dependent on both the reaction conditions and the method of work up. The ratio of **3** to **4** varied from 1.8 to 2.5:1.
(10) S. Zuffanti, *J. Amer. Chem. Soc.*, **62**, 1044 (1940).
(11) F. G. Bordwell and C. S. Rondestvedt, *J. Amer. Chem. Soc.*, **70**, 2429 (1948).
(12) H. (12) J. H. Boyer and D. Siraw, *J. Amer. Chem. Soc.*, **74**, 4502 (1952).
(13) G. D. Parkes and S. G. Tinsley, *J. Chem. Soc.*, 1861 (1934).

Chemistry of "Naked" Anions. III. Reactions of the 18-Crown-6 Complex of Potassium Cyanide with Organic Substrates in Aprotic Organic Solvents[1,2]

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Following Pedersen's discovery that macrocyclic polyethers ("crown" ethers) possess the ability to form crystalline complexes with a variety of inorganic salts and also the ability to solubilize these salts in aprotic organic solvents,[3] attention has been gradually focused toward utilizing the anion of the complex for synthetic purposes.[4] It has recently been reported that poor nucleophiles such as fluoride and acetate ions, solubilized as the potassium salt in CH_3CN or C_6H_6 containing 18-crown-6 (1,4,7,10,13 16-hexaoxacyclooctadecane, **1**),[3] become sufficiently nucleophilic to react smoothly and quantitatively with a variety of organic substrates.[1,2] These reactive species have been termed "naked" anions.[1] We now wish to report the preparation of the "naked" cyanide reagent and its utilization in a variety of synthetically useful reactions. Substitution, elimination, and addition processes have been explored.

The results are summarized in Table I. The reactions were carried out by simply pouring a substrate–crown solution directly over excess, dry KCN, and stirring the two-phase system vigorously at ambient or reflux temperature until reaction was complete. Little or no reaction was found to take place in the absence of **1** under the same conditions covering the same periods of time (runs 20 and 21, Table I). In all cases, **1** was present in catalytic quantities, indicating that it behaves as a phase-transfer catalyst.[5] In general, the reactions are more rapid in CH_3CN than in C_6H_6.

The reaction of "naked" cyanide with benzyl chloride proceeded quickly and quantitatively to product under mild conditions (run 20, Table I). With primary-substituted alkyl halides, the conversions to nitrile compounds were quantitative, with no elimination products detected (runs 1–12, Table I).[6] Displacement at secondary carbon produced primarily substitution products with only a small percentage of elimination products. These results compare favorably to those obtained with "naked" acetate,[2] but are in direct contrast to those of "naked" fluoride,[1] where large quantities of alkenes were obtained. It appears therefore, that "naked" fluoride may be a stronger base than either "naked" cyanide or "naked" acetate. Cyclohexyl halides gives exclusively elimination product with "naked" cyanide (runs 17 and 18, Table I). No reaction was observed with *o*-dichlorobenzene (run 22, Table I).

Table I[a]
Reactions of "Naked" Cyanide with Organic Substrates in the Presence of 18-Crown-6

Substrate	Registry no.	Run	Solvent	Products (yield, %)	Registry no.	Concn, M[b] Crown	Concn, M[b] Substrate	Temp, °C	$t_{1/2}$,[c] hr	t_{end}, hr
1,3-Dibromopropane	109-64-8	1	CH_3CN	Glutaronitrile (97.3)[d]	544-13-8	0.151	1.80	83	7	25
		2	CH_3CN	Glutaronitrile (94.9)[d]		0.147	1.80	Ambient	10.5	48
		3	C_6H_6	Glutaronitrile (100)[e]		0.147	1.80	90	12	40
		4	C_6H_6	Glutaronitrile (100)[e]		0.147	1.80	Ambient	10	49
1-Bromo-3-chloropropane	109-70-6	5	CH_3CN	Glutaronitrile (100)[e]		0.152	1.80	83	1.1	30
1,3-Dichloropropane	142-28-9	6	CH_3CN	Glutaronitrile (96.8)[d]		0.154	1.80	83	0.23	1.5
1,4-Dibromobutane	110-52-1	7	CH_3CN	Adiponitrile (100)[e]	111-69-3	0.141	1.80	83	6.5	14.5
		8	CH_3CN	Adiponitrile (100)[e]		0.141	1.80	Ambient	11	57
1,4-Dichlorobutane	110-56-5	9	CH_3CN	Adiponitrile (94.7)[d]		0.144	1.80	83	0.2	0.7
		10	CH_3CN	Adiponitrile (86)[d]		0.144	1.80	Ambient	8	75
1-Bromohexane	111-25-1	11	CH_3CN	1-Cyanohexane (100)[e]	629-08-3	0.138	1.80	83	10	40
1-Chlorohexane	544-10-5	12	CH_3CN	1-Cyanohexane (90.6)[d]		0.139	1.80	83	0.5	2.2
2-Bromobutane	78-76-2	13	CH_3CN	2-Cyanobutane (69.7)[e]	18936-17-9	0.141	2.00	83	16	32
		14	C_6H_6	2-Cyanobutane (43.4)[e]		0.140	2.01	90	58	66[f]
2-Bromooctane	557-35-7	15	CH_3CN	2-Cyanooctane (56)[d] (62)[e] -octene (17)[e,g]	2570-96-9	0.119	2.00	83	14	78
2-Chlorooctane	628-61-5	16	CH_3CN	2-Cyanooctane (77.5)[e,h] -octene (3.1)[e,g,h]		0.122	2.00	83	59	244[h]
Cyclohexyl bromide	108-85-0	17	CH_3CN	Cyclohexene (46)[e,f]	110-83-8	0.132	1.80	83		53[f]
Cyclohexyl chloride	542-18-7	18	CH_3CN	Cyclohexene (32)[e,f]		0.146	1.80	83		122.5[f]
Benzyl bromide	100-39-0	19	CH_3CN	Benzyl cyanide (100)[e]	140-29-4	0.146	1.80	Ambient	13	25
Benzyl chloride	100-44-7	20	CH_3CN	Benzyl cyanide (94.2)[d]		0.147	1.80	Ambient	0.08	0.4
		21	CH_3CN	Benzyl cyanide (20)[e,f]		0.0	1.80	Ambient		75[f]
o-Dichlorobenzene	95-50-1	22	CH_3CN	No reaction[i]		0.145	1.80	83		109
Methacrylonitrile (Acetone cyanohydrin)[j]	126-98-7	23	CH_3CN	1,2-Dicyanopropane (91.9)[d,l]	623-35-8	0.132	1.51 (1.78)	83	0.3	0.6
		24	CH_3CN	1,2-Dicyanopropane (46)[e,f]		0.132	1.52 (1.72)	Ambient		189[f]
		25	CH_3CN	1,2-Dicyanopropane (77)[d,k]		0.0	1.51 (1.74)	83	6.1	15

[a] For the isolated products, nmr, ir, and mass spectral data confirmed the pure compound's identity. Also, where possible, these spectra and glc data of the products were compared to those of the commercial compounds (runs 1–12). [b] The reactions were run in a total of 25 ml of solution, with a twofold excess of solid KCN per functional group for the substitution reactions, and a catalytic amount (approximately equivalent to 18-crown-6) of salt for the hydrocyanation. [c] $t_{1/2}$ is defined as the time required for 50% of the starting material to react. [d] Isolated yields. For these examples, glc and nmr analysis showed a quantitative conversion to the products. [e] Calculated from glc and nmr data. [f] In these runs, the reactions were stopped before completion. [g] From glc analysis, 1-octene and both *cis*- and *trans*-2-octene were formed. [h] There was difficulty in driving the reaction to completion. At 244 hr, the composition consisted of 7.4% starting material, 89.1% substitution product, and 3.5% olefin by glc analysis. The yields given in Table I are thus based on reacted starting material. [i] The absence of reaction of "naked" cyanide with *o*-dichlorobenzene was in contrast to the results recently reported for the analogous KOH–CH_3OH–crown system in which a 40–50% yield of *o*-chloroanisole was obtained.[4a] [j] 1.18 molar equiv of acetone cyanohydrin was used. It functioned as a proton donor and a cyanide ion regenerator after initiation of the reaction by the "naked" cyanide. [k] Run 25 was monitored frequently during the course of the reaction by glc, and thus a small quantity of product was lost in the transfers. The reaction was quantitative by glc and nmr analyses. [l] Reference 18.

Interestingly, primary chlorides react much faster than the corresponding bromides under the reaction conditions. For example, benzyl chloride reacts about 100 times faster than benzyl bromide (runs 19 and 20, Table I). This observation is contrary to the normally accepted leaving group order.[7] It is also opposite to what has been observed with "naked" acetate and "naked"fluoride.[1,2] With the secondary halides, it appears that bromides react more rapidly than chlorides; however, less alkene[8] and a higher overall yield of substitution product are obtained with the chloride. The causes of these observations are currently being investigated. It is emphasized here, however, that for synthetic purposes chlorides are preferred over bromides under the reaction conditions reported.

Substitutions of halides by cyanide ion have been reported to occur (1) in ethanol–water mixtures under strenuous conditions;[10] (2) in dipolar, aprotic solvents such as DMSO;[11] and (3) by use of tetraalkylammonium or -phosphonium salts to transfer the cyanide ion across a water–organic interface (phase-transfer catalysis).[5,12] Comparatively, the "naked" cyanide system appears to be superior to the ethanol–water method in reaction time, temperature, simplicity of work-up, and yields.[10,13] It also compares favorably to the dipolar, aprotic solvent and phase-transfer catalyst systems in both reaction time and yield for conversion of primary halides to nitriles.[11,12] Advantages of the "naked" cyanide procedure over these latter methods are lower reaction temperature and simplicity of work-up. For secondary substrates, comparable yields to those presented in Table I were obtained in much shorter times in the dipolar, aprotic solvent,[11b] while the phase-transfer catalyst system gave a higher yield of substitution product (no reaction time was reported).[12a] The reaction temperatures, however, were higher in both the DMSO and phase-transfer catalyst systems.[11,12]

The quantitative hydrocyanation reaction (run 23) is included to demonstrate the versatility of the "naked" cyanide reagent. In the absence of crown, reaction was found to proceed at a comparatively slow rate (run 25). The yield obtained in run 23 compares favorably with reported hydrocyanation reactions.[14]

In summary, it has been shown that 1 effectively solubilizes KCN in aprotic solvents, that the resulting "naked" cyanide is both a weak base and a potent nucleophile, and that the reagent produces nitrile compounds smoothly, mildly, and in high yields from a variety of organic substrates.

Experimental Section

The following instruments were used in the analyses: a Varian Model 90-P gas chromatograph for glc analyses, a Varian Model M-66 mass spectrometer for mass spectra, a Varian Model A-60 or T60-A nuclear magnetic resonance spectrometer for nmr spectra, and a Perkin-Elmer Model 237-B spectrophotometer for ir spectra.

The organic reagents and solvents (Aldrich Chemical Co., K & K Laboratories, Fisher Scientific, J. T. Baker Chemical Co., and Eastman Chemical Co.) were commercial compounds used without further purification. The KCN was ground and then dried under vacuum at 100° for 24 hr.

General Procedure. The starting solutions were prepared by weighing the reactive substrate directly into a 25-ml volumetric flask and diluting to the mark with a stock solution (known concentration)[15] of 1 in CH_3CN or C_6H_6. The prepared solutions were placed directly over solid, dry KCN (twofold excess of salt per functional group being displaced) and the reaction mixture was stirred vigorously at ambient or reflux temperature. Small aliquots of solution were removed at intervals and the extent of reaction was followed by glc and/or nmr analysis. Work-up involved separating the solid–liquid phases, removing the bulk of the solvent, diluting the remains with distilled water, extracting the product, and distilling the product after drying and removal of the extraction solvent.

1,4,7,10,13,16-Hexaoxacyclooctadecane (18-Crown-6,[3a] 1) The crown was synthesized and purified by a previously described procedure.[16]

Preparation of Nitrile Compounds. Preparation of 1,3-Dicyanopropane (Glutaronitrile, 2). A. Into a 50-ml round bottom flask equipped with a magnetic stirring bar and a condenser–drying tube system were placed 11.7 g (0.18 mol) of dry KCN (Fisher Scientific) and 25 ml of an acetonitrile solution containing 5.08 g (0.045 mol) of 1,3-dichloropropane (Aldrich Chemical Co.) and 1.01 g (0.0038 mol) of **1**. The two-phase system was heated to reflux with vigorous stirring and the extent of reaction was followed by glc techniques. After 1.5 hr, the reaction mixture was cooled, filtered, and evaporated to *ca.* one-third volume. Distilled water was then added, and the mixture was extracted with CH_2Cl_2.[17] The CH_2Cl_2 solution was dried over $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure. The residue was distilled under vacuum to give 4.10 g (96.8%) of **2**: bp 78–82° (0.15 mm); ir (neat, NaCl plates) 2950, 2875, 2240, 1450, 1420 cm^{-1}; ^1H nmr (neat, external TMS, $CHCl_3$) 2.65 (t, 4 H), 2.15 ppm ("spiked" q, 2 H); mass spectrum *m/e* 94, 93, 54, 41, 28; these spectra and glc analysis of the synthesized product corresponded to those of commercial **2** (K & K Laboratories).

Preparation of 1,2-Dicyanopropane (3). B. Into a 50-ml round-bottom flask equipped as in A were placed 0.32 g (0.005 mol) of dry KCN, 25 ml of an acetonitrile solution containing 3.03 g (0.045 mol) of methacrylonitrile (Eastman Chemical Co.) and 1.04 g (0.0039 mol) of **1**, and 4.42 g (0.052 mol) of acetone cyanohydrin (J. T. Baker Chemical Co.). The system was brought rapidly to reflux with vigorous stirring and the extent of reaction was monitored by glc and nmr techniques. After 0.6 hr, the system was cooled and the solution was worked up as in A.[17] Distillation of the isolated crude product[18] gave 3.89 g (91.9%) of the colorless, transparent liquid **3**: bp 68–71° (0.15 mm); ir (neat, NaCl plates) 2975, 2940, 2250, 1520, 1425, 1380 cm^{-1}; ^1H nmr (neat, external TMS, $CHCl_3$) 3.05 (m, 1 H), 2.65 (d, with spikes, 2 H), 1.35 ppm (d, 3 H); mass spectrum *m/e* 94, 93, 54, 41, 28.

Registry No.—Cyanide, 57-12-5; 18-crown-6, 17455-13-9; 1-octene, 111-66-0; *cis*-2-octene, 7642-04-8; *trans*-2-octene, 13389-42-9.

References and Notes

(1) Part I: C. L. Liotta and H. P. Harris, *J. Amer. Chem. Soc.*, **95**, 2250 (1974).
(2) Part II: C. L. Liotta, *et al.*, *Tetrahedron Lett.*, in press.
(3) (a) C. J. Pedersen, *J. Amer. Chem. Soc.*, **89**, 2495, 7017 (1967); **92**, 386, 391 (1970); *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **27**, 1305 (1968); (b) C. J. Pedersen and H. K. Frensdorff, *Angew. Chem., Int. Ed. Engl.*, **11**, 16 (1972); (c) for other excellent reviews on crown ether chemistry, see T. J. Christensen, J. O. Hill and R. M. Izatt, *Science*, **174**, 459 (1971); D. J. Cram and J. M. Cram, *ibid.*, **183**, 803 (1974).
(4) (a) D. J. Cram and H. E. Simmons, *J. Amer. Chem. Soc.*, **94**, 4024 (1972); **96**, 2252 (1974); (b) M. J. Maskornick, *Tetrahedron Lett.* 1797 (1972); (c) F. Naso and L. Ronzini, *J. Chem. Soc., Perkin Trans. 1*, 540 (1974); (d) V. Fiandanese, G. Marchese, F. Naso, and O. Sciacovelli *ibid.*, 1336 (1973); (e) L. M. Thomassen, T. Ellingsen, and J. Ugelstead, *Acta Chem. Scand.*, **25**, 3024 (1971); (f) T. Matsuda and K. Koida, *Bull. Chem. Soc. Jap.*, **46**, 2259 (1973); (g) J. N. Roitman and D. J. Cram, *J. Amer. Chem. Soc.*, **93**, 2231 (1971); (h) G. Fraenkel and E. Pechhold, *Tetrahedron Lett.*, 153 (1970).
(5) J. Dockx, *Synthesis*, **8**, 441 (1973).
(6) Monocyanated products could be isolated in the runs involving difunctional halides when the reactions were not allowed to proceed to completion.
(7) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 29–31.
(8) The octenes produced in runs 16 and 17, Table I, were not isolated from the reaction mixtures. Low-temperature glc analysis revealed three alkenes to be present in both runs, assigned as 1-octene and *cis*- and *trans*-2-octene. The glc graphs were identical with that given by a known mixture of the three alkenes. Also, nmr splitting and position of the vinyl proton absorptions were overlapping with those of the known mixture.[9]
(9) The known mixture of octenes was supplied by Mr. H. P. Harris, and was isolated from the reaction of 2-bromooctane with "naked" fluoride.[1]
(10) (a) D. J. Mowry, *Chem. Rev.*, **42**, 189 (1948); (b), C. S. Marvel and E. M. McColm, "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1941, p 536; (c) F. H. Allen, *ibid.*, p 156; (d) R. Adams and A. F. Thal, *ibid.*, p 107.
(11) (a) R. A. Smiley and C. Arnold, *J. Org. Chem.*, **25**, 257 (1960); (b) L. Freidman and H. Schechter, *ibid.*, **25**, 877 (1960).
(12) (a) C. M. Starks, *J. Amer. Chem. Soc.*, **93**, 195 (1971); (b) C. M. Starks and R. W. Owens, *ibid.*, **95**, 3613 (1973); (c) N. Sugimoto, *et al.*, *Chem. Pharm. Bull.*, **20**, 427 (1962).
(13) More recent advances than those listed[10] have shown that addition of catalytic amounts of iodide to the ethanol–water system has a beneficial effect on nucleophilic displacements of alkyl halides: H. O. House, *Org. React.*, **9**, 139 (1957), and references cited therein.
(14) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, Chapter 9, pp 623–628, and references cited therein.
(15) It has been found that the upper limit of concentration of **1** in CH_3CN is approximately 0.2 *M* at room temperature, while concentrations as high as 1.5 *M* have easily been achieved in C_6H_6.[1]
(16) C. L. Liotta, H. P. Harris, F. L. Cook, G. W. Gokel, and D. J. Cram, *J. Org. Chem.*, **39**, 2445 (1974).
(17) Extraction of the nitrile compounds can be accomplished by hand (three to five extractions) or by a CH_2Cl_2 continuous extractor (20–24 hr). As nitriles are soluble in H_2O (especially dinitriles) to various extents, the continuous-extraction method is recommended in cases where small quantities are involved and complete extraction from the water layer is desired. For larger runs, the hand-extraction technique is preferred. Both methods were used with comparable results in preparing this report.
(18) On evaporation of the extraction solvent, the crystalline adduct (complex) of **7** and **1** precipitates spontaneously. However, on heating the distillation flask the complex readily melts, and the liquid **7** is then easily distilled. The characteristics of this and a number of other crystalline complexes of nitrile compounds and **1** have been reported: F. L. Cook, H. P. Harris, and C. L. Liotta, *J. Org. Chem.*, submitted for publication.

Carbanion Mechanism in the Alkylation of Certain Tosylhydrazones. 9,9-Disubstituted Fluorenes from Fluorenone Tosylhydrazone

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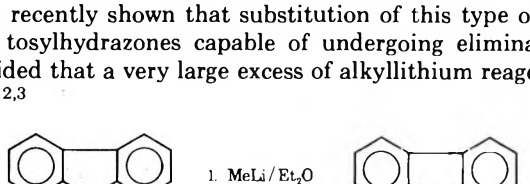
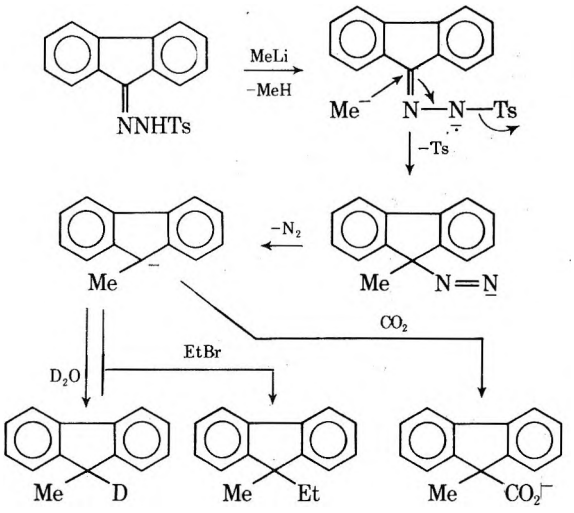
In the first publication of the reaction of tosylhydrazones with alkyllithium reagents it was reported that fluorenone tosylhydrazone (I) undergoes substitution, since elimination is precluded.[1] Herz and his coworkers have more recently shown that substitution of this type occurs with tosylhydrazones capable of undergoing elimination, provided that a very large excess of alkyllithium reagent is used.[2,3]



I

It was suggested that the reaction proceeds by way of an S_N2' mechanism with the key intermediate being a carbanion.[2,4]

We have now trapped the carbanion generated from I with D_2O, CH_3CH_2Br, and CO_2 demonstrating its existence as well as providing a new route to 9,9-disubstituted fluorenes. The probable reaction route is illustrated in the following sequence.



Experimental Section

Fluorenone Tosylhydrazone (I). Fluorenone tosylhydrazone was prepared from fluorenone by the method of Bamford and Stevens.[5] The tosylhydrazone was recrystallized from methanol to give yellow needles, mp 185–186° dec, reported[5] mp 180–182° dec.

9-Methylfluorene. To a solution of fluorenone tosylhydrazone (3.48 g, 0.01 mol) in 50 ml of anhydrous tetrahydrofuran under an atmosphere of nitrogen was added 1.65 *M* methyllithium in ether (Ventron, 18 ml, 0.03 mol) during 5 min. Gas evolved and the solution turned from yellow to deep magenta during the addition. The mixture was stirred at room temperature for 3 hr (gas evolution ceased after ~2 hr) and water was added carefully. The organic phase was washed with saturated sodium chloride solution and dried over calcium chloride. Evaporation of the solvent gave a brown oil which was crystallized from 2-propanol–water as yellow needles, mp 45–46° (reported[6] 45–46°), yield 73%. The mass spectrum showed important peaks at *m/e* 180 ($M^{\cdot+}$) and 165 ($M - CH_3$).

9-Methylfluorene-9-d_1. Following the procedure for 9-methylfluorene with the exception of decomposing the reaction mixture with D_2O instead of H_2O, we obtained 9-methylfluorene-9-d_1. The pmr spectrum of unlabeled 9-methylfluorene contained a three-proton triplet at 1.5 and a one-proton quartet at 3.9 ppm, whereas that of the labeled compound showed a three-proton singlet at 1.5 and no signal at 3.9 ppm. The mass spectrum showed that this compound contained 94% d_1 (reaction yield 71%).

9-Methyl-9-ethylfluorene. Following the same procedure as above but decomposing the reaction mixture with ethyl bromide (2.18 g, 0.02 mol), we obtained an oil which was crystallized from 2-propanol–water as yellow plates, mp 60–61° (reported[7] 61–62°). The yield was 77%. The pmr spectrum showed a three-proton singlet (9-methyl) at 1.4, a two-proton quartet at 2.0, and a three-proton triplet at 0.4 ppm. The mass spectrum showed important peaks at *m/e* 208 ($M^{\cdot+}$), 193 ($M - CH_3$), and 179 ($M - C_2H_5$).

9-Methyl-9-fluorenecarboxylic Acid. Decomposition of the reaction mixture with dry finely divided solid CO_2 gave 9-methyl-9-fluorenecarboxylate, which was dissolved in aqueous sodium hydroxide. After acidification of the aqueous phase with hydrocholoric acid, the free acid separated as an oil. The oil was dissolved in acetic acid and crystallized by the dropwise addition of H_2O to the boiling solution, followed by cooling. The acid separated as pale yellow needles, mp 163–165° (reported[8] 166–167°) in 79% yield. The mass spectrum showed characteristic peaks at *m/e* 224 ($M^{\cdot+}$) and 179 ($M - CO_2H$). The 9-methyl group appeared as a singlet in the pmr at 1.8 ppm.

Registry No.—I, 52341-51-2; 9-methylfluorene, 2523-37-7; methyllithium, 917-54-4; 9-methylfluorene-9-d_1, 15480-50-9; 9-methyl-9-ethylfluorene, 42348-903; ethyl bromide, 74-96-4; 9-methyl-9-fluorenecarboxylic acid, 1989-33-9.

References and Notes

(1) R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967).
(2) J. E. Herz and C. V. Ortiz, *J. Chem. Soc. C*, 2294 (1971); J. E. Herz and E. Gonzalez, *Chem. Commun.*, 1395 (1969).
(3) J. Meinwald and F. Uno, *J. Amer. Chem. Soc.*, **90**, 800 (1968), suggested that a biproduct from a similar reaction results from substitution.
(4) R. H. Shapiro, M. J. Heath, and E. C. Hornaman, Abstracts of the 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept. 1967.
(5) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952).
(6) G. W. H. Scherf and R. K. Brown, *Can. J. Chem.*, **38**, 697 (1960).
(7) E. J. Greenhow and D. McNeil, *J. Chem. Soc.*, 3204 (1956).
(8) R. Kuhn, Herbert Fischer, F. A. Neugegauer, and Hans Fischer, *Justus Liebigs Ann. Chem.*, **654**, 64 (1962).

Oxidation of Phenylhydrazine with Nitrosobenzene

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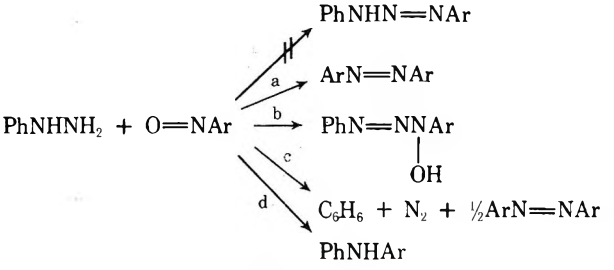
It has been well established that primary aromatic amines condense with aromatic nitroso compounds to form azo compounds. However, the literature about the reaction of phenylhydrazine with nitrosobenzene is conflicting. 1,3-Diphenyltriazene should be the product expected if the reaction is simple condensation between the two with elimination of water. In no case, the formation of 1,3-diphenyltriazene expected was reported. Azobenzene has been reported as the only product when phenylhydrazine is added slowly to a large excess of nitrosobenzene in unheated acetic acid.[2] In another case, *N*-hydroxydiaryltriazenes have been reported to be the major products.[3] In another case, a quantitative gasometric analytical method for *C*-nitroso compounds has been developed according to path c by warming a nitroso compound with an excess of phenylhydrazine in acetic acid.[4] In another case, diarylamine has been reported to be a significant product.[5]



An investigation on this reaction was carried out in our laboratories, and we found that the reaction between nitrosobenzene and phenylhydrazine does not yield 1,3-diphenyltriazene, but the products are azoxybenzene, diphenylamine, benzene, and nitrogen.[6] The mechanism for formation of diphenylamine appeared to be puzzling. A tentative mechanism presented was of ionic nature. Work has been continued, and in this paper we wish to describe the results and propose a modified mechanism involving the phenyl radical.

The products of the reaction between phenylhydrazine and nitrosobenzenes were studied. The samples giving relatively greater yields of diphenylamines are shown in Table I. When a phenylhydrazine solution was added to a nitrosobenzene solution, the yield of diphenylamine was greater; when the order of addition was reversed, the yield was smaller. From the results of the reactions with *p*-nitrosotoluene and *p*-dimethylaminonitrosobenzene, it is clear that one of the two phenyl groups in diphenylamine comes from phenylhydrazine and the other phenyl group comes from nitrosobenzene.

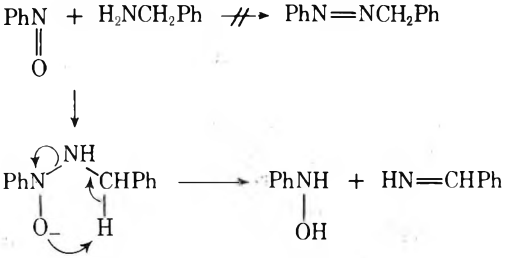
The mechanism of the formation of diphenylamine from the reaction between nitrosobenzene and phenylhydrazine is of interest. Recently Lamson, *et al.*, reported that the reaction of nitrosobenzene with benzylamine did not yield

Table I
Products of the Reactions between Phenylhydrazine and Nitrosoarenes

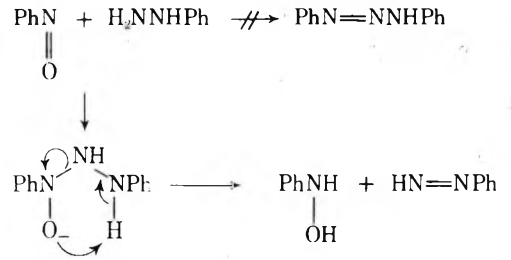
Run	Reactants, mmol	Solvent	Temp, °C	Products (mol/100 mol ArNO) PhNHAr	ArN=NAr	ArN(→O)=NAr	PhH
1	$PhNO(9.22) + PhN_2H_3(9.06)$	MeOH	−8	13.6	7.6	11.2	*a*
2	$PhNO(7.86) + PhN_2H_3(4.41)^b$	MeOH	35	8.4	12.0	22.2	17.0
3	$p\text{-}MeC_6H_4NO(4.77) + PhN_2H_3(4.77)$	MeOH	−8	11.6	0	12.8	15.0
4	$p\text{-}Me_2NC_6H_4NO(7.46) + PhN_2H_3(7.46)$	CH_2Cl_2	−8	10.4	*c*	*c*	*c*

[a] Not determined. [b] At 35°, nitrogen evolved upon addition of each drop of PhN_2H_3 solution, and addition was stopped when no more N_2 evolution was observed. [c] The reaction mixture was tarry, and the identification of other products was not possible.

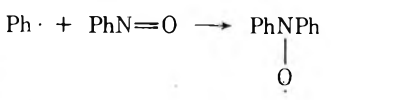
the expected benzylazobenzene, but yielded phenylhydroxylamine and benzaldimine, which further reacted to form azoxybenzene and *N*-benzylbenzaldimine.[7]



If nitrosobenzene and phenylhydrazine react in a similar manner, phenyldiazene must be produced.



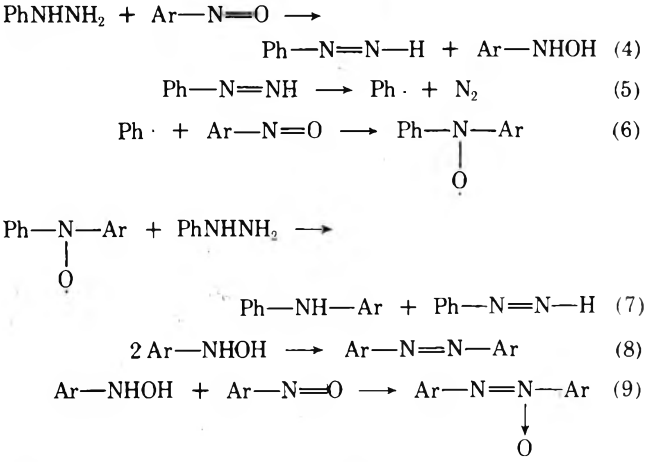
Huang and Kosower prepared phenyldiazene and showed that it yields phenyl radical by bimolecular reaction with itself.[8] It is also known that phenyl radical adds to nitrosobenzene, forming diphenylnitroxide radical.[9]



Therefore, if phenyl radical is formed in the reaction between phenylhydrazine and nitrosobenzene, formation of diphenylnitroxide radical is expected, and it is an attractive precursor for diphenylamine.

To check this possibility, benzene solutions of phenylhydrazine and nitrosobenzene were mixed in an esr tube near 0°; the esr spectrum was identical with that of diphenylnitroxide radical reported in the literature.[10] The esr signal remained unchanged as long as the mixture was kept frozen, but quickly disappeared when the mixture was warmed up, probably owing to further reaction with phenylhydrazine and other reactants. Neither a benzene solution of phenylhydrazine nor that of nitrosobenzene showed any esr signals. Only when a benzene solution of phenylhydrazine and that of nitrosobenzene are mixed, strong signals of diphenylnitroxide are observed.

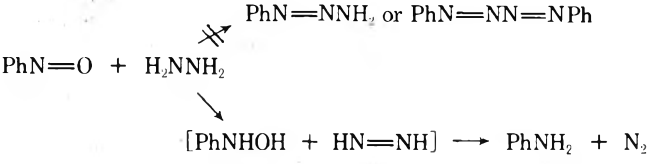
The esr spectrum together with other data obtained suggest that the reactions between phenylhydrazine and nitrosobenzenes are represented by the eq 4–9, involving phenyldiazene and phenyl radical as the intermediates.



The eq 8 and 9 are well known, but step 7 must be checked. By use of an authentic diphenylnitroxide sample, the formation of diphenylamine from its reaction with phenylhydrazine was ascertained.

Direct proof of the intermediacy of phenyldiazene is, of course, desirable. The evidence for phenyldiazene presented by Huang and Kosower is ultraviolet-visible spectra, reduction to phenylhydrazine, and volatility. The reaction mixture of our system was strongly colored, and it was not possible to establish the presence of phenyldiazene. Reduction of phenyldiazene to phenylhydrazine is not applicable in our system, since phenylhydrazine is one of the reactants. Isolation of phenyldiazene by distillation was attempted repeatedly, but was unsuccessful.

In a previous paper,[6] we described that the reaction between hydrazine and nitrosobenzene does not yield phenyltriazene, but aniline and nitrogen with some azobenzene. The present results suggest that the reaction between hydrazine and nitrosobenzene proceeds *via* diimide as an intermediate.



Experimental Section

Materials. Nitrosobenzene,[11] *p*-nitrosotoluene,[11] and *p*-dimethylaminonitrosobenzene[12] were prepared according to the methods described in the literature.

Reaction between a Nitrosoarene and Phenylhydrazine. Run 1. When phenylhydrazine (9.22 mmol) in methanol (80 ml) was added to a green solution of nitrosobenzene (9.06 mmol) in methanol (10 ml) at −8°, the solution turned yellowish green, but no evolution of nitrogen was observed. When the solution was slowly warmed up, evolution of nitrogen started at −2°. After the reaction was completed at room temperature, the solvent was distilled off, and the dark reddish oil obtained was subjected to elu-

tion chromatography. The first fraction (orange needles) was azobenzene, the second (yellow crystals) was azoxybenzene, and the third (white crystals) was diphenylamine. Identification of the products was made on the basis of their mp and comparison of their ir and nmr spectra with those of the authentic samples.

The procedures for other runs were essentially similar to that described above. When the two reactants were mixed at 35°, nitrogen evolved instantaneouly. Benzene was always one of the products formed, but its amount was not always determined.

Esr Measurement of Diphenylnitroxide Radical. A benzene solution (1.1 g) of nitrosobenzene (0.02 g) was cooled to 0° in an esr tube, and before it solidified a benzene solution (0.45 g) of phenylhydrazine (0.03 g) was added. Its esr spectrum was determined at 0° with a JES-PE esr spectrometer. The signals of diphenylnitroxide radical were observed,[10] and did not change as long as the mixture was kept as solid at 0°. When it was warmed up and melted, the signals of the radical disappeared (g = 2.0057, a^N = 10.0 G). When a benzene solution of nitrosobenzene or that of phenylhydrazine was subjected to esr measurements, no esr signals were observed. Only when the two solutions were mixed, were esr signals of diphenylnitroxide radicals observed.

Reaction between Diphenylnitroxide and Phenylhydrazine. A methanol solution (25 ml) of diphenylnitroxide (0.4 g, 2.3 mmol) was cooled to −5°, and then a methanol solution (3 ml) of phenylhydrazine (0.1 g, 0.92 mmol) was added to the cooled solution. The dark red solution became yellow with evolution of some nitrogen. After the mixture was warmed to and allowed to stand at room temperature for 1 hr, the solvent was evaporated under reduced pressure, and the residue was subjected to column chromatography (alumina). The first fraction eluted with hexane–benzene (3:2) was rechromatographed with hexane, and the first fraction eluted was identified as diphenylamine by comparison of its ir spectrum with that of an authentic sample; yield, 0.046 g (0.12 mol/mol of Ph_2NO used).

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No.—Phenylhydrazine, 100-63-0; nitrosobenzene, 586-96-9; *p*-nitrosotoluene, 623-11-0; *p*-dimethylaminonitrosobenzene, 138-89-6; diphenylnitroxide, 712-51-6.

References and Notes

(1) Address all correspondence to this author at Department of Chemistry, Tokyo Metropolitan University, Fukazawa, Setagaya, Tokyo 158, Japan.
(2) C. Mills, *J. Chem. Soc.*, **67**, 925 (1895).
(3) E. Bamberger and E. Stiegelmann, *Ber.*, **32**, 3554 (1899).
(4) R. Clauser and G. Schweitzer, *Ber.*, **35**, 4280 (1902); R. Clauser, *ibid.*, **34**, 889 (1901).
(5) B. A. Geller and L. S. Samosvat, *Zh. Obshch. Khim.*, **31**, 1681 (1961).
(6) H. Minato and T. Fujisawa, *Bull. Chem. Soc. Jap.*, **39**, 1054 (1966).
(7) D. W. Lamson, R. Sciarro, D. Hryb, and R. O. Hutchins, *J. Org. Chem.*, **38**, 1952 (1973).
(8) P. C. Huang and E. M. Kosower, *J. Amer. Chem. Soc.*, **90**, 2367 (1968).
(9) R. Tanikaga, *Bull. Chem. Soc. Jap.*, **42**, 210 (1969).
(10) B. H. J. Bielski and J. M. Gebicki, "Atlas of Electron Spin Resonance Spectra," Academic Press, New York, N.Y., 1967, pp 392–4.
(11) E. C. Horning, Ed., "Organic Syntheses," Collect. Vol. III, Wiley, New York, N.Y., 1955, p 668.
(12) A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. II, Wiley, New York, N.Y., 1943, p 223.

Intramolecular Migration of the Pentafluorophenyl Group under Acidic Conditions

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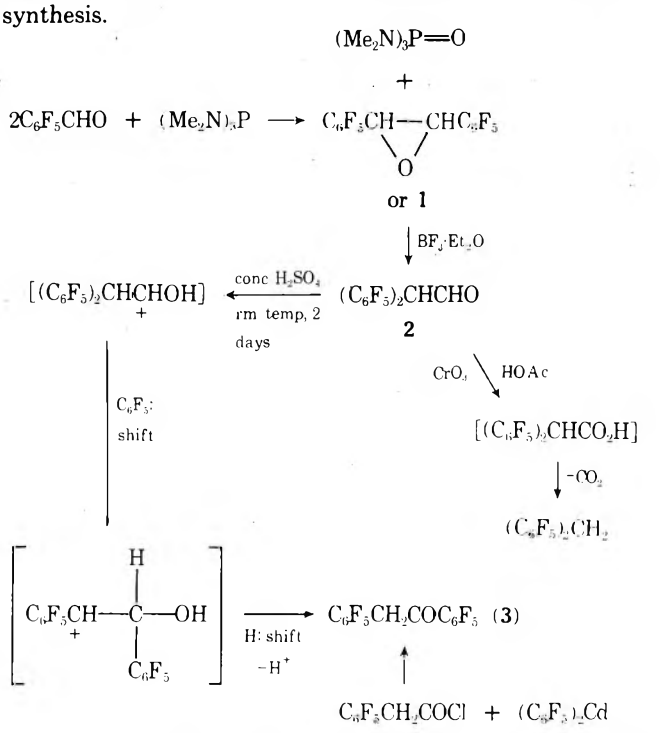
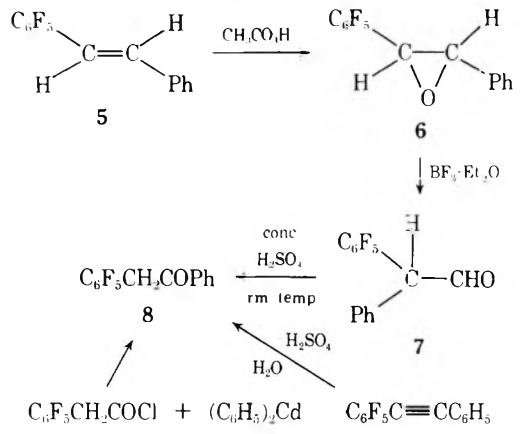
Acid-catalyzed skeletal rearrangements involving the 1,2 shift of aryl groups are well known. Phenyl groups containing electron-attracting substituents generally migrate much more slowly than phenyl, if at all. One might anticipate that the moderately electron-withdrawing pentafluorophenyl group[2a] would cause considerable deactivation in such reactions. To our knowledge, acid-catalyzed rearrangements involving intramolecular 1,2 migration of the C_6F_5 group have not been reported. We describe here a series of interrelated reactions in which we observed such aryl participation.

Pentafluorobenzaldehyde reacted rapidly with tris(dimethylamino)phosphine (hexamethylphosphorus triamide) to give a mixture of diastereomeric stilbene oxides.[2b] This mixture or the pure *trans*-stilbene oxide (**1**), obtained by peroxidation of the olefin,[3] reacted with boron trifluoride etherate to form the isomeric decafluorodiphenylacetaldehyde (**2**) by migration of the C_6F_5 moiety. Compound **2** was oxidized by Jones reagent to the diphenylacetic acid which rapidly lost CO_2 to form decafluorodiphenylmethane. When treated with concentrated H_2SO_4, **2** slowly underwent a reverse, 1,2-pentafluorophenyl shift *via* the unstable cation **4**,[4] to give the isomeric ketone (**3**), whose structure was confirmed by independent synthesis.



In order to compare the relative migratory aptitudes of the phenyl and pentafluorophenyl groups, the unsymmetrical stilbene **5**, prepared by Wittig syntheses ($C_6F_5CH_2Br$ and PhCHO or $PhCH_2Br$ and C_6F_5CHO), was converted to the epoxide **6**, which was isomerized to the diphenylacetaldehyde **7**. Compound **7** was characterized by its infrared spectrum and 2,4-dinitrophenylhydrazone. The latter reaction provides no information on which aryl group migrated. However, on standing with concentrated H_2SO_4 at room temperature, **7** was readily transformed into the ketone **8** in a 95% conversion with no evidence of the presence of its isomer, $PhCH_2COC_6F_5$. Also, compound **8** readily formed a 2,4-dinitrophenylhydrazone, showed carbonyl absorption around 1700 cm^{-1}, and was in all respects identical with an authentic sample (*cf.* isomer, Experimental Section). This observation demonstrated the strong preference of C_6H_5 over C_6F_5 migration in such 1,2 shifts. Ketone **8** was also prepared by two alternate routes, one of which has been reported previously.[5] These results are in marked contrast to the overwhelming migratory preference of C_6F_5 over C_6H_5 in 1,2 shifts in alkaline medium.[6] In the latter case, the

pentafluorophenyl ring stabilizes the developing negative charge in the transition state.



Experimental Section

Decafluorostilbene Oxides.[7] To a stirred solution of pentafluorobenzaldehyde (19.6 g, 0.1 mol) in 20 ml of dry benzene was added dropwise 9.5 g (0.0583 mol) of hexamethylphosphorus triamide[8] dissolved in 5 ml of anhydrous ether. The temperature was regulated below 36° during addition. After 45 min, addition was complete and the reaction mixture was heated at 50° for 1 hr and cooled. The solvents were removed by flash evaporation, water and ether were added to the residue, and the ether layer was separated, washed with water, and dried over anhydrous magnesium sulfate. Ether was removed by flash evaporation and the residual oil was triturated with ethanol. Thin layer chromatography showed the presence of two components. The mixture of oxides was crystallized from ethanol: mp 164–176°; calcd mass spectrum 376, found 376.

Decafluorodiphenylacetaldehyde[9] **(2).** To a solution of 8.5 g of decafluorostilbene oxides in 60 ml of benzene and 20 ml of anhydrous ether was added 2 ml of freshly distilled boron trifluoride etherate. The mixture was shaken and left at room temperature for 1 min. Water (100 ml) was added and the mixture shaken. The two layers were separated and the aqueous layer was extracted with benzene. The combined organic layers were dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated and triturated with ethanol to remove any unreacted epoxide. The alcoholic solution was evaporated to give a semisolid material, which could not be distilled or crystallized: ir (CCl_4) 1710 cm^{-1} (s). Further purification was effected by adsorption over neutral alumina and elution with anhydrous ether. A mass spectrum of this sample revealed a peak at 376; 2,4-dinitrophenylhydrazone melted at 227°.

Attempted Oxidation of 2. To 5 g of impure aldehyde **2**, dissolved in acetone, was added slowly a solution of Jones reagent (13.4 g of CrO_3, 11.5 ml of concentrated H_2SO_4, and 33.5 ml of water). After addition was complete, excess reagent was destroyed by adding isopropyl alcohol. The reaction mixture was poured into water and the aqueous solution extracted with three 100-ml portions of ether. The combined ether layers were washed with water and then with a 10% solution of potassium carbonate. Acidification of the aqueous layer failed to give a solid. The ether layer, after drying over $MgSO_4$, gave, on concentration, a solid which melted at 61°, identical with an authentic sample of decafluorodiphenylmethane: mp[10] 62°.

Reaction of 2 with Concentrated H_2SO_4. A sample of **2** (7.52 g, 0.02 mol) was mixed with 10 ml of concentrated H_2SO_4 and the mixture set aside for 2 days at room temperature. The mixture was then poured into water and extracted with ether, and the ether layer was washed with a dilute solution of sodium bicarbonate and dried over anhydrous $MgSO_4$. Ether was removed by flash evaporation and the residual oil distilled (72°, 2 Torr; 7.2 g, 96% yield). The ir spectrum was identical with that of an authentic sample of decafluorodesoxybenzoin (**3**).[11]

Decafluoro-*trans*-stilbene.[12] In a 100-ml round-bottomed flask were placed triethyl phosphite (8.3 g, 0.05 mol) and pentafluorobenzyl bromide (13 g, 0.05 mol). A condenser was attached and the mixture was heated gently for 1 hr. At 130–140°, ethyl bromide was evolved. The internal temperature reached 210° at the end of 1 hr. The product was cooled and dissolved in 100 ml of dry 1,2-dimethoxyethane. Pentafluorobenzaldehyde (9.8 g, 0.05 mol) and 50% sodium hydride (2.4 g, 0.05 mol) were added to the phosphonate solution and the mixture was heated slowly to 85°. After heating for 0.5 hr, the mixture was cooled and dissolved in a large excess of water. The precipitated stilbene was filtered, dried, and purified by sublimation: mp 101° (lit.[3,13,14] mp 96.5–97.5°, 101.5–103.5°, 101°); yield 11.3 g (63%).

Pentafluoro-*trans*-stilbene (5). (a) From Pentafluorobenzyl Bromide and Benzaldehyde. The procedure was the same as that described for decafluoro-*trans*-stilbene: mp 137° (lit.[15] 139–140°); yield 60%.

b. From Benzyl Chloride and Pentafluorobenzaldehyde. The procedure was the same as above: mp 139°, mixture melting point not depressed.

