Hydrolysis of N-Methyl-2,4,4-substituted Δ^2-Oxazolinium Iodides

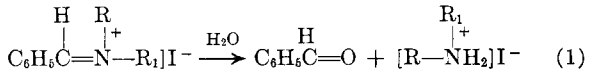
PAUL ALLEN, JR., AND JAMES GINOS

Stevens Institute of Technology, Hoboken, New Jersey, and Nopco Chemical Company, Harrison, New Jersey

Received April 11, 1963

The methiodide salts of 2-methyl-, 2-*t*-butyl-, and 2-phenyl-4,4-dimethyl-Δ^2-oxazoline were hydrolyzed under variable pH conditions to the corresponding amine esters. At a high pH the hydrolysis takes place instantaneously, while at a low pH, the hydrolysis is slow.

Previous work on modes of ring opening of oxazolines and their hydrogen halide salts[1a-h] led us to study the hydrolysis of quaternary oxazolinium compounds. These were expected to hydrolyze in a manner analogous to the alkylated Schiff bases.[2a,b] (This method is often used in monoalkylating amines, equation 1.)

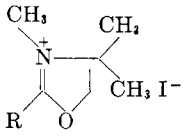


(1)

Fry[2c] has claimed that such is the case with salts of 2-aryloxazolines and aroyl chlorides.

Recently Taylor[3] has reported that a tosylate of a polymeric oxazoline was hydrolyzed by dilute alkali to a mixture of amide and ester. In our studies only ester was found under pH conditions ranging from basic to acidic.

Compound I was chosen for study because its planar symmetry should result in simple n.m.r. spectra and because it was hoped that the *gem*-dimethyl effect[4a,b] operative in cyclizations would lead to high yields in the preparation of the parent oxazolines. The results justified our expectations.



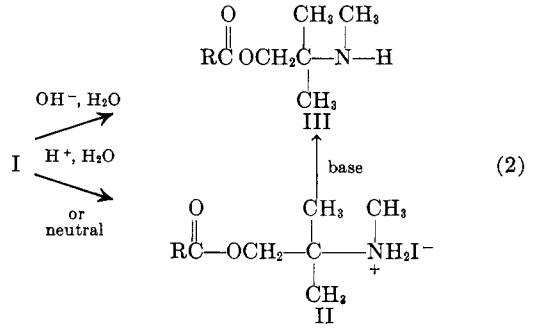
Ia, R = CH_3-

b, R = $(CH_3)_3C-$

c, R = C_6H_5-

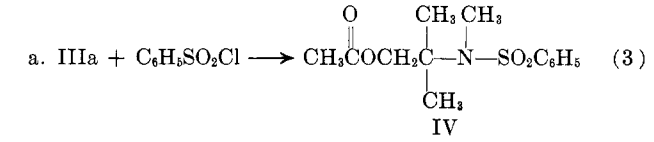
The hydrolysis was carried out under basic, neutral, and acid conditions. The reactions leading to the products are shown in equation 2.

The identity of characteristic groups was confirmed by n.m.r. chemical shifts of their bands and the ratios of the integrals of the band areas. The absence of any other absorption peaks was taken as evidence of the high purity of these compounds.

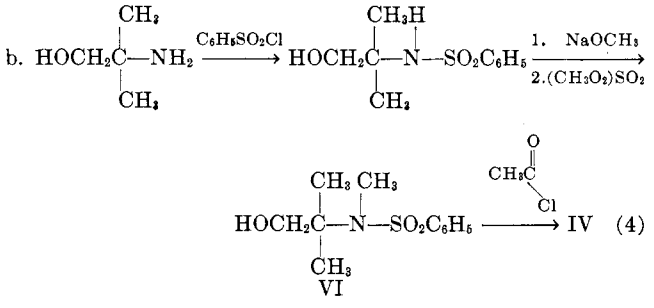


(2)

In addition, the structure of IIIa was shown by preparing its sulfonamide in the following two ways.



(3)



(4)

Of the three parent substances, 2-*t*-butyl-4,4-dimethyl-Δ^2-oxazoline was prepared for the first time. The 2-methyl compound has been reported only once in the patent literature[5]; no physical or chemical properties were recorded. The 2-phenyl compound has been prepared and characterized[6] but not its methiodide. Neither compound II nor III has been reported.

