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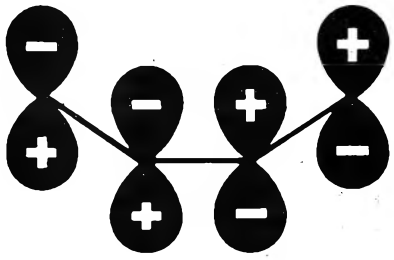

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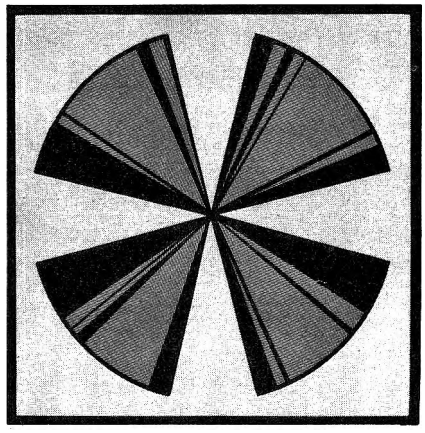

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SEPTEMBER 19, 1975

Peptide Synthesis Using *o*-Nitrophenylsulfenyl *N*-Carboxy α-Amino Acid Anhydrides

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Received February 19, 1975

A derivative of *N*-carboxy α-amino acid anhydrides (NCAs) in which amino proton is substituted by o-nitrophenylsulfenyl (Nps) group has been prepared almost quantitatively. The reaction of the Nps–NCAs with amino acid esters proceeds rapidly to give the Nps-dipeptide esters with full optical activity in high yields. The chain lengthening of peptides by the reaction of the Nps–NCAs was accomplished with good results. The stepwise peptide synthesis using the Nps–NCAs was successfully applied to the synthesis of a C-terminal hexapeptide amide of eledoisin sequence. The results show that the Nps–NCAs are most useful compounds for stepwise synthesis of peptides.

Successful synthesis of peptides using *N*-carboxy α-amino acid anhydrides (NCAs) has been reported by us[1-4] and other groups.[5-16] The NCA method for peptide synthesis has a great advantage of rapid acylation of an amino acid by the NCAs so that the reaction completes in a few minutes[6] to a few hours[1] to give a peptide in very high yield. Another advantage of the NCA method is that the reaction of NCAs with amino acids or peptides can be accomplished without protection of the functional group of the amino acids or the peptides. The NCA method, therefore, gives directly a free peptide from an amino acid. The latter advantage, however, is counterbalanced by the defect that in the NCA method, a small amount of by-product is sometimes formed[7] and is difficult to remove from the desired peptide. This difficulty may be overcome by choice of a strategy of peptide synthesis using an N-substituted NCA. The N-substituted NCA having as high a reactivity as the NCA may be used as an acylating component in conventional solution state peptide synthesis to give a pure N-protected peptide in very high yield, perhaps above 90%, which is obtained by the NCA method of peptide synthesis.[1,6] The by-product accompanied by the reaction of the N-substituted NCA, if present, may be easily removed by the conventional washings of the product with an acid and a base.[17]

Recently, Kricheldorf[18] found that o-nitrophenylsulfenyl (Nps) chloride reacts almost quantitatively with NCAs to give the N-substituted NCAs by the Nps group. We considered that the Nps–NCAs may be successfully used for our strategy of peptide synthesis. We have studied synthesis and reaction of the Nps–NCAs and found that the Nps–NCAs are most useful compound for stepwise synthesis of Nps-protected peptides.[19] This paper reports the preparation of new Nps–NCAs and the synthesis of peptides including a hexapeptide amide having the C-terminal sequence of eledoisin[20] by the Nps–NCA method.

Synthesis of Nps–NCAs. The synthesis of Nps–NCA of glycine and L-phenylalanine was reported by Kricheldorf.[18] New Nps–NCAs of other amino acids were prepared by the method similar to that reported by Kricheldorf. The method involves the fast reaction of Nps-Cl with the 3-amino proton of the NCA to give the Nps–NCA and hydrogen chloride, which is trapped with triethylamine (Scheme I). The reaction was carried out at 0° and tetrahydrofuran (THF) was used as a suitable solvent. Triethylamine must be carefully added to the system. Hasty addition of the reagent caused the undesired polymerization of the NCA through the activated NCA mechanism.[21] The formation of the polymeric by-product, which is insoluble in ethyl acetate, makes it difficult to purify the Nps–NCA by recrystallization. Though the use of acetonitrile as the solvent can suppress the polymerization,[22] it is not suitable for the reaction because the resulting Nps–NCA is poorly soluble in acetonitrile.

Scheme I

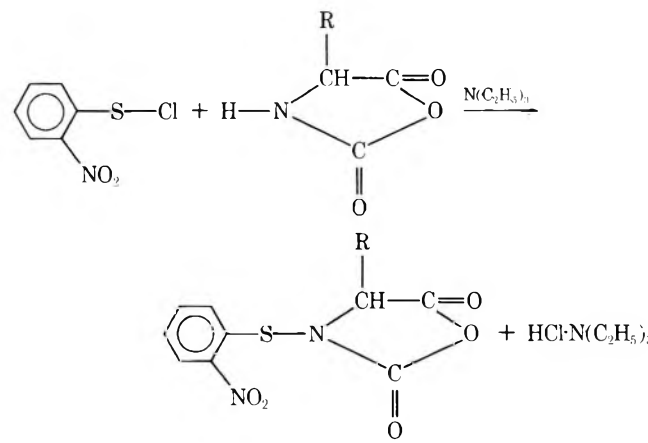


Table I
Results of Syntheses of Nps-NCAs

Registry no.	Nps-NCA[a]	Yield, %	Mp, °C	[α]D in THF, deg (c)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
40331-72-4	Gly	94	168–170[b]		48.66	2.72	12.61	48.72	2.66	12.65
52071-13-3	Ala	92	176–178	+22.7 (1.0)	50.85	3.41	11.86	50.69	3.49	11.90
52152-51-9	Val	94	150–152	+16.9 (1.0)	54.54	4.58	10.60	54.46	4.60	10.56
55903-68-9	Leu	82	97–99	+44.8 (1.0)	56.11	5.07	10.07	56.20	5.10	10.01
54745-13-0	Ile	92	101–103	+32.9 (1.0)	56.11	5.07	10.07	56.15	5.02	10.10
40331-74-6	Phe	92	151–153[c]	+31.2 (2.0)	61.54	3.87	8.97	61.60	3.90	8.92
54745-15-2	Lys (Z)	94	121–123	+23.5 (2.0)	59.01	4.95	9.83	59.05	4.88	9.85
54745-18-5	Glu (OMe)	93	113–115	+31.9 (2.0)	50.65	3.92	9.09	50.68	3.86	9.05
54743-96-3	Glu (OBzl)	94	Oil	+18.7 (2.5)			6.73			6.61
54743-91-8	Asp(OBzl)	94	137–138	+70.8 (2.0)	58.38	3.81	7.57	58.35	3.83	7.60

[a] All amino acid residues have the L configuration except for glycine. [b] 168–170°; see ref 17. [c] 151–153°; see ref 17.

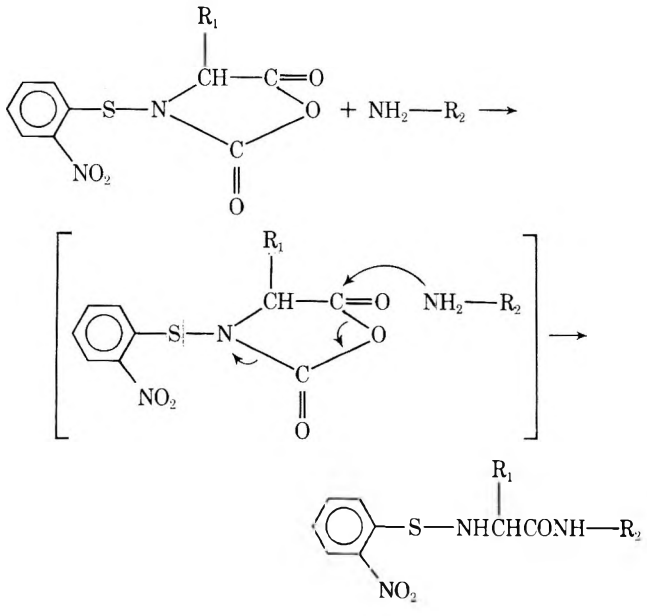
The product was obtained almost quantitatively and readily purified by recrystallization from ethyl acetate. The optical purity of the product was checked by acid hydrolysis and the product was found to have full optical purity.

The Nps–NCAs are conveniently characterized by infrared absorption bands at 1850–1860 and 1780–1790 cm^{-1} characteristic of the anhydride carbonyl strechings and 1600, 1570, and 1460 cm^{-1}, and some sharp bands near 750 cm^{-1} resulting from the substituted benzene ring. Kricheldorf[18] reported that theNps–NCAs have a broad infrared band near 3440–3540 cm^{-1}. We found no broad band near 3450 cm^{-1} in the infrared spectra of our samples of the Nps–NCAs. The contamination with water which comes from the KBr crystals gives the infrared absorption band. We consider that the band at 3440–3450 cm^{-1} reported by Kricheldorf may result from the presence of a small amount of water.

Results of syntheses of the Nps–NCAs are shown in Table I together with the physical properties and the elemental analysis. The synthesis of the Nps–NCA of other amino acids than those listed in Table I is now undertaken.

Synthesis of Peptides Using Nps–NCAs. The Nps–NCA is an intramolecularly activated amino acid derivative by the anhydride group and may be easily attacked at the C-5 carbonyl carbon by an amino compound to give the Nps-peptide with leaving carbon dioxide (Scheme II). We tried to synthesize Nps-dipeptide esters by the reaction of

Scheme II



the Nps–NCAs with amino acid esters. The reaction was carried out by the same procedure as that of the conventional method of peptide synthesis, for 2 hr in tetrahydrofuran at room temperature. After the reaction, the solvent was removed at reduced pressure to give an oil, which was dissolved in ethyl acetate. Then the solution was treated by the same method as that of the conventional peptide synthesis, i.e., washings with aqueous solution of citric acid and of sodium bicarbonate and with water, isolation, and purification by recrystallization. The products, which were isolated in very high yields (above 85%), were identical with the authentic sample of Nps-dipeptide esters prepared by the conventional dicyclohexylcarbodiimide method. The reaction of the Nps–NCAs proceeded rapidly as expected from the rapid reaction of unsubstituted NCAs,[1,6] but Nps-L-valine NCA needed 3 hr for completing the acylating reaction. The slower reaction of the Nps–NCA may result from the steric hindrance of the methyl side chain branching at the β carbon of the amino acid residue.

Racemization during the peptide bond formation by the Nps–NCAs was studied by the method reported by Muraoka and coworkers.[23] The method involves separation of diastereomeric isomers of a glycyl tripeptide containing a racemic amino acid residue such as glycyl-DL-alanyl-L-valine or glycyl-DL-alanyl-L-leucine[24] by using an amino acid analyzer.[25] The method can detect racemization of 0.01%. We prepared glycyl-L-alanyl-L-leucine by a method including the synthesis of Nps-L-alanyl-L-leucine benzyl ester by the reaction of Nps-L-alanine NCA with L-leucine benzyl ester (Scheme III). If the racemization occurs in the reaction of

Scheme III

pTos · H-L-Leu-OBzl $\xrightarrow{\text{Nps-L-Ala NCA}}$ Nps-L-Ala-L-Leu-OBzl $\xrightarrow{\text{HCl}}$ HCl · H-L-Ala-L-Leu-OBzl $\xrightarrow{\text{Z-Gly-OH, DCC}}$ Z-Gly-L-Ala-L-Leu-OBzl $\xrightarrow{H_2}$ H-Gly-L-Ala-L-Leu-OH

the Nps–NCA, examination of the tripeptide by the amino acid analyzer detects the presence of the diastereomeric isomer glycyl-D-alanyl-L-leucine. The diastereomeric isomer, however, could not be detected in our peptide. This result suggests that the Nps–NCA method of peptide synthesis is free from racemization. The optical rotation of an isolated dipeptide derivative was also examined and the result supported the conclusion that the peptide synthesis was free from racemization.

Table II
Results of Syntheses of Nps-Dipeptide Esters by the Nps–NCA Method

Registry no.	Dipeptide	Yield, %	Mp, °C	[α]D (c 1.0, THF)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
54743-90-7	Nps-Asp(OBzl)Leu-OBzl	98	112–113	−25.6	62.16	5.74	7.25	62.28	5.83	7.18
55871-22-2	Nps-Val-Val-OEt	84	85–86	−71.1	54.40	6.85	10.57	54.50	6.78	10.49
54743-92-9	Nps-Val-Ala-OBzl	88	134.5–135.5	−103.1	58.46	5.84	9.74	58.44	5.88	9.80
39741-15-6	Nps-Ile-Gly-OEt	91	121–122	−78.7	52.02	6.28	11.38	52.11	6.35	11.45
7754-66-7	Nps-Phe-Gly-OEt	86	122–123	−4.9	56.57	5.25	10.42	56.60	5.30	10.36
55871-23-3	Nps-Phe-Pro-OBzl	88	53–54	−30.8	64.15	5.38	8.31	64.08	5.48	8.35
55871-24-4	Nps-Leu-Met-OEt	86	93–94	−57.6	51.46	6.59	9.48	51.55	6.63	9.36
6234-24-8	Nps-Ala-Gly-OEt	89	101–102	−74.2	47.71	5.23	12.84	47.66	5.30	12.77
55871-25-5	Nps-Ala-Phe-OEt	94	116–117	+4.2	57.55	5.55	10.07	57.57	5.60	10.03
55871-26-6	Nps-Glu(OMe)Phe-OEt	90	90–91	+14.0	56.43	5.56	8.59	56.40	5.67	8.48

Table III
Results of Syntheses of Nps-Tripeptide and Nps-Tetrapeptide Esters by the Nps–NCA Method

Registry no.	Peptide	Yield, %	Mp, °C	[α]D, deg	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
54743-93-0	Nps-Lys(Z)Asp(OBzl)Leu-OBzl	84	128–130	−16.4[a]	62.62	6.09	8.54	62.48	6.15	8.39
54743-94-1	Nps-Glu(OBzl)Val-Ala-OBzl	82	165–167	−11.0[a]	60.91	5.89	8.61	60.98	5.92	8.58
55871-27-7	Nps-Gly-Leu-Met-OEt	88	142–143	−7.0[b]	50.39	6.44	11.20	50.55	6.45	11.08
55871-28-8	Nps-Phe-Ile-Gly-OEt	94	167–169	−11.5[b]	58.13	6.24	10.85	58.20	6.32	10.88
55871-29-9	Nps-Val-Val-Val-OEt	80	180–181	−90.5[b]	55.63	7.31	11.28	55.58	7.45	11.18
54743-97-4	Nps-Val-Phe-Lys(Z)Ala-OBzl	89	190–192	−13.8[a]	62.84	6.23	9.99	62.75	6.30	9.85

[a] *c* 1.0, DMF. [b] *c* 1.0, THF.

Results of syntheses of the Nps-dipeptide esters are shown in Table II. The satisfactory result of the peptide synthesis results from the use of the Nps–NCAs, which can rapidly acylate the amino component. An advantage of the use of the Nps–NCAs is to suppress completely side reactions in the conventional NCA method of peptide synthesis. In the NCA method, occurrence of some side reactions of the NCAs has been elucidated.[7] One is "overreaction" resulting from premature decarboxylation of the product carbamate which is formed by the reaction of the NCA with an amino component. The other is oligomerization of the NCA via the NCA anion generated by N-proton abstraction in the anhydride. The *o*-nitrophenylsulfenyl protecting group of the Nps–NCAs prevents above both side reactions. Another feature with great advantage of the Nps–NCA method is the use of highly purified Nps–NCAs. In conventional peptide synthesis by the mixed anhydride method, which uses the same activated carboxyl component by the anhydride group as the Nps–NCA method, a mixed anhydride is prepared in situ between an acylated amino acid and an alkylchlorocarbonate and used without purification for the coupling reaction with the amino component. The coexistence of the by-product accompanied by the activation of the acylated amino acid decreases the yield of the coupling reaction. In contrast to the conventional mixed anhydride method, the new method using the Nps–NCAs can use generally the highly purified crystalline NCAs to increase the yield of the coupling reaction. If the reaction of the Nps–NCA with the amino component proceeds quantitatively, perhaps it is true that the by-product accompanied by the reaction is only carbon dioxide, which leaves as a gas from the reaction system. The feature makes it easy to purify the product and increases more the yield.

Among the NCAs, L-proline NCA has no N proton to be substituted by the Nps protecting group. Thus the synthesis of peptides containing proline residue cannot be accomplished by the Nps–NCA method and the introduction of Nps-proline residue to peptide chain must be done by conventional coupling with Nps-proline.[19]

The Nps–NCA method was developed for the stepwise synthesis of higher oligopeptides. The Nps protecting group of the dipeptide derivatives was easily removed[26] by action of hydrogen chloride in dioxane and the resulting dipeptide ester hydrochloride was allowed to react with the Nps–NCA. The Nps-tripeptide ester thus obtained was isolated and purified. Results of syntheses of Nps-tripeptide esters and an Nps-tetrapeptide ester are shown in Table III. The Nps-NCAs react as easily with dipeptides and a tripeptide esters as with amino acid esters to give the higher peptide esters in high yields. These results demonstrate that the Nps–NCA method can be successfully used for stepwise synthesis of Nps-peptides.

In order to further demonstrate the usefulness of the Nps–NCA method, a C-terminal hexapeptide amide of eledoisin, L-alanyl-L-phenylalanyl-L-isoleucylglycyl-L-leucyl-L-methionine amide, was synthesized by two approaches, a stepwise method and a fragment condensation method. In the stepwise approach, L-methionine ethyl ester hydrochloride was allowed to react with Nps-L-leucine NCA to give Nps-L-leucyl-L-methionine ethyl ester in 86% yield. The dipeptide ester was amidated by action of ammonia in methanol. The Nps protecting group of the dipeptide amide was removed by treating with hydrogen chloride to yield quantitatively the dipeptide amide hydrochloride, which was allowed to react with Nps-glycine NCA. The elongation of the peptide chain of the resulting tripeptide amide was carried out by the sequential reactions with Nps–NCAs of L-isoleucine and L-phenylalanine. The intermediate peptide amides were isolated in above 90% yield after purification. The removal of the Nps group was accomplished almost quantitatively. Nps-L-phenylalanyl-L-isoleucylglycyl-L-leucyl-L-methionine amide was obtained in 65.7% yield from the starting L-methionine ethyl ester. The pentapeptide amide was also prepared in 66% yield by

Table IV
Intermediates of Synthesis of Eledoisin Related Peptide

Registry no.	Intermediate	Yield, %	Mp, °C	[α]D, (c 1.0, DMF)	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
55871-30-2	Nps-Gly-Leu-Met-NH_2	91	197–198	−8.4	48.40	6.20	14.86	48.51	6.28	14.80
55871-31-3	Nps-Ile-Gly-Leu-Met-NH_2	94	226–228	−63.0	51.36	6.90	14.38	51.28	6.85	14.40
55871-32-4	Nps-Phe-Ile-Gly-Leu-Met-NH_2	93	232–234	+21.3	55.79	6.75	13.40	55.70	6.82	13.48
55871-33-5	Nps-Ala-Phe-Ile-Gly-Leu-Met-NH_2	92	246–247	−22.3	55.34	8.02	13.96	55.38	8.10	14.05

the fragment condensation of Nps-L-phenylalanyl-L-isoleucylglycine with L-leucyl-L-methionine ethyl ester hydrochloride which had been prepared stepwise by the Nps–NCA method, followed by amidation. The pentapeptide amide obtained by the fragment condensation method was identical with that synthesized stepwise. After the Nps group of the pentapeptide amide was removed, the resulting peptide amide hydrochloride was treated with Nps-L-alanine NCA to give Nps-L-alanyl-L-phenylalanyl-L-isoleucylglycyl-L-leucyl-L-methionine amide in 92% yield. By stepwise synthesis, the yield of the hexapeptide amide of the C-terminal sequence of eledoisin was 60.3% calculated from L-methionine ethyl ester. Table IV shows the results of syntheses of the intermediate peptides.

The new method for peptide synthesis using the Nps–NCAs described here has some characteristic advantages which result from the use of the Nps–NCAs. The active anhydride derivative, Nps–NCA, of amino acids can be used in highly purified state for peptide synthesis. The rapid acylation of the amino component by the Nps–NCAs proceeds without formation of by-product to give the Nps-peptides in high yields. This rapid method may be used with great advantages for the stepwise synthesis of many other peptides.

Experimental Section

General Procedure for the Synthesis of Nps–NCAs. An NCA of amino acid (0.1 mol) was dissolved in 300 ml of tetrahydrofuran and the solution was cooled to 0° by an ice bath. Crystals of Nps-Cl, 19 g (0.1 mol), were added with stirring to the solution. Then 14 ml of triethylamine was slowly dropped with vigorous stirring into the solution. After the addition of triethylamine, the system was stirred at 0° for 15 min. The resulting crystals of triethylamine hydrochloride were removed by filtration. The filtrate was concentrated under reduced pressure at 35°. The residual oil was crystallized by adding *n*-hexane. The crystals of Nps–NCA were dissolved in a small amount of ethyl acetate and undissolved material was removed by filtration. Addition of *n*-hexane to the solution and cooling in a refrigerator gave crystalline pale yellow product. Recrystallization of the product from ethyl acetate gave a pure Nps–NCA. The product was collected by filtration and dried over P_2O_5.

Nps-L-Leucine NCA could not be crystallized from ethyl acetate. Then the Nps–NCA was dissolved in diethyl ether. The solution was gradually diluted with diisopropyl ether and *n*-hexane (1:1) until the system became cloudy. The system was cooled at −20° in a refrigerator for 2 days. The resulting crystals were collected and dried. Nps-γ-benzyl L-glutamate NCA failed to crystallize from any solvents.

Acid Hydrolysis of Nps-L-Valine NCA. Nps-L-valine NCA (0.29623 g, 1 mmol) was hydrolyzed by dissolving in 20 ml of methanol containing 1 ml of concentrated hydrochloric acid. The solution gave an optical rotation αD of 0.229°. An authentic sample of Nps-L-valine (0.27024 g, 1 mmol) was analogously hydrolyzed and the solution gave an optical rotation of 0.232°. These results are identical within the experimental errors.

General Procedure for the Synthesis of Peptide Using Nps–NCAs. An amino acid ester hydrochloride or *p*-toluenesulfonate (0.1 mol) was dissolved in 200 ml of tetrahydrofuran or acetonitrile. Triethylamine (14 ml, 0.1 mol) was added to the solution. The resulting salt was removed by filtration. To the solution, an Nps–NCA (0.105 mol) was added and allowed to react with stirring at room temperature. After 2 hr, the solvent was evaporated under reduced pressure at 35°. The residual oil was dissolved in 400 ml of ethyl acetate and the solution was washed with 5% citric acid, 5% sodium bicarbonate, and water and dried over sodium sulfate. The solution was concentrated in vacuo at 40° to give an oil, which was crystallized by adding *n*-hexane. The product was recrystallized from ethyl acetate.

Check of Racemization in the Nps–NCA Method by Muraoka Method. L-Leucine benzyl ester *p*-toluenesulfonate (1.42 g, 3.6 mmol) was dissolved in 30 ml of tetrahydrofuran and 0.51 ml (3.64 mmol) of triethylamine was added. Nps-L-alanine NCA (1.07 g, 3.6 mmol) was added to the reaction system and allowed to react for 2 hr at room temperature. After the reaction, the system was filtered and the filtrate was concentrated under reduced pressure to give an oil of Nps-L-alanyl-L-leucine benzyl ester. The product was dissolved in 10 ml of 1 *N* hydrochloric acid in methanol. The solution was concentrated at 30°. To the residual oil, 200 ml of diethyl ether was added to precipitate the dipeptide ester hydrochloride. The solvent was removed by decantation and the residue was repeatedly washed with diethyl ether until the yellow color of the residue disappeared. Then the product was dissolved in 50 ml of acetonitrile and the hydrochloride of the dipeptide was converted into the free ester. The solution was cooled to 0° and 0.75 g (3.6 mmol) of benzyloxycarbonylglycine and 0.72 g (3.8 mmol) of dicyclohexylcarbodiimide was added to the solution. The reaction system was allowed to stand for 2 days at −5°. The resulting dicyclohexylurea was removed by filtration and the filtrate was concentrated to give an oil. The oil was dissolved in 30 ml of ethyl acetate and undissolved urea was removed. The filtrate was concentrated again under reduced pressure. The residual oil was crystallized by adding *n*-hexane followed by cooling at −20° in a refrigerator. The product was isolated and dried.

A part of the crude product (50 mg) was hydrogenated in 90% acetic acid, and the filtrate was evaporated. The residue was dissolved in 0.2 *M* citric buffer at pH 4.25 (10 ml). Ten milliliters of the solution was analyzed by a Hitachi amino acid analyzer Model KLA-2 under the same conditions reported by Muraoka et al.[24] Glycine was eluted at 32 ml of effluent volume and glycyl-L-alanyl-L-leucine was eluted at 130 ml of the effluent volume. An elution peak corresponding to glycyl-D-alanyl-L-leucine, which was reported to elute at 159 ml, was not found in the analysis.

Comparison of the Samples of Nps-L-valyl-L-alanine Benzyl Ester Prepared by the Nps–NCA Method and the DCC Method. The optical rotation of the samples was examined by a Jasco automatic polarimeter Model DIP-SL. The dipeptide obtained by our method gave the optical rotation αD of −1.031° at 1.00 g dl^{-1} in tetrahydrofuran and −1.763° at 2.00 g dl^{-1} in ethyl acetate. The authentic sample shows the αD of −1.029° in tetrahydrofuran and −1.763° in ethyl acetate under the same conditions.

Nps-γ-benzyl L-glutamyl-L-valyl-L-alanine Benzyl Ester as an Example for Stepwise Synthesis of Higher Oligopeptides. Nps-L-valyl-L-alanine benzyl ester was prepared in 88% yield by the general procedure for dipeptide synthesis described above. The Nps-dipeptide benzyl ester (8.6 g, 0.02 mol) was dissolved in 50 ml of 1 *N* hydrochloric acid in dioxane. The solution was concentrated. Diethyl ether was added to the residue to give the crystals of dipeptide ester hydrochloride. The crystals were collected on a glass filter and washed with diethyl ether until the yellow color disappeared and dried in vacuo over P_2O_5. Then the product was dissolved in 100 ml of tetrahydrofuran and 2.8 ml (0.02 mol) of triethylamine was added to give the crystals of triethylamine hydrochloride, which were removed by filtration. To the filtrate was added 8.7 g (0.021 mol) of Nps-γ-benzyl L-glutamate NCA and this was allowed to react with stirring for 2 hr at room temperature. The solvent of the system was evaporated under reduced pressure. The resulting residue was dissolved in 400 ml of ethyl acetate. The solution was washed with 5% citric acid, 5% sodium bi-

carbonate, and water, and dried over sodium sulfate. The solution was concentrated and n-hexane was added to crystallize the product. The Nps-tripeptide benzyl ester was recrystallized from ethyl acetate to give 10.7 g (82%) of pure Nps-L-Glu(OBzl)-L-Val-L-Ala-OBzl.

Nps-L-phenylalanyl-L-isoleucylglycyl-L-leucyl-L-methionine Amide. A. Stepwise Approach. L-Methionine ethyl ester hydrochloride (10.7 g, 0.05 mol) was dissolved in 200 ml of tetrahydrofuran and treated with 17.0 g (0.055 mol) of Nps-L-leucine NCA by the general procedure for dipeptide synthesis described above. The purified Nps-L-leucyl-L-methionine ethyl ester (13.3 g, 0.03 mol) was dissolved in 150 ml of methanol saturated with ammonia and the solution was allowed to stand for 3 days. The solvent was evaporated to give a yellow solid, which was again dissolved in 150 ml of methanol. The solution was concentrated and diethyl ether was added to the residue. The resulting crystals of the Nps-dipeptide amide were obtained in 96% yield. The Nps-dipeptide amide was dissolved in 50 ml of 1 N hydrochloric acid in methanol. After the solvent was evaporated, 300 ml of diethyl ether was added. The resulting solid of the hydrochloride was isolated and washed with diethyl ether until the yellow color disappeared. The dipeptide amide hydrochloride (8.35 g, 0.028 mol) was dissolved in 150 ml of tetrahydrofuran and treated with 4.2 ml (0.03 mol) of triethylamine. After the crystals of the salt were removed by filtration, 7.6 g (0.03 mol) of Nps-glycine NCA was added and allowed to react for 2 hr at room temperature. The solvent was evaporated at 35°. The residue was dissolved in 400 ml of ethyl acetate, washed with 5% citric acid, 5% sodium bicarbonate, and water, and dried over sodium sulfate. The filtrate was concentrated to crystallize the Nps-tripeptide amide. The product was recrystallized from warm tetrahydrofuran. The Nps protecting group of the tripeptide amide was removed by dissolving in 50 ml of 1 N hydrochloric acid in methanol. Glycyl-L-leucyl-L-methionine amide hydrochloride was isolated by adding 400 ml of diethyl ether, followed by filtration, and washed with diethyl ether. The tripeptide amide hydrochloride was dissolved in 200 ml of tetrahydrofuran and treated with triethylamine, followed by 9.3 g (0.03 mol) of Nps-L-isoleucine NCA. The isolation and purification of the product were done by the same procedure of Nps-tripeptide amide to give a pure Nps-tetrapeptide amide. The Nps group of 11.7 g (0.02 mol) of Nps-L-isoleucylglycyl-L-leucyl-L-methionine amide was removed by action of hydrochloric acid. The tetrapeptide amide hydrochloride was treated in the presence of 3 ml (0.0214 mol) of triethylamine with 7.8 g (0.022 mol) of Nps-L-phenylalanine NCA in 300 ml of tetrahydrofuran. The solvent was removed by evaporation and the residue was diluted with 400 ml of water to crystallize the Nps-pentapeptide amide. The product was collected by filtration, and washed with 5% citric acid, 5% sodium bicarbonate, and water, and dried in vacuo over P_2O_5. The yield and physical properties of the intermediates described here are shown in Table IV.

B. Fragment Condensation Approach. A carboxyl component of the fragment condensation, Nps-L-phenylalanyl-L-isoleucylglycine, was prepared stepwise. Glycine ethyl ester hydrochloride (7.0 g, 0.05 mol) was dissolved in 200 ml of tetrahydrofuran and treated with 7 ml (0.05 mol) of triethylamine, followed by 15.6 g (0.052 mol) of Nps-L-isoleucine NCA. Nps-L-isoleucylglycine ethyl ester was isolated in 91% yield after recrystallization from ethyl acetate. The Nps group of the dipeptide ester (14.7 g, 0.04 mol) was removed by treating with 50 ml of 2 N hydrochloric acid in dioxane. The resulting hydrochloride was treated in the presence of 6 ml of triethylamine with 15.3 g (0.044 mol) of Nps-L-phenylalanine NCA in 200 ml of tetrahydrofuran. Nps-L-phenylalanyl-L-isoleucylglycine ethyl ester was obtained in a yield of 19.4 g (94%). The tripeptide ester was saponified as follows. The crystals (15.5 g, 0.03 mol) were dissolved in 50 ml of methanol and 30 ml of acetone, and 30 ml of 1 N sodium hydroxide was added. The solution was allowed to stand for 1 hr at room temperature. Then the solvent was evaporated to give the residual aqueous solution, which was diluted with 100 ml of water. The aqueous solution was extracted with 40 ml of diethyl ether and acidified to pH 3 by 15% citric acid. The solution was extracted with ethyl acetate (2 × 300 ml). The extract was washed with water and dried over sodium sulfate. The solvent was evaporated to give an oil, which was crystallized by adding 300 ml of n-hexane. The Nps-tripeptide was recrystallized from ethyl acetate, 12.3 g (84% yield). An amino component, L-leucyl-L-methionine ethyl ester hydrochloride, was obtained as an oil by treating the Nps-dipeptide ester with hydrochloric acid in dioxane. The product (6.5 g, 0.02 mol) was dissolved in 50 ml of tetrahydrofuran and treated with 3 ml of triethylamine. A solution of the carboxyl component of the Nps-tripeptide free acid (9.3 g, 0.02 mol) in 50 ml of dimethylformamide was added to the solution of the amino component. The solution was cooled to −5°, and 4.6 g (0.04 mol) of N-hydroxysuccinimide and 4.18 g (0.022 mol) of dicyclohexylcarbodiimide were added with stirring. The reaction was allowed to stir for 5 hr at −5° and an additional 10 hr at 0°. The temperature of the solution was raised to room temperature and the reaction was continued for 10 hr at the temperature. The resulting crystals of dicyclohexylurea were removed by filtration and the filtrate was concentrated to give an oil. The oil was dissolved in 400 ml of ethyl acetate and undissolved crystals were removed by filtration. The filtrate was washed with 5% citric acid, 5% sodium bicarbonate, and water. The dried solution was concentrated. The residue was crystallized by adding 400 ml of n-hexane. Recrystallization of the product from warm ethyl acetate gave pure Nps-L-phenylalanyl-L-isoleucylglycyl-L-leucyl-L-methionine ethyl ester (10.6 g, 70% yield). The Nps-pentapeptide ester (7.6 g, 0.01 mol) was dissolved in 100 ml of methanol saturated by ammonia and the solution was allowed to stand for 5 days. Then the crystals were formed. The system was concentrated and 200 ml of diethyl ether was added. The crystals were collected by filtration and washed with diethyl ether. The product was recrystallized from hot methanol to give a pure amide, 6.9 g (94%).

Nps-L-alanyl-L-phenylalanyl-L-isoleucylglycyl-L-leucyl-L-methionine Amide. The pentapeptide amide was treated with hydrochloric acid. The resulting hydrochloride (6.15 g, 0.01 mol) was dissolved in 100 ml of dimethylformamide and allowed to react with 3.5 g (0.013 mol) of Nps-L-alanine NCA. The system was diluted with 500 ml of water and the precipitate was filtered off and washed with 5% citric acid, 5% sodium bicarbonate, water, and methanol. The dried product was recrystallized from 50 ml of warm dimethylformamide to give a pure product, 7.4 g (92%).

The final product was obtained by removal of the Nps group of the protected hexapeptide amide by treating with hydrochloric acid. The resulting hydrochloride was collected by filtration and washed with diethyl ether until the yellow color disappeared. The product was recrystallized from 80% ethanol to give a pure hexapeptide amide hydrochloride: 5.05 g (80% yield); mp 255–260 dec (lit.[27] mp 250–255 dec); $[\alpha]_D$ −12.0° (c 0.2, dimethylformamide). Anal. Calcd for $C_{31}H_{51}N_7O_6 \cdot HCl \cdot H_2O$: C, 52.86; H, 7.73; N, 13.92. Found: C, 52.91; H, 7.84; N, 13.86.

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Registry No.—Glycine NCA, 2185-00-4; alanine NCA, 2224-52-4; valine NCA, 24601-74-9; leucine NCA, 3190-70-3; isoleucine NCA, 45895-90-7; phenylalanine NCA, 14825-82-2; benzyloxycarbonyllysine NCA, 1676-86-4; methylglutamic acid NCA, 1663-47-4; benzylglutamic acid NCA, 3190-71-4; benzylaspartic acid NCA, 13590-42-6; Nps-Cl, 7669-54-7.

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Photochemical Syntheses of 2-Aza- and 2-Oxabicyclo[2.1.1]hexane Ring Systems[1]

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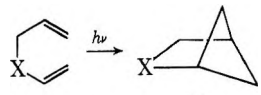
Irradiation of N-substituted 3-allylamino- and 3-allyloxy-5,5-dimethyl-2-cyclohexen-1-ones gives 2-aza- and 2-oxabicyclo[2.1.1]hexane derivatives, respectively, whose structures are assigned on the basis of the NMR spectral and chemical evidence. The photocycloaddition reaction of the *N*-methyl, *N*-allyl, and *N*-phenyl substituted allylamino and allyloxy derivatives produces exclusively or predominantly the thermodynamically unstable isomers, while the *N*-acetyl allylamino derivative gives a ca. 1:1 mixture of two possible isomers. It is suggested that the lone-pair electrons of the heteroatom play an important role in deciding the stereochemical course of this cycloaddition reaction.

Photochemical transformation of 1,5-hexadienes (**1**, X = CH_2) to bicyclo[2.1.1]hexanes (**2**, X = CH_2) has been extensively studied.[2] Several years ago, we initiated a photochemical study on 1,5-hexadienes containing a heteroatom (**1**, X = a heteroatom) with the hope that the reaction might be extended to the syntheses of the 2-heterobicyclo[2.1.1]hexane systems (**2**, X = a heteroatom). We now report the syntheses of the then unknown 2-azabicyclo[2.1.1]hexane ring system (**2**, X = NR)[3] from N-substituted 3-allylamino-5,5-dimethyl-2-cyclohexen-1-ones and the 2-oxabicyclo[2.1.1]hexane ring system (**2**, X = O)[4] from 3-allyloxy-5,5-dimethyl-2-cyclohexen-1-one. In addition, some chemical transformation reactions of the new heterocycles are described.

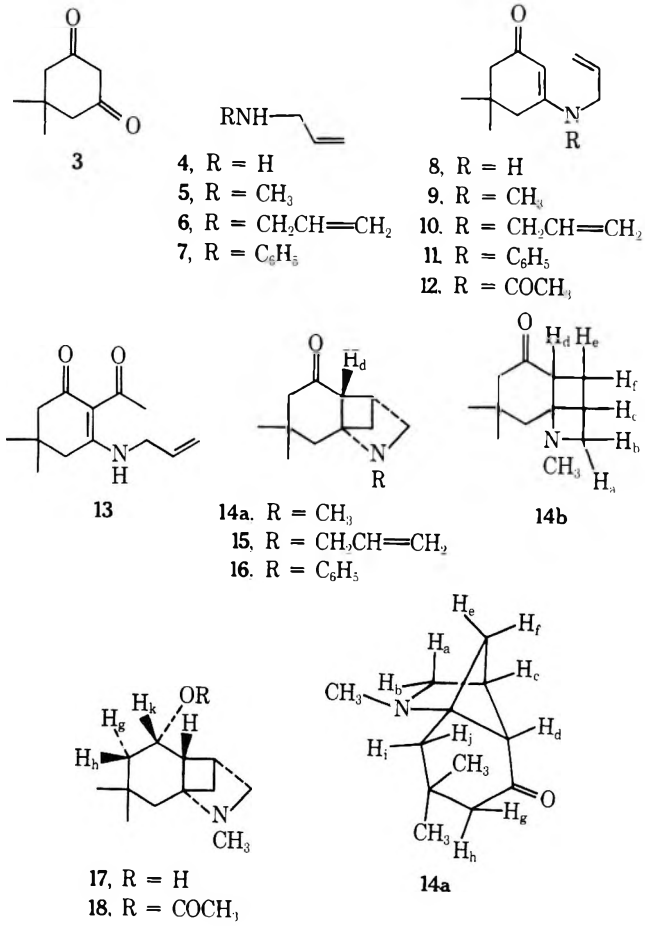


1 **2**

Results

3-Allylamino-2-cyclohexen-1-ones (**8**–**11**) were readily obtained from dimedone (**3**) and the corresponding allylamines (**4**–**7**) in 75, 71, 46, and 64% yields, respectively. Acetylation of **8** with acetic anhydride and pyridine gave *N*-acetate **12** (43%), *C*-acetate **13** (8%), and an unidentified product (11%). The structural assignments of **8**–**13** are consonant with elemental analyses and ir, uv, NMR, and mass spectral data (see Experimental Section).

Irradiation of a 0.02 *M* cyclohexane solution of **9** with a 350-W high-pressure mercury lamp through a Pyrex filter for 10 hr resulted in the disappearance of **9** and the concomitant formation of a single photoproduct. The progress of the reaction was conveniently followed by TLC examination. The other aprotic solvents such as ether, benzene, acetone, and methylene chloride could be equally used, but the use of alcoholic solvents such as methanol or ethanol did not give a clear-cut result. The resulting photoproduct was isolated in 50–60% yield as a crystalline solid, mp 48.5–49.5°, by passing through a short alumina column after removal of the cyclohexane.



3

4, R = H
5, R = CH_3
6, R = $CH_2CH{=}CH_2$
7, R = C_6H_5

8, R = H
9, R = CH_3
10, R = $CH_2CH{=}CH_2$
11, R = C_6H_5
12, R = $COCH_3$

13

14a, R = CH_3
15, R = $CH_2CH{=}CH_2$
16, R = C_6H_5

14b

17, R = H
18, R = $COCH_3$

14a

The photoproduct was shown to be isomeric with **9** by elemental analysis and mass spectrometry. The ir (an absorption at 1710 cm^{-1} typical of a six-membered ketone) and NMR (no olefinic proton signal) spectrum show no unsaturation, and thus it must be tricyclic. It formed a crystalline hydrochloride, indicating the presence of a basic nitrogen. The lithium aluminum hydride reduction in ether

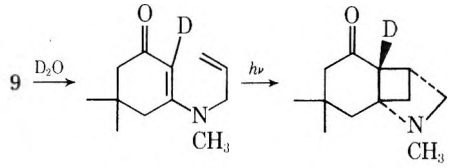
Table I
NMR Data[a] for 2-Aza- and 2-Oxabicyclo[2.1.1]hexanes

Compd	Chemical shift,[b] τ						Coupling constant, Hz				
	H_a	H_b	H_c	H_d	H_e	H_f	J_{ef}	J_{ce}	J_{cf}	J_{ab}	J_{de}
14a	7.81 (d)	6.60 (dd)	7.10 (bs)	7.53 (bs)	8.29 (dd)	8.47 (ddd)	7.0	1.5	2.6	8.0	0
15	7.86 (bd)	6.75 (dt)	7.16 (bs)	7.61 (bs)	8.36 (dd)	8.51 (ddd)	7.0	1.0	2.6	8.5	0
16	5.99 (d)	7.16 (d)	6.99 (bs)	7.41 (bs)	8.21 (s)	8.21 (s)				7.5	0
17	7.74 (d)	6.38 (dd)	7.17 (bs)	8.61 (bs)	8.40 (dd)	8.79 (ddd)	7.0	1.5	2.5	8.0	0
27	7.50 (d)	7.07 (dd)	7.03 (bs)	7.60 (bs)	8.51 (t)	8.16 (ddd)	8.5	0	3.0	8.0	8.5
31	6.26 (bd)	6.77 (dt)	6.95 (m)	7.48 (bs)	8.50 (dd)	8.13 (ddd)	7.0	1.5	2.5	7.5	0
32	6.59 (s)	6.59 (s)	6.88 (dt)	7.51 (bs)	8.59 (t)	7.85[c]	8.5	1.2	3.0		8.5
37a	6.05 (d)	6.35 (d)	6.81 (dt)	7.49 (bs)	8.35 (dd)	8.21 (dd)	7.5	0	2.7	6.0	1.5

[a] Spectra were determined with a Varian HA-100 (100 MHz). Other signals are given in the Experimental Section. [b] Chemical shifts relative to Me_4Si in $CDCl_3$, s = singlet, d = doublet, t = triplet, m = multiplet, bs = broad singlet, bd = broad doublet, dd = doublet of doublets, ddd = doublet of double doublets. [c] Splitting pattern of this signal is uncertain because of its overlapping with other signals.

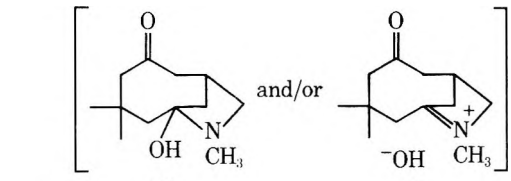
gave an oily secondary alcohol **17**,[5] which could be acetylated by treatment with acetic anhydride and pyridine to give an oily acetate **18**.

Careful examination of the NMR spectra (Table I) prompted us to assign structure **14a** rather than **14b** to the photoproduct. The spectrum (100 MHz) revealed an ABX pattern consisting of a broad signal (X part) at τ 7.10 (H_c), a doublet of doublets at 8.29 (H_e) (J_{ef} = 7.0 and J_{ce} = 1.5 Hz), a doublet of double doublets at τ 8.47 (H_f) (J_{ef} = 7.0, J_{cf} = 2.6, and J_{bf} = 1.5 Hz[6]), and an AB pattern consisting of a doublet with a small splitting at τ 6.60 (H_b) (J_{ab} = 8.0 and J_{bf} = 1.5 Hz) and a doublet at τ 7.81 (H_a) (J_{ab} = 8.0 Hz). These assignments were confirmed by decoupling and deuterium labeling experiments and experiments using a shift reagent, Eu(DPM)$_3$.[7] Irradiation of H_b caused the doublet of H_a to collapse to a singlet and the signal of H_f into a doublet of doublets of J = 7.0 and 2.6 Hz, and irradiation of H_c converted the broad signal of H_d into a sharp singlet and the signal of H_f into a doublet of doublets of J = 7.0 and 1.5 Hz. In the NMR spectrum of deuterated compound **20** prepared by irradiation of **19** which, in turn, was obtained by shaking a methylene chloride solution of **9** with deuterium oxide for 3 min, the signal of H_d disappeared and the broad signal of H_c was sharpened but the signals due to H_e and H_f remained unchanged. This result also eliminates the possibility of alternative structure **14b**. Addition of Eu(DPM)$_3$ to a solution of **14a** in deuteriochloroform caused significant low-field shifts of the signals due to H_b, H_d, H_g, and H_h, as a result of complexation of the shift reagent with the carbonyl oxygen atom. The observed coupling constants (J_{ef} = 7.0, J_{cf} = 2.6, and J_{ce} = 1.5 Hz) are in good agreement with those reported for the bicyclo[2.1.1]hexane system.[8]

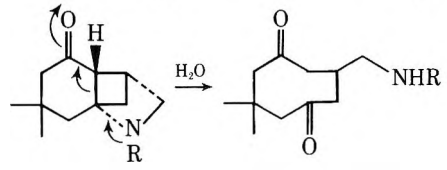


19 **20**

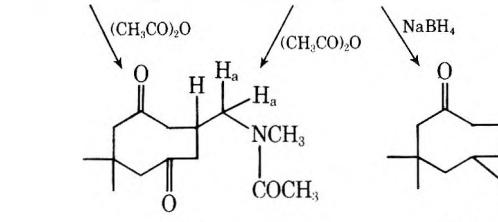
Final confirmation of structure **14a** was given by the chemical transformation. Compound **14a** was found to be labile in water and thus refluxing in water gave a crystalline compound **21** in 94% yield. On the basis of the spectral data (see Experimental Section), taken along with the following chemical evidence, this compound was shown to exist as an equilibrium mixture of the tautomeric isomers (**21a**, **21b**, and/or **21c**).[9] Reduction of **21** with sodium borohydride afforded a new amino ketone **23**, whose ir spectrum shows the carbonyl absorption at 1680 cm^{-1}. This relatively low-frequency shift of the carbonyl band suggests the occurrence of a well-known transannular interaction between the nitrogen and the carbonyl group.[10] This was confirmed by converting it into the perchlorate **24** in which disappearance of the ir carbonyl band and the appearance of a new strong hydroxylic absorption were observed. On the other hand, acetylation of **21** with acetic anhydride gave the *N*-acetate **25a**, which was also obtained directly from **14a** upon similar treatment with acetic anhydride.



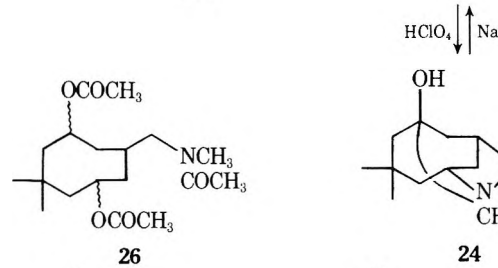
21b **21c**



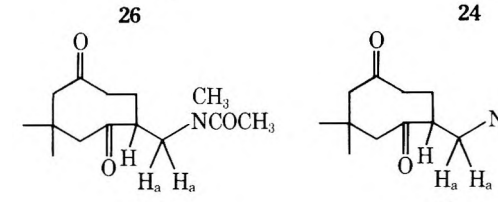
14a, R = CH_3 **21a**, R = CH_3
16, R = C_6H_5 **22a**, R = C_6H_5



25a **23**



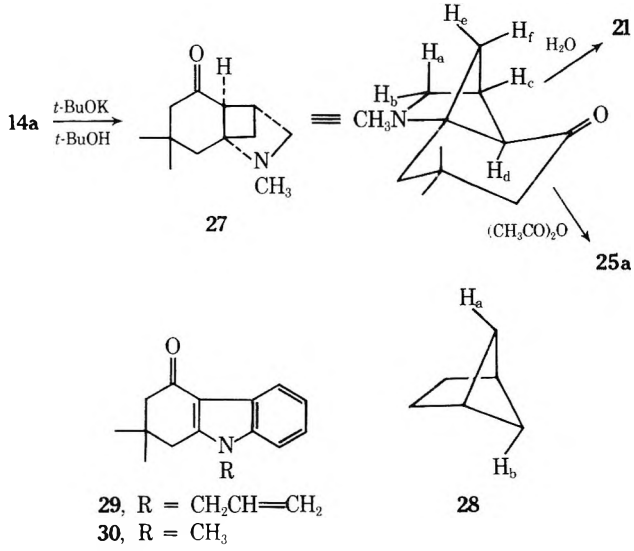
26 **24**



25b **22b**

The mass spectrum of **25a** shows a base peak at *m/e* 86, corresponding to $CH_2{=}N^+(CH_3)COCH_3$. The structure assignment rests largely on the basis of the spectral data (see Experimental Section), a sodium borohydride reduction followed by acetylation to triacetate **26,** and the following deuterium exchange experiment. The *N*-acetate **25a** underwent facile incorporation of deuterium atoms at the four methylene groups adjacent to the carbonyl groups upon heating with deuterium oxide in the presence of sodium deuterioxide. The NMR spectrum showed that the doublet at τ 6.65 ascribable to two H_a's remained unchanged, in accordance with the expectation based on structure **25a.** In contrast, if the photoproduct were **14b,** the *N*-acetate should be **25b,** in which the two H_a's would be nonequivalent and appear as an AB part of an ABX pattern[11] which should become an AB quartet after deuterium exchange.

The stereochemistry of **14a** was confirmed by isolation of the epimer at H_d. Thus, treatment of **14a** with potassium *tert*-butoxide in *tert*-butyl alcohol gave an oily new basic substance **27,** whose structure was readily assigned on the basis of the NMR spectral (Table I) and chemical evidence. The most striking feature of the NMR spectrum is the long-range coupling between endo H_e and endo H_d (J = 8.5 Hz). Such large coupling has been known to occur only if two protons (H_a and H_b) in bicyclo[2.1.1]hexane (**28**) are in W configuration.[8] In comparison, this coupling was not observed in **14a,** in which H_d has the exo configuration. Compound **27** was also transformed to **21** and **25a.**

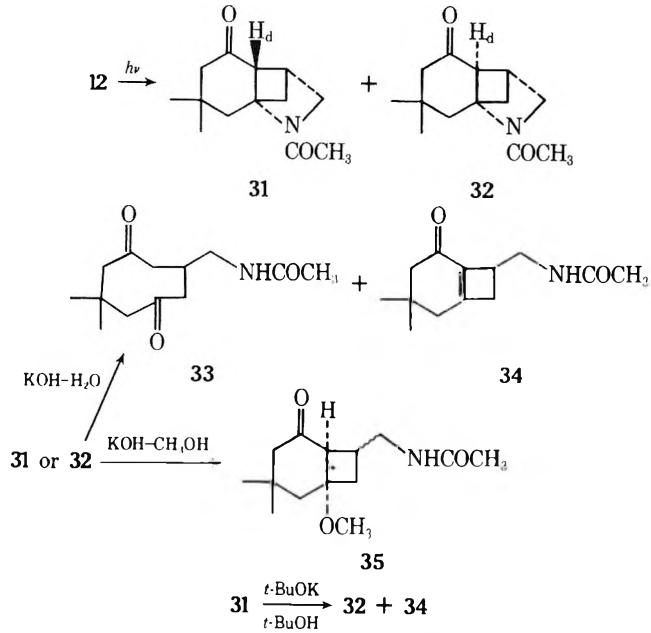


In a similar manner, irradiation of a 0.02 *M* cyclohexane solution of **10** gave a single crystalline product, mp 44–44.5°, in 63% yield, which showed a similar NMR spectrum (Table I) to that of **14a** except for the presence of signals due to an *N*-allyl group instead of the *N*-methyl singlet, thus establishing the structure as **15.**

On the other hand, irradiation of an ethereal solution of **11** gave two products in 39 and 6% yields. The structure of the major product **16,** mp 99–100°, was assigned on the basis of the NMR spectrum (Table I) and transformation to **22a.** Treatment of **16** with potassium hydroxide in aqueous methanol gave a cyclooctane-1,5-dione **22a** in 60% yield, whose ir and NMR spectra (see Experimental Section) suggested that **22a** exists as a diketo form. Deuterium exchange study of **22a** revealed that the doublet at τ 6.68 ascribed to two H_a's remained unchanged, eliminating alternate structure **22b** from consideration. The stereochemical assignment of **16** was again deduced on the base of the NMR spectral examination which indicated the absence of the long-range coupling between H_e and H_d.

The minor product, mp 146–147°, has the molecular formula $C_{17}H_{19}ON$ (elemental analysis and mass spectrometry). In agreement with the assigned structure **29,** this photoproduct exhibits an ir band at 1640 cm^{-1}. Its uv spectrum (see Experimental Section) was similar to that reported for carbazole **30.**[12] The final confirmation was given by the NMR spectrum, which shows four aromatic protons and signals characteristic of an allyl group. The formation of the carbazole **29** must be a result of the presence of the phenyl group which comprises a divinylamine system. Oxidative photocyclizations of the divinylamine system are well known.[13]

Irradiation of a 0.02 *M* ethereal solution of **12** under similar conditions was found to cause the rapid disappearance of the starting material (within 1 hr) and the concomitant formation of two photoproducts in a ratio of 1.07:1 (by NMR spectroscopy). The products could be isolated by preparative TLC to give **31,** mp 38–39°, and **32,** mp 69–70°, in 31 and 25% yields, respectively. The structures of **31** and **32** were apparent from the following spectral data and several interconversions. The principal features of the mass and ir spectra of both compounds **31** and **32** were markedly similar. The ir spectra of **31** and **32** show two strong carbonyl absorptions at 1715 and 1650 cm^{-1}. Heating of **31** or **32** in aqueous potassium hydroxide solution gave the same diketo acetate **33** accompanied by enone **34,** and treatment with potassium hydroxide in methanol resulted in the formation of the same methanol adduct **35.** Treatment of **31**



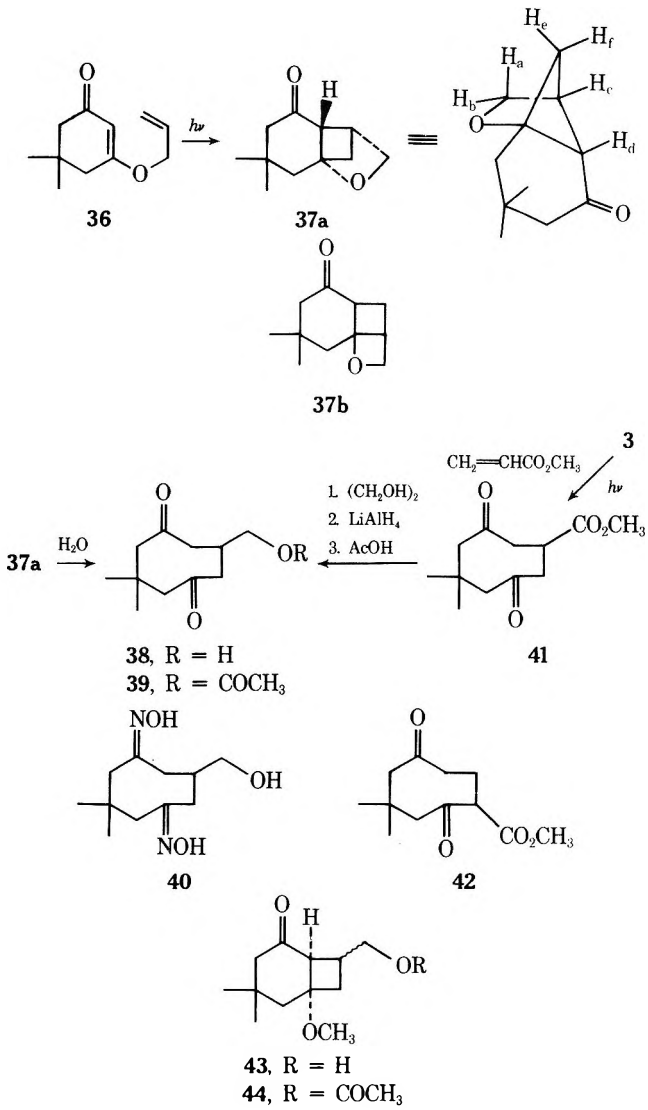
with potassium *tert*-butoxide in *tert*-butyl alcohol gave **32** in addition to **34,** while **32** was recovered unchanged under the similar conditions. Evidence for the structures of **33, 34,** and **35** are given in the Experimental Section. The stereochemistry of **31** and **32** was firmly confirmed by examination of the NMR spectra; the long-range coupling between H_d and H_e (J = 8.5 Hz) was observed in **32,** while **31** did not show such a coupling.

Irradiation of **8** in various solvents was attempted but the reaction proceeded only very slowly to give an unstable product in low yield accompanied by polymeric substance. Prolonged irradiation led to polymer formation.

Irradiation of a 0.02 *M* cyclohexane solution of **36** led to complete disappearance of starting material after 10 hr and appearance of a new spot on TLC. Evaporation of the solvent followed by submitting to preparative TLC on alumina gave a colorless oil in a yield greater than 72%. Although

TLC or GLC analyses indicated that it consists of a single component, its NMR spectrum clearly showed it to contain a trace amount of an unidentified product in addition to a major product.[14] Attempts to isolate the photoproducts in a pure form were unsuccessful. However, careful examination of the ir (1710 cm^{-1}) and NMR (Table I) spectra prompted us to assign structure **37a** rather than **37b** to the major product. The exo configuration of H_d was suggested on the basis of the absence of a large long-range coupling between H_d and H_e.

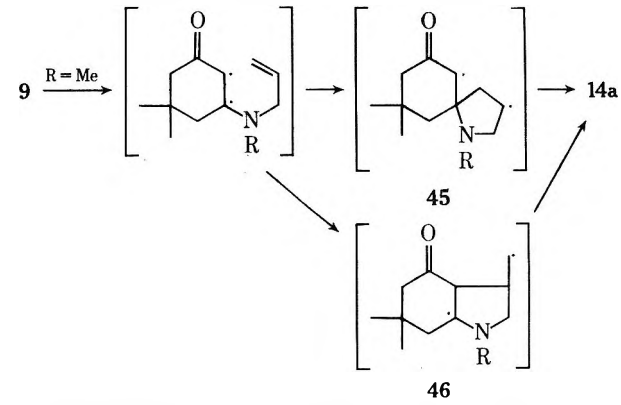
Confirmation of structure **37a** was given by the following chemical evidence. When the photoproduct was refluxed in water, a diketo alcohol **38** was obtained in 53% yield, which gave *O*-acetate **39** by treatment with acetic anhydride and pyridine, and dioxime **40** by treatment with hydroxylamine. The structure of **38** was established by an independent synthesis from dimedone (**3**). Thus, according to the procedure of de Mayo and coworkers,[15] we obtained diketo ester **41** in poor yield by irradiation of **3** and a large excess of methyl acrylate in cyclohexane. The ir spectrum of **41** (1735 and 1710 cm^{-1}) clearly excluded an alternative β-keto ester structure **42**. Ketalization of **41** followed by lithium aluminum hydride reduction and treatment with 90% acetic acid gave a diketo alcohol, which was identical with **38** in all respects.



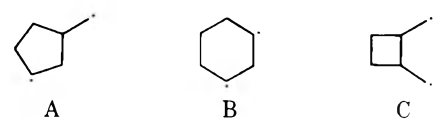
In order to obtain some supporting evidence on the stereochemistry of **37a**, epimerization of **37a** was attempted but without success. Thus, treatment with potassium *tert*-butoxide in *tert*-butyl alcohol gave a complex mixture, and treatment with sodium methoxide in methanol resulted in the addition of methanol to give 52% yield of an oily compound **43**. The structure of **43** was assigned on the basis of spectral (see Experimental Section) and chemical evidence. Thus, it gave *O*-acetate **44** upon treatment with acetic anhydride and pyridine, and afforded **38** upon treatment with hydrochloric acid in methanol.

Discussion

In an attempt to clarify the reactive species in this photocycloaddition reaction, energy transfer experiments were carried out on **9** and **12**. The reaction (**9** → **14a**) was found to be effectively sensitized by acetophenone and benzophenone, and quenched by phenanthrene, naphthalene, and piperylene. Figure 1 shows a plot of the reciprocal of the relative quantum yield for the cycloaddition reaction of **9** against piperylene concentration. The linearity of the Stern–Volmer plot as well as sensitizing experiments confirms that the cycloaddition reaction (**9** → **14a**) occurs via the triplet excited state. Taking into account the results of earlier studies on the intermolecular[16] and intramolecular[2] photocycloaddition of α,β-unsaturated ketones to alkenes, it would appear that the most likely initial step of the reaction of **9** would involve the $n \rightarrow \pi^*$ excitation of the enone group,[17] raising the enone portion to an excited triplet state. The excited enone can undergo a cross addition to the double bond via either diradical intermediate **45** or **46**, leading to 2-azabicyclo[2.1.1]hexanes (e.g., **14a**).



There was no evidence for the formation of the parallel addition products [2-azabicyclo[2.2.0]hexanes (i.e., **14b**)]. The preference for forming cross addition products (bicyclo[2.1.1]hexanes) over parallel addition products (bicyclo[2.2.0]hexanes) in the photocycloaddition reaction of 1,5-hexadienes [**1**, (X = CH_2)] is a well-known phenomenon but still a disputable problem. Recently, it has been suggested that the formation of the five-membered ring intermediate (A) leading to bicyclo[2.1.1]hexanes is preferred to the other possible six- (B) or four-membered ring intermediates (C) in terms of strain and entropy factors;[2c,18] apparently, the stability of the diradical is not an important factor.

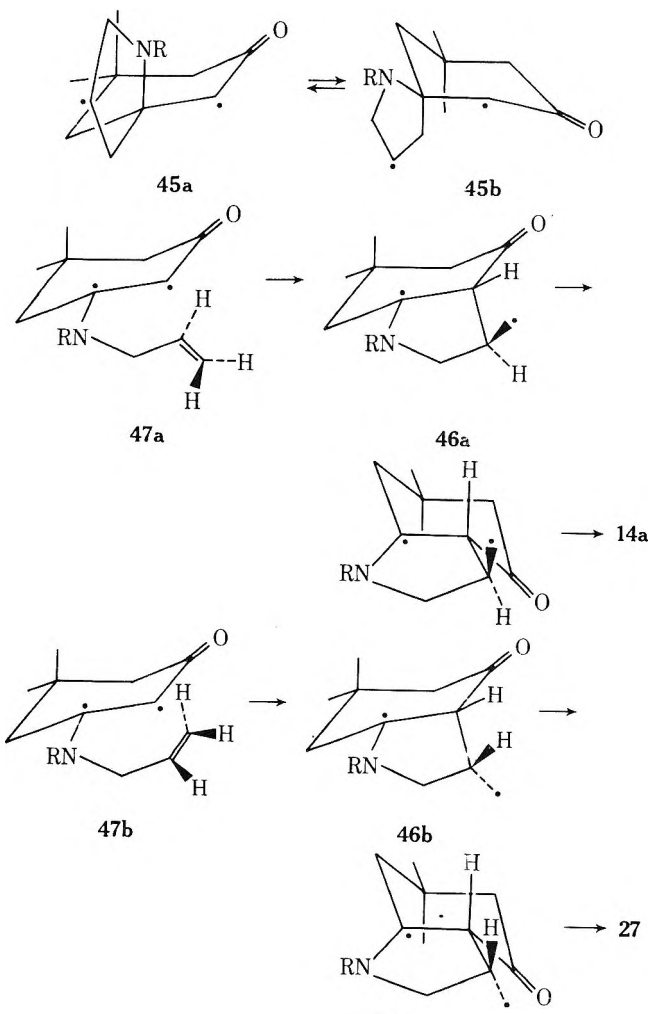


It should be emphasized here that the cycloaddition reaction of **9–11** and **36** produces exclusively or predominantly the thermodynamically unstable isomers,[19] while **12** gave a ca. 1:1 mixture of two possible stereoisomers. In addition, it is noteworthy that the reaction is significantly faster with the *N*-acetyl derivative **12** than with the *N*-methyl **9** or *N*-allyl derivative **10**. These observations suggest that the

lone-pair electrons of the heteroatom play important role in deciding the stereochemical course of this cycloaddition reaction.

The formation of the trans-fused 6–4 ring system from the reaction of **9–11** and **36** is formally related to the intermolecular cycloaddition reactions of cyclohexenones to alkenes in which thermodynamically unstable trans-fused bicyclo[4.2.0]octanones are predominatly produced.[16] However, it has not yet been clarified why the trans adducts should be formed in the latter reaction, although a few interpretations are presented.[16]

Although some interpretations for the stereospecific formation of **14a** from **9** may also be possible (for example, see ref 2c), our interpretation is based on the stereochemical arguments. Thus, if the reaction of **9** is assumed to proceed through intermediate **45** (mechanism a), two conformations **45a** and **45b** may be considered. However, examination of molecular models using sp^2-hybridized carbons for the radical center reveals no marked steric effects which would favor the formation of **14a** over **27** from either conformers; thus, if this reaction is kinetically controlled, the formation of both isomers **14a** and **27** is expected by this mechanism. On the other hand, if alternative intermediate **46** is involved (mechanism b), the initial bond formation may produce two configurational isomers **46a** (leading to the observed product **14a**) and **46b** via the corresponding transition states **47a** and **47b**. Examination of models suggests that approach of the olefinic bond to the radical center at the α position to the ketone as shown in **47b** would be expected to be severely hindered as a result of eclipsing of the double bond with the C^2H–C^1=O bond.[20] Nonbonded interactions of this type are not involved in the transition state **47a**, and thus formation of **46a** would be favored.



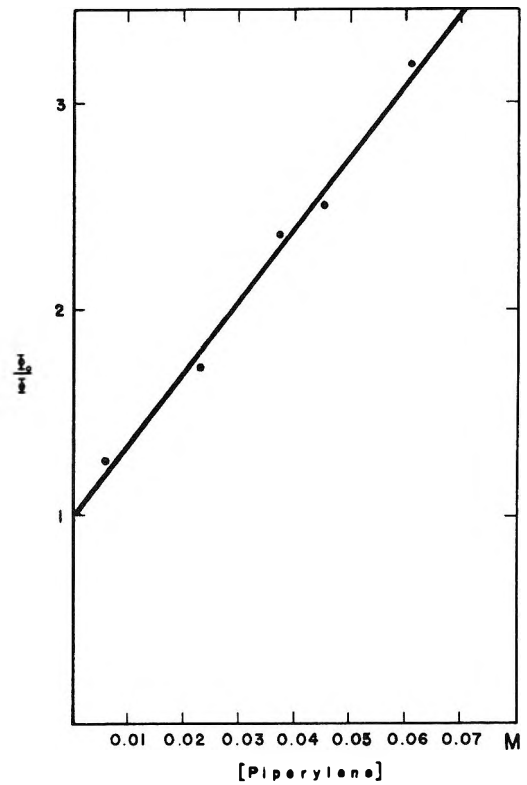


Figure 1. Stern–Volmer plot of quenching of photocycloaddition of **9** (0.009 *M*) by piperylene in ether. The identity and yield of the product **14a** were determined by GLC analysis at 150° and SE-30.

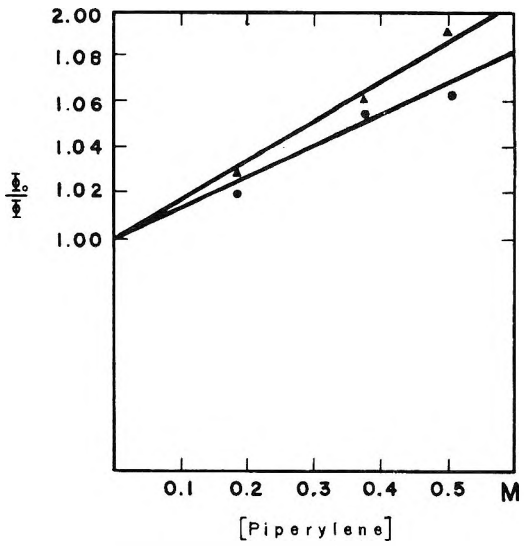


Figure 2. Stern–Volmer plot of quenching of photocycloaddition of **12** (0.01 *M*) by piperylene in ether: ●, **31**; ▲, **32**. The identity and yield of the products **31** and **32** were determined by GLC analysis at 150° on 15% BSP.

The lack of stereospecificity in the cycloaddition of **12**, however, can not be explained by mechanism b, unless it is assumed that the different excitation processes in **12** and the nonacylated compounds **9–11** and **36** operate. In fact, energy transfer experiments of **12** suggested the participation of a different precursor from that of **9**: the reaction (**12** → **31** and **32**) was not sensitized by benzophenone and the slope of the Stern–Volmer plots[21] for the quenching of the isomerization of **12** by piperylene (Figure 2) is about 20 times lower than that of **9**. Assuming that the quenching is diffusion controlled, this indicates the difference of the magnitude in the lifetime of the reacting species of **12** and **9**. Thus, whereas it is clear that compound **9** reacts via the

triplet state, the reaction of **12** may involve a different excited state from that of **9**, presumably a singlet or a triplet pathway; this could also be responsible for the rapid reaction rate of **12**. As one possibility, one can imagine the intermediate **45** (R = acetyl) being involved in the reaction of **12**. However, until more suitable evidence is available, further speculation concerning mechanistic problems must be postponed.

Experimental Section

Melting points are uncorrected. Unless otherwise stated, NMR spectra were determined with an Hitachi R-20A spectrometer (tetramethylsilane as internal standard). Ir spectra were recorded with an Hitachi EPI-G2 spectrophotometer, and uv spectra with an Hitachi 124 spectrophotometer. Mass spectra were obtained with an Hitachi RMU-6D with a direct inlet system operating at 70 eV. Preparative TLC was carried out on Merck alumina PF_{254}. Unless otherwise stated, the petroleum ether used was the fraction having bp 30–60°. Uv irradiation were carried out in a Pyrex vessel at room temperature, using an Eikosha 350-W high-pressure mercury lamp.

3-Allylamino-5,5-dimethyl-2-cyclohexen-1-one (8). A solution of 7 g of dimedone (**3**) and 5 g of allylamine (**4**) in 40 ml of benzene was heated in a sealed tube at 100° for 7 hr. After the solvent was removed, the residual oil was distilled [bp 146° (0.08 mm)] to give 6.72 g (75%) of **8**, which solidified on standing: mp 75–75.5° (from Et_2O); ir ($CHCl_3$) 3440, 1590 cm^{-1}; uv max (EtOH) 289 nm (log ϵ 4.43); NMR ($CDCl_3$) τ 3.85–4.45 (m, 1, $-CH{=}CH_2$), 4.50 (br, 1, NH), 4.60–4.95 (m, 2, $-CH{=}CH_2$), 4.92 (s, 1, 2-H), 6.28 (br, 2, J = 5.5 Hz, $-CH_2CH{=}CH_2$), 7.79 (s, 2, 6-H), 7.86 (s, 2, 4-H), 8.96 [s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 179 (M^+).

Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.83; H, 9.69; N, 7.68.

3-(*N*-Methylallylamino)-5,5-dimethyl-2-cyclohexen-1-one (9). A solution of 2.9 g of **3** and 1.9 g of allylmethylamine (**5**) in 50 ml of benzene was heated in a sealed tube at 100° for 5 hr. After evaporation of the solvent, distillation of the residual oil [bp 116° (0.08 mm)] gave 2.75 g (71%) of **9** as a yellow, viscous oil: ir ($CHCl_3$) 1600, 1550 cm^{-1}; uv max (EtOH) 299 nm (log ϵ 4.48); NMR ($CDCl_3$) τ 3.9–4.6 (m, 1, $-CH{=}CH_2$), 4.6–5.2 (m, 2, $-CH{=}CH_2$), 4.85 (s, 2-H), 6.0–6.4 (m, 2, $-CH_2CH{=}CH_2$), 7.05 (s, 3, NCH_3), 7.70 (s, 2, 6-H), 7.84 (s, 2, 4-H), 8.92 [s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 193 (M^+).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.54; H, 9.91; N, 7.25. Found: C, 74.12; H, 9.99; N, 7.01.

3-Diallylamino-5,5-dimethyl-2-cyclohexen-1-one (10). A solution of 2.8 g of **3** and 2.95 g of diallylamine (**6**) in 50 ml of benzene was heated in a sealed tube at 100° for 7 hr. After removal of the solvent, distillation of the residual oil [bp 146–152° (0.45 mm)] gave 2.85 g (46%) of **10**: ir ($CHCl_3$) 1595, 1550 cm^{-1}; uv max (EtOH) 301 nm (log ϵ 4.50); NMR ($CDCl_3$) τ 3.85–4.5 (m, 2, $2\text{-}CH{=}CH_2$), 4.6–5.1 (m, 4, $2\text{-}CH{=}CH_2$), 4.75 (s, 1, 2-H), 6.15 (br d, 4, J = 5.5 Hz, $2\text{-}CH_2CH{=}CH_3$), 7.70 (s, 2, 6-H), 7.83 (s, 2, 4-H), 8.92 [s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 219 (M^+).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.27; H, 9.77; N, 6.51.

3-(*N*-Allylanilino)-5,5-dimethyl-2-cyclohexene-1-one (11). A solution of 1 g of **3** and 1 g of *N*-allylaniline (**7**) in 50 ml of toluene was refluxed in the presence of 1 drop of sulfuric acid in a flask equipped with a Dean-Stark trap for 20 hr. The solvent was removed and the residue was chromatographed on alumina. Elution with benzene–ethyl acetate (7:3) gave 1.16 g (64%) of **11** as a colorless oil, which solidified on standing: mp 64–65° (from *n*-hexane); ir ($CHCl_3$) 1605, 1555 cm^{-1}; uv max (EtOH) 302 nm (log ϵ 4.51); NMR ($CDCl_3$) τ 2.30–2.97 (m, 5, aromatic), 3.75–4.45 (m, 1, $-CH{=}CH_2$), 4.71 (s, 1, 2-H), 4.70–5.10 (m, 2, $-CH{=}CH_2$), 5.85 (dt, 2, J = 5.0 and 1.5 Hz, $-CH_2CH{=}CH_2$), 7.91 (s, 2, 6-H), 7.96 (s, 2, 4-H), 9.06 [s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 255 (M^+).

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.04; H, 8.36; N, 5.40.

3-(*N*-Allylacetamido)-5,5-dimethyl-2-cyclohexen-1-one (12) and 2-Acetyl-3-allylamino-5,5-dimethyl-2-cyclohexen-1-one (13). A solution of 1 g of **8** in 0.6 ml of pyridine and 4 ml of acetic anhydride was refluxed for 1 hr. After removal of the solvent in vacuo, the residual oil was chromatographed on alumina using petroleum ether–ether (3:7) as solvent to give 525 mg (43%) of **12** as a colorless oil: ir ($CHCl_3$) 1650, 1580 cm^{-1}; uv max (EtOH) 282 nm (log ϵ 4.02); NMR ($CDCl_3$) τ 3.84–4.96 (m, 1, $-CH{=}CH_2$), 4.20 (s, 1, 2-H), 4.70–5.05 (m, 2, $-CH{=}CH_2$), 5.83 (dt, 2, J = 5.0 and 1.5 Hz, $-CH_2CH{=}CH_2$), 7.55 (s, 2, 6-H), 7.78 (s, 2, 4-H), 7.88 (s, 3, $COCH_3$), 8.94 [s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 221 (M^+).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.23; H, 8.71; N, 6.10.

Further elution with the same solvent gave 104 mg (8%) of **13**: mp 40–41° (from petroleum ether); ir ($CHCl_3$) 1630, 1570 cm^{-1}; uv max (EtOH) 260 nm (log ϵ 4.11), 292 (4.14); NMR ($CDCl_3$) τ −2.7 (br, 1, NH), 3.78–4.90 (m, 1, $-CH{=}CH_2$), 4.55–5.00 (m, 2, $-CH{=}CH_2$), 6.03 (m, 2, $-CH_2CH{=}CH_2$), 7.51 (s, 3, $COCH_3$), 7.61 (s, 2, 6-H), 7.76 (s, 2, 4-H), 8.99 [s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 221 (M^+).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.34; H, 8.78; N, 6.73.

Further elution with the same solvent gave 138 mg of an unstable oily product which was not further examined.

Irradiation of 9. A solution of 4 g of **9** in 1 l. of cyclohexane was irradiated for 10 hr. The solvent was removed and the residue was chromatographed on alumina. Elution with petroleum ether–ether (10:1) gave a solid which was recrystallized from petroleum ether to give 2.0–2.4 g (50–60%) of **14a**: mp 48.5–49.5°; ir ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) τ 7.70 (s, 3, NCH_3), 7.86 (s, 2, H_g and H_h), 8.12 (center of AB q, 2, J = 14.0 Hz, H_i and H_j), 8.66 and 8.86 [2 s, 6, $-C(CH_3)_2$]. The NMR spectrum of 38 mg of **14a** in 0.4 ml of $CDCl_3$ in the presence of 15 mg of $Eu(DPM)_3$ showed the following signals: τ 6.38 (dd, 1, H_b), 7.05 (br s, 1, H_c), 7.37 (br s, 1, H_d), 7.65 (s, 2, H_g and H_h), 7.70 (s, 3, NCH_3), 7.80 (d, 1, H_a), 8.08 (s, 2, H_i and H_j), 8.27 (dd, 1, H_e), 8.45 (ddd, 2, H_f), 8.64 and 8.86 [2 s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 193 (M^+).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.25; H, 9.86; N, 7.37.

The hydrochloride was prepared by passing dry hydrogen chloride into an anhydrous ethereal solution of **9**. The precipitated white solid was collected and recrystallized from ethyl acetate: mp 139–140.5°; ir ($CHCl_3$) 2100–2600, 1720 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}NOCl{\cdot}H_2O$: C, 58.17; H, 8.95; N, 5.65. Found: C, 58.04; H, 8.92; N, 5.80.

Reduction of 14a. A solution of 728 mg of **14a** in 10 ml of anhydrous ether was added to a suspension of 230 mg of lithium aluminum hydride in 10 ml of anhydrous ether and the mixture was stirred at room temperature overnight. After an usual work-up procedure, distillation [bp 75–85° (bath temperature) (0.2 mm)] afforded 621 mg (85%) of **17**: ir ($CHCl_3$) 3660 cm^{-1}; NMR ($CDCl_3$) τ 6.04 (q, 1, J = 3.0 Hz, H_k), 7.68 (s, 3, NCH_3), 8.19 (dd, 1, H_g, J = 3 and 14 Hz), 8.32 (center of AB q, 2, J = 13.5 Hz, H_i and H_j), 8.66 (m, 1, H_h), 8.70 and 9.08 [2 s, 6, $-C(CH_3)_2$].

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.33; H, 10.82; N, 7.24.

Acetylation of 17. A mixture of 275 mg of **17** in 0.5 ml of pyridine and 0.5 ml of acetic anhydride was allowed to stand at room temperature overnight. The solvent was removed, the residue was dissolved in benzene, and the solution was washed (Na_2CO_3, NaCl) and dried ($MgSO_4$). After evaporation of the solvent, the residual oil was distilled [bp 100–110° (bath temperature) (0.25 mm)] to give 113 mg (34%) of **18**, ir ($CHCl_3$) 1720 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.70; H, 9.70; N, 5.75.

3-(*N*-Methylallylamino)-2-deuterio-5,5-dimethyl-2-cyclohexen-1-one (19). A solution of 564 mg of **9** in 2 ml of methylene chloride and 1 ml of deuterium oxide was well shaken for 3 min and concentrated to give a crude oil of **19**. The NMR spectrum indicated the absence of 2-H.

Irradiation of 19. A solution of 503 mg of **19** in 300 ml of cyclohexane was irradiated for 10 hr. The solvent was removed and the residue was distilled [bp 80–90° (bath temperature) (0.1 mm)] to give 243 mg (48%) of **20**, whose NMR spectrum indicated the absence of H_d.

3-Methylaminomethyl-7,7-dimethylcyclooctane-1,5-dione (21a). A mixture of 1 g of **14a** and 30 ml of water was refluxed with stirring. After 3 hr, **14a** was completely dissolved in water. After removal of water, the residual solid was recrystallized from petroleum ether to give 1.03 g (94%) of **21a**: mp 79.5–80.5°; ir (KCl) 3300, 1685 cm^{-1}; ($CHCl_3$) 1700 cm^{-1}; NMR ($CDCl_3$) τ 7.2–7.5 (m, 8), 7.54 (s, 3, NCH_3), 7.66–8.06 (m, 4), 8.90 [s, 6, $-C(CH_3)_2$]; (H_2O) τ 7.00 (m, 1, 3-H), 7.44 (center of AB q, 4, J = 12.0 Hz, 6-H and 8-H), 7.46 (d, 2, J = 6.0 Hz, $-CHCH_2N$), 7.67 (s, 3, NCH_3), 7.35–8.15 (m, 4, 2-H and 4-H), 8.88 and 8.98 (2 s, 6, $-C(CH_3)_2$]; in the NMR spectrum in D_2O the signals due to 2-H and 4-H disappeared. This may be a result of the occurrence of an intramolecular abstraction of the 2-H and 4-H by the amino group, since the *N*-

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acetate **25a** did not show such a deuterium exchange; mass spectrum *m/e* 193 (M − 18).

Anal. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63. Found: C, 68.31; H, 10.15; N, 6.49.

Its hydrochloride: mp 155–156° dec (from EtOH); ir (KCl) 3370, 2430, 1700, 1630 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}NO_2Cl$: C, 58.17; H, 8.95; N, 5.65. Found: C, 58.08; H, 8.66; N, 5.74.

3-(*N*-Allylacetamido)-5,5-dimethyl-2-cyclohexen-1-one (12) and Dione (25a). A solution of 100 mg of **21** in 3 ml of acetic anhydride was refluxed for 4.5 hr. The solvent was removed and the residue was recrystallized from ligroin to give 103 mg (86%) of **25a:** mp 130°; ir (KCl) 1700, 1640 cm^{-1}; NMR ($CDCl_3$) τ 6.65 (d, 2, J = 7.0 Hz, $-CHCH_2N$), 6.92 (s, 3, NCH_3), 6.97 (br, 1, 3-H), 7.56 (center of AB q, 4, J = 12.0 Hz, 6-H and 8-H), 7.55–7.88 (m, 4, 2-H and 4-H), 7.87 (s, 3, $COCH_3$), 8.98 [s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* (rel intensity) 253 (M^+, 2), 86 (100, $CH_2{=}N^+(CH_3)COCH_3$).

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.48; H, 9.37; N, 5.43.

Deuteration of 25a. A solution of 30 mg of **25a** in 0.5 ml of deuterium oxide containing 3 mg of NaOD and a small amount of sodium 3-trimethylsilylpropanesulfonate as internal reference was heated at 80° for 10 min. The NMR spectrum was then recorded. The signals due to the four methylene groups adjacent to the carbonyl groups disappeared.

3-(*N*-Acetylmethylaminomethyl)-1,5-diacetoxy-7,7-dimethylcyclooctane-1,5-dione (26). To a solution of 141 mg of **25a** in 1.5 ml of ethanol was added 142 mg of sodium borohydride, and the mixture was stirred at room temperature for 2 hr. After the excess hydride was decomposed by acetic acid, the solution was made alkaline with saturated sodium bicarbonate and extracted with ether. The dried extract was concentrated and the residue was dissolved in 1 ml of acetic anhydride and 1 ml of pyridine. The mixture was allowed to stand overnight at room temperature. The solvent was removed and the residue was recrystallized from petroleum ether–ether to give 32 mg (17%) of **26:** mp 83–86°; ir ($CHCl_3$) 1725, 1630 cm^{-1}.

Anal. Calcd for $C_{18}H_{31}NO_5$: C, 63.31; H, 9.15; N, 4.10. Found: C, 63.19; H, 9.18; N, 4.13.

5,5,8-Trimethyl-8-azabicyclo[5.2.1]decan-3-one (23). To a solution of 150 mg of **21** in 1.5 ml of ethanol was added 11 mg of sodium borohydride and the mixture was stirred at room temperature overnight. After the excess hydride was decomposed with acetic acid, the solution was made alkaline with saturated sodium bicarbonate and extracted with ether. After the extract was dried ($MgSO_4$) and concentrated, the residue was distilled [bp 100–110° (bath temperature) (0.1 mm)] to give 101 mg (70%) of **23,** which solidified on standing: mp 61–62° (from petroleum ether); ir ($CHCl_3$) 1680 cm^{-1}; NMR ($CDCl_3$) τ 7.22 (d, 2, J = 12.0 Hz), 8.06 (d, 2, J = 12.0 Hz), 7.34–7.48 (m, 6), 7.84 (s, 3, NCH_3), 8.25 (dd, 1, J = 15.0 and 6.0 Hz), 8.58 (d, 1, J = 15.0 Hz), 8.85 (s, 3), 9.08 (s, 3); mass spectrum *m/e* 195 (M^+).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.79; H, 10.84; N, 7.17. Found: C, 73.65; H, 11.01; N, 7.06.

Its perchlorate **24** was prepared by adding 70% perchloric acid to an ethereal solution of **23.** The precipitated crystals were recrystallized from EtOH: mp 280° dec; ir (KCl) 3380, 1100–1080 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}NO_5Cl$: C, 48.73; H, 7.50; N, 4.73. Found: C, 48.67; H, 7.62; N, 4.60.

An aqueous solution of 65 mg of the perchlorate **24** was made alkaline with saturated Na_2CO_3 and extracted with ether and the extract was dried ($MgSO_4$). Evaporation of the solvent gave 33 mg of **23,** mp 61–62°.

Epimerization of 14a. A solution of 130 mg of **14a** and 25 mg of potassium *tert*-butoxide in 5 ml of *tert*-butyl alcohol was warmed at 50–60° for 5 min with stirring. After removal of the solvent in vacuo, anhydrous ether was added to the residue and insoluble material was removed by filtration. Removal of the solvent followed by distillation [bp 75–85° (bath temperature) (0.1 mm)] gave 84 mg (65%) of **27:** ir ($CHCl_3$) 1705 cm^{-1}; NMR ($CDCl_3$) τ 7.12 (s, 3, NCH_3), 7.85 (center of AB q, 2, H_g and H_h, J = 13.5 Hz), 8.29 (center of AB q, 2, H_i and H_j, J = 14.0 Hz), 8.87 and 8.94 (2 s, 6, $-C(CH_3)_2$]; the mass spectrum was identical with that of **14a.**

Its hydrochloride was prepared by passing dry hydrogen chloride into an ethereal solution of **27:** mp 139–140° (from ethyl acetate); ir (KCl) 3490, 3420, 2700–2200, 1720 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}NOCl{\cdot}H_2O$: C, 58.17; H, 8.95; N, 5.65. Found: C, 58.31; H, 9.10; N, 5.65.

Transformation of 27 to 21. A mixture of 65 mg of **27** in 1 ml of H_2O was allowed to stand overnight, and removal of the solvent gave a quantitative yield of **21,** mp 79.5–80.5°.

Transformation of 27 to 25a. A solution of 75 mg of **21** in 3 ml of acetic anhydride was heated at 80° for 1 hr. The solvent was removed and the residue was recrystallized from ligroin to give 71 mg (72%) of **25a,** mp 130°.

Irradiation of 10. A solution of 200 mg of **10** in 20 ml of cyclohexane was irradiated for 7 hr and the solvent was removed. Distillation [bp 115–140° (bath temperature) (0.1 mm)] of the residue gave 125 mg (63%) of **15** as a colorless oil, which crystallized on standing: mp 44–44.5° (from petroleum ether); ir ($CHCl_3$) 1705, 1640 cm^{-1}; NMR ($CDCl_3$) τ 3.98–4.44 (m, 1, $-CH{=}CH_2$), 4.70–5.10 (m, 2, $-CH{=}CH_2$), 6.45–6.69 (m, 2, NCH_2–), 7.93 (s, 2, H_g and H_h), 8.14 (center of AB q, 2, J = 14.0 Hz, H_i and H_j), 8.75 and 8.94 [2 s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 219 (M^+).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39. Found: C, 76.78; H, 9.73; N, 6.62.

Irradiation of 11. A solution of 465 mg of **11** in 50 ml of ether was irradiated for 3 hr. Removal of the solvent left a mixture of two compounds which could be separated by preparative tlc using petroleum ether–ether (1:1) as solvent. The fast-moving component was identified as **16.** Recrystallization from petroleum ether gave 180 mg (39%) of white crystals: mp 99–100°; ir ($CHCl_3$) 1705, 1595 cm^{-1}; NMR ($CDCl_3$) τ 2.65–3.25 (m, 5, aromatic), 7.50 (center of AB q, 2, J = 14.0 Hz, H_i and H_j), 7.86 (s, 2, H_g and H_h), 8.94 and 9.02 [2 s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 255 (M^+).

Anal. Calcd for $C_{17}H_{21}NO$: C, 79.96; H, 8.29; N, 5.49. Found: C, 80.16; H, 8.43; N, 5.76.

The slower moving component was identified as **29.** Recrystallization from *n*-hexane afforded 30 mg (6%) of white crystals: mp 146–147°; ir ($CHCl_3$) 1640 cm^{-1}; uv max (MeOH) 216 nm (log ϵ 4.46), 245 (4.27), 267 (4.07), 301 (4.13); NMR ($CDCl_3$) τ 1.66–1.84 (m, 1), 2.64–2.77 (m, 3), 3.85–4.25 (m, 1), 4.70–5.06 (m, 2), 5.15–5.35 (m, 2), 7.24 (s, 2), 7.55 (s, 2), 8.85 (s, 6); mass spectrum *m/e* 253 (M^+).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.56; H, 7.84; N, 5.64.

3-Anilinomethyl-7,7-dimethylcylooctane-1,5-dione (22a). A mixture of 50 mg of **16** and 400 mg of KOH in 5 ml of 90% methanol was refluxed for 20 hr. The solvent was removed and the residue was extracted with ether. The extract was dried ($MgSO_4$) and concentrated. The residue was purified by preparative TLC using ether as solvent to give 32 mg (60%) of **22a:** mp 109–110° (from petroleum ether); ir ($CHCl_3$) 3320, 1695, 1600 cm^{-1}; NMR ($CDCl_3$) τ 2.67–3.55 (m, 5, aromatic), 6.10 (br, 1, NH), 6.90 (d, 2, J = 6.5 Hz, $-CHCH_2N$), 7.24 (br, 1, 3-H), 7.59 (center of AB q, 4, J = 12 Hz, 6-H and 8-H), 7.15–7.95 (m, 4, 2-H and 4-H), 8.90 (s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 273 (M^+).

Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.79; H, 8.53; N, 5.25.

Deuteration of 22a. A solution of 30 mg of **22a** in 0.3 ml of deuterium oxide and 0.3 ml of pentadeuteriopyridine containing 5 mg of NaOD and a small amount of sodium 3-trimethylsilylpropanesulfonate as internal reference was heated at 80° for 10 min. The NMR spectrum was then recorded. The signals due to the four methylene groups adjacent to the carbonyl groups disappeared.

Irradiation of 12. A solution of 152 mg of **12** in 50 ml of ether was irradiated for 45 min. The solvent was removed and the residue was submitted to preparative TLC using petroleum ether–ether (3:7) as solvent to give 46 mg (31%) of **31** and 37 mg (25%) of **32.** Compound **31** had mp 38–39° (from petroleum ether); ir ($CHCl_3$) 1715, 1650 cm^{-1}; NMR ($CDCl_3$) τ 6.64 and 8.08 (2 d, 2, H_i and H_j, J = 14.0 Hz), 7.89 (center of AB q, 2, J = 14.0 Hz, H_g and H_h), 8.05 (s, 3, $COCH_3$), 8.97 [s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 221 (M^+).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.73; H, 8.69; N, 6.31.

Compound **32** had mp 69–70° (from petroleum ether); ir ($CHCl_3$) 1715, 1650 cm^{-1}; NMR ($CDCl_3$) τ 7.53 (center of AB q, 2, J = 14.0 Hz, H_i and H_h), 7.83 (center of AB q, 2, J = 14.0 Hz, H_g and H_h), 7.99 (s, 3, $COCH_3$), 8.86 and 8.98 [2 s, 6, $-C(CH_3)_2$]; mass spectrum *m/e* 221 (M^+).

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.32; H, 8.68; N, 6.31.

3-(*N*-Acetylaminomethyl)-7,7-dimethylcyclooctane-1,5-dione (33) and 8-(*N*-Acetylaminomethyl)-4,4-dimethylbicyclo[4.2.0]oct-1-en-2-one (34). A. From 31. A solution of 80 mg of **31** in 1 ml of 10% aqueous KOH solution was refluxed for 15 min and concentrated. Anhydrous ether was added to the residue and

insoluble material was removed by filtration. Evaporation of the solvent and separation by preparative TLC using ether as solvent gave 45 mg (52%) of **33** and 8 mg (10%) of **34**.

Compound **33**: mp 120.5–121.5° (from petroleum ether); ir ($CHCl_3$) 3440 (NH), 1695 (C=O), 1670 cm^{-1} (NHC=O); NMR ($CDCl_3$) τ 3.95 (br, 1, NH), 6.79 (d, 2, J = 6.5 Hz, $-CHCH_2N$), 6.89 (br, 1, 3-H), 7.60 (center of AB q, 4, J = 12 Hz, 6-H and 8-H), 7.45–7.92 (m, 4, 2-H and 4-H), 8.01 (s, 3, $COCH_3$), 8.95 [s, 6, $-C(CH_3)_2$]; mass spectrum m/e 239 (M^+).

Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.16; H, 8.90; N, 5.75.

Compound **34**: bp 140–150° (bath temperature) (0.13 mm); ir ($CHCl_3$) 3360 (NH), 1670 cm^{-1} (α,β-unsaturated ketone and amido carbonyl group); uv max (EtOH) 245 nm (log ϵ 3.93); NMR ($CDCl_3$) τ 3.35 (br, 1, NH), 5.84–6.16 (m, 2, $-CH_2NH$), 6.60–7.56 (m, 3, cyclobutene), 7.75 (br s, 4), 8.91 [s, 6, $-C(CH_3)_2$]; mass spectrum m/e 221 (M^+). The uv absorption maximum closely resembles the reported value for bicyclo[4.2.0]oct-1-en-2-one.[15]

Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.55; H, 8.65; N, 6.33. Found: C, 70.51; H, 8.83; N, 6.03.

B. From 32. Treatment of 184 mg of **32** with aqueous KOH solution as described above gave 64 mg (33%) of **33** and 14 mg (8%) of **34**.

8-(*N*-Acetylaminomethyl)-6-methoxy-4,4-dimethylbicyclo[4.2.0]octan-2-one (35) A. From 31. A solution of 115.8 mg of **31** and 10 mg of KOH in 1 ml of methanol was refluxed for 15 min and concentrated. Anhydrous ether was added to the residue and the insoluble material was removed by filtration. Evaporation of the solvent and recrystallization of the residual solid from petroleum ether gave 104.5 mg (77%) of **35**: mp 85°; ir ($CHCl_3$) 3350 (NH), 1690 (C=O), 1665 cm^{-1} (NHCO); NMR ($CDCl_3$) τ 3.65 (br, 1, NH), 6.20–6.54 (m, 1), 6.75–7.10 (m, 1), 6.85 (s, 3, OCH_3), 7.35 (d, 1, J = 7.5 Hz), 7.80 (s, 2), 8.06 (s, 3, $COCH_3$), 8.20 (center of AB q, 2, J = 15.0 Hz), 7.89–8.22 (m, 3, cyclobutane), 8.97 and 9.02 [2 s, 6, $-C(CH_3)_2$]; mass spectrum m/e 253 (M^+). The cis stereochemistry of the ring juncture was assigned on the basis of thermodynamic considerations and the fact that **35** was also produced from **32**.

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.51, H, 9.25; N, 5.51.

B. From 32. Treatment of 129 mg of **32** with KOH in methanol as described above gave 20 mg (14%) of **35**.

Epimerization of 31. A solution of 80 mg of **31** and 100 mg of potassium *tert*-butoxide in 1 ml of *tert*-butyl alcohol was allowed to stand at room temperature for 5 min. The solvent was removed, anhydrous ether was added to the residue, and the insoluble material was removed by filtration. After the solvent was evaporated, the residue was separated by preparative TLC using ether as solvent to give 22 mg (27%) of **32** and 27 mg (34%) of **34**.

Upon similar treatment of **32**, only the starting material was recovered unchanged.

3-Allyloxy-5,5-dimethyl-2-cyclohexen-1-one (36). According to the known procedure[22] **36** was prepared from dimedone and allyl alcohol in the presence of *p*-toluenesulfonic acid: bp 82° (0.1 mm) [lit.[23] bp 155° (20 mm)]; ir ($CHCl_3$) 1640, 1600 cm^{-1}; uv max (EtOH) 250 nm (log ϵ 4.21); NMR ($CDCl_3$) τ 3.80–4.50 (m, 1, $-CH=CH_2$), 4.70–5.10 (m, 2, $-CH=CH_2$), 4.65 (s, 1, 2-H), 5.58 (br d, 2, $-CH_2CH=CH_2$, J = 5.5 Hz), 7.71 (s, 2, 6-H), 7.79 (s, 2, 4-H), 8.91 [s, 6, $-C(CH_3)_2$]; mass spectrum m/e 180 (M^+).

Irradiation of 36. A solution of 300 mg of **36** in 50 ml of cyclohexane was irradiated for 10 hr and the solvent was removed. The residue was submitted to preparative TLC using petroleum ether–ether (1:1) as solvent to give 212 mg (72%) of a colorless oil. Although TLC and GLC analyses of the oil indicated that it consists of a single component, its NMR spectrum clearly showed it to contain a trace amount of an unidentified product in addition to a major product (**37a**). Attempts to isolate the photoproducts in a pure form were unsuccessful.

Compound **37a** (containing a trace amount of an unidentified product): ir ($CHCl_3$) 1710 cm^{-1}; NMR ($CDCl_3$) τ 7.86 (s, 2, H_g and H_h), 8.05 (center of AB q, 2, J = 15.0 Hz, H_i and H_j), 8.78 and 8.87 [2 s, 6, $-C(CH_3)_2$]; ms spectrum m/e 180 (M^+).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.09; H, 9.31.

Methyl 7,7-Dimethylcyclooctane-1,5-dione-3-carboxylate (41). A solution of 2.45 g of **3** and 200 g of methyl acrylate in 350 ml of cyclohexane was irradiated for 8 hr. A large amount of a white polymer was formed. The cyclohexane layer was decanted and the polymer was washed with ether. The combined organic layer was dried ($MgSO_4$). Removal of the solvent and recrystallization of the residual solid from ligroin gave 145 mg of **41**: mp 103.5–105°; ir ($CHCl_3$) 1735, 1705 cm^{-1}; NMR ($CDCl_3$) τ 6.27 (s, 3, OCH_3), 7.52 (center of AB q, 4, J = 12.6 Hz, 6-H and 8-H), 6.95–7.65 (m, 5, 2-H, 3-H, and 4-H), 8.90 [s, 6, $-C(CH_3)_2$]; mass spectrum m/e 226 (M^+).

Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.38; H, 8.12.

3-Hydroxymethyl-7,7-dimethylcyclooctane-1,5-dione (38). A. From 37a. A mixture of 1 g of **37a** and 10 ml of water was refluxed for 3 hr. The water was removed and the residue was recrystallized from benzene–petroleum ether (bp 60–80°) to give 587 mg (53%) of **38**: mp 110–111°; ir ($CHCl_3$) 3610, 3480–3380, 1695 cm^{-1}; NMR ($CDCl_3$) τ 6.47 (d, 2, J = 6 Hz, $-CH_2OH$), 7.58 (center of AB q, 4, J = 12.0 Hz, 6-H and 8-H), 7.65 (s, 1, OH), 7.25–7.90 (m, 5, 2-H, 3-H, and 4-H), 8.89 [s, 6, $-C(CH_3)_2$]; mass spectrum m/e 180 ($M^+ - 18$).

Anal. Calcd for $C_{11}H_{18}O_3$: C, 66.64; H, 9.15. Found: C, 66.44; H, 9.32.

B. From 41. A solution of 70 mg of **41** and 120 mg of ethylene glycol in 5 ml of benzene was refluxed in the presence of a small amount of *p*-toluenesulfonic acid in a flask equipped with a Dean-Stark trap for 3 hr. The solution was washed with water and dried ($MgSO_4$). After removal of the solvent, 5 ml of anhydrous ether was added. The solution was added dropwise to a suspension of 10 mg of lithium aluminum hydride in 5 ml of anhydrous ether and the reaction mixture was stirred overnight. After an usual work-up procedure, the reduction product was dissolved in 5 ml of 90% acetic acid and the solution was refluxed for 1 hr. After the solvent was evaporated, a residual solid was recrystallized from benzene–petroleum ether (bp 60–80°) to give colorless crystals, mp 109–110°, which were identical with **38** in all respects.

C. From 43. A solution of 102 mg of **43** in 3 ml of methanol and 3 ml of 10% hydrochloric acid was allowed to stand at room temperature for 3 hr. The solvent was removed and the residue was recrystallized from benzene–petroleum ether (bp 60–80°) to give 63 mg of colorless crystals, mp 109–110.5°, which were identical with **38** in all respects.

3-Acetoxymethyl-7,7-dimethylcyclooctane-1,5-dione (39). A solution of 22.7 mg of **38** in 0.5 ml of acetic anhydride and 0.5 ml of pyridine was allowed to stand at room temperature overnight. The solvent was removed and the residue was recrystallized from petroleum ether (bp 60–80°) to give 24 mg (87%) of **39**: mp 99.5–100°; ir ($CHCl_3$) 1735, 1700 cm^{-1}; mass spectrum m/e 240 (M^+).

Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.11; H, 8.63.

3-Hydroxymethyl-7,7-dimethylcylooctane-1,5-dione Dioxime (40). A solution of 200 mg of **38**, 105 mg of hydroxylamine hydrochloride, and 120 mg of sodium acetate in 5 ml of aqueous ethanol (1:1) was heated at 80° for 1 hr and concentrated to one-third. The precipitated crystals were collected and recrystallized from ethyl acetate to give 211 mg (92%) of **40**: mp 219–220°; ir ($CHCl_3$) 3200–3300 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}N_2O_3$: C, 57.87; H, 8.83; N, 12.27. Found: C, 57.73; H, 9.04; N, 12.00.

4,4-Dimethyl-6-methoxy-8-hydroxymethylbicyclo[4.2.0]octan-2-one (43). A solution of 870 mg of **37a** and 20 mg of sodium methoxide in 5 ml of methanol was heated at 80° for 5 min. After removal of the solvent, anhydrous ether was added to the residue and the insoluble material was removed by filtration. Evaporation of the solvent and distillation gave 528 mg (52%) of **43**: bp 95–103° (bath temperature) (0.07 mm); ir ($CHCl_3$) 3480, 1690 cm^{-1}; NMR ($CDCl_3$) τ 6.35 (d, 2, J = 5.5 Hz), 6.85 (s, 3), 7.21 (d, 1, J = 8.5 Hz), 7.79 (s, 2), 8.04 (s, 2), 7.70–8.70 (m, 4), 8.95 and 9.04 (2 s, 6); mass spectrum m/e 180 ($M^+ - CH_3OH$). The cis stereochemistry of the ring juncture was tentatively assigned on the basis of thermodynamic considerations; i.e., it was formed under the basic conditions.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found; C, 67.62; H, 9.27.

4,4-Dimethyl-6-methoxy-8-acetoxymethylbicyclo[4.2.0]octan-2-one (44). A solution of 145 mg of **43** in 2 ml of acetic anhydride and 2 ml of pyridine was allowed to stand at room temperature for 3 days. Removal of the solvent followed by distillation gave 130 mg (82%) of **44**: bp 100–120° (bath temperature) (0.15 mm); ir ($CHCl_3$) 1735, 1695 cm^{-1}; mass spectrum m/e 195 (M^+).

Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.56; H, 8.62.

Energy Transfer Experiments on 9. Energy transfer experiments were carried out using 0.009 M of **9** and 0.1 M of transfer

agents (acetophenone, benzophenone, phenanthrene, naphthalene, and piperylene) in ether. Each solution was irradiated in a Pyrex tube at room temperature for 70 min and submitted to GLC after removal of solvent. Irradiation of **9** in the presence of acetophenone or benzophenone led to complete disappearance of starting material within 10 min and formation of a new product, which was identical on the GLC retention time with a product obtained from irradiation of **14a** in the presence of acetophenone or benzophenone; thus, the new compound is a secondary product from **14a**. The nature of this compound is presently under investigation. Phenanthrene and naphthalene completely quenched the cycloaddition, and piperylene partially quenched by the concentration used.

Energy Transfer Experiments on 12. Energy transfer experiments on **12** using benzophenone and piperylene as transfer agents were carried out in a similar manner described above for **9**. Benzophenone has no effect on the product distribution and yields, and piperylene gave results as shown in Figure 2.

Registry No.—**3**, 126-81-8; **4**, 107-11-9; **5**, 627-37-2; **6**, 124-02-7; **7**, 589-09-3; **8**, 55800-10-7; **9**, 55800-11-8; **10**, 55800-12-9; **11**, 55800-13-0; **12**, 55800-14-1; **13**, 55800-15-2; **14a**, 37914-13-9; **14a** HCl, 55869-62-0; **15**, 55869-63-1; **16**, 55800-16-3; **17**, 55800-17-4; **18**, 55869-64-2; **19**, 55800-18-5; **20**, 55869-65-3; **21a**, 37914-12-8; **21a** HCl, 55800-19-6; **22a**, 55800-20-9; **23**, 37910-73-9; **24**, 37910-74-0; **25a**, 37910-75-1; **26**, 55800-21-0; **27**, 37914-08-2; **27** HCl, 37910-76-2; **29**, 55800-22-1; **31**, 55800-23-2; **32**, 55869-66-4; **33**, 55800-24-3; **34**, 55800-25-4; **35**, 55800-26-5; **36**, 31928-99-1; **37a**, 55869-67-5; **38**, 37914-09-3; **39**, 37914-10-6; **40**, 55800-27-6; **41**, 37914-11-7; **43**, 55800-28-7; **44**, 55800-29-8.

References and Notes

(1) Portions of this work have appeared as preliminary communications; see Y. Tamura, Y. Kita, H. Ishibashi, and M. Ikeda, *Chem. Commun.*, 167 (1971); *Tetrahedron Lett.*, 1977 (1972).

(2) For a review and leading references, see (a) W. L. Dilling, *Chem. Rev.*, **66**, 373 (1966); (b) J. W. Gibson and W. F. Erman, *J. Org. Chem.*, **37**, 1148 (1972); (c) J. R. Scheffer and R. A. Wostradowski, *ibid.*, **37**, 4317 (1972).

(3) At the same time, Paquette and coworkers reported a synthesis of 1,4-dimethyl-2-azabicyclo[2.1.1]hexan-3-one by the reaction of 1,3-dimethylbicyclo[1.1.0]butane with chlorosulfonyl isocyanate; see L. A. Paquette, G. R. Allen, Jr., and M. J. Broadhurst, *J. Am. Chem. Soc.*, **93**, 4503 (1971).

(4) For the 2-oxabicyclo[2.1.1]hexane ring system, see (a) E. P. Blanchard, Jr., *Chem. Abstr.*, **67**, 108316e (1967); (b) D. G. Farnum and A. J. Mostashari, *Org. Prep. Proced. Int.*, **2**, 5 (1971).

(5) The stereochemistry of **17** was assigned on the basis of the coupling pattern of >CHOH (quartet, J = 3.0 Hz) and the mode of the formation of **17** (an approach of hydride is expected to occur exclusively from the outer face of the folded molecule).

(6) The long-range coupling between H_b and H_f in the bicyclo[2.1.1]hexane system is as yet unrecorded.

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(14) Although it has been reported in a preliminary paper[1] that two products were obtained in a ratio of ca. 4:1, careful reinvestigation indicated that the reaction proceeds with high stereoselectivity.

(15) E. D. Challand, H. Hikino, G. Kornis, G. Lange, and P. de Mayo, *J. Org. Chem.*, **34**, 794 (1969).

(16) (a) E. J. Corey, J. D. Base, R. Lemahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964); (b) T. S. Cantrell, W. S. Haller, and J. C. Williams, *J. Org. Chem.*, **34**, 509 (1969); (c) P. de Mayo, *Acc. Chem. Res.*, **4**, 41 (1971); (d) P. G. Bauslaugh, *Synthesis*, 287 (1970).

(17) We have not been able to detect phosphorescence from $n \rightarrow \pi^*$ excited **9** in methylcyclohexane at 77 K and thus there is no direct evidence for the generation of $n \rightarrow \pi^*$ triplets. However, since there are ample examples in which phosphorescence was not observed from $n \rightarrow \pi^*$ triplets of α,β-unsaturated ketones, and since most of the photoaddition reaction of α,β-unsaturated ketones is known to involve $n \rightarrow \pi^*$ triplets, it is reasonably assumed that this excited state is also $n \rightarrow \pi^*$ in nature.

(18) M. Julia, *Pure Appl. Chem.*, **15**, 167 (1967), and references cited therein.

(19) That the dimethyl group on the cyclohexenone ring has no effect on the stereochemical consequence was shown by the stereospecific transformation of 3-(*N*-methylallylamino)-2-cyclohexen-1-one to the corresponding 2-azabicyclo[2.1.1]hexane, whose structure was deduced from comparison of the NMR spectrum of the crude photoproduct with that of **14a**. However, attempts to isolate it in a pure form were unsuccessful because of its lability, thus precluding elemental analysis (unpublished results).

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(21) The different slopes in Figure 2 may be attributed to the experimental error.

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The Chemistry of Hindered Systems. Syntheses and Properties of Tetramethylazacycloheptanes and Related Acyclic Amines

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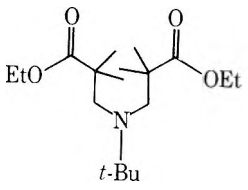
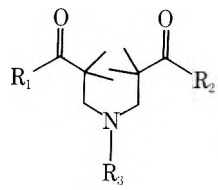
Hindered acyclic *N-tert*-butyl amines **1–5** have been synthesized to determine the relative importance of steric and electronic factors in these systems. The syntheses of the acyclic amines, which involved manipulation of a common intermediate, namely tetramethylazacycloheptane acyloin **9**, (formed from diester **1**), are discussed. The reduction of acyloin **9** was studied in detail and the stereochemistry of the critical diol intermediates formed, **12a** and **12b**, was established using chemical and spectroscopic techniques. One of the spectroscopic approaches utilized ^{1}H NMR chiral shift reagents to distinguish between the diol meso and *dl* diastereomers. Low-temperature dynamic ^{1}H NMR techniques were used to measure $\Delta G^{\ddagger}$ (free energy for inversion–rotation processes about the N–CH_2 bonds; e.g., 9.1 kcal/mol for parent amine **4**) for the acyclic amines. Similarities in $\Delta G^{\ddagger}$ for **1–4** indicate that steric factors and not electronic factors best account for the inversion–rotation barrier found in these molecules. Studies of favorable conformations for amines **1–3**, however, suggested that these systems might be capable of some nitrogen–carbonyl interaction. Comparisons of uv spectra obtained for the diketone **3**, dialdehyde **2**, and cyclic ketone **23** provide evidence that interaction (i.e., mixing of the nitrogen and carbonyl orbitals) does occur in the examples cited.

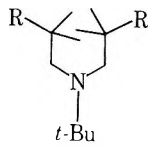
Our reports[1,2] on the synthesis of the hindered *N-tert*-butyl-3,3′-imino diester **1**, and on the possibility that intramolecular 1,4-nitrogen–carbonyl interactions[3,4] resulting as a consequence of preferred conformations[5] might account for some of the unusual properties of this molecule (and other hindered systems we have now synthesized as part of this study), prompted us to synthesize dialdehyde **2** and diketone **3**.



1

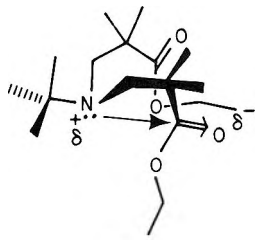


2, $R_1 = R_2 = H$; $R_3 = t$-Bu
3, $R_1 = R_2 = CH_3$; $R_3 = t$-Bu
5, $R_1 = H$; $R_2 = CH_3$; $R_3 = t$-Bu
8, $R_1 = R_2 = H$; $R_3 = CH_3$

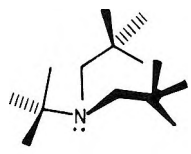


4, R = CH_3
6, R = CH_2-OH

We expected that the increased reactivity toward nucleophiles of the aldehyde and ketone groups, compared to the ester group, would enhance any potential or existing interactions. If 1,4-nitrogen–carbonyl interactions were important in these hindered systems, they would be expected to increase inversion–rotation barriers related to the CH_2–N bonds relative to the parent amine 4[6] (compare **1a** with **4a**).



1a



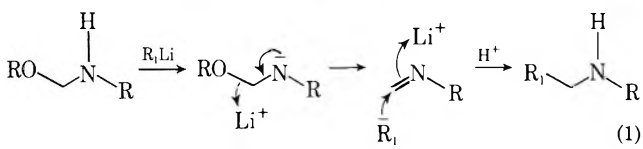
4a

On the other hand, if steric factors were mainly responsible for the chemistry of these systems, the inversion–rotation barriers about the CH_2–N bonds of these molecules should be similar.

The CH_2–N rotation or nitrogen inversion barriers can be estimated by low-temperature ^1H or ^{13}C dynamic magnetic resonance techniques. Our efforts directed toward the synthesis of **1**, **2**, **3**, and a mixed system, **5**, as well as estimates of $\Delta G^{\ddagger}$ for inversion–rotation at the CH_2–N bonds of **1** through **5**, will be discussed.

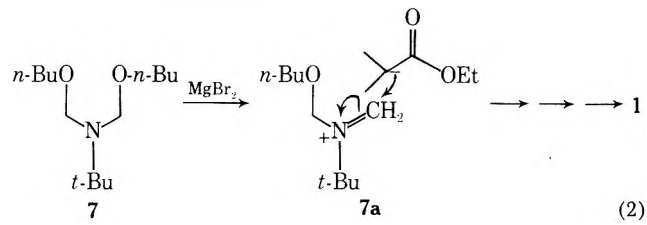
Synthesis and Reactions of Diester 1. It appeared that **1** would represent a good starting material for the synthesis of **2** (and possibly **3**), since partial reduction of **1**, or complete reduction of **1** to diol **6**[6] followed by partial oxidation of **6**, could yield **2**.

Diester **1** was obtained via a dialkylation procedure which involved reaction of the Grignard reagent generated from ethyl 2-bromoisobutyrate with bis(*n*-butoxymethyl)-*tert*-butylamine (**7**) under mild conditions. This approach was employed after more conventional approaches employing Reformatsky reagents[7] were shown to give only monoalkylated products. Interestingly, amine **7** was reasonably stable to organolithium reagents[8] which seem to react, under mild conditions, with molecules containing the $-OCH_2NR_2$ linkage (other than possible acid–base reactions) only when the nitrogen contains a proton.[8e,h] In these cases the "displacement" reaction is believed to be an "elimination–addition" reaction not possible with tertiary amines (eq 1).



(1)

We believe that the Lewis acid ($MgBr_2$)[9] generated in the course of the Grignard reaction is important in catalyzing the formation of dialkylmethyleneimmonium ion **7a**,[10] which we feel is the actual species attacked by the organomagnesium reagent (eq 2).



7 **7a** (2)

Treatment of diester **1** with diisobutylaluminum hydride under conditions which effect the reduction of ethyl isobutyrate[11] gave no reduction. Similarly, reduction with lithium tri-*tert*-butoxyaluminum hydride was also ineffective. In contrast, treatment of **1** with lithium aluminum hydride in refluxing ether gave diol **6** in good yield. Reaction of **6** with oxidizing agents known to convert alcohols to aldehydes (e.g., CrO_3–pyridine,[12] CrO_3–graphite,[13] DMSO–DCC,[14] or methyl phenyl sulfide–Cl_2 complex[15]) failed to give **2** in our hands. In most cases **6** could be recovered. We were also unable to synthesize **2** via either direct or indirect procedures employing the Mannich reaction, which had proved fruitful in the synthesis of the less hindered N–CH_3 dialdehyde **8**.[16]

Synthesis of Dialdehyde 2. Taking a different approach, we found that we were able to synthesize **2** using the sequence outlined in Scheme I. Reaction of **1** under acyloin conditions, sodium in refluxing toluene, gave 80% yield of acyloin **9**. Treatment of ketol **9** with acetic acid–acetic anhydride gave acetate **10** in 85% yield. The high yield of tetramethylated **9** is not surprising, since alternate base condensation reactions are not possible in these systems.[17] Steric compression also favors ring formation (see **1a**). Oxidation of **9** using lead tetraacetate in refluxing pyridine for at least 24 hr gave dione **11** in 60–70% yield. Reduction of **9**, **10**, or **11** gave cis–trans mixtures of diol **12** as shown in Table I.

Scheme I

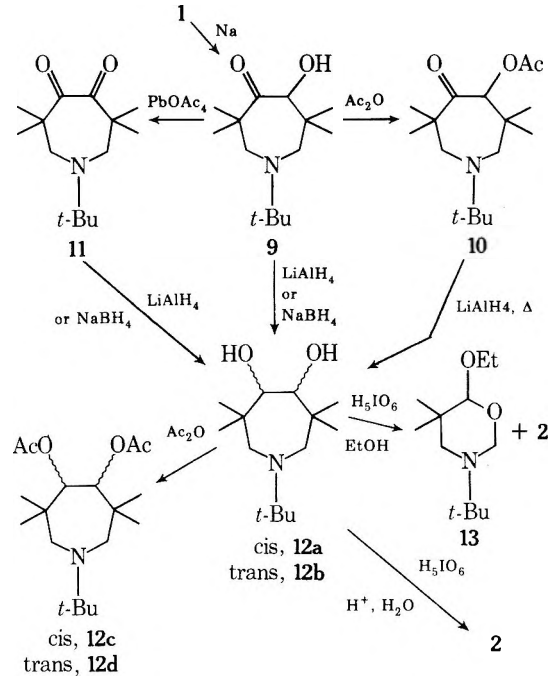


Table I
Reduction of 9, 10 and 11

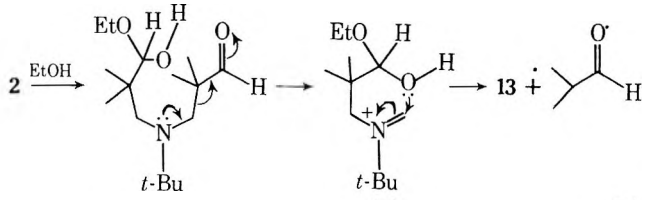
Run	Starting material	Reducing agent	Solvent	Ratio[a] of 12a:12b
A	9	$NaBH_4$	EtOH (25–50°)	80:20[b]
B_1	9	$LiAlH_4$	THF (–78–50)	83:17
B_2	9	$LiAlH_4$	THF (80°)	74:26
C	11	$NaBH_4$	EtOH (25–50°)	80:20[b]
D	11	$LiAlH_4$	Pentane (–78 to 50°)	85:15[b]
E	11	$LiAlH_4$	THF (–78 to 50°)	75:25[b]
F	10	$LiAlH_4$	THF (25–80°)	100:0

[a] Ratios were determined by ^1H NMR integration of the N-CH_2 protons. [b] Average of several runs.

While we were unable to separate the cis and trans diols by GLC (SE-30, SE-52, UCON columns), they were readily analyzed by ^1H NMR or TLC (the minor component having the larger R_f value) and separated by column chromatography using silicic acid with hexane–ether elution. The diols, which have nearly identical melting points (**12a,** mp 140–141°; **12b,** mp 140–142°), were readily converted to their respective diacetates **12c** and **12d** but different approaches were required.

While cis diol **12a** was readily converted to its diacetate **12c** using acetic acid–acetic anhydride, several products were isolated when **12b** was treated in a similar manner. Treatment of **12b** with acetic anhydride in pyridine gave **12d,** however, in 82% yield. The stereospecific acylation–rearrangements observed for **12b,** but not **12a,** under acid conditions (these will be discussed elsewhere) appear to be related to preferred conformations.[18]

Oxidation of **12a** with paraperiodic acid in ethanol for 24 hr at 25° gave two products in a 60:40 ratio. These were identified as the desired dialdehyde **2** and 6-ethoxytetrahydro-3-*tert*-butyl-5,5-dimethyl-2*H*-1,3-oxazine (**13**).[19] We have now shown that tetrahydrooxazine **13** results from the decomposition of **2** in the alcoholic solvents. Stirring pure **2** in anhydrous ethanol for 24 hr at 25° leads to its quantitative (by ^1H NMR, 82% isolated yield) conversion to **13.** This interesting reaction appears to involve loss of isobutyraldehyde (readily detected by ^1H NMR) from **2** or hemiacetal **14a** via a reverse Mannich[20] reaction followed by ring closure of hemiacetal **14b** to give **13** (eq 3). Dialdehyde **2** was found to be stable when stored neat or in nonpolar solvents (CCl_4).

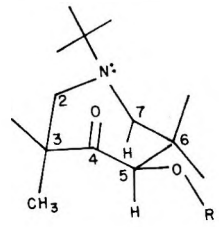


14a **14b** (3)

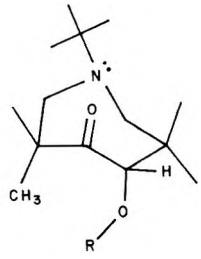
To circumvent participation by the nitrogen lone pair in this reaction, oxidation of **12a** was carried out in aqueous hydrochloric acid at 25°. Under these conditions **2** could be isolated in 62–77% yield depending on the scale of the reaction.

Stereochemistry of Diols 12a and 12b. We have studied the reduction of **9** and **11** and the stereochemistry of diols **12a** and **12b** using semiempirical, chemical, and physical techniques.[21] Since the rapidity and exothermicity (E_{act} = 8–15 kcal/mol)[22] of hydride reactions indicates in many cases that they proceed via "steric approach control" [23] (i.e., little bond breaking and making has occurred at the transition state), the stereoselectivity of the hydride reactions is expected to be reflected by the geometries of the ground state of the starting materials.[24]

Assuming that this is the case for the hindered mesocyclic acyloins, such as **9,** predictions about their ground-state geometries might allow predictions concerning the cis:trans ratios of diols expected from their reduction by hydride.[25c,26] Studies of models[18] of acyloin **9** show that there appears to be two preferred conformations for this molecule, namely, **15a** and **15b.** Because nitrogen can undergo inversion, conformations **15a** and **15b** can be "viewed" as epimers and their relative populations calculated using free-energy differences ($\Delta G_{E/A}$) between conformations involving equatorial and axial C_5 substituents.[25] Assigning a value[25a,b] of 0.9 kcal/mol for the C_3, C_5 (CH_3 → H) diaxial interaction in **15a,** and values of 2.0–2.2 kcal/mol for the C_3, C_5 (CH_3 → OH) diaxial interaction and 0.2–0.4 kcal/mol for the C_5, C_7 (OH → H) diaxial interaction in **15b,** a $\Delta G_{E/A}$ ranging from 1.3 to 1.7 kcal/mol can be calculated. Using the relationship $\Delta G_{E/A} = -RT \ln K_{E/A}$ and solving for $K_{E/A}$ at 25° gives a value for $K_{E/A}$ which indicates that the more stable conformer, **15a,** should comprise 90–95% of the acyloin mixture.

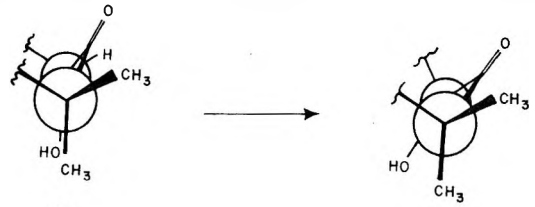


15a, R = H
15c, R = AlH_3

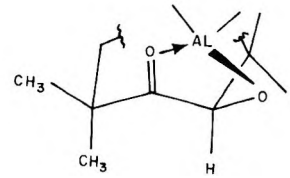


15b, R = H
15d, R = AlH_3

Distortion of the cycloheptanoid half-boat, half-chair conformations (**15a** and **15b**) to half-twist boat, half-chair conformations, while possibly creating C_3, C_7 and C_2, C_5 interactions, relieves the C_3, C_5 diaxial interaction.[18] We feel that this distortion is probably important for **15a,** and especially for **15b,** and estimate that a 30° twist (i.e., **15e** → **15f**) between C_3, C_5 substituents would result in ca. 40% re-



15e **15f**



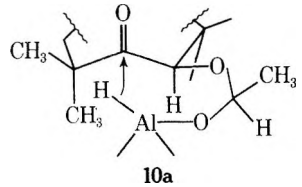
15g

duction (based on dihedral angle–rotational barrier relationships) of their interaction. Given the assumptions,[24] reduction of **9** with sodium borohydride ($NaBH_4$) in ethanol at 25° (attack by hydride at the least hindered face of the carbonyl) would be expected to give cis (from **15a**) and trans (from **15b**) diols **12a** and **12b** in ca. 80–90:20–10 ratios, respectively. These predictions appear to agree reasonably well with experimental results (see run A, Table I).[27] Reduction of either acyloin **9** or dione **11** by lithium aluminum hydride ($LiAlH_4$) might be expected to give, after initial acid–base reaction in the case of **9** or partial reduction in the case of **11**, aluminate esters **15c** and **15d**. Aluminate ester **15c**, but not **15d**, is capable of forming a cyclic cyclopentanoid species such as **15g** where the acyloin acts as a bidentate ligand for the metal atom.

The effect of **15g** on the equilibrium of **15** would be expected to be more important in less polar solvents where the carbonyl oxygen does not have to compete with solvent for complexation.[26b]

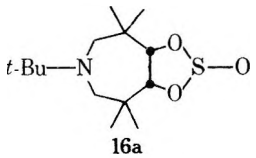
Since conformers **15c** and **15g** should yield cis diol **12a** while **15d** would give trans diol **12b**, reduction of **9** or **11** with $LiAlH_4$ in THF (polar solvent) would be expected to yield about the same cis:trans ratio as observed with $NaBH_4$.[28] In less polar solvents, such as pentane, the yield of cis diol should increase upon $LiAlH_4$ reduction of **9** or **11** owing to the increased importance of **15g** in this poorly solvating solvent. The stereoselectivity of the $LiAlH_4$ reduction of **9** in THF at higher temperature would be expected to decrease owing both to decreased importance of **15g** at the higher temperature and the change expected in $K_{E/A}$ due to the change in temperature. At 80° the more stable conformer, **15a**, would be expected to comprise only 75 to 85%[25a] of the mixture. Reduction of **9**, by adding it to THF and $LiAlH_4$ at reflux (80°), gave a 74:26 ratio of **12a** to **12b** (run B_2, Table I). In general, the experimental results agree well with prediction (see runs B–E, Table I).

The complete stereoselectivity noted in the $LiAlH_4$ reduction of acetate **10** (run F, Table I) is believed to result from the initial reduction of the acetate group in preference to the hindered ketone to give **10a** followed by directed delivery of hydride[29] to give **12a**.

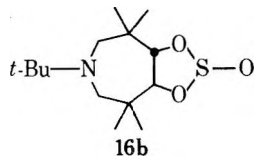


10a

The predicted cis stereochemistry of the major diol was established unambiguously by classical techniques. Examination of the ^1H NMR spectrum of the sulfite ester **16a**, formed from **12a**, showed a singlet occurring at δ 4.63 due to the protons α to the oxygen while sulfite ester **16b** showed an AB pattern at δ 4.30 (J = 11 Hz) for its C-4, C-5 protons.



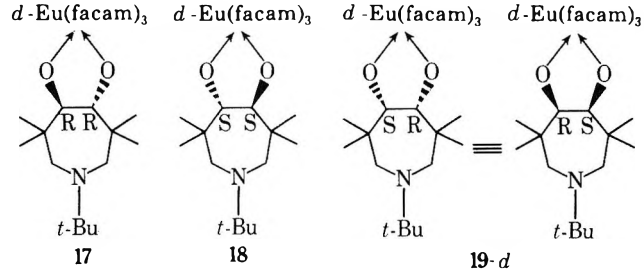
16a



16b

As the chemical–spectroscopic techniques require fair amounts of diol, other simple physical methods for determining the stereochemistry of **12** (and related systems)[21] were studied. Comparison of the mass spectra of **12** indicated that the cis and trans diols could be identified on the basis of their ability to lose water upon electron impact. Comparison of ions occurring at m/e 228 ($M^+ - CH_3$) and 210 (228 − H_2O) for **12a** and **12b** indicates that the loss of water is considerably more favorable from the trans than the cis diol. This seems to be a general property of the cyclic tetramethylated 1,2-diols we have studied and is in agreement with the observation that water is eliminated preferentially via cis elimination processes only available to the trans diol upon electron impact.[30] While extremely dependable in our systems, mass spectra of both isomers are required for comparative purposes (both isomers are not always available; see run F, Table I).

A much more interesting approach to diol stereochemistry, which we believe will prove to be generally applicable to symmetrical diols and related systems, and which should allow isomer assignment in most cases even when only one isomer is available, involves the use of chiral lanthanide shift reagents.[31] Cis diol **12a** (meso) and trans diol **12b** (*dl* racemate) are diastereomers[32] which would be expected to exhibit predictably different ^1H NMR patterns in the presence of chiral shift reagents such as tris(3-trifluoroacetyl-*d*-camphonato)europium (III) [Eu(facam)$_3$]. Trans diol **12b** should show two (probably similar) sets of ^1H NMR signals resulting from formation of "pseudo-contact" diastereomers[33] **17** and **18**[34,35] in the presence of the chiral shift reagent. On the other hand, cis diol **12a** should show ^1H NMR signals resulting from the formation of "pseudo-contact" enantiomer[33] **19-*d***. For **19-*d*** induced asymmetries,



17 **18** **19-*d***

caused by the presence of the chiral center and which should diminish with distance from it, would be expected. Specifically for **12a** and **12b**, only **12b** can show two *tert*-butyl signals in the presence of chiral shift reagents. Comparison of spectra C and E (Figure 1) shows that this point alone is sufficient, in this case, to assign structures to diols **12a** and **12b** (spectra A and D, Figure 1).

Other aspects of spectra C and E (Figure 1) are completely in agreement with the above general predictions, including the induced asymmetries expected for **12a** in the presence of the chiral shift reagent.[34] A spectrum of **12a** in the presence of 0.45 equiv of tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionatoeuropium [Eu(fod)$_3$],[31] an achiral shift reagent, is included for comparative purposes (spectrum B, Figure 1).

Synthesis of Diketone 3, Ketone Aldehyde 5, and Monoketone 23. Diketone **3** (57% yield) and ketone aldehyde **5** (77% yield) were synthesized from diols **22** and **20** using oxidative procedures similar to those employed in the synthesis of **2**. The syntheses of diols **20** and **22** are shown in Scheme II along with synthesis of ketone **23**.

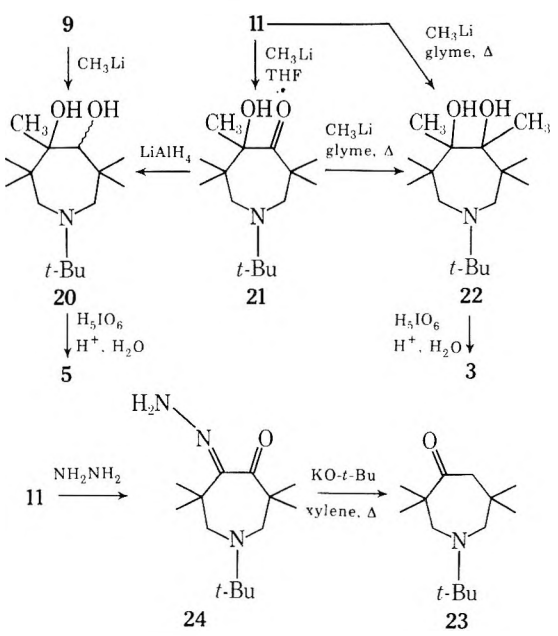
Treatment of acyloin **9** with 4 equiv of methyllithium in THF at −78° followed by warming to 35° [36] gave, after work-up, pentamethyl diol **20** of unknown stereochemistry in 81% yield. Treatment of dione **11** under similar conditions led to formation of acyloin **21** in 87% yield. While we were able to convert dione **11** to hexamethyl diol **22** in 81% yield by treating it with excess (4 equiv) methyllithium in glyme under reflux conditions, we were unable to convert either **11** or **21** to **22** using excess methyllithium in THF, even when vigorous (35°) conditions[36] were used. Acyloin

Table II

Starting material	T_c, °C	T_c, K	ΔV, Hz	$\Delta G^{\ddagger}$, kcal/mol	A value
1[a]	−88	185	67	8.8[b]	1.3 (CO_2Et)[42a]
2[d]	−97	176	78	8.3	1.3 (COH)[42b]
3	−102	171	29	8.4	1.2 ($COCH_3$)
4[d]	−81	192	79	9.1	1.7 (CH_3)
5 (aldehyde CH_2)	−100	173	60	8.2[c]	
5 (ketone CH_2)	−100	173	24	8.4[c]	

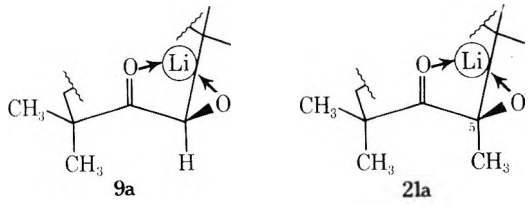
[a] Ca. 5% v/v in vinyl chloride. [b] Error is estimated at ±3°, ±5 Hz = ±0.3$\Delta G^{\ddagger}$. [c] Overlapping AB patterns make these values less reliable. [d] See Figure 4 for representative dynamic ^{1}H NMR spectra (i.e., 2 and 4).

Scheme II



21 was reduced in high yield to 20 using $LiAlH_4$ in refluxing THF.

Literature precedent[25,26] suggests that the successful reaction of 9 with methyllithium (in THF) occurs via a lithium alkoxide–ketone complexed cyclopentanoid half-chain conformer such as **9a**. The front face of complex **9a** would be partially obstructed by the lithium cation. Since we feel this interaction might also exist in complex **21a**, it seems



likely that steric hindrance due to the added methyl group at C_5, and not electronic factors, accounts for the relative reactivities of 9 and 21 with methyllithium (in THF). While not unambiguously established, we believe that only *cis*-**22**,[37] the product expected from attack of conformer **21a**, was obtained from the reactions of either 11 or 21 with excess methyllithium in hot glyme [^{1}H NMR spectra of 22 taken in the presence of Eu(facam)$_3$ (0.25–0.7 equiv) show only one *tert*-butyl signal indicating "pseudo-contact" diastereomers were not formed].

Ketone **23** was prepared from dione 11 via reaction of its monohydrazone **24** with potassium *tert*-butoxide in refluxing xylene.

Low-Temperature Dynamic ^{1}H NMR Studies of 1, 2, 3, 4, and 5. The free energies of activation, $\Delta G^{\ddagger}$, for inversion–rotation related to the CH_2–N[38] bonds for **1, 2, 3, 4,** and **5** were determined using low-temperature dynamic proton magnetic resonance techniques. Measurement of T_c (coalescence temperature for the CH_2–N protons) and ΔV [the chemical shift difference between H_A and H_B (CH_AH_B–N) well below T_c] allows estimation of $\Delta G^{\ddagger}$[39] from the Eyring equation.[40]

$$\Delta G^{\ddagger} = RT_c \ln (\sqrt{2}\,KT_c/h\pi\Delta V)$$

Table II shows the measured ^{1}H NMR parameters and estimated $\Delta G^{\ddagger}$ for **1–5.** *A* values[41,42] are included in Table II as a possible measure of substituent size in order that the various steric and electronic factors responsible for conformational preferences and possibly CH_2–N inversion–rotation barriers might be separated and compared.