Epoxidation of Stilbenes. (a) Decafluoro-*trans*-stilbene Oxide (1). The procedure of House and Rief[9b] was employed. Decafluoro-*trans*-stilbene (10.8 g, 0.03 mol) in 45 ml of methylene chloride was epoxidized with 6.5 ml of 40% peracetic acid to give 11 g (96%) of **1**: mp 166°. *Anal.* Calcd for $C_{14}H_2OF_{10}$: C, 44.41; H, 0.53. Found: C, 44.5; H, 0.57.

(b) Pentafluoro-*trans*-stilbene Oxide (6). The procedure was the same as described above: mp 112°; yield 75%. *Anal.* Calcd for $C_{14}H_7OF_5$: C, 58.74; H, 2.44. Found: C, 58.69; H, 2.40.

Pentafluorodiphenylacetaldehyde (7). The same procedure as for the isomerization of decafluorostilbene oxide to compound **2** was used: bp 97° (2 Torr); calcd mass spectrum 286, found 286; ir $\nu_{C=O}$ 1715 cm^{-1}; 2,4-dinitrophenylhydrazone melted at 185°.

Reaction of 7 with Concentrated H_2SO_4. A sample of **7** (5.72 g, 0.02 mol) was mixed with 10 ml of concentrated H_2SO_4 and set aside at room temperature for 2 days. After work-up (as described earlier for **2**), a solid, mp 117°, was isolated (yield 5.4 g, 95%). The melting point was not depressed when mixed with compound **8**, but was depressed when mixed with benzyl pentafluorophenyl ketone. Compound **8** gave a 2,4-dinitrophenylhydrazone which melted at 174°.

Preparation of Desoxybenzoins. The procedure was the same as that used for pentafluoroacetophenone.[16]

(a) Decafluorodesoxybenzoin (3). Compound **3** was prepared from pentafluorophenylacetyl chloride and bis(pentafluorophenyl)cadmium: bp 71–74° (2–3 Torr), ir $\nu_{C=O}$ 1740 cm^{-1} (s). *Anal.* Calcd for $C_{14}H_2OF_{10}$: C, 44.41; H, 0.53. Found: C, 44.48; H, 0.52. This compound failed to form a 2,4-dinitrophenylhydrazone.

(b) Pentafluorobenzyl Phenyl Ketone (8). Compound **8** was prepared from pentafluorophenylacetyl chloride and diphenylcadmium: mp 118° (lit.[11] mp 118–120°); ir $\nu_{C=O}$ 1700 cm^{-1} (s); nmr 7.8 ppm (5 H), phenyl protons, and a triplet at 4.36 ppm (methylene protons split by ortho fluorines). *Anal.* Calcd for $C_{14}H_7OF_5$: C, 58.74; H, 2.44. Found: C, 58.6; H, 2.39. 2,4-Dinitrophenylhydrazone mp 174°.

(c) Benzyl Pentafluorophenyl Ketone. This compound was prepared from phenylacetyl chloride and bis(pentafluorophenyl)cadmium: mp 54° (lit.[17] mp 52–56°); ir $\nu_{C=O}$ 1713 cm^{-1}; nmr 7.16 ppm (5 H), phenyl protons, and a singlet at 4.05, methylene protons. This compound failed to form a 2,4-dinitrophenylhydrazone.

Registry No.—**1**, 52438-84-3; *cis*-**1**, 52393-42-7; **2**, 52438-80-9; **2** 2,4-DNPH, 52393-43-8; **3**, 24043-89-8; **5**, 19292-25-2; **6**, 52393-44-9; **7**, 52393-45-0; **7** 2,4-DNPH, 52393-46-1; **8**, 34073-32-0; **8** 2,4-DNPH, 52555-18-7; pentafluorobenzaldehyde, 653-37-2; decafluoro-*trans*-stilbene, 14992-40-6; pentafluorobenzyl bromide, 1765-40-8; benzaldehyde, 100-52-7; benzyl chloride, 100-44-7; pentafluorophenylacetyl chloride, 832-72-4; bis(pentafluorophenyl)cadmium, 15989-98-7; diphenylcadmium, 2674-04-6; benzyl pentafluorophenyl ketone, 52393-47-2; phenylacetyl chloride, 103-80-0.

References and Notes

(1) Address all correspondence to R. Filler at the Department of Chemistry, Illinois Institute of Technology, Chicago, Ill. 60616.
(2) (a) W. A. Sheppard, *J. Amer. Chem. Soc.*, **92**, 5419 (1970); (b) V. Mark, *ibid.*, **85**, 1884 (1963).
(3) N. N. Vorozhtsov, Jr., V. A. Barkhash, and S. A. Anichkina, *Dokl. Akad. Nauk SSSR*, **166**, 598 (1966); *Chem. Abstr.*, **64**, 12586*d* (1963).
(4) S. V. Kulkarni, R. Schure, and R. Filler, *J. Amer. Chem. Soc.*, **95**, 1859 (1973).
(5) R. Filler and E. W. Heffern, *J. Org. Chem.*, **32**, 3249 (1967).
(6) R. D. Chambers, M. Clark, and D. J. Spring, *J. Chem. Soc., Perkin Trans. 1*, 2464 (1972).
(7) V. Mark, *Org. Syn.*, **46**, 31 (1966).
(8) V. Mark, *Org. Syn.*, **46**, 42 (1966).
(9) (a) H. O. House, *J. Amer. Chem. Soc.*, **77**, 3070 (1955); (b) H. O. House and D. J. Rief, *Org. Syn.*, **38**, 83 (1958); (c) *ibid.*, **38**, 26 (1958)
(10) V. P. Molosnova, V. I. Vysochih, V. A. Barkhash, and N. N. Vorozhtsov,

Jr., *Izv. Akad. Nauk SSSR, Ser. Khim.*, (1), 146 (1969); *Chem. Abstr.*, **70**, 106077*r* (1969).
(11) E. W. Heffern, Ph.D. Thesis, Illinois Institute of Technology, Chicago, Ill., 1969.
(12) W. S. Wadsworth, Jr., and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1737 (1961).
(13) J. M. Birchall, F. L. Bowden, R. N. Haszeldine, and A. B. P. Lever, *J. Chem. Soc.*, 747 (1967).
(14) N. P. Buu-Hoi and G. Saint-Ruf, *Bull. Soc. Chim. Fr.*, 606 (1968).
(15) R. Filler and E. W. Choe, submitted for publication.
(16) R. Filler, Y. S. Rao, A. Biezais, F. N. Miller, and V. Beaucaire, *J. Org. Chem.*, **35**, 930 (1970).
(17) F. N. Miller, Ph.D. Thesis, Illinois Institute of Technology, Chicago, Ill., 1967.

Cleavage by Acid of the Phosphorus–Carbon Bond in Cyclic Phosphines Containing a β-Carbonyl Group[1]

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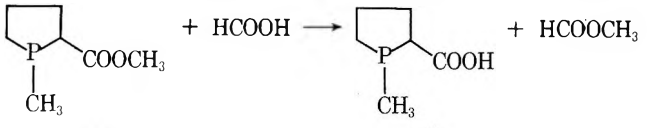
The C–P bond of simple phosphines is known to withstand the conditions of the common organic reactions. However, we have found that the bond is rendered sensitive to cleavage by an acidic medium when a β-carbonyl group is present. This reaction was encountered in an attempt to effect the conversion of methyl 1-methyl-2-phospholanecarboxylate[2] (1) to the acid (2) by HCl-catalyzed transesterification with formic acid[3] (91%). The crystalline



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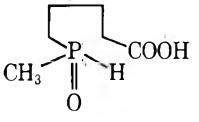
solid that was obtained in 71% yield had properties quite unlike those expected for 2. Through a combination of spectral techniques, it was established to have the ring-opened structure 3.



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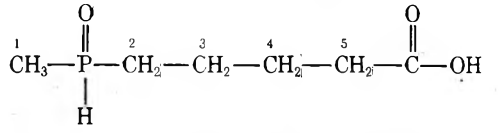
The product, which by analysis differed from the expected structure 2 by the elements of H_2O, had infrared spectral bands for a strongly hydrogen-bonded carboxylic acid group, showing that the expected transesterification had occurred. However, there were also P–H (2375 cm^{-1}) and P=O (1100 cm^{-1}) stretching bands, and this suggested the presence of phosphorus in the secondary phosphine oxide function. The P–H bond was also apparent in the ^1H nmr spectrum; a peak appeared at 9.98 ppm in H_2O that was removed on running the sample in D_2O. This proton had been coupled with the P–CH_3 group, for this latter signal, which in H_2O was a doublet of doublets (J_{PCH} = 14, J_{HPCH} = 2 Hz), lost the smaller coupling after D exchange. The peak at 9.98 ppm is half of the P–H signal; the other half is obscured by the H_2O signal. However, in $CDCl_3$ both halves were visible, with δ 7.62 and J_{PH} = 476 Hz. The shift and coupling constant are in line with those known for other secondary phosphine oxides (*e.g.*, for Me_2PHO,[4] δ 7.5, J_{PH} = 490; for Et_2PHO,[4] δ 7.2, J_{PH} = 468; for 3,4-dimethyl-3-phospholene oxide (4), which was available from previous work,[5] δ 7.97, J_{PH} = 490 Hz).

The proton-decoupled ^{31}P nmr signal (δ −31.8 in $CHCl_3$, −38.2 in H_2O) was also in the region expected for secondary phosphine oxides (*e.g.*, for Et_2PHO,[4] δ −41.0 and −47.7; for the phospholene oxide 4, δ −39.8 and −44.4). Replacement of the proton with deuterium introduces a valuable structure diagnostic effect; the phosphorus singlet is split to a 1:1:1 triplet with a characteristic coupling (for 3, J = 73 Hz; other secondary phosphine oxides gave similar values [4]).

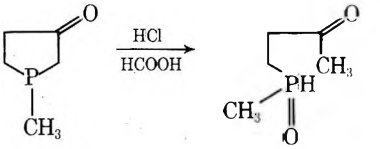
The ^{13}C nmr spectrum also proved the secondary phosphine oxide structure. Carbons attached to phosphoryl groups have large (60–100 Hz) coupling constants,[6] and are readily recognized. For 3, there would be two such signals of roughly equal intensity and these were observed at δ 13.0 with J_{PC} = 64 Hz (C-1) and δ 29.0 with J_{PC} = 65 Hz (C-2). The complete assignment is shown below.



δ:	13.0	29.0	21.2	26.1	34.3	179.0
J_{PC}:	64	65	<2	10	s	s

C-5 is easily recognized since it should be quite similar in position to the α-carbon of pentanoic acid (δ 34.5).[7] The assignment of C-3 and C-4 rests first on a coupling effect with ^{31}P; it is known that in aliphatic tertiary phosphine sulfides and oxides, $^3J_{PC}$ exceeds $^2J_{PC}$,[8] and since this should prevail also in secondary oxides, C-4 is the signal with J_{PC} = 10 Hz. Chemical shift relations support this assignment. Thus, C-4 should have a shift much like that of the β-carbon of pentanoic acid, since phosphorus groups are known to exert only a slight effect on a carbon in this position.[8] The C-4 shift of 26.1 ppm corresponds well to that of the β carbon of pentanoic acid (δ 25.2).[7] C-3 is upfield of C-4 because it undergoes γ-shielding effects[8] with both CH_3 and O on phosphorus.

The generality of the cleavage process was tested with another β-carbonyl phosphine, compound 5, which was available from previous work.[9] The HCl–formic acid treatment should produce structure 6, and the product obtained had spectral properties (see Experimental Section) that confirmed this expectation. The product was a noncrystal-



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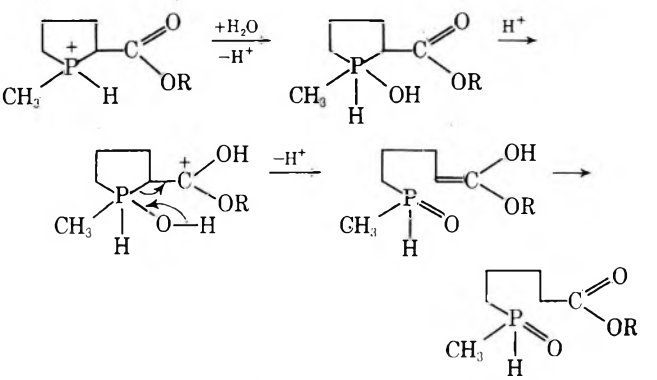
lizing oil, and complete characterization was not possible. There is no doubt, however, that the ring cleavage occurred, and that secondary phosphine oxide 6 was formed.

The mechanism of the cleavage of these β-carbonylphosphines presumably involves attack of water on the proton-



ated phosphine. A possible sequence of events to account for the product is shown above. The transesterification may occur before or after the ring cleavage.

Experimental Section

General. Reactions of phosphines were conducted under nitrogen. Mp values are corrected. Proton nmr spectra were taken with JEOL MH-100 or Varian T-60 spectrometers. Proton-decoupled ^{31}P nmr spectra were taken on a Bruker HFX-10 system at 36.43 MHz; shifts are relative to external 85% H_3PO_4. The proton-decoupled ^{13}C nmr spectrum was obtained by the Fourier transform technique on the Bruker spectrometer at 22.62 MHz utilizing C_6F_6 as external heteronuclear lock in a 3-mm coaxial capillary. Analyses were performed by MHW Laboratories, Garden City, Mich.

Synthesis of Methyl(4-carboxybutyl)phosphine Oxide (3) from Methyl 1-Methylphospholane-2-carboxylate (1). To 30 ml of deoxygenated 91% formic acid was added 0.40 g (0.0025 mol) of a 60:40 cis:trans mixture of **1**.[2] Dry hydrogen chloride generated from sodium chloride and concentrated sulfuric acid was bubbled for 10 min through the resulting solution, which was then refluxed for 24 hr under nitrogen. The reflux condenser was equipped with a take-off valve, and a total of 10 ml of distillate containing the methyl formate produced was drawn off during the reaction period. After the reflux period was complete, the formic acid was distilled off at water-aspirator pressure. Water was added and the distillation repeated to remove remaining traces of formic acid. A light brown oil remained which solidified upon drying overnight at high vacuum. This solid was recrystallized from chloroform–petroleum ether and yielded 0.29 g (71%) of white crystalline **3**, mp 87–88°.

The ^1H nmr spectrum (external TMS) gave the following signals: in H_2O, δ 2.15 (d of d, P-CH_3, $^2J_{PH}$ = 14 Hz, $^3J_{HH}$ = 2 Hz), 1.9–2.7 and 2.8–3.2 (multiplets, CH_2), δ 9.98 (half of doublet of sextets with other half under H_2O absorption, P-H, $^3J_{HH}$ = 2 Hz); in D_2O, δ 2.15 (d, P-CH_3, $^2J_{PH}$ = 14 Hz), 9.98 was absent, rest unchanged; in $CDCl_3$ δ 1.9–2.7 and 2.7–3.3 (two broad peaks, indistinct P-CH_3 and CH_2), δ 7.62 (d of broad peaks, P-H, $^1J_{PH}$ = 476 Hz), 10.31 (broad s, COOH). The ^{31}P nmr had signals at δ −38.2 in H_2O, −37.8 in D_2O (t, $^1J_{PD}$ = 73 Hz), and −31.8 in $CHCl_3$. The ^{13}C nmr (H_2O, p-dioxane as internal reference, δ^{TMS} = 67.8 ppm) is described in the discussion. The infrared spectrum (KBr disk) contained absorptions at 2550, 2900, and 1925 for hydrogen bonded OH stretch, ν_{PH} 2375, $\nu_{C=O}$ 1700, $\nu_{P=O}$ 1110 cm^{-1}.

Anal. Calcd for $C_6H_{13}O_3P$: C, 43.91; H, 7.99; P, 18.87. Found: C, 43.60; H, 7.93; P, 18.56.

Cleavage of 1-Methyl-3-phospholanone (5). By the same procedure as above, 0.9 g (0.0073 mol) of **5**[9] was treated with formic acid–HCl. A light green oil was obtained after removal of all the formic acid. Addition of chloroform dissolved most of the oil leaving a small amount of green residue. The chloroform was removed by rotary evaporation, which yielded 0.52 g (51%) of **6** as a thick, almost colorless oil. All attempts to crystallize the oil proved unsuccessful.

The ^1H nmr spectrum (H_2O, external TMS) gave the following signals: in H_2O, δ 2.03 (d of d, P-CH_3, $^2J_{PH}$ = 14 Hz, $^3J_{HH}$ = 4 Hz), 2.4–3.0 (m, CH_2), 2.61 (s, CH_3CO), 10.02 (broad signal with indistinct additional splitting, half of P-H doublet); in D_2O, δ 2.02 (d, P-CH_3, $^2J_{PH}$ = 14 Hz), 10.02 was absent, rest unchanged; in $CDCl_3$, δ 2.16 (broad d, P-CH_3, $^2J_{PH}$ = 13–14 Hz), 2.4–3.0 (m, CH_2), 2.75 (s, CH_3CO), 7.72 (broad d, P-H, $^1J_{PH}$ = 474 Hz). The ^{31}P nmr signal was at δ −38.2 in H_2O, −37.0 in D_2O (t, $^1J_{PD}$ = 76 Hz) and −27.5 in $CDCl_3$. The ir spectrum (neat) had $\nu_{C=O}$ 1720 and $\nu_{P=O}$ 1155 cm^{-1}.

Spectra of 3,4-Dimethyl-3-phospholene 1-Oxide (4). This compound was prepared as previously reported.[5] The ^1H nmr spectrum (external TMS) had the following signals: in H_2O, δ 2.22 (s, C-CH_3), 2.78–3.50 (m, CH_2), 10.35 (broad, half of P-H doublet, removed with D_2O); in $CDCl_3$ the PH signal occurred at δ 7.97 (J_{PH} = 490 Hz). The ^{31}P nmr signal was at δ −44.4 in H_2O, −44.1 in D_2O (t, $^1J_{PD}$ = 76 Hz), and −39.8 in $CDCl_3$.

Registry No.—*cis*-**1**, 52500-00-2; *trans*-**1**, 52500-01-3; **3**, 52571-12-7; **4**, 52500-02-4; **5**, 49849-35-6; **6**, 52571-13-8.

References and Notes

(1) Supported by Public Health Service Research Grant CA-05507 from the National Cancer Institute. The National Science Foundation provided funds toward the purchase of the Bruker spectrometer (Grant No. GP-10301).
(2) S. G. Borleske and L. D. Quin, *Phosphorus*, in press.
(3) C. E. Rehberg, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N.Y., 1955, p 33.
(4) L. A. Hamilton and P. S. Landis, in "Organic Phosphorus Compounds," Vol. 4, G. M. Kosolapoff and L. Maier, Ed., Wiley-Interscience, New York, N.Y., 1972, p 490.
(5) D. K. Myers and L. D. Quin, *J. Org. Chem.*, **36**, 1290 (1972).
(6) See, for example, G. A. Gray and S. E. Cremer, *J. Org. Chem.*, **37**, 3458, 3470 (1972); J. J. Breen, S. I. Featherman, L. D. Quin, and R. C. Stocks, *Chem. Commun.*, 657 (1972).
(7) R. Hagen and J. D. Roberts, *J. Amer. Chem. Soc.*, **91**, 4504 (1969).
(8) L. D. Quin, M. D. Gordon, and S. O. Lee, *Org. Magn. Resonance*, in press.
(9) L. D. Quin and R. C. Stocks, *J. Org. Chem.*, **39**, 686 (1974).

New Facile Method for Conversion of Oximes to Nitriles. Preparation and Acid-Catalyzed Transformation of Aldehyde Oxime Ortho Esters

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We wish to report a new and facile conversion of aldoximes to the corresponding nitriles by an acid-catalyzed reaction of aldoximes and ortho esters (eq 1).

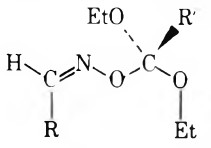
$$RCH{=}NOH + R'C(OEt)_3 \xrightarrow{H^+} RCN + R'COOEt + 2EtOH \quad (1)$$

Heating a mixture of equivalent amounts of an aldoxime and an ortho ester in the presence of a catalytic amount of an acid resulted in formation of the corresponding nitrile, ester, and alcohol. Simple distillation of the ester and the alcohol thus produced (eq 1), followed by vacuum distillation of the residue, afforded the nitrile usually in high yield. The general nature of the reaction is indicated by the results summarized in Table I. The primary product in this transformation is the oxime dialkyl ortho ester[1] which can be easily isolated in high yield by distilling off 1 equiv of the alcohol from an equimolar mixture of the oxime and the ortho ester *in the absence of acid catalysts* (eq 2).

$$RCH{=}NOH + R'C(OEt)_3 \rightleftharpoons RCH{=}NOCR'(OEt)_2 + EtOH \quad (2)$$

For example, distillation of 1 equiv of ethanol from a reaction mixture of equimolar amounts of *n*-butyraldehyde oxime (a mixture of *Z* and *E* isomers in the approximate ratio of 3:2) and triethyl orthoacetate, followed by vacuum distillation, gave a 95% yield of *n*-butyraldehyde oxime diethyl orthoacetate. Similarly, *Z*-benzaldehyde oxime and triethyl orthoformate gave an 86% yield of benzaldehyde oxime diethyl orthoformate. Analysis of these reactions *via* nmr spectroscopy indicated that no oxime isomerization had occurred under the reaction conditions.[3] The formation of oxime dialkyl ortho esters is evidently also a general reaction as indicated in Table II.

The oxime dialkyl ortho esters undergo an acid-catalyzed Beckmann fragmentation reaction providing the corresponding nitrile, ester, and alcohol[5] (eq 3). This reaction



$$\xrightarrow{H^+} RCN + R'COOEt + EtOH \quad (3)$$

Table I
Conversion of Aldehyde Oximes with Ortho Esters to Nitriles

Oxime	Registry no.	mmol	Reagent	mmol	Solvent	Nitrile	Registry no.	Yield,[a] %
$CH_3(CH_2)_2CH{=}NOH$	5780-44-6 (*Z*) 5775-75-7 (*E*)	100	$HC(OEt)_3$[b,f]	120		$CH_3(CH_2)_2CN$	109-74-0	93
$CH_3(CH_2)_2CH{=}NOH$		100	$CH_3C(OEt)_3$[b,g]	120		$CH_3(CH_2)_2CN$		94
$CH_3(CH_2)_2CH{=}NOH$		100	$CH_3C(OEt)_3$[c]	100	SO_2	$CH_3(CH_2)_2CN$		96
$CH_3(CH_2)_5CH{=}NOH$	629-31-2	100	$HC(OEt)_3$[b]	120		$CH_3(CH_2)_5CN$	629-08-3	95
$EtO_2C(CH_2)_3CH{=}NOH$	42586-31-2	50	$HC(OEt)_3$[d]	60	Et_2O	$EtO_2C(CH_2)_3CN$	10444-38-9	92
$EtO_2C(CH_2)_4CH{=}NOH$	42586-31-3	50	$HC(OEt)_3$[d]	60	$CHCl_3$	$EtO_2C(CH_2)_4CN$	4450-39-9	96
$C_6H_5CH{=}NOH$	932-90-1	100	$HC(OEt)_3$[c]	100	SO_2	C_6H_5CN	100-47-0	90
$C_6H_5CH{=}NOH$		100	$CH_3C(OEt)_3$[c]	100	SO_2	C_6H_5CN		60
p-$CH_3OC_6H_4CH{=}NOH$	3235-04-9	50	$HC(OEt)_3$[c,e]	50	SO_2	p-$CH_3OC_6H_4CN$	874-90-8	90
p-$CH_3OC_6H_4CH{=}NOH$		50	$CH_3C(OEt)_3$[c,e]	50	SO_2	p-$CH_3OC_6H_4CN$		90
$C_6H_5CH_2CH_2CH{=}NOH$	1197-50-8	50	$HC(OEt)_3$[b]	60		$C_6H_5CH_2CH_2CN$	645-59-0	93

[a] Yields are of the isolated products. [b] Reaction carried out in the presence of 2 mol % methanesulfonic acid by heating the reaction mixture in the absence of solvents. [c] Reaction carried out using the corresponding oxime diethyl ortho ester in the absence of added catalyst. [d] Reaction carried out in the presence of 2 mol % of hydrochloric acid under reflux in the indicated solvent. [e] After 78 hr at 70°. [f] Registry no. 122-51-0. [g] Registry no. 78-39-7.

Table II
Preparation of Oxime Diethyl Ortho Esters[a]

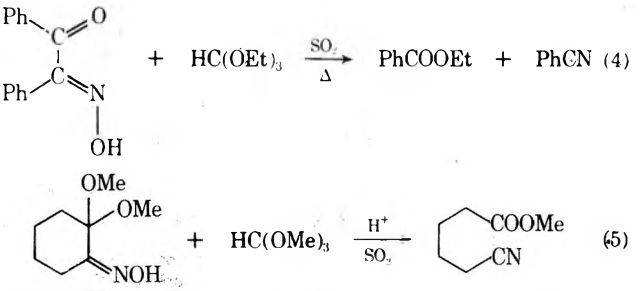
Oxime	Reagent	Product[b]	Registry no.	Bp, °C (mm)	Yield,[c] %
$CH_3(CH_2)_2CH{=}NOH$	$HC(OEt)_3$	$CH_3(CH_2)_2CH{=}NOCH(OEt)_2$	52540-27-9	67-69 (1-2)	95
$CH_3(CH_2)_2CH{=}NOH$	$CH_3C(OEt)_3$	$CH_3(CH_2)_2CH{=}NOCCH_3(OEt)_2$	52540-28-0	47-49 (0.6)	90
$CH_3(CH_2)_2CH{=}NOH$	$PhC(OEt)_3$[f]	$CH_3(CH_2)_2CH{=}NOCPh(OEt)_2$	52540-29-1	115-119 (1.1)	82
$C_6H_5CH{=}NOH$[d]	$HC(OEt)_3$	$C_6H_5CH{=}NOCH(OEt)_2$	52540-30-4	114-115 (0.8)	86
$C_6H_5CH{=}NOH$	$CH_3C(OEt)_3$	$C_6H_5CH{=}NOCCH_3(OEt)_2$	52540-31-5	100 (0.6)	88
p-$ClC_6H_4CH{=}NOH$[e]	$HC(OEt)_3$	p-$ClC_6H_4CH{=}NOCH(OEt)_2$	52540-32-6	135 (1.0)	89
p-$ClC_6H_4CH{=}NOH$	$CH_3C(OEt)_3$	p-$ClC_6H_4CH{=}NOCCH_3(OEt)_2$	52540-33-7	135 (0.8)	86
p-$CH_3OC_6H_4CH{=}NOH$	$HC(OEt)_3$	p-$CH_3OC_6H_4CH{=}NOCH(OEt)_2$	52540-34-8	144 (0.8)	84
p-$CH_3OC_6H_4CH{=}NOH$	$CH_3C(OEt)_3$	p-$CH_3OC_6H_4CH{=}NOCCH_3(OEt)_2$	52540-35-9	170 (0.8)	66

[a] The ratio oxime:ortho ester was in all examples 1:1 (usually a 100-mmol scale). [b] Analytical and all spectral data are in agreement with the structures. [c] Yields are of the isolated products. [d] Registry no. 622-32-2 (*Z*). [e] 3848-36-0. [f] 1663-61-2.

can be carried out neat by removing the alcohol and the ester from the reaction mixture as they are formed, or in solution. For example, the fragmentation of *n*-butyraldehyde oxime diethyl orthoacetate as a 1 *M* solution in toluene, ether, tetrahydrofuran, nitromethane, or dimethyl sulfoxide, in the presence of 2 mol % of methanesulfonic acid at room temperature was complete in less than 30 min.[6] The reaction in ethyl acetate or in acetone was much slower, requiring more than 3 hr for completion at 77° and 56°, respectively. On the other hand, the same transformation in sulfur dioxide solution in the absence of acid catalyst required only several minutes at room temperature. The nmr analysis indicated that the derivative of the *Z* oxime reacted somewhat slower than the *E* isomer.

The fragmentation reaction of benzaldehyde oxime diethyl ortho ester was considerably slower even in sulfur dioxide solution. For example, the corresponding orthoformate and orthoacetate required 48 hr at room temperature to give 90 and 60% yields of benzonitrile, respectively.[7,8]

We also found that ortho esters are very effective reagents for Beckmann fragmentation of α-oximino ketones and α-oximino ketone acetals (eq 4 and 5). Heating a mixture of commercial benzil monooxime with 10% excess of triethyl orthoformate in liquid sulfur dioxide at 75° gave an almost quantitative yield of ethyl benzoate and benzonitrile. Similarly, a solution of 2-oximinocyclohexanone dimethyl ketal and trimethyl orthoformate in sulfur dioxide



containing catalytic amounts of methanesulfonic acid, after short reflux at −10°, afforded a quantitative yield of 5-cyanopentanoic acid methyl ester. These reactions presumably involve intermediate formation of the corresponding oxime ortho esters which undergo the indicated Beckmann fragmentation *in situ*.

Experimental Section

The oximes and ortho esters used in this work were commercial samples purified when necessary by either distillation or crystallization. Boiling and melting points of the products are uncorrected. Glpc analyses were carried out generally on a Hewlett-Packard 5700A instrument using 3- or 6-ft columns of 10% SE-30 on Chromosorb W. Proton nmr spectra were recorded on either Varian A-60 MHz or HA-100 MHz instruments.

Typical Procedure for the Conversion of Oximes to Nitriles. A mixture of *n*-heptaldehyde oxime (15.0 ml, 100 mmol) and triethyl orthoformate (20.0 ml, 120 mmol), containing a drop

of methanesulfonic acid, was placed in a flask attached to a short distilling column and heated to distil the ethyl formate and ethanol formed in the reaction. When the distillation of the ester and alcohol ceased, the residue was distilled *in vacuo* to give a 95% yield of *n*-heptanoic acid nitrile, bp 70–72° (10 mm).

Typical Procedure for Conversion of Oxime Diethyl Ortho Esters. A. In Chloroform.[9] A solution of *n*-butyraldehyde oxime diethyl orthoacetate (20.3 g, 100 mmol) in chloroform (100 ml) was placed in a flask attached to a short distilling column and 0.2 g of methanesulfonic acid added. The solution was stirred at room temperature and the extent of the reaction was followed by neutralizing small aliquots which were then analyzed by glpc. After 30 min the reaction was complete and distillation afforded 5.48 g (94% yield) of *n*-butyronitrile.

B. In Sulfur Dioxide. A 100-ml heavy glass ampoule containing benzaldehyde oxime diethyl orthoformate (19.5 g, 100 mmol) was charged with approximately 50 ml of liquid sulfur dioxide at −70°, sealed, and kept at room temperature[10] for 48 hr. The ampoule was cooled in Dry Ice, opened, and the content transferred into a distilling flask containing 100 ml of cold chloroform. The flask was attached to a short column and excess of solvents removed *in vacuo*. The residue was distilled to give 9.3 g (90%) of benzonitrile, bp 68–70° (10 mm).

Typical Procedure for Preparation of Oxime Diethyl Ortho Esters. A solution of *n*-butyraldehyde oxime (a mixture of *Z* and *E* isomers in approximate ratio of 3:2) (8.7 g, 100 mmol) and triethyl orthoacetate (16.2 g, 100 mmol) was placed in a distilling flask attached to a short distilling column and heated at 120–150° until 4.6 g of ethanol distilled. Vacuum distillation of the residue gave a 95% yield of *n*-butyraldehyde oxime diethyl orthoacetate: bp 47–49° (0.6 mm); nmr ($CDCl_3$) δ 7.38 (t) and 6.68 (t) [1 H (total)], 3.54 (q, 4 H), 2.21 (m, 2 H), 1.5 (m + s, 5 H), 1.21 (t, 9 H).

Anal. Calcd for $C_{10}H_{21}NO_3$: C, 59.08; H, 10.41; N, 6.92. Found: C, 59.30; H, 10.50; N, 6.81.

Beckmann Fragmentation of Benzil Monooxime. A 50-ml heavy glass ampoule containing benzil monooxime (2.25 g, 10 mmol) and triethyl orthoformate (1.52 g, 11 mmol) was charged with approximately 25 ml of liquid sulfur dioxide at −70°, sealed, and heated at 72° for 70 hr. The ampoule was placed in Dry Ice, opened, and the contents were diluted with chloroform. Glpc analysis indicated a 95 and 98% yield of benzonitrile and ethyl benzoate, respectively.

Beckmann Fragmentation of 2-Oximinocyclohexanone Dimethyl Ketal. A 50-ml three-neck flask equipped with a magnetic stirrer, a Dry Ice condenser, and a nitrogen bubbler was charged with approximately 20 ml of sulfur dioxide at −70°, and 2-oximinocyclohexanone dimethyl ketal (1.73 g, 10 mmol), trimethyl orthoformate (1.2 g, 11 mmol), and a drop of methanesulfonic acid were then added. The solution was maintained under reflux (~−10°) for 30 min, and then 10 ml of chloroform and an internal standard were added. Glpc analysis indicated a 97% yield of 5-cyanopentanoic acid methyl ester.

Registry No.—Benzil monooxime, 14090-77-8; 2-oximinocyclohexanone dimethyl ketal, 52540-36-0.

References and Notes

(1) Mukaiyama, *et al.*, have reported[2] the synthesis of several oxime dialkyl ortho esters by the addition of an oxime to a ketene acetal.
(2) T. Mukaiyama, K. Tonooka, and K. Inoue, *J. Org. Chem.*, **26**, 2202 (1961).
(3) This observation is in accord with the known tendency of isomeric oximes to undergo various acylation reactions without isomerization.[4]
(4) P. A. S. Smith, "Open Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, New York, N.Y., 1966, p 46.
(5) We have also shown that oximes react with various ketone acetals to give the corresponding oxime alkyl ketone acetals. These, in turn, also undergo similar transformations as the oxime dialkyl ortho esters.
(6) The extent of the reaction was followed either by nmr or glpc analysis or both.
(7) This slow transformation is very likely a consequence of the syn arrangement of the carbon–hydrogen and nitrogen–oxygen bonds in the benzaldehyde oxime ortho ester, which eventually undergoes rate-determining isomerization to the more reactive anti isomer under the reaction conditions.
(8) Nmr analysis indicated that these oxime ortho esters were undergoing a series of reversible disproportionation reactions which will be discussed elsewhere.
(9) The experimental procedure in other solvents, *e.g.*, toluene, ether, tetrahydrofuran, or nitromethane, was essentially the same.
(10) When the reaction was unusually slow, as in the case of *p*-methoxybenzaldehyde derivatives, the ampoule was heated at 70°, cooled in Dry Ice, opened, and worked up in the same way.

Synthesis and Resolution of 2-Hydroxyheptanoic Acid

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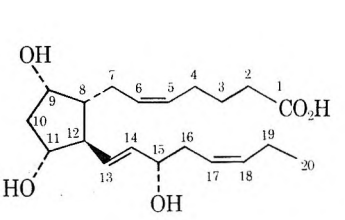
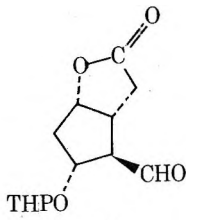
In an elegant synthesis of PGE_3 (1) reported by Corey and coworkers[1] the (*S*)-15-hydroxy-13,17-octadienyl side chain at C-12 was introduced stereospecifically by the condensation of the optically active aldehyde (2) with the ylide derived from the phosphonium salt (**3c**). The salt (**3c**) was prepared from (*S*)-(−)-malic acid by the multistep process (*S*)-(−)-malic acid → **3a** → **3b** → **3c**. It is apparent that the (*S*)-15-hydroxy-13-octenyl side chain at C-12 of prostaglandins and prostaglandin analogs could be introduced by the condensation of the ylide derived from the phosphonium salt (**5c**) with the appropriate aldehyde. The salt (**5c**) could be prepared from (+)-2-hydroxyheptanoic acid [(+)-**4**] by the sequence (+)-**4** → **5a** → **5b** → **5c**. In the present paper, we present an efficient and economical synthesis and resolution of (±)-2-hydroxyheptanoic acid [(±)-**4**].



1



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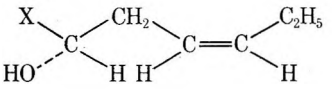
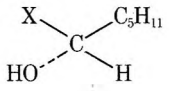


3a, X = CH_2OH
b, X = CH_2I
c, X = $CH_2\overset{+}{P}(C_6H_5)_3$



4, X = CO_2H
5a, X = CH_2OH
b, X = CH_2I
c, X = $CH_2\overset{+}{P}(C_6H_5)_3$

The preparation of (±)-**4** was accomplished in excellent yield from the cyanohydrin of hexanal. Numerous salts of (±)-2-hydroxyheptanoic acid with optically active amines were prepared, but only two, quinine and dehydroabeitylamine, were sufficiently crystalline to warrant further investigation. Recrystallization of both salts and liberation of the acid gave optically active material with opposite rotations. A large scale resolution employing quinine was performed and, in the very early recrystallizations of the quinine salt, two types of crystals were apparent. The progress of the resolution was followed by obtaining the rotation of the liberated and recrystallized acid. When a value of $[\alpha]^{25}D$ +5.55° was obtained, further recrystallization of the quinine salt did not increase the rotation of the acid.

The initial filtrate from the resolution of the plus (+) isomer was acidified, and the enriched minus (−) isomer was converted to its dehydroabeitylamine salt. The progress of the resolution of this isomer was followed as before with the final acid rotation being $[\alpha]^{26}D$ −5.52°.

In a study which established the absolute configuration of the C-15 hydroxyl group of prostaglandins, Nugteren and coworkers[2] degraded certain prostaglandins by ozonolysis and obtained 2-hydroxyheptanoic acid which possessed an optical rotation of $[\alpha]^{25}D$ +6.9, *c* 5.8, $CHCl_3$. Since the magnitude of our final rotations is different from

the value obtained by Nugteren and coworkers,[2] it was necessary to establish the optical purity of the individual optical isomers. The method of Westly and Halpern,[3] which involves the glc analysis of the *l*-menthol carbonate ester derivative of the methyl ester of (±)-4 proved to be a facile check on the completeness of the resolution. When we applied this method to (±)-4, we found that the glc of (±)-4 showed two peaks (one for each diastereoisomer) for the *l*-menthol ester derivative, while the glc of the individually resolved and derivatized acids shows only one peak indicating that each acid was >98% optically pure.

Experimental Section[4]

(±)-2-Hydroxyheptanoic Acid. Sodium metabisulfite (54 g, 0.28 mol) in water (60 ml) was added dropwise to a magnetically stirred mixture of ether (100 ml), hexanal (50 g, 0.5 mol), potassium cyanide (34.5 g, 0.53 mol), ice (50 g), and water (10 ml) at 0 to 10°. After completion of the addition, the reaction mixture was stirred for 15 min at 0° and 15 min at room temperature. The reaction was extracted with ether (4 × 100 ml), and the ether extracts were dried ($MgSO_4$) and evaporated at reduced pressure to give an oil: ir (film) 3400 (OH) and 2140 cm^{-1} (C≡N).

The crude cyanohydrin in ethanol (200 ml) was saturated at 0° with hydrogen chloride, and allowed to stand overnight. Excess ethanolic hydrogen chloride was removed at reduced pressure, and the resulting oil was stirred with ice water (50 ml), then rapidly extracted with ether (2 × 100 ml) and chloroform (2 × 100 ml). The combined extracts were dried ($MgSO_4$), then evaporated at reduced pressure to give a yellow oil. Distillation of the crude product gave 68.2 g (93%) of pure ester: bp 105–107° (17 mm); ir (film) 3480 (OH) and 1735 cm^{-1} (CO_2Et).

The pure ester (50 g, 0.287 mol) in water (70 ml) and dioxane (70 ml) was magnetically stirred while slowly adding sodium hydroxide (12.6 g, 0.315 mol). After stirring overnight, the solution was acidified with hydrochloric acid and extracted with ether (3 × 100 ml). The ether extracts were dried ($MgSO_4$), then evaporated at reduced pressure to give a solid. Recrystallization of the crude acid from benzene–hexane (1:2) gave 39.8 g (95%) of pure 2-hydroxyheptanoic acid: mp 64–65° (lit.[2] mp 64–65°); ir ($CHCl_3$) 3400 (OH) and 1710 cm^{-1} (CO_2H).

D-(−)-2-Hydroxyheptanoic Acid. Four separate but identical resolutions were performed simultaneously. Anhydrous quinine (55.75 g, 0.172 mol) and 2-hydroxyheptanoic acid (25.0 g, 0.171 mol) were combined in methanol (400 ml) and heated to boiling. Hot (70°) water (1 l.) was added with stirring, and the solution became cloudy. Enough hot methanol was added to clarify the solution. After cooling, the salt which had crystallized from solution was collected, washed (2:5 methanol–water), and dried. The collected salt weighed 38 g (47%). This and the remaining recrystallizations are shown in Table I.

Table I

Crystallization	Methanol, ml	Water, ml	Weight, g	% yield
1	400	1000	38	47
2	150	700	35	44.5
3	175	700	36	43.7
4	200	600	26	33.2

The final rotation of the salt was $[\alpha]^{27}D$ +122.53 ± 0.15 (c 4.0, MeOH), and the liberated acid had an average rotation of $[\alpha]^{27}D$ −5.55 ± 0.05° (c 5.8, $CHCl_3$), after extraction into base, washing with ether, reacidification, extraction, and recrystallization of the collected acids from hexane.

L-(+)-2-Hydroxyheptanoic Acid. The filtrates from the first crystallization were treated with acid and extracted into ether, dried, and evaporated to give 49.26 g of L-(+)-2-hydroxyheptanoic acid.

Dehydroabeitylamine (50.38 g, 0.175 mol) and the partially resolved L-(+)-2-hydroxyheptanoic acid (23.45 g, 0.159 mol) were dissolved in hot methanol (250 ml), and hot water (100 ml) was added. The solution became cloudy and a small additional amount of methanol was added to clarify the solution. This and the remaining crystallization are shown in Table II.

Table II

Crystallization	Methanol, ml	Water, ml	Weight, g	% yield
1	250	100	63.4	91.6
2	450	200	62.3	89.9

The final rotation of the dehydroabeitylamine salt was $[\alpha]^{26}D$ +14.47 ± 0.06 (c 4.0, MeOH) while the liberated acid had a rotation of $[\alpha]^{26}D$ +5.53 ± 0.05° (c 5.8, $CHCl_3$).

Optical Purity Analysis. The methyl esters of individual acid samples were prepared by reaction with diazomethane in ether. One drop of the neat ester in five drops of pyridine was treated with four drops of L-menthol chlorocarbonate solution[3] (an excess). Glc analysis was performed at 180° on a 6-ft 1% QF, 1% OV-17 column with a 30-cm^3/min flow rate. Flame ionization was used for detection. The retention times for the derivatized methyl esters follow: (+), 6.57 min; (−), 7.20 min. The major components of the glc trace were identified by glc–mass spectrometry and by comparison of the individual components with authentic samples.

Acknowledgment. This work was supported under Contract NIH-NICHD-72-2712 with the Contraceptive Development Branch of the National Institutes of Child Health and Human Development.

Registry No.—(±)-4, 52358-05-1; (−)-4, 52437-20-4; (+)-4, 52437-21-5; hexanal, 66-25-1; (±)-hexanal cyanohydrin, 52358-06-2; ethyl (±)-2-hydroxyheptanoate, 52438-78-5.

References and Notes

(1) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, and T. K. Schaaf, *J. Amer. Chem. Soc.*, **93**, 1490 (1971).
(2) D. H. Nugteren, D. A. van Dorp, S. Bergstrom, M. Hamburg, and B. Samuelesson, *Nature (London)*, **212**, 38 (1966).
(3) J. Westly and B. Halpern, *J. Org. Chem.*, **33**, 3978 (1968).
(4) Melting points were taken on a Kofler hot stage microscope and are uncorrected. Nmr spectra were determined on a Varian Associates Model HA-100 spectrophotometer in chloroform with tetramethylsilane as an internal standard. Glc–mass spectra were determined on a Varian MAT CH-7 mass spectrometer. Infrared spectra were obtained with a Perkin-Elmer Model 267 double beam spectrophotometer. Rotations were taken on a Perkin-Elmer Model 141 polarimeter.

Synthesis of 3,5-Dialkyl-1,2-dioxolanes[1]

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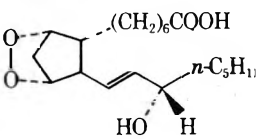
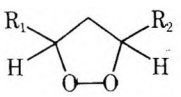
The prostaglandin endoperoxide, **1**, has been proposed as an intermediate in the biosynthesis of other prostaglandins.[2,3] Such structures have been detected in *in vitro* biosyntheses.[3] In view of the biological importance of the prostaglandins, it is pertinent to develop synthetic schemes for the chemical preparation of **1**.



1

Saturated 1,2-dioxanorborananes have not been described in the literature. The synthesis of simple model structures may furnish necessary background for synthesis of compounds such as **1**. For this reason, we undertook to synthesize and investigate the decomposition of the 3,5-dialkyl-1,2-dioxolanes, **2**, cyclic alkyl peroxides with secondary carbon atoms adjacent to the oxygen atoms.



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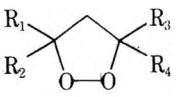
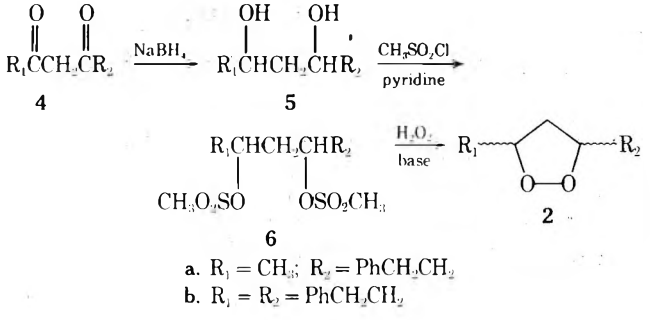


3

Compounds of the type **3**, with tertiary carbon atoms next to the peroxide linkage are known[4-7] and their thermal and photochemical decomposition have been studied.[5-7] These dioxolanes are synthesized by the acid-catalyzed reaction of the corresponding 1,3-diol with concentrated hydrogen peroxide; however, this method is feasible only with tertiary alcohols.

A useful general but low-yield method for the synthesis of secondary acyclic hydroperoxides and dialkyl peroxides is that of Williams and Mosher.[8,9] In this synthesis, methanesulfonyl groups are displaced by nucleophilic attack of peroxy anions; adjustment of the proportion of hydrogen peroxide in the mixture determines whether the product is primarily hydroperoxide[8] or dialkyl peroxide.[9] This method has been used[10] to synthesize one unsubstituted six-membered ring, 1,2-dioxane, in moderate yield from a diprimary 1,4-diol bismethanesulfonate.