The hydrolysis reaction of I under basic conditions is practically instantaneous. We have found that the quaternary compounds can be titrated quantitatively at room temperature with a strong base to a phenolphthalein end point. This behavior on the part of Ib and Ic excludes the likelihood that the acidic hydrogens of the 2-methyl group are titratable with sodium methoxide. Ia can be recovered unchanged after remaining overnight in absolute methanol with one equivalent of

(1)(a) A. P. Phillips and R. Baltzly, *J. Am. Chem. Soc.*, **69**, 200 (1947); (b) G. Fodor and J. Kiss, *ibid.*, **72**, 3495 (1950); (c) E. E. van Tamelen, *ibid.*, **73**, 5773 (1951); (d) J. S. Pierce and C. D. Lunsford, *ibid.*, **73**, 2596 (1951); (e) R. B. Martin and A. Parcell, *ibid.*, **83**, 4835 (1961); (f) S. Konstas, I. Photaki, and L. Zervas, *Ber.*, **92**, 1288 (1959); (g) G. R. Porter, H. N. Rydon, and J. A. Schofield, *J. Chem. Soc.*, 2686 (1960); (h) S. Gabriel and Th. Heymann, *Ber.*, **23**, 2493 (1890).

(2)(a) H. Decker and H. Becker, *Ann.*, **395**, 362 (1912); (b) E. E. Hamilton and R. R. Robinson, *J. Chem. Soc.*, **109**, 1033 (1916); (c) E. M. Fry, *J. Org. Chem.*, **15**, 802 (1950).

(3) L. D. Taylor, *J. Polymer Sci.*, **62**, 174 (1962). (This article appeared when the present work was nearly complete.)

(4) (a) N. L. Allinger and V. Zalkow, *ibid.*, **24**, 701 (1960); (b) E. L. Eliel, "Steric Effects in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1956, pp. 118–120.

(5) P. F. Tryon, U. S. Patent 2,372,409 (1945).

(6) R. N. Boyd and R. H. Hansen, *J. Am. Chem. Soc.*, **75**, 5896 (1953).

sodium methoxide, but the addition of one equivalent of water converts it almost instantaneously to IIIa.

The quaternary salts I were heated in neutral water solutions at 70–90° for one to two hours. They were all hydrolyzed with about the same ease yielding hydrogen iodides of the corresponding amine esters. Infrared and n.m.r. spectra and titrimetric, as well as elemental composition, analyses confirmed their identity. Their bases III were characterized in a similar manner.

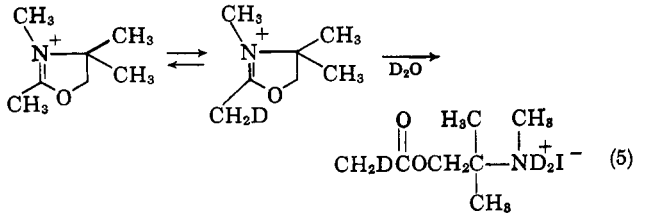
During an attempt to free the amine ester from IIc in methanol with an equivalent amount of sodium methoxide at room temperature, considerable transesterification took place yielding as much as 50–60% methyl benzoate. However, as expected, no transesterification took place in the case of IIIb.

We believe that monoalkylation of amino alcohols may be carried out by conversion to oxazolines, followed by addition of alkyl halide to form salts similar to I and then by complete hydrolysis to acid and the desired product.

A study of the extent of hydrolysis in twenty-four hours under neutral conditions and with hydrogen iodide concentrations of 0.005 *M*, 0.1 *M*, and, in the case of Ib, 5 *M*, was undertaken using n.m.r. techniques. The hydrolysis medium was deuterium oxide with traces of ordinary water at 35°. The concentration of quaternary salt was 1 *M*. Spectra were taken at intervals without removing the solutions from the n.m.r. tube.

In all instances, the characteristic absorption peaks of the hydrolyzed products were displaced upfield relative to the peaks of the unhydrolyzed compounds by 0.15 p.p.m. to 0.65 p.p.m. In the case of Ia, the first hydrolysis product IIa was found to hydrolyze further under acid conditions to the acid and the amino alcohol. The absorption peaks of the second hydrolysis product were found to be displaced farther upfield with respect to the absorption peaks of the first hydrolysis product. As expected, Ib did not hydrolyze beyond the amine ester stage even under strong acid conditions.

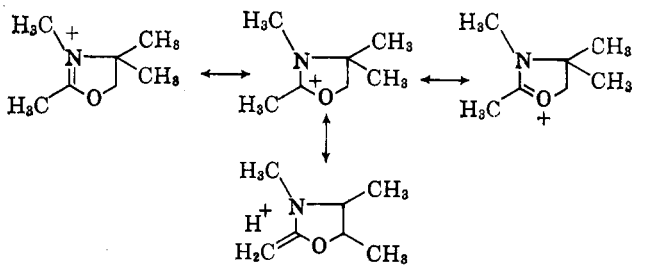
Notable in the case of Ia is the gradual disappearance and flattening of the 2-methyl n.m.r. absorption band as the methyl hydrogens, α to the ring, exchange with the deuterium ions. The absorption band corresponding to the methyl group of the acetoxy group, the first hydrolysis product, is by contrast sharp although considerably diminished in size in comparison with the N-methyl absorption band of the amine ester salt IIa. Since the methyl hydrogens of the acetoxy group do not exchange measureably with deuterium ions, the exchange must have occurred prior to the hydrolysis reaction as shown by equation 5.