Examination of the various conformations possible for a generalized amine **25** (Chart I), taking into account nitrogen inversion, CH_2–N rotation, and concerted inversion–rotation processes,[38] reveals that six conformers, **26–31,** can be drawn (Newman projection down the CH_2–N bond of **25**). Since, to a first approximation, R on **25** can be viewed as a *tert*-butyl group (more will be said about this point), conformers **26, 31** and **27, 30** can be considered unimportant because of the high vicinal nonbonded repulsions due to *tert*-butyl–*tert*-butyl–neopentyl interactions in the former case and *tert*-butyl–*tert*-butyl interactions in the latter. Conformers **28** and **29** suffer from *tert*-butyl–neopentyl nonbonded interaction but studies of models[18] show that because of free rotation about the CH_2–$C(CH_3)_3$ bond in the neopentyl group, this interaction can be considered about equivalent to a *tert*-butyl–methyl vicinal interaction[43] and consequently should be of considerably lower energy than the other two types of vicinal nonbonded repulsions existing in these systems. For these reasons we believe that only conformations **28** and **29** are populated below the coalescence temperature. While H_A and H_B are nonequivalent for each of the conformers, in **28** and **29** they have exchanged environments. Consequently the CH_2–N dynamic ^{1}H NMR spectrum of **28** and **29** should be the same under static conformation conditions and only one AB pattern due to the CH_2–N protons should exist for each of the amines (**1–4**). The near-perfect symmetry[38] below the coalescence temperature of the different AB patterns resulting from the CH_2–N protons of **1–4** supports these conclusions (see Figure 4). Having demonstrated that only conformations **28** and **29** appear to be populated under static conformation conditions, the effect of the various R groups (**25,** R_M, R_A, R_K, R_E, Chart I) can be analyzed. Amines **1–3** can be looked at as conformers **32–34** (Newman projections down the C_3–C_2 bond, Chart I) formed via a threefold rotation process. If *A* values are used as a criteria for deciding the magnitude of nonbonded interaction, it would seem that **32** and **33,** which have the smaller (Table II) sp^2 hybridized carbon as one of the two groups gauche to the bulky nitrogen, would be preferred over **34.** These steric arguments tend to indicate that 1,4-nitrogen–carbonyl interactions seem at least conformationally feasible as

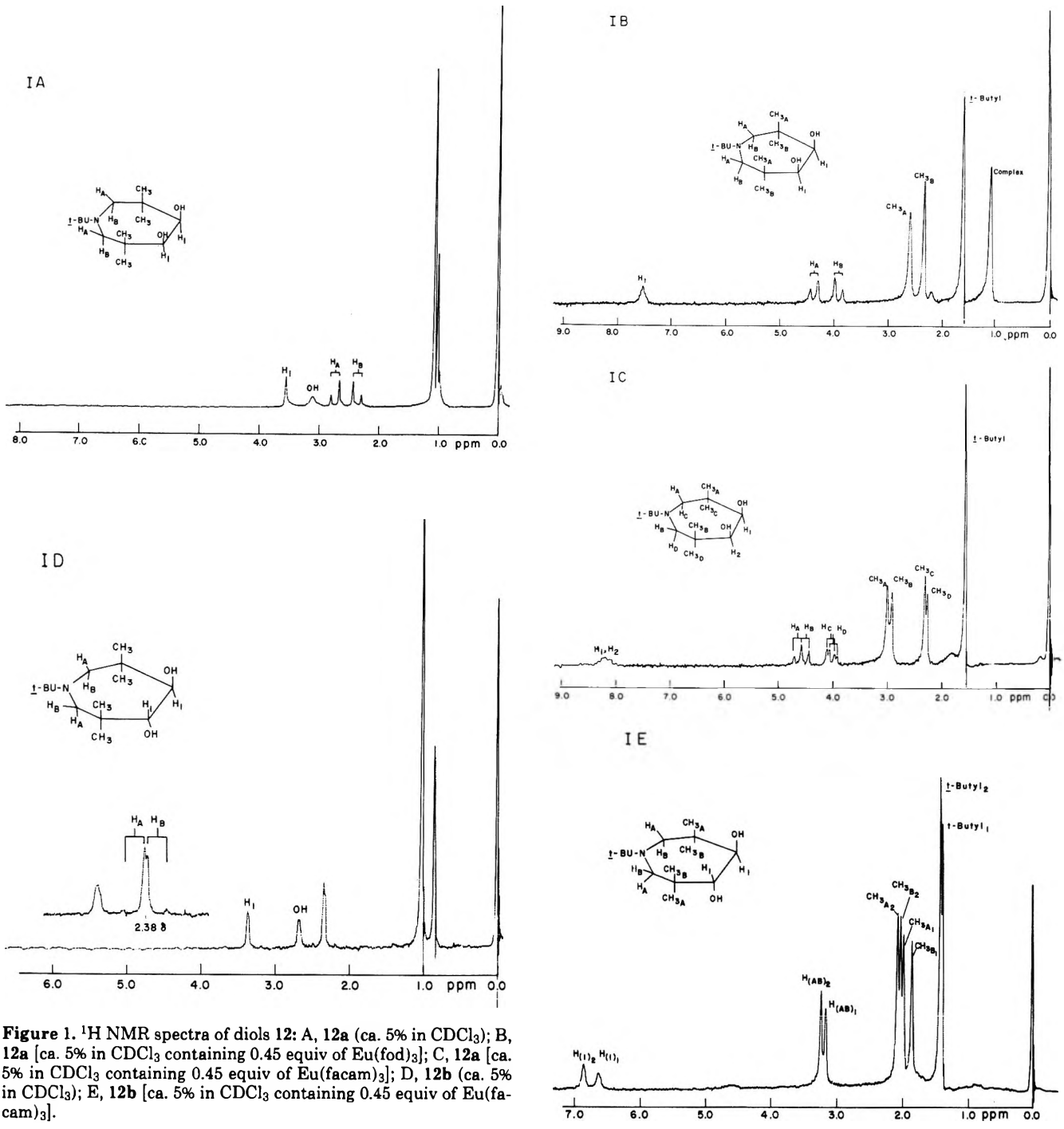


Figure 1. ^{1}H NMR spectra of diols **12**: A, **12a** (ca. 5% in $CDCl_3$); B, **12a** [ca. 5% in $CDCl_3$ containing 0.45 equiv of Eu(fod)$_3$]; C, **12a** [ca. 5% in $CDCl_3$ containing 0.45 equiv of Eu(facam)$_3$]; D, **12b** (ca. 5% in $CDCl_3$); E, **12b** [ca. 5% in $CDCl_3$ containing 0.45 equiv of Eu(facam)$_3$].

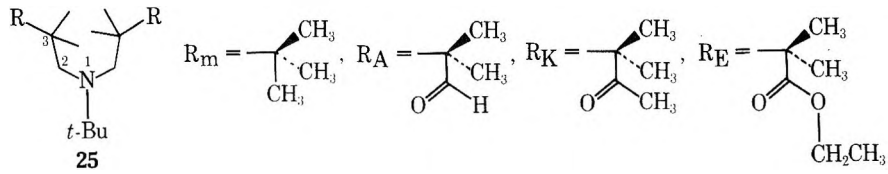
was postulated. Efforts to stop C_2–C_3 rotation in order to look for a nonequivalence of the aldehyde protons of **2** under static conditions resulted in 60 Hz broadening at −150 to −160° of the aldehyde signal but no nonequivalence was noted.

While it is perhaps dangerous to compare ground-state (A values) and transition ($\Delta G^{\ddagger}$) parameters[25] for amines **1–4**, we feel they should show similar trends for these similar systems if steric factors tend to dominate but that they might show divergent trends if electrostatic interaction (e.g., **1a**) were important for the carbonyl containing systems (i.e., **1–3**). It is interesting to note, then, that the former case is observed and that A values do generally parallel the $\Delta G^{\ddagger}$ values obtained for **1–3** (sp^2) and **4** (sp^3), ruling out the likelihood that strong 1,4-nitrogen–carbonyl interactions are important in these systems.

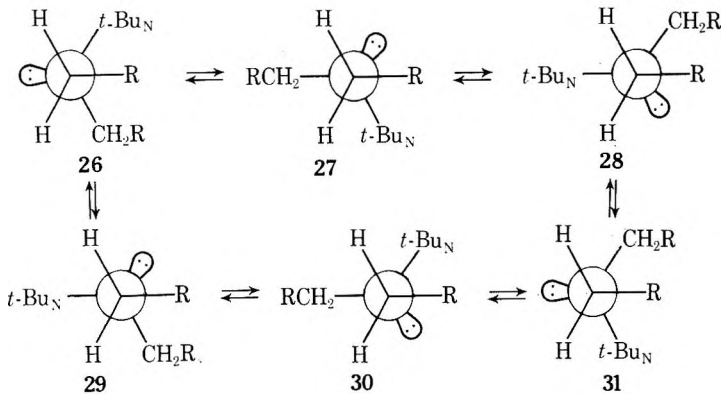
Comparison of $\Delta G^{\ddagger}$ for **4** (9.1 kcal/mol) and for *tert*-butyldiethylamine[38] (**35**, $\Delta G^{\ddagger}$ = 7.2 kcal/mol) is somewhat instructive. While calculations and studies of models show that some sp^2 character at nitrogen relieves nonbonded interactions in the ground state of **35**, thus raising the energy of its ground state relative to its transition state for inversion–rotation (pure sp^2 character) processes, similar sp^2 character in the ground state of **4** would seem unfavorable. While it might relieve CH_2–CH_2–*N*-*tert*-butyl interactions, the increased planarity at nitrogen would cause serious 1,7 alkyl–alkyl interactions. The planar transition state for inversion–rotation of **4** appears to be considerably more crowded than that of **35**. We feel that both of these factors account for the 2 kcal/mol difference between the $\Delta G^{\ddagger}$ of **4** and **35**.

Ultraviolet Studies of 11, 23, and 3. Since the data and discussions presented above indicate that, even though there appear to be no strong ground-state electrostatic (N–C=O) interactions in amines **1–3**, the nitrogen lone pair and carbonyl π orbitals (especially the larger π^* orbit-

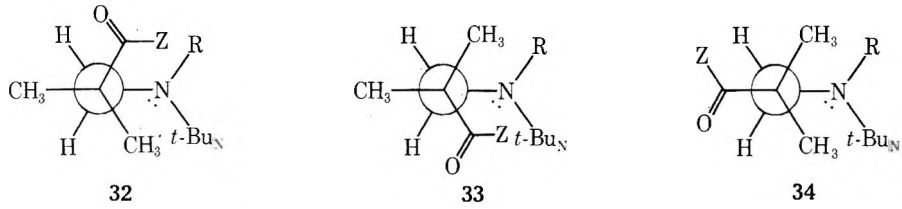
Chart I
Newman Projections of 25



A. Down the C_2–N Bond



B. Down the C_3–C_2 Bond



Z = H, CH_3, OEt

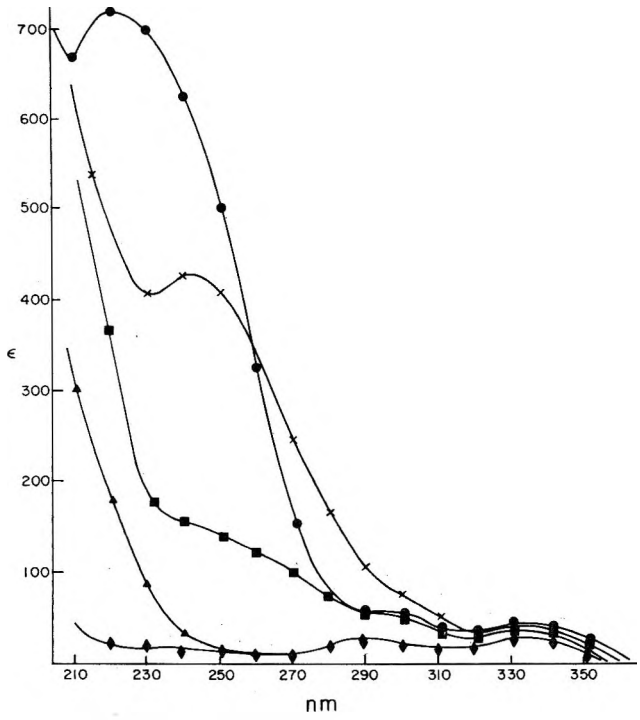
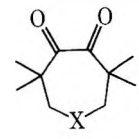
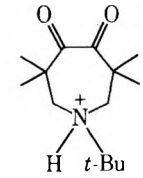


Figure 2. Uv spectra (EtOH) of **36**, ●; **11**, ×; **11** plus 40 μmol AcOH, ■; **37**, ▲; **38**, ♦.

als) should be in close proximity much of the time (see conformers **32** and **33**, Z = H, CH_3), uv studies were undertaken to add support to our conclusions. We felt that the uv spectra of the restricted linear systems should resemble those of cyclic systems if they contained similar structural features. Figure 2 shows uv spectra (EtOH) of tetramethylcycloheptane-4,5-diones **36**,[44] **11**, **37**,[45] and **38**.[46]



36, X = S
11, X = N-*t*-Bu
37, X = O
38, X = CH_2



39

It can be seen that both **36** (219 nm, ε 720) and **11** (242 nm, ε 420) show charge-transfer[47] (C-T) bands in their uv spectra as a consequence of the close proximity of the heteroatom and the carbonyl orbitals while **37** and **38** show spectra typical of normal mesocyclic α-diones. When the spectra of **11** is looked at in the presence of added acetic acid, the C-T absorption decreases significantly because protonation of the nitrogen lone pair (see **39**) prevents nitrogen–carbonyl interaction. Comparing the uv spectra of **11**, **23**, and **3** (see Figure 3), one notices that all three of these molecules show C-T absorption near 240 nm. We believe the strong similarities between the uv spectra of **3** and **23** reflect the fact that their most favored conformations at 25°, **40a**, **40b** (same as **40a** but nitrogen inverted), and **41**, respectively, contain similar important geometric relationships supporting the conformational arguments based on steric factors presented earlier. The lower intensity of the C-T absorption of **3** can be accounted for by the greater

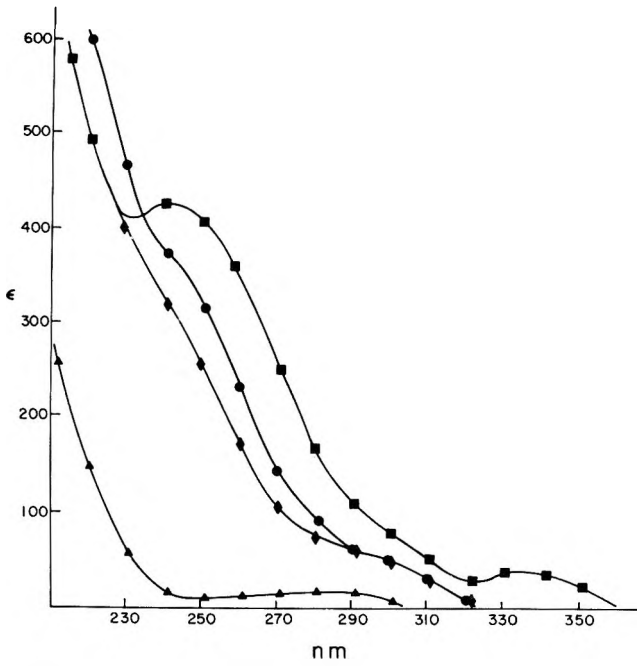
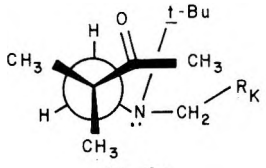
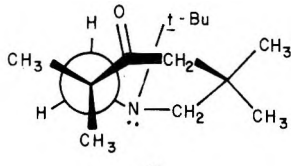


Figure 3. Uv spectra (EtOH) of **23**, ●; **3**, ♦; **42**, ▲; **11**, ■.

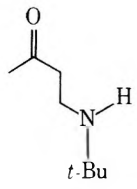
flexibility of the acyclic system at 25° [i.e., conformer **34**, Z = CH_3 (Chart I) would not permit nitrogen–carbonyl interaction].



40a(b)



41



42

To make certain that similar C-T phenomena do not occur in "anti" oriented systems, the uv spectra of **42** was taken (see Figure 3). No evidence for nitrogen–carbonyl interaction was noted in this case.

In conclusion, it seems that while steric considerations dominate the chemistry of these amines, some mixing of the nitrogen and carbonyl orbitals as determined by uv studies does exist.

Further studies on the chemistry and physical properties of these hindered amines are currently underway in our laboratories.

Experimental Section

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

Bis(*n*-butoxymethyl)-*N*-*tert*-butylamine (7). Amine **7** was synthesized in 79% yield using a modification of a general procedure developed by Gaines and Swanson.[10a] Into a flask was placed

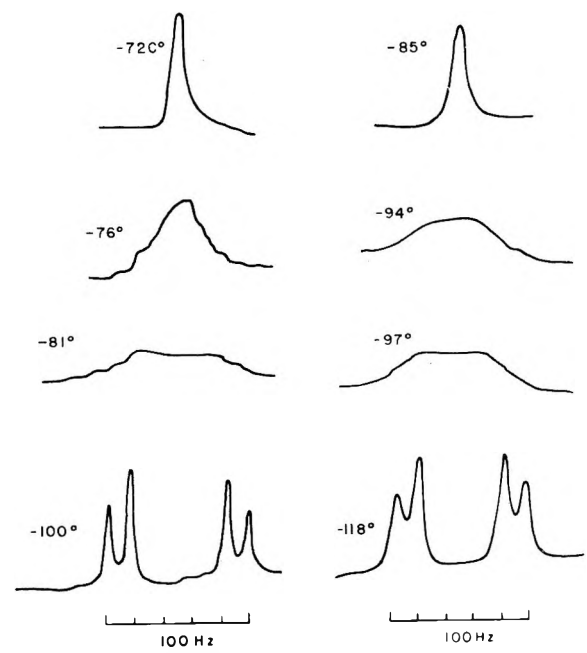


Figure 4. The dynamic ^{1}H NMR spectra (100 MHz) of the CH_2 groups of (A) amine **4** and (B) dialdehyde **2** (~5% v/v in vinyl chloride).

paraformaldehyde (60.0 g, 2.0 mol, CH_2=O), 1-butanol (149.7 g, 2.02 mol), and 200 ml of benzene. The mixture was warmed gently with stirring under N_2 while *tert*-butylamine (74.2 g, 1.0 mol) was added dropwise over 15 min. A Dean-Stark trap was added to the flask and the mixture was heated to reflux. After the theoretical amount of water was removed as an azeotrope (ca. 6 hr), the benzene was distilled off at 760 mm and the remaining oil was vacuum distilled to give 193.0 g of pure **7**: bp 80–83° (0.5 mm); ir (CCl_4) 2955, 2940, 2870, 1465, 1360, 1278, 1231, 1094, 1043, and 998 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.91 (t, 6), 1.19 (s, 9), 1.42 (m, 8), 3.29 (t, 4), and 4.32 (s, 4); mass spectrum (70 eV) *m/e* (rel intensity) 245 (M^+, trace), 230 (1), 173 (5), 172 (5), 159 (15), 101 (8), 100 (26), 87 (8), 86 (60), 72 (30), 70 (20), 57 (40), 56 (10), 44 (100), 43 (40), 42 (35), and 41 (70).

Diethyl *N*-*tert*-Butyl-3,3′-imino-2,2,2′,2′-tetramethyldipropionate (1). Into a dried flask containing 100 ml of dry ether under N_2 at 10° was added 8 g (0.30 mol) of Mg. While the mixture was stirred at high speed, ethyl α-bromoisobutyrate (50 g, 0.25 mol) in 200 ml of dry ether was added dropwise over 0.5 hr and the mixture was stirred at 10° until the bromo ester had reacted. Maintaining a 10° temperature, amine **7** (26.2 g, 0.11 mol) in 50 ml of ether was added to the reaction mixture over 0.5 hr. After stirring for 2 hr, allowing warming to 35° over the last 1 hr, the reaction mixture was quenched with cold aqueous ammonium chloride. An acid–base work-up gave a small amount of neutral product (ethyl isobutylisobutyrate) and 31 g of crude amine products. Careful distillation of the amine products gave 1 g of a mixture of ethyl *N*-*tert*-butyl-3-imino-2,2-dimethylpropionate and ethyl *N*-methyl-*tert*-butyl-3-imino-2,2-dimethylpropionate[7] and 29 g (83%) of amino diester **1**: bp 96–98° (0.1 mm); ir (CCl_4) 2980, 1728, 1465, 1393, 1367, 1268, 1150, 1111, 1062, and 1032 cm^{-1}; ^{1}H NMR (CCl_4) δ 0.92 (s, 9), 1.09 (s, 12), 1.21 (t, 6), 2.73 (s, 4), 4.03 (q, 4); mass spectrum (70 eV) *m/e* (rel intensity) 329 (M^+, trace), 328 (1), 314 (2), 214 (34), 158 (95), 112 (42), 84 (45), 57 (25), 41 (100), and metastable peaks at *m/e* 116.9 ($158^2/214$), and 79.5 ($112^2/158$).

Anal. Calcd for $C_{18}H_{35}NO_4$: C, 65.75; H, 10.65; N, 4.25. Found: C, 66.00; H, 10.93; N, 4.57.

***N*-*tert*-Butyl-3,3,6,6-tetramethyl-1-azacycloheptan-4-on-5-ol (9).** Into a dry three-neck Morton flask equipped with an overhead stirrer and condenser was added 600 ml of toluene. After removal of 50 ml of toluene from the flask by distillation under a N_2 atmosphere, 3.0 g (0.13 mol) of sodium metal was added to the hot toluene and converted to a fine sand using high-speed stirring. Diester **1** (9.87 g, 0.03 mol) was then added dropwise into the flask over 1 hr and the mixture was refluxed for an additional 1 hr, at which time it was cooled and 50 ml of 5% NH_4Cl was added. The organic layer was washed with water until the water wash was neutral and the aqueous layer was backwashed with ether. The combined organic washes were dried with $MgSO_4$ and evaporated to

give 5.8 g (80%) of solid hydroxy ketone **9**, which was further purified by sublimation: mp 55–56°; ir (CCl_4) 3430, 2965, 1700, 1465, 1390, 1365, 1266, 1200, and 1039 cm^{-1}; ^1H NMR (CCl_4) δ 0.60 (s, 3), 0.91 (s, 3), 0.97 (s, 3), 1.05 (s, 9), 1.20 (s, 3), 2.56 (AB, 2, J = 12 Hz), 2.61 (AB, 2, J = 14 Hz), 3.57 (s, 1, absent in D_2O), and 4.01 (s, 1); mass spectrum (70 eV) m/e (rel intensity) 241 (M^+, 9), 226 (43), 154 (14), 126 (14), 100 (14), 98 (14), 86 (20), 85 (40), 84 (39), 83 (20), 70 (67), 57 (100), 56 (26), 55 (36), and 41 (91); uv λ_{max} (EtOH) 290 nm (shoulder, ϵ 50), 245 (shoulder, 360).

***N*-*tert*-Butyl-3,3,6,6-tetramethyl-1-azacycloheptan-5-acetoxy-4-one (10).** A mixture of 4 g (0.0165 mol) of hydroxy ketone **9**, 25 ml of acetic acid, and 25 ml of acetic anhydride was refluxed for 3 hr. Most of the solvent was evaporated from the reaction mixture under reduced pressure and the remaining liquid was poured into ice water. The aqueous solution was made basic with NaOH and extracted with ether which was dried with K_2CO_3, filtered, and evaporated, giving 4.4 g of brownish solid. The solid was sublimed, giving 4.0 g (85%) of pure **10** as a white solid: mp 86–88°; ir (CCl_4) 2960, 1740, 1710, 1470, 1360, 1240, and 1033 cm^{-1}; ^1H NMR (CCl_4) δ 0.75 (s, 3), 0.90 (s, 3), 0.96 (s, 3), 1.02 (s, 9), 1.05 (s, 3), 1.93 (s, 3), 2.49 (AB, 2, J = 12 Hz), 2.61 (AB, 2, J = 14 Hz), and 4.82 (s, 1); mass spectrum (70 eV) m/e (rel intensity) 283 (M^+, 35), 269 (18), 268 (96), 225 (18), 224 (96), 189 (15), 168 (70), 100 (30), 98 (100), 84 (37), 70 (37), 57 (83), 56 (25), 55 (30), 43 (58), and 41 (63), with metastable ions at m/e 254 ($268^2/283$), 126, and 57; uv λ_{max} (EtOH) 288 nm (shoulder, ϵ 60), 240 (shoulder, 360).

Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.32; N, 4.95. Found: C, 68.11; H, 10.03; N, 4.80.

***N*-*tert*-Butyl-3,3,6,6-tetramethyl-1-azacycloheptane-4,5-dione (11).** A mixture of 5.7 g (0.024 mol) of hydroxy ketone **9**, 50 ml of pyridine, and 10.5 g (0.024 mol) of lead tetraacetate was refluxed for 24 hr under N_2. The pyridine was evaporated in vacuo, leaving a brown residue. Water and ether were added to the residue and the pH of the aqueous layer was adjusted to **10**. The aqueous phase was extracted several times with ether which was dried with K_2CO_3, filtered, and evaporated. The resulting residue, a pale yellow oil, was distilled to give 3.9 g (68%) of diketone **11**, which solidified on standing: bp 73–74° (0.1 mm); ir (CCl_4) 2970, 1725 (shoulder 1700), 1475, 1390, and 1375 cm^{-1}; ^1H NMR (CCl_4) δ 1.08 (s, 12), 1.09 (s, 9), 2.62 (s, 4); mass spectrum (70 eV) m/e (rel intensity) 239 (M^+, 44), 224 (26), 196 (2), 183 (3), 168 (3), 154 (11), 139 (8), 112 (18), 100 (100), 99 (19), 85 (25), 70 (34), 57 (95), 56 (75), 55 (24), and 41 (55); uv λ_{max} (EtOH) 335 nm (ϵ 40), 300 (shoulder, 80), 242 (425).

Amino dione **11** was characterized as its quinoxaline derivative, **29**, which was synthesized in the following manner. A mixture of 0.120 g (0.5 mmol) of diketone **11** and 0.054 g (0.5 mmol) of *o*-phenylenediamine in 5 ml of acetic acid was refluxed for 3 hr. The solution was diluted with ice water, made basic with sodium hydroxide, and extracted with ether. The ether solution was dried over potassium carbonate, and the solvent was evaporated. The brown residue was recrystallized from 95% ethanol to give 0.065 g (43% yield) of **29** as yellowish-white needles: mp 109–110°; ^1H NMR (CCl_4) δ 1.20 (s, 9), 1.45 (s, 12), 2.84 (s, 4), and 7.72 (m, 4).

Anal. Calcd for $C_{20}H_{29}N_3$: C, 77.20; H, 9.39; N, 13.50. Found: C, 76.97; H, 9.27; N, 13.42.

Reduction of 9 with $NaBH_4$–EtOH. 12a and 12b. A mixture of 0.85 g (3.5 mmol) of acyloin **9**, 0.13 g (3.5 mmol) of sodium borohydride, and 20 ml of ethanol were stirred under N_2 at 25° for 2 hr and then warmed to 50° over an additional 2 hr. The ethanol was removed in vacuo and water and ether were added to the residue. The aqueous layer was extracted with ether which was dried with K_2CO_3, filtered, and evaporated to give 0.88 g (100%) of a crude solid which was shown by ^1H NMR to be a mixture of cis (**12a**) and trans (**12b**) diols (see Table I, run A). Separation of the diols by column chromatography using silicic acid with hexane–ether elution allowed isolation of pure trans and cis material. For trans diol **12b**: mp (sublimed) 140–142°; ir ($CHCl_3$) 3500, 2980, 1468, 1390, 1360, and 1035 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (s, 6), 1.02 (s, 15), 2.34 (AB, 4), 2.80 (s, 2, absent in D_2O), 3.39 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 243 (M^+, 3), 228 (38), 210 (42), 170 (7), 156 (48), 114 (10), 100 (12), 99 (10), 98 (10), 86 (37), 85 (11), 84 (28), 72 (10), 71 (14), 70 (40), 57 (72), 56 (22), 55 (37), 44 (41), 43 (87), 42 (66), and 41 (100).

Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01. Found: C, 68.72; H, 11.98.

For cis diol **12a**: mp (hexane) 140–141°; ir ($CHCl_3$) 3480, 2980, 1470, 1385, 1365, and 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (s, 6), 1.07 (s, 15), 2.52 (AB, 4, J = 12 Hz) 3.41 (s, 2), and 3.50 (br s, 2, absent in D_2O); mass spectrum (70 eV) m/e (rel intensity) 243 (M^+, 10), 228 (100), 210 (4), 170 (16), 156 (47), 114 (17), 86 (28), 84 (18), 70 (18), 57 (34), 55 (12), 44 (22), 43 (25), and 41 (26).

Anal. Calcd for $C_{14}H_{29}NO_2$: C, 69.09; H, 12.01. Found: C, 69.25; H, 12.02.

Other reductions were run by adding the appropriate substrate to the appropriate solvent at the temperature specified in Table I. In run B_2, solid **9** was added to the refluxing mixture through the condenser top.

Reduction of Acetate 10 with $LiAlH_4$–THF. To 10 ml of THF containing 2 equiv of $LiAlH_4$ was added 0.28 g (0.001 mol) of **10** and the mixture was heated to reflux for 1 hr and cooled.

Standard work-up gave a near quantitative yield of cis diol **12a**.

Cis Diacetate 12c. Diol **12a** (90 mg) was refluxed for 3 hr in a 1:1 mixture of acetic acid–acetic anhydride and poured onto ice. Acid–base work-up gave 115 mg (95%) of a solid which could be sublimed or recrystallized from hexane: mp 91.5–92.5°; ir (CCl_4) 2885, 1745, 1458, 1248, and 1230 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (s, 6), 1.04 (s, 9), 1.06 (s, 6), 2.06 (s, 6), 2.52 (AB, 4, J = 13 Hz), 5.01 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 327 (6, M^+), 312 (100), 284 (2), 267 (22), 252 (7), 208 (5), 152 (40), 138 (5), 123 (8), 102 (7), 84 (10), 70 (22), 57 (30), 55 (10), 44 (14), 43 (49), 42 (27), and 41 (21).

Anal. Calcd for $C_{18}H_{33}NO_4$: C, 66.02; H, 10.16. Found: C, 66.27; H, 10.23.

Trans Diacetate 12d. Diacetate **12d** could not be synthesized using the procedure described to make **12c**. The following procedure was employed. Diol **12b**, 120 mg (0.5 mmol), was refluxed for 20 min in 5 ml of pyridine containing 5 ml of acetic anhydride. After cooling, the mixture was made basic with aqueous KOH and extracted with ether. Purification of the crude material by column chromatography after evaporation of solvents gave diacetate **12d** as a white solid (82% yield): mp (sublimed) 79–82°; ir (CCl_4) 2965, 1748, 1391, 1370, 1250, and 1028 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 6), 0.98 (s, 6), 1.03 (s, 9), 2.02 (s, 6), 2.42 (AB, 4) and 4.97 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 327 (5, M^+), 312 (100), 284 (3), 268 (58), 252 (19), 208 (10), 152 (54), 84 (19), 70 (27), 57 (44), 56 (27), 55 (24), 44 (20), 43 (72), 42 (41), and 41 (58).

Anal. Calcd for: $C_{18}H_{33}NO_4$: C, 66.02; H, 10.16. Found: C, 66.02; H, 10.12.

Cis Sulfite Ester 16a. To a mixture of 0.125 g (0.52 mmol) of diol **12a**, 0.107 g (1.21 mmol) of dry pyridine, and 25 ml of ether under N_2 at 0° was added dropwise 80 mg (0.68 mmol) of thionyl chloride in 5 ml of ether. After allowing the mixture to stir at 0° for 1 hr and 25° for an additional 1 hr it was poured into cold aqueous K_2CO_3 which was extracted with ether to give, after evaporation of the solvents, a crude solid. Column chromatography on silicic acid using hexene–ether elution gave pure **16a** in good yield: mp (sublimed) 85–87°; ^1H NMR ($CDCl_3$) δ 1.08 (s, 15), 1.12 (s, 6), 2.44 (AB, 4, J = 14 Hz), and 4.63 (s, 2).

Anal. Calcd for $C_{14}H_{27}NO_3S$: C, 58.09; H, 9.40. Found: C, 58.18; H, 9.41.

Trans Sulfite Ester 16b. Sulfite ester **16b** was synthesized using the procedure described to make **16a**. For **16b**: mp (sublimed) 131–132°; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3), 1.01 (s, 3), 1.04 (s, 9), 1.08 (s, 3), 1.11 (s, 3), 2.49 (AB, 4), 4.30 (AB, 2, J = 11 Hz).

Anal. Calcd for $C_{14}H_{27}NO_3S$: C, 58.09; H, 9.40. Found: C, 9.67; H, 58.33.

***N*-*tert*-Butyl-3,3′-imino-2,2,2′,2′-tetramethyldipropanal (2).** A mixture of 4.31 g (0.017 mol) of diol **12a**, 4.17 g (0.018 mol) of paraperiodic acid, 100 ml of water, and 4 ml of 1 *N* hydrochloric acid was stirred for 40 hr at 25°. The solution was made basic with cold concentrated sodium hydroxide solution and extracted with chloroform. The chloroform was dried with $MgSO_4$ and evaporated, giving, after distillation, 2.64 g (62%) of dialdehyde **2**: bp 95–96° (0.25 mm); ir (CCl_4) 2965, 2680, 1726, 1467, 1390, and 1365 cm^{-1}; ^1H NMR (CCl_4) δ 0.97 (s, 9), 1.01 (s, 12), 2.75 (s, 4), and 9.60 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 241 (M^+, trace), 240 (1), 239 (1), 238 (2), 198 (5), 154 (7), 142 (5), 86 (21), 79 (10), 72 (59), 70 (58), 58 (22), 57 (79), 56 (20), 55 (19), 43 (95), and 41 (100); uv λ_{max} (EtOH) 290 nm (ϵ 55), 235 (shoulder, 320).

Anal. Calcd for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.28; N, 5.80. Found: C, 69.48; H, 11.42; N, 5.73.

***N*-*tert*-Butyl-3,3,4,6,6-pentamethylazacycloheptane-4,5-diol (20).** A mixture of 0.75 g (3.1 mmol) of acyloin **9** in either 15 ml of dry ether or THF and 9 mmol of methyllithium was stirred for 10 hr at 25°, at which time a few milliliters of water were added and the organic layer separated. The solvent was evaporated and the crude solid remaining was recrystallized from hexane–ether, giving 0.63 g (81%) of diol **20** as a white solid: mp 122–123°; ir (CCl_4) 3300, 2965, 1470, 1391, 1368, and 1020 cm^{-1}; ^1H NMR

($CDCl_3$) δ 0.92 (s, 3), 1.02 (s, 3), 1.06 (s, 3), 1.09 (s, 9), 1.12 (s, 3), 1.17 (s, 3), 2.54 (AB, 2, J = 14 Hz), 2.57 (AB, 2, J = 13 Hz), 3.41 (broad, sharp in D_2O, 1); mass spectrum (70 eV) m/e (rel intensity) 257 (M^+, 14), 242 (100), 200 (11), 170 (52), 156 (59), 140 (21), 128 (37), 114 (17), 86 (66), 84 (43), 70 (23), 57 (49), 43 (63), and 41 (38).

Anal. Calcd for $C_{15}H_{31}NO_2$: C, 69.99; H, 12.14. Found: C, 70.17; H, 12.26.

***N*-*tert*-Butyl-3,3,4,6,6-pentamethylazacycloheptan-4-ol-5-one (21).** A mixture of 1.0 g (4.2 mmol) of dione **11**, 4.6 mmol of methyllithium, and 25 ml of dry tetrahydrofuran was stirred at 35° for several hours. After cooling, water and ether were added. The ether was dried with K_2CO_3 and filtered, and the solvents were removed in vacuo, leaving a solid which was sublimed to give 1.0 g (87%) of acyloin **21**: mp 57–60°; ir (CCl_4) 3440, 2960, 1685, 1465, 1385, 1370, 1050, and 1024 cm^{-1}; ^1H NMR (CCl_4) δ 0.71 (s, 3), 0.92 (s, 3), 1.03 (s, 3), 1.07 (s, 9), 1.24 (s, 3), 1.32 (s, 3), 2.70 (m, 4), and 4.25 (s, 1, absent in D_2O); mass spectrum (70 eV) m/e (rel intensity) 225 (M^+, 11), 240 (100), 226 (7), 171 (10), 156 (10), 154 (27), 140 (23), 126 (18), 86 (63), 85 (56), 84 (64), 71 (15), 70 (53), 57 (88), 56 (15), 55 (20), 43 (44), and 41 (38). The addition of excess methyllithium to the THF mixture did not allow isolation of diol **22** in our hands.

Reduction of 21 with $LiAlH_4$. Acyloin **21** was reduced by $LiAlH_4$ in refluxing THF to give after work-up a near quantitative yield of diol **20**.

***N*-*tert*-Butyl-3,3,4,5,6,6-hexamethylazacycloheptane-4,5-diol (22).** Into a solution of 0.15 g (0.5 mmol) of acyloin **21** (or dione **11**) in dried glyme under N_2 was added 4 equiv of methyllithium. The mixture was heated slowly to reflux over several hours and refluxed for an additional 1 hr, cooled, and quenched with cold water. The basic aqueous layer was extracted with ether which was dried with $MgSO_4$ and evaporated to give a solid residue. Sublimation gave 0.13 g (81%) of **22** as a white solid: mp 91–94°; ir (CCl_4) 3300 and 2985 cm^{-1}; ^1H NMR (CCl_4) δ 0.91 (s, 6), 1.08 (s, 6), 1.10 (s, 9), 1.14 (s, 6), 2.25 (d, 2, J = 13 Hz), and 2.99 (d, 2, J = 13 Hz); mass spectrum (70 eV) m/e (rel intensity) 271 (M^+, 6), 256 (31), 242 (31), 170 (76), 156 (24), 140 (28), 128 (57), 100 (10), 86 (100), 84 (46), 70 (20), 57 (46), 55 (15), and 43 (73).

***N*-*tert*-Butyl-4,4′-imino-3,3,3′,3′-tetramethyldibutane-2,2′-dione (3).** Diketone **3** was synthesized from diol **22** in 57% yield using the same procedure described to make dialdehyde **2**. For **3**: mp (sublimation) 60–62.5°; ir (CCl_4) 2970, 1705, 1470, 1390, 1365, 1352, 1254, and 1100 cm^{-1}; ^1H NMR (CCl_4) δ 0.94 (s, 9), 1.07 (s, 12), 2.10 (s, 6), and 2.76 (s, 4); mass spectrum (70 eV) m/e (rel intensity) 269 (M^+, trace) 183 (5), 168 (39), 156 (6), 112 (5), 110 (3), 86 (36), 84 (12), 70 (26), 57 (23), 43 (100), and 41 (33); uv λ_{max} (EtOH) 285 nm (ε 69), 235 (shoulder, 370).

Anal. Calcd for $C_{16}H_{31}NO_2$: C, 71.33; H, 11.60; N, 5.20. Found: C, 71.40; H, 11.56; N, 5.20.

***N*-*tert*-Butyl-3-imino-2,2-dimethylpropanal-4′-imino-3′,3′-dimethyl-2′-butanone (5).** Aldehyde ketone **5** was synthesized from diol **20** in 77% yield using the same procedure described to make dialdehyde **2**. For **5**: mp (sublimation) 18–19°; ir (CCl_4) 2960, 2680, 1728, 1705, 1470, 1423, 1390, 1390, 1365, 1352, 1245, and 1103 cm^{-1}; ^1H NMR (CCl_4) δ 0.98 (s, 12), 1.08 (s, 9), 2.12 (s, 3), 2.80 (s, 4), and 9.58 (s, 1); mass spectrum (70 eV) m/e (rel intensity) 255 (M^+, none), 183 (6), 168 (23), 156 (21), 112 (5), 86 (57), 72 (24), 70 (84), 57 (72), 43 (100), and 41 (86).

Anal. Calcd for $C_{15}H_{29}NO_2$: C, 70.54; H, 11.45; N, 5.48. Found: C, 70.35; H, 11.35; N, 5.66.

Synthesis of Monohydrazone 24. To 1.2 g (5.3 mmol) of amino dione **11** in 10 ml of a 1:2 mixture of ethanol–benzene containing a few drops of acetic acid was added 2.0 g (6.2 mmol) of 98% hydrazine. The reaction mixture was heated at reflux for 10 hr at which time water was removed from the reaction mixture as an azeotrope using a Dean-Stark trap. The reaction mixture was then cooled and water was added. The resulting mixture was extracted with ether which was dried with $MgSO_4$, filtered, and evaporated to give a solid material. Recrystallization of the solid from methanol gave 0.53 g (42%) of pure hydrazone **24**: mp 78–80°; ir ($CHCl_3$) 3473, 3418, 2973, 2860, 2810, 1735, 1693, 1625, and 1032 cm^{-1}.

***N*-*tert*-Butyl-3,3,6,6-tetramethyl-1-azacycloheptan-4-one (23).** Monohydrazone **24** (0.48 g, 1.9 mmol) was dissolved in 15 ml of dry xylene. Potassium *tert*-butoxide (0.24 g, 2.1 mmol) was added to the mixture, which was refluxed under N_2 for 5 hr. After cooling, the mixture was poured onto 50 ml of ice. The organic layer was separated and the aqueous layer was washed with ether. The combined organic washes were dried over $MgSO_4$, filtered, and evaporated to give a residue which was further purified by column chromatography using 100 mesh silicic acid. Elution with hexane–ether gave a white solid which was sublimed to give 0.20 g (42% yield) of pure **23**: mp 37–38°; ir (CCl_4) 2960, 1702, 1465, 1390, 1370, 1260, 1188, 1068, and 1042 cm^{-1}; ^1H NMR (CCl_4) δ 0.87 (s, 6), 0.97 (s, 6), 1.05 (s, 9), 2.28 (s, 2), 2.47 (s, 2), and 2.63 (s, 2); mass spectrum (70 eV) m/e (rel intensity) 225 (M^+, 21) 211 (19), 210 (100), 154 (13), 152 (14), 140 (25), 126 (12), 125 (9), 114 (28), 85 (34), 97 (12), 84 (42), 70 (41), 57 (68), 56 (20), 55 (30), 44 (28), 43 (30), and 41 (60) (a metastable peak appears at m/e 196.5); uv λ_{max} (EtOH) 290 nm (shoulder, ε 58), 240 (shoulder, 375).

Anal. Calcd for $C_{14}H_{27}NO$: C, 74.66; H, 12.06; N, 6.22. Found: C, 74.56; H, 12.04; N, 6.14.

***N*-*tert*-Butyl-4-iminobutan-2-one (42).** *tert*-Butylamine (0.75 g, 0.011 mol) and methyl vinyl ketone (0.70 g, 0.01 mol) were stirred in 10 ml of methanol at 25° for 24 hr. The solvent was removed by careful evaporation and the crude material was distilled to give **42** as a clear oil in good yield. For **42**: bp 33–34° (2 mm); ir ($CHCl_3$) 3300, 2850, 1715, 1370, 1230, and 1168 cm^{-1}; ^1H NMR ($CDCl_3$) 1.05 (s, 9), 2.08 (s, 3), 2.65 [m, 5, becomes 4 (2 partially overlapping triplets), J = 6 Hz, in D_2O]; mass spectrum (70 eV) m/e (rel intensity) 143 (1, M^+), 97 (3), 70 (3), 58 (100), 56 (20), 43 (28), 42 (22), and 41 (27); uv (EtOH) 288 nm (ε 25).

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Registry No.—**1**, 37489-09-1; **2**, 55886-30-1; **3**, 55886-31-2; **4**, 53934-35-3; **5**, 55886-32-3; **7**, 37489-08-0; **9**, 55886-33-4; **10**, 55886-34-5; **11**, 55886-35-6; **12a**, 55886-36-7; **12b**, 55886-37-8; **12c**, 55886-38-9; **12d**, 55886-39-0; **16a**, 55886-40-3; **16b**, 55923-87-0; **20**, 55886-41-4; **21**, 55886-42-5; **22**, 55886-43-6; **23**, 55886-44-7; **24**, 55886-45-8; **29**, 55886-46-9; **42**, 55886-47-0; 1-butanol, 71-36-3; *tert*-butylamine, 75-64-9; ethyl α-bromoisobutyrate, 600-00-0; *o*-phenylenediamine, 95-54-5; thionyl chloride, 7719-09-7; methyllithium, 917-54-4; potassium *tert*-butoxide, 865-47-4; methyl vinyl ketone, 78-94-4.

References and Notes

(1) Presented in part at the 26th Southeastern Regional Meeting of the American Chemical Society, Norfolk, Va., Oct 24, 1974.
(2) P. Y. Johnson and I. Jacobs, *J. Chem. Soc., Chem. Commun.*, 925 (1972).
(3) 1,4-Nitrogen–carbonyl interaction might be expected to vary from "not measureable" to "interaction resulting in the formation of a covalent bond". While we are unable to find specific examples of 1,4-tertiary nitrogen–carbonyl interaction in acyclic systems, it should be noted that the formation of β-lactams from β-amino acids proceeds via tetrahedral intermediates (R_3N^+–C–O^-) formed as a result of reaction of nitrogen at the carbonyl carbon.
(4) Examples of transannular 1,4-nitrogen–carbonyl interactions have been documented. See (a) K. Achiwa and S. Yamada, *Tetrahedron Lett.*, 1799 (1974); (b) H. Dahn, H. P. Schlunke, and J. Temler, *Helv. Chim. Acta*, **55**, 907 (1972).
(5) For a specific example of conformational effects on the chemistry of a related amino diester, see P. Y. Johnson and M. Davis, *Tetrahedron Lett.*, 293 (1973).
(6) For a recent synthesis of amine **4** and diol **6** see P. Y. Johnson, I. C. Jacobs, and S. Elias, *Synthesis*, 568 (1974).
(7) P. Y. Johnson and I. Jacobs, *Synth. Commun.*, **4**, 51 (1974).
(8) For representative examples of alkylamine formation by monoalkylation of alkoxymethyl amines with organomagnesium reagents see (a) D. Couturier, *Ann. Chim. (Paris)*, **7**, 19 (1972); (b) G. Adrian and C. Glacet, *Bull. Soc. Chim. Fr.*, 638 (1971); (c) ref 1; (d) ref 3. With organozinc reagents: (e) J. Brocard, *Ann. Chim. (Paris)*, **7**, 387 (1972); (f) C. Glacet and J. Brocard, *Bull. Soc. Chim., Fr.*, 4133 (1969); (g) ref 5. With organolithium reagents: (h) A. Venot and C. Glacet, *C. R. Acad. Sci., Ser. C*, **273**, 718 (1971). See also ref 8e and references cited in the above articles.
(9) Stable dialkylmethylene immonium ion–Lewis acid complexes have been isolated: F. Knoll and U. Krumm, *Chem. Ber.*, **104**, 31 (1971). See also ref 8a.
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(11) E. J. Corey and E. A. Broger, *Tetrahedron Lett.*, 1779 (1969).
(12) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).
(13) J. M. Lalancette, G. Rollin, and P. Dumas, *Can. J. Chem.*, **50**, 3058 (1972).
(14) W. W. Epstein and F. W. Sweat, *Chem. Rev.*, **67**, 247 (1967).
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(16) P. Y. Johnson, R. B. Silver, and M. M. Davis, *J. Org. Chem.*, **38**, 3753 (1973).
(17) While early workers reported poor yields for the formation of azacyclo-

heptane acyloins [see N. J. Leonard et al., *J. Am. Chem. Soc.*, **76**, 630 (1954)], more recent reports on acyloin reactions involving the use of chlorotrimethylsilane as an anion trapping agent indicate that nitrogen-containing acyloins can be obtained in 90% yield: K. Ruhlmann, *Synthesis*, 236 (1971).
(18) Ground-state conformations were decided by careful examination of Buchi and space filling models and the conclusions drawn checked against experimental results obtained for related systems. (a) Cycloheptanes: J. B. Hendrickson et al., *J. Am. Chem. Soc.*, **95**, 494 (1973). (b) Azacyclooctanes: J. B. Lambert and S. A. Khan, *J. Org. Chem.*, **40**, 369 (1975).
(19) This molecule, which has been demonstrated to show activity against leukemia, has been previously synthesized by another route: P. Y. Johnson and R. Silver, *J. Heterocycl. Chem.*, 1029 (1973).
(20) Mannich and reverse Mannich reactions involving 2,2-disubstituted ketones (but not aldehydes) have been the subject of considerable debate and controversy. A discussion of this problem has been treated by G. L. Buchanan, A. C. Curran, and R. T. Wall, *Tetrahedron*, **25**, 5503 (1969), and references cited therein. *N*-Methyl dialdehyde **8** does not undergo this interesting reaction: P. Y. Johnson, unpublished results.
(21) While the particular problem of the stereochemistry of **12** could be solved using combination wet chemical–spectroscopic techniques, the frequent reoccurrence of the cis/trans diol problem in our research prompted us to seek a general, more facile approach to this problem.
(22) H. C. Brown and K. Ichikawa, *J. Am. Chem. Soc.*, **84**, 373 (1962).
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(24) This statement is not a violation of the Curtin–Hammett principle,[25] which states that the ratios of products from one starting material depends only on the free energy differences of the transition states, but rather reflects the cases where E_{act} is not necessarily much larger than rotational barriers [compare an E_{act} of 8–15 kcal/mol for reduction of a carbonyl with a $\Delta G^{\ddagger}$ of 9 kcal/mol for rotation in acyclic analogs of our systems (Table II)] and where the geometry of the transition state resembles that of the ground state.
(25) For a general introduction to free-energy calculations and the Curtin–Hammett principle see (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis", Interscience, New York, N.Y., 1965; (b) E. L. Eliel, "Stereochemistry of Carbon Compounds", McGraw-Hill, New York, N.Y., 1962; (c) N. L. Allinger and E. L. Eliel, *Top. Stereochem.*, **1**, 1 (1967). For specific application of these principles to the reduction of acyclic acyloins see G. J. Karabatsos, *J. Am. Chem. Soc.*, **89**, 1367 (1967).
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(27) The reduction of 3,3,6,6-tetramethyl-2-hydroxycyclohexanone by $NaBH_4$ has been reported to give 82% cis diol: D. E. Applequist et al., *J. Am. Chem. Soc.*, **94**, 4272 (1972). Our approach predicts this result.
(28) Because of the geometries involved, a change in mechanism from least hindered attack to directed attack[29] would not alter this conclusion.
(29) M. Akhtar and S. Marsh, *J. Chem. Soc. C*, 937 (1966).
(30) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Molecules", Holden-Day, San Francisco, Calif., 1967.
(31) (a) M. D. McCreary, D. W. Lewis, D. L., Wernick, and G. M. Whitesides, *J. Am. Chem. Soc.*, **96**, 1038 (1974); (b) H. L. Goering, J. N. Eikenberry, G. S. Koermer, and C. J. Lattimer, *ibid.*, **96**, 1493 (1974). For a review of this subject see R. E. Sievers, Ed., "Nuclear Magnetic Resonance Shift Reagents", Academic Press, New York, N.Y., 1973.
(32) While shift reagents have been used for direct determination of enantiomeric composition,[31] we have found only one report, involving epoxides, concerning the use of these reagents to distinguish meso and *dl* diastereomers: M. Kainosho, K. Ajisaka, W. H. Pirkle, and S. D. Beare, *J. Am. Chem. Soc.*, **94**, 5924 (1972).
(33) We have chosen to introduce this general nomenclature, since it provides a picture of our systems from which ^1H NMR spectra taken in the presence of chiral shift reagents can be predicted. Descriptions of our multifunctional systems in terms of enantiotopic and diastereotopic [K. Mislow and M. Raban, *Top. Stereochem.*, **1**, 1 (1967)] relationships are unwieldly when seeking fast, qualitative (cis or trans?) information.
(34) A more quantitative study of the application of chiral shift reagents as a method of determining the stereochemistry of diol systems is under study in our laboratories. Spectra presented (Figure 1) for **12a** and **12b** are included to demonstrate the feasibility and utility of this approach.
(35) Structures **17**, **18**, and **19-*d*** should be considered averages and do not imply knowledge of the exact nature of binding for these systems.
(36) Since the half-life of alkyllithium reagents in THF is ca. 10 min at 35° [R. B. Bates, L. M. Kroposki, and D. E. Potter, *J. Org. Chem.*, **37**, 560 (1972), and references cited therein], this solvent is only appropriate for alkyliithium addition reactions when the rate of addition is much faster than the rate of decomposition due to reaction with THF.
(37) The addition of methyllithium to cyclodecane-1,3-dione has been shown to give 98% cis diol: A. E. Runquist and J. A. Marshall, Northwestern University, Evanston, Ill., unpublished results.
(38) For a more quantitative treatment of related, but less hindered, *N-tert*-butyl-*N,N*-dialkylamines see (a) C. H. Bushweller et al., *J. Am. Chem. Soc.*, **96**, 3892 (1974), and references cited therein; (b) see S. Brownstein, E. Horswill, and K. U. Ingold, *J. Am. Chem. Soc.*, **92**, 7217 (1970), for a discussion of several mononeopentylamines.
(39) For comparisons of related compounds, in particular for investigations of substituent effects, measurements of $\Delta G^{\ddagger}$ are usually adequate. See L. O. Sutherland, *Annu. Rep. NMR Spectrosc.*, **4**, 71 (1971).
(40) For the use and limitations of this approximation of $\Delta G^{\ddagger}$ see (a) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance", McGraw-Hill, New York, N.Y., 1959; (b) for a more precise expression, see S. Alexander, *J. Chem. Phys.*, **37**, 967 (1963).
(41) See ref 25c, p 199.
(42) (a) F. Jensen et al., *J. Am. Chem. Soc.*, **91**, 344 (1969); (b) G. W. Buchanan and J. B. Stothers, *Chem. Commun.*, 179 (1967).
(43) This contention is supported in part by the lower $\Delta G^{\ddagger}$ (7.6 kcal/mol) ($T_c = -112°$) (P. Y. Johnson, unpublished results) found for trineopentylamine. For the synthesis of trineopentylamine see ref 6.
(44) (a) J. Strating, S. Reiffers, and H. Wynberg, *Synthesis*, 209 (1971); (b) P. Y. Johnson, *Tetrahedron Lett.*, 1991 (1972).
(45) P. Y. Johnson, J. Zitsman, and C. Hatch, *J. Org. Chem.*, **38**, 4087 (1973).
(46) N. J. Leonard and P. M. Mader, *J. Am. Chem. Soc.*, **72**, 5388 (1950).
(47) For examples of C-T phenomena in related systems see (a) N. J. Leonard, T. W. Milligan, and T. L. Brown, *J. Am. Chem. Soc.*, **82**, 4075 (1960); (b) N. J. Leonard, *Rec. Chem. Prog.*, **17**, 243 (1956); (c) E. A. Fehnel and M. Carmack, *J. Am. Chem. Soc.*, **71**, 84 (1949); (d) C. G. Overgerger, P. Barkan, A. Lusi, and H. Ringsdorf, *J. Am. Chem. Soc.*, **84**, 2814 (1962); (e) L. A. Paquette and L. D. Wise, *ibid.*, **89**, 6659 (1967); (f) G. Bergson, G. Claeson, and L. Schotte, *Acta Chem. Scand.*, **16**, 1159 (1962); (g) P. Y. Johnson and G. A. Berchtold, *J. Org. Chem.*, **35**, 584 (1970).

Synthesis and Properties of 3-Amino-3-pyrazolin-5-ones

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The enamines, 1-amino-1-trichloromethyl-2,2-dicarboxyalkylethenes, reacted with hydrazine in DMF to yield 1-amino-1-hydrazino-2,2-dicarboxyalkylethenes (**2**) at 25° or 3-amino-3-pyrazolin-5-ones (**3**) at 100°. These heterocyclics react with acid halide and phenyl isocyanate to give mono (3-amino) or di (3-amino,5-hydroxy) derivatives. With isatoic acid, a 3-(o-aminobenzamido) compound can be made. Infrared and mass spectral data indicate considerable intra- and intermolecular hydrogen bonding in most of these compounds.

In a program concerned with the synthesis and pharmacological activities of certain enamines,[2,3] one of us converted these compounds into mono- and diaminopyrazoles.[3] Here we report on the synthesis and properties of several 3-aminopyrazole-5-ones, or in *Chemical Abstracts* terminology, 3-amino-3-pyrazolin-5-ones (**3**).[4a] Among the numerous patterns of substitution in this ring system, a few N-unsubstituted pyrazol-5-ones[4b] and 3-aminopyrazoles[4c] have been reported. Recently, Gillis and Weinkam have oxidized tautomers of 3,4-disubstituted pyrazolin-5-ones and

Table I
1-Amino-1-hydrazinoethenes, $RR'C{=}C(NH_2)NHNH_2$ (2)

Registry no.	R	R'	Formula	Yield, %	Mp, °C	Found N, %	Calcd N, %
52566-35-5	CH_3OOC	CH_3OOC	$C_6H_{11}N_3O_4$	78	126–127	22.1	22.21
1572-20-9	C_2H_5OOC	C_2H_5OOC	$C_8H_{15}N_3O_4$	81	114–115	19.6	19.34
55254-77-8	C_3H_7OOC	C_3H_7OOC	$C_{10}H_{19}N_3O_4$	76	85–86	16.7	17.01
55254-78-9	i-C_3H_7OOC	i-C_3H_7OOC	$C_{10}H_{19}N_3O_4$	73	97–98	17.1	17.01
55254-79-0	C_4H_9OOC	C_4H_9OOC	$C_{12}H_{23}N_3O_4$	78	73–75	15.5	15.37
55254-80-3	i-C_4H_9OOC	i-C_4H_9OOC	$C_{12}H_{23}N_3O_4$	83	89–90	15.4	15.37
55254-81-4	t-C_4H_9OOC	CH_3OOC	$C_9H_{17}N_3O_4$	74	68–69	18.3	18.60
55254-82-5	t-C_4H_9OOC	C_2H_5OOC	$C_{10}H_{19}N_3O_4$	76	57–58	17.1	17.01

Table II
3-Aminopyrazolin-5-ones [3-NH_2, 4-R-$C_3N_2H_2O$ (3)] and Their Monoacyl [3-R'CONH, 4-R-$C_3N_2H_2O$ (4, 5, 8, 10)] and Diacyl [3-R'CONH, 4-R, -5-R'COO-C_3N_2H (6, 7, 9)] Derivatives

R	R'	Formula	Yield, %	Mp, °C	Found C, H or (N), %		Calcd C, H or (N), %	
CH_3OOC		$C_5H_7N_3O_5$	91	256–258[a]	(26.3)		(26.74)	
C_2H_5OOC		$C_6H_9N_3O_5$	94	268–269[a]	(24.7)		(24.55)	
C_3H_7OOC		$C_7H_{11}N_3O_3$	89	283–284[a]	(22.8)		(22.69)	
i-C_3H_7OOC		$C_7H_{11}N_3O_3$	92	205–208[a]	(22.7)		(22.69)	
C_4H_9OOC		$C_8H_{13}N_3O_3$	85	310–312[a]	(21.3)		(21.09)	
i-C_4H_9OOC		$C_8H_{13}N_3O_3$	87	248–250[a]	(20.7)		(21.09)	
t-C_4H_9OOC		$C_8H_{13}N_3O_3$	76	212–213[a]	(21.0)		(21.09)	
n-C_3H_7OCO	CH_3[b]	$C_9H_{13}N_3O_4$	59	172–173	47.8	5.70	47.57	5.76
i-C_3H_7OCO	CH_3[b]	$C_9H_{13}N_3O_4$	83	284[a]	47.5	5.69	47.57	5.76
i-C_4H_9OCO	CH_3[b]	$C_{10}H_{15}N_3O_4$	87	166–167	49.8	6.03	49.78	6.26
C_2H_5OCO	C_6H_5[b]	$C_{13}H_{13}N_3O_4$	92	227–228	57.5	4.85	57.09	4.79
n-C_3H_7OCO	C_6H_5[b]	$C_{14}H_{15}N_3O_4$	67	130–131	57.9	5.10	58.12	5.23
i-C_4H_9OCO	C_6H_5[b]	$C_{15}H_{17}N_3O_4$	61	181–182	59.7	5.47	59.39	5.64
C_2H_5OOC	NHPh[b]	$C_{13}H_{14}N_4O_4$	63	232–233	53.7	4.77	53.78	4.86
n-C_3H_7OOC	NHPh[b]	$C_{14}H_{16}N_4O_4$	71	328–329	55.1	5.41	55.22	5.29
i-C_4H_9OOC	NHPh[b]	$C_{15}H_{18}N_4O_4$	68	227–228	56.3	5.89	56.61	5.70
n-C_3H_7OOC	CH_3[c]	$C_{11}H_{15}N_3O_5$	74	212–213	49.0	5.76	49.07	5.58
i-C_4H_9OOC	CH_3[c]	$C_{12}H_{17}N_3O_5$	65	219–220	50.9	6.03	50.87	6.04
C_2H_5OOC	C_6H_5[c]	$C_{20}H_{17}N_3O_5$	68	123–124	63.4	4.73	63.30	4.51
n-C_3H_7OOC	C_6H_5[c]	$C_{21}H_{19}N_3O_5$	73	108–109	64.2	5.02	64.11	4.87
i-C_3H_7OOC	C_6H_5[c]	$C_{21}H_{19}N_3O_5$	71	137–138	63.9	5.02	64.11	4.87
i-C_4H_9OOC	C_6H_5[c]	$C_{22}H_{21}N_3O_5$	70	112–113	64.8	5.15	64.85	5.19
C_2H_5OOC	NHPh[c]	$C_{20}H_{19}N_5O_5$	73	210–212	58.5	4.45	58.67	4.67
n-C_3H_7OOC	NHPh[c]	$C_{21}H_{21}N_5O_5$	69	196–197	59.6	5.14	59.57	4.99
i-C_4H_9OOC	NHPh[c]	$C_{22}H_{23}N_5O_5$	71	182–183	62.5	5.27	62.69	5.30
i-C_4H_9OOC	o-$NH_2C_6H_4$[d]	$C_{15}H_{18}N_4O_4$	66	134–135	59.5	6.68	59.73	6.79
C_2H_5OOC	o-$NH_2C_6H_4$[d]	$C_{13}H_{14}N_4O_4$	80	204–205	51.47	5.07	51.72	4.85

[a] With decomposition. The melting point appears to change with age (several months) of the sample. Recrystallization restores some of the original 3. [b] Monoacyl derivative. [c] Diacyl derivative. [d] 10.

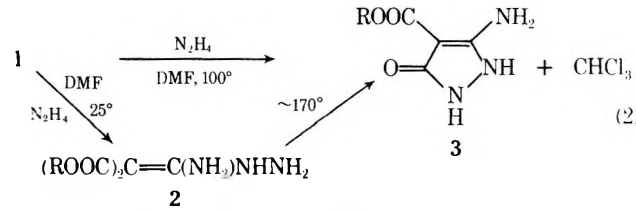
trapped the unstable diazacyclopentadienone with dienes;[5a] Junek and Aiger have treated 1,3-disubstituted pyrazol-5-ones or 3-aminopyrazoles with tetracyanoethylene and obtained condensations at the 4 position.[5b] However, actual analogs of 3 are rare; the closest examples we know are the 3-amino-4-arylazo-2-pyrazolin-5-ones,[6a] whose chemistry has been developed by Elnagdi et al.[6b]

In previous work the synthesis and some properties of the products (1) of eq 1 were discussed.[2] Here these enam-

$$Cl_3CCN + CH_2(COOR)_2 \xrightarrow{Na} \underset{1}{(RO_2C)_2C{=}C(CCl_3)NH_2} \quad (1)$$

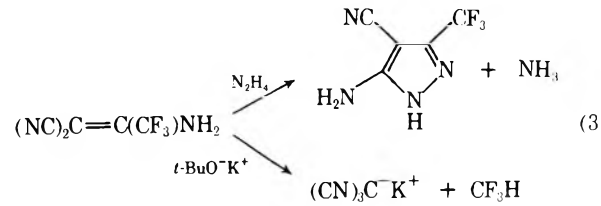
ines readily reacted with hydrazine to yield chloroform and 1-amino-1-hydrazino-2,2-dicarboxyalkylethenes (2) at ca. 25° (eq 2). The properties of these compounds are given in Table I.

There are perhaps two reactions which begin by looking



(2)

like precedents for eq 2 but which end up with different products.[7] In general, CCl_3^- (or CF_3^-) is typical of



(3)

Table III
Observed Ir Frequencies[a] and Tentative Assignments for the 3-Aminopyrazolin-5-ones (3) and Their Acylation Products (4–7)[b]

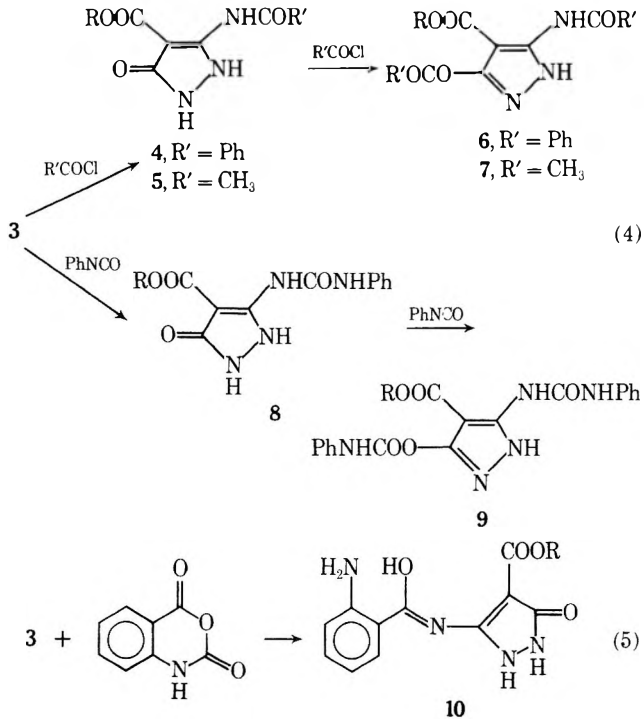
3	4 or 5	6 or 7	Tentative assignment, ν	Ref
3500 s	3490 s	3480 ± 10 m	Asymmetrical NH	9, 10
3300 ± 10 w		3300 ± 10 m	Symmetrical NH	9, 10
3220–3000 b	3400–3100 b		Intermolecular OH···N	10
2980 m, 2900 w ± 10	2990 m	3000 ± 15 m	Intramolecular OH···	11
		1750 s	5-COOR	12, 14
1685 ± 10 s	1720 ± 10 s	1690 ± 10 s	4-COOR	
	1680–1630 b	1660 s	–CON< and >C=N–	12
1610 ± 15 m	1610 m	1600 ± 10 s	Ring >C=N–	8, 11
1550 ± 10 s	1520 ± 15 s	1500 ± 10 w	Ring >C=C<	8, 9, 11, 14
1470 ± 10 m	1450 w	1450 ± 10 m	Asymmetrical $-CH_2-$ deformation	8, 9, 14, 15
1385 w	1380 ± 10 m	1400 ± 10 m	Symmetrical $-CH_2-$ deformation	8, 9, 14
1330 ± 10 m	1320 ± 10 s	1300 ± 15 s	C–N stretch	8, 9, 10, 15
1260 ± 5 w	1250 ± 10 m	1250 ± 10 s	Asymmetrical ester C–O stretch	14
1150 ± 5 s	1150 ± 10 s	1175 ± 5 m	C–N, C–C stretch	10
1100 ± 10 s	1100 ± 15 w	1135 ± 5 w	Symmetrical ester C–O stretch	14
980 ± 15 w	1000 ± 10 w	1040 ± 5 m	CH	
960 ± 15 w	970 ± 10 m	1020 ± 10 m	Heteroring	9, 10, 14
	880 ± 10 m	940 ± 15 m		
		920 ± 10 w		
810 ± 10 s	800 ± 10 m	800 ± 15 m	Heteroring	10
750 ± 15 w	760 ± 10 m	760 ± 10 m	Heteroring	
	700 ± 5 s	700 ± 5 s	Ph ring	
680 w	680 m	680 m	Heteroring	
650 ± 5 w	660 ± 10 m	660 ± 10 m	Heteroring	

[a] In reciprocal centimeters. [b] b, broad; m, medium; s, strong; w, weak.

leaving groups in nucleophilic attacks at an ethylenic carbon. On the other hand, the analogy between eq 2 and the familiar haloform reaction is so close, particularly for the imine tautomer of **1**, that the formation of **2** is quite plausible.

As indicated in eq 2, the hydrazinoenamines (**2**) cyclize on heating to give pyrazolones (**3**). More conveniently, **1** and excess hydrazine in DMF at ca. 100° yielded **3**. The properties of this series are listed in Table II.

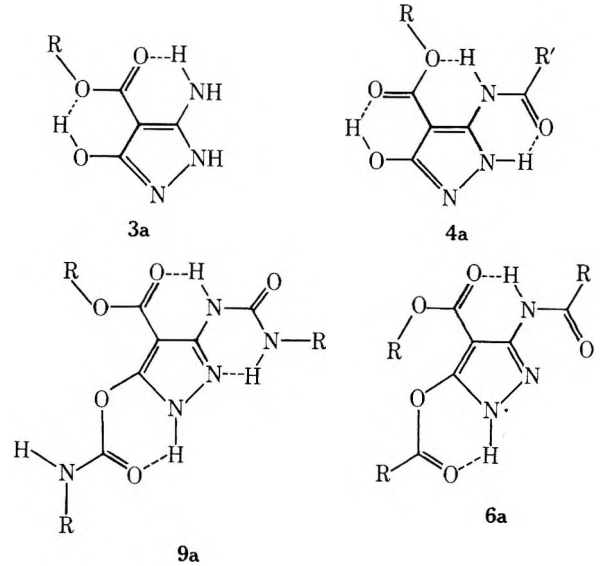
In order to characterize the pyrazolones, we prepared several derivatives (eq 4). Depending on whether 1 or 2 equiv of acid chloride or isocyanate are added, one may proceed cleanly to the mono- or disubstitution products.[4b] Likewise, isatoic anhydride acylates **3** to give a yellow product (**10**). All of these compounds (**4–10**) are described in Table II.



(4)

(5)

Spectral Data. There has been considerable interest in the tautomers and hydrogen-bonded forms of pyrazolones.[4,8] Our 3-amino compounds (**3**) and their derivatives (**4–9**) increase the possibilities in both categories. Structures **3a**, **4a**, **6a**, and **9a** depict some of the possible tautomers and types of *intramolecular* hydrogen bonds. Intermolecular hydrogen bonds, N–H···N, N–H···O, and O–H···O, must, of course, also be considered.



The preceding structural effects may be deduced in a general way from the spectra of **3–7**. Those features of the families which seem to be common are summarized in

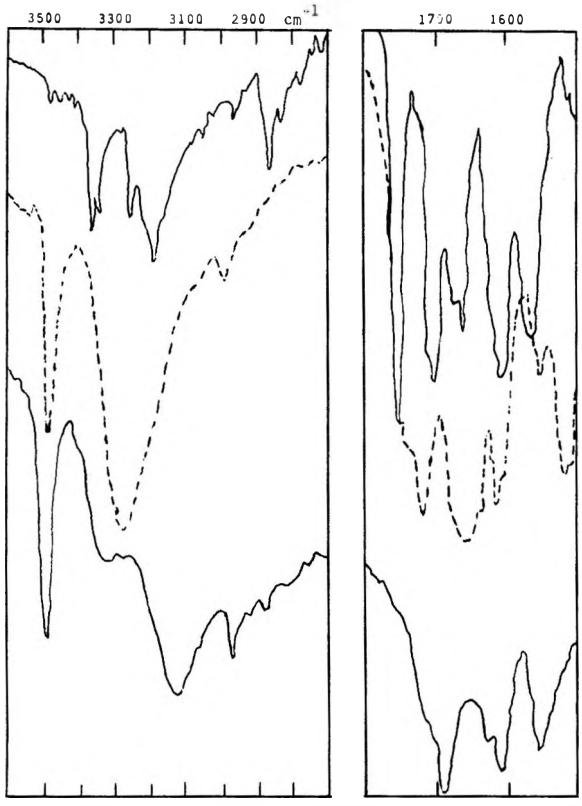
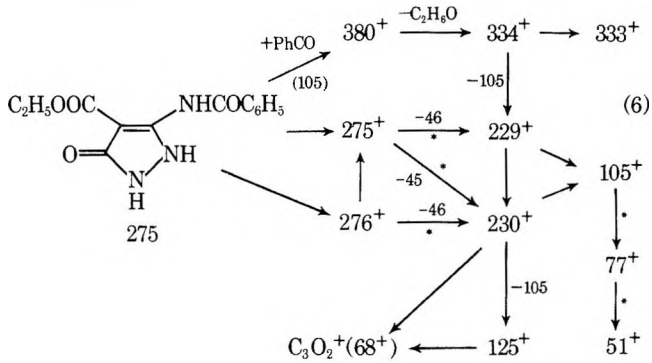


Figure 1. Infrared spectra of substituted pyrazoles (3-R′NH, 4-RCOO, 5-R″) and/or their tautomeric forms in potassium bromide pellets: lower curve, R′ = R″ = H, R = *i*-C_4H_9; middle curve, R′ = COPh, R = C_2H_5, R′ = H; upper curve, R′ = R″ = COPh, R = *n*-C_3H_7.

Table III. In the absence of a normal coordinate treatment (except for the parent pyrazole[9]) our vibrational assignments must be regarded as tentative. However, we were aided by previous work in which many of the band (group) assignments were made. This extensive experience will simply be cited here.[8-15]

In Figure 1 we show typical changes in the regions of carbonyl and no (3400–3600 cm^{-1}), intermolecular (3000–3400 cm^{-1}), and intramolecular (2000–3000 cm^{-1}) hydrogen-bonding absorptions. To begin with, the solids **3** are probably present as hydroxy tautomers, e.g., **3a**, in which inter- and intramolecular hydrogen bonds can be strong. Monoacylation, as in **4a**, appears to narrow bands in the 3300- and 2950-cm^{-1} regions and decrease the intensity of the latter substantially. Diacylation as in **6a** produces sharper but weaker peaks throughout.

Certain mass spectra of the series studied were of special interest. The solids **9** and **10** tended to crack: parent peaks were not observed. The parent ions of the mono- and diacylated solids (**4–7**) usually split along fairly conventional lines. Above the parent, however, was an array of ions carrying one or more "extra" protons or acyl groups, e.g., eq 6. It is not clear whether these ions arise from acid–base reactions in the heated probe or from the fragmentation of dimers in the source. Whatever their origin, it appears that *intermolecular* analogs of the *intramolecular* bonding pictured in **3a, 4a, 6a,** and **9a** are significant.



Several typical mass spectra are listed in the Experimental Section.

Experimental Section

1-Amino-1-hydrazino-2,2-dicarboxyalkylethenes (2) (Table 1). 1-Amino-1-trichloromethyl-2,2-dicarboxyalkylethene[1] (0.01 mol) in DMF (30 ml) was stirred as an 85% aqueous solution of hydrazine hydrate (1.5 ml) was slowly added. The mixture was stirred for 30 min more, heated briefly (3–5 min) to ca. 80°, treated with water (100 ml), and stored for ca. 12–24 hr at 0–5°. The white solid products were obtained by filtration and several recrystallizations from ethanol–water (1:1).

3-Amino-4-carboalkoxypyrazolinones (3). A stirred solution of **2** (0.1 mol) and hydrazine hydrate (20 ml) in DMF (200 ml) was heated at ca. 100° for 2 hr. Treatment of the cooled solution with ice water (100 ml) and evaporation yielded a solid which was washed with water and recrystallized from methanol. In an alternate preparation of **3**, compound **2** was quickly dissolved in refluxing phenetole (ca. 172°). Compound **3** began to separate immediately and was filtered from the cooled solution.

Mono- and Diacylated Derivatives (4–7) of 3. A solution of the pyrazolone **3** (0.01 mol) and benzoyl chloride (0.01 mol) in pyridine was stirred for 1 hr at ca. 70°. Evaporation of the solvent yielded a solid (**4**), which was washed with water and recrystallized from methanol. Acetyl chloride (0.01 mol) was added slowly to a solution of pyrazolone **3** (0.01 mol) in pyridine (20 ml). The mixture was stirred for ca. 1 hr more and then treated with ice water (ca. 50 ml). The viscous oil which separated crystallized at ca. −5°. It was decolorized with active carbon in and recrystallized from methanol or ethanol to give **5.**

The diacyl products were prepared by heating **3** (0.01 mol) and the appropriate acid chloride (0.02 mol) in pyridine (20 ml) at reflux for ca. 2 hr or until solution was complete. The cooled solution was treated with ice slush (100 g) and the solid (**6, 7**) which separated was recrystallized from ethanol or acetone.

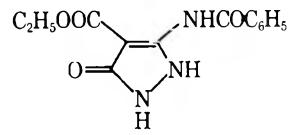
Urea and Urethane Derivatives of 3. A solution of **3** (0.01 mol) and phenyl isocyanate (0.01 mol) in pyridine (20 ml) was stirred for ca. 0.2 hr at ca. 25° and 0.5 hr at reflux. The cooled solution was treated with ice slush and the solid (**8**) which separated was recrystallized from ethanol. A solution of **3** (0.01 mol) and phenyl isocyanate (0.02 mol) in pyridine (15 ml) was heated at reflux for 1 hr. On evaporation under vacuum, the solution deposited a viscous oil which was stirred with water at ca. −5°. Treatment of this material with active carbon in ethanol and recrystallization gave white crystals of **9.**

***o*-Aminobenzoylations with Isatoic Anhydride.** Reactions of 4-carboethoxy derivatives of 3- and 5-aminopyrazole were carried out. A mixture of isatoic anhydride (1.63 g, 0.01 mol),[16] pyrazole (0.01 mol), and pyridine (20 ml) was stirred at ca. 100° for 4 hr. After the colored solution was cooled and evaporated, the residue was recrystallized from ethanol to yield (**10**).

Mass Spectra. A Varian MAT CH7 instrument operated at an ionizing energy of ca. 55 eV at 100 μA was used. A few sample spectra are recorded below. Probe temperatures, *m/e* (rel intensities) and metastable transitions m* are indicated. Below the double slash (//), peaks of low relative intensity and at an arbitrary cut-off (5–8%), as well as *m/e* 32, 29, 18, and 17, were omitted.

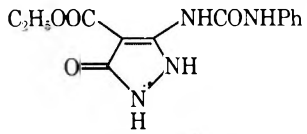
$C_{20}H_{17}O_5N_3$, 379; 160°

488 (1), 487 (3), 440 (1), 415 (1), 383 (16), 382 (68), 381 (85), //335 (27), 334 (53), 293* ± 1.5 (382, 381 → 335, 334), 276 (9), 230 (9), 229 (33), 138.5* (382, 381 → 230, 231) 107 (12), 106 (74), 105 (100), 104 (9), 83 (21), 78 (38), 77 (93), 76 (18), 68 (9), 67 (29), 56.6* ± 1 (105 → 77), 56 (5), 51 (56), 50 (10), 40 (5), 34* (77 → 51), 29.1* ± 0.6 (382, 381 → 106, 105), 29 (12)



$C_{13}H_{13}N_3O_4$, 275; 260°

382 (1), 381 (5), 380 (12), 334 (2), 333 (5), 293* (380 → 334), 276 (44), 275 (76), 230 (53), //229 (47), 191* ± 1 (275 → 230, 229), 125 (18), 106 (68), 105 (100), 103 (64), 78 (27), 77 (82), 76 (16), 69 (13), 68 (67), 56.5* (275 → 125, 105 → 77), 51 (38), 50 (15), 48* (230, 229 → 106, 105), 45 (8), 44 (22), 43 (10), 41 (13), 40.2* (275 → 105), 40 (20), 39 (80), 34* (77 → 51), 31 (13), 29 (35), 27 (24)



290; 240°

290 (1.2), 289 (0.5), 275 (0.8), 245 (0.8), 229 (1.2), 199 (0.5), //172 (10), 171 (90), 125 (42), 124 (100), 120 (16), 119 (95), 91.4* (171 → 125), 91 (71), 69.7* ± 0.5 (119 → 91), 68 (90), 65 (11), 64 (40), 63 (18), 58 (11), 51 (12), 50 (10), 45* (91 → 64), 41 (14), 40 (15), 39 (17), 38 (15), 37* (125 → 68), 27 (15)

Registry No.—**1** (R = Me), 22071-01-8; **1** (R = Et), 22071-11-0; **1** (R = Pr), 22071-02-9; **1** (R = Pr-*i*), 22071-03-0; **1** (R = Bu), 55254-75-6; **1** (R = Bu-*i*), 55254-76-7; **1** (R = Bu-*t*), 40764-67-8; **1** (R = Bu-*t*; R′ = Et), 51920-23-1; **3** (R = CH_3OOC), 52566-49-1; **3** (R = C_2H_5OOC), 52565-83-0; **3** (R = C_3H_7OOC), 55254-83-6; **3** (R = *i*-C_3H_7OOC), 55254-84-7; **3** (R = C_4H_9OOC), 55254-85-8; **3** (R = *i*-C_4H_9OOC), 55254-86-9; **3** (R = *t*-C_4H_9OOC), 55254-87-0; **4** (R = C_2H_5OOC), 52566-51-5; **4** (R = *n*-C_3H_7OOC), 55254-88-1; **4** (R = *i*-C_4H_9OOC), 55254-89-2; **5** (R = *n*-C_3H_7OOC), 55254-90-5; **5** (R = *i*-C_3H_7OOC), 55254-91-6; **5** (R = *i*-C_4H_9OOC), 55254-92-7; **6** (R = C_2H_5OOC), 55254-93-8; **6** (R = *n*-C_3H_7OOC), 55254-94-9; **6** (R = *i*-C_3H_7OOC), 55254-95-0; **6** (R = *i*-C_4H_9OOC), 55254-96-1; **7** (R = *n*-C_3H_7OOC), 55254-97-2; **7** (R = *i*-C_4H_9OOC), 55254-98-3; **8** (R = C_2H_5OOC), 55254-99-4; **8** (R = *n*-C_3H_7OOC), 55255-00-0; **8** (R = *i*-C_4H_9OOC), 55255-01-1; **9** (R = C_2H_5OOC), 55255-02-2; **9** (R = *n*-C_3H_7OOC), 55255-03-3; **9** (R = *i*-C_4H_9OOC), 55255-04-4; **10**, (R = Et), 55255-05-5; **10** (R = Bu-*i*), 55255-06-6; hydrazine hydrate, 10217-52-4; benzoyl chloride, 98-88-4; acetyl chloride, 75-36-5; phenyl isocyanate, 103-72-0; isatoic anhydride, 118-48-9.

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(16) Gift of Sherwin Williams Chemicals.

Dye-Sensitized Photooxygenation of *tert*-Butylpyrroles

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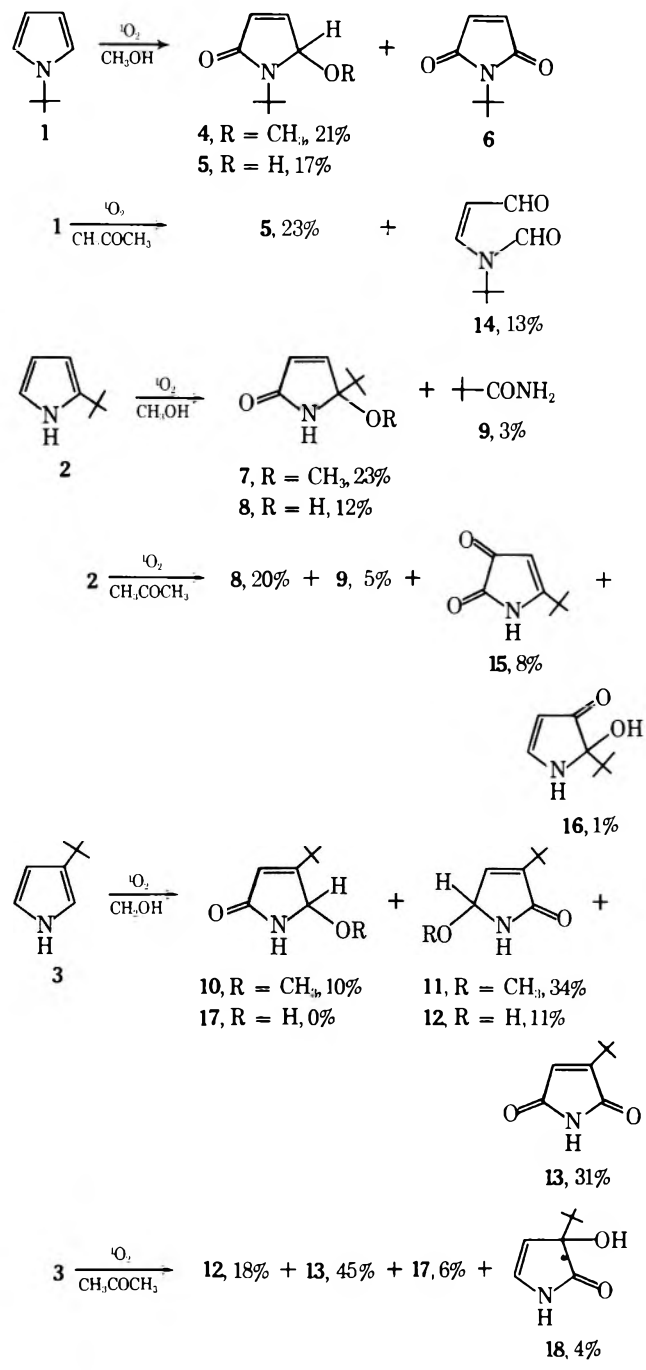
The isomeric 1,2 and 3-mono-*tert*-butylpyrroles were photooxygenated in methanol and acetone solvents using Rose Bengal and Methylene Blue singlet oxygen sensitizers. Their rates of photooxygenation are comparable to that of 2,5-dimethylfuran in methanol, but slower in acetone. Fifteen different photooxygenation products from both methanol and acetone solvents have been isolated, and their structures have been determined by spectroscopic methods. They include the expected 5-methoxy- and 5-hydroxylactams, 3-hydroxylactams, imides, pivalamide, and an unusual yellow keto lactam. The intermediate endo peroxides have been prepared at −78° and identified by low-temperature NMR.

The dye-sensitized photooxygenation of pyrroles has been the subject of recent extensive investigations,[1] especially in connection with a phototherapy method for treating neonatal jaundice due to an excess of the tetrapyrrole, bilirubin.[1,2,3] However, the first photochemical oxidation of pyrrole was reported by Ciamician and Silber in 1912:[4] photoautoxidation of pyrrole in water gave succinimide along with two unidentified crystalline compounds and a black resin. Subsequent investigations were reported by Bernheim and Morgan,[5] who found that eosin or Methylene Blue sensitized irradiation of pyrrole in water, acetone, or alcohol gave a 58% yield of an unidentified crystalline product, $C_4H_5NO_2$, mp 102.5°; and Linnel and Umar,[6] who postulated a reactive, polymerizable pyrrole endo peroxide. De Mayo and Reid[7] were the first to prove the 5-hydroxylactam structures of the products from eosin-sensitized aqueous photooxygenation of pyrrole and *N*-methylpyrrole. They accounted for their isolated photoproducts by proposing the intermediacy of an unstable endo peroxide formed by reaction of the pyrrole with singlet oxygen[8,9] [$^1O_2$] analogous to the photooxygenation of furans.[10,11] Pyrrole photooxygenations were later extended to alkylpyrroles by Lightner et al.,[1,12] and the photooxygenation of phenyl-substituted pyrroles received extensive and pioneering attention by Wasserman et al.[1,13] and Dufraisse, Rio et al.[1,14] The only reported photooxygenation study on *tert*-butylpyrroles is that of Ramasseul and Rassat,[15] who isolated hydroperoxides from 2,5-di-*tert*-butylpyrrole and 2,3,5-tri-*tert*-butylpyrrole as well as other products whose structures are reminiscent of those from 2,3,4,5-tetraphen-

Chart I



ylpyrrole.[13,16] The photooxygenation of mono-*tert*-butylpyrroles gives different products from those discussed above and are more akin to photoproducts from methyl- and ethyl-substituted pyrroles.[1]

Results

The dye-sensitized photooxygenations of 1-, 2- and 3-*tert*-butylpyrrole (**1**, **2**, and **3**) were examined in anhydrous methanol with Rose Bengal sensitizer and in anhydrous acetone with Methylene Blue sensitizer. The photoproducts (see Chart I) were isolated by column and thin layer chromatography and were characterized by a combination of spectroscopic techniques. The expected[17,18] 5-hydroxylactams (**5**, **8**, **12**) were obtained from photooxygenation in both methanol and acetone. 5-Methoxylactams (**4**, **7**, **10**, **11**) were obtained from methanol. Surprisingly high yields of 3-*tert*-butylmaleimide were found in either solvent. Unexpected new compounds including a yellow keto amide (**15**), ketol (**16**), and pivalamide (**9**) were obtained from 2-*tert*-butylpyrrole in acetone.

Table I
Reaction Rate of *tert*-Butylpyrroles with Singlet Oxygen[a]

Acceptor	CH_3OH, Rose Bengal		CH_3COCH_3, Methylene Blue	
	k_A, M^{-1} sec^{-1} ($\times 10^{-8}$)	β, M^b ($\times 10^3$)	k_A, M^{-1} sec^{-1} ($\times 10^{-8}$)	β, M^b ($\times 10^3$)
	1.2	0.12	0.39	0.97
	1.5	0.93	0.42	0.90
	1.8	0.78	0.30	1.3
	1.4	1.0	2.1	0.18

[a] In CH_3OH, $k_d = 1.4 \times 10^5$ sec^{-1}; in CH_3COCH_3, $k_d = 3.8 \times 10^4$ sec^{-1}; ref 19. [b] Ratio of the $^1O_2$ decay rate to the reaction rate. [c] CH_3OH values from ref 9.

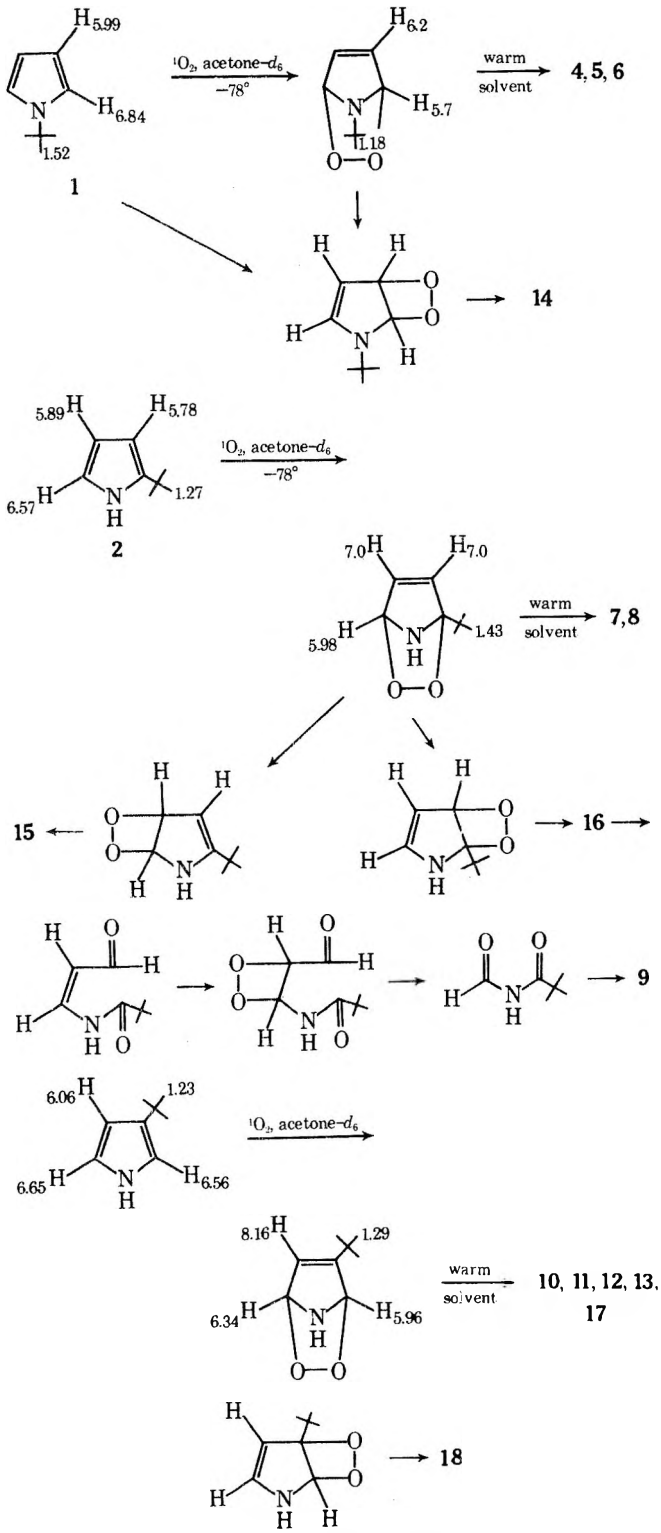
The rates of photooxygenation in methanol of the isomeric *tert*-butylpyrroles are nearly identical with each other and with that of 2,5-dimethylfuran,[9] $k_A = 1.4 \times 10^8$ M^{-1} sec^{-1}, as shown in Table I. However, the rates for the *tert*-butylpyrroles in acetone are all roughly an order of magnitude slower than that of 2,5-dimethylfuran, whose reaction rate with $^1O_2$ is slightly greater in acetone ($k_A = 2.1 \times 10^8$ M^{-1} sec^{-1}) than in methanol. Since the lifetime of $^1O_2$ is longer in acetone than in methanol,[19] the pyrrole results are surprising when contrasted to the furan behavior and are as yet unexplained.

Discussion

The origin of the majority of the photooxygenation products of the isomeric *tert*-butylpyrroles (**1**–**3**) can be explained by ground-state reactions of unstable endo peroxides which are formed from 1,4 addition of $^1O_2$ to the pyrrole diene system.[6,7,12] Such a mechanism is entirely analogous to that proposed in the dye-sensitized photooxygenations of furans[10,11,20] and other pyrroles,[1,7,12-18] and it readily explains the origin of the typical 2-oxo-5-alkoxy or hydroxy products. Although evidence for the formation of furan endo peroxides has been marshalled by Kane and Foote[20] in their nuclear magnetic resonance (NMR) studies at low temperatures, there have been no similar observations of pyrrole endo peroxides reported except very recently for that of *N*-phenylpyrrole.[21] In the present work we have observed the formation of the *tert*-butylpyrrole endo peroxides by NMR at −80° following dye-sensitized photooxygenation of **1**, **2**, and **3** at −78° in acetone-d_6 or Freon-11[22] (Chart II). We have also observed (NMR) their transformation upon warming to the more stable isolated photoproducts. The reactivity of the endo peroxides in methanol-*O*-*d* was too rapid at −78° to allow for their detection by NMR.

We therefore suggest that methoxylactams **4**, **7**, **10**, and **11** arise by methanolysis of their respective precursor pyrrole endo peroxides and that hydroxylactams **5**, **8**, **12**, and **17** originate either by an internal rearrangement or by adventitious hydrolysis of the same endo peroxides. Methanolysis is a well-established decomposition mechanism for furan endo peroxides[10,11,23,24] and has also been invoked frequently to explain the formation of 5-methoxylactams

Chart II



during pyrrole photooxygenation.[1,12,17,18] Too, we have established in control experiments that the methoxylactams are not formed from other photoproducts, viz., hydroxylactams, under the reaction and work-up conditions. Just how 5-hydroxylactams originate in anhydrous organic solvents, except by internal reorganization, is not clear. In a related work[25] using $H_2{}^{18}O$, the corresponding methylpyrroles were found to give hydroxylactams in methanol or acetone largely by rearrangement of the endo peroxides, and this route was still important even in water solvent. Whether the rearrangement mechanism involves sensitizer or oxygen in an H-abstraction step or whether it is entirely unimolecular has not been ascertained.

The mechanistic origin of isomeric 3-hydroxylactams (**16** and **18**) is less obvious, but they, plus **14** and **15**, might be viewed as deriving from unstable dioxetane intermediates. Whether such dioxetanes are formed directly by 1,2 addition to the pyrroles or, alternatively, by rearrangement of endo peroxides or peroxiranes[26,27] is not easy to determine. We can provide no direct evidence for either dioxetane or peroxirane precursors to the cited photoproducts, but a careful NMR examination of the *tert*-butylpyrrole photooxygenations at −78° reveals that only endo peroxides and very little else are formed in acetone-d_6 of Freon-11. Since it appears unlikely that 1,2 addition of $^1O_2$ is significant at −78°, but products from apparent 1,2 addition are observed upon warming, rearrangement of an endo peroxide to a dioxetane is presumed. In support of this, it should be noted that products presumably derived from dioxetanes generally occur in a solvent (acetone) where the endo peroxide is relatively (to methanol) long lived (cf. low-temperature NMR discussion), and apparently has time to rearrange to some extent to other reactive intermediates, e.g., dioxetanes or peroxiranes.

The ring-opened product (**14**) is a characteristic type of dioxetane cleavage product[28] which has also been found in the photooxygenation of 3,4-diethyl-2,5-dimethylpyrrole.[29] Further addition (1,2) of $^1O_2$ to the enamine-like carbon–carbon double bond[28] of **14** with subsequent cleavage of the dioxetane and hydrolysis might explain the formation of pivalamide (**9**) (Chart II). While it is clear that both **9** and **14** are just the types one expects from thermal reaction of dioxetanes[26] derived from enamines,[28,29] the origin of **15** is less obvious. Its unusual α-keto amide structure is unlike that of any pyrrole photooxidation product identified previously,[1] and we can offer no reasonable explanation for its formation other than by oxidation (H· loss or abstraction) of a precursor dioxetane (Chart II) or by oxidation of the as yet not isolated 5-*tert*-butyl-3-hydroxy-Δ^4-pyrrolin-2-one.

An isomer (**18**) of the latter has been isolated in this work, and there is ample precedent for expecting a product of this type from a 3-substituted pyrrole.[30-32] On the other hand, the 2-hydroxy-3-oxo structure of **16** is an unreported photooxygenation structure type which we have observed only once previously, with 2,3,5-trimethylpyrrole.[33] However, whether either structure type is derived from an unstable dioxetane precursor is unclear, for α-hydroxy carbonyl compounds are usually not found among the typical dioxetane decomposition structures, cf. **14**. Rather, such structures are more akin to those derived apparently from peroxiranes.[26] In either case, as noted earlier, we have found no direct evidence for dioxetane or peroxirane intermediates and speculate that should they be involved they might likely be formed from observable (NMR) endo peroxides.

The formation of maleimides, e.g., **6** and **13**, has been observed occasionally in pyrrole photooxygenations,[12,18,28-30,34] and especially in cases in which the pyrrole β positions were substituted with one or two alkyl groups. We believe that the failure to isolate maleimides from other alkylpyrroles may be due in part to the reactivity of the unsubstituted maleimide toward $^1O_2$, or its sensitivity to pH during the photooxygenation. For example, we have isolated maleimide in up to 8% yield under favorable conditions in the photooxygenation of pyrrole in methanol, but it has also been shown to undergo photooxygenation under the reaction conditions.[35] However, when a trace of ammonia is present during the photooxygenation, we can no longer isolate maleimide. Maleimides **6** and **13** may be viewed as arising from endo peroxides (Chart II) by H· loss or H· abstraction by sensitizer or oxygen.

Summary

Direct NMR evidence for endo peroxide intermediates in the photooxygenation of 1-, 2-, and 3-*tert*-butylpyrroles (1–3) has been provided. The rate of photooxygenation is faster in methanol by roughly an order of magnitude over acetone solvent. From the differing product distribution and structures, the NMR study, and the observation that the endo peroxides are longer lived in acetone than in methanol, we believe that pyrrole endo peroxides may rearrange to dioxetanes or peroxiranes when given sufficient time, and these may rearrange to a different set of products than those derived directly from endo peroxides.

Experimental Section

General. Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Nuclear magnetic resonance spectra were determined in $CDCl_3$ solution, unless otherwise specified, on Varian EM-360, XL-100, or a Jeolco 4H-100 spectrometers; chemical shift data are reported in parts per million downfield from internal tetramethylsilane (δ scale). Mass spectra were measured on a Varian MAT 311 or AEI MS-9 mass spectrometer. Infrared spectra were run on a Perkin-Elmer Model 457 spectrometer. Gas–liquid chromatography (GLC) was performed on a Varian Aerograph Model 1200 chromatograph with flame ionization detector, using a 6 ft × 0.125 in. aluminum 5% SE-30 on AWS Chromosorb W column with nitrogen as the carrier gas. The silica gel used for column chromatography is from M. Woelm, Eschwege 70–325 mesh ASTM and for thin layer chromatography is silica gel F, M. Woelm Eschwege. The preparative thin layer chromatography plates were 1 mm thick in adsorbent, whereas the analytical plates were 0.125 mm thin.

The methanol and acetone used were Baker Analyzed anhydrous reagent grade solvents. Pyrrole and 2,5-dimethoxytetrahydrofuran were obtained from Aldrich. Hexane-2,5-dione and Rose Bengal were obtained from Matheson, and Methylene Blue was obtained from Allied Chemical.

Synthesis of *N*-*tert*-Butylpyrrole (1). The pyrrole was prepared by the method of Josey[36] by using 2,5-dimethoxytetrahydrofuran and substituting *tert*-butylamine for methyl anthranilate. The yield of distilled product was 35%, bp 68° (30 Torr) [lit.[37] bp 74–79° (42 Torr)], as a colorless liquid which was greater than 99% pure by GLC: NMR δ 1.52 (s, 9 H, CH_3), 6.06 (m, 2 H, C=CHCH=C), 6.73 ppm (m, 2 H, C=CHN).

Synthesis of 2- and 3-*tert*-Butylpyrrole (2 and 3). These pyrroles were prepared by the method of Skell and Bean[38] and using pyrrole Grignard and *tert*-butyl chloride. The pyrroles were separated by repeated distillation through a spinning band column under partial vacuum to yield 2-*tert*-butylpyrrole, bp 78° (20 Torr), mp 44–46° [lit.[38] bp 89° (30 Torr)], and 3-*tert*-butylpyrrole, bp 93° (30 Torr) [lit.[38] bp 94° (30 Torr)]. The purity of each compound was greater than 99% by GLC. 2-*tert*-Butylpyrrole: NMR δ 1.27 (s, 9 H, $-CH_3$), 5.87 (m, 1 H, =CH), 6.03 (m, 1 H, =CH), 6.65 (m, 1 H, =CH). 3-*tert*-Butylpyrrole: NMR δ 1.27 (s, 9 H, $-CH_3$), 6.13 (m, 1 H, =CH), 6.50 (m, 1 H, =CH), 6.61 (m, 1 H, =CH).

Synthesis of 2,5-Dimethylfuran. The furan was prepared from hexane-2,5-dione by the method of Scott and Naples[39] except using Dowex 50W-X8 instead of Amberlyst 15.

Photooxidation of *N*-*tert*-Butylpyrrole in Methanol. In a large water-cooled photocell[11,20] were placed 450 ml of anhydrous methanol, 16 mg of Rose Bengal, and 1.00 g (8.14 mmol) of *N*-*tert*-butylpyrrole. Oxygen was circulated in a closed system. The solution was irradiated using a 500-W Sylvania (N. Q/CL 500) tungsten–halogen quartz lamp operated at 80 V. The progress of the reaction was monitored by measuring the oxygen uptake. The reaction was complete within 22 min, during which ca. 100% equivalent of O_2 ($t_{1/2}$ = 11 min) was consumed. The solvent was removed at 40–50° using a rotary evaporator to yield 1.37 g of crude photoproducts. The crude mixture was partially separated by column chromatography on silica gel (2.3 × 45 cm) using ethyl acetate (500 ml). Further purification by preparative thin layer chromatography on silica gel (ethyl acetate or chloroform) gave the following products.

5-Hydroxy-*N*-*tert*-butyl-Δ^3-pyrrolin-2-one (5): R_f 0.45 (ethyl acetate); 218 mg, 17% isolated yield; mp 75–76°; NMR δ 1.50 (s, 9 H, $-CH_3$), 3.70 (br s, 1 H, –OH), 5.60 (s, 1 H, CH—O), 5.98 (d, 1 H, J = 6 Hz, CHC=O), 6.88 (dd, 1 H, J = 6 and 2 Hz, O=C–CuCH); mass spectrum *m/e* (rel intensity) 155 (M^+, 45), 140 (M – CH_3, 62), 57 (C_4H_9, 100); ir ($CHCl_3$) ν 3350, 1688, 1610 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO_2$: mol wt, 155.09462. Found: 155.09310.

5-Methoxy-*N*-*tert*-butyl-Δ^3-pyrrolin-2-one (4): R_f 0.58 (ethyl acetate); 281 mg, 21% isolated yield; brown oil; NMR δ 1.42 (s, 9 H, $-CH_3$), 3.13 (s, 3 H, OCH_3), 5.58 (s, 1 H, CHO), 6.12 (d, 1 H, J = 6 Hz, CHC=O), 6.79 (dd, 1 H, J = 6 and 2 Hz, O=C–C=CH); mass spectrum *m/e* (rel intensity) 169 (M^+, 6), 153 (M – CH_4, 100), 138 (M – OCH_3, 60%); ir ($CHCl_3$) ν 1690, 1615 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO_2$: mol wt, 169.11027. Found: 169.11051.

***N*-*tert*-Butylmaleimide (6):** R_f 0.63 (chloroform); 60 mg, 5% isolated yield; oil; NMR δ 1.58 (s, 9 H, CH_3), 6.58 (s, 2 H, C=CH); mass spectrum *m/e* (rel intensity) 153 (M^+, 1), 138 (M – CH_3, 100), 57 (C_4H_9, 12); ir ($CHCl_3$) ν 1710 cm^{-1}.

Anal. Calcd for $C_8H_{11}NO_2$: mol wt, 153.0789. Found: 153.0787.

Photooxidation of *N*-*tert*-Butylpyrrole in Acetone. The reaction was carried out essentially as described for *N*-*tert*-butylpyrrole in methanol using 37 mg of Methylene Blue and 1.00 g (8.15 mmol) of *N*-*tert*-butylpyrrole, except that an operating voltage of 100 V was used. After 130 min, 8.15 mmol of O_2 was consumed ($t_{1/2}$ = 47 min). The solvent was removed at 30–40° using a rotary evaporator to yield 1.49 g of crude photoproducts. The crude mixture was partially separated by column chromatography on silica gel (2.3 × 45 cm) using ethyl acetate eluent (300 ml), and further purified by preparative thin layer chromatography silica gel (ether) to give the following photoproducts.

5-Hydroxy-*N*-*tert*-butyl-Δ^3-pyrrolin-2-one (5): R_f 0.38 (ether); 290 mg, 23%, isolated yield; NMR and ir matched those of the authentic sample.

β-(*N*-*tert*-butylformamido)acrolein (14): R_f 0.46 (ether); 160 mg, 13% isolated yield; mp 59–62°; NMR δ 1.57 (s, 9 H, $-CH_3$), 6.50 (dd, 1 H, J = 7 and 4 Hz, CHC=O), 7.39 (d, 1 H, J = 7 Hz, CHN), 8.70 (s, 1 H, NCHO), 9.33 (d, 1 H, J = 4 Hz, CCHO); mass spectrum *m/e* (rel intensity) 155 (M^+, 8), 126 (M – CHO, 62); 98 (M – C_4H_9, 17); ir ($CHCl_3$) ν 1695, 1678, 1618 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO_2$: mol wt, 155.09462. Found: 155.0946.

Photooxidation of 2-*tert*-Butylpyrrole in Methanol. The photooxidation was carried out in the same manner as for *N*-*tert*-butylpyrrole using 1.00 g (8.15 mmol) of 2-*tert*-butylpyrrole and 18 mg of Rose Bengal in 450 of methanol. The reaction was complete within 50 min taking up 10 mmol of oxygen ($t_{1/2}$ = 9 min). Evaporation of the solvent resulted in 1.50 g of crude photoproducts. The crude mixture was partially separated by silica gel column chromatography and further purified by preparative thin layer chromatography on silica gel to give the following photoproducts.

5-Hydroxy-5-*tert*-butyl-Δ^3-pyrrolin-2-one (8): R_f 0.32 [$CHCl_3$–MeOH (9:1)]; 132 mg, 12%; mp 195–197° dec [sublimed at 95° (0.01 Torr)]; NMR (Me_2SO-d_6) δ 0.96 (s, 9 H, $-CH_3$), 5.70 (br s, 1 H, OH), 5.94 (d, 1 H, J = 6 Hz, CHC=O), 7.05 (d, 1 H, J = 6 Hz, CH=C–C=O), 8.14 (br s, 1 H, NH); mass spectrum *m/e* (rel intensity) 155 (M^+, 1), 98 (M – C_4H_9, 84), 57 (C_4H_9, 100); ir (KBr) ν 3210, 1710, 1590 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO_2$: mol wt, 155.09462. Found: 155.0946.

5-Methoxy-5-*tert*-butyl-Δ^3-pyrrolin-2-one (7): R_f 0.58 [$CHCl_3$–MeOH (9:1)]; 557 mg, 23%; mp 126–129° dec [sublimed at 78° (0.02 Torr)]; NMR δ 1.01 (s, 9 H, $-CH_3$), 3.10 (s, 3 H, OCH_3), 6.15 (d, 1 H, J = 6 Hz, CHC=O), 6.80 (d, 1 H, J = 6 Hz, CH=C–C=O), 7.69 (br s, 1 H, NH); mass spectrum *m/e* (rel intensity) 169 (M^+, 1), 112 (M – C_4H_9, 42), 57 (C_4H_9, 100); ir (KBr) ν 3200, 3080, 1688 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO_2$: mol wt, 169.11027. Found: 169.10882.

Pivalamide (9): R_f 0.33 (ethyl acetate); 27 mg, 3%; mp 156–156.5° (lit.[40] mp 155–156°), white leaflet crystal [sublimed at 90° (0.02 Torr)]; NMR δ 1.23 (s, 9 H, $-CH_3$), 5.58 (br s, 2 H, NH); ir ($CHCl_3$) ν 3550, 3430, 1760 cm^{-1}; mass spectrum *m/e* (rel intensity) 101 (M^+, 6), 57 (C_4H_9, 100).

Photooxidation of 2-*tert*-Butylpyrrole in Acetone. The photooxidation was carried out similarly to that of *N*-*tert*-butylpyrrole, using 1.00 g (8.15 mmol) of 2-*tert*-butylpyrrole and 35 mg of Methylene Blue in 450 ml of anhydrous acetone. The reaction was complete within 120 min, taking up 10 mmol of O_2 ($t_{1/2}$ = 38 min). Evaporation of solvent resulted in 1.49 g of crude photoproducts. The crude photoproducts were separated and purified as for *N*-*tert*-butylpyrrole. The following photoproducts were identified.

5-*tert*-Butyl-Δ^4-pyrroline-2,3-dione (15): R_f 0.42 [$CHCl_3$–ether (1:1)]; 101 mg, 8%; orange solid, mp 110–135° [sublimed at 78° (0.03 Torr)]; NMR δ 1.30 (s, 9 H, *t*-Bu), 5.21 (d, 1 H, OHC=C, J = 2 Hz); mass spectrum *m/e* (rel intensity) 153 (M^+, 43), 110 (40), 67 (100), 57 (C_4H_9, 35); ir (KBr) ν 1768, 1750 (sh), 1718, 1695 cm^{-1} (sh).

Anal. Calcd for $C_8H_{11}NO_2$: mol wt, 153.07897. Found: 153.0789.

2-Hydroxy-2-*tert*-Butyl-Δ^4-pyrrolin-3-one (16): R_f 0.68 [$CHCl_3$–MeOH (9:1)]; 15 mg, 1%; mp 157–159° dec; NMR (Me_2SO-d_6) δ 0.82 (s, 9 H, *t*-Bu), 6.05 (d, 1 H, CHC=O, J = 6 Hz), 7.10 (d, 1 H, CH=C–C=O, J = 6 Hz), 8.36 (br s, 1 H, NH); mass spectrum *m/e* (rel intensity) 155 (M^+, 6), 138 (M − OH, 33), 98 (M − C_4H_9, 100), 57 (C_4H_9, 46); ir (KBr) ν 3345, 3090, 3210, 1685 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO_2$: mol wt, 155.09462. Found: 155.0946.

5-Hydroxy-5-*tert*-butyl-Δ^3-pyrrolin-2-one (8): R_f 0.35 [$CHCl_3$–MeOH (9:1)]; 249 mg, 20%; mp 195–197° [sublimed at 95° (1.01 Torr)]; ir and NMR matched those of authentic sample.

Pivalamide (9): R_f 0.33 (ethyl acetate); 39 mg, 5%; mp 156–156.5°; ir and NMR matched those of the authentic sample.

Photooxidation of 3-*tert*-Butylpyrrole in Methanol. The photooxidation was carried out as described for *N*-*tert*-butylpyrrole in methanol using 0.997 g (8.15 mmol) of 3-*tert*-butylpyrrole, 17 mg of Rose Bengal in 450 ml of anhydrous methanol. The reaction was completed within 14 min consuming 9.16 mmol of O_2 ($t_{1/2}$ = 7.5 min). Evaporation of the solvent gave 1.44 g of crude photoproducts. The crude mixture was separated and purified as for *N*-*tert*-butylpyrrole, and the following photoproducts were identified.

5-Hydroxy-3-*tert*-butyl-Δ^3-pyrrolin-2-one (12): R_f 0.59 [$CHCl_3$–MeOH (9.1)]; 136 mg, 11%; oil; NMR δ 1.23 (s, 9 H, $-CH_3$), 4.61 (br s, 1 H, –OH), 5.53 (br s, 1 H, CHO), 6.56 (m, 1 H, CH=C–C=O), 7.52 (br s, 1 H, NH); mass spectrum *m/e* (rel intensity) 154 (M − 1, 3), 83 (100), 85 (65); ir (KBr) ν 3220, 1680 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO_2$: mol wt, 155.09462. Found: 155.0946.

5-Methoxy-3-*tert*-butyl-Δ^3-pyrrolin-2-one (11): R_f 0.59 (ether); 464 mg, 34%; mp 98–99°; NMR δ 1.28 (s, 9 H, $-CH_3$), 3.32 (s, 3 H, OCH_3), 5.32 (m, 1 H, CHO), 6.47 (m, 1 H, CH=C–C=O), 7.46 (br s, 1 H, NH); mass spectrum *m/e* (rel intensity) 169 (M^+, 38), 152 (M − CH_3, 100), 138 (M − OCH_3, 74); ir (KBr) ν 1708, 1675 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO_2$: mol wt, 169.11027. Found: 169.10713.

5-Methoxy-4-*tert*-butyl-Δ^3-pyrrolin-2-one (10): R_f 0.72 [$CHCl_3$–MeOH (9:1)]; 137 mg, 10%; oil; NMR δ 1.24 (s, 9 H, $-CH_3$), 3.35 (s, 3 H, OCH_3), 5.51 (m, 1 H, CHO), 5.89 (m, 1 H, CHC=O), 8.09 (br s, 1 H, NH); mass spectrum *m/e* (rel intensity) 169 (M^+, 1), 137 (M − OCH_3, 77), 112 (M − C_4H_9, 100); ir (KBr) ν 1708 cm^{-1}.

Anal. Calcd for $C_9H_{15}NO_2$: mol wt, 169.11027. Found: 169.10713.

3-*tert*-Butylmaleimide (13). R_f 0.87 (ether); 386 mg, 31%; mp 153–154°; NMR δ 1.32 (s, 9 H, $-CH_3$), 6.22 (m, 1 H, CHC=O); mass spectrum *m/e* (rel intensity) 153 (M^+, 3), 95 (M − C_4H_9, 47), 67 (100); ir (KBr) ν 1765, 1715 cm^{-1}.

Anal. Calcd for $C_8H_{11}NO_2$: mol wt. 153.07897. Found: 153.07873.

Photooxidation of 3-*tert*-Butylpyrrole in Acetone. The photooxidation was carried out similarly to that of *N*-*tert*-butylpyrrole using 1.001 g (8.15 mmol) of 3-*tert*-butylpyrrole and 36 mg of Methylene Blue in 450 ml of anhydrous acetone. The reaction was complete within 100 min consuming 10.9 mmol of oxygen ($t_{1/2}$ = 30 min). Evaporation of solvent resulted in 1.604 g of crude photoproducts. The crude mixture was separated and purified as the same manner as *N*-*tert*-butylpyrrole. The following photoproducts were identified.

5-Hydroxy-3-*tert*-butyl-Δ^3-pyrrolin-2-one (12): R_f 0.29 (ether); 223 mg, 18%; oil; ir, NMR and mass spectrum those of matched authentic sample.

5-Hydroxy-4-*tert*-butyl-Δ^3-pyrrolin-2-one (17): R_f 0.14 (ether); 72 mg, 6%; mp 184.5–185.5° (recrystallized from acetone–chloroform); NMR (acetone-d_6) 1.25 (s, 9 H, $-CH_3$), 5.66 (br, 2 H, CH=C–CO, CHO overlap), 2.87 (br, 1 H, OH), 7.20 (br, 1 H, NH); mass spectrum *m/e* (rel intensity) 155 (M^+, 14), 138 (M − OH, 9), 99 (M − C_4H_8, 100), 57 (C_4H_9, 76); ir (KBr) ν 3250, 1690 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO_2$: mol wt, 155.09462. Found: 155.0944.

3-Hydroxy-3-*tert*-butyl-Δ^4-pyrrolin-2-one (18): R_f 0.40 (ether); 53 mg, 4%; oily solid; NMR δ 1.24 (s, 9 H, *t*-Bu), 5.90 (d, 1 H, CH=CN, J = 2 Hz), 6.33 (d, 1 H, C=CHN, J = 2 Hz); mass spectrum *m/e* (rel intensity) 155 (M^+, 37), 138 (M − OH, 88), 99 (M − C_4H_8, 78), 67 (100), 57 (C_4H_9, 65); ir (KBr) ν 3250, 1700 cm^{-1}.

Anal. Calcd for $C_8H_{13}NO_2$: mol wt, 155.09462. Found: 155.0946.

3-*tert*-Butylmaleimide (13): R_f 0.87 (ether); 593 mg, 43%; mp 153–154°; ir, NMR, and mass spectrum matched those of the authentic sample.

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Selective Hydrogenation of Quinoline and Its Homologs, Isoquinoline, and Phenyl-Substituted Pyridines in the Benzene Ring

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Hydrogenation of quinoline, its 2-, 3-, 6-, and 8-methyl and 2-isopropyl homologs, isoquinoline, acridine, benzo[*h*]quinoline, 2-phenylpyridine, 4-phenylpyridine, and 4-(3-phenylpropyl)pyridine over platinum oxide (and, in some instances, palladium or rhodium on charcoal) in strong acid (12 *N* HCl, 12 *N* H_2SO_4, CF_3COOH) leads to selective hydrogenation of the benzene ring. The fastest procedure is one employing PtO_2 in trifluoroacetic acid.

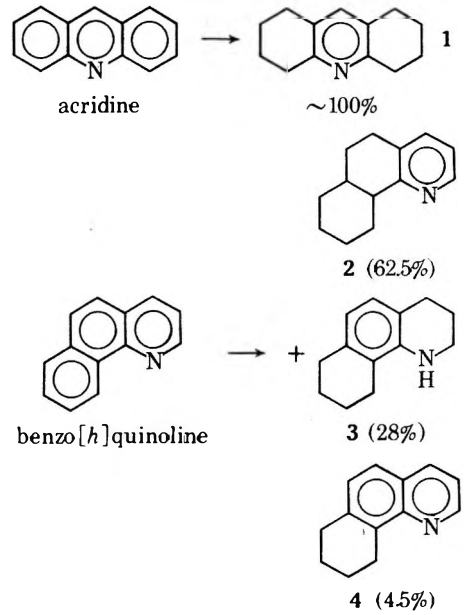
It is well documented[1-4] that catalytic hydrogenation of pyridines bearing phenyl substituents (either on or away from the pyridine rings) and of quinolines and isoquinolines and their homologs occurs preferentially in the pyridine ring. Thus hydrogenation of 4-benzylpyridine over rhodium on carbon gives 4-benzylpiperidine almost exclusively.[5,6] Hydrogenation of quinoline or isoquinoline over platinum oxide in acetic acid at room temperature and 50 psi initially gives the 1,2,3,4-tetrahydro products (benzpiperidines) in high yields.[8-10] Further reduction to the decahydro stage appears to be facilitated by the addition of mineral acid,[10] under which conditions the major product is the cis isomer[10,11] whereas in the absence of mineral acid the trans isomer is reported to predominate in the formation of decahydroquinoline.[6,10,11] *trans*-Decahydroquinoline is thus obtained in 62% yield by hydrogenation of quinoline over Raney Ni at 210° and 1000 psi[12] and isoquinoline is similarly hydrogenated to *trans*-decahydroisoquinoline in 80% yield over platinum.[13] A mixture of decahydroquinolines containing 90% of the trans isomer (along with tetrahydroquinoline and starting material) is reported[11] to be formed by hydrogenating quinoline acid oxalate in water at 40° and 30–45 psi over colloidal platinum; trans-rich decahydroquinoline mixtures also result[6,11] from similar hydrogenation of quinoline in acetic acid. In general, however, the synthesis of trans-fused decahydroquinolines and -isoquinolines is difficult.

Preparations of cyclohexylpyridines by catalytic hydrogenation do not appear to be on record and 5,6,7,8-tetrahydroquinolines[14] and -isoquinolines[10] were generally prepared by tedious, indirect methods, such as dehydrogenation of the corresponding decahydro compounds over hot platinum or palladium.[10,14] Only a few special cases of hydrogenation of quinolines to 5,6,7,8-tetrahydroquinolines have been reported;[16,17] these include the hydrogenation of certain alkylquinolines.[17] Bulky substituents in the 2, 3, and 4 positions evidently inhibit hydrogenation of the pyridine moiety and cause the reduction products to be mixtures of 5,6,7,8- and 1,2,3,4-tetrahydroquinolines.

It is clear that a method involving clean hydrogenation of the benzene ring in phenyl- and benzpyridines would be valuable not only in its own right, but also because reduction of 5,6,7,8-tetrahydroquinolines with sodium and ethanol[17,18] is a convenient route to the corresponding trans-decahydro compounds which constitute part of the carbon skeleton of many alkaloids. Such a method is reported here.

Booth and Bostock[19] recently hydrogenated quinoline to *cis*-decahydroquinoline with platinum in 12 *N* hydrochloric acid. Interruption of this very slow reduction when 2 mol of hydrogen had been adsorbed has now revealed that the major product (70%) at this stage is 5,6,7,8-tetrahydroquinoline. The optimized reduction procedure is described in the Experimental Section and the results for various substituted quinolines and isoquinolines are shown in Table I. Since reaction times were rather long (30–130 hr, the longer times applying to quinolines substituted in the benzene ring), other acids were substituted for HCl. Sulfuric acid (Table I) allowed reduction of quinoline to proceed in 4.5 hr but by far the best solvent proved to be trifluoroacetic acid, in which hydrogenation of the benzene ring was complete in 45–90 min (Table II). In this solvent, rhodium and palladium catalysts also yielded 5,6,7,8-tetrahydroquinoline from quinoline (Table II). Acridine was cleanly hydrogenated in both benzene rings, the pyridine ring being preserved; the same was true for benzo[*h*]quinoline, although the reduction proceeded less cleanly, the tetrasubstituted central benzene ring resisting hydrogenation (Scheme I). Both 2- and 4-phenylpyridine and 4-(3-phenylpropyl)pyridine were reduced in the benzene ring, the 2-substituted compound less cleanly than the 4-substituted ones (Table II).

Scheme I



Discussion

Hydrogenation of quinoline in neutral medium (absolute methanol) stops cleanly (97.5%) at the tetrahydro stage, 97% of the product being reduced in the pyridine and only 3% in the benzene ring (Table III, entry 1). It appears that the piperidine formed poisons the catalyst for further reduction.[8a,15,36] In acetic acid,[6,8,11] which prevents such poisoning by forming salts with the strongly basic benzpiperidine intermediates, reduction continues to the (predominantly trans) decahydro products;[6,11] this is true, contrary to an earlier report,[10] for isoquinoline also (Table III, item 4), though here the cis isomer predominates.

Table I
Selective Hydrogenation of Quinolines and Isoquinoline with PtO_2 in 12 *N* Hydrochloric and Sulfuric Acids at 50 psi and Room Temperature

Substance reduced (in HCl unless indicated)	Registry no.	Product composition[a] % 5,6,7,8-Tetrahydro product	% other products[a] (-quinolines)
Quinoline	91-22-5	70[b]	24 Decahydro[c] 6 $\Delta^{1,9}$-Octahydro[d]
Quinoline (H_2SO_4)		74	13 1,2,3,4-Tetrahydro[e] 6.5 $\Delta^{1,9}$-Octahydro 5.5 Decahydro[f]
Quinoline[g] (H_2SO_4)		58	42 1,2,3,4-Tetrahydro
Isoquinoline	119-65-3	95[h]	5, not isolated
2-Methylquinoline	91-63-4	95[i]	5, not isolated
2-Isopropylquinoline	17507-24-3	90[j]	3, overreduced, not isolated 7 Starting material
3-Methylquinoline	612-58-8	95[k]	5, not isolated
6-Methylquinoline	91-62-3	53[l]	24 1,2,3,4-Tetrahydro[m] 11.5 Decahydro[n] 8 Starting material 3.5 $\Delta^{1,9}$-Octahydro[o,p]
8-Methylquinoline	611-32-5	55[q]	22.5 1,2,3,4-Tetrahydro[r] 10 Starting material 6.5 Decahydro[n,o] 6 $\Delta^{1,9}$-Octahydro[o,s]

[a] Determined by VPC; see Experimental Section. [b] Picrate, mp 159–160° (lit.[20] mp 158–159°). [c] Mostly cis, by comparison with independently synthesized *trans*-[21] and *cis*-[19]decahydroquinoline. [d] Picrate, mp 136–137° (lit.[22] mp 136.5–137°). [e] Hydrochloride, mp 181° (lit.[23] mp 181°). [f] Cis and trans. [g] Catalyst 5% Pd/C. [h] Picrate, mp 143–144° (lit.[24] mp 144°). [i] Picrate, mp 158–159° (lit.[17b] mp 154°). [j] Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78. Found: C, 82.09; H, 9.75. Picrate, mp 142–143°. [k] Picrate, mp 182–183° (lit.[20] mp 182–183°). [l] Picrate, mp 161–162° (lit.[25] mp 159.5–160.5°). [m] Hydrochloride, mp 188–189° (lit.[26] mp 189°). [n] Mixture of isomers. [o] By comparison with independently synthesized compound(s), see ref 18b. [p] Picrate, mp 134–135°. [q] Picrate, mp 126–127° (lit.[25] mp 125–126°). [r] Hydrochloride, mp 218° dec (lit.[26] mp 214°). [s] Picrate, mp 151–152°.

A very different situation obtains when strong mineral acid (sulfuric, hydrochloric) is added to the acetic acid solution or when the hydrogenation is carried out in 12 *N* hydrochloric or sulfuric acid or in trifluoroacetic acid. The literature[8b,10] suggests that mineral acid facilitates reduction to the decahydro stage at least in the case of isoquinoline. However, when a large excess of acid is used, hydrogenation proceeds very slowly.[19] Indeed, it has been shown[37] that, whereas addition of small amounts of acid facilitates hydrogenation of pyridines, a large excess of acid slows it down. Of more interest, from the preparative point of view, is the fact that in strong acid the reduction proceeds via the 5,6,7,8-tetrahydroquinolines or -isoquinolines (benztetrahydro products) rather than via the 1,2,3,4-tetrahydro products mentioned above. Although the benztetrahydro products must have been intermediates in at least two previous reductions[10,19] in strong acid (cf. Table III, item 5), they have not heretofore been isolated except where reduction of the pyridine ring was impeded by alkyl substituents.[17] In the present work, we found (Table I) that the highest yields of 5,6,7,8-tetrahydroquinolines result when there is a methyl substituent in the pyridine ring, or a second fused benzene ring (as in acridine), lesser yields with no substituent, and the lowest yields when there is an alkyl substituent in the benzene ring, or a second benzene ring fused to it (as in benzo[*h*]quinoline).

The crucial factor in guiding the reaction toward hydrogenation of the benzene ring is the use of strong acid (compare Tables I and II with item 1 in Table III).[38] Under strongly acid conditions, not only quinoline and isoquinoline, but also acridine, benzo[*h*]quinoline, 2- and 4-phenylpyridine, and 4-(3-phenylpropyl)pyridine may be reduced in the benzene ring(s) in preference to the pyridine ring (Table II). It is tempting to propose, by way of explanation, that conversion to the salt impedes hydrogenation of the pyridine ring and thereby allows the normally slower hydrogenation of the benzene ring to occur preferentially. If this is so, it cannot be just a matter of placing a positive charge on the pyridine ring, however, since it is known[15,39,40] that *N*-alkylpyridinum salts are readily hydrogenated to N-substituted piperidines.

Of the three strong acids used in this work trifluoroacetic acid (Table II) is preferred because reduction times in this solvent are quite short.[41] In contrast, hydrochloric acid (Table I), perhaps by acting as a catalyst inhibitor, leads to very slow hydrogenation;[41] sulfuric acid (Table I) is intermediate.

Finally we note that $\Delta^{1,9}$-octahydroquinolines (**5**) frequently appear among the products of quinoline hydrogenation, in yields up to 11% (Tables I and II). While we have no definitive evidence as to whether these compounds are side products or intermediates in the hydrogenation, experiment 2 in Table III, in which $\Delta^{1,9}$-octahydroquinoline was obtained in 28% yield in the hydrogenation of 1,2,3,4-tetrahydroquinoline, raises the possibility that the Schiff base **5** arises from the enamine salt **6** derived from a $\Delta^{9,10}$-octahydroquinoline. The latter may logically be formed from either 1,2,3,4- or 5,6,7,8-tetrahydroquinoline if the sterically hindered 9,10 double bond escapes ultimate hydrogenation. Resistance of such a double bond to hydrogenation has been previously reported in the case of 1-methyl-Δ^5-tetrahydrojulolidinium perchlorate (**7**).[42] If this

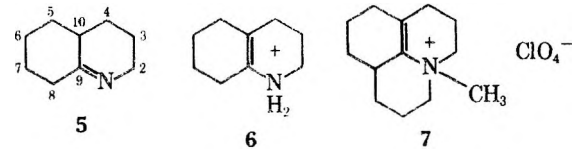


Table II
Hydrogenation of Quinolines, Isoquinoline, Quinoline Homologs, and Pyridines with Phenyl Substituents in Trifluoroacetic Acid at Room Temperature[a,b]

Substance reduced (catalyst[a])	Registry no.	Composition: % product[b] reduced in benzene ring(s)	Composition: % other products[b,c]
Quinoline		84	4.5 1,2,3,4-Tetrahydro 5 $\Delta^{1,9}$-Octahydro 3 Decahydro 3.5 Unidentified
Quinoline[d]		79.5	11.2 $\Delta^{1,9}$-Octahydro 7.3 Decahydro[e] 1.2 1,2,3,4-Tetrahydro
Quinoline (5% Rh/C)		69	15.6 1,2,3,4-Tetrahydro 9.2 Starting material 3.1 $\Delta^{1,9}$-Octahydro 2.3 Decahydro
Quinoline (5% Pd/C)		69	25 1,2,3,4-Tetrahydro 5.4 $\Delta^{1,9}$-Octahydro
Isoquinoline[f]		90.5	4 Decahydro[g] 4 Unidentified 1.5 1,2,3,4-Tetrahydro[h]
2-Methylquinoline		95	5, not isolated
2-Isopropylquinoline		95	5, not isolated
6-Methylquinoline		74	18.7 1,2,3,4-Tetrahydro 3.3 $\Delta^{1,9}$-Octahydro 2.1 Decahydro[i] 1.8 Starting material
8-Methylquinoline		55.8 (58)[j]	27.2 (12.4) 1,2,3,4-Tetrahydro 8.1 (21.6) $\Delta^{1,9}$-Octahydro 7.1 (0) Starting material 1.8 (5.7) Decahydro[i]
Acridine	260-94-6	100[k] (1)	None isolated
Benzo[*h*]quinoline	230-27-3	62.5 (42)[l,m] (2)	4.4 (33) 7,8,9,10-Tetrahydro (4)[n] 28 (25) 1,2,3,4,5,6,7,8-Octahydro (3)[o]
2-Phenylpyridine[p]	1008-89-5	49.8[q]	14.7 2-Cyclohexyl-3,4,5,6-tetrahydropyridine[r] 11.2 2-Cyclohexylpiperidine[s] 10.8 2-Phenylpiperidine[t] 13.5 Starting material
4-Phenylpyridine	939-23-1	87[u]	9 Overreduced, unidentified 4 Starting material
4-(3-Phenylpropyl)pyridine	2057-49-0	96[v]	4 Overreduced, unidentified

[a] Catalyst PtO_2, at 50 psi hydrogen, unless otherwise indicated. [b] Identification of products also listed in Table I is not indicated again. [c] Determined by VPC; see Experimental Section. [d] Reduction carried out at atmospheric pressure. Reaction time 8.5 hr. The material was deliberately slightly overreduced (uptake of more than 2 mol of hydrogen) to ascertain that all starting material had reacted. Starting material had to be purified by heating to reflux in ethanol over Raney Ni and distillation or else only 70% of theoretical amount of H_2 was taken up in 60 hr. [e] Cis:trans ratio 9:1. [f] Reduction carried out at atmospheric pressure. Reaction time 16 hr. Starting material was purified over Raney nickel. [g] Mixture of cis and trans. For identification see Table III, item 4. [h] Picrate, mp 194–195° (lit.[27] mp 194°). [i] Mixture of isomers; see footnote *o*, Table I. [j] Values in parentheses refer to a 75-min run, slightly overreduced. The unparenthesized figures refer to a 50-min run. [k] 1,2,3,4,5,6,7,8-Octahydroacridine, mp 69–71° (lit.[28] mp 69–71°). [l] The parenthesized figures refer to a 4-hr reaction time. The unparenthesized figures refer to an experiment with a greater than usual amount of catalyst, reaction time 1.5 hr. [m] 5,6,6a,7,8,9,10,10a-Octahydrobenzo[*h*]quinoline. Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.20; H, 9.00. Picrate, mp 179–180°. [n] Picrate, mp 185–186° (lit.[29] mp 186°). [o] Picrate, mp 161–162° (lit.[30] mp 155–156°). A sample of the amine prepared according to this procedure[30] was not pure by VPC; ^1H NMR spectrum of the purified compound was identical with that of **3**. [p] Reduction of amount of CF_3COOH by 25% led to consumption of only 80% starting material in 5.5 hr. [q] 2-Cyclohexylpyridine. Picrate, mp 111–112° (lit.[31] mp 128–129°, lit.[32] mp 104°; see Experimental Section). [r] Hydrochloride, mp 219–221° dec (lit.[33] mp 222–224°). [s] Hydrochloride, mp 255–256° (lit.[34] mp 251–252.5°). [t] Hydrate, mp 63° (lit.[7] mp 61–62°). [u] 4-Cyclohexylpyridine. Picrate, mp 154–155° (lit.[31] mp 154–155°). [v] 4(3-Cyclohexylpropyl)pyridine. Anal. Calcd for $C_{14}H_{21}N$: C, 82.70; H, 10.41. Found: C, 82.51; H, 10.28. Picrate, mp 147–148°.

explanation is correct, the change from **6** to **5** (presumably in neutralization and work-up) must be essentially thermodynamically irreversible, since we were unable to regenerate **6** from **5** upon acidification (see Experimental Section). Alternatively, $\Delta^{1,9}$-octahydroquinoline salts may be formed as such in the reduction and resist further hydrogenation; indeed, when these Schiff bases are synthesized independently and hydrogenated in strong acid, reduction to the decahydro product is extremely slow (Table III, item 6).

Experimental Section

Melting points were determined on a Sargent Mel-Temp variable temperature heating block and are uncorrected. Analytical gas–liquid chromatography was carried out with a Hewlett-Pack-

Table III
Miscellaneous Reductions[a]

Item	Compd reduced	Conditions	% composition of products
1	Quinoline[b]	CH_3OH (anhydrous), 35 hr[c,d]	94.5 1,2,3,4-Tetrahydro 3 5,6,7,8-Tetrahydro 2.5 Decahydro (cis + trans)
2	1,2,3,4-Tetrahydroquinoline	12 *N* HCl, 75 hr	57.5 *cis*-Decahydro 14.5 *trans*-Decahydro 28 $\Delta^{1,9}$-Octahydro
3	Isoquinoline[e]	CH_3COOH, 1 atm, 4.5 hr[f]	61.9 1,2,3,4-Tetrahydro 20.8 *cis*-Decahydro[g] 7.7 *trans*-Decahydro[h] 5.8 5,6,7,8-Tetrahydro 3.8 Unidentified
4	Isoquinoline[e]	CH_3COOH, 1 atm, 35 hr[c]	62.5 *cis*-Decahydro[g,i] 33.2 *trans*-Decahydro[h,i] 4.3 Unidentified
5	Isoquinoline[e]	CH_3COOH + H_2SO_4,[j] 1 atm, 3 hr[f]	80 5,6,7,8-Tetrahydro 8.3 1,2,3,4-Tetrahydro 7.9 Starting material 2 Unidentified 1.8 Decahydro
6	8-Methyl-$\Delta^{1,9}$-octahydroquinoline	12 *N* HCl, ~70°, 48 hr[c]	71 Decahydro[k] 29 Starting material

[a] Over PtO_2, at 50 psi hydrogen, at room temperature unless otherwise indicated. [b] Conditions of ref 35. [c] Reduced until hydrogen uptake had practically ceased. [d] After 20 hr only 70% of starting material had reacted. [e] Conditions of ref 10. [f] Stopped after 2 mol of hydrogen had been absorbed. [g] Picrate, mp 150–151° (lit.[10] mp 150°). [h] Picrate, mp 177° (lit.[10] mp 177°). [i] Reference 10 reports reduction to stop at the 1,2,3,4-tetrahydro stage under similar conditions. Our starting material was purified by heating to reflux in ethanol over Raney Ni followed by distillation. [j] Initially precipitated isoquinolinium sulfate dissolved as hydrogenation proceeded. [k] Mixture of isomers; see footnote *o*, Table I.

ard 5750 research chromatograph, equipped with a thermal conductivity detector, on 0.125-in. columns. Columns used were a 12-ft, aluminum, 20% Carbowax 20M + 10% KOH on Chromosorb W, 80/100 mesh, and a 10-ft stainless steel 30% SE-30 on Chromosorb W, 60/80 mesh, at temperatures between 120 and 200°. A Varian Aerograph Series 2700 with 0.375-in. aluminum columns with matching phase on Chromosorb A were used for preparative VPC. NMR spectra were recorded on a Varian XL-100 equipped with Fourier transform for ^{13}C analysis, or on a Jeolco C60HL instrument. Microanalyses were carried out by Galbraith Laboratories, Inc.