We adapted this method for the synthesis of two 3,5-dialkyl-1,2-dioxolanes from the bismethanesulfonates of disecondary 1,3-diols. The general synthetic scheme is shown below.



a. $R_1 = CH_3$; $R_2 = PhCH_2CH_2$
b. $R_1 = R_2 = PhCH_2CH_2$

Reduction of **4a**[11] with sodium borohydride in methanol[12] gave the diol **5a**; the bismethanesulfonate, **6a**, was prepared from **5a** and methanesulfonyl chloride in the presence of pyridine. Reaction of **6a** with an excess of hydrogen peroxide and potassium hydroxide in methanol gave **2a**. To avoid excessive base decomposition, **2a** was extracted from the reaction mixture as it was formed by an overlayer of hexane. After purification by repetitive short column chromatography, the product **2a** was homogeneous on tlc and gave a positive reaction to a peroxide spray reagent.[13] Microanalysis and molecular weight determination were in accord with structure **2a**.

The infrared spectrum of **2a** shows no alcohol, hydroperoxide, ketone, or methanesulfonate absorptions; the nmr shows no exchangeable protons and all the absorptions are in the expected regions. The protons α to the oxygen atoms are shifted downfield relative to the parent alcohol by about 0.2 ppm. The direction and magnitude of this shift is similar to that observed for dialkyl peroxides.[14] Reaction of **2a** with lithium aluminum hydride in ether gives a diol identical in all respects with diol **5a**. The dioxolane is unchanged after being stored for one year at −20° but decomposes significantly after a few days at room temperature.

Similarly, diketone **4b**[15] was transformed to diol **5b** which in turn was converted to bismethanesulfonate **6b**. The dioxolane, **2b**, was obtained by reaction of **6b** with hydrogen peroxide and solid potassium carbonate in methanol with a hexane overlayer. Analysis, spectra, and tlc data were all in accord with the structure **2b**, and reduction with lithium aluminum hydride furnished the expected diol **5b**. The thermal stability of **2b** is similar to that of **2a**.

No attempt was made to optimize the yields of these peroxides by systematically varying the temperature, the concentration of hydrogen peroxide, and the specific base used for the cyclization. The key purpose of this study was to determine the feasibility of preparing such compounds and to assess their stability.

Experimental Section

General. Melting points were taken on a Mel-Temp apparatus and are corrected. Boiling points are uncorrected. *All reactions involving 98% hydrogen peroxide (FMC Corporation) were performed behind safety shields and reasonable caution was exercised with potentially explosive products.* Elemental and molecular weight analyses were performed by Midwest Microlabs, Inc. (Indianapolis, Ind.). Nuclear magnetic resonance (nmr) spectra were recorded on a Varian T-60 instrument and are reported in parts per million downfield from tetramethylsilane. Infrared spectra were recorded on a Beckman IR-8 or IR-10 and are reported in reciprocal centimeters. Silica gel coated glass plates (E. Merck, F-254) were used for all tlc and were stored in a desiccator prior to use.

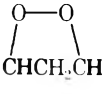
6-Phenyl-2,4-hexanediol (5a). A solution of 42.2 g (0.222 mmol) of dione **4a**[11] in 60 ml of methanol was added dropwise to a solution of 6 g (0.158 mmol) of sodium borohydride and 0.3 g sodium hydroxide in a mixture of water (60 ml) and methanol (50 ml). The solution was stirred overnight. The methanol was removed under reduced pressure and water was added. The mixture was extracted twice with chloroform. The chloroform solution was dried over magnesium sulfate and evaporated to give 43 g (100%) of a hydroscopic yellow oil. Purification of a portion of this oil on silica gel/chloroform gave diol **5a** in 65% yield: ir 3400–3600 (OH), 1610 (phenyl), 1500 (CH_3), 1050–1150 (CO); nmr ($CDCl_3$) δ 7.15 (s, 5, C_6H_5), 4.6 (br s, 2, exchangeable, two OH), 3.95 [m, 2, $\mathbf{CH(OH)CH_2CH(OH)}$], 2.6 (m, 2, $C_6H_5\mathbf{CH_2}$), 1.7 [m, 4, $\mathbf{CH_2CH(OH)CH_2CH(OH)}$], 1.2 (d, 3, CH_3).

A bisnitrobenzoate was prepared from the diol and had mp 115–118°; ir 3110, 3050, 3020 (aromatic H), 2980, 2930 (aliphatic H), 1720 (ester), 1600 (phenyl), 1520, 1350 (NO_2), 1270 (ester); nmr ($CDCl_3$) δ 8.2 (s, 8, two $NO_2C_6H_4$), 7.2 (s, 5, C_6H_5), 5.4 [m, 2, $CH(OCOPhNO_2)CH_2\mathbf{CH}(OCOPhNO_2)$], 2.8 (m, 2, $C_6H_5\mathbf{CH_2}$), 2.2 [m, 4, $\mathbf{CH_2}CH(OCOR)\mathbf{CH_2}CH(OCOR)$], 1.5 (d, 3, CH_3).

Anal. Calcd for $C_{26}H_{24}N_2O_8$: C, 63.41; H, 4.91; N, 5.69. Found: C, 63.28; H, 4.87; N, 5.70.

The bismethanesulfonate **6a** was prepared from the diol and purified by column chromatography on silica gel/chloroform to give 84% of a clear oil: ir no alcohol, 1185 and 1350 (sulfonate); nmr ($CDCl_3$) δ 7.2 (s, 5, C_6H_5), 4.9 [m, 2, $\mathbf{CH}(OMs)CH_2\mathbf{CH}(OMs)$], 2.9 (m, 8, two OSO_2CH_3 and $C_6H_5CH_2$), 2.1 [m, 4, $CH_2CH(OMs)\mathbf{CH_2}CH(OMs)$], 1.5 (d, 3, CH_3).

3-Methyl-5-(2-phenylethyl)-1,2-dioxolane (2a). A solution of 3.7 g (10.5 mmol) 6-phenyl-2,4-hexanebismethanesulfonate **6a**, 12 ml 30% hydrogen peroxide (0.13 mol), and a trace of thymol blue indicator in 35 ml methanol was heated to 50° and overlaid with hexane. A solution of 1 *N* potassium hydroxide in methanol–water was added dropwise to keep the indicator color blue to green. In 7 hr, one third of the required amount of base had been added. The hexane layer was removed and replaced with fresh solvent. The remainder of the base was added all at once. Another hexane extract was taken at 24 hr and again at 96 hr. The combined hexane layers were evaporated and chromatographed on silica gel/chloroform to give 280 mg (13%) peroxide positive[13] material, R_f ($CHCl_3$) 0.62, contamined with starting material. Two further column chromatographs, on silica gel with methylene chloride and with benzene, gave 140 mg (7%) pure **2a**, a yellow oil: it was homogeneous on tlc in $CHCl_3$, ethyl acetate, and 20% ethyl acetate in hexane; ir, no alcohol absorptions, 3070, 3040 (aromatic H), 2980, 2940 (aliphatic H), no carbonyl absorptions, 1600 (phenyl), 1500 (methyl); nmr ($CDCl_3$) δ 7.1 (s, 5, C_6H_5), 4.2 (m, 2, a), 2.6 (m, 2, $C_6H_5\mathbf{CH_2}$), 2.4–



a

1.4 [m, 4, $\mathbf{CH_2}CH(OO)\mathbf{CH_2}$], 1.2 (d, 3, $\mathbf{CH_3}$). The couplings are clearly second order; irradiation at the δ 4.2 peak causes peak

shape changes in the peaks at δ 2.6 (crude t), 2.4–1.4 (crude t), and 1.2 (s).

Anal. Calcd for $C_{12}H_{16}O_2$ (mol wt, 192.26): C, 74.96; H, 8.39. Found [mol wt, 198 (±5%)]: C, 75.14; H, 8.35.

Treatment of a solution of dioxolane **2a** in ether with an excess of lithium aluminum hydride for 3 hr gave a quantitative yield of diol having the same R_f on tlc as 6-phenyl-2,4-hexanediol **5a**. A bisnitrobenzoate was prepared from this material, chromatographed on silica gel/chloroform, and crystallized from ethyl acetate–hexane. It had mp and mmp 115–118°, with the bisnitrobenzoate from **5a** and its ir was superimposable on that of the authentic compound.

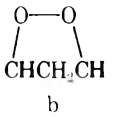
1,7-Diphenyl-3,5-heptanediol (5b). A solution of 1,7-diphenyl-3,5 heptanedione[15] (0.11 mol, 31 g) in 100 ml methanol was added dropwise to a solution of 4.6 g sodium borohydride (0.122 mol) in 150 ml methanol. The solution was refluxed overnight. The methanol was removed under vacuum. To the residue was added water and an excess of mannitol;[12] this aqueous solution was extracted three times with chloroform. A yellow oil was obtained in 98% yield and crystallized from ether–hexane to give 20 g (63%), mp 65–82°. Three fractional crystallizations failed to give any usable gradation in melting point. The highest melting point attained, after extensive crystallizations was 78–82°. The diasteromers appear to form a solid solution since spectra and analytical results are the same for the high melting as for the initially crystallized material: ir 3680, 3590, 3450 (OH), 1600 (phenyl), 1200 (CO); nmr ($CDCl_3$) δ 7.2 (s, 10, two C_6H_5), 3.9 [m, 2, $CH(OH)CH_2CH(OH)$], 3.3 (br s, exchangeable, two OH), 2.7 distorted t, 4, two $C_6H_5CH_2$), 1.7 [m, 6, $CH_2CH(OH)CH_2CH(OH)CH_2$].

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.51. Found; C, 80.21; H, 8.68.

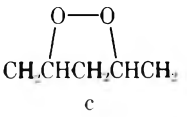
The bismethanesulfonate **6b** was prepared and crystallized from chloroform–hexane to give mp 60–69°; nmr ($CDCl_3$) δ 7.2 (s, 10, two C_6H_5), 4.8 [m, 2, $CH(OMs)CH_2CH(OMs)$], 2.9 (s, 6, two OSO_2CH_3), 2.7 (m, 4, two $C_6H_5CH_2$), 2.1 [m, 6, $CH_2CH(OMs)CH_2CH(OMs)CH_2$].

Anal. Calcd for $C_{21}H_{28}S_2O_6$: C, 57.26, H, 6.41, S, 14.53. Found: C, 57.19, H, 6.13, S, 14.28.

3,5-Bis(2-phenylethyl)-1,2-dioxolane (2b). A mixture of 11 g of bismethanesulfonate **6b** (25 mmol), 8.3 g of potassium carbonate (60 mmol), and 10 ml of 98% hydrogen peroxide (400 mmol) in 100 ml of methanol with a hexane overlayer was heated to 40° overnight. The hexane was removed and the reaction continued with fresh hexane for an additional 12 hr. The hexane layers were combined to give 0.86 g oil (17%, corrected for 3.2 g bismethanesulfonate recovered). After two column chromatographs on silica gel/benzene, 280 mg (5.6%) of peroxide positive material was obtained. Preparation of **2b** by the method used for **2a** gave only 0.5% yield: the material was homogeneous on tlc in four solvent systems; ir, no alcohol, no carbonyl, 1880, 1810, 1740, all weak aromatic bands; no sulfonate; nmr ($CDCl_3$) δ 7.2 (s, 10, two C_6H_5), 4.2 (quintet, 2, b, 2.7 (distorted d of t, 4, two $C_6H_5CH_2$), 2.4–1.6 (m, 6, c).



b



c

Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.52; H, 8.11.

A solution of dioxolane **2b** in ether was treated with an excess of lithium aluminum hydride at room temperature, yielding a diol that was identical with **5b** on four tlc systems and having mp 81–82°, mmp 77–81° with **5b**.

Registry No.—**2a**, 52393-48-3; **2b**, 52393-49-4; **4a**, 52393-50-7; **4b**, 38572-30-4; **5a**, 52393-51-8; **5a** bisnitrobenzoate, 52393-52-9; *meso*-**5b**, 52393-53-0; *dl*-**5b**, 52393-54-1; **6a**, 52393-55-2; *meso*-**6b**, 52393-56-3; *dl*-**6b**, 52393-57-4; hydrogen peroxide, 7722-84-1.

References and Notes

(1) This investigation was supported by Grant No. NR408-979 from the Department of the Navy. It is abstracted in part from the Ph.D. thesis of P. M. Jacobs.
(2) B. Samuelsson, *J. Amer. Chem. Soc.*, **87**, 3011 (1965).
(3) M. Hamberg and B. Samuelsson, *Proc. Nat. Acad. Sci. U.S.A.*, **70**, 899 (1973).
(4) R. Criegee and G. Paulig, *Chem. Ber.*, **88**, 712 (1955).
(5) W. Adam and N. Duran, *Tetrahedron Lett.*, 1357 (1972).
(6) W. Adam and N. Duran, *J. Org. Chem.*, **38**, 1434 (1973).
(7) W. Adam and N. Duran, *J. Chem. Soc., Chem. Commun.*, 279 (1972).
(8) H. R. Williams and H. S. Mosher, *J. Amer. Chem. Soc.*, **76**, 2987 (1954).
(9) F. Welsh, H. R. Williams, and H. S. Mosher, *J. Amer. Chem. Soc.*, **80**, 551 (1955).
(10) R. Criegee and G. Muller, *Chem. Ber.*, **89**, 238 (1956).
(11) C. R. Hauser and T. M. Harris, *J. Amer. Chem. Soc.*, **80**, 6360 (1958).
(12) J. Dale, *J. Chem. Soc., (London)*, 910 (1961).
(13) M. M. Buzlanova, V. F. Stepanovskaya, and V. L. Antonovskii, *J. Anal. Chem. USSR*, **21**, 1324 (1966).
(14) R. Hiatt, in "Organic Peroxides," Vol III, D. Swern, Ed., Wiley, New York, N.Y., 1972.
(15) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 59 (1954).

Synthesis of 1-, 2-, 3-, and 4-Phenylphenanthrenes by Photocylization of Isomeric Phenylstilbenes[1]

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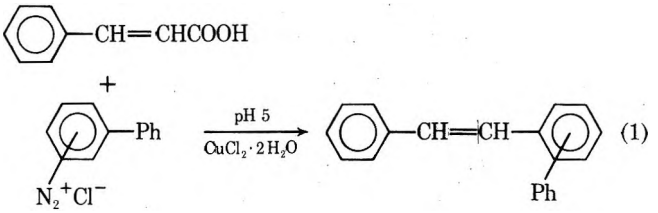
Authentic samples of 1-, 2-, 3-, 4-, and 9-phenylphenanthrenes were needed in connection with a larger study of the correlation of structure and reactivity in homolytic phenylation of polycyclic aromatic hydrocarbons.[3] At the time our investigation began, the required compounds had already been described in the literature,[4] but their synthesis involved lengthy reaction sequences. After we had prepared 1- and 4-phenylphenanthrene *via* the classical method of Haworth,[5] Mallory and coworkers described the photocyclization of substituted stilbenes to phenanthrene derivatives, including the formation of 9-phenylphenanthrene from triphenylethylene.[6] The simplicity of Mallory's method led us to extend it to the desired 1-, 2-, 3-, and 4-phenylphenanthrenes (**1–4**). Since the original report, the photolysis of a variety of stilbenes in the presence of air or iodine to form phenanthrenes has proved to be the method of choice and has been studied extensively.[7–9] The isomeric *o*-, *m*-, and *p*-phenylstilbenes (**6a–c**) were obtained by a modification of the Meerwein reaction between cinnamic acid and diazotized 2-, 3-, and 4-aminobiphenyl hydrochlorides (**5a–c**), respectively. The reaction is represented in eq 1 (see the Experimental Section).

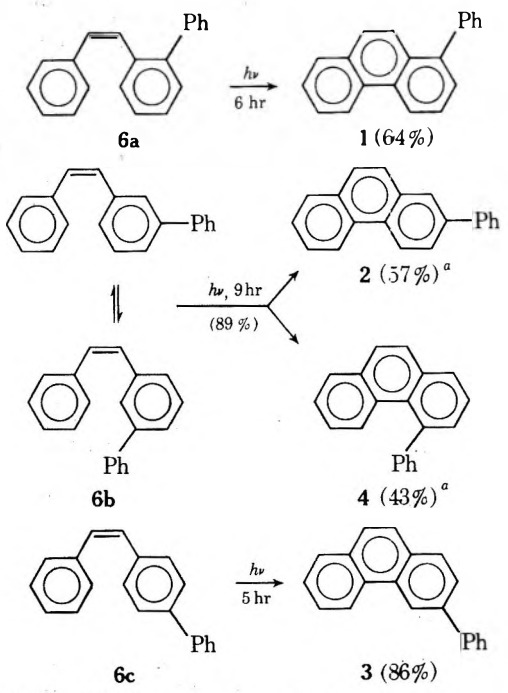


5a, 2-N_2^+ Cl^-
b, 3-N_2^+ Cl^-
c, 4-N_2^+ Cl^-

6a, *o*-Ph
b, *m*-Ph
c, *p*-Ph

Photoconversions of **6a–c** to phenylphenanthrenes were conducted in benzene–cyclohexane solutions in the presence of iodine and air as outlined in Scheme I. Separation of **4** from **2** was easily accomplished because of the low solubility of **2** in ethanol. The slightly lower yield of **4** compared with **2** may be attributed to a steric effect in the cyclization between the phenyl and hydrogen at positions 4 and 5. Recently very low yields of photocyclization product were reported in a case where the steric effect was more pronounced.[9]

Scheme I



[a] Relative yields based on vpc analysis.

Experimental Section[10]

m-**Phenylstilbene (6b).** A solution of 10 g of KOH in water (150 ml) was added to cinnamic acid (22.84 g, 0.155 mol). The suspension was stirred mechanically until solution occurred. The solution was adjusted to pH 7 with 5% HCl, and cupric chloride dihydrate (8.5 g, 0.05 mol) was added. Acetone (495 ml) was added and the suspension stirred. To the reaction mixture was then added 50 ml of a diazotized solution of 3-aminobiphenyl hydrochloride (10.150 g, 0.0493 mol). The suspension was adjusted to pH 5 with dilute KOH and acetone (150 ml) was added, to maintain a 1:3 ratio of water to acetone. Stirring at room temperature was continued for 48 hr until evolution of nitrogen ceased. The suspension was steam distilled for 4 hr and the suspension remaining in the reaction vessel was made alkaline. The suspension was filtered under suction and the precipitate washed repeatedly with boiling benzene and discarded. The aqueous filtrate was extracted with hot benzene and the organic layers were combined, washed with water until neutral, dried (Na_2SO_4), and filtered. Evaporation of the solvent left an orange-brown residue which was chromatographed over neutral alumina (Woelm, activity grade I, 67.0 × 2.0 cm) using benzene as eluent (350 ml). The eluate was evaporated leaving a colorless solid: 4.73 g (37.5% yield based on amine hydrochloride); mp 100–101°. The uv spectrum (95% EtOH) showed maxima at 223, 228, 236, 297, and 308 nm (ε 17,600, 17,800, 16,700, 27,850, and 27,000).

Anal. Calcd for $C_{20}H_{16}$: C, 93.71; H, 6.29. Found: C, 93.75; H, 6.21.

The isomeric *o*- and *p*-phenylstilbenes were prepared in a similar manner in 6 and 35% yields, respectively.

2- and 4-Phenylphenanthrenes (2 and 4). The irradiation source was a 550-W Hanovia high-pressure mercury lamp housed in a water-cooled quartz immersion well. The reaction well was provided with a gas inlet tube and magnetic stirrer, and was fitted at the bottom with a stopcock to permit removal of aliquots during irradiation. A magnetically stirred solution of **6b** (1.28 g, 0.005 mol) and 0.064 g of iodine (2.5×10^{-4} mol) in 500 ml of benzene–cyclohexane (2:3, v/v) was irradiated. A slow stream of purified air was passed through the solution during the course of the reaction. The color of the solution turned gradually from purple to pale yellow at the end of the reaction. The required irradiation time was determined by following the progress of the reaction by glc. Aliquots (3 ml) taken at specified time intervals were shaken with 5% aqueous NaOH and the organic layer was separated, dried over $MgSO_4$, and filtered. The filtrate was concentrated to about 0.5 ml and injected into the gas chromatograph. Irradiation was continued for about 1 hr after the peak corresponding to **6b** was no longer detectable by glc. The solvent was removed *in vacuo* leaving 1.159 g (89% yield) of a mixture of **2** and **4** (57 and 43%, respectively, by glc). The mixture was chromatographed over neutral alumina (Woelm, activity grade I, 18.0 × 2.0 cm) using a hexane–benzene mixture (2:1, v/v) as eluent. The chromatogram was followed by uv light. The solvent was removed from the eluate leaving an oil which was dissolved in 25 ml of hot ethanol. On cooling 0.350 g of **2** (mp 195–197° (lit.[11] 196.6–197.2°)) deposited.

The ethanol was evaporated and the pale-yellow residue was chromatographed again (Woelm, neutral alumina, activity grade I, 35.0 × 2.0 cm) first using cyclohexane as eluent (450 ml) and then benzene (350 ml). The cyclohexane fraction, after removal of solvent, left an oil (0.405 g) which crystallized as colorless rods, **4**: mp 81.8–82.6° (lit.[4] 80–81.5°). The material showed a single peak in glc; its retention time was identical with that of an authentic sample prepared *via* Haworth synthesis.[5b]

The evaporated benzene fraction contained impure **2** (0.245 g), mp 180–185°.

Compounds **1** and **3** were prepared in a similar manner in the yields shown in Scheme I: **1**, mp 79.5–80.0° (lit.[4] 79.5–80.5°); **3**, mp 73° (lit.[12] 73°).

Acknowledgments. We wish to thank Professor M. S. Newman for a sample of 2-phenylphenanthrene. We are greatly indebted to Professor F. B. Mallory for manuscript copy in advance of publication.

Registry No.—**1**, 4325-76-2; **2**, 4325-77-3; **3**, 2903-83-5; **4**, 4325-78-4; **5a**, 52500-12-6; **5b**, 20893-76-9; **5c**, 4163-91-1; **6a**, 33506-75-1; **6b**, 52500-13-7; **6c**, 2039-69-2; cinnamic acid, 621-82-9.

References and Notes

(1) This work was supported by a grant (5FI-GM-22, 577-02) from the National Institute of General Medical Sciences.
(2) Address correspondence to this author at Department of Chemistry, Bronx Community College of the City University of New York, New York, N.Y. 10453.
(3) S. C. Dickerman and I. Zimmerman, *J. Amer. Chem. Soc.*, **86**, 5048 (1964); S. C. Dickerman, W. M. Feigenbaum, M. Fryd, N. Milstein, G. B. Vermont, I. Zimmerman, and J. F. W. McOmie, *ibid.*, **95**, 4624 (1973).
(4) A. L. J. Beckwith and M. J. Thompson, *J. Chem. Soc.*, 74 (1961), and references cited therein.
(5) (a) W. E. Bachmann and A. L. Wilds, *J. Amer. Chem. Soc.*, **60**, 624 (1938), for the preparation of 1-phenylphenanthrene; (b) A. D. Campbell, *J. Chem. Soc.*, 3659 (1954), for the synthesis of 4-phenylphenanthrene.
(6) F. M. Mallory, C. S. Wood, and J. T. Gordon, *J. Amer. Chem. Soc.*, **86**, 3094 (1964), and references cited therein.
(7) R. O. Kan, "Organic Photochemistry," McGraw-Hill, New York, N.Y., 1966, p 219.
(8) F. R. Stermitz, "Organic Photochemistry," O. L. Chapman, Ed., Marcel Dekker, New York, N.Y., 1967, p 254.
(9) M. S. Newman and H. M. Chung, *J. Org. Chem.*, **39**, 1036 (1974).
(10) Uv spectra were recorded on a Cary 15 spectrometer. Ir spectra were obtained on Baird Model 4-55 and Perkin-Elmer Infracord and Model 337 spectrophotometers. Elemental analyses were performed by the Schwarzkopf Microanalytical Laboratory, Woodside, N.Y.
(11) M. S. Newman, *J. Org. Chem.*, **9**, 518 (1944).
(12) D. M. W. Anderson, N. Campbell, D. Leaver, and W. H. Stafford, *J. Chem. Soc.*, 3992 (1959).

Synthesis and Biological Evaluation of De-*AB*-camptothecin

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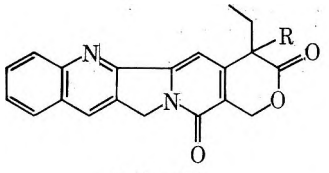
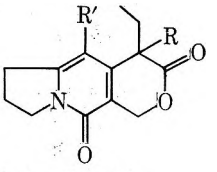
Received May 7, 1974

Recently, Rapoport and coworkers reported a route to analogs of the antitumor alkaloid camptothecin (**2**).[1] The Berkeley group synthesis,[2,3] patterned after the approach used in connection with its highly successful total synthesis,[4] involves a series of rearrangements, hydrogenolyses and dehydrogenations. Among the compounds reported were analogs[5] **3** and **4**.

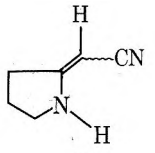
The new synthesis of α-pyridones of diverse substitution pattern,[6] developed as part of our total synthesis,[7,8] allows for mounting the crucial D and E ring segment found in camptothecin, onto a preformed enamino ester of the type **6** in a very simple fashion. As part of a program aimed at establishing the minimum structural features required for camptothecin-like activity, we have undertaken the preparation and study of analogs where entire rings, found in the natural product, are deleted. In this connection, we have synthesized and evaluated compounds **3** and **4**.



1, R = H
2, R = OH



3, R = R′ = H
4, R = OH, R′ = H
11, R = H, R′ = CO_2Me



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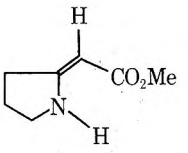

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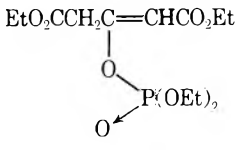

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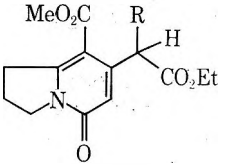

9, R = H
10, R = Et

Methanolysis of the readily available 2-cyanomethylenepyrrolidine (**5**)[9] gives the crystalline enamino ester **6**, mp 102–103.5°. The latter condenses smoothly with either[1,3] dicarbethoxyallene **7**[10] (method A) or its precursor enol phosphate **8**[10] (method B) to give pyridone **9**, mp 127–128°. Although method A is somewhat simpler in that no chromatography is required for purification, this factor does not justify the lower overall yield because of difficulties associated with the transformation of **8** → **7**.

Base-induced ethylation of **9** gave the alkylated pyridone **10**. With the nucleophilic 5 position of the pyridone blocked by the carbomethoxyl function, lactomethylation is forced to occur in the 3 position, affording the resultant lactone ester **11**. The structure of **11** follows from its mass spectrum, parent *m/e* 291, and its nmr spectrum in which the pyridone and ethyl ester proton resonances present in **10** have been eliminated. Without purification, **11** was converted into deoxy analog **3** through the action of concentrated HBr. Hydroxylation of the deoxy compound gave the desired de-*AB*-camptothecin **4**.

Compounds **3** and **4** were examined with respect to their performance as inhibitors of DNA and RNA synthesis. The efficiency of *dl*-**1** and *dl*-**2** as inhibitors of nucleic acid synthesis has already been established, and this property may well be crucial to the antitumor function of naturally occurring **2** (see ref 8 and bibliography), though this point has, by no means, been proved.[5f]

The de-AB analogs showed no discernible inhibition at the micromolar concentrations where *dl*-**1** and -**2** show 50% inhibition. For instance, for the case of **4**, 20% inhibition requires a concentration of 5×10^{-5} *M*.[11] Furthermore, compounds **3** (NSC 177364) and **4**[12] (NSC 174570) exhibited no meaningful activity in the N.C.I. L-1210 carcinoma screen at concentrations where camptothecin is quite active in control experiments.[13]

It would appear, on the basis of these studies and other information in the literature,[5b,d] that the AB portion may be more crucial to activity than was previously suspected. Studies directed toward this problem are in progress.

Experimental Section[14]

Preparation of 2-Carbomethoxymethylenepyrrolidine (6). Treatment of 8.5 g (0.0788 mol) of 2-cyanomethylenepyrrolidine (**5**)[9] with methanolic hydrogen chloride, according to the procedure of Horii[15] afforded 7.18 g (65%) of **6**, mp 88–95°. Chromatography of the mother liquors on 150 g of silica gel gave, after elution with 2:1 hexane–ethyl acetate, an additional 0.69 g (6.2%) of **6**. Several recrystallizations from ether–hexane afforded an analytical sample: mp 102–103.5°; λ_{max} ($CHCl_3$) 3375, 1650, 1590 cm^{-1}; δ ($CDCl_3$) 8.2–7.8 (~1 H, very broad), 4.53 (s, 1 H); 3.60, 3.53 (s + t, *J* = 7 Hz respectively, 5 H), 2.8–2.4 (m, 2 H), 2.4–1.8 (m, 2 H).

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85. Found: C, 59.66; H, 7.90.

Reaction of 6 with 1,3-Dicarbethoxyallene (7). Formation of 3-Carbomethoxymethyl-4-carbethoxy-1,6-cyclopentano-2-pyridone (9) (Method A). A solution of 1.15 g (0.0082 mol) of **6**, 1.513 g (0.0082 mol) of allene **7**,[10] and 16 drops of triethylamine in 8 ml of absolute ethanol was stirred at room temperature for 48 hr. The volatiles were removed *in vacuo*. Trituration of the residual solid with ether afforded 1.69 g (74%) of **9** as a white solid: mp 127–128°; λ_{max} ($CHCl_3$) 1720, 1700, 1650 cm^{-1}; δ ($CDCl_3$) 6.40 (s, 1 H), 4.35–3.95 (q + t, *J* = 7 Hz for each, 4 H), 3.78 (s, 5 H), 3.52 (t, *J* = 7 Hz, 2 H), 2.2 (quint, *J* = 7 Hz), 1.25 (t, *J* = 7 Hz, 3 H). Several recrystallizations from absolute ethanol afforded an analytical sample of **9**, mp 125–127°.

Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.14. Found: C, 60.13; H, 6.34.

Reaction of 6 with Enol Phosphate 8. Formation of Pyridone 9 (Method B). To a magnetically stirred solution of 0.141 g (0.001 mol) of **6** and 0.600 g (0.00177 mol) of enol phosphate **8** in ml of absolute ethanol was added *ca.* 0.3 ml of triethylamine. Stirring was continued for 48 hr at room temperature. The volatiles were removed *in vacuo*. Trituration of the residue afforded 0.150 g (54%) of **9**, mp 120–124°. Chromatography of the residue on silica gel and elution with 2:1 hexane–ethyl acetate gave an additional 0.073 g (26%) of **9**, mp 118–123°.

Preparation of the Ethylated Pyridone 10. To a slurry under N_2 of 1.62 g (0.00582 mol) of pyridone **9** in 25 ml of dry dimethoxyethane cooled in a Dry Ice–2-propanol bath was added, with stirring, 0.715 g (0.00638 mol) of potassium *tert*-butoxide (Alfa Inorganics). After 5 min 3.76 g (0.024 mol, 1.95 ml) of ethyl iodide was added and the reaction mixture was stirred for 2 hr in the cold. It was then allowed to warm to room temperature and stirred for 20 hr after which it was quenched by pouring it into 300 ml of water layered with 100 ml of methylene chloride. The aqueous layer was extracted with 2 × 100 ml of methylene chloride. The combined organic layers were washed with brine, dried over magnesium sulfate, and freed of solvent to afford 1.57 g (88%) of the ethylated pyridone **10** as a green-yellow oil, homogeneous to thin layer chromatography: δ ($CDCl_3$) 6.36 (s, 1 H), 3.8–4.2 (q + t, *J* = 7 Hz for each + m, 5 H), 3.67 (s, 3 H), 3.5–3.1 (m, 2 H), 2.4–1.4 (m, 5 H), 1.20 (t, *J* = 7 Hz, 3 H), 0.95 (t, *J* = 7 Hz, 3 H).

Reaction of Pyridone 10 with Paraformaldehyde. Formation Intermediate Lactone Ester 11. A thick-walled sealed tube containing 0.255 g (0.00083 mol) of the ethylated pyridone **10**, 0.120 g of paraformaldehyde, 1.5 ml of dioxane (undistilled), 3 drops of concentrated sulfuric acid, and 3 drops of water was heated at 104° for 22 hr. Upon cooling, the reaction mixture was poured into 50 ml of water and extracted with 1 × 50 plus 2 × 25 ml of methylene chloride. The combined organic extracts were washed with brine, dried over magnesium sulfate, and freed of solvent to afford 0.261 g of a yellow oil containing the tricyclic lactone **11** (*m/e* 291) which was used, as such, in the next step.

Preparation of De-*AB*-deoxycamptothecin (3). A mixture of 0.261 g of the crude **11** just described and 7.5 ml of aqueous hydrobromic acid was heated at reflux under nitrogen for 18 hr (oil bath at 115°). It was then poured into 50 ml of water and 50 ml of methylene chloride and the layers were separated. The aqueous one was extracted with 2 × 20 ml of methylene chloride. The combined organic layers were extracted with brine, dried over magnesium sulfate, and freed of solvent to afford 0.150 g of a crude partially crys-

talline oil: λ_{max} (KBr) 1730, 1658, 1592, 1580 cm^{-1}; δ ($CDCl_3$) 5.93 (s, 1 H), 5.25 (broadened S, 2 H), 4.08 (t, J = 8 Hz, 2 H), 3.48–2.85 (m, 3 H), 2.45–1.62 (m, 4 H), 0.95 (t, J = 8 Hz, 3 H). Chromatography on 12 g of silica gel eluting with chloroform afforded 0.089 g (46% based on starting **10**[16]) of **3** as a white solid, mp 145–148° (lit.[2] 149–150°).

Preparation of De-*AB*-camptothecin (4). A solution of 0.190 g (0.000815 mol) of deoxy **3** at 0.200 g (0.0018 mol) of potassium *tert*-butoxide in 40 ml of methanol was allowed to stir at room temperature for 10 min prior to the addition of 10.15 ml of a solution of 1 ml of 30% hydrogen peroxide in 20 ml of ether dried over Na_2SO_4. The resulting solution was stirred for 26 hr at room temperature. The reaction mixture was then acidified with methanolic hydrochloric acid and freed of volatiles *in vacuo*. The residue was triturated with 3 × 20 ml of methylene chloride. The combined methylene chloride extracts were dried over anhydrous magnesium sulfate and freed of solvent of afford 0.191 g of a yellow oil. Crystallization from ethanol afforded 0.126 g of a white solid which, from its nmr spectrum, was judged to contain *ca.* 80% of the desired analog **4** and 20% of the starting deoxy **3**. This material was dissolved in 20 ml of methanol and treated as described above with 0.097 g (0.000865 mol) of potassium *tert*-butoxide and 5 ml of a solution of 1 ml of 30% H_2O_2 in 20 ml of anhydrous ether dried over sodium sulfate. Upon work-up, there was obtained 0.125 g of a yellow oil whose nmr spectrum indicated it to be almost pure **4**. Chromatography on 15 g of silica gel, after chloroform elution afforded 0.088 g (43%) of analog **4** as a white solid, mp 172–182°. Two recrystallizations from ethanol afforded the analog **4** as a white solid: mp 176–179° (reported[2] mp 175–177°); λ_{max} (KBr) 3401, 1748, 1730, 1647, 1582; δ ($CDCl_3$) 6.45 (s, 1 H), 5.75–4.95 (AB quartet, 2 H), 4.25–4.03 [t + s (OH), 3 H], 3.30–3.05 (t, 2 H), 2.5–1.6 (quintet + quartet, 4 H), 1.10–0.85 (t, 2 H).

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Registry No.—**3**, 43083-10-9; **4**, 40163-27-7; **5**, 13939-73-6; **6**, 36625-47-5; **7**, 52358-42-6; **8**, 52358-43-7; **9**, 52358-44-8; **10**, 52358-45-9; **11**, 52358-46-0; paraformaldehyde, 30525-89-4.

References and Notes

(1) (a) M. E. Wall, M. G. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966); (b) for a recent review of the area: A. G. Schultz, *Chem. Rev.*, **73**, 385 (1973).
(2) J. J. Plattner, R. D. Gless, G. K. Cooper, and H. Rapoport, *J. Org. Chem.*, **39**, 303 (1974).
(3) J. J. Plattner, R. D. Gless, and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 8613 (1972).
(4) C. Tang and H. Rapoport, *J. Amer. Chem. Soc.*, **94**, 8615 (1972).
(5) For other analog synthesis see (a) J. M. Beisler, *J. Med. Chem.*, **14**, 1116 (1971); (b) M. E. Wall, H. F. Campbell, M. C. Wani, and S. G. Levine, *J. Amer. Chem. Soc.*, **94**, 3632 (1972); (c) T. Sugasawa, T. Toyoda, and K. Sakasura, *Tetrahedron Lett.*, 5109 (1972); (d) S. Danishefsky, J. Quick, and S. B. Horwitz, *ibid.*, 2525 (1973); (e) R. E. Lyle, J. A. Bristol, M. J. Kane, and D. E. Portlock, *J. Org. Chem.*, 38, 3268 (1973); (f) M. E. Wall, "Internationales Symposium, Biochemie and Physiologie der Alkaloide, Halle (Salle)," Vol. 4, K. Mothes, K. Schreiber, and H. R. Schutte, Ed., Akademie-Verlag, Berlin, 1969, pp 77, 78.
(6) S. Danishefsky, S. J. Etheredge, R. Volkmann, J. Eggler, and J. Quick, *J. Amer. Chem. Soc.*, **93**, 5575 (1971).
(7) R. Volkmann, S. Danishefsky, J. Eggler, and D. M. Solomon, *J. Amer. Chem. Soc.*, **93**, 5576 (1971).
(8) S. Danishefsky, R. Volkmann, and S. B. Horwitz, *Tetrahedron Lett.*, 2521 (1973).
(9) E. Bertele, H. Boos, J. D. Dunitz, F. Elsinger, A. Eschenmoser, I. Felner, H. P. Griki, H. Gschwend, E. Meyer, M. Pesaro, and R. Schaffold, *Agnew. Chem. Int. Ed. Engl.*, **3**, 490 (1964).
(10) J. Cymmerman Craig and M. J. Moyle, *J. Chem. Soc.*, 5356 (1963).
(11) Private communication, Professor Susan B. Horwitz, Department of Pharmacology, Albert Einstein College of Medicine.
(12) This was assigned to the sample first submitted by Professor Rapoport.
(13) We wish to thank Dr. Robert Engle, National Cancer Institute, National Service Center, Drug Development Brand, Bethesda, Md., for expediting these studies.
(14) Melting points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Model 247 spectrophotomer. Nmr spectra were measured on a Varian Associates T-60 spectrometer with tetramethylsilane as the internal standard. Combustion analysis were performed by Galbraith Laboratories, Knoxville, Tenn.
(15) Z. Horii, K. Morikawa, and I. Ninomiya, *Chem. Pharm. Bull.*, 2230 (1969).
(16) Two other runs afforded **3** in yields of 44 and 26%.

The Chemistry of 2-Alkoxy-3,4-dihydro-2*H*-pyrans. II. Addition of Dimethyl Acetylenedicarboxylate to 2-Alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans

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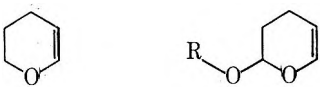
Received May 29, 1974

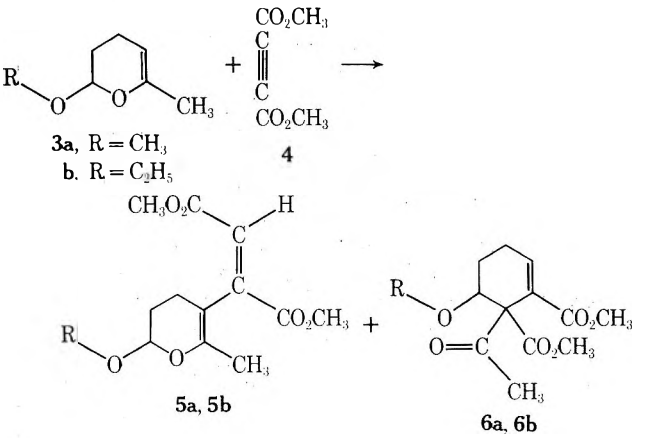
The introduction of an alkoxy group at the 2 position of 3,4-dihydro-2*H*-pyran (**1**) drastically alters the chemistry of the title compounds, 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2**), as compared to the parent compound, 3,4-dihydro-2*H*-



1 **2**

pyran (**1**). This can be most dramatically appreciated by comparing the addition of tetracyanoethylene,[1] condensation with benzenesulfonyl azide,[2] and oxidation by *m*-chloroperbenzoic acid,[3,4] with 3,4-dihydro-2*H*-pyran (**1**) and 2-alkoxy-3,4-dihydro-2H-pyrans (**2**).[5] Herein we wish to report yet another unusual reaction of the title pyrans with dimethyl acetylenedicarboxylate.

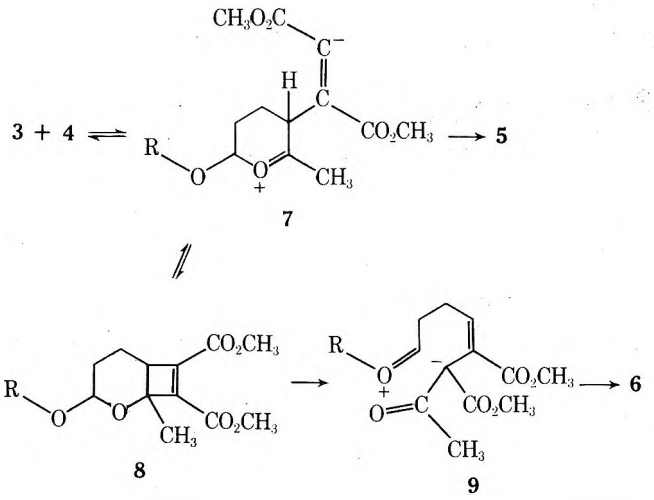
Refluxing a toluene solution of 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3a**) and dimethyl acetylenedicarboxylate (**4**) for 65 hr afforded a mixture of 2-methoxy-5-(dimethylfumaryl)-6-methyl-3,4-dihydro-2*H*-pyran (**5a**)[6] and dimethyl 2-acetyl-3-methoxycyclohex-6-ene-1,2-dicarboxylate (**6a**) in a ratio of 1:1 (glpc). Similar results were obtained with 2-ethoxy-6-methyl-3,4-dihydro-2*H*-pyran (**3b**).



3a, R = CH_3
b, R = C_2H_5
4
5a, 5b
6a, 6b

The assigned structures of the two products are consistent with the spectral data and composition analyses. The isolated yields are presumably low owing to the lability of 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans.[7]

The above reactions might best be described as involving the intermediacy of zwitterion **7**, analogous to intermediates invoked in enamine chemistry,[8] which can lead to product **5** by proton transfer or to the cyclobutene intermediate **8** by cyclization. The cyclobutene intermediate **8**, similar to that proposed as intermediates in reactions of ketene diethyl acetal[9] and enamines[8b,10] with acetylenic esters, can subsequently rearrange to **6**. Frequent monitoring (glpc) of the reaction indicated that no stable intermediate accumulated, and resubjecting products **5** and **6** to the conditions confirmed that each is a true end product of the reaction.



In addition, we have found in a study of related compounds that the parent 3,4-dihydro-2*H*-pyran (**1**) and the closely related 2-alkoxy-3,4-dihydro-2*H*-pyrans (**2**) are inert to these reaction conditions, suggesting a remarkable effect of the 6-methyl group, which had been noted in the peracid studies,[4] on the reactivity of these compounds.[11]

Experimental Section[12]

The 2-alkoxy-6-methyl-3,4-dihydro-2*H*-pyrans (**3**) were prepared as reported.[5a,b] In all the experiments described below, the toluene was freshly distilled from CaH_2 and the reaction mixtures were degassed prior to refluxing under a static argon atmosphere. The progress of the reactions were monitored by thin layer chromatography (tlc) and by gas chromatography (glpc) on a Hewlett-Packard Model 7610A high-efficiency chromatograph (flame detector) using a 4 ft × 6 mm (all glass) 4% silicone gum rubber UCC-W-982 (methylvinyl) on 80–100 HP Chromosorb W (AW, DMCS) column and a 4 ft × 6 mm (all glass) 1% silicone gum rubber OV-1 (methyl) on 80–100 HP Chromosorb W (AW, DMCS) column. Column chromatography of the product mixtures was performed on Woelm neutral aluminum oxide (activity grade III) and eluted with petroleum ether and petroleum ether–Et_2O. Further purification, when necessary, was accomplished using a Büchi kugelrohr bulb to bulb distillation apparatus at reduced pressure. All boiling points are uncorrected.

Reaction of 2-Methoxy-6-methyl-3,4-dihydro-2*H*-pyran (3a) with Dimethyl Acetylenedicarboxylate (4). A solution of 2-methoxy-6-methyl-3,4-dihydro-2*H*-pyran (1.41 g, 11 mmol) and dimethyl acetylenedicarboxylate (1.42 g, 10 mmol) in toluene (8 ml) was refluxed for 65 hr. The solvent was then removed *in vacuo* and the residue (2.65 g) after repeated chromatography yielded 450 mg (17%) of **5a** as a yellow liquid, a mixture which contained 48 mg (2%) of **5a** and 259 mg (10%) of **6a**, and 231 mg (8%) of **6a** as a pale yellow liquid (mixture of geometric isomers).

2-Methoxy-5-(dimethylfumaryl)-6-methyl-3,4-dihydro-2*H*-pyran (**5a**): bp 135–140° (0.2 mm); ir (film) 1725 cm^{-1}; uv (EtOH) λ_{max} 204 nm (ϵ 15,250), 332 (815); nmr (220 MHz, CCl_4) δ 6.71 (1 H, H, s), 4.89 (1 H, t, J = 3 Hz), 3.75 (3 H, s), 3.69 (3 H, s), 3.43 (3 H, s), 2.27–2.09 (1 H, m), 2.09–1.91 (1 H, m), 1.91–1.77 (2H, m), 1.56 (3 H, perturbed s); mass spectrum *m/e* (rel intensity) 270 (M^+, 8), 239 (8), 238 (19), 195 (23), 179 (17), 147 (21), 75 (38), 71 (31), 58 (100), 43 (96).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.79; H, 6.63.

Dimethyl 2-Acetyl-3-methoxycyclohex-6-ene-1,2-dicarboxylate (**6a**): ir (film) 1720 cm^{-1}; uv (EtOH) λ_{infl} 215 nm (ϵ 8,815); nmr (60 MHz, $CDCl_3$) δ 7.17 (1 H, t, J = 4 Hz), 4.03 (1 H, d of d, J = 5 and 4 Hz), 3.78 (3 H, s), 3.74 (3 H, s), 3.39 (3 H, s), 2.41 (3 H, s), 2.38–2.10 (2 H, m), 2.08–1.78 (2 H, m); mass spectrum *m/e* (rel intensity) 270 (M^+, 2), 238 (10), 196 (76), 165 (74), 164 (67), 163 (100), 137 (31), 105 (40), 77 (36), 59 (40), 43 (16).

Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 58.04; H, 7.00.

Reaction of 2-Ethoxy-6-methyl-3,4-dihydro-2*H*-pyran (3b) with Dimethyl Acetylenedicarboxylate (4). A solution of 2-ethoxy-6-methyl-3,4-dihydro-2*H*-pyran (1.57 g, 11 mmol) and dimethyl acetylenedicarboxylate (1.42 g, 10 mmol) in toluene (8 ml) was refluxed for 65 hr. The solvent was removed *in vacuo* and the residue (3.0 g) after repeated chromatography yielded 493 mg (17%) of **5b** as a yellow liquid, a mixture which contained 170 mg (6%) of **5b** and 177 mg (6%) of **6b**, and 520 mg (18%) of **6b** as a pale yellow liquid (mixture of geometric isomers).