Hydrogenations at 50 psi were carried out in a Parr low-pressure shaker type hydrogenation apparatus, in 500-ml glass bottles.[3] Atmospheric pressure hydrogenations were done in a sloping manifold hydrogenator,[3] with magnetic stirring.

Catalysts. Platinum oxide (83%), rhodium (5% on carbon), and palladium (5% on carbon) were purchased from Engelhard Industries, Inc.

Starting Materials. Quinoline, isoquinoline, 2-methylquinoline, acridine, benzo[*h*]quinoline, 4-phenylpyridine, and 4-(3-phenylpropyl)pyridine were purchased from various sources (Aldrich Chemical Co., Columbia Organic Chemicals Co., and Eastman Kodak). 6-Methylquinoline[43] and 8-methylquinoline[44] were prepared by the Skraup synthesis from *p*- and o-toluidine. 3-Methylquinoline[17b] was obtained by condensation of o-aminobenzaldehyde[45] with propionaldehyde. 2-Isopropylquinoline was first synthesized from 1-methylquinolinium iodide with isopropylmagnesium bromide and subsequent elimination of methane from the intermediate 1-methyl-2-isopropyl-1,2-dihydroquinoline,[46] but the alternative method,[47] reaction of 2-methylquinoline two times in succession with equimolar amounts of butyllithium and quenching with methyl iodide, was vastly superior (the intermediate 2-ethylquinoline was isolated and purified by distillation). 2-Phenylpyridine was made from phenyllithium and pyridine.[48] 1,2,3,4-Tetrahydroquinoline was obtained by hydrogenating quinoline in anhydrous methanol over PtO_2 (see Table III, item 1). $\Delta^{1,9}$-Octahydroquinoline was prepared by the method of Cohen and Witkop.[22] 8-Methyl-$\Delta^{1,9}$-octahydroquinoline was synthesized from the piperidine enamine of 2-methylcyclohexanone and 3-bromopropylamine hydrobromide as reported for the parent compound;[49] this synthesis will be described elsewhere.[18b]

Purification of Starting Materials. Commercially obtained products were dissolved in ethanol and heated to reflux over Raney nickel[19] for 12 hr. After filtering from the catalyst and evaporation of the solvent, the material was distilled and checked by gas chromatography. Occasionally reduction of the pyridine ring of the compounds took place in minor amounts; such by-products were separated by acetylation, and the pyridines and quinolines purified by distillation as described below. For hydrogenations at elevated pressure (50 psi) this purification normally proved unnecessary but prolonged hydrogenation times were required when unpurified amines were hydrogenated at atmospheric pressure (note Table II, footnote *d*). The purification was also necessary for 2-isopropylquinoline synthesized by the butyllithium–methyl iodide method (see above) or else hydrogenation at 50 psi was extremely slow.

Hydrogenations at 50 psi. Fifty millimoles of starting material was dissolved in a 500-ml Parr bottle in 40 ml of ice-cold acid (HCl, 12 *N*, or H_2SO_4, 12 *N*, or CF_3COOH), 750 mg of PtO_2 [or 3 g of Rh (5% on C) or 3 g of Pd (5% on C)] was added, the bottle was connected to the hydrogenator and the air was removed,[3] 50 psi pressure was applied, and the mixture was hydrogenated until the required amount of hydrogen had been consumed. The catalyst was then filtered from the solution through a glass fiber filter, and the solution was diluted with water. Catalysts could be reused without noticeable loss in activity (except with H_2SO_4 as a solvent; here occasionally the catalyst proved inactive upon reuse). The aqueous solution was chilled in ice, and was carefully made basic with strong NaOH. The products were extracted with either petroleum ether or ether, the organic solution was dried over KOH, and the solvent was distilled off. The remaining residue was purified by total distillation at reduced pressure (without fractionation) by means of a Kugelrohr unit, using bulb tubes equipped with ground glass joints. The distilled products were checked by VPC, using the columns described above. Compositions listed in Tables I–III were determined in this way.

Hydrogenations at Atmospheric Pressure. Starting material (50 mmol or the amount indicated in ref 10) was dissolved in 40 ml of CF_3COOH (or the solvent indicated in Table III) and added to 750 mg (or the amount indicated in ref 10) of PtO_2, which had been prereduced in 10 ml of CF_3COOH (or the solvent indicated in Table III). The mixture was hydrogenated with magnetic stirring under a slight positive pressure of the gas buret (filled with glycerol) until the theoretical amount of hydrogen had been consumed or

Table IV
^{13}C Shifts[a] of $\Delta^{1,9}$-Octahydroquinoline

	Carbon								
	2	3	4	5	6	7	8	9	10
$CDCl_3$	49.56	21.39	27.50	34.98	25.97	27.98	39.28	172.94	38.66
CF_3COOH	47.46	19.96	28.69	36.10	25.46	25.83	38.24	199.14	41.51

[a] In parts per million downfield from Me_4Si.

uptake had completely ceased. After the catalyst was filtered, the solution was worked up as described above.

Isolation of Pure Products. In a number of cases the products were separated by preparative gas chromatography and characterized by melting point of derivatives, ^1H NMR spectra, and (if necessary) elemental analysis. The isolation of 5,6,7,8-tetrahydroquinoline on a larger scale is described below.

Quinoline (6.45 g, 50 mmol) was dissolved in 40 ml of CF_3COOH, 750 mg of PtO_2 was added, and the mixture was hydrogenated at 50 psi in a Parr shaker. After 45 min, when the pressure had dropped 9.2 psi, the catalyst was filtered off and the solution was worked up as described above. The crude product (6.3 g) was stirred with 1.3 g of acetic anhydride (12.7 mmol) at 100° for 5 hr. At the end of that time the mixture was diluted with 100 ml of water, 15 ml of concentrated HCl was added, and the solution was extracted five times with ether. (From the ether extract the decahydro-, but not the octahydroquinoline, could be recovered by heating the amides with concentrated HCl and subsequently extracting the basified solution with petroleum ether.) The aqueous solution was chilled in ice, made carefully basic with a concentrated aqueous solution of NaOH, and extracted five times with petroleum ether. The organic extract was dried over KOH and the solvent distilled off. The residue was distilled in a Kugelrohr apparatus at 25 mm (air bath temperature 120°) to give 5.05 g (76%) of 5,6,7,8-tetrahydroquinoline. The product was pure by VPC.

In a similar way the other products with nonreduced pyridine ring were isolated preparatively. When small amounts of starting material were still present, they were separated by fractional distillation at reduced pressure.

$\Delta^{1,9}$-Octahydroquinoline. To determine the position of the double bond in octahydroquinoline and octahydroquinolinium trifluoroacetate, 300 mg of 5[22] was dissolved in 3 ml of $CDCl_3$ or CF_3COOH containing 2% Me_4Si and the ^{13}C NMR spectra were recorded (Table IV). Assignment of the signals of the nine carbon atoms was made by comparison with the spectra of the 8,8,10-trideuterio analog and a number of methyl homologs,[50] and by off-resonance decoupling.

The similarity of the two sets of shifts indicates that the protonated species produced from $\Delta^{1,9}$-octahydroquinoline does not have structure **6**, since there is only one olefinic carbon atom (9), and the signals of carbon atoms 8 and 10 are a triplet and a doublet in the off-resonance decoupled spectrum indicating their substitution with two protons and one proton, respectively.

2-Cyclohexylpyridine. The melting point of the picrate prepared from a gas chromatographically pure sample, 111–112°, did not agree with the literature data (lit.[31,32] mp 128–129°, 104°). Analysis of the picrate agreed with theory. Anal. Calcd for $C_{17}H_{18}N_4O_7$: C, 52.31; H, 4.65. Found: C, 52.47; H, 4.94.

Amine: $n^{25}D$ 1.5221 (lit.[31] $n^{20}D$ 1.5246; lit.[32] $n^{20}D$ 1.5295).

The 60-MHz ^1H NMR spectrum (10% in $CDCl_3$, Me_4Si) agreed only roughly with values reported in the literature[51] shown in parentheses (solvent not reported[51]): pyridine ring, δ 8.77 (d, 1 H, H_α) (8.51, d), 7.24 (m, 2 H, H_β) (7.06, m), 7.77 (m, 1 H, H_γ) (7.56, m); cyclohexane ring, 2.78 (broad m, 1 H, H_1) (2.40, m), 1.73 ppm (m, 10 H, H_{2-6}) (1.60, m).

^{13}C shifts (parts per million from Me_4Si, in $CDCl_3$, multiplicity in parentheses from off-resonance decoupled spectrum): pyridine ring, C_2 166.15 (s), $C_{3,5}$ 120.79[52] (d), C_4 136.07 (d), C_6 148.76 (d); cyclohexane ring, C_1 46.50 (d), $C_{2,6}$ 32.88[52] (t), $C_{3,5}$ 26.58[52] (t), C_4 26.07 (t).

Acknowledgment. This work was supported by the Chemistry Department of the University of North Carolina at Chapel Hill under a NSF Science Development grant. We are indebted to Mr. Robert Williams for assistance with the hydrogenation experiments and to Dr. David Harris for recording the NMR spectra on the XL-100 instrument.

Registry No.—2-Isopropyl-5,6,7,8-tetrahydroquinoline, 55904-64-8; 2-isopropyl-5,6,7,8-tetrahydroquinoline picrate, 55904-65-9; 6-methyl-$\Delta^{1,9}$-octahydroquinoline picrate, 55904-66-0; 8-methyl-$\Delta^{1,9}$-octahydroquinoline picrate, 55904-67-1; 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinoline, 55904-68-2; 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinoline picrate, 55904-69-3; 4-(3-cyclohexylpropyl)pyridine, 55904-70-6; 4-(3-cyclohexylpropyl)pyridine picrate, 55904-71-7; 8-methyl-$\Delta^{1,9}$-octahydroquinoline, 52761-53-2; $\Delta^{1,9}$-octahydroquinoline, 1074-06-2; 2-cyclohexylpyridine, 15787-49-2; 2-cyclohexylpyridine picrate, 55904-72-8; 1,2,3,4-tetrahydroquinoline, 635-46-1.

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Reduction of 5,6,7,8-Tetrahydroquinolines and 2,3,4,5,6,7,8,10-Octahydroquinolines to *trans*-Decahydroquinolines†

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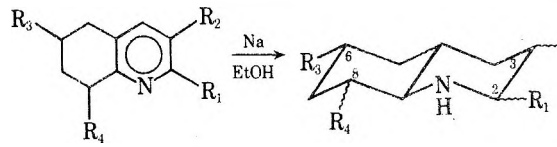
The reduction of the title compounds with sodium in ethanol gives largely (~90%) *trans*-decahydroquinolines. When alkyl substituents or fused rings are present in the starting materials, the decahydroquinoline juncture of the product is still largely trans, but two (or more) epimers at the point of alkyl substitution (or fused ring juncture) result; they are separated readily by preparative gas chromatography. Similar reduction of 5,6,7,8-tetrahydroisoquinoline gives mainly $\Delta^{9,10}$-octahydroisoquinoline (58%) with lesser amounts of *cis*- (20%) and *trans*-decahydroisoquinoline (22%). Reduction of 5,6,7,8-tetrahydroquinoline with sodium in ethanol-*O*-*d* surprisingly gives mainly 2,3,3,4,9,10-hexadeuterio-*trans*-decahydroquinoline with some deuteration also occurring at position 8. Evidently exchange at an intermediate reduction stage is involved. Similar reduction of pyridine gives 2,3,3,4,5,5,6-heptadeuteriopiperidine. Reduction of $\Delta^{1,9}$-octahydroquinolines with sodium in ethanol provides an alternative path for the synthesis of *trans*-decahydroquinolines, including compounds with methyl substituents at C-10. The synthesis of certain deuterated analogs is also described. The ^{1}H NMR spectra of the compounds synthesized (including the deuterated analogs) as well as of their *N*-methyl, *N*-ethyl, and *N*-isopropyl derivatives are described in some detail.

As explained in the accompanying paper,[1] there is a dearth of convenient known syntheses for the trans isomers of decahydroquinoline and decahydroisoquinoline. Catalytic hydrogenation of quinolines and isoquinolines normally leads to the cis products, or at best (under special conditions) to mixtures in which the trans isomer may predominate. While the separation of *cis*- and *trans*-decahydroquinolines and decahydroisoquinolines by modern gas-chromatographic methods presents no insuperable difficulty, the problem is aggravated when there are alkyl substituents in the ring, in which case *four* diastereoisomers are formed: the α and β isomers[2] (referring to the stereochemical placement of the alkyl group) in both the cis and trans ring-fused series.

Chemical Reduction of 5,6,7,8-Tetrahydroquinolines. Having devised a convenient synthesis[1] of 5,6,7,8-tetrahydroquinolines and -isoquinoline by hydrogenation of the corresponding quinoline or isoquinoline over platinum oxide in strongly acidic medium, we decided to explore the sodium–ethanol[4,5] reduction of the benztetrahydro compounds as a means to obtaining the *trans*-decahydro compounds which we required in another investigation.[5] The results are summarized in Table I.

5,6,7,8-Tetrahydroquinoline (**1**) is reduced to *trans*-decahydroquinoline (90%) along with 10% of the cis isomer (Scheme I). In the case of the 2- (**2**), 3- (**3**), 6- (**4**), and 8-substituted (**5**) homologs, again the combined yield of the *trans*-decahydro product adds up to 90%, but in this case two diastereoisomers, α and β, result. Except in the case of the 6-methyl compound (**9**), where only the α (equatorial) isomer was isolated, the α and β isomers were cleanly separated by gas chromatography and identified by elemental analysis, ^{1}H NMR (see below), and ^{13}C NMR[7] spectral study. In the tricyclic series, 1,2,3,4,5,6,7,8-octahydroacridine[1] (**11**) was reduced in high yield to *trans-syn-trans*-perhydroacridine (**12**, Scheme II).[8] The stereoisomeric mixture of 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinolines (**13**) obtained by catalytic hydrogenation of the aromatic precursor[1] was reduced to a mixture of three perhydrobenzo[*h*]quinolines (**14**–**16**) in which the juncture of the piperidine to the adjacent cyclohexane ring was trans and the decalinoid ring fusion displayed the two possible cis junctures and one of the possible trans junctures (Scheme II).[8]

Scheme I



1	$R_1 = R_2 = R_3 = R_4 = H$	6	
2	$R_1 = CH_3$; $R_2 = R_3 = R_4 = H$	7	(α, β)
3	$R_2 = CH_3$; $R_1 = R_3 = R_4 = H$	8	(α, β)
4	$R_3 = CH_3$; $R_1 = R_2 = R_4 = H$	9	(α only)
5	$R_4 = CH_3$; $R_1 = R_2 = R_3 = H$	10	(α, β)

Unfortunately, 5,6,7,8-tetrahydroisoquinoline (**17**) is reduced in the main (58%) to the 1,2,3,4,5,6,7,8-octahydro compound[9] (**18**) with only minor amounts of *cis*- (**20**) and *trans*-decahydroisoquinoline (**19**) being formed (Scheme III). Apparently the sequence of reduction steps is such that the last of the three double bonds to be reduced ends up in the 9,10 position, where it is, of course, inert to further reduction.[10] A plausible though unproven sequence of events is suggested in Scheme IV. It should be noted that in the reduction of the tetrahydroquinoline analog (discussed below), even if a double bond remained in the 9,10

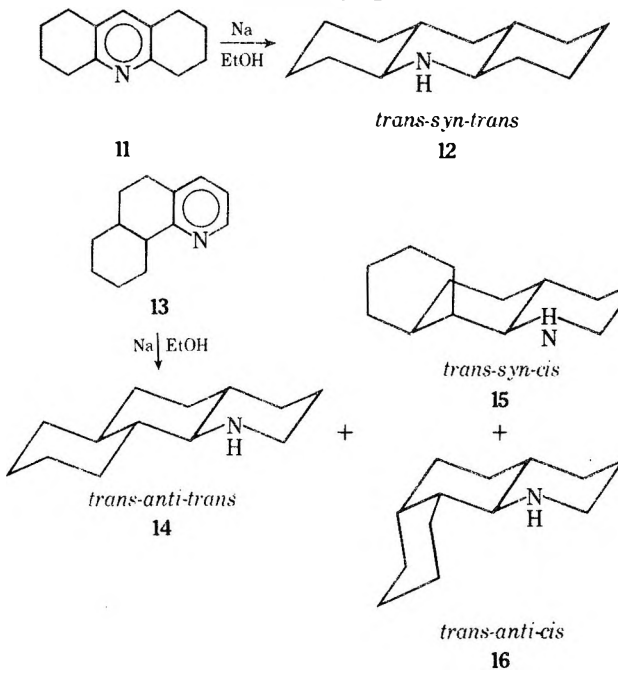
† This paper, and the preceding one, is dedicated by F.W.V. to Professor Dr. K. Kratzl on the occasion of his 60th birthday.

Table I
Reduction of 5,6,7,8-Tetrahydroquinolines and Related Compounds with Sodium in Ethanol

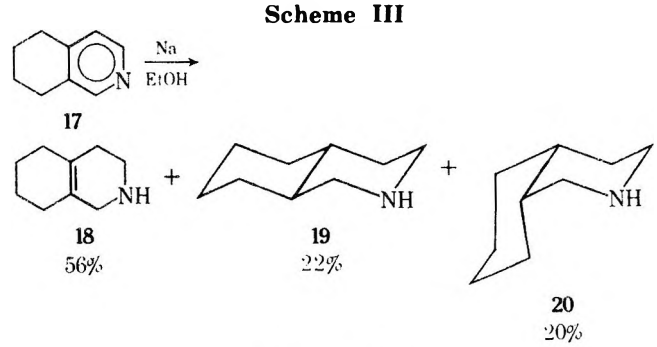
Starting material[a]	Products, composition, %[b,c]
5,6,7,8-Tetrahydroquinoline (**1**)	*trans*-Decahydroquinoline[d] (**6**), ~90
	cis-Decahydroquinoline,[e] ~10
2-Methyl-5,6,7,8-tetrahydroquinoline (**2**)	2β-Methyl-*trans*-decahydroquinoline[f] (**7β**), 54.5
	2α-Methyl-*trans*-decahydroquinoline[g] (**7α**), 41.5
	Two substances (cis?), unidentified, 4
3-Methyl-5,6,7,8-tetrahydroquinoline (**3**)	3α-Methyl-*trans*-decahydroquinoline[h] (**8α**), 60
	3β-Methyl-*trans*-decahydroquinoline[i] (**8β**), 30
	Other substance, unidentified,[j,k] 10
6-Methyl-5,6,7,8-tetrahydroquinoline (**4**)	6α-Methyl-*trans*-decahydroquinoline[l] (**9α**), 91
	One other substance, unidentified, 9
8-Methyl-5,6,7,8-tetrahydroquinoline (**5**)	8α-Methyl-*trans*-decahydroquinoline[m] (**10α**), 48
	8β-Methyl-*trans*-decahydroquinoline[n] (**10β**), 51
	8α-Methyl-*cis*-decahydroquinoline,[k] traces
5,6,7,8-Tetrahydroisoquinoline (**17**)	*trans*-Decahydroisoquinoline[o] (**19**), 22
	cis-Decahydroisoquinoline[p] (**20**), 20
	$\Delta^{9,10}$-Octahydroisoquinoline[q] (**18**), 58
1,2,3,4,5,6,7,8-Octahydroacridine (**11**)	*trans-syn-trans*-Perhydroacridine[r] (**12**), >90
	Other products, not identified, <10
5,6,6a,7,8,9,10,10a-Octahydrobenzo[*h*]-quinoline (**13**)	*trans-anti-trans*-Perhydrobenzo[*h*]quinoline[s] (**14**), ~30
	trans-anti-cis-Perhydrobenzo[*h*]quinoline[t] (**16**), ~18
	trans-syn-cis-Perhydrobenzo[*h*]quinoline[t] (**15**), 52

[a] For synthesis of starting materials see ref 1. [b] For nomenclature, see ref 2. [c] Analysis by gas chromatography. For columns used see Experimental Section. [d] Mp 48° (lit.[19] mp 48–48.5°); because of slight overlap of peaks the percent values are only approximate. [e] By comparison with an authentic sample, prepared according to ref 19. [f] Hydrochloride, mp 292–293° (lit.[22] mp 293–294°). [g] Hydrochloride, mp 284–285° (lit.[22] mp 284–285°). [h] Mp 81° (from petroleum ether; a melting point of 70–71° is reported for an unspecified mixture of 3-methyldecahydroquinolines.[4] Picrate, mp 179°. [i] Because of the extremely small amounts of material isolated, no derivatives were prepared. [j] From the ^{1}H NMR spectrum, one substance was assigned the structure of 3-methyl-$\Delta^{3,4}$-octahydroquinoline. Insufficient material was isolated for further identification. Based on comparison of retention times, the other two substances are believed to be 3α- and 3β-methyl-*cis*-decahydroquinoline. [k] Cis compounds for comparison were synthesized according to ref 19; synthesis and characterization is described elsewhere.[7] [l] Mp 68–69° [lit. for 6-methyl-*trans*-decahydroquinoline without specification of configuration of the methyl group, 68–69°: S. Fujise and M. Iwakiri, *Bull. Chem. Soc. Jpn.*, 11, 293 (1936)]. [m] Anal. Calcd for $C_{10}H_{19}N$: C, 78.37; H, 12.50. Found: C, 78.82; H, 12.20. Picrate, mp 193–194°. Hydrochloride, mp 247–248° dec. *N*-Benzoyl-8α-methyl-*trans*-decahydroquinoline, mp 48°. [n] Anal. Calcd for $C_{10}H_{19}N$: C, 78.37; H, 12.50. Found: C, 78.42; H, 12.35. Picrate, mp 148.5–149.5°. Hydrochloride, mp 279–280° dec. *N*-Benzoyl-8β-methyl-*trans*-decahydroquinoline, mp 127–128°. [o] Picrate, mp 174–175° [lit. mp 175–176°: W. L. F. Armarego, *J. Chem. Soc. C*, 377 (1967)]. [p] Picrate, mp 149–150° (lit.[o] mp 149–150°). [q] Picrate, mp 176–176.5° (lit.[9] mp 172°). Hydrochloride, mp 149° (lit.[9] mp 150°). [r] Mp 89° (petroleum ether) [lit. mp 90.5–91.5°: H. Adkins and H. L. Coonradt, *J. Am. Chem. Soc.*, 63, 1563 (1941)]. [s] Mp 41–42° (from petroleum ether). Anal. Calcd for $C_{13}H_{23}N$: C, 80.76; H, 11.99. Found: C, 80.74; H, 11.83. [t] Mp 76° (from petroleum ether). Anal. Calcd for $C_{13}H_{23}N$: C, 80.76; H, 11.99. Found: C, 80.69; H, 11.82.

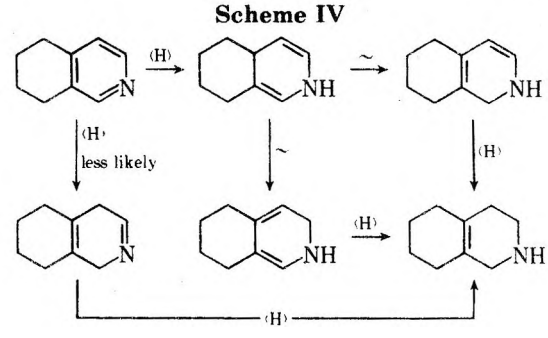
Scheme II



Scheme III



Scheme IV



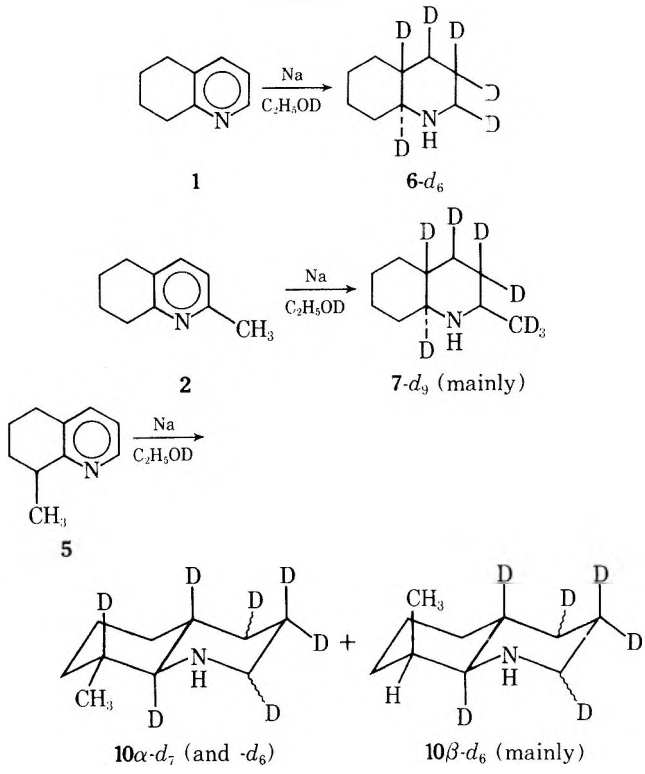
position, it would be enaminic and thus subject to further reduction.

Reduction of 5,6,7,8-Tetrahydroquinoline with Sodium in Ethanol-*O*-*d*. To obtain deuterated analogs of some of the above-described *trans*-decahydroquinolines for a ^{13}C NMR study, we reduced the benztetrahydro compounds with sodium in ethanol-*O*-*d*. This reduction, shown in Scheme V for **1**, provided a surprise in that both the ^{13}C NMR and the mass spectrum of the product indicated it to be largely a hexadeuterio (rather than the expected 2,3,4,9,10-pentadeuterio) species, containing also some heptadeuterated material. The ^{13}C NMR spectrum unequivocally indicated that the extra deuterium was at C-3, since the ^{13}C NMR signal of C-3 was suppressed, owing to the missing nuclear Overhauser effect[11] of the absent proton there. The additional deuteration occurred at C-8, which displayed a triplet superimposed upon a singlet in the ^{13}C NMR spectrum. In Scheme VI are shown two alternative sequences for the reduction of **1** with sodium in ethanol. Both proceed via the 1,4,5,6,7,8-hexahydro intermediate,[12] which is then assumed to rearrange to either the 3,4,5,6,7,8-hexahydro or the 4,10,5,6,7,8-hexahydro derivative. The former would exchange, in the presence of EtOD–EtO$^-$, at C-3, the latter at C-8, the exchange involving a HC–C=N– proton in either case. Further reduction would lead to $\Delta^{1,9}$ compound in the former case (with subsequent exchange at C-8) and to the $\Delta^{1,2}$ (with subsequent exchange at C-3) in the latter, with ultimate reduction to the partially deuterated decahydro species in either case. Since the dienoid species (C=N–C=C) is probably more fleeting than the enamine species, so that exchange is more likely to occur in the latter, and since the proton at C-3 is much more extensively exchanged than that at C-8, we prefer the reaction path via the 4,10,5,6,7,8-hexahydro intermediate.

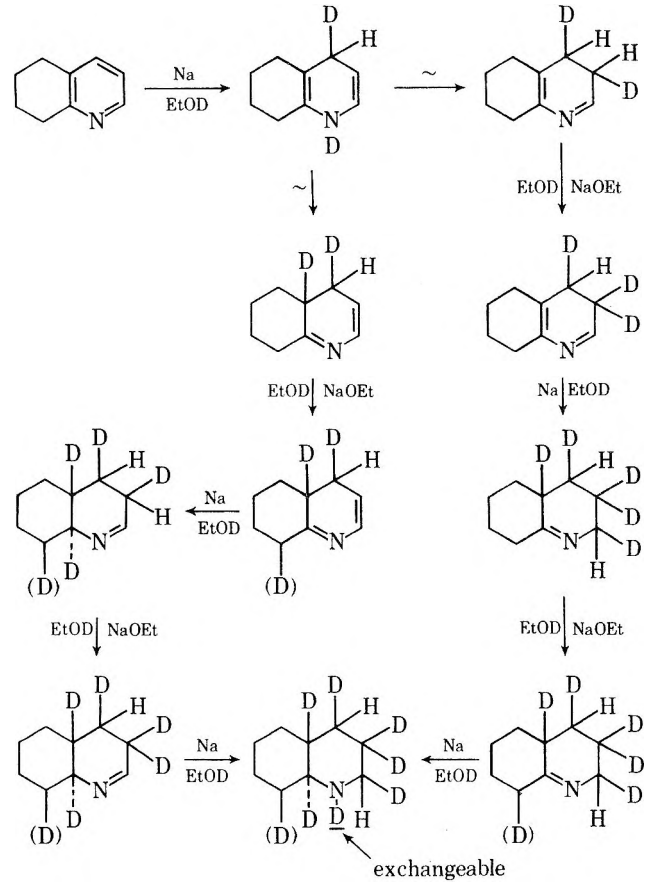
The reductions are summarized in Table II.

When the 2-methyl homolog **2** was similarly reduced (Scheme V), the ^{13}C NMR and ^1H NMR spectra of the product (deuterated **7**) indicated extensive H–D exchange in the methyl group (which passes through a N=C–CH_3 intermediate in the course of the reaction). This is further evidence that the last intermediate may be the $\Delta^{1,2}$-octahydro derivative.

Scheme V



Scheme VI



Reduction of the 8-methyl homolog **5** was particularly interesting because of different degrees of deuterium incorporation in **10α** and **10β** (Scheme V). The **10β** epimer contained six deuterium atoms only, whereas **10α** was appreciably heptadeuterated, with the extra deuterium at C-8. The α isomer (Scheme V) has an equatorial C-8 methyl group and an axial C-8 hydrogen; in the intermediate $\Delta^{1,9}$-imine intermediate, the corresponding carbanion is well disposed for p–π overlap with the C=N double bond[13] and thus presumably prone to ready H–D interchange. In contrast, the β isomer has an equatorial C-8 hydrogen which, in the imine precursor, is nearly in the plane of the double bond and thus ill disposed for p–π overlap in the anion. Exchange of this proton is presumably so slow as to be negligible in the time period of survival of the imine.

We also reduced pyridine with sodium–ethanol-*O*-*d* and showed by mass spectral, ^1H NMR, and ^{13}C NMR analysis that the product formed (85.5%) is piperidine-*2,3,3,4,5,5,6-d*$_7$, as would be expected on the basis of the analogy with Scheme IV.

Reduction of 2,3,4,5,6,7,8,10-Octahydroquinolines. A few cases of reactions of $\Delta^{1,9}$-octahydroquinolines with sodium in ethanol are summarized in Scheme VII and the product compositions are shown in Table III. Except for the case of the 9-methyl compounds **26** and **27α** (which cannot, of course, be obtained from quinoline precursors), the lengthy (see below) route via the $\Delta^{1,9}$-octahydroquinolines offers no advantages over the shorter and more convenient two-stage reduction of quinolines, especially since the product compositions in the two cases are quite similar (compare Table III with Table I).

Table II
Reductions of Tetrahydro- and Octahydroquinolines with Sodium and Ethanol-*O*-*d*

Starting material	Product[a]
Pyridine	Piperidine-*2,3,3,4,5,5,6*-d_7[b]
5,6,7,8-Tetrahydroquinoline (**1**)[c]	*trans*-Decahydroquinoline-*2,3,3,4,9,10*-d_6[c,d]
2-Methyl-5,6,7,8-tetrahydroquinoline (**2**)	2β-Methyl-*trans*-decahydroquinoline-*2,3,3,4,9,10,*-α,α,α-d_9[e]
	2α-Methyl-*trans*-decahydroquinoline-*2,3,3,4,9,10,*-α,α,α-d_9[e]
8-Methyl-5,6,7,8-tetrahydroquinoline (**5**)	8α-Methyl-*trans*-decahydroquinoline-*2,3,3,4,9,10*-d_6[d]
	8β-Methyl-*trans*-decahydroquinoline-*2,3,3,4,9,10*-d_6 and -*2,3,3,4,8,9,10*-d_7
5,6,7,8-Tetrahydroisoquinoline (**14**)	$\Delta^{9,10}$-Octahydroisoquinoline-*1,3,4,4*-d_4 and -*1,3,4*-d_3
$\Delta^{1,9}$-Octahydroquinoline (**21**)	*trans*-Decahydroquinoline-*9,10*-d_2[f]
10-Methyl-$\Delta^{1,9}$-octahydroquinoline (**24**)[g]	10-Methyl-*trans*-decahydroquinoline-*8,8,9*-d_3[h]

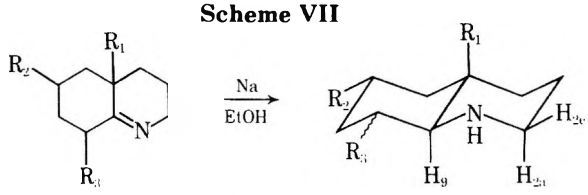
[a] Products isolated; for product composition see Tables I and III, if not otherwise indicated. [b] Crude product contains about 8% starting material but can be purified by preparative gas chromatography. [c] Neither the starting material (**1**) nor *trans*-decahydroquinoline (**6**) exchange hydrogen when treated with NaOEt in EtOD. [d] Small amounts of *2,3,3,4,8,9,10*-d_7 product admixed; see Discussion. [e] This is the major product, but there is also some side-chain mono- and dideuterated material and some deuteration at C-8; see Discussion. [f] Ca. 60%; rest is *trans*-decahydroquinoline-*9-d* and very little *trans*-decahydroquinoline-*8,9,10*-d_3. [g] Heated to reflux with EtOD and NaOEt for 3 hr, and then reduced with Na. [h] Small amount of *8,9*-d_2 product admixed.

Table III
Reduction of $\Delta^{1,9}$-Octahydroquinolines with Sodium and Ethanol

Starting material ($\Delta^{1,9}$-octahydroquinoline)	Product, composition, %[a-c]
Unsubstituted (**21**)	*trans*-Decahydroquinoline[d,e] (**6**), ~95
	cis-Decahydroquinoline,[d,e] ~5
6-Methyl- (**22**)	6α-Methyl-*trans*-decahydroquinoline (**9**α), 94
8-Methyl- (**23**)	8α-Methyl-*trans*-decahydroquinoline (**10**α), 66
	8α-Methyl-*cis*-decahydroquinoline,[f] 6
	8β-Methyl-*trans*-decahydroquinoline (**10**β), 28
10-Methyl- (**24**)	10-Methyl-*trans*-decahydroquinoline[d,e,g] (**26**), ~90
	10-Methyl-*cis*-decahydroquinoline,[d,e,h] ~10
8,10-Dimethyl- (**25**)	8α,10-Dimethyl-*trans*-decahydroquinoline[i] (**27**α) ~95
	One other substance, unidentified, ~5

[a] For nomenclature see ref 2. [b] Products characterized in Table I are not described further. [c] By gas chromatography; for columns used see Experimental Section. [d] Because of overlap of peaks percent values are only approximate. [e] No formation of cis product by this procedure is indicated in ref 15. [f] By comparison with authentic sample; see ref 7. [g] Picrate, mp 227–228° (lit.[15] mp 224–225°). [h] Picrate, mp 193° (lit.[15] mp 190–192°). [i] Anal. Calcd for $C_{11}H_{23}N$: C, 78.98; H, 12.65. Found: C, 78.76; H, 12.91. Picrate, mp 220–222°.

Scheme VII



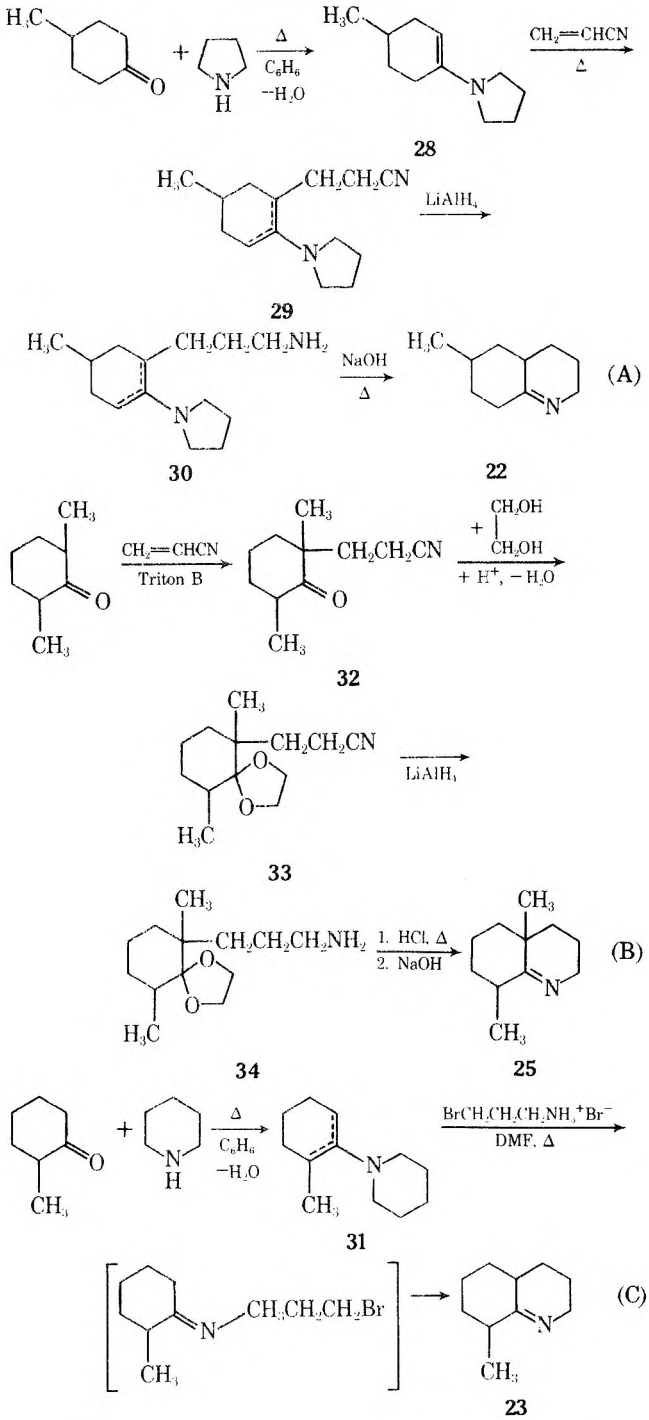
21	$R_1 = R_2 = R_3 = H$	**6**
22	$R_2 = CH_3$; $R_1 = R_3 = H$	**9**α
23	$R_3 = CH_3$; $R_1 = R_2 = H$	**10**α, β
24	$R_1 = CH_3$; $R_2 = R_3 = H$	**26**
25	$R_1 = R_3 = CH_3$; $R_2 = H$	**27**α

The starting materials required for the $\Delta^{1,9}$-octahydroquinoline route were synthesized either from the pyrrolidine enamine of cyclohexanone and acrylonitrile followed by lithium aluminum hydride reduction and hydrolysis[14] (Scheme VIII, A, used for the parent compound[14] and its 6-methyl derivative), or from 2-methylcyclohexanone and acrylonitrile, followed by ketal formation with ethylene glycol, hydride reduction,[15] and acid-catalyzed deketalization and cyclization[15] (Scheme VIII, B used for the 10-methyl[15] and 8,10-dimethyl compounds), or from the piperidine enamine of 2-methylcyclohexanone and 3-bromopropylamine in a one-step reaction[16,17] (Scheme VIII, C used for the 8-methyl compounds).

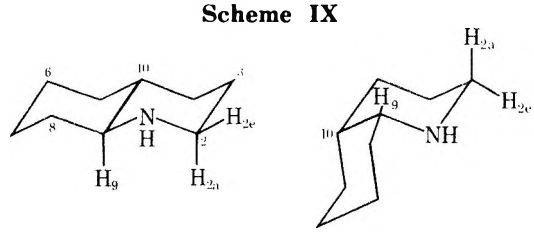
We also studied the reduction of $\Delta^{1,9}$-octahydroquinoline (**21**) and its 10-methyl homolog (**24**) with sodium–ethanol-*O*-*d* (Table II). Reduction of **21** involved partial exchange of the 10 hydrogen prior to reduction; in the case of **24** exchange of the α hydrogens (in this case the two hydrogens located at C-8) was furthered by treating the compound with NaOEt–EtOD before reduction.

Identification of Products. NMR Spectra. Configurational assignment of the products rests both on ^{1}H NMR and on ^{13}C NMR spectra. The ^{1}H NMR spectra of the NH compounds (**6–10**, Scheme I), as well as two of the three perhydrobenzo[*h*]quinolines (**12**, **15**, Scheme II), are summarized in Table IV with emphasis on the downfield protons α to the ring nitrogen (the remaining protons, with the exception of those of the methyl group, are generally not well resolved). The ^{13}C NMR spectra will be reported in detail elsewhere,[7] but we have included in Table IV the *C*-methyl signals which are characteristic of conformation (and configuration): axial methyl groups are upfield from equatorial ones.[18] The spectra for *N*-alkyl derivatives (*N*-methyl, *N*-ethyl, *N*-isopropyl) are reported elsewhere[6] and will be commented on briefly.

Scheme VIII



Scheme IX



The ^{1}H NMR spectra of *cis*- and *trans*-decahydroquinoline (**6**) have been investigated by Booth and Bostock.[19] Characteristic of the trans isomer is the downfield equatorial proton at C-2 (H_{2e}, Scheme IX) as a doublet (geminal splitting), further split by gauche protons, at 3.04 ppm; a relatively complex, widely split signal for the corresponding axial proton H_{2a} at 2.62 ppm; and a broad, ill-resolved signal for the tertiary axial proton (H_9) at ca. 2.08 ppm. The spectrum (and the other spectra to be discussed in the sequel) may be understood on the following premises: (1) axial protons, especially when α to nitrogen, are shifted upfield, relative to equatorial ones; (2) tertiary protons tend to be downfield from secondary ones; and (3) methyl or methylene substituents (R) on the carbon adjacent to one occupied by the proton under consideration (RC–CH) produce upfield shifts if gauche and downfield shifts if anti to the proton in question.[20] In addition, of course, the usual rules of coupling (large for a,a, small for a,e or e,e) apply.[21] Thus H_9 is upfield from H_{2a} even though the former is tertiary, because of the upfield shifting effect of the methylene groups CH_2-4 and CH_2-5 (gauche). In the cis isomer (Scheme IX, only the major conformer in which syn-axial interactions are minimized is shown) H_9 is shifted downfield to 2.82 ppm, since it is now anti to the methylene group at C-10 rather than gauche. The H_2's are unchanged.

The 6-methyl compound **9** (Scheme I) has essentially the same spectrum as **6**, confirming the trans ring juncture. The position (0.87 ppm) and coupling constant (6 Hz) of the methyl group suggests its equatorial placement which is confirmed by the ^{13}C NMR signal (22.39 ppm).[18]

The 8-methyl compounds, **10**α and **10**β (Scheme I), also have the H_2 protons essentially unchanged; H_9 in **10**α is shifted upfield beyond 1.8 ppm to the point where it almost disappears in the envelope of the cyclohexanoid protons; this is to be expected as the result of the presence of an extra gauche methyl group. In contrast, **10**β has H_9 at 2.23 ppm as a neat double doublet (J_1 = 9, J_2 = 4.5 Hz). The downfield shift (relative to **6**) is consistent with the presence of an anti methyl group and the double doublet results from one axial–axial and one axial–equatorial split. The position and coupling constants for the methyl groups (Table IV) support the assignment, the axial methyl in **10**β being slightly further downfield and having a slightly larger coupling constant. The ^{13}C NMR signals are also in agreement.

In the 3-methyl compounds, **8**α and **8**β (Scheme I), the signal of H_9 is, expectedly, little shifted relative to **6**, thus confirming the trans ring juncture. In **8**α (equatorial Me) H_{2e} is surprisingly at almost the same field (3.00 ppm) as in **6**; the expected upfield shift caused by a gauche methyl group does not occur. It is, however, seen in H_{2a}, which is shifted upfield to 2.25 ppm and appears as a near triplet with $J_{gem} \approx J_{anti}$ (there is no gauche proton). In **8**β, in contrast, H_{2e} and H_{2a} are nearly degenerate at 2.84 ppm, as might be expected as a result of an upfield shift of H_{2e} by the gauche methyl group and a downfield shift of H_{2a} (relative to **6**) by the same methyl group positioned anti. The splittings and chemical shifts of the methyl groups (Table IV) support the assignment of configuration to **8**α (equatorial methyl) and **8**β (axial methyl), as do the ^{13}C NMR signals.

In one of the two 2-methyl compounds (**7**α,β, Scheme I), the β isomer (equatorial CH_3), the shift of H_9 (2.16 ppm) is little changed from that in **6** and the axial H_{2a} shows up as a very broad (multiply split) signal at 2.70 ppm. In **7**α (axial methyl), on the other hand, the syn-axial methyl shifts H_9 downfield to 2.45 ppm, which is characteristic of a van der Waals shift. H_{2e} in **7**α, being equatorial, is narrower than the axial H_{2a} in **7**β and displays a quartet further split narrowly by ring protons (gauche). The methyl proton and ^{13}C NMR signals and the proton splittings (Table IV) support the assignments.[22]

The 10-methyl compound **26** (Scheme VII) has nearly the same H_{2e} and H_{2a} (shifts) as **6**, although H_{2a}, in this case, is a nearly perfect triplet of doublets (J_1 = 12, J_2 = 3.5 Hz) as a result of equal geminal and anti coupling con-

Table IV
Pertinent Chemical Shifts[a] of *trans*-Decahydroquinolines and Perhydrobenzo[*h*]quinolines[b]

Substance[c]	^{1}H H_{2e}	H_{2a}	H_9	CH_3	^{13}C CH_3
Parent (**6**)	3.04 (d, 12)	2.62	2.08		
2α-CH_3 (**7α**)	3.30_5 (q, 7)		2.45	1.20 (d, 7)	18.59
2β-CH_3 (**7β**)		2.70	2.16	1.07 (d, 6)	22.91
3α-CH_3 (**8α**)	3.00 (d, 12)	2.24_5 (t, 10.5)	1.99	0.82 (d, 6)	19.58
3β-CH_3 (**8β**)	2.84		~2	1.09 (d, 7)	17.65
6α-CH_3 (**9α**)	3.07_5 (d, 12)	2.65_5	2.06	0.87 (d, 6)	22.39
8α-CH_3 (**10α**)	3.08 (d, 12)	2.59	<1.8	0.91 (d, 6)	18.56
8β-CH_3 (**10β**)	3.08 (d, 12)	2.63	2.23 (d, 9, of d, 4.5)	0.95 (d, 7)	12.61
10-CH_3 (**26**)	3.06 (d, 12)	2.64 (t, 12, of d, 3.5)	2.21	0.93 (0.5)	15.57
8α,10-Dimethyl (**27α**)	3.14_5 (d, 12)	2.61_5 (t, 12, of d, 3.5)	1.85 (d, 9.5)	0.96[d] 0.85 (d, 6)[e]	16.72[d] 18.92[e]
trans-anti-trans[f] (**14**)	3.11 (d, 12)	2.58_5	<2.0		
trans-syn-cis[f] (**15**)	3.11 (d, 12)	2.63_5	2.21 (d, 9, of d, 4)		

[a] In $CDCl_3$ from Me_4Si; since part of the ABXY pattern of H_{2e} and H_{2a} is not resolved, the reported values are centers of signals in the spectra. [b] The parenthesized data are multiplicity and coupling constants (in hertz); only clearly recognizable patterns are reported. [c] Substituted *trans*-decahydroquinoline, if not otherwise indicated. [d] CH_3-10. [e] CH_3-8. [f] Perhydrobenzo[*h*]quinoline.

Table V
Pertinent Chemical Shifts[a] of Ring-Deuterated *trans*-Decahydroquinolines

R	6-R-*d*		10β-R-*d*			10α-R-*d*		
	H_{2e}	H_{2a}	H_{2e}	H_{2a}	CH_3[b]	H_{2e}	H_{2a}	CH_3[b,c]
H	2.94	2.55_5	2.98_5	2.56	0.93_5 (7 Hz)	3.01	2.53	0.89_5 (6 Hz) 0.88_8
CH_3	2.73_5	1.95_5	2.76	1.95	0.94 (7 Hz)	2.85	2.76	0.92 (6 Hz) 0.91_3
CH_2CH_3	2.78	2.13	2.83_5	2.05	0.94 (7 Hz)	3.10_3	2.53	0.92 (6 Hz) 0.91_3
$CH(CH_3)_2$	2.84	1.97	2.83	1.98	0.92 (7 Hz)	3.18	2.52_3	0.91_3 (6 Hz) 0.90_6

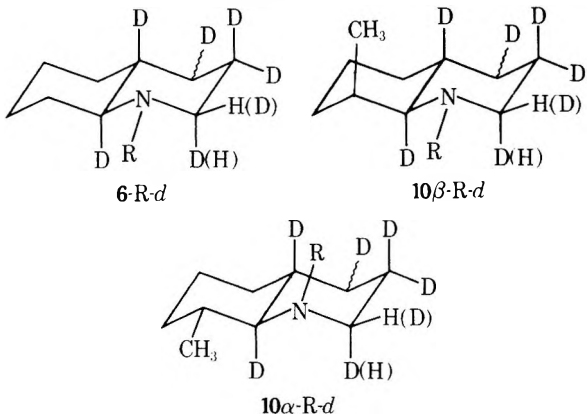
[a] In CF_2BrCF_2Br, from Me_4Si. Chemical shifts of *trans*-decahydroquinoline in this solvent are, H_{2e}, 2.995, H_{2a} 2.585, H_9 2.025; of 8α-methyl-*trans*-decahydroquinoline, H_{2e} 3.045, H_{2a} 2.555, CH_3 0.895. The difference between chemical shifts in Tables IV and V is therefore partly due to a solvent effect, and partly to D isotope effects (see footnote c). [b] Parenthesized values: coupling constants. [c] The first set of signals are doublets of the compounds with a proton on C-8; in the second set (shifted upfield by 0.7 Hz by the deuterium) this proton is exchanged against deuterium and the corresponding methyl signal is a singlet.

stants and a much smaller gauche coupling constant, H_9 is shifted downfield by the anti-placed 10-methyl group to 2.21 ppm and is considerably narrower than in **6**, since one of the anti splittings is absent. A long-range coupling of the 10-methyl group, presumably to H_9 (J = 0.5 Hz), could also be discerned. Finally, the 8,10-dimethyl compound **27α** (Scheme VII) is almost identical with **26** in the H_{2e} and H_{2a} region, but H_9 is shifted back upfield to 1.85 ppm by the gauche methyl group at C-8, which is thus shown to be equatorial. Also, H_9 is a clean doublet, J = 9.5 Hz, since it is split by only one proton (at C-8) in anti location. This split is the best indication for the trans ring junction as well as equatorial methyl at C-8; the latter is also supported by the ^{1}H NMR shift and coupling constant and the ^{13}C NMR shift (Table IV).

In the tricyclic series, the trans-anti-trans isomer of the perhydrobenzo[*h*]quinoline **14** (Scheme II) was recognized by the close similarity of its ^{1}H NMR spectrum with that of the analogous 8α-methyl compound (**10α**). In contrast, the trans-syn-cis compound (**15**, Scheme II) bears an extremely close resemblance in both chemical shifts and coupling constants of all three salient protons to **10β**. These two structures are thus established unequivocally by a conformational analogy. ^{13}C NMR spectroscopy[7] confirms the configurations of these two isomers and the third one (**16**), which was not obtained pure enough for ^{1}H spectral investigation.

The ^{1}H NMR spectra of the *N*-methyl derivatives of **6**, **8α**, **8β**, **9α**, **10α**, **10β**, **14**, **15**, **16**, **26**, and **27α** and the *N*-ethyl and *N*-isopropyl derivatives of **6**, **8**, **10α**, **10β**, and **26** have been tabulated elsewhere.[6] These spectra are of lesser interest than those of the NH precursors because the gauche effect of the equatorial *N*-alkyl group is to shift H_{2a} and H_9 upfield to a point where they are largely overlaid with the envelope of the other protons. An exception occurs in the compounds in which the *N*-alkyl group is axial (NCH_3 of

Scheme X



10α, **14** and **16**) or at least largely axial (NCH_3 of **27α**, *N*-ethyl and *N*-isopropyl of **10α**); H_{2a} and H_9 are now shifted downfield by (a) the anti effect of the *N*-alkyl group and (b) by the absence of the upfield shifting axial pair of electrons on nitrogen to the point where they may again be clearly discerned. However, in case of the NCH_3 derivatives of **10α**, **14**, **16**, and **27α**, H_{2e} and H_{2a} have nearly identical chemical shifts, and the ABXY pattern is nearly degenerate and hard to resolve. The methylene protons in the *N*-ethyl compounds are diastereotopic, and the AA′ part of the AA′X_3 appears in the downfield region, partly overlaid with the signal of H_{2e}. This difficulty was overcome by either decoupling the methyl protons of the ethyl group, whereupon the AA′X_3 collapsed to an AA′, or by recording the deuterium noise-decoupled spectra of the NCH_2CD_3 analogs.

Of more interest are the deuterium noise decoupled spectra of *N*-methyl-*trans*-decahydroquinoline-*2,3,3,4,-9,10-d*$_6$ (**6**-Me-*d*) and its 8-methyl homologs (**10β**-Me-*d* and **10α**-Me-*d*) shown in Scheme X (R = Me). It should be noted that these compounds are singly but nonspecifically deuterated at C-2, so that in each case they are mixtures of the 2α-*d* and 2β-*d* epimers. Also, because of dideuteration at C-3, the sole remaining proton at C-2 is an entirely uncoupled singlet[24] which can be clearly discerned even if it falls into the envelope of the rest of the protons. The pertinent chemical shifts for these compounds and the corresponding *N*-ethyl and *N*-isopropyl homologs are shown in Table V and are of interest in that they provide values not only for ν_a and ν_e in the *N*-methyl equatorial (**10β**, R = Me) and mobile (**6**) species, but also in the *N*-methyl axial case (**10α**, R = Me). Shifts in the former situation have previously been seen in appropriately substituted *N*-methylpiperidines[23] and values of $\Delta(\nu_e - \nu_a)$ of 1.19–1.20 ppm in the N-Me(e) and of 1.02 or 1.10 ppm (in CH_2Cl_2 or toluene-d_8 at −80°C) in the mobile series were reported. The values in the decahydroquinoline series (in CF_2BrCF_2Br at room temperature) are somewhat different: $\Delta_{Me(e)}$ = 0.81 ppm (from **10β**-Me-*d*) and $\Delta_{Me(mobile)}$ = 0.78 ppm (from **6**-Me-*d*). In addition, one can determine a value $\Delta_{Me(a)}$ = 0.09 ppm from the shifts in **10α**-Me-*d*. It is interesting that, on the usual assumption[25] that the value for the mobile system is the weighted average of that for the anancomeric (conformationally biased) systems $\Delta_{Me(mobile)} = n_e\Delta_{Me(e)} + n_a\Delta_{Me(a)}$, one may compute $K = m_e/n_a$ = 23 and $-\Delta G°$ = 1.86 kcal/mol, in excellent agreement with values obtained by more accurate methods.[6] It is of interest that the corresponding Δ values in the secondary amines (NH compounds) are nearly constant: **6**-*d*, 0.39 ppm; **10β**-*d*, 0.43 ppm; **10β**-*d*, 0.48 ppm. Thus, if it is true that these values are determined mainly by the position of the lone pair on nitrogen and not by the position of the *N*-methyl group,[23] the equatorial–axial NH equilibria in **6**, **10β**, and **10α** must be similar, with the peri or syn-axial methyl group exercising little if any bias on the NH.

Experimental Section

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

NMR spectra were recorded on a Varian XL-100 instrument equipped with Fourier transform for ^{13}C analysis. Substances for the spectra summarized in Table IV were dissolved in $CDCl_3$, the deuterium-decoupled spectra of the polydeuterated compounds (Table V) were recorded in $C_2F_4Br_2$. The solvents provided the internal lock signal (D or F); 2% Me_4Si was added to the samples as internal reference. ^{13}C spectra in Table IV were recorded in $CDCl_3$.

Mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E. Microanalyses were carried out by Galbraith Laboratories, Inc.

Starting Materials. Syntheses of the various methyl-substituted 5,6,7,8-tetrahydroquinolines (**1**–**5**), of 5,6,7,8-tetrahydroisoquinoline (**17**), 1,2,3,4,5,6,7,8-octahydroacridine (**11**), and 5,6,6a,7,8,9,10,10a-octahydrobenzo[*h*]quinoline (**13**) have been described in detail elsewhere.[1] Δ^{1,9}-Octahydroquinoline (**21**) was prepared from *N*-1-cyclohexenylpyrrolidine and acrylonitrile as described by Cohen and Witkop.[14] 10-Methyl-Δ^{1,9}-octahydroquinoline (**24**) was synthesized as described by Henshall and Parnell;[15] the intermediate 1-(2-cyanoethyl)-2,2-ethylenedioxy-1-methylcyclohexane was reduced with $LiAlH_4$ (see below for 8,10-dimethyl-Δ^{1,8}-octahydroquinoline).

6-Methyl-Δ^{1,9}-octahydroquinoline (22). *N*-(4-Methyl-1-cyclohexenyl)pyrrolidine (28). 4-Methylcyclohexanone (100.8 g, 0.9 mol), pyrrolidine (85.2 g, 1.2 mol), and benzene (45 ml) were heated to reflux for 5 hr, the water formed being separated with a Dean-Stark trap. When the theoretical amount of water had been collected, solvent and excess pyrrolidine was evaporated at reduced pressure; the product was used without purification.

1-*N*-Pyrrolidinyl-2-(2-cyanoethyl)-4-methylcyclohexene (29). The crude **28** was dissolved in 60 ml of dioxane, 52.5 g (0.99 mol) of freshly distilled acrylonitrile was added, and the mixture was heated to reflux for 2 hr. The solvent was distilled off and the residue was distilled at reduced pressure, yield 153 g (78%), bp 125–130° (0.5 mm).

1-*N*-Pyrrolidinyl-2-(3-aminopropyl)-4-methylcyclohexene (30). The above product (**29**, 65.4 g, 0.3 mol) was dissolved in 150 ml of anhydrous ether and added slowly to 11.5 g (0.3 mol) of $LiAlH_4$ in 650 ml of anhydrous ether. After addition was complete, the suspension was stirred for 1 hr. The excess $LiAlH_4$ was decomposed carefully with ethyl acetate and water, the ether phase was decanted, and the aqueous phase was extracted four times with ether. The combined ether phases were concentrated without drying, and the product was used without purification.

6-Methyl-Δ^{1,9}-octahydroquinoline (22). The above product (**30**) was mixed with 25 ml of aqueous NaOH (2 *N*) and heated under nitrogen for 1 hr on a boiling water bath. After cooling to room temperature the mixture was extracted repeatedly with petroleum ether, and the extracts were combined and dried. The solution was concentrated, and the residue was distilled at reduced pressure. The product (20.4 g, 45% from the nitrile) boiled at 110.5–111° (20 mm); it was pure by VPC. ^1H NMR: δ 0.97 (d, J = 6 Hz, 3 H, CH_3), 3.57 (broad s, 2 H, H-2's), remainder broad, unresolved 0.8–2.5 ppm, 12 H. Picrate, mp 136–137°. Anal. Calcd for $C_{16}H_{20}N_4O_7$: C, 50.53; H, 5.30. Found: C, 50.68; H, 5.52.

8-Methyl-Δ^{1,9}-octahydroquinoline (23). *N*-(2-Methylcyclohexenyl)piperidine (**31**),[26] bp 74–77° (1.2 mm) [lit. bp 48° (1.7 mm)] (0.11 mol), 3-bromopropylamine hydrobromide (0.10 mol), and 30 ml of dimethylformamide were placed in a 250-ml three-necked flask, equipped with a thermometer and heated to 80°, when an exothermic reaction started. The flask was cooled by immersion in an ice bath to keep the temperature of the reaction mixture below 110°. When the reaction subsided, the mixture was heated with magnetic stirring at 100–110° for 12 hr and cooled to

room temperature, and 100 ml of water and 7 ml of concentrated HCl were added. The solution was extracted three times with ether (discarded). The aqueous solution was overlaid with petroleum ether, and was made strongly basic by addition of a concentrated solution of NaOH. The basic solution was extracted repeatedly with petroleum ether, the organic extracts were dried, the solvent was evaporated, and the residue was distilled at reduced pressure. 8-Methyl-$\Delta^{1,9}$-octahydroquinoline (**23**), bp 116–119° (30 mm), was collected. The product was a mixture of two stereoisomers, the major component having the CH_3 group α, the minor β; two methyl signals were visible in the ^1H NMR spectrum, and the ^{13}C spectrum[7] showed two sets of signals. ^1H NMR: δ 1.05 (d, J = 6 Hz, CH_3-α, 2.25 H), 1.14 (d, J = 7.5 Hz, CH_3-β, 0.75 H), 3.54 (broad s, 2 H, H-2's), rest broad, unresolved, 1.0–2.3 ppm. Ratio of CH_3 signals in ^{13}C spectrum:[7] 25% β, 75% α. Picrate, mp 151–152°. Anal. Calcd for $C_{16}H_{20}N_4O_7$: C, 50.53; H, 5.30. Found: C, 50.60; H, 4.89.

8,10-Dimethyl-$\Delta^{1,9}$-octahydroquinoline (25). 2-(2-Cyanoethyl)-2,6-dimethylcyclohexanone (32). 2,6-Dimethylcyclohexanone (mixture of isomers) was washed with dilute alkali and water, dried over $MgSO_4$, and distilled. To 6.35 g (0.5 mol) of the ketone and 2 g of Triton B, 7.5 g (0.14 mol) of freshly distilled acrylonitrile was added dropwise. The reaction vessel was cooled intermittently to keep the temperature below 35°. After addition was complete the mixture was stirred at room temperature overnight, diluted with ether, neutralized with dilute HCl, washed with a saturated aqueous solution of NaCl, and dried over $MgSO_4$. The ether was evaporated at reduced pressure and the residue was distilled, yield 12.65 g (50.5%), bp 117° (0.7 mm).

2-(2-Cyanoethyl)-2,6-dimethyl-1,1-ethylenedioxycyclohexane (33). Compound **32** (12.65 g, 0.071 mol) was dissolved in 50 ml of benzene, 5.2 g of ethylene glycol and 200 mg of *p*-toluenesulfonic acid were added, and the mixture was heated to reflux. The water formed was collected in a Dean-Stark trap. After 48 hr the solvent was evaporated, and the residue was dissolved in ether and washed three times with water. The ether solution was dried over $MgSO_4$, the solvent was removed at reduced pressure, and the residue was distilled, bp 108–112° (0.3 mm), yield 14.2 g (90%).

2-(3-Aminopropyl)-2,6-dimethyl-1,1-ethylenedioxycyclohexane (34). A solution of **33** (14.2 g, 68 mmol), dissolved in 40 ml of anhydrous ether, was added slowly to a suspension of 2.6 g (68 mmol) of $LiAlH_4$ in 150 ml of anhydrous ether, and the mixture was heated to reflux for 4 hr. The excess $LiAlH_4$ was decomposed carefully with ethyl acetate and water, the ether layer was separated, the aqueous phase was extracted repeatedly with ether, and the combined ether phases were concentrated without drying. The product (**34**) was used without further purification.

8α,10-Dimethyl-$\Delta^{1,9}$-octahydroquinoline (25). Compound **34** was dissolved in 40 ml of 2 *N* HCl and the solution was heated to reflux for 1 hr, cooled, made strongly basic with a concentrated solution of NaOH, and extracted repeatedly with petroleum ether. The organic extract was dried and the solvent was distilled. The residue was distilled at reduced pressure in a Kugelrohr distillation apparatus, air bath temperature 140° (22 mm). The product was pure by VPC. ^1H NMR: δ 1.02 (d, J = 6 Hz, 3H, CH_3-8), 1.18 (s, 3 H, CH_3-10), 3.65 (broad s, 2 H, H-2's), rest broad, unresolved 1.0–3.0 ppm. Picrate, mp 185–186°. Anal. Calcd for $C_{17}H_{22}N_4O_7$: C, 51.77; H, 5.62. Found: C, 51.99; H, 5.74.

Reductions with Sodium and Ethanol. These were carried out as described in the literature.[4,15,27] Anhydrous ethanol had to be used for the reduction of pyridine or else the yields of piperidine were drastically lowered.[28]

Reductions with Sodium in Ethanol-*O*-*d*. Ethanol-*O*-*d* was prepared from tetraethyl orthosilicate and D_2O as described by Pasto and Meyer.[29] The uncatalyzed decomposition of the tetraethyl orthosilicate was unsatisfactory: even after prolonged reaction times (5–7 days) at elevated temperatures (reflux) only part of the starting materials had reacted.[30] Addition of small amounts of DCl[30] or $SOCl_2$ led to a very fast and quantitative reaction. The ethanol-*O*-*d* was then heated to reflux for 48 hr with and distilled from crushed CaO.

Piperidine-*2,3,3,4,5,5,6-d*$_7$. Pyridine (4 g) (dried over solid KOH and distilled) was dissolved in 30 ml of ethanol-*O*-*d* and the solution was heated to reflux. Ten grams of sodium (cut in small pieces and stored under anhydrous ether) was gradually added. When part of the sodium was dissolved and sodium ethoxide started precipitating, 20 ml more ethanol-*O*-*d* was gradually added and the mixture was heated until all the sodium had reacted. After addition of 60 ml of water the mixture was distilled until the boiling temperature had reached 100°. The distillate was neutralized with dilute HCl and the solvent was evaporated. The residue was dried in a vacuum desiccator over P_2O_5, yield 5.97 g (97%). One gram of the impure piperidinium-d_7 hydrochloride was dissolved in 2 ml of water, and the solution was covered with petroleum ether and made strongly basic with aqueous NaOH. The basic solution was repeatedly extracted with petroleum ether, the organic extracts were dried over KOH, and the solvent was carefully distilled off. Analytical VPC showed two signals: piperidine (92%) and pyridine (8%). The mixture of amines was separated by preparative VPC (Carbowax 20M KOH column, see above; column temperature 80°), and the mass spectrum of the piperidine-d_7 recorded giving a parent peak of *m/e* 92 (d_7). The ^{13}C spectrum (in $C_2F_4Br_2$) (proton noise-decoupled) showed two triplets: δ 24.91 (J_{CD} = 20 Hz, C-4); 47.34 ppm (J_{CD} = 20 Hz, C-2,6); both triplets were further split by long-range C–D coupling. A very weak and broad signal at ~27 ppm (of C-3 and C-5) was partly overlaid by the signal of C-4. The deuterium noise-decoupled ^1H spectrum in $C_2F_4Br_2$ showed two singlets of equal intensity, H on C-2 and C-6, 2.70 ppm, and NH and H on C-4 at 1.49 ppm.

***trans*-Decahydroquinoline-*2,3,3,4,9,10-d*$_6$.** 5,6,7,8-Tetrahydroquinoline (1.5 g) was dissolved in 25 ml of ethanol-*O*-*d* and reduced by gradual addition of 6 g of sodium and an additional 20 ml of ethanol-O-*d* as described above. When all the sodium had reacted, the mixture was poured into water and the resulting aqueous solution was extracted repeatedly with petroleum ether. The petroleum ether extracts were dried over KOH, the solvent was distilled off on a rotary evaporator, and the solid residue was recrystallized three times from small amounts of petroleum ether, yield 1.14 g, mp 47–48°.

Mass spectrum: The strongest peak corresponded to a mass of 145 (d_6), with a signal of approximately half that intensity for d_7 (146) (*trans*-decahydroquinoline-*2,3,3,4,8,9,10-d*$_7$). The signal for C-7 in the ^{13}C spectrum was split into two peaks with a shift difference of 2.4 Hz, the more upfield signal being due to deuterium at C-8. Full details of the ^{13}C spectrum will be reported elsewhere.[7]

In a similar way 2-methyl- and 8-methyl-5,6,7,8-tetrahydroquinoline and 5,6,7,8-tetrahydroisoquinoline were reduced. The products were separated by preparative VPC.

2α-Methyl-*trans*-decahydroquinoline-*d* and 2-β-Methyl-*trans*-decahydroquinoline-*d*. The mass spectra of both compounds had the largest peak at a mass of 162 (d_9), with large peaks at 161 and 160, and a smaller peak at 163. The ^{13}C spectrum indicates that the compound with mass 163 has deuterium in 2, 3, 3, 4, 8, 9, and 10 and three deuterium atoms in the side chain.

8α-Methyl-*trans*-decahydroquinoline-*d*. The largest peak in the low-voltage mass spectrum corresponds to a mass of 159, with a signal of half that intensity at 160. Both the signals of the CH_3 and C-7 in the ^{13}C spectrum are split, the lower intensity upfield signal being due to deuterium at C-8.

8β-Methyl-*trans*-decahydroquinoline-*d*. The largest peak in the low-voltage mass spectrum is at 159; the peak at 160 was small. No second signal for the CH_3 and C-7 in the ^{13}C spectrum could be seen.

$\Delta^{9,10}$-Octahydroisoquinoline-*d*. The mass spectrum shows ca. 60% d_4 product (mass 141) and *ca.* 40% d_3. The ^{13}C spectrum shows triplets for the signals of C-1 (48.52 ppm, 49.18 in the undeuterated analog) and C-3 (43.01, 43.78 in the undeuterated compound). Only a small triplet due to residual proton at C-4 is visible; the larger part (60%) has this proton exchanged (*1,3,4,4-d*$_4$), and the signal is dissipated.

***trans*-Decahydroquinoline-*d*.** $\Delta^{1,9}$-Octahydroquinoline was reduced with Na–EtOD and the *trans*-decahydroquinoline-*d* was isolated as described above for the 5,6,7,8-tetrahydroquinoline. The ^{13}C spectrum showed complete disappearance for C-9 (fully deuterated), two signals for both C-4 and C-5 in a ratio of 4:6, due to exchange of *ca.* 60% of the proton at C-10, a signal for C-8 which was hardly reduced in intensity, and only a very small additional upfield signal for C-7, indicating very little exchange of H at C-8.

10-Methyl-*trans*-decahydroquinoline-*8,8,9-d*$_3$. 10-Methyl-$\Delta^{1,9}$octahydroquinoline (2 g) was added to 25 ml of ethanol-*O*-*d* in which 500 mg of sodium has been dissolved. The solution was heated to reflux for 3 hr under a protective atmosphere of nitrogen. Then 6 g of sodium and 15 ml of ethanol-*O*-*d* were gradually added. When all the sodium was dissolved, the reaction mixture was poured into water, the aqueous solution was extracted with petroleum ether, the petroleum ether extract was dried, and the solvent was distilled. The mixture of 10-methyl-*trans*- (ca. 90%) and -*cis*- (ca. 10%) decahydroquinoline-*d* (1.81 g, isomer ratio by VPC) was dissolved in ether, 3.25 g of picric acid in ether was added, and the picrate was recrystallized twice from ethanol. The recrystallized picrate was decomposed in aqueous NaOH and the 10-

methyl-*trans*-decahydroquinoline-*d* was extracted with petroleum ether. The extract was dried and the solvent was evaporated. The residue was distilled in a Kugelrohr apparatus to yield 950 mg of product, pure by VPC.

The ^{13}C spectrum showed no visible signal for C-9 (completely deuterated), a triplet of weak intensity for C-8 (due to C-8 substituted by a proton and a deuterium; the dideuterio substituted C-8 is not visible) and two signals for C-7 with a shift difference of 2.5 Hz (due to C-8 HD and C-8 D_2). The signal for C-6 was noticeably broadened by the deuterium at C-8.

Exchange Experiments with *trans*-Decahydroquinoline and 5,6,7,8-Tetrahydroquinoline. *trans*-Decahydroquinoline (or 5,6,7,8-tetrahydroquinoline) (1 g) was added to 25 ml of ethanol-*O*-*d* in which 500 mg of sodium had been dissolved. The solution was heated to reflux for 3 hr, cooled to room temperature, and diluted with 100 ml of water. The amine was extracted with petroleum ether, the extracts were dried, and the solvent was evaporated. The residue was distilled in a Kugelrohr apparatus and the distillate was shown to be pure by VPC. Both mass spectrum and ^{13}C spectrum were identical with those of untreated starting material.

Acknowledgment. This work was supported by the Chemistry Department of the University of North Carolina at Chapel Hill under an NSF Science Development grant. Purchase of the NMR instrument was made possible by NSF Instrument Grants GU-2059, 2059-Amendment I and GP-37602 and by NIH Grant 5S05RR07072. We are indebted to Dr. David Harris for recording the ^{13}C NMR spectra, Mr. Rodney Willer for recording most of the ^{1}H NMR spectra, and Mr. Eusebio Juaristi for the mass spectra.

Registry No.—**1**, 10500-57-9; **2**, 2617-98-3; **3**, 28712-62-1; **4**, 52601-65-7; **5**, 52601-66-8; **6**, 767-92-0; **6**-R-*d* (R = H), 55905-17-4; **6**-R-*d* (R = CH_3), 55905-18-5; **6**-R-*d* (R = CH_2CH_3), 55905-19-6; **6**-R-*d* [R = $CH(CH_3)_2$], 55905-20-9; **7***α*, 18609-01-3; **7***β*, 18610-37-2; **8***α*, 52679-13-7; **8***α* picrate, 55905-21-0; **8***β*, 52601-71-5; **9***α*, 55905-22-1; **10**-R-*d* (R = H), 55905-23-2; **10**-R-*d* (R = CH_3), 55905-24-3; **10**-R-*d* (R = CH_2CH_3), 55905-25-4; **10**-R-*d* [R = $CH(CH_3)_2$], 55905-26-5; **10***α*, 52761-68-9; **10***α* picrate, 55905-27-6; **10***α* HCl, 55905-28-7; **10***α* *N*-benzoyl analog, 55905-29-8; **10***β*, 52730-00-4; **10***β* picrate, 55905-30-1; **10***β* HCl, 55905-31-2; **10***β* *N*-benzoyl analog, 55905-32-3; **11**, 1658-08-8; *trans*-**13**, 55905-33-4; *cis*-**13**, 55905-34-5; **14**, 55925-21-8; **15**, 55925-22-9; **16**, 55925-23-0; **17**, 36556-06-6; **18**, 2721-62-2; **21**, 1074-06-2; **22**, 52601-67-9; **22** picrate, 55905-35-6; *cis*-**23**, 55905-36-7; *cis*-**23** picrate, 55905-37-8; *trans*-**23**, 55905-38-9; *trans*-**23** picrate, 55905-39- **24**, 37442-12-9; **25**, 55905-40-3; **26**, 45846-79-5; **27***α*, 55905-41-4; **27***α* picrate, 55905-42-5; **28**, 39716-23-9; **29**, 55905-07-2; **30**, 55905-09-4; **31**, 55905-11-8; **32**, 7647-22-5; **33**, 55905-43-6; **34**, 55905-44-7; piperidine-*2,3,3,4,5,5,6-d*$_7$, 55905-45-8; *trans*-decahydroquinoline-*2,3,3,4,9,10-d*$_6$, 55905-17-4; 4-methylcyclohexanone, 589-92-4; pyrrolidine, 123-75-1; acrylonitrile, 107-13-1; *cis*-2,6-dimethylcyclohexanone, 766-42-7; *trans*-2,6-dimethylcyclohexanone, 766-43-8; ethylene glycol, 107-21-1.

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The Chemistry of 1,2,5-Thiadiazoles. II. 3,4-Disubstituted Derivatives of 1,2,5-Thiadiazole 1,1-Dioxide[1]

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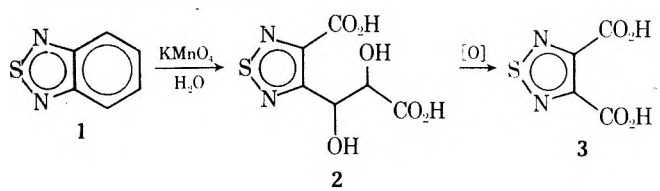
The dipotassium salt of 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide (**4a**) was synthesized in high yield from sulfamide and diethyl oxalate. The free acid (**7**) was prepared from **4a**, from the disilver salt (**4c**), or from 3,4-dichloro-1,2,5-thiadiazole 1,1-dioxide (**13**), the latter being synthesized from **4a** and phosphorus pentachloride. The reactive **13** was converted in methanol to the dimethoxy derivative (**12**). Either **12** or **13** reacted with ammonia to form the 3,4-diamino derivative (**14**) and with methylamine, dimethylamine, and ethylenediamine, respectively, to produce the 3,4-bis(methylamino) (**15**), the 3,4-bis(dimethylamino) (**16**), and the 3,4-piperazino (**23**) derivatives. One mole of morpholine with **12** yielded 3-morpholino-4-methoxy-1,2,5-thiadiazole 1,1-dioxide (**17**), which could be rearranged smoothly by heating to 2-methyl-3-oxo-4-morpholino-1,2,5-thiadiazoline 1,1-dioxide (**18**). Two moles of piperidine with **12** gave 3-oxo-4-piperidino-1,2,5-thiadiazoline 1,1-dioxide (**19**) and *N*-methylpiperidine. Dimethoxy derivative **12** rearranges thermally, first to 2-methyl-3-oxo-4-methoxy-1,2,5-thiadiazoline 1,1-dioxide (**10**) and then to 2,5-dimethyl-3,4-dioxo-1,2,5-thiadiazolidine 1,1-dioxide (**11**). o-Phenylenediamine with **12** in DMF gave the tricyclic 1,3-dihydro[1,2,5]thiadiazolo[3,4-*b*]quinoxaline 2,2-dioxide (**24**). **12** and **14** condensed in the presence of sodium methoxide to form a linear tricyclic quinonoid salt (**25a**). **13** reacted with 2 mol of anthranilic acid to yield a diamine (**26**) which was dehydrated to a linear pentacyclic bis(quinazolino)-1,2,5-thiadiazole derivative (**27**).

Previously, only alkyl or aryl disubstituted derivatives of the 1,2,5-thiadiazole 1,1-dioxide ring had been reported.[2,3] We now wish to report the synthesis and reactions of 1,2,5-thiadiazole 1,1-dioxide derivatives having chlorine, oxygen, or nitrogen substituents on the 3,4 positions.

This work has permitted us to compare the parent aromatic ring system, 1,2,5-thiadiazole,[1a] with its 1,1-dioxide in a series of functional derivatives, and to assess the relative influence of the two ring systems upon such important groups as chloro, hydroxy, and amino. For example, comparison has been made of the effects of the state of oxidation of the ring sulfur atom upon the acidic ionization constants of the 3,4-dihydroxy derivatives (or their tautomers). The amide-like character of the 3,4-diamino derivatives has been noted. A pronounced tendency of the 3,4-dialkoxyl derivatives to transfer their *O*-alkyl groups to the ring nitrogen atoms has been observed. Spectral studies have given information regarding possibilities for prototropy in the hydroxy- and amino-substituted derivatives. Finally, the dioxo compounds have been shown to be excellent precursors for building up more complex fused ring derivatives in which, at the end, the $-SO_2-$ function can be replaced with an unoxidized –S– to yield otherwise inaccessible fused-ring 1,2,5-thiadiazole derivatives of unusual character.[1b] The 1,2,5-thiadiazole 1,1-dioxide nucleus is to be regarded as alicyclic rather than aromatic. It is strongly electron withdrawing and activating but somewhat less powerful than the oxalyl group (–COCO–), with which it is compared.

Carmack et al.[1,4,5] and Pesin et al.[6] found that the neutral potassium permanganate oxidation of 2,1,3-benzothiadiazole (**1**) at 50–60° gave diacid **2**, 1,2,5-thiadiazole-3,4-dicarboxylic acid (**3**), and a small amount of the dipotassium salt of 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide (**4a**). Compound **4a** was obtained as the major product when the permanganate oxidation of **1** or **3** was carried out at 90°. Product **4a** could also be synthesized in low yield from sulfamide and dimethyl oxalate using potassium hydroxide in methanol–water.[1,7] Initial consideration was given to the possibility that the by-product salt might be the dipotassium salt of *N*-sulfamoyloxamic acid **5**, but this was ruled out by both chemical and spectral evidence showing that the compound is a heterocyclic derivative which crystallizes with a firmly held water of crystallization.



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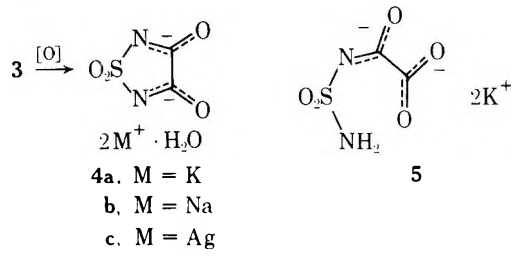
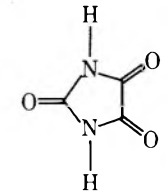


4a, M = K
b, M = Na
c, M = Ag

5

The anhydrous disodium and dipotassium salts of **4** were synthesized in high yield from sulfamide and diethyl oxalate using the respective metal methoxide in a procedure similar to the synthesis of parabanic acid (**6**).[8] The water of hydration was picked up on recrystallization from water and was evolved upon heating above 180°. The proton NMR of **4a** in Me_2SO-d_6 showed only water, identified by observing increased peak intensity upon adding water to the sample.[9] The ^{13}C NMR spectrum of **4b** in water showed one sharp singlet at 171.9 ppm, consistent with the resonating dianion structure **4**. The formation of **4** under completely anhydrous conditions further rules out structure **5**.



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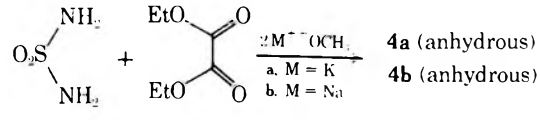
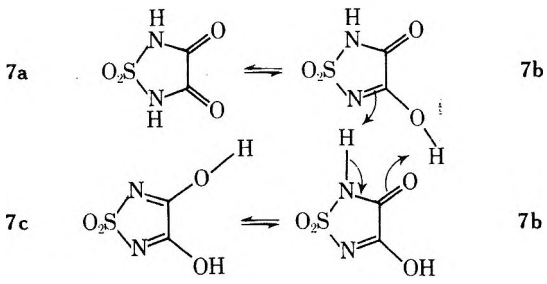


Free 3,4-dihydroxy-1,2,5-thiadiazole 1,1-dioxide (**7**) was

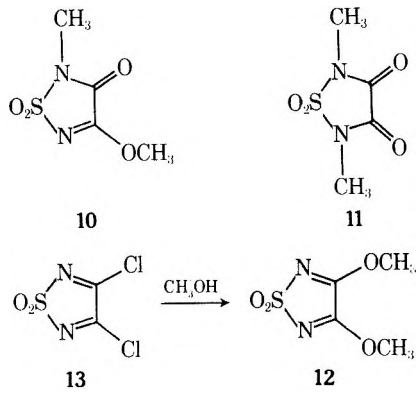
isolated from **4a** by means of a cation-exchange resin, or by the action of hydrogen sulfide on the disilver salt **4c**. Although its salts are stable, **7** itself hydrolyzed readily to sulfamide and presumably oxalic acid. Neutralization of **7** with potassium hydroxide reconverted the material to the dipotassium salt **4a**. Free dihydroxy compound **7** could exist as three tautomers (**7a–c**), whose order of stability



would be predicted to be **7a** > **7b** > **7c**. This order was arrived at from the strength of the infrared absorption bands at 5.67 and 5.80 μm, both typical of >C=O (cf. compound **11**, vide infra) and the lack of absorption in the region of 6.15 μm.

A comparison of acid strengths determined in water for 3,4-dihydroxy-1,2,5-thiadiazole (**9**), 3,4-dihydroxy-1,2,5-thiadiazole 1-oxide (**8**), and 3,4-dihydroxy-1,2,5-thiadiazole-1,1-dioxide (**7**) is shown in Table I.

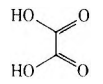
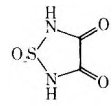
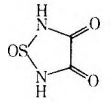
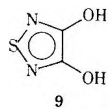
Methylation of the disilver salt **4c** in refluxing methyl iodide–benzene gave 2-methyl-3-oxo-4-methoxy-1,2,5-thiadiazoline 1,1-dioxide (**10**), mp 179–180°, and 2,5-dimethyl-3,4-dioxo-1,2,5-thiadiazolidine 1,1-dioxide (**11**), mp 118–120°, in a 2:1 ratio. The third possible dimethylated isomer, 3,4-dimethoxy-1,2,5-thiadiazole 1,1-dioxide (**12**), mp 188–189°, was synthesized from **13** by a method known to



give only the 3,4-dimethoxy compound (vide infra). All three compounds gave correct analyses for $C_4H_6N_2O_4S$ and showed molecular ions at *m/e* 178 in their mass spectra. The structural assignments of **10** and **11** were made on the basis of ir and NMR spectra. The infrared spectrum of **12** showed a single band at 6.1 μm as expected for the C=N bonds, whereas **10** showed an amide carbonyl band at 5.7 μm[12] in addition to a 6.15-μm band. Compound **11** showed a pair of amide carbonyl bands at 5.54 and 5.7 μm. The proton NMR spectra of the two symmetrical compounds **11** and **12** showed singlets at δ 3.23 and 4.18, respectively. The unsymmetrical compound **10** showed two singlets, one at δ 3.28 for the *N*-methyl protons and one at δ 4.24 for the *O*-methyl protons.

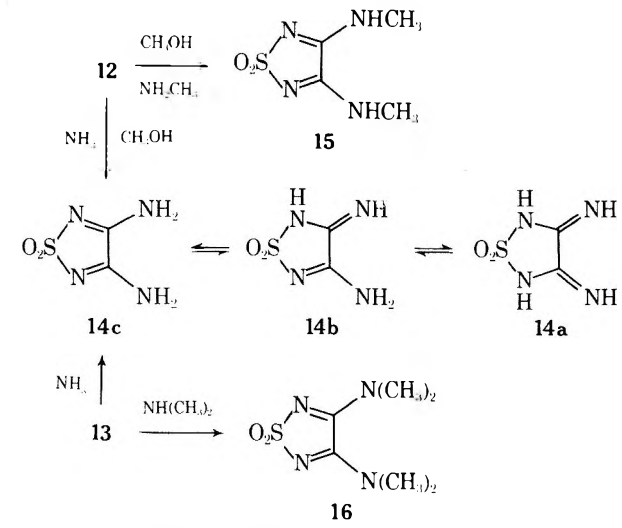
Reaction of **4a** with 3–5 mol of phosphorus pentachloride at 55–60° gave 3,4-dichloro-1,2,5-thiadiazole 1,1-dioxide (**13**). Repeated elemental analyses have shown a small

Table I
Ionization Constants of Heterocyclic Acids

	pK_{a_1}	pK_{a_2}	Ref
	1.23	4.19	10
 7	2.20	5.55	
 8	2.62	6.58	11
 9	4.68	7.50	7, 11

amount (~0.2%) of hydrogen due to the extreme sensitivity of the compound toward atmospheric moisture. However, the mass spectrum of **13** gave the correct exact mass and the expected major fragment at *m/e* 135 ($CClNO_2S$, M^+ – cyanogen chloride). Hydrolysis of **13** to **7** occurred rapidly, indicating that **13** has reactivity comparable to an acid chloride. Surprisingly, the reactions of crystalline **4a** and **4b** with phosphorus pentachloride seemed related to the degree of hydration. Most consistent good yields were obtained from **4a** monohydrate. **4b** dihydrate gave variable yields, whereas anhydrous **4b** gave no dichloride **13**.

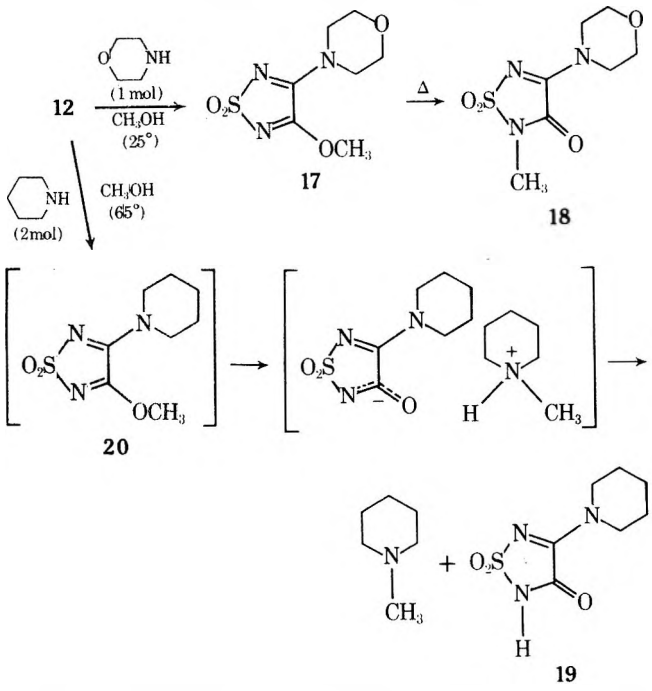
Addition of **13** to methanol gave dimethoxy compound **12** in an exothermic reaction. The corresponding 3,4-diethoxy-1,2,5-thiadiazole 1,1-dioxide was prepared from ethanol and **13**. The dimethoxy compound **12** is readily purified, yet retains reactivity at least comparable to an ester. When a methanolic solution of **12** was saturated with ammonia, 3,4-diamino-1,2,5-thiadiazole 1,1-dioxide (**14**) was formed in nearly quantitative yield. Compound **14** was obtained directly from **13** by treatment with liquid ammonia, although the work-up was longer and the yield lower than in the synthesis from **12**. The compound **14** probably has considerable imino character and should best be represented as a mixture of tautomers, **14a**, **14b**, and **14c**. The same



interpretation would apply to compounds **15**, **23**, and **26**, all of which contain 3,4 secondary nitrogens. The compounds which have protons available for tautomerization exhibit multiple infrared bands between 5.6 and 6.3 nm whereas

compounds incapable of tautomerism, such as **12** and **16**, exhibit only single bands in this region.

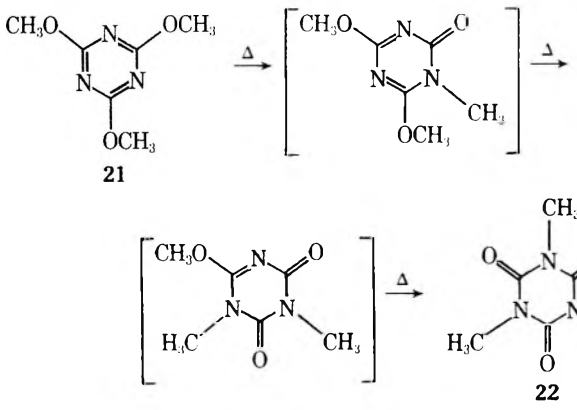
Several N-substituted analogs of **14** were prepared from amines and **12** or **13**. Methylamine with **12** gave 3,4-di-(*N*-methylamino)-1,2,5-thiadiazole 1,1-dioxide (**15**), a white solid, mp 307–308°, showing a molecular ion at *m/e* 176 in its mass spectrum. The corresponding bis(dimethylamino) derivative **16** could be prepared from **13** with excess dimethylamine in ether. The reaction of **12** with 1 mol of morpholine in methanol at 25° gave a white precipitate in which only one of the methoxy groups had been replaced to give 3-methoxy-4-morpholino-1,2,5-thiadiazole 1,1-dioxide (**17**). On rapid heating, a sample of **17** melted at ~205°, then crystallized and melted again at 260–261°, whereas slow heating gave only the higher melting point. The infrared, NMR, and mass spectra of the material obtained by melting **17** and recrystallizing the solid showed it to be 2-methyl-3-oxo-4-morpholino-1,2,5-thiadiazoline 1,1-dioxide (**18**). The mass spectra of both **17** and **18** gave molecular



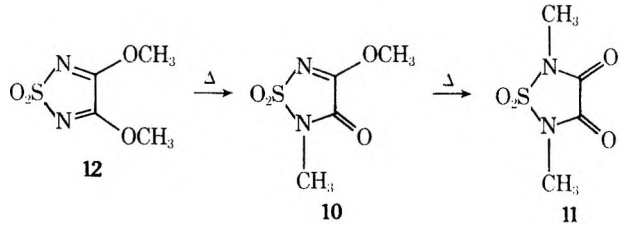
ions at *m/e* 233, although the fragmentation patterns differed considerably, suggesting that a rearrangement had taken place. The ir of **18** showed bands at 5.75 and 6.12 μm analogous to the bands at 5.7 and 6.15 μm for **10**, whereas **17** showed only a 6.2-μm band analogous to the 6.1-μm band for **12**. Thus the thermal rearrangement can be seen to involve a methyl shift from oxygen (**17**) to nitrogen (**18**). This is confirmed by the proton NMR spectra of **17** and **18**. The *O*-methyl of **17** appears at δ 4.18 (cf. the *O*-methyls of **10** and **12** at δ 4.24 and 4.18, respectively) and the *N*-methyl of **18** appears at δ 3.19 (cf. the *N*-methyls of **10** and **11** at δ 3.28 and 3.23, respectively).

An attempt to prepare the 3,4-dipiperidino derivative of **12** by refluxing a methanol solution of **12** and 2 mol of piperidine did not give the expected product, but rather 3-oxo-4-piperidino-1,2,5-thiadiazoline 1,1-dioxide (**19**) and *N*-methylpiperidine. Apparently the expected intermediate, 3-methoxy-4-piperidino-1,2,5-thiadiazole 1,1-dioxide (**20**), is attacked on the methoxy methyl group by the second equivalent of piperidine. The hydrogen of the *N*-methylpiperidinium ion is then transferred to yield **19** and *N*-methylpiperidine.

Precedent for these rearrangements is supplied by a similar thermal rearrangement of 2,4,6-trimethoxy-1,3,5-triazine (**21**) to the *N,N',N''*-trimethyl compound **22**. The isomerization of **21** has been shown to be an intermolecular reaction by isotope labeling, methyl trapping, and chemical methods.[13]

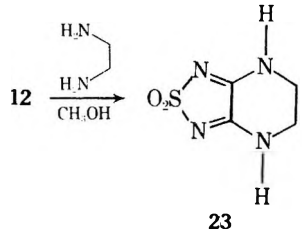


In view of the relative ease of methyl isomerization, dimethoxy compound **12** was reexamined and found to isomerize completely to **11** in less than 1 min above its melting point.[14] A mixture of all three isomers (**10**, **11**, and **12**) was



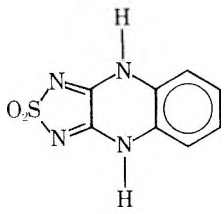
obtained by quickly melting and cooling a sample of **12**, showing that the isomerization proceeded via **10**. Evidently, the isomerization of **10** to **11** is rapid compared to the isomerization of **12** to **10**. Although Paoloni et al. could not isolate the two intermediates in the thermal isomerization of **21** to **22**, they did show that the second and third isomerizations of the intermediates occurred faster than the isomerization of **21** to the first intermediate.[13]

Formation of fused piperazine and pyrazine rings on the 1,2,5-thiadiazole 1,1-dioxide ring was readily accomplished by reaction of **12** with 1,2-diamines. Ethylenediamine in methanol reacted rapidly and quantitatively with **12** to give a precipitate of 4,5,6,7-tetrahydro[1,2,5]thiadiazolo[3,4-*b*]pyrazine 2,2-dioxide (**23**). Not unexpectedly, o-phenyl-

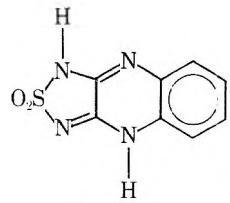


enediamine did not react readily with **12** in methanol; however, an equimolar solution of the reagents in DMF rapidly formed white crystals in a slightly exothermic reaction. The product was identified as 1,3-dihydro[1,2,5]thiadiazolo-[3,4-*b*]quinoxaline 2,2-dioxide (**24**) by its mass spectrum and analysis. Typical of a fused-ring heterocycle, the mass spectrum of **24** showed an intense molecular ion (*m/e* 222.0211, 100%) and a sparse fragmentation pattern (loss of SO_2 predominating, *m/e* 158.0592). Compound **24** would be expected to exist preferentially as tautomer **24c**, since **24c** contains the additional stabilizing factor of a quinoxaline ring.

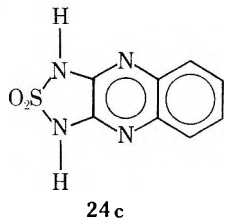
The extremely weak basicity of the amino groups in compound **14** rendered direct condensation with the dimethoxy



24a

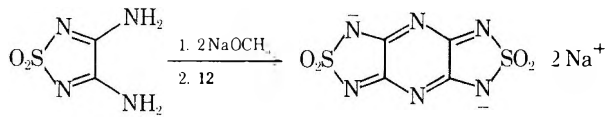


24b



24c

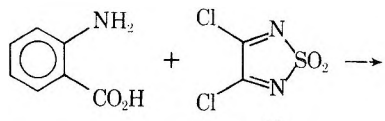
compound **12** unlikely. However, a solution of **14** in methanol containing 2 equiv of sodium methoxide reacted with **12** to give a bright yellow disodium salt, assigned a linear tricyclic structure for which **25a** would represent a preferred resonance-stabilized contributor having maximum separation of the two negative charges in a *p*-quinonoid arrangement. After the recrystallization of the sodium salt, the



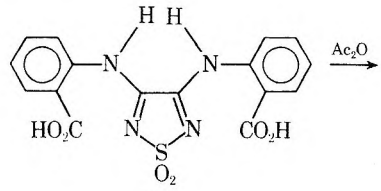
14 25a

NMR showed no protons, and an analysis indicated a C:H:N:S ratio of 2:0:3:1. When a concentrated aqueous solution of **25a** was acidified with dilute hydrochloric acid, a white, crystalline solid formed, mp >360°. A mass spectrum of the free compound (**25b**) showed a molecular ion, as predicted, at *m/e* 262 with volatilization at very high temperature.

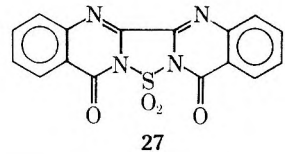
Reaction of the dichloride **13** with excess anthranilic acid in hot acetone gave yellow needles of a product postulated to be diacid **26** in which each chlorine of **13** was replaced by an amino group of anthranilic acid. The diacid **26** was not characterized further, but rather dehydrated with acetic anhydride to **27**. Structural assignment of **27** was made on



13



26



27

the basis of its chemical properties, analysis, and mass spectrum. In contrast to diacid **26**, which is soluble in dilute base, **27** is insoluble in base. Analysis showed a C:H:N ratio of 4:2:1 and a mass spectrum gave a molecular ion at *m/e* 352 (100%).

Experimental Section

General. Melting points (uncorrected) were determined in a Mel-Temp apparatus in open capillary tubes. Analyses were performed by Midwest Microlab, Indianapolis, Ind. Infrared spectra were recorded on a Perkin-Elmer 137 spectrometer. Ultraviolet spectra were recorded using a Cary 14 spectrometer. Low-resolution mass spectra (70 eV) were obtained on a Varian MAT CH-7 instrument using a heated probe. High-resolution mass spectra (70 eV) were obtained on an AEI MS-9 spectrometer. Proton NMR spectra were recorded on a Varian HR-220 instrument with internal Me_4Si as reference. The ^{13}C NMR spectra were acquired on a Varian XL-100 instrument in FT mode. Methanol and 2-propanol were distilled from calcium hydride prior to use.

Dipotassium Salt of 3,4-Dihydroxy-1,2,5-thiadiazole 1,1-Dioxide Monohydrate (4a). A potassium alkoxide solution was prepared by adding 58.7 g (1.50 mol) of potassium to 300 ml of 2-propanol and diluting the solution with 300 ml of methanol. After the solution had cooled, 72.0 g (0.75 mol) of sulfamide in 600 ml of methanol was added dropwise with vigorous mechanical stirring to give a white suspension. Diethyl oxalate (109.6 g, 0.75 mol) was added dropwide with stirring and the resulting suspension was refluxed gently for 16 hr with stirring. After cooling, the white solid was filtered, washed with methanol, and dried under high vacuum to give 158.0 g (93.0%) of anhydrous **4a.** The product was recrystallized from boiling water (2.5 ml/g): mp >360°, gas evolved above 185°; ir (KBr) 2.85, 3.00, 6.00, 6.09, 7.39, 8.01, 8.15, 8.85, 10.40, and 13.23 μm.

Anal. Calcd for $C_2K_2N_2O_4S{\cdot}H_2O$: C, 9.84; H, 0.83; N, 11.48; S, 13.12. Found: C, 9.75; H, 0.60; N, 11.43; S, 12.75.

Disodium Salt 4b. The above procedure was used starting with 1.0 mol of sulfamide to prepare the disodium salt **4b** in 97.5% yield except that only methanol was used to prepare the sodium methoxide. The salt was recrystallized from water and dried at 100° in vacuo: mp >360°, gas evolved above 185°; ^{13}C NMR (H_2O) 171.9 ppm (s).[15]

Anal. Calcd for $C_2Na_2N_2O_4S{\cdot}2H_2O$: C, 10.44; H, 1.75. Found: C, 10.82; H, 1.79.

Repeated recrystallization of the disodium salt **4b** from saturated KCl gave dipotassium salt **4a** identical with **4a** prepared above.

Disilver Salt of 4 Monohydrate (4c). A solution of 15.0 g of silver nitrate in 100 ml of water was added dropwise to a stirred solution of **4a** (10.0 g, 41.0 mmol) in 300 ml of water at 90°. After the addition was complete, the mixture was boiled for 15 min and filtered hot. The white solid was washed with 200 ml of hot water and dried at 100° to give 14.8 g (94.5%) of **4c** containing a small amount of potassium by flame test, mp >360°. The product could not be recrystallized because of its insolubility and was therefore analyzed without purification.

Anal. Calcd for $C_2Ag_2N_2O_4S{\cdot}H_2O$: C, 6.29; H, 0.53; N, 7.34; S, 8.40. Found: C, 6.86, 6.70; H, 0.32, 0.24; N, 7.75; S, 8.27.

Method A. 3,4-Dihydroxy-1,2,5-thiadiazole 1,1-Dioxide Monohydrate (7). Cation Exchange in 4a. A solution of **4a** (3.00 g, 12.3 mmol) in 50 ml of water was passed through 40 ml (wet volume) of Amberlite IR-120H cation-exchange resin, and eluted with water to a pH of 6. The eluent was lyophilized to give 2.09 g of white solid, which on fractional crystallization from acetone–chloroform gave 0.555 g (26.9%) of **7** as colorless prisms: mp 159–161° dec; ir (KBr) 2.97, 3.02, 3.08, 5.67, 5.80, 7.48, and 8.75 μm. A potentiometric titration in water with NaOH gave pK_{a_1} 2.20 and pK_{a_2} 5.55.

Anal. Calcd for $C_2H_2N_2O_4S{\cdot}H_2O$: C, 14.29; H, 2.37; N, 16.67; S, 19.08. Found: C, 14.62; H, 2.25; N, 16.80; S, 18.88.

Concentration of the mother liquor gave 0.642 g (54.5%) of white crystals, mp 91–92°, identified as sulfamide by ir and mixture melting point with an authentic sample.

Method B. Reaction of 4c with Hydrogen Sulfide. Hydrogen sulfide was bubbled into a suspension of the disilver salt **4c** (5.00 g, 13.1 mmol) in 75 ml of THF. After 1 hr, the black silver sulfide was filtered off and the colorless filtrate was evaporated to dryness. Recrystallization from acetone–chloroform gave 0.755 g (34.3%) of **7**, mp 159–160°.

Method C. Hydrolysis of 13. Recrystallized **13** (695 mg, 3.70 mmol) was added to 15 ml of cold 6 *N* HCl with stirring. After the dichloro compound had dissolved, the solution was extracted with ether (2 × 20 ml). The combined ether extracts were dried and evaporated to a white residue, which, after two recrystallizations from ether–cyclohexane, gave 135 mg (21.7%) of **7**, mp 162–163°. The infrared spectra of **7** prepared by all three methods were identical.

Methylation of Disilver Salt 4c. A suspension of **4c** (5.00 g, 13.1 mmol) in 20 ml of redistilled methyl iodide and 100 ml of benzene was refluxed for 20 hr with good stirring. The yellow silver iodide was filtered from the hot solution and washed with 20 ml of hot chloroform. The combined filtrate was evaporated under vacuum to give 2.65 g of faint yellow solid. Fractional crystallization from chloroform–cyclohexane gave two white products. The major product, 831 mg (35.6%), was identified as 2-methyl-3-oxo-4-methoxy-1,2,5-thiadiazoline 1,1-dioxide (**10**): mp 179–180° (see text and ref 14); ir (KBr) 5.70, 6.15, 7.40, 7.52, 8.27, 8.50, 9.62, 10.90, and 14.25 μm; uv (ethanol) λ_{max} 218 nm (log ε 3.88); NMR ($CDCl_3$) δ 3.28 (s), 4.24 (s); mass spectrum *m/e* (rel intensity) 178 (41), 106 (11), 58 (100), 57 (40), 56 (30), 29 (13), and 28 (22).

Anal. Calcd for $C_4H_6N_2O_4S$: C, 26.98; H, 3.40; N, 15.71; S, 18.00. Found: C, 27.39; H, 3.48; N, 15.85; S, 17.83.

The minor product, 425 mg (18.2%), was identified as 2,5-dimethyl-3,4-dioxo-1,2,5-thiadiazolidine 1,1-dioxide (**11**): mp 118–120°; ir (KBr) 5.54, 5.70, 7.34, 7.85, 8.56, 9.50, 10.13, 10.78, and 11.65 μm; uv (ethanol) only end absorption; NMR ($CDCl_3$) δ 3.23 (s); mass spectrum *m/e* (rel intensity) 178 (28), 106 (6), 94 (11), 93 (9), 86 (10), 58 (100), 57 (53), 56 (55), 29 (28), and 28 (58).

Anal. Calcd for $C_4H_6N_2O_4S$: C, 26.98; H, 3.40; N, 15.71. Found: C, 27.13; H, 3.50; N, 16.03.

3,4-Dichloro-1,2,5-thiadiazole 1,1-Dioxide (13). An intimate mixture of **4a** (10.0 g, 41.0 mmol, recrystallized from water, dried at 80° for 4 hr, and finely powdered) and 43.0 g (0.206 mol) of powdered PCl_5 was heated at 55–60° in a flask with a short condenser and drying tube. Magnetic stirring was begun as soon as enough $POCl_3$ had formed. After 12 hr, the $POCl_3$ was evaporated off under vacuum at less than 40°. The dry solid was sublimed at 42–43° (0.3 mm) to give 5.85 g of colorless crystals. Recrystallization from cyclohexane yielded 3.34 g (43.5%) of **13** as needles: mp 103–104°; ir (Nujol) 6.30, 6.41, 7.19, 8.34, 8.73, 9.60, 12.64, 13.15, and 14.52 μm; mass spectrum *m/e* (rel intensity) 186 (2 ^{35}Cl, 1), 125 (1 Cl, 86), 90 (62), 87 (1 Cl, 24), 64 (99), 63 (60), 61 (1 Cl, 100), 52 (18), and 48 (67).

Exact Mass. Calcd for $C_2{}^{35}Cl_2N_2O_2S$: 185.9058. Found: 185.9062.

Anal. Calcd for $C_2Cl_2N_2O_2S$: C, 12.85; H, 0.00; Cl, 37.93. Found: C, 13.21; H, 0.20; Cl, 37.12.

Method A. 3,4-Dimethoxy-1,2,5-thiadiazole 1,1-Dioxide (12) and the Diethoxy Analog. From Recrystallized 13. A solution of 166 mg (0.887 mmol) of recrystallized **13** in 10 ml of anhydrous ether was added to 15 ml of methanol. The mixture was heated on a steam bath for 15 min and then refrigerated overnight to give 119 mg (75.5%) of **12** as colorless needles: mp 188–189° (methanol) (see text and ref 14); ir (KBr) 3.36, 6.10, 6.95, 7.18, 7.50, 7.70, 7.85, 8.44, 10.44, 11.00, and 13.40 μm; uv (ethanol) only end absorption.

Anal. Calcd for $C_4H_6N_2O_4S$: C, 26.96; H, 3.40; N, 15.72; S, 18.00. Found: C, 26.92; H, 3.45; N, 15.84; S, 18.29.

A similar experiment using ethanol in place of methanol gave 83% of the 3,4-diethoxy derivative as white plates from ethanol, mp 178–179.5° (see ref 14).

Anal. Calcd for $C_6H_{10}N_2O_4S$: C, 34.94; H, 4.89. Found: C, 34.71; H, 4.73.

Method B. From 4a via Crude 13. A mixture of 20.0 g (82.0 mmol) of **4a** and 60.0 g (0.288 mol) of PCl_5 was heated as described above. The mixture was filtered and washed with anhydrous ether (3 × 120 ml). The ether extract was added to 140 ml of methanol over 15 min (exothermic), and refluxed for 30 min. On cooling, the white, crystalline precipitate of **12** was collected. Additional crops were recovered by concentrating the mother liquor and cooling to give 7.80 g (53.4%) of **12**, which was recrystallized from methanol: mp 188–189° (see text and ref 14); NMR ($CDCl_3$) δ 4.18 (s); mass spectrum *m/e* (rel intensity) 178 (53), 147 (17), 121 (15), 114 (9), 106 (29), 105 (12), 95 (16), 90 (23), 85 (23), 84 (79), 79 (23), 72 (75), 69 (34), 64 (34), 58 (85), 57 (100), 56 (30), 48 (18), 44 (14), 42 (21), 41 (13), 31 (9), 30 (11), 29 (14), and 28 (27).

Exact Mass. Calcd for $C_4H_6N_2O_4S$: 178.0058. Found: 178.0061.

The infrared and mass spectra of **12** prepared by both methods were identical.

3,4-Diamino-1,2,5-thiadiazole 1,1-Dioxide (14). Method A. Reaction of 12 with Ammonia. An ice-cooled solution of **12** (14.6 g, 82.0 mmol) in 1.2 l. of methanol was bubbled with ammonia for 1 hr. The ice bath was removed and ammonia was bubbled into the solution for an additional 1 hr. Much of the methanol was removed on a rotary evaporator, and, after cooling, the product was filtered. Further concentration and cooling gave a nearly quantitative yield of **14**: mp 284–286° dec; uv (ethanol) λ_{max} 240 nm (log ε 3.93); ir (KBr) 2.92, 3.10, 5.90, 5.97, 6.18, 7.36, 7.70, 7.82, 8.60, 11.25, and 13.80 μm.

Anal. Calcd for $C_2H_4N_4O_2S$: C, 16.21; H, 2.72; N, 37.82. Found: C, 16.15; H, 2.90; N, 37.95.

A similar replacement by ammonia on the 3,4-diethoxy analog of **12** in ethanol gave an identical product.

Method B. Reaction of 13 with Ammonia. A solution of **13** (3.50 g, 18.7 mmol) in 50 ml of anhydrous ether was added dropwise to 5 ml of liquid ammonia at −78°. The mixture was allowed to warm to room temperature and evaporated to dryness under vacuum. The light yellow solid was extracted with THF for 36 hr in a Soxhlet apparatus. The product was filtered from the THF and recrystallized from DMF–chloroform to give 1.14 g (41.2%) of **14**: mp 286–288° dec; ir (KBr) identical with that of **14** prepared from **12**.

3,4-Bis(dimethylamino)-1,2,5-thiadiazole 1,1-Dioxide (16). A solution of **13** (387 mg, 2.07 mmol) in 10 ml of anhydrous ether was added dropwise to a solution of 2 ml of dimethylamine in 20 ml of anhydrous ether. The dimethylamine and ether were evaporated to give a yellow solid which was extracted repeatedly with 10-ml portions of hot acetone. The combined extracts were treated with carbon and filtered. The product was crystallized by addition of hexane to give 158 mg (37.5%) of **16** as colorless crystals: mp 183–185°; uv (ethanol) λ_{max} 280 nm (log ε 3.93); ir (KBr) 3.35, 6.23, 7.14, 7.72, 8.10, 8.73, 9.40, 10.55, 12.06, 13.04, and 14.10 μm.

Anal. Calcd for $C_6H_{12}N_4O_2S$: C, 35.27; H, 5.92; N, 27.43. Found: C, 35.42; H, 5.91; N, 27.44.

3,4-Bis(methylamino)-1,2,5-thiadiazole 1,1-Dioxide (15). A solution of **12** (1.78 g, 10.0 mmol) in 250 ml of methanol was cooled on ice while methylamine was bubbled in for 30 min. The ice bath was removed and the mixture was stirred for 1 hr. The solution was evaporated to dryness and the white product was recrystallized from acetone to give a nearly quantitative yield of **15**: mp 307–308° slow dec; ir (KBr) 3.15, 6.10, 6.40, 7.05, 7.40, 7.82, 8.70, 10.90, and 13.10 μm; mass spectrum *m/e* (rel intensity) 176 (26), 84 (29), 57 (100), 56 (73), 55 (63), 28 (21).

Exact Mass. Calcd for $C_4H_8N_4O_2S$: 176.0368. Found: 176.0368.

Anal. Calcd for $C_4H_8N_4O_2S$: C, 27.26; H, 4.58. Found: C, 27.53; H, 4.82.

3-Methoxy-4-morpholino-1,2,5-thiadiazole 1,1-Dioxide (17). Morpholine (470 mg, 5.40 mmol) in 10 ml of methanol was added at room temperature to a solution of **12** (890 mg, 5.00 mmol) in 100 ml of methanol. A white solid soon precipitated. After 3 hr, the product was filtered, washed with 50 ml of methanol, and dried under high vacuum to give 1.03 g (88.5%) of **17**: mp ~205° and 260–261° (see text); ir (KBr) 6.20, 6.96, 7.60, 7.90, 8.65, 9.00, 9.58, 10.25, 10.83, 11.05, 11.57, 12.42, and 13.85 μm; mass spectrum *m/e* (rel intensity) 233 (41), 218 (52), 176 (30), 168 (18), 154 (44), 139 (18), 112 (23), 86 (49), 85 (19), 58 (40), 57 (20), 56 (100), 55 (61), 54 (41), 53 (15), 42 (89), 29 (20), 28 (92), 27 (22), and 15 (42); NMR ($CDCl_3$) δ 3.76 (t, 2 H, J = 5 Hz), 3.81 (s, 4 H), 4.02 (t, 2 H, J = 5 Hz), 4.18 (s, 3 H).

Exact Mass. Calcd: 233.0470. Found: 233.0474.

Anal. Calcd for $C_7H_{11}N_3O_4S$: C, 36.04; H, 4.75. Found: C, 35.94; H, 4.71.

2-Methyl-3-oxo-4-morpholino-1,2,5-thiadiazoline 1,1-Dioxide (18). Recrystallized (methanol) **17** (ca. 150 mg) was placed in a small test tube and warmed over a small flame until completely melted. After cooling, the white solid was recrystallized from methanol to give **18**: mp 260–261°; ir (KBr) 5.75, 6.12, 6.98, 7.35, 7.50, 7.65, 7.80, 8.20, 8.40, 8.93, 9.30, 9.72, 9.90, 10.23, 10.83, 11.10, 11.55, and 12.26 μm; mass spectrum *m/e* (rel intensity) 233 (42), 169 (33), 139 (15), 126 (14), 85 (52), 57 (12), 56 (27), 55 (100), 54 (24), 42 (58), and 28 (56); NMR ($CDCl_3$) δ 3.19 (s, 3 H), 3.78 (t, 2 H, J = 5 Hz), 3.82 (s, 4 H), 4.45 (t, 2 H, J = 5 Hz).

Exact Mass. Calcd: 233.0470. Found: 233.0474.

Anal. Calcd for $C_7H_{11}N_3O_4S$: C, 36.04; H, 4.75. Found: C, 35.61; H, 4.72.

3-Oxo-4-piperidino-1,2,5-thiadiazoline 1,1-Dioxide (19). Piperidine (410 μl, 4.15 mmol) in 2 ml of methanol was added to dimethoxy compound **12** (356 mg, 2.00 mmol) dissolved in 40 ml of methanol. After refluxing for 45 min, the methanol was removed by distillation through a 6-in. helices-packed column. The remaining oil was distilled to give a drop of *N*-methylpiperidine, identified by comparison of its mass spectrum with literature data:[16,17] mass spectrum *m/e* (rel intensity) 99 (33), 98 (100), 84 (14), 71 (8), 70 (19), 58 (12), 57 (11), 56 (6), 55 (7), 44 (12), 43 (46), 42 (29), 41 (8), and 39 (7); at ~18 eV, 99 (100). The residue was precipitated twice from methylene chloride with hexane to give **19** as a pale yellow oil: ir (KBr) 3.50, 6.00, 6.25, 7.98, 8.76, 10.13, 11.69, and 12.34 μm; mass spectrum *m/e* (rel intensity) 217 (11), 153 (19), 109 (8), 84 (17), 83 (100), 69 (10), 57 (9), 56 (12), 55 (55), 54 (12), and 53 (8).

Isomerization of 12 to 10. Recrystallized **12** (ca. 180 mg) was placed in a small test tube and immersed in an oil bath at 200°. After all the solid had melted, heating was continued for an additional 60 sec. The melt was cooled and scratched to induce crystallization. An infrared spectrum (KBr) showed only **10**, which after recrystallization from chloroform–cyclohexane was identical with **10** prepared by the methylation of **4c**.

Another sample of **12** was heated in an oil bath at 190° until melted and immediately cooled on ice. An infrared spectrum of the solid showed characteristic bands for each of the three methyl isomers, **10**, **11**, and **12**.

4,5,6,7-Tetrahydro[1,2,5]thiadiazolo[3,4-*b*]pyrazine 2,2-Dioxide (23). A solution of ethylenediamine (680 μl, 10.0 mmol) in 10 ml of methanol was added to a solution of **12** (1.78 g, 10.0 mmol) in 200 ml of methanol. Almost immediately a white solid began to precipitate. After the mixture had been stirred for 30 min, the solid was filtered, washed with 50 ml of methanol, and dried under high vacuum to give 1.74 g (100%) of **23**: mp >360°; ir (KBr) 6.13, 7.20, 7.74, 8.70, and 10.80 μm.

Anal. Calcd for $C_4H_6N_4O_2S$: C, 27.58; H, 3.47. Found: C, 26.92; H, 4.02.

1,3-Dihydro[1,2,5]thiadiazolo[3,4-*b*]quinoxaline 2,2-Dioxide (24). Freshly purified *o*-phenylenediamine (540 mg, 5.00 mmol) and recrystallized **12** (890 mg, 5.00 mmol) were dissolved in 5 ml of DMF. The light yellow solution warmed slightly and within 5 min crystalline **24** began to precipitate. After standing at room temperature for 3 hr, the crystals were collected and vacuum dried to give 675 mg of **24**. An additional 407 mg (total 97.5%) was obtained by concentrating the mother liquor under vacuum, filtering the solid, washing with 5 ml of acetone, and vacuum drying. The product was soluble in dilute sodium hydroxide and could be precipitated by adding dilute hydrochloric acid. An analytical sample was recrystallized from DMF: mp >360° (some darkening); ir (KBr) 3.26, 6.02, 6.27, 6.71, 7.20, 7.70, 8.61, 10.72, 11.96, and 13.24 μm; mass spectrum *m/e* (rel intensity) 222 (100), 158 (90), 131 (18), 105 (41), 104 (31), 90 (16), 78 (17), 77 (17), 64 (11), 53 (10), 52 (14), and 51 (14).

Exact Mass. Calcd for $C_8H_6N_4O_2S$: 222.0211. Found: 222.0211. Calcd for $C_8H_6N_4$ ($M^+ - SO_2$): 158.0592. Found: 158.0592.

Anal. Calcd for $C_8H_6N_4O_2S$: C, 43.24; H, 2.72. Found: C, 43.22; H, 2.83.

25a. A sodium methoxide solution was prepared from 276 mg (12.0 mmol) of sodium and 300 ml of methanol. After cooling, **14** (888 mg, 6.00 mmol) was added and stirred until dissolved. Dimethoxy compound **12** (1.068 g, 6.00 mmol) was added and the mixture was allowed to stir for 12 hr at room temperature. The bright yellow salt was filtered and dried to give 1.39 g (75.8%) of **25a**. Additional material of lesser purity was obtained by concentrating the mother liquor. After recrystallization from methanol, **25a** showed mp >360°; NMR [D_2O–TMSP (sodium 3-(trimethylsilyl)propanesulfonate)] no protons; ir (KBr) 6.54, 7.18, 7.70, 8.68, 8.91, 10.20, 11.43, 12.43, and 13.32 μm.

Anal. Calcd for $C_4Na_2N_6O_4S_2$: C, 15.69; H, 0.00. Found: C, 15.78; H, 0.00.

25b. The parent acid of disodium salt **25a** (**25b**) was prepared by acidifying a concentrated aqueous solution of **25a** with 5 *N* HCl and filtering the crystals after 4 hr: mp >360° (darkening); mass spectrum *m/e* 262 (100%).

26 and 27. An acetone solution (20 ml) of **13** (187 mg, 1.00 mmol) and anthranilic acid (550 mg, 4.00 mmol) was refluxed for 30 min to give 514 mg of yellow solid. The solid was dissolved in dilute NH_4OH and after neutralization to pH 6 with HCl, 280 mg of **26** crystallized as fine yellow needles, mp 340–350° dec. Compound **26** was dehydrated by refluxing in 10 ml of acetic anhydride for 15 min. The pale yellow crystalline precipitate was filtered off and dried to give 152 mg of **27**. An analytical sample was recrystallized twice from DMF–water: mp 351–353° (sealed tube); ir (KBr) 5.78, 6.12, 6.28, 6.83, 7.09, 7.50, 7.77, 8.13, 8.34, 8.63, 9.24, 12.40, 12.83, 13.00, 13.46, and 14.50 μm; mass spectrum *m/e* 352 (100%).

Anal. Calcd for $C_{16}H_8N_4O_4S$: C, 54.55; H, 2.29; N, 15.91. Found: C, 54.36; H, 2.41; N, 15.61.

Registry No.—**4a**, 35036-06-7; **4b**, 55904-78-4; **4c**, 55904-79-5; **7**, 55904-80-8; **10**, 55904-81-9; **11**, 55904-82-0; **12**, 55904-83-1; **12** diethoxy analog, 55904-84-2; **13**, 55904-85-3; **14**, 55904-35-3; **15**, 55904-86-4; **16**, 55904-87-5; **17**, 55904-86-6; **18**, 55904-89-7; **19**, 55904-90-0; **23**, 55904-91-1; **24**, 55904-92-2; **25a**, 55925-85-4; **25b**, 55904-93-3; **26**, 55904-94-4; **27**, 55904-95-5; sulfamide, 7803-58-9; diethyl oxalate, 95-92-1.

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The Chemistry of 1,2,5-Thiadiazoles. III. [1,2,5]Thiadiazolo[3,4-c][1,2,5]thiadiazole[1]

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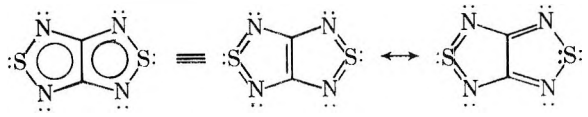
The stable new heteroaromatic compound, [1,2,5]thiadiazolo[3,4-c][1,2,5]thiadiazole (1), was synthesized by three routes. Ring closure of 2 with *excess* sulfur mono- or dichloride in DMF gave 1. The aminoamidine 9a was isolated from the reaction of 2 with only 1 mol of sulfur dichloride. Diamine 3 could be cyclized to 1 with either thionyl chloride in pyridine or with sulfur monochloride in DMF. Oxamide dioxime (4) closed to 1 when treated with sulfur dichloride in DMF. Hydrolysis of 1 gave 3, which on further hydrolysis gave oxamide.

We report the synthesis of a new bicyclic heteroaromatic compound, [1,2,5]thiadiazolo[3,4-c][1,2,5]thiadiazole (1),



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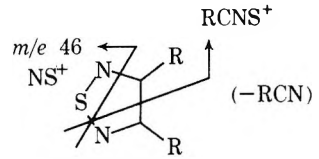
by three independent methods. This ring system represents a unique extension of the isoelectronic replacement of all peripheral atoms of naphthalene with hetero equivalents. A symmetrical and relatively stable ring system results which has only sulfur and nitrogen atoms in exterior positions, with no substituents except unshared electron pairs. The new ring system can be regarded as aromatic by the criteria of planarity, shortened bond lengths, and chemical stability. It shares with the thieno[3,4-c]thiophene series the characteristic that the uncharged resonance contributors contain at least one tetravalent sulfur;[2] yet it appears to possess much greater stability than the thieno[3,4-c]thiophene family. It is the first in a series of bicyclic, tricyclic, and tetracyclic aromatic compounds, with only hetero elements in the periphery, which we shall describe in later papers of this series.[3,4]

Properties of 1. Pure [1,2,5]thiadiazolo[3,4-c][1,2,5]-thiadiazole (1) is a white, crystalline solid, mp 115.7–116°. Trace contaminants (often sulfur) give it a faint yellow color. Although small samples of 1 could be obtained by preparative GLC on an SE-30 column, purification was best accomplished by recrystallization from methanol, vacuum sublimation, or column chromatography on silica gel, or combinations of the three methods.

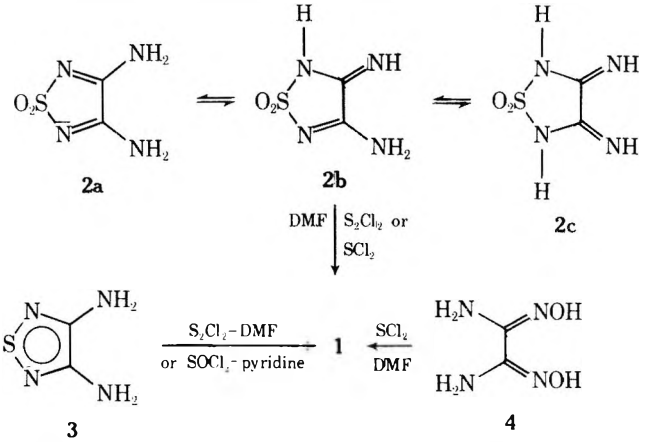
The physical properties of 1 resemble those of naphthalene: it is a planar,[5] nonpolar, volatile, and only very weakly basic white solid, soluble in organic solvents and only very slightly soluble in water.

The molecular formula of 1 was established to be $C_2N_4S_2$ by elemental analysis. A high degree of symmetry for 1 was indicated by the simple infrared spectrum, which contained only four absorptions at 10.9, 12.3, 18.5, and 23 μm. Maxima occurred at 215 and 317 m in the ultraviolet spectrum. The ^{13}C NMR spectrum in chloroform showed a single line at 169.4 ppm from Me_4Si for the two identical carbons. [For comparison, the carbons of 1,2,5-thiadiazole appear at 149.1 ppm ($CHCl_3$), and the ring fusion carbons of 2,1,3-benzothiadiazole appear at 154.2 ppm ($CHCl_3$).][6] An X-ray structural analysis confirmed the planar structure of 1.[5]

In addition to confirming the formula $C_2N_4S_2$ by exact mass measurement of the molecular ion *m/e* 143.9563 (100%), the mass spectrum of 1 showed three major fragment ions: *m/e* 78, 72, and 46. The ion at *m/e* 77.94708 (NS_2, 34%) must result from an ion rearrangement in which the two sulfur atoms are brought into close proximity. The ion at *m/e* 72 (CN_2S, 37%, metastable ion at *m/e* 36.0) corresponds to cleavage of the molecular ion in half. The ion at *m/e* 46 (NS, 63%) arises from both the molecular ion and CN_2S^+, with metastable ions at *m/e* 14.7 and 29.4, respectively. The formation of the ions NS^+ and CN_2S^+ can be compared with two major fragmentation pathways we have found for monocyclic 1,2,5-thiadiazoles; simple cleavage to form NS^+, and loss of RCN (with charge retention on the fragment $RCNS^+$).



Synthesis of 1. Method I. The first synthesis of 1 resulted from work on substituted 1,2,5-thiadiazole 1,1-dioxides.[1] Reaction of 3,4-diamino-1,2,5-thiadiazole 1,1-dioxide (2) with excess sulfur monochloride in *N,N*-dimethylformamide (DMF) gave 1 in 59% yield.[7] Subsequently, it was found that cyclization of 2 with excess sulfur dichloride in DMF improved the yield of 1 to 75%.

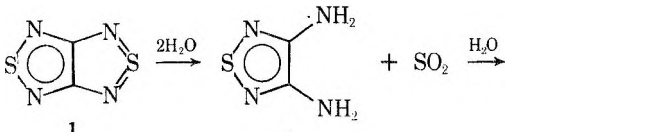


Method II. The second synthesis of 1, a structure proof, was accomplished by cyclization of authentic 3,4-diamino-1,2,5-thiadiazole (3)[4] by two methods known to form a 1,2,5-thiadiazole ring from α-diamines.[8,9] A good yield of 1 (81.5%) was obtained by heating a pyridine solution of 3 during the addition of 2 mol of thionyl chloride in portions. Cyclization of 3 to 1 was also accomplished in 83% yield with sulfur monochloride in DMF.

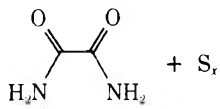
Method III. The most convenient synthesis of 1 was accomplished by the sulfur dichloride cyclization of oxamide dioxime (4) in DMF at 55°, a reaction which proceeds in 66% yield. On the other hand, cyclization of 4 with sulfur monochloride in DMF gave 1 in yields of less than 10%, even though the reagent has been used successfully in the

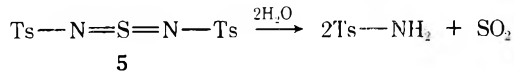
synthesis of other 1,2,5-thiadiazoles from α-diamines and α-dioximes.[8,10]

Reactions of 1. In contrast to 2,1,3-benzothiadiazole, which steam distils cleanly, only a small portion of 1 was recovered from steam distillation. Examination of the undistilled portion showed only oxamide with no remaining 1. In a similar fashion, 1 was suspended in water at 75° for 12 hr to give a mixture of 3, oxamide, and elemental sulfur.



1 3





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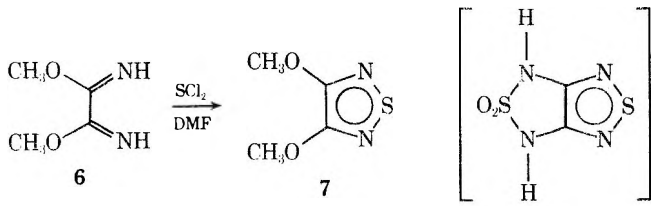
This indicated that the hydrolysis of 1 to oxamide proceeded via 3, yet an authentic sample of 3 heated in water at 75° for 12 hr was recovered unchanged. The sulfur dioxide generated by the hydrolysis of 1 to 3 appears to be required for the subsequent hydrolysis of 3. Indeed, when 3 was heated for 8 hr at 75° in aqueous sulfur dioxide, it was completely hydrolyzed to oxamide and elemental sulfur. Thus, neutralization of the sulfur dioxide formed during the hydrolysis of 1 should halt the hydrolysis at the stage of diamine 3. This was found to be true, for when 1 was refluxed for 20 min in dilute ammonium hydroxide, 3 was obtained in nearly quantitative yield without oxamide or elemental sulfur.

The hydrolysis of 1 to 3 is analogous to the rapid hydrolysis of bis(*p*-toluenesulfonyl)sulfodiimide (5).[11] Both 1 and 5 contain the sulfodiimide linkage (RN=S=NR) with electron-withdrawing substituents on the nitrogens, yet the hydrolysis of 1 is slower than that of 5 because of its aromatic stabilization and the milder electron-withdrawing effect of the 1,2,5-thiadiazole ring compared with the two tosyl groups of 5.

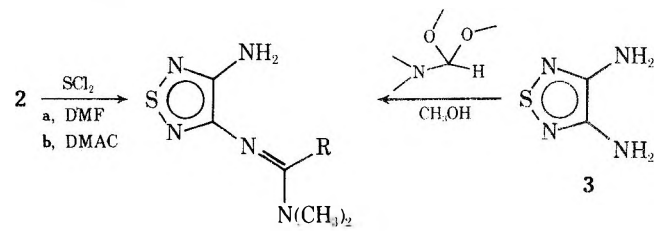
Studies Related to the Ring Closure Reactions Leading to 1. Method I. In an effort to learn more about the sulfur dichloride cyclization of 2 to 1 in DMF, a DMF solution of 2 was treated dropwise with only 1 mol of sulfur dichloride in DMF. This is in contrast to the usual reaction conditions requiring addition of 2 to a large excess of sulfur dichloride. The closure of dimethyl oxaldiimidate (6) with 1 mol of sulfur dichloride in DMF proceeded very well to give 3,4-dimethoxy-1,2,5-thiadiazole (7) in 94% yield. We



6 7 8

had anticipated analogous sulfur dichloride bridging of the exocyclic nitrogens of 2[12] to give the bicyclic intermediate 8. The reaction of 2 did not, however, lead to the analogous product 8 but on aqueous work-up[13] gave a white solid with the molecular formula $C_5H_9N_5S$ (*m/e* calcd 171.0579; found 171.0579). This material was shown to bear two exchangeable hydrogens as evidenced by the increase in mass to *m/e* 173 after equilibration with D_2O. In view of the elemental composition, this result was interpreted as the presence of a primary amino function.

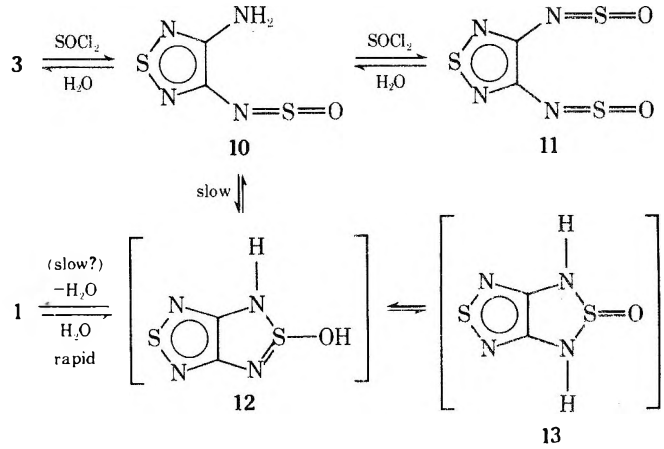
A similar reaction of 2 with 1 mol of sulfur dichloride carried out in *N,N*-dimethylacetamide (DMAC), in place of DMF, gave a compound with its molecular ion at *m/e* 185. These data suggested the formation of amidine functions involving the solvents. On this basis, the structure proposed for the product from cyclization of 2 in DMF and DMAC were **9a** and **9b**, respectively, implicating a Vilsmeier-type intermediate derived from sulfur dichloride and the reaction solvent.[14]



9a, R = H
b, R = CH_3

The structure of **9a** was confirmed by independent synthesis. Aminoamidine **9a** was isolated as a white solid, mp 124.5–125°, upon slow treatment of 3 with 1 mol of dimethylformamide dimethyl acetal in methanol.[15] The 220-MHz NMR spectrum of **9a** ($CDCl_3$) showed a singlet at δ 8.31, a broad singlet at 4.85, and two singlets at 3.07 and 3.03, in a 1:2:3:3 ratio; and corresponding to the imine proton, the amino protons, and the two nonequivalent *N*-methyl groups, respectively.[16] Aminoamidine **9a** prepared from 3 was spectroscopically identical with material from the reaction of 2 with sulfur dichloride in DMF.

Method II. The mechanism for the thionyl chloride cyclization of o-phenylenediamine to 2,1,3-benzothiadiazole in the presence of tertiary amines has been reported.[17] In the present reaction scheme, pyridine may assist in two places: by removing the 2 mol of hydrogen chloride formed in generation of intermediate **10**, which allows free **10** to cyclize to **12**, and by aiding in the dehydration of **12** to 1.[18] It

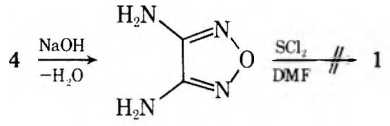


10 11 12 13

was found that, even in pyridine solution, 3 treated with excess thionyl chloride gave poor yields (0–59%) of 1. In order to obtain 1 in good yield, it was necessary to maintain at least a catalytic concentration of **10** throughout the reaction. This was done by initially adding only 1.9 mol (of required 2.0 mol) of thionyl chloride, followed by the slow addition of the remaining thionyl chloride. Evidently, the cyclization of **10** to **12** is much slower than the same process for the benzene analog of **10**,[17,19] owing to the powerful deactivation of the amino group by the 1,2,5-thiadiazole ring. Thus, in the presence of excess thionyl chloride, the red compound **10** is rapidly trapped as the yellow bis-*N*-

sulfinyl compound 11 (aqueous work-up of such a reaction gave mostly starting material 3 by hydrolysis of 11 via 10, and yielded very little 1).

Method III. In view of the obscure mechanism for the cyclization of α-dioximes to 1,2,5-thiadiazoles[8] and 1,2,5-thiadiazole *N*-oxides,[10a] the possible intermediacy of 3,4-diamino-1,2,5-oxadiazole (14) was considered. When 14 (obtained by base-catalyzed dehydration of 4)[20] was treated with sulfur dichloride in DMF under conditions identical with those which convert 4 to 1, no trace of 1 was observed. This rules out 14 as an intermediate. Dehydration



14

of 4 by sulfur dichloride in DMF is probably a competing reaction leading to a less than optimum yield of 1, in analogy to the partial dehydration of dimethylglyoxime to 3,4-dimethyl-1,2,5-oxadiazole by sulfur monochloride in DMF.[8]

Experimental Section

General. Melting points (uncorrected) were determined in a Mel-Temp apparatus in open capillary tubes. Elemental analyses were performed by Midwest Microlab, Indianapolis, Ind., unless otherwise indicated. Infrared spectra were recorded on Perkin-Elmer 137 or 621 spectrometers. Ultraviolet spectra were recorded on methanol solutions using a Cary 14 spectrometer. Low-resolution mass spectra (70 eV) were obtained on a Varian MAT CH-7 instrument. High-resolution mass spectra (70 eV) were determined with an AEI MS-9 spectrometer. Proton NMR spectra were obtained on a Varian HR-220 spectrometer. The ^{13}C NMR spectra were recorded on a Varian XL-100 instrument operating in FT mode.[6] *N,N*-Dimethylformamide (DMF) was distilled successively from phosphorus pentoxide and calcium hydride. *N,N*-Dimethylacetamide (DMAC) was distilled from calcium hydride. Anhydrous magnesium sulfate was routinely used as a drying agent.

1 from 2 with Sulfur Monochloride (Method I). A solution of sulfur monochloride (12.0 ml, 150 mmol) in 50 ml of DMF was cooled on ice with stirring while 4.00 g (27.0 mmol) of 2[1] was added in portions over 20 min. After the mixture had been stirred at room temperature for 2.5 hr, it was poured onto 120 g of ice and extracted with ether (4 × 80 ml). The combined ether extracts were washed with water (2 × 25 ml), dried, and evaporated to dryness, yielding 2.74 g of crude 1 as yellow-white plates. It was then chromatographed on 75 g of silica gel. A small amount of elemental sulfur was eluted with 2% ether in hexane, followed by 2.30 g (59%) of 1 eluted with 4–8% ether in hexane. The colorless prisms, mp 115.2–116°, were sublimed at 50–60° (3 mm): mp 115.7–116° (Hershberg apparatus); ir (KBr, recorded between 2.5 and 25 μm) 10.9, 12.3, 18.5, and 23 μm; uv λ_{max} (log ε) 215 nm (3.17), 317 (4.32); ^{13}C NMR ($CHCl_3$) 169.4 ppm;[6] mass spectrum *m/e* (rel intensity) 144 (100, M^+), 104 (2, CN_2S_2), 98 (1, C_2N_3S), 78 (34, NS_2), 72 (37, CN_2S), 64 (2, S_2), 58 (2, CNS), 52 (2, C_2N_2), 46 (63, NS), 40 (0.5, CN_2), 38 (0.5, C_2N), and 32 (9, S); metastable ions 42.2 (144 → 78), 36.0 (144 → 72), 29.4 (72 → 46), and 14.7 (144 → 46).

Exact Mass. Calcd for $C_2N_4S_2$: 143.9564. Found: 143.9563. Calcd for NS_2: 77.94722. Found: 77.94708.

Anal. Calcd for $C_2N_4S_2$: C, 16.66; H, 0.00; N, 38.86; S, 44.48. Found: C, 16.78; H, 0.00; N, 38.87; S, 44.27 (A. Bernhardt).

1 from 2 with Sulfur Dichloride (Method I). A solution of sulfur dichloride (1.4 ml, 22 mmol) in 8 ml of DMF was cooled on ice while 2 (592 mg, 4.00 mmol) was added in portions over 10 min. After the mixture had been stirred at room temperature for 3 hr, it was cooled to 0°, poured onto 20 g of ice, and extracted with ether (4 × 20 ml). The combined ether extracts were washed with water (4 × 5 ml), dried, and evaporated to dryness to give 430 mg (74.6%) of 1.

3,4-Dimethoxy-1,2,5-thiadiazole (7). The procedure is an improvement on the sulfur dichloride cyclization of diethyl oxaldiimidate in refluxing benzene yielding 3,4-diethoxy-1,2,5-thiadiazole in 66% yield.[21] Sulfur dichloride (51.0 g, 495 mmol) in 250 ml of DMF was cooled to −30°. Dimethyl oxaldiimidate[22] (6, 52.2 g, 450 mmol) in 75 ml of DMF was added dropwise over 20 min at −30°. After the mixture had been stirred for 4 hr at room temperature, it was treated with 600 ml of water and steam distilled. The organic layer was separated and the aqueous layer was extracted with methylene chloride (2 × 40 ml.) The combined organic extracts were dried and fractionated to give 61.8 g (94.1%) of colorless 7: mp 33–34°; bp 90° (~20 mm); NMR ($CDCl_3$) δ 4.01 (s); ir (neat) 5.99, 6.47, 6.59, 6.90, 6.95, 7.10, 7.22, 7.30, 7.83, 8.02, 8.44, 10.10, 11.41, and 13.00 μm; mass spectrum *m/e* (rel intensity) 146 (100), 145 (11) 131 (7), 117 (21), 116 (6), 103 (16), 89 (31), 85 (7), 74 (27), 61 (34), 58 (32), 54 (7) 46 (76), and 15 (39).

Exact Mass. Calcd for $C_4H_6N_2O_2S$: 146.0150. Found: 146.0156.

Anal. Calcd for $C_4H_6N_2O_2S$: C, 32.87, H, 4.14. Found: C, 32.97; H, 4.20.

9a from 2. Freshly distilled sulfur dichloride (60 μl, 0.95 mmol) was added slowly at 0° to 148 mg (1.00 mmol) of 2 in 1 ml of DMF. After the red reaction mixture had been stirred for 10 min, half of it was evaporated to dryness under high vacuum. A mass spectral analysis of the crude solid showed molecular ions at *m/e* 171 (**9a**) and 126.[13] The remaining half of the reaction mixture was stirred with 5 ml of water and extracted twice with ether. No material was present in the ether extract. The aqueous layer was neutralized with excess sodium bicarbonate and extracted three times with ether. The combined ether extracts were dried and evaporated under high vacuum to give crystals of **9a**, spectroscopically identical with **9a** prepared from 3.

Exact Mass. Calcd for $C_5H_9N_5S$: 171.0579. Found: 171.0579.

Solid **9a** dissolved in ether was stirred vigorously with D_2O for 30 min. The ether layer was separated, dried, and evaporated to give dideuterated **9a**: mass spectrum *m/e* 173, 158, 131, 129, 109, 99, 83, 76, 57, 44, 43, 42, 30, 28, and 15.

9b from 2. A sulfur dichloride cyclization of 2 was conducted in DMAC rather than DMF. A mass spectrum of the crude mixture prior to work-up showed a larger molecular ion at *m/e* 140 than *m/e* 185 (**9b**).[13]

Exact Mass. Calcd for $C_6H_{11}N_5S$: 185.0735. Found: 185.0737.

9a from 3. *N,N*-Dimethylformamide dimethyl acetal (232 mg, 2.00 mmol) in 2 ml of methanol was added over 10 min to a refluxing solution of 3 (232 mg, 2.00 mmol) in 3 ml of methanol. After the colorless solution had been refluxed for an additional 30 min, it was cooled on ice and filtered to give white **9a**: mp 124.5–125° (methanol); ir (KBr) 2.89, 2.99, 3.09, 3.39, 6.16, 6.55, 6.67, 6.82, 7.01, 7.12, 7.46, 7.98, 8.17, 8.99, 9.42, 11.65, 11.96, and 12.87 μm; NMR ($CDCl_3$) δ 8.31 (s, 1), 4.85 (broad s, 2), 3.07 (s, 3), and 3.03 (s, 3); mass spectrum *m/e* (rel intensity) 171 (100), 156 (16), 129 (20), 127 (16), 108 (21), 98 (19), 83 (30), 74 (13), 57 (12), 44 (67), 43 (17), 42 (40), 30 (14), 28 (16), and 15 (10).

Exact Mass. Calcd for $C_5H_9N_5S$: 171.0579. Found: 171.0578.

Anal. Calcd for $C_5H_9N_5S$: C, 35.07; H, 5.30. Found: C, 35.23; H, 5.55.

Aminoamidine **9a** could also be synthesized from 3 by treatment with thionyl chloride in DMF.

1 from 3 with Thionyl Chloride (Method II). Thionyl chloride (550 μl 7.57 mmol) was added dropwise to a solution of 3,4-diamino-1,2,5-thiadiazole (3,[4] 468 mg, 4.00 mmol) in 4 ml of pyridine (exothermic). After the red solution had been heated for 15 min (oil bath 125°), thionyl chloride (30 μl, 0.4 mmol) was added dropwise and heating was continued for 30 min before a final portion of thionyl chloride (30 μl, 0.4 mmol, total ~8.4 mmol) was added dropwise. After being heated for 30 min, the brownish solution was cooled on ice and stirred briefly with 10 ml of ice water. The solid was filtered, washed well with water, and air dried to give 470 mg (81.5%) of 1.

Similar experiments, in which the entire quantity of thionyl chloride was added at the onset, gave lower yields (0–59% depending on the addition rate). The product from rapid addition, 11, was obtained as an extremely moisture-sensitive pale yellow solid: mass spectrum *m/e* 208, 120, and 46. Even during transfer to the mass spectrometer in a glove bag under dry nitrogen, 11 frequently hydrolyzed partly to a red solid (10), mass spectrum *m/e* 162, 120, 74, and 46, and some 1. When solid 11 was treated with catalytic amounts of water, sulfur dioxide was evolved and variable yields of 1 were produced.

1 from 3 with Sulfur Monochloride (Method II). A solution of 3 (116 mg, 1.00 mmol) in 1 ml of DMF was cooled to −15° and added to sulfur monochloride (325 μl, 4.0 mmol) in 2 ml of DMF at −15°. The red mixture was stirred at room temperature for 1.5 hr, poured onto 20 g of ice, and extracted with ether (4 × 50 ml). The combined ether extracts were washed with water (3 × 15 ml) and dried. Evaporation of the ether left 120 mg (83.3%) of 1.

1 from 4 (Method III). A solution of oxamide dioxime (4,[23] 11.8

g, 100 mmol) in 150 ml of DMF was added dropwise over 40 min to a stirred solution of sulfur dichloride (38.2 ml, 600 mmol) in 250 ml of DMF at 0–10°. After the mixture had been heated at 55° for 8 hr, it was cooled to 5° and poured onto 400 g of ice. The product was extracted with ether (7 × 150 ml). The combined ether extracts were washed with water (3 × 25 ml), dried, and evaporated to dryness under vacuum to give 15.9 g of yellow solid. After standing overnight, the product was dissolved in 100 ml of boiling methanol, decanted from 2.3 g of elemental sulfur, treated with carbon, and filtered hot. The methanolic filtrate was cooled on Dry Ice and the resulting white plates of **1** were collected on a cold filter. After air drying, the product weighed 9.50 g (66%).

Similar experiments using sulfur monochloride in place of sulfur dichloride gave low yields (<10%) of **1**.

14 from 4. The procedure of Coburn was altered slightly to improve safety and yield.[20] Oxamide dioxime (**6**, 11.8 g, 100 mmol) was added to a solution of sodium hydroxide (4 g in 40 ml of water) in a 300-ml Pyrex-lined autoclave. The autoclave was heated at 160–185° for 2 hr, then cooled on ice and the white solid was filtered, washed with ice water (2 × 20 ml), and dried (7.0 g, 70%). The solid was dissolved in hot water and filtered. After the filtrate had been cooled, pure white **14** was collected, mp 178.5–180.5° (lit.[20] mp 180°). Mass spectral and infrared analyses showed the product to be free of starting material.

Exact Mass. Calcd for $C_2H_4N_4O$: 100.0385. Found: 100.0386.

Reaction of 14 with Sulfur Dichloride. A solution of **14** (1.0 g, 10 mmol) in 15 ml of DMF was added over 15 min to a stirred solution of sulfur dichloride (3.8 ml, 60 mmol) in 25 ml of DMF at 0–5°. After the mixture had been heated for 8 hr at 55°, it was cooled to 0°, poured onto 40 g of ice, and extracted with ether (6 × 20 ml). The combined ether extracts were washed with water (2 × 10 ml), dried, and evaporated to dryness to give only a small amount of yellow solid shown to be elemental sulfur by its mass spectrum. No trace of **1** was detected in this and two additional experiments.

Hydrolysis of 1. A. In Water. A suspension of **1** (72 mg, 0.50 mmol) in water was heated at 75°. After 1 hr, the solid had dissolved to give a light yellow solution, and after 12 hr, a precipitate had formed. The water was removed by lyophilization to give an off-white solid. Mass spectral analysis showed **3**, oxamide, and elemental sulfur.

B. In Dilute Ammonium Hydroxide. A suspension of **1** (1.44 g, 10.0 mmol) in 30 ml of 3 *M* ammonium hydroxide was refluxed until all of the solid had dissolved (20 min or less). The colorless solution was lyophilized to give **3** in nearly quantitative yield. After recrystallization (water), the melting point, ir, and mass spectra of **3** were identical with those of an authentic sample.[4]

In other experiments, mixtures of **1** and **3** were found to give a pale lavender color.

Hydrolysis of 3. A. In Water. A 58-mg sample of **3** was dissolved in water and heated at 75° for 12 hr. The solution was lyophilized to give recovery of the starting material.

B. In Water with Sulfur Dioxide. A 58-mg sample of **3** was dissolved in water and bubbled with sulfur dioxide for several seconds. After the solution had been heated 8 hr at 75° (precipitate present), it was lyophilized to give a mixture of oxamide and elemental sulfur by mass spectral analysis.

15.[16] Aminopyrazine (Aldrich, 9.51 g, 100 mmol) was suspended in 20 ml of ethanol and heated to reflux. Dimethylformamide dimethyl acetal (14.0 g, 117 mmol) was added dropwise over 10 min and the solution was refluxed for an additional 3 hr. After the solvent and excess reagent had been distilled under vacuum, the faintly yellow amidine **15** (14.73 g, 98.2%) was vacuum distilled: mp slightly above room temperature; bp 84–85° (0.04 mm); NMR (15° probe temperature) ($CDCl_3$) δ 8.37 (s, 1), 8.23 (narrow m, 1), 8.04 (m, 2), and 3.07 (s, 6); NMR (CCl_4) δ 8.39 (s, 1), 8.13 (narrow m, 1), 7.96 (m, 2), 3.00 (s, 3), and 2.99 (s, 3); NMR (C_6D_6) δ 8.65 (narrow m, 1), 8.38 (s, 1), 8.00 (m, 2), 2.63 (s, 3), and 2.18 (s, 3); NMR (C_5D_5N) δ 8.60 (m, 2), 8.24 (m, 2), 2.95 (s, 3), 2.81 (s, 3); ir (neat) 3.23, 3.38, 3.53, 6.15, 6.35, 6.66, 6.83, 6.94, 7.21, 7.43, 7.88, 8.04, 8.47, 8.72, 9.02, 9.42, 9.87, 10.13, 11.64, 11.87, and 13.10 μm; mass spectrum *m/e* (rel intensity) 150 (100), 149 (50), 135 (28), 134 (8), 108 (15), 94 (27), 82 (11), 81 (10), 80 (30), 79 (32), 71 (10), 57 (50), 53 (9), 52 (29), 44 (71), 43 (8), 42 (45), 40 (9), 30 (21), 28 (25), 26 (8), and 15 (19).

Exact Mass. Calcd for $C_7H_{10}N_4$: 150.0905. Found: 150.0905.

16.[16] An experiment similar to the above was carried out on 2-amino-3-chloropyrazine to give **16**: NMR (CCl_4) δ 8.33 (s, 1), 7.87 (d, J = 2.6 Hz, 1), 7.73 (d, J = 2.6 Hz, 1), 3.12 (s, 3), and 3.11 (s, 3); ir (neat) 6.15, 6.44, 6.71, 6.89, 7.04, 7.26, 8.03, 8.62, 8.96, 9.18, 9.44, 10.16, 11.50, 11.85, and 13.49 μm; mass spectrum *m/e* (rel intensity, ^{35}Cl ions only) 184 (44), 169 (8), 168 (6), 149 (84), 133 (12), 128 (12), 113 (11), 108 (12), 79 (18), 57 (54), 52 (19), 44 (100), 42 (69), 30 (26), 28 (19), and 15 (23).

Exact Mass. Calcd for $C_7H_9{}^{35}ClN_4$: 184.0516. Found: 184.0514.

Acknowledgment. We thank the National Science Foundation (Grant GP-32225) for funds used in the computerization of the departmental mass spectrometers.

Registry No.—**1**, 55904-34-2; **2**, 55904-35-3; **3**, 55904-36-4; **4**, 2580-79-2; **6**, 30986-09-5; **7**, 55904-37-5; **9a**, 55904-38-6; **9b**, 55904-39-7; **14**, 17220-38-1; **15**, 51519-09-6; **16**, 55904-40-0; sulfur monochloride, 10025-67-9; sulfur dichloride, 10545-99-0; *N,N*-dimethylformamide dimethyl acetal, 4637-24-5; thionyl chloride, 7719-09-7; aminopyrazine, 5049-61-6; 2-amino-3-chloropyrazine, 6863-73-6.

References and Notes

(1) For part II in this series see R. Y. Wen, A. P. Komin, R. W. Street, and M. Carmack, preceding paper in this issue.
(2) M. P. Cava, M. Behforouz, G. E. Husbands, and M. Srinivasan, *J. Am. Chem. Soc.*, **95**, 2561 (1973).
(3) Part IV: A. P. Komin and M. Carmack, *J. Heterocycl. Chem.*, in press.
(4) The synthesis of **3** by three routes will appear in part V: *J. Heterocycl. Chem.*, submitted for publication.
(5) An X-ray structure analysis by Professor Riley Schaeffer showed **1** to be planar, with the following dimensions: bond angles: NSN 103.2°, SNC 104.4°, and NCC 114°; bond lengths: NS 1.62 Å, NC 1.35 Å, and CC 1.44 Å.
(6) The chemical shifts with respect to chloroform were converted to Me_4Si by adding 77.2 ppm.
(7) (a) M. Carmack, R. W. Street, and R. Y. Wen, Abstracts, 158th National Meeting of the American Chemical Society, New York, N.Y., Sept 1969, No. ORGN-54; (b) R. W. Street, M.S. Dissertation, Indiana University, 1968.
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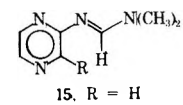
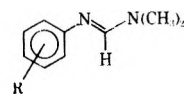
(9) (a) A. M. Khaletskii, V. G. Pesin, and C.-C. Chao, *Dokl. Akad. Nauk SSSR*, **106**, 88 (1956); *Chem. Abstr.*, **50**, 13885*c* (1956); (b) D. Picher and R. N. Castle, *J. Heterocycl. Chem.*, **8**, 441 (1971).
(10) (a) K. Pilgram, *J. Org. Chem.*, **35**, 1165 (1970). (b) Reactions of dioximes with selenium monochloride: C. L. Pedersen, *J. Chem. Soc., Chem. Commun.*, **17**, 704 (1974).
(11) G. Kresze and W. Wucherpfenning, *Angew. Chem., Int. Ed. Engl.*, **6**, 149 (1967).
(12) Compound **2** has considerable imino character, i.e., **2b** and **2c** are prevalent.[1]
(13) Mass spectral examination of the crude reaction mixture, prior to water work-up, showed an additional compound with a molecular ion at *m/e* 126 (fragment at *m/e* 99, $M^{\cdot+}$ − HCN). The analogous reaction with DMAC as solvent gave a corresponding molecular ion at *m/e* 140 (fragment at *m/e* 99, $M^{\cdot+}$ − CH_3CN). On this basis, the compounds are probably the imidazole derivatives obtained by elimination of dimethylamine from **9a** and **9b**, respectively. Neither of the imidazoles was isolated.
(14) There is good evidence for a Vilsmeier-type reagent prepared from sulfur dichloride and DMF: U. Hasserodt, *Chem. Ber.*, **101**, 113 (1968).
(15) H. Brederick, F. Effenberger, and A. Hofmann, *Chem. Ber.*, **97**, 61 (1964).
(16) The imine proton was assigned by comparison to the imine protons of the two *N,N*-dimethylformamidines, **15** and **16** (see Experimental Section). The reported NMR of **17** (C_6D_6), in which R's were electron-withdrawing groups, showed nonequivalence of the two *N*-methyl groups: J. P. Marsh, Jr., and L. Goodman, *Tetrahedron Lett.*, 683 (1967).



15, R = H
16, R = Cl



17

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(18) The dehydration of **12** to **1** may be slow, since it was shown that the reverse reaction, hydrolysis of **1** to **3** via **12**, is faster than that of any known 1,2,5-thiadiazole. The hydrolysis of **1** to **12** is similar to the covalent hydration observed for pyrazino[2,3-*b*]pyrazine: W. L. F. Armarego, *J. Chem. Soc.*, 4304 (1963).
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Studies in the Heterocyclic Series. X. 1,3,9-Triazaphenothiazine Ring System, a New Phenothiazine Ring

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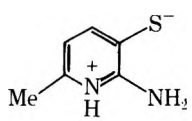
Functionally substituted novel triazaphenothiazines were sought for a study of their properties and reactions and for testing as antihypertensive and antipsychotic agents. The reaction of 2-amino-3-mercapto-6-picoline with 5,6-disubstituted pyrimidines under acid-catalyzed conditions produced good yields of the new 1,3,9-triazaphenothiazine ring system. This heterocyclic ring is now the second known phenothiazine with three annular nitrogen atoms; the remaining 22 structural isomers remain unknown. The aminomercaptopicoline precursor was obtained as the dipolar salt by base-catalyzed hydrolysis of 2-amino-3-thiocyano-6-picoline followed by acidification. A similar reaction with some 4-chloropyrimidines which are unsubstituted in the 5 position yielded 6-(3-mercapto-6-methyl-2-pyridyl)pyrimidinylamines as their dipolar salts. The structures of these products were established by chemical evidence and ultraviolet, infrared, NMR, and mass spectrometry.

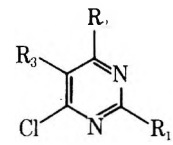
Our interest in the chemistry of phenothiazine[1,2] and phenoxazine[3,4] with annular nitrogen atoms led us to investigate the related compounds, particularly those with isomeric azaphenothiazine rings. Some of the least explored group of compounds in these series are those bearing three ring nitrogen atoms. While four monoaza- and nine diazaphenothiazine systems are known,[1] the only known phenothiazine ring in this group is the 1,3,6-triazaphenothiazine;[5] the remaining 23 structural isomers of this ring have not been reported. In view of the remarkable psychopharmacological properties of the derivatives of azaphenothiazine heterocycles,[6,7] we became particularly interested in the synthesis of phenothiazines bearing annular nitrogen atoms in the active sites 1, 3, and 9 positions as these may combine the antihypertensive[8] and CNS depressant actions of 1-aza-[6,9] and 1,3-diazaphenothiazines.[10]

We have chosen the reaction path which utilizes 2-amino-3-mercaptopyridine precursor. Of all the possible routes at our disposal for the preparation of this compound, an adaptation of Kaufmann's electrophilic thiocyanation of aromatic amines with nascent thiocyanogen appears most convenient and attractive.[11] 2-Amino-6-picoline was converted to the 3-thiocyano derivative and hydrolyzed with 15% potassium hydroxide solution followed by acidification. The greenish-yellow solid obtained is soluble in sodium hydroxide, insoluble in mineral acids, and sparingly soluble in common organic solvents. The infrared spectrum shows strong absorption signals at 3340 d (2-NH_2), 3197 (ring NH), and 1667 cm^{-1} (C=NH).[12,13] The solubility in sodium hydroxide, insolubility in acid, and the absence of weak SH absorption at 2550 cm^{-1} even in concentrated solutions are strong evidence for zwitterionic character. The dipolar structure **1** was therefore assigned to this product.

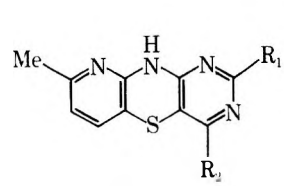


1

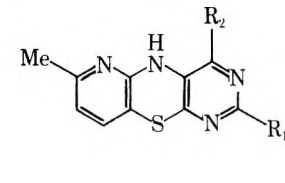
Upon refluxing an intimate mixture of this compound (**1**) with 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**2**) in 0.20 *N* sulfuric acid, a white, high-melting solid was obtained in a good yield. The ultraviolet spectrum showed a maximum absorption band at 250 nm, characteristic of phenothiazine systems. While the NMR spectrum is in agreement with either the 1,3,9-triazaphenothiazine (**3**) or the 1,6,8-triazaphenothiazine (**4**) structures, it did not favor one over the other. Further experimentation was therefore necessary. If



2, $R_1 = R_2 = OMe$; $R_3 = Br$
7, $R_1 = R_2 = OMe$; $R_3 = H$
11, $R_1 = H$; $R_2 = NH_2$; $R_3 = NO_2$
14, $R_1 = NH_2$; $R_2 = OH$; $R_3 = H$
15, $R_1 = NH_2$; $R_2 = OH$; $R_3 = Br$

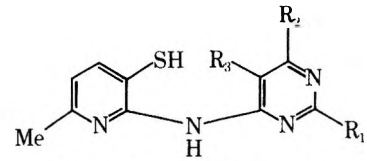


3, $R_1 = R_2 = OMe$
12, $R_1 = H$; $R_2 = NH_2$
16, $R_1 = NH_2$; $R_2 = OH$

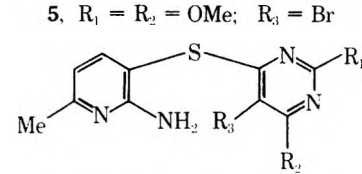


4, $R_1 = R_2 = OMe$
13, $R_1 = H$; $R_2 = NH_2$

the initial reaction is the acid-catalyzed condensation of the amine **1** with the chloropyrimidine **2**, a diarylamine intermediate, **5**, will be formed followed by cyclization and loss of hydrogen bromide leading to the 1,3,9-triazaphenothiazine compound **3**. Compound **4**, on the other hand, will be formed from **5** by Smiles rearrangement leading to the diaryl sulfide **6**, which can then cyclize by loss of hydrogen bromide. The initial reaction could also involve a



5, $R_1 = R_2 = OMe$; $R_3 = Br$

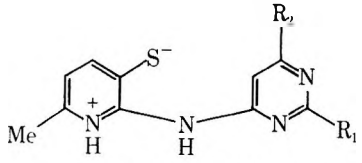


6, $R_1 = R_2 = OMe$; $R_3 = Br$

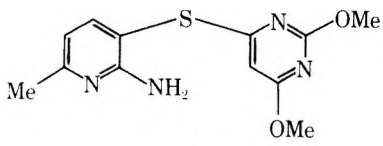
nucleophilic attack of the mercaptide ion on the four-carbon center of the pyrimidine ring; however, this reaction is untenable owing to protonation of the mercaptide ion in the acid medium employed. Furthermore, the same reactions, carried out in basic media, where the concentration of the mercaptide ion is extremely high, yielded no prod-

ucts; the starting materials were quantitatively recovered. These results favor an initial formation of an o-mercaptodiarylamine intermediate, **5**, and in agreement with our results, such acid-catalyzed reactions are known to be retarded by increasing the pH of the solution.[14]

In order to decide conclusively whether the reactions took place with or without rearrangement, the dipolar compound **1** was treated with compound **7**, which lacked a reactive group at the five-carbon center and hence would prevent cyclization. Under similar reaction conditions used for the preparation of the tricyclic structures, a 62% yield of a white, crystalline material of molecular formula $C_{12}H_{14}N_4O_2S$ was obtained. The compound is soluble in sodium hydroxide and insoluble in mineral acids; the infrared spectrum showed the absence of a mercapto group even in concentrated solutions. The dipolar nonrearranged structure, **8**, was therefore assigned to this product. This result rules out the diaryl sulfide structure **9** and thus shows that

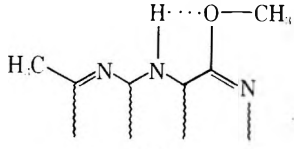


8, $R_1 = R_2 = OCH_3$
17, $R_1 = NH_2$; $R_2 = OH$



9

after the initial acid-catalyzed condensation of compound **1** with the bromochloropyrimidine **2**, the diarylamine intermediate, **5**, cyclizes without rearrangement to yield the tricyclic compound which we have now identified as a derivative of the 1,3,9-triazaphenothiazine ring (compound **3**). Structure **4** was further rejected on the premise that the 10-NH proton should have a more diffuse NMR signal[15] and should show a stronger intramolecular hydrogen bonding with the methoxy group oxygen leading to the chelate structure **10**. The o-aminomercaptopyridine **1** also reacts



10

with an acidic solution of 4-amino-6-chloro-5-nitropyrimidine (**11**) and gave 4-amino-8-methyl-1,3,9-triazaphenothiazine (**12**). Further evidence of structure was provided by diazotization of compound **12**, which failed to give the 1,10-diazole structure characteristic of o-aminodiaryl amines.[5,16] It therefore confirms that the amino group in the product is not in an ortho position with regard to the central ring NH as one would expect from structure **13**. Other derivatives of this novel triazaphenothiazine ring[17] as well as the "open" systems were also prepared and characterized.

Experimental Section

General. Melting points were determined with a Fisher-Johns apparatus. Uv spectra were taken with a Pye Unicam SP 8000 spectrophotometer using matched 1-cm quartz cells. The solvent is methanol; absorptions are given in nanometers; the figures in parentheses are ϵ values. Ir spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer using KBr disks unless otherwise stated. NMR spectra were determined on a Varian Associates A-60 instrument. Chemical shifts are reported on the τ scale relative to Me_4Si used as an internal standard. The letters br, s, sh, and d are used to indicate broad, singlet, shoulder, and doublet, respectively. The mass spectra were obtained on an AEI MS-9 double-focusing mass spectrometer at 70 eV.

2-Amino-3-mercapto-6-picoline (1). 2-Amino-6-picoline (5.4 g, 50 mmol) was converted to 2-amino-3-thiocyano-6-picoline by the action of 45 g of potassium thiocyanate in 60 ml of glacial acetic acid and 8 ml of bromine as was previously described.[11]

The product, 2-amino-3-thiocyano-6-picoline (3.30 g, 20 mmol), was treated with 2 g of sodium sulfite and refluxed in 30 ml of 15% potassium hydroxide solution on a steam bath for 4 hr. The dark brown solution was treated with activated charcoal, boiled for an additional 15 min, and filtered. The yellowish-brown solution was cooled, neutralized with glacial acetic acid, and chilled. The yellowish precipitate obtained was collected by filtration and recrystallized from aqueous methanol–acetone mixture (Norit) to yield greenish-yellow crystals of the dipolar salt of 2-amino-3-mercapto-6-picoline (**1**, 1.29 g, 92%): mp 245°; uv spectrum λ_{min} 226 nm (2030), λ_{max} 256 (6998), λ_{min} 290 (3220), λ_{max} 302 (3639); ir spectrum ν_{max} 3340 d, 3197, 1667, 1645, 1600, 1325, 1229, 1206, 1087, 1019, 943, 841 cm^{-1}; NMR spectrum (Me_2SO-d_6) τ 7.47 s (6-CH_3), 3.22 d (J = 9.2 Hz, 5-CH), 2.20 br (2-NH_2), 2.06 d (J = 9.2 Hz, 4-CH). 1.73 s, br (1-NH).

Anal. Calcd for $C_6H_8N_2S$: C, 51.42; H, 5.72; N, 20.00; S, 22.86. Found: C, 51.61; H, 5.88; N, 19.76; S, 22.89.

2-Amino-5-bromo-4-chloro-6-hydroxypyrimidine (15). To a suspension of 2-amino-4-chloro-6-hydroxypyrimidine (**14**, 7.28 g, 50 mmol) in 150 ml of 50% aqueous methanol was added sodium bicarbonate (6.0 g) with constant stirring. Bromine (7.0 ml) was added to the stirred mixture in drops during a period of 80 min. After 40 min of constant stirring at room temperature, the solution became acidic. An additional 4 g of sodium bicarbonate was then added. The mixture was stirred at room temperature for an additional 1 hr. The crude product was collected by vacuum filtration and recrystallized twice from aqueous acetone after treatment with activated charcoal. White crystals of 2-amino-5-bromo-4-chloro-6-hydroxypyrimidine (10.55 g, 94%) were collected: mp >300°; uv spectrum λ_{min} 211 nm (9313), λ_{max} 229 (14,170), λ_{min} 258 (3367), λ_{max} 297 (14,310); ir spectrum (Nujol) ν_{max} 3290, 3010, 1650, 1567, 1500, 1314, 1208, 1070, 1014, 970, 911, 804, 750 cm^{-1}; NMR spectrum (Me_2SO-d_6) τ 2.82 br (area 2, 2-NH_2), −0.30 br (area 1, 6-OH).

Anal. Calcd for $C_4H_3N_3OClBr$: C, 21.38; H, 1.34; N, 18.71; Cl, 15.81; Br, 35.63. Found: C, 21.54; H, 1.18; N, 18.60; Cl, 15.95; Br, 35.69.

5-Bromo-4-chloro-2,6-dimethoxypyrimidine (2). This compound was prepared from 4-chloro-2,6-dimethoxypyrimidine (**7**) as described in the literature.[5]

4-Amino-6-chloro-5-nitropyrimidine (11). This compound was partly prepared and partly purchased from Aldrich Chemical Co.[18] and recrystallized from boiling methanol, NMR spectrum τ 2.37 s (2-H), 1.90 br (4-NH_2).

2,4-Dimethoxy-8-methyl-1,3,9-triazaphenothiazine (3). A mixture of 2-amino-3-mercapto-6-picoline (1.40 g, 10 mmol) and 5-bromo-4-chloro-2,6-dimethoxypyrimidine (**2**, 2.79 g, 11 mmol) was ground in a mortar and placed in the reaction flask containing 200 ml of 0.20 N sulfuric acid. Sodium sulfite[19] (1.0 g) was then added and the mixture was refluxed with constant mechanical agitation for 5 hr on a steam bath.[20] Extensive sublimation of the pyrimidine compound, **2**, was observed and the sublimate settled on the condenser and upper half of the reaction flask. This light crystalline compound was periodically washed down into the reaction solution with minimal amount of water from a wash bottle. At the end of the reflux period, the solution was cooled, when a slimy white product formed. Vacuum filtration proved difficult as the product blocked the fine holes in the filter paper. However, by ordinary filtration, it was possible to isolate the product. It was then washed with boiling methanol and recrystallized from aqueous acetone (Norit) to yield 2,4-dimethoxy-8-methyl-1,3,9-triazaphenothiazine (**3**, 1.88 g, 68%) as white powder:[21] mp >300°; uv spectrum λ_{min} 213 nm (6112), λ_{max} 221 (7244), λ_{min} 235 (5409), λ_{max} 250 (5864), λ_{min} 266 (5036), λ_{max} 283 (7174); ir spectrum ν_{max} 3480, 3418, 3360 d, 3180, 1650, 1630, 1616, 1560, 1550, 1456, 1428, 1402, 1374, 1365, 1340, 1274, 1260, 1190, 1150, 1143, 1090, 1050, 1020, 984, 893, 815, 785, 746 cm^{-1}; NMR spectrum (Me_2SO-d_6) τ 7.67 s (8-CH_3), 6.37 s (4-OCH_3), 6.02 s (2-OCH_3), 3.63 d (J = 8.2 Hz, 7-CH), 3.70 s, br (10-NH), 2.60 d (J = 8.2 Hz) (6-CH); mass

spectrum *m/e* (rel intensity) 94 (100), 112 (29), 180 (5), 261 (5), 262 (20), 276 (M^+, 9).

Anal. Calcd for $C_{12}H_{12}N_4O_2S$: C, 52.18; H, 4.35; N, 20.29; S, 11.60. Found: C, 51.79; H, 4.19; N, 20.46; S, 11.51.

4-Amino-8-methyl-1,3,9-triazaphenothiazine (12). To a mixture of 2-amino-3-mercapto-6-picoline (0.7 g, 5 mmol) and 0.96 g (5.5 mmol) of 4-amino-6-chloro-5-nitropyrimidine (11) in 100 ml of water was added 2 ml of concentrated sulfuric acid and 1.0 g of sodium sulfite. The solution was then refluxed on a steam bath at 92° with vigorous mechanical agitation. The pH of the solution was checked and maintained at 1.0 throughout the reflux period. After 1 hr, a yellowish material started to form. At the end of the reflux period (6 hr), the product was collected by filtration, washed with hot methanol, and recrystallized twice from water after treatment with activated charcoal. Yellowish-white crystals of 4-amino-8-methyl-1,3,9-triazaphenothiazine (**12**, 1.05 g, 91%) were collected: mp >300°; uv spectrum λ_{max} 270 nm (6900), λ_{min} 290 (5558), λ_{max} 314 (6640); ir spectrum (Nujol) ν_{max} 3390, 3100, 1650, 1603, 1250, 1180, 1136, 1019, 980, 895, 794 cm^{-1}; NMR spectrum (Me_2SO) τ −0.46 (10-NH),[22] 1.80 br (4-NH_2), 2.40 d (J = 9.0 Hz, 6-H), 2.42 s (2-H), 3.31 d (J = 9.0 Hz, 7-H), 2.37 s (8-CH_3).

Anal. Calcd for $C_{10}H_9N_5S$: C, 51.95; H, 3.89; N, 30.31; S, 13.86. Found: C, 52.08; H, 3.70; N, 30.14; S, 14.00.

2-Amino-4-hydroxy-8-methyl-1,3,9-triazaphenothiazine (16). A mixture of 2-amino-5-bromo-4-chloro-6-hydroxypyrimidine (**15**, 1.24 g, 5.5 mmol) and 2-amino-3-mercapto-6-picoline (0.7 g, 5 mmol) was pulverized by grinding and placed in the reaction flask containing 150 ml of water. The aqueous suspension was acidified with 1.0 ml of concentrated sulfuric acid. Sodium sulfite (0.5 g) was then added and the acidic mixture was refluxed on a steam bath for 4.5 hr. The solution was cooled and the white precipitate was collected by filtration. The crude powdery material was recrystallized twice from water (800 ml) after treatment with activated charcoal. 2-Amino-4-hydroxy-8-methyl-1,3,9-triazaphenothiazine (**16**, 1.14 g, 92%) was collected as a white microcrystalline powder: mp >300°; uv spectrum λ_{min} 215 nm (6528), λ_{max} 230 (8412), λ_{min} 251 (5757), λ_{max} 300 (11,110); ir spectrum (Nujol) ν_{max} 3340, 3100, 1675, 1585, 1543, 1478, 1327, 1220, 1084, 1020, 918, 840, 811, 755 cm^{-1};

Anal. Calcd for $C_{10}H_9N_5OS$: C, 48.59; H, 3.64; N, 28.34; S, 12.95. Found: C, 48.70; H, 3.55; N, 28.19; S, 13.00.

3′-Mercapto-6′-methyl-2′-pyridyl-2,4-dimethoxy-6-pyrimidinylamine (8). 2-Amino-3-mercapto-6-picoline (1.40 g, 10 mmol) and 4-chloro-2,6-dimethoxypyrimidine (**7**, 1.92 g, 11 mmol) were mixed and refluxed in 200 ml of water containing 2 ml of concentrated sulfuric acid and 1.0 g of sodium sulfite. Considerable sublimation of the chlorodimethoxypyrimidine 7 was observed. It was washed down to the reaction flask from time to time with a small amount of water.

At the end of the reflux period (4 hr), the mixture was cooled and filtered. The impure product was washed with warm methanol to remove the unreacted chlorodimethoxypyrimidine. The white residue was then recrystallized from dilute acetic acid after treatment with activated charcoal to yield glistening white plates of 3′-mercapto-6′-methyl-2′-pyridyl-2,4-dimethoxy-6-pyrimidinylamine (**8**, 1.72 g, 62%): mp 260°; uv spectrum λ_{max} 206 nm (19,110), λ_{min} 227 (5572), λ_{max} 257 (23,280), λ_{min} 281 (10,630), λ_{max} 305 (11,470); ir spectrum ν_{max} 3300 (6-NH), 3194 (C=NH^+), 1650, 1590, 1530, 1344, 1235, 1202, 1150, 1020, 980, 900, 841 cm^{-1}; NMR spectrum (Me_2SO-d_6) τ 6.10 (6′-CH_3, 2-OCH_3, 4-OCH_3), 3.26 d (J = 5.9 Hz, 5′-CH), 2.53 br (5-CH, 6-NH, 1′-NH), 2.45 d (J = 5.9 Hz, 4′-CH); mass spectrum *m/e* (rel intensity) 64 (80), 106 (12), 139 (100), 140 (33), 278 (M^+, 21), 279 (3), 280 (1).

Anal. Calcd for $C_{12}H_{14}N_4O_2S$: C, 51.81; H, 5.03; N, 20.14; S, 11.51. Found: C, 51.94; H, 5.10; N, 20.11; S, 11.50.

3′-Mercapto-6′-methyl-2′-pyridyl-2-amino-4-hydroxy-6-pyrimidinylamine (17). A mixture of 2-amino-4-chloro-6-hydroxypyrimidine (**14**, 1.455 g, 10 mmol) and 2-amino-3-mercapto-6-picoline (1.40 g, 10 mmol) was ground in a mortar and refluxed for 3 hr in 100 ml of 0.20 *N* sulfuric acid containing 1.0 g of sodium sulfite. The product was collected by filtration and recrystallized from aqueous ethanol–acetone mixture after treatment with activated charcoal. Glistening white crystals of 3′-mercapto-6′-methyl-2′-pyridyl-2-amino-4-hydroxy-6-pyrimidinylamine (**17**, 2.17 g, 87%) separated out: mp 263°; uv spectrum λ_{max} 203 nm (14,010), λ_{sh} 230 (7158), λ_{min} 238 (6691), λ_{max} 268 (11,520); ir spectrum (Nujol) ν_{max} 1650, 1575, 1531, 1275, 1210, 1197, 1146, 1010, 971, 793 cm^{-1}; NMR spectrum (Me_2SO-d_6) τ 6.57 s (6′-CH_3), 3.80 s (5-CH), 2.90 d (J = 5.8 Hz, 5′-CH), 2.82 br (2-NH_2), 2.20 br (4-OH, 6-NH, and 1′-NH), 2.07 d (J = 5.8 Hz, 4′-CH).

Anal. Calcd for $C_{10}H_{11}N_5OS$: C, 48.19; H, 4.42; N, 28.11; S, 12.85. Found: C, 48.17; H, 4.25; N, 28.20; S, 12.78.

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Registry No.—**1**, 33761-31-8; **2**, 42362-16-3; **3**, 55740-61-9; **7**, 6320-15-6; **8**, 55740-62-0; **11**, 4316-94-3; **12**, 55740-63-1; **14**, 1194-21-4; **15**, 55740-64-2; **16**, 55740-65-3; **17**, 55740-66-4; 2-amino-3-thiocyano-6-picoline, 42449-30-9, bromine, 7726-95-6.

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(6) Prothipendyl, the 1-azaphenothiazine analog of promazine, is a highly potent tranquilizing drug. It has a low initial hypnotic effect, a more constant and longer lasting effect, and a superior parenteral toleration which make it superior to chlorpromazine. Again, in contrast to chlorpromazine there is no tendency by this drug to excite latent epilepsy, thereby making prothipendyl more suitable for the treatment of pyschic stages of excitement especially in acute psychosis. St. Hift and K. Kryspin-Exner, *Wien. Med. Wochenschr.*, **108**, 664 (1958); J. Quandt, L. von Horn, and H. Schliep, *Psychiatr. Neurol.* **135**, 197 (1958).
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(18) Aldrich Chemical Co., Milwaukee, Wis. W. R. Boon, W. G. M. Jones, and G. R. Ramage *J. Chem. Soc*, 96 (1951).
(19) Sodium sulfite was added to minimize autoxidation which would convert the *o*-aminomercaptopicoline **1** to the corresponding dipyridyl disulfide.
(20) The bath temperature is 92°.
(21) This compound is highly hydroscopic and retains a lot of solvent after recrystallization, chromatography, and on exposure to air. It is quite stable to heat and was oven dried at 100° for 48 hr and preserved in a vacuum desiccator. In spite of these precautions, the drying procedure was repeated each time before any spectrum is taken and before analysis.
(22) When the NMR spectrum was run in hexadeuteriodimethyl sulfoxide the 10-NH proton was not observed owing to proton exchange with deuterium from the solvent. The 4-NH_2 protons, however, did not exchange with deuterium.

Ion Radicals. XXXIV. Preparation of Phenoxathiin Cation Radical Perchlorate. Formation and Reactions of *S*-Iminophenoxathiin (Phenoxathiin Sulfilimine)[1,2]

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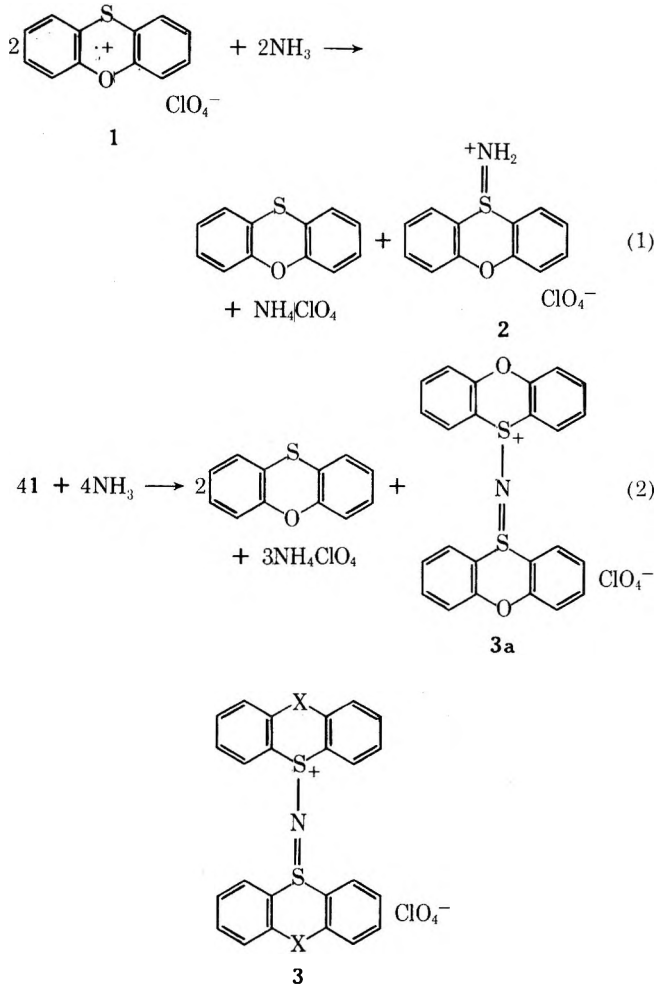
Received April 23, 1975

A method of preparing crystalline phenoxathiin cation radical perchlorate (**1**) by oxidation of phenoxathiin with perchloric acid in benzene–acetic anhydride is reported. Reaction of **1** with ammonia was controlled so as to give either phenoxathiin sulfilimine perchlorate (**2**) or the dimeric product 5,5-dihydro-5-(5-phenoxathiiniumylimino)phenoxathiin perchlorate (**3a**). Deprotonation of **2** gave phenoxathiin sulfilimine (**4a**). Reaction of **4a** with *p*-toluenesulfonyl chloride gave the known tosyl derivative, obtainable also by reaction of phenoxathiin with chloramine-T. Methylation of **4a** led to the same product obtainable by direct reaction of **1** with methylamine, i.e., 5,5-dihydro-5(methylimino)phenoxathiin perchlorate (**6**). Reaction of **4a** with **1** led to **3a**. Reaction of **4a** with thianthrene cation radical perchlorate led, similarly, to 5,5-dihydro-5-(5-thianthreniumylimino)phenoxathiin perchlorate (**9**).

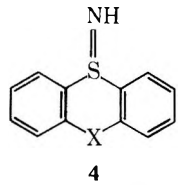
Work with the phenoxathiin cation radical has been confined in the past for the most part to characterization by ESR spectroscopy. For the most part, also, the cation radical has been made by oxidation of phenoxathiin with concentrated sulfuric acid, in which medium ESR characterization has been carried out.[3-6] The cation radical has also been made from both phenoxathiin and phenoxathiin 5-oxide by reaction with a variety of Lewis acids ($AlCl_3$, $FeCl_3$, $SbCl_5$, etc.) in haloalkane solvents for characterization by absorption spectroscopy.[7] No definitive study of the chemistry of the phenoxathiin cation radical has been reported. Ten years ago one of us[8] showed that the conversion of phenoxathiin 5-oxide into the cation radical in sulfuric acid solution was accompanied by hydroxylation reactions. The cation radical of 3-hydroxyphenoxathiin was identified by ESR, and 3-hydroxyphenoxathiin 5-oxide was isolated. Subsequently, Cauquis reported in detail on the electrochemistry of phenoxathiin, and deduced[9] that reaction of either the cation radical or the dication, formed by disproportionation of the cation radical, with water in the solvent gave the 5-oxide.[9] Phenoxathiin can be oxidized with iodine–silver perchlorate, but separation of the cation radical perchlorate (**1**) from the precipitated mixture of **1** and silver iodide was, in our hands, always accompanied by considerable decomposition of the cation radical. Oxidation of phenoxathiin in carbon tetrachloride with perchloric acid–acetic anhydride in the way which is so successful with thianthrene[10] was also not successful, since under those conditions **1** would not crystallize out. We are now able to make crystalline phenoxathiin cation radical perchlorate (**1**) quite easily, with close to 100% cation radical content, by controlled oxidation of phenoxathiin in benzene with 70% perchloric acid–acetic anhydride. This has allowed us to begin studying the chemistry of the cation radical in homogeneous solution.

An initial pleasing development is that, by controlled reaction of **1** with ammonia, we have been able to prepare not only the anticipated dimeric compound, 5,5-dihydro-5-(5-phenoxathiiniumylimino)phenoxathiin perchlorate (**3a**), but also phenoxathiin sulfilimine perchlorate (**2**). These compounds are obtained according to the stoichiometry shown in eq 1 and 2. Phenoxathiin was isolated in each case, as well as small amounts of phenoxathiin 5-oxide. In previous work with thianthrene cation radical,[11] and the cation radicals of *N*-methyl- and *N*-phenylphenothiazine,[2] it was possible to obtain the dimeric molecules (**3b, 3c,** and **3d**) analogous to **3a**. We now find that if ammonia is streamed very vigorously into a homogeneous solution of **1** in acetonitrile, the product is **2**. If in contrast ammonia is bubbled gently into a suspension of **1** in acetonitrile, the product is **3a**. Appropriate adjustment of conditions leads to a mixture of **2** and **3a**.



3b, X = S; **c**, X = *N*-Me; **d**, X = *N*-C_6H_5

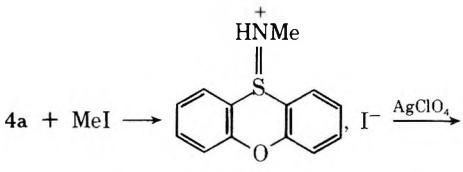
The perchlorate **2** is readily deprotonated. We have been able to prepare the hitherto unreported phenoxathiin sulfilimine (**4a**) and to study some of its reactions. The sulfilimines **4b** and **4c** have been prepared[12] by Tamura's mesitylhydroxylamine method,[13] whereas only the mesitylsulfonate of **4a** was reported.[12] The sulfilimine **4a**, mp 66–67°, is spectroscopically very similar to phenoxathiin 5-oxide.



4

4a, X = O; b, X = S; X = *N*-Me

Reaction of **4a** with methyl iodide led to 5,5-dihydro-5-(methylimino)phenoxathiin iodide (**5**), which was converted into the corresponding perchlorate **6** (eq 3). The latter was also prepared by reaction of methylamine with **1** (eq 4), a type of reaction reported earlier in the thianthrene[14]



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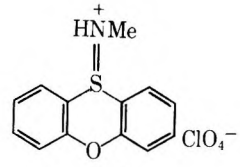

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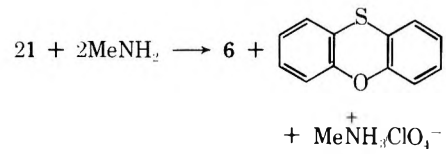
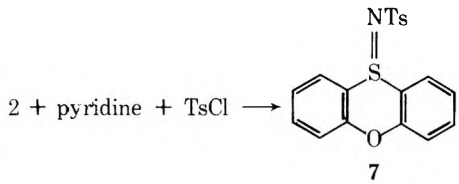


(4)

(*tert*-butylamine) and phenothiazine (various alkylamines) series.[2]

The tosyl derivative (**7**) of **4a** has been prepared by reaction of chloramine-T with phenoxathiin.[15] Reaction of **4a** (generated from treating **2** with pyridine) with tosyl chloride also gave **7**, allowing us to thus characterize **4a** via a known derivative (eq 5).



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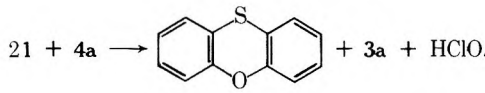

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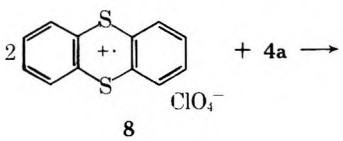

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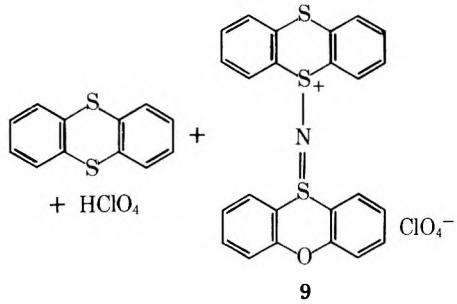

9 (7)

Finally, we have been able to prepare the dimeric compound **3a** by reaction of **4a** with the cation radical **1** (eq 6), and we carried out the analogous reaction of the thianthrene cation radical (**8**) with **4a** to obtain the mixed dimer **9** (eq 7). These last two reactions obviously are related to the formation of dimeric products in the reactions of ammonia with organosulfur cation radicals[2,11] and we hope to make use of **4a** in studying the mechanism of these reactions.

Experimental Section

Acetonitrile was Eastman Spectrograde. All column chromatography was performed with Merck silica gel no. 7733, 10-30 ASTM mesh. Phenoxathiin was obtained from Eastman Kodak, mp 55–57°, and was used without further purification.

Phenoxathiin cation radical perchlorate (1) was prepared by a modification of the method used for preparing thianthrene cation radical perchlorate.[10] To a solution of 500 mg (2.49 mmol) of phenoxathiin in 30 ml of dry benzene was added 1 ml of 70% perchloric acid. The acid became blue and remained undissolved in the benzene. The mixture was swirled for 10 min and acetic anhydride was added dropwise while the mixture was shaken continuously. Purple crystals of **1** began to deposit. The small purple acidic layer dissolved on the addition of acetic anhydride and the crystallization of **1** continued. The mixture was allowed to stand for 4 hr and was filtered. The crystalline **1** was washed with dry benzene until the washings were colorless, giving 501 mg (1.67 mmol, 67%) of **1** after drying under vacuum. The purity of the **1**, which was determined iodimetrically, was always close to 100%.

Reactions of 1 with Ammonia. Formation of Phenoxathiin Sulfilimine Perchlorate (5,5-Dihydro-5-iminophenoxathiin Perchlorate, 2) and 5,5-Dihydro-5-(5-phenoxathiiniumylimino)phenoxathiin Perchlorate (3a). The three experiments which follow are examples of the many runs which were made seeking to understand the conditions under which **2** and **3a** were formed.

A. Ammonia gas was bubbled through a suspension of 2.04 g (7.78 mmol) of **1** in 40 ml of acetonitrile. The solution turned yellow within 15 sec. The ammonia stream was continued for 5 min, and stirring for a further 15 min. The acetonitrile was removed on a rotary evaporator, and the residue was taken up in a small amount of acetone and chromatographed on a column of silica gel. Elution with benzene gave 663 mg (3.31 mmol, 49%) of phenoxathiin, and elution with chloroform gave 52 mg (0.255 mmol, 3.81%) of phenoxathiin 5-oxide. Elution with acetone gave 1.70 g (3.3 mmol, 49%) of **3a**, mp 235–238° dec (from aqueous ethanol), λ_{max} (MeCN) (10^{-4} ϵ) 314 nm (1.43), 272 (1.03), and 239 (4.48).

Anal. Calcd for $C_{24}H_{16}NS_2ClO_6$: C, 56.1; H, 3.14; N, 2.73; S, 12.5; Cl, 6.89. Found: C, 56.1; H, 3.14; N, 2.98; S, 12.7; Cl, 6.59.

B. A suspension of 1.5 g (5.0 mmol) of **1** in 30 ml of acetonitrile was stirred for 5 min after which ammonia gas was bubbled in until the purple color disappeared (within 20 sec). After stirring a further 15 min, the solution was worked up as before, giving 487 mg (2.49 mmol, 50%) of phenoxathiin and 22 mg (0.1 mmol) of phenoxathiin 5-oxide. The acetone eluate from the silica column was evaporated to give a mixture of **3a** and phenoxathiin sulfilimine perchlorate (**2**). The mixture was triturated with acetone to remove the more soluble **2**, which was then precipitated from solution by adding ether. The two solids were crystallized to give 25 (0.05 mmol, 1%) of **3a**, mp 240–241° dec, from aqueous ethanol, and 690 mg (2.18 mmol, 44%) of **2**, mp 190–191° dec, from aqueous methanol: λ_{max} (MeCN) (10^{-3} ϵ) 301 nm (5.72), 280 (3.55), and 225 (25.2).·^{1}H NMR (Me_2SO-d_6) δ 9.1–8.2 (m, 2 H, aromatic) and 7.75 (m, 6 H, aromatic). The NH protons could not be detected in Me_2SO solvent, presumably because of exchange, but gave rise to a 3180-cm^{-1} band in the infrared.

Anal. Calcd for $C_{12}H_{10}NSClO_5$ (**2**): C, 45.6; H, 3.19; N, 4.44; S, 10.2; Cl, 11.2. Found: C, 45.7, H, 3.43; N, 4.45; S, 9.85; Cl, 11.4.

C. A suspension of 1.09 g (3.63 mmol) of **1** in 40 ml of acetonitrile was stirred until all of the **1** had dissolved (20 min). Into this solution ammonia gas was introduced as a strong blast, and the solution became yellow immediately. Work-up gave 356 mg (1.77 mmol, 49%) of phenoxathin, 50.2 mg (0.232 mmol, 6.4%) of phenoxathiin 5-oxide, and 504 mg (1.60 mmol, 44%) of **2**, mp 190–192° dec.

Deprotonation of 2. Formation of Phenoxathiin Sulfilimine (5,5-Dihydro-5-iminophenoxathiin, 4a). A. About 0.5 ml of triethylamine was added to a solution of 102 mg (0.322 mmol) of **2** in

5 ml of chloroform. After 10 min the solvent was removed, and the solid residue was washed well with water and crystallized from ether–petroleum ether (bp 30–60°), giving 66 mg (0.283 mmol, 88%) of **4a**: mp 66–67° dec; λ_{max} (MeCN) (10^{-3} ϵ) 298 nm (2.35), 290 (2.46), and 239 (28.2); ^{1}H NMR ($CDCl_3$) δ 7.95–7.8 (m 2 H, aromatic), 7.3 (m, 6 H, aromatic), and 1.5 (s, 1 H, NH). The NH band was at 3200 cm^{-1}.

Anal. Calcd for $C_{12}H_9NOS \cdot H_2O$: C, 61.8; H, 4.75; N, 6.00; S, 13.7. Found: C, 61.9; H, 4.81; N, 5.86; S, 13.8.

B. Compound **4a** was also obtained by adding 10% sodium hydroxide solution to a suspension of **2** in ethanol and working up as before.

Methylation of 4a. Formation of 5,5-Dihydro-5-(methylimino)phenoxathiin Iodide (5). To a solution of 110 mg (0.511 mmol) of **4a** in ether was added 2 ml of methyl iodide. Pale yellow crystals of **5** deposited during 15 min of stirring, giving 149 mg (0.42 mmol, 81.5%), mp 121–122° dec.

Conversion of 5 into 5,5-Dihydro-5-(methylimino)phenoxathiin Perchlorate (6). An excess of silver perchlorate was added to a stirred solution of 100 mg (0.28 mmol) of **5** in acetonitrile. After 10 min the precipitated silver iodide was filtered, the solution was evaporated, and the residue was washed with water and crystallized from aqueous methanol, giving 88 mg (0.27 mmol, 96%) of **6**, mp 160–162° dec, mmp with authentic **6** (see below) 159–160° dec.

Reaction of 1 with Methylamine. Formation of 6. A suspension of 1.02 g (3.41 mmol) of **1** in acetonitrile was stirred for 10 min and methylamine gas was bubbled in until the purple color disappeared. Reaction was slower than with ammonia. Work-up and chromatography, as earlier, gave 457 mg (2.28 mmol, 67%) of phenoxathiin, 31 mg (0.144 mmol, 4%) of phenoxathiin 5-oxide, and 143 mg (0.433 mmol, 13%) of **6**, mp 158–159° dec, from aqueous acetone: λ_{max} (MeCN) (10^{-3} ϵ) 302 nm (5.43), 280 (3.54), and 233 (20.0); ^{1}H NMR (Me_2SO-d_6) δ 8.0–8.2 (m, 2 H, aromatic), 7.7 (m, 6 H, aromatic), and 2.2 (s, 3 H, Me). The NH proton could not be detected in Me_2SO solvent, presumably because of exchange, but gave rise to a 3280-cm^{-1} band in the infrared.

Anal. Calcd for $C_{13}H_{12}NSClO_5$: C, 47.3; H, 3.67; N, 4.25; S, 9.72; Cl, 10.7. Found: C, 47.3; H, 3.42; N, 4.39; S, 9.92; Cl, 10.7.

Reaction of 4a with Tosyl Chloride. Formation of *N*-Tosyl Phenoxathiin Sulfilimine (7). A suspension of 53 mg (0.17 mmol) of **2** in ether was deprotonated by addition of 1 ml of pyridine. Tosyl chloride (42 mg, 0.22 mmol) was added, and after 1 hr of stirring the solvent was removed. The residue was washed well with water and crystallized from aqueous ethanol to give 26 mg (0.07 mmol, 41%) of **7**, mp 166–168°, infrared identical with that of an authentic sample, mp 168–170°, made by reaction of phenoxathiin with chloramine-T according to method B of Tsujihara et al.[15]

Reaction of 1 with 4a. Preparation of 3a. A suspension of 139 mg (0.463 mmol) of **1** in 10 ml of acetonitrile was stirred for 10 min and a solution of 51 mg (0.237 mmol) of **4a** in 3 ml of acetronitrile was added. The disappearance of the color of **1** was quite slow. After 20 min the pale purple color was discharged by adding 1 drop of water. The solution was stirred with a small amount of sodium carbonate (to neutralize perchloric acid) and evaporated. Column chromatography gave 47.6 mg (0.237 mmol, 51%) of phenoxathiin (benzene), 19 mg (0.09 mmol) of phenoxathiin 5-oxide (chloroform), and 101 mg (0.196 mmol, 42%) of **3a** (acetone), mp 236–238° dec, from aqueous methanol.

Reaction of 4a with Thianthrene Cation Radical Perchlorate (8). Formation of 5,5-Dihydro-5-(5-thianthreniumylimino)phenoxathiin Perchlorate (9). Reaction was carried out as with the reaction of **4a** with **1**, using 52 mg (0.165 mmol) of **8** and 19.5 mg (0.091 mmol) of **4a**. After stirring with sodium carbonate the solution was poured into water and the precipitate was taken up in acetone and precipitated with ether. Crystallization from aqueous methanol gave 41 mg (0.077 mmol, 47%) of **9**, mp 208–210° dec.

Anal. Calcd for $C_{24}H_{16}NS_3ClO_5$: C, 54.4; H, 3.04; N, 2.64; S, 18.2; Cl, 6.69. Found: C, 54.1; H, 3.02; N, 2.47; S, 18.4; Cl, 6.56.

The acetone–ether filtrate from the precipitation of **9** was evaporated, and the residue was taken up in chloroform and subjected to TLC on silica gel with benzene development, giving 19.5 mg (0.09 mmol, 55%) of thianthrene and 7 mg (0.03 mmol) of thianthrene 5-oxide.

Registry No.—**1**, 55975-63-8; **2**, 55975-55-8; **3a**, 55975-57-0; **4a**, 54002-03-8; **5**, 55975-58-1; **6**, 55975-60-5; **7**, 54462-91-8; **8**, 35787-71-4; **9**, 55975-62-7; phenoxathiin, 262-20-4; methyl iodide, 74-88-4; silver perchlorate, 7783-93-9; methylamine, 74-89-5; tosyl chloride, 98-59-9.

References and Notes

(1) Supported by Grant GP-25989X from the National Science Foundation, and Grant D-028 from the Robert A. Welch Foundation.
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Dimethyl Sulfoxide–Trifluoroacetic Anhydride. A New and Efficient Reagent for the Preparation of Iminosulfuranes[1]

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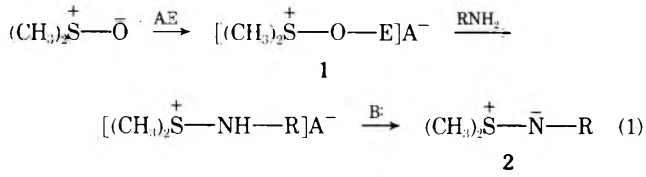
The scope and limitations are described of the recently reported dimethyl sulfoxide–trifluoroacetic anhydride (DMSO–TFAA) reagent for the preparation of iminosulfuranes. Yields range from 40 to 90% with aryl amines, including ortho-substituted ones, aryl amides, aryl sulfonamides, and urea. Previously uncharacterized iminosulfuranes have been prepared from sulfanilamide (mono- and diylides) and sulfadiazine. Relatively basic amines (cyclohexylamine, benzylamine), *o*- and *p*-diaminobenzenes, anthranilamide, ansidine, and 2- and 4-aminopyridines failed to yield isolable iminosulfuranes.

This paper defines the scope and limitations of the recently reported dimethyl sulfoxide–trifluoroacetic anhydride (DMSO–TFAA) reagent for the efficient preparation of iminosulfuranes (sulfilimines) and compares the reagent's utility with that of other "activated" DMSO reagents. In our preliminary communications[1a] only a few iminosulfuranes were reported and no information was then available on the limitations of the new reagent.

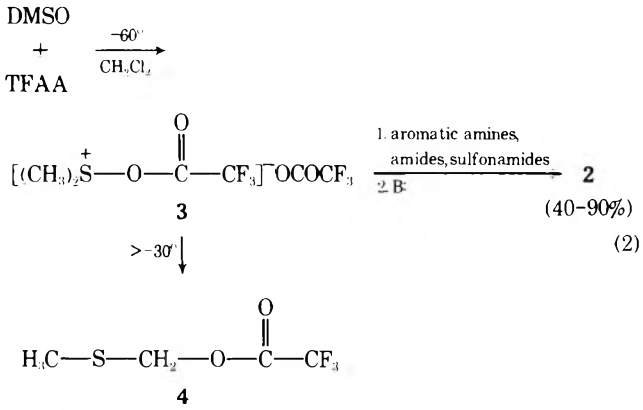
The activation of DMSO by a number of electrophiles is well documented, typically chlorine,[2] acetic anhydride,[3] toluenesulfonic anhydride,[4] methanesulfonic anhydride,[4] alkyl chloroformates,[5] toluenesulfonyl chloride,[4] cyanuric chloride,[4] sulfur trioxide,[1b,6,7] phosphorus pentoxide,[6,8,9] and dicyclohexylcarbodiimide.[10,11] All of these electrophiles have been used to activate DMSO for the oxidation of alcohols but only the last three electrophiles (AE) and acetic anhydride have also been used for the preparation of iminosulfuranes (2) (eq 1). Preparation of 2 in good yield requires an intermediate (1) containing a good leaving group (OE^-) readily displaced by the nucleophilic nitrogen compounds.[12]



(1)

Results and Discussion

Scope. Activation of DMSO with acyl halides and certain anhydrides at room temperature, particularly in the absence of a moderating solvent, can and does proceed explosively. TFAA falls into that category, but we correctly concluded that it should be possible to moderate its reaction with DMSO by working at low temperature in an unreactive solvent. Even under those conditions, DMSO and TFAA react almost instantly and exothermically at −60° in methylene chloride to produce a white precipitate which, for convenience, is written as 3 (eq 2). This precipitate is stable below −30° but on warming the system it becomes homogeneous, and the Pummerer rearrangement product (4) forms; it is readily observed by NMR (δ 5.35, 2 H, s; 2.28, 3 H, s).



(2)

We have no direct evidence for the structure of 3, as we have failed in all attempts to isolate it. We can intercept and trap 3, however, with a wide range of nitrogen-containing nucleophiles, such as certain aromatic amines, amides, and sulfonamides (eq 2). These nucleophiles react rapidly and cleanly. Crude 2, after basification (when required) with triethylamine or 5–10% aqueous sodium hydroxide, is obtained in 40–90% yields in almost analytical purity without further purification (Table I).[17] With many aromatic amines, the reactions are complete within a few minutes after all the amine has been added (TLC); with sulfonamides reaction takes about 30–60 min and with amides up to 240 min is required. In contrast, DMSO activated by sulfur trioxide or phosphorus pentoxide requires considerably longer reaction times (ca. 20 times longer).[1b]

Table I lists the iminosulfuranes (2) (or their salts) prepared and also yields, melting points, NMR, and elemental analyses. In one case (6), both the ylide (y) and its picrate (p) were isolated. In three other cases (5, 7, 8) only the picrate was stable enough for characterization. In one case (15) only the trifluoroacetate could be obtained. All compounds had the predicted NMR spectra. Compounds that had been previously reported by us and/or others (5, 7, 9, 11, 13, 14, 16, 17) were additionally characterized by melting point and ir comparison with authentic samples and, in several cases, by mixture melting point as well. New compounds were characterized spectrally and by elemental analyses. Thin layer chromatography was a useful monitor of purity.

One noteworthy feature of the DMSO–TFAA reagent is is reactivity even with aromatic amines containing certain ortho substituents (CH_3, NO_2). Such amines could not be converted to *N*-aryliminosulfuranes by our earlier procedure in which DMSO is activated by SO_3.[1b] For completeness, *o*-fluoroaniline was also converted to the *N*-aryliminosulfurane (Table I, 8).

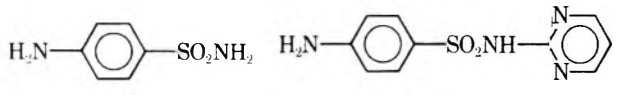
Amides (benzamide, *p*-nitrobenzamide, and urea) readily form *N*-acyliminosulfuranes (Table I, 13, 14, 15) in excellent yield with the DMSO–TFAA reagent. Reaction times (90–240 min, as derived from TLC data) are longer than with aromatic amines and a small excess of the reagent (3) is required to obtain optimum yields. With benzamide, addition of base is essential to obtain the ylide (13) but with *p*-nitrobenzamide, the ylide 14 precipitates during the reaction and does not require basification to obtain at least a 90% yield of almost pure product. The additional acidity of the NH proton resulting from the *p*-nitro group coupled with the low solubility of the product (14) shifts the equilibrium cleanly and almost quantitatively from salt to ylide.

Urea, an amide with two identical nucleophilic sites, can in principle form a mono- and diylide as well as the corresponding salts. A pure dylide or disalt could not be obtained even with a large excess of the reagent (3); a complex mixture of products was shown by TLC. However, when equimolar quantities of urea and the reagent (3) were used, an excellent yield (80%) of the monotrifluoroacetate salt of the monoylide (Table I, 15) was obtained.

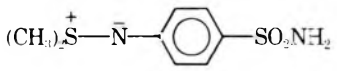
The reaction of sulfonamides (benzene- and *p*-nitrophenylsulfonamide) with the reagent (3) turned out to be two to four times more rapid than that with amides, even though sulfonamides are poorer nucleophiles. Sulfonamides, however, are considerably stronger acids than amides and may exist in equilibrium with their conjugate base, the sulfonamido anions. Although only small quantities of these anions are likely to be present, they should be superior nucleophiles to free amides and, if the equilibrium is rapidly restored, the overall reaction rate should be higher with sulfonamides. This argument is supported by our work with *p*-aminobenzenesulfonamide (PABS) described below. With sulfonamides basification is not required as the NH proton is readily lost and the ylides precipitate from the reaction mixture.

Sulfanilamide (18) poses an intriguing synthetic challenge as it can, in prinicple, form two monoiminosulfuranes, one with the ylide function on the amino side (20) and the other with the ylide function on the sulfonamido side (21), and one diiminosulfurane (22). Sulfadiazine (19) can yield only one iminosulfurane, the monoylide (23).

The diylide 22 (eq 3) appeared to be the easiest of the group to prepare as we had already established that both the amino and sulfonamido functions react cleanly and rapidly with the reagent 3. When 18 was allowed to react with an excess of 3 in methylene chloride below −40° (usually −50 to −60°) for about 2 hr followed by customary addition of triethylamine (TEA) to the reaction solution, a



18 19



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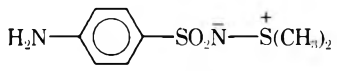

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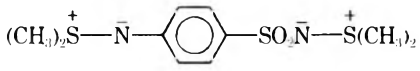

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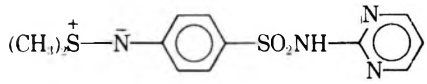
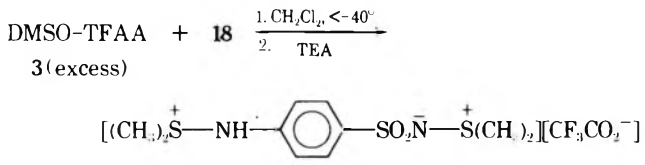
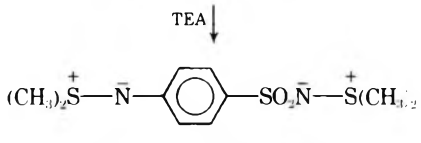


23

75–95% yield of **24**, mp 174–176° dec, the monotrifluoroacetate salt of **22** rather than **22**, was unexpectedly formed. To obtain **22** it was necessary to react **24** with virtually neat TEA (some methylene chloride was needed to enhance the solubility of **24**) in a separate step.



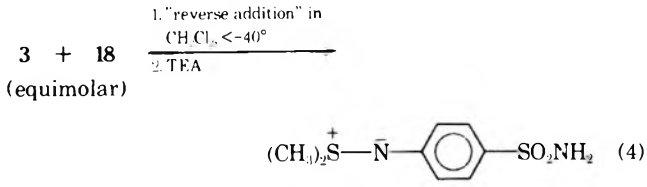
24, mp 174–176° dec (75–95%)



22, mp 179–182° dec (59%) (3)

To prepare **20** (iminosulfurane on the amino group of **18**) it was planned to take advantage of the known higher rate of reaction of an amino group, relative to sulfonamido, with reagent **3**. However, when an equimolar quantity of sulfanilamide (**18**) was added to **3** at low temperatures both functional groups reacted and selective reaction could not be achieved. Based on our earlier work with various para-substituted aromatic amines,[6] we conclude that the electron-withdrawing sulfonamido group must be reducing the nucleophilicity of the amino group to the point where both functional groups in **18** react at similar although probably not identical rates.

It was possible to obtain the desired monoylide (**20**), however, by a "reverse addition" technique, using a specially designed all-glass apparatus, in which the reagent **3**, prepared at or below −40°, was added slowly to a cold stirred solution of **18** (eq 4). Thus, immediate consumption

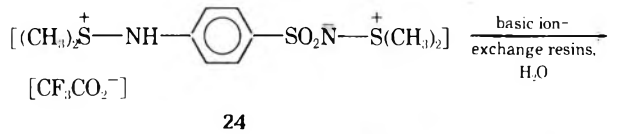


20, mp 135–137° dec (50%) (4)

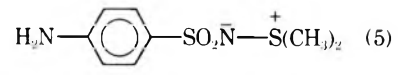
of **3** was assured and at no time was it present in excess (as is the case when **18** is added to **3**). The exclusive product isolated in the "reverse addition" method was **20** obtained in about 50% yield after addition of TEA to deprotonate the intermediate sulfonium salt. Compound **20**, mp 135–137° dec, gives a negative ninhydrin test and fails to form an azo dye with β-naphthol (free amino group absent) and it is soluble in aqueous base (free sulfonamido group present).[18] Spectra and elemental analysis confirmed its structure.

The direct preparation of **21** (iminosulfurane on the sulfonamido group) from **18** and **3** was expected to be difficult, if not impossible, because of the intrinsically lower nucleophilicity of the sulfonamido group. Even in cases where we attempted to reduce the nucleophilicity of the amino group markedly be making the trifluoroacetate salt of **18**, we were not successful in the direct selective reaction of the sulfonamido group.

Compound **21** was obtained unexpectedly, however, in about 30% yield when we attempted to convert **24**, the monotrifluoroacetate salt (eq 3), to the diiminosulfurane (**22**) by treatment with basic ion-exchange resins in an aqueous system (eq 5). Treatment of **24** with Amberlite



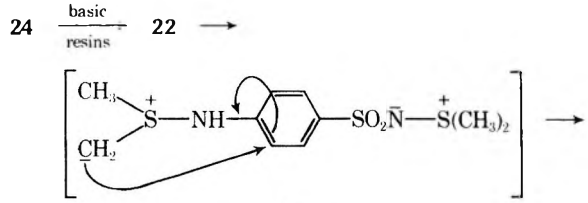
24



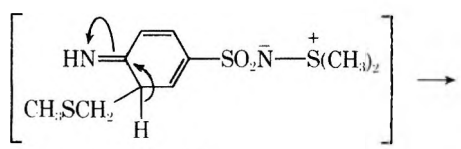
21, mp 190–193° dec (30%) (5)

IR-45 (IRA-400 or IRC-50) at room temperature caused selective hydrolysis on the amino side; **21**, mp 190–193° dec, was obtained in 30% yield after recrystallization from isopropyl alcohol or purification by column chromatography on silica gel. Compound **21** gives a positive ninhydrin test and is insoluble in dilute aqueous base, as would be expected. Spectral properties and elemental analysis confirmed the structure. Independent synthetic studies, to be described below, distinguished unequivocally between **20** and **21**.

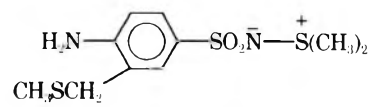
Prior to purification, **21** was shown by TLC to be contaminated by another compound with a higher R_f value. Chromatography yielded a compound, mp 158–159°, whose NMR spectrum suggested that it contained the $-CH_2SCH_3$ group. On the basis of spectral data, elemental analysis, mechanistic considerations, and literature reports,[19] the contaminant in crude **21** was deduced to be a new compound **25** formed by a Sommelet–Hauser type of reaction.



25a

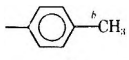
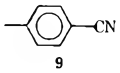
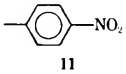
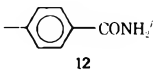
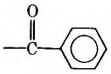
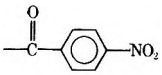
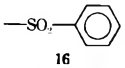
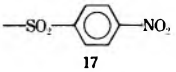


25b



25, mp 162–163° (6)

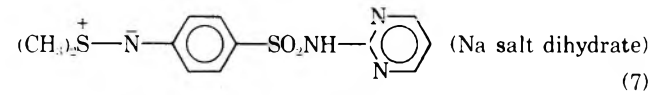
Table I
Iminosulfuranes (2) from DMSO–TFAA Reagent and Nitrogen Compounds

R in $(CH_3)_2S^+$ -N^--R	Yield, %	Mp, °C Found	Mp, °C Lit.	Elemental analysis and NMR data[a]
 5	60	130–130.5 dec	128–130[13]	Calcd for $C_{14}H_{14}N_4O_7S$: C, 44.0; H, 3.70; N, 14.8; S, 8.37. Found: C, 44.4; H, 4.11; N, 15.1; S, 8.18. NMR 3.3, 6 H, s; 7.3, 5 H, m; 8.6, 2 H, s
 6	40 (y)[d] 75 (p)	132–132.5 dec 165–168 dec[e]	RT[14]	NMR (y) 2.4, 3 H, s; 3.6, 6 H, s; 7.1, 4 H, m. Calcd for $C_{15}H_{16}N_4O_7S$ (p): C, 45.5; H, 4.07; N, 14.1; S, 8.07. Found: C, 45.3; H, 4.03; N, 14.0; S, 8.07. NMR (p) 2.4, 3 H, s; 3.4, 6 H, s; 7.1, 4 H, m; 8.6, 2 H, s
 7	60	165–166 dec	165–167[13]	NMR 2.2, 3 H, s; 3.2, 6 H, s; 7.0, 4 H, m, 8.6, 2 H, s
 8	85	140–141 dec[e]		Calcd for $C_{14}H_{13}FN_4O_7S$: C, 42.0; H, 3.25; N, 14.0; S, 8.00. Found: C, 41.9; H, 3.12 N, 13.9; S, 7.73. NMR 3.3, 6 H, s; 7.2, 4 H, m; 8.6, 2 H, s
 9	65	108–109 dec	111–112[1b] 108–112[13]	NMR 2.8, 6 H, s; 7.1, 2 H, d; 7.7, 3 H, d
 10	60	73–74[e]		Calcd for $C_8H_{10}N_2O_2S$: C, 48.5; H, 5.05; N, 14.1. Found: C, 48.2; H, 5.17; N, 13.9. NMR 2.6, 6 H, s; 7.50, 1 H, m; 7.90, 1 H, m; 8.16, 1 H, m; 8.56, 1 H, m
 11	65	166–167 dec	172–174[1b] 164–166[10]	NMR 2.8, 6 H, s; 7.6, 2 H, d; 8.3, 2 H, d
 12	55	90		NMR 2.6, 6 H, s; 6.7, 2 H, d; 7.7, 2 H, d
 13	60	108–110	106–108[15]	NMR 2.8, 6 H, s; 7.3, 3 H, m; 8.0, 2 H, m
 14	90	217–218 dec	220–222[1b]	
 15	80	136–137[e]		Calcd for $C_5H_9F_3N_2O_3S$: C, 25.6; H, 3.87; F, 24.4; N, 12.0; S, 13.7. Found: C, 26.0; H, 3.84; F, 24.2; N, 11.7; S, 13.4. NMR 3.2, 6 H, s; 7.0, 3 H, s (broad)
 16	80	129–131	128–130.5[1b] 131[16]	NMR 2.7, 6 H, s; 7.35, 3 H, m; 7.85, 2 H, m
 17	85	184–185	183–185[1b] 186[10]	NMR 2.8, 6 H, s; 8.0, 2 H, m; 8.4, 2 H, m

[a] $CDCl_3$ or DMSO-d_6 solution; XL-100 NMR spectrometer; δ values (Me_4Si = 0). [b] Isolated as picrate only. [c] Both ylide and picrate isolated; y = ylide and p = picrate. [d] The free ylide is unstable; an elemental analysis was not obtained. [e] New compounds. [f] This compound was not completely characterized and its structure is still uncertain. [g] Isolated as trifluoroacetate only.

The sequence that best explains the formation of **25** from **24** via **25a** and **25b** in the presence of basic ion-exchange resins is shown in eq 6.

Sulfadiazine (**19**) readily forms an iminosulfurane (**23**), sodium salt (dihydrate), mp 265–268° dec, in 70% yield from reagent **3** and **19** (eq 7). In contrast to **19**, **23** is readily

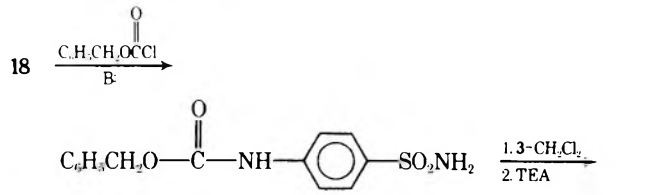


(7)

23, mp 265–268° dec (70%)

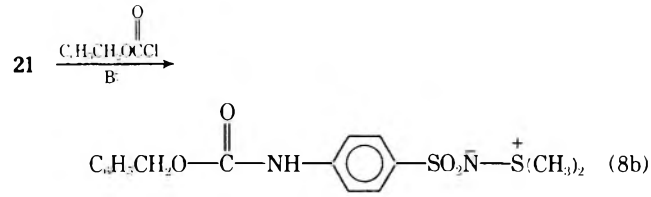
soluble in water, producing a slightly alkaline solution (pH 9). Compound **23** undergoes the Sommelet–Hauser type of rearrangement in aqueous solution at room temperature ($t_{1/2} \simeq 24$ hr) (determined by NMR) but it appears to be stable in the solid state.

Independent Synthesis. Monoylides **20** and **21** are isomeric and have similar NMR spectra. Although **20** gives a negative ninhydrin test and is soluble in aqueous base and **21** gives a positive ninhydrin test and is insoluble in aqueous base, such structure proof is inadequate. The structure of **21** was demonstrated by the synthetic sequence shown in eq 8a and 8b. To block the free amino group, sulfanilamide (**18**) was treated with benzyl chloroformate in acetone in the presence of sodium bicarbonate thereby forming **26**, mp 192–193° (80%) (eq 8a). Compound **26** (free amino group blocked) was then converted to the iminosulfurane (**27**) (ylide on the sulfonamido side), mp 148–149° (50%), by reaction with the DMSO–TFAA reagent (**3**) followed by deprotonation with TEA. The same compound was formed by reaction of **21** with benzyl chloroformate (eq 8b); it was



26, mp 192–193° (80%)

27, mp 148–149° (50%) (8a)



(8b)

27

identical with **27** in every way (NMR, ir, uv, melting point, mixture melting point). It can therefore be concluded that **21** is the monoylide with a free amino group (ylide on the sulfonamide side) and **20** must be its isomer with a free sulfonamido group (ylide on the amino side). Both **26** and **27** give negative ninhydrin tests, as would be expected as neither compound contains a free amino group.

We have also tried to remove the benzyloxycarbonyl group selectively from **27** to re-form **21** using either hydrogenolysis in methanol with 5% Pd/C catalyst at 60 psi or the more recently reported reagent, boron trifluoroacetate in trifluoroacetic acid.[20] Hydrogenolysis yielded a mixture of sulfanilamide (**18**) and **26** but not **21**. We believe this is the first reported hydrogenolytic cleavage of the S–N bond in iminosulfuranes. The results indicate that hydrogenolysis of the S–N bond is more rapid than cleavage of the benzyloxycarbonyl group. The boron trifluoroacetate reagent cleaved both the benzyloxycarbonyl and ylide groups (no selectivity was noted); **18** was isolated in good yield.

Limitations. Cyclohexylamine and benzylamine did not yield ylides or their salts on reaction with the reagent (**3**); under a variety of conditions the trifluoroacetates of the amines were obtained instead. These amines are considerably more basic than aromatic amines and, rather than perform a nucleophilic displacement reaction on the sulfur atom of the reagent, they may abstract a proton from the dimethylsulfonium moiety instead. No success was obtained with *o*- and *p*-diaminobenzene or anthranilamide for reasons that are not evident. With *p*-anisidine attempts were made to isolate the picrate of the ylide but the reaction products decomposed. 2- and 4-aminopyridine yielded picrates of the amines and not of the ylides.

Experimental Section[21]

General Procedures. Compounds 16 and 17 (Table I). DMSO (1.45 ml, 0.02 mol) was dissolved in CH_2Cl_2 (10 ml) in a three-neck flask with a magnetic stirrer, thermometer, nitrogen inlet, and drying tube. Dry nitrogen was passed through the stirred solution cooled to −60° and TFAA (2.8 ml, 0.02 mol) was added slowly while maintaining the temperature below −50°. The reaction was exothermic and a white precipitate of **3** formed immediately. (Similar results have been obtained using a 2:1 molar ratio of DMSO to TFAA and 5 ml of CH_2Cl_2).

p-Nitrobenzenesulfonamide (2.0 g, 0.01 mol) was slowly added as a slurry in DMSO–CH_2Cl_2 (10 ml of 4:1 v/v) at or below −50°. (TLC was not useful in monitoring this reaction owing to interference by DMSO.) After 1 hr the stirred reaction mixture was allowed to warm to room temperature and the precipitate was filtered, washed with 5% aqueous NaOH to remove any residual starting material, then with water, and dried. Pure **17**, mp 184–185° (2.34 g, 88%), was obtained without further work-up. Compound **16**, mp 129–131°, was similarly prepared (80%).

Compounds 13, 14, 15 (Table I). In the preparation of **13**, all the benzamide was consumed in 1 hr (TLC) below −35°. The reaction mixture was diluted to 50 ml with CH_2Cl_2 and excess 10% aqueous sodium hydroxide was added. The organic layer was washed with water (2 × 10 ml), dried over $MgSO_4$, filtered, and evaporated to dryness. The residue, obtained in 100% yield, consisted of **13** contaminated with a small quantity of DMSO. It was washed several times with ether to yield pure **13**, mp 108–110° (60% yield). Omission of the base in the work-up gave a mixture of products in the initial residue; **13** was one of them but it could not be obtained in a pure state unless the residue was washed with aqueous base.

A variation in procedure was used in preparing **14**. A stirred slurry of *p*-nitrobenzamide (2.4 g, 0.015 mol) in DMSO (1.45 ml, 0.02 mol) and CH_2Cl_2 (15 ml) was cooled to −60° and TFAA (2.8 ml, 0.02 mol) was added slowly while maintaining the temperature below −50°. After 2.5 hr all of the amide was consumed (TLC) and the reaction mixture was allowed to warm to room temperature. Ether (30 ml) was added and the precipitate was filtered, washed with ether, and dried, mp 217–218° (2.96 g, 92%). A single crystallization from methanol yielded product of mp 220–222°.[1b]

To prepare **15**, a slurry of urea (1.2 g, 0.02 mol) in DMSO–CH_2Cl_2 (4 ml of 1:1 v/v) was added to the reagent (**3**) prepared from equimolar quantities (0.02 mol) of DMSO and TFAA in CH_2Cl_2 (10 ml) at −50°. After 3 hr the reaction mixture was allowed to warm to room temperature and the precipitate was filtered and dried; mp 136–135° (80%). Recrystallization from ethanol–ether (1:3) did not raise the melting point. Analysis showed that **15** was the trifluoroacetate of the monoylide.

Use of 0.03 mol of reagent (**3**) to 0.01 mol of urea yielded a mixture of products one of which corresponded to **15** (TLC). No further examination was made of this reaction.

Compounds 5–11. The reagent (**3**) was prepared from DMSO (0.018 mol) and TFAA (0.01 mol) in CH_2Cl_2 (5 ml) at −60°. *p*-Nitroaniline (0.01 mol dissolved in 5 ml of CH_2Cl_2 + 3 ml of DMSO) was slowly added while maintaining the temperature below −40° during the addition. By the time all the amine had been added, the precipitate of **3** had disappeared. Aqueous 10% sodium hydroxide solution (5 ml) was added and the stirred reaction mixture was allowed to warm to room temperature. The solution was extracted with CH_2Cl_2 (2 × 20 ml) and the combined CH_2Cl_2 extracts were washed with water (2 × 10 ml) and dried over anhydrous $MgSO_4$. Evaporation of the filtrate to dryness under vacuum yielded a brown residue in quantitative yield. Recrystallization from CH_2Cl_2–ether using decolorizing carbon yielded pure **11**, mp 166–167° dec (65%) (melting point, NMR, ir, TLC identical with those of an authentic sample[1b]).

Compound **10** was similarly prepared but reaction time was 1 hr. The crude product was a reddish oil whose NMR and ir indicated

that it was mainly **10**. Recrystallization from CH_2Cl_2–ether (1:5) yielded orange needles: mp 73–74° (60%); ir 3010, 2920, 1600, 1510, 1350, 1270, 1170, 910, 840, 750, 670 cm^{-1}.

The ylide from *o*-fluoroaniline was obtained as an oil that could not be crystallized; its NMR spectrum was consistent with the proposed structure. The picrate salt of the ylide (compound **8**) was prepared from **3** (0.02 mol) and o-fluoroaniline (0.01 mol) in CH_2Cl_2 (10 ml) at −50° followed by addition of a methanol solution of picric acid at −20°. The yellow precipitate was filtered, washed with cold solvent, and dried. Analysis and NMR confirmed its structure as the picrate salt of **8**, mp 140–141° dec (85%).

Compounds **5**, **6** and **7** were also isolated as picrates, essentially as just described; their melting points with decomposition are 130–130.5°, 165–168°, and 165–166°, respectively. The ylide **6**, mp 132° dec, could be prepared also but it was too unstable to obtain an elemental analysis; its NMR was consistent with the ylide structure. During the determination of its melting point it blackened.

Preparation of 24 and 22. To a stirred slurry of **3** (0.03 mol) at −60° a solution of sulfanilamide (**18**, 1.72 g, 0.01 mol) in DMSO (4.5 ml) or DMSO–CH_2Cl_2 (10 ml of 1:1 v/v) was added dropwise. After about 1–2 hr TEA (0.02 mol) was added and the stirred reaction mixture was allowed to warm to room temperature. Ether (20–100 ml) was added and the white precipitate (3.5–4.5 g) was separated by filtration. Recrystallization either from methanol, methanol–acetone, or methanol–methylene chloride yielded pure **24** (75–95%): mp 174–176° dec; NMR (Me_4Si 0) [DMSO-d_6–D_2O (1:1)] δ 2.8 s, 6 H; 3.36, s, 6 H; 7.3, dd, 2 H; 7.8, dd, 2 H; ir 1250 (SO_2 asymmetrical), 1120 (SO_2 symmetrical), 1690 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{17}F_3N_2O_4S_3$: C, 35.5; H, 4.20; F, 14.0; N, 6.89; S, 23.6. Found: C, 35.8; H, 4.19; F, 13.8; N, 6.9; S, 23.4.

Compound **24** (0.41 g, 0.001 mol) was stirred for 1 hr at room temperature with excess TEA (2.5 ml) and CH_2Cl_2 (2 ml). Solution was not obtained; the solid (0.170 g, 59%), mp 179–182° dec, was filtered, washed, and dried under vacuum. It was shown to be pure **22** by spectral measurements and elemental analysis: NMR (DMSO-d_6) δ 2.65, 2, 6 H; 2.8, s, 6 H; 6.8, dd, 2 H; 7.5, dd, 2 H. Anal. Calcd for $C_{10}H_{16}N_2O_2S_3$: C, 41.4; H, 5.47; N, 9.58; S, 32.9. Found: C, 41.2; H, 5.28; N, 9.37; S, 32.6.

The conversion of **24** to **22** was also conducted in D_2O–NaOH solution in an NMR tube. Compound **24** (27 mg) was dissolved in D_2O (1 ml) in an NMR tube and its spectrum was recorded. A few drops of 50% aqueous NaOH solution was added and the NMR spectrum was immediately rerecorded: NMR (D_2O δ 5) **24**, 3.1, s, 6 H; 3.6, s, 6 H; 7.6, dd, 2 H; 8.2, dd, 2 H; **22**, 2.7, s, 12 H; 6.8, dd, 2 H; 7.5, dd, 2 H.

Preparation of 20. A. Unsuccessful Preparation. Sulfanilamide (**18**, 0.01 mol) in DMSO–CH_2Cl_2 (7 ml of 1:1 v/v) was added to **3** (0.01 mol) at −50° with stirring, followed after 5 min by the addition of TEA (0.02 mol). The reaction mixture was allowed to warm to room temperature. An oil separated from which the supernatant solvent layer was decanted. The residual oil was washed with CH_2Cl_2–diethyl ether (1:1), leaving a sticky solid residue (2.2 g). Its NMR spectrum indicated that it was mainly the diiminosulfurane monosalt, **24**. TLC showed three spots corresponding to **24** and **18** (major products) and a minor unidentified species.

B. Successful Preparation. In a specially constructed apparatus consisting of two three-neck flasks vertically arranged and interconnected by means of a stopcock between the upper and lower flasks (both of which could be independently cooled), reagent **3** (0.02 mol) was prepared in the upper flask, the contents of which were mechanically stirred at −50°. The intermediate was then added dropwise to the lower flask which contained **18** (0.02 mol) in DMSO–CH_2Cl_2 (10 ml of 1:1 v/v) at −50°, magnetically stirred. The addition required about 30 min. Stirring was continued at −50° for an additional 15 min and the lower flask was allowed to warm to room temperature. TEA (8 ml) was added and the white precipitate that formed was filtered, washed successively with cold CH_2Cl_2 and diethyl ether, and dried; compound **20** (2.3 g, 50%), mp 135–137° dec, was thus obtained in analytical purity. It gave a negative ninhydrin test and did not form an azo dye with β-naphthol. It was insoluble in water but soluble in aqueous base (sulfonamide group present): NMR (DMSO-d_6 + D_2O) (D_2O δ 4.0) 2.7, s, 6 H; 6.7, dd, 2 H; 7.5, dd, 2 H. Anal. Calcd for $C_8H_{12}N_2O_2S_2$: C, 41.4; H, 5.20; N, 12.1; S, 27.6. Found: C, 41.3; H, 5.14; N, 12.0; S, 27.4.

Preparation of 21. A. Compound **24** (1.2 g, 0.003 mol) was dissolved in water (40 ml) and prewashed Amberlite IR-45 ion-exchange resin (10 ml of aqueous slurry) was added. After overnight stirring, the mixture was filtered and the filtrate was freeze dried. The precipitate was recrystallized from *i*-PrOH, yielding **21** (0.200 g, 30%), mp 190–193° (positive ninhydrin test).

B. A. 7.2 × 2.5 cm column was packed with 60 ml of a slurry of Amberlite IRA-400 (Cl^-) ion-exchange resin. A 5% NaOH solution (120 ml) was passed through the column to convert the resin to the hydroxide form. The column was then washed thoroughly with distilled water (ca. 500 ml) until the pH of the effluent was 7. The monotrifluoroacetate **24** (4.8 g) was dissolved in H_2O–MeOH (35 ml of 85:15 v/v) and the solution was added to the column. The column was eluted with H_2O–MeOH (300 ml of 95:5 v/v adjusted to pH 9) and the eluate was evaporated to dryness at 30° under high vacuum. The residual solid was triturated with *i*-PrOH to yield an insoluble white solid (2.7 g). TLC showed the presence of three components, one major and two minor. Ir and NMR indicated that trifluoroacetic acid had been completely removed. Column chromatography on silica gel (80 g) and elution with MeOH–$CHCl_3$ (5:95) yielded **25** (600 mg), mp 162–163°, and **21** (1.2 g), mp 190–193°. Anal. Calcd for $C_{10}H_{16}N_2O_2S_3$ (**25**): C, 41.4; H, 5.20; N, 12.1; S, 27.6; *m/e* 292. Found: C, 41.2; H, 5.47; N, 9.46; S, 32.8; *m/e* 292. Anal. Calcd for $C_8H_{12}N_2O_2S_2$ (**21**): C, 41.4; H, 5.20; N, 12.1; S, 27.6. Found: C, 41.4; H, 5.18; N, 11.9; S, 27.5. NMR spectra (DMSO-d_6) (Me_4Si 0) **21**, δ 6.6–7.4, dd, 4 H; 5.68, broad s, 2 H (signal disappears on addition of D_2O); 2.65, s, 6 H; **25**, 7.4, s, 1 H, 6.7–7.4, dd, 2 H; 5.60, broad s, 2 H (signal disappears on addition of D_2O); 3.62, s, 2 H; 2.64, s, 6 H; 1.98, s, 3 H. Ir (Nujol mull) **21**, 3440, 3330, 1248, 1125, 1090, 950, 840, 772 cm^{-1}; **25**, 3440, 3330, 3250, 1253, 1117, 1094, 958, 769 cm^{-1}; uv λ_{max} (EtOH) **21**, 211 nm (ϵ 16,300), 265 (24,500); **25**, 216 nm (ϵ 382), 267 (361).

Preparation of 23. To a stirred slurry of **3** (0.02 mol) in DMSO–CH_2Cl_2 (12 ml of 1:1 v/v) at −60°, *N'*-2-pyrimidinylsulfanilamide (sulfadiazine, **19**) in DMSO–CH_2Cl_2 (35 ml) was added while maintaining the temperature at or below −45°. After 30 min 10% NaOH (25 ml) was slowly added and the reaction mixture was stirred for an additional 30 min at −45°. After warming to room temperature, the reaction mixture was filtered yielding crude **23** (4.4 g, 70%). It was dissolved in a minimum quantity of water without heating, *i*-PrOH was added to the cloud point, and the mixture was cooled to 0–5° to yield **23** as the sodium salt (dihydrate): mp 265–268°; NMR (D_2O) δ 2.68, s, 6 H; 6.65, t, 1 H; 6.85, d, 2 H; 7.75, d, 2 H; 8.25, d, 2 H. Compound **23** is unstable in water and undergoes a Sommelet–Hauser type of rearrangement ($t_{1/2} \simeq$ 24 hr at room temperature): ir (Nujol mull) 1405, 1210, 1115, 815 cm^{-1}; uv λ_{max} (EtOH) 285 nm (ϵ 17,400). Anal. Calcd for $C_{12}H_{13}N_4O_2S_2Na \cdot 2H_2O$: C, 39.1; H, 4.64; N, 15.2; S, 17.4; Na, 6.24. Found: C, 39.5; H, 4.64; N, 15.19; S, 17.4; Na, 6.30.

Independent Syntheses. 26. Sulfanilamide (**18**, 1.72 g, 0.01 mol) was dissolved in acetone (20 ml) followed by addition to the stirred solution of aqueous sodium bicarbonate (1.26 g, 0.015 mol in 5 ml of H_2O) and then benzyl chloroformate (2.5 ml, ca. 0.02 mol). After 18 hr, the reaction mixture was evaporated to dryness at 40°. The white residue was triturated with H_2O and filtered. The dried precipitate was washed with cold methylene chloride and ether. The residue was crystallized from *i*-PrOH to yield **26**, mp 192–193° (negative ninhydrin test). TLC (10% MeOH–$CHCl_3$ development) gave a single spot (R_f 0.5).

Compound 27. The DMSO–TFAA complex was prepared at −45° from DMSO (1.9 ml) dissolved in CH_2Cl_2 (5 ml) and TFAA (1.5 ml, 0.01 mol). To the resulting stirred suspension, **26** (2.5 g, 0.008 mol) dissolved in DMSO–CH_2Cl_2 (15 ml of 1:2 v/v) was added at −45° or below. After 10 min, TEA (1.7 ml) was added and the reaction mixture was allowed to warm to room temperature. After concentration to a small volume at 45° under vacuum, *i*-PrOH–Et_2O (1:1) was added to remove soluble impurities (mainly DMSO). The white solid residue (1.5 g, 50%) was crystallized from *i*-PrOH to yield **27**: mp 148–149°; NMR (DMSO-d_6) (Me_4Si 0) **26**, δ 5.20, s, 2 H; 7.20, broad s, 2 H; 7.40, s, 5 H; 7.62–7.80, dd, 4 H; **27**, 2.65, s, 6 H; 5.18, s, 2 H; 7.40, s, 5 H; 7.60, s, 4 H.

Conversion of 21 to 27. To a stirred solution of **21** (0.1 g) in acetone (3 ml), aqueous $NaHCO_3$ (0.2 g in 2 ml of H_2O) was added followed by benzyl chloroformate (1 ml). After 3 hr the reaction mixture was evaporated to dryness and worked up as above. The product obtained was identical in every way with **27** (NMR, ir, uv, melting point, mixture melting point).

Attempted Debenzylation of 27. Attempted reconversion of **27** to **21** by hydrogenolysis in methanol with 5% Pd/C catalyst at 60 psi or with boron trifluoroacetate in trifluoroacetic acid was unsuccessful. Hydrogenolysis yielded a mixture of **18** and **26** and the boron reagent yielded only **18**.

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122273) and the Samuel S. Fels Fund for partial support of this research.

Registry No.—**5** picrate, 55975-86-5; **6**, 27691-49-2; **6** picrate, 55871-34-6; **7** picrate, 55871-35-7; 8 picrate, 55871-37-9; **9**, 39159-87-0; **10**, 55871-38-0; **11**, 27691-52-7; **13**, 19397-91-2; **14**, 55259-85-5; 15 trifluoroacetate, 55871-40-4; **16**, 19871-30-8; **17**, 18922-58-2; **18**, 63-74-1; **19**, 68-35-9; **20**, 55871-41-5; **21**, 24194-22-7; **22**, 55871-42-6; **23**, 55871-43-7; **24**, 55871-44-8; **25**, 55871-45-9; **26**, 55871-46-0; **27**, 55871-47-1; DMSO, 67-68-5; TFAA, 407-25-0; *p*-nitrobenzenesulfonamide, 6325-93-5; benzamide, 55-21-0; *p*-nitrobenzamide, 619-80-7; urea, 57-13-6; *p*-nitroaniline, 100-01-6; *o*-fluoroaniline, 348-54-9; benzyl chloroformate, 501-53-1.

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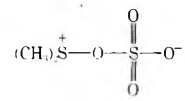

A

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(18) Sulfanilamide (**18**) gives a positive ninhydrin test and is soluble in aqueous base.
(19) P. Gassman and G. Gruetzmacher, *J. Am. Chem. Soc.*, **96**, 5487 (1974), and following papers.
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Acid-Catalyzed Reactions of Epoxides with Dimethyl Sulfoxide[1a]

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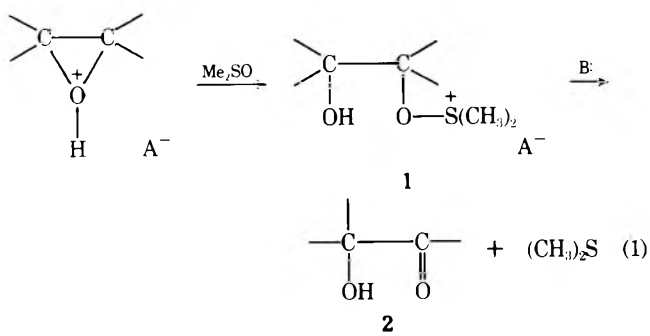
Ring-opening reactions of styrene oxide, *p*-nitrostyrene oxide, cyclopentene, cyclohexene, and cycloheptene oxides, and *cis*- and *trans*-9,10-epoxystearic acids with Me_2SO in the presence of strong acids have been studied both by NMR and preparatively. In most instances, initial products are vicinal hydroxyalkoxysulfonium salts. Regiospecificity of ring opening is observed with styrene oxide and *p*-nitrostyrene oxide; stereospecificity is observed with cyclohexene oxide and *cis*- and *trans*-9,10-epoxystearic acids. Treatment of selected salts with bases yields mixtures of 1,2-ketols and glycols even in the absence of water, with glycols usually predominating. In contrast with cyclohexene oxide, which reportedly gives fair to good yields of adipoin on treatment with boron fluoride etherate followed by base, cyclopentene and cylcoheptene oxides isomerize largely to the corresponding ketones.

In an earlier study[2] we showed that 2,4,6-trinitrobenzenesulfonic acid is a useful strong acid catalyst for the regio- and stereospecific preparation of crystalline vicinally substituted hydroxyalkoxysulfonium salts (**1**, eq 1) from Me_2SO and epoxides.



1 **2** (1)

To assess the generality of the acid-catalyzed Me_2SO ring-opening reaction, we had been concurrently exploring other strong acid catalysts (boron trifluoride, fluoroboric, trifluoroacetic, methanesulfonic, sulfuric, and nitric acids) which also provide anions of low nucleophilicity; this paper describes the results of that investigation. Although crystalline salts (**1**) were usually not obtained with the latter group of acids, the course of the reactions and the initial products were readily monitored by NMR. In addition we are reporting (a) the overall oxidation of epoxides to α-hydroxy ketones (ketols) (**2**) via the intermediate salts (**1**) upon treatment with base, (b) the stereospecific conversion of epoxides to 1,2-glycols by hydrolysis of **1** or its attack by nucleophiles, and (c) some miscellaneous reactions of the epoxides and salts (**1**).

The regiospecificity of attack of many nucleophiles on unsymmetrical epoxides under acid conditions has been

Table I
Acid-Catalyzed Ring Opening of Styrene Oxide (3) by Me_2SO[a]

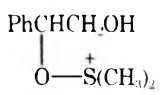
Acid	Products 4, %	5, %	Others, %
Trifluoroacetic	52[b]	16[b]	Phenylacetaldehyde (**6**), 1
Sulfuric	47	*c*	2-Phenyl-2-hydroxyethanol, 2-sulfonate ester (**7**), 20[d] 2-Phenyl-2-hydroxyethanol (**8**), 14
Methanesulfonic	69	*c*	2-Phenyl-2-hydroxyethanol 2-methanesulfonate ester (**9**), 25[d]
$Me_2SO \cdot BF_3$	66	*c*	**6**, 12
$Me_2SO \cdot HBF_4$[e]	86	*c*	**6**, 1
$Me_2SO \cdot HNO_3$	62	*c*	2-Phenyl-2-hydroxyethanol, 2-nitrate ester (**10**), 22[d]

[a] Molar ratio Me_2SO:3:acid 5:1:1. [b] After 5 min at 40°, the molar ratio of 4:5 was 6.7 with a total yield of 60%. After 20 min, decomposition of 4 and 5 had occurred, the ratio had decreased to 2.6, and the yield was no longer determinable by NMR. The initial ratio was slightly higher if the acid was added to the Me_2SO–epoxide solution rather than vice versa. [c] 5 could not be detected. [d] Inferred from NMR. [e] We assume that this is the species that predominates in the reaction of Me_2SO with commercial HBF_4 (see Experimental Section).

widely studied and reviewed.[3-6] In contrast, reaction of Me_2SO with epoxides in the presence of acid catalysts has received only limited study. In most cases only the secondary products of the reaction were examined, thereby rendering equivocal conclusions concerning the initial point of attack.[7-12] Direct observation of the intermediate hydroxyalkoxysulfonium salts (**1**) avoids the problems of earlier approaches to the determination of the regiospecificity of the ring-opening processes, and such observation could confirm the role of the intermediates in the overall reaction.

Results and Discussion

Regiospecificity. Ring Opening of Styrene Oxide (3) (Table I). In Me_2SO solution in the presence of 1 or more equiv of strong acid, the characteristic NMR signals of the oxirane ring of **3**, consisting of three doublets of doublets, rapidly disappear and are replaced by three new sets of signals: a broad triplet centered about δ 5.7; a broad doublet centered about δ 3.9; and two singlets at δ 3.5 and 3.3. On the basis of chemical shift, multiplicity, and integration, and by comparison with the reported spectrum of the corresponding bromo compound,[13] the triplet, doublet, and two singlets can be assigned to the methine, methylene, and *S*-methyl protons,[14] respectively, of the (α-hydroxymethyl)benzyloxydimethylsulfonium cation **4**. This assignment was confirmed by the loss of these signals on treatment of the solution with water or base and also by isolation and further characterization of two salts of this cation in our laboratory[2] and elsewhere.[15]



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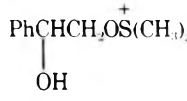


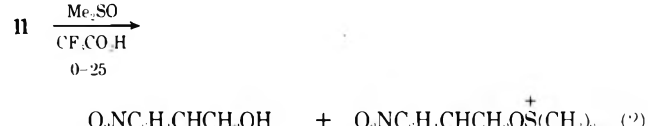
5

With trifluoroacetic acid (Table I), two additional sets of signals are observed: a triplet centered about δ 5.0 and a doublet centered about δ 4.5. These can be assigned to the methine and methylene protons, respectively, of the regioisomer of **4** (α-hydroxybenzyl)methyloxydimethylsulfonium cation **5**. The assignment is a reasonable one from the multiplicity, chemical shifts, and integration, and by comparison with the NMR spectrum of **4**. In addition, the total *S*-methyl signal (**4** + **5**) integrates correctly only if the presence of **5** is accepted. The signals assigned to **5** also disappear upon the addition of water, and the related alkoxydimethylsulfonium salt from *p*-nitrostyrene oxide gives NMR signals closely corresponding to those of **5** as would be expected (see below). Thus, the regioisomers from styrene oxide and Me_2SO can be readily distinguished by NMR.

The results of the ring-opening reaction using various strong acids are summarized in Table I.[16] Other products formed (NMR detection only) are (a) phenylacetaldehyde (**6**) [usually 1% or less except with BF_3 (>10%)], (b) those from reaction of the anions of the strong acids rather than Me_2SO with the protonated epoxide (**7**, **9**, **10**), and (c) 1,2-glycols in the case of sulfuric acid which contains about 4% water.

The main conclusion from Table I is that the acid-catalyzed ring opening of styrene oxide by Me_2SO exhibits the regiospecificity shown by other nucleophiles.[3-5] With the exception of trifluoroacetic acid, complete regiospecificity is obtained and even in that case the expected regioisomer (that of benzylic attack by Me_2SO) predominates (6.7:1). The presumption is that this ratio reflects the products of kinetic control. This conclusion is supported by the stability of cation **4** (with regard to conversion to **5**) under similar conditions with other counterions (Table I). Also, when **4** is isolated as the trinitrobenzenesulfonate and observed by NMR in Me_2SO solution, no conversion to **5** is noted.[2,6b] Similar reasoning applies to the cations formed from *p*-nitrostyrene oxide (see below).

***p*-Nitrostyrene Oxide (11).** Reaction of Me_2SO (5.60 mol) with **11** (0.857 mol) and trifluoroacetic acid (1.00 mol) is not only considerably slower than with **3** but nonbenzylic attack predominates at 0–25° (eq 2). The ratio of **12**:**13** is 0.83–0.87 (1:1.2) and this ratio remains constant for many hours (16 hr at 0° and 4 hr at 25°).



(2)

12 **13**

With the two epoxides examined, acid-catalyzed oxirane ring opening by Me_2SO conforms to the regiospecificity expected from a "borderline SN2" process.

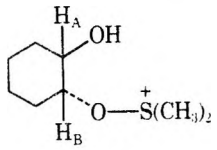
Stereospecificity. Ring Opening of Cyclohexene Oxide (14). To examine the stereospecificity of the Me_2SO–epoxide reaction the cyclohexene oxide–Me_2SO–trifluoroacetic acid system was chosen for initial NMR study. As with styrene oxide (**3**), the signals characteristic of the oxirane ring protons disappear rapidly and three new sets of signals appear: an unresolved multiplet centered about δ 4.4 (4.1–4.7); a multiplet ranging from δ 3.3 to 3.9; and two singlets at δ 3.45 and 3.50. By analogy with **3** and comparison with the NMR spectra of related cations, namely, a bromo compound[13] and a corresponding cation

Table II
Reaction of Intermediate Salts (4 and 5) from Styrene Oxide (3)-Me_2SO-Acids with Various Bases

Acid	Base	Base:cation molar ratio	Phenylacyl alcohol (16), % conversion	2-Phenyl-2-hydroxyethanol (17), % conversion
Trifluoroacetic	Triethylamine	3.4	20	43
Trifluoroacetic	Pyridine-d_5[a]	3.0	18	38
Trifluoroacetic	Pyridine-d_5[b]	2.8	17	80
Trifluoroacetic	$NaHCO_3$[c]	2.8	42	57
Trifluoroacetic	NaH	2.4	None detected	None detected
Sulfonic	Triethylamine	2.9	26	71
Methanesulfonic	Triethylamine	2.4	58	41
$Me_2SO \cdot BF_3$	Triethylamine	2.7	Trace	Trace
$Me_2SO \cdot HBF_4$	Triethylamine	1.8	Trace	Trace
$Me_2SO \cdot HBF_4$	$NaCO_3$[c]	2.0	50[d]	50[d]

[a] Salt (1) solution added to base. [b] Base added to salt solution. [c] Base incompletely soluble in Me_2SO. [d] The spectra were poorly resolved: figures are best estimates.

derived from acid-catalyzed *N*-oxide ring opening,[17] the new signals are assigned to the *trans*-(2-hydroxycyclohexyl)oxydimethylsulfonium cation (**15**). The upfield multiplet



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is probably due to H_A and the downfield one to H_B. The pair of singlets of the two nonequivalent *S*-methyl groups comprise the third set of signals. To corroborate conclusions from the in situ NMR study, the reaction was repeated on a preparative scale; the trifluoroacetate of **15**, **15a**, mp 82–84°, was isolated in about 40% yield.[18] Its NMR spectrum was identical with that found in the NMR study. Compound **15a** was also obtained independently in about 20% yield from *trans*-1-iodo-2-hydroxycyclohexane, Me_2SO, and silver trifluoroacetate. It would be expected that the trans stereochemistry of the iodohydrin would be preserved in such a displacement by O-3 neighboring group participation.

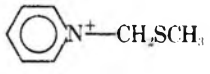
The trans stereochemistry of **15** was confirmed by mild, neutral aqueous hydrolysis of **15a** to *trans*-1,2-cyclohexanediol in almost 50% yield as the sole product. Hydrolysis of secondary alkoxysulfonium salts, such as **15a**, proceeds by exclusive attack at sulfur and the stereochemistry of the salt is preserved in the alcohol produced; this conclusion has ample precedent.[2-5,19]

Reaction of 1 with Bases. Reaction of the intermediate salts (**1**) with bases has been studied in a few cases;[2,7,20] reported products are ketols (α-hydroxy ketones) and dimethyl sulfide. Detailed study of that reaction[20,21] has shown that the reaction is not a simple or general one; yields of ketols are only modest. We have reinvestigated the reaction in NMR tubes with salts formed in situ from Me_2SO, styrene oxide, and strong acids, followed by the immediate addition of various bases; Table II summarizes the results.

The anticipated product, phenacyl alcohol (**16**), was formed in most cases (17–58%) but the major product (38–80%) was 2-phenyl-2-hydroxyethanol (**17**) even though the reactions were run under anhydrous conditions.[22] Other by-products were also formed depending on the base used. In about half the reactions listed in Table II, a good mass balance for the conversion of the cations **4** and **5** to **16** and **17** was obtained. In the other cases, the presence of unidentified substances was indicated by the NMR spectra but they could not be determined quantitatively. Unidentified by-product formation may be associated with failure to control the internal temperature of the base–cation reaction adequately, which was carried out in NMR tubes immersed in an ice–water bath but without monitoring or controlling the internal temperature. The possibility of side reactions, including base-catalyzed condensations of **16**, cannot be excluded.

Mandelaldehyde (or its dimer) could not be detected by NMR even though it is the anticipated product of the reaction of **5** with base. In view of the facile rearrangement of α-hydroxy aldehydes to α-hydroxy ketones,[23,24] failure to observe mandelaldehyde is not too surprising. This result emphasizes the danger in attempting to infer the regiospecificity of Me_2SO attack on the oxirane ring from the final reaction products.

When pyridine was used as the base (Table II) 1-(methylthio)methylpyridinium ion (**18**) was a by-product. With triethylamine, NMR signals consistent with the presence of (methylthiomethyl)trimethylammonium ion (**19**) were observed.



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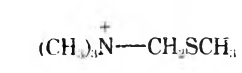


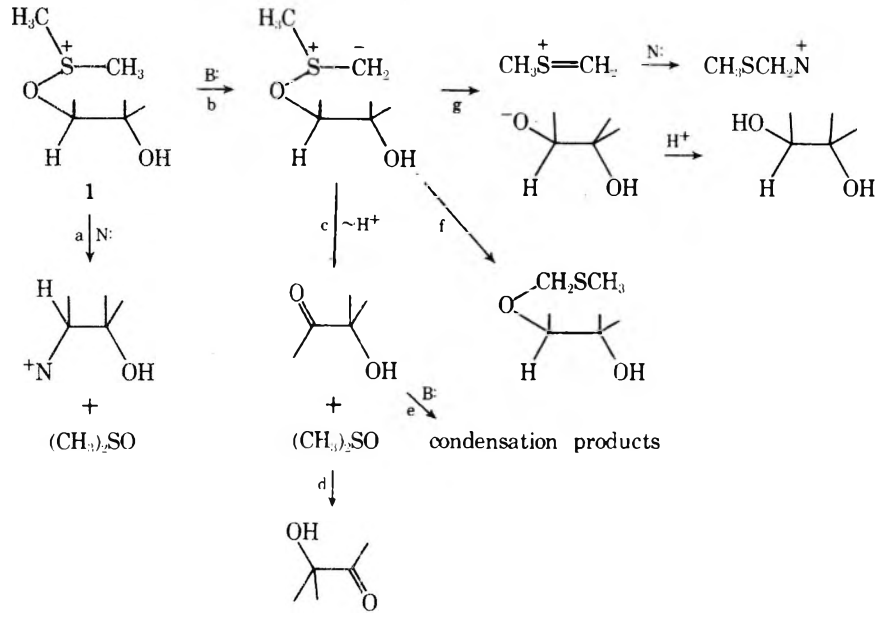
19

The isolated trifluoroacetate salt of **15** [*trans*-(2-hydroxycyclohexyloxy)dimethylsulfonium trifluoroacetate (**15a**)] was decomposed in neat pyridine or in pyridine–Me_2SO-d_6. The formation of a mixture of products was observed by NMR and the following were isolated in low yield by preparative GLC: *trans*-1,2-cyclohexanediol (**20**), pyridinium trifluoroacetate (**21**), *cis*-(2-hydroxycyclohexyl)pyridinium trifluoroacetate (**22**), in addition to dimethyl sulfide and Me_2SO. 1-(Methylthiomethyl)pyridinium trifluoroacetate (**18**) was tentatively identified also.

Basic decomposition of the cations (**12**, **13**) from *p*-nitrostyrene oxide (**11**) yielded only 2-hydroxy-2-*p*-nitrophenylethanol (**23**). No *p*-nitrophenacyl alcohol was observed but it might have undergone rapid condensation in the basic system as it would be expected to be more prone to such condensations than phenacyl alcohol.

In the original work describing the oxidation of epoxides to α-hydroxy ketones,[7] Me_2SO–BF_3–diethyl ether at 100° was employed; cyclohexene oxide was one of the three epoxides studied. When we applied this oxidation technique to cycloheptene (**23**) and cyclopentene oxides (**24**), we obtained mixtures of products which contained the expected ketols, but the major products were cycloheptanone and cyclopentanone, respectively, the BF_3-induced isomeriza-

Scheme I[a]



[a] B: is base, N: nucleophile.

tion products of the epoxides. Furthermore, we have not been able to reproduce the reported yields of ketols from cyclohexene oxide or styrene oxide and Me_2SO using boron fluoride, air or *tert*-butyl hydroperoxide catalysis.[7,11]

Reaction Pathways. The products observed in the decomposition of cations **4, 5, 12, 13,** and **15** can be rationalized on the basis of a series of competing reactions of the cations and intermediate ylides with the nucleophiles present in the system (Scheme I).

Step a accounts for the presence of Me_2SO in the reaction of **15** with pyridine (N:) in DMSO-d_6 and also accounts for the esters formed in the reaction of styrene oxide (**3**) in Me_2SO with the nucleophiles derived from certain strong acids listed in Table I, although esters can also arise by direct attack of the nucleophile on the protonated epoxide. Me_2SO is an effective leaving species; displacements of Me_2SO from alkoxydimethylsulfonium salts of the type **1** have been amply documented.[2,13,25-27]

Step b, the conversion of the cations to carbosulfuranes (ylides), is a well-established one and has been shown to be operative in many base-induced Me_2SO oxidations involving alkoxydimethylsulfonium salts.[13,28,29] Step c is the decomposition of the ylides to complete the redox reaction with the formation of dimethyl sulfide and α-hydroxycarbonyl compounds. This pathway is observed in Me_2SO oxidations; the ylides decompose intramolecularly via a cyclic transition state. Steps d and e are, respectively, the isomerization and condensation of the α-hydroxycarbonyl compounds.

Step f shows the Pummerer rearrangement of the salts (**1**) via the carbosulfuranes to form a methylthiomethyl ether. The formation of Pummerer rearrangement products upon treatment of alkoxysulfonium salts with base is well known.[30,31]

Origin of Diols in the Me_2SO Oxidation of Epoxides. Step g in Scheme I is best rationalized as a competition between nucleophiles for an intermediate sulfur-stabilized carbonium ion from the Pummerer rearrangement[30] to yield glycol and the methylthiomethylated nucleophile. When the nucleophile, N:, is an alcohol a methylthiomethyl ether is formed. With pyridine the product is **18,** as observed with **4, 5,** and **15.** Yields of methylthiomethylated products are consistently lower than those of glycols.

The inclusion of step g in Scheme I is not only consistent with the products observed on treatment of the hydroxysulfonium salts (**1**) with base under mild conditions but can also account for the formation of glycols in other Me_2SO oxidations of epoxides at relatively high temperatures without added base, i.e., under conditions originally described for oxidation of epoxides.[7,9,21,32] In the present study, the formation of glycols from epoxides and Me_2SO under these conditions (no added base) was verified with styrene oxide–boron trifluoride etherate (low yields) and *cis*- and *trans*-9,10-epoxystearic acids (**25, 26**) (no catalyst or water used). The last two epoxides cleanly yielded *threo*- and *erythro*-9,10-dihydroxystearic acids, respectively in 10–30% yields.

The most likely source of these glycols is the ylide–nucleophile reaction (step g, Scheme I). Adventitious hydrolysis of the intermediate sulfonium salts (**1**) was ruled out as a significant source of glycol by a control experiment with *cis*-9,10-epoxystearic acid in which exclusion of water during work-up affected the yield of glycol only slightly.

Thermolysis of 15 Trifluoroacetate (15a). Thermolysis of a dimethylalkoxysulfonium salt was carried out to determine the reaction products in the absence of added nucleophiles. Thermolysis of **15a** at 100° yielded numerous products none of which was major: adipoin (2-hydroxycyclohexanone), dimethyl sulfide, trifluoroacetic acid, Me_2SO, 1,2-cyclohexylditrifluoroacetate, *trans*-1,2-cyclohexanediol, bis(methylthio)methane, and many other unidentified compounds. Neither cyclohexene epoxide nor cyclohexanone could be detected.

Experimental Section[33]

Acid-Catalyzed Ring Opening of Epoxides with Me_2SO. Styrene Oxide (3) (Table I). General Procedure. A stock solution of **3** (5.00 g, 0.0416 mol) in anhydrous Me_2SO (15.8 g, 0.202 mol) containing sodium 2,2-dimethyl-2-silapentanesulfonate (DSS, 0.21 g) as an internal NMR standard was prepared in a flask sealed with a serum cap. The appropriate weight of acid was introduced into an NMR tube which was then sealed with a serum cap, evacuated, and immersed in an ice bath, and the stock solution was injected by means of a syringe (molar ratio DMSO:acid:epoxide 5:1:1). The tube was removed from the bath and mixed thoroughly and its NMR spectrum was immediately determined. The molar ratios of the reactants and yields of products were calculated by in-

tegration of the NMR signals using the aromatic proton signals as an internal standard. The results are given in Table I.

p-Nitrostyrene Oxide (11). Compound **11** (0.168 g, 1.02×10^{-3} mol) was similarly treated with a solution (0.655 g) of trifluoroacetic acid (0.469 g, 4.11×10^{-2} mol) in Me_2SO (1.80 g, 2.30×10^{-2} mol) containing DSS (0.053 g). (molar ratio Me_2SO:acid:epoxide 5.60:1.00:0.857.) Initially, the NMR spectrum of the reaction mixture showed only faint signals other than those of **11**. The NMR spectrum stabilized after the reaction had been run for 16 hr at 0° and 1 hr at 25°. The epoxide had completely disappeared and the ratio of benzylic to nonbenzylic attack was calculated to be 0.83–0.87 (1:1.2).

Cyclohexene Oxide (14). The NMR experiments were conducted as described above with **3** and **11**. Preparative scale ring openings were conducted by slowly adding trifluoroacetic acid (14.4 g, 0.117 mol) to Me_2SO (10 ml) with stirring and cooling to 0° and then allowing the solution to warm to room temperature. A solution of **14** (11.0 g, 0.112 mol) in Me_2SO (5 ml) was added dropwise with stirring over 15 min; the exothermic reaction was controlled at 25–30°. After an additional 15 min the reaction mixture was washed under nitrogen with anhydrous ether (4 × 100 ml). After the last washing, the insoluble liquid residue crystallized spontaneously to give essentially pure **15a**, mp 79–80°. Concentration of the ether washings and storage at −30° for 24 hr gave more product for a total yield of 12.9 g (38.6% based on **14**). Recrystallization from chloroform–ether (dissolution at room temperature followed by cooling in the freezer) gave analytical quality material, mp 82–84°, equiv wt calcd 291; found 295. Anal. Calcd for $C_{10}H_{17}F_3O_4S$: C, 41.4; H, 5.90. Found: C, 41.2; H, 5.90.

Alternatively, **15a** could be obtained by treating a solution of *trans*-3-iodocyclohexanol[34] (0.653 g, 0.0029 mol) in chloroform (0.5 ml) with a solution of silver trifluoroacetate (0.668 g, 0.0030 mol) in Me_2SO (1 ml) at room temperature. After the addition of more chloroform (2 ml) the silver iodide was filtered off and ether (25 ml) was added to the residue. Cooling the solution to −20 to −30° yielded **15a** (0.169 g, 20%), mp 83–85°.

***trans*-1,2-Cyclohexanediol (20) from 15a.** The salt (0.657 g, 0.0022 mol) was heated on the steam bath with water (4 ml) for 15 min. The water was then removed azeotropically with benzene and the benzene solution was evaporated to dryness under vacuum. The residual oil was crystallized at 0° from a minimum quantity of ether to yield the trans diol (0.116 g, 46%), mp 101–105°; its ir spectrum was identical with that of an authentic sample.[35]

Reaction of Salts (1) with Base (Table II). To the NMR tubes from the acid-catalyzed ring-opening reaction of **3** with Me_2SO described above under General Procedure, various bases were added in excess by injection through the serum cap while the tube was immersed and shaken in an ice–water bath at 0°. After complete decomposition of the cation, NMR spectra were redetermined and the yields of phenacyl alcohol (**16**) and 2-phenyl-2-hydroxyethanol (**17**) were calculated from the ratio of the integral of the aromatic protons to that of the methylene protons of **16** (s, δ 4.98) and the methine (t, δ 4.70) and methylene (d, δ 3.53) protons of **17**. (Authentic samples of **16** and **17** were used to give peak enhancement and to confirm the NMR assignments.) Table II summarizes the results. In no case could signals attributable to mandelaldehyde or its dimer be detected.[23]

In most cases, a signal attributable to methyl sulfide (s, δ 2.08) (using peak enhancement) was observed along with one or more singlets in the *S*-methyl region (δ 1.9–2.2). With pyridine, 1-(methylthio)methylpyridinium ion (**18**) (s, δ 2.28, 5.82) was also present; addition of an authentic sample of **18** (as the chloride) resulted in peak enhancement with the production of no new signals.

When triethylamine was the base in the reactions originally catalyzed by trifluoroacetic, methanesulfonic, and nitric acids, two singlets (δ 5.48 and 2.18) were also observed. These are attributed to the *S*-methylene and *S*-methyl protons of the (methylthiomethyl)trimethylammonium ion (**19**).

Reaction of 15a with Pyridine. The NMR spectrum of the salt formed in situ from **14**, trifluoroacetic acid, and Me_2SO and then treated with excess pyridine was virtually identical with that of a solution of isolated salt (see above) in Me_2SO-d_6 to which excess pyridine was added. The following products also appeared to be present in the solutions: **18**, **20**, methylthiomethyl ether of **20**, adipoin, and methyl sulfide. When the reaction of **15a** with pyridine was run on a preparative scale (2 g of salt) and then chromatographed on a 15% Carbowax 20M column at 110° (He flow rate 80 ml/min, injection port 180°, detector 210°) four major fractions were collected and analyzed by ir. In order of increasing retention times, the fractions were identified as **20**, **21**, **22**, and **18**.

Reaction of Salts 12 and 13 from p-Nitrostyrene Oxide (11) with Triethylamine. Treatment of the NMR tube (described above) containing **11**, trifluoroacetic acid, and Me_2SO with excess triethylamine gave the NMR spectrum of the diol **23** (δ 4.80, t, methine, 1 H, and δ 3.60, d, methylene, 2 H). No signals were found in the region δ 5.5–6.5 (ketol absent).

Boron Trifluoride Etherate Catalyzed Me_2SO Oxidation of Cycloheptene (23) and Cyclopentene (24) Oxides. Epoxide (0.1 mol), Me_2SO (0.5 mol), and boron trifluoride etherate (0.003 mol) were placed in a three-neck flask equipped with a reflux condenser, magnetic stirrer, and thermometer and protected from entry of atmospheric moisture. The flask was immersed in a preheated oil bath maintained at 95° and appearance of dimethyl sulfide and disappearance of epoxide were followed by GLC; **23** had not completely reacted after 24 hr but **24** reacted completely in less than 3 hr. In both cases, the reactions were terminated by pouring the solutions into ice water (100 ml) containing 1% sodium hydroxide. The aqueous solutions were multiply extracted with chloroform or methylene chloride, dried over anhydrous magnesium sulfate, stripped of solvent under vacuum, and then distilled under reduced pressure. All fractions obtained were mixtures (TLC, NMR) with Me_2SO the major contaminant (TLC, NMR). The presence of enolic compounds was demonstrated by the development of green or orange solutions on treatment of the fractions with aqueous ferric chloride. In addition, the fractions were soluble in 10% aqueous sodium hydroxide. The main C=O absorption band, however, was that of the corresponding ketones formed by isomerization of **23** and **24** (cycloheptanone, 1705 cm^{-1}; cyclopentanone, 1745 cm^{-1}) but each spectrum also contained a shoulder at approximately 50 cm^{-1} lower wave number, indicative of the hydrogen bonded carbonyl of an α-ketol.[36] Further attempts at purification of the fractions by preparative GLC or column chromatography gave only mixtures.

Me_2SO Oxidation of *cis*- and *trans*-9,10-Epoxystearic Acids (25, 26). A. The cis epoxy acid **25** (9.0 g, 0.03 mol) and Me_2SO (0.06 mol) were heated at 120–130°. The methyl sulfide formed was condensed in a cold trap and identified as its mercuric chloride complex. After 6.25 hr the reaction mixture was poured into cold water and the gummy mass that separated was dried under vacuum and then digested in hot *n*-heptane. Filtration of the hot solution yielded insoluble *threo*-9,10-dihydroxystearic acid, mp 89–91° (11%); mmp with an authentic sample 90–93°. The filtrate was evaporated to dryness and the residue was recystallized from ethanol to provide the mixed 9,10(10,9)-ketohydroxystearic acids, mp 57–61°, in low yield (identified by ir). Unreacted epoxide was not isolated.

To ensure that the diol was *not* formed by hydrolysis during the work-up procedure the following pair of experiments was conducted. The cis epoxy acid and Me_2SO (mole ratio **25**:Me_2SO 1:5) were heated at 120° for 24 hr. Me_2SO was removed by vacuum distillation (pot temperature 94–107°), care being taken to exclude moisture, and the reaction flask was sealed and removed to a drybox, where two samples were taken. The first was washed with *n*-heptane under anhydrous conditions to give the insoluble threo diol, mp 88–92° (15%). The second sample was removed from the drybox and allowed to stand in water overnight. Water was drained from the resultant slurry, ethanol was added, and the solution was stripped under vacuum to remove ethanol and water. The remaining solid was washed with *n*-heptane to give the insoluble threo diol (18%).

B. The oxidation of **26** (0.01 mol) was carried out in the same way as that of **25** except that more Me_2SO (0.035 mol) was used and the reaction time was 68 hr at 85° because the reaction proceeded slowly. Work-up as described above gave *erythro*-9,10-dihydroxystearic acid, mp 129–133° (lit.[37] mp 131°) (32%). Its ir spectrum was identical with that of an authentic sample. No ketohydroxystearic acids could be isolated. Unreacted epoxide was recovered (37% yield).

Miscellaneous Compounds. Cyclopentene (**24**) and cycloheptene (**23**) epoxides were prepared by peroxyacetic acid oxidation at 0° of the corresponding olefins in CH_2Cl_2 solution containing a large excess of powdered sodium carbonate;[38] GLC was used to monitor olefin consumption. The crude epoxides were then fractionally distilled through a Vigreux column: **23**, bp 160–161°, and **24**, bp 99–99.5°. *cis*- and *trans*-9,10-epoxystearic acids (**25** and **26**, respectively) were prepared by peroxyacetic acid epoxidation of oleic and elaidic acids, respectively, following a literature procedure.[39]

Me_2SO–Acid Salts. The Me_2SO–BF_3 adduct was prepared by the dropwise addition of boron trifluoride etherate to Me_2SO in

CCl_4 at room temperature. The adduct precipitated as it formed; it was filtered and triturated with several portions of dry ether. Drying under vacuum yielded hygroscopic white crystals, mp 59–63° (lit.[40] mp 60°). It is unnecessary and undesirable to heat the reaction mixture to 175° in the preparation of this adduct as reported.[40] Me_2SO–HNO_3 was prepared by adding nitric acid (9.23 g of 70%, 0.1 mol) dropwise with stirring to a solution of Me_2SO (8.0 g, 0.103 mol) in ethanol (50 ml of 95%) at 10°. The mixture was allowed to warm to room temperature and then evaporated to dryness under vacuum. The residual oil slowly crystallized on storage in a freezer (ca. −20°). The solid was recrystallized from absolute ethanol (8.9 g, 61%); it had mp 43–44° and equiv wt 141 (calcd 141). Its ir spectrum was identical with that reported.[41] The Me_2SO–HBF_4 adduct was similarly prepared from Me_2SO and 50% aqueous HBF_4 but the adduct, mp 71–72°, could not be obtained in analytical purity. Attempts to determine its equivalent weight by titration gave anomalous results owing to fading endpoints.