2-Ethoxy-5-(dimethylfumaryl)-6-methyl-3,4-dihydro-2*H*-pyran (**5b**): bp 140–145° (0.2 mm); ir (film) 1725 cm^{-1}; uv (EtOH) λ_{max} 208 nm (ϵ 10,360), λ_{infl} 295 nm (ϵ 500); nmr (220 MHz, CCl_4) δ 6.72 (1 H, s), 4.99 (1 H, t, J = 3 Hz), 3.86 (1 H, q, J = 7 Hz), 3.76 (3 H, s), 3.70 (3 H, s), 3.57 (1 H, q, J = 7 Hz), 2.32–2.11 (1 H, m), 2.11–2.91 (1 H, m), 1.91–1.77 (2 H, m), 1.55 (3 H, perturbed s), 1.21 (3 H, t, J = 7 Hz); mass spectrum *m/e* (rel intensity) 284 (M^+, 4), 239 (4), 238 (8), 225 (4), 207 (11), 195 (14), 181 (17), 147 (18), 89 (24), 72 (61), 59 (16), 43 (100).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.27; H, 6.95.

Dimethyl 2-Acetyl-3-ethoxycyclohex-6-ene-1,2-dicarboxylate (**6b**): ir (film) 1720; uv (EtOH) λ_{infl} 210 nm (ϵ 14,480); nmr (100 MHz, $CDCl_3$) δ 7.16 (1 H, t, J = 4 Hz), 4.08 (1 H, d of d, J = 6, 4 Hz), singlets at 3.68 (3 H, s) and 3.66 (3 H, s) superimposed on an apparent quartet at 3.64 (1 H, q, J = 7 Hz), two overlapping quartets at 3.38 and 3.36 (1 H, d of q, J = 7 Hz), a singlet at 2.36 (3 H, s) superimposed on a multiplet at 2.42–2.16 (2 H, m), 1.92–1.68 (2 H, m), overlapping triplets at 1.18 and 1.13 (3 H, t, J = 7 Hz); mass spectrum *m/e* (rel intensity) 284 (M^+, 1), 253 (6), 196 (100), 165 (32), 164 (58), 163 (53), 137 (12), 105 (8), 77 (3), 59 (4), 43 (11).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 7.09. Found: C, 59.10; H, 6.98.

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Registry No.—**3a**, 28194-35-6; **3b**, 52438-71-8; **4**, 762-42-5; **5a**, 52438-72-9; **5b**, 52438-73-0; *cis*-**6a**, 52438-74-1; *trans*-**6a**, 52438-75-2; *cis*-**6b**, 52438-76-3; *trans*-**6b**, 52438-77-4.

References and Notes

(1) J. K. Williams, D. W. Wiley, and B. C. McKusick, *J. Amer. Chem. Soc.*, **84**, 2210 (1962).
(2) J. E. Franz, D. M. Dietrick, A. Henshall, and C. Osouch, *J. Org. Chem.*, **31**, 2847 (1966).
(3) F. Sweet and R. K. Brown, *Can. J. Chem.*, **45**, 1007 (1967).
(4) S. S. Hall and H. C. Chernoff, *Chem. Ind. (London)*, 896 (1970), which is part I in this series.
(5) For the general method of preparation see (a) R. I. Longely, Jr., and W. S. Emerson, *J. Amer. Chem. Soc.*, **72**, 3079 (1950); (b) C. W. Smith, D. G. Norton, and S. A. Ballard, *ibid.*, **73**, 5267 (1951); (c) K. Ryoji, O. Hiroski, A. Nakamura, and K. Fukuda, Japanese Patent 7,368,573 (1973) and German Patent 2,163,515 (1973).
(6) Comparison of the δ values for the vinyl proton of methyl citraconate (5.77 ppm) and methyl mesaconate (6.68 ppm) shows the effect of a group on the malonate and fumarate system [see R. R. Fraser and D. E. McGreer, *Can. J. Chem.*, **39**, 505 (1961)] and served as a basis for the assigned trans stereochemistry.
(7) The 2-alkoxy-3,4-dihydro-2*H*-pyrans are extremely sensitive compounds and are easily hydrolyzed [W. S. Johnson, Ed., Org. Syn., **34**, 71 (1954)] and polymerized.[5a]
(8) (a) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963); (b) C. F. Huebner, L. Dorfman, M. M. Robison, E. Donoghue, W. P. Pierson, and P. Strachan, *J. Org. Chem.*, **28**, 3134 (1963).
(9) K. C. Brannock, R. D. Burpitt, and J. G. Thweatt, *J. Org. Chem.*, **28**, 1697 (1963).
(10) (a) G. A. Berchtold and G. F. Uhlig, *J. Org. Chem.*, **28**, 1459 (1963); (b) K. C. Brannock, R. D. Burpitt, V. W. Goodlett, and J. G. Thweatt, *ibid.*, **28**, 1464 (1963).
(11) We have found, in a related study that will be published, the order of reactivity of these compounds to be **3** > **1** > **2** in competitive electrophilic addition reactions with *tert*-butyl hypochlorite in alcohol.
(12) The ir spectra were determined with a Perkin-Elmer Model 237B ir recording spectrophotometer and a Beckman Model IR-10 ir recording spectrophotometer. The uv spectra were determined with a Cary Model 14 recording spectrophotometer. The nmr spectra were determined at 60 MHz with a Varian Associates Model T-60 nmr spectrometer, at 100 MHz with a Varian Associates Model HA-100 nmr spectrometer, and at 220 MHz with a Varian Associates Model HR-220 nmr spectrometer. The chemical shift values are expressed in δ values (parts per million) relative to a Me_4Si internal standard. The mass spectra were obtained with a Consolidated Electronics Corporation Model 110-21B mass spectrometer and a LKB Model 9000 mass spectrometer.

Condensation of Benzoylcyanamide with Aromatic Amino Esters, Acids, and Amides

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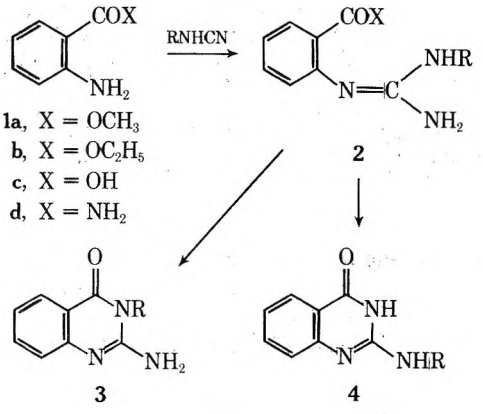
The condensation of alkyl and aryl cyanamides with methyl anthranilate (**1a**) has been shown to give two possible products, **3** and **4** (Scheme I). The distribution of these two products varies dramatically with changes in the substituent, examples being found where **4** was the sole product.[2]

Scheme I



Previous work in this laboratory had shown that benzoylcyanamide and anthranilic acid reacted to give what appeared to be a single product, which was not completely characterized.[3] When this investigation was continued, a white crystalline material was obtained from the condensation of benzoylcyanamide (*N*-cyanobenzamide) with either anthranilic acid (**1c**), ethyl anthranilate (**1b**), or anthranilamide (**1d**). This material analyzed for $C_{15}H_{11}N_3O_2$, and the nmr and ir spectra (Table I) indicated that the compound was 2-amino-3-benzoyl-4(3*H*)-quinazolinone (**7**) (Scheme II). The mass spectrum (70 eV) gave a molecular ion at *m/e* 265, verifying the molecular weight (calcd, 265). In addition to the spectral evidence, the insolubility of the material in alkali indicated that it was not the isomeric 2-benzamido-4(3*H*)quinazolinone (**4**, R = COPh).

Scheme II

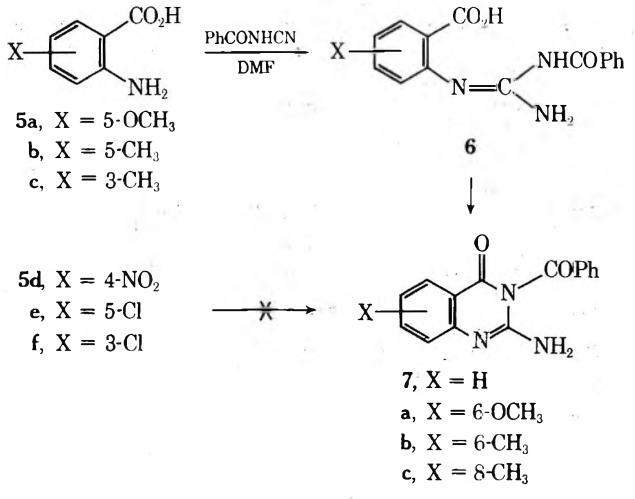


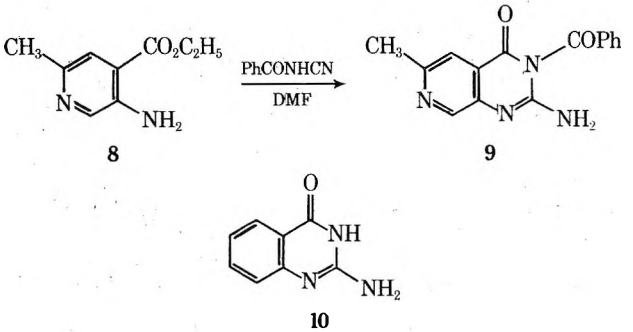
Table I
Ir and Nmr Spectra of Products

Product	Ir max, cm^{-1} [a]	Nmr, δ, ppm [b]
7	3175, 3060, 1675, 1645, 1610, 1275	7.28–7.93 (m, 6), 8.05–8.38 (m, 3), 12.40 (br, 2)
7a	3200–2930, 1680, 1655, 1630–1615, 1030	3.99 (s, 3), 7.61–7.99 (m, 6), 8.29–8.55 (m, 2), 12.42 (br, 2)
7b	3190, 3050, 1685, 1665, 1635, 1280	2.48 (s, 3), 7.48–7.95 (m, 5), 8.00–8.50 (m, 3), 12.35 (br, 2)
7c	2990, 1680, 1640, 1625, 1610, 1585, 1560	2.57 (s, 3), 7.38 (t, *J* = 7 Hz, 1), 7.47–7.88 (m, 4), 7.98–8.43 (m, 3), 12.38 (br, 2)
9	3200, 3110, 3050, 1680, 1660–1610, 1270	2.60 (s, 3), 7.60–7.90 (m, 3), 7.85 (s, 1), 8.10–8.40 (m, 2), 8.95 (s, 1), 12, 40 (br, 2)

[a] Obtained as KBr pellets. [b] Spectra obtained in DMSO-d_6/$CDCl_3$ (70/30, v/v) solutions, with TMS as an internal standard.

Further investigation of the synthetic utility of this condensation was suggested by the fact that only one isomer (**7**) was isolated, and the yields (Table II) were equal to or greater than the best yields reported by Grout and Partridge.[2] A variety of anthranilic acids possessing electron-donating groups (**5a,b,c**) reacted as expected, and reasonable yields (Table II) of the 2-amino-3-benzoyl-4(3*H*)-quinazolinones (**7a,b,c**) were obtained. Once again, only one isomer was isolated in these condensations. The presence of electron-withdrawing groups on anthranilic acid apparently decreased the nucleophilicity of the aromatic amine, since no products were observed with **5d–f**.[4]

Condensation of a few heterocyclic amino esters, acids, and amides with benzoylcyanamide was then examined. 2-Methyl-4-carbethoxy-5-aminopyridine (**8**) gave the corresponding 2-amino-3-benzoyl-6-methylpyrido[3,4-*d*]pyrimidin-4(3*H*)-one (**9**) in reasonable yield (Table II). Ethyl 2-



aminonicotinate and 2-aminonicotinic acid failed to react, presumably because of the non-nucleophilic character of some 2-aminopyridine derivatives.[5] 2-Amino-3-carbethoxy-4-methylthiophene and 2-amino-3-carbamyl-4,5-dimethylfuran[6] decomposed rapidly, giving intractable materials upon work-up. Further compounds are presently being investigated in an effort to determine what systems will undergo this condensation.

In addition to observing the products and scope of this condensation, mild conditions for hydrolysis[3] were devel-

Table II

Substrate	Reaction time, hr.	Product[a]	Mp, °C	Yield, %[b]
1b	48	7	188.5–190	58
1c	48	7		45
1d	48	7		57
5a	20	7a	203–204	57, 62[c]
5b	20	7b	209.5–210.5	24, 39[c]
5c	27	7c	226–227	21, 24[c]
8	20	9	269–270.5	35, 43[c]

[a] Satisfactory analyses (±0.4% for C, H, N) were reported for compounds 7, 7a–c, and 9: Ed. [b] Based upon substrate. [c] Based upon unrecovered substrate.

oped that allowed conversion of 7 to the corresponding 2-amino-4(3*H*)-quinazolinone (10) in 86% yield.

Experimental Section

Melting points were taken on a Fisher-Johns melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained on a Jeol C60HL spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 257 spectrophotometer. The mass spectrum was obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer. The ultraviolet spectrum was obtained on a Unicam SP-800B spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. The dimethylformamide (DMF) used as solvent was reagent grade and was stored over 4A molecular sieves (Linde). The benzoylcyanamide[7] was recrystallized from benzene/petroleum ether (30–60) and had a melting point of 139–40° dec (lit.[7] 143°).

Synthesis of 7, 7a–c, and 9. Two millimoles of the amino ester, acid, or amide were dissolved in 10 ml of DMF and benzoylcyanamide (146 mg, 1 mmol) was added. The solution was stirred and heated at 90–95° for 5 hr, then an additional 1 mmol of benzoylcyanamide was added and stirred until this portion had completely reacted (tlc). The solution was then concentrated (*in vacuo*) to a volume of 3–4 ml and poured into 5–10 ml of 95% ethanol, which was then poured into 35 ml of ice water. The mixture was stirred overnight, cooled, filtered, and washed with water. A further washing of the solid material with diethyl ether removed any of the unreacted substrates studied, which could then be recovered. The powdered material remaining was recrystallized from 70% ethanol (Norit). Analytical samples were recrystallized twice. Yields (based upon powdered material) and melting points are listed in Table II.

Hydrolysis of 7. Fifty milligrams of an analytical sample of 7 was heated on a steam bath with 3 ml of 0.5 *N* sodium hydroxide for 15 min. Complete dissolution required approximately 10 min. The solution was filtered hot (Norit), then allowed to cool, and acidified to pH 5.5–6.0 with acetic acid. The fine white powder (86%) was filtered, washed with water and ether, and dried *in vacuo*. Purification was achieved by dissolution in dilute alkali and reprecipitation with acetic acid. The uv spectrum of 10 (95% ethanol) was identical with that reported.[8]

Registry No.—**1b,** 87-25-2; **1c,** 118-92-3; **1d,** 88-68-6; **5a,** 6705-03-9; **5b,** 2941-78-8; **5c,** 4389-45-1; **7,** 52393-73-4; **7a,** 52393-74-5; **7b,** 52393-75-6; **7c,** 52393-76-7; **8,** 52393-72-3; **9,** 52393-77-8; benzoylcyanamide, 15150-25-1.

References and Notes

(1) NDEA Title IV Fellow, 1973.
(2) R. J. Grout and M. W. Partridge, *J. Chem. Soc.*, 3540 (1960).
(3) C. E. Cook, Ph.D. Thesis, The University of North Carolina, Chapel Hill, N.C., 1960.
(4) Reaction of 3-methoxyanthranilic acid gave an anomalous product whose analysis corresponded to $C_{24}H_{22}N_4O_6$, suggesting the product was derived from 2 equiv of the anthranilic acid and one equivalent of benzoylcyanamide. A complete structure proof has not been accomplished, because of the lack of additional structural evidence.
(5) S. J. Angyal and C. L. Angyal, *J. Chem. Soc.*, 1461 (1952).
(6) J. L. Isidor, Ph.D. Thesis, The University of North Carolina, Chapel Hill, N.C., 1971.
(7) W. Buddeus, *J. Prakt. Chem.*, **42**, 84 (1890).
(8) P. Grammaticakis, *C. R. Acad. Sci.*, **247**, 2013 (1958).

Photochemical and Thermal Internal Cycloadditions in *retro*-γ-Ionylidenemalononitrile

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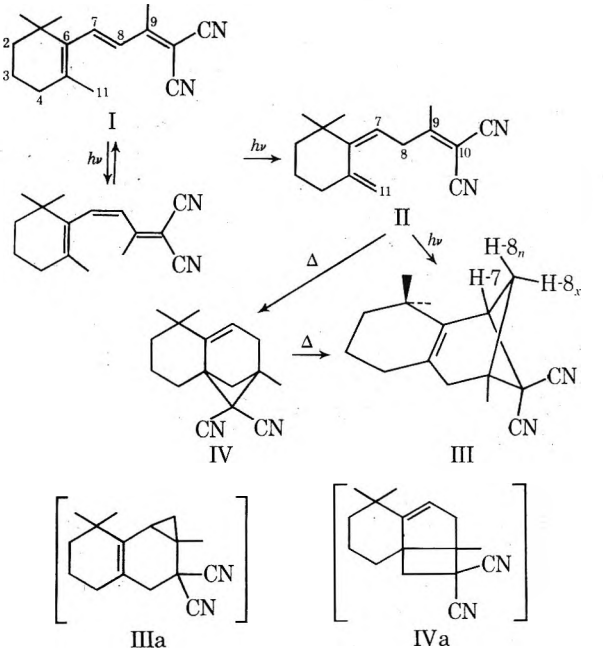
In connection with studies of hindered 7-cis isomers of retinal analogs,[1] we have reinvestigated reactions from direct irradiation of several dienes and trienes in this series. Similar to previous reports,[2] we observed in most cases primarily rapid, reversible geometric isomerization, electrocyclization (trienes), and irreversible 1,5-sigmatropic hydrogen migration products (dienes and trienes). Therefore, with a typical ionylidene derivative during the initial period of irradiation a mixture of 7,8 and 9,10 geometric isomers is produced,[2,3] along with less efficient formation of a cyclohexadiene, all of which eventually disappear to give the final product, a *retro*-γ-ionylidene derivative. However, in one instance we observed an additional secondary photoreaction and unexpected thermal rearrangements. These are described below.

retro-γ-Ionylidenemalononitrile (II) is the principal end product from direct irradiation of a dilute ether solution of β-ionylidenemalononitrile (I) when light of >360 nm (Corning 0-51 filter) is used. Upon further irradiation with light >290 nm (Pyrex filter) a new photoproduct is formed. The spectroscopic properties of the product, after its isolation by column chromatography (silica gel), suggest that it is formally an internal 4 + 2 cycloadduct, III.[4]



The mass spectrum of III shows that it is isomeric to I and II (*m/e* for M^+ 240). The compound is clearly not a cyclohexadiene because of the absence of vinyl hydrogens from its nmr and ir spectra. The pmr spectrum is in fact quite indicative of the structure. The three methyl groups (δ 1.17, 1.19, and 1.35) are now nonequivalent as expected for III. A broad singlet at δ 2.32, attributable to the allylic hydrogens at C-11, overlaps with a quartet (d of d) at 2.38. The latter ($H\text{-}8_{exo}$) is shown by double irradiation to couple with two single H's at 3.19 (d, J = 8.5 Hz, H-7) and 1.51 (d, J = 6.0 Hz, $H\text{-}8_{endo}$). This pattern of coupling is in agreement with compounds of a bicyclo[*n*.1.1] structure in which the bridgehead hydrogens are known to couple only with

the exo hydrogen of the methylene bridge (endo hydrogen being orthogonally oriented to the bridgehead hydrogen).[5] The alternative 4 + 2, head-to-head adduct (IIIa), though also not containing any vinyl hydrogens, cannot account for this pattern of coupling of three hydrogens and also the H-11's would appear at a much lower field. Also, consistent with structure III, the ^{13}C nmr spectrum of the photoproduct shows the presence of two quaternary olefinic carbons at δ 140.4 and 129.3, two cyano carbons at δ 115.9 and 112.9, and three aliphatic quaternary carbons at δ 49.0 (C-9), 41.2 (C-1), and 19.2 (C-10) along with other methyl, methylene, and methine carbon signals. Finally, structure III also accounts for the peaks at *m/e* 121 and 62 in its mass spectrum. The cyclopropenyl cation formed by the loss of the cyclobutane ring and an allylic hydrogen probably corresponds to the 121 peak and the associated metastable peak should have a *m/e* 62.

This reaction appears to have some generality because in a similar manner 3,4-dehydro-I gives 3,4-dehydro-III as the only end product: nmr, three methyl singlets at δ 1.08, 1.11, and 1.47, three coupled H's at 1.66 (d, J = 10.0 Hz, H-8_{endo}), 2.58 (d of d, J = 5.0, 10.0 Hz, H-8_{exo}), and 3.44 (d, J = 5.0 Hz, H-7), a broad methylene singlet at 2.56, and a singlet for two vinyl H's at 5.28 ppm.

Upon heating to 100°, II rearranges to three products: I (5%), III (35%), and a new isomeric compound, IV (60%). The formation of I is in line with other *retro*-γ-ionylidene compounds.[6] The nmr spectrum of the major product shows the presence of methyl singlets at δ 1.17, 1.19, and 1.35, a complex group of signals for 6 H's between δ 1.4 and 2.0. Most indicative of the structure is the presence of a vinyl hydrogen (t, δ 5.74, J = 3.0 Hz) coupled with two H's at δ 2.42 and two coupled hydrogens at 1.61 (d, J = 9.0 Hz) and 1.91 (d). These features are only consistent with a structure from 2 + 2 internal cycloaddition of II. Of the two possible structures (IV and IVa) we favor the head-to-tail adduct IV because of the chemical shifts of coupled methylene hydrogens being too high for hydrogens adjacent to a dicyanomethylene group and more importantly upon heating to 180°, IV undergoes further rearrangement to III. From structure IV, 1,3 migration of the dicyanomethylene group gives III, while from IVa, there is no direct pathway to III.

The unusual photo and thermal chemical properties of II are probably associated with the dicyano group. That electrocyclic products are not formed in direct irradiation reaction must be due to the absence of a di-s-cis conformer necessary for cyclization due to unfavorable steric interaction.[3] The internal cycloadditions are probably associated with the electron deficient property of the 9,10 double bond. It is interesting to note that the directions of addition (4 + 2 or 2 + 2) for the major products in thermal and photochemical reactions are opposite to those normally encountered in cycloaddition reactions. At this time it is not clear whether these cycloadditions are from concerted or stepwise processes. If concerted, the photochemical and thermal reactions must have proceeded by way of $_{\pi}4_s + _{\pi}2_a$ ($_{\pi}4_a + _{\pi}2_s$) and $_{\pi}2_s + _{\pi}2_a$ additions.[7] Such mechanistic and stereochemical questions can be answered with compounds of defined stereochemistry at C-9 and C-10.

Experimental Section

All pmr spectra were recorded on a Varian HA-100 spectrometer and cmr spectra on a Varian XL-100 spectrometer. Deuterated chloroform was used as solvent and TMS as internal standard.

retro-γ-**Ionylidenemalononitrile (II).** A 10% ether or chloroform solution of β-ionylidenemalononitrile (I)[1b] was sealed in a Pyrex test tube and irradiated with a 200-W Hanovia medium pressure mercury lamp equipped with a Corning 0-51 filter. Progress of reaction was followed by nmr. After 2 days the reaction was complete. The major product was identified as the *retro*-γ-triene II by its nmr spectrum: 1 H (t, J = 7.0 Hz) at 4.90 ppm coupled with 2 H's at 3.19; two additional vinyl hydrogens at 4.48 and 4.98 ppm. Another minor product was also present in the irradiation mixture. The compound, however, was not isolated nor identified. Conditions of photochemical and thermal reactions of II are described in the text.

3,4-Dehydro-β-ionylidenemalononitrile. In 200 ml of CCl_4, 24 g of I was allowed to react with 17.8 g of NBS with 0.5 g of benzoyl peroxide. The nmr spectrum of the product agreed with that of 4-bromo-β-ionylidenemalononitrile. The crude product was allowed to react with a mixture of *N,N*-dimethylaniline (70 ml) and pyridine (30 ml) at 95°. After the usual work-up, the crude product was purified by column chromatography (silica gel with benzene as solvent). The overall yield of 3,4-dehydro-β-ionylidenemalononitrile is 50%: ir (film) 2220, 970, and 730 cm^{-1}; nmr δ 1.12 (s, 6 H), 1.96 (s, 3 H), 2.32 (s, 3 H), 5.92 (s, 2 H), 6.90 (d, J = 16 Hz, 1 H), 7.14 (d, 1 H).

Conditions for photochemical reactions of the tetraenenitrile are similar to those described for I.

Acknowledgment. This work was partially supported by a grant from the Public Health Services (EY-AM 00918). Cmr spectra were obtained by Mr. J. Loo on a Varian XL-100 instrument made available through a NSF-DSD grant (GU 3855).

Registry No.—I, 52699-42-0; 3,4-dehydro-I, 52665-36-8; II, 52665-37-9; III, 52665-38-0; 3,4-dehydro-III, 52665-39-1; IV, 52665-40-4; 4-bromo-β-ionylidenemalononitrile, 52665-41-5.

References and Notes

(1) (a) V. Ramamurthy and R. S. H. Liu, *J. Amer. Chem. Soc.*, **96**, 5625 (1974); (b) V. Ramamurthy, G. Tustin, C. C. Yau, and R. S. H. Liu, *Tetrahedron*, in press; (c) V. Ramamurthy and R. S. H. Liu, *Tetrahedron*, in press; (d) V. Ramamurthy, Y. Butt, C. Yang, P. Yang, and R. S. H. Liu, *J. Org. Chem.*, **38**, 1247 (1973).
(2) See, *e.g.*, M. Mousseron, *Advan. Photochem.*, **4**, 195 (1966).
(3) V. Ramamurthy and R. S. H. Liu, *Tetrahedron Lett.*, 1393 (1973).
(4) *retro*-γ-Ionone was recently shown to undergo a photochemical 2 + 2 internal addition: A. van Wageningen and H. Cerfontain, *Tetrahedron Lett.*, 3679 (1972).
(5) See, *e.g.*, K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Amer. Chem. Soc.*, **84**, 1594 (1962).
(6) Other *retro*-γ-ionylidene derivatives including ionylideneacetonitrile thermally reverse back to conjugated triene isomers without forming any cycloadducts (unpublished results of V. Ramamurthy).
(7) See, *e.g.*, R. B. Woodward and R. Hoffmann, "The Conservatior of Orbital Symmetry," Academic Press, New York, N. Y., 1970.

Biological Probes. II. Ring Labeled Nicotinamide

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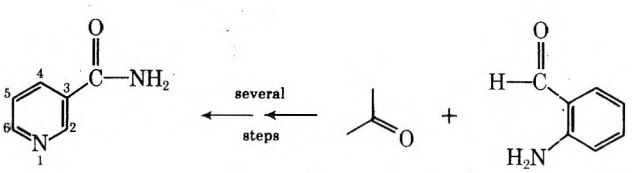
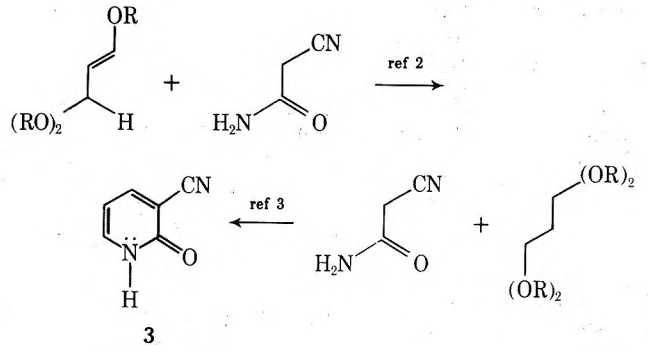
A growing interest in nonradioactive labels for use as general biological probes has led us to the development of efficient methods for the preparation of ring labeled nicotinamide (1). Previously we had described a high yield, six-step synthesis of $^{13}C_6$-amide 1 starting with carbon-13 labeled acetone.[1] We now wish to report a versatile labeling



1 (50% from 2) 2

technique that can be applied to regiospecific labeling of pyridines and one which constitutes a vast improvement in the synthesis of 2-halonicotinic acid derivatives. Initially,



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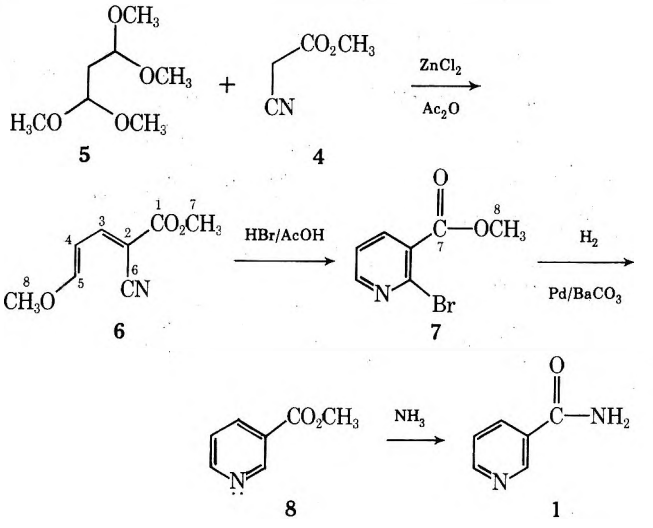
we had hoped to use the known 3-cyano-2-pyridone (3) as a precursor of amide 1 since the preparation of this pyridone 3 proceeds from readily accessible malonic acid derivatives. Unfortunately, neither the procedure of Dornow[2] nor that of Protopopova[3] could be modified to give a suitable yield of 3. High yield preparations of pyridines were finally realized through the reaction sequence in Scheme I.

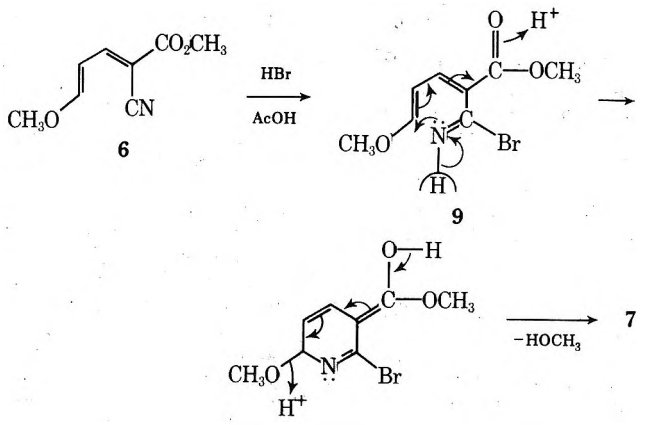
Scheme I



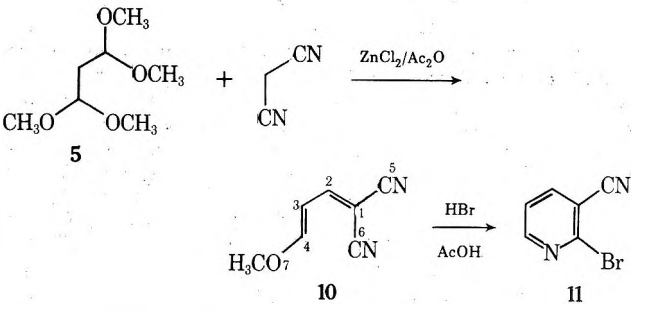
The zinc chloride catalyzed condensation of methyl cyanoacetate (4) and 1,1,3,3-tetramethoxypropane (5) in acetic anhydride afforded enol ether 6 (90%).[4] Ether 6, on treatment with HBr in acetic acid, undergoes a very facile intramolecular cyclization–elimination reaction forming methyl 2-bromonicotinate (7, 97%).[5] This ester 7 was converted to the desired amide 1 by catalytic hydrogenation (7 → 8, 93%) followed by treatment with aqueous ammonia (8 → 1); thus providing a convenient, high yield conversion of methyl cyanoacetate to nicotinamide (1, 60% from 5).

Presumably, this cyclization reaction is initiated by addition of HBr to the nitrile group of 6, forming iminobromide 9 (below) which, in turn, could add to the terminus of the conjugated ester system in a Michael-like reaction. Bromopyridine 7 would then be formed by simple elimination of methanol. It is interesting to note that the pmr and cmr spectrum of enol ether 6 indicated the presence of only one of several possible geometric isomers,[6] a fact which might fortuitously account for the nearly quantitative conversion of 6 to 7. It would seem more likely that under these strongly acidic conditions (HBr/AcOH) the geometry of the conjugated enol ether–nitrile is of little consequence.

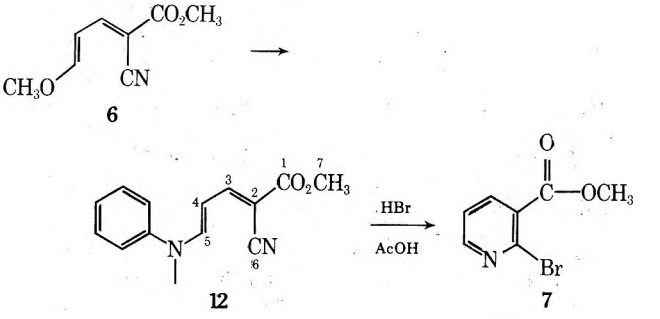
The reaction sequence operates with equal facility in forming 2-bromonicotinonitrile (11) from malononitrile.



The intermediate enol ether 10 likewise appears to be only one of two possible isomers and cyclizes to give bromonitrile 11 as the only product in high yield; thus demonstrating the ease by which various halopyridines can be prepared.



There are indications in the literature[7] that conjugated enamines analogous to ether 6 undergo similar acid-catalyzed cyclizations. To test this possibility methyl 2-cyano-5-*N*-methylanilino-2,4-pentadienoate (12)[8] was prepared by treating ether 6 with *N*-methylaniline in refluxing methanol (88% yield). Enamine 12 smoothly forms methyl 2-bromonicotinate (7) under the same acid conditions (HBr/AcOH) in high yield (87%).



The availability of methyl cyanoacetate specifically labeled at various positions with either ^{13}C and/or ^{15}N enhances the versatility of the procedure described above. Accordingly, nicotinamide-2-^{13}C has been prepared in excellent yield in four steps from methyl cyanoacetate[9] (^{13}C-nitrile labeled) and corresponding nmr labels at positions one and three of amide 1 are close at hand. In addition labeled nicotinamide (1) has been incorporated into NAD^+ through biosynthetic techniques.[1] Finally we note that (labeled or unlabeled) methyl 2-bromonicotinate can be readily converted into 2-aminonicotinic acid derivatives and similar structures[10] which are important antiinflammatory agents and therefore this facile enol ether cyclization provides a convenient synthetic route to a variety of important medicinal agents. Other aspects concerning the generality of this enol ether–nitrile cyclization will be forthcoming.

Experimental Section

Mass spectra or satisfactory elemental analysis was obtained for all compounds. Melting points were obtained on a Fisher-Johns hot stage melting point apparatus and are uncorrected. All boiling points reported are for bulb to bulb distillations and are the oven temperature recorded unless otherwise indicated. Coupling constants (J) are reported in Hz.

Methyl 2-Cyano-5-methoxy-2,5-pentadienoate (6). A mixture of tetramethoxypropane (12.3 g), acetic anhydride (25 ml), and $ZnCl_2$ (68 mg) was heated under reflux and methyl cyanoacetate (4.95 g, 0.5 mol) was added dropwise. Reflux was maintained for 18 hr after which the volatiles were distilled out until the distillation temperature reached 122°. The residue was cooled and filtered. The filtrate solidified on standing. The solid was distilled (Kugelrohr oven, 0.1 m) affording a yellow oil (bp 90°), acetate of diacetal 4 and a yellow solid (**6**, 7.5 g, 90%) 110–140° (partial decomposition): pmr $\delta_{TMS}(CDCl_3)$ 7.92 (d, J = 13, 1 H, C_3H), 7.42 (d, J = 13, 1 H, C_5H), 6.11 (t, J = 13, 1 H, C_4H) 3.95 and 3.89 (s and s, 6 H's, $-OCH_3$'s); ir (CH_2Cl_2) 2250, 1720, 1615 cm^{-1}; cmr (relative TMS, CH_2Cl_2 ppm) 117.03 (labeled CN); 167.3 (C_5), 164.1 (C_1), 156.2 (C_5), 117.0 (C_6), 104.0 (C_4), 99.0 (C_2), 59.7 (C_8), 53.5 (C_7); ir (C_7); ir (CH_2Cl_2) 2235, 1720, 1620, 1560 cm^{-1}.

Methyl 5-(*N*-Methylanilino)-2-cyano-2,4-pentadienoate. Enol ether (**6**, 5.0 g, 0.03 mol) was dissolved in methanol (400 ml) and *N*-methylaniline (4.8 g, 0.045 mol) added. The stirred mixture was heated under reflux for 6 hr, then cooled and volatiles were removed at reduced pressure. The darkened residue was titurated with ether–hexane (1:1) resulting in a solid that was recrystallized from CH_2Cl_2–ether and afford 6.35 g of **12** (88%, mp 145–146°); pmr δ_{CDCl_3}(TMS) 7.92 (d, J = 13, 1 H, C_3H), 7.5 (d, J = 13, 1 H, C_5H), 7.27 (m, 5 H, Ph-), 5.85 (t, J = 13, 1 H, C_4H), 3.74 (s, 3 H, OCH_3), 3.41 (s, 3 H, NCH_3); ir (CH_2Cl_2) 2230, 1700, 1615, 1560 cm^{-1}; cmr (relative to TMS, CH_2Cl_2 ppm) 118.09 (labeled nitrile), 164.3 (C_1),[11] 158.4 (C_5), 154.2 (C_3), 146.9 ($C_{1'}$), 130.8 ($C_{3',3'}$ or C_m), 127.0 ($C_{4'}$ or C_p) 121.6 ($C_{2',2'}$ or C_o), 118.1 (C_6), 101.1 (C_4), ~91 (C_2),[11] 52.9 (C_7 or $-OCH_3$), 38.7 (C_8 or NCH_3).

Methyl 2-Bromonicotinate (7) from Enamine 12. Enamine **12** (1 g, 0.004 mol) was dissolved in 5 ml of acetic acid and warmed to 40°. An acetic acid solution (10 ml) saturated with HBr (sat. at 0°) was added dropwise while maintaining the reaction mixture at 40–45°. After addition was complete the temperature was raised to 55° for 30 min. The darkened solution was cooled, poured into water, and neutralized by careful addition of Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2 (3 × 125 ml). The organic extracts were combined, washed with water, and dried (Na_2SO_4). Evaporation of the volatiles at reduced pressure left a residue that was distilled (Kugelrohr oven at 0.1 m) affording a colorless liquid at 60° (*N*-methylaniline) and a viscous oil at 90–120° (**7**, 0.77 g, 87%): pmr δ_{CDCl_3}(TMS) 8.47 (dd, $J_{6,4}$ = 2, $J_{6,5}$ = 5, 1 H, C_6H), 8.07 (dd, $J_{4,5}$ = 8.5, $J_{4,6}$ = 2, 1 H, C_4H), 7.40 (dd, $J_{4,5}$ = 8.5, $J_{5,6}$ = 5, 1 H, C_5H), 3.95 (s, 3 H, OCH_3); ir = 1735 cm^{-1}; cmr (relative to TMS, CH_2Cl_2 ppm) 170.2 (C_7), 153.1 (C_6), 141.2 (C_2), 140.6 (C_4), 133.0 (C_3), 123.6 (C_5), 53.9 (C_8); cmr (relative to TMS, CH_2Cl_2 ppm) (C_2 label) 141.11, ir (CH_2Cl_2) 1735, 1580 cm^{-1}; pmr (labeled **7**) δ_{CDCl_3}(TMS) 8.47 (ddd, $J_{6,5}$ = 5, $J_{6,4}$ = 2, $J_{C_2,6}$ = 16, 1 H, C_6H), 8.07 (ddd, $J_{4,5}$ = 8.5, $J_{4,6}$ = 2, $J_{C_2,4}$ = 8, 1 H, C_4H), 7.40 (ddd, $J_{5,4}$ = 8.5, $J_{4,6}$ = 2, $J_{C_2,5}$ = 3, 1 H, C_5H).

Methyl 2-Bromonicotinate (7) from Vinyl Ether 6. Vinyl ether **6** (1.20 g, 0.007 mol) was treated with HBr in the exact manner described above for enamine **12** affording **7** (1.46 g, 97%, bp 105–120° (35 mm)); ir (film) 1735, 1580, 1560 cm^{-1}.

Methyl Nicotinate (8). At room temperature methyl 2-bromonicotinate (**7**, 1.65 g, 0.008 mol) was added to a vigorously stirred suspension of 1% $Pd/BaCO_3$ (10 g) in ethanol (150 ml) under hydrogen at atmospheric pressure. After 171 ml of H_2 was absorbed, the suspended catalyst was filtered and the volatiles were removed at reduced pressure. The resulting oil was distilled (bp 110–125° (~25 mm)) affording **8** (0.98 g, 93%, mp 42–43°); pmr δ_{CDCl_3}(TMS) 9.31 (dd, $J_{2,6}$ = 2 = $J_{2,4}$, 1 H, C_2H), 8.82 (dd, $J_{2,6}$ = 2, $J_{6,5}$ = 5), 8.43 (dt, $J_{4,5}$ = 8, $J_{2,4}$ = 2 = $J_{4,6}$, 1 H, C_4H), 7.40 (dd, $J_{4,5}$ = 8, $J_{4,6}$ = 5, 1 H, C_5H), 3.95 (s, 3 H, OCH_3), ir (CH_2Cl_2) 1725 and 1580 cm^{-1}; cmr (relative to TMS, CH_2Cl_2 ppm) 166.0 (C_7 or –CO–), 153.9 (C_6), 151.0 (C_2), 137.3 (C_4), 126.5 (C_3), 123.9 (C_5), 52.8 (C_8 or OCH_3); cmr (relative to TMS, CH_2Cl_2 ppm) (C_2 label) 151.16; ir (CH_2Cl_2) 1730 cm^{-1}.

Nicotinamide (1) was prepared from methyl nicotinate (**8**) as described earlier (approximately 75% from **8**):[1] ir (KBr) 3450, 1665, 1620 cm^{-1}; mp 130–131°.

1,1-Dicyano-4-methoxy-1,3-butadiene (10). Malononitrile (1.00 g, 0.015 mol) was converted to butadiene **10** following the procedure used to prepare vinyl ether **6** (1.23 g, 60%, bp 100–130° (10.01 mm)): ir (CH_2Cl_2) 2250, 1620 cm^{-1}; pmr δ_{CDCl_3}(TMS) 7.48 (d, J = 13, 1 H, C_3H), 7.40 (d, J = 13, 1 H, C_5H), 6.07 (t, J = 13, 1 H, C_4H), 3.92 (s, 3 H, OCH_3); cmr (relative to TMS, $CDCL_3$ ppm) 167.7 (C_4), 160.1 (C_2), 114.4 and 112.5 (C_5, C_6), 103.7 (C_3), 76.4 (C_1), 59.3 (C_7 or OCH_3).

Bromonicotinonitrile (11). Butadiene **10** (1.34 g, 0.01 mol) was converted to bromonicotinonitrile **11** following the procedure used to prepare methyl bromonicotinate (**7**, 1.59 g, 87%): ir (CH_2Cl_2) 2250 and 1580 cm^{-1}; pmr δ_{CDCl_3}(TMS) 7.49 (dd, $J_{4,5}$ = 8, $J_{6,5}$ = 5, 1 H, C_5), 8.03 (dd, $J_{4,5}$ = 8, $J_{4,6}$ = 2, 1 H, C_4), 8.70 (dd, $J_{6,5}$ = 5, $J_{6,4}$ = 2, 1 H, C_6H); cmr (relative to TMS, $CDCl_3$ ppm) 153.0 (C_6), 143.8 (C_2), 142.4 (C_4), 122.5 (C_5), 115.7 (C_3), 114.4 (C_7 or C≡N).

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Registry No.—**1**, 98-92-0; **4**, 105-34-0; **5**, 102-52-3; **6**, 52718-94-2; **7**, 52718-95-3; **8**, 93-60-7; **10**, 52718-96-4; **11**, 20577-26-8; **12**, 26932-71-8; *N*-methylaniline, 100-61-8; malononitrile, 109-77-3.

References and Notes

(1) T. A. Bryson, J. C. Wisowaty, R. B. Dunlap, R. R. Fisher, and P. D. Ellis, *J. Org. Chem.*, **39**, 1158, (1974).
(2) A. Dornow, *Ber.*, **73**, 153 (1940).
(3) T. V. Protopopova and A. P. Skoldinov, *J. Gen. Chem. USSR*, **27**, 1360 (1957).
(4) T. B. Windholz, L. H. Peterson, and G. J. Kent, *J. Org. Chem.*, **28**, 1443 (1963).
(5) Bulb to bulb distillation; oven temperature cited.
(6) In the cmr spectrum only one resonance for each carbon is observed, and the pmr spectrum contained single resonances (coupled) for the diene-methines as well as a single ester and ether methyl group resonance.
(7) R. A. Buica and F. J. Batulin, *Rev. Real Acad. Cienc. Exactas. Fis. Natur. Madrid*, **62**, 249 (1968).
(8) For two other approaches to the synthesis of similar enaminonitriles see ref 7; H. Bredereck, F. Effenberger, K. Hirsch, and D. Zeyfang, *Chem. Ber.*, **103**, 222 (1970).
(9) Prepared from $K^{13}CN$ (90%) and methyl chloroacetate.
(10) For example, see activity studies on 2-(α,α,α-trifluoro-*m*-toluidino)nicotinic acid (niflumic acid on nifluril): E. Evans, K. Hailwood, C. Cashin and H. Jackson, *J. Med. Chem.*, **10**, 428 (1967); K. Rauma, *Chem. Abstr.*, **75**, 35782g (1967); C. Hoffmann and A. Faure, *Chem Abstr.*, **72**, 24628y (1967); and J. R. Boissier, R. Gentaz, J. Fichelle, and M. Piarroux, *Therapie*, **22**, 1257 (1967).
(11) Estimated chemical shift from very weak signal.