1-(Methylthio)methylpyridinium Chloride. Dry pyridine (40 ml, 0.5 mol) was added to chloromethyl methyl sulfide (4.83 g, 0.05 mol) in a round-bottom flask protected from atmospheric moisture. The turbid mixture was heated at 50° for 1 hr and ether (20 ml) was added to the solid reaction mixture. The insoluble solid was filtered, washed with ether, and dried under vacuum (7.8 g, 88%), mp 149–158°. Recrystallization from acetone–ethanol (10:1 v/v) and thorough drying over P_2O_5 gave the pure compound (5.8 g, 67%), mp 155–160° (lit.[42] mp 158–160°). It is an extremely hygroscopic compound: NMR (D_2O, DSS internal standard) δ 2.28, s, 3 H; 5.82, s, 2 H; 8.0–9.3, m, 5 H.

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Registry No.—**3,** 96-09-3; **11,** 6388-74-5; **14,** 286-20-4; **15a,** 55913-50-3; **16,** 582-24-1; **17,** 93-56-1; **20,** 931-17-9; **23,** 286-45-3; **24,** 285-67-6; **25,** 24560-98-3; **26,** 13980-07-9; dimethyl sulfoxide, 67-68-5; *trans*-3-iodocyclohexanol, 55913-51-4; *threo*-9,10-dihydoxystearic acid, 2391-05-1; 9,10-ketohydroxystearic acid, 13985-42-7; 10,9-ketohydroxystearic acid, 13985-41-6; *erythro*-9,10-dihydroxystearic acid, 3639-32-5; 1-(methylthio)methylpyridinium chloride, 5983-12-0.

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Electron Impact Induced Processes of Thermally and Photochemically Labile Organic Sulfur Compounds. A Mass Spectral Study of Dialkyl Thiolsulfonates, Disulfides, Trisulfides, and α-Disulfones

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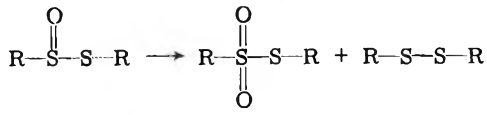
The mass spectral fragmentation patterns of various dialkyl thiolsulfonates, diethyl disulfide and trisulfide, and dimethyl α-disulfone have been studied, using deuterium labeling and defocusing techniques to clarify the mechanisms of a number of novel rearrangement processes. Among the more interesting processes seen are a fragmentation occurring via an apparently unprecedented 2,2,1-bicyclic transition state (or its stepwise counterpart), the electron impact induced rearrangement of thiolsulfonates to sulfenyl sulfinates, nonspecific hydrogen transfer in the formation of HSSH from diethyl disulfide, and the formation of H_2S_3 and EtSSSH from diethyl trisulfide. Where information is available, electron impact induced processes for the compounds studied are compared with thermal and photochemical pathways.

We recently reported a detailed study of the mass spectra of dialkyl thiolsulfinates (**1**) and indicated the considerable utility of mass spectrometry in clarifying the mechanism of thermal disproportionation of these unstable compounds to thiolsulfonates (**2**) and disulfides (**3**).[2] In this



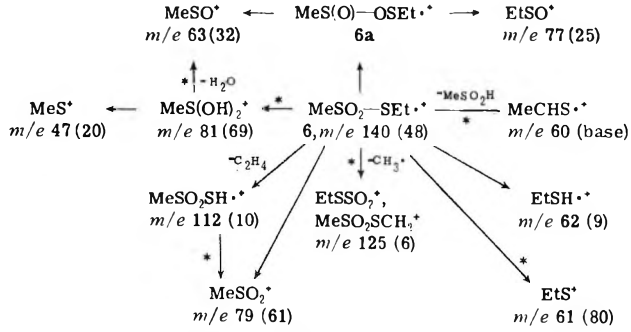
1 **2** **3**

same paper[2] we indicated notable similarities as well as differences between electron impact and thermally (and photochemically) induced processes for the thiolsulfinate esters. The present paper extends our examination of electron impact induced processes of thermally and photochemically labile organic sulfur compounds to include dialkyl thiolsulfonates (**2**), disulfides (**3**), trisulfides, and α-disulfones (RSO_2SO_2R). Of these compounds, mass spectral studies have been previously reported only for dialkyl disulfides[3] and dimethyl trisulfide,[4] and these without substantiation for proposed fragmentation processes through deuterium labeling.

It is of interest that, as with dialkyl thiolsulfinates,[2] dialkyl thiolsulfonates, disulfides, and trisulfides are found naturally as components of the essential oils from plants of the *Allium* species (onion, garlic, chives, caucas);[5a] dialkyl trisulfides have also been detected in algae of the *Dictyopteris* species[5b] and in ponerine ants.[5c] The fact that mass spectrometry (generally in the form of GC–MS) is widely used as the primary analytical tool in these studies of naturally occurring organic polysulfide derivatives provided further impetus for the study described herein.

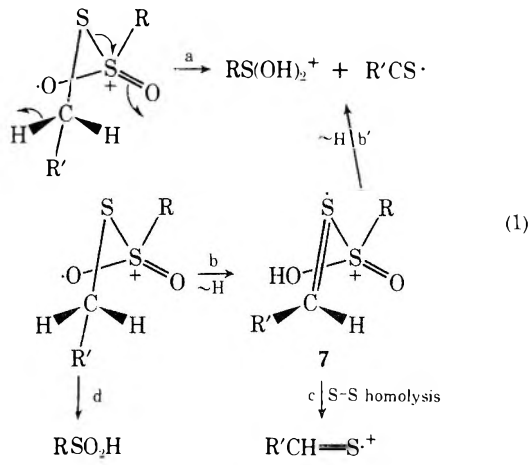
Alkyl Alkanethiolsulfonate Esters. Thiolsulfonate esters **2** are generally stable substances[6] while the isomeric α-disulfoxide [RS(O)S(O)R (**4**)] and sulfenic–sulfinic mixed anhydride [RS(O)OSR (**5**)], both variously postulated as intermediates in thermal and photochemical reactions involving thiolsulfonate as a final product,[7] have thus far eluded isolation and are thought to be unstable.[7] Under electron impact conditions we find evidence for the conversion of certain thiolsulfonates **2** to isomeric species **4** or **5**. Thus, the unsymmetrical ethyl methanethiolsulfonate [$MeSO_2SEt$ (**6**)] gives substantial fragments corresponding to *both* $MeSO^+$ and $EtSO^+$ with similar intensities (see Scheme I); the identity of the fragments was established by exact mass measurements as summarized in Table I. Similar results were obtained with $MeSO_2SCD_3$ ($MeSO^+$, rel intensity 56; CD_3SO^+, rel intensity 44). Other unsymmetrical alkyl alkanethiolsulfonates studied fail to give significant fragments corresponding to RSO^+ and therefore provide no information on oxygen migration. The formation of a fragment $R'SO^+$ from thiolsulfonate RSO_2SR' requires oxygen transfer which may be accomplished through isomerization of **2** to **5** as suggested in Scheme I (**6** → **6a**; this would be analogous to the known ionic or electron impact induced sulfone–sulfinate interconversion[8]) or, less likely, by oxygen migration with *retention* of the S–S bond giving **4**.[9] The electron impact induced oxygen migration observed with thiolsulfonates parallels that seen with α-disulfones (see below) but is to be contrasted with the absence of similar rearrangements in thiolsulfinates.[2]

Scheme I
Mass Spectral Fragmentation Pathways for Ethyl Methanethiolsulfonate (6)[a]



[a] An asterisk indicates that a metastable peak was observed. Figures in parentheses are relative intensities.

Another interesting rearrangement seen with alkyl thiolsulfonates is the formation of substantial fragments corresponding to protonated alkanesulfinic acid, $RS(OH)_2^+$. This species constitutes a significant fragment in the mass spectra of $MeSO_2SMe$, $MeSO_2SEt$ [seen as $MeS(OH)_2^+$ at *m/e* 81[11a]], $MeSO_2SCD_3$ [$CH_3S(OD)_2^+$, *m/e* 83], $EtSO_2SMe$, and $EtSO_2SEt$ [$EtS(OH)_2^+$, *m/e* 95[11a]]; this species is *not* seen to any significant extent in the mass spectra of $MeSO_2S$-*i*-Pr or $MeSO_2S$-*t*-Bu. In the case of esters of the type RSO_2SMe, $RS(OH)_2^+$ must arise either via an unprecedented 2,2,1-bicyclic transition (eq 1, path a with R′ = H) or by sequential hydrogen transfer processes (eq 1, paths b and b′).[11b] To compare the preference for the novel fragmentation pathways of eq 1 with the preference for pathways involving the more common 3,2,1-bicyclic



(1)

transition state[12] (or its two-step counterpart), we have studied the fragmentation of specifically deuterated derivatives (**8** and **9**) of ethyl ethanethiolsulfonate with the results shown in Scheme II. From the data in Scheme II (processes a for **8** and c for **9**) it is seen that the pathways of eq 1 are favored over the alternative 3,2,1 transition state,[14] presumably reflecting the lability of C–H bonds adjacent to the sulfur. The data available do not allow a choice between the concerted or stepwise routes to $RS(OH)_2^+$ in eq 1. Transfer of a single hydrogen to a sulfonyl oxygen via intermediate **7** (eq 1, paths b, c) or by a direct route d (eq 1), processes analogous to those seen in diethyl sulfone[14] and certain sulfonate esters,[12] accounts for the base peaks in the mass spectra of $MeSO_2SEt$ (*m/e* 60, C_2H_4S[11a]) and $MeSO_2S$-*i*-Pr (*m/e* 74, C_3H_6S[11a]). Consistent with the mechanism of eq 1, paths b–c or d, is the formation of $C_2D_3HS^{\cdot+}$ rather than $C_2D_2H_2S^{\cdot+}$ from $CD_3CH_2SO_2SCH_2CD_3$ (**8**).

Scheme II
Deuterium Distribution in Fragments from Deuterated $EtSO_2SEt$[13]

$CD_3CH_2SO_2SCH_2CD_3 \xrightarrow{a}$ $CD_3CH_2S(OH)_2^+$ (67.5%),
8, 88% d_6, 12% d_5 $CD_3CH_2S(OH)(OD)^+$ (30.8%),
$CD_3CH_2S(OD)_2^+$ (1.7%)

8 $\xrightarrow{b}$ CD_3CH_2SD (70%), CD_3CH_2SH (30%)

$CH_3CD_2SO_2SCD_2CH_3 \xrightarrow{c}$ $CH_3CD_2S(OD)_2^+$ (58%),
9, 93% d_4, 3% d_3, $CH_3CD_2S(OD)(OH)^+$ (40%),
4% d_2 $CH_3CD_2S(OH)_2^+$ (2%)

9 $\xrightarrow{d}$ CH_3CD_2SH (85%), CH_3CD_2SD (15%)

Two other fragmentation processes of dialkyl thiolsulfonates have analogies in pyrolytic processes.[6] Of the several thiolsulfonates studied by us, extrusion of SO_2 was significant only in the mass spectrum of $PhCH_2SO_2SCH_2Ph$ (eq 2), a result consistent with previously described substituent

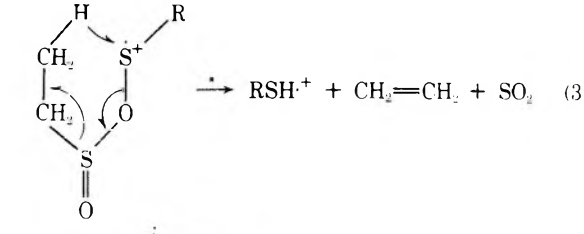
$$PhCH_2SO_2SCH_2Ph^{\cdot+} \xrightarrow[-SO_2]{*} (PhCH_2)_2S^{\cdot+} \text{ (11\% base)} \quad (2)$$

effects on thiolsulfonate pyrolyses.[6] The *m/e* 48 peak of $EtSO_2SMe$ (90% base intensity) identified as $MeSH$[11a] and the analogous *m/e* 62 ($EtSH$[11a]) fragment identified in the mass spectra of $MeSO_2SEt$ and $EtSO_2SEt$ are presumably

Table I
High-Resolution Mass Spectral Data

Compd	*m/e*	Formula	Assignment	% base
$MeSO_2SEt$	60.0028	C_2H_4S	$MeCH{=}S^{\cdot+}$	100
	62.0177	C_2H_6S	$EtSH^{\cdot+}$	9
	62.9884	CH_3SO	$MeSO^+$	32
	77.0059	C_2H_5SO	$EtSO^+$	25
	80.9991	CH_5SO_2	$MeS(OH)_2^+$	69
$(CD_3CH_2S)_2$	79.9739	CH_2DS_2	$CH_2DS_2^+$	7
$EtSSSEt$	97.9327	H_2S_3	$HSSSH^{\cdot+}$	6
	125.9629	$C_2H_6S_3$	$EtSSSH^{\cdot+}$	1.4
$EtSO_2SMe$	48.0028	CH_4S	$CH_3SH^{\cdot+}$	85
	95.0159	$C_2H_7SO_2$	$EtS(OH)_2^+$	10
$MeSO_2S$-*i*-Pr	74.0168	C_3H_6S	$Me_2C{=}S^{\cdot+}$	100

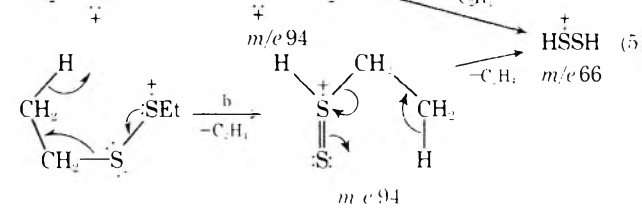
the consequence of competitive processes of the type depicted in eq 3 and 4. Studies with deuterated thiolsulfonates **8** and **9** indicate that the fragmentation in eq 3 is substantially favored over that in eq 4 (see Scheme II, paths b and d). Reaction 4 may also occur thermally.[6]



(3)

(4)

Dialkyl Disulfides and Trisulfides. While the mass spectra of a variety of dialkyl disulfides have been previously examined,[3] mechanistic speculations on fragmentation processes have not been supported by deuterium labeling. In the relatively simple mass spectrum of diethyl disulfide there are major peaks at *m/e* 94 ($EtSSH^+$), 66 ($HSSH^+$), and 29 ($C_2H_5^+$) in addition to the molecular ion (*m/e* 122), which is the base peak, and minor, yet significant peaks at *m/e* 107 ($EtSSCH_2^+$) and 79 (MeS_2^+). The formation of the *m/e* 94 and 66 fragments may be rationalized in terms of the sequential elimination processes of eq 5a[3c] or 5b.[11b] That this sequence cannot be the only frag-



(5)

mentation path leading to *m/e* 94 and 66 is shown by the data on bis(ethyl-*1,1-d*$_2$) disulfide in Scheme III. Support for the occurrence of one-step hydrogen transfer processes 126 → 96 and 97, 96 → 66 and 67, and 97 → 67 and 68 is provided by metastable analysis (metastable ions are seen for *all* of these processes) and by direct analysis of daughter ions (DADI) studies[17] of the *m/e* 126 and 96 species.

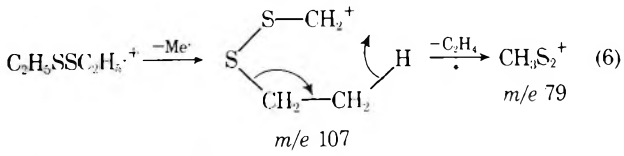
Scheme III
Deuterium Distribution in Fragments from Bis(ethyl-*1,1-d*$_2$) Disulfide

$(CH_3CD_2S)_2^{+\cdot} \longrightarrow$
m/e 126,
96.5% d_4
3.5% d_3

$$\left.\begin{matrix}CH_3CD_2SSH^{+\cdot}\ (87\%,\ m/e\ 96)\\ CH_3CD_2SSD^{+\cdot}\ (13\%,\ m/e\ 97)\end{matrix}\right\} \longrightarrow \left\{\begin{matrix}H_2S_2\ (64\%,\ m/e\ 66)\\ HDS_2\ (31\%,\ m/e\ 67)\\ D_2S_2\ (5\%,\ m/e\ 68)\end{matrix}\right.$$

Support for one-step nonspecific hydrogen transfer processes of the type indicated by the data in Scheme III is also obtained from DADI studies on $CD_3CH_2SSCH_2CD_3$.[18] All of these studies show that the hydrogen transfers shown in eq 5 are more favorable than the 1,2 or 1,3 shifts presumably responsible for the *m/e* 97, 68, and 67 species of Scheme III.

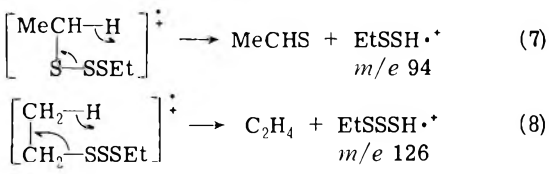
Analysis of the mass spectra of variously deuterated samples of diethyl disulfide also allows the origin of the *m/e* 79 rearrangement ion ($CH_3S_2^+$) to be written with some confidence as in eq 6, since the *m/e* 79 fragment is



(6)

shifted to *m/e* 80 ($CH_2DS_2^+$[11a]) in $(CD_3CH_2S)_2$ and to *m/e* 81 ($CD_2HS_2^+$) in $(CH_3CD_2S)_2$.[19]

We have also examined the mass spectra of several dialkyl trisulfides with the results for diethyl trisulfide summarized in Scheme IV. The composition of the *m/e* 126 and 98 fragments were established by exact mass measurements (see Table I). Species of the type H_2S_3 and RSSSH have not been previously reported in the fragmentation of sulfur compounds. That the EtSSSH fragment is of lower abundance than the EtSSH fragment can perhaps be rationalized in terms of the process in eq 7 being more favorable (because of the weak trisulfide S–S bond[2]) than the process in eq 8.[20] It should be pointed out that particularly gentle



(7)

(8)

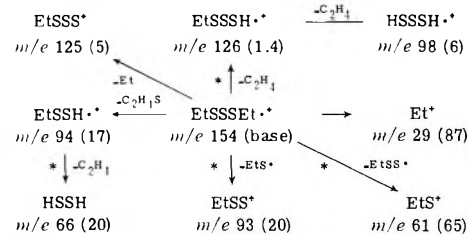
conditions must be used to obtain meaningful mass spectra of the thermally labile trisulfides. Even with a redistilled sample of EtSSSEt, for example, a substantial peak at *m/e* 122 corresponding to the parent ion of EtSSEt was observed along with its fragment ions and metastable peaks. That the *m/e* 122 peak corresponds primarily to EtSSEt produced according to eq 9 rather than to eq 10 could be

$$EtSSSEt \rightleftharpoons EtSSEt + EtSSSSEt \quad (9)$$

$$EtSSSEt^{+\cdot} \xrightarrow{-S} EtSSEt^{+\cdot} \quad (10)$$

shown by (a) the simultaneous appearance in the mass spectrum of EtSSSEt under GC–MS conditions of small peaks corresponding to *both* EtSSEt and EtSSSSEt and (b) the variation in the *m/e* 122/154 peak height ratio with method of sample introduction and source temperature, with ratios as low as 0.05 being observed under some conditions. In none of the spectra of EtSSSEt examined was there observed a metastable peak corresponding to the process *m/e* 154 $-S \rightarrow$ *m/e* 122.

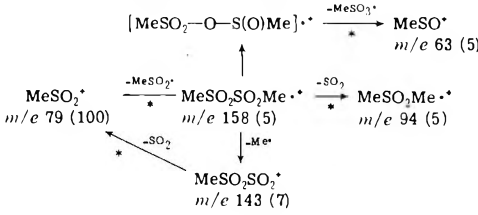
Scheme IV
Mass Spectral Fragmentation of Diethyl Trisulfide[a]



[a] See Scheme I, footnote *a*.

Dialkyl α-Disulfones. The mass spectra of α-disulfones have not been previously described.[21] Scheme V summarizes the fragments formed from dimethyl α-disulfone, $MeSO_2SO_2Me$. The fragmentation processes generally parallel the thermal and photochemical results reported for diaryl α-disulfones.[22] In contrast to the fragmentation of $MeSO_2SMe$, there is no indication of the formation of $MeS(OH)_2^+$ from $MeSO_2SO_2Me$.

Scheme V
Mass Spectral Fragmentation of Dimethyl α-Disulfone[a]



[a] See Scheme I, footnote *a*.

Experimental Section

Mass spectra were determined at the University of Missouri—St. Louis on an A. E. I. MS-12 mass spectrometer at an ionizing voltage of 70 eV using an all-glass inlet maintained at 100–150° and at Drexel University on a Hitachi Perkin-Elmer RMU-6 mass spectrometer operating under similar conditions. In the case of thermally sensitive samples the material was placed in a finely constricted melting point capillary or adsorbed on powdered graphite and introduced via a probe directly into the source of the mass spectrometer. Coupled gas chromatography–mass spectrometry was accomplished using a Hewlett-Packard Model 5750 gas chromatograph (flame ionization detector) coupled, via an all-glass Watson-Biemann separator, to the source of the A. E. I. MS-12 mass spectrometer. Exact mass measurements were made on an A. E. I. MS-9 double-focusing mass spectrometer at Harvard University while defocusing and DADI studies were performed on a Varian MAT CH5 double-focusing mass spectrometer at the University of Illinois—Urbana. The synthesis of all of the thiolsulfonates[2] (except $MeSO_2SCD_3$), the deuterated diethyl disulfide,[2] and dimethyl α-disulfone[23] have been described elsewhere.

Methyl-d_3 Methanethiolsulfonate. To 1.18 g (12 mmol) of bis(methyl-d_3) disulfide[24] in 80 ml of 50% aqueous acetone was added 2.04 g (12 mmol) of silver nitrate and 1.22 g (12 mmol) of sodium methanesulfinate.[25,26] After stirring at room temperature for 1 hr, the bright yellow suspension was filtered to remove $AgSCD_3$ and the filtrate was extracted with two 25-ml portions of ether. The combined ether extracts were dried over Na_2SO_4 and the ether was evaporated to yield 1.46 g (94%) of methyl-d_3 methanethiolsulfonate, bp 84° (1.7 mm), NMR ($CDCl_3$) δ 3.35 (singlet). Mass spectral analysis indicated 98.4% methyl-d_3 methanethiolsulfonate and 1.6% methyl-d_2 methanethiolsulfonate.

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versity of Missouri—St. Louis. We also thank Mr. William Garrison (U.M.S.L.), Ms. M. Lalevic (Drexel), Mr. Joseph Wrona (University of Illinois), and Mr. J. Upeslacis (Harvard) for obtaining the mass spectral data used in this study. The data processing equipment at the University of Illinois—Urbana employed in this study was provided by National Institutes of Health Grant GM-16864.

Supplementary Material Available. Full mass spectral data for the compounds $MeSO_2SMe$, $MeSO_2SCD_3$, $MeSO_2SEt$, $EtSO_2SMe$, $EtSO_2SEt$, $MeSO_2S$-*i*-Pr, *i*-$PrSO_2SMe$, *i*-$PrSO_2S$-*i*-Pr, $MeSO_2$-*t*-Bu, $MeCD_2SO_2SCD_2Me$, $CD_3CH_2SO_2SCH_2CD_3$, $PhCH_2SO_2SCH_2Ph$, $(CD_3CH_2S)_2$, $(MeCD_2S)_2$, EtSSSEt, and $MeSO_2SO_2Me$ 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 Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.50 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2770.

Registry No.—$MeSO_2SEt$, 2043-76-7; $(CD_3CH_2S)_2$, 52754-14-0; EtSSSEt, 3600-24-6; $EtSO_2SMe$, 2144-05-0; $MeSO_2S$-*i*-Pr, 32846-80-3; $CH_3SO_2SCH_3$, 31761-75-8; $C_2H_5SO_2SC_2H_5$, 682-91-7; $CD_3CH_2SO_2SCH_2CD_3$, 55800-38-9; $CH_3CD_2SO_2SCD_2CH_3$, 55800-39-0; *i*-$C_3H_7SO_2SCH_3$, 55800-40-3; *i*-$C_3H_7SO_2S$-*i*-C_3H_7, 10027-69-7; CH_3SO_2S-*t*-C_4H_9, 55800-41-4; $C_6H_5CH_2SO_2SCH_2C_6H_5$, 16601-40-4; $CH_3CD_2SSCD_2CH_3$, 52754-13-9; $CH_3SO_2SO_2CH_3$, 10383-49-0; methyl-d_3 methanethiolsulfonate, 55800-37-8; bis(methyl-d_3) disulfide, 7282-94-2.

References and Notes

(1) (a) University of Missouri—St. Louis; (b) University of Maine; (c) Drexel University.
(2) E. Block and J. O'Connor, *J. Am. Chem. Soc.*, **96**, 3921 (1974).
(3) (a) B. G. Hobrock and R. W. Kiser, *J. Phys. Chem.*, **67**, 648 (1963). (b) B. G. Gowenlock, J. Kay, and J. R. Majer, *Trans. Faraday Soc.*, **59**, 2463 (1963). (c) J. H. Bowie, S.-O. Lawesson, J. Ø. Madsen, C. Nolde, G. Schroll, and D. H. Williams, *J. Chem. Soc. B*, 946 (1966). (d) R. C. Gillis and J. L. Occolowitz, *Tetrahedron Lett.*, 1997 (1966). (e) W. R. Cullen, D. C. Frost, and M. T. Pun, *Inorg. Chem.*, **9**, 1976 (1970), and references cited therein. (f) Also see D. N. Harpp and J. G. Gleason, *J. Org. Chem.*, **36**, 73 (1971), for a recent discussion of some novel mass spectral fragmentation processes in cystine derivatives. (g) For a recent study of the mass spectra of fluorine-containing polysulfides, see N. R. Zack and J. M. Shreeve, *J. Fluorine Chem.*, **5**, 153 (1975).
(4) B. G. Hobrock and R. W. Kiser, *J. Phys. Chem.*, **67**, 1283 (1963).
(5) (a) M. Boelens, P. J. de Valois, H. J. Wobben, and A. van der Gen, *J. Agric. Food Chem.*, **19**, 984 (1971); H. Nishimura, K. Fujiwara, J. Mizutani, and Y. Obata, *ibid.*, **19**, 992 (1971); M. H. Brodnitz, C. L. Pollock, and P. P. Vallon, *ibid.*, **17**, 760 (1969); (b) R. E. Moore, *Chem. Commun.*, 1168 (1971); (c) G. Casnati, A. Ricca, and M. Pavan, *Chim. Ind. (Milan)*, **49**, 57 (1967).
(6) (a) For studies on the pyrolysis of various thiolsulfonates, see J. L. Kice, R. H. Engebrecht, and N. E. Pawlowski, *J. Am. Chem. Soc.*, **87**, 4131 (1965), and earlier papers in the series. (b) A cyclic thiolsulfonate has recently been reported to lose SO_2 on photolysis: J. Meinwald and S. Knapp, *J. Am. Chem. Soc.*, **96**, 6532 (1974). (c) Photolysis of $MeSO_2SMe$ in dioxane or tetrahydrofuran affords $MeSO_2H$, MeSSMe, and $MeSO_3H$ as major products with lesser amounts of SO_2, MeSH, CH_4, and Me_2S (trace): M. D. Bentley, unpublished results.
(7) (a) P. Koch, E. Ciuffarin, and A. Fava, *J. Am. Chem. Soc.*, **92**, 5971 (1970); (b) E. Block and J. O'Connor, *ibid.*, **96**, 3929 (1974); (c) J. L. Kice in "Sulfur in Organic and Inorganic Chemistry", Vol. I, A. Senning, Ed., Marcel Dekker, New York, N.Y., 1971, Chapter 5; (d) J. A. Howard and E. Furimsky, *Can. J. Chem.*, **52**, 555 (1974).
(8) D. Darwish and R. McLaren, *Tetrahedron Lett.*, 1231 (1962); R. M. Dodson, P. D. Hammen, and R. A. Davis, *J. Org. Chem.*, **36**, 2693 (1971), and references cited therein.
(9) An example of oxygen migration in the mass spectrum of an unsymmetrical diaryl thiolsulfonate is described by Oae,[10] who postulates "an intermediate with [a] three-membered ring containing oxygen" which we would view as the transition state in the rearrangement of **2** to **4**. While we cannot exclude the intervention of **4**, structure **5** should be of somewhat lower energy, since it avoids the destabilizing interaction anticipated for the adjacent sulfoxide dipoles of **4**. Furthermore, recent experiments[7d] suggest that the initial product of coupling of alkanesulfinyl radicals has structure **5** rather than **4**.
(10) S. Kozuka, H. Takahashi, and S. Oae, *Bull. Chem. Soc. Jpn.*, **43**, 129 (1970).
(11) (a) See Table I for confirmation by exact mass. (b) This possibility was suggested by a referee.
(12) See, for example W. E. Truce and L. W. Christensen, *J. Org. Chem.*, **33**, 2261 (1968).
(13) In undeuterated $EtSO_2SEt$, the relative intensities of the *m/e* 95 $[EtS(OH)_2^+]$ and 62 $(EtSH^{\cdot+})$ fragments are 33 and 61, respectively. The relative amounts of deuterated forms of key fragments are given for each fragment type. These approximate values have been corrected for contributions from heavy isotopes (C, S, O) and incomplete deuteration but not for isotope effects. The fragmentation process *m/e* 160 (**8**, $M^{\cdot+}$) → *m/e* 99 $[CD_3CH_2S(OH)(OD)^+]$ is supported by metastable analysis. Extensive hydrogen scrambling in **8** and **9** *prior* to fragmentation according to eq 1 is considered unlikely in view of the negligible transfer of *two* deuterium atoms or *two* hydrogen atoms in processes a and c, Scheme II, respectively.
(14) In the mass spectra of aliphatic sulfones the species $RS(OH)_2^+$ is formed.[15] However, the transition state for formation must differ from that proposed for fragmentation of thiolsulfonates (eq 1), since $EtSO_2H^{\cdot+}$ rather than $EtS(OH)_2^+$ is formed from diethyl sulfone, and no $RS(OD)_2^+$ is formed from α-, β-, or γ-d_4 or δ-d_6 dibutyl sulfone.[15] A similar situation exists in the fragmentation of alkyl alkanesulfonate esters.[12]
(15) R. Smakman and T. J. de Boer, *Org. Mass Spectrom.*, **3**, 1561 (1970).
(16) The relative amounts of the two fragment types has been corrected for contributions from heavy isotopes (C, S, O) and from incomplete deuteration but not for isotope effects. Extensive hydrogen scrambling prior to fragmentation can be excluded because of the low intensity of the $D_2S_2^{\cdot+}$ fragment. The relative extent of deuterium incorporation into fragments did not change substantially on reducing the ionizing voltage to 10 eV.
(17) Also referred to as mass-analyzed ion kinetic energy spectra (MIKES). For a recent review of the technique, see J. H. Beynon, R. G. Cooks, J. W. Amy, W. E. Baitinger, and T. Y. Ridley, *Anal. Chem.*, **45**, 1023 (1973).
(18) The daughter ions $CD_3CH_2SSD^{\cdot+}$ and $CD_3CH_2SSH^{\cdot+}$ from $(CD_3CH_2S)_2$ were found by DADI analysis to have their intensities in the ratio of 7.5:1, respectively. Similarly, the ions D_2S_2 and DHS_2 from CD_3CH_2SSD had intensities in the ratio of 3.9:1 while the ions DHS_2 and H_2S_2 derived directly from CD_3CH_2SSH had intensities in the ratio of 5.3:1, respectively.
(19) Additional characteristics of α-disulfide carbonium ions, such as the *m/e* 107 fragment of eq 6, generated under electron impact as well as solvolytic conditions may be found in E. Block, *J. Org. Chem.*, **39**, 734 (1974).
(20) In the mass spectrum of $MeSSSMe$[4] there is a significant fragment corresponding to MeSSH (14% of base intensity) possibly produced according to eq 7.
(21) Following the completion of this work, a brief report of the mass spectra fragmentation of di-*p*-tolyl disulfone appeared: T. Graafland, J. B. F. N. Engberts, and W. D. Weringa, *Org. Mass Spectrom.*, **10**, 33 (1975).
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Organic Disulfides and Related Substances. 39. Study of Insertion Reactions Using Carbenoids, Carbenes, Ylides, and Nitrenes[1]

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With the carbenoidal Simmons–Smith reagent (~ICH_2ZnI), several diaryl disulfides underwent insertion of CH_2 between the sulfur atoms to give bis(arylthio)methanes in yields up to 85% by NMR and 33% by isolation. Insertion of more than one CH_2 sometimes occurred. An alkyl and an aralkyl disulfide were recovered unchanged. This reaction proceeds reasonably well only with aryl disulfides lacking substituents that are ortho, strongly electron-withdrawing, or strongly basic in the Lewis sense. Carbenoids obtained from copper-catalyzed decomposition of diazo esters also gave insertion products. However, reactions were preferred that led to the same outcome through BF_3-catalyzed decomposition of the diazo esters; pure acids were isolated in 11–16% yield. Dichlorocarbene did not react with diaryl disulfides. With an ylide, triphenylphosphonium methylide, only trace insertion of CH_2 occurred with diphenyl disulfide. The major product was tris(phenylthio)methane (64% isolated); methyl phenyl sulfide, triphenylphosphine sulfide, and thiophenol also were isolated, and a course of reaction is suggested. Di-*n*-propyl disulfide evidently reacted similarly. Attempted insertion of R'N moieties by reaction of nitrenes with diphenyl disulfide was unpromising.

In a continuing study of organic disulfides,[1a] we became interested in the feasibility of insertions like that shown by eq 1.

$$RSSR + Z \longrightarrow RSZSR \quad (1)$$

Carbenoids, carbenes, ylides, and nitrenes seemed promising species for insertions of a moiety Z. At the outset, the literature contained little information on such possibilities, although reports appeared later on carbenoids and, especially, carbenes.

Carbenoids. The Simmons–Smith reagent, formulated as **1** for simplicity, is a carbenoid readily available by the means of eq 2

$$CH_2I_2 + Zn/Cu \longrightarrow \underset{\mathbf{1}}{ICH_2ZnI} \quad (2)$$

among others.[2] Use of **1** in synthesis of cyclopropanes by insertion of CH_2 into carbon–carbon double bonds has been reviewed,[2] but reactions of **1** with disulfides have not been explored. The only study with disulfides of carbenoid reactions was of insertion into a cyclic disulfide by the use of substituted diazomethanes, with copper acetylacetonate as a catalyst (eq 3).[3] Diphenyl disulfide gave an unidentified product.[3]

$$R_2CN_2 + Cu^{2+} \longrightarrow R_2C^+Cu^{+} \xrightarrow{(R'S)_2} [R_2C^-S^+R'SR'] \longrightarrow R_2C(SR')_2 \quad (3)$$

As eq 4 shows, aryl disulfides **2–8** with the Simmons–Smith reagent underwent insertion of CH_2 to give the bis(arylthio)methanes **9–15.** Identities of **9–12** and **15** were assured by mixture melting point and congruity of NMR and ir spectra using authentic samples synthesized according to eq 5, a well-known method.[4]

$$\underset{R}{R—ArSSAr—R} \xrightarrow{CH_2I_2,\ Zn\text{–}Cu} \underset{R}{R—ArSCH_2SAr—R} \quad (4)$$

2. H	6. *p*-$(CH_3)_2N$	9. H	13. *p*-$(CH_3)_2N$
3. *p*-CH_3	7. *p*-H_2N	10. *p*-CH_3	14. *p*-H_2N
4. 2,3-$(CH_3)_2$	8. *p*-Cl	11. 2,3-$(CH_3)_2$	15. *p*-Cl
5. *p*-CH_3O		12. *p*-CH_3O	

$$2ArSNa + CH_2I_2 \longrightarrow (ArS)_2CH_2 + 2NaI \quad (5)$$

Yields of bis(arylthio)methanes were determined by NMR on the assumption that the reaction product contained only the disulfide used (e.g., **2–8**) and the bis(arylthio)methane (e.g., **9–15**); this assumption generally was reasonable, although **3** and **8** led to small amounts of other products discussed below. Validity of the NMR method was established with standard mixtures of **2** and **9.** Bis(arylthio)methanes **9–12** and **15** also were isolated in yields of 5–33% by column chromatography; with **9** and **10,** overlapping disulfide also required reduction ($LiAlH_4$) for purification entailing considerable loss, but with the 2,3-dimethyl, *p*-methoxy, and *p*-chloro compounds (**11, 12, 15**) pure products were obtained from the column.

We turn now to the individual reactions summarized by eq 4. Conversion of diphenyl disulfide (**2**) to bis(phenylthio)methane (**9**) afforded a good vantage point for studying characteristics of the general reaction, since it also would afford a good reference point for comparing effects of substitution. These studies gave the results a–f.

(a) When **2** was added near the end of the preparation of **1** in ether, variation of the ratio of **1:2** (from 1 to 2) and of time (20–72 hr) suggested that the best ratio was 1.5 and the best time about 20 hr.

(b) When reagent **1** was prepared beforehand, so that the filtered, clear solution of **1** could be added to disulfide **2,** bis(phenylthio)methane (**9**) was obtained in a yield as high as 70% [but, for unknown reasons, also in yields as low as 2–7%; the tolyl analog (**10**) was obtained in 22% yield]. Although these yields suggest that this inverse addition is inferior to the usual mode, formation by this means is important because it proves that **9** and **10** arise in eq 4 from reagent **1,** not merely from reduction of the disulfide by zinc followed by alkylation of the zinc thiolate. This conclusion was buttressed among other ways (*vide infra*), by recovery of 77% of disulfide **2** (and of formation of only 1% of thiophenol) when **2** was subjected to the usual conditions of eq 4, except for omission of methylene iodide.

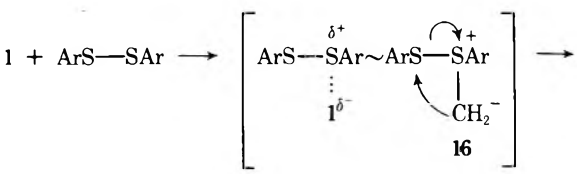
(c) Although a recent preparation of the reagent **1** often improves results,[5] its use led only to 98% recovery of **2.**

(d) Variations in the yield of **9** show that conditions are important. Presumably owing to uncertainties in the preparation of the zinc–copper couple[5] and to the heterogeneity of **1,** yields of **9** occasionally varied erratically from 85 to 10%, even under essentially the preferred conditions. In some experiments, iodine consumption showed that 10–22% of thiophenol also formed, reflecting some reduction of the disulfide. Recoveries of disulfide **2** in various reactions ranged from about 15 to 80%, but attempts to increase con-

sumption of **2** by prolonging reaction beyond about 24 hr led only to tar, and larger ratios of **1** were not beneficial.

(e) In the isolation of **9**, several agents were tried in the hope of reducing contaminating disulfide to the thiol which could be removed with aqueous base. Glucose reduced bis(*p*-nitrophenyl) disulfide quantitatively but gave no help with **2** or other disulfides. Sodium borohydride led to incomplete reduction. Lithium aluminum hydride, as mentioned, partially destroyed **9**, but isolation of **9** in 25% yield (yield by NMR 85%) finally was achieved by using this hydride repeatedly, with chromatography.

(f) The most attractive rationalization of the reaction of eq 4 is that reagent **1** attacks the disulfide bond as an electrophile and that a ylide-like species produced then rearranges (eq 6).



$(ArS)_2CH_2$ (6)

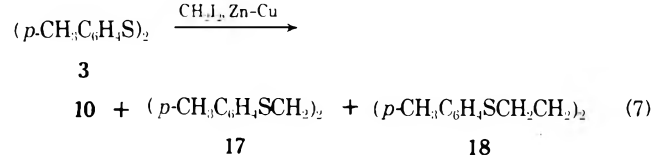
The ylide intermediate **16** is reminiscent of that in eq 3. If this view is correct, zinc iodide probably present in the reaction mixture should be an inhibitory influence because of its competition with **1** for the disulfide bond; indeed, addition of 1.5 molar proportions of zinc iodide (relative to disulfide **2**) reduced the usual yield of up to ~85% of thioformal **9** to 4–9%, and 3 molar proportions reduced it to 0%. Use of 1,2-dimethoxyethane–ether in the usual Simmons–Smith reaction rapidly and quantitatively precipitates zinc iodide;[2a] this approach promised to improve results of eq 4 by eliminating competition of zinc iodide, but use of a 1:1 mixture of these two ethers actually reduced the yield to 8% (NMR); perhaps the glycol ether simply competed too effectively with the disulfide bond for the reagent **1**.

In comparison of substituents, electron-donating groups were studied first. Di-*p*-tolyl disulfide (**3**) gave insertion product **10** in a yield of 50% by NMR and 33% by isolation. This yield was between the extremes for diphenyl disulfide and other disulfides discussed below, and the reaction of **3** thus was used to probe still further features of eq 4 and 6, with the results of a–c.

(a) One such feature is the possible role of homolysis, a pathway postulated (without evidence as yet) for insertion effected by rearrangement of ylides from a carbene and disulfides.[6] Irradiation with uv light reduced the yield of **10** from 48–50% to 10–17%; an increase would have been more consistent with homolysis. Passage of dry air, with oxygen as a radical scavenger, reduced the yield to 0%, a result consistent with intervention in a homolytic pathway but in heterolytic ones as well (it is worth adding that although dry air increases the yield of Simmons–Smith reactions in benzene,[7] the yield of the phenyl compound **9** decreased when air was passed from 13% in benzene to 5%). The results with air probably signify easily oxidizable intermediates, rather than free radicals. When the usual conversion to **9** in ether was repeated, with ESR spectra taken at 30-min intervals during 2 hr, no ESR signal for free radicals could be observed, although NMR showed that **9** had begun to form.[8] These experiments are not conclusive, but together they perhaps point more toward heterolysis than homolysis as the major pathway for eq 4.

(b) Tetrahydrofuran and diglyme, as alternatives to ether for preparing **10**, proved even worse than benzene (6% yield) probably for the reason suggested with the diether–ether mixture. As with **9**, results with **10** were best with reaction in ether for 24–30 hr with a **1**:**3** ratio of 1.5.

(c) Interestingly, GC–mass spectrometric study showed presence of products corresponding to insertion of both two and four methylene units (eq 7)



(7)

each in less than 5% yield, along with the 33% of **10** isolated. The di-insertion product **17** also has been observed in the reaction of **3** with diazomethane.[9] The di-insertion product **17** could not be well separated from the mono-insertion product **10**, but the mass spectrum of the mixture was identical with the sum of the spectra of authentic **10** and **17**; a tetrainsertion product, presumed to be **18**, was separable by GC and showed a molecular ion. The bis(arylthio)methane probably is not an intermediate in these insertions, because when **9** was allowed to react with **1** under the usual conditions, although GC separated insertion products, none had either the mass spectrum of authentic 1,2-bis(phenylthio)ethane or the mass spectrometric pattern seen with the presumed **18** (the products perhaps were $C_6H_5SCH_2SCH_2C_6H_5$ and $C_6H_5SCH_2CH_2SCH_2C_6H_5$). Furthermore, treatment of the thioformal **10** itself gave no indication of **17** or **18** after GC–mass spectrometry.

With bis(2,3-dimethylphenyl) disulfide (**4**), a second effect was superimposed on electron donation. The yield of thioformal **11** was only 5% (NMR, isolation); 90–95% of **4** was recovered. This second effect is the steric hindrance afforded by an ortho substituent, presumably against formation of a bulky zinc-containing intermediate (*cf.* eq 6).

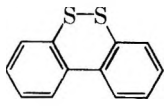
With bis(*p*-methoxyphenyl) disulfide (**5**), still a third effect appeared. The yield of bis(*p*-methoxyphenylthio)-methane (**12**) was 25% both by NMR and isolation. The lower yield than usual (**2**, up to 85%; **3**, ~50%) is attributable to coordination of zinc species with the CH_3O moiety of **5**, which should place positive charge on the CH_3O moiety and make it a less effective electron donor; evidently, good characteristics of the S–S bond as an electron donor are crucial.

All three substituent effects (viz., electron donation, ortho hindrance, and Lewis type basicity) played a role with bis(2,4-dimethoxyphenyl) disulfide. Two good electron-donating groups are present, but one is in the ortho position and both are subject to coordination with zinc. Neither NMR nor isolation revealed any bis(2,4-dimethoxyphenylthio)methane; 90–95% of disulfide was recovered.

Neither bis(*N*,*N*-dimethylaminophenyl) disulfide (**6**) nor bis(*p*-aminophenyl) disulfide (**7**) did well, presumably because of coordination with zinc; no **13** or **14** could be isolated, although NMR showed yields of 13–16%.

Not surprisingly, electron-withdrawing substituents led to poor results. Bis(*p*-chlorophenyl) disulfide (**8**) gave **15** in only 5% yield (NMR, isolation), and reduction was marked (up to 16% of thiol and ~5% of methyl *p*-chlorophenyl sulfide). Bis(*p*-nitrophenyl) disulfide gave no bis(*p*-nitrophenylthio)methane (NMR, isolation); *p*-nitrothiophenol resulted (2–9%), but the nitro disulfide usually was recovered (63–93%). As with **2**, the Zn–Cu couple alone did not significantly reduce the nitro disulfide (3% of thiol), although this disulfide probably is the easiest of the group to reduce. *p*-Methoxyphenyl *p*-nitrophenyl disulfide merely disproportionated to the symmetrical disulfides.

The heterocyclic disulfide **19**, dibenzo[c,e]-*o*-dithiin, gave no monoinsertion product; GC–mass spectrometry in-



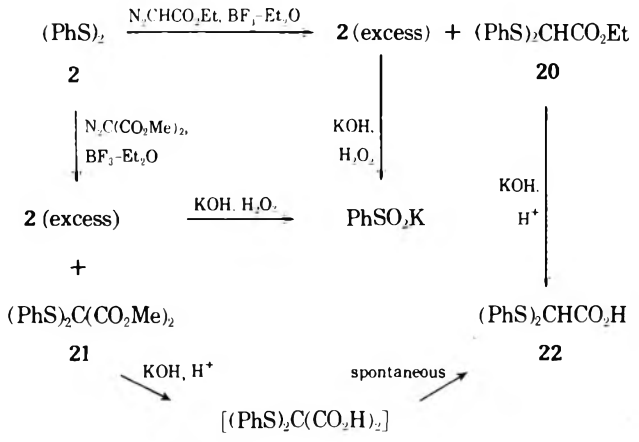
19

dicated about 20% of a tri-insertion product. The alkyl and aralkyl disulfides di-*n*-propyl disulfide, and dibenzyl disulfide were recovered in 98% yield.

In sum, insertion of CH_2 into disulfides by the Simmons–Smith carbenoidal species succeeds best with aryl disulfides lacking substituents that are ortho, strongly electron withdrawing, or strongly basic in the Lewis sense.

Copper-catalyzed decomposition of diazoacetates to carbenoids is well known;[10] these are selective to a degree uncommon to carbenes.[10b] The only copper-associated carbenoid tried with disulfides is mentioned above.[3] Copper-catalyzed decomposition of ethyl diazoacetate in the presence of **2** apparently led to insertion (**20**, Scheme I) and also to

Scheme I



other products. These efforts were discontinued when the mixture proved intractable and when BF_3-catalyzed insertion proved cleaner. Copper-catalyzed insertion of dimethyl diazomalonate with **2** gave **21** in a cleaner reaction than that of the diazoacetate but the BF_3-catalyzed reaction gave equivalent results (NMR), involved less vigorous conditions, and was more convenient.

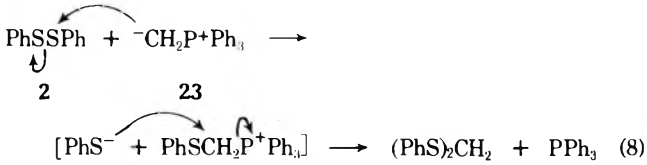
Carbenes. Reviews are available on carbenes (and carbenoids).[11a-d] Early in our work, there were only two reports of reactions of carbenes with disulfides,[12a,b] but others soon appeared.[6,9,12c] Several reported insertions like that of eq 1 with carbenes engendered thermally or photochemically.[6,9,12b,c]

On the other hand, insertions of the $CHCO_2Et$ moiety between the alkoxyl groups and methinyl carbon of orthoformates had been achieved catalytically using a diazoacetate.[13] The catalyst was boron trifluoride etherate, suggesting that this catalyst also might be effective for insertions using diazo esters with disulfides. Although such a reaction with a disulfide formally (and perhaps actually) would correspond to insertion of a carbene (cf. ref 13), it could also be cationic (diazonium and/or carbonium ion).[11e] Viewing the intermediate in such a reaction at least as a carbenoid is reasonable, since this loose term describes "... intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species ..." and since the term "... is very useful in the discussion of many methylene transfer reactions where the precise constitution of the reactive species has not been delineated".[11f]

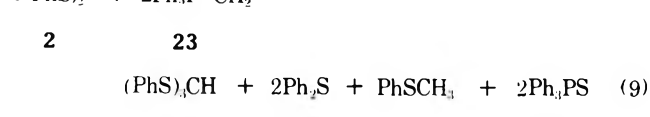
In any event, insertion with ethyl diazoacetate and phenyl disulfide (**2**) did occur, proceeding best with 2 molar equiv of **2** (Scheme I). As with our earlier insertions, removal of unchanged disulfide was difficult, but **2** finally was removed using alkali and peroxide (Scheme I), a procedure that converts aryl disulfides to water-soluble products.[14] This procedure saponified **20** only partially, but completion of the saponification permitted isolation of pure **22** in 16% yield. The identity of **22** was established by comparison with authentic **22**. The BF_3-catalyzed reaction of a diazomalonate led after decarboxylation of the malonic acid to **22** (11% yield, Scheme I). The 11–16% of **22** isolated seems to represent only perhaps a third or a fourth of the insertion products **20** and **21** actually formed. Ando and coworkers in photolytic studies using dialkyl disulfides and dimethyl diazomalonate isolated insertion products corresponding to **21** in 2% yield.[6]

In the earliest study of disulfides with carbenes per se, Searles and Wann found that dichlorocarbene led to dichloromethyl alkyl disulfides. This reaction was general for alkyl disulfides containing β hydrogen atoms and led also to an alkene.[12a] Interestingly, the aryl disulfides **2**, **3**, and **5** were recovered (95–100%) when dichlorocarbene was generated in their presence by thermally induced decomposition of an equimolar amount of sodium trichloroacetate in 1:3 diglyme–tetrachloroethylene, a procedure based on a well-known one for forming cyclopropanes.[15] Evidently dichlorocarbene was formed, since carbon dioxide slowly evolved during about 4 hr under reflux. Perhaps a complex like **16** formed of the carbene and disulfide but, instead of rearranging, reverted to the carbene which then coupled to give tetrachloroethylene; it is also possible that aryl disulfides may simply be too weakly basic to form the complex.

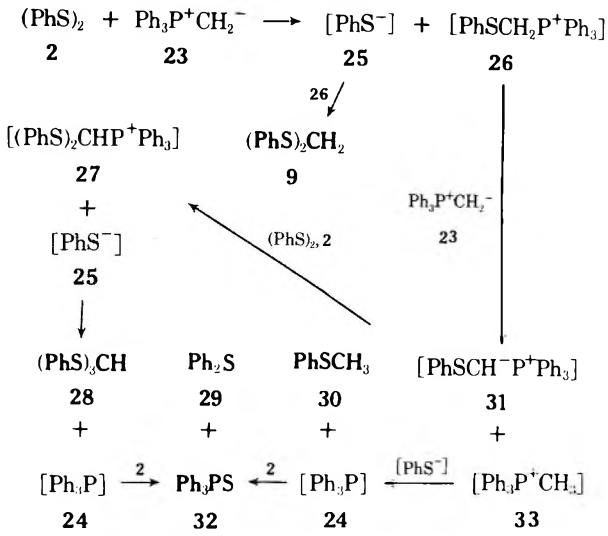
Ylides.[16] The insertion shown by eq 8



seemed a reasonable outcome for reaction of the ylide **23** with disulfide **2** (the phosphine **24** and **2** presumably would subsequently form diphenyl sulfide and triphenylphosphine sulfide).[17] Attempted reaction in boiling ether led only to recovery of 95–100% of **2**. In diglyme at 130° **2** reacted during 24 hr (at 100°, 98% recovery), but only a trace of the insertion product **9** was isolated. Scheme II shows the products (boldface), along with reactions that rationalize their formation. Attack of **25** on **26** to give **9** and the phosphine **24** clearly is minor (~0.3% of **9**). Instead, in the major course of reaction, **26** (perhaps as a tight ion pair with **25**) is considered to lose a proton to ylide **23**, thereby forming a new ylide **31**, along with **33**. The new ylide **31** then consumes more disulfide **2** and leads through **25** and **27** to tris(phenylthio)methane (**28**). The ylide **23**, having abstracted the proton, becomes a methylating agent (**33**) that produces **24** and **30**. Finally, triphenylphosphine (**24**) desulfurizes **2**,[17] giving **29** and **32**. Equation 9 summarizes



Scheme II



these reactions. Based on eq 9 in various reactions tris(phenylthio)methane (**28**) was isolated in up to 64% yield and methyl phenyl sulfide (**30**) in up to 6% yield. Diphenyl sulfide (**29**) was not sought since the phosphine sulfide (**32**) was isolated. Thiophenol was isolated in yields up to 28%, presumably reflecting incomplete reaction of the thiolate ion **25** involved at several stages. When the tolyl disulfide **3** was used with **23**, no indication was seen of interchange of tolyl and phenyl groups.

Before Scheme II was developed, it seemed likely that the tris sulfide **28** had formed by abstraction of a proton from the insertion product **9** by the ylide **23**, followed by attack of the resulting carbanion of **9** on **2**. Three pieces of contrary evidence were adduced. (1) When equimolar amounts of **9** were treated with ylide **23** and disulfide **2**, NMR indicated no loss of **9**. (2) Treatment of **9** with ylide **23** led to no detectable methylation of **9** (95% recovery). (3) Treatment of **9** with ylide **23** at 30° for 2 hr, followed by quenching with D_2O, led neither to loss of intensity of the NMR methylene signal (relative to a standard) nor to the splitting expected if deuterium had replaced hydrogen; hence **23** is unable to abstract a proton from **9** readily.

The reaction also proceeds with an alkyl disulfide. When *n*-propyl disulfide was subjected to the reaction, tris(*n*-propylthio)methane was isolated in 17% yield (38–78% by NMR); 1-propanethiol (4%) and **32** also were isolated.

Nitrenes.[11b,18a] *p*-Azidobenzonitrile thermolyzed with **2** with and without copper powder (up to 48 hr, ~130°) led only to recovery of the **2** (89%) and gave no indication of much S–N bonding (<2% by reaction with thiophenol). Photolysis (30 hr) led to 43–45% recovery of each starting material, with no evidence of S–N bonding. Heating of *p*-toluenesulfonyl azide and **2** at 155° for 5 hr also gave no evidence for S–N bond formation. The conditions required for reaction according to eq 10 thus seemed likely to be so extreme that there would be little chance for survival of sulfenamides. Indeed, insertion products actually might have been destroyed by reactions like that of eq 11. Dialkyl disulfides react with methyl azidoformate but give alkylthio- and alkyldithiocarbamates, $RSNHCO_2Me$ and $RSSNHCO_2Me$, respectively.[18b]

$$(RS)_2 + R'N_3 \longrightarrow (RS)_2NR' + N_2 \quad (10)$$

$$2(RS)_2NR' \longrightarrow 2(RS)_2 + R'N{=}NR' \quad (11)$$

Experimental Section[19]

Materials. A. Disulfides. *p*-Nitrophenyl *p'*-methoxyphenyl disulfide was prepared by the reaction of *p*-nitrobenzenesulfenyl chloride and *p*-methoxythiophenol. The sulfenyl chloride was prepared by condensing Cl_2 (0.9 g, 12.7 mmol) using Dry Ice–acetone and then allowing it to volatilize spontaneously (ca. 20 min) upon removal of cooling into a stirred solution of bis(*p*-nitrophenyl) disulfide (3.7 g, 12.0 mmol) in 75 ml of CH_2Cl_2 maintained at −20°. The resulting solution was added (ca. 30 min) to a stirred solution of *p*-methoxythiophenol (3.36 g, 24 mmol) in 75 ml of CH_2Cl_2. The mixture was allowed to warm to ~25° with stirring and then was washed with H_2O, 5% aqueous $NaHCO_3$, and H_2O to neutrality. Drying and removal of solvent gave the unsymmetrical disulfide as a viscous oil (2.50 g, 36%). TLC showed one spot using CH_2Cl_2, benzene, benzene–Me_2CO (2:1), EtOAc, petroleum ether, or EtOH; NMR (CCl_4) δ 6.4–7.9 (m, 8, Ph), 3.6 (s, 3.2, CH_3). The product was not further purified to avoid possible disproportionation.

Anal. Calcd for $C_{13}H_{11}NO_3S_2$: C, 53.27; H, 3.76; S, 21.84. Found: C, 53.34; H, 4.24; S, 21.23.

Bis(2,3-dimethylphenyl) Disulfide (4, obtained by oxidizing the thiol, prepared by diazotizing the corresponding amine and treating with a xanthate) was kindly provided by L. H. Brannigan: mp 98–98.5°; NMR (CCl_4) δ 6.9–7.4 (m, 6, PhH), 2.3 (s, 6, CH_3), 2.25 (s, 6, CH_3).

Anal. Calcd for $C_{16}H_{18}S_2$: C, 70.07; H, 6.56; S, 23.35. Found: C, 70.14; H, 6.65; S, 23.27.

The other disulfides used have been reported previously; melting points before use were in good agreement with reported values (±2°). The dimethylamino disulfide **6** was prepared using sulfur monochloride and *N,N*-dimethylaniline,[20] mp 118–119° (lit.[20] mp 118°); use of formic acid–formaldehyde with bis(*p*-aminophenyl) disulfide, in a modified Leuckart reaction,[21] gave **6** in much lower yield and purity. Bis(2,4-dimethoxyphenyl) disulfide was prepared by reducing the sulfonyl chloride to the thiol and oxidizing with I_2,[22,23a] mp 115–116° (lit.[23a] mp 113–115°). Dibenzo[*c,e*]-*o*-dithiin (**19**) was prepared by reducing 2,2'-biphenyldisulfonyl chloride with HI,[1a] mp 111.5–112° (lit.[1a] mp 112–113°). All other disulfides (purified as stated) were either commercial products or were prepared by oxidizing commercially available thiols with I_2 (**2, 3, 5, 7,** 8, and others not numbered).

B. Bis(arylthio)methanes and 1,2-Bis(arylthio)ethanes. Preparation of bis(phenylthio)methane (**9**), based on a general procedure,[4] is illustrative. Addition of CH_2I_2 (85 mmol) during ~15 min to thiophenol (170 mmol) in EtOH (75 ml) containing 170 mmol of NaOH led to an exothermic reaction. The mixture was stirred for 2 hr and diluted with H_2O (25 ml). An Et_2O extract gave **9** in 78% yield; mp after recrystallization (EtOH), 34–35° (lit.[4] mp 36°). Other bis(arylthio)methanes prepared similarly were **10** (oil, lit.[4] mp 30°); **11** [mp 58–59°; NMR (CCl_4) δ 6.9–7.3 (m, 6, Ph), 4.1 (s, 2, CH_2), 2.2 (s, 6, CH_3), 2.1 (s, 6, CH_3)]; 12 [mp 68–69° (lit.[23b] mp 66–67°)]; and **15** [mp 38–39° (lit.[23b] mp 39–39.5°)].

Preparation of 1,2-bis(*p*-tolylthio)ethane (**17**) and 1,2-bis(phenylthio)ethane was identical with that of the bis(arylthio)methanes, except in use of $Br(CH_2)_2Br$ instead of CH_2I_2: **17**, mp 79–79.5° (lit.[4] mp 80°); 1,2-bis(phenylthio)ethane, mp 68–69° (lit.[4] mp 69°).

C. Miscellaneous. *p*-Azidobenzonitrile[24] had mp 64–64.5° (lit.[25] mp 70°), and *p*-toluenesulfonyl azide[26] was used as an oil (lit.[18] mp 24–26°). Bis(phenylthio)acetic acid (**22**) was prepared, essentially as reported,[27] from sodium dichloroacetate and sodium benzenethiolate; after recrystallization to constant melting point, the melting point was 103–104° (lit.[27] mp 104°). Tris(phenylthio)methane (**28**) was kindly provided by D. L. Tuleen, mp 39–40° (lit.[28] mp 40°). Zinc iodide was prepared as described (method II).[29] All other substances were obtained commercially.

Reactions of the Simmons–Smith Reagent (1) with Diaryl Disulfides. The reaction of **1** with diphenyl disulfide (**2**) is illustrative. A slurry of **1** was prepared, using a reported procedure,[30] by adding Zn dust (1.96 g, 30 mmol) to a nearly boiling solution of $Cu(OAc)_2$ (0.23 g, 1.25 mmol) in glacial AcOH (30 ml). After 5 min, the AcOH was decanted from the Zn–Cu couple. The couple was washed repeatedly with anhydrous Et_2O until no trace of AcOH was evident (by odor) and then was transferred to the reaction flask and stirred in Et_2O (100 ml). About half of the CH_2I_2 (2.44 ml, 30 mmol) was added dropwise during ~15 min (exothermic reaction). The disulfide **2** (4.36 g, 20 mmol) in 30 ml of Et_2O was added to the remainder of the CH_2I_2, and this mixture then was added during ~15 min with good stirring. The mixture then was stirred vigorously for 24 hr under reflux. Removal of solid by filtration, and evaporation of solvent and excess CH_2I_2, then left the crude reaction product.

Products were isolated by column chromatography,[19] with treatment by $LiAlH_4$ in Et_2O being used if the bis(arylthio)methane did not separate cleanly [**9, 10,** and (occasionally) 12]. When $LiAlH_4$

was necessary, a clear Et_2O solution was added dropwise to the fraction in Et_2O (until excess $LiAlH_4$ could be shown by gassing when a few drops were added to wet alcohol), and the solution was heated under reflux for 2 hr; excess $LiAlH_4$ then was hydrolyzed, and thiol was washed out with 10% aqueous NaOH. Products were identified by melting point, mixture melting point, and congruency of NMR spectra with authentic samples.

For the NMR assays of incompletely purified products, based on relative integrals of aryl and $-SCH_2S-$ protons,[1c] the validity of the method was checked by analysis of standard mixtures containing 25, 50, and 75% of **9** with **2**; the results, respectively, were 23, 48, and 73%. Insertion products **13** and **14** were not isolated, and the $-SCH_2S-$ signal of δ 4.1–4.5 was used in estimating percent composition [a reasonable assumption since this signal varied from δ 4.0 to 4.2 for six other bis(arylthio)methanes].

For the inverse mode (i.e., when the reagent **1** was added to the disulfide), the Zn–Cu couple was made as before, and CH_2I_2 then was added to the couple in Et_2O. Solid was removed by a quick gravity filtration, and the resulting clear solution was added during 15 min to a solution of **2** in Et_2O. Other procedures were as before.

Cu-Catalyzed Reactions of Diazo Esters with Diphenyl Disulfide (2). According to a general procedure for reaction of diazoacetates with various substrates,[10a] a mixture of 0.79 g (5.0 mmol) of dimethyl diazomalonate, 2.18 g (10.0 mmol) of **2**, and 0.16 g (1.0 mmol) of freshly dried anhydrous $CuSO_4$ was heated at 90° under nitrogen until N_2 evolution ceased (~30 min). The mixture was cooled and agitated with Et_2O. The Et_2O extract was filtered and concentrated to give 2.4 g of crude **21** as an oil that appeared by NMR to be composed of about 17% of **21** (for an estimated yield of 24% of **21**). This crude **21** was roughly equivalent by NMR to products obtained from the BF_3-catalyzed decomposition described below.

Essentially the same procedure of reaction was used with ethyl diazoacetate (100 mmol), **2** (200 mmol), and $CuSO_4$ (2 mmol). Crude products resulted that appeared to consist of a little diethyl fumarate and maleate, one unidentified material with NMR δ 3.4 (s), and another with δ 5.7 (s). A component with δ 4.65 (s) was believed to be the insertion product **20**, but it could not be separated cleanly by column chromatography or preparative TLC from other products; in the best reaction, NMR suggested that this presumed **20** amounted to 25% of the product (~25% yield).

BF_3-Catalyzed Reactions of Diazo Esters with Diphenyl Disulfide (2). A. Ethyl Diazoacetate. In a modification of a reported procedure for BF_3-catalyzed reactions of diazoacetates,[13] ethyl diazoacetate (0.57 g, 5.0 mmol) was added dropwise during ~3 min to a mixture of **2** (2.18 g, 10.0 mmol) and boron trifluoride etherate (0.5 ml). Immediate evolution of N_2 occurred. The liquid then was heated at 40° for 2 hr to assure decomposition of the diazoacetate (loss of the characteristic diazo frequency at ~2150 cm^{-1}). The mixture cooled to ~25°, mixed with H_2O (20 ml), and extracted well with Et_2O. The extract was dried and concentrated to give 2.6 g of oil [NMR of the δ 4.65 peak suggested that this oil contained 34% of the insertion product **20**, ethyl bis(phenylthio)-acetate, corresponding to a yield of 58%].

In most of these diazoacetate experiments, the δ 3.4 peak seen in the copper-catalyzed reaction was present, but the δ 5.7 peak was absent. In experiments with varied ratios of disulfide **2** to diazoacetate, a 2:1 ratio most favored the δ 4.65 peak and hence presumably the formation of **20**; a 1:2 ratio gave about equal intensity of the δ 3.4 and δ 4.65 peaks and a 1:1 ratio greatly increased the δ 3.4 peak. These results were the basis of the 2:1 ratio used above of **2** to diazoacetate.

Column chromatography purified the crude **20** considerably, but much **2** remained. Efforts to remove this **2** by reduction with Zn–AcOH or Ph_3P-H_2O caused loss of the δ 4.65 peak, and oxidation with peroxide or cleavage with ethanolic base also were unsatisfactory. Finally, an effective means of removing **2** without apparent damage to the **20** was based on the report that base-induced cleavage of diaryl disulfides, in the presence of H_2O_2, converts them in good yield to (water-soluble) sulfinic acid salts.[14] Subsequent further treatment with base was needed for complete saponification of **20**, however. In this procedure, part of the crude **20** (1.0 g) was assumed to be all disulfide (i.e., to represent 4.6 mmol of **2**) and was dissolved in 20 ml of EtOH, to which was added KOH (0.52 g, 9.2 mmol) in H_2O (30 ml) and 30% H_2O_2 (1.56 g, 13.8 mmol). The mixture was heated at 35° for 18 hr with stirring. It then was acidified with 10% HCl, and the EtOH was evaporated. An Et_2O extract of the aqueous residue was washed twice with H_2O to remove most of the benzenesulfinic acid, dried, and evaporated to give an oil. This partially saponified **20** then was heated under reflux for 18 hr in EtOH (20 ml) containing 1.03 g (18.4 mmol) of KOH. Evaporation of EtOH and acidification, followed by reprecipitation from aqueous $NaHCO_3$ with several recrystallizations (H_2O), gave 0.17 g (16%) of **22**, mp 101–102°. Further recrystallizations gave **22** with a constant melting point of 102–103°, which had ir and NMR spectra congruent with those of authentic **22**, bis(phenylthio)acetic acid; the melting point was undepressed by authentic **22**[27] (lit.[27] mp 104°).

B. Dimethyl Diazomalonate. The procedure of A for the diazoacetate was duplicated using dimethyl diazomalonate (0.79 g, 5.0 mmol), **2** (2.18 g, 10.0 mmol), and boron trifluoride etherate (0.5 ml). The Et_2O extract yielded 2.4 g of oil [NMR of the OCH_3 peak at δ 3.65 suggested that this oil contained 17% of the insertion product **21**, dimethyl bis(phenylthio)malonate, corresponding to a yield of 23%]; in several other experiments, the range of percent composition for **21** was 27–47%.

In various preparations of **21**, all of which were done with a 2:1 ratio of **2** to diazomalonate, there were present a little tetramethyl 2,3-dicarboxymaleate, and a compound with δ 4.3. Up to 50% of **2** could be recovered in some instances. Column chromatography effected partial separation of **2**, but the removal of **2** by conversion to benzenesulfinic acid still was necessary, with isolation of the acid **22** as in A. For this conversion of **21** to **22**, part of **21** (1.0 g, 4.6 mmol had the product been pure **2**) was treated in 20 ml of EtOH, as in A, with 0.52 g (9.2 mmol) of KOH in 30 ml of H_2O and 1.56 g (13.8 mmol) of 30% H_2O_2. Complete saponification of the partially saponified **21** then was achieved as in A, with 1.03 g (18.4 mmol) of KOH in 20 ml of EtOH. Acidification and reprecipitation from aqueous base with acid and recrystallizations gave 0.1 g (11%) of the acid **22**, mp 100–101°. Further recrystallization gave **22** with a constant melting point of 102–103°, which had ir and NMR spectra congruent with those of both authentic **22**[27] and the **22** from A; the melting point was not depressed by either of these other two samples.

Reaction of Methylenetriphenylphosphorane (23) with Aryl and Alkyl Disulfides. The reaction of diphenyl disulfide (**2**) with **23** exemplifies the general procedure. The ylide **23** was formed by addition of triphenylmethylphosphonium bromide (3.57 g, 10.0 mmol) to a diglyme solution (100 ml, dried with $LiAlH_4$ and freshly distilled) containing *n*-butyllithium (in hexane, 10 ml, 10.0 mmol) under N_2; the solution became orange, signifying formation of **23**. The mixture then was heated at 130° for 1 hr, after which **2** (2.18 g, 10.0 mmol) dissolved in 10 ml of diglyme was added dropwise during 30 min. The solution then was heated for 24 hr at 130° under N_2, cooled to 25°, and poured into H_2O (500 ml). The aqueous mixture was extracted well with Et_2O, and the Et_2O extract was washed well with H_2O and dried. Evaporation of the Et_2O gave an oily mixture. In various experiments, NMR suggested that the ratio of **28** to **30** in the mixture varied from 9:1 (the present experiment) to 0.7:1; **9** never was seen in more than trace amounts.

Upon chromatography of part of the crude product using Brinkmann silica gel G, benzene eluted three products (in the order of mention, with yields in parentheses being based on eq 9): **30**, methyl phenyl sulfide (6%); **9**, bis(phenylthio)methane (0.3%, based on eq 8); and, **28**, tris(phenylthio)methane (64%), mp 39°. The identities of **9**, **28**, and **30** were established by congruence of NMR spectra with those of authentic samples; the mixture melting point of **28** was undepressed by authentic **28**. The yields varied with the conditions of reaction. In other experiments, **32**, triphenylphosphine sulfide, crystallized from the crude product and was identified by NMR and melting point.

Acidification of the water-diglyme raffinate and extraction with Et_2O separated thiophenol formed; titration with I_2 showed the yield to be 28%.

The reaction of **23** with di(*n*-propyl) disulfide was carried out using similar molar proportions and similar conditions. Tris(*n*-propylthio)methane was identified, after distillation of the products, by boiling point and NMR (congruency with authentic material prepared by the well-known method of heating the thiol with chloroform; δ CH, 4.7). Triphenylphosphine sulfide (**32**) was identified by NMR and melting point. 1-Propanethiol was estimated by acidification of the basic reaction mixture, extraction, and titration with I_2.

Registry No.—**2**, 882-33-7; **3**, 103-19-5; **4**, 55990-91-5; **5**, 5335-87-5; **6**, 5397-29-5; **7**, 722-27-0; **8**, 1142-19-4; **9**, 3561-67-9; **19**, 230-26-2; **23** (uncharged form), 3487-44-3; **23** (charged form), 19493-09-5; *p*-nitrophenyl *p'*-methoxyphenyl disulfide, 20168-74-5; *p*-nitrobenzenesulfenyl chloride, 937-32-6; *p*-methoxythiophenol,

696-63-9; bis(2,4-dimethoxyphenyl) disulfide, 55990-92-6; CH_2I_2, 75-11-6; thiophenol, 108-98-5; $Br(CH_2)_2Br$, 106-93-4; dimethyl diazomalonate, 6773-29-1; ethyl diazoacetate, 623-73-4; triphenylmethylphosphonium bromide, 1779-49-3; di(*n*-propyl) disulfide, 629-19-6.

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Nucleophilic Cleavage of the Sulfur–Sulfur Bond by Phosphorus Nucleophiles. III. Kinetic Study of the Reduction of a Series of Ethyl Aryl Disulfides with Triphenylphosphine and Water[1]

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A stopped-flow kinetic study of the reaction of a series of ethyl substituted-phenyl disulfides (2) with triphenylphosphine (Ph_3P) in 50% dioxane–water at pH 13.3 is reported. This reaction results in reduction of the disulfide to yield the corresponding benzenethiol, ethanethiol, and triphenylphosphine oxide. Triphenylphosphine sulfide is not formed. In analogy with our previous study of the reaction of symmetrical aryl disulfides with Ph_3P a two-step mechanism is suggested. At pH 13.3 the first step is rate determining. A plot of log k_1 against σ yields a ρ value of 1.76 (standard deviation 0.07). The substituent effect data are interpreted to indicate that some negative charge is developed on both sulfur atoms in the transition state as bond making is somewhat advanced over bond breaking.

We recently reported[1] evidence to indicate that the reduction of symmetrical aryl disulfides with triphenylphosphine (Ph_3P) in aqueous dioxane involves at least two steps (Scheme I). The rate-determining step of this redox reaction was shown to be pH dependent. At both low and high pH, nucleophilic attack by Ph_3P on the S–S bond to form an intermediate thioalkoxyphosphonium cation (1) is rate limiting, while at intermediate pH the reversal of the first step becomes important and the reaction is kinetically more complex.[1] Based primarily on the large sensitivity of the first step of Scheme I to the electron-withdrawing nature of the disulfide substituents ($\beta = -1.02$, $\rho = 2.94$) it was tentatively suggested that nucleophilic attack by the phosphine occurs via a transition state in which negative charge is developed on both sulfur atoms, and that thus the sulfur undergoing attack is partially valence expanded as

Scheme I

$$Ph_3P + ArSSAr \rightleftharpoons Ph_3\overset{+}{P}—SAr + ArS^-$$

1

$$Ph_3\overset{+}{P}—SAr + H_2O \longrightarrow Ph_3PO + ArS^- + 2H^+$$

Table I
Cleavage of Ethyl-Substituted Phenyl Disulfides by Ph_3P[a]

Ethyl substituted-phenyl disulfide	pH	No. of runs	10^3 $[Ph_3P]_0$, M	$10^{-4}k$, l. mol^{-1} min^{-1}	pK_a substituted[b] benzenethiol
3, 4-NO_2	13.30, 13.60	6	0.80–1.6	6.54 ± 0.70	5.36
4, 3-NO_2	13.30	3	0.80–1.6	6.19 ± 0.65	6.08
5, 4-$COOCH_3$	13.30	3	0.80–1.6	1.44 ± 0.10	6.70
6, 3-Cl	13.30	3	0.80–1.6	1.08 ± 0.012	7.00
7, 4-Cl	13.30, 13.60	12	0.80–1.6	0.684 ± 0.068	7.40
8, 3-OCH_3	13.30	3	0.80–1.6	0.355 ± 0.034	
9, 4-OCH_3	13.30	3	1.0–3.0	0.0973 ± 0.010	8.45
10, 4-NH_2	13.30	3	2.0–4.0	0.0219 ± 0.0009	8.86

[a] In 50% dioxane–water, 30.0 ± 0.1°, ionic strength 0.10 (KCl), $[ArSSEt]_0$ = 2–30 × 10^{-5} M, $[Na_2EDTA]$ = 5.0 × 10^{-4} M. [b] Experimentally determined under identical conditions (ref 1).

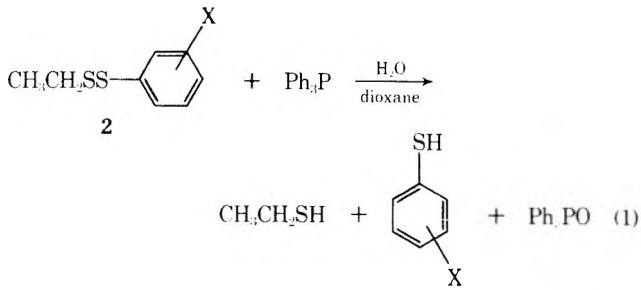
bond making is advanced over bond breaking. The timing of bond-making and bond-breaking steps in nucleophilic displacements at sulfenyl sulfur has been the object of intense investigation.[3] In order to pursue this question further, for the specific case of phosphine nucleophiles and disulfides, we report here an investigation of the reaction of Ph_3P with a series of ethyl aryl disulfides. It was hoped that a study of these unsymmetrical disulfides would provide substituent effect data about the leaving group sulfur, and that these data, when compared with the results of our previous study of symmetrical aryl disulfides, would allow us to draw some conclusions about the nature of the sulfur atom undergoing nucleophilic attack.[4]

Most previous studies of this reaction of unsymmetrical disulfides with nucleophiles are consistent with both kinetic and thermodynamic cleavage occurring in the direction to liberate the most stable mercaptide.[5,6] Although examples of kinetic cleavage in the opposite sense are known,[7] nucleophilic attack in these cases was likely dictated by steric effects. Thus, as a consequence of the small steric bulk of the ethyl substituent and the high pK_a of ethanethiol[8] it was anticipated that ethyl aryl disulfides would undergo kinetic attack by nucleophiles solely on the ethyl bearing sulfur.

Although several workers have studied the reduction of symmetrical aryl[1,9] and alkyl[10] disulfides with Ph_3P, the reaction of Ph_3P with unsymmetrical alkyl aryl disulfides has not been previously reported.

Results

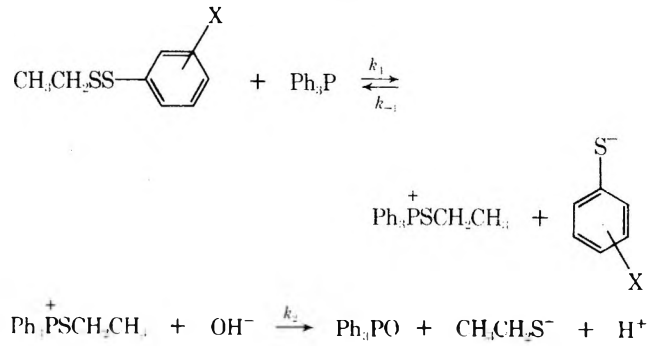
The ethyl aryl disulfides (**2**) were conveniently prepared by the reaction[11] of *N*-(ethylthio)phthalimide[12] with the corresponding benzenethiol and were purified by a combination of preparative layer chromatography and distillation. Disulfides **2** are readily cleaved when treated at 30° with Ph_3P in aqueous dioxane (eq 1). Assay by uv indicated



the formation of 1.0 ± 0.05 equiv of the corresponding benzenethiol (see Table II). Ethanethiol was also produced as evidenced by its characteristic odor and by gas chromatographic assay, but owing to its volatility no attempt was made to quantify its yield. For disulfides **4**, **7**, and **10** the yield of triphenylphosphine oxide (Ph_3PO) was determined by gas chromatography, under conditions (see Experimental Section) similar to those used in the kinetic studies, and varied from 70 to 100%. Significantly no (<1%) triphenylphosphine sulfide was detected.

The rate of cleavage of disulfides **3**–**10** by Ph_3P in 50% dioxane–water was measured at pH 13.3 (0.01 M NaOH), conditions which had previously been shown (for aryl disulfides) to involve nucleophilic attack by the phosphine in the rate-determining step.[1] Under these conditions the rate of formation of 1 equiv of the corresponding benzenethiol was clearly first order (r = 0.9995 or better) for 2–3 half-lives. The resulting second-order rate constants (k_1 = $k_{obsd}/[Ph_3P]$), determined at three or more Ph_3P concentrations, are summarized in Table I.[13] As a spot check, the second-order rate constants for disulfides **3** and **7** were shown to be unaffected by doubling the sodium hydroxide concentration. The observation of clean pseudo-first-order kinetics for 2–3 half-lives indicates that these unsymmetrical disulfides do not disproportionate, to any appreciable extent, under the conditions of the kinetic measurements, since the corresponding symmetrical aryl disulfides react with Ph_3P 10–20 times faster.[1] Moreover, the absence of upward curvature in the first-order plots during the second and third half-lives also indicates that although ethyl mercaptide is slightly more thiophilic[14] than Ph_3P it is not competitive under our pseudo-first-order conditions. The results described are consistent with the mechanism of Scheme II, in which the first step (k_1) is rate limiting.[15]

Scheme II



Discussion

A plot of log k_1 against the Hammett substituent constant σ is shown in Figure 1. The correlation for both meta and para substituents is excellent (the standard deviation

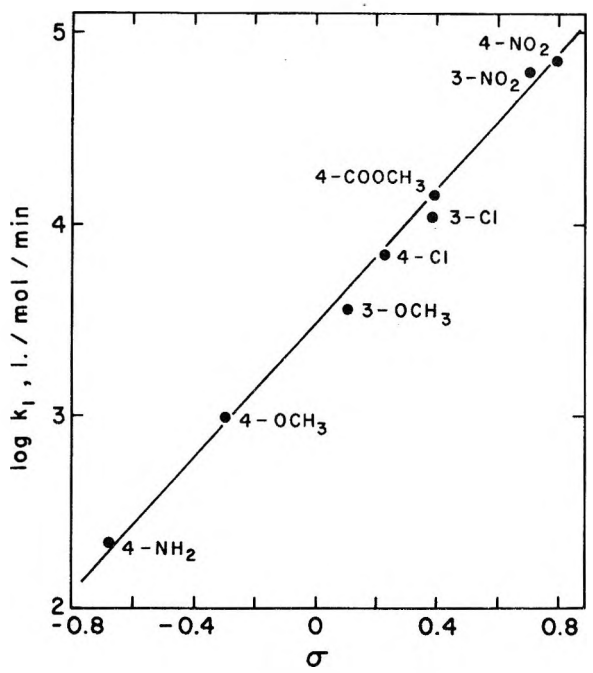
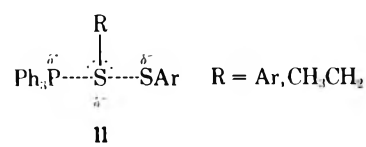


Figure 1. A plot of log k_1 vs. σ. The slope (ρ) is 1.76.

from the least-squares slope is 0.07) and yields a ρ value of 1.76.[16] Significant is the excellent correlation of strong π-electron conjugating para substituents (NH_2, OCH_3, NO_2), which is in marked contrast to the large deviations observed for those substituents in our previous study of symmetrical aryl disulfides. The nondeviation of π-conjugating para substituents is consistent with the assumption that attack by Ph_3P occurs solely at the ethyl bearing sulfur, since in our previous study the observed deviations were ascribed[5] to the effect of para substituents on the sulfur undergoing nucleophilic attack.[1]

The effect of aryl substituents on the Ph_3P cleavage of this series of ethyl aryl disulfides is only 60% as large as that observed under identical conditions for a similar series of symmetrical aryl disulfides.[1] To the extent that the reaction of eq 1 is a good model for the effect of substituents on the leaving group sulfur of a symmetrical aryl disulfide, a comparison of the ρ values for the two series would indicate that the large positive ρ value observed in the symmetrical series results from positive contributions from both the sulfur of the leaving group (ρ ~1.8) and the sulfur undergoing nucleophilic attack (ρ ~1.1). The substituent effect ascribed by this analysis to the sulfur undergoing nucleophilic attack appears to be somewhat larger than would be anticipated for a process in which bond formation and bond cleavage were equally advanced,[17] and thus would seem more consistent with a transition state such as **11** in which negative charge is developed on both sulfur atoms. Such a transition state would result if bond making were somewhat advanced over bond breaking.



11

Experimental Section

The purification of solvents, and the methods and instruments used for the stopped-flow and pH measurements, were described previously.[1] The wavelengths used for the kinetic measurements are summarized in Table II. "50% dioxane-water" refers to a dioxane-water solution made by diluting (0.5V) ml of dioxane to V ml with water in a volumetric flask.[1] Errors reported are ± one standard deviation from the mean for a series of measurements. All disulfide samples used for kinetic measurements were homogeneous by TLC (silica gel) and showed no trace of the corresponding symmetrical aryl disulfide, under TLC conditions which clearly resolved the two. Analytical gas–liquid chromatography (GC) utilized a Hewlett-Packard Model 700 with a flame ionization detector. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz.

Table II
Experimental Conditions for Kinetic Measurements

Ethyl substituted-phenyl disulfide	Wavelength followed, nm	ϵ_{EtSSAr}[a]	ϵ_{ArS^-}[a]
3, 4-NO_2	425	<10	16,300
4, 3-NO_2	428	<10	1,100
5, 4-$COOCH_3$	332	4,300	22,500
6, 3-Cl	330	35	290
7, 4-Cl	330	150	550
8, 3-OCH_3	352	140	48
9, 4-OCH_3	330	380	1,200
10, 4-NH_2	350	450	210

[a] Molar extinction coefficient. In 50% dioxane-water, 30°, pH 13.3 ionic strength 0.10 (KCl).

Preparation of Ethyl Substituted-Phenyl Disulfides. These materials were prepared in 40–80% yield by the reaction of *N*-(ethylthio)phthalimide[12] with the appropriate benzenethiol in refluxing benzene.[11a,b] Disulfides **3** and **4** were described previously.[11] The ethyl substituted-phenyl disulfides were stable to disproportionation and were easily purified by conventional chromatographic means.

They were also quite stable to disproportionation in solution. For example, 10^{-2} M solutions of disulfide **4** in dioxane and in 50% dioxane–water showed no traces of the corresponding symmetrical aryl disulfide (TLC assay) when stored in laboratory light on the bench top for 2 days. The TLC system was silica gel with 1:1 hexane–benzene as eluent: disulfide **4** R_f 0.5; 3-nitrophenyl disulfide R_f 0.3.

Ethyl-4-carbomethoxyphenyl Disulfide (5). The analytical (and kinetic) sample was purified by Kugelrohr distillation (oven temperature 118–124°, 0.03 Torr): ν_{max} (film) 1704, 1269, and 1099 cm^{-1}; ^1H NMR (CCl_4) τ 1.8–2.7 (A_2B_2 pattern, 4 H, ArH), 6.12 (s, 3 H, OCH_3), 7.26 (q, J = 7 Hz, 2 H, CH_2), and 8.70 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_{10}H_{12}O_2S_2$: C, 52.60; H, 5.30; S, 28.09. Found: C, 52.31; H, 5.27; S, 28.25.

Ethyl 3-Chlorophenyl Disulfide (6). The analytical (and kinetic) sample was prepared by preparative layer chromatography (silica gel–benzene) and Kugelrohr distillation (oven temperature 110–116°, 0.03 Torr): ν_{max} (film) 1558, 770, and 670 cm^{-1}; ^1H NMR (CCl_4) τ 2.1–3.2 (m, 4 H, ArH), 7.25 (q, J = 7 Hz, 2 H, CH_2), 8.69 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_8H_9ClS_2$: C, 46.93; H, 4.43; Cl, 17.32; S, 31.32. Found: C, 47.02; H, 4.86; Cl, 17.45; S, 31.16.

Ethyl 4-Chlorophenyl Disulfide (7). The analytical (and kinetic) sample was prepared by short-path distillation: bp 73–77° (0.15 Torr); ν_{max} (film) 1441 and 805 cm^{-1}; ^1H NMR (CCl_4) τ 2.4–2.9 (A_2B_2 pattern, 4 H, ArH), 7.36 (q, J = 7 Hz, 2 H, CH_2), 8.79 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_8H_9ClS_2$: C, 46.93; H, 4.43; Cl, 17.32; S, 31.32. Found: C, 47.14; H, 4.41; Cl, 17.23; S, 31.05.

Ethyl 3-Methoxyphenyl Disulfide (8). The analytical (and kinetic) sample was prepared by preparative layer chromatography (silica gel–benzene) and Kugelrohr distillation (oven temperature 110–116°, 0.03 Torr): ν_{max} (film) 1553, 846, 765, and 679 cm^{-1}; ^1H NMR (CCl_4) τ 2.7–3.6 (m, 4 H, ArH), 6.28 (s, 3 H, OCH_3), 7.33 (q, J = 7 Hz, 2 H, CH_2), 8.72 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_9H_{12}OS_2$: C, 53.96; H, 6.04; S, 32.01. Found: C, 54.02; H, 6.13; S, 32.26.

Ethyl 4-Methoxyphenyl Disulfide (9). The analytical (and kinetic) sample was prepared by Kugelrohr distillation (oven temperature 115–120°, 0.03 Torr); ν_{max} (film) 1225 and 822 cm^{-1}; ^1H NMR (CCl_4) τ 2.4–3.4 (A_2B_2 pattern, 4 H, ArH), 6.34 (s, 3 H, OCH_3), 7.36 (q, J = 7 Hz, 2 H, CH_2), 8.77 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_9H_{12}OS_2$: C, 53.96; H, 6.04. Found: 54.15; H, 6.23.

Table III
Yield of Triphenylphosphine Oxide by GC

Disulfide (mmol)	Ph_3PO formed, mmol (% theory)	Ph_3P recovered, mmol
4 (0.22)	0.15 (68)	0.34
7 (0.28)	0.21 (75)	0.32
10 (0.26)	0.26 (100)	0.22

Ethyl 4-Aminophenyl Disulfide (10). The analytical (and kinetic) sample was prepared by preparative layer chromatography (silica gel–10% ethyl acetate–90% benzene) and Kugelrohr distillation (oven temperature 114–120°, 0.03 Torr): ν_{max} (film) 3390, 3250, and 823 cm^{-1}; ^1H NMR (CCl_4) τ 2.5–3.7 (A_2B_2 pattern, 4 H, ArH), 6.40 (s, 2 H, NH_2), 7.32 (q, J = 7 Hz, 2 H, CH_2), 8.71 (t, J = 7 Hz, 3 H, CH_3).

Anal. Calcd for $C_8H_{11}NS_2$: C, 51.85; H, 5.98; N, 7.56; S, 34.60. Found: C, 52.01, H, 5.98; N, 7.69; S, 34.24.

Products. Triphenylphosphine Oxide (Ph_3PO). A 0.02 M solution of sodium hydroxide in 50% aqueous dioxane, containing 5 × 10^{-4} M disodium ethylenediaminetetraacetic acid, was deoxygenated for 1 hr with oxygen-free nitrogen.[19] Triphenylphosphine (0.50 mmol) and disulfide **4**, **7**, or **10** (0.22–0.28 mmol) were added and the solution was stirred under a nitrogen atmosphere at 40° for 2–10 min. After cooling to room temperature 50 ml of ether was added, the aqueous layer was saturated with sodium chloride, and the organic layer was separated. The aqueous layer was washed with 50 ml of ether and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. A weighed amount of benzophenone was added as an internal standard and the product mixture was analyzed by GC.[21] Peak areas were corrected for detector response by standard methods. Triphenylphosphine sulfide could be detected at the 1% level. The results are summarized in Table III.

Acknowledgment. Financial support of this research by the National Institutes of Health (Grant GM-20674) is gratefully acknowledged.

Registry No.—**3**, 51351-84-9; **4**, 51351-85-0; **5**, 55975-71-8; **6**, 55975-72-9; **7**, 55975-73-0; **8**, 55975-74-1; **9**, 55975-41-2; **10**, 55975-42-3; triphenylphosphine oxide, 791-28-6; triphenylphosphine, 603-35-0.

References and Notes

(1) For Part II in this series, see L. E. Overman, D. Matzinger, E. M. O'Connor, and J. D. Overman, *J. Am. Chem. Soc.*, **96**, 6081 (1974).
(2) (a) Alfred P. Sloan Foundation Fellow, 1975–1977; (b) U. C. President's Undergraduate Fellow, 1974–1975.
(3) The current status of this question is briefly summarized in ref 1. Other recent summaries include (a) J. L. Kice in "Sulfur in Organic and Inorganic Chemistry", Vol. 1, A. Senning, Ed., Marcel Dekker, New York, N.Y., 1971, Chapter 6; (b) E. Ciuffarin and A. Fava, *Prog. Phys. Org. Chem.*, **6**, 81 (1968); (c) L. Senatore, E. Ciuffarin, and A. Fava, *J. Am. Chem. Soc.*, **92**, 3035 (1970); (d) W. A. Pryor and K. Smith, *ibid.*, **92**, 2731 (1970).
(4) An alternate approach, in which one tries to isolate the substituent effect to the sulfur atom undergoing nucleophilic attack, was anticipated to be unsuccessful. Wright and coworkers[5] have previously shown that substituted-phenyl *p*-acetylphenyl disulfides and substituted-phenyl *p*-nitrophenyl disulfides undergo nucleophilic cleavage by cyanide to some extent by attack of cyanide on the *p*-acetylphenyl (or *p*-nitrophenyl) bearing sulfur. In our case, with Ph_3P as the nucleophile, corrections for the cleavage in this direction could not be made.
(5) D. A. R. Happer, J. W. Mitchell, and G. J. Wright., *Aust. J. Chem.*, **26**, 121 (1973).
(6) A. J. Parker and N. Kharasch, *J. Am. Chem. Soc.*, **82**, 3071 (1960); R. G. Hiskey and F. I. Caroll, *ibid.*, **83**, 4644 (1961); D. N. Harpp and J. G. Gleason, *ibid.*, **93**, 2437 (1971).
(7) R. G. Hiskey and D. N. Harpp, *J. Am. Chem. Soc.*, **86**, 2014 (1964).
(8) pK_a = 11.7 in 50% dioxane–water (40°): unpublished studies of E. M. O'Connor.
(9) (a) A. Schonberg, *Chem. Ber.*, **68**, 163 (1935); A. Schonberg and M. Barak, *J. Chem. Soc.*, 892 (1949); R. E. Humphrey and J. M. Hawkins, *Anal. Chem.*, **36**, 1812 (1964); R. S. Davidson, *J. Chem. Soc. C*, 2131 (1967).
(10) C. G. Moore and B. R. Trego, *Tetrahedron*, **18**, 205 (1962); R. E. Humphrey, A. L. McCrary, and R. M. Webb, *Talanta*, **12**, 727 (1965); M. Grayson and C. E. Farley, *Chem. Commun.*, 831 (1967); M. Grayson, *Colloq. Int. CNRS*, **182**, 275 (1969).
(11) (a) K. S. Boustany and A. B. Sullivan, *Tetrahedron Lett.*, 3547 (1970); (b) D. N. Harpp, D. K. Ash, T. G. Back, J. G. Gleason, B. A. Orwig, and W. F. Van Horn, *ibid.*, 3551 (1970); (c) L. Overman, J. Smoot, and J. D. Overman, *Synthesis*, 59 (1974).
(12) M. Behforouz and J. E. Kerwood, *J. Org. Chem.*, **34**, 51 (1969).
(13) The uv change which accompanied the reduction of ethyl phenyl disulfide was so small that the reaction could not be conveniently studied.
(14) A. Fava and G. Pajaro, *J. Am. Chem. Soc.*, **78**, 5203 (1956); R. D. Ritter and J. H. Krueger, *ibid.*, **92**, 2316 (1970).
(15) Unpublished studies from our laboratory show that the hydrolysis of ethanethiolatotriphenylphosphonium hexachloroantimonate in 50% dioxane–water is specific base catalyzed and would be sufficiently fast at pH 13.3 that the first step (k_1) in Scheme II would be clearly rate limiting.
(16) Log k_1 also correlates well with the corresponding benzenethiol pK_a (determined under identical conditions)[1] and affords a Brønsted slope of $\beta = -0.71 \pm 0.07$.
(17) A model for such a process would be the SN2 reaction of carbon compounds. Although substituent effects for the carbon undergoing nucleophilic attack are observed, these effects are small.[18] For example, introducing a meta NO_2 substituent results in rate accelerations (k_X/k_H) in the range of 0.8–3.5.[18] It is also typical for the SN2 reactions of carbon compounds to be accelerated by both electron-withdrawing and electron-donating substituents.[18]
(18) Much of this data is summarized in the following references: A. Steitwieser, Jr., "Solvolytic Displacement Reactions", McGraw-Hill, New York, N.Y., 1962, pp 18–20; R. Fuch and D. M. Carelton, *J. Am. Chem. Soc.*, **85**, 104 (1963).
(19) Nitrogen was deoxygenated by bubbling sequentially through gas traps filled with chromous solution[20] and distilled H_2O.
(20) Cf. A. J. Gordon and R. A. Ford, "The Chemist's Companion", Wiley, New York, N.Y., 1972, p 438.
(21) A 8 ft × 0.12 in. column of 10% SP 2100 on 100/120 Supelcoport operated at 250° with a nitrogen carrier gas (45 ml/min) was used. This column cleanly separated Ph_3P, Ph_3PO, and Ph_3PS.

Aromatic Nucleophilic Substitution. V.[1] Confirmation of the Spiro Janovsky Complex in Base-Catalyzed Rearrangement of *N*-Acetyl-β-aminoethyl-2,4-dinitrophenyl Ether with Simultaneous Migration of Acetyl Group

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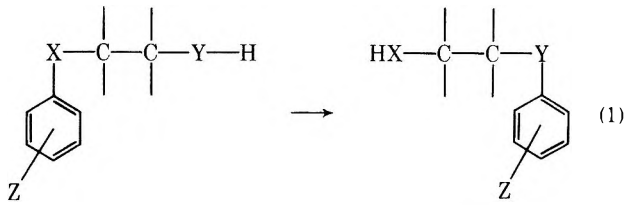
N-Acetyl-β-aminoethyl-2,4-dinitrophenyl ether readily undergoes a Smiles rearrangement in Me_2SO in the presence of tertiary-butanolic $KOC(CH_3)_3$ to give *N*-β-acetyloxyethyl- and *N*-β-hydroxyethyl-2,4-dinitroaniline. During the reaction, the spiro Janovsky complex is spectrometrically confirmed to exist.

Smiles rearrangements (eq 1) are typical intramolecular nucleophilic substitution reactions. The two carbon atoms joining X and Y may be part of an aliphatic or an aromatic system. It has been well established that aromatic nucleophilic substitution reactions proceed via Bunnett's intermediate.[2] Therefore, Smiles rearrangements can be assumed to be a good model for studying aromatic nucleophilic substitution mechanisms.

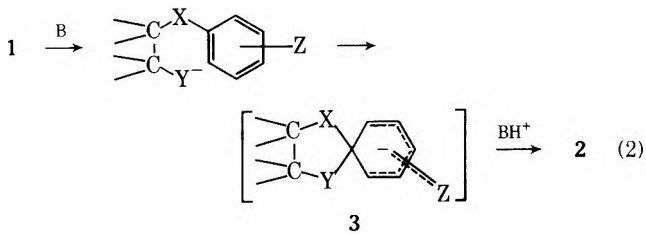


(1)

1 2

Z, activating group

Several pathways are possible for the conversion of 1 to 2. As shown in eq 2, in most cases a nucleophilic function YH may be ionized by a base to give 2 via the intermediate 3. In certain systems, in which aromatic rings are much ac-

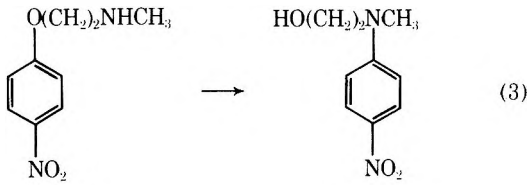


(2)

3

tivated with nitro, cyano, or other electron-withdrawing groups, the intermediates (spiro Meisenheimer or Janovsky complex, hereafter referred to as anionic σ complex), might possibly be confirmed spectrometrically or isolated. This field has been recently reviewed in detail.[3]

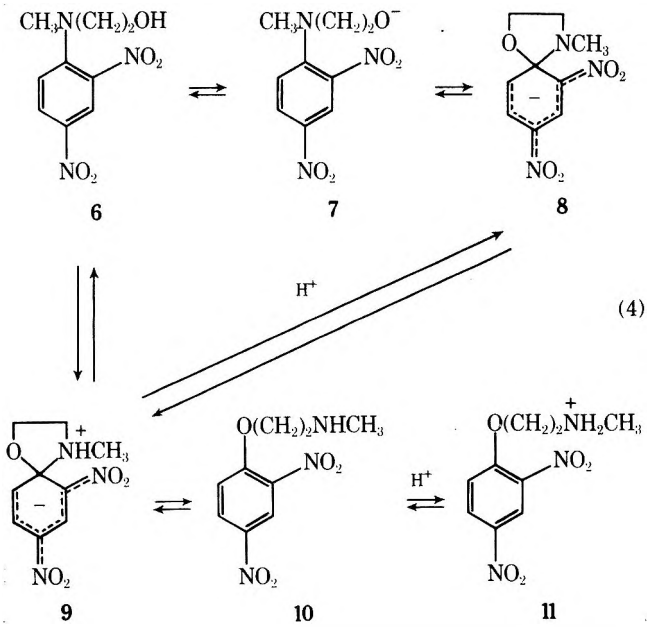
Kleb[4] has reported the rearrangement of 4 to 5, in which the reaction proceeded very rapidly and, therefore, no cyclic intermediate was confirmed by experimental evidence.



(3)

4 5

Bernasconi et al.[5] have recently reported the kinetics of the base-catalyzed formation of 8 from 6 shown in eq 4. Aryl ethers such as 10 or 11 cannot be prepared by ordinary methods. Therefore, they prepared 11 by rapidly acidifying the spiro anionic σ complex (8) and proposed the reverse Smiles rearrangement of 6 to 11 as follows.



(4)

6 7 8

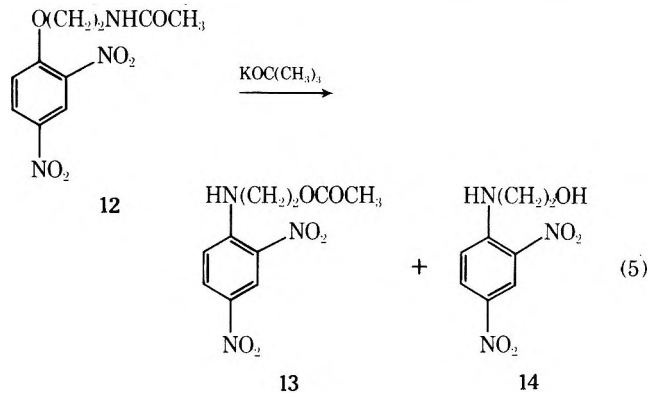
9 10 11

We have more recently carried out the base-catalyzed Smiles rearrangement of *N*-acetyl-β-aminoethyl-2,4-dinitrophenyl ether (12) in Me_2SO, in which the stabilized intermediate (or spiro Janovsky complex) could be spectrometrically confirmed to exist. The compound 12 was selected for study, because pure 12 can be prepared and the life of the anionic σ complex derived from 12 is comparatively longer, so that direct information on the reaction path of the normal Smiles rearrangement can be obtained spectrometrically.

This paper reports the reaction mechanism of the base-catalyzed Smiles rearrangement of 12.

Results and Discussion

Addition of an equivalent amount of tertiary-butanolic $KOC(CH_3)_3$ at room temperature to a Me_2SO solution of 12 immediately led to a red color, and soon to a dark red one. After 1 hr treatment of the colored solution with aqueous HCl solution gave *N*-β-acetyloxyethyl-2,4-dinitroaniline (13) in 78% yield, and a small amount of *N*-β-hydroxyethyl-2,4-dinitroaniline (14), the hydrolysis product of 13, as shown in eq 5. As discussed in the next paragraph, the

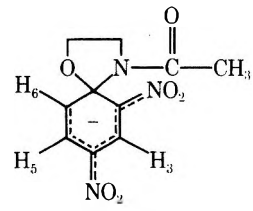


(5)

12 13 14

color change from red to dark red suggests that the reaction in eq 5 proceeds via a spiro anionic σ complex.

To confirm this mechanism, NMR spectra were observed at intervals during the reaction. The results are shown in Figure 1. Immediately after addition of $KOC(CH_3)_3$, the red solution gives the spectrum of Figure 1b; the poor resolution is due to the fast sweep time (500 Hz/50 sec). In Figure 1b, the resonance peak positions of 12 are shifted to a higher magnetic field (H_3 δ 8.72 → 8.57, H_5 δ 8.47 → 7.00, and H_6 δ 7.62 → 5.33), while the amide proton resonance peak (δ 8.03) disappeared. Such chemical shifts are characteristic of 1,1-disubstituted anionic σ complexes of 2,4-dinitrobenzene such as 15.[3,5-11] Figure 1c shows the spectrum scanned (500 Hz/50 sec) immediately after that in 1b. In addition to the signals due to 15, the spectrum shows reso-



15

nance peaks which are the same as those in Figure 1d. Further, several minutes after mixing, the H_3 signal is shifted upfield (δ 8.57 → 8.37) and H_5 and H_6 signals are shifted downfield (H_5 δ 7.00 → 7.52, H_6 δ 5.33 → 6.37) as shown in Figure 1d, and from that time on these peak positions do not change. After the measurement, the solution was already dark red.

In order to clarify what the spectrum of Figure 1d is attributed to, the reaction of 13 with an equivalent amount of $KOC(CH_3)_3$ in Me_2SO was carried out. Immediately after

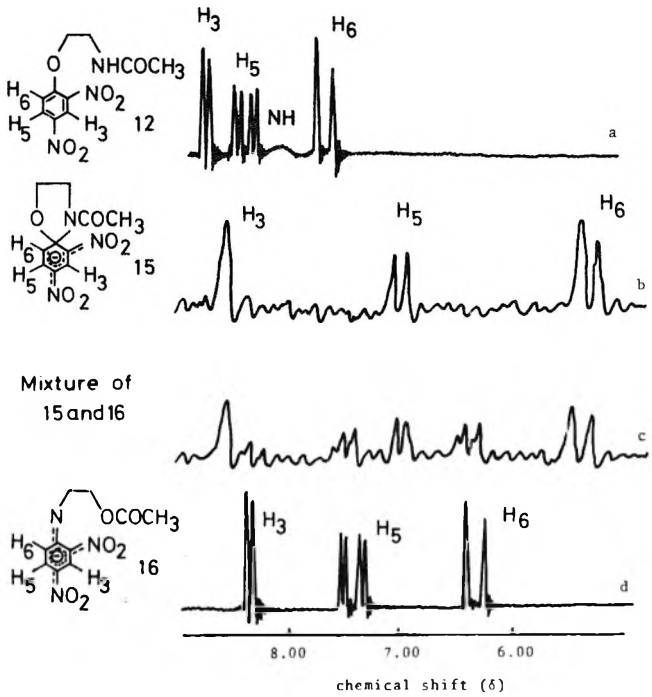
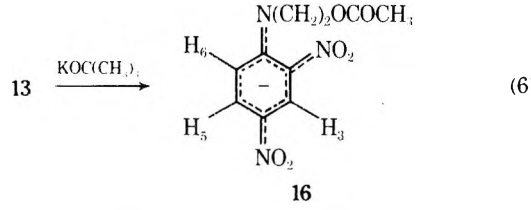


Figure 1. NMR spectra of the reaction of **12** with tertiary-butanolic $KOC(CH_3)_3$ in Me_2SO-d_6: (a) before addition of $KOC(CH_3)_3$; (b) immediately after addition of $KOC(CH_3)_3$; (c) immediately after measurement of Figure 1b; (d) several minutes after addition of $KOC(CH_3)_3$.

addition of $KOC(CH_3)_3$, the dark red solution gives the same spectrum as that in Figure 1d. The H_3, H_5, and H_6 resonance peaks of **13** are shifted upfield (H_3 δ 8.85 → 8.40, H_5 δ 8.28 → 7.57, and H_6 δ 7.28 → 6.38) while the amide proton resonance peak (δ 8.87) disappeared.

From these results it is considered that the following reaction occurs.[5,12]



(6)

Therefore the final product in the rearrangement is assumed to be **16.**

The time-dependent absorption spectral change is shown in Figure 2, when 50 equiv of $KOC(CH_3)_3$ is added to a Me_2SO solution of **12.** The reaction takes place in two distinct stages, indicated by two spectral changes. The first change occurs immediately upon addition of $KOC(CH_3)_3$ to a Me_2SO solution of **12** (from curve a to b). Not only the shape but also the positions and intensities of the spectrum of curve b [λ_{max} 347 nm (ϵ 14,300), 359 (13,800), and 506 (28,000)] are characteristic of 1,1-disubstituted 2,4-dinitrobenzene anionic σ complexes.[3c,5] Furthermore, Hosoya et al.[13] have stated by MO calculation that the shape of an absorption spectrum of 1,1-disubstituted 2,4-dinitrobenzene anionic σ complex does not depend on the substituents at C-1.

The second spectral change is much slower (from curve b to c and d). In order to clarify what curve d is attributed to, absorption spectra were observed immediately after addition of 50 equiv of $KOC(CH_3)_3$ to a Me_2SO solution of **13.** The spectrum is the same as curve d. Accordingly curve d represents the spectrum of **16** [λ_{max} 432 nm (ϵ 19,100) and ca. 490 (sh)].

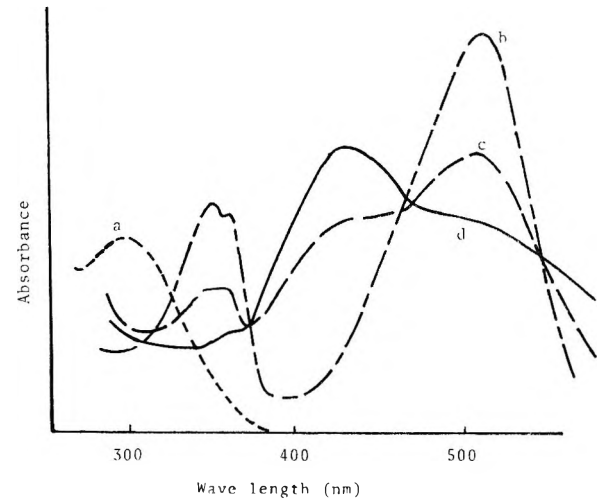
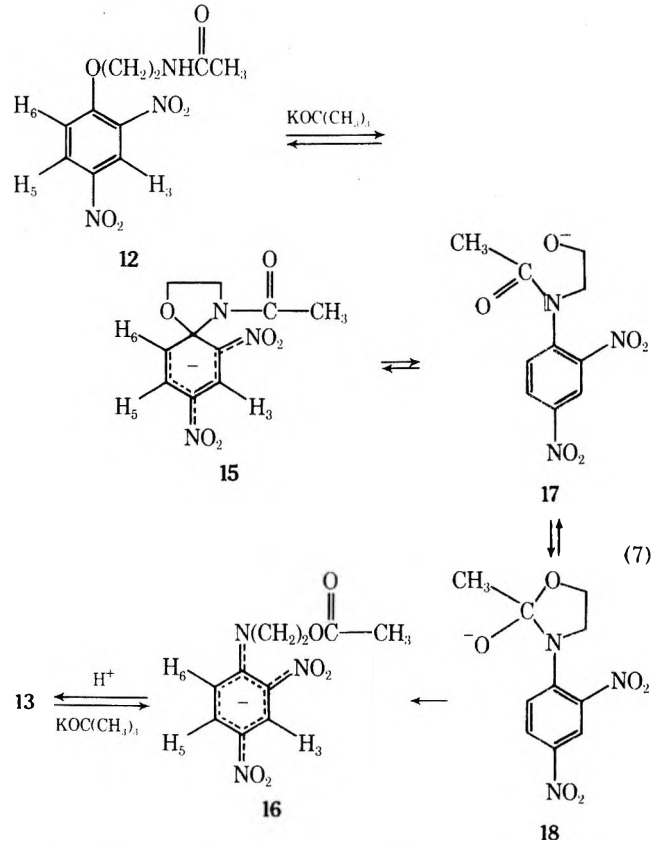


Figure 2. Absorption spectra relevant to the reaction of **12** with $KOC(CH_3)_3$ in Me_2SO: (a) before addition of $KOC(CH_3)_3$; (b, c, and d), immediately, ca. 12, and 40 hr after addition of $KOC(CH_3)_3$.

The following scheme is, therefore, most consistent with these results.

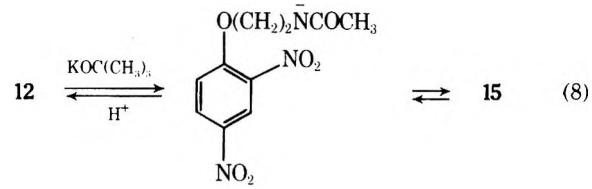


(7)

In order to elucidate the conversion of **12** to **15** or **15** to **12,** absorption spectra were obtained on successive addition of 50, 100, and 200 equiv of $KOC(CH_3)_3$ (1.25 *N*), HCl (1.00 *N*), and $KOC(CH_3)_3$, respectively, to a Me_2SO solution of **12** as shown in Figure 3. The first spectral change (curve a → b) represents the conversion of **12** to **15**[3c,5] and the second one (curve b → c) the conversion of **15** to **12.** A decrease in optical density at λ_{max} 298 nm is attributable to a partial rearrangement of **15** to **16.** The third spectral change (curve c → d) shows that on readdition of $KOC(CH_3)_3$ the spiro anionic σ complex (**15**) is reproduced.

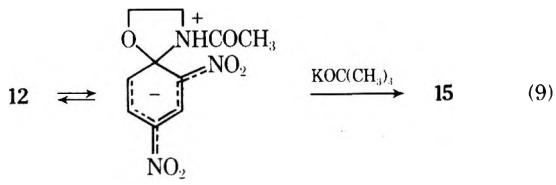
From a consideration on the acidity of the amide hydrogen, the base-catalyzed conversion of **12** to **15** probably

proceeds via the amide ion (**19**), which is in equilibrium with **15** and the equilibrium lies far to **15**, as shown in eq 8.



19

Furthermore, the other conversion of **12** to **15** is possible as shown in eq 9. Spectral change of curve a → b in Figures



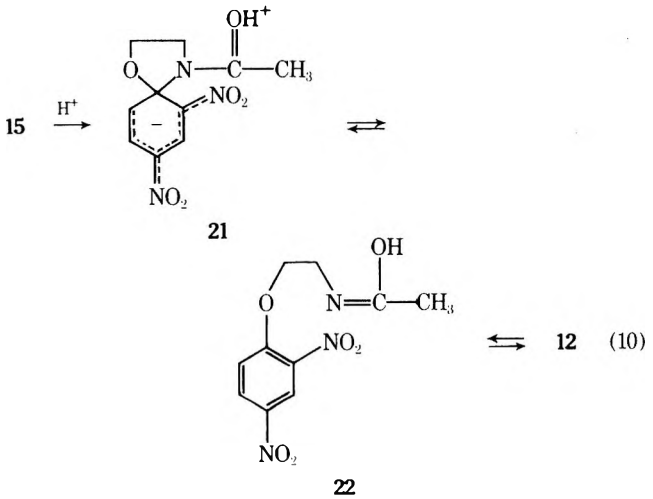
20

2 and 3, however, does not occur in the absence of a base. Bernasconi et al. show that deprotonation of **9** to **8** is very easy.[5] Accordingly, if **20** were spontaneously formed, **20** would change into **15** even in the absence of a base. Accordingly, the conversion in eq 9 is considered to be unlikely.

In the acid-catalyzed conversion of **15** to **12**, there are at least two possible paths. One is the process in which **15** returns to **19**, and, in turn, **19** is protonated to change into **12** as shown in eq 8.

The other is the process in which **15** directly changes to **12** by protonation of the amide group, in which protonation occurs on the amide nitrogen or the carbonyl oxygen. However, much available evidence supports the conclusion that O-protonation on carbonyl oxygen predominates over N-protonation on amide nitrogen in acidification of amide groups.[14]

Therefore, the other process in the acid-catalyzed conversion of **15** to **12** is considered to be as follows.



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It is not clear at present which path (reverse of eq 8, and eq 10) is predominant.

Experimental Section

Melting points are uncorrected. The NMR spectra were recorded on a Varian A-60D spectrometer. Elemental analyses were performed at the Microanalytical Center of Gunma University. The absorption spectra were measured in Me_2SO on a Hitachi-124 uv–visible spectrophotometer. All reagents were purified by recrystallization or by distillation prior to use.

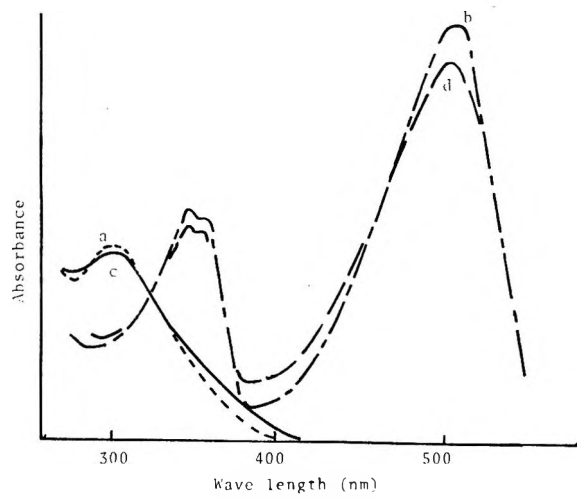

Figure 3. Absorption spectral change in successive addition of $KOC(CH_3)_3$, HCl, and $KOC(CH_3)_3$ to a Me_2SO solution of **12**: (a) **12** before addition of $KOC(CH_3)_3$; (b) immediately after addition of $KOC(CH_3)_3$; (c) immediately after addition of HCl to **15** (anionic σ complex); (d) immediately after addition of $KOC(CH_3)_3$ to reproduced **12**.

Preparation of *N*-Acetyl-β-aminoethyl-2,4-dinitrophenyl Ether (12), *N*-β-Acetyloxy- (13) and *N*-β-Hydroxyethyl-2,4-dinitroaniline (14). After 0.69 g (0.030 mol) of metallic sodium had been added to a stirred solution of 4.6 g (0.045 mol) of *N*-acetylethanolamine in 50 ml of dioxane, the mixture was refluxed for 5 hr so that sodium might be completely dissolved. After a solution of 5.6 g (0.030 mol) of 2,4-dinitrofluorobenzene in 30 ml of dioxane had been added thereto under stirring, the mixture was stirred for an additional 4 hr at 30°. Then the mixture was poured into 200 ml of ice–water and extracted with chloroform. After the organic layer had been dried over anhydrous Na_2SO_4, the solvent was evaporated to produce the crude products, which were separated by column chromatography on silica gel with benzene–acetone mixture as a developing solvent. After the solvent had been distilled off, recrystallization of each crude product from benzene or benzene–ligroin gave each analytical sample: **12**, 14%, mp 105–105.5°, λ_{max} 298 nm (ε 11,300); **13**, 9%, mp 131–132°, λ_{max} 358 nm (ε 17,400), ca. 410 (sh); **14**, 37%, mp 91–92°, λ_{max} 362 nm (ε 17,700), ca. 390 (sh). Anal. Calcd for $C_{10}H_{11}N_3O_6$ (**12**): C, 44.61; H, 4.12. Found: C, 44.33; H, 4.05. Anal. Calcd for $C_{10}H_{11}N_3O_6$ (**13**): C, 44.61; H, 4.12. Found: C, 44.76; H, 4.40. Anal. Calcd for $C_8H_9N_3O_5$ (**14**): C, 42.29; H, 3.99. Found: C, 42.20; H, 3.80%.

Reaction of *N*-Acetyl-β-aminoethyl-2,4-dinitrophenyl Ether (12) with Tertiary-Butanolic $KOC(CH_3)_3$. To a stirred solution of 0.778 g (2.89×10^{-3} mol) of **12** in 10 ml of Me_2SO was added at room temperature 2.37 ml (2.89×10^{-3} mol) of tertiary-butanolic $KOC(CH_3)_3$ (1.22 *N*). After the mixture had been stirred for 1 hr and then 2.89 ml of 2.00 *N* HCl solution added thereto, it was poured into 100 ml of water, extracted with chloroform, and dried over anhydrous Na_2SO_4. The solvent was evaporated to produce the crude products, which were separated by column chromatography on silica gel with benzene as a developing solvent and purified. **13** and **14** were obtained in 78% yield and in a small amount, respectively.

NMR and Absorption Spectra Measurement. In NMR measurement a certain amount of a sample (ca. 42 mg) was dissolved in a small amount of Me_2SO-d_6 (ca. 0.5 ml) in a NMR tube. After an equivalent amount of $KOC(CH_3)_3$ (0.840 *N*) had been added to the solution through a microsyringe, shaken vigorously, and filtered if necessary, the spectra of the mixture were observed.

In absorption spectra measurement of the rearrangement reaction, 3.66 μl of tertiary-butanolic $KOC(CH_3)_3$ (1.25 *N*) was added to 3 ml of a Me_2SO solution of **12** (3.05×10^{-5} *M*), and then the spectra of the mixture were observed (Figure 2). In absorption spectra measurement on successive addition (Figures 3), at first 3.66 μl (50 equiv) of tertiary-butanolic $KOC(CH_3)_3$ (1.25 *N*) was added to 3 ml of a Me_2SO solution of **12** (3.05×10^{-5} *M*), the spectra of the mixture were observed, and then 9.15 μl (100 equiv) of HCl solution (1.00 *N*) was added to the mixture. Immediately after the spectrum had been observed, 14.6 μl (200 equiv) of tertiary-butanolic $KOC(CH_3)_3$ was again added to the mixture, and, the spectrum was observed.

Acknowledgment. We thank the Asahi Glass Foundation for the Contribution to Industrial Technology and the Ministry of Education for their financial support.

Registry No.—12, 55759-61-0; 13, 19289-04-4; 14, 1945-92-2; $KOC(CH_3)_3$, 865-47-4; *N*-acetylethanolamine, 142-26-7; 2,4-dinitrofluorobenzene, 70-34-8.

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Cleavage Reaction of Cyclic Ethers by Alkyl Chlorosulfinates

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The reaction of alkyl chlorosulfinates with tetrahydrofuran (THF) produced predominantly 4-chlorobutylalkyl ethers, but with ethylene oxide β-chloroethylalkyl sulfites were the main product. The kinetic study on the formation of 4-chlorobutylalkyl ethers revealed that the nucleophilic attack of THF on the carbon atom of alkyl chlorosulfinates is the rate-determining step, followed by simultaneous fission of C–O and S–Cl bonds of alkyl chlorosulfinates.

Of the various classes of organic reactions, nucleophilic substitution reactions on carbon have, to date, been studied most intensively. On the formation of alkyl chlorides from the reactions of the corresponding alcohols with thionyl chloride, Hughes and Ingold[1] proposed a mechanism involving the formation of intermediate alkyl chlorosulfinates, followed by the loss of sulfur dioxide, and simultaneously with it formed the carbon–chlorine bond, presumably by way of a cyclic transition state due to their stereochemical reasons. They called this reaction the SNi mechanism. Since then, Boozer and Lewis[2] showed by the study dealing with the decomposition of alkyl chlorosulfinates that intermediates in the formation of alkyl chlorides must have much ionic character. Cram[3] concluded that the SNi reaction proposed by Hughes and Ingold for the decomposition of alkyl chlorosulfinates differs from the SN1 reaction only in the sense that the leaving group is complex, and that the anion of the first ion pair can decompose internally under some conditions faster than a potential anion can react at the carbon undergoing substitution. However, the study on the reactions employing the alkyl chlorosulfinates as the substrate is lacking compared with those of the alkyl chloroformates[4] except for the studies on the interactions of alkyl chlorosulfinates and pyridine by Gerrard.[5,6] We will report the cleavage reaction of cyclic ethers by alkyl chlorosulfinates.

Results

The reaction of ethylene oxide with methyl chlorosulfinate in benzene at 0° gave 70.8% of β-chloroethylmethyl sulfite[7] for 20 min. The results obtained from a variety of epoxides are shown in Table I; the preferential attack of the sulfinyl sulfur of methyl chlorosulfinate by epoxides seems to be predictable from the fact that methanesulfinyl chloride is known to react with ethylene oxide yielding the corresponding sulfinate ester.[8] However, from the five-membered ether, tetrahydrofuran (THF), 4-chlorobutylmethyl ether is obtained as the main reaction product. As shown in Figure 1 this reaction proceeded with an exceedingly slow rate at 30°. At this temperature, the yield of methyl chloride formed by a side reaction is less than about 5% of that of 4-chlorobutylmethyl ether.

These interesting results by the use of THF caused us to elucidate the mechanism of the reaction of THF with alkyl chlorosulfinates yielding 4-chlorobutylalkyl ethers. As shown in Scheme I it is possible to consider two mechanisms containing different modes of attack: (1) THF as the nucleophilic reagent attacks the carbon atom of alkyl chlorosulfinates (C-attack) forming both *O*-alkyl tetrahydrofuranium ion and chlorosulfinate anion (I), followed by the loss of SO_2 to produce the chloride anion. On the other hand, (2) the nucleophilic attack of THF on the sulfur atom of alkyl chlorosulfinates (S-attack) may lead to the formation of an intermediate *O*-alkoxysulfinyl tetrahydrofuranium ion (II), followed by the formation of *O*-alkyl tetrahydrofuranium ion[9] by way of a cyclic transition state.

It is conceivable that the intramolecular reaction of an intermediate (II) may proceed more rapidly than the attack of the chloride ion on an intermediate oxonium ion (II) because of the high stability of such an oxonium ion compared with that of the three-membered oxonium ions. Thus, we elucidate at first the distinction between the C-attack and S-attack of THF and then the feature of this reaction. The reaction rate of methyl chlorosulfinate with THF was followed by gas–liquid partition chromatography (GLC) determining the concentration of methyl 4-chlorobutyl ether formed by the use of *p*-cymene as an internal reference. The reactions were carried out at the temperatures below 50° in order to avoid the side reactions probably due to thermal instability of alkyl chlorosulfinates.

Table I
Reaction Products of Methyl Chlorosulfinate with Various Epoxides in Benzene

Epoxide	Registry no.	Product: Structure (mol %) (registry no.)		% yield	Bp, °C (mmHg)	Time, min	Temp, °C
Ethylene oxide	75-21-8	$CH_3OSO(CH_2)_2Cl$ (55913-34-3)		70.8	115–118 (46)	20	0
Cyclohexene oxide	286-20-4	CH_3OSO–C$_6$H$_{10}$–Cl (55913-35-4)		68.2	130–135 (8)	100	25
		(trans isomer)					
Propylene oxide	75-56-9	$CH_3OSOCH_2CHClCH_3$ (25.3) (55913-36-5)	$CH_3OSOCHCH_2ClCH_3$ (74.7) (55913-37-6)	85.6	105–108 (58)	120	30
1,2-Epoxy-3-methoxypropane	930-37-0	$CH_3OSOCH_2CHClCH_2OCH_3$ (11.7) (55913-38-7)	$CH_3OSOCHCH_2ClCH_2OCH_3$ (88.3) (55913-39-8)	88.1	102 (11)	120	30
Epichlorohydrin	106-89-8	$CH_3OSOCH_2CHClCH_2Cl$ (2.1) (55913-40-1)	$CH_3OSOCHCH_2ClCH_2Cl$ (97.9) (55913-41-2)	60.6	100 (8)	600	30

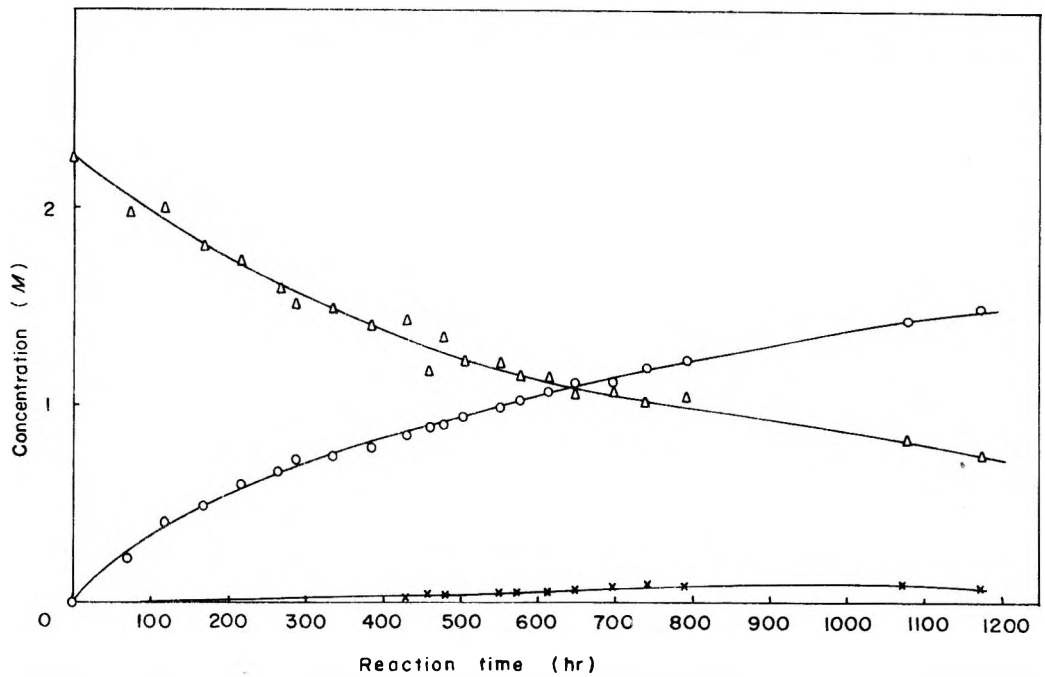


Figure 1. Time dependence of products and methyl chlorosulfinate for the reaction of methyl chlorosulfinate with THF in carbon tetrachloride at 30°: $[CH_3OS(=O)Cl]_0 = [THF]_0 = 2.30\ M$; Δ, $CH_3OS(=O)Cl$; o, $CH_3O(CH_2)_4Cl$; x, CH_3Cl.

The reaction rates were followed up to 40–60% conversions; reactions obeyed good second-order kinetics, i.e., the rates of reaction were proportional to the concentrations of THF and methyl chlorosulfinate, respectively, as shown in Table II. The second-order rate constant (k_2) for these reactions was found to be $(2.86 \pm 0.25) \times 10^{-7}\ M^{-1}\ sec^{-1}$ in benzene at 30°. Moreover, on the reaction of isobutyl chlorosulfinate with THF, only isobutyl 4-chlorobutyl ether was formed and not the other possible isomers, *sec*-butyl and *tert*-butyl 4-chlorobutyl ether, to which an intermediate isobutyl cation would isomerize[10] if isobutyl chlorosulfinate might decompose according to the first-order reaction. Thus, these experimental results confirmed that the reaction of the primary alkyl chlorosulfinates with THF proceeded by second-order reaction. The k_2 values derived from the reactions with various alkyl chlorosulfinates are given in Table III.

The comparisons of relative reactivities among a series of alkyl chlorosulfinates studied and some bimolecular nucleophilic substitutions are informative. The results, relative rates (k_2 for the ethyl compounds in each series at unity) for some bimolecular nucleophilic substitutions of primary compounds containing a displaceable group, are given in Table IV; it is arranged in decreasing orders for the relative rates from methyl to isobutyl, suggesting that steric hindrance plays a dominant role. Thus, the resemb-

Table II
Second-Order Rate Constants for the Reaction of Methyl Chlorosulfinate with THF in Benzene at 30°

$[CH_3OS(O)Cl]$, M	$[THF]$, M	$k_2 \times 10^7$, M^{-1} sec^{-1}
2	3	2.56 ± 0.05
2	2.5	2.77 ± 0.23
2	2	2.94 ± 0.07
2	1.5	2.83 ± 0.11
2	1	2.92 ± 0.11
2	0.5	2.97 ± 0.20
1	2	2.92 ± 0.17
0.5	2	2.92 ± 0.25
1	3	3.03 ± 0.25
		av 2.86 ± 0.25

Table III
Second-Order Rate Constants for the Reactions of Various Alkyl Chlorosulfinates with THF in Benzene

R	Temp, °C	$k_2 \times 10^7$, M^{-1} sec^{-1}	Activation parameter
Me	20	1.22 ± 0.09	$\Delta H^{\ddagger}$ = 17.8 kcal/mol
	20.5	1.39 ± 0.11	$\Delta S^{\ddagger}$ = −20.6 eu
	25	2.22 ± 0.19	
	30	2.86 ± 0.25	
	35	4.33 ± 0.31	
	40	7.28 ± 0.52	
Et	30	1.78 ± 0.04	$\Delta H^{\ddagger}$ = 19.0 kcal/mol
	40	4.71 ± 0.21	$\Delta S^{\ddagger}$ = −18.9 eu
	50	10.78 ± 0.54	
n-Pr	30	0.72 ± 0.01	
i-Bu	30	0.038 ± 0.003	
i-Pr	30	15.36 ± 1.50	

tion with the isopropyl chlorosulfinate proceeds with a faster rate than that with methyl compound as shown in Table III. It is reported in the literature[2] that secondary alkyl chlorosulfinates are more reactive than primary compounds for the thermal decomposition yielding the corresponding alkyl chlorides and sulfur dioxide.

The data of the influence of solvents on reaction rates are shown in Table V. The tendency of the increasing rate in more polar solvents implies that initially neutral reactants form a transition state which has some separation of charge in analogy with the Menschutkin reaction.

Discussion

The experimental results, having great resemblance of reactivity to the well-known other nucleophilic substitution reactions, predominantly to give inverted products, and the solvent effects make certain a mechanism that the nucleophilic attack of THF on the carbon atom of primary alkyl chlorosulfinates is a rate-determining step and then, as depicted in Scheme I, *O*-alkyl tetrahydrofuranium ion and chlorosulfinate anion would be formed, followed by the loss of sulfur dioxide forming chloride anion. When *O*-alkyl tetrahydrofuranium ion undergoes the nucleophilic attack of the chloride anion, we can consider two modes of reaction, that is, methylene–O and alkyl–O cleavage. It has been reported[16] that methylene–O cleavage is greatly preferred in the cyclic oxonium intermediate, which can be ascribed to a decrease of steric hindrance and an increase in reactivity due to some eclipsing strain when the methylene–O carbon is constrained to a five-membered ring. From the structural analogy to alkyl chlorosulfates,[17] we attempt in the reaction of alkyl chlorosulfinates with THF to distinguish between the typical SN2 reaction and the multiple bond fission (fragmentation SN2) reaction accompanied by simul-

Table IV
Relative Rates for Some Substitution Reactions Concerned with Primary Compounds

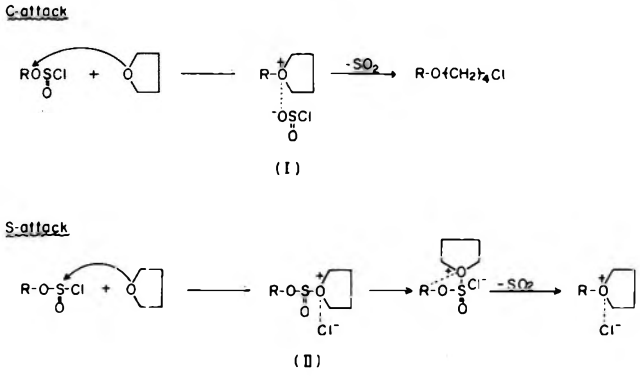
Reaction	Temp, °C	Relative rate: Me	Et	*n*-Pr	*i*-Bu	Ref
RBr + pyridine in MeOH	80	17.2	1.00	0.55	0.017	11
ROTs in EtOH	75	2.3	1.00		0.46	12
RBr in 50% aq EtOH	95	1.94	1.00		0.075	13
ROS(=O)Cl in 85.3% aq dioxane	25	2.93	1.00	0.555	0.043	14
ROS(=O)(=O)Ph in H_2O	60	1.05	1.00		0.235	15
ROS(=O)Cl + THF in benzene	30	1.61	1.00	0.40	0.022	This work

lances of reactivities among one another collected in Table IV provide strong evidence that alkyl chlorosulfinates react with THF by bimolecular substitution on carbon. Moreover, the reaction of optically active *sec*-butyl chlorosulfinate with THF gave a 64.3% inverted product, which was evaluated in comparison with the optically active material obtained by way of Williamson's method. This result, the low optical purity caused by the use of a secondary alkyl chlorosulfinate, may show that the reaction proceeds partially by a carbonium ion mechanism without participation of nucleophiles in the transition state. Actually, the reac-

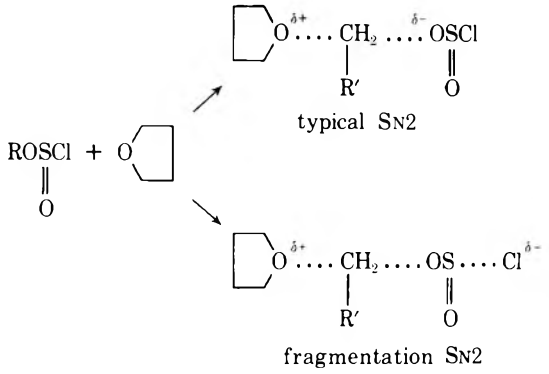
Table V
Solvent Effect on the Reaction Rate of Methyl Chlorosulfinate with THF at 30°

Solvent	$k_2 \times 10^7$, M^{-1} sec^{-1}	Dielectric constant (25°)	Registry no.
n-Hexane	0.86 ± 0.03	1.88	110-54-3
Benzene	2.86 ± 0.25	2.28	71-43-2
Dichloromethane	6.56 ± 0.27	8.93	75-09-2
1,2-Dichloroethane	8.06 ± 0.27	10.3	107-06-2
Nitrobenzene	10.83 ± 0.80	35.9	98-95-3

Scheme I

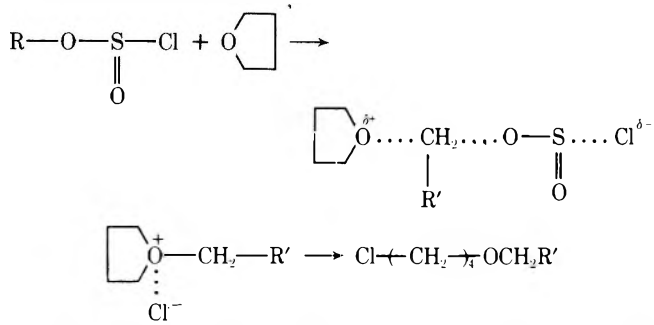


taneous fission of C–O and S–Cl bonds. The effect of leaving groups on substitution reaction rates is shown in Table



VI; the order of the ease of the substitutions for leaving groups attached to the carbon atoms parallels the order of departing tendency[18] of fragments attached to the sulfinyl sulfur atom.

If the typical SN2 reaction occurs we cannot expect the remarkable retardation of the reaction rate by the change of the X in the leaving groups –OS(O)X.[19] Further insight into the mechanism of the reaction of alkyl chlorosulfinates with THF may be gained by consideration of the actual magnitudes of the activation parameters. A discussion of activation parameters must consider their large dependence on both the medium and reaction mechanism. The comparison of the activation parameters for the reactions of alkyl chlorosulfinates with those for some Menschutkin reactions in the same reaction medium (benzene) is listed in Table VII. The actual magnitudes of the activation entropies should be considered in correlation with both the solvation and degrees of freedom of the initial and transition states. If the simultaneous fission of two bonds accompanied by formation of three fragments occurs in the transition state we can expect an increased $\Delta S^{\ddagger}$ owing to the gain of a degree of freedom, but contrary to this, increased solvation to the transition state results in a more negative $\Delta S^{\ddagger}$. Although the balance of the two opposite effects is difficult to estimate, Buncel[17] indicated that the increase of the activation entropy caused by the gain of a degree of freedom predominates over the solvation by 10–20 eu in the hydrolysis of alkyl chlorosulfates. Our result that the reaction of alkyl chlorosulfinates and THF proceeds with a more positive $\Delta S^{\ddagger}$ (10–20 eu) compared with the typical Menschutkin reactions may be due to simultaneous fission of two bonds. In addition to this, it is most likely that the remarkable retardation of the reaction by the change of the X in the leaving groups –OS(O)X is responsible for the fact that the reaction of alkyl chlorosulfinates with THF proceeds with a greater charge separation and also forms the incipient sulfur dioxide in this transition state. The generation of *O*-alkyl tetrahydrofuranium ions from the reactions



of alkyl chlorosulfinates with THF, for which the corresponding alkyl chlorides are unreactive without catalyst, is taken to indicate that the loss of sulfur dioxide provides a substantial driving force for the reactions.

Although it is possible to interpret the difference in the reaction products between epoxides and THF as a catalytic action of a small amount of hydrochloric acid which is difficult to remove by purification of alkyl chlorosulfinates, it can be ruled out by the following facts. As shown in Table I, the distribution of the isomers in products obtained from asymmetric epoxides such as propylene oxide and epichlorohydrin greatly differs from that which would be expected from the acid-catalyzed reaction[24] in which the chloride anion prefers to attack the methylene–O carbon, not the

Table VI
Effect of Leaving Groups on Substitution Reaction Rates of $CH_3OS(O)X$ with THF in Benzene at 30°

X	Cl	$OC(O)CH_3$	OCH_3
k_2, M^{-1} sec^{-1}	2.86×10^{-7}	10^{-11}–10^{-12}	No reaction for 7 days

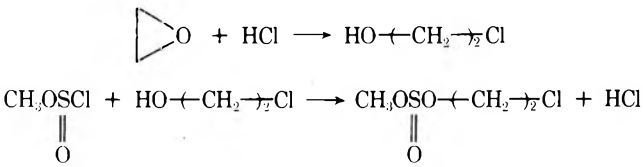
Table VII
Comparison of Activation Parameters Obtained from Reactions of Alkyl Chlorosulfinates and THF with Those of Some Menschutkin Reactions in Benzene

Reaction	k_2, M^{-1} sec^{-1}	Temp, °C	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	Ref
MeI + pyridine	7.1×10^{-5}	50	15.7	−54.0	20
MeI + Et_3N	1.85×10^{-3}	30	10.3	−42.9	21
EtBr + pyridine	0.744×10^{-5}	79	17.5	−34.5	22
EtBr + $PhNEt_2$	5.58×10^{-6}	70	9.05	−59.2	23
MeOSCl + THF ‖ O	2.86×10^{-7}	30	17.8	−20.6	This work
EtOSCl + THF ‖ O	1.78×10^{-7}	30	19.0	−18.9	This work

Table VIII
Reaction Product of Various Alkyl Chlorosulfinates with Tetrahydrofuran

R in ROS(O)Cl	Registry no.	Product RO(CH2)4Cl	Registry no.	Bp, °C	Elemental analysis, %	C	H
Me		Me-O-(CH2)4Cl	17913-18-7	50 (40 mmHg)	Calcd	48.98	8.98
					Found	49.02	8.76
Et	6378-11-6	Et-O-(CH2)4Cl	36865-43-7	149	Calcd	52.75	9.52
					Found	52.51	9.36
n-Pr	22598-38-5	*n*-Pr-O-(CH2)4Cl	14860-82-3	168	Calcd	55.81	9.97
					Found	55.69	9.71
i-Bu	13291-52-6	*i*-Bu-O-(CH2)4Cl[a]	55913-42-3	178	Calcd	58.36	10.33
					Found	58.45	10.33
i-Pr	22598-56-7	*i*-Pr-O-(CH2)4Cl	55913-43-4	166–168	Calcd	55.81	9.97
					Found	56.08	10.08
sec-Bu	55954-47-7	*sec*-Bu-O-(CH2)4Cl	55913-44-5	165–168	Calcd	58.36	10.33
					Found	57.99	10.01

[a] Secondary and tertiary isomers were not detected.



carbon having the substituent. The reaction of methyl chlorosulfinate with ethylene oxide proceeds more rapidly even in benzene than predicted from the acid-catalyzed hydrolysis of ethylene oxide in a more polar solvent, H_2O. Accordingly, the possibility of the action by hydrochloric acid can be ruled out in this reaction. The preferential attack on sulfinyl sulfur by ethylene oxide seems to be reasonable from the fact that the addition of β-chloroethyl chloroformate to ethylene oxide produces bis(2-chloroethyl) carbonate quantitatively and this is a violent exothermic reaction.[25] It is known that lone pair electrons on the oxygen atom of epoxides possess much more s character than those of THF because of its large ring strain. Thus, we assume that the difference in the mobilities of lone pair electrons located on the oxygen atoms of epoxides and THF is due to the difference in the contributions to the Coulombic repulsions in the transition state between the neutral nucleophile and the sulfur atom of alkyl chlorosulfinates having the positive charge.[26] The nucleophilic attack of THF on the sulfur atom of alkyl chlorosulfinates requires much more activation energy than that of epoxides to overcome the Coulombic repulsion in the transition state.

However, we cannot interpret clearly the reason for the more favorable attack of THF on the carbon atom of alkyl chlorosulfinates. The mechanism of the reaction of alkyl chlorosulfinates with epoxides is now under active study.

Experimental Section

Materials. All of the solvents were purified by the usual methods. Commercial THF was dehydrated over sodium wire and then purified by distillation. Cyclohexene oxide, propylene oxide, and epichlorohydrin, commercially available, were dried with calcium hydride and then purified by distillation. Ethylene oxide, prepared from ethylene chlorohydrin and sodium hydroxide pellets, was purified by low-temperature distillation from dried sodium hydroxide and finally by drying over barium oxide. 1,2-Epoxy-3-methoxypropane, obtained by the method of Gallardo and Pollard,[27] was purified by distillation, bp 53° (86 mmHg). Alkyl chlorosulfinates used in this study were prepared and purified by the method of Lewis.[2] Optically active (*R*)-*sec*-butyl chlorosulfinate was synthesized by the reaction of thionyl chloride with the corresponding alcohol prepared by a modification of the method of Prichard and Kenyon[28] and optically active (*R*)-*sec*-butyl 4-chlorobutyl ether was prepared by the reaction of (*R*)-*sec*-butyl alcoholate with 1,4-dichlorobutane. Methyl acetoxysulfinate was obtained by the reaction of methyl chlorosulfinate with anhydrous sodium acetate as reported by Kobayashi[29] and purified by distillation, bp 40–45° (5 mmHg).

Anal. Calcd for $C_3H_6O_4S$: S, 23.19. Found: S, 21.17

The structure of methyl acetoxysulfinate was confirmed by the agreement with the ir spectrum shown in the literature. The purity was calculated to be 91% from sulfur content; thus only a rough estimate of the rate constant was done for this compound. Methyl sulfite was obtained as a by-product in the preparation of methyl chlorosulfinate and then purified by distillation.

Authentic Compounds for GLC. 4-Methoxybutyl acetate was prepared by the slow addition with stirring of acetyl chloride in anhydrous ether to a mixture of dry pyridine and 4-methoxybutyl alcohol, which was itself obtained by treating butane-1,4-diol with sodium and methyl iodide.[16,30]

Kinetic Measurement. A flask was equipped with a needle valve and a neoprene rubber stopper. The appropriate solvent, THF, and sealed glass ampoule containing alkyl chlorosulfinate were placed in the flask, and then dry nitrogen was bubbled into the reaction flask immersed in cold methanol. The initial time for the reaction was taken when the glass ampoule in the flask immersed in a thermostat was broken. A small amount of the reaction mixture was taken out from the flask at a given time through the neoprene rubber stopper with a syringe and then treated with 50% aqueous sodium carbonate solution. The reaction rates were determined from the measurement of GLC peak areas. The concentration of the product in the reaction mixture was corrected using *p*-cymene as internal standard for difference in detector responses between products and internal standard. GLC was performed on a Yanaco Model 201 with flame ionization detector.

General Method of Reaction of Methyl Chlorosulfinate with Epoxides in Benzene. To epoxide in benzene, methyl chlorosulfinate was added. After the reaction had continued for the prescribed time, the reaction mixture was immediately evaporated at reduced pressure to remove the solvent, and alkyl sulfites were isolated by distillation under reduced pressure and obtained in pure form by preparative GLC. The structure of the products was identified by its infrared and NMR spectra. Product yields were determined by the GLC method using an internal reference with corrections for differences in detector responses and measurement of peak areas. The isomer distributions of alkyl sulfites obtained from asymmetric epoxides were determined by the intensity of the NMR signals for the methine and methylene protons attached to the sulfite group. Yields and product distributions of the individual compounds are summarized in Table I.

2-Chloroethyl Methyl Sulfite. Gaseous ethylene oxide was bubbled into methyl chlorosulfinate in benzene. After the reaction was carried out for 20 min at 0°, 2-chloroethyl methyl sulfite was obtained by distillation: ir ν_{max} S=O 1210, S–O 730 cm^{-1}.

Anal. Calcd for $C_3H_7ClO_3S$: C, 22.71; H, 4.42; S, 20.19. Found: C, 23.15; H, 4.56; S, 20.45.

2-Chlorocyclohexyl Methyl Sulfite. The reaction was carried out as described in the general procedure. Distillation of the crude product under reduced pressure afforded pure compound: ir ν_{max} S=O 1200, S–O 700, 740 cm^{-1}.

Anal. Calcd for $C_7H_{13}ClO_3S$: C, 39.52; H, 6.12; S, 15.06. Found: C, 39.73; H, 5.87; S, 15.37.

2-Chloropropyl Methyl Sulfite and Isomer. The product was obtained according to the above procedure. To determine the isomer distribution, the reaction products were isolated by preparative GLC: ir ν_{max} S=O 1192, S–O 690, 735 cm^{-1}; NMR δ 4.69 (sextet, –OC**H**(CH$_3$)CH$_2$Cl), 4.04 (AA'X, –OC**H**$_2$CH(CH$_3$)Cl).

Anal. Calcd for $C_4H_9ClO_3S$: C, 27.83; H, 5.52; S, 18.52. Found: C, 27.55; H, 4.97; S, 18.72.

2-Chloro-3-methoxypropyl Methyl Sulfite and Isomer. The results of elementary analyses were satisfactorily consistent with calculated values without further preparative GLC: ir ν_{max} S=O 1200, S–O 710 cm^{-1}; NMR δ 4.58 [q, –O(CH$_2$Cl)C**H**(CH$_2$OCH$_3$)], 4.10 [m, –OCH$_2$CH(Cl)–].

Anal. Calcd for $C_5H_{11}ClO_4S$: C, 29.63; H, 5.43; S, 15.80. Found: C, 29.69; H, 5.59; S, 15.36.

2-Chloromethyl-2-chloroethyl Methyl Sulfite and Isomer. Methyl chlorosulfinate was added to epichlorohydrin as described in the general procedure. The reaction mixture slowly darkened in 10 hr at 30°. An appreciable by-product was isolated by the use of GLC at this stage. Crude product was purified by preparative GLC: ir ν_{max} S=O 1190, S–O 705, 730 cm^{-1}; NMR δ 4.73 [q, –OC**H**(CH$_2$Cl)$_2$], 4.20 [m, –OC**H**$_2$CH(CH$_2$Cl)Cl].

Anal. Calcd for $C_4H_8Cl_2O_3S$: C, 23.18; H, 3.86; S, 15.46. Found: C, 23.01; H, 4.33; S, 15.26.

Reaction of Alkyl Chlorosulfites with THF. To excess THF alkyl chlorosulfinates were added. After reflux had continued for 4–5 hr, the corresponding 4-chlorobutyl alkyl ethers were isolated by distillation at atmospheric pressure after treating the reaction mixture with 10% aqueous sodium hydroxide solution and dehydrating by anhydrous sodium sulfate. Boiling points and elementary analyses of individual products are summarized in Table VIII. The structures of all of the compounds were confirmed by infrared and NMR spectra: for CH$_3$CH(CH$_3$)CH$_2$O(CH$_2$)$_4$Cl ir ν_{max} ether bond 1112 cm^{-1}; NMR δ 0.89 [d, 6 H, (C**H**$_3$)$_2$CH–], 3.12 (d, 2 H, –CHC**H**$_2$O–), 3.30–3.70 (m, 4 H, –OC**H**$_2$CH$_2$–, –C**H**$_2$Cl), 1.60–2.10 (m, 5 H, –C**H**$_2$C**H**$_2$–, –CHC**H**$_2$–).

Time Dependence of 4-Chlorobutyl Methyl Ether and Methyl Chlorosulfinate. An equimolar mixture of methyl chlorosulfinate and THF was allowed to react in carbon tetrachloride, and the progress of the reaction was followed by means of NMR spectroscopy. The amounts of the products and methyl chlorosulfinate were determined from the integrated values on NMR spectra by using dichloromethane as the internal standard: NMR δ 4.08 [CH$_3$OS(O)Cl], 3.28 [C**H**$_3$O(CH$_2$)$_4$Cl], 3.05 (C**H**$_3$Cl).

Registry No.—Methyl chlorosulfinate, 13165-72-5; 1,4-dichlorobutane, 110-56-5; methyl acetoxysulfinate, 5308-06-5.

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Fluoro Olefins. VI. Ring Size Effects in Cyclic Fluoro Olefins with Alkoxide Nucleophiles

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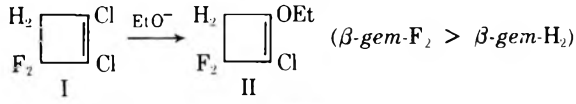
In contrast to 1,2-dichloro-3,3-difluorocyclobutene (I), which undergoes almost exclusive displacement of chloride ion when reacted with ethoxide, the five-membered analog, 1-chloro-5,5-dihydropentafluorocyclopentene (V), undergoes facile allylic rearrangement. Similarly, the six-membered analog undergoes facile dehydrohalogenation. These results show that the conformational changes, as the ring size changes, dominate the reactions of these cyclic fluoro olefins containing *gem*-dihydro groups, and that the "carbanion stabilization" theory of Park cannot be applied indiscrimately to the larger ring system.

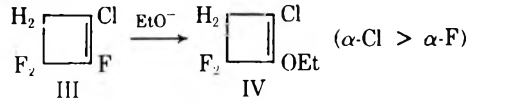
The susceptibility of fluorinated olefins to nucleophilic attack is well documented.[2] Park and coworkers theorized the kinetic control of intermediate carbanion formation by α- and β-position substituents.[3] However, a report by Burton and Johnson suggested that the carbanion stabilization theory did not completely explain the reactions of metal hydrides with cyclic polyfluoro olefins.[4] They suggested that steric effects (between entering nucleophile and the leaving group) might be contributing to the different mixtures of products obtained from the reactions of sodium borohydride or lithium aluminum hydride with cyclic fluoro olefins. In addition to this apparent discrepancy between alkoxides and complex metal hydrides, both Burton and Park have observed that the ring size of the cyclic fluoro olefins can have an effect upon product ratios.[4,5] Since most of Park's kinetic control theory has been obtained with cyclobutene systems, it suggested to us that these discrepancies between alkoxides and hydrides might be another example of ring size effects. Accordingly, this paper presents the results of our study into this problem with respect to alkoxides. A later paper will report results obtained with these substrates and their reaction with complex metal hydrides.

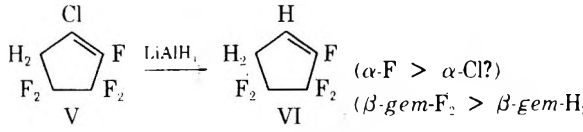
The experimentally determined order of α-stabilization was reported to be I > Br > Cl > H > OR > F.[6] To a lesser extent, these intermediates are stabilized by substituents

in the β position to the negative charge. The experimentally determined order of β-stabilization was reported to be *gem*-Cl_2 > *gem*-ORCl > *gem*-FCl > *gem*-F_2 > *gem*-$(OR)_2$ > *gem*-H_2.[7]

Examples of the discrepancies between alkoxide and metal hydride reaction products are shown below. Park has reported that the reactions of 1,2-dichloro-3,3-difluorocyclobutene (I) and 1-chloro-2,3,3-trifluorocyclobutene (III) with ethoxide ion give ether products which would be expected from the α- and β-carbanion stabilization theory.[8] Feast and coworkers have reported that the reaction of 1-chloro-5,5-dihydropentafluorocyclopentene (V) with lithium aluminum hydride gives the chloride displaced product.[9] This cyclopentene reaction product is not that expect-



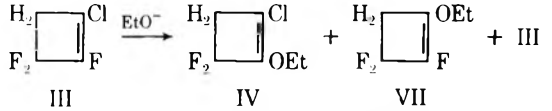




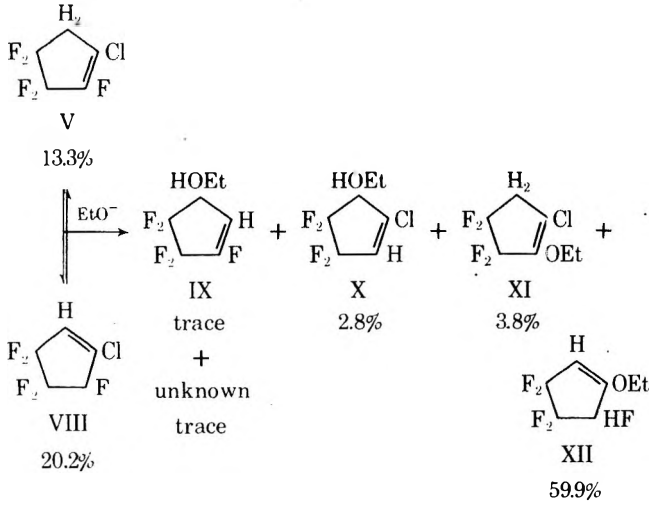
ed by application of the carbanion stabilization theory, which would predict fluoride displacement. Park concluded that this latter reaction was evidence that complex metal hydrides might proceed by a different reaction mechanism than that of the alkoxides.[8]

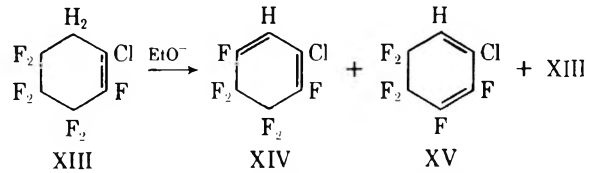
Results

The reaction of III with potassium hydroxide in ethanol was repeated. The results observed by Park were essentially verified.[8] The main product, 1-chloro-2-ethoxy-3,3-difluorocyclobutene (IV), resulted from fluoride displacement; however, a small amount of chloride displaced product, 1-ethoxy-2,3,3-trifluorocyclobutene (VII), was also observed. The reaction of V with potassium ethoxide in etha-



nol gave five new products plus one trace unknown. Here the main product, 1-ethoxy-2,5-dihydropentafluorocyclopentene (XII), resulted from chloride displacement. The

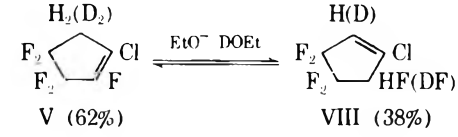




+ six ethers (not isolated)

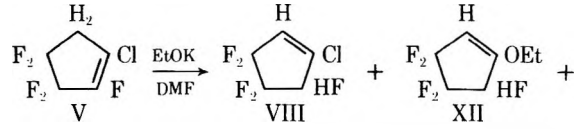
reaction of 1-chloro-6,6-dihydroheptafluorocyclohexene (XIII) with potassium ethoxide in ethanol produced two new cyclohexadienes and six unidentified ether products. The listed product ratios (in this reaction) represent the relative integrated areas of GLC chromatograms of the respective final product solutions.

When it became apparent that an allylic rearrangement was contributing to the major product in the cyclopentene case, both the cyclobutene and cyclopentene reactions were repeated using potassium ethoxide in ethanol-*O*-*d*. The potassium ethoxide was pregenerated by reaction of potassium metal with ethanol-*O*-*d*. Previous reactions had shown that potassium metal or potassium hydroxide gave the same reaction products when premixed in ethanol. When III was treated at −10° for 11 days in ethanol-*O*-*d* the same relative ratio of products was observed and no deuterium incorporation into the ring protons was found.[10] When the reaction of V with ethoxide in ethanol-*O*-*d* was carried out, considerable deuterium incorporation in isolated XI and XII was found. In a separate reaction, pure XII was mixed with 0.1 equiv of potassium ethoxide in ethanol-*O*-*d*. Reisolation of XII showed by ^1H NMR that no exchange or additional reaction had taken place. The allylic isomer equilibrium was studied in two ways. One reaction was carried out in ethanol-*O*-*d* (5–10°) but quenched with water after 35 min. Only a trace of ether products was present, but the ratio of allylic isomers V:VIII was 62:38. The isolated compounds showed considerable deuterium incorporation as shown below. A second reaction used previously isolated VIII to demonstrate that the isomerization was reversible and gave V plus ether products.



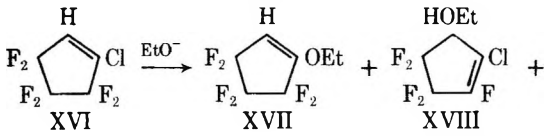
	Analysis method	
14.4% D (of H is D)	Mass spectrum	67.3% D (sum of 2- and 5-H)
14.2% D (of H is D)	D elemental	70.5% D
	^{19}F NMR integration	82.9% of 5-H is D

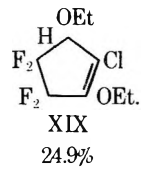
The reaction of V with potassium ethoxide was also studied in dimethylformamide solvent. While the rearrangement of V to VIII did occur in DMF, the reaction mixture turned very black and a GLC chromatogram of the reaction mixture showed many broad unresolved peaks which were assumed to be polymers of cyclopentadienes.



The ratio of nucleophilic attack at chloride compared to attack at hydrogen in the allylic isomer, VIII, appears to be

about 20:1 (60%:3%). This isomer has the same olefinic substitution as 1-chloro-2-hydrohexafluorocyclopentene (XVI). The reaction was carried out because we believed that attack would occur mainly at hydrogen (as predicted by both steric and carbanion stabilities). A GLC analysis of the final reaction showed that, indeed, attack at hydrogen was favored by about 10:1.





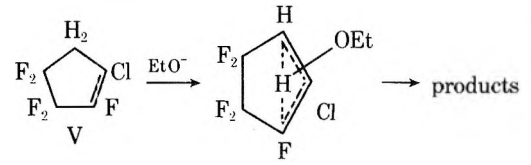
Discussion

The kinetic carbanion theory of Park and steric effects would both predict that fluoride should be the major displacement product in all cases. The results, however, show that fluoride is the major displacement product for the cyclobutene III, but that chloride displacement is preferred with ethoxide and the cyclopentene V. Neither the carbanion theory nor steric effects adequately suggest a means of rationalization of products.

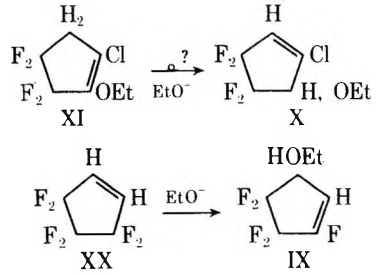
A third alternative, that of ethanol addition across the double bond and a subsequent elimination of either HCl or HF, also does not suggest an explanation for the results. However, elimination of HX cannot be entirely ruled out as making a contribution to some of the products observed. A recent paper reports the observation of small amounts of saturated compounds in alkoxide reactions with 1,2-dihydropolyfluorocyclobutenes, -pentenes, and -hexenes.[11] This paper did, however, state that the reaction path involved addition of alkoxide ion to generate a carbanionic species. Only a minor portion of the carbanion protonated to form the saturated ether; the main product was formed by rearrangement of the carbanion to eliminate fluoride ion (SN2′) and form a new ether olefin. In addition, separate reaction of the saturated ether with alkoxide did not give olefins, showing that the olefin generated was by rearrangement and not HX elimination. Koch has observed a saturated ether product in the reaction of 2-phenylperfluoropropene with ethoxide ion.[12] It was pointed out that even in this noncyclic fluoro ether the rate of dehydrofluorination (to form olefin) was at least six orders of magnitude slower than the rate of reaction of the original olefin with ethoxide.

It therefore seems most reasonable to us to explain these reactions as being due to ring size effects. The deuterium exchange studies clearly show that the cyclobutene III is not acidic enough to form an allylic carbanion system or even exchange any of the ring protons for deuterium under these conditions. Similar deuterium studies on the cyclopentene V show that it is acidic enough to enter into a reversible and mobile equilibrium to form the allylic isomer VIII. Furthermore, from the ^{19}F NMR integration of the 5 position of VIII it can be seen that a fair amount of hydrogen (17%) of V migrates without exchange for deuterium. Such an intramolecular transfer is common in allylic rearrangements and has been described as the "conducted tour" or "internal return" by Cram and others.[13] The cyclohexene system, XIII, also has an acidic, allylic hydrogen pair and in the presence of a strong base (alkoxide) reacts to form 1,2- and 1,4-cyclohexadiene elimination products. The cyclohexene is more acidic than either the cyclopentene or the cyclobutene, probably because conformational effects of the larger ring allow it to more easily orient itself for trans elimination of HF. Overall, then, the switch from major fluoride displacement between the cyclobutene and cyclopentene with alkoxides is due to ring size effects.

Park's original conclusion of alkoxide and hydride mechanism[8] differences was based on the switch from fluoride to chloride displacement as stated in the introduction. While we have shown that alkoxides also show this product switch and we attribute it to ring size effects, there is a mechanism change between the alkoxide reactions on III and V. We feel, as does Park, that the cyclobutene reaction is under kinetic control of the most stable carbanion. However, the cyclopentene case differs by the proton shift and the intramolecular nature of this shift. In addition, we know that VIII undergoes preferential displacement of chloride (to form XII) (20:1). In contrast, attack at the vinyl hydrogen in the model compound, XVI, which carries the same vinyl substitution as VIII, is favored by 10:1.[14] This information allows us to suggest that an acid–base-like alkoxide bridged intermediate is kinetically favored. This intermediate, shown below, explains the intramolecular nature of the allylic rearrangement and positions the ethoxide above the vinyl chloride to make it inherently more probable that nucleophilic displacement take place at that site. This intermediate is highly solvated by the alcoholic solvent. The solvent impedes the reactivity of the alkoxide ion as shown by the DMF solvent reaction. In that solvent the alkoxide is not strongly hydrogen bonded to alcoholic solvent molecules and apparently the increased basicity of the ethoxide is enough to favor complete removal of a proton from the substrate. This removal, we speculate, makes elimination to form cyclopentadienes favored over allylic rearrangement. The DMF reaction did prematurely stop as would be expected from HX neutralization of potassium ethoxide. Some fluorocyclopentadienes have been known to polymerize easily.



We have shown that the main cyclopentene product, XII, does not undergo exchange with deuterium or further reaction. It is possible that the minor product, XI, could undergo an allylic rearrangement to form the other minor product, X, as shown below. We, however, doubt that this rearrangement takes place, as our experience and that of others[5] has shown that once ether substitution has taken place the protons are no longer very acidic. As stated before, X was probably formed by ethoxide attack on VIII. We have no rationale for the formation of the trace product, IX, from either V or VIII. It would most easily be formed from an impurity, 1,2-dihydrohexafluorocyclopentene (XX), in our starting material.[4] We cannot, however, detect any of



this in our starting material. The trace unknown was not identified because it eluted next to the main product (by GLC) and we were unable to isolate it.

The cyclohexene (XIII) reaction was undertaken in order to better investigate possible ring size effects. The reaction, as observed by gas chromatography, was fairly rapid. We were unable to resolve the ether products well enough to use preparative gas chromatography. Nevertheless, isolation of the dienes and recovered starting material was possible by distillation from the relatively nonvolatile ether products and their identification does allow us to say that again there is a mechanism change when the ring size is increased. Identification of the ether products will be undertaken as part of a study of the nucleophilic displacement reactions of alkoxides on cyclohexadienes.

In summary, ring size effects caused by conformational changes dominate the reactions of these cyclic fluoro olefins containing allylic *gem*-dihydro groups with potassium ethoxide. While the kinetic carbanion theory of Park correctly predicts the reaction products of the cyclobutene III, other reaction paths become kinetically favored for larger ring systems. The reader is also referred to a recent paper on the parent hydrocarbon systems of cyclopentene and cyclohexene for more examples of ring size effects.[15]

Experimental Section

Gas–liquid chromatography analyses were obtained on a Hewlett-Packard Model 5752 gas chromatograph. Preparative GLC was carried out on a Varian Aerograph Model 700 instrument. For product ratios the peak areas were determined by a disk integrator and the areas obtained were normalized to 100%. Infrared spectra were obtained on a Perkin-Elmer Model 21 spectrophotometer. The spectra were calibrated by use of a standard polystyrene peak at 6.238 μm. Proton magnetic resonance spectra were obtained on either a Varian A-60 or HA-100 instrument. Chemical shifts are reported in δ values downfield from tetramethylsilane. Fluorine spectra were obtained on the HA-100 retuned to 94.075 MHz and were calibrated by the audio side-band technique. Fluorine chemical shifts are reported as φ units upfield from trichlorofluoromethane internal standard.

Preparation of Starting Materials. 1-Chloro-5,5-dihydropentafluorocyclopentene (V). Commercially available 1,2-dichlorohexafluorocyclopentene was reduced with 2 equiv of sodium borohydride in diglyme in the presence of water. The major product, V, was isolated by steam distillation of the diglyme final solution and spin band distillation of the volatile organic layer. The major fraction (~85%) boiled at 89–90° and was shown by ir and NMR to be V (lit. bp 89.5°).[16]

1-Chloro-2,3,3-trifluorocyclobutene (III). Commercially available 1,1,2,2-tetrachlorotetrafluorocyclobutane was dechlorinated with metallic zinc using the procedure of Rapp.[17] The product formed was 1,2-dichlorotetrafluorocyclobutene. This olefin was reduced with 2 equiv of sodium borohydride as above to give a solution containing III (~50%) and other fluorocarbons (~50%). Spin band distillation gave pure III, bp 52.5° (745 mm) (lit. bp 53°).[17b]

1,2-Dichloro-3,3-difluorocyclobutene (I). Commercially available 1,1-dichloroethene was cyclodimerized with 1,1-dichlorodifluoroethyene according to a procedure reported by Dick.[18] The dimerization products were dissolved in dioxane and dechlorinated with metallic zinc. A fraction boiling at 80–90° was collected and spin band distilled to give a 7.8% yield of I, bp 89–90° (750 mm), ^{1}H NMR δ_{CH_2} 3.17 (triplet, J_{HF} = 3.0 Hz) (lit. δ 3.15, J = 3.0 Hz).[19]

1-Chloro-6,6-dihydroheptafluorocyclohexene (XIII). Commercially available 1,2-dichlorooctafluorocyclohexene was reduced with 2 equiv of sodium borohydride in diglyme. The reaction mixture was hydrolized with dilute nitric acid and diluted with water, and the lower, fluorocarbon layer separated. This material was distilled at 115° (750 mm) to give a 67% yield of XIII. The compound gave n^{20}D 1.3606, ir 1706 cm^{-1} (FC=CCl) (lit. 116°, 1705 cm^{-1}).[9]

Reaction of 1-Chloro-2,3,3-trifluorocyclobutene (III) with Ethoxide. The reaction was carried out once using potassium hydroxide in ethanol and once using potassium metal in ethanol-*O*-*d*. In a 100-ml three-necked flask equipped with a condenser, Teflon stopcock, dropping funnel, and magnetic stirrer were placed 2.85 g (0.02 mol) of III and 10 ml of absolute ethanol. To the flask was rapidly added 10 ml of absolute ethanol in which 1.45 g (0.022 mol) of potassium hydroxide had previously been dissolved. The reaction mixture was stirred overnight at 25°. A GLC analysis (QF-1, 10%, 10 ft, 70–150°) of the final mixture gave, in order of elution, III (20%), minor product (2.7%), and major product (77.3%).

The reaction was repeated at temperatures of −9 to −13° utilizing a thermocouple-cooled bath. In the flask was placed 0.78 g (0.02 mol) of potassium metal while a slow nitrogen gas stream was maintained through the flask. Ten milliliters of ethanol-*O*-*d* (C_2H_5OD) was dropped onto the metal. Once addition was completed the flask was immersed in the cold bath and a magnetic stirrer and 2.85 g (0.02 mol) of precooled III was added. The progress of the reaction was followed by periodically removing 0.05 ml of reaction solution, dilution with water, and injecting the lower, fluorocarbon layer into the GLC. After some 50 hr an additional 0.01 mol of potassium dissolved in 5 ml of ethanol-*O*-*d* was added. The reaction was quenched with water after 11 days, although 13% starting material remained. The two reaction products were isolated by preparative GLC (QF-1, 3, 140°) to give a minor component with ir 1754 cm^{-1} (FC=COR) assumed to be 1-ethoxy-4,4-dihydrotrifluorocyclobutene (VII) (lit. ir 1750 cm^{-1}),[4] and a major component, 1-chloro-2-ethoxy-3,3-difluorocyclobutene (IV): ir 1690 cm^{-1} (ClC=COR); ^{1}H NMR δ_{CH_3} 1.30 (t, 7.0), δ_{CH_2} 4.20 (q, 7.0) and 2.77 (t, J_{HF} = 3.0 Hz) [lit. ir 1680 cm^{-1}; ^{1}H NMR δ 1.30, 4.20, and 2.77 (J = 3.0 Hz)].[8] The ^{1}H NMR integration (2:2:3) showed that no deuterium exchange had taken place. The ether products were present in the approximate ratio of 3:97 (VII:IV).

Reaction of 1-Chloro-5,5-dihydropentafluorocyclopentene (V) with Ethoxide. In a 100-ml flask equipped as above was placed 2.15 g (0.055 mol) of potassium. Dry nitrogen was slowly swept through the flask as 45 ml of absolute ethanol was slowly dropped onto the potassium. When the reaction was completed, 9.63 g (0.05 mol) of 1-chloro-5,5-dihydropentafluorocyclopentene (V, precooled) was added rapidly. The reaction mixture was maintained at 0–3° for 23 hr, after which time it was quenched with water. The reaction was periodically monitored by removing a 0.1-ml sample, diluting it with water, and injecting the lower layer into the gas chromatograph (QF-1, 10%, 10 ft, 90–165° at 15°/min). A peak (which eluted just after the starting material) was observed to grow rapidly with time and slowly decay during the reaction as other materials of greater retention times grew in proportion. After the reaction was quenched GLC analysis gave starting material (V, 13.3%); starting material isomer, 1-chloro-2,5-dihydropentafluorocyclopentene (VIII, 20.2%); 1,5-dihydro-5-ethoxypentafluorocyclopentene (IX, trace); 1,3-dihydro-2-chloro-3-ethoxytetrafluorocyclopentene (X, 2.8%); a trace unknown not isolated because it could not be separated from main product; and 1,3-dihydro-2-ethoxypentafluorocyclopentene (XII, 59.9%). Products from a number of these reactions were combined and isolated by preparative GLC (QF-1, 30%, 165°) for product identification and characterization. The starting material isomer (VIII) gave ir 1630 cm^{-1} (HC=CCl); ^{1}H NMR δ_{5H} 5.7 (J_{HF} = 52.4 Hz), 8.5, 5.0, 2.3, 2.2, δ_{2H} 6.30 (m); ^{19}F NMR ϕ_{3F} 104.8 and 109.6 (m of AB pattern, J_{FF} = 265 Hz), ϕ_{4F} 121.6 and 129.3 (m of AB pattern, J_{FF} = 251 Hz), and ϕ_{5F} 193.8 (d of m, J_{HF} = 52.5 Hz). The ether products respectively: IX gave ir 1695 cm^{-1} (HC=CF); ^{1}H NMR δ_{CH_3} 1.24 (t), δ_{CH_2} 3.68 (ABX_3 pattern, J_{AB} = 9.1, J_{AX} = 7.0, J_{BX} = 6.9 Hz), δ_{5H} 4.34 (m), δ_{1H} 5.69 (m); X gave bp 151.5°(743 mm); n^{20}D 1.3943, ir 1630 cm^{-1} (HC=CCl); ^{1}H NMR δ_{CH_3} 1.24 (t, J = 7.0 Hz), δ_{CH_2} 3.78 (ABX_3 pattern, J_{AB} = 9.2, J_{ABX} = 7.0 Hz), δ_{1H} 6.05 (m), δ_{3H} 4.30 (m); XI gave bp 38° (3 mm); n^{20}D 1.3789; ir 1673 cm^{-1} (ClC=COR); ^{1}H NMR δ_{CH_3} 1.34 (t, J_{HH} = 7.0 Hz), δ_{CH_2O} 4.30 (q, 7.0), δ_{CH_2} 3.20 (t of t, J_{4F5H} = 11.2, J_{3F5H} = 3.4 Hz); ^{19}F NMR ϕ_{3F} 115.5, ϕ_{4F} 115.1; XII gave bp 50° (3 mm), 106° (100 mm); n^{20}D 1.3770; ir 1647 cm^{-1} (HC=COR); ^{1}H NMR δ_{CH_3} 1.38 (t, J_{HH} = 7.0 Hz), δ_{CH_2} 4.02 (q, 7.0), δ_{1H} 5.13 (m), δ_{3H} 5.15 (m, J_{HF} = 53.1 Hz, 9.15, 4.85, 1.65, 1.65); ^{19}F NMR ϕ_{5F} (AB pattern at 97.8 and 105.7, J_{FF} = 251 Hz), ϕ_{4F} (AB pattern at 121.7 and 128.8, J_{FF} = 250 Hz), ϕ_{3F} 195.6 (m, J_{HF} = 53.5 Hz, and others). Anal. Calcd for $C_7H_7F_5O$: C, 41.60; H, 3.49. Found: C, 41.33; H, 3.40.

A similar 0.05-mol reaction was carried to 98.7% completion and the GLC showed that the major product, XII, was 91.1% of the final mixture. After dilution with water and separation of the organic layer the water layer was acidified with nitric acid and treated with silver nitrate. A total of 6.21 g of a possible 7.09 g of silver chloride was isolated. This 87.6% yield of chloride compares favorably with the 91.1% GLC assay for the chloride displaced product, XII.

Reactions of 1-Chloro-5,5-dihydropentafluorocyclopentene

(V) in Ethanol-*O-d*. A duplication of the above reactions using potassium ethanol-*O-d*-[20] from 0° to room temperature showed that considerable deuterium incorporation occurred. The ring proton positions of 1-chloro-5,5-dihydrodeuteriotetrafluorocyclopentene (XI) showed 78% D. The major product, 1,3-dihydrodeuterio-2-ethoxypentafluorocyclopentene (XII), showed 83 and 87% D, 1 and 3 positions, respectively. These values were taken from integration of the respective ^{1}H NMR spectra and subsequent comparison of ring proton to side chain proton count (which was always 2:3).

In a separate experiment 6.2 ml of ethanol-*O-d* and 1.9 g (0.01 mol) of V were stirred together for 44 hr at room temperature. An infrared spectrum of the isolated fluorocarbon showed no bands in the fingerprint region which could be assigned to deuterium incorporation when compared to an authentic sample of V.

Rearrangement of 1-Chloro-5,5-dihydropentafluorocyclopentene (V). In a 100-ml three-necked flask equipped with a magnetic stirrer, condenser, dropping funnel, and nitrogen inlet was placed 2.15 g (0.055 mol) of potassium. To the flask was carefully added 35 ml of ethanol-*O-d*. Subsequently 10 ml of ethanol-*O-d* containing 9.63 g (0.05 mol) of V was added. Over a 35-min period the reaction temperature varied from 4 to 9°. The reaction was quenched at this time with dilute nitric acid. A GLC (QF-1, 85°) of the fluorocarbon layer gave starting material (V, 62%) and isomer, 1-chloro-2,5-dihydropentafluorocyclopentene (VIII, 38%) with a trace of ether products. The two compounds were isolated by preparative GLC (TCEP, 30%, 100°). The amounts of deuterium incorporation as determined by elemental analysis[21] and mass spectral analysis (20 eV),[22] respectively, for each compound were found to be as follows: V, 14.2 and 14.4%, and VIII, 70.5 and 67.3%. In addition, VIII was selectively assayed for D incorporation at the 2 position by ^{19}F NMR. The high-field peak (ϕ 194 ppm) doublet collapsed to a singlet (with concurrent 0.65 ppm upfield shift) with D substitution. The ^{19}F integration of the singlet and doublet showed 82.9% D at the 2 position.

Reaction of 1-Chloro-2,5-dihydropentafluorocyclopentene (VIII) with Ethoxide. In a 100-ml three-necked flask equipped as above were placed 3.3 g (0.017 mol) of VIII and 6.3 ml of ethanol-*O-d*. To the flask with stirring was added 5 ml of ethanol-*O-d* which had previously been treated with 0.4 g (0.01 mol) of potassium. A GLC analysis after 45 min showed all the products observed from the reaction of ethoxide with V. The reaction mixture was allowed to warm to 25° and quenched with water after 5 hr. A GLC analysis at this time showed V (10%), starting material (VIII, 33%), four very minor peaks (5%), and XII (52%). Identifications were made by retention times. This reaction showed that the isomerization of V to VIII was reversible and suggested that VIII was the thermodynamically preferred isomer.

Reaction of 1-Chloro-5,5-dihydropentafluorocyclopentene (V) with Ethoxide (DMF). In a 100-ml three-necked flask equipped as above was placed 1.08 g (0.028 mol) of potassium. While nitrogen was being swept through the flask 10 ml of ethanol was slowly added. After the reaction was completed, unreacted ethanol was removed under vacuum while warming the flask with an infrared lamp. To the flask and contents was added 25 ml of dry DMF. The solution was cooled with the aid of an ice bath and 5 ml of DMF which contained 4.82 g (0.025 mol) of V was added. An immediate blackening of the reaction mixture was observed. A GLC analysis (QF-1, 10%, 100–200°, 15°/min) within 30 min showed starting material (V), a small amount of VIII, and mainly one ether product surrounded by broad unresolved peaks. A GLC analysis showed very little change, indicating almost no additional reaction. A ^{1}H NMR of the steam-distilled reaction mixture showed that the main product was 1,3-dihydro-2-ethoxypentafluorocyclopentene (XII). It was suspected that dehydrofluorination had occurred. This side reaction removed ethoxide and caused low conversion to products. The cyclopentadiene, which resulted, probably polymerized to give the black reaction mixture and high-boiling components observed on the GLC.

Reaction of 1-Chloro-2-hydrohexafluorocyclopentene (XVI) with Ethoxide. In a 250-ml flask equipped as above was placed 9.0 g (0.23 mol) of potassium. To the flask was carefully added 100 ml of absolute ethanol. This solution was added to another 200-ml flask containing 25 ml of absolute ethanol and 42 g (0.199 mol) of XVI.[13] The reaction was carried out at −10° overnight. Subsequently the reaction mixture was poured into water and separated, and the water layer was acidified with nitric acid and treated with silver nitrate in the usual manner. A total of 3.25 g of a theoretical 25.4 g of silver chloride was isolated (89% completed reaction by GLC), indicating that 12.8% of the product resulted from chloride displacement. A GLC (Carbowax 20M, 10%, 120–200°, 15°/min) of the reaction products showed (excluding recovered XVI) 1-chloro-5-ethoxy-5-hydropentafluorocyclopentene (XVIII, 66.7%), 1-ethoxy-2-hydrohexafluorocyclopentene (XVII, 8.3%), and 1-chloro-2,5-diethoxy-5-hydrotetrafluorocyclopentene (XIX, 24.9%). The products gave XVIII, bp 134° (743 mm); n^{20}D 1.3796; ir 1704 cm^{-1} (ClC=CF); XVII, ir 1660 cm^{-1} (HC=COR); ^{1}H NMR δ_{CH_3} 1.41 (t, J_{HH} = 7.0 Hz), δ_{CH_2} 4.42 (q, 7.0), δ_{2H} 5.19 (m); XIX, ir 1669 cm^{-1} (ClC=COR), ^{1}H NMR (acetone-d_6) δ_{2CH_3} 1.34 (t, J_{HH} = 7.0 Hz), δ_{2CH_2} 4.43 (q, 7.0), δ_{5CH_3} 1.22 (t), δ_{5CH_2} ~ 3.81 (ABX$_3$ pattern, J_{AX} = 7.0, J_{BX} = 6.9, J_{AB} = 9.4 Hz), δ_{5H} 4.58 (m, J_{HF} 11.3 Hz, 6.5, 2.3, 1.5).

Registry No.—I, 14851-11-7; III, 694-62-2; IV, 14851-13-9; V, 5239-60-1; VII, 55871-52-8; VIII, 55871-53-9; IX, 55871-54-0; X, 55871-55-1; XI, 55871-56-2; XII, 55871-57-3; XIII, 5239-63-4; XVI, 3761-95-3; XVII, 55871-58-4; XVIII, 55871-59-5; XIX, 55871-60-8; 1,2-dichlorohexafluorocyclopentene, 706-79-6; 1,2-dichlorooctafluorocyclohexene, 336-19-6; ethoxide, 16331-64-9.

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Fluoro Olefins. VII. Preparation of Terminal Vinyl Fluorides

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The synthetic scope of the reactions of several aldehydes and ketones with fluoromethylenetriphenylphosphorane, $(C_6H_5)_3P{=}CHF$, either pregenerated via the dehydrohalogenation of fluoromethyltriphenylphosphonium iodide with *n*-butyllithium in THF at −78°, or better generated in situ via the dehalogenation of fluoroiodomethyltriphenylphosphonium iodide with zinc–copper couple in DMF at 0°, was studied in detail. In addition several methods of preparation of the phosphonium salts which served as the precursors to the designated ylide were investigated.

Vinyl fluorides are generally synthesized by (1) nucleophilic substitution reactions on fluoro olefins; (2) dehalogenation of saturated halofluorocarbons; and (3) dehydrohalogenation of saturated halofluorocarbons.[2a] These methods, however, are normally accompanied by unfavorable side reactions and/or involve multistep procedures employing poorly accessible starting materials. The Wittig reaction of fluoromethylenetriphenylphosphorane with a carbonyl moiety offers a simple, one-step synthetic tool to terminal H–F olefins.

At present, two reports have appeared in the literature which describe the fluoromethylene ylide route to vinyl fluorides. Rabinowitz[3] has claimed that the reaction of a trialkylphosphine with a dihalofluoromethane in the presence of a carbonyl compound afforded the corresponding fluoromethylene olefin and a *gem*-dihalide, the latter product formed from the reaction of a dihalophosphorane with the aldehyde or ketone.

$$2R_3P + CHFXY + 2R'C(O)R'' \longrightarrow R'C(R'')=CHF + 2R_3PO + R'C(R'')XY$$

These reactions presumably proceed through the intermediacy of a fluorohalomethyltrialkylphosphonium salt which is subsequently dehalogenated by additional phosphine generating the ylide and a phosphorane.[4] In our hands this method of approach was unsuccessful as a method of preparation of vinyl fluorides. Schlosser and Zimmermann[5,6] have recently reported that some aldehydes and a steroid could be successfully fluoroolefinated via the Wittig reaction employing fluoromethylenetriphenylphosphorane pregenerated at temperatures below −50°.

$$R_3P + CHFXY \longrightarrow [R_3\overset{+}{P}CHFX]Y^- \xrightarrow{R_3P} \begin{matrix} R_3P{=}CHF \\ + \\ R_3PXY \end{matrix}$$

Results and Discussion

Fluoromethylenetriphenylphosphorane, pregenerated from the reaction of *n*-butyllithium and fluoromethyltriphenylphosphonium iodide in THF at Dry Ice temperatures, reacted readily with a variety of carbonyl compounds representing most structural groups, affording the corresponding vinyl fluorides in fair yields (approximately 10–30% via GLC analysis). Treatment of these reaction mixtures with potassium *tert*-butoxide at 0° or room temperature resulted in significant increases of the desired products. It appears that the intermediate betaines form strong complexes with lithium salts which inhibit their cyclization into oxaphosphetanes that precede betaine collapse into olefin and phosphine oxide.[7]

The reactions reported here were carried out by simply adding a freshly standardized[8] solution of *n*-butyllithium in hexane dropwise to a stirred slurry of fluoromethyltriphenylphosphonium iodide in THF cooled to approximately −78°. The generation of the ylide was believed to coincide with the color changes of the slurry; that is, initially it was a faint canary yellow which gradually darkened into a deep brownish-red upon completion of the addition. The reaction mixture was then stirred for 30 min at −78° before being quenched with an aldehyde or ketone. Stirring was continued for approximately 2 hr at −78° and then for 1.5 hr at room temperature. When very active carbonyl compounds were employed (i.e., fluorinated aldehydes and ketones) the reaction mixture was cooled in an ice–water slush bath before the betaine was decomposed with potassium *tert*-butoxide. The results of these reactions are summarized in Table I.

Table I
Synthesis of Fluoro Olefins via the Reaction of Pregenerated Fluoromethylenetriphenylphosphorane with Carbonyl Compounds

Product	GLC yield,[a] %	Cis:trans
$C_6H_5C(CF_3){=}CHF$	28.3[b]	39:61
	50.4[c]	46:54
$C_6H_5C(CH_3){=}CHF$	48.8	49:51
$(C_6H_5)_2C{=}CHF$	46.8	
$c\text{-}C_6H_{10}{=}CHF$	69.3	
$C_6H_5CH{=}CHF$	43.5	44:56[d]
$n\text{-}C_6H_{13}CH{=}CHF$	25.7	48:52
$C_6H_5C(CF_3){=}CHF$	48.0	49:51[e]

[a] GLC yields based on thermal conductivity corrections relative to an appropriate standard. [b] Betaine decomposition for 42 hr at 28°. [c] Betaine decomposition for 2 hr at 0°. [d] Isomers were not completely separable by GLC; the isomer ratio was determined by employing an integrated ^1H NMR spectrum of the isomer mixture. [e] Ylide was pregenerated by reaction with $LiN[CH(CH_3)_2]_2$ in place of BuLi.

Fluoromethylenetriphenylphosphorane was also found to be sufficiently stable when generated under similar conditions at 0°, for it could be trapped 40 min later with an activated ketone. In an identical reaction conducted at room temperature (28°), however, no olefins were produced when the ylide was quenched 20 min after its pregeneration.

The present olefination technique did exhibit three major limitations: (1) the ylide precursor (i.e., fluoromethyltriphenylphosphonium iodide) could only be prepared from triphenylphosphine and the poorly accessible fluoroiodomethane; (2) *n*-butyl substitution products of the desired olefins were formed during these reactions in fair yields (14–23%); and (3) the stable betaine–lithium salt complex necessitated the employment of potassium tert-butoxide to catalyze betaine collapse into olefin and phosphine oxide.

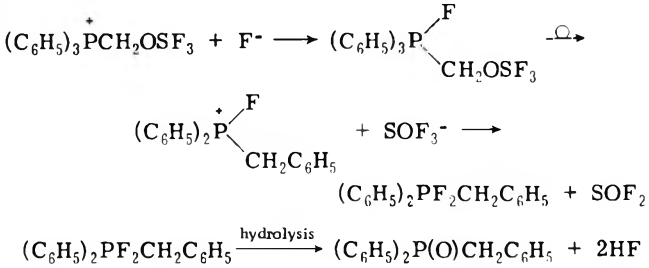
Fluoromethyltriphenylphosphonium iodide was isolated in 86% yield from the reaction of triphenylphosphine with

fluoroiodomethane. However, this methylene halide could only be prepared in yields of approximately 20% from the reaction of mercuric fluoride and methylene iodide, the major reaction product being methylene fluoride, formed in yields as high as 67%. Schlosser[5] has recently reported that this phosphonium salt could be synthesized by the reaction of perchloryl fluoride with salt-free methylenetriphenylphosphorane. However, the employment of elaborate safety precautions in the event of spontaneous ignition or detonation of perchloryl fluoride reaction mixtures limits the scale of such reactions and detracts from their usefulness.

Several other synthetic routes to a fluoromethyltriphenylphosphonium salt have been unsuccessfully investigated in this laboratory. The ease associated with the preparation of hydroxymethyltriphenylphosphonium chloride[9,10] and its conversion into the corresponding halomethyl derivatives when treated with thionyl chloride[10] or phosphorus tribromide[11,12] lead to the attempted fluorination of this salt with sulfur tetrafluoride. In each reaction conducted in this study the isolated organic product, as determined by ^{1}H NMR spectroscopy, was a chloromethyltriphenylphosphonium salt. A fluoromethyl derivative was detected (~1% yield) in the product from only one reaction which was conducted in the presence of sodium fluoride and a very large excess of sulfur tetrafluoride.

The observed reaction product was apparently formed by the chloride ion displacement of $^-OSF_3$ in the intermediate generated during the initial reaction between sulfur tetrafluoride and the phosphonium salt. In an attempt to avoid this side reaction, the less nucleophilic bifluoride and fluoroborate derivatives of hydroxymethyltriphenylphosphonium chloride were prepared via analogous methods and treated with sulfur tetrafluoride. Unexpectedly, the major reaction product was benzyldiphenylphosphine oxide, although low yields (<20%) of a fluoromethyltriphenylphosphonium salt could be detected in some of the product mixtures in addition to small amounts of the chloromethyl derivative.

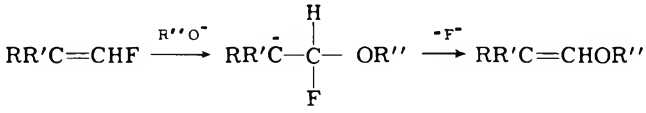
Benzyldiphenylphosphine oxide could conceivably be produced during these reactions by fluoride ion attack on phosphorus in the initial reaction intermediate followed by subsequent rearrangement to benzyldifluorodiphenylphosphorane. Hydrolysis of this latter compound during the work-up of the products would afford the observed phosphine oxide. Recent observations in this laboratory[13] have indicated that positive four-coordinated organophosphorus compounds react with fluoride ion forming a fluorophosphorane, which can then expel the most stable phosphorus ligand as a carbanion ($C_6H_5^-$ in this case). The chloromethylphosphonium salt presumably arises from chlorine-containing impurities in the gaseous fluorinating reagent.



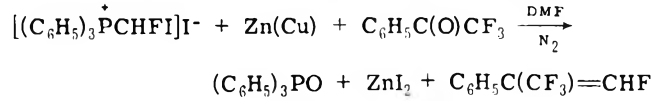
The attempted fluoride ion displacement of iodide and of chloride in their respective halomethyltriphenylphosphonium salts resulted in the isolation of a methyltriphenylphosphonium salt in the former case and unreacted starting material in the latter. Apparently the carbon–iodine bond was thermally cleaved in the reaction involving iodomethyltriphenylphosphonium iodide and the organic radical that was produced abstracted a hydrogen atom from the solvent. The carbon–chlorine bond in the chloromethylphosphonium salt was evidently resistant to thermal cleavage as well as displacement by fluoride ion.

The second major limitation of the described fluoroolefination technique is the significant formation of *n*-butyl derivatives of the vinyl fluorides. Although *n*-butyllithium is expected to be capable of reacting with fluoro olefins to afford the observed by-products,[14] the presence of an organolithium reagent could not be detected by quenching an aliquot of an ylide solution with ethylene bromide prior to the addition of a carbonyl compound. It appears, therefore, that the observed by-products are formed from the reaction of the carbonyl compounds with *n*-butylmethylenetriphenylphosphorane generated from the reaction of a base with an *n*-pentyltriphenylphosphonium salt formed from the displacement of fluoride ion in fluoromethyltriphenylphosphonium iodide by *n*-butyllithium. Although this pathway would not normally be expected to compete with proton abstraction in the ylide generation sequence, the fact that fluorine destabilizes adjacent carbanionic sites[2b] and that the lithium–fluorine bond is stronger than the carbon–fluorine bond,[15] could assist fluoride ion displacement. In an attempt to avoid this problem, lithium diisopropylamide was employed as the base in place of *n*-butyllithium (cf. Table I). The yield of vinyl olefin and the cis:trans ratio of products were similar to the *n*-butyllithium method of generation and did not appear to offer any significant advantage.

The necessity to employ potassium *tert*-butoxide in this reaction sequence to assist in the decomposition of the intermediate betaine–lithium salt complexes is potentially the most severe limitation to this synthetic method, for terminal fluoro olefins are known to be very susceptible to nucleophilic substitution by alkoxides.[14,16] This fact is dramatically demonstrated in the lower yield of 1-hydro-2-phenylperfluoropropene obtained when the corresponding betaine–lithium halide complex was treated with the alkoxide for 42 hr at 28° vs. 2 hr at 0° (cf. Table I).



A synthetic fluoroolefination technique has been developed that completely avoids the use of basic materials in any step of the reaction sequence, thus eliminating the formation of n-butyl derivatives of the vinyl fluorides and the potential consumption of the fluoro olefins by alkoxides. In the presence of activated carbonyl compounds the zinc–copper couple catalyzed dehalogenation of fluoroiodomethyltriphenylphosphonium iodide, readily prepared from the reaction of triphenylphosphine with fluorodiiodomethane,



80%

afforded good yields of the corresponding H–F olefins. These results are summarized in Table II.

The fact that acetophenone reacted poorly under these conditions when, in fact, it readily reacted with the pregenerated fluoromethylene ylide at lower temperatures suggested that a "free ylide" is not the olefinating agent during the in situ method of vinyl fluoride formation. It appears that the olefinating agent is a complex of ylide and

Table II
Synthesis of Fluoro Olefins via the Reaction of Carbonyl Compounds with Fluoromethylenetriphenylphosphorane Generated In Situ

Product	GLC yield,[a] %	Cis:trans
$C_6H_5C(CF_3)=CHF$	79.9	52:48
$C_6H_5CH=CHF$	52.4	41:59[b]
$C_6F_5CH=CHF$	65.0	54:46
n-$C_6H_{13}CH=CHF$	54.4	43:57
$C_6H_5C(CH_3)=CHF$	12.0	57:43

[a] GLC yields based on thermal conductivity corrections relative to an appropriate standard. [b] Isomers were not completely separable by GLC; the isomer ratio was determined by employing an integrated normalized ^1H NMR spectrum of the isomer mixture.

$$[(C_6H_5)_3\overset{+}{P}CHFI]I^- + Zn(Cu) \longrightarrow \begin{matrix}(C_6H_5)_3P{=}CHF \cdots ZnI_2 \\ \Downarrow \\ [(C_6H_5)_3\overset{+}{P}CHFZnI]I^-\end{matrix}$$

zinc iodide which is not as reactive as the "free ylide". Mercury halide complexes of nonstabilized ylides have been reported in the literature, some of which have also demonstrated olefinating capabilities at elevated temperature.[17,18] It is suggested that nonactivated carbonyl compounds could be satisfactorily fluoroolefinated using the pregeneration procedure described previously, for the consumption of the resulting olefin by reaction with potassium *tert*-butoxide in the betaine decomposition sequence should be minimal under carefully controlled conditions.

In addition to the decreased reactivity of the fluoroolefinating species generated by this technique, very reactive halogenated carbonyl compounds that are capable of reacting to an appreciable extent with the dehalogenating agent cannot be satisfactorily employed. For example, *sym*-dichlorotetrafluoroacetone was completely consumed during its attempted in situ fluoroolefination but no olefinic products were detected via GLC analysis of the reaction mixture. An unsuccessful attempt was made to develop a procedure in which the fluoroolefinating agent could be pregenerated at 0° via the salt dehalogenation sequence so that the reaction of zinc–copper couple with very reactive carbonyl compounds could be avoided. However, it appears that in the absence of a carbonyl compound the fluoroolefinating reagent is not appreciably stable, for only a 16% yield of 1-hydro-2-phenylperfluoropropene was realized when a reaction mixture of fluoroiodomethyltriphenylphosphonium iodide and zinc–copper couple was quenched with α,α,α-trifluoroacetophenone 90 min after initiating the reaction. A similar reaction conducted in the presence of the carbonyl compound afforded an 80% yield of the product.

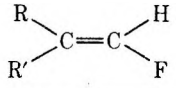
The olefins synthesized during the course of this study were isolated by distillation and/or preparative GLC techniques and characterized by ir, NMR (^1H and ^{19}F), and mass spectral analysis. When possible the spectra of the products were compared to those of authentic samples or to those reported in the literature.

The observed cis:trans isomer ratios of the H–F olefins synthesized by the reaction of unsymmetrical carbonyl compounds with fluoromethylenetriphenylphosphorane, either pregenerated at −78° or generated in situ, were consistently close to unity. Although the method of ylide generation apparently affects the isomer ratio in the reactions involving α,α,α-trifluoroacetophenone and acetophenone, this observation appears to be an artifact attributed to the preferential consumption of the cis isomer by potassium *tert*-butoxide in the betaine decomposition sequence of the pregenerated olefination technique. The fact that neither isomer is predominantly formed suggests that the equilibrium normally established between the diastereomeric erythro and threo betaines in the presence of lithium salts[19] is insignificant and that the electrostatic replusions between the groups attached to the carbonyl carbon atoms and the hydrogen and fluorine atoms of the ylide are similar. The structural assignments and physical constants for the H–F olefins are shown in Table III.

The ir spectra of all of the compounds synthesized in this study are typical and will not be described in detail. Spectra of the H–F olefins generally exhibit very strong C=C stretching vibrations between 5.96 and 6.02 μm with the exception of that for 1,1-diphenyl-2-fluoroethylene, which occurred at 6.11 μm (cf. Table III). The n-butyl derivatives showed a similar but much weaker vibration from 5.87 to 6.25 μm.

The ^1H and ^{19}F NMR spectra of the olefinic compounds normally exhibited first-order spectra with characteristic chemical shifts and coupling constants. The vinyl fluorine resonances occurred between ϕ* 108.8 and 142.3 ppm in the ^{19}F NMR spectra and exhibited geminal HCF coupling constants between 77.6 and 88.0 Hz. The magnitude of the HCF coupling is consistent with the values reported pre-

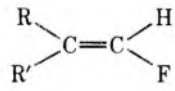
Table III
Structural Assignments, Physical Constants, and Infrared Data for H–F Olefins of the Type



Registry no.	R	R′	Isomer	Bp, °C (mm)	$n^{20}D$	λ, C=C, μm
55904-26-2	C_6H_5	CF_3	Cis	163 (745)	1.4460	5.98
55904-27-3	CF_3	C_6H_5	Trans	149 (745)	1.4456	5.96
55904-28-4	CH_3	C_6H_5	Cis		1.5223	6.00
55904-29-5	C_6H_5	CH_3	Trans		1.5185	5.99
390-75-0	C_6H_5	C_6H_5			1.5902	6.11
16416-47-0				119 (746)	1.4397	5.98
20405-78-1	H	C_6H_5	Cis		1.5259[a]	6.02[a]
20405-77-0	C_6H_5	H	Trans			
55904-30-8	H	C_6F_5	Cis	152 (745)	1.4338	5.97
55904-31-9	C_6F_5	H	Trans	152 (745)	1.4392	6.00
32814-16-7	H	n-C_6H_{13}	Cis	135 (742)[b]	1.4021[b]	5.98
32814-17-8	n-C_6H_{13}	H	Trans		1.4003	5.97

[a] Recorded for a cis:trans (41:59) mixture. [b] Recorded for a cis:trans (32:68) mixture.

Table IV
^{1}H and ^{19}F Nuclear Magnetic Resonance Data[a] for H–F Olefins of the Type



Chemical shifts				Coupling constants, Hz				
R	R′	H	F	J_{HCF}	$J_{H,R}$	$J_{H,R'}$	$J_{F,R}$	$J_{F,R'}$
C_6H_5	CF_3	6.42	112.2	80.1		0		24.7
CF_3	C_6H_5	7.04	124.1	77.9	1.8		8.0	
CH_3	C_6H_5	6.62	124.9	84.3	1.6		5.0	
C_6H_5	CH_3	6.88	132.7	85.4		1.6		3.8
C_6H_5	C_6H_5	6.88	128.7	83.4				
		6.39	142.3	88.0	1.1	1.1	*b*	*b*
H	C_6H_5	6.53	123.0	79.5	5.4		44.0	
C_6H_5	H	7.10	130.5	79.8		11.4		17.9
H	C_6F_5	6.77	108.8	80.4	5.4	~0.5	40.3	*c*
C_6F_5	H	7.47	111.9	81.0	0.7	11.6	*c*	19.6
H	n-C_6H_{13}	6.45	130.9	85.1	4.8	1.4	42.6	1.7
n-C_6H_{13}	H	6.50	130.6	85.4	1.2	11.2	2.0	19.3

[a] ^{1}H and ^{19}F NMR chemical shifts are reported on the δ and ϕ^* scales using internal references Me_4Si and $CFCl_3$, respectively. Similar coupling constants for a compound from the ^{1}H and ^{19}F spectra were averaged and are given in hertz. [b] Nondetectable. [c] Variable and not unequivocally determined.

viously for terminal fluoro olefins.[20–23] When applicable, cis and trans isomer assignments were made on the basis of the magnitude of the coupling of the terminal hydrogen and fluorine atoms with the groups (H, R, or R′) on the vicinal carbon atom. The coupling constants reported in the literature for the following designated cis and trans configurations agreed with the values for similar cases observed in this investigation (cf. Table IV): HC=CH;[23,24] HC=CF;[22,23,25] HC=CCH$_2$;[23] FC=CCH$_2$;[23] CH$_2$CH=;[23] HC=CCF$_3$;[24,26] and FC=CCF$_3$.[22,27,28]

Each olefin was also characterized by mass spectral analysis. All of the mass spectra exhibited molecular ions coincident with those calculated for the respective compounds.

Experimental Section

Infrared spectra were recorded on a Perkin-Elmer 21 spectrophotometer using a neat film of sample, and calibrated vs. a 0.07-mm polystyrene film. Proton NMR spectra were obtained with approximately 10% (w/v) solutions on a Varian A-60 spectrometer and are reported in δ values downfield from an internal standard of tetramethylsilane. Fluorine NMR spectra were obtained with approximately 10% (w/w) solutions on a Varian HA-100 spectrometer at 94.1 MHz and are reported in ϕ^* values upfield from an internal standard of trichlorofluoromethane. Analytical GLC analyses were obtained on a Hewlett-Packard Model 5750 dual column gas chromatograph equipped with 10 ft × 0.25 in. stainless steel columns using helium as a carrier gas. Product yields were determined from comparisons of the relative areas under peaks vs. an appropriate standard, corrected for thermal conductivity differences. Column A was packed with 15% w/w silicone gum rubber, column B with 15% w/w Carbowax 20M, and column C with 10% w/w FS-1265 fluorosilicone rubber. Preparative GLC analyses were obtained with a Varian Aerograph Model 700 gas chromatograph equipped with 10 ft × 0.50 in. stainless steel columns using helium as a carrier gas. Column D was packed with 30% w/w Carbowax 20M, column E with 30% w/w QF-1 fluorosilicone rubber, and column F with 30% w/w silicone gum rubber. All column packings were supported on 80–100 mesh acid-washed Chromosorb P. Carbon and hydrogen analyses were obtained in this laboratory. Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-66 mass spectrometer operated at 70 eV by Dr. Donald A. Wiebe in this department.

Fluoroiodomethane and Methylene Fluoride. The apparatus employed consisted of a 500-ml two-necked round-bottomed flask equipped with a magnetic stirring bar, a Fieser solid addition apparatus, and a water-cooled Friedrichs condenser connected to two traps cooled in ice and in liquid nitrogen followed by a connection to a vacuum pump. The apparatus was dried at 110° prior to use and assembled while warm under a continuous nitrogen flow to exclude moisture. The flask was charged with 599.4 g (2.238 mol) of methylene iodide and the solid addition apparatus with 78.4 g (0.328 mol) of mercuric fluoride. The pressure within the apparatus was reduced to 12–17 mm and the flask was heated with an oil bath at 62–69° while the fluorinating agent was *slowly* added to the rapidly stirred methylene iodide over a 13-hr period. Upon completion of the addition the reaction mixture was allowed to stir for an additional 10 hr at the prescribed conditions. The reaction was terminated and the liquid nitrogen cooled trap was sealed at one end as the other end was connected to a previously weighed trap cooled in a Dry Ice–isopropyl alcohol slush bath. As the liquid nitrogen cooled trap was slowly allowed to warm to 0°, 11.5 g of a volatile material distilled out of this trap and into the trap cooled to −78°. The ir spectrum of this material was identical with that reported for methylene fluoride in the literature,[29] yield 0.221 mol (67.4%) based on mercuric fluoride.

The nonvolatile product (21.3 g, 20.3% crude yield) was combined with two other similarly prepared product mixtures and distilled at atmospheric pressure through a 24-in. Nester-Faust Teflon spinning band column. A total of 68.1 g of pure fluoroiodomethane was obtained, bp 53.2–53.7° (lit.[30] bp 53.4°), n^{20}D 1.4974 (lit.[30] nD 1.4910). The ^{1}H NMR spectrum (neat) exhibited a doublet at δ 6.35 (J_{HCF} = 49.1 Hz). The ^{19}F NMR spectrum (CCl_4) showed a triplet at ϕ^* 191.3 ppm (J_{FCH} = 48.8 Hz).

Fluoromethyltriphenylphosphonium Iodide. A 1-l. one-necked round-bottomed flask fitted with a water-cooled reflux condenser and a magnetic stirring bar was charged with 111.7 g (0.426 mol) of triphenylphosphine, 68.1 g (0.426 mol) of fluoroiodomethane, and 550 ml of dry benzene. The resulting solution was refluxed for 64 hr with moderate stirring. Upon completion of the reaction the white insoluble phosphonium salt was collected on a sintered glass funnel, washed with hot benzene (3 × 200 ml), and dried in a vacuum desiccator at 0.1 mm for 12 hr, yield 154.2 g (0.365 mol, 85.7%), mp 168.4–169.5° dec (reported[5] for fluoromethyltriphenylphosphonium iodide, 169–171°). The ^{1}H NMR spectrum ($CDCl_3$) consisted of a doublet (2 H) at δ 6.84 (J_{HCF} = 44.8, J_{HCP} = 0 Hz) and a complex multiplet (15 H) located at δ 7.54–8.16, peaking at δ 7.78. The ^{19}F NMR spectrum ($CHCl_3$) exhibited a doublet of triplets at ϕ^* 243.6 ppm (J_{FCP} = 58.0, J_{FCH} = 45.8 Hz).

Fluoriodomethyltriphenylphosphonium Iodide. A black 500-ml one-necked round-bottomed flask, equipped with a water-cooled reflux condenser and a magnetic stirring bar, was charged with 104.4 g (0.398 mol) of triphenylphosphine and 165 ml of reagent grade methylene chloride. Fluorodiiodomethane (111.6 g 0.390 mol), previously prepared by the method described by Hine,[31] was shaken with elemental mercury immediately prior to use and then filtered directly into the reaction mixture. The re-

sulting solution was moderately stirred while being heated at 58–60° for 46 hr. Upon completion of the reaction the warm slurry was filtered through a sintered glass funnel and the light canary yellow phosphonium salt was washed with hot methylene chloride (2 × 150 ml) and then with hot benzene (100 ml) before being dried in vacuo over phosphorus pentoxide, yield 123.4 g (0.225 mol 57.7%, 25.4% based on $CHFI_2$), mp 168.8–172.0° dec. The ^1H NMR spectrum (saturated in DMSO-d_6) consisted of an unresolved multiplet at δ 7.62–8.21, peaking at δ 7.86 (15 H), and a doublet of doublets (1 H) at δ 9.19 (J_{HCF} = 44.8, J_{HCP} = 7.8 Hz). The ^{19}F NMR spectrum of this sample exhibited a doublet of doublets at ϕ^* 184.4 ppm (J_{FCP} = 66.0, J_{FCH} = 45.5 Hz).

Anal. Calcd for $C_{19}H_{16}FI_2P$: C, 41.64; H, 2.94. Found: C, 40.16; H, 3.15.

α,α,α-Trifluoroacetophenone. This polyfluorinated ketone was prepared in 57.3% yield by the method of Dishart and Levine.[32]

Zinc–Copper Couple. Zinc–copper couple was prepared by the method of Le Goff.[33]

General Procedure for the Synthesis of Vinyl Fluorides via Pregenerated Fluoromethylenetriphenylphosphorane. The apparatus consisted of a 200-ml three-necked round-bottomed flask equipped with a magnetic stirring bar, a glass stopper, a constant-pressure addition funnel fitted with a nitrogen inlet, and a water-cooled reflux condenser topped with a T joint leading to a mineral oil bubbler. The apparatus was flushed with nitrogen, flame dried, and allowed to cool to room temperature while deaeration with nitrogen was continued.

A typical preparative reaction using the synthesis of 1-hydro-2-phenylperfluoropropene, $C_6H_5C(CF_3)$=CHF, as an example proceeded as follows. The flask was charged with 6.44 g (0.015 mol) of fluoromethyltriphenylphosphonium iodide and 80 ml of dry THF containing 1.12 g (0.012 mol) of toluene. The glass stopper was replaced with a rubber septum and the nitrogen inlet on top of the addition funnel was replaced with a glass stopper. However, the nitrogen atmosphere was maintained throughout the system by connecting the previously exposed T joint atop the condenser to the inert gas source. The slurry of phosphonium salt and solvent was moderately stirred while cooled in a Dry Ice–isopropyl alcohol slush bath. During this cooling process the addition funnel was charged with 10.0 ml (0.015 mol) of 1.53 *N* *n*-butyllithium in hexane. Any appreciable amount of hydrolysis of the organolithium reagent was avoided by maintenance of a constant sweep of nitrogen over the addition funnel when the stopper was removed and by transferring the base via a pipette under a dry nitrogen atmosphere. The base was added dropwise over a 23-min period. Upon completion of the addition, the reaction mixture was stirred for 25 min at −78°. At the end of this period a 1.0-ml aliquot of the reaction mixture was withdrawn under a nitrogen atmosphere and added to 1.0 ml of ethylene bromide with the evolution of heat. GLC analysis of the resulting mixture (column B) indicated that no *n*-butyl bromide was formed, suggesting that all of the *n*-butyllithium had reacted with the phosphonium salt. The reaction was continued for an additional 25 min at −78° and then 3.36 g (0.0193 mol) of α,α,α-trifluoroacetophenone was added. The reaction between the ylide and the carbonyl compound was allowed to proceed for 2 hr at −78° and then for 1.5 hr at room temperature. The reaction mixture was then cooled in ice. Potassium *tert*-butoxide (MSA Research, 1.57 g, 0.0140 mol) was added and the mixture was stirred for 2 hr at 0°. At the end of this period GLC analysis (column B) indicated that 1-hydro-2-phenylperfluoropropene was formed in 50.4% yield (cis:trans 46:54). In addition to the desired products, 17.4% of 1,1,1-trifluoro-2-phenylheptene-2 was also formed (cis:trans 39:61) and some higher boiling materials.

The dark reaction mixture was centrifuged and decanted, and the precipitate was washed with small portions of THF. The decantates were combined and washed with saturated aqueous sodium chloride solutions (3 × 100 ml) until the aqueous layer was neutral to litmus paper. The dried (anhydrous magnesium sulfate) and filtered organic material was concentrated by removal of the solvent through a 6-in. Vigreux column. The residue was flash distilled at reduced pressure through a short-path distillation apparatus and two fractions were collected in Dry Ice cooled receivers. Preparative GLC analysis of fraction I on column D at 136° afforded pure samples of *cis*- and *trans*-1-hydro-2-phenylperfluoropropene. Pure samples of *cis*- and *trans*-1,1,1-trifluoro-2-phenylheptene-2 were isolated from fraction II by preparative GLC analysis on column D at 178°.

General Procedure for the Synthesis of Vinyl Fluorides via Fluoromethylenetriphenylphosphorane Generated in Situ. The apparatus consisted of a 200-ml three-necked round-bottomed flask equipped with a magnetic stirring bar, a Schlenk solids addition tube, a glass stopper, and an air-cooled reflux condenser topped with a T joint connected to a nitrogen source and to a mineral oil bubbler. The assembled apparatus was simultaneously deaerated with nitrogen and flame dried and then allowed to cool to room temperature while a slow sweep of nitrogen was maintained.

A typical preparative reaction using the synthesis of α,β-dihydrohexafluorostyrene, C_6F_5CH=CHF, as an example proceeded as follows. Fluoroiodomethyltriphenylphosphonium iodide (27.41 g, 0.0500 mol), purified pentafluorobenzaldehyde (Peninsular Chem-Research, 9.80 g, 0.05 mol), toluene (3.00 ml, 2.60 g, 0.0282 mol), and 150 ml of dry DMF were placed into the reaction flask. The flask was cooled to 0° as the Schlenk solids addition tube was charged with 4.90 g (0.0750 g-atom) of zinc–copper couple. The cold solution was rapidly stirred as the couple was added in one portion. The reaction was allowed to proceed for 45 min at 0°, at which time GLC analysis on column C indicated that all of the carbonyl compound had been consumed. The reaction mixture was stirred for 45 min and then filtered with nitrogen pressure through a Schlenk fritted funnel. An aliquot of the filtrate was withdrawn and analyzed on column C vs. a standard solution of α,β-dihydrohexafluorostyrene and toluene in ether, yield 65.0% (cis:trans 54:46).

The apparatus was rinsed with ether (2 × 50 ml) and the washes were passed through the funnel. The organic materials were combined and added to 75 ml of water with the evolution of heat. The mixture was steam distilled and upon completion of the distillation the flask appeared to be etched. The distillate was saturated with sodium chloride and extracted with ether (3 × 100 ml). The extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated by removal of the solvent through a 6-in. Vigreux column. The residue was then flash distilled at reduced pressure through a short-path distillation apparatus. GLC analysis of the distillate on column C indicated that the trans isomer was significantly consumed during the work-up procedures (cis:trans 80:20), presumably owing to its susceptibility to hydrolysis. Pure samples of *cis*- and *trans*-α,β-dihydrohexafluorostyrene were isolated from the flash distillate by preparative GLC analysis on column E at 90°.

Acknowledgment. We are indebted to Mr. Gregory Wheaton for the lithium diisopropylamide experiment.

Registry No.—Fluoroiodomethane, 373-53-5; methylene fluoride, 75-10-5; fluoromethyltriphenylphosphonium iodide, 28096-32-4; triphenylphosphine, 603-35-0; fluoroiodomethyltriphenylphosphonium iodide, 55904-32-0; fluorodiiodomethane, 1493-01-2; α,α,α-trifluoroacetophenone, 434-45-7; fluoromethylenetriphenylphosphorane (uncharged species), 28096-33-5; fluoromethylinetriphenylphosphorane (charged species), 28096-34-6; pentafluorobenzaldehyde, 653-37-2.

References and Notes

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A Rapid Method of Preparation of Phospholanium Perchlorates via Intramolecular Cyclizations of 4-Hydroxybutylorganophosphines[1]

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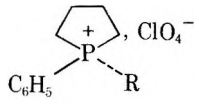
A rapid synthetic procedure for the preparation of phospholanium perchlorates in high yield has been developed. The process involves the cleavage of tetrahydrofuran by lithium organophosphides, affording 4-hydroxybutylorganophosphines, which are then intramolecularly cyclized in an aqueous solution. The following phospholanium salts (very tediously prepared by other methods) have been obtained by this procedure: methylphenyl-, ethylphenyl-, *n*-propylphenyl-, *n*-butylphenyl-, and diphenylphospholanium perchlorate. Evidence is also presented to show that cleavage of THF by diethylphenylphosphine and lithium metal afforded not only the expected diethyl-4-hydroxybutylphosphine, but also ethyl-4-hydroxybutylphenylphosphine. Confirmation of this was obtained in the form of subsequent intramolecular cyclization of these phosphines to the corresponding diethylphospholanium perchlorate and ethylphenylphospholanium perchlorate. Extension of this synthetic procedure to tetrahydropyran also afforded the desired phosphorinanium perchlorate in good yield.

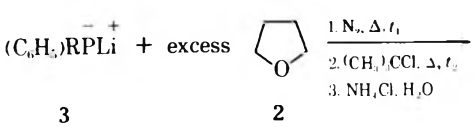
Historically, phospholanium salts have been prepared by quaternization of a selected phospholane with an alkyl halide.[3] Although the quaternization procedures generally afforded the desired salts in high yield, major drawbacks to this approach have been centered around the synthesis of the initial phospholanes,[4] which have been recently reviewed.[3,5,6] In order to alleviate this necessity of first preparing the phospholane, we have developed a process involving the cleavage of a cyclic ether by lithium organophosphides to yield γ-hydroxyalkylorganophosphines, which were intramolecularly cyclized to the desired alkylphenylphospholanium salts **1** in high yield. The initial step



1

R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, C_6H_5

in the synthetic sequence involved the cleavage of tetrahydrofuran **2** by a lithium alkylphenylphosphide **3**, generated in situ from the corresponding diphenylalkylphosphines and lithium metal,[7] to yield the necessary alkyl-4-hydroxybutylphenylphosphines **4**.



3 **2**

$(C_6H_5)RP(CH_2)_4OH$

4

R = CH_3, C_2H_5, *n*-C_3H_7, *n*-C_4H_9, C_6H_5

This cleavage of cyclic ethers **5** by alkali organophosphides **6** has been previously shown to afford the corresponding γ-hydroxyalkylorganophosphines **7**, although the yields reported were quite variable.[8-15] A variety of substituted cyclic ethers such as propylene oxide, styrene oxide, and cyclohexene oxide have also been utilized.[8] Most of the alkali organophosphides **6** studied have been symmetric, i.e., the organic substituents of the phosphide have been dimethyl,[13] diethyl,[8] diphenyl, etc.[8,11] In the present work, the lithium organophosphides **3** have been *dissymmetric*, except in the case of the diphenyl derivative, and have afforded the dissymmetric 4-hydroxybutylalkylphenylphosphines **4** (Table I). The cleavage of tetrahydrofuran by

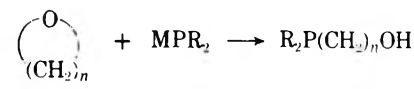
Table I
Preparation of 4-Hydroxybutylalkylphenylphosphines 4 via Lithium Organophosphides and Tetrahydrofuran

$(C_6H_5)RP(CH_2)_4OH$

4

R	t_1, hr[a]	t_2, hr[b]	Bp, °C (mm)	Yield, %	Registry no.
CH_3	12	12	87–89 (0.10)	86	55759-63-2
C_2H_5	12	24	121–124 (0.15)	86	54807-90-8
n-C_3H_7	48	12	126–128(0.35)	73	55759-64-3
n-C_4H_9	48	12	135–137 (0.10)	78	55759-65-4
C_6H_5	48	12	160–164 (0.20)	73	7526-70-7

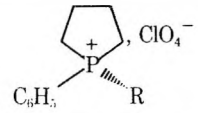
[a] Time of reflux before addition of $(CH_3)_3CCl$. [b] Time of reflux after addition of $(CH_3)_3CCl$.



5 **6** **7**

n = 2, 3, 4, 5 M = Li, K
R = dialkyl or diaryl

Table II
Preparation of Phospholanium Salts 1 via Intramolecular Cyclizations of 4-Hydroxybutylorganophosphines 4

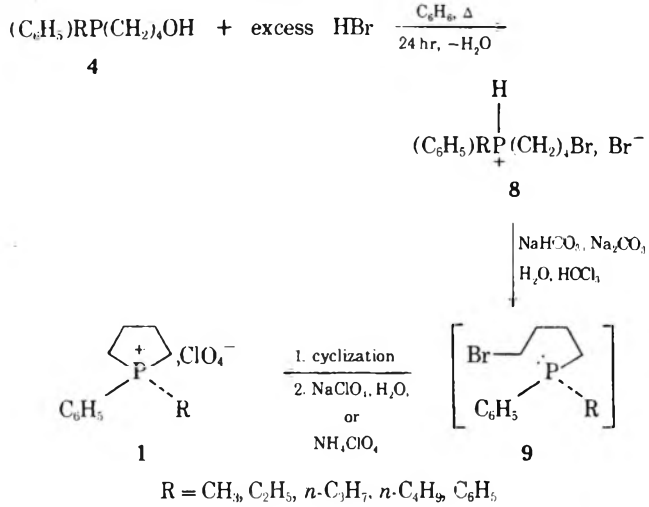


R	Mp, °C	Yield, %[a]	Molecular formula	Anal., % P	Registry no.
CH_3	75–77	74	$C_{11}H_{16}ClO_4P$	Calcd 11.11 Found 10.88	55759-67-6
C_2H_5	81–83	90	$C_{12}H_{18}ClO_4P$	Calcd 10.58 Found 10.78	55759-69-8
n-C_3H_7	96–97	81	$C_{13}H_{20}ClO_4P$	Calcd 10.10 Found 10.08	55759-71-2
n-C_4H_9[b]	54–55.5	75	$C_{14}H_{22}ClO_4P$	Calcd 9.66 Found 9.41	55759-73-4
C_6H_5	112–113.5[c]	71	$C_{16}H_{18}ClO_4P$	Calcd 9.09 Found 9.04	55759-75-6

[a] Overall yields for the reactions based on the amount of initial 4-hydroxybutylorganophosphine 4. Mass spectral data (determined with a CEC Model 21 HR unit) are available upon request. [b] See ref 26. [c] Lit. mp 114–115° (ref 27).

the bulkier (R = n-C_3H_7, n-C_4H_9) lithium organophosphides or the resonance-stabilized lithium diphenylphosphide was found to be very dependent upon the length of time of the reflux. If shorter reaction times comparable to the methyl and ethyl derivatives were employed, a considerable amount of the unreacted phosphide remained as noted by the isolation of a mixture of the corresponding secondary phosphines $(C_6H_5)RPH$, secondary phosphine oxides, and phosphinic acids. With lithium diphenylphosphide, a large quantity of diphenylphosphine was isolated after reaction times comparable to the methyl and ethyl derivatives. This observation is in agreement with earlier work in which after only 7 hr of boiling in THF, lithium diphenylphosphide afforded only 22% of the 4-hydroxybutyldiphenylphosphine along with diphenylphosphine and diphenylphosphinic acid.[11] Although the cleavage of THF by the phenyllithium coproduct is not expected under normal conditions,[16] it was deemed necessary in the present study to selectively remove this product by the addition of *tert*-butyl chloride[17] owing to the requirements of vigorous reflux and extended reaction times for the phosphide–ether cleavage reaction to occur.

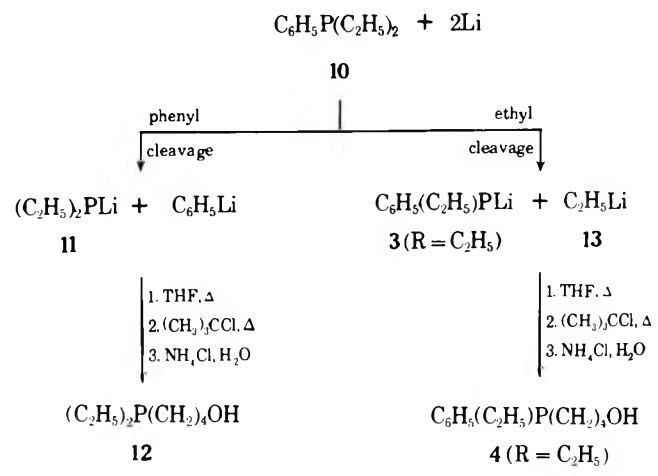
Once the 4-hydroxybutylorganophosphines 4 had been obtained, the next step involved the conversion of these phosphine alcohols to 4-halobutylorganophosphonium hydrobromides 8, which were then *intramolecularly cyclized* via generation in situ of the 4-halobutylorganophosphines 9, to the desired phospholanium salts 1. The conversion of



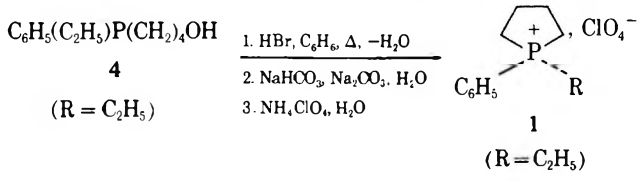
4 to the haloalkylphosphonium hydrobromide 8 was markedly facilitated by the continual removal of the water formed. The hydrobromides 8, although isolated, were not characterized, since they were generally found to be very hygroscopic. Rather 8 was quickly dissolved in a minimum of chloroform and treated with a dilute solution of aqueous sodium bicarbonate and sodium carbonate.[18] Surprisingly the cyclization occurred in the *aqueous layer* in all cases. Confirmation of this was obtained by the observation that after mixing the solutions for 15 min, separation of the layers was effected. Upon standing at room temperature for 48 hr, the aqueous layer was treated with a saturated sodium or ammonium perchlorate solution and 1 precipitated (Table II). In every case <10% of 1 was obtained from the chloroform layer upon work-up. Intramolecular cyclizations of this type are rare but not unknown.[19–23] However, the application of this technique for the preparation of phospholanium salts 1 via the 4-hydroxybutylorganophosphines has *not* been previously reported. Examination of Table II reveals the procedure to be superior, since the yields recorded were for the overall multistep sequence of 4 to 1 and were based upon the initial quantity of 4.

Earlier reports have indicated that cleavage of diethylphenylphosphine (10) by lithium metal resulted in formation of lithium diethylphosphide (11), whereas cleavage by potassium afforded potassium ethylphenylphosphide.[15,24] Thus, if applied to the cleavage of THF, diethylphenylphosphine (10) and lithium metal would be expected to give diethyl-4-hydroxybutylphosphine (12). Upon treatment of diethylphenylphosphine with lithium metal in THF, a dark green color developed which was considered an indication that lithium diethylphosphide (11) formed (Scheme I). This tentative conclusion was based on the earlier literature results[15,24] and the observations that with the diphenylalkylphosphines, formation of the lithium alkylphenylphosphides 3 produced a dark red color. The resulting dark-colored solution was vigorously boiled for 96 hr with subsequent treatment of *tert*-butyl chloride. However, the isolation of the products afforded the expected diethyl-4-hydroxybutylphosphine (12, 33.3%), recovered diethylphenylphosphine (10, 20.3%), *plus* ethyl-4-hydroxybutylphenylphosphine (4, R = C_2H_5, 26.3%). The latter product apparently resulted from the cleavage of diethylphenylphosphine (10) by lithium to form C_2H_5Li (13) and $C_6H_5(C_2H_5)PLi$ (3, R = C_2H_5). Besides the spectral analyses, additional confirmation that 4 (R = C_2H_5) had been

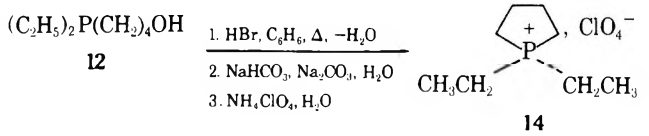
Scheme I



formed was afforded when a portion of this fraction was subjected to the intramolecular cyclization procedure to yield ethylphenylphospholanium perchlorate (**1**, R = C_2H_5, 84%). Treatment of the diethyl-4-hydroxybutylphosphine

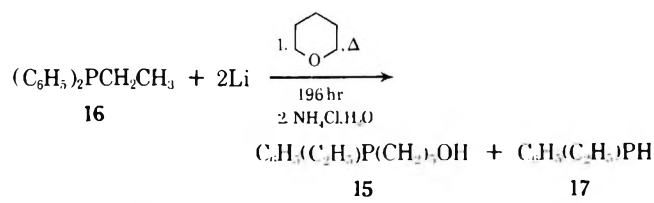


(**12**) by a similar procedure afforded the desired diethylphospholanium perchlorate (**14**, 85%). Thus, although the

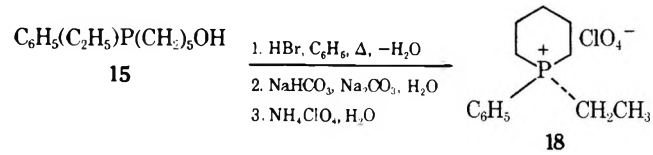


initial partial cleavage of diethylphenylphosphine by lithium afforded predominantly lithium diethylphosphide (**11**) based on the earlier reports[15,24] and our initial color observations, apparently a competitive reaction of ethyl–P vs. phenyl–P bond cleavage resulted under the conditions of vigorous reflux and long reaction time.

This synthetic procedure has also been extended to another ether system, tetrahydropyran (THP). Treatment of THP with diphenylethylphosphine and lithium under an extended reflux period (196 hr) did afford the desired ethyl-5-hydroxypentylphenylphosphine (**15**) but only in a yield of 13.4%. Besides a considerable amount of recovered starting phosphine **16** (38.8%), ethylphenylphosphine (**17**) was also isolated (38.4%). Thus, based on these observa-



tions, the initial C–P cleavage in phosphine **16** by lithium to afford the lithium ethylphenylphosphide (**3**) did not occur as readily in THP as compared to THF (almost 40% recovered phosphine in THP case). Apparently, the phosphide, once formed, is not sufficiently basic and/or nucleophilic in THP to facilitate ether cleavage (appreciable amount of secondary phosphine isolated). This latter point may be more dependent upon the coordination ability of THP with the lithium ethylphenylphosphide as compared with that of THF, rather than the reactivity of the phosphide itself. Our results appear in good agreement with the previous report that, after 13.5 hr of vigorous boiling, lithium diphenylphosphide cleaved THP in a low yield (4%).[11] The ethyl-5-hydroxypentylphenylphosphine (**15**), however, was subjected to our intramolecular cyclization procedure and *did afford* the desired ethylphenylphosphorinanium perchlorate (**18**, 50.4%).



This study has revealed a convenient and rapid procedure for the preparation of cyclic phosphonium salts in high yield based on the cleavage of cyclic ethers, THF and THP, by lithium organophosphides. The intermediate γ-hydroxyalkylorganophosphines can be isolated and subsequently cyclized to the desired salts. Work is continuing in this area.

Experimental Section

General Procedure. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-5A unit as thin films for 4 and as KBr pellets for 1. ^1H NMR and ^{31}P NMR spectra were obtained with a XL-100(15) Varian spectrometer with Me_4Si as internal standard unless otherwise indicated. Anhydrous THF and tetrahydropyran were obtained fresh for each cleavage reaction by distillation from NaH immediately before use.

Starting Materials. The initial starting phosphines $(C_6H_5)_2PR$ were easily prepared via the appropriate Grignard reaction on $(C_6H_5)_2PCl$.[25] Triphenylphosphine was from a commercially available source. Diethylphenylphosphine was prepared hy the reaction of ethylmagnesium bromide on $C_6H_5PCl_2$.[25]

Since the procedures for the preparation of the 4-hydroxybutylalkylphenylphosphines **4** [derived from $(C_6H_5)_2PR$] were identical except for the time of reaction as indicated in Table I, only the preparation of ethyl-4-hydroxybutylphenylphosphine will be described in detail. A similar approach will be used for the description of the preparation of the phospholanium salts **1** given in Table II.

Ethyl-4-hydroxybutylphenylphosphine (4, R = C_2H_5). Diphenylethylphosphine (21.4 g, 0.10 mol) and lithium shavings (1.4 g, 0.02 g-atom) in 200 ml of anhydrous THF were stirred at room temperature under N_2 until the dark-red color persisted (~1 hr). The mixture was heated at vigorous reflux for 12 hr with the disappearance of the lithium shavings. After cooling to room temperature, *tert*-butyl chloride (9.3 g, 0.10 mol) was added, and the mixture was boiled for an additional 24 hr with a color change to a reddish-orange. This mixture was then cooled, hydrolyzed (5.9 g, 0.11 mol, NH_4Cl in 50 ml of H_2O), saturated (NaCl), and extracted (3 × 150 ml) with benzene. The organic extracts were dried ($MgSO_4$) and evaporated to an oil on a rotary evaporator. Distillation of the residual oil under reduced pressure through a short-path Vigreux column afforded 18.0 g (86%) of ethyl-4-hydroxybutylphenylphosphine (**4**, R = C_2H_5): bp 121–124° (0.15 mm); ir (film) ν 3283 (OH), 1583 (C_6H_5), 1050 (C–O), 733 and 695 cm^{-1} (C_6H_5); ^1H NMR ($DCCl_3$) δ 0.98 (d of t, J_{PCCH} = 16, J_{HCCH} = 7 Hz, 3 H, CH_3CH_2P), 1.22–1.84 (m, 8, $CH_3CH_2PCH_2CH_2CH_2CH_2OH$), 3.20 (s, broad, 1, OH), 3.50 (t, J_{HCCH} = 6 Hz, 2, CH_2OH), and 7.20–7.60 (m, 5, ArH). The data of other 4-hydroxybutylalkylphenylphosphines **4** prepared by a similar procedure are given in Tables I and III.

Ethylphenylphospholanium Perchlorate (1, R = C_2H_5). A solution of 5.65 g (0.027 mol) of ethyl-4-hydroxybutylphenylphosphine (**4**, R = C_2H_5) in 50 ml of benzene was added to 75 ml of a saturated benzene solution of anhydrous HBr with immediate formation of a white slurry. This mixture was vigorously boiled for 12 hr with continual removal of the H_2O (ca. 0.5 ml) formed (Dean-Stark trap). After resaturation of the mixture with HBr (bubbling in at 20 ml/min for 10 min), the boiling was continued for an additional 12 hr. The benzene was concentrated via distillation to a volume of ~25 ml. Upon cooling to room temperature, the residual slurry was triturated with 75 ml of hexane and resulted in the formation of a white precipitate. This very hygroscopic solid was col-

Table III
Spectral Properties of 4-Hydroxybutylalkylphenylphosphines 4[a]
$(C_6H_5)RP(CH_2)_4OH$

R	Ir absorption spectra, selected bands, cm^{-1} [b]	^1H NMR spectral assignments, chemical shifts, δ, ppm
CH_3[c]	3300 (OH), 1059 (C–O), 737 and 693 (C_6H_5)	1.19 (d, J_{PCH} = 3 Hz, 3, CH_3P), 1.30–1.80 [m, broad, 6, $(CH_2)_3$-P], 3.53 (t, broad, 2, CH_2OH), 4.42 (s, broad, 1 OH), 7.12–7.60 (m, 5, ArH)[d]
n-C_3H_7[e]	3285 (OH), 1577 (C_6H_5), 1065 (C–O), 749 and 696 (C_6H_5)	0.94 [t, J_{HCCH} = 6 Hz, $CH_3(CH_2)_2P$], 1.10–1.82 [m, 10, CH_3-$(CH_2)_2P$ and $P(CH_2)_3$-CH_2OH], 3.10 (s, broad, 1, OH), 3.51 (t, J_{HCCH} = 6 Hz, 2, CH_2OH), 7.16–7.60 (m, 5, ArH)[f]
n-C_4H_9[c]	3276 (OH), 1584 (C_6H_5), 1066 (C–O), 744 and 702 (C_6H_5)	0.83 [t, J_{HCCH} = 7 Hz, 3, $CH_3(CH_2)_3P$], 1.10–1.86 [m, 12, $CH_3(CH_2)_3P$ and P-$(CH_2)_3CH_2OH$], 3.22 (s, 1, OH), 3.50 (t, J_{HCCH} = 6 Hz, 2, CH_2OH), 7.20–7.62 (m, 5, ArH)[f]
C_6H_5[g]	3259 (OH), 1584 (C_6H_5), 1067 (C–O), 741 and 700 (C_6H_5)	1.10–1.80 (m, 4, PCH_2-$CH_2CH_2CH_2CH$), 2.04 (m, 2, PCH_2), 2.52 (s, 1, OH), 3.51 (t, J_{HCCH} = 6 Hz, CH_2-OH), 7.14–7.52 (m, 10, ArH)[f]

[a] Other properties in addition to yields are found in Table I. [b] The spectra were obtained as thin films between NaCl plates. [c] Cleavage reaction conducted on a scale of 0.10 mol of phosphine. [d] This spectrum was obtained on a neat sample with Me_4Si as internal standard. [e] Cleavage reaction conducted on a scale of 0.052 mol of phosphine. [f] Spectrum was obtained as a solution in $DCCl_3$ with Me_4Si as internal standard. [g] Cleavage reaction conducted on a scale of 0.05 mol of phosphine.

lected by vacuum filtration, dissolved in 75 ml of chloroform, transferred to a separatory funnel, and treated with 75 ml of a 5% $NaHCO_3$ solution (with 5 g of Na_2CO_3 added) for 15 min under N_2 in the standard manner, and the layers were separated. After reextraction of the aqueous layer (2 × 100 ml) with chloroform, the aqueous layer was stoppered and set aside at room temperature for 48 hr.[18] Combination of the chloroform extracts, drying ($MgSO_4$), and boiling for 12 hr under N_2 afforded, after removal of solvent and trituration with a saturated $NaClO_4$ solution, 0.1 g of the desired product.

Treatment of the aqueous layer with 50 ml of a saturated $NaClO_4$ solution gave the desired product as a white precipitate.[26] Recrystallization from absolute C_2H_5OH–$(C_2H_5)_2O$ (1:3) yielded 7.1 g (90%) of the phospholanium salt 1 (R = C_2H_5): mp 81–83°; ir (KBr pellet) ν 1588 (C_6H_5), 1068 (ClO_4^-), 739 and 687 cm^{-1} (C_6H_5); ^1H NMR ($DCCl_3$) δ 1.23 (d of t, J_{PCCH} = 20, J_{HCCH} = 8 Hz, 3, CH_3CH_2P), 2.23 (m, 4, β-CH_2CH_2 of ring), 2.71 (m, 6, CH_3CH_2P and CH_2PCH_2 of ring), 7.50–8.06 (m, 5, ArH). ^{31}P NMR (40.5 MHz, 12% in $HCCl_3$) δ −51.39 ppm relative to 85% H_3PO_4. Additional analytical data are given in Table II. The data of other phospholanium perchlorates prepared by a similar procedure are given in Tables II and IV.

Cleavage of THF with Diethylphenylphosphine and Lithium Metal. Diethylphenylphosphine (12.3 g, 0.074 mol) and lithium shavings (1.05 g, 0.15 g-atom) in 200 ml of anhydrous THF were stirred at room temperature under N_2 with the appearance of a dark green color (~1 hr). The mixture was heated at reflux for 96 hr, cooled to room temperature, treated with *tert*-butyl chloride (6.85 g, 0.074 mol), and boiled for an additional 12 hr with formation of a white slurry. This mixture was then cooled, hydrolyzed (4.0 g, 0.074 mol, NH_4Cl in 50 ml of H_2O), and extracted (3 × 100 ml) with benzene. The organic extracts were dried ($MgSO_4$) and the solvents were removed via distillation under N_2. Distillation of the resultant oil under reduced pressure on an 18-in. stainless steel spinning band afforded four fractions: (1) bp 62–65° (3.0 mm), 2.5 g (20.3%) of recovered diethylphenylphosphine (**10**); ^1H NMR ($DCCl_3$) δ 0.95 (d of t, J_{PCCH} = 16, J_{HCCH} = 7 Hz, 6, CH_3CH_2P), 1.62 [m, 4, $(CH_3CH_2)_2P$], 7.10–7.62 (m, 5, ArH); (2) bp 75–78° (3.3 mm), 4.0 g (33.3%) of diethyl-4-hydroxybutylphosphine (**12**); ir (film) ν 3300 (OH), 2925 (CH), 1040 cm^{-1} (C-O); ^1H NMR ($DCCl_3$) δ 1.03 (d of t, J_{PCCH} = 14, J_{HCCH} = 7 Hz, 6, CH_3CH_2P), 1.25–1.90 [m, 10, $(CH_3CH_2)_2P$ and $PCH_2CH_2CH_2CH_2OH$], 3.58 (t, 2, CH_2OH), 3.68 (s, 1, OH); (3) bp 98–100° (0.05 mm), 4.1 g (26.3%) of ethyl-4-hydroxybutylphenylphosphine (4, R = C_2H_5); ir (film) ν 3290 (OH), 1586 (C_6H_5), 1049 (C-O), 735 and 695 cm^{-1} (C_6H_5); ^1H NMR ($DCCl_3$) δ 0.95 (d of t, J_{PCCH} = 16, J_{HCCH} = 7 Hz, 3, CH_3CH_2P), 1.15–2.0 (m, 8, CH_3CH_2P and $PCH_2CH_2CH_2OH$), 3.55 (t, 2, CH_2OH), 4.37 (s, 1, OH), 7.10–7.78 (m, 5, ArH); (4) bp 110–115° (0.05 mm), 2.0 g of a mixture tentatively identified as diethyl-4-hydroxybutylphosphine oxide (major) and diethylphenylphosphine oxide (minor).

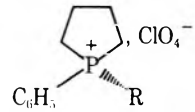
Diethylphospholanium Perchlorate (14). A solution of 2.5 g (0.0154 mol) of diethyl-4-hydroxybutylphosphine in 50 ml of benzene was added to 100 ml of a saturated benzene solution of anhydrous HBr with formation of a white slurry. This mixture was boiled for 12 hr with the continual removal of H_2O (ca. 0.3 ml) (Dean-Stark trap). After resaturation of the mixture with HBr (bubbling in at 20 ml/min for 10 min), the boiling was continued for an additional 12 hr. After the benzene was evaporated via distillation to a volume of ~25 ml and the mixture was cooled to room temperature, the resultant slurry was triturated with 125 ml of hexane with formation of a white precipitate. After decantation of the solvents, this solid was treated with 125 ml of a 5% $NaHCO_3$ solution (with 3 g of Na_2CO_3 added) for 12 hr under N_2 at ~80°. This clear aqueous solution was cooled to room temperature and treated with 75 ml of a saturated NH_4ClO_4 solution with the appearance of some turbidness. This mixture was concentrated in vacuo to a volume of ~50 ml and extracted (5 × 100 ml) with chloroform.[28] The combination of chloroform extracts were dried ($MgSO_4$) and then concentrated in vacuo to afford a white solid. Recrystallization from absolute C_2H_5OH–$(C_2H_5)_2O$ (2:1) yielded 3.2 g (85%) of diethylphospholanium perchlorate (**14**): mp 248–250°; ir (KBr pellet) ν 2950 (CH), 1077 (ClO_4^-), also bands at 1453, 1403, 858, 787, and 754 cm^{-1}; ^1H NMR ($DCCl_3$ + 3 drops of F_3CCO_2H) δ 1.29 (d of t, J_{PCH} = 20, J_{HCCH} = 7 Hz, 6, CH_3CH_2P), 1.88–2.54 (m, 12, $CH_2CH_2PCH_2CH_2$ and CH_3CH_2P); ^{31}P NMR (40.5 MHz, 12% in $HCCl_3$–F_3CCO_2H) δ −58.75 ppm relative to 85% H_3PO_4.

Anal. Calcd for $C_8H_{18}ClO_4P$: P, 12.66. Found: P, 12.35.

Ethylphenylphospholanium Perchlorate (1, R = C_2H_5). Confirmation of Ethyl-4-hydroxybutylphenylphosphine Isolated in Diethylphenylphosphine–THF Cleavage Reaction. The procedure was as described above for diethylphospholanium perchlorate with 2.5 g (0.0119 mol) of ethyl-4-hydroxybutylphenylphosphine (fraction 3 of diethylphenylphosphine–THF cleavage reaction) in 150 ml of a saturated benzene solution of HBr. With work-up identical with that previously described, treatment of the aqueous layer with 75 ml of a saturated NH_4ClO_4 solution gave a turbid mixture. The aqueous mixture was concentrated in vacuo to ~75 ml and extracted with 4 × 100 ml of chloroform. The chloroform extracts were combined and dried ($MgSO_4$), and the solvent was removed in vacuo to afford a white solid. Recrystallization from absolute C_2H_5OH–$(C_2H_5)_2O$ (1:3) yielded 2.9 g (84%) of ethylphenylphospholanium perchlorate (1, R = C_2H_5): mp 81–83°; mmp [with authentic sample of 1 (R = C_2H_5) as prepared previously] 80.5–82.5°; ir (KBr pellet) ν 1588 (C_6H_5), 1070 (ClO_4^-), 740 and 687 cm^{-1} (C_6H_5); ^1H NMR ($DCCl_3$) δ 1.23 (d of t, J_{PCCH} = 20, J_{HCCH} = 8 Hz, 3, CH_3CH_2P), 2.22 (m, 4, β-CH_2CH_2 of ring), 2.70 (m, 6, CH_2PCH_2 and PCH_2CH_3), 7.50–8.06 (m, 5, ArH).

Ethyl-5-hydroxypentylphenylphosphine (15). Diphenylethylphosphine (21.4 g, 0.10 mol) and lithium shavings (1.4 g, 0.20 g-atom) in 100 ml of anhydrous tetrahydropyran were stirred at room temperature under N_2 until the dark red color persisted (~1

Table IV
Spectral Data of Phospholanium Perchlorates 1[a]



R	Ir absorption spectra, selected bands, cm^{-1} [b]	^1H NMR spectral assignments, chemical shifts, δ, ppm	$^{31}P_{(\delta)}$ [c]
CH_3 [d]	1617 (C_6H_5), 1092 (ClO_4^-), 717 and 687 (C_6H_5)	2.23 (d, J_{PCH} = 14 Hz, 3, CH_3P), 2.26 (m, 4, β-CH_2CH_2 of ring), 2.62 (m, 4, CH_2PCH_2), 7.70 (m, 5, ArH)[e]	−44.26
n-C_3H_7 [f]	1588 (C_6H_5), 1090 (ClO_4^-), 740 and 693 (C_6H_5)	1.06 [t, J_{HCCH} = 7 Hz, 3, $CH_3(CH_2)_2P$], 1.57 (m, 2, $CH_3CH_2CH_2$), 2.15 (m, 4, β-CH_2CH_2 of ring), 2.66 (m, 6, CH_2PCH_2 and $PCH_2CH_2CH_3$), 7.48–8.02 (m, 5, ArH)[g]	−49.09
n-C_4H_9 [h]	1575 (C_6H_5), 1070 (ClO_4^-), 748 and 790 (C_6H_5)	0.87 [t, J_{HCCH} = 7 Hz, 3, $CH_3(CH_2)_4P$], 1.48 (m, 4, $CH_3CH_2CH_2CH_2P$), 2.21 (m, 4, β-CH_2CH_2 of ring), 2.66 [m, 6, CH_2PCH_2 and $PCH_2(CH_2)_2CH_3$], 7.50–8.10 (m, 5, ArH)[g]	−49.22
C_6H_5 [i]	1587 (C_6H_5), 1089 (ClO_4^-), 730 and 694 (C_6H_5)	2.30 (m, 4, β-CH_2CH_2 of ring), 3.01 (m, 4, CH_2PCH_2), 7.48–7.98 (m, 10, ArH)[g]	−44.34

[a] Additional analytical data are given in Table II. [b] The spectra were obtained on samples (4 mg) with KBr (400 mg) pellets. [c] The spectra were obtained at 40.5 MHz on 12% solutions in $HCCl_3$ with resonance positions given in parts per million relative to 85% H_3PO_4. [d] Cyclization procedure conducted on a scale of 0.028 mol of 4 (R = CH_3) with recrystallization from absolute C_2H_5OH-$(C_2H_5)_2O$ (1:3). [e] Spectrum was obtained as a solution in $DCCl_3$ with 3 drops of F_3CCO_2H added and Me_4Si as internal standard. [f] Cyclization procedure conducted on a scale of 0.022 mol of 4 (R = n-C_3H_7) with recrystallization from absolute C_2H_5OH-$(C_2H_5)_2O$ (1:3). [g] Spectrum was obtained as a solution in $DCCl_3$ and Me_4Si as internal standard. [h] Cyclization procedure conducted on a scale of 0.021 mol of 4 (R = n-C_4H_9) with recrystallization from absolute C_2H_5OH-$(C_2H_5)_2O$ (1:4). [i] Cyclization procedure conducted on a scale of 0.018 mol of 4 (R = C_6H_5) with recrystallization from absolute C_2H_5OH-$(C_2H_5)_2O$ (1:3).

hr). The mixture was heated at vigorous reflux for 24 hr, cooled to room temperature, treated with 9.3 g (0.10 mol) of *tert*-butyl chloride, and boiled for an additional 172 hr with formation of a reddish-orange slurry. This mixture was then cooled, hydrolyzed [5.9 g (0.11 mol) of NH_4Cl in 50 ml of H_2O], and extracted (3 × 150 ml) with diethyl ether. The ether extracts were dried ($MgSO_4$) and the solvents were removed via distillation under N_2. Distillation of the residual oil under reduced pressure on an 18-in. stainless steel spinning band afforded three fractions: (1) bp 43–45° (1.5 mm), 5.3 g (38.4%) of ethylphenylphosphine (**17**); ^1H NMR ($DCCl_3$) δ 0.98 (d of t, J_{PCCH} = 13, J_{HCCH} = 8 Hz, CH_3CH_2P), 1.60 (m, 2, CH_3CH_2P), 4.02 (d of t, J_{PH} = 204, J_{HPCH} = 7 Hz, 1, PH), 7.02–7.60 (m, 5, ArH);[29] (2) bp 88–91° (0.1 mm) [lit.[30] bp 108–111° (0.3 mm)], 8.1 g (38.8%) of recovered diphenylethylphosphine (**16**), ^1H NMR ($DCCl_3$) δ 0.96 (d of t, J_{PCCH} = 16, J_{HCCH} = 7 Hz, 3, CH_3CH_2P), 1.90 (m, 2, CH_3CH_2P), 7.0–7.56 (m, 10, ArH); (3) bp 120–122° (0.2 mm), 3.0 g (13.4%) of **15**; ir (film) ν 3283 (OH), 1588 (C_6H_5), 1045 (C–O), 735 and 694 cm^{-1} (C_6H_5); ^1H NMR (C_6D_6) δ 0.92 (m, 3, CH_3CH_2P), 1.2–2.0 (m, 10, CH_3CH_2P and $PCH_2CH_2CH_2CH_2CH_2OH$), 3.16 (s, broad, 1, OH), 3.50 (t, broad, 2, CH_2OH), 7.0–7.80 (m, 5, ArH).

Ethylphenylphosphorinanium Perchlorate (18). A solution of 2.5 g (0.011 mol) of ethyl-5-hydroxypentylphenylphosphine in 50 ml of benzene was added to 150 ml of a saturated benzene solution of anhydrous HBr. This mixture was vigorously boiled for 24 hr with continual removal of the H_2O (ca. 0.2 ml) formed. After resaturation of the mixture with HBr, the boiling was continued for an additional 24 hr. The benzene mixture was concentrated via distillation to ~25 ml, cooled to room temperature, and triturated with 125 ml of hexane with formation of a white precipitate. After decantation of the solvents, the solid was treated with 125 ml of a 5% $NaHCO_3$ solution (with 3 g of Na_2CO_3 added) and the resulting solution was boiled for 24 hr under N_2. This solution was cooled to room temperature, treated with 50 ml of a saturated NH_4ClO_4 solution (turbidness developed), and extracted (3 × 150 ml) with chloroform. The chloroform extracts were dried ($MgSO_4$) and solvent was removed in vacuo, affording a white solid. Recrystallization from absolute C_2H_5OH-$(C_2H_5)_2O$ (1:2) yielded 1.7 g (50.4%) of **18**: mp 143.5–144.5°; ir (KBr pellet) ν 1590 (C_6H_5), 1076 (ClO_4^-), 743 and 693 cm^{-1} (C_6H_5); ^1H NMR ($DCCl_3$) δ 1.12 (d of t, J_{PCCH} = 20, J_{HCCH} = 7 Hz, 3, CH_3CH_2P), 1.46–2.34 (m, 6, β- and γ-CH_2 of the ring), 2.34–3.06 (m, 6, CH_2PCH_2 and CH_3CH_2P), 7.56–8.08 (m, 5, ArH); ^{31}P NMR (40.5 MHz, 12% in $HCCl_3$) δ −21.74 ppm relative to 85% H_3PO_4.

Anal. Calcd for $C_{13}H_{20}ClO_4P$: P, 10.10. Found: P, 10.16.

Registry No.—**10**, 1605-53-4; **12**, 55759-76-7; **14**, 55759-78-9; **15**, 55759-79-0; **16**, 607-01-2; **17**, 3619-88-3; **18**, 55759-81-4.

References and Notes

(1) We gratefully acknowledge support of this work by the USPHS, NIH, National Cancer Institute, CA 11967.
(2) Research Associate, 1973–1975.
(3) For a discussion on the synthetic aspects involved in the preparation of phospholanium salts, see P. Beck in "Organic Phosphorus Compounds", Vol. 2, G. M. Kosolapoff and L. Maier, Ed., Wiley-Interscience, New York, N.Y., 1972, Chapter 4, and references cited therein. Additional insight may be obtained by examining the brief discussions of the preparation of phospholanes, phospholenes, and phospholene oxides (all potential precursors of phospholanium salts). For the former two, see L. Maier in "Organic Phosphorus Compounds", Vol. 1, G. M. Kosolapoff and L. Maier, Ed., Wiley-Interscience, New York, N.Y., 1972, Chapter 1, and references cited therein. For the latter, see H. R. Hays and D. J. Peterson in "Organic Phosphorus Compounds", Vol. 3, G. M. Kosolapoff and L. Maier, Ed., Wiley-Interscience, New York, N.Y., 1972, Chapter 6, and references cited therein.
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(26) These phospholanium salts are slightly hygroscopic and have a tendency to precipitate as an oil. In those cases, the precipitates were dissolved in $HCCl_3$ and the aqueous layer was also extracted (3 × 100 ml) with $HCCl_3$. The $HCCl_3$ extracts were combined, dried ($MgSO_4$), and evaporated in vacuo to afford the solid products.
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Synthesis and Solvolysis of Tricyclo[4.3.2.0^{2,5}]undeca-3,8,10-trien-7-ol. An Unusual $[CH]_{11}^+$ Rearrangement[1]

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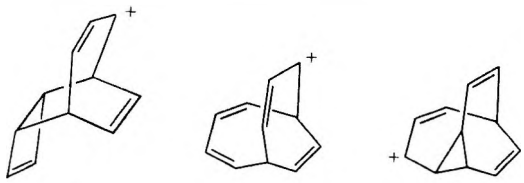
Synthesis of the title compound (**11**) has been achieved by two routes, the cycloaddition of cyclobutadiene to tropone and addition of tetrachlorocyclopropene to an appropriate bicyclo[4.2.0]diene (**6**) and subsequent transformations. Acetolysis of esters of **11** afforded a rearranged allylic acetate (**15**) and dihydroindenylenol acetate (**20**). Deuterium-labeling studies indicate that **20** derives from **15** via a bicyclo[2.1.0]pentane (**25**) and subsequent thermal fission. Activation parameters for this process ($\Delta H^{\ddagger}$ = 31.2 kcal/mol, $\Delta S^{\ddagger}$ = −6.2 eu) are in accord with the proposed mechanism.

Interest in the preparation and reorganization of $[CH]_n$ hydrocarbons and ions has been aroused by the surprising variety of rearrangements observed in these systems and by attempts to correlate experimental evidence regarding these energy surfaces to theoretical prediction. Particularly, the concepts of homoaromaticity,[2] bicycloaromaticity,[3] and spiroaromaticity[4] have served at least to focus attention on structures of importance. We were led to synthesize precursors of **1** in view of its relationship to the interesting ions **2** and **3**. Our expectations that **1** might lead to **2** or **3**



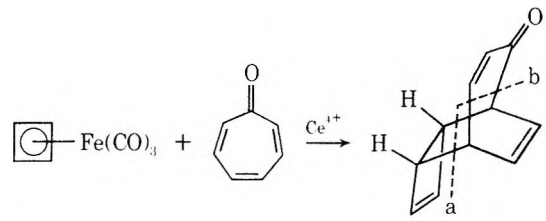
1 **2** **3**

were based upon the known σ participation of appropriately positioned cyclobutenes[5] and predictions regarding the stabilization of **2**.[3]

At the outset of this work no derivatives of the $[CH]_{11}$–X family of valence tautomers had been described. Since that time we[6] and others[7] have reported six other members of this series and a number of rearrangements relating them. We report here two independent synthetic approaches to the alcohol corresponding to **1** and evidence bearing on the mechanism of its unusual rearrangement to an enol acetate by thermal fission of a bicyclo[2.1.0]pent-2-yl intermediate.

Results and Discussion

Synthesis. Inspection of **4** suggested two attractive synthetic approaches, the annulation of a cyclobutene ring onto tropone (a) and the elaboration of an enone bridge onto an appropriate bicyclo[4.2.0]octane precursor (b). We have investigated both routes.



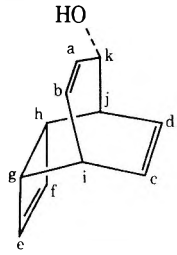
4

When cyclobutadiene was generated in situ[8] in the presence of freshly distilled tropone, only one volatile product was detected by analytical GLC. After column chromatography, a 14% yield of a 1:1 adduct was isolated. Of several possible isomers only **4** was consistent with the spectral data.

The presence of a single α,β-unsaturated carbonyl unit was indicated by the ^1H NMR spectrum (δ 7.0, 1 H, dd, J = 11, 8 Hz; δ 5.7, 1 H, dd, J = 11, 2 Hz) and an accordant ir spectrum (1680, 1640 cm^{-1}). A sharp singlet at δ 6.0 and an ir band at 1560 cm^{-1} were assigned to a cyclobutene. The spin-decoupled ^1H NMR spectrum revealed that the β carbon of the enone unit was adjacent to a bridgehead proton. Both the coupling constants and chemical shifts found in the ^1H NMR spectrum of enone **4** were in excellent agreement with those found in appropriate model compounds.[9]

While the direct, one-step approach to this ring system was successful, the yields of enone **4** remained uneconomical since excess cyclobutadieneiron tricarbonyl was used. In another approach (Scheme I) we have applied the known

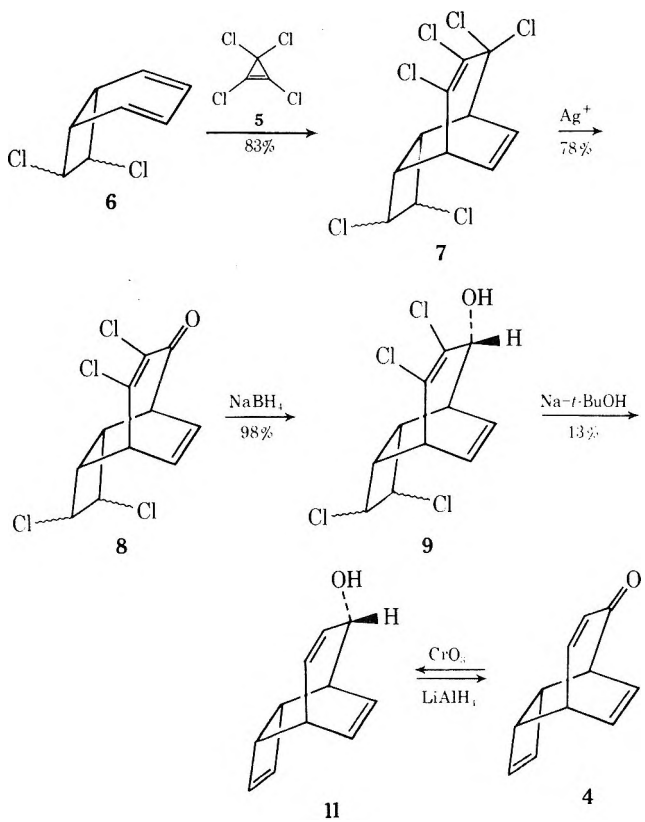
Table I
^{3}H NMR Spectrum of 11[a]



δ	a	b	c	d	e	f	g	h	i	j	k	Apparent multiplicity	ΔEuδ
a	5.24	11 Hz							3 Hz		2.5 Hz	dt	5.4
	b	5.8							8 Hz				3.2
		c	6.10	8 Hz					8 Hz			t	1.2
			d	5.72						8 Hz		t	2.4
				e	5.96	2.7 Hz						d	1.1
					f	5.80						d	1.4
						g	3.16	3 Hz	3 Hz			t	2.4
							h	3.45		1–2 Hz		br s	5.6
								i	2.32			br t	2.0
									j	2.39	3 Hz	br d	5.1
										k	4.25	br s	2.2

[a] Diagonal elements are chemical shifts (δ) obtained in CCl_4; off-diagonal elements are coupling constants (hertz) assigned by decoupling. [b] Pseudocontact shifts for Eu(fod)$_3$.[16]

Scheme I



cycloaddition–ring opening reaction of tetrachlorocyclopropene[10] (**5**) with dienes to 7,8-dichlorobicyclo[4.2.0]octa-2,4-diene (**6**). Thus, heating **6** in a large excess of **5** at 75° for 3 weeks[11] afforded hexachloride **7**, a mixture of stereoisomers, in 83% yield.

A more classical approach, Diels–Alder addition of acetoxyacrylonitrile, with the intent of subsequent ring expansion, produced no cycloadduct.[12]

When the hexachloride **7** was hydrolyzed with silver nitrate in aqueous dioxane, a 78% yield of a tetrachloro ketone **8** was isolated. Subsequent reduction with sodium borohydride without isolation of **8** led to the corresponding alcohol **9** in equally good yield from **7**.

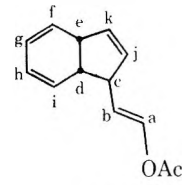
Reductive dehalogenation of **9** and several obvious derivatives under a variety of conditions was exceedingly complex. Under optimum conditions, treatment of **9** with sodium–*tert*-butyl alcohol[13] and oxidation of the crude product mixture with CrO_3–pyridine[14] afforded a 13% yield of **4** identical in every respect with the product. The remainder of the reaction product contained appreciable amounts of the corresponding hydrocarbon (**10**).[15]

The allylic alcohol **11** (ir 3540, 3400, 1025 cm^{-1}) was obtained in excellent yield from the reduction of enone **4** with lithium aluminum hydride in ether. The spectral data for **4** left the stereochemical relationship of the four-carbon and three-carbon bridges in doubt. By analysis of the europium-shifted and spin-decoupled ^{1}H NMR[16] spectrum of **11** (Table I), it was possible to definitively assign the stereochemistry.

The magnitudes of the pseudocontact shifts for the protons k (ΔEu 22 ppm), a (5.4 ppm), and j (5.1 ppm) are as expected for an allylic alcohol of this structure. However, the relatively large contact shift for proton h (5.6 ppm) indicates that one of the cyclobutene methine protons is spatially close to the hydroxyl group. This fact simultaneously fixes the stereochemistry of the alcohol and the cyclobutene bridge, and it becomes possible to identify **11** as (1α,2β,5β,6α,7β)tricyclo[4.3.2.0^{2,5}]undeca-3,8,10-trien-7-ol. From this stereochemical assignment, it is evident that the reduction of enone **4** has occurred with preferential approach of the hydride reagent from the α side, presumably reflecting the steric hindrance of the cyclobutene methine protons. In addition, the related stereochemistry of enone **4** indicates that cyclobutadiene has reacted as a reactive dienophile in accord with the endo rule.[17,18] The thermal reactivity of cyclobutadiene in this instance is in marked contrast with its photochemical reaction in the presence of tropone ketal, which leads to a [2 + 6] cycloadduct (eq 1).[19]

The 3,5-dinitrobenzoate (**12**) and the acetate **13** could be

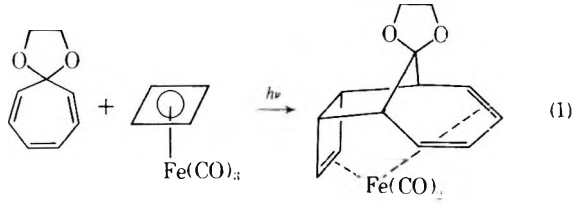
Table II
^{3}H NMR (CCl_4) Spectral Data of 20[a]



20

δ	a	b	c	d	e	f–k	Ac	Apparent multiplicity
a	7.05	12.8 Hz	1.0 Hz					d, d
	b	5.18	9.8 Hz					d, d
		c	3.48 Hz	3.2 Hz		$J_{c,j}$ = 1 Hz		t
			d	3.12	12.3 Hz	$J_{d,i}$ = 3.9 Hz		Heptet
				e	3.62			d
					f–k	5.70		m
						Ac	2.08	s

[a] Ir ($CDCl_3$) 3030, 2950, 2890, 1765, 1740, 1430, 1375, 1290, 1250, 1225, 400 cm^{-1}; uv (95% EtOH) λ_{max} 213, 255, 262, 272 nm (ϵ_{262} 3100); MS *m/e* (rel intensity) 202 (6.1), 160 (72), 142 (100, base), 104 (81), 95 (62), 91 (71); ^{13}C NMR ($CDCl_3$) from Me_4Si 167.8, 135.0, 133.2, 132.8, 126.1, 125.8, 123.0, 120.7, 116.2, 49.7, 43.6, 38.2, 14.7 ppm.

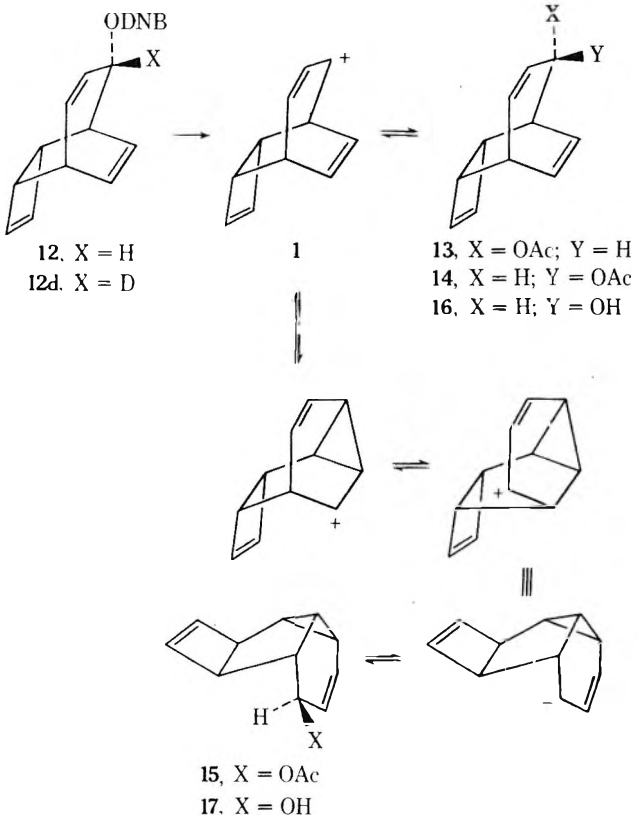


(1)

synthesized in excellent yield by the reaction of **11** with 3,5-dinitrobenzoyl chloride and acetic anhydride, respectively. Both **12** and **13** were shown to be unrearranged by their reduction with lithium aluminum hydride to afford only **11**.

Solvolysis. When **12** was solvolyzed in acetic acid at 118° for 4 hr, three isomeric acetates (**13, 14,** and **15**) were isolated in 100% yield (relative amounts 1.5:1.5:1). Compound **13** was identical with the product of acetylation of alcohol **11**. Compound **14** was epimeric with **13** as demonstrated by its reduction to alcohol **16** and oxidation to afford enone **4**.

Scheme II



12, X = H
12d, X = D

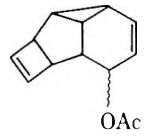
1

13, X = OAc; Y = H
14, X = H; Y = OAc
16, X = H; Y = OH

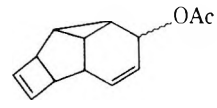
15, X = OAc
17, X = OH

The structure of the remaining acetate (**15**) was determined by analysis of its ^{1}H NMR spectrum. That a cyclobutene ring was present in the molecule was signaled by the two ^{1}H NMR doublets at δ 6.32 and 6.02 (J = 3 Hz[20a]). A three-hydrogen absorbance at δ 1.56 was assigned to a cyclopropyl ring, and the presence of an additional vinyl unit was evidenced by protons at δ 5.98 and 5.56. When **15** was reduced to the corresponding alcohol **17** with lithium aluminum hydride, a chemical shift of δ 4.48 was observed for the hydroxy methine proton and the resonance at δ 5.56 decreased from two protons to one proton. Accordingly, the acetoxy methine proton in **15** also comes at δ 5.56, a chemical shift too low for any acetate other than an allylic acetate.[20b]

On this basis the only reasonable structures for **15** are among the epimers of **18** and **19**. On mechanistic grounds



18



19

and the observation that **15** is in equilibrium with **13** and **14** in acetic acid at 118°, we tentatively assign the structure **15** (Scheme II).

When a solution of dinitrobenzoate **12** or acetate **13** was heated in acetic acid at 190°, the same mixture of three acetates (**13, 14,** and **15**) was initially formed. These products subsequently rearranged over 2 hr to afford a fourth isomer **20**. Analysis of spectral data for **20** indicated that it was a trans enol acetate ($\nu_{C=O}$ 1765 cm^{-1}, δ 7.05, d, 1 H, J = 12.8 Hz)[21] with no cyclobutene protons evident among the eight vinyl hydrogens (Table II).

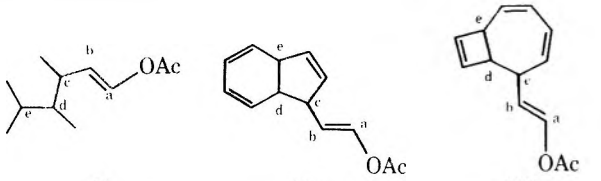
Spin decoupling of the ^{1}H NMR spectrum of **20** located the β carbon of the enol acetate adjacent to a bridgehead proton with J_{bc} = 9.8 Hz. The bridgehead proton, H_c, was shown to be adjacent to only one bridgehead proton, H_d, with $J_{c,d}$ = 8.2 Hz and H_d, in turn, was adjacent to the remaining bridgehead proton H_e with $J_{d,e}$ = 12.3 Hz, completing the structural unit **21**.

Table III
Vinyl Carbon Resonances for 20, 22, and 23

	Assignment					
	Cyclopentene		Cyclohexadiene			
20	133.2[a]	132.8	126.1	125.8	123.0	120.7
22	138.7	128.8	126.5	125.1	121.8	121.3
23	134.8	128.8	127.9	125.7	121.7	121.0

[a] Chemical shifts in parts per million downfield from Me_4Si.

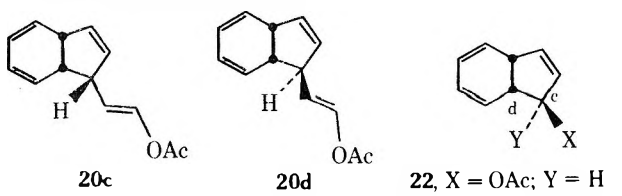
There are only two reasonable $[CH]_{11}$ structures (**20a** and **20b**) with three remaining double bonds which contain this connectivity.[22]



21 20a 20b

The structure **20b** is eliminated on the basis of two pieces of information. The observed uv extinction coefficient (ϵ 3100) is too small for a homoannular diene in a seven-membered ring (ϵ 8000),[23] and is similar to those found in *cis*- and *trans*-3a,7a-dihydroindenes (ϵ_{cis} 4580, ϵ_{trans} 3700).[24] In addition the magnitude of the coupling constant, $J_{d,e}$ = 12.8 Hz, is too large for a cyclobutene ring and is only consistent with a cis-fused 3a,7a-dihydroindene.[25]

The stereochemical assignment for the attachment of the enol acetate group was more difficult and rests on an analysis of the ^{13}C NMR spectrum (Table III). The resonances at δ 135.0 and 116.2 were unambiguously assigned to the α and β carbons of the enol acetate group, respectively, by heteronuclear spin decoupling of the corresponding proton resonances. Calculation of the chemical shifts for these carbons is expected to be relatively accurate, since they are not part of the ring system. By applying the empirical parameters of Roberts[26] with vinyl acetate[27] as a model compound, calculated values of δ 134.6 and 116.8 are obtained for carbons a and b in **20**, in excellent agreement with the observed shifts. Particularly significant is the close agreement for carbon b. One consequent difference between epimers **20c** and **20d** is the very close approach of carbons b and i in **20c**. This spacial proximity would be expected to exert a strong shielding effect[28] (~4–5 ppm) on the interacting carbon atoms. Given the agreement of calculated and observed chemical shifts for carbon b, no such effect is evident and structure **20d** must be preferred. A similar argument can be constructed for carbon i, since there is close agreement in chemical shift for all the diene carbons in **20**, **22**, and **23** (Table III).