Site of N-Amination of Adenine and Alkyladenines[1]

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In contrast to the many examples of heterocyclic *N*-oxides,[2] which are useful as synthetic intermediates and interesting because some, especially in the purine series,[3] have shown biological activity, there are fewer recorded examples of the isoelectronic *N*-imines and their corresponding *N*-amino salts.[4] The *N*-amino derivatives of the nucleic acid bases are of particular interest as intermediates and with respect to their possible biological activity. We wish to report the synthesis of 1-aminoadeninium salts and the effect of alkyl substituents on adenine upon the position of N-amination.[5]

Amination of a heterocyclic nitrogen is the most direct route to *N*-amino salts. Chloramine and hydroxylamine-*O*-sulfonic acid (HSA) are the traditional reagents used for N-amination,[4,6] while *O*-mesitylenesulfonylhydroxylamine (MSH)[7] and *O*-dinitrophenoxyamine[8] are enjoying increasing favor. Adenine (**1**) failed to aminate with HSA but with MSH in methanol yielded (≥65%) an *N*-aminoadeninium

mesitylenesulfonate (**2a**), convertible to the *N*-aminoadeninium chloride (**2b**) on ion exchange resin. Of the five conceivable sites of N-amination of adenine, attack at N^6 was readily ruled out by comparison of the uv spectra of **2** with those reported for 6-hydrazinopurine.[9] Positions N-1 and N-3 were the likely targets: N-1 is the site of oxidation by H_2O_2/HOAc to form the *N*-oxide[10] while N-3 is the site of alkylation on adenine under neutral conditions.[11,12,19]

We attempted to direct the N-amination separately to the 1 and 3 positions by analogy with the reciprocal directivity observed for 1- and 9-alkyl-substituted adenines *vs.* 3- and 7-substituted derivatives.[13,14] If N-amination were similar to alkylation, a 7-alkyladenine would yield a 7-alkyl-3-aminoadeninium salt while a 9-alkyladenine would give a 9-alkyl-1-aminoadeninium salt. Employment of a labile alkyl group would permit us to remove the alkyl group and thus obtain the corresponding *N*-aminoadeninium salts. We used 9- and 7-pivaloyloxymethyladenines (**3, 5**) since the pivaloyloxymethyl (Pom) group can be removed easily by treatment with methanolic ammonia.[15] Amination of **3** and **5** and subsequent removal of the Pom group from each product resulted in the isolation, in very good yield, of the *identical N-aminoadeninium mesitylenesulfonate* originally obtained by direct amination of adenine. This result showed that 7- or 9-alkyl substituents do not direct the course of N-amination in the same way that they control the course of N-alkylation. The problem remained to establish the structure of **2a** arrived at by the three routes. Adjacency of the two NH_2 groups was shown by treatment of compound **2a** with triethyl orthoformate in dimethylformamide, which produced the known *s*-triazolo[5,1-*i*]purine (**7**)[16] in 95% yield. Accordingly, the product of amination of adenine and of representative 7- and 9-alkyladenines with *O*-mesitylenesulfonylhydroxylamine is 1-aminoadeninium mesitylenesulfonate. The locus of N-amination is not a function of the anionic portion of the MSH reagent being used, since, when the analogous alkylating agent methyl mesitylenesulfonate was employed with adenine, methylation occurred at N-3 as indicated by the uv spectrum of the product.[14] When 7-Pom-adenine (**5**) was oxidized with *m*-chloroperbenzoic acid, followed by removal of the Pom group with methanolic ammonia, the product was adenine 1-oxide as indicated by uv and tlc comparison with an authentic sample.

Analogy of the N-amination reaction is thus better drawn with N-oxidation than with N-alkylation. Theoretical predictions have not yet provided the basis for differentiation between the N-oxidation (or, now, N-amination) and N-alkylation processes,[17-20] so that further examination of the N-amination process will be necessary. The mild conditions used in the amination of adenine and alkyladenines with the reagent MSH of Tamura, *et al.*,[7] *i.e.*, 30 min at 25° in various solvents, recommend its use in sensitive or more complex systems.

Experimental Section

Melting points are uncorrected. The nmr spectra were recorded on a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard and $(CD_3)_2SO$ as the solvent unless otherwise noted. The ultraviolet spectra were obtained on a Cary Model 15 spectrophotometer, and the infrared spectra were obtained on a Perkin-Elmer Model 337 infrared spectrophotometer in KBr pellets. Microanalyses were performed by Mr. Josef Nemeth and associates, who also weighed samples for the quantitative electronic absorption spectra. Low resolution mass spectra were obtained on a Varian-MAT CH-5 spectrometer coupled with a 620i computer and STATOS recorder.

1-Aminoadeninium Mesitylenesulfonate (2a) and Chloride (2b). Freshly prepared *O*-mesitylenesulfonylhydroxylamine[7] (MSH) (0.63 g, 3 mmol) was added to a solution of adenine (135 mg, 1 mmol) in methanol. The solution was stirred at 25° for ~30 min and then immersed in a Dry Ice/isopropyl alcohol bath. The precipitate (200 mg) was collected from the cold mixture, and a second crop (27 mg) was collected from the cooled filtrate, for a total yield of 65%:[21] mp 244°; λ_{max} (MeOH) 263 nm; nmr δ 2.18 (s, 3, *p*-CH_3), 2.52 (s, *o*-CH_3's superimposed on solvent), 6.50 (br, 1, exchanges with D_2O, NH), 6.73 (s, 2, *m*-H's), 8.43 and 8.52 (ss, 2, purine H's); mass spectrum (70 eV) *m/e* (rel intensity) 200 (52, M − 150), 150 (76, M − 200), 135 (25), 120 (97), 118 (100).

The chloride salt **2b** (88% recovery) was obtained by passing **2a** through a Dowex-1 (Cl^-) column. One recrystallization from water afforded an analytical sample: mp 252°; λ_{max} (H_2O) ($\epsilon \times 10^{-3}$) at pH 1 256 (10.3), at pH 7 263 (11.1), at pH 12 269 (13.7); mass spectrum (70 eV) *m/e* (rel intensity) 150 (100, M − HCl), 123 (15, 150 − HCN).

Anal. Calcd for $C_5H_7ClN_6$: C, 32.18; H, 3.78; N, 45.01. Found: C, 31.89; H, 3.84; N, 44.78.

***N*-Amino-9-pivaloyloxymethyladeninium Mesitylenesulfonate (4).** Freshly prepared MSH[7] (0.6 g) was added to a solution of 9-pivaloyloxymethyladenine[15] (100 mg, 0.4 mmol) in 50 ml of acetone. The solution was stirred at 25° for 30 min, and a white precipitate of **4** was collected: 174 mg (94% yield); darkening at 254° and mp 261° (sealed tube); λ_{max} (H_2O) ($\epsilon \times 10^{-3}$), at pH 1 256 (12.0), at pH 7 256 (11.9), at pH 12 268–269 (13.9); nmr δ 1.11 (s, 9, Pom CH_3's), 2.15 (s, 3, *p*-CH_3), 2.49 (s, *o*-CH_3's superimposed on solvent), 6.18 (s, 2, Pom CH_2), 6.57 (s, 1, exchanges with D_2O, NH), 6.70 (s, 2, *m*-H's), 8.55 and 8.63 (ss, 2, purine H's); mass spectrum (70 eV) *m/e* (rel intensity), 264 (34, M − 200), 200 (24, M − 264), 150 (78), 135 (23), 57 (100).

Anal. Calcd for $C_{20}H_{28}N_6O_5S$: C, 51.71; H, 6.08; N, 18.09. Found: C, 51.46; H, 5.94; N, 17.85.

Cleavage of the 9-Pom Group of 4. A solution of 120 mg of the *N*-amino-9-Pom-adeninium mesitylenesulfonate (**4**) in methanol saturated with ammonia was allowed to stand overnight at 25°. The solution was then evaporated to dryness *in vacuo*, the residue was washed with ether, and the solid was collected by centrifugation. Recrystallization from methanol gave 57 mg (62%) of chromatographically (tlc) pure **2a**: mp 241–242°; λ_{max} (H_2O) at pH 1 258, at pH 7 264, at pH 12 269; nmr δ 2.18 (s, 3, *p*-CH_3), 2.49 (s, *o*-CH_3's superimposed on solvent), 6.50 (br, 1, exchanges with D_2O, NH), 6.72 (s, 2, *m*-H's), 8.43 and 8.52 (ss, 2, purine H's); mass spectrum (70 eV), *m/e* (rel intensity), 200 (50, M − 150), 150 (100,

M − 200), 135 (73), 118 (93); the ir spectrum was superimposable on that of the product of the direct amination of adenine.

***N*-Amino-7-pivaloyloxymethyladeninium Mesitylenesulfonate (6).** In a procedure similar to that used for the preparation of **4**, 0.5 g of MSH and 150 mg of 7-Pom-adenine[15] gave 185 mg (67%) of compound **6**: mp 230–231°; λ_{max} (H_2O) ($\epsilon \times 10^{-3}$) at pH 1 266 (8.76), at pH 7 261 (10.3), at pH 12 269 (12.5); nmr δ 1.10 (s, 9, Pom CH_3's), 2.17 (s, 3, *p*-CH_3), 2.50 (s, *o*-CH_3's superimposed on solvent), 6.38 (s, 3, 1 H exchanges with D_2O, Pom CH_2, and NH), 6.72 (s, 2, *m*-H's), 8.38 and 8.55 (ss, 2, purine H's); mass spectrum (70 eV), *m/e* (rel intensity), 264 (21, M − 200), 200 (26, M − 264), 179 (24), 150 (30), 135 (20), 57 (100).

Anal. Calcd for $C_{20}H_{28}N_6O_5S \cdot \frac{1}{2}H_2O$: C, 50.73; H, 6.17; N, 17.75. Found: C, 50.60; H, 5.99; N, 17.65.

Cleavage of the 7-Pom Group of 6. A solution of 120 mg of the *N*-amino-7-Pom-adeninium mesitylenesulfonate in methanol saturated with ammonia was allowed to stand at 25° for 6 hr. The solution was evaporated to dryness *in vacuo*, the residue was washed with ether, and the solid was collected by centrifugation. Recrystallization from methanol gave **2a** in chromatographic purity (tlc): yield, 66%; mp 243–244°, λ_{max} (H_2O) at pH 1 257, at pH 7 265, at pH 12 270; nmr δ 2.18 (s, 3, *p*-CH_3), 2.50 (s, *o*-CH_3's superimposed on solvent), 6.51 (s, 1, exchanged with D_2O, NH), 6.72 (s, 2, *m*-H's), 8.43 and 8.52 (ss, 2, purine H's); mass spectrum (70 eV), *m/e* (rel intensity), 200 (43, M − 150), 150 (65, M − 200), 135 (17), 118 (100); the ir spectrum was superimposable on that of the product of direct amination of adenine and on the spectrum of the 9-Pom (**4**) cleavage product.

***s*-Triazolo[5,1-*i*]purine (7).** Triethyl orthoformate (5 ml) was added to a suspension of **2a** (680 mg, 1.95 mmol) in 25 ml of dry dimethylformamide. The mixture was heated at reflux for 5 min, allowed to cool, and the volatile material was removed *in vacuo*. The resulting solid was suspended in methanol and filtered to afford **7**: 226 mg (95% yield); mp >300°; the uv spectra were identical with reported spectra;[16] λ_{max} (H_2O) at pH 1 261, 273, at pH 7 262 and 277, at pH 12 290; nmr δ 8.48 (s, 1), 8.60 (s, 1), 9.58 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity), 160 (100, M). This compound is weakly fluorescent, showing an emission maximum of 349 nm upon excitation at 291 nm.

Registry No.—**2a**, 52500-49-9; **2b**, 52500-50-2; **4**, 52500-52-4; **6**, 52500-54-6; **7**, 4022-94-0; *O*-mesitylenesulfonylhydroxylamine, 36016-40-7; adenine, 73-24-5; 9-pivaloyloxymethyladenine, 18997-21-2; 7-pivaloyloxymethyladenine, 18997-22-3; triethyl orthoformate, 122-51-0.

References and Notes

(1) This work was supported by Research Grant GP-8407X from the National Science Foundation.
(2) A. R. Katritzky and J. M. Lagowski, "Heterocyclic N-Oxides," Academic Press, New York, N.Y., 1970, Chapter II.
(3) (a) K. Suguira and G. B. Brown, *Cancer Res.*, **27**, 925 (1967); (b) K. Suguira, M. N. Teller, J. C. Parham, and G. B. Brown, *ibid.*, **30**, 184 (1970); (c) G. B. Brown, K. Suguira, and R. M. Cresswell, *ibid.*, **25**, 986 (1965).
(4) R. Gosl and A. Meuwsen, *Chem. Br.*, **92**, 2521 (1959).
(5) The N-amination of adenosine has been reported. The product was "conclusively suggested" to be the N-1 isomer by G.-F. Huang, T. Okamoto, M. Maeda, and Y. Kawazoe, *Tetrahedron Lett.*, 4541 (1973).
(6) (a) B. H. Rizkalla, R. K. Robins, and A. D. Broom, *Biochim. Biophys. Acta*, **195**, 285 (1969), (b) A. D. Broom and R. K. Robins, *J. Org. Chem.*, **34**, 1025 (1969).
(7) Y. Tamura, J. Minamikana, Y. Miki, and S. Matsugashita, *Tetrahedron Lett.*, 4133 (1972).
(8) T. Sheradsky, *Tetrahedron Lett.*, 1909 (1968).
(9) J. A. Montgomery and L. B. Holum, *J. Amer. Chem. Soc.*, **79**, 2185 (1957).
(10) M. A. Stevens and G. B. Brown, *J. Amer. Chem. Soc.*, **80**, 2759 (1958).
(11) J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, **84**, 1914 (1962).
(12) N. J. Leonard and T. Fijii, *J. Amer. Chem. Soc.*, **85**, 3719 (1963).
(13) N. J. Leonard and T. Fujii, *Proc. Nat. Acad. Sci., U.S.*, **51**, 73 (1964).
(14) J. H. Lister, "Fused Pyrimidines, Part II. Purines," D. J. Brown, Ed., Wiley-Interscience, New York, N.Y. 1971, pp 342–345.
(15) M. Rasmussen and N. J. Leonard, *J. Amer. Chem. Soc.*, **89**, 5439 (1967).
(16) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **30**, 3601 (1965).
(17) B. Pullman, *J. Chem. Soc. (London)*, 1621 (1959).
(18) B. Pullman and T. Nakajima, *Bull Soc. Chim. Fr.*, 1502 (1958).
(19) B. C. Pal, *Biochemistry*, **1**, 558 (1962).
(20) M. Miyaki and B. Shimizu, *Chem. Pharm. Bull. (Tokyo)*, **18**, 1446 (1670).
(21) The filtrate contained mainly adenine and only a trace of a second product.

Synthesis of 2-Cyano, 2-Acyl, and 2-Carboxamido Derivatives of 3-Aminobenzo[*b*]thiophene Involving Nitro Displacement

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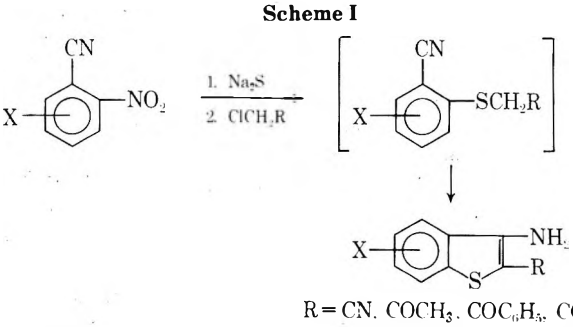
Until recently, 3-aminobenzo[*b*]thiophenes, substituted at the 2 position with cyano or acyl functions, were inaccessible. Clarke and coworkers[1] reported the synthesis of 3-aminobenzo[*b*]thiophene-2-carbonitrile by the reaction of *o*-mercaptobenzonitrile[2] with chloroacetonitrile in aqueous alkali. Similarly prepared were 3-aminobenzo[*b*]thien-2-yl methyl and phenyl ketones using chloroacetone and phenacyl chloride, respectively. The same authors[3] also described the preparation of the methyl ketone from 3-chloro-1,2-benzisothiazole[4] and pentane-2,4-dione in the presence of sodium ethoxide. A facile synthesis of N-substituted 3-aminobenzo[*b*]thien-2-yl ketones from 3-chloro-1,2-benzisothiazolium chlorides[5] and methyl ketones has been reported by Böshagen and Geiger.[6] In an earlier paper,[7] we described the preparation of methyl 3-aminobenzo[*b*]thiophene-2-carboxylate esters from *o*-nitrobenzonitriles and methyl thioglycolate in the presence of base. The reaction involved displacement of the activated nitro group by thioglycolate anion and subsequent base-catalyzed ring closure. Attempts to extend the scope of this procedure for the synthesis of the analogous 2-cyano and 2-acyl derivatives were frustrated by the instability or inaccessibility of the required mercaptan reagents.

We now wish to report two related processes, both involving nitro displacement, for the preparation of these compounds. In the first, an *o*-nitrobenzonitrile was allowed to react with sodium sulfide in aqueous DMF. The nitro group was readily displaced at ice bath temperature, and the anion of the corresponding *o*-mercaptobenzonitrile was formed (Scheme I). *In situ* alkylation with chloroacetonitrile, chloroacetone, or phenacyl chloride, with subsequent sulfide-catalyzed cyclization, yielded the corresponding 3-aminobenzo[*b*]thiophene-2-carbonitriles, 3-aminobenzo[*b*]thien-2-yl methyl ketones, or phenyl ketones, respectively. The procedure was also used as an alternate method of synthesis for 3-aminobenzo[*b*]thiophene-2-carboxamides[8] when chloroacetamide was utilized as the alkylating agent. The derivatives prepared and the yields obtained are summarized in Table I. When the starting nitrile was 2-chloro-5-nitrobenzonitrile, the 2-cyano (**10**) and 2-benzoyl (**11**) derivatives of 3-amino-5-nitrobenzo[*b*]thiophene were readily formed by a process involving active chlorine displacement.

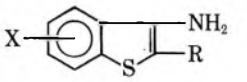
Scheme I



R = CN, $COCH_3$, COC_6H_5, $CONH_2$

When *o*-nitrobenzonitrile or 6-nitro-*o*-anisonitrile was subjected to the initial reaction conditions, sulfide displacement did not occur even at 100° during an extended

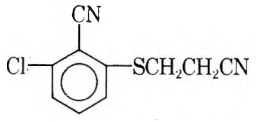
Table I
3-Aminobenzo[*b*]thiophenes[a]



Compd	X	R	Mp, °C	Yield, %	Crystn solvent[b]
1	4-Cl	CN	181–182	66	A
2	6-Cl	CN	215–216	75	A
3	4-NO_2	CN	177–179	84	A
4	4-Cl	$COCH_3$	101–103	68	B
5	4-NO_2	$COCH_3$	136–137	83	A
6	4-Cl	COC_6H_5	126–127	60	B
7	4-NO_2	COC_6H_5	139–141	60	A
8	4-Cl	$CONH_2$	225–227	69	A
9	4-NO_2	$CONH_2$	238–239	65	C
10	5-NO_2	CN	272–273	87	D
11	5-NO_2	COC_6H_5	205–207	90	C
13	H	CN	155–156[c]	70	A
14	H	$COCH_3$	147–149[d]	67	E
15	4-OCH_3	CN	173–176	50	D

[a] Satisfactory analytical data (±0.3% for C, H, N) were reported for all new compounds listed in the table. [b] A = alcohol; B = alcohol–water; C = acetonitrile; D = DMF–water; E = benzene–hexane. [c] Lit.[1] mp 155–156°. [d] Lit.[1] mp 145.5–147°.

period of time. In the second process, this problem was overcome with the use of 3-mercaptopropionitrile[9] anion. In this reaction sequence, the *o*-nitrobenzonitrile was allowed to react with the mercaptan anion in aqueous DMF containing excess potassium hydroxide. Displacement occurred rapidly at ice bath temperature, and an equilibrium mixture was formed involving the cyanoethyl thioether and the corresponding o-mercaptobenzonitrile anion. When the reaction was quenched soon after addition of the mercaptan, the cyanoethyl thioether could be isolated and characterized, as in the case of **12**. Addition of the alkylating



12

agent and subsequent ring closure yielded the desired product. Compounds prepared by this method were 3-aminobenzo[*b*]thiophene-2-carbonitrile (**13**), 3-aminobenzo[*b*]thien-2-yl methyl ketone (**14**), and 3-amino-4-methoxybenzo[*b*]thiophene-2-carbonitrile (**15**).

These two procedures provide a convenient, rapid route to 3-aminobenzo[*b*]thiophenes, substituted at the 2 position with cyano, acyl, or carboxamido functions, from readily available *o*-nitrobenzonitriles.

Experimental Section[10]

Materials. 2-Chloro-6-nitrobenzonitrile, 4-chloro-2-nitrobenzonitrile, 2-chloro-5-nitrobenzonitrile, and *o*-nitrobenzonitrile were commercially available. 2,6-Dinitrobenzonitrile[7] and 6-nitro-*o*-anisonitrile[11] were prepared by procedures described in the literature.

General Procedure for Aminobenzo[*b*]thiophenes (1–11). To a mechanically stirred, cold solution (ice bath) containing 30 mmol of the substituted *o*-nitrobenzonitrile in 100 ml of DMF was added dropwise a solution containing 36 mmol of sodium sulfide (nonahydrate) in 20 ml of water. The mixture was stirred in the cold for 15 min and the alkylating agent (3 ml of chloroacetonitrile for **1–3** and **10**; 3 ml of chloroacetone for **4** and **5**; 36 mmol of phenacyl chloride for **6**, **7**, and **11**; 36 mmol of chloroacetamide for **8** and **9**) was added dropwise or portionwise. The ice bath was removed and the mixture was stirred for an additional time (30 min for **1–5** and **10**; 1 hr for **6–9** and **11**). It was poured into ice water and the crude product was collected and crystallized from the appropriate solvent (Table I).

2-Chloro-6-[(2-cyanoethyl)thio]benzonitrile (12). A solution of 3 g of potassium hydroxide in 15 ml of water was added dropwise to a stirred, cold solution (ice bath) containing 5.5 g (30 mmol) of 2-chloro-6-nitrobenzonitrile and 3.1 g (36 mmol) of 3-mercaptopropionitrile[9] in 60 ml of DMF. The mixture was stirred in the cold for 10 min and then poured into ice water. The solid was collected and crystallized from alcohol to yield 2.7 g (40%) of product, mp 96–97°.

General Procedure for Aminobenzo[*b*]thiophenes 13–15. To a stirred, cold solution (ice bath) containing 30 mmol of the substituted *o*-nitrobenzonitrile and 3.1 g (36 mmol) of 3-mercaptopropionitrile[9] in 60 ml of DMF was added dropwise a solution of 5 g of potassium hydroxide in 15 ml of water. The mixture was stirred in the cold for 15 min (30 min for preparation of **14**), and the alkylating agent (3 ml of chloroacetonitrile for **13** and **15**; 3.5 ml of chloroacetone for **14**) was added dropwise. After it had been stirred in the cold for an additional 2 hr, the mixture was poured into ice water. The crude product was collected and crystallized from the appropriate solvent (Table I).

Acknowledgment. The authors thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.

Registry No.—**1**, 52673-85-5; **2**, 52673-86-6; **3**, 52673-87-7; **4**, 52673-88-8; **5**, 52673-89-9; **6**, 52673-90-2; **7**, 52673-91-3; **8**, 52673-92-4; **9**, 52673-93-5; **10**, 52673-94-6; **11**, 52673-95-7; **12**, 52673-96-8; **13**, 34761-14-3; **14**, 22720-75-8; **15**, 52673-97-9; 2-chloro-6-nitrobenzonitrile, 6575-07-1; 4-chloro-2-nitrobenzonitrile, 34662-32-3; 2-chloro-5-nitrobenzonitrile, 16588-02-6; *o*-nitrobenzonitrile, 612-24-8; 2,6-dinitrobenzonitrile, 35213-00-4; 6-nitro-*o*-anisonitrile, 38469-85-1; sodium sulfide, 1313-82-2; chloroacetonitrile, 107-14-2; chloroacetone, 78-95-5; phenacyl chloride, 532-27-4; chloroacetamide, 79-07-2; 3-mercaptopropionitrile, 1001-58-7.

References and Notes

(1) D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *J. Chem. Soc. C*, 3903 (1971).
(2) D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *J. Chem. Soc. C*, 3262 (1971).
(3) D. E. L. Carrington, K. Clarke, and R. M. Scrowston, *Tetrahedron Lett.*, 1075 (1971).
(4) A. Reissert, *Chem. Ber.*, **61**, 1680 (1928).
(5) H. Böshagen, *Chem. Ber.*, **99**, 2566 (1966).
(6) H. Böshagen and W. Geiger, *Ann. Chem.*, **764**, 58 (1972).
(7) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972).
(8) J. R. Beck and J. A. Yahner, *J. Org. Chem.*, **38**, 2450 (1973).
(9) L. Bauer and T. L. Welsh, *J. Org. Chem.*, **26**, 1443 (1961). The authors thank the Phillips Petroleum Co. for a sample of this compound.
(10) Melting points were determined on a Mel-Temp apparatus and are uncorrected.
(11) A. Russell and W. G. Tebbens, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N.Y., 1955, p. 293.

A New Synthesis of $N^{\alpha},N^{G,G}$-Tribenzyloxycarbonyl-L-arginine and Related Derivatives

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Among the guanidino protected arginine derivatives[1] used in peptide synthesis, $N^{\alpha},N^{G,G}$-tribenzyloxycarbonylarginine (II)[2,3] has proven to be a useful intermediate for the addition of an arginine residue to the amino terminus of a synthetic peptide. The considerable difficulty with which II is prepared, however, has discouraged its use in peptide synthesis except in special cases, *e.g.*, the synthesis of L-arginyl-L-arginyl sequences.

We report herein a procedure for the preparation of II and closely related derivatives which is experimentally simple and which consistently provides product yields substantially greater than the procedure[2,3] heretofore used. The salient features of the procedure involve the use of an

alkyl pentachlorophenylcarbonate as the alkyloxycarbonyl donor and *N*-trimethylsilylacetamide to promote *in situ* silyl ester formation[4] and to scavenge pentachlorophenol produced in the alkyloxycarbonylation reaction. Work-up of the reaction mixture is simplified by the ready hydrolysis of silyl esters and ethers, the high solubility of lithium acetate in absolute ethanol, and the ready precipitation of the crystalline lithium salts of II and closely related derivatives from ethanolic lithium acetate solution without coprecipitation of lithium pentachlorophenoxide. Other derivatives that have been prepared by the procedure are N^{α}-*p*-methoxybenzyloxycarbonyl-$N^{G,G}$-dibenzyloxycarbonyl-L-arginine (IV),[5] N^{α}-benzoyl-$N^{G,G}$-dibenzyloxycarbonyl-L-arginine (VI), and $N^{\alpha},N^{G,G}$-tri-*p*-methoxybenzyloxycarbonyl-L-arginine (VIII). The latter two derivatives are new compounds, and their use in peptide synthesis will be reported elsewhere.

Experimental Section[6]

Lithium $N^{\alpha},N^{G,G}$-Tribenzyloxycarbonyl-L-arginate (I). To 210 ml of dry DMF were added 20.88 g (0.12 mol) of L-arginine and 160 g (0.4 mol) of benzyl pentachlorophenylcarbonate.[7] The resulting suspension was stirred and heated to 60°. *N*-Trimethylsilylacetamide (78.6 g; 0.6 mol) was added to the mixture and the mixture was stirred for 60 hr at 60°.

After addition of 20 ml of water to the reaction mixture the DMF was evaporated *in vacuo*. The resulting residue was dissolved in absolute ethanol and the solution was added to a hot saturated solution of 50 g of lithium acetate in ethanol. The resulting mixture was cooled slowly to room temperature and then maintained at 4° overnight. A precipitate formed and was filtered. The collected solid was triturated with hot ethyl acetate and then was recrystallized from a minimum volume of boiling methanol. The solid was recovered by filtration and dried *in vacuo* to obtain 39 g (56%) of the title compound, mp 153–155°. An analytical sample was recrystallized from a mixture of methanol and acetone, mp 156–157°; $[\alpha]^{24}D$ +10.6 (*c* 1.5, methanol).

Anal. Calcd for $C_{30}H_{31}N_4O_8Li$: C, 61.85; H, 5.36; N, 9.62; mol wt 582.52. Found: C, 61.75; H, 5.50; N, 9.34.

$N^{\alpha},N^{G,G}$-tribenzyloxycarbonyl-L-arginine (II). Lithium $N^{\alpha},N^{G,G}$-tribenzyloxycarbonyl-L-arginate (10.0 g; 0.017 mol) was suspended in ethyl acetate. The suspension was neutralized by addition of 2% aqueous sulfuric acid. The ethyl acetate layer was separated, dried ($MgSO_4$), and evaporated *in vacuo*. The resulting residue was recrystallized from ethyl acetate to afford, after drying *in vacuo*, 9.1 g (92%) of the title compound: mp 138–139°; $[\alpha]^{25}D$ +15.1 (*c*, 1.5, chloroform) (lit.[2] mp 138–139°; $[\alpha]^{25}D$ +15.5 (*c* 1.5, $CHCl_3$)).

Anal. Calcd for $C_{30}H_{32}N_4O_8$: C, 62.49; H, 5.59; N, 9.72; mol wt 576. Found: C, 62.21; H, 5.80; N, 9.43.

Lithium N^{α}-*p*-Methoxybenzyloxycarbonyl-$N^{G,G}$-dibenzyloxycarbonyl-L-arginate (III). The title compound was prepared from N^{α}-*p*-methoxybenzyloxycarbonyl-L-arginine[5] as described in the procedure for I, except that the reaction time was limited to 34 hr. III was obtained in 63% yield: mp 209–210°; $[\alpha]^{24}D$ +9.9 (*c* 1.5, methanol).

Anal. Calcd for $C_{31}H_{33}N_4O_9Li$: C, 60.78; H, 5.43; N, 9.15; mol wt 612.55. Found: C, 60.51; H, 5.67; N, 9.08.

N^{α}-*p*-Methoxybenzyloxycarbonyl-N^{G},N^{G}-dibenzyloxycarbonyl-L-arginine (IV). Neutralization of III with 0.75 *N* aqueous citric acid gave the title compound in 91% yield: mp 139–141°; $[\alpha]^{25}D$ +16.6 (*c* 1.5, chloroform) (lit.[5] mp 135–136°; $[\alpha]^{25}546$ +14.0° (*c* 1.5, EtOH)).

Anal. Calcd for $C_{31}H_{34}N_4O_9$: C, 61.38; H, 5.65; N, 9.24; mol wt 606.63. Found: C, 61.65; H, 5.88; N, 9.46.

Lithium N^{α}-Benzoyl-$N^{G,G}$-dibenzyloxycarbonyl-L-arginate (V). The title compound was prepared from N^{α}-benzoyl-L-arginine[8] as described in the procedure for I, except that the reaction time was limited to 48 hr. V was obtained in 50% yield: mp 207–209°; $[\alpha]^{25}D$ +28.3 (*c* 1.5, chloroform).

Anal. Calcd for $C_{29}H_{29}N_4O_7Li$: C, 63.03; H, 5.29; N, 10.14; mol wt 552.49. Found: C, 62.80; H, 5.13; N, 10.29.

N^{α}-Benzoyl-N^{G},N^{G}-dibenzyloxycarbonyl-L-arginine (VI). Neutralization of V with 0.75 *N* aqueous citric acid gave the title compound in 83% yield: mp 172–173°; $[\alpha]^{25}D$ +20.0 (*c* 1.5, DMF).

Anal. Calcd for $C_{29}H_{30}N_4O_7$: C, 63.73; H, 5.53; N, 10.25; mol wt 546.58. Found: C, 63.59; H, 5.25; N, 10.07.

Lithium $N^{\alpha},N^{G,G}$-Tri-*p*-methoxybenzyloxycarbonyl-L-arginate (VII). The title compound was prepared exactly as described in the procedure for I. VII was obtained in 50% yield: mp 146–148°; $[\alpha]^{25}D$ +17.5 (*c* 1.0, DMF).

Anal. Calcd for $C_{33}H_{37}N_4O_{11}Li$: C, 58.93; H, 5.55; N, 8.33; mol wt 672.60. Found: C, 58.70; H, 5.76; N, 8.54.

$N^{\alpha},N^{G,G}$-Tri-*p*-methoxybenzyloxycarbonyl-L-arginine (VIII). Neutralization of VII with 0.5 *N* sulfuric acid gave the title compound in 80% yield: mp 125–128°; $[\alpha]^{25}D$ +1.9 (*c* 1, DMF).

Anal. Calcd for $C_{33}H_{38}N_4O_{11}$: C, 59.45; H, 5.75; N, 8.40; O, 26.40; mol wt 666.68. Found: C, 59.15; H, 5.84, N, 8.45; O, 26.57.

Registry No.—I, 52748-08-0; II, 52795-86-5; III, 52748-09-1; IV, 52748-10-4; V, 52748-11-5; VI, 52748-12-6; VII, 52748-13-7; VIII, 52748-14-8; L-arginine, 74-79-3; benzyl pentachlorophenylcarbonate, 13795-28-3; *p*-methoxybenzyl pentachlorophenylcarbonate, 52795-87-6.

References and Notes

(1) G. Jäger and R. Geiger, *Chem. Ber.*, **103**, 1727 (1970).
(2) L. Zervas, M. Winitz, and J. P. Greenstein, *J. Org. Chem.*, **22**, 1515 (1957).
(3) E. Wünsch and G. Wendlberger, *Chem. Ber.*, **10** 160 (1967).
(4) L. Birkofer and F. Müller, "Peptides," E. Bricas, Ed., North-Holland Publishing Co., Amsterdam, 1968, p 151.
(5) F. Weygand and E. Nintz, *Z. Naturforsch. B*, **20**, 429 (1965).
(6) All melting points are in °C and are uncorrected. DMF refers to *N,N*-dimethylformamide.
(7) Y. Wolman, D. Ladkany, and M. Frankel, *J. Chem. Soc. C*, 689 (1967).
(8) M. Bergman, J. Fruton, and H. Pollok, *J. Biol. Chem.*, **127**, 643 (1939).

Ethylene Iminocarbonate

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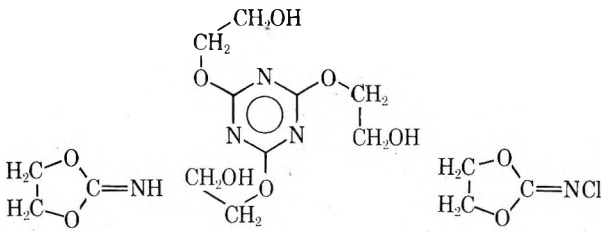
We wish to record here a preparation and characterization of ethylene iminocarbonate (**1**), and its spontaneous conversion to a trimer (**2**). Although the hydrochloride of **1** was described some time ago,[2] neither **1** itself nor **2** have apparently been reported previously.



1 **2** **3**

Ethylene chloriminocarbonate (**3**), easily available from ethylene glycol, potassium cyanide, and chlorine,[3] reacted with sodamide in liquid ammonia, slowly at −80°, vigorously at −50° to −60°. At the latter temperature, the reaction was complete in about 1 hr. Low-temperature work-up gave up to 25% yield of white crystals, mp 38–45° dec, assigned the structure of ethylene iminocarbonate based on spectral data. A by-product, white crystals of mp 117–120° (sintering), was isolated in 25–40% yield. From spectral evidence, it was assigned a trimer structure, most likely **2**.

After about 30 min at room temperature, the crystals of **1** started to melt and 2.5 hr after isolation, decomposition was extensive (effect of traces of base cannot be excluded). Upon further standing or trituration with acetonitrile, crystals of the trimer **2** were formed. On the other hand, the nmr spectrum of a solution of **1** in acetonitrile-d_3 remained unchanged for more than 2 weeks at room temperature.

To complete the characterization of **1**, it was converted at −80° to its hydrochloride, which had been prepared in a different way by Addor.[2] As described in ref 2, the hydrochloride rearranged into β-chloroethyl carbamate upon standing at room temperature.

Besides direct nucleophilic displacement on chlorine, which appears most likely, addition and elimination appears to be a possibility for the mechanism of formation of **1**.[4] It is interesting to note that a previous attempt to prepare **1** by reduction of **3** was unsuccessful.[3]

The trimerization of **1** most likely proceeds *via* ring opening to β-hydroxyethyl cyanate. Alkyl cyanates usually rearrange to isocyanates rather than trimerize, but electronegative substituents on the alkyl appear to slow down the isomerization so that trimerization can compete successfully, yielding trialkoxy-1,3,5-triazines.[5] A trimer similar to **2** was obtained upon basic treatment of 2-imino-1,3-oxathiane hydrochloride.[6]

Experimental Section

Ethylene Iminocarbonate (1). Into a 300-ml 3-neck flask fitted with Dry Ice–acetone condenser, mechanical stirrer, and gas inlet was condensed 200–250 ml of dry ammonia. To this was then added 2.5 g of sodium hydride washed 6–7 times with ether. A blue color resulted and disappeared after stirring for 6–10 hr, or upon addition of a small crystal of ferric nitrate (10–15 min. required). The mixture was cooled to −80° and 5 g of **3** were added. At −80°, the reaction proceeds to less than 50% after 2 hr. However, at −60° to −50°, it proceeds rapidly, often in a vigorously exothermic fashion. It was monitored by removing a small sample of the mixture, evaporating off the NH_3, triturating the residue with ice-cold pyridine and taking the nmr spectrum of the pyridine extract. The reaction was usually complete after 1 hr at −50 to −60° as evidenced by the loss of the nmr peak at δ 4.65, and the appearance of a singlet at δ 4.4. Ammonia was removed under reduced pressure (water aspirator) at −50 to −40°. The residue was triturated 3 times with ether at −20 to −30°. The ether extract was filtered and the ether removed on a rotary evaporator below 0°, leaving white crystals: mp 38–45°; yield varied from ~250 mg to 1 g (6–26%); ^1H nmr (acetonitrile-d_3) singlet at δ 4.4 (4 H), broad peak near δ 5.3 (1 H); ir (Nujol mull) 1700 and 3300 cm^{-1}; mass spectrum molecular ion peak at *m/e* 87, other peaks at 58, 44, and 43 (base peak) (a peak at *m/e* 58 is also seen in the mass spectrum of 3).

2,4,6-Tris(β-hydroxyethoxy)-1,3,5-triazine (2). A. From Reaction Residue. Further extraction of the ether extracted sodamide residue with either acetonitrile or methylene chloride followed by filtration and evaporation of the solvent yielded a light yellow oil. Upon standing or triturating with acetonitrile, the oil gave white crystals, mp 113–117°. Yield 1.0–1.5 g. Analytical sample was crystallized from acetone: mp 117–120° (sintering); ^1H nmr (D_2O) A_2B_2 pattern centered at δ 3.7 and 4.2; ir (Nujol) 3300 (broad) and 1560 cm^{-1}; uv (acetonitrile) shoulder at 260 nm (ε 32), then strong rise in absorption but no maximum down to 205 nm; mass spectrum (electron impact ionization), no molecular ion at *m/e* 261, peaks at 244 ($M^+ - OH$, presumably bicyclic immonium ion), 231 ($M^+ - CH_2O$), 218, 201, 187, 174, 156, 143, 130 (base peak), 113, 87, 70; mass spectrum (chemical ionization) peak at *m/e* 262 ($M^+ + H$); high-resolution mass spectrum (Varian MAT 311, resolution 10,000), peak at nominal *m/e* 231 matched with PFK; 231.0852, for $C_8H_{13}N_3O_5$ calculated 231.0855.

B. From Ethylene Iminocarbonate (1). After standing at room temperature for several hours, ethylene iminocarbonate trimerized spontaneously, giving crystals of mp 114–118°, whose nmr and ir spectra were identical with those of the above-described trimer.

Ethylene Iminocarbonate Hydrochloride. Into 25 ml of dry ethylene glycol dimethyl ether (distilled from $LiAlH_4$) was placed ~20 mg of ethylene iminocarbonate. The solution was cooled to −80° (complete dissolution did not occur). A stream of dry HCl was bubbled into the mixture for 2 min. A cloudy suspension developed. The solid was collected on filter and washed with ether, giving fine white crystals: mp 73–75° (lit.[2] 77–78°); ir (Nujol mull) 1510, 1550, 1720, and a broad band at 2600–3400 cm^{-1}. Upon standing over the weekend, the hydrochloride rearranged to β-chlorethyl carbamate, mp 68–70° (lit.[2] 65–70°).

Registry No.—**1**, 6703-57-7; **1** HCl, 52699-47-5; **2**, 891-65-6; **3**, 22718-26-9.

References and Notes

(1) Support by NSF Grant No. GP-26557 is gratefully acknowledged.
(2) R. W. Addor, *J. Org. Chem.*, **29**, 738 (1964).
(3) T. Fujisawa, Y. Tamura, and T. Mukaiyama, *Bull. Chem. Soc. Jap.*, **37**, 793 (1964).
(4) It has recently come to our attention that the reaction of sodium ethoxide with diethyl chloriminocarbonate yields diethyl iminocarbonate in a reaction closely analogous to that described here: A. Milling, Jr., Dissertation, New Mexico State University, 1973. We are obliged to Professor W. Lwowski for communication of these results.
(5) E. Grigat and R. Pütter, *Angew. Chem., Int. Ed. Engl.*, 6, 206 (1967).
(6) M. Menard, A. M. Wrigley, and F. L. Chubb, *Can. J. Chem.*, **39**, 273 (1961).

Ozonization of the 7-Phenylnorcaranes. Effects of Solvent and Temperature

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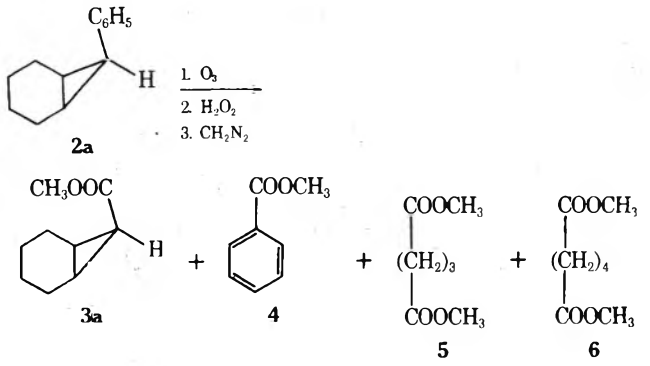
Recently we reported the first direct chemical evidence[1] supporting Closs',[2] Jensen's,[3] and Ledlie's[4] stereochemical assignments of *endo-* and *exo*-7-phenylnorcarane (**2a** and **2b**, respectively). This involved degrading **2a** and **2b** with ozone, employing the procedure of Shabarov,[5] producing the known *endo-* and *exo*-norcarane-7-carboxylic acids,[6,7] respectively, and a cyclopropane cleavage product, benzoic acid (**4**), all of which were isolated as their methyl esters. We then became interested in searching for other cleavage products and now wish to report the isolation and identification of the remaining compounds formed as **2a** and **2b** are ozonized, noting the effects of solvent and temperature on the product distribution. A modified procedure for the synthesis of **2a** is also discussed.

Jensen[3] has reported that triphenyltin hydride reduction of crude 7-chloro-7-phenylnorcarane (**1**), prepared by reaction of cyclohexene, benzal chloride, and potassium *tert*-butoxide,[8] yields, by vpc, 80% **2a**, 1% **2b**, and 19% olefin. Our observations indicate that the origin of the olefin arises not from the reduction of **1**, but occurs as a result of reduction of an olefinic product produced during the preparation of **1**. This olefinic impurity was removed with ozone. Purified **1** was then reduced with lithium aluminum hydride in diglyme furnishing a 65% yield of products which analyze (vpc) as 97% **2a**, 3% **2b**, and no olefin. Subsequent distillation of the reaction mixture yields a sample of **2a** that is 99% pure.[9]

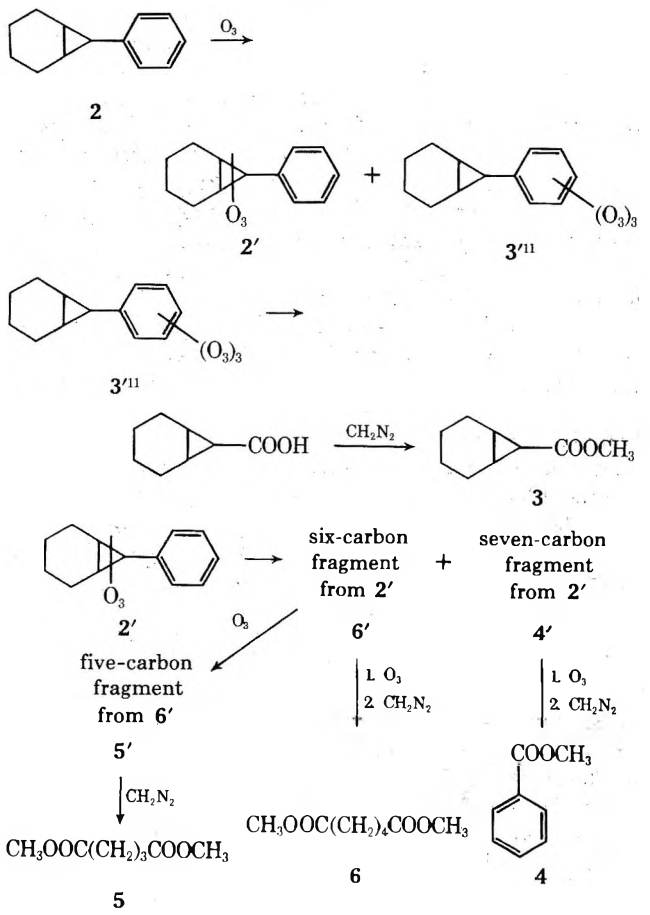
Ozonization of **2a** in 95% acetic acid at 25°, followed by treatment of the ozonized material with hydrogen peroxide and subsequent methylation of the products, furnishes a mixture containing four volatile components. These were separated by preparative gas chromatography and labeled in order of increasing elution time as **3a**, **4**, **5**, and **6**. Compounds **3a** and **4** have previously been identified as *endo*-7-carbomethoxynorcarane and methyl benzoate, respectively.[1] Compound **5** was identified as dimethyl glutarate by comparison of its ir and nmr spectra with reference spectra, correct elemental analysis, and by saponification of **5** to glutaric acid. Compound **6** furnished a correct elemental analysis for dimethyl adipate, gave ir and nmr spectra identical with authentic material, and saponification of **6** furnished adipic acid. These materials, **3a**, **4**, **5**, and **6**, were formed in 13, 16, and 9 and 8% yields, respectively,



when ozonized with a stream of 3% ozone. As expected, *exo*-7-phenylnorcarane furnished the same products (neglecting stereochemistry) when exposed to ozone. Both **2a** and **2b** consumed 8.3 mol of ozone/mol of starting compound when ozonized at 25° in 95% acetic acid.

Comparison of product ratios obtained from complete and partial ozonizations of **2b** provides some insight into these reactions. Essentially the same **3b/4** ratio is obtained from both of these ozonizations indicating that these two compounds result from the initial attack of ozone on **2b**. The **5/6** ratio was five times larger for the completely ozonized sample indicating that **5** resulted from ozone attack on **6'**. Gas chromatographic analysis of a sample of **2b** that had been treated with ozone and then diazomethane confirmed the presence of all four methyl esters, thereby demonstrating that it was the ozone and not the hydrogen proxide that was responsible for these ring opening reactions.[10] A proposed reaction scheme is given (Scheme I). Of course ozone could also react with **3'** [11] at the cyclopropane portion of the bicyclic ring system leading to the formation of **5** and **6**.