20c 20d

22, X = OAc; Y = H
23, X = COOEt; Y = H

Mechanism. To establish the mechanism for the formation of **15** and the unusual subsequent transformation to **20**, we have examined the acetolysis of deuterated benzoate **12**-*d*. Integration of the ^1H NMR spectrum of **15**-*d* isolated from a solvolysis at 120° indicated the presence of 0.5 deuterium atom at the vinyl position adjacent to the acetoxymethine and 0.5 deuterium atom among the cyclopropyl protons consistent with Scheme II. Interestingly, the deuterium distribution in the recovered epimers **13**-*d* and **16**-*d*, as determined by integration of the ^1H NMR spectra of the corresponding alcohols, revealed incomplete allylic scrambling presumably owing to some SN2 solvolysis.

Table IV
^{13}C NMR Spectrum of 20-*d*

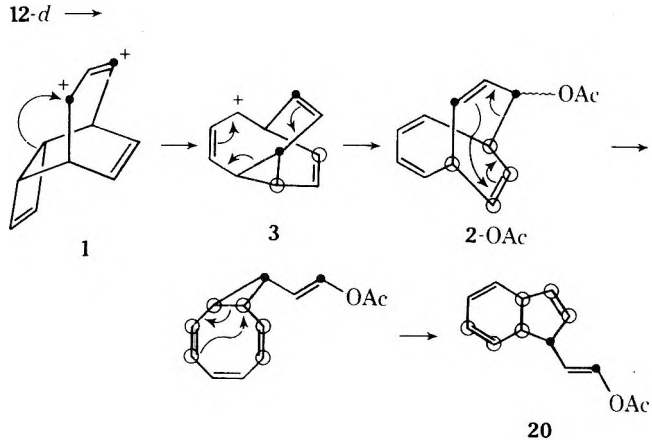
Carbon	δ Obsd	δ Calcd[26]	Rel D intensity	1st order multiplicity
a	135.0[a]	134.6		s
b	116.2[a]	117.8		s
c	49.7	49.3		Slight br
d	43.6	44.1		s and d
e	38.2	39.5		Slight splitting
f	120.7	125.0	0.1	t
g	126.1	126.4	0.4	t
h	125.8	127.9	0.1	1:1 d
i	123.0	123.5	0.4	t
j	133.2	132.8		s
k	133.3	130.3		s

[a] Assignment confirmed by heteronuclear spin decoupling.

At higher temperatures, under conditions leading to the formation of **20**-*d*, the deuterium was found to be more widely distributed in all solvolysis products and, accordingly, ^1H NMR integration became less reliable. A definitive assignment of the deuterium distribution in **20**-*d* was made by analysis of its ^{13}C NMR spectrum, since individual carbon resonances could be assigned with some certainty. Virtually all the deuterium was found among the carbons of the conjugated diene unsymmetrically disposed (Table IV).

This distribution severely limits the range of mechanisms which might give rise to **20**. One mechanism to which we gave much initial attention because of the clear precedent for the thermal steps (Scheme III) is clearly inconsistent with the complete lack of deuterium content in the five atoms not part of the cyclohexadiene ring.

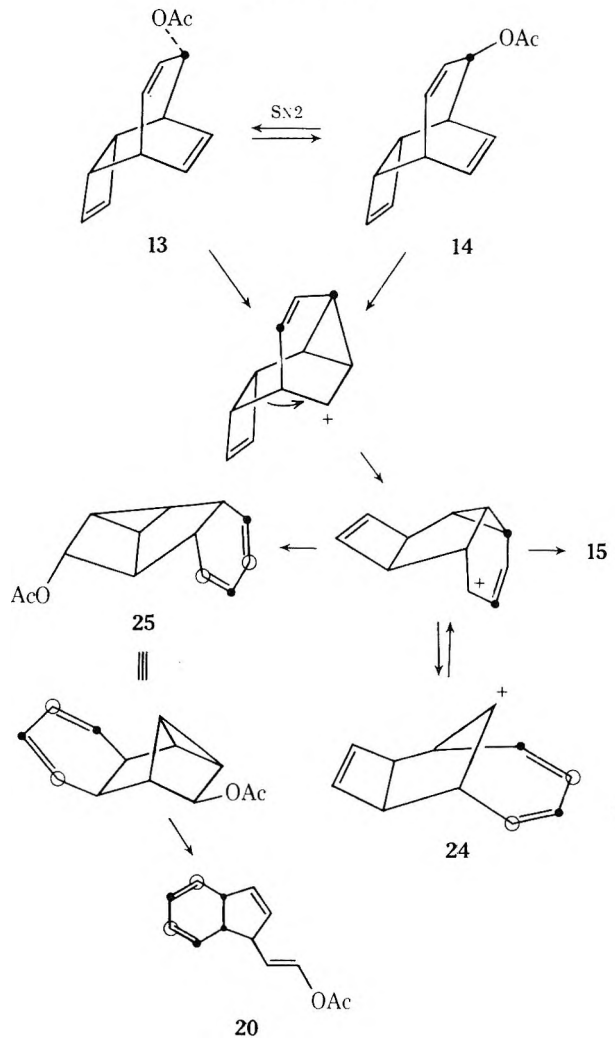
Scheme III



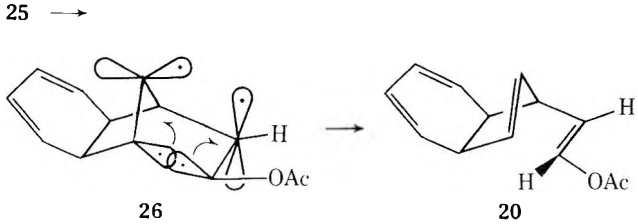
Scheme IV, involving an intermediate bicyclopentane (**25**), accounts for all the observations: incomplete allylic scrambling in the starting material, the intermediacy of **15**, the deuterium distribution in **20**, the formation of an enol acetate, and the exact stereochemistry of **20**.

The formation of an unseen intermediate (**25**) is supported by the thermal stability of **13**, **14**, and **15** at 200° in benzene. Additional evidence is derived from the kinetics for the formation of **20** (Table V) which gave good pseudo-first-order parameters, $\Delta H^{\ddagger}$ = 31.2 kcal/mol, $\Delta S^{\ddagger}$ = −6.2 eu.

Scheme IV



The solvolysis of *exo*-2-bicyclo[2.1.0]pentanes is known to be slow and proceeds via homolytic opening of the central bond.[28] Typical activation barriers for this process (32–38 kcal)[29] are in reasonable agreement with those measured for **20**. Further ring opening of the resultant 1,3-diradical is normally observed to have a substantially higher energy barrier[30] but this is almost quantitatively accounted for by the expected relief of a ca. 18 kcal of ring strain for the norbornyl system in **26**.[31] The more usually encountered hydrogen migration in 1,3-diradicals[32] would lead in this case to an untenably strained olefin.

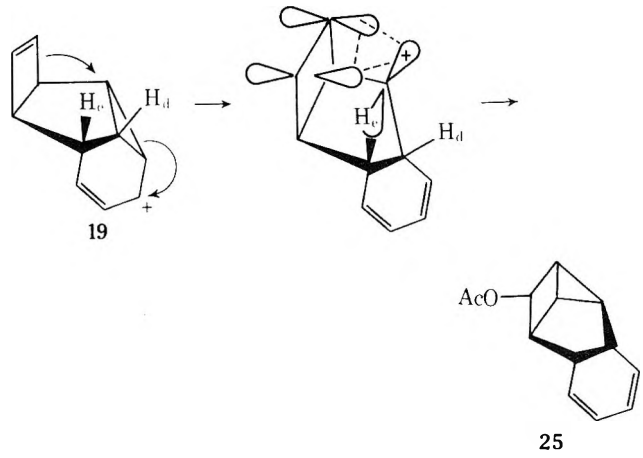


The formation of **25** is also of interest. Stereoelectronic control of the capture of the developing cyclobutyl carbonium ion would give rise to **25**, an *exo*-2-bicyclo[2.1.0]pentane. Least motion opening of the bicyclopentane would then lead to the observed trans enol acetate (**20**). More details regarding the mode of ring opening of constrained bicyclopentanes will have to await the isolation of compounds such as **25**.

Table V
First-Order Rate Constants for Rearrangement of 13, 14, and 15[a] in Acetic Acid

Temp, K[b]	Rate constant, sec^{-1}	Temp, K[b]	Rate constant, sec^{-1}
425.75	$3.7 \pm 0.7 \times 10^{-5}$	440.95	$1.5 \pm 0.2 \times 10^{-4}$
430.95	$5.4 \pm 0.6 \times 10^{-5}$	445.05	$2.2 \pm 0.3 \times 10^{-4}$
435.45	$1.4 \pm 0.2 \times 10^{-4}$	455.25	$4.2 \pm 0.4 \times 10^{-4}$

[a] Substrate concentration. [b] ±0.05°.



Recent developments in our laboratories[33] have succeeded in generating **3** under solvolytic conditions. This ion has been found to lead only to covalent derivatives of **2**. The failure to achieve the anticipated ring-opening reaction **1** → **3** thus leads to the conclusion that no great lowering of the barrier to cyclobutene ring opening is achieved by virtue of the adjacent allylic cation. More specifically, the transition state leading to **3** from **1** must be higher in energy than that reported here leading from **1** to **25** and, accordingly, any stabilization present in **3** is not manifested in the chemistry of **1** below 31 kcal/mol.

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer grating spectrophotometers, Model 237B or Model 457. Ultraviolet spectra were obtained on a Cary 14 recording spectrophotometer. Varian T-60 and Jeol PS-100 nuclear magnetic resonance spectrometers were used to obtain ^1H NMR and ^{13}C NMR spectra. Mass spectra were obtained on an AEI MS-902 mass spectrometer.

Analytical GLC data were obtained with a Varian Aerograph gas chromatograph, Model 1200, equipped with a flame ionization detector. A Varian Aerograph 90-P gas chromatograph equipped with a thermal conductivity detector was used for preparative GLC. Brinkmann thin layer plates precoated with silica gel (0.25 and 2 mm) and fluorescent indicator were used for analytical and preparative thin layer chromatography, respectively. Woelm silica gel and basic alumina (0.05–0.2 mm) activity I was used for column chromatography, and dry column chromatography was done with Woelm silica gel with fluorescent indicator, "dry column chromatography grade".

Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Synthesis of Tricyclo[4.3.2.0^{2,5}]undeca-3,8,10-trien-7-one from Tropone. A solution of 2.86 g (0.015 mol of freshly distilled cyclobutadieneiron tricarbonyl and 0.86 g (0.008 mol) of freshly distilled tropone in 250 ml of reagent-grade acetone was cooled to −5° using an ice–salt bath. The system was maintained under argon. A flask containing 13.9 g (0.025 mol) of ceric ammonium nitrate was attached to the reaction system with a piece of Gooch tubing. The solution was stirred rapidly while the ceric ammonium nitrate was added in several small portions over a period of 30 min.

After stirring for an addition 2 hr, the dark brown reaction mixture was poured into 400 ml of 16% aqueous sodium chloride solu-

tion and washed with 3 × 200 ml of ether. The combined organic layers were washed with 250 ml of water and 200 ml of saturated sodium chloride. The ether layer was dried over anhydrous sodium sulfate and filtered, and the ether was removed under reduced pressure to yield 0.51 g of a dark brown oil.

The crude product was then chromatographed on 50 g of silica gel. Elution with 300 ml of benzene, followed by 2% ether–benzene, yielded 0.23 g (14.5%) of enone 4 as a pale yellow oil: ir (CCl_4) 3040, 2920, 1680, 1640, 1565, 1385, 1300, 1260, 1240, 1200, 1165 cm^{-1}; uv (ether) λ_{max} 229 nm (ϵ 4850), 256 (1950), 290 (266); MS *m/e* (rel intensity) (70 eV) 160 (0.5), 159 (7.5), 158 (55.9), 157 (32.0), 129 (83.2), 128 (41.2), 115 (44.4), 103 (34.5), 78 (100); ^{1}H NMR ($CDCl_3$) δ 7.0 (dd, 1 H, J = 11, 8 Hz), 6.2 (t, 1 H, J = 8 Hz), 6.0 (s, 2 H), 5.9 (t, 1 H, J , 8 Hz), 5.7 (dd, 1 H , J = 11, 2.2 Hz), 3.44 (d, 1 H, J = 8 Hz), 3.25 (t, 1 H, J = 8 Hz), 3.18 (br, s, 2 H); ^{13}C NMR ($CDCl_3$) δ 196.5, 152.0, 139.0, 136.0, 133.5, 130.0, 124.0, 55.9, 48.0, 42.4, 39.5.

Anal. Calcd for $C_{11}H_{10}O$: C, 83.52; H, 6.37. Found: C, 83.41; H, 6.36.

Tricyclo[4.3.2.0^{2,5}]undeca-3,4,7,7,8,9-hexachloro-8,10-diene (7). A stirred neat solution of 300 g (1.69 mol) of tetrachlorocyclopropene and 58 g (0.33 mol) of 7,8-dichlorobicyclo[4.2.0]octa-2,4-diene was flushed with a fine stream of argon and the mixture was maintained at 75° with stirring for 3 weeks.

The reaction mixture was then allowed to cool to room temperature and the unreacted tetrachlorocyclopropene was removed by flash distillation (35–80°C, 0.1 mm), leaving 100 g of crude **7** as a pale tan, viscous oil, 83.5% yield.

Hexahalide **7** could be partially purified by trituration with pentane and recrystallization from petroleum ether, mp 120–136° (mixture of epimers at C-3 and C-4). Analytical GLC showed that crude **7** consisted of two major components with retention times of 11 and 12 min (SE-30, 100–200°).

Tricyclo[4.3.2.0^{2,5}]-3,4,8,9-tetrachloro-8,10-dien-7-one (8). A 2-l. three-neck round-bottom flask was equipped with a stirring rod and Teflon paddle, thermometer, and reflux condenser. Silver nitrate (100 g, 0.6 mol) was dissolved in 200 ml of distilled water and 700 ml of *p*-dioxane. This solution was then maintained at 55–65° while stirring and 100 g (0.28 mol) of hexahalide **7** dissolved in 100 ml of *p*-dioxane was added at once to the silver nitrate solution. The reaction mixture was then maintained at 55–65°, with stirring, for 20 hr.

The reaction mixture was then cooled and the silver chloride was removed by suction filtration. Saturated sodium chloride was added to the clear filtrate until the silver chloride precipitation ceased. The reaction mixture was filtered and used without purification for the sodium borohydride reduction. Dry silver chloride (62 g) was isolated (78%): ir (film) 3050, 2980, 2940, 1715, 1615, 1590, 1265, 860, 780, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.65 (t, 1 H, J = 8 Hz), 6.3 (t, 1 H, J = 8 Hz), 3.9 (m, 4 H), 3.2 (m, 2 H).

Tricycyo[4.3.2.0^{2,5}]undeca-3,4,8,9,-tetrachloro-8,10-dien-7-ol (9). The clear yellow dioxane–water solution of **8** (described above) was cooled to 0° in a 3-l. three-neck flask, equipped with an addition funnel, stirring rod with Teflon paddle, and a reflux condenser. A solution of 38 g (1.0 mol) of sodium borohydride in 1 l. of 95% ethanol was added dropwise over 1 hr while stirring. After the addition was complete, the reaction mixture was allowed to warm to room temperature and was then heated at 80° for an additional 4 hr. Upon evaporation of solvent, the oily two-phase residue was washed with 3 × 300 ml of chloroform. The combined organic layers were dried over anhydrous sodium sulfate and filtered. Removal of the solvent under reduced pressure yielded 60 g (71.5%, calcd from **7**) of a viscous tan oil. Analysis of this oil by analytical GLC (SE-30, 100–200°) showed that it consisted of three major components (10.5, 11.0, 12.0 min), assumed to be epimers at C-3 and C-4.

Tricyclo[4.3.2.0^{2,5}]3,8,10-trien-7-one (4) from 9. A three-neck 1-l. round-bottom flask, equipped with a 250-ml addition funnel, Herchberg stirrer, reflux condenser, and gas bubbler, was flame dried under a nitrogen atmosphere. A suspension of 15 g (0.66 g-atom) of finely cut sodium in 400 ml of dry tetrahydrofuran was heated to reflux while stirring rapidly. Dry *tert*-butyl alcohol (5.0 g) was added to the refluxing suspension just prior to the addition of tetrachloro alcohol **9**. A solution of 5.0 g (0.017 mol) of crude **9**, 25 g of *tert*-butyl alcohol (total 30 g, 0.66 mol), and 100 ml of tetrahydrofuran was added dropwise over 1 hr. The vigorously stirred solution was maintained at reflux for an additional 8 hr, or until the sodium formed a large shiny lump. (Caution: the reaction cannot be left unattended after the first 2 hr of reaction time as the sodium ball can destroy the reaction vessel with rapid stirring).

The reaction was cooled in an ice bath and methanol was added slowly with gentle stirring, until the sodium was completely reacted.

The reaction mixture was poured into 400 ml of water and extracted with 3 × 100 ml of ether. The combined organic extracts were washed with 250 ml of 5% hydrochloric acid, 250 ml of water, and 2 × 250 ml of saturated sodium chloride. The ether layer was then dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure to yield 2.4 g of a dark brown oil.

A 500-ml three-neck round-bottom flask was equipped with a Herschberg stirrer and maintained under a nitrogen atmosphere. Chromium trioxide (1.5 g, 0.015 mol) was added to a stirred solution of 2.37 g (0.03 mol) of pyridine in 200 ml of methylene chloride. After stirring for 15 min, 2.4 g (0.015 mol) of the crude oil (**11**) in 50 ml of methylene chloride was added in one portion to the deep red, clear solution. Stirring was continued for an additional 15 min, followed by the addition of 2-propanol until the red color of the chromium oxide–pyridine complex was completely discharged.

The reaction mixture was decanted and the tarry residue was washed with 3 × 100 ml of ether. The combined organic layers were then washed with 3 × 200 ml of 5% sodium hydroxide, 100 ml of 5% hydrochloric acid, 100 ml of 5% sodium bicarbonate, and 200 ml of saturated sodium chloride. The organic layer was then dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure to yield 2.3 g of a dark brown oil.

When this oil was chromatographed as described above, 0.34 g (13% from **9**) of enone **4** was isolated.

Tricyclo[4.3.2.0^{2,5}]-3,8,10-trien-7-ol (11) from 4. A clear lithium aluminum hydride ($LiAlH_4$) solution was prepared by refluxing 0.24 g (0.064 mol) of $LiAlH_4$ in 50 ml of dry ether under nitrogen for 30 min. The cooled solution was filtered under nitrogen with a Schlenk tube into a dry 100-ml three-neck round-bottom flask and cooled to −78°. A solution of 1 g (0.064 mol) of enone **4** in 10 ml of dry ether was added to the stirred $LiAlH_4$ solution dropwise over 15 min. After the reaction mixture had been maintained at −78° for an additional 1 hr, 5 ml of water was added dropwise over 5 min. The Dry Ice–acetone bath was then removed and the stirred reaction mixture was allowed to warm to room temperature. The mixture was then filtered and the aluminum oxide salts were washed with several portions of hot methanol.

The filtrate was washed with 3 × 50 ml of water, 50 ml of 5% hydrochloric acid, 50 ml of 5% sodium bicarbonate, and 50 ml of saturated sodium chloride. The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure to yield 1.0 g (99%) of the allylic alcohol **11**: ir (CCl_4) 3580, 3400, 3030, 2900, 1640, 1390, 1305, 1190, 1025 cm^{-1}; MS *m/e* (rel intensity) 162 (2.32), 161 (0.41), 60 (15.7), 142 (33.5), 141 (27.6), 131 (47), 117 (43.5), 104 (90.5), 91 (95), 82 (100).

Reduction of 4 with Lithium Aluminum Deuteride. When the procedure above was repeated using lithium aluminum deuteride, a 95% yield of **11-*d*** was obtained: ^{1}H NMR identical with that of **11** except absorption at δ 4.25 absent; MS (70 eV) *m/e* 161.

Tricyclo[4.3.2.0^{2,5}]undeca-3,8,10-trienyl 7-Acetate (13). A solution of 0.5 g (0.0032 mol) of allylic alcohol **11** and 5 ml of acetic anhydride in 25 ml of dry pyridine was heated at reflux for 1 hr. The reaction mixture was cooled and the pyridine was removed by flash distillation. The brown oil was dissolved in 50 ml of ether and washed with 3 × 100 ml of water, 100 ml of 5% hydrochloric acid, 100 ml of 5% sodium bicarbonate, and 2 × 100 ml of saturated sodium chloride. The organic layer was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure to yield 0.6 g (93%) of **13** as an amber oil: ir (CCl_4) 3020, 2900, 1720, 1370, 1225, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.0 (m, 5 H), 5.4 (m, 2 H), 3.4 (d, 1 H, J = 3 Hz), 3.2 (t, 1 H, J = 3 Hz), 2.6 (m, 2 H), 2.05 (s, 3 H); MS (70 eV) *m/e* (rel intensity) 202 (2.7), 160 (35), 142 (100), 115 (58.5), 104 (57), 91 (89.2).

7-Deuterioallylic Acetate (13-*d*). When deuterated alcohol **11-*d*** was acetylated as above, **13-*d*** was isolated in a 90% yield: ^{1}H NMR (CCl_4) adsorption at δ 5.4 integrated for 1 H; MS (70 eV) *m/e* 203.

Tricyclo[4.3.2.0^{2,5}]undeca-3,8,10-trienyl *syn*-7-(3,5-Dinitrobenzoate) (12). A solution of 1.43 g (0.0064 mol) of 3,5-dinitrobenzoyl chloride and 1.0 g (0.0064 mol) of allylic alcohol **11** in 50 ml of dry pyridine was heated at 60° for 1 hr. The reaction mixture was cooled and the pyridine was removed by flash distillation. The yellow oil was dissolved in 100 ml of ether and washed successively with 10% HCl, water, and saturated salt solution. Concentration of the organic layer afforded 2.05 g (93%) of the allylic benzoate **12**: mp (acetone–water) 142–143°, iridescent plates; ir (CCl_4) 3080,

3030, 2900, 1730, 1640, 1550, 1350, 1270, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.05 (s, 3 H), 6.2 (m, 2 H), 6.0 (m, 4 H), 5.5 (m, 1 H), 3.4 (m, 2 H), 2.8 (m, 2 H).

Anal. Calcd: C, 61.10; H, 3.96; N, 7.92. Found: C, 61.10; H, 4.06; N, 7.91.

7-Deuterioallylic Benzoate 12-*d*. When the benzoate of deuterated alcohol 11-*d* was prepared as described above, a 90% yield of deuterated benzoate 12-*d* was isolated; ^1H NMR (CCl_4) adsorption at δ 6.2 integrated for 1 H.

Solvolysis of Benzoate 12 at Reflux. A solution of 0.5 g of 12 in 50 ml of glacial acetic acid was heated at reflux for 2 hr under an argon atmosphere. The reaction mixture was cooled to room temperature and dissolved in 100 ml of ether. The organic layer was washed with 4 × 100 ml of water, 100 ml of 5% sodium bicarbonate, and 100 ml of saturated sodium chloride. The ether layer was dried over anhydrous sodium sulfate and filtered and the solvent was removed under reduced pressure.

The epimeric allylic acetates, **13** and **14**, were separated from the cyclopropyl allylic acetate **15** by preparative GLC (SE-30, 130°).

15: ^1H NMR ($CDCl_3$) δ 1.56 (3 H, br s), 1.9 (3 H, s), 2.80 (1 H, br s), 3.00 (2 H, m), 5.56 (2 H, m), 5.98 (1 H, d, J = 8 Hz), 6.04 (1 H, d, J = 3 Hz), 6.32 (1 H, d, J = 3 Hz).

The epimeric acetates were then reduced to their corresponding alcohols (**11** and **16**) with lithium aluminum hydride and separated by preparative GLC (20% Carbowax 60–80, 125°).

Solvolysis of 12 at 190°. A solution of 0.5 g of the benzoate **12** in 50 ml of glacial acetic acid in a combustion tube was degassed by bubbling a fine stream of argon through the solution for 1 hr. The tube was cooled to −78° and sealed under vacuum. The reaction mixture was then warmed to room temperature and maintained at 190° for 2 hr.

The reaction mixture was then cooled to 0° and then to −78°. After the combustion tube was opened, the reaction mixture was dissolved in 100 ml of ether. The ether layer was washed and the organic layer was evaporated.

The epimeric allylic acetates, **13** and **14**, were separated from the enol acetate **20** by preparative GLC (3% SE-52, 120°).

Thermal Stability of Solvolysis Products. One milligram of **13**, a mixture of the epimeric allylic acetates **13** and **14**, and a mixture of **13**, **14**, and **15** were each dissolved in 30 μl of benzene and sealed under vacuum in a capillary tube. The tubes were maintained at 180° for 2 hr, cooled, and analyzed by analytical GLC. All samples were unchanged.

Kinetics. A. Solvolysis at 118°. A solution of 0.77 g of dinitrobenzoate **12** in 50.0 ml of glacial acetic acid was immersed in a bath at 130°. Aliquots, taken at various intervals, were quenched by plunging into a Dry Ice–acetone bath. The rate of product formation was analyzed by analytical GLC (SE-52, 125°).

B. Solvolysis at Elevated Temperatures. A solution of the allylic acetate **13** and biphenyl (internal standard) in glacial acetic acid was sealed under vacuum in a series of capillary tubes. Eight tubes were immersed in an oil bath at temperatures ranging from 165 to 190°. Samples were quenched at various times by rapid cooling to −78°. The rate of disappearance of the acetates **13**, **14**, and **15** was then analyzed by analytical GLC (3%, SE-52, 125°).

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Aspects of the Kinetics of Hydrolysis of Acetals of Ketones[1]

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The rate constants are reported for the acid-catalyzed hydrolysis of the dimethyl acetals of acetone, butanone, 2-pentanone, 3-pentanone, 4-methyl-2-pentanone, 4-heptanone, 2-octanone, cyclohexanone, 2-methylcyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone. The hydrolytic reactions were conducted in 95% methanol–5% water at 15, 25, and 35°. Differences in rates for the series of acyclic ketones are small with the largest change being about a factor of 5. Activation parameters have been calculated for the above compounds and various linear free energy correlations attempted. Taft plots were poor but isokinetic plots of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ were quite good with a slope, β, of 276 K and a correlation coefficient of 0.968. From previously measured equilibrium constants and the hydrolytic rate constants, rate constants were calculated for acetal formation for eight of the ketones. Rates parallel equilibria for both the formation reaction and for the hydrolysis reactions but the rates forward have an inverse relationship to the hydrolysis rates. It is concluded that steric factors control the small differences in rates observed for these reactions.

In an earlier paper,[3] rate constants and equilibrium constants were reported for the formation and hydrolysis of para-substituted benzaldehyde dimethyl acetals in 95% methanol–5% water at 15, 25, and 35°. This solvent was selected so that reaction rates could be determined for both the forward and reverse reaction under identical conditions. We now report a kinetic study for the hydrolysis of dimethyl acetals of selected ketones in the same solvent. These acetals are not hydrolyzed to completion under these conditions, with exceptions, and the reactions follow simple second-order kinetics (first order in acetal and first order in hydronium ion).

We were interested in the hydrolysis of acetals of ketones as a structural study for three particular reasons. First, these ketones form minimal amounts or no hemiacetals[4] in solution of methanol so the reaction kinetics remain clear of this possible complication.[5] Second, we have suggested[4] that the rates of acetal hydrolyses should correlate in classes for linear free energy correlations depending upon $\Delta S^{\ddagger}$ terms and these data have been unavailable. Third, we were interested in comparing rates and equilibria for this series as we have reported for the interconversion of para-substituted benzaldehydes and their dimethyl acetals.

Experimental Section

Preparation and Purification of Reagents. Methanol (Union Carbide Chemicals Co.) was purified in 3-l. batches by the method of Lund and Bjerrum[6] and as previously reported.[3]

95% Methanol–5% Water–0.1 *m* Sodium Perchlorate was prepared in kilogram lots as previously reported[3] with the sodium perchlorate having been recrystallized three times from water and dried under vacuum at 120°. The salt did not change the pH of water for concentration changes from 0.02 to 0.1 *M*.

Acetals. The general procedure used for conversion of the ketones to their dimethyl acetals is essentially the same as that used by Kreevoy and Taft[7] for making diethyl acetals. Mixtures of 0.14 mol of the appropriate ketone, 0.146 mol of trimethyl orthoformate, 0.74 mol of methanol, and a crystal of *p*-toluenesulfonic acid were refluxed for 4 hr. One drop of 50% sodium hydroxide was added and 15 ml of hexane. The methanol layer was removed and the hexane layer was distilled on a Nester-Faust annular Teflon spinning band column. No attempts were made to optimize yields since we were interested in high-purity samples but yields of the center cuts were usually in the range of 50–70%. At no time was carbonyl absorption observed in infrared spectra of the acetals. The boiling points and refractive indices of these acetals follow: 2,2-dimethoxypropane, bp 83° (1 atm), n^{20}D 1.3770 [lit.[8] bp 80° (760 mm) n^{25}D 1.3748]; 2,2-dimethoxybutane, bp 105° (1 atm), n^{20}D 1.3930 [lit.[8] bp 50° (100 mm), n^{24}D 1.3915]; 2,2-dimethoxypentane, bp 37° (25 mm), n^{20}D 1.4005; 3,3-dimethoxypentane, bp 37° (25 mm), n^{20}D 1.4046 [lit.[8] bp 50° (63 mm), n^{26}D 1.4013]; 2,2-dimethoxy-4-methylpentane, bp 53° (29 mm), n^{20}D 1.4068 [lit.[8] bp 58° (35 mm), n^{25}D 1.4048]; 4,4-dimethoxyheptane, bp 79° (23 mm), n^{20}D 1.4135; 2,2-dimethoxyoctane, bp 37° (2 mm), n^{20}D 1.4186; 1,1-dimethoxycyclohexane, bp 65° (25 mm), n^{20}D 1.4397 [lit.[8] bp 56° (13 mm), n^{24}D 1.4373]; 1,1-dimethoxy-2-methylcyclohexane, bp 78° (25 mm), n^{20}D 1.4472; 1,1-dimethoxy-3-methylcyclohexane, bp 75° (25 mm), n^{20}D 1.4383; 1,1-dimethoxy-4-methylcyclohexane, bp 75° (25 mm), n^{20}D 1.4385. These structures showed all of the appropriate absorptions without extraneous bands for their NMR, ir, and Raman spectra.

Rate Measurements and Calculations. The reactions for acetal hydrolysis were monitored by measuring the appearance of the carbonyl group in the ultraviolet as a function of time. The wavelengths of absorption and the extinction coefficients have been previously reported.[4] A Beckman DU spectrophotometer with a modified cell compartment[9] was used in the manner previously described.[3]

The reactions were catalyzed by dichloroacetic acid–sodium dichloroacetate buffer with the ionic strength maintained essentially constant with 0.1 *m* sodium perchlorate. The particular concentrations of the acid and the salt used for the various kinetic runs and the measured pH values are reported in Table I along with the rate constants. The pH values were measured with a Corning Model 10 pH meter using a Corning Ag–AgCl combination electrode. Before each pH measurement the meter was standardized against an aqueous solution of pH 4.00 prepared with Coleman buffer tablets.

Second-order rate constants (first order in acetal and first order in hydronium ion) were calculated for acetal hydrolysis (k_2) as reported previously.[3,10] For the hydrolysis of the dimethyl acetals of acetone, butanone, cyclohexanone, 2-methylcyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone the back reaction was sufficient that we obtained ($k_1 + k_2$) values (the sum of the forward and reverse rate constants) as for the benzaldehyde series. These values along with our independently measured equilibrium constants[4] were used to obtain the rate constants. For the acetals of the other five ketones, the hydrolyses were all 99% complete or better at infinite time so that plots of log ($A_\infty - A_t$) vs. time provided k_2 (hydrolysis) values directly.

All rate constants were calculated by the method of least squares. The activation parameters E_a, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$ were calculated by the least-squares treatment of the rate constant–temperature data in the usual manner.[11] Error analyses for the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ were calculated by the procedure recommended by Wiberg.[12] Linear free energy plots were made for visual inspection but the actual correlations were made by the method of least squares.

Results

Rate constants at 15.02, 25.39, and 35.04° were obtained for the acid-catalyzed hydrolysis of the dimethyl acetals and are summarized in Table I along with the activation parameters. These are shown in two series for acetals of acyclic ketones and acetals of cyclic ketones, each listed in order of increasing reactivity (25°). The reactions were conducted in 95% methanol–5% water which was 0.100 *m* in sodium perchlorate and the catalyst was dichloroacetic acid–sodium dichloroacetate buffer. This particular solvent mix-

Table I
Rate Data for the Hydrolysis of Acetals of Ketones[a]

Parent ketone of dimethyl acetal	Rate constants, k_2,[b] 15.02°	25.39°	35.04°	E_a, kcal mol^{-1}	$\Delta G^{\ddagger}_{298}$, kcal mol^{-1}	$\Delta H^{\ddagger}_{298}$, kcal mol^{-1}	$\Delta S^{\ddagger}_{298}$, eu	Registry no.
Acetone	1.55[c] (6.18 × 10^3)	4.45[e] (18.1 × 10^3)	12.4[f] (49.4 × 10^3)	18.4	16.6	17.8	4.3	77-76-9
Butanone	2.48[c] (9.86 × 10^3)	7.82[e] (31.1 × 10^3)	20.0[f] (79.6 × 10^3)	18.5	16.2	17.9	5.7	3453-99-4
3-Pentanone	2.35[c] (9.35 × 10^3)	8.89[f] (35.4 × 10^3)	23.4[f] (93.2 × 10^3)	20.4	16.2	19.8	12.2	25636-49-1
2-Pentanone	3.14[c] (12.5 × 10^3)	8.97[e] (35.7 × 10^3)	29.8[f] (119 × 10^3)	19.9	16.2	19.3	10.5	55904-98-8
2-Octanone	2.72[c] (10.8 × 10^3)	9.46[f] (37.7 × 10^3)	27.5[f] (110 × 10^3)	20.5	16.1	19.9	12.8	54583-19-6
4-Heptanone	3.53[c] (14.1 × 10^3)	10.8[e] (43.0 × 10^3)	30.8[f] (123 × 10^3)	19.2	16.1	18.6	8.6	55904-99-9
4-Methyl-2-pentanone	8.08[f] (32.2 × 10^3)	25.4[e] (101 × 10^3)	64.4[e] (257 × 10^3)	18.4	15.5	17.8	7.7	1112-78-3
4-Methylcyclohexanone	0.167[d] (0.66 × 10^3)	0.542[c] (2.16 × 10^3)	2.03[d] (8.08 × 10^3)	22.1	17.7	21.5	12.8	18349-20-7
Cyclohexanone	0.169[d] (0.67 × 10^3)	0.67[c] (2.67 × 10^3)	2.20[f] (8.76 × 10^3)	22.8	17.7	22.2	15.0	933-40-4
3-Methylcyclohexanone	0.224[d] (0.89 × 10^3)	0.796[c] (3.17 × 10^3)	2.61[d] (10.4 × 10^3)	21.5	17.6	20.9	11.1	18349-16-1
2-Methylcyclohexanone	1.92[c] (7.6 × 10^3)	6.28[f] (25 × 10^3)	19.1[f] (76 × 10^3)	20.4	16.4	19.8	11.4	38574-09-3

[a] The reactions were conducted in 95% methanol–5% water with 0.1 *m* $NaClO_4$ and dichloroacetic acid–sodium dichloroacetate buffer. [b] k_2 is the rate constant for acetal hydrolysis normalized to 1 *M* H_3O^+ using observed pH values. The values in parentheses are normalized to 1 *M* H_3O^+ using corrected pH values. [c] The buffer ratio of [acid]/[salt] = 0.01/0.01; av pH 3.24. [d] The buffer ratio of [acid]/[salt] = 0.08/0.01; av pH 2.80. [e] The buffer ratio of [acid]/[salt] = 0.002/0.01; av pH 3.97. [f] The buffer ratio of [acid]/[salt] = 0.004/0.02; av pH 3.93.

ture had been selected to enable the measurement of the rates for the forward and reverse reactions for the interconversion of benzaldehydes and their dimethyl acetals. These data also permitted the simultaneous determination of the equilibrium constants. One must simply be careful to obtain the proper rate constants for acetal hydrolysis depending upon correction for the back reaction, if any.

We were unable to use perchloric acid as the catalyst as was used for the benzaldehyde series[3] because at the catalyst concentration used for that series, the acetals of ketones hydrolyze too fast for accurate rate measurements in our system. The use of lower acid concentrations (below 10^{-4} *M*) was tried but was unsuccessful because of uncertainties in the acid concentrations. For these reasons it was necessary that a buffer system be used but we obtained consistent rate constants by utilizing measured pH values for $[H_3O^+]$.

The hydrolysis reaction is first order in acetal concentration and first order in hydronium ion concentration. The rate law at constant salt concentration is $k_{obsd} = k_2[H_3O^+]$. All rate constants are listed as k_2 for hydrolysis and are normalized to 1 *M* hydronium ion based upon pH measurements. The pH values measured in methanol–water are not the same as those measured in water.[1,13] For this reason we also have corrected the $[H_3O^+]$ based upon the liquid junction potentials reported by de Ligny.[14] These corrected rate constants are those given in parentheses in Table I with a correction factor of 3.98×10^3 because of the liquid junction potentials. These corrections are only approximate because of unknown effects of the perchlorate ion in our solutions on the liquid junction potentials. This correction does give, however, the correct order of magnitude for the $[H_3O^+]$ and does not affect the activation parameters or the linear free energy correlations.

All rate constants reported are the averages of at least three experiments but most generally are the averages of four experiments. Values were reproducible to within ± 2% and discordant data were eliminated by the *Q* test.[15]

For eight of the ketones we had previously reported equilibrium constants for dimethyl acetal formations.[4] For these ketones the equilibrium constants and the measured hydrolytic rate constants (k_2) were used to calculate the formation rate constants (k_1). These values are summarized in Table II.

Discussion

The first and most obvious effect observed for these systems is that the rate changes are small for a change of the alkyl groups. This small structural effect was first suggested by Kreevoy and Taft[7] in their classic work on acetal hydrolysis and is to be expected if all alkyl groups have about the same σ's.[16] A number of linear free energy correlations were attempted without much success for our data for the acyclic ketone series at all three temperatures. The 15° data, as a typical example, were used for an unsuccessful Taft correlation giving $\rho^* = -0.91$ with a correlation coefficient of 0.72. Omitting the value for the dimethyl acetal of 4-methyl-2-pentanone did not improve the correlation to an acceptable level.

Interestingly, an isokinetic plot[17] of $\Delta H^{\ddagger}$ vs. $\Delta S^{\ddagger}$ for the hydrolysis of the dimethyl acetals of the acyclic ketones gave a good correlation. Least-squares treatment of the data gave β = 276 K and a correlation coefficient of 0.968. When the value of the dimethyl acetal of 4-methyl-2-pentanone was omitted, β = 266.7 K and the correlation coefficient was 0.996. The fact that we obtain a good isokinetic plot but a poor Taft plot is in agreement with the arguments presented by Ritchie and Sager.[16]

The hydrolysis data for the dimethyl acetals of the four

Table II
Rate and Equilibrium Constants[a] for Dimethyl Acetal Formation and Hydrolysis Reactions, 25°

Ketone[b]	$K_e \times 10^3$[d]	k_2, l. mol^{-1} sec^{-1}[c]	k_1, l. mol^{-1} sec^{-1}[d]
Acetone	0.40	4.45	0.48
Butanone	0.13	7.82	0.28
3-Pentanone	0.034	8.89	0.082
2-Octanone	0.048	9.46	0.12
Cyclohexanone	6.7	0.67	1.22
2-Methylcyclohexanone	0.20	6.28	0.34
3-Methylcyclohexanone	3.4	0.80	0.73
4-Methylcyclohexanone	6.1	0.54	0.90

[a] These equilibrium constants were determined for the ketones dissolved in various mixtures of methanol–water at 25°.[4] [b] The corresponding dimethyl acetals were hydrolyzed. [c] k_1 is the rate constant for acetal formation and k_2 is for acetal hydrolysis. [d] $k_1 = k_2K_e$ [MeOH]^2/[H_2O]. See ref 3.

cyclic ketones also correlate reasonably well by an isokinetic treatment of $\Delta H^\ddagger$ vs. $\Delta S^\ddagger$. The correlation provided β = 201 K and a correlation coefficient of 0.91. The largest effect observed for this particular series is that due to replacing a hydrogen by methyl on the 2 position of the cyclohexane ring, for which the rate increases by a factor of about 10. Moving the methyl group to the 3 or to the 4 position has a very small effect on the rate relative to cyclohexanone dimethyl acetal.

It is possible that the linear correlation between $\Delta H^\ddagger$ and $\Delta S^\ddagger$ indicates a small steric factor operating to control the rates relative to structure. We would not strongly promote the identity, but we do present some evidence which rules out the control of rates by a polar effect.

In a paper on rates and equilibria for the benzaldehyde–dimethyl acetal interconversion,[3] a striking relationship was noted between rates forward and reverse and between equilibria. For that system having substantially negative ρ's the rates parallel each other in both directions ($\rho_{25°}$ = −2.15 for rates of acetal formation; $\rho_{25°}$ = −4.29 for rates of acetal hydrolysis) but these rates have an inverse relationship for the equilibria for acetal formation ($\rho_{25°}$ = +2.14). This effect is expected if the polar effect is the predominant source of stabilization of the transition state.

For the hydrolysis of dimethyl acetals of ketones, just the opposite effect is observed. The data of Table II show an inverse relationship of the acetal formation rates to the acetal hydrolysis rates for substituent changes; thus, the formation rates parallel the formation equilibria and the hydrolysis rates parallel the hydrolysis equilibria.

The transition state is positively charged for these acetals just as it is for the benzaldehyde acetals and for both directions of reaction. These positively charged transition states should be stabilized by electron-donating groups for either direction if the polar effect is the predominant source of stabilization. The fact that the formation and hydrolysis rates are not parallel for changes in alkyl substituents suggests that the predominant control is not by polar effects. Furthermore, if one accepts the arguments of Ritchie and Sager[16] that all alkyl groups have the same polar qualities then one is left with the main possibility of a steric effect controlling the small changes in rates which are observed.

It is evident that there is at least a qualitative relationship between the forward and reverse rates and the sizes of the alkyl groups. In the formation reaction the steric effect operates to retard the rates and equilibria because the larger the group the less favored is the change from sp^2 geometry to the developing sp^3 geometry of the transition state or of the product acetal. Just the opposite should be and is observed for acetal hydrolysis. With a bulkier alkyl group change, such as isobutyl in place of methyl, there is a particularly large enhancement in rate just as Kreevoy and Taft observed for the neopentyl and *tert*-butyl groups.[7]

We have suggested[4] that one should not expect all classes of carbonyl compounds to have their rates of acetal hydrolysis lie on a single linear free energy correlation line. It did not seem that aromatic aldehydes should correlate on the same line with aliphatic ketones and with aliphatic aldehydes as Kreevoy and Taft[7] were able to accomplish by the use of a hyperconjugation parametric term on the Taft equation for the rates of hydrolysis of diethyl acetals. The reason for our suggestion was that the contributions of $\Delta S^\ddagger$ to $\Delta G^\ddagger$ were unknown and could distort the validity of the correlations. We reported that ΔS values were about −24 to −28 eu for the equilibrium formation of dimethyl acetals of aromatic aldehydes while ΔS values were about −30 to −36 eu for both cyclic and acyclic ketones. We suggested that a similar effect might be observed for the entropies of activation for acetal hydrolysis.

We have reported $\Delta S^\ddagger$ values for the hydrolysis of dimethyl acetals of para-substituted benzaldehydes to be near zero (−1 to +4 eu).[3] These values are in line with what one would expect for a unimolecular process even though that may not be the case for this system. As can be seen in Table 1, $\Delta S^\ddagger$ values for the hydrolysis of the dimethyl acetals of ketones are considerably more positive than for the dimethyl acetals of substituted benzaldehydes. These values vary from near zero to nearly +15 eu and are all positive. On this basis we reemphasize our previous point[4] that parametric corrections should not be made for linear free energy correlations in the absence of activation parameters. Our results were obtained in 95% methanol–5% water while Kreevoy and Taft worked in 50% water–dioxane and it may be that comparisons between results for the two different solvents should not be made. However, we think that the conclusions made are valid since the ρ values obtained for ketal hydrolysis are not significantly different (theirs −3.60 and ours −4.29).

It appears to us that the so-called hyperconjugation term of Kreevoy and Taft may be an entropic contribution to the free energy of activation, at least for ketal hydrolysis. This effect may be steric in origin as Wiberg has suggested.[18]

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Structures of Isomeric Grignard Compounds Derived from 2,2-Diphenylethyl 2,4,6-Trimethylphenyl Ketone and Their Corresponding Enol Benzoates[1]

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Enol benzoates I and II formed from reactions of magnesium enolates I and II with benzoyl chloride are determined to have *E* and *Z* configurations, respectively. The configurations are established using the vinyl substituent shielding constants of Pascual et al.[7] and Tobey.[8] The corresponding magnesium enolates, I and II, likewise have *E* and *Z* configurations. Magnesium enolate I is formed from the reaction of benzalacetomesitylene (1) and phenylmagnesium bromide; magnesium enolate II is formed from the reaction of 2,2-diphenylethyl 2,4,6-trimethylphenyl ketone (2) and ethylmagnesium bromide. Cryoscopic studies in naphthalene show that magnesium enolates I and II are both monomeric; this together with other evidence indicates that they contain tricoordinate magnesium analogous to the Grignard compound derived from isopropyl mesityl ketone.[6] Ir spectra confirm the enolic nature of the magnesium compounds, I and II.

In 1935 Kohler, Tishler, and Potter[3] reported the preparation of the bromomagnesium derivative of 2,2-diphenylethyl 2,4,6-trimethylphenyl ketone (2) by three routes (Scheme I): (A) 1,4 addition of phenylmagnesium bromide to benzalacetomesitylene (1); (B) action of Grignard reagent on 2,2-diphenylethyl 2,4,6-trimethylphenyl ketone (2); (C) action of Grignard reagent on 2,2-diphenyl-1-bromoethyl 2,4,6-trimethylphenyl ketone (3). They noted that the magnesium compounds prepared by route A vs. those from routes B and C formed stereoisomeric (cis–trans) enol benzoates (4) in high yield (ca. 96%) on reaction with benzoyl chloride. A high-melting benzoate (162°) was formed by the first method and a lower melting benzoate (142°) by the other two methods (Scheme II). They reasoned that the magnesium compounds were the corresponding magnesium enolates.

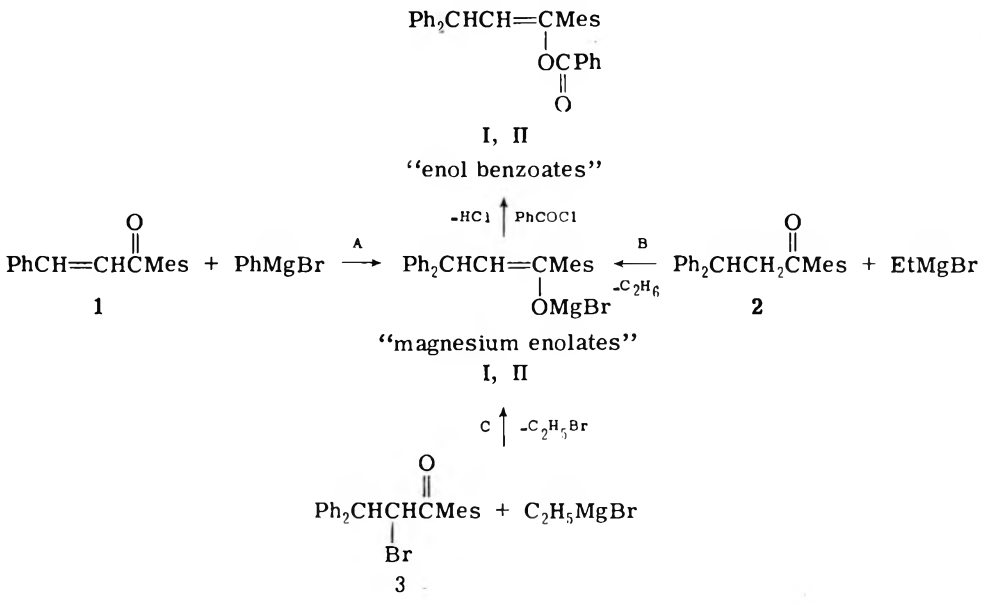
Nesmeyanov, Sazonova, and Landor[4] characterized the isomeric enol benzoates and bromomagnesium derivatives from routes A and B by elemental analysis, which showed that the latter each contained one molecule of ether. (The benzoates were also previously analyzed by Kohler et al.[3]) The compound from route A was about ten times as soluble in benzene as that from route B and only the former compound was oxidized to peroxide by atmospheric oxygen. Both isomers formed the same ketone quantitatively on hydrolysis. The authors concluded that solubility of the magnesium compounds in benzene as well as absence of interconversion excluded consideration of mesomeric anionic forms. However, neither the Nesmeyanov group nor the earlier Kohler group were able to assign cis–trans structures to the isomeric magnesium enolates or enol benzoates and the molecular states of aggregation of the former were not determined.

In connection with our interest in the structures of Grignard compounds derived from methyl[5] and isopropyl[6] mesityl ketones, it was thought that the characterization and assignments of the isomeric structures of the magnesium enolates and corresponding enol benzoates would aid in the determination of the structures of Grignard compounds derived from alkyl mesityl ketones which were under investigation at the time.

Results and Discussion

Configuration of Enol Benzoates. Enol benzoates I and II were prepared by treating magnesium enolates I and II with benzoyl chloride according to the procedure of Kohler et al.[3] as modified by Nesmeyanov et al.[4] (The designations I and II by the latter group are retained in the present paper in order to maintain continuity with the previous workers.) The relationships are outlined in Schemes I and

Scheme I

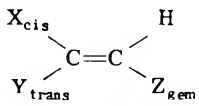


Scheme II

"magnesium enolate I" ⟶ "enol benzoate I" (mp 162°) (via route A)

"magnesium enolate II" ⟶ (via routes B and C) "enol benzoate II" (mp 142°)

II. The configurations were established mainly from ^{1}H NMR data. The principal feature was the chemical shift of the vinyl proton which was compared with the values calculated by using the concept of additivity of vinyl substituent shielding constants as developed by Pascual et al.[7] and Tobey.[8] The chemical shift of the vinyl proton can be calculated from eq 1 where −5.27 represents the value for unsubstituted ethylene. The substituent shielding constants in Table I taken from the literature were used. Since no values for the diphenylmethyl group have been reported, the value for the benzyl group was used.[9] The calculations for *Z* and *E* configurations are shown. These values check



$$\delta_{ppm} = -5.27 + \sigma_{cisX} + \sigma_{transY} + \sigma_{gemZ} \quad (1)$$

$$Z: \delta_{ppm} = -5.27 + 0.11 + 0.51 - 1.05 = -5.70$$

$$E: \delta_{ppm} = -5.27 + 0.10 - 0.15 - 1.05 = -6.37$$

very well with those observed for the vinyl protons of enol benzoate I at −5.75, establishing it as having the *Z* configuration, and enol benzoate II at −6.35, which indicates the *E* isomer. From molecular models, the vinyl proton of the *Z* isomer is apparently in the shielding zone of the mesityl ring, this being in accord with observations. The other ^{1}H NMR assignments are clear-cut and are given in the Experimental Section.

Magnesium Enolates. A. Molecular Weight Determinations. The two enolates were prepared by the Kohler[3] and Nesmeyanov[4] procedures. As reported, the magnesium enolate obtained as a precipitate from the reaction of phenylmagnesium bromide and benzalacetomesitylene (1) in diethyl ether was soluble in dry benzene at room temperature to the extent of 10–15 wt % and was recrystallized from this solvent. This is designated "magnesium enolate I". "Magnesium enolate II", obtained as a precipitate from the reaction of ethylmagnesium bromide and 2,2-diphenylethyl 2,4,6-trimethylphenyl ketone (2), was only soluble to the extent of 1–2 wt % in benzene. The molecular weights of these samples were determined by a cryoscopic method[10] using naphthalene. The results obtained show a molecular weight of 521 ± 26 (average of four runs with four to six determinations per run) for magnesium enolate I and 501 ± 5 (average of two runs with six determinations per run) for magnesium enolate II. The calculated molecular weight for the formula $C_{28}H_{33}O_2MgBr$ is 506 so the respective *i* values are 1.03 for enolate I and 0.990 for enolate II. (*i* values are defined[11] as the degree of association = *i* = experimental mol wt/theoretical mol wt.) These results show that each enolate is coordinated with one molecule of ether and is monomeric in naphthalene. Thus, these two enolates can be added to the examples in which magnesium is tricoordinate.[6]

The following points can be made concerning the possibility of solute association at higher concentrations. Enolate I was measured over a concentration range of 8–12.2 wt % and no trend in values with concentration was discernible. Enolate II was measured at a lower concentration of 1.8–2.0 wt % because of its lower solubility. However, at concentrations of 2–3%, the Grignard compound derived from methyl mesityl ketone was found[5] to be a dimer, showing that no dissociation occurred at a low concentration under similar conditions, whereas the corresponding compound derived from isopropyl mesityl ketone was a monomer[6] at comparable concentrations. The molecular weights for both of these compounds were also determined at comparable concentrations by cryoscopy in benzene with comparable results, showing no appreciable effects of temperature or solvent changes.

Concerning the assignment of the two magnesium enolates of the present work as having tricoordinate magnesium, this is based on the following considerations. The elemental analyses and molecular weight determinations clearly establish that the compounds are monoetherates and not dietherates. For monomeric dietherates, the molecular weight would have deviated by about 15% from the value found, and the elemental analyses also by a substantial amount. Since the compounds are monoetherates, there are only three atoms bound to magnesium, since the possibility of forming a dimer was excluded. The reason for the inability to dimerize in the present cases is apparently the same as that suggested for the isopropyl case,[6] that is, steric crowding by the diphenylmethyl group preventing cyclization which results in dimer formation.

B. Structural Considerations. The infrared spectra of the magnesium enolates both show C=C stretching bands as a doublet at 1658 and 1650 cm^{-1}, in excellent agreement with those observed[5,6] for magnesium enolates derived from alkyl mesityl ketones. This establishes the enolate nature of these compounds.

Since enol benzoate I, obtained in high yield from reaction of magnesium enolate I with benzoyl chloride, was shown to have different physical properties from enol benzoate II, which was obtained in high yield in the same manner from magnesium enolate II, the configurations of the magnesium enolates are retained and are directly related to the configurations of the enol benzoates. Since reaction must necessarily occur at the O–Mg bond, magnesium enolate I must have the *Z* configuration and magnesium enolate II the *E* configuration. The correlations between the benzoates and the magnesium enolates are in Scheme III. If isomerization had occurred during the reaction, a mixture of enol benzoates would have been obtained, or the same

Table I
^{1}H NMR Substituent Shielding Constants[e] for Some Vinylic Substituents

Substituent	σ_{cis}	σ_{trans}	σ_{gem}	Ref
$PhCO_2$	+0.10	+0.51	−2.46	*a*
2,4,6-Me_3Ph	+0.11	−0.15	−1.36	*b*
$ArCH_2$	+0.29	+0.32	−1.05	*c*
XMgO	+0.86	+1.11		*d*

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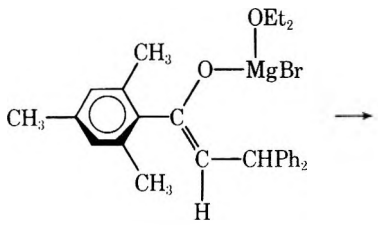
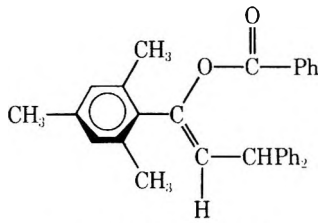
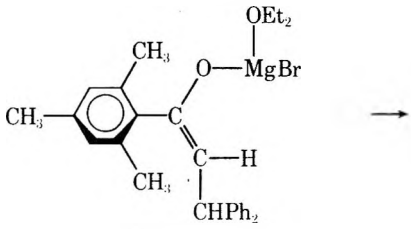
Scheme III



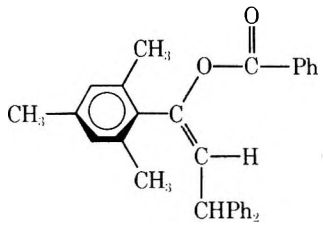
"magnesium enolate I"
(via route A) *Z* configuration



"enol benzoate I"
(*Z*)-(1-mesityl-2-diphenylmethyl)vinyl benzoate



"magnesium enolate II"
(via routes B and C) *E* configuration



"enol benzoate II"
(*E*)-(1-mesityl-2-diphenylmethyl)vinyl benzoate

isomer would be obtained from both reactions (depending on whether or not equilibrium was attained).

Experimental Section

2-Phenylvinyl 2,4,6-trimethylphenyl ketone (benzalacetomesitylene, 1) was prepared by (a) sodium hydroxide catalyzed condensation of acetomesitylene and freshly distilled benzaldehyde according to the procedure of Kohler and Barnes[12] in 97.4% crude yield, mp 60.5–61.5° after recrystallization from petroleum ether (bp 30–60°) (lit.[13] mp 63°) [the recrystallized product showed a single spot, R_f 0.56, on a thin layer chromatogram [80% chloroform–20% carbon tetrachloride mixture on silica gel–poly(ethylene terephthalate); Eastman Chromatogram type K301R]]; (b) Friedel–Crafts aluminum chloride catalyzed acylation of mesitylene with cinnamoyl chloride in carbon disulfide using a modification of the procedures of Kohler[14] and Nesmeyanov and Sazonova,[13] 82% yield, mp 62.5–63.0° after recrystallization from petroleum ether.

Ir and ^{1}H NMR spectra showed that the same trans product was obtained from the two different methods of preparation. A trans or *E* configuration is assigned on the basis[15] of the coupling constant ($J_{H_\alpha H_\beta}$) of 16.5 Hz for the vinyl protons at δ 6.82 and 7.18, respectively, for H_α and H_β. The other ^{1}H NMR assignments (CCl_4) are: δ 2.14 (*o*-CH_3), 2.28 (*p*-CH_3), 6.88 (two ArH on Mes), 7.41 m (C_6H_5). Ir (CCl_4) 1681 sh, 1650 s (C=O), 1629 s, 1610 s, 1582 cm^{-1} m (C=C stretch, aliphatic). The two carbonyl bands and C=C stretching bands result from s-cis–s-trans isomerism of the conjugated enone system.[16]

2,2-Diphenylethyl 2,4,6-trimethylphenyl ketone (2) was prepared by the hydrolysis of the bromomagnesium compound obtained from the reaction of phenylmagnesium bromide and benzalacetomesitylene (1) according to the method of Kohler et al.[3] A yield of 95% (lit.[4] quantitative) was obtained after three recrystallizations from absolute ethanol: mp 80–82° (lit.[3,4] mp 82°); ^{1}H NMR ($CDCl_3$) δ 1.89 (*o*-CH_3), 2.22 (*p*-CH_3), 3.46 (d, J_{CH_2CH} = 7.2 Hz), 4.80 (t, CH), 6.75 (two ArH on Mes), 7.24 (m, Ph_2); ir (mineral oil) 1689 cm^{-1} s (C=O).

Preparation of "Magnesium Enolate I" [Bromo Grignard Compound from Reaction of Phenylmagnesium Bromide and Benzalacetomesitylene (1)]. The general procedures of Kohler et al.[3] and Nesmeyanov et al.[4] were followed. The initial precipitate was recrystallized from dry benzene, the crystals forming after standing for several days in a nitrogen-filled drybox: ir (mineral oil) 1658, 1650 (C=C stretch, aliphatic), 1613 cm^{-1} (C=C stretch, aromatic).

Preparation of "Magnesium Enolate II" [Bromo Grignard Compound from Reaction of Ethylmagnesium Bromide and 2,2-Diphenylethyl 2,4,6-Trimethylphenyl Ketone (2)]. The general procedures of Kohler et al.[3] and Nesmeyanov et al.[4] were followed. The precipitated "enolate" was collected by vacuum filtration and washed with anhydrous ether: yield 73%; ir (mineral oil) 1658, 1650 (C=C stretch, aliphatic), 1613 cm^{-1} (C=C stretch, aromatic).

"Enol benzoate I" was prepared by the reaction of "magnesium enolate I" with benzoyl chloride according to the general procedure of Kohler et al.[3] and Nesmeyanov et al.[4] The initial crude product was recrystallized twice from acetone: mp 162–163° (lit. mp 161°,[3] 162°[3,4]); ^{1}H NMR ($CDCl_3$) δ 2.24 (o-Me), 2.41 (*p*-Me), 5.23 (d, CH, $J_{CH,CH=}$ = 10.1 Hz), 5.75 (d, CH=), 6.82 (*m*-Mes-H), 7.23 (Ph_2), 7.41 (m, *m*- + *p*-C_6H_5C=O); ir (mineral oil) 1736 (C=O stretch), 1689 (C=C stretch, aliphatic), 1613 cm^{-1} (C=C stretch, aromatic).

"Enol benzoate II" was prepared by the reaction of "magnesium enolate II" with benzoyl chloride following the general procedure of Kohler et al.[3] and Nesmeyanov et al.[4] The initial product was recrystallized twice from acetone, mp 143–145° (lit. mp 142°,[3] 145°[4]). (The 148° value also given in the Kohler paper is apparently in error.) The melting point range of a 1:1 mixture of enol benzoates I and II was 126–134°: ^{1}H NMR ($CDCl_3$) δ 2.29 (o-Me), 2.25 (*p*-Me), 4.48 (d, -CH-, $J_{CH,CH=}$ = 11.0 Hz), 6.35 (d, CH=), 6.88 (*m*-MesH_2), 7.19 (Ph_2), 7.41 (m, *m*- + *p*-C_6H_5C=O), 8.01 (m, *o*-C_6H_5C=O); ir (mineral oil) 1733 (C=O stretch), 1689 (C=C stretch, 8.01, aliphatic), 1615 cm^{-1} (C=C stretch, aromatic).

Instruments and Methods. Reactions and operations using moisture- and oxygen-sensitive compounds were carried out in a nitrogen-filled drybox. Phosphorus pentoxide spread on vermiculite was used as a desiccant in the drybox and as part of a drying train for the nitrogen. Traces of oxygen were removed by bubbling through Fieser's solution.[17]

Ir spectra were taken on a Perkin-Elmer Model 337 grating spectrophotometer. Band positions were calibrated against polystyrene film.

^{1}H NMR spectra were taken with Varian Associates Models DP-60 or A56/60A spectrometers on samples having concentrations of 10–15% w/v, Me_4Si internal reference.

Melting points were determined with a modified Thiele apparatus using a calibrated thermometer.

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Registry No.—**1**, 55800-30-1; **2**, 55800-31-2; magnesium enolate I, 55869-68-6; magnesium enolate II, 55800-34-5; enol benzoate I, 55800-32-3; enol benzoate II, 55800-33-4; acetomesitylene, 1667-01-2; benzaldehyde, 100-52-7; mesitylene, 108-67-8; cinnamoyl chloride, 102-92-1; benzoyl chloride, 98-88-4.

References and Notes

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A Low-Pressure, Palladium-Catalyzed *N,N'*-Diarylurea Synthesis from Nitro Compounds, Amines, and Carbon Monoxide

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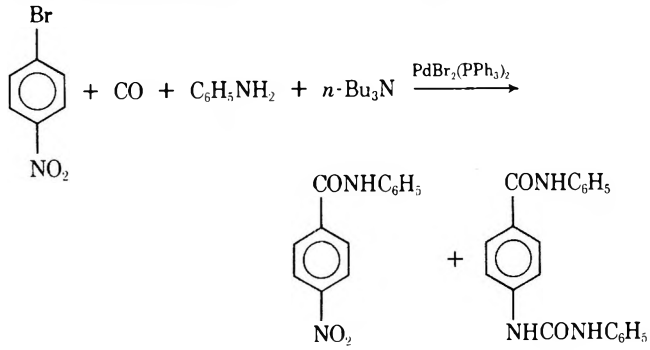
Aromatic primary amines, aromatic nitro compounds, and carbon monoxide react in the presence of catalytic amounts of palladium(II) salts, organic phosphines, a basic tertiary amine, and tetraethylammonium chloride at 90° under 1 atm pressure to form *N,N'*-diarylureas in moderate to good yields.

It was previously noted that the reaction of *p*-bromonitrobenzene, carbon monoxide, aniline, and a tertiary amine with $PdBr_2(PPh_3)_2$ as catalyst at 100° and 1 atm pressure led to the formation of considerable amounts of the *N*-phenylamide of 4-carboxydiphenylurea as well as the expected *N*-phenyl-*p*-nitrobenzamide.[1] We have now investigated the diarylurea formation in more detail.



It is known that aromatic nitro compounds can be treated with carbon monoxide under vigorous conditions to give urea derivatives. For example, nitrobenzene with water and 10,000 psi of carbon monoxide at 180° with a palladium–iron catalyst forms diphenylurea[2] and the same product is obtained in 54% yield when nitrobenzene is treated at 140° under 150 atm pressure with carbon monoxide and hydrogen using $[Ru(CO)_4]_3$ as catalyst.[3] We report in this paper a more versatile synthesis of diarylureas that occurs with only 1 atm pressure of carbon monoxide and at temperatures below 100°.

Results and Discussion

Preliminary experiments investigating the reaction of aniline and nitrobenzene with $Pd(OAc)_2$ plus 2 equiv of triphenylphosphine as catalyst under 1 atm of carbon monoxide revealed that both halide ion and a basic tertiary amine were necessary to cause the reaction to occur in reasonable yields. Without halide ion, the reaction stopped with less than 10% of the theoretical amount of CO being absorbed. It was also necessary to purge the apparatus frequently with fresh CO to remove accumulated CO_2 from the reaction vessel. The optimum reaction rate in xylene solution was achieved at about 90° using 15 mol % tetraethylammonium chloride, ~50 mol % tri-*n*-butylamine, 2 mol % palladium acetate, and 4 mol % triphenylphosphine based upon the aromatic amine used. The nitro compound was present in 10–100% excess of the molar amount of the aromatic amine. The reaction could be carried out in solvents other than xylene such as DMF, Me_2SO, and HMPA, but there appeared to be no rate or yield advantage in doing so. In xylene, the urea derivatives generally crystallized from the solution during the reaction while in DMF, Me_2SO, or HMPA they did not. The tetraethylammonium chloride salt was more effective than the bromide and it in turn was better than the iodide. The reaction rates were not very sensitive to the amount of the chloride added; however, the amount of tertiary amine which gave the greatest rate acceleration was about 1 g per 10 ml of xylene solvent. The reaction is presumed to occur according to the following equation.

$$ArNH_2 + ArNO_2 + 3CO \xrightarrow[n\text{-}Bu_3N]{Pd(PPh_3)_2X_2,\ Et_4N^+Cl^-} ArNHCONHAr + 2CO_2$$

The data obtained from these and related reactions appear in Table I. Reaction rates were estimated from the time required for half of the theoretical amount of CO required, according to the above equation, to be absorbed.

Various palladium complexes were tried as catalysts. Differences in the anions attached to the metal had only minor effects upon the reaction rates. Major effects were caused by changing the phosphine groups. Triphenylphosphine was the best ligand found. Tri-*o*-tolylphosphine and

Table I
Diarylurea Syntheses[a]

Amine (mmol)	Nitro compd (mmol)	Halide (mmol)	Tertiary amine (mmol)	Catalyst (mmol)	$T_{1/2}$, min[b]	Total CO, % of theory	Products (% yield)
$C_6H_5NH_2$ (10)	$C_6H_5NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	158	88	$(C_6H_5NH)_2CO$ (64)
$C_6H_5NH_2$ (10)	$C_6H_5NO_2$ (20)	$Et_4N^+Cl^-$ (0.5)	n-Bu_3N (2.7)	$PdClPh(PPh_3)_2$ (0.2)	170		
$C_6H_5NH_2$ (10)	$C_6H_5NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$PdClPh(PPh_3)_2$ (0.2)	165		
$C_6H_5NH_2$ (10)	$C_6H_5NO_2$ (20)	$Et_4N^+Cl^-$ (3.0)	n-Bu_3N (2.7)	$PdClPh(PPh_3)_2$ (0.2)	169		
p-$CH_3C_6H_4NH_2$ (10)	p-$CH_3C_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	155	85	$(p$-$CH_3C_6H_4NH)_2CO$ (69)
p-$CH_3OCOC_6H_4NH_2$ (10)	p-$CH_3OCOC_6H_4NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	99	111	$(p$-$CH_3OCOC_6H_4NH)_2CO$ (81)
p-$ClC_6H_4NH_2$ (10)	p-$ClC_6H_4NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	90	97	$(p$-$ClC_6H_4NH)_2CO$ (66)
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	100	94	p-$ClC_6H_4NHCONHC_6H_5$ p-$ClC_6H_4NH)_2CO$ $(C_6H_5NH)_2CO$ (50)[c,j]
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	56	112	p-$ClC_6H_4NHCONHC_6H_5$ $(p$-$ClC_6H_4NH)_2CO$ $(C_6H_5NH)_2CO$ (~60)[c,j]
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$Pd(OAc)_2$ (0.2) + Ph_3P (0.4)	93	97	
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$PdCl_2(PPh_3)_2$ (0.2)	131	106	
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$Pd(Cl)Ph(PPh_3)_2$ (0.2)	89	106	
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$Pd(Br)Ph(PPh_3)_2$ (0.2)	91	115	
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$Pd(PPh_3)_4$ (0.2)	105		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (4.0)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	62		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	56		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (8.0)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	72		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (11)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	82		
$C_6H_5NH_2$ (10)	p-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	n-Bu_3N (2.7)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	96		

$C_6H_5NH_2$ (10)	*p*-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	*n*-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	87[d]	
$C_6H_5NH_2$ (10)	*p*-$ClC_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	*n*-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	72[e]	
$C_6H_5NH_2$ (10)	*p*-$ClC_6H_4NO_2$ (20)	$Et_4N^+Br^-$ (1.5)	*n*-Bu_3N (2.7)	$Pd(Br)Ph(PPh_3)_2$ (0.2)	120	
$C_6H_5NH_2$ (10)	*p*-$ClC_6H_4NO_2$ (20)	$Et_4N^+I^-$ (1.5)	*n*-Bu_3N (2.7)	$Pd(Br)Ph(PPh_3)_2$ (0.2)	~600[f]	
p-$CH_3C_6H_4NH_2$ (10)	*p*-$CH_3OCOC_6H_4NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	*n*-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	51	87	*p*-$CH_3C_6H_4NHCONHC_6H_4COOCH_3$ (28)[g] (*p*-$CH_3C_6H_4NH)_2CO$ (21)[h] (*p*-$CH_3OCOC_6H_4NH)_2CO$ (6)[h]
p-$CH_3OCOC_6H_4NH_2$ (10)	*p*-$CH_3C_6H_4NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	*n*-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	296	58	*p*-$CH_3C_6H_4NHCONHC_6H_4COOCH_3$ (22)[i] (*p*-$CH_3C_6H_4NH)_2CO$ (5)[h] (*p*-$CH_3OCOC_6H_4NH)_2CO$ (10)[h]
p-$CH_3C_6H_4NH_2$ (10)	$C_6H_5NO_2$ (11)	$Et_4N^+Cl^-$ (1.5)	*n*-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	88	89	*p*-$CH_3C_6H_4NHCONHC_6H_4$ (*p*-$CH_3C_6H_4NH)_2CO$ ($C_6H_5NH)_2CO$ } (~44)[j]
$C_6H_5CH_2NH_2$ (10)	$C_6H_5NO_2$ (20)	$Et_4N^+Cl^-$ (1.5)	*n*-Bu_3N (5.4)	$Pd(OAc)_2$ (0.2) + PPh_3 (0.4)	53	71	($C_6H_5CH_2NH)_2CO$ (17)[k]

[a] Carried out at 90° with 1 atm of CO and 10 ml of xylene as solvent. [b] The time required for absorption of 5 mmol of CO. This is approximate since no correction was made for the difference in solubility of CO and CO_2 in the reaction medium. [c] No *p*-chloroaniline could be detected by VPC in this reaction mixture. [d] Carried out at 80°. [e] Carried out at 100°. [f] Extrapolated value. [g] Methyl *p*-aminobenzoate was shown to be formed in the reaction by VPC. [h] Based on a theoretical yield of 10 mmol of diarylurea. [i] *p*-Toluidine was shown to be formed in the reaction by VPC. [j] Composition of mixture was not determined. [k] Other ureas were also present but were not specifically identified.

triphenyl phosphite did not catalyze the reaction significantly under the usual conditions.

Reaction rates and yields varied with the substituents present in the aromatic amine and the nitro compound. With an electron-supplying group in the amine (*p*-toluidine) the reaction rate increased, while with a withdrawing group (methyl *p*-aminobenzoate) the rate decreased relative to aniline. The *p*-chloro group in *p*-chloraniline, however, had little effect. In the nitro compound the effects were larger and reversed in the few examples investigated. The reaction of *p*-toluidine with methyl *p*-nitrobenzoate proceeded nearly six times faster than the reverse combination of methyl *p*-aminobenzoate with *p*-nitroaniline. In the last case the reaction stopped with absorption of only 58% of the required amount of CO while the reverse combination absorbed 87%, even with a much smaller excess of the nitro compound.

In most of the instances where amines and nitro compounds with different substituents were reacted, mixtures of the unsymmetrical and symmetrical ureas were formed with the expected, unsymmetrical products predominating. The reaction mixtures also usually contained some of the amine expected from reduction of the nitro compound employed. The urea mixtures obtained were not readily separable by crystallization so analyses were made where possible from the NMR spectra of the mixtures by comparing the areas under the different NH-proton absorptions. The NMR spectral data, melting points, and analyses of the products prepared are listed in Table II.

Control experiments showed that neither methyl *p*-aminobenzoate nor *p*-toluidine reacted with diphenylurea significantly under the urea formation reaction conditions, indicating that mixing of aryl groups did not occur by a simple nucleophilic attack of amine on the urea. *p*-Toluidine and *N*-phenyl-*N'*-*p*-tolylurea likewise did not react in the presence of palladium acetate, triphenylphosphine, tri-*n*-butylamine, and tetraethylammonium chloride at 90° in xylene solution in 24 hr.

A reaction of *p*-toluidine with *p*-nitrotoluene was carried out in the presence of diphenylurea with the result that only a trace of aniline was detected in the reaction mixture. Aniline was found in significant amount when nitrobenzene and *p*-toluidine were allowed to react. Thus, the mixing of aryl groups must be occurring in some intermediate palladium complex.

The mechanism of the urea formation is obscure. Presumably the catalyst is reduced initially and the nitro compound complexes with it, but attempts to isolate or identify such an intermediate have failed. Heating nitrobenzene with a molar amount of tetrakis(triphenylphosphine)palladium(0) under CO at 90° causes a darkening of the solution to a yellow-brown color but no gas is absorbed and only an intractable dark-colored gum could be obtained from the solution. Analyses by VPC failed to show the presence of free nitrobenzene, nitrosobenzene, or phenyl isocyanate. Intermediate arylnitroso, nitrene, and isocyanate palladium complexes can be imagined, but we have not obtained evidence to indicate that any of these are actually formed.

Experimental Section

General Procedure for the Preparation of Diarylureas. The indicated amounts of the nitro compound, aromatic amine, tri-*n*-butylamine, tetraethylammonium chloride, and 10 ml of xylene were placed in a 100-ml jacketed flask equipped with a magnetic stirring bar and a stopcock attachment from which was suspended a Teflon cup containing the palladium catalyst. The flask was then attached to a microhydrogenation-type apparatus.[4] The apparatus was evacuated and filled several times with carbon monoxide, then brought to the proper temperature (constant-temperature bath)

Table II
Physical Properties and Analytical Data for *N,N'*-Diarylureas

Compd	Mp, °C (reported)	NMR spectrum, τ, ppm
$(C_6H_5NH)_2CO$	235–236 (235)[a]	(Me_2SO-d_6) s 1.29 (2 H), m 2.25–3.15 (10 H)
$(p\text{-}ClC_6H_4NH)_2CO$	303–305 (306–307)[b,d]	(polysol) s 1.09 (2 H), d 2.27 (4 H), d 2.53 (4 H) (J = 10 Hz)
$(p\text{-}CH_3C_6H_4NH)_2CO$	253–264 (264)[c,d]	(Me_2SO-d_6) s 1.39 (2 H), d 2.52 (4 H), d 2.83 (4 H) (J = 8 Hz), s 7.74 (6 H)
$(p\text{-}CH_3OCOC_6H_4NH)_2CO$	258–258.5[d]	(polysol) s 0.78 (2 H), d 1.93 (4 H), d 2.27 (4 H) (J = 9 Hz), s 6.07 (6 H)

[a] T. L. Davis and K. C. Blanchard, "Organic Syntheses", Collect. Vol. I, Wiley, New York, N.Y., 1964, p 453. [b] M. H. Vittenet, *Bull. Soc. Chim. Fr.*, **21**, 302 (1899). [c] T. L. Davis and H. W. Underwood, Jr., *J. Am. Chem. Soc.*, **44**, 2595 (1922). [d] Satisfactory analytical values (±0.2% for C, H, N, and Cl when present) were reported for these compounds.

and allowed to come to equilibrium at 1 atm pressure. The Teflon cup containing the palladium catalyst was then dropped into the reaction mixture. Gas volume changes and times were periodically recorded until gas absorption stopped. Because of the formation of carbon dioxide in the reactions, stirring was stopped and the system was evacuated and refilled with carbon monoxide at 50-ml intervals. When gas absorption stopped the reaction mixture was cooled to room temperature, diluted with ca. 300 ml of hexane, and filtered. The solid, insoluble urea was then recrystallized from ethanol.

Attempted Reaction of *N*-Phenyl-*N'*-*p*-tolylurea with *p*-Toluidine. *N*-Phenyl-*N'*-*p*-tolylurea (1.13 g, 5 mmol), 0.59 g (5 mmol) of *p*-toluidine, 1.0 g (5.4 mmol) of tri-*n*-butylamine, 0.249 g (1.5 mmol) of tetraethylammonium chloride, 0.045 g (0.2 mmol) of palladium acetate, 0.104 g (0.4 mmol) of triphenylphosphine, and 10 ml of xylene were mixed at 90° in a CO atmosphere in the same manner described in the general procedure for the preparation of ureas. After stirring for 24 hr at 90° only about 4 ml of CO had been absorbed. The reaction mixture was dissolved in about 400 ml of methylene chloride which was then extracted with two 400-ml portions of 40% hydrochloric acid, washed with 400 ml of water, dried over magnesium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was analyzed by NMR. The NMR spectra of the residue showed that it consisted entirely of *N*-phenyl-*N'*-*p*-tolylurea and that no *N,N'*-di-*p*-tolylurea or *N,N'*-diphenylurea was formed.

***N,N'*-Di-*p*-tolylurea Formation in the Presence of *N,N'*-Diphenylurea.** *p*-Nitrotoluene (1.51 g, 11 mmol), 1.07 g (10 mmol) of *p*-toluidine, 0.249 g (1.5 mmol) of tetraethylammonium chloride, 1.0 g (5.4 mmol) of tri-*n*-butylamine, 0.045 g (0.2 mmol) of palladium acetate, 0.104 g (0.4 mmol) of triphenylphosphine, and 10 ml of xylene were allowed to react at 90° as described in the general procedure with 1.84 g (10 mmol) of *N,N'*-diphenylurea also present in the reaction mixture. After 30 hr CO absorption had stopped and about half of the theoretical amount of CO had been absorbed by the system. The reaction mixture was then examined by VPC. Although a trace of aniline was detected, this was not enough to indicate that any appreciable amount of exchange had taken place.

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Registry No.—$C_6H_5NH_2$, 62-53-3; $p\text{-}CH_3C_6H_4NH_2$, 106-49-0; $p\text{-}CH_3OCOC_6H_4NH_2$, 619-45-4; $p\text{-}ClC_6H_4NH_2$, 106-47-8; $C_6H_5CH_2NH_2$, 64-04-0; $C_6H_5NO_2$, 98-95-3; $p\text{-}CH_3C_6H_4NO_2$, 99-99-0; $p\text{-}CH_3OCOC_6H_4NO_2$, 619-50-1; $p\text{-}ClC_6H_4NO_2$, 100-00-5; $Et_4N^+Cl^-$, 56-34-8; *n*-Bu_3N, 102-82-9; $Pd(OAc)_2$, 3375-31-3; Ph_3P, 603-35-0; $PdClPh(PPh_3)_2$, 22605-84-1; $PdCl_2(PPh_3)_2$, 13965-03-2; $PdBrPh(PPh_3)_2$, 30643-33-5; $Pd(PPh_3)_4$, 14221-01-3; $(C_6H_5NH)_2CO$, 102-07-8; $(p\text{-}ClC_6H_4NH)_2CO$, 1219-99-4; $(p\text{-}CH_3C_6H_4NH)_2CO$, 621-00-1; $(p\text{-}CH_3OCOC_6H_4NH)_2CO$, 56050-99-8; CO, 630-08-0.

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Phase Transfer Catalyzed Reactions. I. Highly Stereoselective Formation of the Thermodynamically Less Stable Manno Isomers from Nitro Sugars with Active Methylene Compounds

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A phase transfer process was applied to the reaction of 3-nitro-2-enopyranoside (2) with some active methylene compounds to give thermodynamically less stable manno pyranosides in fairly good yields. In the case of acetylacetone deacetylation occurred to yield 5, but under milder conditions product 8 was obtained exclusively. The reaction of 2 with malononitrile gave a mixture comprised of gluco and manno isomers (11 and 12); the latter was proved to epimerize to the former under the same conditions.

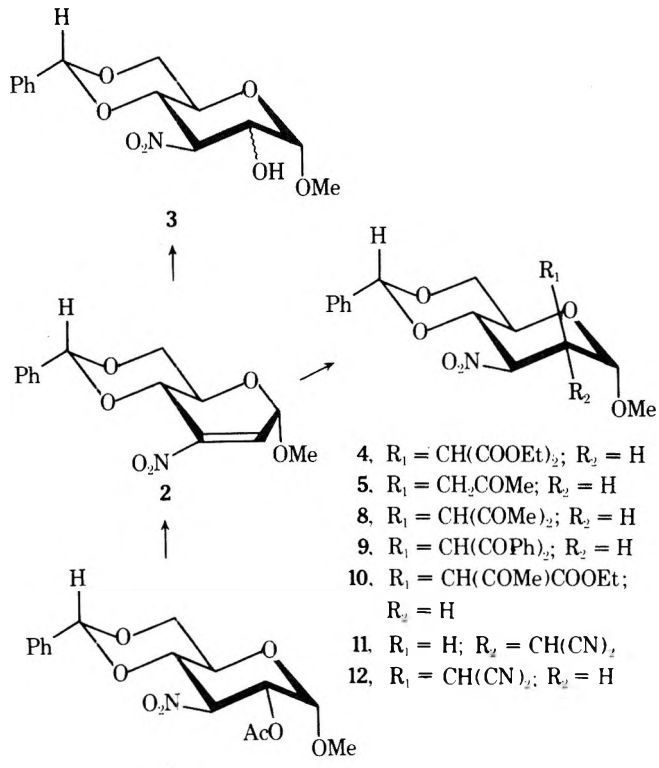
It is well known that the Michael reaction generally affords the thermodynamically more stable product because it is reversible.[1] Thus, very few examples[2] are known of stereoselective synthesis of the thermodynamically less stable isomer from nitro olefins, which are useful acceptors in the Michael reaction.

In recent years, on the other hand, great interest has developed in *phase transfer catalyzed two-phase reactions*.[3] One of the advantages of this method is that species existing in the organic phase and sensitive to hydrolysis, isomerization, etc., are more or less protected from water as well as a reagent or catalyzer in the aqueous phase.[4] This suggests such phase transfer might suppress the retro-Michael reaction to give the kinetically controlled product.[5]

We should like to report that the thermodynamically less stable manno derivatives can be prepared by the reaction of nitro sugars (1, 2) with some active methylene compounds under the phase transfer conditions in fairly good yields.[6]

Results and Discussion

Reaction of 1 or 2 with ethyl malonate in benzene–0.2 *N* NaOH (excess) was not induced at room temperature even after vigorous stirring for 16 hr. When 2 was similarly treated with acetylacetone for 20 hr, almost all of 2 was recovered, but on stirring for 70 hr, half of 2 was converted into nitro alcohol 3. These facts may be attributed to the inability of a carbanion generated in the aqueous phase and of nitro olefin remaining in the organic phase to combine. Addition of a small amount of hexadecyltributylphosphonium bromide as a phase transfer catalyst to the above two-phase reaction of 1 with ethyl malonate caused completion of the addition reaction within only 2 hr, giving methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-*C*-bis(ethoxycarbonyl)methyl-3-nitro-α-D-mannopyranoside (4) in over



70% yield. The manno configuration of 4 was assigned from NMR data (Table I): $J_{1,2}$ = 1.3, $J_{2,3}$ = 5.0, and $J_{3,4}$ = 10.6 Hz. The reaction doubtless proceeded via the intermediate nitro olefin 2 which arose from 1 by elimination of acetic acid and was subjected to the addition of ethyl malonate. In fact, treatment of 2 with ethyl malonate under the same conditions also afforded 4 in 74% yield. The yield of 4 was

Table I
100-MHz NMR Spectra in $CDCl_3$ (Me_4Si as an Internal Standard)

	Chemical shifts, δ							Coupling constants, Hz				
Compd	H^1	H^2	H^3	H^4	PhCH	H^8 [a]	CH_3CO	$J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{2,8}$
4	4.86	3.53	5.18	4.50	5.61	3.70		1.3	5.0	10.6	8.8	6.3
5	4.54	3.18–3.25	5.09	?	5.61	2.57–2.65	2.05	1.0	5.0	10.0	?	?
8	4.46	3.72	5.13	?	5.61	4.27	2.14 2.30	1.3	5.0	10.3	?	10.6
9	4.70	4.21	5.30	4.43	5.49	5.97		1.0	5.3	10.6	8.8	8.3
10	4.74	3.64	5.15	4.43	5.61	?	2.19	1.0	5.0	11.3	8.8	?
11	5.04	2.95	5.05	4.03	5.53	3.86		3.8	11.5	9.5	8.8	6.3
12	5.10	3.08	5.23	4.73	5.65	4.09		1.0	5.6	11.3	7.5	3.8

[a] H^8 means the acid methine or methylene proton(s) of a chain moiety.

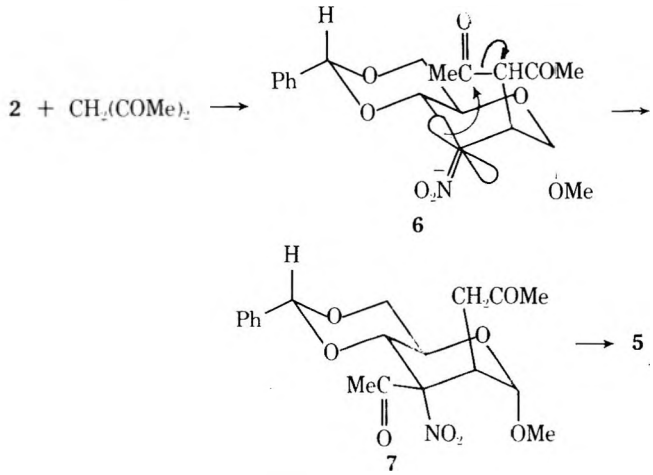
Table II
Reactions of 2 with Acetylacetone[a]

Expt	0.2 NaOH, ml	Benzene, ml	t-BuOH, ml	Catalyst, mg	Time, hr	Ratios of the products 5:8	
1	2.7	8		4	16	q[c]	*d*
2	2.7	2	1	4	1.5	q	*d*
3	2.7	2	2	4	1.5	q	*d*
4	1.0	3		6	2	1	2.2
5	0.1	3		2	2		q
6	0.1	3		2	24		q

[a] All the reactions were carried out by the use of 0.1 mmol of 2 and 0.18 mmol of acetylacetone. [b] Ratios of the products were determined by NMR spectroscopy. [c] q, quantitative or almost so. [d] Not detected by NMR spectroscopy.

improved up to 92% when the amount of sodium hydroxide was reduced to a trace.

Reaction of **2** with acetylacetone under the same conditions, on the other hand, afforded methyl 2-*C*-acetonyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-mannopyranoside (**5**). Its structure was deduced from the following data: the elemental analysis corresponded to $C_{17}H_{21}NO_7$; ir spectroscopy (KBr) showed the presence of carbonyl (1717 cm^{-1}) and nitro group (1550 cm^{-1}); NMR spectroscopy showed *C*-methyl (3 H, δ 2.05) and methylene signals (2 H, δ 2.57–2.62) as well as $J_{1,2}$ = 1.0, $J_{2,3}$ = 5.0, and $J_{3,4}$ = 10 Hz. On addition of *tert*-butyl alcohol as a proton source to the above reaction system, only **5** was formed similarly (expt 2, 3). If at the stage of nitronate ion (**6**) migration of an acetyl group from the newly formed diacetyl methyl moiety to C_3 is much faster than external protonation or internal proton migration from the acidic methine proton to C_3,[7] **5** should be easily formed because deacetylation from **7** probably occurs more easily than **8** owing to the stronger electron-withdrawing character of a nitro group than that of an acetyl group. When the reaction was carried



out under milder conditions (expt 5), the intended adduct (**8**) was obtained exclusively in good yields. Under these conditions **8** was not affected within 2–24 hr, but it was completely converted into **5** with or without acetylacetone under conditions similar to those used for the preparation of **4**. In these reactions no evidence for the simultaneous formation of both epimers of **5** and **8** was observed. These results suggest that **8** was first formed, which was subjected to deacetylation to give **5** prior to epimerization of **8**. On treatment of **2** with dibenzoylmethane in the presence of a catalytic amount of alkali, manno isomer **9** was obtained in good yield.

A similar reaction of **2** with ethyl acetoacetate gave a mixture, the NMR spectrum of which suggested the manno configuration ($J_{1,2}$ = 1.0, $J_{2,3}$ = 5.0, and $J_{3,4}$ = 11.3 Hz), but which showed two signals in the acetyl region (δ 2.35 and 2.19 with the ratio of 1:2) with 3 H intensity. This mixture, therefore, may consist of two manno isomers which differ in the chirality of the ethyl acetoacetate moiety. The major product could be isolated in a crystalline form but the isolation of the minor one has not been yet achieved.

Treatment of **2** with malononitrile in the presence of a trace of alkali for 2 hr gave a mixture of gluco (**11**) and manno isomer (**12**) in the ratio of 1:1.3 (by NMR spectroscopy), which were separated by column chromatography. The ratio of **12** to **11** decreased with the reaction time: 0.3 (6 hr), and 0.1 (24 hr), and finally **12** in the mixture was completely converted into **11**.[8]

These results are the first example to demonstrate the usefulness of a phase transfer catalyst in the Michael reaction. The result is a highly stereoselective formation of thermodynamically less stable isomers from nitro olefin derivative and active methylene compounds.

Experimental Section

All the melting points were determined in capillaries and are uncorrected. The ir spectra were determined in potassium bromide disks with a Hitachi 215 infrared spectrophotometer. The NMR spectra (Table I) were recorded at 100 MHz with a JNM-4H-100 (Jeol) spectrometer in chloroform-*d*, using tetramethylsilane as the internal standard. The column chromatography was carried out on silica gel (C-200, Wakogel). In this section the catalyst means hexadecyltributylphosphonium bromide.

Methyl 4,6-*O*-Benzylidene-2-*C*-bis(ethoxycarbonyl)methyl-2,3-dideoxy-3-nitro-α-D-mannopyranoside (4). A. From Nitro Acetate 1.[9] A mixture of **1** (105.9 mg, 0.3 mmol), ethyl malonate (69 mg, 0.43 mmol), benzene (24 ml), and 0.2 *N* NaOH (9.6 ml) was stirred for 2 hr at room temperature in the presence of the catalyst (12 mg) and then washed with water (3 × 5 ml). The benzene layer was evaporated in vacuo to give a syrup (98 mg, 72%), which was found to contain no by-product by NMR spectroscopy. The syrup was chromatographed on a silica gel column (13 × 65 mm) with benzene: yield 88.4 mg (65%); $[\alpha]^{20}D$ −33.4° (*c* 1, $CHCl_3$); ir (KBr) 1750, 1730 (COOEt), 1560, 1370 cm^{-1} (NO_2).

Anal. Calcd for $C_{21}H_{27}NO_{10}$: C, 55.62; H, 6.00; N, 3.09. Found: C, 56.01; H, 6.32; N, 3.07.

B. From Nitro Olefin 2.[9] In the same manner as described above except for the decreased amount of 0.2 *N* NaOH to 8.1 ml, reaction between **2** and ethyl malonate gave NMR spectroscopically pure **4** (101 mg, 74%). The yield increased to 92% when the amount of 0.2 *N* NaOH was further reduced to 0.1 ml.

Methyl 2-*C*-Acetonyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-mannopyranoside (5). To a solution of **2** (131.9 mg, 0.45 mmol), acetylacetone (90 mg, 0.9 mmol), the catalyst (18 mg), and benzene (36 ml) was added 0.2 *N* NaOH (12 ml). The reaction mixture was stirred for 2 hr at room temperature and then washed with water (3 × 10 ml). The organic layer was evaporated in vacuo to afford a NMR spectroscopically pure solid residue (147 mg, 93%). Recrystallization from ethanol gave 134 mg (85%) of **4**: mp 114–115°; $[\alpha]^{20}D$ +22.8° (c 1, $CHCl_3$); ir (KBr) 1717 (CO), 1550, 1370 cm^{-1} (NO_2).

Anal. Calcd for $C_{17}H_{21}NO_7$: C, 58.11; H, 6.02; N, 3.99. Found: C, 58.33; H, 6.06; N, 4.22.

Methyl 4,6-*O*-Benzylidene-2-*C*-(diacetyl)methyl-2,3-dideoxy-3-nitro-α-D-mannopyranoside (8). To a solution of **2** (58.6 mg, 0.2 mmol), acetylacetone (36 mg, 0.36 mmol), the catalyst (4 mg), and benzene (6 ml) was added 0.2 *N* NaOH (0.2 ml). The reaction mixture was stirred for 2 hr at room temperature and then washed with water (3 × 5 ml). The benzene layer was evaporated in vacuo to give a NMR spectroscopically pure residue (74 mg, 94%), which was crystallized from ethanol to give **8** (63.5 mg, 80.8%): mp 147.5–148.5°; $[\alpha]^{20}D$ −129° (*c* 1, $CHCl_3$); ir (KBr) 1728, 1708 (CO), 1552 cm^{-1} (NO_2).

Anal. Calcd for $C_{19}H_{23}NO_8$: C, 58.01; H, 5.89; N, 3.56. Found: C, 58.07; H, 5.85; N, 3.59.

Conversion of 8 into 5. Treatment of **8** (19.7 mg, 0.05 mmol) with or without acetylacetone (9 mg, 0.09 mmol) in benzene (4 ml)–0.2 *N* NaOH (1.4 ml) solution in the presence of the catalyst

(2 mg) for 2 hr at room temperature gave **5** exclusively on the basis of its NMR spectrum.

Methyl 4,6-*O*-Benzylidene-2-*C*-(dibenzoyl)methyl-2,3-dideoxy-3-nitro-α-D-mannopyranoside (9). Treatment of **2** (58.6 mg) with dibenzoylmethane (49 mg, ca. 0.22 mmol) under the conditions used to prepare **8** gave a pure crystalline residue of **9** (88 mg, 85%). The residue (176 mg) was recrystallized from ethanol: yield 149 mg (72%); mp 214° dec; $[\alpha]^{20}D$ −262° (c 1, $CHCl_3$); ir (KBr) 1690 (CO), 1550 cm^{-1} (NO_2).

Anal. Calcd for $C_{29}H_{27}NO_8$: C, 67.30; H, 5.26; n, 2.71. Found: C, 67.09; H, 5.19; N, 2.83.

Methyl 2-*C*-(Acetylethoxycarbonyl)methyl-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-α-D-mannopyranoside (10). Reaction of **2** (58.6 mg) with ethyl acetoacetate (28.6 mg, 0.22 mmol) under the conditions described above for the preparation of **8** gave a mixture (67.7 mg, 80%), which was chromatographed on silica gel (13 × 35 mm) with benzene, and the eluate was evaporated in vacuo to give a syrup of **10** (42.3 mg, 50%), which was crystallized from isopropyl ether: mp 127.5–128.5°; $[\alpha]^{20}D$ −103° (c 1, $CHCl_3$); ir (KBr) 1730, 1710 (CO), 1555 cm^{-1} (NO_2).

Anal. Calcd for $C_{20}H_{25}NO_8$: C, 56.73; H, 5.59; N, 3.31. Found: C, 56.78; H, 5.95; N, 3.31.

Methyl 4,6-*O*-Benzylidene-2-*C*-(dicyano)methyl-2,3-dideoxy-3-nitro-α-D-glucopyranoside (11). Treatment of **2** (58.6 mg) with malononitrile (24 mg, 0.36 mmol) under the condition described above for the preparation of **8** gave a syrup (55.3 mg, 77%) consisting of **11** and **12**, in the ratio of 1:1.3 on the basis of NMR spectrum. The syrup (11 mg) was chromatographed on silica gel (17 × 85 mm) developed slowly with benzene. The eluate was collected in 10-ml portions. Fractions 3 and 4 were combined and evaporated in vacuo to give crystals of **11**: yield 36 mg (25%); mp 163.5–164.5°; $[\alpha]^{20}D$ +110° (c 1, $CHCl_3$); ir (KBr) 2260 (CN), 1560 cm^{-1} (NO_2).

Anal. Calcd for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.70. Found: C, 56.73; H, 4.92; N, 11.79.

Methyl 4,6-*O*-Benzylidene-2-*C*-(dicyano)methyl-2,3-dideoxy-3-nitro-α-D-mannopyranoside (12). In the above chromatography, fractions 6–12 were combined and evaporated in vacuo to give a syrup (57 mg, 40.1%) of **12**: $[\alpha]^{20}D$ +21.7° (c 1, $CHCl_3$); ir (KBr) 2260, 2235 (CN), 1557 cm^{-1} (NO_2).

Anal. Calcd for $C_{17}H_{17}N_3O_6$: C, 56.82; H, 4.77; N, 11.70. Found: C, 56.93; H, 4.85; N, 11.49.

Conversion of 12 into 11. To a solution of benzene (3 ml), 0.2 *N* NaOH (0.8 ml), the catalyst (2 mg), and malononitrile (12 mg) was added a mixture (36 mg) of **12** and **11** (ratio of 1.5:1 by NMR spectroscopy). The reaction mixture was stirred for 15 hr at room temperature, and then washed with water. The benzene layer was evaporated in vacuo to give a residue, which was NMR spectroscopically pure **11**.

Registry No.—**1**, 16697-50-0; **2**, 16697-51-1; **4**, 55853-26-4; **5**, 55853-27-5; **8**, 55853-28-6; **9**, 55853-29-7; **10** isomer a, 55853-30-0; **10** isomer b, 55853-31-1; **11**, 55853-32-2; **12**, 55853-33-3; acetylacetone, 123-54-6; dibenzoylmethane, 120-46-7; ethyl acetoacetate, 141-97-9; malonitrile, 109-77-3; ethyl malonate, 105-53-3.

References and Notes

(1) For example, S. Patai and Z. Rapport, "The Chemistry of Alkenes", S. Patai, Ed., Interscience, New York, N.Y., 1964, Chapter 8.

(2) Some thermodynamically less stable isomers were prepared from nitro olefin derivatives with the following nucleophiles: hydrogen cyanide, hydrazoic acid, theophylline, and 2,6-dichloropurine, T. Sakakibara and R. Sudoh, *Chem. Commun.*, 69 (1974); hydrogen cyanide, H. Paulsen and W. Grewe, *Chem. Ber.*, **107**, 3013 (1974); *N*-bromoacetamide, H. H. Baer and W. Rank, *Can. J. Chem.*, **52**, 2257 (1974); anthranilic acid, H. H. Baer and F. Kienzle, *J. Org. Chem.*, **34**, 3848, 4204 (1969); secondary amines such as morpholine, P. Southwick and J. E. Anderson, *J. Am. Chem. Soc.*, **79**, 6222 (1957).

(3) C. M. Starks, *J. Am. Chem. Soc.*, **93**, 195 (1971); J. Dockx, *Synthesis*, 441 (1973); E. X. Dehmlow, *Angew. Chem.*, **86**, 187 (1974); *Angew. Chem., Int. Ed. Engl.*, **13**, 170 (1974).

(4) For example, K. E. Koenig and W. P. Weker, *Tetrahedron Lett.*, 2275 (1974); M. Makosza and M. Fedorynski, *Synthesis*, 274 (1974).

(5) A phase transfer catalyst has been used in the Michael reaction but the stereochemical studies were not examined; for example, D. A. White and M. M. Baiter, *J. Chem. Soc., Perkin Trans. 1*, 2230 (1973).

(6) The facts that the thermodynamically less stable manno isomers could be isolated exclusively or predominantly by this phase transfer process prompted us to investigate the reactions of **2** with active methylene compounds under homogeneous conditions, and in some cases the manno isomers were formed also as a major product. Details are now in progress.

(7) This reaction mechanism was based on the fact that the reaction of 4-*tert*-butyl-1-cyanocyclohexene with ethyl malonate afforded ethyl 4-*tert*-butyl(e)-2-carbethoxymethyl(a)-1-cyano(a)cyclohexanecarboxylate(e); R. A. Abramovitch and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).

(8) These results are in good agreement with the generalization that manno isomers are thermodynamically less stable than the gluco isomers.

(9) H. H. Baer and F. Kienzle, *Can. J. Chem.*, **45**, 983 (1967).

Synthesis of C Nucleosides. X.[1] Structural Analogs of Formycin B

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A general synthetic route to 2-substituted fused pyrimidones is described. Model reactions of benzylthioacetimidate **8** with different aminocarbethoxypyrazoles give the cyclized structures. The same condensations with glycosyl thioformimidates **10** and **14** lead to pyrazolo[4,3-*d*]pyrimidin-7-ones **11** and **15** and pyrazolo[3,4-*d*]pyrimidin-4-ones **19** and **21**. Removal of the protective ester groups is achieved with methanolic ammonia. The spectroscopic properties of anomers of the ribo and 2′-deoxyribo analogs of formycin B, **3**, **4**, **5**, and **6**, are discussed.

The biological properties of formycins[2] A (**1**) and B (**2**) have stimulated diverse studies on their total synthesis[3] or on the preparation of derivatives with modifications of the heterocycle[4,5] and of the sugar moieties.[6,7]

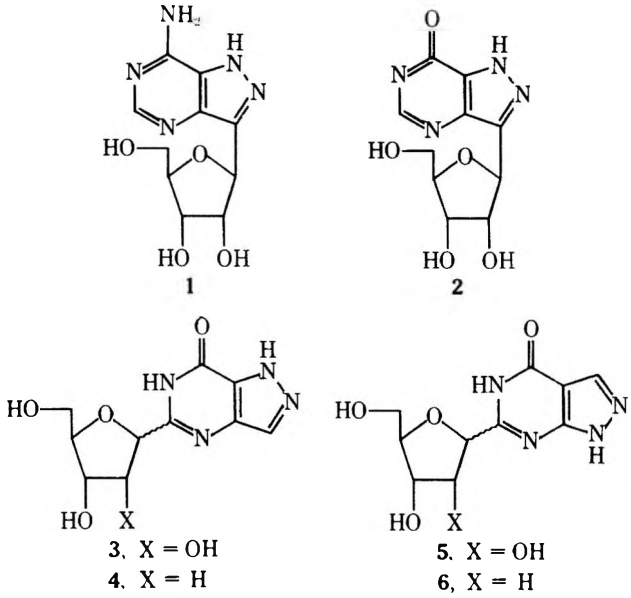
In pursuit of our work on the synthesis of C nucleosides we prepared isomers of formycin B and 2′-deoxyformycin B, whose sugar (ribose and 2-deoxyribose) was linked to carbon 2 of the pyrimidine cycle. We should obtain the 5-glycosylpyrazolo[4,3-*d*]pyrimidin-7-ones **3** and **4**, closely related to formycin B, or the 6-glycosylpyrazolo[3,4-*d*]pyrimidin-4-ones **5** and **6**, related to allopurinol nucleoside (Chart I).

Known methods for the preparation of 2-substituted fused pyrimidines are laborious with poor overall yield[8] or require drastic conditions.[9] A new approach, using much milder conditions, has been developed from the condensation of a thioformimidate[10] with an amino aromatic heterocycle, functionalized in the ortho position by an ester group.

Results

We start with a model reaction, using benzyl thioacetimidate (**8**) and 4-amino-3-carbethoxypyrazole (**7**), prepared by reduction of the nitro ester[11] (Scheme I). By refluxing in

Chart I



pyridine, we quantitatively obtain 5-methylpyrazolo[4,3-*d*]pyrimidin-7-one (**9**), a product not yet described to our knowledge.

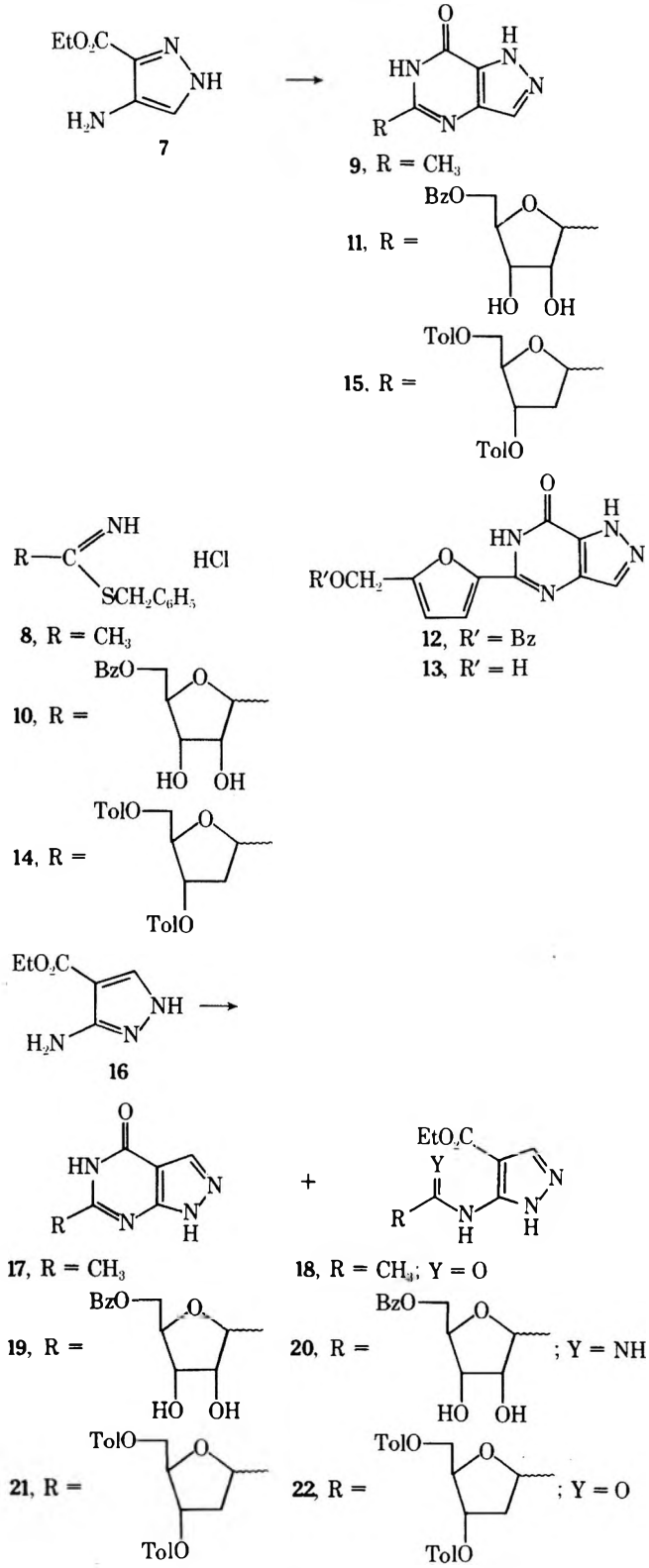
The condensation of **7** with benzyl 5-*O*-benzoyl-D-ribofuranosyl thioformimidate[20] (**10**) under the same conditions leads to 30% of a mixture of pyrazolo[4,3-*d*]pyrimidones **11**α and -β, separated by silica gel column chromatography. The β anomer is predominant (β/α = 70/30). We also isolate from dehydration of the ribose cycle furan **12** as a by-product.

Starting with thioformimidate[1] **14** in the 2-deoxyribose series, the formation of a furan is not observed and the yield of pyrazolopyrimidones **15**α and -β, separated by column chromatography, increases to 75%. The **15**β anomer is slightly predominant (β/α = 60/40). The benzoyl or *p*-toluyl protective groups of **11**α,β, **15**α,β, and **12** are quantitatively removed by methanolic ammonia to give respectively pyrazolo[4,3-*d*]pyrimidones **3**α,β, **4**α,β and furan **13**. The reaction time is shorter for the benzoyl (1 night) than for the *p*-toluyl group (2 weeks).

The same procedure is used in the preparation of substituted pyrazolo[3,4-*d*]pyrimidones: condensation of **8** with commercially available 3-amino-4-carbethoxypyrazole (**16**) gives the expected 6-methylpyrazolo[3,4-*d*]pyrimidin-4-one (**17**), already described.[8b] The yield of **17** is about 60% and we also isolate the amide **18** whose structure is consistent with mass and NMR spectra.

The reaction of benzyl 2-deoxy-3,5-di-*O*-*p*-toluyl-D-*erythro*-pentofuranosyl thioformimidate (**14**) also gives the two anomers (α and β) of amide **22**. The noncyclized amides **18** or **22** could arise from hydrolysis of a N-substituted amidine intermediate; amidine **20** is indeed isolated from condensation of pyrazole **16** with ribofuranosyl thioimidate **10**. The overlap of the sugar protons, even in the 250-MHz spectrum, does not allow the determination of its configuration. Of course, in the ribose, as well as in the 2-deoxyribose series, we isolate the expected pyrazolo[3,4-*d*]pyrimidones **19**α,β and **21**α,β. Treatment of each anomer with methanolic ammonia provides the C nucleosides **5**α,β and **6**α,β.

Scheme I



Discussion

Unlike the previous condensations of thioimidate **10** with *o*-aminocyano heterocycles,[10,20] which gave only the β anomers, the reactions of the same thioimidate with o-aminocarbethoxy heterocycles lead to the formation of α and β anomers of C ribonucleosides. The anomeric mixture of **3** or **5** does not proceed from a thermodynamic equilibrium, since no epimerization is observed from each anomer with the experimental conditions used. Further cyclizations of thioimidate **10** with other bases[25] seem to show that the formation of both anomers is a general rule: the β/α ratio varies with the base, and the β anomer is strongly predominant or exclusive.[20] This fact may be correlated with the steric effect of 2'-OH: in the 2'-deoxy series[1,13] the β anomer is less favored and in the arabinosyl series[10,26] the α anomer is always predominant.

Table II
NMR Chemical Shifts (Parts per Million) at 250 MHz in DMSO-d_6

Compd	Pyrazole H									
		Methyl								
		CH_3								
9	8.0[a]	2.4								
17	8.0[a]	2.3								
		Ribose								
		H-1′	H-2′		H-3′	H-4′	H-5′	H-5″	$J_{1',2'}$, Hz	
3α	8.08	4.87	4.34		4.09[b]	4.09[b]	3.62	3.45	4.9	
3β	8.12	4.65	4.17		4.07	3.98	3.80	3.64	4.0	
5α	8.11	4.90	4.35		4.08[b]	4.08[b]	3.64	3.45	4.5	
5β	8.15	4.65	4.15		4.05	3.97	3.78	3.62	4.2	
		2-Deoxyribose								
		H-1′	H-2′	H-2″	H-3′	H-4′	H-5′	H-5″	$J_{1',2'}$, Hz	$J_{1',2''}$, Hz	$J_{1',2'} + J_{1',2''}$, Hz
4α	8.10	4.90	2.56	2.12	4.25	4.04	3.41	3.41	8.6	4.7	13.3
4β	8.08	4.94	2.21	2.17	4.26	3.90	3.63	3.56	8.4	7.3	15.7
6α	8.13	4.93	2.59	2.12	4.24	4.06	3.43	3.43	8.7	4.5	13.2
6β	8.10	4.96	2.22	2.22	4.26	3.92	3.64	3.58	7.5	7.5	15.0
		Furan									
			H-2′		H-3′		H-5′	H-5″	$J_{2',3'}$, Hz		
13	8.08		7.43		6.52		4.50	4.48	3.2		

[a] Spectra measured at 60 MHz. [b] Not first order spectra: possible error of 0.02 ppm.

Table III
Chemical Shifts of Intermediary Esters in DMSO-d_6 at 250 MHz

Compd	Pyrazole H													
		Methyl												
		CH_3												
18[d]	7.7	2.3												
		Ribose												
		H-1′	H-2′	H-3′	H-4′	H-5′	H-5″	H_o[e]	H_m[f]	H_p[g]	$J_{1',2'}$, Hz			
11α	7.92	4.88	4.37[b]	4.39[b]	4.16	4.52	4.33[b]	8.02	7.55	7.68	3.8			
11β	7.91	4.65	4.38	4.24	4.14	4.53	4.41	7.91	7.42	7.62	3.6			
19α	8.04	5.04	4.40[b]	4.43[b]	4.24	4.62	4.36[b]	8.05	7.58	7.70	3.9			
19β	8.15	4.73	4.42	4.22[b]	4.22[b]	4.56	4.47	7.80	7.42	7.63	3.8			
20[c]	7.73	4.75	4.46	4.75–4.46	4.35	4.75–4.46		7.89	7.21	7.41				
		2-Deoxyribose												
		H-1′	H-2′ H-2″	H-3′	H-4′	H-5′ H-5″		H_o		H_m		ΔH_o	Me		$J_{1'2'} + J_{1'2''}$, Hz
15α[d]	8.0	5.4	2.8–3.1	5.7	5.0	4.6		8.0	7.5	7.2	6.9	0.5	2.2	2.4	11
15β[d]	8.0	5.4	2.6–2.9	5.7	4.8	4.8		8.0	7.9	7.2	7.1	0.1	2.3	2.4	15
21α[a]	8.1	5.3		5.4	4.4	4.4		7.8	7.4	7.3	7.0	0.4	2.3	2.4	11
21β[a]	8.1	5.2		5.5	4.5	4.5		7.9	7.7	7.3	7.2	0.2	2.3	2.4	15
22α[d]	7.7	4.9–4.4	2.5–2.8	5.5	4.9–4.4	4.9–4.4		7.8	7.5	7.1	6.8	0.3	2.2	2.4	
22β[d]	7.6	4.9	2.5–2.8	5.5	4.6	4.6		7.8	7.6	7.2	7.0	0.2	2.3	2.4	16
		Furan												
		H-2′	H-3′	H-5′	H-5″	H_o		H_m		H_p		$J_{2',3'}$, Hz		
12	8.12	7.53	6.86	5.43		8.01		7.54		7.69		3.5		

[a] Measured at 60 MHz. [b] Not first-order spectra: possible error of 0.02 ppm. [c] Measured in $CDCl_3$. [d] Measured at 60 MHz in $CDCl_3$. [e] Aromatic H in ortho position of C=O. [f] Aromatic H in meta position of C=O. [g] Aromatic H in para position of C=O.

The simultaneous formation of both anomers in each series permits us to suggest some tentative rules for interpretation of the spectroscopic data.

The ultraviolet spectra of C nucleosides **3, 4** and **5, 6** are quite similar to those of their methyl analogs **9** and **17** (Table I, microfilm material). The 5-substituted pyrazolo[3,4-*d*]pyrimidone chromophore absorbs at a higher wavelength than the 6-substituted pyrazolo[3,4-*d*]pyrimidone cycle, whose bathochromic shift from 0.1 *N* hydrochloric acid to 0.1 *N* sodium hydroxide is more important (15 vs. 5 nm).

The isolation of **3, 5** and **4, 6** in each series of C nucleosides greatly facilitates determination of their anomeric configuration by NMR. In the ribose series (Table II) the determination is not based on the coupling constants $J_{1',2'}$, which are practically the same, but on the chemical shifts of $H_{1'}$. The β configuration is attributed to the higher shift of $H_{1'}$, due to the shielding of a cis 2′-OH.[17] The β anomers of **3, 5** show well-resolved sugar protons whereas in the α anomers, $H_{3'}$ and $H_{4'}$ are collapsed. The presence of a benzoyl group moves downfield $H_{5'}$ and $H_{5''}$.

For the 2′-deoxy series (Table II), no significant differ-

Table IV
Relative Intensity (%) of Predominant Ions in Mass Spectra of Substituted Pyrazolopyrimidones

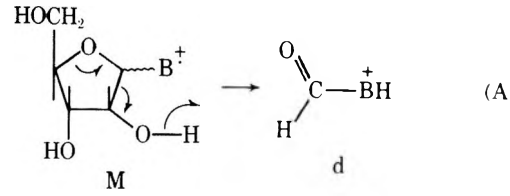
Compd	m/e	232	203 B + 68	192 B + 57	179 B + 44	165 B + 30	163 B + 28	150 B + 15	137 B + 2	136 B + 1	135 B	120 B − 15	110 B − 25	109 B − 26
Methyl														
9								100		<1	9	1	11	2
17								100	2	25			28	7
Ribose														
	M	M − 17	M − 30 a	M − 31				c	d		e			
3α	29	1	<1	1	2	2	7	92	100	2	5	6	4	4	12	8	12
3β	13	25	4	8	1	4	2	100	82	5	13	13	7	7	17	11	21
5α	17	3	4	2	25	22	2	83	1100	10	36	31	19	39	19	56	33
5β	17	6	11	4	15	15	2	100	82	13	39	35	19	44	19	62	37
2-Deoxyribose														
	M	M − 17	M − 30 a	M − 31					d $(\dot{B}HCH{=}CH_2)$		e			
4α	<1		<1	<1		3	3	11	16	100	5	11	12	6	18	7	19
4β	5		4	2		2	1	4	15	100	5	9	6	2	7	3	9
6α	7	<1	1	2		9	10	2	6	100	3	10	4	9	3	13	6
6β	7	<1	4	2		3	2	4	12	100	6	11	4	9	6	16	7
Furan														
		M − 17	M − 30		M									
13		22	<1		100	35				1	4	4	13	6	5	3	9

ence on the chemical shift is observed for the anomeric proton and the assignment of the configuration is based on its splitting pattern:[17,18] quartet for the α anomer and triplet for the β, with a larger peak width for the β anomer.[19] We notice a downfield shift in α anomers for $H_{4'}$;[21] this influence of the base on the sugar protons also appears in the chemical shifts of $H_{2'}$ and $H_{2''}$ which are well resolved in α anomers and collapsed in β anomers.[22] Another good criterion for the determination of the configuration for esters **15, 21,** and **22** is based on the difference of chemical shifts of the aromatic protons which are in the ortho position of the carbonyl: ΔH_o is larger in α anomers[13] (Table III) than in β anomers.

The detailed discussion of the NMR spectra of all these nucleosides will be published later.

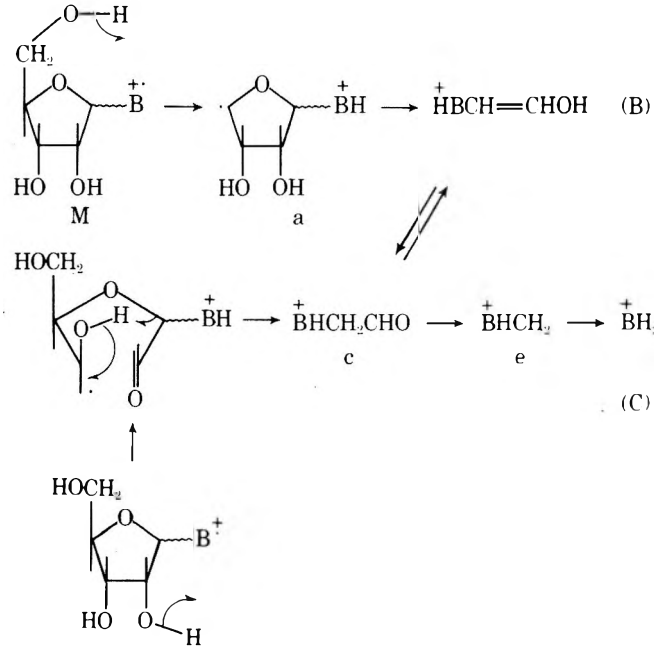
All of the mass spectra (Table IV) of the nucleosides show the molecular ion M. The ribo and 2′-deoxy nucleosides present the same type of fragmentation. The C–C bond between the carbohydrate and the heterocycle is confirmed by the reduced intensity of ions B + H (136) and B + 2H (137).[12a] Peaks at M − 30 and M − 31 demonstrate the presence of an exocyclic hydroxymethyl group and the furanose structure of the sugar. We also observe the characteristic fragmentation of $O–C_{1'}$ and $C_{2'}–C_{3'}$ bonds which gives an abundant ion (c) at B + 44 (179) in the ribose series (80–100% rel intensity) and B + 28 (163) in the 2′-deoxy series (major ion); a fragment at B + 28 is observed in all 2′-deoxy C nucleosides synthetized in our laboratory[1,13] and in 2′-deoxyformycin.[6a] Another characteristic ion is found at B + 30 (165) in the ribonucleosides: ion d results from the cleavage of $O–C_{4'}$ and $C_{1'}–C_{2'}$ bonds and was proposed as the major fragment of C ribonucleosides;[14] this empirical rule[23] is observed only on α anomers of fused pyrimidine nucleosides **3** and **5.** Ion d is reduced in 2′-deoxynucleosides **4** and **6** and absent in furan **13.** It appears that formation of ion d requires the spatial proximity between the base and 2′-OH (pathway A).[12]

It should be noted that pyrazolo[3,4-*d*]pyrimidones **5** more easily lose 2 mol of water (ion at 232) than pyrazolo[4,3-*d*]pyrimidones **3**; this fragmentation via dehydration without cleavage of the glycosidic bond was mentioned for formycin B[14] and pyrazomycin.[15] Ion M − $2H_2O$ is the major molecular ion of furan **13.**



(A)

As for N nucleosides,[12b] the most significant difference between a couple of anomers is the relative intensity of ion M − 30: the β anomers of **3, 4** and **5, 6** possess a more important ion (a) than the α anomers. The 100% relative intensity of ion c, correlated with the higher intensities of ions a (M − 30), e (B + 15), and B + 2H on β anomers of C



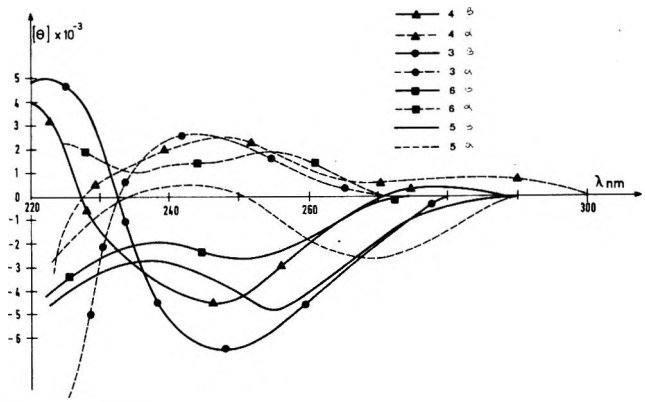


Figure 1. CD spectra of nucleosides in water.

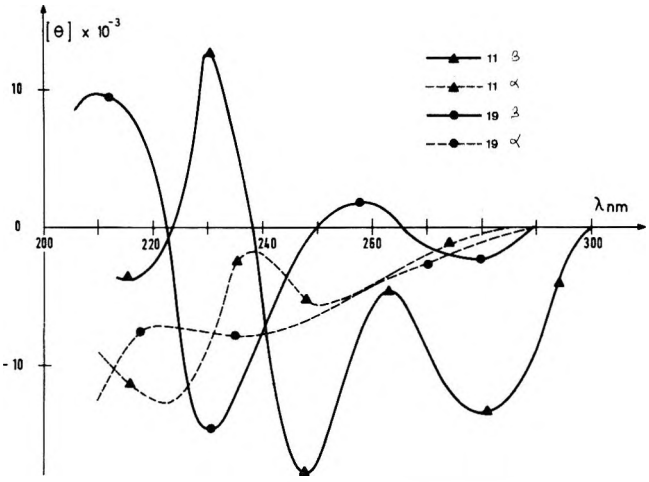
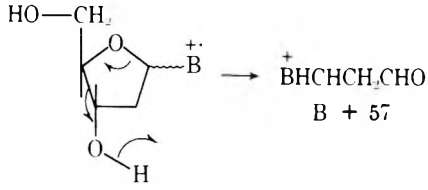


Figure 2. CD spectra of 5′-*O*-benzoyl ribonucleosides in water.

ribonucleosides **3** and **5** may be tentatively depicted by pathway B;[12,16] the same effect was observed on 2-β-D-ribofuranosyladenine.[20] The principal pathway (C), generally admitted for ion c in ribosides,[12] suggests the participation of a 2′-hydroxy group and seems not to predominate in the case of fused pyrimidine nucleosides.

In the 2′-deoxynucleosides, a more significative difference between α and β consists in the higher intensity of peaks at B + 57 for α anomers which could be explained by a fragmentation involving 3′-OH.



Unlike the previous spectroscopic methods, the circular dichroism measurements are less indicative of the configuration. As for N nucleosides,[24] the α anomers of compounds **3**, **4**, and **6** present a positive Cotton effect and the β anomers a negative effect. However, the correlation seems not to be general, since **5**α behaves differently, suggesting a difference of conformation (Figure 1).

The most significant effect is observed with 5′-*O*-benzoyl derivatives **11** and **19** of the ribo series: in the β anomers, where the molecular conformation favors a stacking between the benzene nucleus and the heterocycle, the Cotton effects are very important; on the contrary, in the α anomers, where an intramolecular interaction cannot exist, the magnitude of the Cotton effect is well reduced. This difference in the intensities of the Cotton effect on two anomers was observed in all other 5′-benzoylated C ribonucleosides and tentatively used in the determination of the anomeric configuration[20] (Figure 2).

Experimental Section

Melting points were determined with Kofler microscope and were uncorrected. Ultraviolet spectra were determined with a Perkin-Elmer 237 spectrophotometer. NMR spectra were obtained using a 250-MHz Cameca TSN-250 and a 60-MHz Varian EM-360 with tetramethylsilane as internal reference. Mass spectra were obtained with a Varian CH-7 or MS-9. Optical activities were measured with a Perkin-Elmer 241 MC polarimeter and circular dichroism spectra were recorded with a Roussel-Jouan II-185 dichrograph. Chromatographic columns were packed with Silicar 100 mesh Grade I; 0.25 mm thick TLC plates were prepared with Merck Kieselgel $HF_{254+366}$ and visualized with an uv light at 254 nm.

4-Amino-3-carbethoxypyrazole (7). A solution of 660 mg (3.57 mmol) of 3-carbethoxy-4-nitropyrazole in 20 ml of ethanol was hydrogenated at atmospheric pressure with 10% Pd/C for 3 hr. After filtration, the solution was evaporated to dryness and the residue was applied to a silica gel column and developed with ether; 490 mg of **7** (87%) was obtained, mp 90–92°. Anal. Calcd for $C_6H_9O_2N_3$: C, 46.44; H, 5.85; N, 27.02. Found: C, 46.69; H, 5.92; N, 26.98.

General Procedure. The same procedure was used for the condensation of a thioimidate with an aminocarbethoxypyrazole. No attempt was made to optimize the yields obtained.

A solution of 5 mmol of pyrazole and 5 mmol of thioimidate in 15 ml of anhydrous pyridine was refluxed for 16 hr. The mixture was evaporated and dissolved in aqueous ethanol. The solution was neutralized with 1 *N* sodium hydroxide and evaporated to dryness. The residue was recrystallized or applied to a silica gel column (300 g, 75 × 4 cm). Elution with the adequate mixture of solvents gave first the by-products (**12**, **18**, **20**, and **22**) and then the two anomers. The anomeric separation can also be undertaken after debenzoylation with gel chromatography: 260 mg of compound **3** or **5** was separated on 50 g of Bio-Gel P-2 200–400 mesh (90 × 1.6 cm); 50 mg of compound **6** was separated on 64 g of Sephadex G-10 (120 × 1.2 cm).

Debenzoylation was achieved with saturated methanolic ammonia at room temperature and monitored by TLC; after completion of the reaction, the solution was evaporated to dryness and the residue was washed with benzene and ethyl acetate and recrystallized.

The experimental and physical data are summarized in Tables V and VI (microfilm material).

Registry No.—α-**3**, 55904-41-1; β-**3**, 55904-42-2; α-**4**, 55904-43-3; β-**4**, 55904-44-4; α-**5**, 55904-45-5; β-**5**, 55904-46-6; α-**6**, 55904-47-7; β-**6**, 55904-48-8; **7**, 55904-61-5; **9**, 55904-62-6; α-**11**, 55904-40-9; β-**11**, 55904-50-2; **12**, 55925-84-3; **13**, 55904-63-7; α-**15**, 55904-51-3; β-**15**, 55904-52-4; **17**, 30129-57-8; **18**, 14333-80-3; α-**19**, 55904-53-5; β-**19**, 55904-54-6; α-**20**, 55904-55-7; β-**20**, 55904-56-8; α-**21**, 55904-57-9; β-**21**, 55904-58-1; α-**22**, 55904-59-1; β-**22**, 55904-60-4.

Supplementary Material Available. Tables I, V, and VI 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 Business Office, Books and Journals Division, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $4.00 for photocopy or $2.50 for microfiche, referring to code number JOC-75-2825.

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The Gentamicin Antibiotics. 7.[1a] Structures of the Gentamicin Antibiotics A_1, A_3, and A_4

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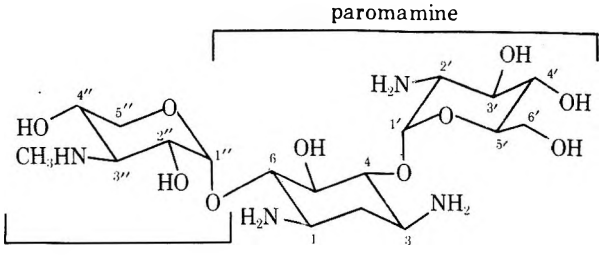
The structures of the gentamicin antibiotics A_1, A_3, and A_4 coproduced with other gentamicins in submerged fermentations of *Micromonospora purpurea* and *Micromonospora echinospora* have been elucidated by proton and carbon-13 magnetic resonance spectroscopy in conjunction with mass spectrometry. Gentamicin A_1 and A_3 are 4-*O*-(2′-amino-2′-deoxy-α-D-glucopyranosyl)-6-*O*-(3″-methylamino-3″-deoxy-β-L-arabinopyranosyl)deoxystreptamine and 4-*O*-(6′-amino-6′-deoxy-α-D-glucopyranosyl)-6-*O*-(3″-methylamino-3″-deoxy-β-L-arabinopyranosyl)deoxystreptamine, respectively. Gentamicin A_4 is 3″-*N*-formylgentamicin A.

Gentamicin A is coproduced with other gentamicins in submerged fermentations of *Micromonospora purpurea* and *Micromonospora echinospora*.[1b,2] Its structure was elucidated by Maehr and Schaffner[3,4] and is shown below.



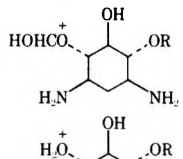
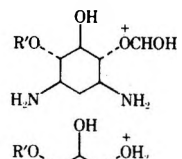
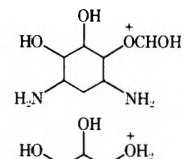
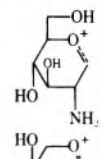
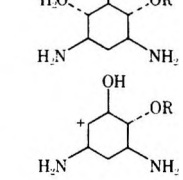
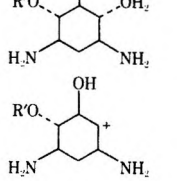
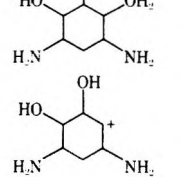
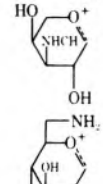
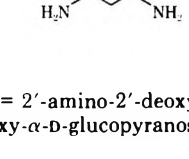
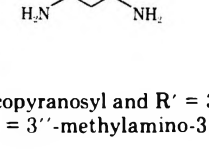
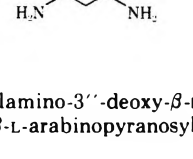
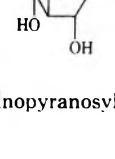
Recent investigations in this laboratory have revealed the presence of four new deoxystreptamine-containing antibiotics in crude preparations of gentamicin A which we have designated gentamicins A_1, A_2, A_3, and A_4. The elucidation of the structures of A_1, A_3, and A_4 is the subject of this communication. The structure of gentamicin A_2 is published in the accompanying note.[5a]

Gentamicins A_1, A_3, and A_4 could be separated from A and from each other by thin layer chromatography on silica gel using chloroform–methanol–ammonium hydroxide (3:4:2) as the developer. On a typical chromatogram A_1, A_3, and A_4 had R_A[5b] values of 0.78, 0.40, and 1.62, respectively. Isolation of these compounds in high states of purity was effected by chromatography of the crude mixture on a column of silica gel using the above-mentioned eluent, and in the case of A_1 and A_3 by rechromatography on Dowex 1-X2 ion exchange resin in the hydroxide cycle using water as the eluent.[6,7]

Structures of Gentamicins A_1 and A_3. The proton noise decoupled ^{13}C NMR spectra of A_1 and A_3 were very similar to that of A and indicated the presence of 18 carbon atoms in each compound (Table III). The mass spectra of A_1 and A_3 were also very similar to that of A. Each exhibited a peak at *m/e* 469 attributable to the $(MH)^+$ ion as previously indicated for A.[8] It was apparent, therefore, that A, A_1, and A_3 were isomers. The elemental analyses were consistent with the compositions $C_{18}H_{36}N_4O_{10}\cdot H_2O$ for A_1 and $C_{18}H_{36}N_4O_{10}\cdot 4HCl$ for the hydrochloride salt of A_3, further supporting the above contention.

Hydrolysis of gentamicins A, A_1, and A_3 with 6 *N* hydrochloric acid at 100° for 1 hr followed by paper chromatographic analysis of the hydrolyzate clearly indicated the presence of deoxystreptamine in all of them. Glucosamine and paromamine were present only in the hydrolyzates of A and A_1. The hydrolyzate of A_3 contained 6-amino-6-deoxyglucose. Furthermore, this comparative study indicated the absence of gentosamine (3-methylamino-3-deoxy-D-xylose), one of the hydrolysis products of gentamicin A, in the hydrolyzates of A_1 and A_3, but the presence of another sugar whose R_f was very close to, but not identical with, that of gentosamine. These data strongly suggested, therefore, that A_1 was an isomer of A in the gentosamine moiety, and A_3 was an isomer of A_1 in the glucosamine moiety. Recently, Mallams and coworkers[9a] in our laboratories isolated two new antibiotics named 66-40B and 66-40D from *Micromonospora inyoensis* and showed these to possess the following structures.

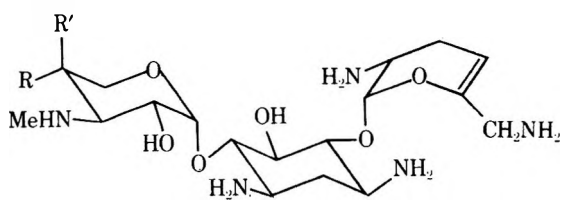
Table I
Prominent Mass Spectral Fragment Ions of Gentamicins A_1 and A_3[a]

m/e	Ion	m/e	Ion	m/e	Ion	m/e	Ion
352		336		191		162	
−CO		−CO		−CO			
324		308		163		146	
$-H_2O$		$-H_2O$		$-H_2O$			
306		290		145		162	
$-H_2O$		$-H_2O$		$-H_2O$			
334		318		173			

[a] In gentamicin A_1, R = 2′-amino-2′-deoxy-α-D-glucopyranosyl and R′ = 3′′-methylamino-3′′-deoxy-β-L-arabinopyranosyl; in gentamicin A_3, R = 6′-amino-6′-deoxy-α-D-glucopyranosyl and R′ = 3′′-methylamino-3′′-deoxy-β-L-arabinopyranosyl.