Scheme I



The effects of varying the source and concentration of ozone, temperature, and solvent upon the product distribution have been investigated. Ozonizing with ozone concentrations in the range of 3–6% in a stream of oxygen, ozonizing with a stream of 3% ozone in air, or ozonizing with oxygen-free ozone[12] in a stream of nitrogen had virtually no effect on the product distribution or total yield of the reaction. The effects of varying the temperature, employing 95% acetic acid as the solvent, afforded the most dramatic effect upon the product distribution while maintaining good overall yields. Increased reaction temperatures tend to favor attack at the bicyclic ring system, while lower temperatures tend to favor attack at the phenyl ring. When **2a** was ozonized in methylene chloride or ethyl acetate at 25°, one observes a decrease in the overall yield of the reaction as well as a reduction of the **3a/4** ratio when compared to the results obtained using 95% acetic acid as the solvent. Overall, there was a decrease in attack on the bicyclic ring system in the exo isomer as compared to the endo isomer, possibly due to the decreased shielding of the phenyl ring in the exo isomer. We are presently investigating the ozonization of other bicyclo[*n*.1.0] systems as a function of structure and reaction temperature.

Table I
Influence of Temperature on the Product Distribution in the Ozonization of the 7-Phenylnorcaranes

Compd	Solvent	Temp (°C)	Ozone concn (%)	% yield[a] 3a	3b	4	5	6
2a	95% HOAc	6	3	19		17	8	8
2a	95% HOAc	25	3	13		16	9	8
2a	95% HOAc	60	3	8		20	10	7
2a	95% HOAc	80	3	8		29	7	9
2b	95% HOAc	6	3		23	8	7	4
2b	95% HOAc	25	3		25	11	10	5
2b	95% HOAc	80	3		11	17	14	4

[a] Each reaction was performed twice with the average yield calculated for each product shown in Table I. The yield data were reproducible to within ±1%.

Experimental Section

An F&M gas chromatograph, Model 810, equipped with a 14 ft × 0.25 in. 5% Carbowax 1500 column operated at 130°, He flow rate of 100 ml/min, was employed for all analytical and preparative gas chromatography. Ir spectra were obtained using a Beckman Model 10 grating ir spectrophotometer with potassium bromide cells. Nmr spectra were recorded in carbon tetrachloride with a Varian A-60 spectrometer employing tetramethylsilane as an internal reference. A Welsbach ozonator, Model T-816, operated at a flow of 1 l./min was used for all ozonolyses. The elemental analyses were performed by M-H-W Laboratories, Garden City, Mich. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are corrected. Boiling points are uncorrected.

Ozonolysis of *endo*-7-Phenylnorcarane[5] (2a). A stream of 3% ozone was bubbled through a 250-ml gas wash bottle containing a magnetically stirred mixture of 1.0 g of **2a**[9] (99% pure) in 100 ml of 95% acetic acid until a test in water showed no turbidity. The time required for this reaction at 25° was 2.0 hr. After completion of the reaction, 10 ml of 30% hydrogen peroxide was added, and the solution was allowed to stir at room temperature overnight. The mixture was then heated in an oil bath at 95° for 4 hr, and the acetic acid removed *in vacuo*, furnishing a mixture of four acids. These acids were dissolved in dioxane and treated with diazomethane[13] and the resulting methyl esters separated by preparative gas chromatography employing a 14 ft × 0.25 in. column containing 5% Carbowax 1500 on Chromosorb P operated at 130°. The order of elution of the four methyl esters is **3a, 4, 5,** and **6**, respectively. The faster eluting compounds **3a** and **4** have previously been identified as *endo*-7-carbomethoxynorcarane and methyl benzoate, respectively.[1]

Compound **5** was proven to be dimethyl glutarate by comparison

of its ir and nmr spectra with reference spectra. Saponification of 0.0624 g of **5** was accomplished by refluxing with 1 ml of concentrated hydrochloric acid for 20 min, cooling, and then removing the water by placing the mixture in a vacuum desiccator along with a beaker of concentrated sulfuric acid. This procedure furnished a 59% yield of glutaric acid, mp and mmp 96.2–97.2° (lit.[14] mp 97°).

Anal. Calcd for $C_7H_{14}O_4$: C, 52.49; H, 7.55. Found: C, 52.39; H, 7.58.

Compound **6** was proven to be dimethyl adipate by comparison of its ir and nmr spectra with reference spectra. Saponification of 0.0697 g of **6** *vide supra* gave adipic acid in 55% yield, mp and mmp 150.5–151.5° (lit.[15] mp 150–151°).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 54.94; H, 7.97.

The yields[16] of esters **3a, 4, 5,** and **6** based on **2a** were 13, 16, 9, and 8%, respectively.

Ozonization of **2a** was also carried out in 95% acetic acid at temperatures of 6, 60, and 80°, requiring 3.66, 1.5, and 1.33 hr, respectively, for completion. The yields[16] of esters **3a, 4, 5,** and **6** based on **2a** are, respectively, as follows: 19, 17, 8, and 8% for the 6° reaction; 8, 20, 10, and 7% for the 60° reaction; and 8, 29, 7, and 9% for the 80° reaction.

***exo*-7-Phenylnorcarane[2] (2b).** To a stirred solution of 41 g of potassium *tert*-butoxide[8] and 230 ml of dry dimethyl sulfoxide (CaH_2) was added 9.6 g of **2a**[9] (99% pure) and then the mixture was heated to 100° under a nitrogen atmosphere for 25 hr. The reaction mixture was hydrolyzed and extracted with ether, and the extract washed with water and then dried over $CaCl_2$. Evaporation of the solvent and subsequent distillation of the residue, utilizing a Nester/Faust Auto Annular spinning band distillation column, resulted in 8.31 g (87% yield) of **2b** (98% pure), bp 126–127° (11 mm).

Ozonolysis of *exo*-7-Phenylnorcarane[5] (2b). Ozonolysis of **2b** (98% pure) was carried out in exactly the same manner described for **2a.** The time required for this reaction at 25° was 1.16 hr. The order of elution of the four methyl esters obtained is **4, 3b, 5,** and **6.** The faster eluting compounds, **4** and **3b,** have previously been identified as methyl benzoate and *exo*-7-carbomethoxynorcarane, respectively.[1]

Compound **5** was shown to be dimethyl glutarate by comparison of its ir and nmr spectra with reference spectra. Saponification of 0.0829 g of **5** *vide supra* gave an 83% yield of glutaric acid, mp and mmp 95.7–96.7° (lit.[14] mp 97°).

Anal. Calcd for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.58; H, 7.53.

Compound **6** was proven to be dimethyl adipate by comparison of its ir and nmr spectra with reference spectra. Saponification of 0.0805 g of **6** *vide supra* furnished a 68% yield of adipic acid, mp and mmp 150.3–151.8° (lit.[15] 150–151°).

Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.43; H, 8.14.

The yields[16] of esters **3b, 4, 5,** and **6** based on **2b** were 25, 11, 10, and 5%, respectively.

Ozonization of **2b** was also carried out in 95% acetic acid at temperatures of 6 and 80°, requiring 1.66 and 0.83 hr, respectively, for completion. The yields[16] of esters **3b, 4, 5,** and **6** based on **2b** for the 6° reaction were 23, 8, 7, and 4%, respectively, while the yields for the 80° reaction were 11, 17, 14, and 4%, respectively.

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Registry No.—**2a,** 10503-37-4; **2b,** 10503-36-3; **5,** 1119-40-0; **6,** 627-93-0.

References and Notes

(1) J. D. Woodyard, P. R. Morris, and R. G. Brownd, *J. Org. Chem.*, **37,** 4473 (1972).
(2) G. L. Closs and J. J. Coyle, *J. Org. Chem.*, **31,** 2759 (1966).
(3) F. R. Jensen and D. B. Patterson, *Tetrahedron Lett.*, 3837 (1966).
(4) D. R. Ledlie and S. MacLean, *J. Org. Chem.*, **34,** 1123 (1969).
(5) Y. S. Shabarov, V. K. Potapov, R. Y. Levina, and E. G. Treshchova, *Vestn. Mosk. Univ., Khim.*, **18,** 61 (1963); *Chem. Abstr.*, **59,** 7397h (1963).
(6) P. S. Skell and R. M. Etter, *Proc. Chem. Soc.*, 443 (1961).
(7) H. Musso and U. Biethan, *Chem. Ber.*, **97,** 2282 (1964).
(8) J. E. Hodgkins, J. D. Woodyard, and D. L. Stephenson, *J. Amer. Chem. Soc.*, **86,** 4080 (1964).
(9) P. R. Morris and J. D. Woodyard, *Org. Prep. Proced. Int.*, **5,** 275 (1973).
(10) We recommend the use of hydrogen peroxide in all work-up procedures in order to destroy any possible remaining ozonides.
(11) The structure given for **3'** is an abbreviated representation of the triozonide produced at the phenyl ring of **2** during ozonization.
(12) M. C. Whiting, A. J. N. Bolt, and J. H. Parish, *Advan. Chem. Ser.*, **No. 77, 4** (1968).
(13) F. Arndt, "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 165.
(14) E. Boedtker, *J. Pharm. Chim.*, **15,** 225 (1932).
(15) A. L. Henne and P. Hill, *J. Amer. Chem. Soc.*, **65,** 752 (1943).
(16) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 43.

Oxidation of Olefins by Mercuric Salts. The Alkaline Decomposition of Oxymercurials

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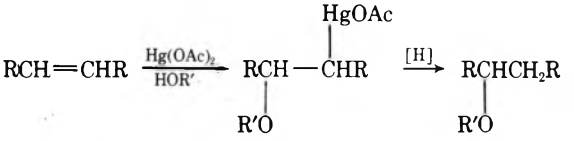
The increasing interest shown in the oxymetalation of olefins in the past few years has mirrored the fast growing field of organometallic chemistry. Among oxymetalation reactions oxymercuration occupies a position of considerable importance and the number of recent reviews is a clear testimony to this.[1-4]

The interaction of alkenes with mercuric salts yields oxymercurials which can either be reduced as typical organo-



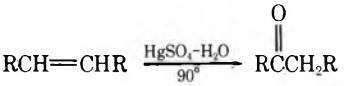
mercury compounds[5] or be thermally decomposed in acidic medium as in the Denigés reaction to give directly oxidized organic moieties and reduced mercury species.[6]

We have studied the thermal decomposition of these organomercurials in alkaline medium and found quite a different behavior from that observed in acidic medium. Thus when basic solutions containing oxymercurials are heated, a mixture of ketone and epoxide as the oxidized organic moiety is obtained.[7]

Results and Discussion

The study was first carried out under experimental conditions analogous to the Denigés reaction[6] and then by synthesizing the desired oxymercurial and following its thermal decomposition in a chosen medium.

Aqueous Medium. The general procedure was to stir a suspension of mercuric salt in the presence of olefin. The solution obtained was then made basic and heated. At the end of the reaction, addition of hydrochloric acid regenerated the starting olefin and thus allowed an estimation of the advancement of the reaction, *i.e.*, per cent conversion.



The results given in Table I show clearly lower yields with propene and 1-butene. This can easily be explained if one considers the possibility of allylic oxidation of α-olefins analogous to that observed in acidic medium; such oxidations generally yield α,β-unsaturated carbonyl compounds which can be expected to be unstable under the reaction conditions.[6] This was shown to be the case by introducing compounds such as acrolein or methyl vinyl ketone in the

Table I
Oxidation of Olefins with Mercuric Salts at pH 13[a]

Substrate	Salt	Products (%)[b]		Total yield, %[c]	Conversion, %[d]
Propene (115-07-1)	$HgSO_4$ (7783-35-9)	 (6)	 (94)	51	7
Propene	$Hg(OAc)_2$ (1600-27-7)	 (4)	 (96)	43	9
1-Butene (106-98-4)	$HgSO_4$	 (7)	 (93)	30	13
2-Butene (trans) (624-64-6)	$HgSO_4$	 (64)[e]	 (36)	72	49
2-Butene (cis) (590-18-1)	$HgSO_4$	 (44)[f]	 (56)	62	56
Cyclohexene (110-83-8)	$HgSO_4$	 (84)	 (16)	48	*h*
Isobutene (115-11-7)	$HgSO_4$	 (32)	 (68)	63	11
2,3-Dimethyl-2-butene (563-79-1)	$HgSO_4$	 (100)		*g*	*h*

[a] Registry nos. are given below each compound. [b] Relative amount by glpc analysis. [c] Total yield by glpc analysis using an internal standard. [d] % olefin reacted based on olefin regenerated upon hydrochloric acid addition. [e] 95% isomeric purity. [f] Not determined. [g] Could not be determined accurately because decomposition occurred partially during the organomercurial preparation.

Table II
Influence of Various Variables on the Reaction of *trans*-2-Butene with Mercuric Salts in Alkaline Medium

Variables	Experimental range	Degree of influence: % epoxide[a]	% total yield[b]	% conversion[c]
Salt concentration	0.1–0.9 mol/l.	***[d] (−32.2)[e]	*** (12.4)	*** (22.4)
pH	9–13	* (3.4)	* (5.9)	* (−2.7)
Reaction temperature	78–93°	* (−5.5)	*** (31)	*** (25.7)
Reaction time	2–6 hr	** (6.7)	*** (14.1)	*** (13.4)
N_2 flow	4–8 l./hr	0 (−2.9)	0 (−2.9)	0 (−1.7)
Salt nature	$HgSO_4$–$Hg(OAc)_2$	** (−12)	*** (−13.4)	** (8.7)

[a] Relative amount by glpc analysis. [b] Total yield of epoxide and ketone by glpc analysis. [c] % olefin reacted based on olefin regenerated upon hydrochloric acid addition. [d] Degree of significance of the influence measured by statistical methods and symbolized from very significant (***) to not significant (0).[9] [e] Direction and amplitude of the influence obtained from two-level fractional factorial plans.[9]

reaction medium and observing a very rapid polymerization.

The isomeric purity of the oxides obtained from *cis*- or *trans*-2-butene strongly suggests two successive stereoselective steps; most probably a trans addition to give the intermediate oxymercurial followed by a trans intramolecular attack to give the epoxide. The higher yield in epoxide in the case of cyclohexene is also indicative of such a process since it has been shown that with this olefin the hydroxyl group and the mercury atom are trans to each other which through a rapid aa ⇄ ee equilibrium facilitates a trans intramolecular attack.[8]

The use of olefins whose structures do not allow ketone formation did not always give high yields of epoxide; with isobutene a large quantity of *tert*-butyl alcohol was obtained and with 2,3-dimethyl-2-butene the only product was *tert*-butyl methyl ketone.

In order to obtain a deeper insight we studied the various variables that could influence this reaction. *trans*-2-Butene was chosen arbitrarily and a series of reactions was carried out using six variables.

The Variance Analysis Technique was utilized and a relatively limited number (20) of experiments permitted the determination of the influence of each variable on the yield and selectivity of the reaction.[9]

The results given in Table II show firstly a great influence of the oxymercurial concentration and a little or no influence of the pH on the yield and selectivity. If by analogy with the reaction in acidic medium, one considers the formation of the ketone, *via* an intramolecular rearrangement of the oxymercurial accompanied by a 1,2-hydride shift, the first observation is not surprising. What is more unexpected, however, is the nondependence of the hydroxide concentration on the rate of product formation as can be seen from the small influence of the pH on the per cent conversion. Although this is in accord with a ketone formation by the path described above, it forbids a full analogy with the process of epoxide formation from 1,2-chlorohydrins which has been shown to be base dependent.[10]

The results in Table II also show a very significant influence of the temperature and the reaction time on the per cent conversion. This is not unexpected; however, the fact that the selectivity in epoxide fell with reaction time left a doubt as to the possibility of isomerization of epoxide into ketone. Such rearrangements have been reported in the presence of organometals.[11] We thus introduced pure epoxide in a mixture containing mercuric sulfate under identical experimental conditions and at a rate close to which it is formed and observed no ketone formation.

All these observations as well as those given in Table I

Table III
Thermal Decomposition of 1-Chloromercuri-2-hydroxypropane in the Presence of Potassium Alkoxide (ROK) in Alcohol (ROH)

R	ϵ[a]	Products, %			Yields, %	Conversion, %
						
Ethyl[b]	24.3	60	38	2	20	36
n-Butyl	18.2	78	21	1	21	47
sec-Butyl	15.8	87	11	2	83	94

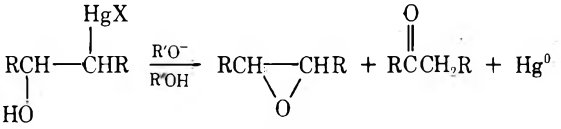
[a] Dielectric constant of the alcohol at 25°. [b] Reaction temperature: refluxing ethanol, 78°.

Table IV
Thermal Decomposition of 1-Halomercuri-2-hydroxypropane in the Presence of Potassium *n*-Butoxide in *n*-Butyl Alcohol

Halogen	Registry no.	Products, %			Yields, %	Conversion, %
						
Cl	52358-07-3	78	21	1	21	47
Br	18832-83-2	35	65		14	50
I	5323-64-8	4	96		36	60

clearly indicate two parallel decomposition paths of the intermediate oxymercurial, one leading to the ketone and one to the epoxide.

Nonaqueous Medium. The general procedure consisted of adding to the potassium alkoxide solution the previously prepared halomercurial and heating the resulting mixture.



R′ = H, alkyl

The results given in Table III show that both the yield and the selectivity in epoxide increase with decreasing dielectric constant of the medium. This again points out the dissimilarity with the epoxide formation from chlorohydrins; thus, the formation of an intermediate 1-chloromercuri-2-alkoxide analogous to the 2-chloroethoxide proposed by Swain would be expected to be facilitated in solvents with higher dielectric constants, whereas the opposite was observed.[12]

On the other hand the ease of formation of ketone seems to be influenced by the character of the mercury atom as a leaving group. This was shown by varying the halogen on the oxymercurial. The results are given in Table IV.

The results obtained both in aqueous and nonaqueous medium, although not allowing the establishment of a detailed mechanism, clearly indicate two distinct decomposition paths: one leading to epoxide formation most probably by an intramolecular attack, somehow different from that of 1,2-chlorohydrins, and a second leading to ketone apparently driven by the departure of the mercury atom.

Experimental Section

Materials. All olefins used were commercially available and were used as obtained after verifying their purity by glpc on a 12 m × 6 mm column of 30% dimethylsulfolane on Chromosorb P at 25°. All solvents were purified by distillation following standard methods. Mercuric salts (Prolabo) and alkali metals (Prolabo) were used without further purification.

Oxidation Procedure. The general procedure was discussed in the text. All product analyses were carried out by glpc using tetrahydrofuran as an internal standard. Products were identified by spectroscopic methods on preparative glpc purified samples and compared with authentic samples.

Aqueous Medium. A suspension of 80 mmol of mercuric salt in 150 ml of water was placed under an atmosphere of gaseous olefin. In the case of liquid olefins, the stoichiometric amount of substrate was added to the aqueous suspension and stirring continued for 1 hr. The resulting solution was then placed in the reaction vessel equipped with a gas inlet tube, a mechanical stirrer, and a reflux condenser kept at 60–65°. The mixture was rendered basic (pH 13) by slowly adding 14 g of potassium hydroxide and then heated to 100° for 6 hr. The products formed were swept out by a continuous flow of nitrogen gas (5 l./hr) and collected in two flasks placed in series and cooled to −45°. After cooling the reaction mixture, hydrochloric acid was added and the amount of olefin regenerated was measured.

Nonaqueous Medium. To the desired potassium alkoxide (80 mmol) in 100 ml of alcohol, placed in the reaction vessel described for the aqueous reaction, was added a 100-ml alcoholic solution containing 80 mmol of the previously prepared 1-halo-2-hydroxypropane. Heating the mixture for 6 hr at 82° while nitrogen gas swept the system gave the reaction products which were collected and analyzed in a manner analogous to the reaction in water.

Preparation of 1-Halomercuri-2-hydroxypropane. The procedure followed was the one described by Hofmann and Sand.[13] A 300-ml aqueous solution containing 200 g (0.63 mol) of mercuric acetate was placed under an atmosphere of propene. Vigorous agitation resulted in the absorption of 13.24 l. of gas. The solution obtained was neutralized by adding slowly 40 g (0.7 mol) of potassium hydroxide dissolved in 100 ml of water, adjusted to neutrality with CO_2 and then divided into three aliquots. Each part was then treated separately with 0.21 mmol of sodium chloride, bromide, and iodide to give white precipitates which were filtered and recrystallized from diethyl ether. The products obtained were respectively: 1-chloromercuri-2-hydroxypropane (42 g, 68% yield), mp 51° (lit.[13] 53°); 1-bromomercuri-2-hydroxypropane (54 g, 75% yield), mp 78° (lit.[13] 76°); and 1-iodomercuri-2-hydroxypropane (40 g, 50% yield), mp 65° (lit.[13] 68°). All solids were stored under nitrogen and in the dark before use.

References and Notes

(1) J. Chatt, *Chem. Rev.*, **48**, 7 (1951).
(2) W. Kitching, *Organometal. Chem. Rev.*, **3**, 61 (1968).
(3) N. S. Zerfirov, *Russ. Chem. Rev.*, **34**, 527 (1965).
(4) W. Kitching in "Organometallic Reactions," Vol. 3, F. I. Becker and M. Tsutui, Ed., Wiley-Interscience, New York, N.Y., 1972, p 319.
(5) H. C. Brown and J. P. Geoghegan, Jr., *J. Org. Chem.*, **35**, 1844 (1970).
(6) H. Arzoumanian and J. Metzger, *Synthesis*, 527 (1971).
(7) A similar reaction has been described in a German Patent [German Patent No. 1, 150,668 (1961)] but the products obtained are mainly α,β-unsaturated carbonyl compounds and only small amounts of epoxide.
(8) W. H. Brown and G. F. Wright, *J. Amer. Chem. Soc.*, **62**, 2412 (1940).
(9) C. A. Bennett and N. L. Franklin, "Statistical Analysis in Chemistry and the Chemical Industry," 3rd ed, Wiley, New York, N.Y., 1963.
(10) A. A. Frost and R. G. Pearson, "Kinetics and Mechanisms," Wiley, New York, N.Y., 1953, pp 243–257.
(11) J. L. Eisenmann, *J. Org. Chem.*, **27**, 2706 (1962).
(12) C. G. Swain, A. D. Ketley, and R. F. W. Bader, *J. Amer. Chem. Soc.*, **81**, 2353 (1959).
(13) K. A. Hofmann and J. Sand, *Ber.*, **33**, 1353 (1900).

A Kinetic Study of the Thermal Decomposition of (*Z*)-*N*-*tert*-Butyl-α-phenylnitrone[1,2]

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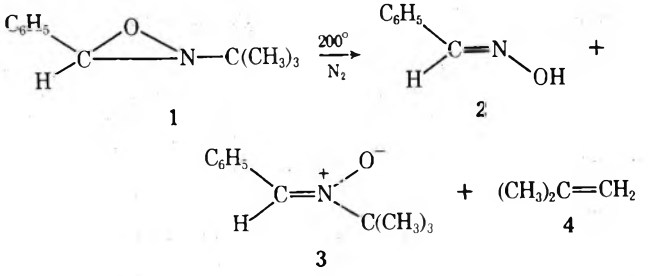
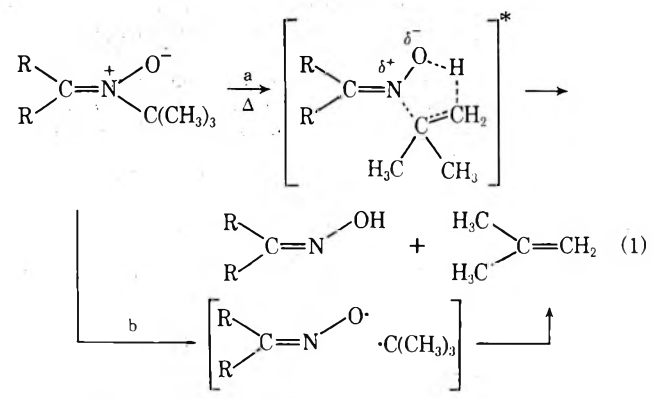
The vapor-phase pyrolysis of 2-*tert*-butyl-3-phenyloxaziridine (1) was described by Emmons in 1957.[3] The prod-

ucts were reported to be benzaldoxime (2), *N-tert*-butyl-α-phenylnitrone (3), and isobutylene (4) contaminated



with small amounts of *tert*-nitrosobutane, nitrous oxide, and carbon dioxide. A concerted cyclic elimination from the initially formed nitrone was suggested as the probable mechanism for the formation of the oxime and olefin. Such cyclic eliminations are well documented for tertiary amine oxides bearing β-hydrogens. Recently Boyd[4] showed that the thermal elimination of olefins from various *N*-alkylnitrones is quite general.

Although a concerted decomposition (illustrated in route a for an *N-tert*-butylnitrone) seems reasonable, a homolytic dissociation followed by disproportionation (route b) warrants consideration.[5] We have recently shown that a



homolytic cleavage of the C–N bond is the principal mode of decomposition of *N*-benzhydryl-α,α-diarylnitrones.[6,7]

A kinetic comparison of the thermolyses of **3** and *N*-benzhydryl-α,α-diphenylnitrone (**5**) in *tert*-butyl alcohol appeared to offer a useful mechanistic probe. The entropy of activation for the decomposition of **5**, which clearly involves the formation of iminoxy and benzhydryl radicals, was expected to be moderately large and positive. In diethylcarbitol this was found to be 11 eu.[8] By contrast, for a cyclic elimination (from **3**) a modest negative ΔS^* might reasonably be expected. Entropies of activation for thermolyses of neutral compounds, transition states for which involve five- or six-membered structures, fall in the range of −2 to −17 eu.[9] Useful comparison examples are the thermal decompositions of *erythro*- and *threo*-*N*,*N*-dimethyl-3-phenyl-2-butylamine oxides in aprotic solvents which exhibit entropies of activation ranging from +0.6 (±2.1) to −10.5 (±2.5) eu.[10]

Rate constants for the thermal decompositions of **3** and **5** in *tert*-butyl alcohol obtained in the present study are listed in Table I. The activation parameters calculated from the data in Table I are for **3**, E_a = 34.9 ± 0.3 kcal/mol; ΔS^* = −0.3 ± 0.9 eu; for **5**, E_a = 40.9 ± 0.4 kcal/mol; ΔS^* = +14.5 ± 0.8 eu. The *N*-benzhydrylnitrone (**5**) leads to the formation of *O*-benzhydrylbenzophenone oxime in nearly quantitative yield by recombination of iminoxy and benzyhydryl radicals. From the decomposition of **3**, benzaldoxime was produced in 97% yield as determined by ultraviolet spectroscopy and isobutylene was isolated in 90% yield. The near zero value of ΔS^* for the decomposition of **3** is consistent with a cyclic transition state but not in accord with expectations if homolytic dissociation or ion pair formation were involved. The substantially lower activation energy for this decomposition (compared with that of **5**) is also in accord with expectations based upon the bond energy gain attending partial carbon-carbon double bond formation. The high yield of oxime and olefin renders unlikely and significant cycloaddition of isobutylene with unreacted nitrone.

Table I
First-Order Rate Constants[a] for the Thermal Decompositions of *N-tert*-Butyl-α-phenylnitrone (3) and *N*-Benzhydryl-α,α-diphenylnitrone (5) in *tert*-Butyl Alcohol

Nitrone	Concn, *m*M	Temp, °C	$10^5 k$, sec^{-1}
3	2.53	135	0.368
3	2.63	135	0.385
3	0.229	150	1.86
3	1.20	150	1.70
3	1.20	150	1.88
3	2.44	150	1.76
3	1.03	165	7.09
3	2.62	165	7.39
5	3.44	130	0.250
5	0.733	130	0.232
5	0.745	130	0.236
5	2.41	144	1.26
5	3.50	144	1.28
5	2.58	144	1.32
5	0.906	144	1.30
5	0.664	144	1.34
5	0.596	144	1.35
5	3.07	160	7.66
5	2.84	160	7.97
5	0.930	160	8.13
5	0.650	160	8.22

[a] The average probable error on individually determined rate constants was ±1%.

Experimental Section[13]

***N*-Benzyl-*tert*-butylimine** was prepared according to the procedure of Emling and coworkers[14] in 83% yield: bp 77.5–79° (4 mm), n^{25}D 1.5212, ir (neat) 1650 cm^{-1} (C=N).

2-*tert*-Butyl-3-phenyloxaziridine (1) was prepared by *m*-chloroperbenzoic acid oxidation of the above imine using the procedure described by Pews.[15] The unpurified product (96% yield) was obtained as a pale yellow oil: pmr (CCl_4) δ 7.4–7.2 (m, 5, aromatic), 4.50 (s, 1, α C–H), 1.15 (s, 9, $C(CH_3)_3$).

***N*-*tert*-Butyl-α-phenylnitrone (3)** was prepared by the thermal isomerization of I in acetonitrile as described by Emmons.[3] The nitrone was recrystallized from 10% ether–petroleum ether (bp 90–110°) followed by recrystallization from 20% ether–hexane. The product used was a colorless crystalline material: mp 73.5–74.5° (lit.[3] mp 75–76°); pmr (CCl_4) δ 8.25–8.02 (m, 2, aromatic), 7.38–7.15 (m, 4, aromatic + vinyl protons), 1.53 (s, 9, $C(CH_3)_3$); uv (C_2H_5OH) λ_{max} 293.5 nm (ε, 17,700), 224 nm (ε, 7,240).

***N*-Benzhydryl-α,α-diphenylnitrone (5)** was prepared as previously described.[16]

General Procedures for the Kinetic Runs. A solution of the nitrone was prepared with *tert*-butyl alcohol which had been dried over CaO and distilled from Dri-Na under nitrogen. Approximately 1 ml of the solution was pipetted into each of 5–10-m. Pyrex tubes. These solutions were then degassed and sealed under vacuum. For a given run the tubes were simultaneously placed in a constant temperature oil bath (±0.05°). Tubes were removed periodically and quenched at low temperature. Infinity tubes remained in the bath for 10 half-lives. The opened tubes were allowed to warm to room temperature in a desiccator. Aliquots were weighed by dif-

ference into volumetric flasks and diluted with absolute ethanol. Rate constants were determined for the disappearance of the nitrone by following the decrease in its absorption at 293.5 (for **3**) and 310 nm (for **5**).

Product Analyses. Small samples of **5** were decomposed (99.9% reaction based upon rates) in *tert*-butyl alcohol at 144°. After removal of solvent under reduced pressure, the residue was carefully chromatographed over alumina. Hexane–benzene (49:1) mixtures eluted approximately 1–2% tetraphenylethane. Hexane–benzene (4:1) eluted *O*-benzhydrylbenzophenone oxime in yields as high as 96%.

The yield of benzaldoxime from the decomposition of **3** in *tert*-butyl alcohol (measured by ultraviolet spectroscopy) was 97%. The opened reaction ampoules were then attached to a vacuum line, and the isobutylene was distilled from the solution and collected under reduced pressure. The isobutylene (90% determined volumetrically) was identified by infrared and mass spectra.

Acknowledgment. The authors wish to thank Dr. Morey Ring for his assistance in isolating the isobutylene using vacuum line techniques.

Registry No.—**1**, 7731-34-2; **3**, 52392-70-8; **5**, 5350-59-4; *N*-benzyl-*tert*-butylimine, 6852-58-0.

References and Notes

(1) This work was supported in part by the National Science Foundation in a grant (GY-9550) to M.H.G. for an Academic Year Extension of Research Participation for College Teachers.
(2) The rate data for the thermal decomposition of *N*-benzhydryl-α,α-diphenylnitrone (also described in this note) were taken from the Ph.D. thesis of J. A. Villarreal. This part of the study was supported by the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA-10741-04).
(3) W. D. Emmons, *J. Amer. Chem. Soc.*, **79**, 5739 (1957).
(4) D. R. Boyd, *Tetrahedron Lett.*, 3467 (1973).
(5) Recently K. Sommermeyer, W. Seiffert, and W. Wilker, *Tetrahedron Lett.*, 1821 (1974), have observed the esr spectra of nitroxide radicals formed during the thermal decomposition of **3** (variously substituted in the para position) in tetrachloroethylene. Presumably this represents a minor side reaction of the nitrones. Whether such a competing pathway is general for other solvents is yet to be determined.
(6) T. S. Dobashi and E. J. Grubbs, *J. Amer. Chem. Soc.*, **95**, 5070 (1973), and references therein.
(7) With these nitrones no β C–H bond is available for a cyclic elimination, and the two aromatic rings are effective in stabilizing the alkyl radical being formed in the rate-determining step.
(8) E. J. Grubbs, J. A. Villarreal, J. D. McCullough, Jr., and J. S. Vincent, *J. Amer. Chem. Soc.*, **89**, 2234 (1967).
(9) C. A. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, **82**, 1810 (1960).
(10) The ΔS^* for the decomposition of the erythro isomer (freed from its water of hydration) in THF was found to be −27.8 eu, but the limit of uncertainty was large.[11] See also ref 12 for evidence regarding the possible polar character for the transition state in thermolyses of 1-arylethyldimethylamine oxides.
(11) M. R. V. Sahyun and D. J. Cram, *J. Amer. Chem. Soc.*, **85**, 1263 (1963).
(12) G. G. Smith and E. Silber, *J. Org. Chem.*, **38**, 4172 (1973).
(13) Melting points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 621 grating spectrophotometer. Proton magnetic resonance spectra were obtained using a Varian Model A-60 spectrometer (δ relative to TMS internal reference). Ultraviolet spectra were determined on a Cary Model 14 recording spectrophotometer.
(14) B. L. Emling, R. J. Horvath, A. J. Saraceno, E. F. Ellermeyer, L. Haile, and L. D. Hudac, *J. Org. Chem.*, **24**, 657 (1959).
(15) R. G. Pews, *J. Org. Chem.*, **32**, 1628 (1967).
(16) E. J. Grubbs, J. D. McCullough, Jr., B. H. Weber, and J. R. Maley, *J. Org. Chem.*, **31**, 1098 (1966).

Thermolysis of Heterocyclic Azides. Rearrangement Involving Acyl Migration from Carbon to Nitrogen

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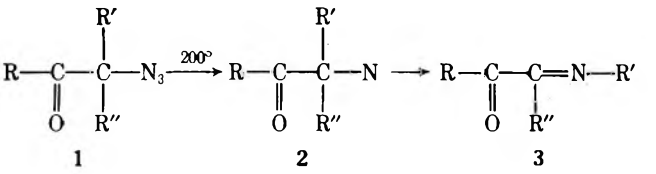
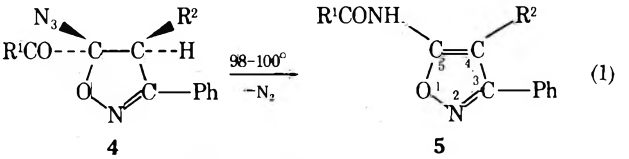
Boyer and Straw have shown that aliphatic α-azidocarbonyl compounds (**1**) decompose at 200 ± 20° to give imines (**3**), probably *via* the intermediacy of nitrenes (**2**).[1] In



1 **2** **3**

this reaction migration of hydrogen, methyl, or phenyl occurred and no acyl migration was observed. We now want to report two examples of acyl migration from carbon to nitrogen when R′ and R″ are part of a heterocyclic ring such as in eq 1.[2]

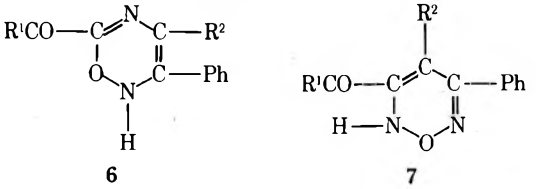


(1)

4 **5**

a, $R^1 = Me$; $R^2 = Ph$
b, $R^1 = Ph$; $R^2 = Me$

The 5-azido-5-acylisoxazolines **4a** and **4b** used in this work were obtained, among other products, from the reactions of α-azidovinyl ketones with benzonitrile oxide.[3] Thermolysis of **4a,b** in toluene at *ca.* 100° resulted in evolution of nitrogen and formation of white crystals which exhibited microanalyses and spectral data consistent with structure **5a,b.** The alternative structures **6** and **7**, which



6 **7**

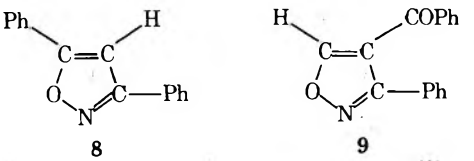
would result from **4** by loss of nitrogen and ring expansion, are easily excluded by the absence of a ketone C-atom absorption at about 190–200 ppm in the ^{13}C nmr spectra.

The chemical shift data of compounds **4a** and **4b** are summarized in Table I. Assignment of the ring carbon absorptions was based on comparison with the model compounds **8** and **9**.[3] These compounds possess CH ring C atoms whose position in the nmr spectra can be determined by the off-resonance spin-decoupling technique. The values reported in Table I are consistent with expectation. Indeed,

Table I
^{13}C Chemical Shifts with Respect to TMS (DMSO-d_6 as Solvent)

Compd	C_3	C_4	C_5
5a[a]	162.4	110	159.1
5b[b]	163.6	103.8	159.5
8	164	97.5	170.5
9	161.6	119.3	163.6
11	161.7	91.4	167.7

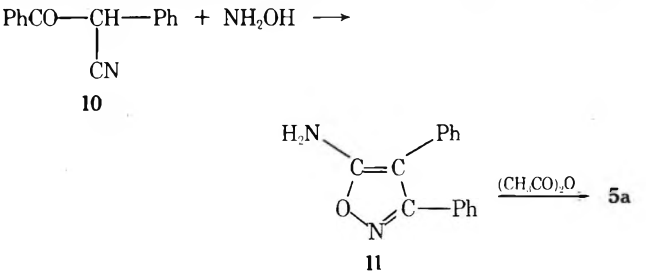
[a] For this compound the CH_3CO carbon atoms absorb at δ 22.6 and 170. Compare these values with δ 24.1 and 169.5 for the acetyl group in acetanilide: L. F. Johnson and W. C. Jankowski, "Carbon-13 Nmr Spectra. A Collection of Assigned, Coded, and Indexed Spectra," Wiley-Interscience, New York, N.Y., 1972, Spectrum no. 295. [b] For this compound the CH_3 and C=O carbon atoms absorb at δ 8 and 165.6.



8 **9**

the C_5 atoms are expected to absorb at low field (relative to benzene, δ 128) since they are located next to an electronegative O atom. The C_4 atoms, on the contrary, experience an electron-donating resonance effect of the O atom and, hence, their absorption lines are shifted upfield.

The structure **5a** was further proven beyond any doubt by an independent synthesis starting from α-benzoylphenylacetonitrile (**10**) and hydroxylamine.[4] The aminoisoxazole **11** formed in this reaction was treated with acetic



anhydride at room temperature to give a product which was identical in all respects with the product obtained by thermolysis of **4a**. The aminoisoxazole **11** was also subjected to ^{13}C nmr analysis and exhibited absorptions consistent with its structure (see Table I). Noteworthy is the lower field absorption of the C_5 atom compared with the corresponding acetyl derivative **5a**. The difference in chemical shift (8.6 ppm) is comparable with that found for the C_1 absorptions of aniline (δ 147.9) and acetanilide (δ 139.8, $\Delta\delta$ 8.1 ppm).[5] Note also that the C_4 atom in **11** not only experiences the mesomeric effect of the O atom, but also that of the amine function which results in a high-field absorption.

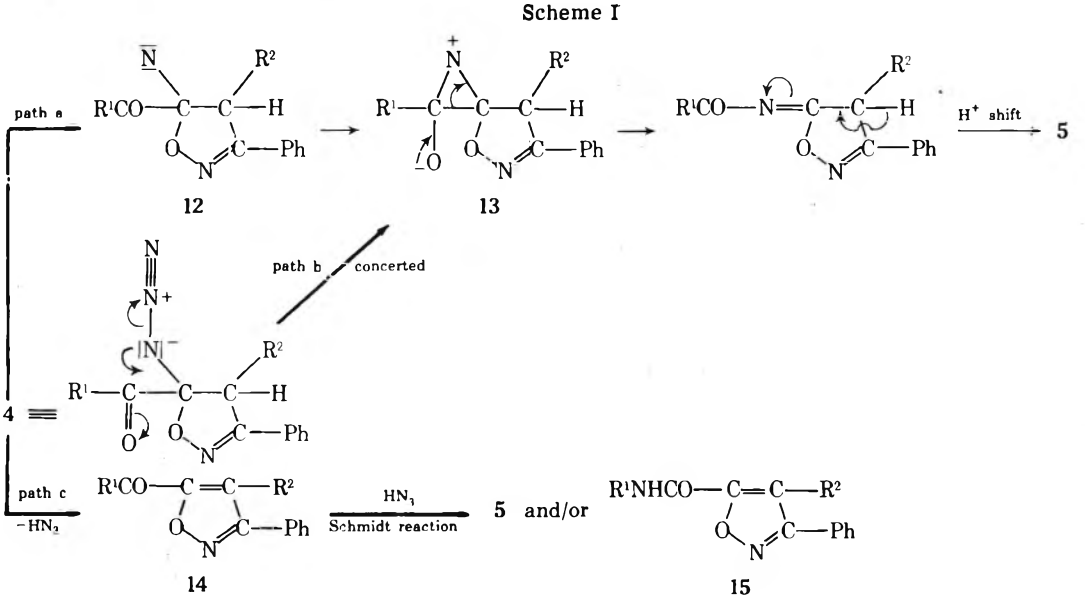
Mechanistically, three pathways can be considered for the reaction **4** → **5** (see Scheme I). The azidoisoxazoline **4** can lose nitrogen to give a nitrene **12**, which then rearranges *via* a nitrenium ion **13** as shown in path a, or the azide can decompose with simultaneous formation of the nitrenium ion **13** as shown in path b. A third possible route involves the elimination of HN_3 at the elevated temperature to produce an 5-acylisoxazole **14** which then undergoes a Schmidt reaction to give **5** (path c). Path c is easily excluded by two facts: (i) 5-acylisoxazoles do not react with HN_3 in boiling toluene, and (ii) reaction under the Schmidt conditions (concentrated sulfuric acid) does not lead to **5** but, instead, is known[6] to produce amides of type **15**. We have prepared compound **15a** from **14a** by the well-known Schmidt reaction[7] in order to compare its spectral characteristics with those of compound **5a** (see Experimental Section). Worth mentioning are the ^1H nmr spectra of both compounds, which showed CH_3–NH coupling in the case of **15a** but not in the case of **5a**, the latter giving rise to a Me singlet absorption and a sharp NH absorption.

Table II
Rate Constants and Activation Parameters for the Thermal Decomposition of 4a in Decalin

Temp, °C	$10^5 k_1$, sec^{-1}	E_a, kcal/mol	ΔS^* (at 101.9°), eu
101.9	4.76	27.9	−3
110.9	11.61		
121.3	31.94		
131.6	74.19		

Since path c can be excluded on the basis of structure determination, we are left with paths a and b, which only differ in the way the nitrenium ion is formed. In order to differentiate between a two-step or concerted process, we have carried out a kinetic investigation of the thermolysis of **4a** in decalin. The results are summarized in Table II. The moderate energy of activation and the low entropy of activation are only consistent with path b (compare these values with E_a = 47.5 kcal/mol and ΔS^* = +32 eu for thermolysis of cyclohexyl azide in ethyl acetate, which proceeds *via* a nitrene).[8] That anchimeric assistence occurs during the thermolysis of **4a** is also evident from the low decomposition temperature (*ca.* 100°) compared with that of aliphatic α-azidocarbonyl compares (*ca.* 200°).[1]

Scheme I



Experimental Section

Melting points were obtained on a Leitz apparatus and are uncorrected. Ir spectra were taken on a Perkin-Elmer 521 spectrometer. ^1H nmr spectra were recorded with a Varian A-60 or XL-100 spectrometer using TMS as an internal reference. For ^{13}C nmr spectra, the XL-100 apparatus was equipped with a device for pulsed Fourier transform operation. Mass spectra were obtained with an AEI MS-12 instrument operating at an ionizing potential of 70 eV.

Thermolysis of 4a. Compound **4a** (1.7 g) was dissolved in dry toluene (10 ml) and then heated at 98–100°. After complete reaction (11 days), the solution was cooled and **5a** crystallized out in

72% yield: mp 154–157° ($CHCl_3$–*n*-pentane); ir (KBr) 3240 (NH), 1692, 1640, 1515 cm^{-1}; nmr ($CDCl_3$) τ 1.68 (NH, exchangeable with D_2O), 2.5–2.8 (m, 10 H), and 7.90 (s, 3 H); mass spectrum *m/e* (per cent) 278 (60, $M^{\cdot+}$), 236 (100, $M^{\cdot+} - CH_2CO$, m* at *m/e* 200.3), 235 (11, $M^{\cdot+} - CH_3CO\cdot$).

Anal. Calcd for $C_{17}H_{14}N_2O_2$ (278): C, 73.37; H, 5.07; N, 10.07. Found: C, 73.65; H, 5.08; N, 9.93.

Thermolysis of 4b. When a toluene solution of **4b** (1.0 g in 5 ml) was heated at 98–100° and then cooled, compound **5b** was obtained in 98% yield: mp 148–149.5° (1:1 $CHCl_3$–ether); ir (KBr) 3270 (NH), 1680, 1642, 1530 cm^{-1}; nmr ($CDCl_3$) τ 1.00 (NH, exchangeable with D_2O), 1.8–2.2 (m, 2 H), 2.25–2.75 (m, 8 H), and 7.98 (s, 3 H); mass spectrum *m/e* (per cent) 278 (54, $M^{\cdot+}$), 175 (16, $M^{\cdot+} - PhCN$), 105 (100, $PhCO^+$).

Anal. Calcd for $C_{17}H_{14}N_2O_2$ (278): C, 73.37; H, 5.07; N, 10.07. Found: C, 73.06; H, 5.08; N, 10.00.

Independent Synthesis of 5a. α-Benzoyl phenylacetonitrile (**10**, 0.02 mol), prepared by the method of Levine and Hauser,[9] was dissolved in pyridine (7 ml) and treated with $NH_2OH \cdot HCl$ (0.02 mol) at room temperature for 24 hr. The suspension was poured into ice–water, and the precipitate was filtered, washed with water, and dried over P_2O_5 to give **11** in 56% yield. Crystallization from water–EtOH (60%) furnished white needles: mp 152–154°; ir (KBr) 3400 (NH), 3300–3180, 1634 cm^{-1}; nmr ($CDCl_3$) τ 2.50–2.90 (m, 10 H) and 5.47 (NH_2, exchangeable with D_2O); mass spectrum *m/e* (per cent) 236 (41, $M^{\cdot+}$), 208 (27, $M^{\cdot+} - CO$, m* at *m/e* 183.3), 105 (100, $PhCO^+$).

Anal. (determined by high-resolution exact mass measurement). Calcd for $C_{15}H_{12}N_2O$: 236.09495. Found: 236.09391.

Another procedure for the preparation of **11** consisted in allowing equimolar amounts (0.04 mol) of **10** and $NH_2OH \cdot HCl$ in EtOH (75 ml) to react at reflux temperature for 2 hr. Then the solution was partially evaporated and cooled to give **11** in 58% yield.

Compound **11** (1.2 g) was dissolved in acetic anhydride (15 ml) and allowed to stand at room temperature for 28 days. After cooling of the reaction mixture, **5a** crystallized out in 70% yield, mp 154–157° (benzene).

Note: When **11** was heated in acetic anhydride or in boiling *m*-xylene containing acetyl chloride, the N,N-diacetylated derivative (mp 145–146.5°) was obtained in high yield (67–84%).

Synthesis of 15a by the Schmidt Reaction. To a magnetically stirred solution of **14a** (0.5 g) in chloroform (15 ml) was added slowly concentrated sulfuric acid (15 ml) and then NaN_3 (1 g). The mixture was stirred for 24 hr at room temperature before being quenched into ice. The yellow precipitate was filtered and crystallized from MeOH (20 ml) to give pure **15a** in 61% yield: mp 196–198°; ir (KBr) 3320 (NH), 1662, 1628, 1530 cm^{-1}; nmr ($CDCl_3$) τ 2.75 (s, 10 H), 3.32 (br, NH, exchangeable with D_2O), and 7.20 (d, 3 H, J = 5 Hz); mass spectrum *m/e* (per cent) 278 (35, $M^{\cdot+}$), 220 (100, $M^{\cdot+} - CH_3NHCO\cdot$, m* at *m/e* 174.1), 192 (30, 220 – CO, m* at *m/e* 167.5).

Anal. Calcd for $C_{17}H_{14}N_2O_2$ (278): C, 73.37; H, 5.03; N, 10.07. Found: C, 73.40; H, 5.05; N, 10.00.

Kinetic Measurements. Decalin solutions of **4a** (*ca.* 1.25 g in 50 ml) were allowed to decompose at the appropriate temperature and the rates of decomposition were followed by recording the decrease of the azide absorption band at about 2130 cm^{-1} in the ir as a function of time. Details concerning the procedure have been described elsewhere.[10]

Acknowledgment. The authors are indebted to the IWONL (Belgium) for a fellowship to one of them (G.M.).

Registry No.—**4a**, 51002-99-4; **4b**, 51003-00-0; **5a**, 52392-71-9; **5b**, 52392-72-0; **10**, 5415-07-6; **11**, 52392-73-1; **11** N,N-diacetylated derivative, 52470-18-5; **14a**, 1631-96-5; **15a**, 52438-82-1; $NH_2OH \cdot HCl$, 5470-11-1.

References and Notes

(1) J. H. Boyer and D. Straw, *J. Amer. Chem. Soc.*, **74**, 4506 (1952); **75**, 1642, 2683 (1953).
(2) Acyl migrations to nitrogen are rare in thermal and photochemical decomposition reactions of azides. Only a few isolated examples have been reported: R. M. Moriarty, J. M. Kliegman, and C. Shovlin, *J. Amer. Chem. Soc.*, **89**, 5958 (1967); R. M. Moriarty and P. Serridge, *ibid.*, **93**, 1534 (1971); H. W. Moore and D. S. Pearce, *Tetrahedron Lett.*, 1621 (1971); D. S. Pearce, M. S. Lee, and H. W. Moore, *J. Org. Chem.*, **39**, 1362 (1974).
(3) G. L'abbé and G. Mathys, *J. Org. Chem.*, **39**, 1221 (1974).
(4) For a review of isoxazoles, see N. K. Kochetkov and S. D. Sokolov, *Advan. Heterocycl. Chem.*, **2**, 365 (1963).
(5) J. B. Stothers, "Carbon-13 Nmr Spectroscopy," A. T. Blomquist and H. Wasserman, Ed., Academic Press, New York, N. Y., 1972, p 295.
(6) P. Vita-Finzi and M. Arbasino, *Ann. Chim. (Rome)*, **54**, 1165 (1964).
(7) D. V. Banthorpe in "The Chemistry of the Azido Group," S. Patai, Ed., Interscience, New York, N. Y., 1971, Chapter 7, p 405.
(8) P. Walker and W. A. Waters, *J. Chem. Soc.*, 1632 (1962).
(9) R. Levine and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 760 (1946).
(10) G. L'abbé and G. Mathys, *J. Org. Chem.*, **39**, 1778 (1974).

Convenient Synthesis of the Tricarbonyliron Complex of Cyclobutadienecarboxylic Acid[1]

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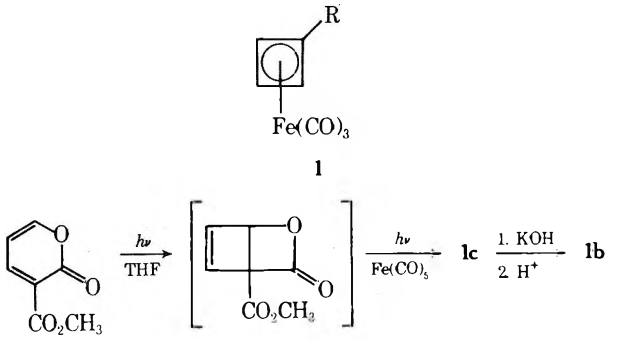
Recently, in connection with another synthetic program, we needed a convenient source of synthetically useful amounts of the tricarbonyliron complex of cyclobutadienecarboxylic acid (**1b**). Earlier preparations of this compound require parent complex **1a** and involve either formylation–oxidation in <1% overall yield[2] or methylthioformylation–hydrolysis in 34% yield.[2b] Because existent methods for preparing **1a** are either expensive or inefficient, we sought a more direct route to **1b** and have found that application of the photopyrone route of Rosenblum and Gatsonis[3] to the readily prepared 3-carbomethoxy-2-pyrone (**2**)[4] provides a convenient entry to monocarboxyl derivatives of **1a** and, by implication, to other types of monosubstituted derivatives.

Experimentally, a solution of **2** in THF is irradiated until disappearance of the pyrone, and the presumed photopyrone **3** is irradiated for 1 hr in the presence of a 100% excess of iron pentacarbonyl. Although the immediate product, methyl ester **1c**, is isolable, it is a liquid and is sensitive to light. Consequently, the product was most conveniently isolated as crystalline **1b** after a saponification step. Quali-



a, R = H
b, R = CO_2H
c, R = CO_2CH_3

tative analysis of the effect of varying irradiation time (during complexation) and relative amount of iron pentacarbonyl indicated that the maximum yield (21%) of **1b** is obtained under the specified conditions.

Experimental Section

Melting points and boiling points are uncorrected. Ir spectra were recorded on a Perkin-Elmer 521 spectrophotometer. Nmr spectra were recorded on a Varian Associates A60-A spectrophotometer using TMS as internal standard. Microanalysis was performed by Galbraith Laboratories, Knoxville, Tenn.

Tricarbonyl[1,2,3,4-η-1,3-cyclobutadienecarboxylic acid]-iron (1b). A solution of 1.00 g (6.50 mmol) of 3-carbomethoxy-2-

pyrone[4] in 180 ml of dry THF was placed in a photochemical reaction vessel immersed in an ice bath and irradiated for 22 hr under nitrogen with a Hanovia 450-W high-pressure mercury lamp fitted with a Pyrex filter. By this time, the pyrone had disappeared as indicated by ir spectroscopy. Iron pentacarbonyl (2.55 g, 13.0 mmol) was then added, and irradiation was continued for 1 hr. The reaction mixture was concentrated on a rotary evaporator at reduced pressure at room temperature,[5] and the residue was washed through a 4.5-in. × 1.5-in. wet-packed column of alumina with methylene chloride (400–500-ml total volume). Crude ester **1c** was obtained by collection and evaporation of the first colored band eluted. This material was immediately mixed with a solution of 0.80 g of 85% potassium hydroxide in 1 ml of water and 5 ml of methanol and stirred for 2 hr. The resulting mixture was combined with 50 ml of water, washed with 50 ml of methylene chloride, acidified with concentrated hydrochloric acid, and extracted with 2 × 50 ml of ether. The ether extracts were dried over magnesium sulfate and evaporated, and the residue was recrystallized from carbon tetrachloride to give 325 mg (21%) of **1b**, mp 147–149° (lit[2b] mp 151–152°), the ir and nmr spectra of which were identical with those reported by Fitzpatrick.[2b]

Tricarbonyl[methyl 1,2,3,4-η-1,3-cyclobutadienecarboxylate]iron (1c). The crude ester obtained in the preceding experiment was purified by preparative tlc (20 cm × 20 cm silica gel plate, development with $CHCl_3$) followed by evaporative distillation [bath temperature 34–38° (1.2 mm)] to give **1c** as a yellow oil: ir ($CHCl_3$) 2068, 1988, and 1709 cm^{-1}; nmr ($CDCl_3$) δ 3.67 (s, 3 H, OCH_3), 4.28 (s, 1 H, para proton), and 4.51 (s, 2 H, ortho protons).

Anal. Calcd for $C_9H_6FeO_5$: C, 43.24; H, 2.42; Fe, 22.34. Found: C, 43.11; H, 2.47; Fe, 22.10.

Registry No.—**1b**, 52571-39-8; **1c**, 52571-40-1; **2**, 25991-27-9; iron pentacarbonyl, 13463-40-6.

References and Notes

(1) This work was supported by Public Health Service Research Grant No. CA-12008 from the National Cancer Institute.
(2) (a) J. D. Fitzpatrick, L. Watts, G. F. Emerson, and R. Pettit, *J. Amer. Chem. Soc.*, **87**, 3254 (1965); (b) J. D. Fitzpatrick, Ph.D. Thesis, University of Texas, Austin, 1966.
(3) M. Rosenblum and C. Gatsonis, *J. Amer. Chem. Soc.*, **89**, 5074 (1967).
(4) E. J. Corey and D. S. Watt, *J. Amer. Chem. Soc.*, **95**, 2303 (1973).
(5) Because **1c** is sensitive to prolonged exposure to light, it was kept in the dark as much as possible during this and subsequent manipulations.

Tetrahydrofuran-Promoted Aryl–Alkyl Coupling Involving Organolithium Reagents

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The reaction of aryl halides with organolithium compounds in diethyl ether or other less polar solvents is dominated by the halogen–metal interconversion[1] (eq 1). The coupling of the aryl and alkyl groups in these solvents generally takes place very slowly.[1] We have noted that the coupling reaction (eq 2) is markedly promoted by tetrahydrofuran (THF),[2] producing cleanly the cross-coupled products in many cases.[2]

$$\mathrm{ArBr} + \mathrm{RLi} \xrightarrow[25^\circ]{\text{ether}} \mathrm{ArLi} + \mathrm{RBr} \quad (1)$$

$$\mathrm{ArBr} + \mathrm{RLi} \xrightarrow[25^\circ]{\mathrm{THF}} \mathrm{ArR} + \mathrm{LiBr} \quad (2)$$

For example, the reaction of 1-bromonaphthalene with *n*-butyllithium in a 1:5 mixture of hexane and THF produces 1-*n*-butylnaphthalene (**1**) in 72% yield within 1 hr at room temperature, whereas the corresponding reaction in a

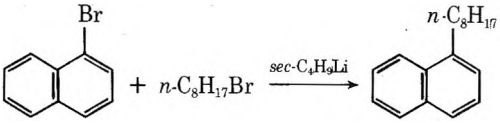
Table I
Tetrahydrofuran-Promoted Aryl–Alkyl Coupling

Aryl reagent	Registry no.	(ArX)	Alkyl reagent	Registry no.	(RY)	Procedure[a]	Product[b]	Registry no.	Yield, %[c]
o-Tolyl	95-46-2	Br	*n*-Butyl	109-72-8	Li	I	*o*-*n*-Butyltoluene[d]	1595-11-5	65
m-Tolyl	591-17-3	Br	*n*-Butyl		Li	I	*m*-*n*-Butyltoluene[e]	1595-04-6	63
p-Tolyl	106-38-7	Br	*n*-Butyl		Li	I	*p*-*n*-Butyltoluene[f]	1595-05-7	69
1-Naphthyl	90-11-9	Br	*n*-Butyl		Li	I	1-*n*-Butylnaphthalene[g]	1634-09-9	66 (72)
1-Naphthyl		Br	*sec*-Butyl	598-30-1	Li	I	1-*sec*-Butylnaphthalene	1680-58-6	(<1)
1-Naphthyl		Br	*t*-Butyl	594-19-4	Li	I	1-*tert*-Butylnaphthalene	17085-91-5	(<1)
4-Methyl-1-naphthyl	6627-78-7	Br	*n*-Butyl		Li	I	1-*n*-Butyl-4-methylnaphthalene[h]	52718-76-0	52
4-Methyl-1-naphthyl		Br	Ethyl	811-49-4	Li	I	1-Ethyl-4-methylnaphthalene[i]	27424-87-9	60
2-Methyl-1-naphthyl	2586-62-1	Br	Ethyl		Li	I	1-Ethyl-2-methylnaphthalene[j]	17057-93-1	66
Phenyl	591-51-5	Li	*n*-Octyl	111-83-1	Br	II	*n*-Octylbenzene[g]	2189-60-8	82 (87)
Phenyl	108-86-1	Br	*n*-Octyl		Br	III	*n*-Octylbenzene		70 (76)
1-Naphthyl		Br	*n*-Octyl		Br	III	1-*n*-Octylnaphthalene[g]	2876-51-9	60 (74)

[a] For definition of procedures I, II, and III, see the Experimental Section. [b] All isolated products yielded satisfactory pmr and ir data, and 1-*n*-butyl-4-methylnaphthalene gave the correct analytical data. [c] By isolation. The numbers in parentheses are yields by glpc (SE-30). [d] n^{25}D 1.4933 (lit.[7] n^{20}D 1.4960). [e] $n^{25.5}$D 1.4892 (lit.[7] n^{20}D 1.4910). [f] $n^{25.5}$D 1.4886 (lit.[7] n^{20}D 1.4916). [g] For physical constants, see the Experimental Section. [h] Bp 91–94° (0.04 mm); n^{20}D 1.5729. [i] Bp 83–86° (0.25 mm); n^{25}D 1.5976 [lit.[6] bp 122° (40 mm)]. [j] Bp 76–79° (0.15 mm); n^{25}D 1.5974 [lit. bp 133–134° (15 mm) from R. B. Carlin and K. P. Sivaramakrishnan, *J. Org. Chem.*, **35**, 3368 (1970)].

1:5 mixture of hexane and diethyl ether yields only 3% of 1 over the same period at the same temperature.

As summarized in Table I, a wide variety of aryl halides react readily with primary alkyllithiums to produce the cross-coupled products in high yields. On the other hand, secondary and tertiary alkyllithiums do not give the cross-coupled products in any appreciable yields under the comparable conditions. These results suggest that the actual coupling step involves the interaction of aryllithiums with alkyl halides formed by the halogen–metal exchange reaction. Indeed, phenyllithium prepared from bromobenzene and lithium metal reacted with *n*-octyl bromide in the presence of THF to produce *n*-octylbenzene in 87% yield within 2 hr at room temperature. Based on these results we have developed the following convenient procedure involving the use of a hindered alkyllithium, *i.e.*, *sec*-butyllithium. 1-Bromonaphthalene was treated sequentially with equimolar quantities of *sec*-butyllithium and *n*-octyl bromide to provide 1-*n*-octylnaphthalene (**2**) in 74% yield (eq 3). Only trace quantities of 1-*sec*-butylnaphthalene and 3-



(3)

2

methylundecane were present. The benzyne mechanism[4] does not appear significant, since no 2-naphthyl derivatives were detected.

It should be noted that any of the three procedures described here provides a convenient alternative to the Wurtz–Fittig route for the coupling of aryl halides with alkyl halides.

Experimental Section

The following examples are representative of the three procedures discussed in this report.[5]

Preparation of 1-*n*-Butylnaphthalene by the Reaction of 1-Bromonaphthalene with *n*-Butyllithium (Procedure I). To a dry 100-ml flask equipped with a magnetic stirring bar, a septum inlet, and an outlet connected to a mercury bubbler were introduced sequentially 20 ml of THF, 2.07 g (1.41 ml, 10 mmol) of 1-bromonaphthalene, and 4.30 ml (11 mmol) of 2.56 *M* *n*-butyllithium in hexane while controlling the reaction temperature at 25 ± 5°. After stirring the mixture for 2 hr, it was washed with water and aqueous sodium chloride. The combined aqueous layer was extracted with chloroform and the combined organic layer was dried over magnesium sulfate, evaporated, and distilled to yield 1.21 g (66% yield) of 1-*n*-butylnaphthalene: bp 78–80° (0.05 mm); n^{25}D 1.5807 [lit.[6] bp 289°; n^{20}D 1.5819]; pmr (CCl_4, TMS) δ 0.8–2.0 (m, 7 H), 3.00 (t, 2 H, *J* = 7.5 Hz), 7.2–8.1 (m, 7 H) ppm; ir (neat) 797, 785 (sh), 775 cm^{-1}.

Preparation of *n*-Octylbenzene by the Reaction of Phenyllithium with *n*-Octyl Bromide (Procedure II). In a setup similar to that described above 5.56 ml (10 mmol) of 1.80 *M* phenyllithium in a 70:30 mixture of benzene and diethyl ether and 2.12 g (1.89 ml, 11 mmol) of *n*-octyl bromide in 20 ml of THF were reacted at 25 ± 5° for 2 hr. The mixture was worked up in a manner analogous to that described above to give 1.56 g (82%) of *n*-octylbenzene: bp 82–85° (0.5 mm); n^{25}D 1.4832 [lit.[7] bp 131–134° (12 mm); n^{20}D 1.4851]; pmr (CCl_4, TMS) δ 0.7–1.9 (m, 15 H), 2.58 (t, 2 H, *J* = 7.5 Hz), 7.12 (s, 5 H) ppm; ir (neat) 745, 695 cm^{-1}.

Preparation of 1-*n*-Octylnaphthalene by the Coupling of 1-Bromonaphthalene and *n*-Octyl Bromide under the Influence of *sec*-Butyllithium (Procedure III). In a setup similar to that described above 2.07 g (1.41 ml, 10 mmol) of 1-bromonaphthalene in 10 ml of diethyl ether was treated at room temperature with 13.7 ml (11 mmol) of 0.80 *M* *sec*-butyllithium in hexane. After stirring the mixture for 10 min 2.12 g (1.89 ml, 11 mmol) of *n*-octyl bromide and 10 ml of THF were added in this order at 25 ± 5°. The mixture was stirred for 3 hr and then worked up as described above to yield 1.59 g (66%) of 1-*n*-octylnaphthalene: bp 120–123° (0.05 mm); n^{24}D 1.5515 [lit.[8] bp 144.5° (0.2 mm); n^{20}D 1.5533]; pmr (CCl_4, TMS) δ 0.7–2.0 (m, 15 H), 3.01 (t, 2 H, *J* = 7.5 Hz), 7.2–8.1 (m, 7 H) ppm; ir (neat) 797, 788, 776 cm^{-1}.

Acknowledgment. We thank Research Corporation and Syracuse University for financial support.

References and Notes

(1) R. G. Jones and H. Gilman, *Org. React.*, **6**, 339 (1951).
(2) The marked rate-accelerating effect of THF in the aryl-alkyl coupling reaction producing the cross-coupled products in high yields does not appear to have been clearly documented.[1,3]
(3) A rate-accelerating effect of THF in certain aryl–aryl coupling reactions has been reported: H. Gilman and B. J. Gaj, *J. Org. Chem.*, **22**, 447 (1957). These reactions almost certainly proceed *via* the benzyne mechanism. In a report describing the reaction of alkyl or aryl halides with lithium metal in THF, the same authors [H. Gilman and B. J. Zaj, *J. Org. Chem.*, **22**, 1165 (1957)] made the following observations: (1) the yields of alkyl- or aryllithiums decrease in the order Cl > Br > I, (2) the higher the reaction temperature, the lower the yields were. These results were rationalized in terms of the rate-accelerating effect of THF in the alkyl–alkyl or aryl–aryl coupling. However, no product study was made.
(4) See, for example, G. Wittig, *Angew. Chem., Int. Ed. Engl.*, **4**, 731 (1965).
(5) All reactions were carried out under a nitrogen atmosphere with precautions to exclude air and moisture. Diethyl ether and THF were purified by distillation from lithium aluminum hydride. The pmr spectra were obtained using a Varian A-60 nmr spectrometer.
(6) G. Harris, J. R. A. Pollock, and R. Stevens Ed., "Dictionary of Organic Compounds," Oxford University Press, New York, N.Y., 1965.
(7) R. C. Weast Ed., "Handbook of Chemistry and Physics," 52nd ed, The Chemical Rubber Co., Cleveland, Ohio, 1971.
(8) B. Barrowsmith, G. H. Jeffery, and A. I. Vogel, *J. Chem. Soc.*, 2072 (1965).
(9) R. B. Carlin and K. P. Sivaramakrishnan, *J. Org. Chem.*, **35**, 3368 (1970).

Regeneration of Ketones from Tosylhydrazones

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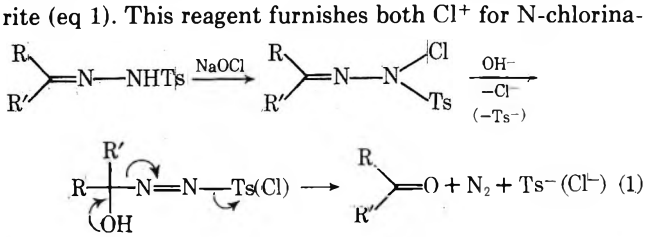
Tosylhydrazones serve as intermediates for the synthesis of olefins[1] and the creation of carbenes.[2] Those derived from α,β-epoxy ketones undergo fragmentation readily to afford acetylenic carbonyl compounds.[3] Generally, tosylhydrazones are highly crystalline, therefore they should be valuable for the characterization and purification of carbonyl substances. However, this last potential utility and also their applicability as protective device have been virtually completely ignored, presumably owing to their high hydrolytic stability.

Thus the recovery of carbonyl compounds from tosylhydrazones represents a pragmatic problem yet to be resolved. During the regenerative process, a hydroxyl group is to be attached to the imino carbon, and, to augment the electrophilicity of this center toward water or hydroxide ion, an additional electron-withdrawing, good leaving group has to be temporarily introduced to the tosyl-bearing nitrogen. According to our plan, such an operation is in fact mandatory, because a combination of an SN2′ displacement and then a fragmentation is required for the ultimate generation of the carbonyl and the release of molecular nitrogen. Further elaboration of this scheme indicated that the most elegant and convenient way to effect the overall transformation would be the reaction with alkali hypochlorite (eq 1). This reagent furnishes both Cl^+ for N-chlorination and OH^- for deprotonation and the nucleophilic attack.



(1)

Treatment of tosylhydrazones with a commercial bleach solution rapidly reverted them in one step to the parent ketones, thereby confirming the validity of our proposal. The timing of the double extrusion (Cl^-, Ts^-) cannot be determined but it is immaterial from the synthetic standpoint.

Table I
Ketones from Tosylhydrazones

Ketone	Yield, %
Benzophenone	85
Acetophenone	69
Cyclohexanone	60
2-Methylcyclohexanone	63
Norcamphor	62

Acetophenone has been similarly obtained in reasonable yield, even though it is susceptible to further degradation (haloform reaction). Unfortunately the procedure is not very suitable for cleavage of aldehyde derivatives, since aldehydes were recovered in rather low yields, perhaps due to oxidation by hypochlorite.

Experimental Section

General Procedure for the Hydrolysis of Ketone Tosylhydrazones. The tosylhydrazone (1.0 g), dissolved or suspended in chloroform (30 ml), was shaken with 5% NaOCl (20 ml) for 5 min. The organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated. Distillation of the residue gave the ketone.

Registry No.—Benzophenone, 119-61-9; benzophenone tosylhydrazone, 4545-20-4; acetophenone, 98-86-2; acetophenone tosylhydrazone, 4545-21-5; cyclohexanone, 108-94-1; cyclohexanone tosylhydrazone, 4545-18-0; 2-methylcyclohexanone, 583-60-8; 2-methylcyclohexanone tosylhydrazone, 52826-41-2; norcamphor, 497-38-1; norcamphor tosylhydrazone, 38397-34-1.

References and Notes

(1) R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967).
(2) W. R. Bamford and T. S. Stevens, *J. Chem. Soc.*, 4735 (1952); L. Friedman and H. Shechter, *J. Amer. Chem. Soc.*, **81**, 5513 (1959); **83**, 3159 (1961).
(3) A. Eschenmoser, D. Felix, and G. Ohloff, *Helv. Chim. Acta*, **50**, 708 (1967); J. Schreiber, *et al.*, *ibid.*, **50**, 2101 (1967).

Communications

Sulfonyl Thiocyanates and Their Additions to Olefins, Acetylenes, and Allenes

Summary: Sulfonyl thiocyanates may be readily prepared from the appropriate sodium sulfinate and thiocyanogen; these new members of the sulfonyl halide/pseudohalide class react with unsaturated hydrocarbons to provide β-thiocyanatosulfones.

Sir: Investigations into the synthetic use of sulfonyl iodides (**2**, X = I)[1-3] coupled with the recent reports concerning the synthesis[4] and chemistry[5] of sulfonyl cyanides (**2**, X = CN) kindled our interest in the possible preparation of other sulfonyl pseudohalides. Perhaps the most facile method for preparing **2** is *via* the reaction of an aqueous solution of the sodium salt of the appropriate sulfinic acid (**1**) with molecular iodine (X = Y = I), or with cyanogen chloride (X = CN; Y = Cl). Considering the similar reac-

$$\underset{\mathbf{1}}{ArSO_2^-Na^+} + XY \longrightarrow \underset{\mathbf{2}}{ArSO_2X} + NaY$$

tivities of molecular iodine and thiocyanogen,[6] it was felt the generation of **2** (X = SCN) was a rational goal.[7]

The finding that thiocyanogen is relatively stable as a benzene solution in contact with water[8] (at least at temperatures below 10°) provided the opportunity for attempting the synthesis of *p*-toluenesulfonyl thiocyanate in a manner similar to that employed for the analogous cyanide[4b] and iodide.[2]

A clear, pale yellow benzene solution of **2** (X = SCN) was obtained on mixing a cold, aqueous solution of sodium *p*-toluenesulfinate with a benzene solution of thiocyanogen. Similarly, solutions of the methyl and ethyl homologs were prepared. In practice the sulfonyl thiocyanate could be used in this form or, with the aryl derivative, it could be isolated (64%) as a crystalline solid. *p*-Toluenesulfonyl thiocyanate is a moderately stable, white solid, mp 37–39°, which undergoes only slow decomposition when refrigerated. Decomposition is obvious after 1 month as noted by a dark yellow color and the odor of sulfur dioxide. At elevated temperatures this process is accelerated. Confirmation of the structure was provided by elemental analysis, and nmr, ir, and mass spectral data (see supplementary pages). Supporting this structure is the known reactions of thiocyanogen with various nucleophiles invariably providing the corresponding thiocyanate. In addition, *p*-toluenesulfonyl thiocyanate, on standing in absolute ethanol for 24 hr at room temperature, provided a virtually quantitative yield of ethyl *p*-toluenesulfonate.

Table I
Reactions of Sulfonyl Thiocyanates with Unsaturated Hydrocarbons

Reaction	RSO_2-SCN, R	Unsaturated hydrocarbon	% yield of isolated adduct	Mp, °C, of adduct
1	*p*-Tol	Styrene	43	112–112.5
2	*p*-Tol	Cyclohexene	84	90–92
3	Me	Cyclohexene	57	89–91
4	*p*-Tol	Phenylethyne	79	111–112
5	*p*-Tol	Cyclohexylethyne	68	116–117
6	*p*-Tol	3-Hexyne	5	70–72
7	Me	3-Hexyne	13	53–55
8	Et	Cyclohexene	35	71–72
9	*p*-Tol	3-Methyl-1,2-butadiene	53	99–100
10	Me	3-Methyl-1,2-butadiene	12	66–67

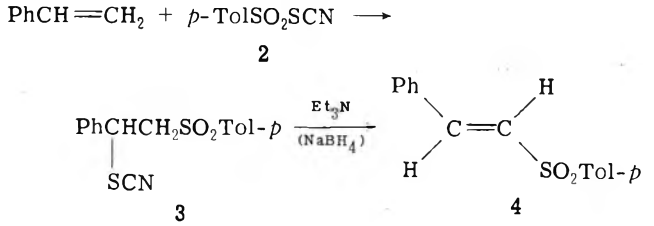
Bacon, *et al.*, have shown that arylalkyl hydrocarbons may undergo homolytic thiocyanation with either thiocyanogen or thiocyanogen chloride.[9] It has also been noted that sulfonyl iodides (but not sulfonyl cyanides) undergo a very facile free-radical addition to unsaturated hydrocarbons.[2] Under more rigorous conditions, sulfonyl cyanides react with olefins, but not with acetylenes.[5] It has now been found that combination of a sulfonyl thiocyanate (aryl or alkyl) and an unsaturated hydrocarbon (olefin, acetylene, or allene) provides a fair to good yield of a product giving the correct elemental analysis for a 1:1 adduct. That this material is a thiocyanate rather than an isothiocyanate was

confirmed by the ir spectrum. Thus, all adducts in Table I showed a very strong, sharp band between 4.64 and 4.67 μ. Isothiocyanates are known to absorb at longer wavelength—4.67–5.26 μ—and these bands are usually broad.[10] We have been unable to detect any appreciable amount of isothiocyanate (by ir) in any of the crude reaction mixtures.[11]

That the reactions are homolytic in quality is supported by the nature of the adducts obtained which are analogous to those obtained in the known free-radical additions of sulfonyl iodides. Consistent also is the fact that large quantities of polystyrene were obtained in the reaction of methanesulfonyl thiocyanate with styrene. The biting odor of sulfur dioxide was noted during the reactions in which alkanesulfonyl thiocyanates were employed; this observation is consistent with the intermediacy of $RSO_2\cdot$, which decomposes to $R\cdot$ and SO_2.

The yields listed in Table I have not been optimized though it has been found that these additions require a large excess of hydrocarbon for best results. Thus, in reaction 2, as the molar ratio of cyclohexene was increased in the manner 1:1, 2:1, 4:1, and 10:1, the corresponding yields of isolated product were 15, 38, 53, and 84%. The yields given in Table I are the result of hydrocarbon excesses ranging from 2:1 to 10:1.

Careful monitoring of several of the reactions (1–4, 9) by both tlc and glpc methods has revealed, in addition to starting materials and very slow moving components (most certainly polymeric in nature) no more than 10% minor products with R_f values and retention times comparable with those of the isolated adducts.



That structure **3** correctly represents the adduct obtained in the *p*-toluenesulfonyl thiocyanate addition to styrene was confirmed by its further, facile conversion to **4** (93%). Based on the known trans additions of sulfonyl iodides, it seems reasonable to assign structures resulting from trans addition of the sulfonyl and thiocyanato moieties in reactions 2–8; however, this matter is currently under investigation.

The spectral data of the adducts from reactions 9 and 10 confirm that addition has occurred to the less substituted double bond. The nmr spectrum of the adduct from reaction 10 shows three unequal methyl groups as singlets, in addition to a methylene group (singlet). With 9, one of the methyl groups is replaced by a *p*-tolyl function. That the thiocyanato group was attached to the terminal carbon was determined by the interesting borohydride conversion of this latter adduct to 2-(*p*-toluenesulfonyl)-3-methylbut-1-ene in 57% yield. Similar borohydride treatment of **3** provided **4** in 88% yield.

Though the chemistry of these 1:1 adduts may, in some respects, resemble that found when sulfonyl iodides are employed, the presence of the thiocyanato moiety in the current compounds provides an unusually reactive functionality which should be subject to the known transformation of thiocyanates,[6] thereby providing access to numerous unique β-substituted sulfones.

Acknowledgment. Thanks are expressed to Dr. R. T. Blickenstaff for his encouragement and suggestions and to G. Wagoner for technical assistance.

Supplementary Material Available. A full experimental section describing the synthesis of all adducts in Table I, as well as the preparation of **4**, **6**, and *p*-toluenesulfonyl thiocyanate will appear following these pages in the microfilm edition of this volume of the journal. Additionally, full nmr, ir, and analytical data are tabulated. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3454.

References and Notes

(1) W. E. Truce and G. C. Wolf, *Chem. Commun.*, 150 (1969).
(2) W. E. Truce and G. C. Wolf, *J. Org. Chem.*, **36**, 1727 (1971).
(3) W. E. Truce, D. L. Heuring, and G. C. Wolf, *J. Org. Chem.*, **39**, 238 (1974).
(4) (a) A. M. van Leusen, A. J. W. Iedema, and J. Strating, *Chem. Commun.*, 440 (1968); (b) J. M. Cox and R. Ghosh, *Tetrahedron Lett.*, 3351 (1969); (c) R. G. Pews and F. P. Corson, *Chem. Commun.*, 1187 (1969).
(5) R. G. Pews and T. E. Evans, *Chem. Commun.*, 1397 (1971), and references cited therein.
(6) J. L. Wood, *Org. React.*, **3**, 240 (1946).
(7) Unknown at the outset of this work was a patent briefly describing the preparation of five arylsulfonyl thiocyanates [J. Goerdeler and P. Rosenthal, German Patent 1,219,021 (1966); *Chem. Abstr.*, **66**, 2371 (1967)]; further details concerning the properties and reactions of these materials have not been forthcoming.
(8) R. P. Welcher and P. F. Cutrufello, *J. Org. Chem.*, **37**, 4478 (1972).
(9) (a) R. G. R. Bacon and R. G. Guy, *J. Chem. Soc. (London)*, 2428 (1961); (b) R. G. R. Bacon, R. G. Guy, and R. S. Irwin, *ibid.*, 2436 (1961).
(10) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 117.
(11) The possibility of obtaining isothiocyanates was validly raised by one of the reviewers; we have found, and intend to report in detail later, that indeed some of our adducts may be readily isomerized to the corresponding isothiocyanates.

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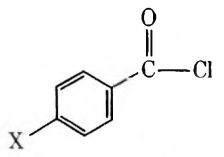
Condensation of *tert*-Butyl α-Lithioisobutyrate with Acid Chlorides. A Synthesis for β-Keto Acids and Ketones

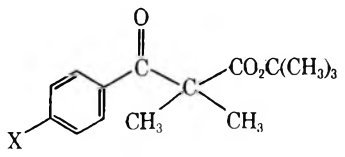
Summary: The acylation of *tert*-butyl α-lithioisobutyrate with benzoyl chlorides gives the corresponding β-keto esters in good yield, and subsequent treatment of these esters with trifluoroacetic acid either at room temperature or at reflux affords β-keto acids or isobutyrophenones, respectively.

Sir: Recently dianions of carboxylic acids[1] and *O*-silyl ketene acetals[2] have been used to prepare β-keto acids and β-keto esters, respectively. However, the former method does not work well for the preparation of α-benzoyl carboxylic acids and the latter method is inapplicable to the synthesis of α,α-disubstituted β-keto esters. Herein we report a new procedure[3] for the facile synthesis of both of these classes of compounds and for their conversion into the corresponding ketones.

Treatment of *tert*-butyl α-lithioisobutyrate with benzoyl chlorides (**1**) gave the *tert*-butyl α-benzoylisobutyrates[4] (**2**) in fair to good yields.[5] The *tert*-butyl esters **2** upon treatment with trifluoroacetic acid for 15 min at room temperature afforded the β-keto acids[6] **3** in quantitative yield. The corresponding ketones **4** can be readily prepared, essentially quantitatively, by heating solutions of **2** in trifluoroacetic acid under reflux for 1 hr.

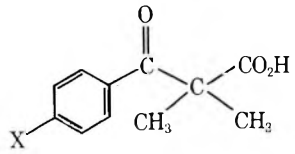


1a–e

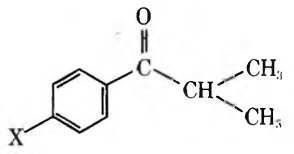


2a–e

a, X = H 55% d, X = Cl 68%
b, X = CH_3 68% e, X = NO_2 22%
c, X = OCH_3 80%



3a–e



4a–e

The nmr spectrum of **2a** in trifluoroacetic acid exhibited a *tert*-butyl resonance at δ 1.38 that disappeared after 45 sec with a simultaneous appearance of a new resonance (a singlet integrating for nine protons) at δ 1.60 that remained even after decarboxylation to **4a** was complete. The only reasonable assignment of the δ 1.60 resonance is to *tert*-butyl trifluoroacetate. Thus, isobutylene is not expelled from solution when esters **2** are dissolved in trifluoroacetic acid, but rather the elements of isobutylene are transferred from **2** to trifluoroacetic acid generating *tert*-butyl trifluoroacetate.[7] These observations clearly indicate that the original 15-min period used for the conversions of **2** to **3** was much longer than necessary.

This use of *tert*-butyl α-lithio esters offers great promise for the synthesis of a wide variety of substituted ketones, especially α-monoalkylated ketones that are difficult to prepare by other means. These aspects are presently under investigation.

The procedure for the synthesis of **2a** is representative.[8] To a solution of 20 mmol of *tert*-butyl α-lithioisobutyrate[9] dissolved in 25 ml of dry benzene at 0° was added a solution of 22 mmol of benzoyl chloride dissolved in 10 ml of dry benzene over 2 min. The cooling bath was removed and the reaction mixture allowed to come to room temperature. The reaction mixture was extracted with 10% potassium carbonate solution, washed with water and saturated brine, and filtered through anhydrous calcium sulfate. After the removal of solvent under reduced pressure, the yellow residue was chromatographed on silica gel with hexane to give **2a** as a colorless solid: mp 65.5–66.3°; ir (CCl_4) 1725, 1680, 1390, and 1385 cm^{-1}; nmr (CCl_4) δ 1.28 (s, 9), 1.47 (s, 6), 7.5–8.1 (m, 5).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Supplementary Material Available. The experimental procedures for the reactions described in this investigation will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3455.

References and Notes

(1) Y. N. Kuo, J. A. Yahner, and C. Ainsworth, *J. Amer. Chem. Soc.*, **93**, 6321 (1971).
(2) M. W. Rathke and D. F. Sullivan, *Tetrahedron Lett.*, 1297 (1973).
(3) M. W. Rathke and J. Deitch, *Tetrahedron Lett.*, 2953 (1971), have used a similar method for the synthesis of ethyl β-keto esters, but these β-keto esters are not suitable for the preparation of β-keto acids, and difficulties are often encountered in converting them to ketones.
(4) L. Lochmann and D. Lim, *J. Organometal. Chem.*, **50**, 9 (1973), briefly mention the fact that *tert*-butyl α-lithioisobutyrate reacts with benzoyl chloride to give **2a**.
(5) No attempts have been made to optimize yields at this stage.
(6) All compounds were characterized by ir and nmr spectroscopy, and satisfactory combustion analyses were obtained for all new substances, except for the labile β-keto acids.
(7) G. A. Latremouille and A. M. Eastham, *Can. J. Chem.*, **45**, 11 (1967), have shown that *tert*-butyl trifluoroacetate is rapidly formed upon addition of isobutylene to cold (−40°) trifluoroacetic acid.
(8) In the case of **1e** an inverse addition of the *tert*-butyl α-lithioisobutyrate at −78° to *p*-nitrobenzoyl chloride was necessary in order to obtain **2e**.
(9) *tert*-Butyl α-lithioisobutyrate was prepared in the manner of *tert*-butyl α-lithioacetate; see M. W. Rathke and D. F. Sullivan, *J. Amer. Chem. Soc.*, **95**, 3050 (1973).

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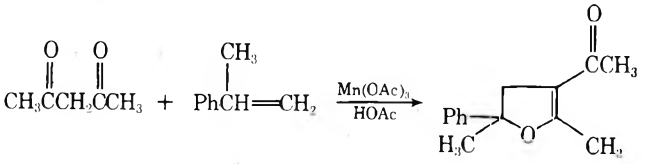
Oxidation by Metal Salts. XI. The Formation of Dihydrofurans

Summary: Dihydrofurans are formed in high yields by the reaction of readily enolizable ketones, such as β diketones and β-keto esters, with olefins in the presence of manganic acetate. The free-radical mechanism for their formation is presented and contrasted with the ionic mechanism observed in the case of lead tetraacetate, which leads to an isomeric product.

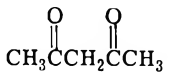
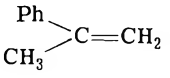
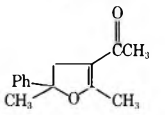
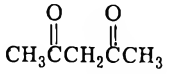
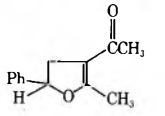
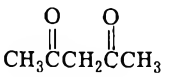
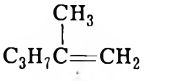
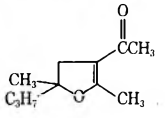
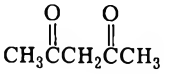
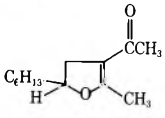
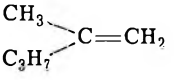
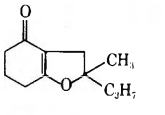
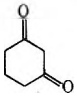
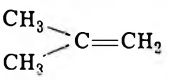
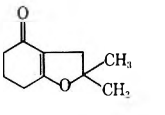
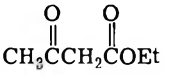
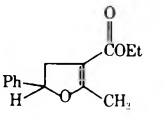
Sir: In an earlier communication[1] we described a novel free-radical addition reaction of enolizable ketones to olefins which took place in the presence of such oxidants as manganic acetate. The major products observed in these reactions were a saturated ketone, an unsaturated ketone, and a ketoacetate; the relative distribution of which depended on the reaction conditions and the nature of the reagents employed.

We now wish to report the facile formation of dihydrofurans in this reaction when highly enolizable ketones such as β diketones and β-keto esters are used as one of the reagents. Thus, the reaction of manganic acetate with acetylacetone and α-methylstyrene afforded the dihydrofuran[2] shown in quantitative yield, based on the manganic ion consumed. In a typical experiment, 0.25 mol of $Mn(OAc)_3 \cdot 2H_2O$, prepared from potassium permanganate and manganous acetate,[3] was dissolved in 1 l. of glacial acetic acid at 45° under nitrogen. To this solution was added a mixture of 15.3 g of α-methylstyrene (0.13 mol) and 75 g of acetylacetone (0.75 mol). The reaction was over in 10 min as evidenced by the disappearance of the brown manganic color. The product dihydrofuran was isolated by extraction with ether followed by distillation. Examples of other dyhydrofurans synthesized *via* this method are shown in Table I.



The formation of these dihydrofurans can best be explained by our previously postulated mechanism[1,4] based on the selective generation of α-keto radicals from enolizable ketones and the selective oxidation of organic free radicals, the details of which are shown in Scheme I. The predominant formation of dihydrofurans from β-dicarbonyl compounds contrasts sharply with the low yield found in

Table I
Synthesis of Dihydrofurans

Ketone	Olefin	Dihydrofuran	Yield,[a] %
			100
	PhCH=CH$_2$		30
			40
	C$_6$H$_{13}$CH=CH$_2$		10 (33)[b]
			74
			>40
	PhCH=CH$_2$		57

[a] Yields are based on Mn^{3+} consumed, assuming 2 equiv/mol of product. [b] In the presence of trifluoroacetic acid as cosolvent.

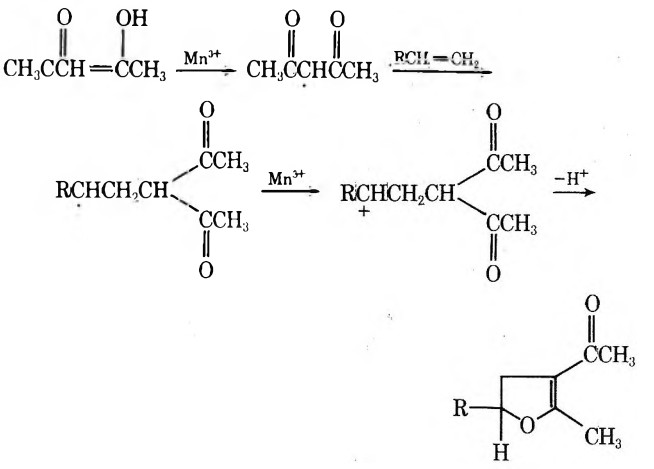
the case of simple ketones (2-methyl-5-phenyl-4,5-dihydrofuran was obtained as a very minor product in the reaction of acetone with styrene). This can be rationalized on the basis of the more rapid cyclization of the carbonium ion intermediate due to the greater enol content of these dicarbonyl compounds, as well as the greater stability of the resulting carbonyl-stabilized dihydrofuran products toward acid-catalyzed ring opening under reaction and work-up conditions.[5]

The dihydrofurans produced in the manganic acetate reaction of acetylacetone with terminal olefins have in all cases consisted of only one isomer, namely, the 5-substituted 2-methyl-3-acetyl-4,5-dihydrofuran. This stands in sharp contrast to the dihydrofuran reported in the thallic acetate reaction of acetylacetone with styrene,[6] where only the 4-substituted isomer was observed. The corresponding reaction of lead tetraacetate led to either one or both isomers, depending on the solvent employed.[7] At that time, two competing ionic mechanisms were proposed,[7] although the controlling factors for these two paths remained unexplained.

Our experience with manganic acetate now suggests that the 5 isomer is produced exclusively *via* a free-radical mechanism as depicted in Scheme I. The formation of the 4 isomer can then be rationalized by an ionic mechanism similar to that suggested,[6,7] in which a benzylic carbonium ion is produced by attack of the electrophilic metal acetate, which then, in turn, adds to the diketone.

The effect of solvent on the $Pb(OAc)_4$ reaction can be understood in terms of the well-established competition between ionic and free-radical pathways characteristic of

Scheme I



lead tetraacetate,[8] both of which occur in the polar acetic acid solvent, whereas only the free-radical product is observed in benzene. This mechanistic explanation is consistent with the reported formation of the 5-substituted dihydrofuran in the electrochemical oxidative addition of sodium acetylacetonate to olefins,[9] which presumably is a free-radical reaction similar to that of manganic acetate.

The simple one-step synthesis of dihydrofurans presented in this communication represents one more example of syntheses based on the selective generation and oxidation of organic free radicals. Further examples of such syntheses will be presented in forthcoming publications.

Acknowledgment. The skillful technical assistance of George Stead is gratefully acknowledged.

References and Notes

(1) E. I. Heiba and R. M. Dessau, *J. Amer. Chem. Soc.*, **93**, 524 (1971).
(2) The dihydrofuran analyzed for $C_{14}H_{16}O_2$: mol wt (mass spectrum) 216; ir peaks at 5.96, 6.15, 6.24, 7.22, and 8.02 μ; nmr τ 8.35 (3 H, s), 7.85 (3 H, s), 7.7 (3 H, tr, J = 1.4 Hz), 6.9 (2 H, m), 2.7 (5 H, m).
(3) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **91**, 138 (1969).
(4) E. I. Heiba and R. M. Dessau, *J. Amer. Chem. Soc.*, **94**, 2888 (1972).
(5) L. H. Brannigan and D. S. Tarbell, *J. Org. Chem.*, **35**, 639 (1970).
(6) K. Ichikawa, S. Uemura, and T. Sugita, *Tetrahedron*, **22**, 407 (1966).
(7) K. Ichikawa and S. Uemura, *J. Org. Chem.*, **32**, 493 (1967).
(8) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **90**, 2706 (1968); R. O. C. Norman and C. B. Thomas, *J. Chem. Soc. B*, 771 (1967).
(9) H. Schafer and A. Alazrak, *Angew. Chem., Int. Ed. Engl.*, **7**, 474 (1968).