Table II
Proton Magnetic Resonance Parameters of Comparative Aminoglycosides

		Gentamicin A		Gentamicin A_1		Gentamicin A_3		6640-D	
H	J (H,H)	δ	Multiplicity, J, Hz	δ	Multiplicity, J, Hz	δ	Multiplicity, J, Hz	δ	Multiplicity, J, Hz
2ax		1.19	q	1.20	q	1.22	q		
	2ax, 2eq		12.5		12.5		12.5		
	1, 2ax		12.5		12.5		12.5		
	2ax, 3		12.5		12.5		12.5		
2eq		1.94	d,t	1.95	d,t	1.98	d,t		
	1, 2eq		3.5		3.5		3.5		
	2eq, 3		3.5		3.5		3.5		
1′		5.23	d	5.26	d	5.35	d		
	1′, 2′		3.5		3.5		3.8		
2′		2.77	d,d	2.78	d,d	Not observed			
	2′, 3′		10.0		10.0				
1′′		4.99	d	5.08	d	5.09	d	5.05	d
	1′′, 2′′		3.5		4.0		4.0		4.0
2′′		3.61	d,d	3.81	d,d	3.86	d,d	3.79	d,d
	2′′, 3′′		9.5		10.5		10.5		10.0
3′′		2.70	t	Not observed		2.92	d,d	2.78	d,d
	3′′, 4′′		9.5				3.0		3.0
4′′		3.26	d,t	4.12	br s	4.13	br s	4.10	br s
	4′′, 5′′ax		9.5						
	4′′, 5′′eq		5.0						
5eq′′				4.18	br d	4.18	br d	4.15	br d
	5eq′′, 5ax′′				12.5		12.5		12.5
3′′NMe		2.49	s	2.37	s	2.43	s	2.35	s



R = OH; R′ = H = 66-40B
R = H; R′ = OH = 66-40D

The presence of gentosamine in 66-40B and its 4′′ epimer in 66-40D suggested that gentamicin A and A_1 might similarly be related. The unknown component in the acid hydrolyzates of both A_1 and A_3 had the same R_f on a thin layer chromatogram as that of 3-methylamino-3-deoxy-L-arabinose.[9b] On the basis of these findings and in view of the likely common biogenesis of these compounds, gentamicin A_1 was thought to be 6-*O*-(3′′-methylamino-3′′-deoxy-β-L-arabinopyranosyl)paromamine (1) and gentamicin A_3, 4-*O*-(6′-amino-6′-deoxy-α-D-glucopyranosyl)-6-*O*-(3′′-methylamino-3′′-deoxy-β-L-arabinopyranosyl)deoxystreptamine (2). Substantiating evidence was obtained from the physical methods delineated below.

The mass spectra of A_1 and A_3 showed the expected prominent fragment ions for the above structures and are explained in Table I.

The proton magnetic resonance parameters for gentamicins A, A_1, A_3 and antibiotic 66-40D are listed in Table II. It may be seen from Table II that the spectra of A, A_1, and A_3 have in common only the H-2_{ax} and H-2_{eq} resonances of deoxystreptamine and an *N*-methyl singlet. Gentamicin A_1 also gives rise to an anomeric doublet (H-1′) and a multi-

plet (H-2′) which are mutually coupled and compare well with the corresponding resonances in gentamicin A. This portion of the spectrum is therefore consistent with that expected from the presence of the paromamine moiety in gentamicin A_1. Similar resonances are not found in the spectrum of gentamicin A_3.

Resonances assigned to H-1″, H-2″, H-4″, and H-5″$_{eq}$ of gentamicins A_1, A_3 and antibiotic 66-40D are also listed in Table II. A resonance for H-3″ could not be distinguished in the spectrum of gentamicin A_1. In all other cases listed in the table, INDOR techniques were used to observe any protons not clearly resolved from the envelope of a spectrum. All assignments were confirmed by spin decoupling. Although the proton chemical shifts of aminoglycoside antibiotics are sensitive to changes in pH and therefore to sample preparation and handling, it may be seen that the characteristic resonances of the 4″-*epi*-gentosamine residue of the antibiotic 66-40D are also found in the spectra of gentamicin A_1 and A_3, supporting the presence of a 3-methylamino-3-deoxy-β-L-arabinopyranosyl moiety in their structures.

The unambiguous assignments of structure **1** to A_1 and **2** to A_3 were finally possible from proton noise decoupled carbon-13 magnetic resonance spectroscopy. The ^{13}C chemical shifts of gentamicins A, A_1, and A_3 and of the reference compounds methyl 3-methylamino-3-deoxy-α-D-xylopyranoside, methyl 3-methylamino-3-deoxy-β-L-arabinopyranoside, paromamine, and kanamycin A are given in Table III. Recent work of Morton and coworkers,[10] Lemieux and Koto,[11] Woo and Westland,[12] Omoto and his associates,[13] and Koch and her collaborators[14] clearly demonstrate that the carbon resonances in aminoglycoside antibiotics can readily be assigned by a combination of techniques including simple comparison of ^{13}C chemical shifts with those of adequate model substances and, as first shown by Lemieux and Koto[11] in the aminoglycoside antibiotics, by utilizing the β-carbon shifts that occur on protonation of the amino groups. The latter two techniques were employed for making assignments in the present work. The presence of the paromamine moiety in both A and A_1 is readily apparent when the chemical shifts of carbon atoms 1–5 and 1′–6′ in these compounds are compared with the corresponding resonances for paromamine. The chemical shifts of paromamine obtained in our laboratory agreed, within experimental errors, with those reported by Woo and Westland[12] and, except for the C-2′ resonance (56.1 ppm), also with those reported by Omoto and coworkers (52.2 ppm).[13] A comparison of the chemical shifts of carbon atoms 1″ to 5″ and the *N*-methyl of A_1 with the corresponding carbon atoms of methyl 3-methylamino-3-deoxy-β-L-arabinopyranoside clearly confirmed the presence of the latter sugar moiety in A_1. The validity of such a comparison in structural assignments is apparent from the close agreement of the chemical shifts of carbon atoms 1″–5″ and the *N*-methyl group of gentamicin A and the corresponding carbon atoms of methyl 3-*N*-methylamino-3-deoxy-α-D-xylopyranoside. The position of linkage of the 3-methylamino-3-deoxy-β-L-arabinopyranosyl unit to paromamine in gentamicin A_1 was readily established by comparison with gentamicin A, in which the linkage of the corresponding α-D-xylo unit to paromamine is at 6. As expected,[10] the C-6 of paromamine experienced a deshielding of 9.6 ppm and C-5 a shielding of 1.7 ppm on substituting the hydroxyl hydrogen atom at 6 by the α-gentosaminyl residue. At pD 2, these shifts were 9.7 and 1.1 ppm, respectively. Furthermore, C-6 in A experienced a shielding of 3.7 ppm on acidification. Similar analysis in the case of gentamicin A_1 revealed that $\delta_{C\text{-}6}(A_1) - \delta_{C\text{-}6}(Par) = 9.3$ ppm, $\delta_{C\text{-}5}(A_1) - \delta_{C\text{-}5}(Par) = -1.6$ ppm, $[\delta_{C\text{-}6}(A_1) - \delta_{C\text{-}6}(Par)]_{pD2} = 9.9$ ppm, $[\delta_{C\text{-}5}(A_1) - \delta_{C\text{-}5}(Par)]_{pD2} = -0.9$ ppm, and $\delta_{C\text{-}6}(A_1) - \delta_{C\text{-}6,pD2}(A_1) = 3.2$ ppm. These values are in excellent agreement with those of gentamicin A, and hence it can be concluded that linkage of 3″-methylamino-3″-deoxy-β-L-arabinopyranosyl residue to paromamine in gentamicin A_1 is at 6.

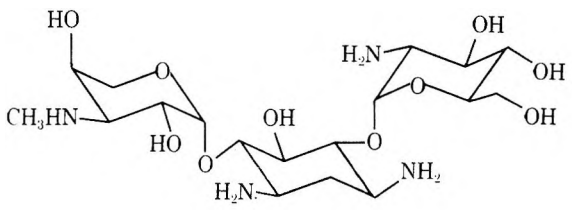
The chemical shifts of carbon atoms 1–6 and 1′–6′ in gentamicin A_3 agree extremely well with those of the corresponding carbon atoms of kanamycin A, confirming the presence of 4-*O*-(6-amino-6-deoxy-α-D-glucopyranosyl) unit in the latter. The chemical shifts of carbon atoms 1″–5″ and *N*-methyl, on the other hand, are, within experimental error, identical with those of the corresponding atoms in gentamicin A_1, confirming the presence of 6-*O*-(3″-methylamino-3″-deoxy-β-L-arabinopyranosyl) moiety in A_3. The structures of A_1 and A_3 are shown above Table III.

It is noteworthy that in gentamicins A_1 and A_3, which have an axial hydroxyl group on C-4″, the β shifts of C-4″ on acidification are 1.4 and 1.3 ppm, respectively, compared to 4.4 ppm in the case of A in which the hydroxyl group at C-4″ is in the equatorial orientation. In kanamycins A and B the corresponding β shifts are 3.8 and 3.5 ppm, respectively.[11] Also, on acidification, the *N*-methyl carbon atoms in A_1 and A_3 are shielded by 1.7 and 1.6 ppm, respectively, as compared to 3.7 ppm in gentamicin A.

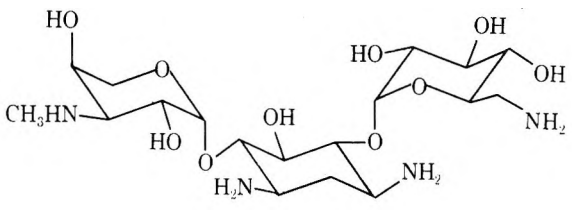
Structure of Gentamicin A_4. The ^{13}C NMR spectrum of gentamicin A_4 (Table III) showed the presence of 19 carbon atoms in the molecule, including a carbonyl carbon atom (167.5 ppm). The molecular weight of A_4 was found to be 28 units higher than that of A from mass spectrometry and the ^1H NMR spectrum showed a peak at 8.00 ppm attributable to a *N*-formyl proton. Therefore, it was apparent that A_4 was a formyl derivative of one of the gentamicin A's. The spectrum also showed the presence of two anomeric protons, a doublet at δ 5.21 ppm (H-1′, $J_{1',2'} = 3.8$ Hz) and a doublet at δ 5.11 ppm (H-1″, $J_{1'',2''} = 3.8$ Hz), and an *N*-methyl group as a singlet at δ 2.79 ppm. The characteristic signals due to the deoxystreptamine methylene protons were at δ 1.88 and 1.12 ppm. The presence of a quartet at δ 2.75 ppm with spacings of 9.0 ($J_{2',3'}$) and 3.75 Hz ($J_{1',2'}$) indicated a glucosamine moiety and therefore suggested that A_4 was a derivative of either A or A_1 but not of A_3.

Analysis of the ^{13}C NMR spectra of A_4 at basic and acidic pD's and comparison of the chemical shifts with the corresponding values of A indicated the location of the formyl group in A_4 at 3″. As seen in Table III, the C-1 to C-6 and C-1′ to C-6′ resonances of A_4 were almost identical with the corresponding resonances of gentamicin A, confirming the presence of the paromamine moiety in the latter. The *N*-methyl carbon in A_4 was shielded by 8.5 ppm relative to this resonance in gentamicin A. In contrast to an upfield shift of 3.7 ppm of the *N*-methyl carbon atom on acidification of gentamicin A, the chemical shift of the *N*-methyl carbon atom of A_4 did not change on acidification. These observations and the fact that the C-5″ and C-1″ resonances of A and A_4 were identical, within experimental error, and the C-2″ and C-4″ resonances in A_4 appeared shielded by 4.1 and 4.5 ppm, respectively (β shifts) in A_4, established the structure of A_4 to be 3″-*N*-formylgentamicin A (**3**). As predicted from the structure, on protonation of the amino groups only the paromamine moiety of A_4 showed the expected changes in the chemical shifts (Table III).

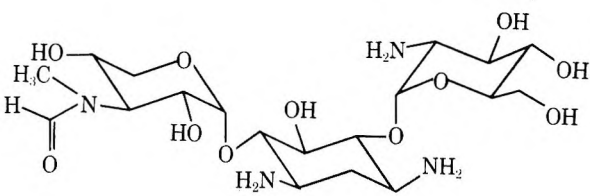
Finally, the mass spectrum of gentamicin A_4 gave a series of ions at *m/e* 352, 334, 324, 306, 191, 173, 163, 145, and 179 for the paromamine moiety[8] and ions at *m/e* 174 and 364, 346, 336, and 318 for the 3″-*N*-formylgentosaminyl deoxystreptamine unit consistent with the assigned structure.



gentamicin A_1 (**1**)



gentamicin A_3 (**2**)



gentamicin A_4 (**3**)

Table III
Carbon-13 Chemical Shifts of Comparative Aminoglycosides[a]

Carbon	G-A	Par	R[c]	$G\text{-}A_1$	R'[c]	$G\text{-}A_3$	K-A[b]	$G\text{-}A_4$	G-A pD 2	$G\text{-}A_1$ pD 2	$G\text{-}A_3$ pD 2	K-A[b] pD 3.6	Par pD 2	$G\text{-}A_4$ pD 2	$\delta_{base} - \delta_{salt}$ G-A	$G\text{-}A_1$	$G\text{-}A_3$	$G\text{-}A_4$	Par	K-A[b]
1	51.5	51.1		51.5		51.4	51.0	51.5	50.3	50.6	50.7	50.4	50.7	50.4						
2	36.5	36.7		36.4		36.2	36.1	36.5	28.5	29.4	28.4	28.1	29.3	28.6	8.0	7.0	7.8	7.9	7.4	8.0
3	50.3	50.3		50.3		49.8	49.6	50.2	49.6	49.7	48.6	48.3	50.3	49.6						
4	88.6	88.8		88.5		87.7	87.6	88.5	80.9	81.9	79.1	78.8	81.4	81.1	7.7	6.6	8.6	7.4	7.4	8.8
5	75.1	76.8		75.2		75.0	74.8	75.1	74.5	74.7	73.1	73.4	75.6	74.5						
6	87.9	78.3		87.6		88.1	88.4	88.0	84.2	84.4	84.7	84.3	74.5	84.2	3.7	3.2	3.4	3.8	3.8	4.1
1'	101.7	102.0		101.7		100.4	99.9	101.6	97.7	97.9	96.6	96.1	97.9	97.8	4.0	3.8	3.8	3.3	4.1	3.8
2'	56.2	56.1		56.2		72.6	72.4	56.2	54.8	55.0	71.7	71.4	55.1	54.8						
3'	74.7	74.6		74.6		73.7	73.5	74.6	69.8	70.2	73.1	72.8	70.1	69.8	4.9	4.4		4.8	4.5	
4'	70.9	70.8		70.8		71.9	71.7	70.8	70.3	70.4	71.7	71.4	70.4	70.3						
5'	73.8	73.8		73.8		73.2	72.9	73.8	74.5	74.5	69.5	69.3	73.3	74.5			3.7			3.6
6'	61.6	61.6		61.6		42.2	42.0	61.6	61.5	61.3	41.3	41.0	61.3	61.3						
1''	100.8		100.1	101.2	100.3	101.1	100.4	100.7	101.4	101.8	102.0	100.7		101.8						
2''	70.9		70.5	68.6	68.2	68.3	72.4	66.8	67.1	64.8	64.7	68.7		66.7	3.8	3.8	3.6			3.7
3''	62.8		62.8	59.3	59.2	59.3	54.9	64.2	61.3	59.1	59.1	55.7		63.8						
4''	68.7		68.6	64.6	63.9	64.6	70.0	64.2	64.3	63.2	63.3	66.2		63.8	4.4	1.4	1.3			3.8
5''	63.0		62.3	65.3	65.3	65.1	72.9	62.8	63.3	66.3	66.4	72.8		63.4						
6''							61.1					60.7								
$N\text{-}CH_3$	34.2		34.3	32.6	32.5	32.4		25.7	30.5	30.9	30.8			25.8	3.7	1.7	1.6			
N-CHO								167.5						167.8						

[a] G-A = gentamicin A; Par = paromamine; R = methyl 3-methylamino-3-deoxy-α-D-xylo-pyranoside; $G\text{-}A_1$ = gentamicin A_1; R' = methyl 3-methylamino-3-deoxy-β-L-arabinopyranoside; $G\text{-}A_3$ = gentamicin A_3; K-A = kanamycin A; $G\text{-}A_4$ = gentamicin A_4. [b] See ref 11. [c] See ref 9.

Experimental Section

Thin layer chromatography was performed on silica gel GP (Analtech, Inc., Newark, Del.) using, unless otherwise specified, chloroform–methanol–ammonium hydroxide (3:4:2) as the developing phase. Column chromatography was carried out on silica gel (60-200 mesh, J. T. Baker Chemical Co., Phillipsburg, N.J.) using, unless otherwise specified, the same solvent system as above and on Dowex 1-X2 (200–400 mesh, hydroxide form, Sigma Chemical Co., St. Louis, Mo.) with water as the eluent.

The ^{1}H NMR spectra were recorded on a Varian Associates XL-100-15 spectrometer. Chemical shifts are given in δ values for solutions in deuterium oxide, flushed with nitrogen, using DSS as the internal standard. ^{13}C NMR spectra were obtained at 25.2 MHz on a Varian XL-100-15 spectrometer in the pulsed mode and Fourier transform to the frequency domain was accomplished with a Varian 620L-16K computer. ^{13}C chemical shifts are given in parts per million downfield from Me_4Si for solutions in deuterium oxide. The spectra were recorded with an internal dioxane reference and the expression δ_C (Me_4Si) = δ_C (dioxane) + 67.4 was employed to express the chemical shifts downfield from Me_4Si.[10] Mass spectra were obtained on a Varian MAT CH5 spectrometer at 70 eV with a probe temperature of 200–250°.

Isolation of Gentamicin A_1. A sample of crude gentamicin A (5.5 g) isolated as previously described[1b,2] and enriched in A_1 (R_A 0.78) was chromatographed on silica gel (600 g) using a column 5 cm in diameter. Ten-milliliter fractions were collected. Tubes 395–441, which contained gentamicin A_1, were pooled, concentrated, and lyophilized to give 0.28 g. Fractions 292–394 contained both gentamicins A and A_1, and after removal of the solvents in vacuo the residue was rechromatographed on the same column used above. After 500 ml of eluate 10-ml fractions were collected. Tubes 222–282 contained pure gentamicin A_1 and after work-up as above gave 0.386 g. Tubes 194–217 (0.5 g) contained mainly gentamicin A_1 and after work-up as above this was combined with the 0.28 g of material obtained above and chromatographed on a 3 × 72 cm column of Dowex ion exchange resin collecting 10-ml fractions. The homogeneous fractions (tubes 36–42) were pooled and concentrated to dryness. The residue was dried and dissolved in a minimum amount of methanol. Addition of excess ether precipitated pure gentamicin A_1, which was isolated by filtration, washed with ether, and dried to give 0.35 g, $[\alpha]^{26}D$ +141° (c 0.44, water), $[\theta]_{TaCu}{}^{280}$ – 12,190.

Anal. Calcd for $C_{18}H_{36}N_4O_{10}\cdot H_2O$: C, 44.44; H, 7.87; N, 11.52. Found: C, 44.75; H, 7.75; N, 11.57.

Isolation of Gentamicin A_2. In a manner similar to that described above, crude gentamicin A (36 g)[1b,2] was chromatographed on silica gel (3 kg) collecting 25-ml fractions. Tubes 811–900 were pooled, concentrated, and lyophilized to give partially pure (3 g) gentamicin A_2 (R_A 1.18). This product was again chromatographed on a Dowex ion exchange resin column (5.5 × 49 cm). Five-milliliter fractions were collected. Tubes 75–105 were pooled, concentrated, and lyophilized to give 1.84 g of pure A_2, $[\alpha]^{26}D$ +141° (c 0.4, water).

Anal. Calcd for $C_{17}H_{33}N_3O_{11}\cdot 2H_2O$: C, 41.54; H, 7.59; N, 8.55. Found: C, 41.36; H, 6.94; N, 8.29.

Isolation of the Gentamicins A_3 and A_4. Crude gentamicin A (112 g)[1b,2] was chromatographed on two 5-kg silica gel columns (12 × 152 cm) attached in series. Two-liter fractions were collected. Fractions 53–62 contained mainly gentamicin A_3 (R_A 0.40) and after work-up as above gave 6.5 g of crude A_3. In a similar manner work-up of tubes 27–31 yielded 7.5 g of crude gentamicin A_4 (R_A 1.62).

The above product of gentamicin A_3 (2 g) was rechromatographed on Dowex ion exchange resin (300 ml) collecting 10-ml fractions. Tubes 41–48, which contained pure A_3, were pooled, concentrated, and freeze dried to afford 0.1 g of material. A sample of this material was converted to the tetrahydrochloride salt by dissolving in water, neutralizing with 0.1 *N* hydrochloric acid, and lyophilization, $[\alpha]^{26}D$ +130° (c 0.1, water).

Anal. Calcd for $C_{18}H_{36}N_4O_{10}\cdot 4HCl$: C, 35.19; H, 6.56; N, 9.12. Found: C, 34.87; H, 6.77; N, 9.12.

Crude gentamicin A_4 isolated above was rechromatographed on silica gel (630 g) using a chloroform–methanol–ammonium hydroxide (2:1:0.35) system as the eluent and taking 3-ml fractions. Tubes 1361–1951, which contained A_4, were pooled, concentrated, and lyophilized to give 3.8 g of partially pure A_4. A sample of the above material (0.357 g) was further purified by chromatography on silica gel (70 g) using a 2.7 × 30 cm column and a solvent system containing chloroform–methanol–ammonium hydroxide–formic acid (300:400:200:0.3). Two-milliliter fractions were collected. The homogeneous fractions (tubes 170–189) were pooled, concentrated, deionized with Amberlite IRA-401S ion exchange resin in the hydroxide form, and lyophilized to give 0.222 g of pure gentamicin A_4, $[\alpha]^{26}D$ +130° (c 0.1, water). Anal. Calcd for $C_{19}H_{36}N_4O_{11}\cdot CO_2\cdot 2H_2O$: C, 41.66; H, 6.99; N, 9.72. Found: C, 41.68; H, 6.99; N, 9.88.

Acknowledgments. The authors wish to thank Messrs. J. McGlotten and P. Bartner for mass spectral determinations and Mr. C. Luce for assistance in column chromatography.

Registry No.—**1**, 55925-13-8; **2**, 55925-14-9; **3**, 55904-33-1; gentamicin A, 13291-74-2; gentamicin A_2, 55715-66-7.

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Notes

The Gentamicin Antibiotics. 8. Structure of Gentamicin A_2

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This communication deals with the elucidation of the structure of gentamicin A_2. The isolation of A_2 is published in the accompanying paper.[1a] The mass spectrum of A_2 indicated a molecular weight of 455 and elemental analysis was in good agreement with the composition $C_{17}H_{33}N_3O_{11}\cdot 2H_2O$. The mass spectrum also indicated ions characteristic of the deoxystreptamine moiety (*m/e* 191, 173, 163, and 145), a monoaminomonodeoxyhexosyldeoxystreptamine (*m/e* 352, 334, 324, 306, and 162), and a pentosyldeoxystreptamine unit (*m/e* 323, 305, 295, 277, and 133) in the molecule.[1-3]

Hydrolysis of gentamicin A_2[1b] with 6 *N* hydrochloric acid at 100° for 1 hr followed by analysis of the hydrolysate by paper chromatography using 1-butanol–pyridine–water–acetic acid (6:4:3:1) as the developer confirmed the presence of deoxystreptamine. The R_f values of the monosaccharides produced agreed well with those of glucosamine and xylose on paper chromatography using an ethyl acetate–pyridine–water (8:2:1) system as developer.[11]

The ^1H NMR spectrum of A_2 contained signals readily recognizable as arising from the deoxystreptamine and glucosamine portions of the molecule [δ 1.19 (H-2_{ax}, $J_{2ax,eq}$ = 12.5 Hz, $J_{1,2ax} = J_{2ax,3}$ = 12.5 Hz), 1.95 (H-2_{eq}, $J_{1,2eq} = J_{2eq,3}$ = 3.5 Hz), 2.77 (H-2′, $J_{2',3'}$ = 10 Hz), 5.23 ppm (H-1′, $J_{1',2'}$ = 3.5 Hz)].[1a,2] A second anomeric proton doublet appeared at δ 5.02 ppm with a splitting of 2.5 Hz.

N-Acetylation of A_2 afforded tri-*N*-acetylgentamicin A_2[1c] in quantitative yield, which confirmed the presence of three amino groups in the molecule [δ 1.51 (H-2_{ax}, $J_{2ax,2eq}$ = 12.0 Hz), 2.0, 2.02, and 2.06, (*N*-acetyls), 5.09 (H-1″, $J_{1'',2''}$ = 3.0 Hz), 5.38 (H-1′, $J_{1',2'}$ = 3.5 Hz)]. The chemical shifts and spin couplings of the signals due to the anomeric hydrogens in A_2 and its tri-*N*-acetyl derivative indicate these protons to be equatorially oriented and cis to the neighboring hydrogens.

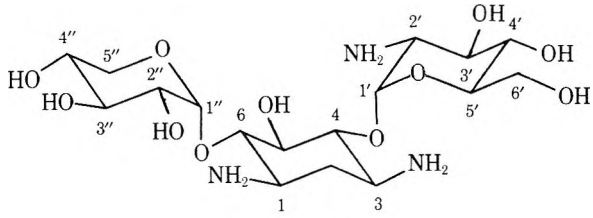
The proton noise decoupled ^{13}C NMR spectra of gentamicin A_2 measured at basic and acidic pD's[4-8] led to the recognition of the paromamine moiety in the molecule and established the configuration and ring size of the pentose unit and its position of attachment to paromamine.[1a] In Table I, the ^{13}C chemical shifts of gentamicins A_2, A, paromamine, and methyl α-D-xylopyranoside[9] are compared. The presence of the paromamine moiety in A_2 is clear from a comparison of the chemical shifts of carbon atoms 1–6 and 1′–6′ of A_2 with those of the corresponding carbons in A and paromamine. The close agreement (Table I) between the chemical shifts of carbon atoms 2–5 of methyl α-D-xylopyranoside and the corresponding atoms 2″–5″ of A_2 confirms the configuration and ring size of the pentose unit as α-xylopyranoid. The resonance position of C-1″ of A_2 (δ 101.4 ppm) corresponds well with that of A (δ 100.8 ppm) and differs by only 1 ppm from that of methyl α-D-xylopyranoside (δ 100.4 ppm). The linkage position of the α-xylopyranosyl unit to deoxystreptamine was established as 6-O by inspection of the chemical shifts of C-6 in A_2 and A. These atoms resonate at δ 87.9 ppm. On acidification, the C-6 resonance of A_2 is shielded by 4.1 ppm and the C-5 resonance experiences virtually no shift. This phenomenon[5] is also observed in the case of A where the magnitude of the shielding of C-6 is 3.7 ppm (Table I).[10] Furthermore, as shown in the accompanying paper,[1a] the magnitudes of the deshielding of C-6 and of shielding of C-5 on conversion of paromamine to a 6-O-linked pseudotrisaccharide is diagnostic for establishing the position of linkage of the second monosaccharide unit. Thus, $\delta_{C\text{-}6}$ (A_2) − $\delta_{C\text{-}6}$ (Par) = 9.6

Table I
^{13}C Chemical Shifts of Gentamicin A and A_2, Paromamine, and Methyl α-D-Xylopyranoside[a]

	Gentamicin A		Gentamicin A_2		Paromamine		Methyl α-D-
Carbon atom	pD 8.5	2.0	pD 8.5	2.0	pD 8.5	2.0	xylopyranoside[b]
1	51.5	50.3	51.4	50.8	51.1	50.7	
2	36.5	28.5	36.2	29.5	36.7	29.3	
3	50.3	49.6	50.2	49.9	50.3	49.9	
4	88.6	80.9	88.1	80.9	88.8	81.4	
5	75.1	74.5	75.0	74.4	76.8	75.6	
6	87.9	84.2	87.9	83.8	78.3	74.5	
1′	101.7	97.7	101.5	97.3	102.0	97.9	
2′	56.2	54.8	56.1	55.1	56.1	55.1	
3′	74.7	69.8	74.5	69.8	74.6	70.1	
4′	70.9	70.3	70.8	70.2	70.8	70.4	
5′	73.8	74.5	73.8	73.6	73.8	73.3	
6′	61.6	61.5	61.6	61.3	61.6	61.3	
1″	100.8	101.4	101.4	101.8			100.4
2″	70.9	67.1	72.5	72.4			72.2
3″	62.8	61.3	74.0	74.3			74.1
4″	68.7	64.3	70.2	69.7			70.2
5″	63.0	63.3	62.5	63.4			61.8

[a] Chemical shifts are in parts per million downfield from Me_4Si for solutions in D_2O. [b] Values obtained in our laboratory are in excellent agreement with the published ones.[9]

ppm and $\delta_{C\text{-}5}$ (A_2) − $\delta_{C\text{-}5}$ (Par) = −1.5 ppm in the bases and at pD 2, these are 9.3 and −1.2 ppm, respectively. These values are in excellent agreement with the values reported for structurally related compounds.[1a] Therefore, it can be concluded that in A_2 the α-xylopyranosyl unit is located at the 6-position of paromamine. The absolute configuration of xylose in A_2 has been shown by Nagabhushan and Daniels[10] to be D by a novel application of ^{13}C NMR spectroscopy. The structure of gentamicin A_2 is therefore as shown below.



gentamicin A_2

Registry No.—Gentamicin A_2, 55715-66-7.

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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXXIII. The Ochrolifuanines and Emetine[1]

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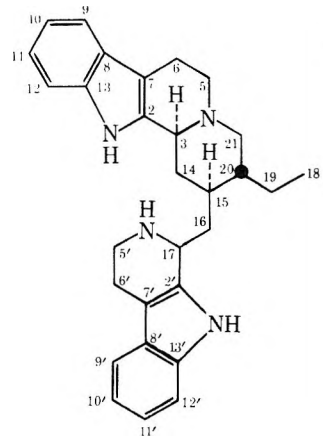
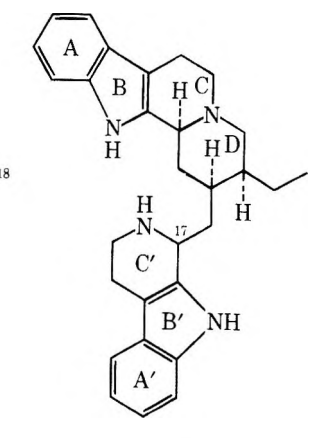
Recently two new alkaloids were isolated from *Ochrosia lifuana* Guillaumin and shown to possess structures **1a** and **1b**.[2,3] Their synthesis and that of two of their stereoisomers soon followed.[3] In view of the success in the use of ^{13}C NMR spectroscopy as an analytical tool for the differentiation of stereoisomers among yohimboid, ajmalicinoid, and corynanthoid alkaloids,[4,5] a ^{13}C NMR analysis of ochrolifuanine A (**1a**), ochrolifuanine B (**1b**), and the synthetic isomers **2a** and **2b** was undertaken. The ^{13}C NMR data[5] on models **3**, **4**, **5a**, and **5b** were used in this connection.



1a, 17β-H
b, 17α-H



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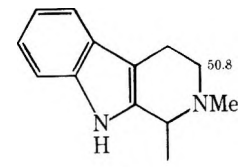

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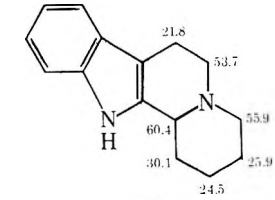

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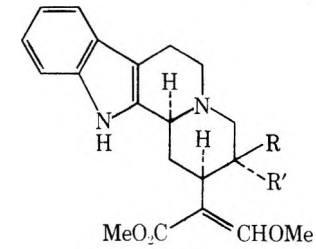


5a, R = H; R′ = Et
b, R = Et; R′ = H

The chemical shift information obtained from proton noise-decoupled and single-frequency off-resonance decoupled spectra of isomers **1a**, **1b**, **2a**, and **2b** as well as the data depicted on **3** and **4** and outlined in Table I for substances **5a** and **5b** permitted shift assignment for all carbons of the four substances under study except for two of their methylenes as well as two of their methines. Differentiation of the methylenes, C(14) and C(16), is based on the known C(14) shift of 37.2 ppm in yohimbane.[4] Ochrolifuanine A (**1a**) and ochrolifuanine B (**1b**) must have their C(14) more shielded owing to an added acyclic γ effect, while compounds **2a** and **2b** possess an even more shielded C(14) in view of the addition of another γ effect as a consequence of the axiality of their ethyl group. The distinction of the methines C(15) and C(20) of **1a** and **1b** is based on the idea of the shift similarity noted for the equivalent carbons in model **4** being retained in a case in which both carbons are equatorially ethylated and C(15) being shielded by the C(17) substituents. The same shift order can be expected for **2a** and **2b**. The total shift assignment portrayed in Table I was confirmed by a lanthanide shift study of **2b** with Yb(DPM)$_3$. The shift agent coordinates almost exclusively at the site of the secondary amine.

It is noteworthy that the C(5), C(6), C(5′), and C(6′) shifts are constant in the four substances **1a**, **1b**, **2a**, and **2b** and that there is a distinct difference between the C(5) and C(5′) shifts and the C(6) and C(6′) resonances. The constancy of the C(3) shift reflects the identity of the *trans*-quinolizidine conformation in the four compounds.[5] The dissimilarity of the C(17) shifts is a result of differences of rotamer populations of the equatorial C(15) side chain

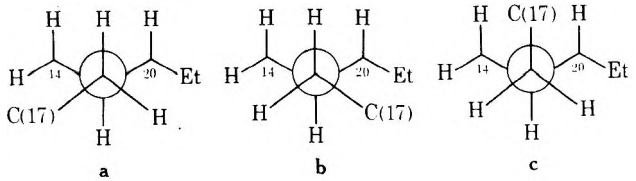
Table I
^{13}C Chemical Shifts[a]

	1a[b]	1b[b]	5a	2a[b]	2b[b]	5b
C(2), C(2′)	134.7, 135.5	134.6, 135.5		135.2, 135.4	135.1, 135.4	
C(3)	59.3	59.5	60.2	59.4	60.3	61.2
C(5)	52.6	52.9	53.1	53.1	53.1	53.4
C(6)	21.5	21.6	21.9	21.5	21.6	21.9
C(7), C(7′)	107.3, 108.1	107.3 108.6		107.9, 108.7	107.3, 108.4	
C(8), C(8′)	127.0, 127.2	127.0, 127.2		127.3, 127.4	127.1, 127.2	
C(9), C(9′)	117.7, 117.9	117.7, 117.9		117.9, 118.0	117.7, 117.7	
C(10), C(10′)	121.0, 121.3	120.9, 121.6		120.9, 121.4	120.6, 121.2	
C(11), C(11′)	118.9, 119.0	118.9, 119.3		119.1, 119.2	118.8, 119.0	
C(12), C(12′)	110.6, 110.9	110.8, 110.8		110.6, 110.6	110.6, 110.6	
C(13), C(13′)	135.9, 136.1	135.8, 135.9		135.7, 136.0	135.8, 135.8	
C(14)	34.3	36.4	33.8	31.1	32.4	29.8
C(15)	35.8	37.8	38.7	35.1	36.1	40.8
C(16)	38.1	38.4		38.4	37.8	
C(17)	48.8	51.9		49.8	50.0	
C(18)	11.0	11.2	11.3	12.5	12.4	12.8
C(19)	23.2	23.8	24.4	18.6	17.5	19.1
C(20)	42.2	42.5	39.3	41.3	38.3	40.0
C(21)	59.9	60.1	61.3	57.3	57.5	57.9
C(5′)	42.2	42.0		42.3	42.2	
C(6′)	22.4	22.4		22.5	22.3	

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b] The shifts of like carbons of the two indole units are undifferentiated.

(vide infra). The methyl group of axial ethyl functions is deshielded by ca. 1.5 ppm. In view of the 1,3-diaxial interaction C(14) and C(19) are shielded in the compounds possessing axial ethyl groups, i.e., **2a, 2b,** and **5b.** Carbon 21 is shielded in these substances also.

The C(14), C(15), C(17), and C(20) shifts are indicative of the conformational disposition of the two ring systems attached to C(16) with respect to each other. Carbon 16 serves the same structural function to the compounds **1a, 1b, 2a,** and **2b** as the oxygen bridge between two pyranosyl units and/or pyranosyl–inosityl units in disaccharides and related systems. Acyclic conformational analysis of such natural products has been aided immensely by ^{13}C NMR spectroscopy.[6] The rotamers **6a, 6b,** and **6c** represent the substituent arrangement around the C(15)–C(16) bond of ochrolifuanine A (**1a**) and B (**1b**) and rotamers **7a, 7b,** and **7c** the C(15)–C(16) environment of isomers **2a** and **2b.** Since, however, rotamers **6c** and **7c** incorporate an extra gauche-butane interaction, they can be discounted as important contributors to the structures in solution. The combination of identity of C(20) shifts and dissimilarity of C(14) shifts of **1a** and **1b** confirms this assignment for the alkaloids on the basis of the transmission of the γ effect via a carbon–hydrogen bond on the terminus of a gauche-butane structure.[7] The shielding of C(14) in **2a** with reference to **2b** and the concomitant deshielding of C(20) indicates that the predominant rotamer of **2a** is **7a** and that of **2b** is **7b.** The same C(14) shift argument leads to the assignment of rotamer **6a** for **1a** and **6b** for **1b.**



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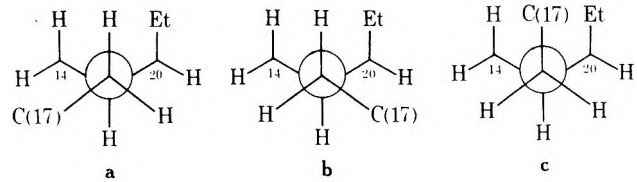

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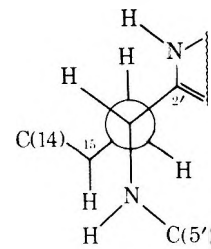
The shielding of C(15) with respect to C(20) in all four substances implies a nonbonded interaction of H(15) with N_b and/or C(2′). Furthermore, the shielding of C(14) in **1a** vs. **1b** and in **2a** vs. **2b** is explicable only in terms of a nonbonded interaction of H(17) with C(14) in **1a** and **2a.** Similarly, the shielding of C(20) in **2b** vs. **2a** must reflect a nonbonded interaction of H(17) with C(20) in **2b.** As a consequence, the rotamer **8** is preferred for compounds **1a** and **2a** and the rotamer **9** for **2b,** in accord with their C(17) configurations. Unfortunately, the rotamer preference of **1b** is difficult to assess. The 2 ppm or more deshielding of both C(15) and C(17) in **1b** as contrasted to its three isomers shows the lowering of reciprocal γ effects and hence increased H(15)–H(17) nonbonded interaction. The serious nonbonded interaction between C(17) and C(19) may be responsible for the lessening of the energy difference between various C(16)–C(17) bond rotamers.



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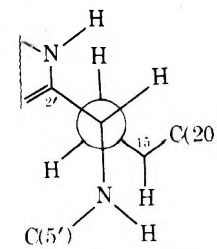
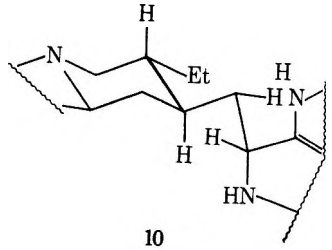


9

Since an axial 20-ethyl group can be expected to exert little effect on the energy content of the C(15)–C(16) bond rotamers **7a** and **7b** and since compound **2a** shows a preference for **7a,** while **2b** prefers **7b** instead, this unusual behavior must be the result of the difference of the C(17) chirality in the two compounds. An inspection of models indicates that in the overall structures **2a**–**7a**–**8** and **2b**–**7b**–**9**

H(15) experiences nonbonded interaction from $N_{b'}$, whereas **2a** represented by rotamer **7b** and **2b** by **7a** lead to much more severe nonbonded interaction of H(15) with $N_{a'}$. The same consideration of nonbonded interactions supports the preference of ochrolifuanine A (**1a**) for rotamer **7a** instead of **7b** except that in the case of this alkaloid rotamer **7b** suffers from an additional, unfavorable interaction, i.e., repulsion of C(17) and C(19). Conformational structures **10**, **11**, and **12** portray the preferred orientations of rings D and C′ toward each other in ochrolifuanine A (**1a**) and isomers **2a** and **2b**, respectively.



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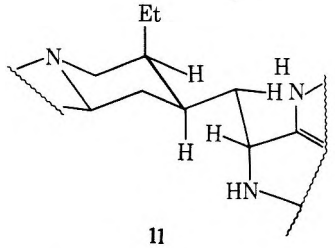

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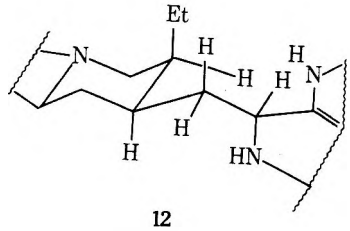
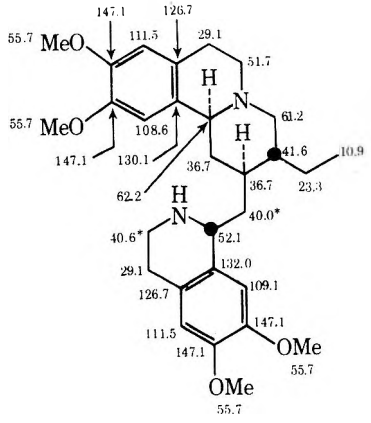


12

Ochrolifuanine A (**1a**) has a phenylalanine-derived alkaloid relative in emetine (**13**). The ^{13}C NMR data for the ochrolifuanines and their steroisomers (vide supra) as well as for the isoquinoline alkaloids laudanosine and tetrahydropalmatine[8] permit the assignment of the carbon shifts of emetine, as shown in formula **13**. It is noteworthy and of possible diagnostic value in the alkaloid field that benzylic methylenes within a tetrahydroisoquinoline nucleus are strongly deshielded on comparison with those in a tetrahydrocarboline unit.



13

Experimental Section

The carbon shifts in Table I were recorded on a Varian XL-100-15 spectrometer operating at 25.20 MHz equipped to operate in the pulsed Fourier transform mode with Transform Technology Inc. computer and pulse hardware. The shifts denoted on formula **13** were obtained from a chloroform solution [$\delta(Me_4Si) = \delta(CHCl_3) + 77.2$ ppm] with a Varian DP-60 spectrometer operating at 15.08 MHz in the Fourier transform mode. The asterisks on formula **13** indicate permissible signal reversal.

Registry No.—**1a**, 35527-46-9; **1b**, 35471-11-5; **2a**, 51820-26-9; **2b**, 51820-25-8; **3**, 17019-01-1; **4**, 239-15-6; **5a**, 7762-19-8; **5b**, 14509-88-7; **13**, 483-18-1.

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(3) M. Koch, M. Plat, and N. Préaux, *Bull. Soc. Chim. Fr.*, 2868 (1973).
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Carbon-13 Nuclear Magnetic Resonance Spectroscopy of Naturally Occurring Substances. XXXIV. Monomeric Quinolinic *Melodinus* Alkaloids[1]

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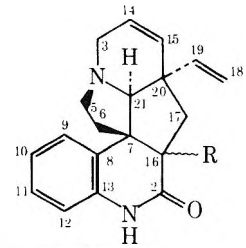
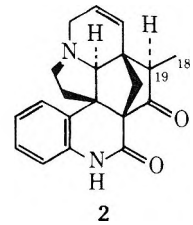
Investigations of the chemical constituents of the New Caledonian plant *Melodinus scandens* Forst. have shown this species to contain known *Aspidosperma* alkaloids as well as new bases structurally related to the former by oxidative rearrangement.[2-4] Structures **1a**, **1b**, **1c**, and **2** were



1a, R = β-H
b, R = α-H
c, R = α-CO_2Me
d, R = β-CO_2Me



2

assigned to meloscine,[2] epimeloscine,[2] scandine,[2] and meloscandonine,[4] respectively, primarily by spectroscopic means and the full structure of meloscine (**1a**) and absolute configuration were determined by X-ray analysis.[4] In view of the recent success in structure correlation of the *Aspidosperma* bases by ^{13}C NMR spectroscopy[5] the four quinolones were submitted to ^{13}C NMR analysis.

Table I
Chemical Shifts[a]

	1c	1a	1b	2
C (2)	170.2	171.9	173.0	169.0
C (3)	47.6	45.6	45.7	47.2
C (5)	53.2	52.4	51.7	54.8
C (6)	39.8	43.2	35.4	38.1
C (7)	57.7	56.8	55.3	54.8
C (8)	128.5	126.5	135.8[d]	130.5
C (9)	126.7[b]	127.2	122.3[c]	123.5[e]
C (10)	123.4	123.6	123.2[c]	123.4[e]
C (11)	127.2[b]	127.2	126.7	127.6
C (12)	115.5	115.4	116.2	116.3
C (13)	134.1	134.8	136.5[d]	136.5
C (14)	122.7	126.4	120.8	124.0
C (15)	131.2	134.2	130.9	127.4
C (16)	63.6	50.0	47.9	67.7
C (17)	44.0	40.8	34.0	36.0
C (18)	114.4	112.2	112.1	11.0
C (19)	142.0	142.4	144.3	50.7
C (20)	46.5	47.3	44.9	44.3
C (21)	83.5	81.1	71.5	69.9
C=O	169.3			210.0
OMe	52.4			

[a] In parts per million downfield from Me_4Si; $\delta(Me_4Si) = \delta(CDCl_3) + 76.9$ ppm. [b-e] The signals bearing the same superscript may be reversed.

The assignment of the carbon shifts of the alkaloids has been carried out in the following manner. The aromatic carbon shifts can be designated by the use of acetanilide[6] and 3,3-dialkyloxindoles[7] as models. Residual coupling characteristics detected in the single-frequency off-resonance decoupled (sford) spectra differentiate the nuclear double bond carbons from the aromatic methines. Thus C(14) and C(15) show appreciably lower J_R values in sford spectra in which the decoupler frequency is at the upfield end of the ^1H NMR spectrum.[8] As in the *Aspidosperma* alkaloid series,[5] C(14) is distinguished from C(15) by taking into consideration their dissimilarity with respect to the C(20) substituents. Readily recognized by chemical shift and multiplicity, the carbons of the vinyl group of three of the alkaloids exhibit strong two-bond coupling with their hydrogens. The phenomenon of long-range coupling of allylic carbons attached to vinyl groups is useful in the differentiation of the quaternary sites C(7) and C(20) of compounds **1** after the initial recognition of all nonprotonated carbons by the low-power, proton noise-modulated decoupling technique.[8,9] Thus, the C(20) signal appears much more broadened than the signals of other nonprotonated centers in sford spectra in which the decoupler frequency is placed at the high-field extremum of the ^1H NMR spectrum. The same signal is sharpened selectively upon irradiation in the olefinic ^1H NMR region. The C(7) shift of the four alkaloids is nearly the same as that of the *Aspidosperma* bases in view of their similar C(7) environment. Carbon 16 of **1c** and **2** exhibits the lowest field signal among the quaternary carbons.

The sole aminomethine, C(21), is the methine of lowest field. Since H(21) is the lowest field, saturated methine hydrogen, the residual J_{C-H} values, from sford spectra with the decoupler at a high ^1H NMR field position, are larger for C(21) than the other methine. Similarly, both chemical shift and residual splitting distinguish the aminomethylenes from the other methylenes and C(3) from C(5). The differentiation of the methylenes C(6) and C(17) depends on more subtle arguments (vide infra). The chemical shifts of all alkaloids are listed in Table I.

The stereochemistry of epimeloscine (**1b**) restricts the ring system to a rigid framework in which H(9) is in close proximity to H(21) and the C(9)–H and C(21)–H bonds are nearly coplanar. This requirement for a strong, reciprocal γ effect is missing in meloscine (**1a**), whose stereochemistry permits far more flexibility of the ring system. Both the ^1H NMR[2] and ^{13}C NMR data reveal the steric relationship between C(9)–H and C(21)–H. In epimeloscine (**1b**) H-21 is deshielded by 0.4 ppm from its field position in meloscine (**1a**) because of the anisotropy of the aromatic ring and C(9) and C(21) are shielded by ca. 5 and 10 ppm, respectively. Meloscandonine (**2**) expectedly shows the same ^{13}C NMR behavior at C(9) and C(21) as epimeloscine (**1b**). The lack of like ^{13}C NMR characteristics of scandine (**1c**) militates against its accepted structure and suggests it to be isomeric at C(16), in conformity with the similarity of its C(9) and C(21) shifts with those of meloscine (**1a**).

The same conclusion is reached by consideration of the C(6) and C(17) methylene resonances. Feeling a reciprocal γ effect, the two methylenes of epimeloscine (**1b**) are shielded strongly in comparison with the equivalent centers of meloscine (**1a**). The introduction of a 16-carbomethoxy group can be expected to deshield C(17) of either **1a** or **1b**, while shielding C(6) of **1a** or leaving C(6) of **1b** unaffected. Comparison of the methylene shift differences of scandine and meloscine (**1a**) as well as epimeloscine (**1b**) without regard to which signal belongs to C(6) or C(17) leads to only one set of rational values. They force the allocation of the methylene shifts of the three alkaloids to be as depicted in Table I and limit scandine to structure **1d**.[10] The previous assessment of the C(16) stereochemistry of scandine was based on the interpretation of upfield H(21) and methoxy shifts being due to shielding by the carbomethoxy group and the benzene ring, respectively.[2] In structure **1d** H(21) is in a lower aromatic deshielding zone than in epimeloscine (**1b**) and, to a smaller extent, in meloscine (**1a**) and the methoxy group is within the shielding influence of the lactam carbonyl function and/or the benzene ring.

Experimental Section

The spectra were recorded on a Varian XL-100-15 spectrometer operating at 25.204 MHz equipped to operate in the pulsed Fourier transform mode with Transform Technology Inc. computer and pulse hardware.

Registry No.—**1a**, 24314-51-0; **1b**, 24314-58-7; **1c**, 24314-59-8; **2**, 28645-27-4.

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(10) The differentiation of the C(6) and C(17) shifts of meloscandonine (**2**) is based on the ^{13}C NMR analysis of 19-epimeric alkaloids (unpublished observations).

A Convenient Preparation of Alkanoylmethylenetriphenylphosphoranes

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Various alkanoylmethylenetriphenylphosphoranes (**2**), versatile Wittig reagents, can be conveniently prepared[1] on a small scale from the corresponding acyl chlorides through the diazo ketone (Scheme I). To avoid undesirable use of

Scheme I[1]

$$RCOCl \xrightarrow{CH_2N_2} RCOCHN_2 \xrightarrow{HCl} RCOCH_2Cl \xrightarrow{Ph_3P}$$

1

$$RCOCH_2\overset{+}{P}Ph_3\bar{Cl} \xrightarrow{Na_2CO_3} RCOCH{=}PPh_3$$

2

diazomethane, an alternate route (Scheme II) to the chloro ketone had been developed.[2] Carboxylic acid esters con-

Scheme II[2]

$$RCOCH_3 \xrightarrow[NaH]{(CH_3O)_2CO} \xrightarrow[H_2O]{KOH} RCOCH_2CO_2H \xrightarrow{SO_2Cl_2} \xrightarrow{\text{distillation}} RCOCH_2Cl$$

1

taining no active hydrogen can be converted to the phosphorane (**2**, R = C_6H_5, R = H) upon treatment with methylenetriphenylphosphorane (Scheme III).[3,4] Various phos-

Scheme III[3,4]

$$RCO_2C_2H_5 + Ph_3P{=}CH_2 \longrightarrow RCOCH{=}PPh_3 + C_2H_5OH$$

2

phoranes (**2**) can also be prepared[4] by treatment of an appropriate acyl chloride with excess methylenetriphenylphosphorane (Scheme IV). However, poor yields in our

Scheme IV[4]

$$RCOCl + 2Ph_3P{=}CH_2 \longrightarrow RCOCH{=}PPh_3 + Ph_3\overset{+}{P}CH_3\bar{Cl}$$

2

hands[2] made this procedure unattractive. Recently Taylor and coworkers[5] and Cooke[6] have discovered that various alkanoylmethylenetriphenylphosphoranes (**3**) could be prepared by alkylation of lithiotriphenylphosphinioacetonide (Scheme V).

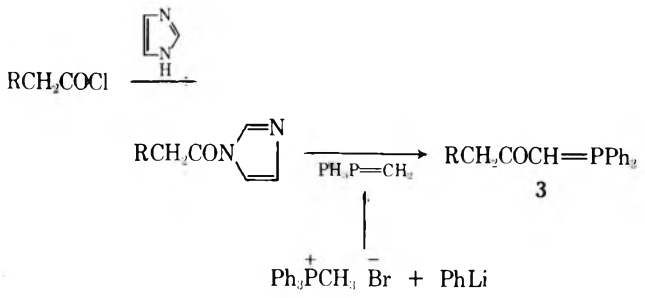
Scheme V[5,6]

$$CH_3COCH_2\overset{+}{P}Ph_3\dot{\bar{X}} \xrightarrow{2n\text{-BuLi}} \bar{C}H_2COCH{=}PPh_3 \xrightarrow{RX} RCH_2COCH{=}PPh_3$$

3

In this communication we report a preparation of **3** from acyl imidazolide (Scheme VI) which affords a significant

Scheme VI



advantage over Schemes III and IV. Contrary to Scheme III, Scheme VI could be applied to imidazolides of weak acids having α hydrogens. Only an equivalent amount of methylenetriphenylphosphorane was required in Scheme VI, in contrast with 2 equiv in Scheme IV. The overall yield of phosphoranes via Scheme VI was usually 50–60%, superior to yield of phosphoranes via Scheme IV. Since the basic fraction of reaction products included no phosphorus-containing by-product, the work-up was easy. The major by-product was a ketone **5**, presumably formed by a Claisen-type condensation (**4**).

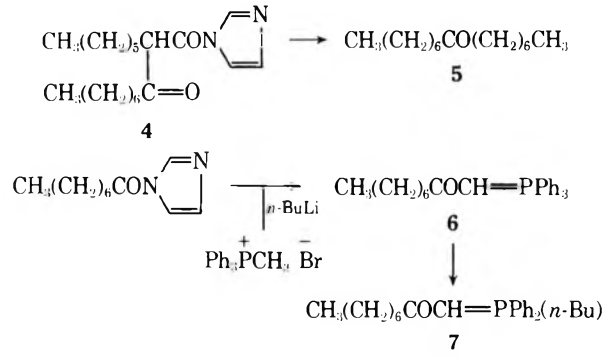
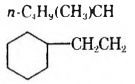
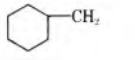
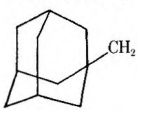
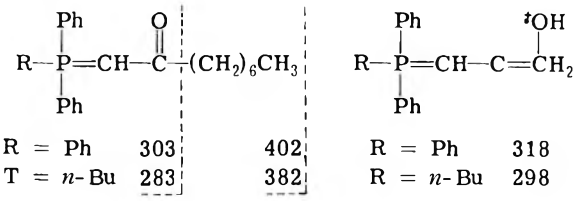


Table I
New Alkanoylmethylenetriphenylphosphoranes Prepared by Imidazole Procedure

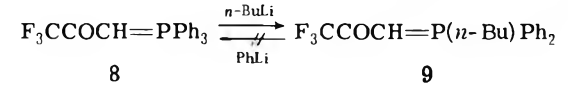
	RCOCH=PPh3						
			Calcd, %		Found, %		
R	Yield, %	Mp, °C	C	H	C	H	Registry no.
n-$C_4H_9(CH_3)CH$	55	83–85	80.38	7.53	80.41	7.57	41692-76-6
	56	84–86	81.13	7.54	80.87	7.64	55759-57-4
	53	133–135	80.97	7.30	80.97	7.40	55759-58-5
n-C_7H_{15}	52	81–83	80.56	7.76	80.61	7.58	41693-09-8
$CH_3OCH_2CH_2CH_2$	31	75–78	76.57	6.42	76.10	6.61	55759-59-6
	45	224–225	82.21	6.91	81.95	7.18	55759-60-9

Methylenetriphenylphosphorane used in this reaction had to be generated with phenyllithium. If *n*-butyllithium was used, significant amounts of *n*-butyldiphenylphosphorane (**7**) were formed, drastically decreasing the yield of crystalline **6**. Although **7** could not be isolated in a pure state and was an oil, *m/e* 382 (molecular ion), 298, and strong 283 peaks afforded convincing evidence for structure **7**. A few precedents for similar alkyl–aryl exchange have been recorded in the literature. Seyferth,[7] for instance, showed that benzene (26%) was formed when methyltriphenylphosphonium bromide was treated with methyllithium.



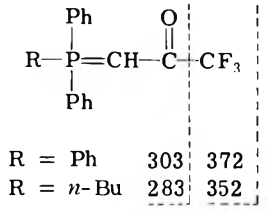
R = Ph	303	402	R = Ph	318	
T = *n*-Bu	283	382	R = *n*-Bu	298	

Trifluoroacetylmethylenetriphenylphosphorane (**8**) was obtained accompanied by trifluoroacetylmethylene-*n*-butyldiphenylphosphorane (**9**) when ethyl trifluoroacetate was treated with methylenetriphenylphosphorane generated by *n*-butyllithium. When **8** was treated with an equimolecular amount of *n*-butyllithium in ether at 25°, approximately 70% of **8** was converted into **9** within 30 min. On the other



8 **9**

hand, treatment of **9** with phenyllithium did not afford any recognizable (by TLC) amount of **8**.



R = Ph	303	372
R = *n*-Bu	283	352

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and were not corrected.

Acyl chlorides were prepared from the corresponding acids by thionyl chloride in hexane or benzene and were purified by distillation.

General Procedure for Preparation of Alkanoylmethylenetriphenylphosphorane (3). A solution of imidazole (0.2 mol) in 250 ml of tetrahydrofuran–ether (50:50) was stirred at 5° under nitrogen as an ethereal solution of acyl chloride (0.1 mol) was slowly added over 15 min. The resulting slurry was stirred for an additional 30 min and filtered under a nitrogen atmosphere. The cake of imidazole hydrochloride was washed with ether. A slurry of methyltriphenylphosphonium bromide (0.1 mol) in 1 l. of ether was treated with 0.1 mol of phenyllithium in benzene–ether (Ventron) at 25° for 1.5 hr. The ethereal acyl imidazolide solution was added to the methylenetriphenylphosphorane solution at −70° over 30 min. The mixture was allowed to warm to 25°, poured into 2 l. of dilute hydrochloric acid, and shaken with 1 l. of ether. The aqueous phase containing a heavy oil which was soluble in neither phase separated. The insoluble oily substance was the hydrochloride of **3** and often crystallized during the work-up. The aqueous phase was made alkaline (pH 10) with potassium carbonate and the oil which separated was extracted with toluene or benzene. The organic extract was washed[8] and evaporated in vacuo. The residue was recrystallized from hexane or ether–hexane.

Isolation and Identification of Pentadecan-8-one (5) as Byproduct. The preparation of **6** was carried out according to the general procedure except that methylenetriphenylphosphorane was generated with *n*-butyllithium. The ethereal phase was separated from the aqueous hydrochloric acid layer and concentrated. The residue was dissolved in benzene, washed,[8] and concentrated. The residue was recrystallized from hexane to give **5**: mp 43° (lit.[9] mp 43°); ir ($CHCl_3$) 1715 cm^{-1}; mass spectrum (70 eV) *m/e* 127 [$CH_3(CH_2)_6C(OH)=CH_2$].

Anal. Calcd for $C_{15}H_{30}O$: C, 79.59; H, 13,36. Found: C, 79.30; H, 13.39.

The aqueous phase containing the heavy oil gave **6** and **7**.

Trifluoroacetylmethylenetriphenylphosphorane (8) and Trifluoracetylmethylene-*n*-butyldiphenylphosphorane (9). To a solution of methylenetriphenylphosphorane (prepared from 0.22 mol of methyltriphenylphosphonium bromide and 0.2 mol of *n*-butyllithium) in 1 l. of ether was added 0.2 mol of ethyl trifluoroacetate at −70° under nitrogen. The reaction mixture was stirred at −70° for 1 hr, brought to 25°, then stirred with 1.5 l. of 2% hydrochloric acid and filtered to collect a colorless precipitate (A). The ethereal phase was worked up in the usual manner[8] (B). The aqueous acidic layer was made alkaline with potassium carbonate and extracted with methylene chloride[8] (C). The crystalline precipitate (A) was dissolved in methylene chloride, washed, and dried[8] (D). Extracts B and D gave totally 30.3 g of crude **8** whereas extract C gave 42.3 g of a mixture of **8** and **9**. Pure **8** of mp 233° was obtained (~30 g) by recrystallization from benzene: ir ($CHCl_3$) 1590 (C=O), 1575 cm^{-1} (C=C); NMR ($CDCl_3$) δ 4.27 (d, 1, J = 20 Hz).

Anal. Calcd for $C_{21}H_{16}OF_3P$: C, 67.74; H, 4.33. Found: C, 67.81; H, 4.49.

Pure **9** (~15 g) was obtained by chromatography of a mixture of **8** and **9** on silica gel using 1% ethyl acetate–methylene chloride and recrystallization from ethyl acetate: mp 138°; ir ($CHCl_3$) 1587 (C=O), 1572 cm^{-1} (C=C); NMR ($CDCl_3$) δ 4.07 (d, 1, J = 19 Hz), 2.73 (m, 2), 1.47 (m, 4), 0.90 (m, 3).

Note Added in Proof. A preparation of benzoylmethylene triphenylphosphorane from benzoylimidazole and 2 mol of methylenetriphenylphosphorane was recorded in the literature, but no example of an imidazolide having an α H was given: H. J. Bestmann, N. Sommer, and H. A. Staab, *Angew. Chem.*, **74**, 293 (1962).

Registry No.—**5**, 818-23-5; **8**, 55759-55-2; **9**, 55759-56-3; methyltriphenylphosphonium bromide, 1779-49-3; phenyllithium, 591-51-5; methylenetriphenylphosphorane, 3487-44-3; ethyl trifluoroacetate, 383-63-1.

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Metal–Hexamethylphosphoramide Reduction. IV. Birch-Like Reduction of 2,6- and 2,7-Dimethoxynaphthalenes[1]

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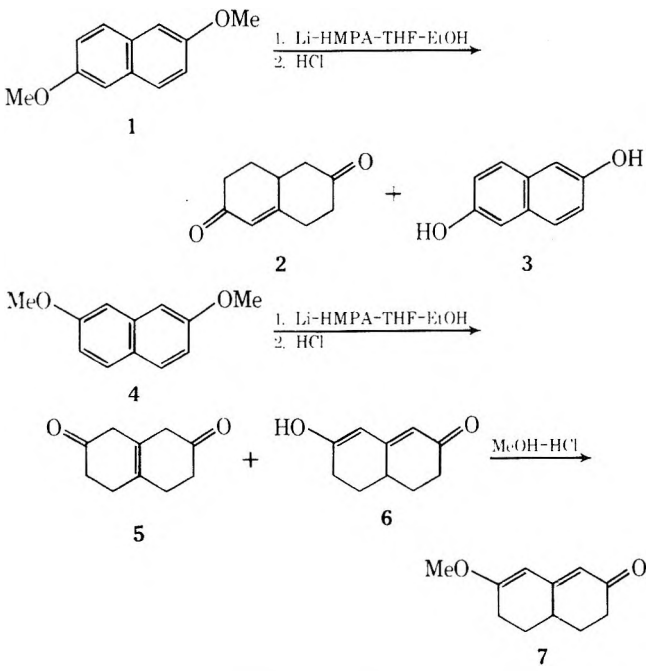
Recently we reported[2] preliminary results on the reduction of β-substituted dimethoxynaphthalenes with lithium in hexamethylphosphoramide (HMPA)–tetrahydrofuran (THF) with or without a proton donor (ethanol). We demonstrated that in the absence of an alcohol reductive cleavage of the type naphth–OMe and naphthO–Me is the major reaction pathway. In the presence of ethanol reduction of

the ring prevails; however, it can be preceded by attack of an electron at one or both methoxyl groups, which in consequence may give phenolic products without or with partial reduction of the aromatic rings. Therefore the product mixture differed distinctly from that obtained from the standard Birch reduction with sodium in liquid ammonia.

For that reason we decided to study this reaction in detail to find conditions that would give results analogous to those obtained by Birch reduction. The first experiments successful in this regard were achieved with 6-methoxytetralin and with estradiol 3-methyl ether.[3] In both cases we obtained the desired α,β-unsaturated ketones in good yield (~80%) after acid hydrolysis.

The present paper describes the successful reduction of 2,6-dimethoxynaphthalene (1) and 2,7-dimethoxynaphthalene (4) under the conditions of our new procedure leading to α,β-unsaturated ketones as major products. This procedure consists of slow addition of a 4:1 HMPA–THF lithium solution at −40° to a solution of the aryl ether in a HMPA–THF–EtOH mixture, followed by acid hydrolysis. In both cases we obtained the same products as those obtained by Birch reduction[4] in good yield (60–70%), along with some unreacted dimethoxynaphthalene and, especially in the case of 1 small amounts (<10%) of the related dihydroxynaphthalene.



The structural assignment of the purified reaction products was made by comparison of physical (melting point, mixture melting point, TLC retention time) and spectral (uv, ir) data with samples prepared by sodium–liquid ammonia reduction of 1 and 4. In the case of 7-hydroxy-2,3,4,5,6,10-hexahydronaphthalen-2-one (6), additional confirmation was made by conversion of it to 7-methoxy-2,3,4,5,6,10-hexahydronaphthalen-2-one (7) and its comparison with an authentic sample.

The above experiments describe for the first time an efficient, Birch-like conversion of naphthalenic diethers into bicyclic ketones by means of alkali metals dissolved in HMPA.

Experimental Section

Melting points were determined on a Boetius melting point apparatus and are uncorrected. Ir spectra were taken in chloroform with a Zeiss Model UR-20 spectrophotometer in absolute methanol. Thin layer chromatography was performed on microscopic slides coated with silica gel G (E. Merck) using benzene or benzene–ethyl acetate(4:1) solvent system for developing. Compounds were detected by iodine vapor. All solvents were made absolute according to standard procedure immediately before use. The lithium, cut into small pieces, was washed free of oil with hexane immediately before addition to the reaction mixture. Compounds 1 and 4 were prepared as described by Fisher and Kern[5]: 1, mp 149.5° from EtOH (lit.[6] mp 150°), and 4, mp 138° from EtOH (lit.[5] mp 138°).

Preparation of 2,6-Diketo-1,2,3,4,6,7,8,9-octahydronaphthalene (2). To a mixture of anhydrous and freshly distilled HMPA (60 ml) and THF (15 ml) placed into a dry three-neck round-bottom flask, equipped with a mechanical stirrer, a thermometer, and a calcium chloride tube, 150 mg (8 g-atoms) of lithium cut into small pieces was added under stirring. The blue coloration of the metal solution developed after a few minutes and the temperature rose to 25–28°. The solution was then cooled to 0° and the stirring was continued for about 1.5 hr until almost all lithium was dissolved.

Simultaneously, a similarly equipped flask containing a solution of 1 (0.5 g) in HMPA (20 ml), THF (20 ml), and EtOH (3 ml) was cooled to −45° with a Dry Ice–acetone bath. The lithium solution prepared as above was now added slowly in small portions so that the temperature of the mixture did not exceed −30°. After addition of THF (40 ml) the complete reaction mixture was stirred until decolored (usually after about 5 hr). The solution was then acidified with 2 *N* hydrochloric acid, allowed to stand for 30 min, and extracted with three 50-ml portions of ether. Usual work-up of the combined ether extracts led after evaporation of the ether to a crude product which was dissolved in 20 ml of THF–EtOH (2:1) mixture and 5 ml of 2 *N* HCl and refluxed for 30 min. After this time the mixture was treated with a saturated ammonium sulfate solution and extracted three times with ether. The combined ether layers were washed ten times with 2 *N* HCl, then with a saturated ammonium sulfate solution, and dried over anhydrous magnesium sulfate. After filtration and evaporation of ether 2 was isolated by column chromatography on silica gel (E. Merck) using benzene and benzene–ethyl acetate (4:1) as eluents. Recrystallization from ethyl acetate afforded 0.26 g (60.5%) of colorless needles: mp 93–93.5° (lit.[4a] mp 93–94°); uv λ_{max} 235 nm (ϵ 26,000); ir ν_{max} 1615, 1680, 1725 cm^{-1}. Preparation of the 2,4-dinitrophenylhydrazone in the usual manner provides red prisms, mp 274° (lit.[4a] mp 275°), after recrystallization from ethyl acetate.

Reduction of 2,7-Dimethoxynaphthalene (4) in a manner completely analogous to that described above for 1 afforded from 0.5 g of 4 after column chromatography on silica gel using the same eluent 0.056 g of 5 and 0.214 g of 6 (total yield 63%). **5:** colorless needles; mp 65° (lit.[4d] mp 62.5–63.5°) after recrystallization from benzene–petroleum ether (bp >80°); ir ν_{max} 1718 cm^{-1}. **6:** fine pale yellow crystals; mp 176° (lit.[4d] mp 179–179.5°) after recrystallization from benzene–petroleum ether; uv λ_{max} 321 nm (ϵ 17,700); ir ν_{max} 1560, 1608, 3250–3350 cm^{-1}.

Preparation of 7-Methoxy-2,3,4,5,6,10-hexahydronaphthalen-2-one (7). A solution of 0.2 g of 6 in 20 ml of MeOH saturated with HCl was heated under reflux for 1 hr. Then the cooled solution was diluted with ether and extracted with water, 1 *N* NaOH, and three times with water. The ethereal solution was dried over anhydrous magnesium sulfate. After filtration, evaporation of ether, and recrystallization from ethyl ether–petroleum ether (bp 60–80°), 7 was obtained as colorless needles: mp 97° (lit.[4f] mp 93–94°); uv λ_{max} 310 nm (ϵ 22,500); ir ν_{max} 1260, 1560, 1608 cm^{-1}.

Registry No.—1, 5486-55-5; 2, 54440-32-3; 4, 3469-26-9; 5, 3468-56-2; 6, 1614-83-1; 7, 1614-84-2; lithium, 7439-93-2.

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Halolactones from 1,4-Dihydrobenzoic Acids

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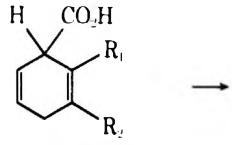
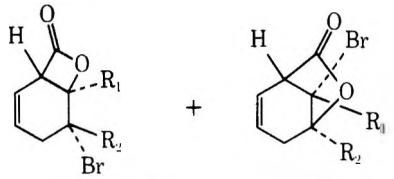
In an effort to increase the utility of 1,4-dihydrobenzoic acids, which are readily available by the Birch reduction[2] of benzoic acids, and in connection with studies aimed at defining the scope of a new β-lactone synthesis,[3] we have examined the iodolactonization and bromolactonization of 1,4-dihydrobenzoic acids. However, such low yields of lactones have been obtained in the iodolactonization of several 1,4-dihydrobenzoic acids that the reaction cannot be considered as a reliable synthetic method. In contrast, the bromolactonization reaction consistently affords good yields of stable crystalline bromolactones.

The ring size of the lactone formed in the bromolactonization of a 1,4-dihydrobenzoic acid depends upon substitution at the sites of unsaturation. Either a β-lactone or a γ-lactone may be favored. Thus 2-methyl-1,4-dihydrobenzoic acid (**1a**), affords a β-lactone. Of the two possible β-lactones only one is formed, lactone formation in this case being directed toward the more substituted double bond to produce **2a**. In the bromolactonization of the isomeric carboxylate salt, **1b**, lactonization is directed once again toward the more substituted double bond; however, there is a difference in lactone ring size. The major product is γ-lactone **3b**.



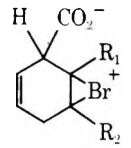
1a. $R_1 = CH_3$; $R_2 = H$
b. $R_1 = H$; $R_2 = CH_3$
c. $R_1 = R_2 = H$
d. $R_1 = R_2 = CH_3$



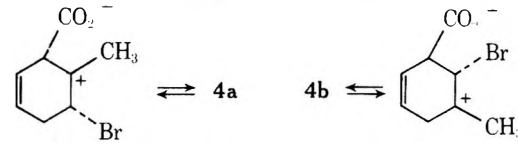
2a. $R_1 = CH_3$; $R_2 = H$ **3a**. $R_1 = CH_3$; $R_2 = H$
b. $R_1 = H$; $R_2 = CH_3$ **b**. $R_1 = H$; $R_2 = CH_3$
c. $R_1 = R_2 = H$ **c**. $R_1 = R_2 = H$
d. $R_1 = R_2 = CH_3$ **d**. $R_1 = R_2 = CH_3$

This selectivity of halolactonization for the more substituted double bond can be rationalized in terms of a probable mechanism of the reaction.[4] In the addition reactions of bromine to olefinic sites, three-membered cyclic bromonium ions have often been postulated as intermediates in a two-step mechanism, but only until recently have such intermediates received experimental support.[5] The change in lactone ring size which results from the shift of a methyl group from the β to the γ position in dihydrobenzoic acid substrates **1a** and **1b** is consistent with a brominum ion intermediate having more carbonium ion character[6] at the more substituted carbon atom, **4a** → **5**. An intermediate with character as shown by **5** could promote intramolecular Markovnikov-type regiospecificity controlling the formation of **2a** from **1a**.

A similar argument applies to the formation of a γ-lactone in the case of the isomeric acid salt **1b**. An intermediate having carbonium ion character as shown by **6** would tend to promote γ-lactone formation leading to **3b**. In both of the cases, owing to the stability of the tertiary carbonium ions, **5** and **6**, the ring closure step would be expected to possess a great deal of SN1 character.



4a. $R_1 = CH_3$; $R_2 = H$
b. $R_1 = H$; $R_2 = CH_3$

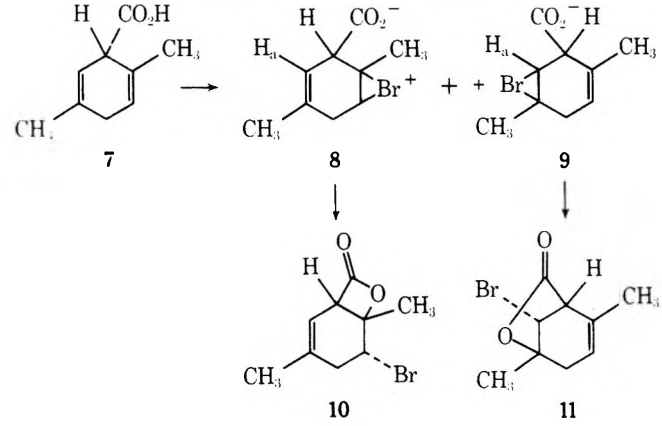


5 **6**

On the other hand, the bromonium ion involved in the reaction of **1c** is not as stable; therefore, the ring closure step would be expected to possess primarily SN2 character. Since it is known that in intramolecular SN2 ring closure reactions the geometry of the molecule is such that the formation of four-membered rings is favored over the formation of five-membered rings,[7] the expected product from **1c** is the β-lactone **2c**; indeed, **2c** is the exclusive lactone product.

Another example in which Markovnikov control is not operative, but one in which the bromonium ion is stabilized, is 2,3-dimethyl-1,4-dihydrobenzoic acid (**1d**). As expected the γ-lactone **3d** is favored (>80% by quantitative ir); however, it is not the exclusive lactone product.

As an example in which Markovnikov control is operative and competitive β- and γ-lactone formation is conceivable, the bromolactonization of 2,5-dimethyl-1,4-dihydrobenzoic acid (**7**) was studied. In this case two different bromonium ions, **8** and **9**, are possible. By analogy to the 2-



7 **8** **9**

10 **11**

methyl- and 3-methyl-1,4-dihydrobenzoic acids, the expected products of Markovnikov addition are **10** and **11**. In practice, γ-lactone formation predominates. The lactone mixture contained 93% of **11** and a small amount of γ-lactone. Since the crude reaction product does not show O=C–O–C**H** absorption in the NMR, this β-lactone must have structure **10**. Both products, **10** and **11**, would be expected to be formed by a SN1 mechanism; however, the entropy factor favors the formation of a five-membered ring over the formation of a four-membered ring.

Although a limited number of examples have been examined, the examples are representative enough to permit several generalizations about the bromolactonization of 1,4-dihydrobenzoic acids. In general, the bromolactonization of alkyl-substituted 1,4-dihydrobenzoic acids is di-

rected to the more substituted olefinic site. The presence of a γ-alkyl group promotes γ-lactone formation and in the absence of any γ-alkyl substituents, β-lactone formation predominates. Within these limitations the bromolactonization reaction appears to be a viable synthetic method which promises to enhance the utility of 1,4-dihydrobenzoic acids as intermediates in organic syntheses.

Experimental Section

NMR spectra were run in CCl_4 unless otherwise indicated. The spectra were recorded with a Hitachi 100 NMR spectrometer. The infrared spectra were run in the media indicated with a Perkin Elmer Model 257 spectrometer, except for the quantitative infrared spectra for 6-bromo-5-hydroxy-5,6-dimethylcyclohex-2-enecarboxylic acid γ-lactone (**3d**) and 2,5-dimethyl-5-hydroxy-6-bromocyclohex-2-enecarboxylic acid γ-lactone (**11**), which were recorded with a Perkin-Elmer Model 261. Melting points were taken on a Reichert hot stage apparatus and are corrected. Analyses were done at the Atlantic Microlab, Inc., Atlanta, Ga.

2-Methyl-1,4-dihydrobenzoic Acid (1a). 2-Methyl-1,4-dihydrobenzoic acid was prepared according to the method of Birch.[2b] *o*-Toluic acid (40.0 g) was reduced by sodium in liquid ammonia to yield 35.0 g (86%) of colorless crystals, mp 74–76° (lit.[2b] mp 74–75°).

1,4-Dihydrobenzoic Acid (1c). 1,4-Dihydrobenzoic acid was prepared according to the method of Kuehne and Lambert,[2a] yield 16.8 g (78%), bp 89° (0.50 mm) [lit. bp[2a,b] 96–98° (0.01 mm)].

3-Methyl-1,4-dihydrobenzoic Acid (1b). To 50 g (0.368 mol) of *m*-toluic acid, 500 ml of absolute methanol, and approximately 1650 ml of liquid ammonia was added 46.3 g (2.0 mol) of sodium which was cut into small pieces. After the addition of sodium had been completed, ammonium chloride (215 g) was added. The reaction mixture was stirred for 3 hr and the ammonia was allowed to evaporate overnight. Water (800 ml) was added and the solution was acidified with 10% HCl. The aqueous layer was extracted four times with 200-ml portions of ether. The combined ether layers were dried (Na_2SO_4) and filtered, and the solvent was evaporated in vacuo, yielding 43.0 g (85%). After one recrystallization from ether–light petroleum ether, the yield was 30.0 g (60%): mp 82.5–84.5°; NMR δ 12.13 (s, 1 H), 5.43–5.75 (m, 3 H), 3.40–3.77 (m, 1 H), 2.48–2.60 (m, 2 H), 1.73 (s, 3 H).

Anal. Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.65; H, 7.37.

2,3-Dimethyl-1,4-dihydrobenzoic Acid (1d). 2,3-Dimethyl-1,4-dihydrobenzoic acid was prepared in the same manner as **1b.** The crude yield from the reduction of 2,3-dimethylbenzoic acid (0.167 mol) was 23.0 g. After recrystallization from ether–light petroleum ether, the yield was 19.2 g (76%): mp 74.5–76.5°; NMR δ 12.12 (s, 1 H), 5.71 (m, 2 H), 3.39–3.67 (m, 1 H), 2.50–2.65 (m, 2 H), 1.68 (s, 6 H).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.11; H, 7.87.

2,5-Dimethyl-1,4-dihydrobenzoic Acid (7). 2,5-Dimethyl-1,4-dihydrobenzoic acid was prepared in the same manner as **1b.** The crude yield from the reduction of 2,5-dimethylbenzoic acid (0.167 mol) was 23.2 g (91.5%). After recrystallization from ether–light petroleum ether, the yield was 17.8 g (72%): mp 82–83°; NMR δ 12.02 (s, 1 H), 5.35–5.50 (m, 2 H), 3.27–3.67 (m, 1 H), 2.42–2.65 (m, 2 H), 1.70 (s, 6 H).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.03, H, 7.95. Found: C, 70.90; H, 8.00.

5-Bromo-6-hydroxy-6-methylcyclohex-2-enecarboxylic Acid β-Lactone (2a). To 1.38 g (0.01 mol) of **1a,** which was dissolved in 40 ml of a saturated $NaHCO_3$ solution, was added 1.60 g (0.01 mol) of bromine in 50 ml of methylene chloride. The stirring was continued at room temperature until the disappearance of the bromine color (about 1 min). The layers were separated and the aqueous layer was extracted with 25 ml of methylene chloride. The combined organic layers were washed with 25 ml of water. The organic layer was dried (Na_2SO_4), and then the solvent was evaporated in vacuo, yielding 1.13 g (52%), ir (film) 1827 (C=O), 1642 cm^{-1} (C=C). Recrystallization from ether–light petroleum ether yielded 0.74 g (29.5%): mp 51–53°; NMR δ 5.85–5.98 (m, 2 H), 4.31–4.45 (t, 1 H), 3.79–3.88 (d, 1 H), 2.64–2.80 (m, 2 H), 1.84 (s, 3 H).

Anal. Calcd for $C_8H_9BrO_2$: C, 44.27; H, 4.18; Br, 36.70. Found: C, 44.31; H, 4.26; Br, 36.54.

5-Bromo-6-hydroxycyclohex-2-enecarboxylic Acid β-Lactone (2c). A procedure similar to that used for the preparation of **2a** was used. The crude yield from **1c** (0.01 mol), bromine (0.01 mol), and $NaHCO_3$ reaction mixture was 1.20 g (59.6%), ir (film) 1825 (C=O), 1643 cm^{-1} (C=C). Recrystallization from ether–light petroleum ether yielded 0.85 g (42%): mp 84–85°; NMR ($CDCl_3$) δ 5.68–6.18 (m, 2 H), 4.17–4.96 (m, 3 H), 2.64–2.75 (m, 2 H).

Anal. Calcd for $C_7H_7BrO_2$: C, 41.41; H, 3.48; Br, 39.35. Found: C, 41.36; H, 3.58; Br, 39.15.

6-Bromo-5-hydroxy-5-methylcyclohex-2-enecarboxylic Acid β-Lactone (3b). A procedure similar to that used for the preparation of **2a** was used. The crude yield from **3b** (0.01 mol), bromine (0.01 mol), and $NaHCO_3$ reaction mixture was 1.55 g (71.4%), ir (film) 1785 (C=O), 1638 cm^{-1} (C=C). Recrystallization from ether–light petroleum ether yielded 1.33 g (61.3%): mp 70–71°; NMR δ 5.78–5.84 (m, 2 H), 4.24–4.28 (d, 1 H), 3.12–3.24 (m, 1 H), 2.40–2.50 (m, 2 H), 1.45 (s, 3 H).

Anal. Calcd for $C_8H_9BrO_2$: C, 46.78; H, 4.80; Br, 34.58. Found: C, 46.74; H, 4.83; Br, 34.51.

The infrared spectrum of the residue from the combined mother liquors vs. the spectrum of the pure γ-lactone indicated that the mother liquor contained 80 ± 3% γ-lactone (ratio of γ- to β-lactone in crude product ~93:7).

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

Registry No.—**1a,** 55886-48-1; **1b,** 31673-44-6; **1c,** 4794-04-1; **1d,** 31673-37-7; **2a,** 55886-49-2; **2c,** 55886-50-5; **3b,** 55886-51-6; **7,** 31673-39-9; *m*-toluic acid, 99-04-7; 2,3-dimethylbenzoic acid, 603-79-2; 2,5-dimethylbenzoic acid, 610-72-0.

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A Facile Double Migration in the Protonation of Lithium Alkynyltrialkylborates with Acid

Summary: Protonation of lithium alkynyltrialkylborates, $(R_3BC{\equiv}CR')Li$, with acid can be directed to achieve a double migration of alkyl groups from boron to carbon.

Sir: Monolithium acetylide reacts rapidly with trialkylboranes to produce the lithium ethynyltrialkylborate (eq 1). The protonation of such compounds with hydrochloric acid may be controlled to produce the Markovnikov alkenylborane[1] (eq 2). However, the use of excess acid causes a facile second migration of an alkyl group from boron to carbon (eq 3). Oxidation with alkaline hydrogen peroxide then

$$R_3B + LiC{\equiv}CH \longrightarrow (R_3BC{\equiv}CH)Li \quad (1)$$

$$(R_3BC{\equiv}CH)Li \xrightarrow[-78°]{HCl/H_2O} \begin{matrix} R \\ \diagdown \\ C{=}CH_2 \\ \diagup \\ R_2B \end{matrix} + LiCl \quad (2)$$

$$\begin{matrix} R \\ \diagdown \\ C{=}CH_2 \\ \diagup \\ R_2B \end{matrix} \xrightarrow[\Delta]{HCl/H_2O} R{-}B(HO){-}C(R){-}CH_3 \quad (3)$$

produces the tertiary alcohol in high yield. Such a migration during the protonation of simple vinylboranes has hitherto been unobserved. This unusual migration is quite broadly applicable and has now been observed in the protonation of a considerable number of lithium alkynyltrialkylborates (eq 4).

$$(R_3BC{\equiv}CR')Li \xrightarrow{H^+} \xrightarrow{[O]} HO{-}\overset{R}{\underset{R}{C}}{-}CH_2R' \quad (4)$$

Alkali metal alkynyltrialkylborates are readily protonated under mild conditions to give a mixture of isomeric alkenylboranes[2] (eq 5). These vinylboranes may be cleaved

$$(R_3BC{\equiv}CR')M \xrightarrow{H^+} R_2BCR{=}CHR' \quad (5)$$

with acetic acid to give a cis–trans mixture of internal olefins[2] or they may be oxidized to regiospecific ketones.[2b] No double migration has been observed in these reactions. Indeed, Zweifel has shown that vinylboranes are cleaved to olefin upon protonation with mineral acid. Only when the vinylborane is first complexed with methyllithium does protonation cause an alkyl group to migrate.[3]

However, protonation of lithium ethynyltri-*n*-butylborate (5 mmol) with concentrated hydrochloric acid (5 mmol) at −78°, followed by oxidation with alkaline hydrogen peroxide at room temperature, produces the unexpected product, 5-methyl-5-nonanol, in 20% yield, along with 55% expected 2-hexanone. The use of excess acid results in exclusive carbinol formation (80% yield).

The reaction is quite general. The complexes from monolithium acetylide[4] or monolithium acetylide–ethylenediamine (EDA)[2c,5] and a variety of trialkylboranes react quite readily upon warming to room temperature with adequate hydrochloric acid. As a general procedure, these complexes are refluxed for 1 hr in tetrahydrofuran (THF) with 2 mol of concentrated hydrochloric acid following the initial protonation at −78°. The complexes from trialkylboranes and 1-hexyne or cyclohexylethyne are somewhat more sluggishly protonated. These require 1–2 hr of reflux. The highly hindered complexes from 3,3-dimethyl-1-butyne require somewhat more drastic conditions, such as 4–8 hr in refluxing 1-butanol. In the case of these more hindered boranes, the yields of carbinol also decrease. The results are summarized in Table I.

Table I
The Protonation of Lithium Alkynyltrialkylborates for the Synthesis of *tert*-Alcohols

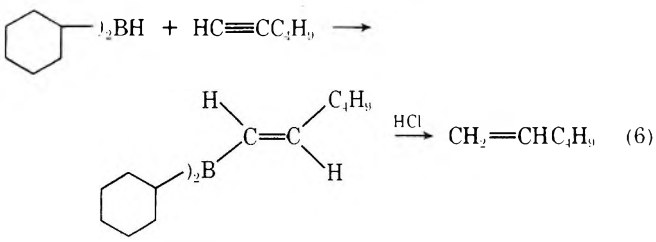
Trialkylborane, R	Yield,[a] %, of $R_2C(OH)CH_2R'$, R'					
	H	H·EDA	*n*-Butyl	*tert*-Butyl	Cyclohexyl	Phenyl
n-Butyl	82	80	86	86	74	73
Isobutyl	72	72	81	75	77	86
sec-Butyl	68	55	86	30[c]	78	30[d]
Cyclopentyl	72	72	84[b]		75	
Cyclohexyl	72	86	80	15[c]	63	0[d]

[a] By VPC. All reactions were run on a 5-mmol scale. The products were isolated by preparative VPC and characterized by spectroscopy. [b] Isolated yield. [c] The main product was unreacted starting material. [d] The reaction took a different course which is presently under investigation.

The following procedure for the preparation of 1,1-dicyclopentyl-1-hexanol is representative. A dry 500-ml flask equipped with a septum-capped inlet, a reflux condenser, and magnetic stirring bar was connected to a bubbler and flushed with nitrogen. The flask was charged with THF (65 ml) and cyclopentene (300 mmol, 26.5 ml). The flask was cooled to 0° and borane–THF (100 mmol, 35.6 ml of 2.81 *M*) was added dropwise. The solution was then stirred at room temperature for 1 hr, then cooled to 0°. A dry 250-ml flask was flushed with nitrogen and charged with THF (80 ml) and 1-hexyne (100 mmol, 12.0 ml). The flask was cooled to 0° and *n*-butyllithium in hexane (100 mmol, 44 ml of 2.27 *M*) was added dropwise. After 10 min, the contents were transferred dropwise by a double-ended needle[6] to the 500-ml flask containing the tricyclopentylborane. After completion of the addition, the solution was stirred for 10 min and then cooled to −78°. Concentrated hydrochloric acid (~240 mmol, 20 ml) was added, and the solution was warmed to room temperature by removing the Dry Ice–acetone bath. The solution was heated at reflux for 1 hr. The solution was then cooled and neutralized to the phenolphthalein end point with 40% potassium hydroxide (~25 ml). Ethanol (100 ml) and sodium hydroxide (24 g) were added to the flask. Hydrogen peroxide (40 ml of 30%) was added at such a rate as to keep the temperature at 50°. After the addition, the solution was heated to 50° for 2 hr and then cooled, and the aqueous layer was saturated with potassium carbonate. The THF phase was separated, and the water layer was extracted with 2 × 50 ml of ether. The combined organic phase was dried over magnesium sulfate and distilled. There was collected 20.1 g (84%) of 1,1-dicyclopentyl-1-hexanol, bp 118–120° (0.01 mm), $n^{20}D$ 1.4876.

The protonation of lithium alkynyltrialkylborates may thus be controlled to give either the alkenylborane[1] (monoalkyl group migration) or the *tert*-alkylborane (dialkyl

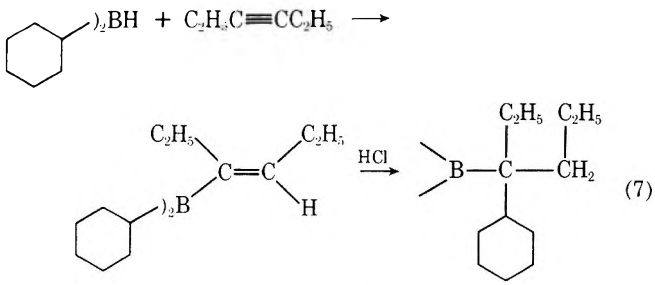
group migration). Since the second step involves the protonation of a vinylborane, the protonation of typical vinylboranes was briefly investigated. Hydroboration of 1-hexyne with dicyclohexylborane produces the terminal vinylborane (eq 6). The vinyl protons [NMR δ 6.70 (dt, J = 18



(6)

Hz, J = 5.6 Hz), 6.15 (d, J = 18 Hz)] disappear upon treatment with concentrated hydrochloric acid and protons due to 1-hexene appear. Oxidation produces none of the expected 1-cyclohexyl-1-hexanol. These results thus confirm previous investigations of mineral acid protonations of vinylboranes.[3]

Hydroboration of 3-hexyne with dicyclohexylborane produces the internal vinylborane (eq 7). The vinyl protons [δ



(7)

5.72 (m)] disappear upon protonation. Oxidation produces 3-cyclohexyl-3-hexanol in 96% yield.

Thus, there is a major difference in the behavior of dialkylvinylboranes toward hydrochloric acid, depending upon whether the vinyl group is terminal (eq 6) or internal (eq 7). The former undergoes simple protonolysis of the B–C bond; the latter undergoes proton addition to the double bond with B–C alkyl group migration.

The protonation of lithium alkynyltrialkylborates may now be controlled to give either alkenylboranes or organoboranes containing bulky *tert*-alkyl groups. Such organoboranes are becoming increasingly important in the formation of complex structures.[6,7] Furthermore, the present reaction suggests that other reactions of lithium alkynyltrialkylborates may be controlled to produce double migrations.[8]

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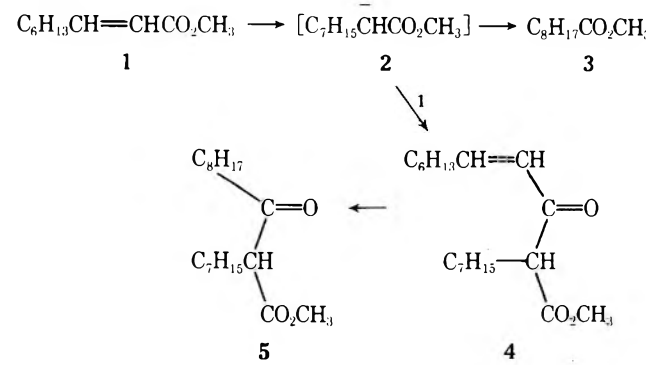
Unique Methodology for the Conjugate Reduction and Reductive Alkylation of α,β-Unsaturated Carboxylic Esters

Summary: A wide variety of α,β-unsaturated esters undergo 1,4 reduction and reductive alkylation to afford saturated esters in preparatively useful yields through the agency of lithium tri-*sec*-butylborohydride.

Sir: Recently we reported that α,β-unsaturated cyclohexenones, unlike their acyclic counterparts,[1] undergo exclusive 1,4 reduction to ketone enolates when treated with potassium tri-*sec*-butylborohydride (K-Selectride™, Aldrich).[2] These enolates can subsequently be protonated or alkylated in excellent yield. We became intrigued with the possibility that such borohydride reagents might similarly convert α,β-enoates to saturated esters by way of saturated ester enolates, since no present synthetic methodology generally accomplishes this transformation. Solutions of alkali metals in amines have been used to reduce the double bond of α,β-unsaturated acids,[3] but chemical reduction of the corresponding esters becomes a low yield process commonly leading to saturated alcohols.[4] This communication describes how trialkylborohydrides can successfully be employed to convert α,β-unsaturated esters directly to saturated esters in excellent yield. Furthermore the intermediate ester enolates which are generated can be alkylated in situ, thus accomplishing in a one-pot procedure for the first time what is usually a four-step series of reactions.[5]

When methyl-2-nonenoate **1** was subjected to K-Selectride™ in ether or THF at −70°, rapid disappearance of enoate was accompanied by formation of methyl nonanoate **3** in low yield as well as preponderant amounts of a single, high-molecular weight ester shown by ir, NMR, and mass spectroscopy to be the keto ester **5**.[6] This substance apparently resulted from initial 1,4 reduction to saturated ester enolate **2**, then attack by **2** on **1** to form the unsaturated keto ester **4**. Conjugate reduction of **4** produced **5**, whose structural assignment was also supported by its positive $FeCl_3$ test.[7]



By substituting the corresponding lithium trialkylborohydride (L-Selectride™) we hoped to retard the dimerization and, indeed, **1** with L-Selectride™ afforded a 4:1 mixture of methyl nonanoate and **5** in 80% yield. However, efforts to eradicate the yield-lowering self-condensation by varying solvent, temperature, and ester type, or by using cosolvents such as hexamethylphosphoric triamide, were uniformly unsuccessful; the best yield of **3** obtainable (−70°, 20 min) seemed to be 75%.

Other experiments in our laboratory had revealed appreciable lifetimes of Selectride™ reagents in the presence of alcohol solvents, and suggested that such a reducing medium might avoid Claisen condensation by rapidly protonating the first-formed ester anions. In fact, addition of **1** and *tert*-butyl alcohol (2 equiv) to a THF solution of L-Selec-

Table I
Reduction of α,β-Unsaturated Esters Using L-Selectride/*tert*-Butyl Alcohol

Enoate[a]	Time, min	Temp, °C	Product (% yield)[b]
1	20	−70	3 (92)
$CH_3CH{=}C(CH_3)CO_2CH_3$	20	−70	$C_2H_5CH(CH_3)CO_2CH_3$ (70)
	30	0	
$C_6H_{13}CH{=}C(CH_3)CO_2CH_3$	20	−70	$C_7H_{15}CH(CH_3)CO_2CH_3$ (90)
$(CH_3)_2C{=}CHCO_2C_2H_5$[c]	15	−70 → 0	$(CH_3)_2CHCH_2CO_2C_2H_5$ (70)
Methyl cinnamate	20	−70	starting material (29)
	30	0	$PhCH_2CH_2CO_2CH_3$ (27)
Ethyl *p*-nitrocinnamate	20	−70	*p*-$NO_2C_6H_4CH_2CH_2CO_2C_2H_5$ (62)

[a] Enoates were mixed with *t*-BuOH (2–2.5 equiv) and added to L-Selectride. [b] Reported yields represent isolated esters after oxidation of tri-*sec*-butylborane. Products were identified by comparison with authentic samples. [c] *tert*-Butyl alcohol was omitted in this experiment.

Table II
Reductive Alkylation of α,β-Unsaturated Esters

Enoate[a]	Alkylating agent	Time, min	Temp, °C	Product (% yield)[b]
1	CH_3I	20	0	$C_7H_{15}CH(CH_3)CO_2CH_3$ (60)
1	$CH_2{=}CHCH_2Br$	20	0	$C_7H_{15}CHCO_2CH_3$ (50) CH_2 CH CH_2
1	CH_3COCH_3	60	0	$C_7H_{15}CHCO_2CH_3$ (62) CH_3-C-CH_3 OH
1	C_4H_9I[c]	60	*d*	$C_7H_{15}CHCO_2CH_3$ (63) C_4H_9 3 (19)
8	$PhCH_2Br$[c]	120	*d*	$(CH_3)_2CHCHCO_2C_2H_5$ (50) CH_2 Ph

[a] Enoate was added to 1.0–1.1 equiv of L-Selectride™ in THF at −70° for 20 min. Alkylating agent was subsequently added and reaction completed as described in each case. Note the two exceptions. [b] Yields have not been optimized. All experiments using 1 also afforded 15–20% 5. [c] In these difficult alkylations, the enolate solution was added at room temperature to dry DMSO solutions of the alkylating agent (1.5–2 equiv); see ref 10. [d] Room temperature.

tride™ at −70° followed by careful oxidative work-up to remove tri-*sec*-butylborane afforded pure methyl nonanoate in 92% yield. No trace of 5 could be detected. Table I summarizes our results when this technique was applied to some structurally diverse enoates.

The reductions are quite clean and even sterically encumbered enoates such as methyl β,β-dimethylacrylate can be reduced in good yield. Whereas methyl cinnamate did not afford a worthwhile yield of β-phenylpropionic ester, ethyl *p*-nitrocinnamate was effectively reduced to the corresponding hydrocinnamate (mp 168°). Inverse hydride addition is possible in this system and we are presently investigating whether a nitro-stabilized benzylic anion is formed rather than an ester enolate.[8]

We have also observed that the intermediate enolates can be trapped with a reactive electrophile; in such procedures the enoate is added to L-Selectride in the absence of alcohol, followed later by the alkylating agent.[9] Overall yields are good and a summary of representative experiments is presented in Table II.

The yields of products in Table II are comparable to those of Rathke et al. who have generated and similarly alkylated ester enolates by low-temperature ester metalation.[10] It seems apparent that all the methodology developed by those workers should be applicable to anions arising from conjugate enoate reduction. Furthermore the remarkably nonbasic nature of L-Selectride™ makes it an especially attractive reagent for generating ester enolates under mild conditions.

The following is a typical experimental procedure.

Methyl-2-nonenoate (0.506 g, 2.98 mmol) and *tert*-butyl alcohol (0.55 g, 2,5 equiv) in dry THF (3 ml) was added dropwise down the side of a 50-ml round-bottomed flask containing stirred L-Selectride (3.0 ml of a 1*M* solution from Aldrich) under N_2 at −70°. After 20 min, methanol (0.2 ml) was injected and the reaction brought to room temperature, concentrated under reduced pressure, and diluted with hexane (20 ml). The flask was cooled in ice during addition of ice-cold aqueous 10% NaOH (1.2 ml, ~1 equiv) and 30% H_2O_2 (3 ml). After the mixture stirred overnight at room temperature, the aqueous layer was extracted twice with ether (10 ml) and the combined organic phases were worked up in the usual fashion to afford 0.46 g (92%) of methyl nonanoate, identical in every respect with an authentic sample.

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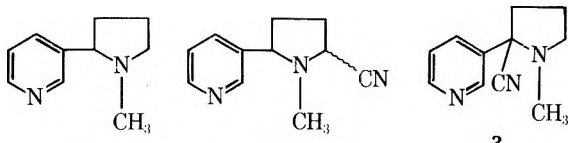
Nicotine Chemistry. 5′-Cyanonicotine

Summary: The synthesis of 5′-cyanonicotine is reported. An attempt to reproduce a literature preparation of this compound led to a mixture of isomeric cyanonicotines in which 2′-cyanonicotine predominated.

Sir: Murphy[1] has recently reported that oxidation of nicotine (1) with mercuric acetate, followed by treatment of the intermediate with potassium cyanide, results in the formation of a cyanonicotine. The product was assigned structure 2 on the basis of its mass and NMR spectra.

Repetition of Murphy's procedure[2] in our laboratory gave a compound which has been unequivocally characterized as 3 based on an independent synthesis of 2 and a detailed spectral analysis of 2 and 3.



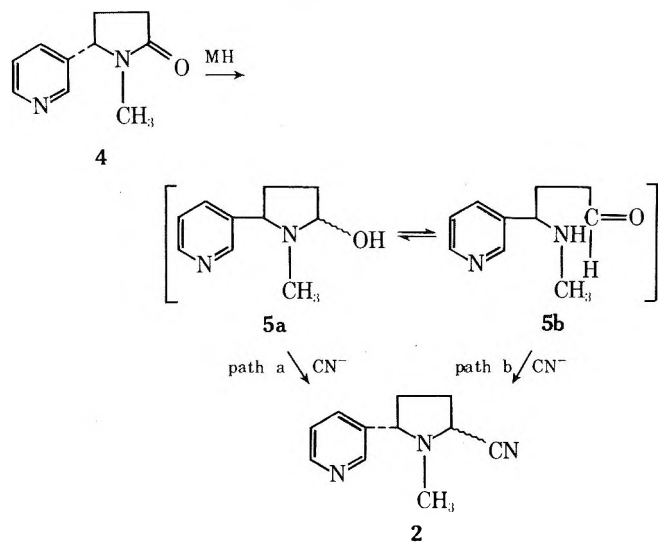
1 2 3

(*S*)-Cotinine (4)[3] was chosen as a logical starting point for the synthesis of 2 in that functionality is already present at the C-5′ position. Since tertiary amides have been reductively cleaved to secondary amines and aldehydes by metal hydrides,[4] introduction of the cyano group at C-5′ was envisaged as proceeding through a cyclic carbinolamine or an acyclic amino aldehyde as shown in Scheme I.[5]

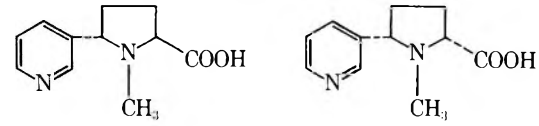
When 4 was treated with 1.6 equiv of a fresh, standardized solution of sodium aluminum hydride[7] in dry tetrahydrofuran, a highly unstable product was isolated which exhibited an intense ir band at 1735 cm^{-1}, typical of a saturated aldehyde. Treatment of the partial reduction product with an excess of aqueous potassium cyanide and ammonium chloride gave an inseparable mixture of (2′*S*)-*cis*- and -*trans*-5′-cyanonicotine (2),[8] isolated in 75% yield (see Scheme I).

All spectral data for the mixture of the two nitriles were consistent with the assigned structure.[8] Acid hydrolysis of the mixture of nitriles gave a mixture of two nicotine-5′-carboxylic acids in a 2:1 ratio which were subsequently separated by fractional crystallization. The major isomer was

Scheme I



determined to be (2′*S*)-*trans*-nicotine-5′-carboxylic acid (6) based on the low field signal of the 5′ proton in its ^1H NMR spectrum,[9] while the minor isomer was assigned the cis configuration (7). In addition, ir and ^1H NMR spectra of



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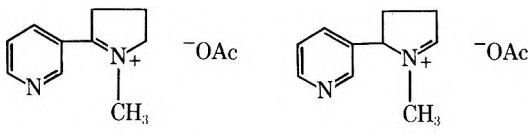
6 were identical with those of a racemic nicotine-5′-carboxylic acid of previously unassigned stereochemistry which was prepared by independent synthesis.[10]

The preparation of authentic 5′-cyanonicotine allowed us to investigate the structure of the product obtained from Murphy's procedure. Nicotine was treated with mercuric acetate in acetic acid. After addition of potassium cyanide to the neutralized (pH 7.0) solution, the components of the product mixture were found to be cotinine (~50%)[12] (4), unreacted 1, and a small amount of a nitrile. The crude product was distilled to give a 5% yield of an unstable oil which displayed a weak band at 2300 cm^{-1} in the ir. The ^1H NMR spectrum of the product, assigned structure 3, was significantly different from the spectrum of 2. The mass spectrum of 2 displayed a prominent molecular ion at *m/e* 187 and a base peak at *m/e* 109, whereas the spectrum of 3 had a barely detectable molecular ion, with a base peak at *m/e* 159.

The ^{13}C NMR spectrum of 3 upon SFOR decoupling is split into one quartet, three triplets, and a singlet [43.0 (q), 21.1, 36.2, and 53.7 (t), and 69.6 ppm (s)]. This pattern is consistent with an *N*-methylpyrrolidine containing a single tetrasubstituted carbon atom. The ^{13}C NMR spectrum of 2 shows a pair of peaks for each of the five saturated carbon atoms. The SFOR-decoupled spectrum displays a pair of quartets (36.5 and 38.1 ppm), a pair of triplets and a single triplet (33.6, 34.5, and 28.9 ppm), and two pairs of doublets (57.0 and 56.1 and 65.6 and 68.3 ppm) consistent with two isomeric *N*-methylpyrrolidines each containing two monosubstituted carbon atoms. Gas chromatography of 3 shows the presence of a small amount of 2 (~10%).[13]

The formation of 2′-cyanonicotine in our laboratory from the mercuric acetate dehydrogenation of nicotine establishes that its precursor is 8. This is consistent with the generalization[14] that mercuric acetate dehydrogenation of α-substituted cyclic amines results in the formation of the more substituted imminium salt. On the other hand, the

formation of cotinine, as well as varying amounts of 5′-cyanonicotine, probably occurs by way of **9**. If this is indeed



8 **9**

the case, then not only must one be concerned with the apparent preferential formation of **9**, but also with its subsequent facile oxidation.

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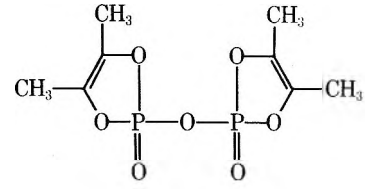
One-Flask Phosphorylative Coupling of Two Different Alcohols

Summary. Aryl (1,2-dimethylethenylenedioxy) phosphates are effective reagents for the "one-flask" conversion of two different alcohols, R^1OH and R^2OH, into dialkylacetoinyl phosphates, $(R^1O)(R^2O)P(O)[OCH(CH_3)COCH_3]$, which are readily hydrolyzed to unsymmetrical dialkyl phosphates, $(R^1O)(R^2O)P(O)(OH)$.

Sir: We would like to describe experiments of practical and theoretical importance for the synthesis of unsymmetrical dialkyl phosphates, $(R^1O)(R^2O)P(O)(OH)$, and for studies on the mechanism and the biological functions of phosphate esters.

Crystalline aryl (1,2-dimethylethenylenedioxy) phosphates, e.g., the known[1,2] *p*-nitrophenyl ester (**2**) and the new[3] pentafluorophenyl ester (**3**, mp 54–56°; δ_{31P} −8.0 ppm, τ 7.98, both in $CDCl_3$) are obtained in 90–95% yield from the reaction of phenols with oxybis(1,2-dimethylethenylenedioxyphosphoryl)[1,2] (**1**).



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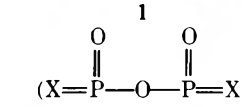


The reagents, X=P(O)OAr [**2** (Ar = p-$NO_2C_6H_4$) and **3** (Ar = C_6F_5)], are capable of converting two different alcohols, R^1OH and R^2OH, into dialkylacetoinyl phosphates, $(R^1O)(R^2O)P(O)[OCH(CH_3)COCH_3]$, without isolation of intermediates ("one-flask" reactions), in high yields by simple isolation techniques and within short periods of time; see Table I. The hydrolysis has already been described.[2]

$$(R^1O)(R^2O)P(O)[OCH(CH_3)COCH_3] + HO^- \rightarrow (R^1O)(R^2O)P(O)O^- + CH_3COCH(CH_3)OH$$

The synthesis consists of two steps (1 and 2), both of which are effectively catalyzed by salts of the phenols, e.g., $ArO^-(C_2H_5)_3NH^+$. The catalyst is generated by the introduction of the amine together with the first alcohol, R^1OH, since the phenol is a by-product of the reaction 1.

Table I
One-Flask Phosphorylative Coupling of Two Different Alcohols

No.	R^1 in R^1OH	R^2 in R^2OH	Yield of triester,[b] %
		X=P(O)OC$_6$H$_4$NO$_2$-*p*[a]	
1	c-C_5H_9	*i*-C_4H_9	93
2	c-C_5H_9	$C_6H_5CH_2$	91
3	c-C_5H_9	CH_2=C(CH_3)CH_2CH_2	93[c]
		X=P(O)OC$_6$F$_5$[d]	
4	c-C_5H_9	$BrCH_2CH_2$	97
5	$(CH_3)_3CCH_2$	*i*-C_4H_9	98[e]
6	c-C_5H_9	*i*-C_4H_9	90

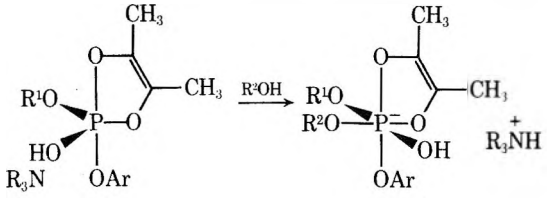
[a] A dichloromethane solution containing R^1OH (1 mol equiv) and triethylamine (1 mol equiv) was added dropwise in 5 min to a stirred dichloromethane solution of X=P(O)$C_6H_4NO_2$-*p* (1 mol equiv; 0.4–0.6 *M*) at 25°. After 15–30 min at 25°, a dichloromethane solution of R^2OH was added dropwise in ~5 min to X=P(O)OR^1. The reaction was allowed to proceed for ~1–2 hr at 25° (0.3–0.5 *M*). The solution was diluted with dichloromethane to ~0.2 *M* and was repeatedly extracted with cold, dilute aqueous alkali (Na_2CO_3 or NaOH) to remove the *p*-nitrophenol. The organic layer was washed first with 5% hydrochloric acid and then with water, dried over Na_2SO_4, filtered, and evaporated in vacuo to yield the dialkylacetoinyl phosphate. The triester was hydrolyzed to the dialkyl phosphate by known procedures.[2] [b] Crude triester, based on R^1OH. Purity >98% based on ^1H NMR spectrometry (in $CDCl_3$) and on conversion to amine salt of diester.[2] [c] Triester purified by short-path distillation (at 0.05 mm, bath temp ~100°), yield 81%. [d] As in the previous procedure (footnote *a*) except using X=P(O)-OC$_6$F$_5$. The reaction of eq 2 was allowed to proceed for ~5 hr at 25° (0.5 *M*). [e] Triester purified by short-path distillation (at 0.10 mm, bath temp ~95°), yield 94%.

$$X{=}P(O)OAr + R^1OH \rightarrow X{=}P(O)OR^1 + ArOH \quad (1)$$

$$X{=}P(O)OR^1 + R^2OH \rightarrow CH_3COCH(CH_3)OP(O)(OR^1)(OR^2) \quad (2)$$

Alcohol R^1OH reacts much faster with $X{=}P(O)OAr$ than with the product $X{=}P(O)OR^1$, and, therefore, the symmetrical phosphates, $CH_3COCH(CH_3)OP(O)(OR^1)_2$, are not formed in any appreciable extent. Moreover, the phenols with electron-withdrawing substituents are much less reactive than alcohols toward both $X{=}P(O)OAr$ and $X{=}P(O)OR^1$, and hence the corresponding aryl phosphates are not produced.

The effective catalysis of reaction 2 by the phenol salts [e.g., a factor of ~140 in the reaction of i-C_4H_9OH with $X{=}P(O)O$-c-C_5H_9 by p-$N_2C_6H_4{}^-O(C_2H_5)_3NH^+$ in 0.2 M $CDCl_3$ at 25°] could involve 5- and 6-coordinate phosphorus intermediates[4] **4** and **5**; the latter, **5**, is analogous to



4 **5**

compounds isolated from the reaction of stable pentaoxyphosphoranes, phenols and tertiary amines.[4,5]

These results may have a bearing on the mechanism of action of enzymes that catalyze the reactions of phosphates and pyrophosphates, since the presence of tyrosine, lysine, arginine, and histidine residues could facilitate the addition of nucleophiles to 4-coordinate phosphorus by analogous mechanisms.

References and Notes

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(2) F. Ramirez, J. F. Marecek, and I. Ugi, *J. Am. Chem Soc.*, **97**, 3809 (1975).
(3) The elemental analyses of all new compounds agree with the calculated values. ^1H NMR signals are in parts per million vs.TMS = 10 (τ); ^{31}P NMR signals are in parts per million vs. H_3PO_4 = 0.
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(5) See also H. R. Allcock and E. C. Bissell, *J. Chem. Soc., Chem. Commun.* 676 (1972).

(6) Research supported by Grant GM-20672 from the Cancer Institute of the National Institutes of Health and, partially, by Grant 7136 from the Petroleum Research Fund, administered by the American Chemica Society.

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Synthesis of DL-γ-Carboxyglutamic Acid Derivatives[1]

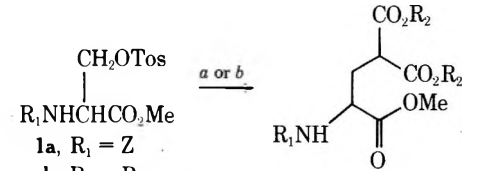
Summary: A method of synthesis of DL-γ-carboxyglutamic acid derivatives has been developed involving the reaction between *O*-tosyl serine derivatives and esters of malonic acid.

Sir: We wish to report the synthesis of derivatives of γ-carboxyglutamic acid (Gla),[1b] a new amino acid recently identified in prothrombin[2] and factor X,[2e] two of the four vitamin-K-dependent blood clotting factors. The success of the preparation of side chain protected cysteine[4,5] derivatives by displacement reactions on corresponding serines and alanines, and the DL-glutamic acid synthesis of Wieland et. al.[6] suggested the sequence of reactions outlined below for the preparation of Gla derivatives.[7]

Compounds **2a** and **2d** were prepared by the tosylate displacement[8] shown; yields and physical data are listed in Table I. Hydrolysis of aliquots of each reaction mixture followed by amino acid analysis[9] indicated the presence of glutamic acid in all cases.

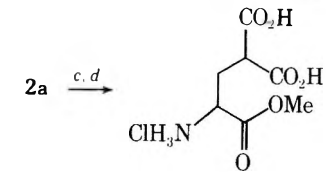
Attempts to achieve SN2 displacement of the tosylate group were unsuccessful under a variety of conditions.[10] Rather, the reaction seems to proceed in a stepwise fashion: elimination to a dehydroalanine derivative, followed by conjugate addition of the malonate anion to the α,β-unsaturated ester. The optical rotations for the Gla derivatives obtained via this procedure were usually between +1 and +2°, indicating probable racemization. This was confirmed by acidic hydrolysis of **2c** to glutamic acid, which was shown to be totally racemized.

That appropriately protected Gla derivatives could be selectively deprotected and incorporated into peptides at either the α-amino or the α-carboxyl positions was shown

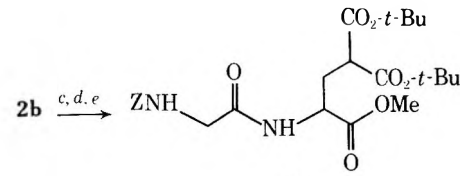


1a, R_1 = Z
b, R_1 = Boc

2a, R_1 = Z; R_2 = Bzl
b, R_1 = Z; R_2 = *t*-Bu
c, R_1 = Boc; R_2 = Bzl
d, R_1 = Boc; R_2 = *t*-Bu
e, R_1 = ClH_3; R_2 = H



2e



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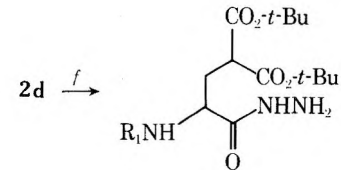
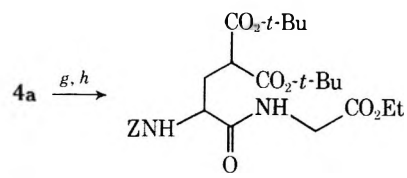


4a, R_1 = Z
b, R_1 = Boc



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[a] $Li^+ {}^-CH(CO_2R_2)_2$, THF. [b] $Na^+ {}^-CH(CO_2R_2)_2$, DMF. [c] H_2, Pd/C, HOAc. [d] HCl/Et_2O. [e] Z-Gly-OH, THF, isobutyl chloroformate, *N*-methylmorpholine. [f] Hydrazine hydrate, methanol, 3 hr. [g] HCl/THF, *n*-butyl nitrite, −23°, 15 min. [h] Et_3N, H-Gly-OEt, THF, 0°, 2.5 hr.

Table I
Yields and Physical Data for Gla Derivatives[a]

Compd	Yield, %[b]	Mp, °C[c]
2a	82	Oil
2b	30	Oil
2c	60	82–83.5
2d[d]	56	Oil
2e[e]	43	122.5–123.5 dec
3	63[f]	91.5–93
4a	75[g]	108.5–110
4b	73	82–83
5[e]	80[h] (60[g])	97.5–99[e]

[a] All new compounds gave satisfactory NMR spectra and combustion analysis, except as noted. [b] Isolated yields of purified products; not maximized. [c] Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. [d] Combustion analysis was not obtained for this compound; the substance was characterized as the hydrazide, **4b**. [e] Characterized as the monohydrate. [f] Overall yield from **2b**. [g] Overall yield from 1a, without purification of **2b**. [h] Overall yield from 4a.

in the following manner: hydrogenation of **2b**, followed by coupling to *N*-benzyloxycarbonylglycine using the mixed anhydride procedure,[11] afforded dipeptide **3** in 63% yield. The total yield for the conversion from *N*-benzyloxycarbonyl-L-serine methyl ester tosylate to the dipeptide derivative was 53%. Selective hydrazinolysis of either methyl ester **2b** or **2d** provided the corresponding hydrazides, **4a** and **4b**, and thus a convenient means of coupling at the COOH terminus. Conversion of **4a** to the acyl azide, and reaction with ethyl glycinate using a modified Honzl–Rudinger[12] procedure, afforded the dipeptide **5** in 80% yield. The total yield for the conversion from *N*-benzyloxycarbonyl-L-serine methyl ester tosylate was 60%.

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References and Notes

(1) (a) The following abbreviations have been used in the text: Gla,[1b] γ-carboxyglutamic acid; Z, benzyloxycarbonyl; Boc, *tert*-butyloxycarbonyl; Bzl, benzyl; *t*-Bu, *tert*-butyl; Tos, *p*-toluenesulfonyl. (b) There is no international symbol for this entity; both Glx[2b,c] and Gla[2d,3] have been used previously.
(2) (a) J. B. Howard and G. L. Nelsestuen, *Biochem. Biophys. Res. Commun.*, **59**, 757 (1974); (b) G. L. Nelsestuen and T. H. Zytkovicz, *J. Biol. Chem.*, **249**, 6347 (1974); (c) J. Stenflo, P. Fernlund, W. Egan, and P. Roepstorff, *Proc. Nat. Acad. Sci. U.S.A.*, **71**, 2730 (1974); (d) S. Magnusson, L. Sottrup-Jensen, T. E. Petersen, H. R. Morris, and A. Dell, *FEBS Lett.*, **44**, 189 (1974); (e) T. H. Zytkovicz and G. L. Nelsestuen, *J. Biol. Chem.*, **250**, 2968 (1975).
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(6) T. Wieland, G. Ohnacker, and W. Ziegler, *Chem. Ber.*, **90**, 194 (1957).
(7) H. R. Morris, M. R. Thompson, and A. Dell, *Biochem. Biophys. Res. Commun.*, **62**, 856 (1975), reported the synthesis of Gla via *N*-benzyloxycarbonyl-DL-chloroalanine benzyl ester and dibenzyl malonate. The product was characterized by mass spectrometry, paper electrophoresis, and comparison with natural Gla obtained by mild hydrolysis of prothrombin.
(8) Displacement reactions were run under similar conditions: 15 ml of solvent, ambient temperature, 20 hr. Sodium malonates were formed by adding 1 equiv of the malonic ester to a stirred suspension of sodium hydride in dimethylformamide. Lithium malonates were generated by reaction of 1 equiv of lithium diisopropylamide (prepared by *n*-butyllithium and diisopropylamine in THF) with the malonic ester in THF. The metal malonate (2 equiv) was then added dropwise to stirred solutions of the tosylate in the same solvent. Starting tosylates were prepared according to published procedures.[4,5]
(9) Beckman Model 116 amino acid analyzer; Beckman custom spherical ion exchange resin, type VR-30.
(10) Reaction of *N*-benzyloxycarbonyl-*O*-tosyl-L-serine methyl ester under any of the following conditions results largely in elimination: diisopropylamine, THF, 20 hr; sodium malonate (1 equiv), methanol, 20 hr; sodium malonate (1 equiv), DMF, 20 hr; diethylamine, 50:50 ether–ethyl acetate, 7 hr or 20 hr; lithium malonate (1 equiv), THF, 20 hr.
(11) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.*, **88**, 1338 (1966).
(12) J. Honzl and J. Rudinger, *Collect. Czech. Chem. Commun.*, **26**, 2333 (1961).

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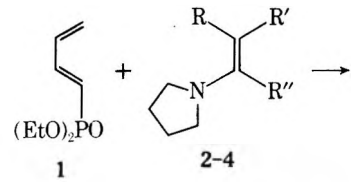
Cycloaddition Reactions of Enamines and Diethyl 1,3-Butadienephosphonate. The Formation of β-Aminophosphonates via a Mannich Reaction[1,2]

Summary: Cycloaddition of 1-diethylphosphinyl-1,3-butadiene and enamines proceeds in good yield to give β-aminophosphonates which deaminate to yield cyclohexadienephosphonates.

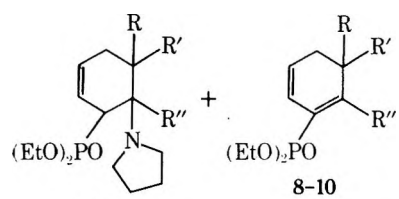
Sir: We wish to report the first observed cycloaddition reaction of a phosphonate activated butadiene to an enamine.

The diene **1** was prepared from triethyl phosphite and 1,4-dichloro-2-butene in two steps, with an overall yield of 74%, by using a procedure for the formation of diethyl vinylphosphonate.[3] The reaction of 0.1 mol of diene **1** with an equal amount of 1-pyrrolidinocyclohexene(**2**), 1-pyrrolidino-2-methylpropene (**3**), or 1-pyrrolidinopropene (**4**) was carried out under nitrogen in a solution containing 100 ml of benzene and refluxed for 24–48 hr. Water was added to the refluxing solution, in the work-up, to hydrolyze any enamine. The major products were β-aminophosphinates (**5**, **6**, or **7**) and the cyclohexadienyl phosphonates (**8**, **9**, or **10**). The yields of the cyclohexadienephosphonates were increased at the expense of the β-aminophosphonates by further heating of the reaction mixture. The latter were never completely transformed. The products were separated and isolated from the organic layer with dilute hydrochloric acid solution. The acid layer was neutralized to recover the amine.



1 **2–4**

2 (R = H; R′R″ = $-CH_2CH_2CH_2CH_2-$)
3 (R, R′ = CH_3; R″ = H)
4 (R = CH_3; R′, R″ = H)



5–7 **8–10**

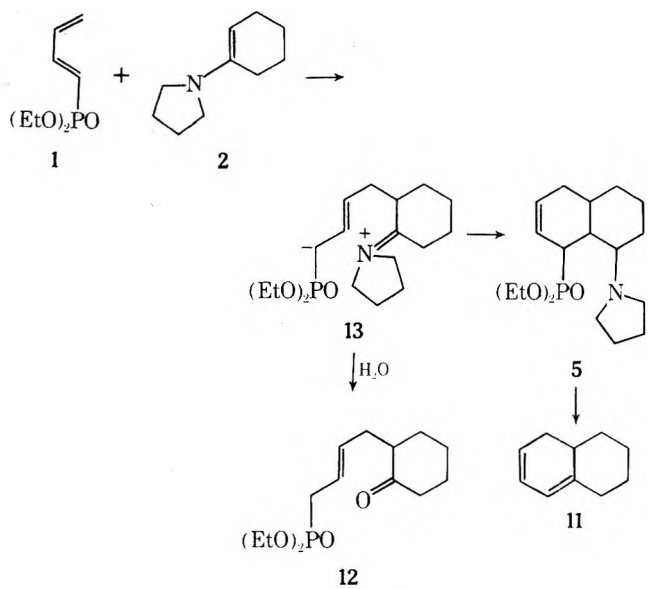
Products	
5	8
6	9
7	10

The respective products isolated follow. **5:** 30%; bp 155–156° (0.3 mm); δ ($CDCl_3$) 1.2–2.9 (m, 26 H), 4.2 (ABX pentet, 4 H), 5.5 (m, 2 H). **8:** 35%; bp 131–132° (0.3 mm); λ_{max}^{EtOH} 278 nm (ε 21.0 × 10^3); δ ($CDCl_3$) 1.2–2.8 (m, 17 H), 4.0 (ABX pentet, 4 H), 5.5–6.1 (m, 2 H); mass spectrum for $C_{14}H_{23}O_3P$, *m/e* 270. **6:** 35%; bp 150–153° (0.5 mm); δ ($CDCl_3$) 1.0 (s, 6 H), 1.3 (t, 6 H), 1.4–3.3 (m, 12 H), 4.0 (ABX pentet, 4 H), 5.2–5.8 (m, 2 H). **9:** 36%; bp 110–112° (0.5 mm); λ_{max}^{EtOH} 260 nm (ε 28.8 × 10^3); δ ($CDCl_3$) 1.0 (s, 6 H), 1.2 (t, 6 H), 2.1 (d, J = 3 Hz, 2 H), 4.1 (ABX pentet, 4 H), 5.7 (m, 2 H), 6.2 (d, J = 19 Hz, 1 H); mass spectrum for $C_{12}H_{21}O_3P$, *m/e* 244. **7:** 46.5%; bp 135–137° (0.4 mm); δ ($CDCl_3$) 1.0 (d, J = 7.5 Hz, 3 H), 1.2 (t, 6 H), 1.5–3.2 (m, 13 H), 4.1 (ABX pentet, 4 H), 5.8 (m, 2 H). **10:** 10.5%; bp 110–112° (0.5 mm); λ_{max}^{EtOH} 265 nm (ε 27.2 × 10^3); δ ($CDCl_3$) 1.2 (d, J = 7.5 Hz, 3 H), 1.3 (t, 6 H), 1.5–2.8 (m, 3 H), 4.0 (ABX pentet, 4 H), 5.7–6.1 (m, 2 H), 6.5 (d, J = 19 Hz, 1 H); mass spectrum for $C_{11}H_{19}O_3P$, *m/e* 230.

From the reaction of **1** and **2** there was also isolated <1% 4,4a,5,6,7,8-hexahydronaphthalene (**11**), bp 44–45° (0.1 mm), and <1% uncyclized ketone (**12**). The latter was removed with Girard-T reagent from the neutral organic fraction. The ketone **12** was obtained in 10.4% yield when the reaction was refluxed only 12 hr: bp 135–137° (0.05 mm); $\lambda_{max}^{CCl_4}$ 5.85 μm; δ ($CDCl_3$) 1.2 (t, 6 H), 1.3–2.8 (m, 13 H), 4.1 (ABX pentet, 4 H), 5.5 (m, 2 H); mass spectrum for $C_{14}H_{25}O_4P$, *m/e* 288.

The isolation of this ketone clearly indicates that the reaction between diene **1** and an enamine is a two-step process. Each cycloaddition reaction above is terminated by the addition of water to the refluxing solution to hydrolyze unreacted enamine and immonium salts. The yield of ketone **12** is higher for the 12-hr reaction than for the 48-hr reaction. The yield of **5** and **8** are lower for the former reaction than for the latter reaction. This would preclude the aminophosphonate **5** as the source of **12**. In addition, when **5** was refluxed in benzene solution with triethylamine, followed by the addition of water, the only other product isolated along with **5** was the deaminated product **8**. No evidence was found to suggest that the β-aminophosphonates underwent a reverse Mannich reaction.

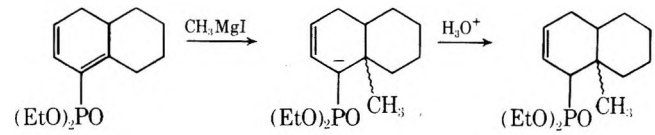
All previous reports on enamine cycloadditions are ambiguous on the reaction mechanisms, giving the impression of a concerted process.[4] We propose here that the mechanism is a *nonconcerted* two-step process involving, first, Michael addition to the activated diene to give the intermediate (**13**), followed by a Mannich reaction of the phosphinyl carbanion on the immonium ion to give **5**. Such a mechanism is consistent with the reported Michael additions to **1**[5] and in accord with other observations on activated butadienes.[6] We do not imply here that all cycloadditions of **1** are nonconcerted. The diene **1** has been shown to undergo typical Diels–Alder reactions with itself and standard dienophiles.[7] Hydrolysis of the reaction mixture would be expected to convert intermediate **13** into ketone **12**. The geometry of this alkene **12** is shown to be trans from the ir absorption at 965 cm^{-1}. Isomerization of the allylic carbanion **13** would be expected to occur during the prolonged reaction. Presumably the hydrocarbon **11** is derived from the aminophosphonate **5** by a nitrogen analog of the Emmons–Wittig reaction.[8]



Deamination of aminophosphinates **5**, **6**, or **7** occurred when 0.1 mol of the amine in 100 ml of benzene was refluxed under nitrogen for 24 hr. The dienes obtained were identical with those isolated previously. The yields were 86% **8**, 60% **9**, and 63.5% **10**.

The dienephosphonates, **8** and **9**, underwent ozonolysis to give 2-oxocyclohexaneacetic acid and 2,2-dimethylsuccinic acid, respectively. Catalytic hydrogenation of dienes **8** or **9** in ethyl acetate over 19% Pd/C resulted in the uptake of 1 mol of hydrogen to give the corresponding cyclohexenylphosphonates.[9] **14:** 77%; bp 133–135° (0.3 mm); δ ($CDCl_3$) 0.75–3.2 (m, 21 H) 4.1 (ABX pentet, 4 H). **15:** 97%; bp 114–115° (0.5 mm); δ ($CDCl_3$) 0.9 (s, 6 H), 1.25 (t, 6 H), 1.1–2.4 (m, 6 H), 4.0 (ABX pentet, 4 H), 6.7 (d, J = 22 Hz, 1 H).

The reactivity of cycloalkadienephosphonates may be illustrated by the following sequence. When **8** is added to an ethereal solution of methylmagnesium iodide, a white precipitate is formed. Acidification and isolation of the product gave **17:** 51%; bp 135–137° (0.3 mm); δ ($CDCl_3$) 1.0–3.0 (m, 21 H), 4.1 (ABX pentet, 4 H), 5.7 (m, 2 H). The improved yield of the Grignard addition product over previous reports[10] may be ascribed to the greater stabilization of the phosphinyl carbanion through allylic resonance. The trapping of the carbanion, **16**, and the stereochemistry of the angular methyl group is under investigation.



8 **16** **17**

We have shown that the cycloaddition of a butadienephosphonate and an enamine is a general method for obtaining varied cyclohexadienylphosphonates. These compounds are not an end product but may be considered potentially useful synthetic intermediates.

References and Notes

(1) This research was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society.
(2) This material was presented in part at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974.
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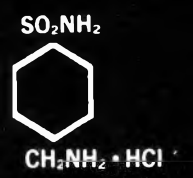
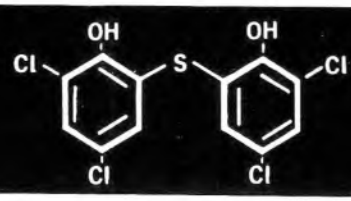
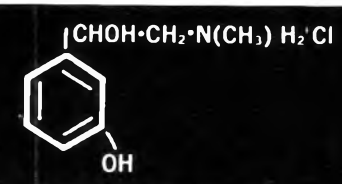

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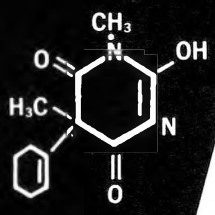
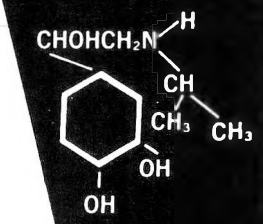

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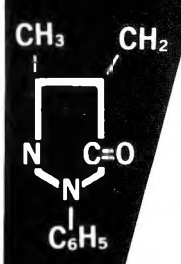
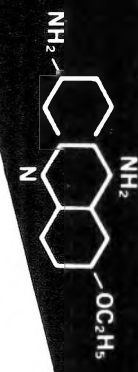
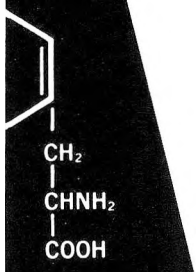


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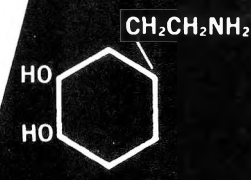

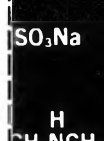
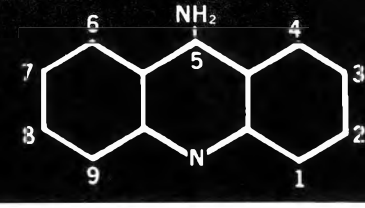

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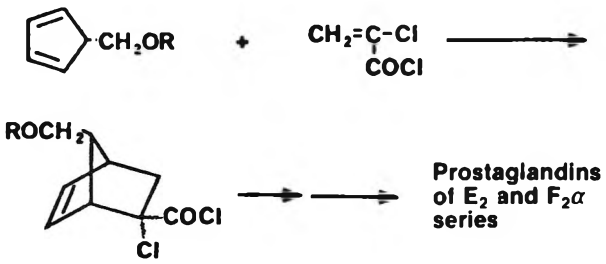
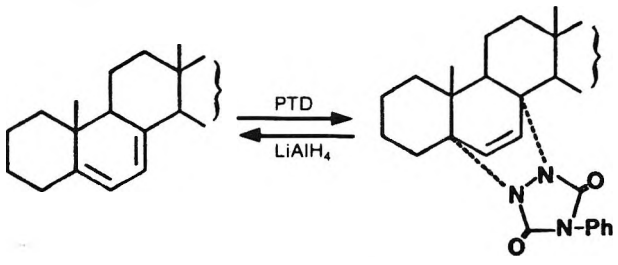


We now offer the most reactive dienophile known,[6] **4-phenyl-1,2,4-triazoline-3,5-dione (PTD)**, prepared *in situ* by mild oxidation of **4-phenylurazole.**[7] **PTD** reacts instantly with cisoid dienes, even at -78°, to give stable crystalline adducts in high yield.[8] Because of its high reactivity **PTD** has found application for trapping transient intermediates.[9]

Barton *et al.*[10] have recently described the use of **PTD** for the protection of steroidal dienes. The Diels-Alder adduct is formed in high yield and permits an easier modification of the steroidal nucleus. Retro-Diels-Alder reaction is achieved in virtually quantitative yield upon treatment of the adduct with $LiAlH_4$.



PTD also oxidizes an alcohol to the corresponding aldehyde or ketone in good yield under mild conditions.[11] In dry benzene, from which the 4-phenylurazole by-product precipitates, the reaction proceeds in a few hours at room temperature. **PTD** is clearly the reagent of choice for oxidizing compounds sensitive to acid, base or heat.

We also offer other trapping reagents such as **1,3-diphenylisobenzofuran, tetracyanoethylene,** and **tetraphenylcyclopentadienone. 1,3-Diphenylisobenzofuran** has recently been used to trap an olefin which violates Bredt's rule,[12] benzyne[13] and highly strained cyclopentyne.[14]

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