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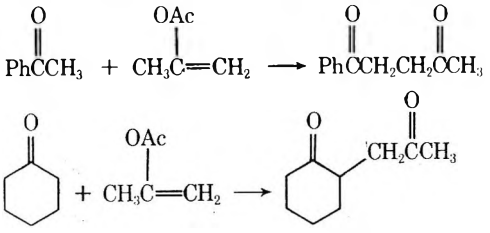
Oxidation by Metal Salts. XII. A Novel One-Step Synthesis of 1,4 Diketones

Summary: A convenient one-step synthesis of 1,4 diketones by the reaction of enol esters with ketones in the presence of manganic acetate is presented.

Sir: As a continuation of our interest in the development of new synthetic methods based on the selective generation and oxidation of organic free radicals,[1] we wish to report a convenient one-step synthesis of 1,4 diketones from readily available starting materials. The development of new synthetic routes to 1,4 diketones has received considerable interest during the past few years, in view of their value as cyclopentenone precursors.[2]

We have previously demonstrated[1b,c] that ketones could be added to olefins in the presence of an oxidant such as manganic acetate to give a variety of products. We now wish to report the formation of 1,4 diketones as the predominant nonpolymeric reaction product when an enol ester is treated with a ketone and manganic acetate. Thus, the reaction of acetophenone with isopropenyl acetate and manganic acetate produced 1-phenylpentane-1,4-dione, while the corresponding reaction with cyclohexanone gave 2-(2-oxopropyl)-cyclohexanone.

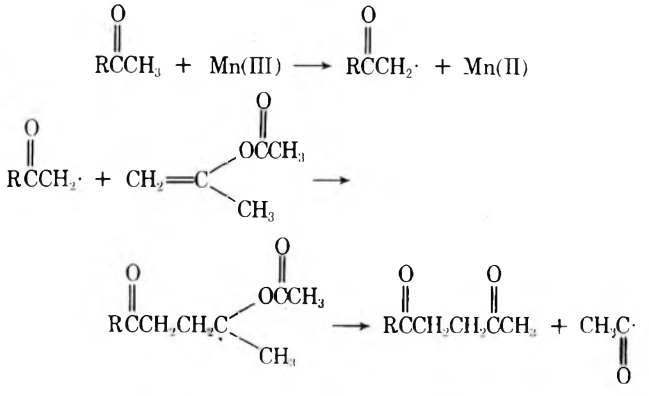


Reactions were generally conducted at 50–70°, with reaction times on the order of 1 hr or less. Yields of 1,4 diketones were 20–35% based on the manganic ion consumed, assuming 2 equiv/mol of diketone produced.[3] Despite the modest yield obtained, this method is well suited for the laboratory preparation of 1,4 diketones in a single step from readily available reagents, especially since manganic acetate can be prepared *in situ* by the addition of potassium permanganate to a solution of manganous acetate in acetic acid.

In a typical experiment, 0.5 mol of cyclohexanone and 0.5 mol of isopropenyl acetate were added together to 0.5 mol of a manganic acetate–acetic acid solution at 70°. The reaction, which was over in ~10 min, yielded 8 g (22% yielded based on manganic ion) of 1,4 diketone as the predominant product after extraction and distillation.

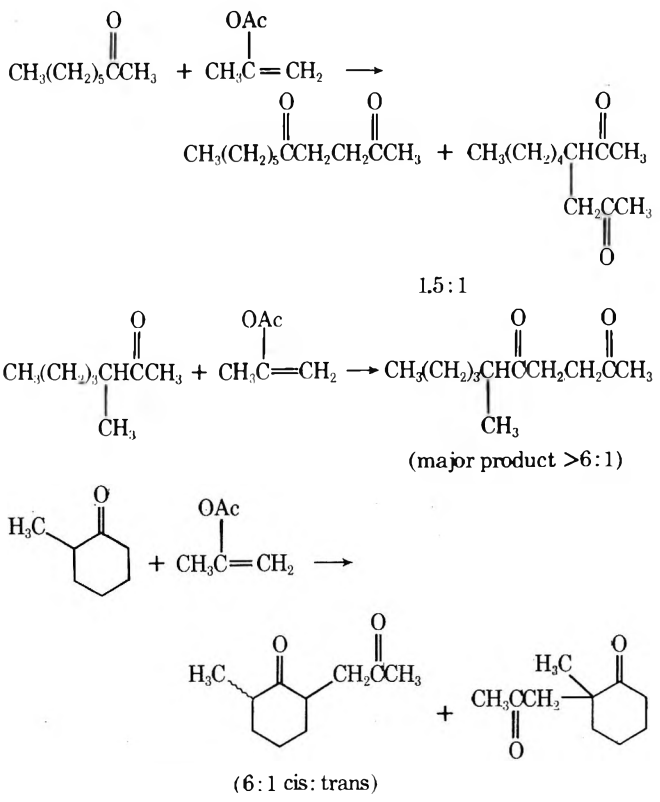
A reasonable mechanism for the formation of 1,4-diketones using manganic acetate is shown in Scheme I. The

Scheme I

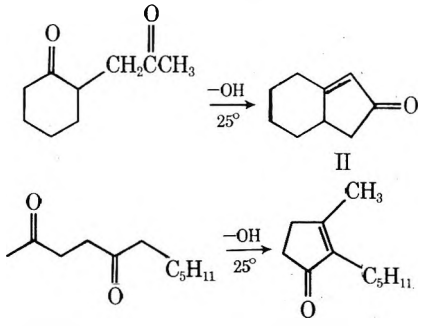


success of this synthesis as shown in Scheme I is due to three factors: (1) the selective oxidation of enolizable ketones by manganic ions to generate α-keto radicals exclusively, (2) the facile elimination of acetyl radical from the α-acetoxyalkyl adduct radical, and (3) the resistance of the initially formed α-keto radical to oxidation by manganic ion due to the electron-withdrawing character of the carbonyl group. Since the initial formation of the α-keto radical involves attack by manganic ion on either the enol or enolate ion of the ketone,[1b] unsymmetrical ketones having two different enolizable hydrogens would be expected to lead to mixture of products. This was indeed observed; the predominant diketone product in each case was that derived from the less substituted α-keto radical, as shown in Scheme II. The preferential formation of the least substituted α-keto radical from unsymmetrical ketones is consistent with a base-catalyzed enolization mechanism, evidence for which has been presented earlier.[1b]

Scheme II



1,4 diketones are useful intermediates in that they can be readily transformgd into cyclopentenone derivatives by treatment with dilute base.[4] Thus, 2-(2-oxopropyl)cyclohexanone (I) was converted in high yield to hydrindenone (II) [bp 70° (0.1 mm); ir 1718, 1626 cm^{-1}; pmr τ 4.2 (1 vinyl



H); uv λ_{max} (EtOH) 230 mμ (ϵ 14,000)], and undecadione-2,5 was transformed into dihydrojasmone.

The relatively simple one-step synthesis of 1,4 diketones presented in this communication represents one more example of syntheses based on the selective generation and oxidation of organic free radicals. Further examples of such syntheses will be presented in forthcoming publications.

Acknowledgment. The skillful technical assistance of Ms. M. Zikos is gratefully acknowledged.

Supplementary Material Available. A detailed experimental procedure will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3457.

References and Notes

(1) (a) E. I. Heiba, R. M. Dessau, and W. J. Koehl, Jr., *J. Amer. Chem. Soc.*, **90**, 5905 (1968); (b) E. I. Heiba and R. M. Dessau, *ibid.*, **93**, 524 (1971); (c) E. I. Heiba and R. M. Dessau, *ibid.*, **94**, 2888 (1972).
(2) G. Stork and R. Borch, *J. Amer. Chem. Soc.*, **86**, 935 (1964); G. Büchi and H. Wüest, *J. Org. Chem.*, **31**, 977 (1966); E. J. Corey and L. S. Hegedus, *J. Amer. Chem. Soc.*, **91**, 4926 (1969); E. Wenkert, R. A. Mueller, E. J. Reardon, Jr., S. S. Sathe, D. J. Scharf, and G. Tosi, *ibid.*, **92**, 7428 (1970); J. E. McMurry and T. E. Glass, *Tetrahedron Lett.*, 2575 (1971); J. E. McMurry and J. Melton, *J. Amer. Chem. Soc.*, **93**, 5309 (1971); T. Mukaiyama, K. Narasaka, and M. Furusato, *ibid.*, **94**, 8641 (1972); P. A. Grieco and C. S. Pogonowski, *J. Org. Chem.*, **39**, 733 (1974).
(3) Two equivalents of manganic ion are required since the acetyl radical eliminated undoubtedly is quantitatively oxidized to the carbonium ion by manganese(III).
(4) H. Hunsdiecker, *Chem. Ber.*, **75**, 455 (1942).

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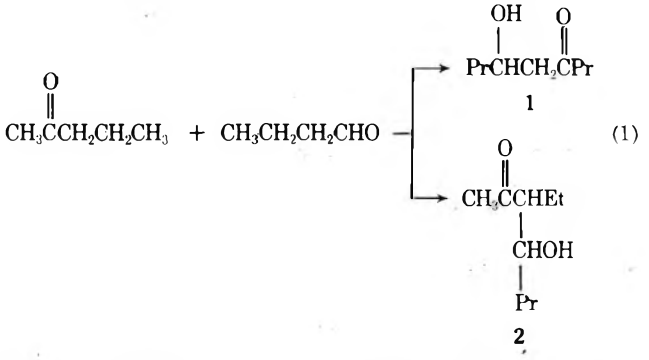
Regiospecific Aldol Condensations of the Kinetic Lithium Enolates of Methyl Ketones

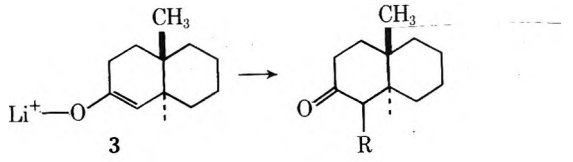
Summary: The aldol condensation can be carried out regiospecifically and in good yield at the methyl group of methyl ketones *via* their kinetic lithium enolates generated in tetrahydrofuran at −78°.

Sir: The aldol condensation is one of the fundamental reactions for the formation of carbon–carbon bonds. It has established itself as one of the most important methods for the formation of five- and six-membered rings.[1] In contrast, directed intermolecular aldol condensation has not been a generally feasible synthetic method[2] because of rapid equilibration of the anions especially of methyl ketones, during their formation. Two recent examples[3,4] illustrate this difficulty (eq 1). We demonstrated 13 years ago[5]

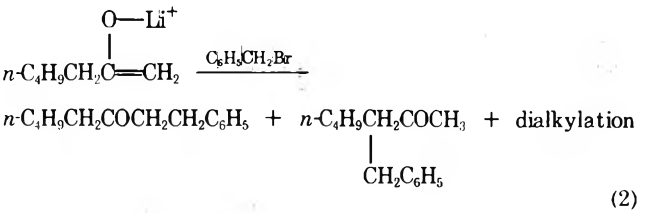


(1)

that certain regiospecifically generated, thermodynamically unstable *lithium* enolates can be alkylated with reactive alkyl halides more rapidly than they undergo equilibration (*cf.* **3** → **4**).

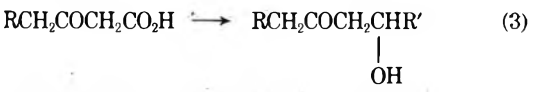


Efforts to apply this technique to the kinetic primary ion derived from a methyl ketone have, however, not met with success, even with halides which proved satisfactory with **3**.[6,7] For instance, the alkylation of enolates such as $RCHCH_2C(O^-)=CH_2Li^+$ with benzyl bromide gave relatively low yields of mixtures of alkylation at the terminal and internal positions[8] (eq 2).



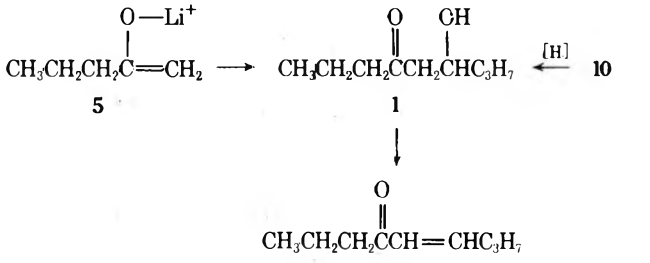
(2)

An ingenious solution to the synthesis of regiospecific aldols, including the linear aldols from methyl ketones, was provided by Schöpf[9] who used β-keto acids to achieve the desired regiospecificity, as shown in eq 3. The overall yields are, however, only fair to moderate.



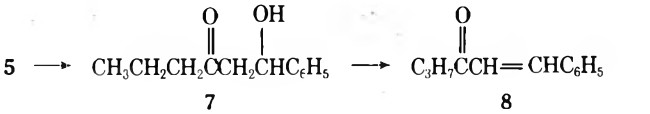
(3)

It occurred to us that the difficulty in trapping the kinetic anions of simple methyl ketones with alkyl halides might not be encountered with a more reactive nucleophile such as an aldehyde. This has indeed proved to be the case.[10] To the kinetic enolate **5** prepared from 2-pentanone and 1.1 equiv of lithium diisopropylamide in dry tetrahydrofuran at −78° was added, dropwise, a solution of butyraldehyde in tetrahydrofuran. After 15 min, the cooling was removed and the solution was immediately neutralized with 1.1 equiv of acetic acid in ether. Isolation and distillation (Kugelrohr, 100° (10 mm)) gave in 65% yield the aldol **1**: ir



(film) 5.81, 2.93 μ; nmr ($CDCl_3$) δ 0.9–1.8 (m, 13 H), 2.2–2.6 (m, 4 H, $CH_2C(=O)CH_2$), 4.1 (m, 1 H HCOH); *m/e* 140 ($M^+ - H_2O$), 97 ($PrCH=CH\text{-}C(=O)^+$). The absorption in the nmr at δ 2.3, which is characteristic of the acetyl group of **2**, was very small, suggesting that the aldol **1** was at least 90% pure. The structure was established further (a) by comparison with an authentic mixture of **1** and **2** (separable[11] on 5% QF_1 at 150°), (b) by showing the identity of **1** with the product of hydrogenation (Pd–C in ethanol) of the hydroxydienone **10**, (c) by dehydration (*p*-toluenesulfonic acid, benzene, 1 hr reflux, 72% yield) to the α,β-unsaturated ketone **6** identical with an unambiguously synthesized[12] sample. These results show that lithium enolates of methyl ketones can retain their integrity in the aldol condensation.[13]

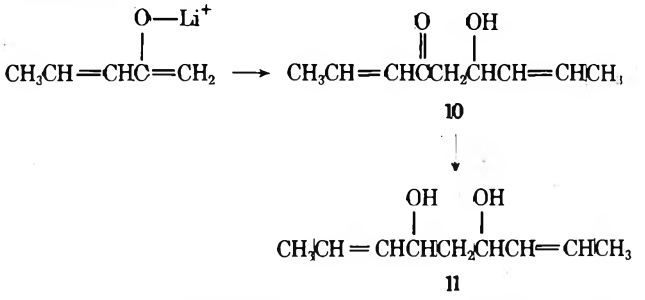
Under similar conditions, the kinetic lithium enolate **5** was condensed with benzaldehyde to give the aldol **7** in 75–80% yield (Kugelrohr, bp 95–100° (0.025 mm)). The



structure followed from the nmr ($CDCl_3$): δ 7.3 (C_6H_5, s), 5.1 (d of d, HCOH), 2.6 ($HOCCH_2C=O$), 2.2 (q, $EtCH_2C=O$), 0.9–1.8 (m, C_2H_5). It was further confirmed (a) by oxidation (MnO_2–$CHCl_3$, room temp) to 1-phenyl-1,3-hexanedione, identical with a sample made from the dianion of 1-phenyl-1,3-butanedione (2 equiv of $LiN(i\text{-}Pr)_2$

in THF) with ethyl iodide; and (b) by dehydration (*p*-toluenesulfonic acid, refluxing benzene) to the known[14] unsaturated ketone 8.

The kinetic lithium enolates of α,β-unsaturated ketones[15] can also be used in regiospecific aldol condensation. The lithium enolate from 3-penten-2-one was prepared and condensed, as described above, with crotonaldehyde to give the dienolone **10** in 70% yield (after preparative tlc on silica gel with 4:1 methylene chloride–ether): ir (film) 3.0, 5.9 μ; nmr ($CDCl_3$) δ 5.9–7.1 (m, $CH_3CH{=}CH{-}C{=}O$) 5.5–5.7 (m, $CH_2CH{=}CHCHOH$–), 4.4–4.6 (m, HCOH), 2.6 (d, J = 6 Hz, $-CH_2C{=}O$), 1.98 (d, b, J = 6 Hz, $O{=}CC{=}CCH_3$), 1.85 (d, J = 5 Hz $CH_3C{=}CCHOH$). Analysis was performed on the bis(trimethylsilyl) ether of the doubly unsaturated diol **11** from reduction (bis(2-methoxyethoxy)aluminum hydride in benzene): *m/e* 300.1938 (calcd 300.1940). Catalytic hydgenation of **10** gave the saturated aldol **1** identical (*vide supra*) with the product of the aldol condensation of butyraldehyde and the kinetic lithium enolate of 2-pentanone.



The ability of regiospecifically produced lithium enolates to maintain their integrity in aldol condensations should greatly extend the usefulness of the reaction.[16,17]

References and Notes

(1) *Cf.* H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, Menlo Park, Calif., 1972.
(2) "No examples (of successful aldol condensation under nonequilibrating conditions) involving methyl ketones are known": A. T. Nielsen, *Org. React.*, **16**, 37 (1968).
(3) M. Gaudemar, *C. R. Acad. Sci.*, **270**, 533 (1974).
(4) C. A. Brown, *J. Org. Chem.*, **39**, 1324 (1974).
(5) G. Stork, P. Rosen, and N. L. Goldman, *J. Amer. Chem. Soc.*, **83** 2965 (1961); G. Stork, P. Rosen, N. L. Goldman, R. Coombs, and J. Tsuji, *ibid.*, **87**, 275 (1965).
(6) Except, of course, when the kinetic enolate is also the more stable one.
(7) For the structure of the kinetic enolates of methyl ketones, see H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 1341 (1965); H. O. House, L. J. Czuba, M. Gall, and H. D. Olmstead, *ibid.*, **34**, 2324 (1969).
(8) "Selective alkylation of the methyl group of ketones RCH_2COCH_3 by any method which involves generation of the enolate $RCH_2C(O^-){=}CH_2Li^+$ in an ethereal solvent will not be a good synthetic procedure": H. O. House, M. Gall, and H. D. Olmstead, *J. Org. Chem.*, **36**, 2361 (1971).
(9) C. Schöpf and K. Thierfelder, *Justus Liebigs Ann. Chem.*, **518**, 127 (1935). For a more recent application to a mechanistic problem, *cf.* M. Stiles, D. Wolf, and G. V. Hudson, *J. Amer. Chem. Soc.*, **81**, 628 (1959).
(10) H. O. House, D. S. Crumrine, A. Y. Teranishi, and H. D. Olmstead, *J. Amer. Chem. Soc.*, **95**, 3310 (1973), recently reported on the aldol condensation of acetophenone and of acetomesitylene with benzaldehyde, using the lithium, magnesium, or zinc enolates. The question of regiospecificity obviously does not arise in the case of these particular methyl ketones.
(11) The linear isomer had the longer retention time.
(12) By reduction of the enol ether of 4,6-nonanedione with bis(2-methoxyethoxy)aluminum hydride in benzene, followed by aqueous acid hydrolysis.
(13) In a paper (ref 3) which was published after the completion of our own work, the statement is made (without experimental details) that direct preparation of lithium enolates with lithium diisopropylamide in tetrahydrofuran had not given satisfactory results. In the absence of experimental details, the reason for this difference with our own results is unclear.
(14) C. Harres and P. Bromberger, *Ber.*, **35**, 3088 (1902).
(15) For the structure of the kinetic enolates of *cyclic* α,β-unsaturated ketones, see R. A. Lee, C. McAndrews, K. M. Patel, and W. Reusch, *Tetrahedron Lett.*, 965 (1973); G. Stork and R. L. Danheiser, *J. Org. Chem.*, **38**, 1775 (1973).
(16) We have, for instance (G. Stork and J. D'Angelo, in preparation), shown that the synthetically versatile α-hydroxymethyl ketones can be produced regiospecifically by trapping enolate ions with formaldehyde.

(17) We thank the National Institutes of Health and the National Science Foundation for their support of this work.

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Capillary Techniques in Organic Synthesis

Summary: Some reactions such as nucleophilic displacements and additions have been found to be considerably accelerated if allowed to take place inside the pores of high surface area materials (silica gel, aluminum oxide and others).

Sir: Solids such as activated charcoal, silica gel, and aluminum oxide having high surface areas promote reactions which would otherwise require much higher temperatures or would not take place at all. Innumerable examples of such reactions in the vapor phase are well known.

In the liquid phase, catalytic effects of the adsorbent were frequently observed during adsorption chromatography when polymerization, isomerization, hydrolysis, dehydration,[1] dehydrohalogenation,[2] reduction,[3] and similar alterations[1] of the chromatographed substances were occasionally recorded. In some instances, the adsorbent was pretreated with certain chemicals to achieve reactions which would not occur over the pure adsorbent.[4]

In all these instances, the reactions take place between the compound and the adsorbent which reacts by virtue of its chemical properties (acidity, dehydrating power, etc.).

It was of interest to find out whether porous materials could be used just to bring two or more compounds together in the liquid phase inside the pores where the minimum pore size is of the order of several molecular diameters. For this purpose, several displacement and addition reactions have been carried out.

When a column of acid aluminum oxide was soaked with a solution of benzyl chloride in chloroform containing hydrazoic acid, and after 16 hr at room temperature the column was eluted with hexane and ether, 49.5% conversion and 68.5% yield of benzyl azide was obtained.

Similar treatment of dialkyl α-bromo-α'-fluorosuccinate or α,α'-dibromosuccinate with a solution of hydrazoic acid gave dialkyl azidofumarate. Preparation of the same compound required refluxing of the halogenated esters with sodium azide in methanol for 12 hr.[5]

The Diels–Alder reaction between 1-acetoxy-1,3-butadiene and fluoranil (tetrafluoro-*p*-benzoquinone) requires heating of the benzene solution of the two compounds at 98° for several hours.[6] When the same solution was placed in a column of silica gel at room temperature for 60 hr, the product, 5-acetoxy-2,3,4a,8a-tetrafluoro-4a,5,8,8a-tetrahydro-1,4-naphthoquinone, was obtained by chloroform elution in 49.5% conversion and 67–78% yield.

Similar reaction of 1-acetoxy-1,3-butadiene with *p*-benzoquinone was described taking place at a reflux temperature of carbon tetrachloride and diisopropyl ether after at least 1 hr.[7] When a solution of 1-acetoxy-1,3-butadiene and *p*-benzoquinone in benzene was allowed to react for 40 hr at room temperature in a column of silica gel presoaked with hexane, not only did the addition occur, but the product, 5-acetoxy-4a,5,8,8a-tetrahydro-1,4-naphthoquinone, eliminated acetic acid, and the intermediate dihydro com-

pound was dehydrogenated by benzoquinone to 1,4-naphthoquinone in a 87% yield.

The general procedure for the "capillary technique" is as follows. A chromatographic tube (50 ml) is filled with silica gel (60–80 mesh), aluminum oxide (activity I), or other adsorbent (15–25 ml for 0.0005–0.002 *M* quantities). A solution of reactants (0.05–0.002 mol) in the least polar possible solvent (3–20 ml) is introduced into the column which is usually accompanied by very gentle warming. The mixture is allowed to react 12–72 hr at room temperature, and the products are isolated by conventional elution technique.

Alternately, the column filled with the adsorbent can be presoaked with a nonpolar solvent such as hexane or benzene before introducing the solution of the reactants, and this modification gives even better results. Also, the column may be presoaked with a solution of one reactant, and a solution of the other reactant can be passed through the column and allowed to react for a certain time.

The described technique is especially of advantage in such cases where conventional procedures require prolonged heating which could damage the reactants. Experiments are underway to find out the theoretical background of the reaction, in particular the function of the adsorbent, whether it is purely physical, or whether chemical aspects such as acid–base catalysis are involved.

References and Notes

(1) L. Zechmeister, *Ann. N.Y. Acad. Sci.*, **49**, 145 (1967).
(2) M. Zaoral, *Chem. Listy*, **47**, 1872 (1953).
(3) V. J. Hruby, *Proc. N. Dak. Acad. Sci.*, **16**, 12 (1962); *Chem. Abstr.*, **62**, 1589*g* (1955).
(4) R. L. Burwell, Jr., *Chemtech.*, 371 (1974).
(5) M. Hudlicky, *J. Fluorine Chem.*, **2**, 1 (1972–1973).
(6) M. Hudlicky and H. M. Bell, *J. Fluorine Chem.*, in press.
(7) I. A. Kaye and R. S. Matthews, *J. Org. Chem.*, **29**, 1341 (1954).

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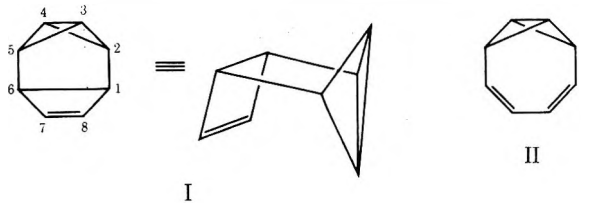
A New $(CH)_8$ Isomer, Tetracyclo[4.2.0.0^{2,4}.0^{3,5}]oct-7-ene

Summary: Tetracyclo[4.2.0.0^{2,4}.0^{3,5}]oct-7-ene (I) has been prepared *via* a four-step reaction sequence, starting from benzvalene; the adduct (III) of dichloroketene and benzvalene was dehalogenated with triphenyltin hydride, and the resulting ketone (IV) was converted into I by the reaction of its *p*-toluenesulfonylhydrazone (V) with lithium 2,2,6,6-tetramethylpiperidide; preliminary experiments show that I is isomerized to cyclooctatetraene both thermally and in a silver ion catalyzed reaction.

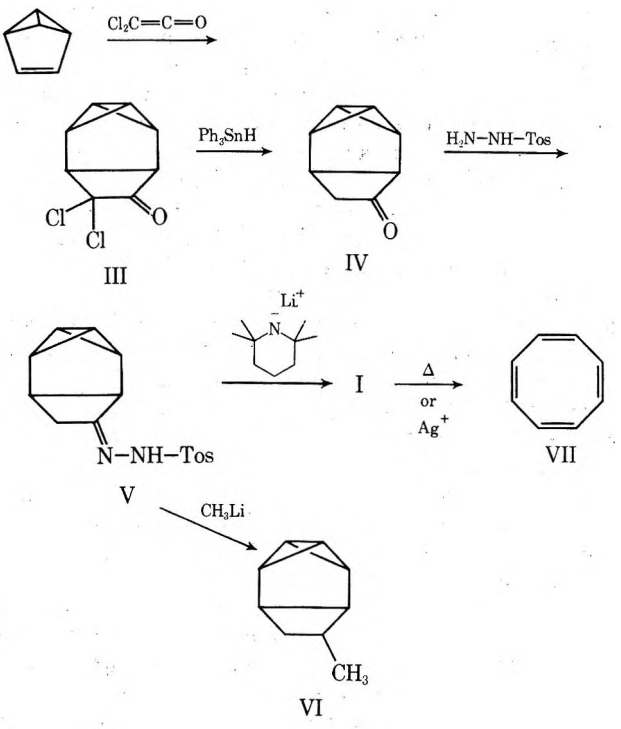
Sir: As a consequence of our interest in $(CH)_8$ isomers and in highly strained molecules in general,[1] we have devised a synthesis of the as yet unreported title compound I, starting from benzvalene. It is hoped that this compound may serve as a precursor of the elusive "octavalene" (tricyclo[5.1.0.0^{2,8}]octa-3,5-diene), II, whose properties and possible rearrangements are expected to be of particular interest. After initial lack of success with approaches involving ozonolysis of benzvalene, sensitized photochemical addition of maleic anhydride to benzvalene, and the reaction of ethyl diazoacetate with benzvalene, the route outlined in Chart I proved fruitful.



I

II

Chart I



Benzvalene in diethyl ether, prepared by the method of Katz,[2] was treated with just over 1 equiv of dichloroketene (generated *in situ* from dichloroacetyl chloride and triethylamine)[3] at 0° for 3.25 hr. After aqueous work-up and drying over potassium carbonate, the product was vacuum distilled (~0.1 Torr; oil bath heated to 80° after removal of ether) to yield up to 86% adduct III: ir (neat) 3145 (w), 3065 (w), 2990 (w), 1800 (s), 1110 (m), and 750 (s) cm^{-1}; nmr (CCl_4) δ 3.83, 3.72, 3.22, 3.10 (2H, "AB" pattern with J_{AB} = 7 Hz), and 2.2–2.7 (4 H, br m); mass spectrum consistent with assigned structure. *Anal.* Calcd for $C_8H_6Cl_2O$: C, 50.84; H, 3.20. Found: C, 50.23; H, 3.12. Although benzvalene's addition reactions do not always follow "expected" paths,[4] the desired [2 + 2] cycloaddition is evidenced in this case by the characteristic carbonyl stretching frequencies exhibited by compounds III and IV.[3,5] The adduct III was reduced to the unhalogenated ketone IV by treatment with a small excess of triphenyltin hydride[3c,d,6] in refluxing cyclohexane for 4 hr, under nitrogen. After vacuum distillation (~0.1 Torr, bath temperature 70°), the yield of product was over 95% at its best (this includes ketone which codistilled with the cyclohexane): ir (CCl_4) 3060 (w), 1780 (vs), and 1119 (m) cm^{-1}; nmr δ 3.30 (1 H, m), 3.0–1.9 (7 H, very complex); mass spectrum (rel intensity) *m/e* 120 (15), 92 (15), 91 (54), 80 (20), 79 (26), and 78 (100). *Anal.* Calcd for C_8H_8O: C, 80.00; H, 6.71. Found: C, 80.14; H, 6.79.

The conversion of IV into its *p*-toluenesulfonylhydrazone[7] V is accomplished in high yield by dissolving the ketone and a slight excess of *p*-toluenesulfonylhydrazine in a minimum amount of anhydrous ethanol; the viscous solution is left at room temperature for 24 hr. The solvent is centrifuged from the resulting cream-colored solid mass. After recrystallization from ethanol, the product (apparently a mixture of geometrical isomers) gives mp 142–146°

dec; ir (KBr) 3200 (s), 3050 (w), 2930 (m), 1670 (m), 1590 (m), 1380 (s), 1325 (vs), 1170 (vs), 1083, 1020, 920, and 894 (m) cm^{-1}; nmr ($CDCl_3$) δ 8.10, 7.75 (combined 1 H, br s, removed by shaking with D_2O), 7.92, 7.78, 7.38, 7.25 (4 H, AA'BB' pattern), 3.20–3.12 (1 H), and 2.8–1.7 (10 H, complex, containing s at 2.45). *Anal.* Calcd for $C_{15}H_{16}N_2O_2S$: C, 62.48; H, 5.59; N, 9.72. Found: C, 62.65; H, 5.60; N, 9.80.

The final transformation of V into I gave some initial difficulty. Treatment of V with excess methyllithium[8] in ether at room temperature for 10 hr gave as the major product (~25%) a compound whose mass spectrum suggests a C_9H_{12} hydrocarbon bearing a methyl group, tentatively assigned structure VI, corresponding to methyl addition rather than to elimination to form an olefin.[8a,9] The use of other bases was therefore explored: potassium hydride (which seemed interesting because of its high reactivity),[10] *n*-butyllithium,[8b,c,d,11] and *sec*-butyllithium all failed to give appreciable amounts of the desired product. Finally, successful elimination was achieved by use of 2 equiv of lithium 2,2,6,6-tetramethylpiperidide[12] in THF–ether at room temperature for 8–10 hr under nitrogen; this gave yields of 35–55% I. To isolate the product, one adds pentane, removes THF and ether by repeated aqueous extraction, then removes the amine by rapid extractions with 1 *M* sodium dihydrogen phosphate; a final wash is carried out using aqueous ammonia. Pure I can be isolated by preparative gc, using a 6% SE-30 on Gas-Chrom Q column at room temperature. Lithium diisopropylamide in THF–ether at room temperature also gives I, but in only ~20% yield.

Tetracyclo[4.2.0.$0^{2,4}$.$0^{3,5}$]oct-7-ene (I) is characterized by the following spectral data: ir (vapor) 3100 (w), 3050 (s), 2950 (s), 2900 (w), 1570 (vw), 1380 (w), 1265 (m), 1180 (w), 1120 (m), 798, 755, and 705 (s) cm^{-1}; nmr ($CDCl_3$) δ 6.03 (s, 2 H), 2.80 (slightly broadened s, 2 H), 2.3–1.7 (m), and 2.1 (s, showing fine structure) (total 4 H);[13] ^{13}C nmr[13c,14] (δ from TMS) 139.4 (assigned to vinylic C's), 47.7 and 37.2 (tentatively assigned to C-1,6 and C-2,5, respectively), and 16.2 and −0.7 (C-3,4, in indefinite order); uv end absorption, starting at ~230 nm; mass spectrum (EI) (rel intensity) *m/e* 105 (7), 104 (71), 103 (71), 102 (11), 79 (6), 78 (100), 77 (32), 76 (8), 75 (5), 74 (9), 52 (20), 51 (40), and 50 (25); mass spectrum (CI, with CH_5^+ as ionizing medium) (rel intensity) *m/e* 106 (10), 105 (100), 104 (12), 103 (20), 102 (1), 93 (4), 92 (2), 91 (28), 80 (2), 79 (33), 78 (3), 67 (2), 56 (3), and 51 (3).

In some preliminary experiments, samples of I were briefly pyrolyzed at 400–500°[15] in an attempt to open the cyclobutene ring to give II. The result of these pyrolyses was a very clean conversion to cyclooctatetraene (VII), as determined by the mass spectrum of the product and by coinjection with an authentic sample of VII on three different gc columns. Treatment of I with silver ion[16] (silver perchlorate or silver tetrafluoroborate in acetone or THF at room temperature for several minutes) also appears to yield some VII. Alternative ring opening techniques, as well as other reactions of the title hydrocarbon, are now being studied.

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References and Notes

(1) (a) J. Meinwald and D. Schmidt, *J. Amer. Chem. Soc.*, **91**, 5877 (1969); (b) J. Meinwald and H. Tsuruta, *ibid.*, **91**, 5878 (1969); (c) P. J. van Vuuren, Ph.D. Dissertation, Cornell University, 1970; (d) P. J. van Vuuren, R. J. Fletterick, J. Meinwald, and R. E. Hughes, *J. Amer. Chem. Soc.*, **93**, 4394 (1971); (e) H. E. Zimmerman and L. R. Sousa, *ibid.*, **94**, 834 (1972).
(2) T. J. Katz, E. J. Wang, and N. Acton, *J. Amer. Chem. Soc.*, **93**, 3782 (1971).
(3) (a) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Amer. Chem. Soc.*, **87**, 5257 (1965); (b) L. Ghosez, R. Montaigne, and P. Mollet, *Tetrahedron Lett.*, 135 (1966); (c) L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and P. Mollet, *Tetrahedron*, **27**, 615 (1971); (d) W. T. Brady, *Synthesis*, 415 (1971), and references therein.
(4) (a) T. J. Katz and N. Acton, *J. Amer. Chem. Soc.*, **95**, 2738 (1973); (b) R. J. Roth and T. J. Katz, *ibid.*, **94**, 4770 (1972); (c) T. J. Katz and K. C. Nicolaou, *ibid.*, **96**, 1948 (1974).
(5) (a) J.-M. Conia and J.-L. Ripoll, *Bull. Soc. Chem. Fr.*, 768 (1963); (b) F. V. Brutcher, Jr., T. Roberts, S. J. Barr, and N. Pearson, *J. Amer. Chem. Soc.*, **78**, 1507 (1956).
(6) (a) G. M. L. Cragg, *J. Chem. Soc. C*, 1829 (1970); (b) D. J. Carlsson and K. U. Ingold, *J. Amer. Chem. Soc.*, **90**, 7047 (1968).
(7) H. O. Hutchins, C. A. Milewski, and B. E. Maryanoff, *J. Amer. Chem. Soc.*, **95**, 3662 (1973).
(8) (a) R. H. Shapiro and J. H. Duncan, *Org. Syn.*, **51**, 66 (1971); (b) W. G. Dauben, M. E. Lorben, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *J. Amer. Chem. Soc.*, **90**, 4762 (1968); (c) R. H. Shapiro and M. J. Heath, *ibid.*, **89**, 5734 (1967); (d) J. E. Hertz, E. Gonzalez, and B. Mendel, *Aust. J. Chem.*, **23**, 857 (1970); (e) A. K. Bose and N. G. Steinberg, *Synthesis*, 595 (1970).
(9) J. Meinwald and F. Uno, *J. Amer. Chem. Soc.*, 90, 800 (1968).
(10) (a) C. A. Brown, *J. Amer. Chem. Soc.*, **95**, 982 (1973); (b) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N.Y., 1967, p 935.
(11) G. Kaufman, F. Cook, H. Schechter, J. Bayless, and L. Friedman, *J. Amer. Chem. Soc.*, **89**, 5736 (1967).
(12) R. A. Olofson and C. M. Dougherty, *J. Amer. Chem. Soc.*, **95**, 581, 583 (1973).
(13) For examples of ^1H spectra of structurally related compounds, see (a) W. R. Moore, H. R. Ward, and R. F. Merritt, *J. Amer. Chem. Soc.*, **83**, 2019 (1961); (b) D. M. Lemal and K. S. Shim, *Tetrahedron Lett.*, 3231 (1964); (c) K. Wüthrich, S. Meiboom, and L. C. Snyder, *J. Chem. Phys.*, **52**, 230 (1970); (d) G. L. Closs and R. B. Larrabee, *Tetrahedron Lett.*, 287 (1965); (e) K. E. Wilzbach, J. S. Ritscher, and L. Kaplan, *J. Amer. Chem. Soc.*, **89**, 1031 (1967).
(14) For some related ^{13}C spectral data, see (a) L. Cassar, P. E. Eaton, and J. Halpern, *J. Amer. Chem. Soc.*, **92**, 6366 (1970); (b) ref 5a; (c) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Chapter 3, Wiley, New York, N.Y., 1972; (d) P. H. Weiner and E. R. Malinowski, *J. Phys. Chem.*, **71**, 2791 (1967).
(15) (a) W. G. Dauben and R. L. Cargill, *Tetrahedron*, **12**, 186 (1961); (b) O. L. Chapman, D. J. Pasto, G. W. Borden, and A. A. Griswold, *J. Amer. Chem. Soc.*, **84**, 1220 (1962).
(16) W. Merk and R. Pettit, *J. Amer. Chem. Soc.*, 89, 4788 (1967).

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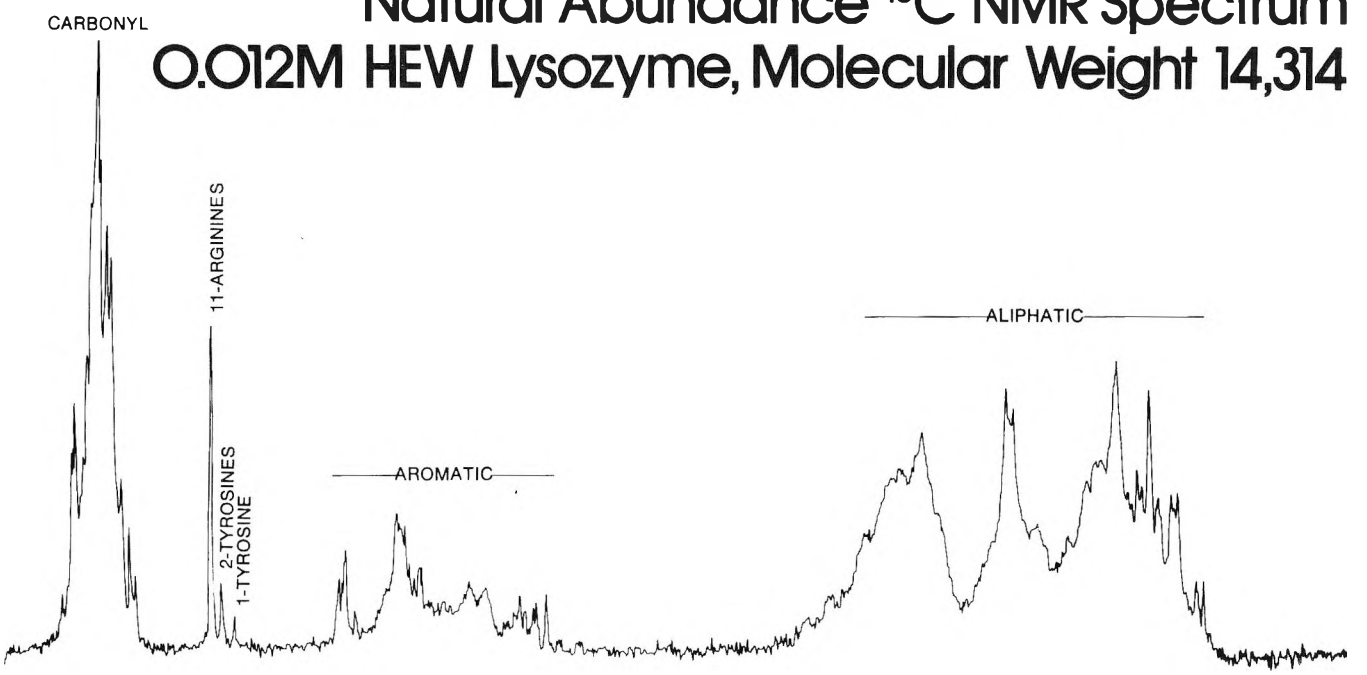
Natural Abundance ^{13}C NMR Spectrum
0.012M HEW Lysozyme, Molecular Weight 14,314



Proton-decoupled natural abundance ^{13}C spectrum of hen egg white lysozyme in 0.15M NaCl in 9:1 H_2O/D_2O, pH 4.0, 45°C. Recorded with a TT-14 system[1] at 15.08 MHz using a 20 mm sample tube; 37,107 90° pulses; 4096 time-domain points; and 1.165 Hz digital line broadening. This spectrum demonstrates that in a small protein, single carbon resonances such as the one assigned above to C^{ζ} in a single tyrosine residue, can be observed after only five hours of signal averaging with use of the 20 mm sample technology developed at Indiana University by Dr. Adam Allerhand.[2,3]

1. Sample run at the University of Chicago, courtesy of Dr. Philip Keim, Pritzker School of Medicine.
2. A. Allerhand, R.F. Childers, E. Oldfield, J. Magn. Resonance, *11*, 272 (1973).
3. E. Oldfield and A. Allerhand, Proc. Nat. Acad. Sci. USA, *70*, 3531 (1973).

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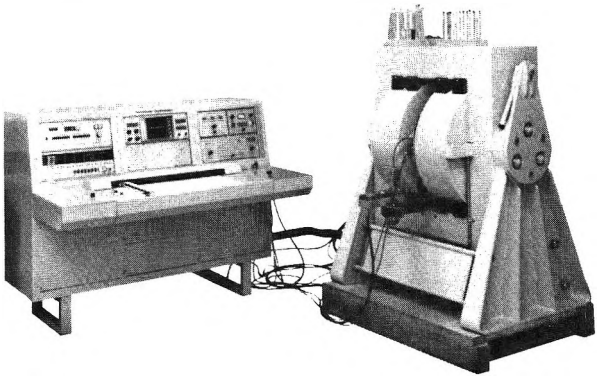

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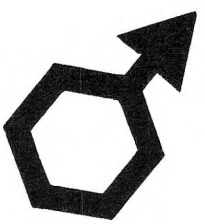

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1) K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, **94**, 7154 (1972).
2) K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **37**, 3973 (1972).
3) K. B. Sharpless, M. W. Young and R. F. Lauer, *Tetrahedron Lett.*, 1979 (1973).
4) K. B. Sharpless and R. F. Lauer, *J. Amer. Chem. Soc.*, **95**, 2697 (1973).
5) K. B. Sharpless and R. F. Lauer, unpublished results.
6) K. B. Sharpless, R. F. Lauer and A. Y. Teranishi, *J. Amer. Chem. Soc.*, **95**, 6137 (1973).
7) H. J. Reich, I. L. Reich and J. M. Renga, *J. Amer. Chem. Soc.*, **95**, 5813 (1973).
8) D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 695 (1973).

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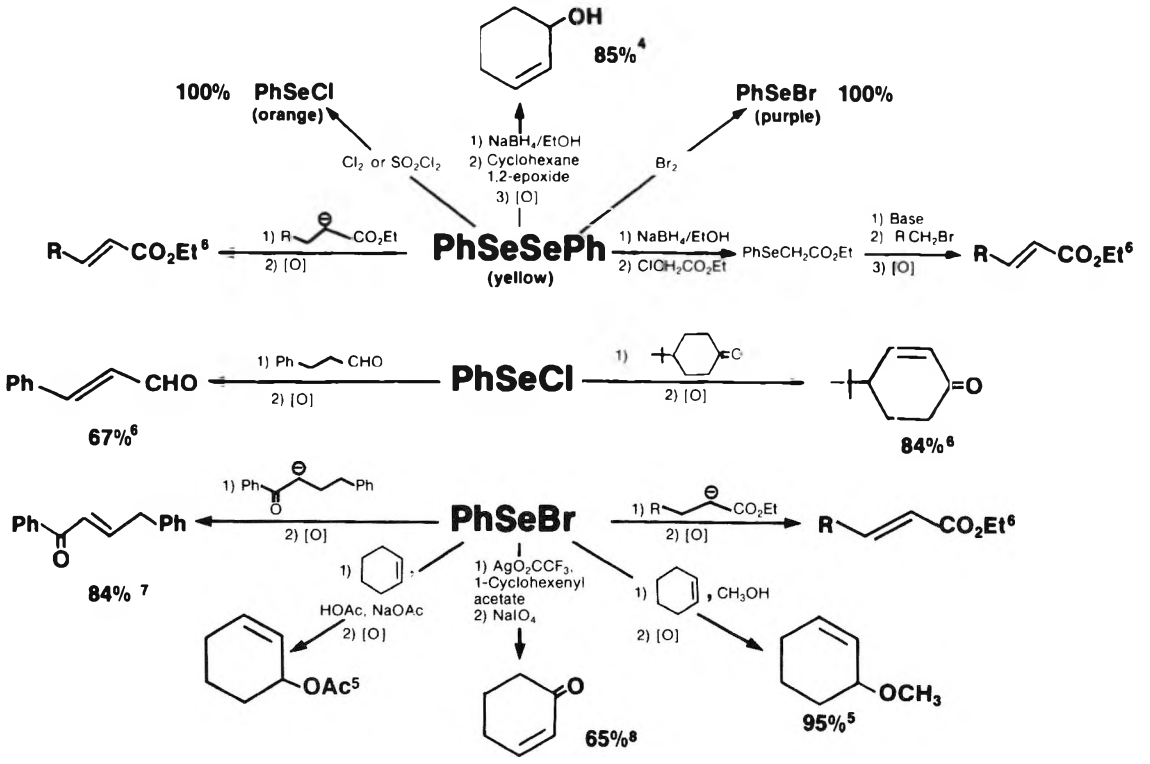

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