(5)

Under acid conditions, the deuterium exchange is virtually suppressed indicating that we are dealing with a normal acidic hydrogen dissociation phenomenon.

Presumably the 2-methyl hydrogens are rendered acidic by the delocalization of the electrons brought about by the positive charge on the nitrogen. The following resonance forms can be formulated for the oxazolinium salt.



The activity of the 2-methyl hydrogens is shown by the condensation of quaternary oxazoline salts with aldehydes.[7a,b]

Calibrated n.m.r. spectra of the oxazolinium salts in deuterated chloroform, integration of the band areas, and theoretical considerations, served to identify the absorption bands. For calculation of the per cent hydrolysis of Ia by integration of the band areas, the N-methyl and the 4,4-dimethyl band, corresponding to the unhydrolyzed and hydrolyzed compounds, were used with very good agreement. In the case of Ib, because of overlapping between the 2-*t*-butyl and 4,4-dimethyl bands, we were limited to the N-methyl band. Because of the relative insolubility of the hydrolysis products in water, the 2-phenyl compounds could not be compared with the methyl and tertiary butyl compounds.

As shown in Table I, the presence of acid inhibits hydrolysis. The extent of hydrolysis, I to II, appears to be the same within experimental error for compounds Ia and Ib under the same conditions. Furthermore,

TABLE I

	% Hydrolysis[a]		
	Molarity of HI		
Compound	Neutral	0.005	0.1	5.0
Ia	68.8	39.3	38.8	
Ib	70.0	41.3	39.3	26.3
IIa		22.8	40.8	

[a] Temperature, 35°; time, 24 hr.

the increase of acid concentration by a factor of twenty does not affect significantly the extent of the first hydrolysis to the amine ester salt. However, increase in acidity greatly increases the hydrolysis of the amine ester salt IIa to the corresponding acid and amino alcohol.

We are engaged at present with a detailed study of the kinetics of this hydrolysis.

Experimental

N.m.r. data were recorded on a Varian DP 60 Model, 60 Mc. Chemical shifts were recorded as values in p.p.m. referred to tetramethylsilane as an internal standard where deuteriochloroform was used as a solvent. A Varian n.m.r. integrator, Model V 352, in conjunction with a digital voltmeter was used to integrate the areas under the n.m.r. bands.

Titrimetry.—The purity of the parent oxazoline was established mainly by titration with 0.100 *N* perchloric acid solution[8] in

(7) (a) F. M. Hamer and R. J. Rathbone, British Patent 541,330 (1940); (b) J. Nys and J. Libeer, *Bull. soc. chim. Belgrade*, **65**, 377 (1956).

(8) This method was suggested to us by the Commercial Solvents Corp.

glacial acetic acid using crystal violet as an indicator. Titration with methanolic hydrogen chloride (bromophenol blue indicator) and methanolic sodium methoxide (phenolphthalein indicator) established the free amine and free acid content, respectively. Any amide present was determined by difference.

2,4,4-Trimethyl-Δ^2-oxazoline.—Sixty grams (1.0 mole) of glacial acetic acid was added with stirring to 89 g. (1.0 mole) of freshly distilled 2-amino-2-methyl-1-propanol. The reaction mixture was refluxed until the reflux temperature dropped from a maximum of 170 to 158°. The oxazoline was distilled azeotropically at 98° through a 12-in. Vigreux column. The distillate was collected in solution in 350 ml. of hexane, while the water separated as a lower layer. The water layer was extracted repeatedly with small amounts of hexane since the oxazoline is soluble in water. After drying over sodium hydroxide, the hexane was removed by distillation. The crude product, 98.7 g., was 99.3% pure by titration; fractionation through a column packed with glass helices gave 85.8 g. of pure product (75.6%); $n^{26.2}$D 1.4186; infrared (3.7% chloroform), 5.9 μ (–C=N); n.m.r. (deuteriochloroform) (τ), $-CH_2$ (5.56), $-CH_3$ (5.64), $-C(CH_3)_2$ (8.46); ratios of band areas, 2:3:6.

Anal. Calcd. for $C_6H_{11}NO$: C, 63.69; H, 9.80; N, 12.37. Found: C, 63.68; H, 9.82; N, 12.56.

2,3,4,4-Tetramethyl-Δ^2-oxazolinium Iodide (Ia).—To 22.6 g. (0.20 mole) of 2,4,4-trimethyl-Δ^2-oxazoline in 100 ml. of nitromethane, 42.6 g. (0.30 mole) of iodomethane was added slowly with stirring. Twenty minutes after the addition, the temperature rose from 26 to 62° as a vigorous exothermic reaction set in. After 12 hr. at room temperature, the product was precipitated as a yellow oil by diluting the reaction solution with 600 ml. of ether. The oil slowly solidified into yellow crystals, 46 g. (91%), m.p. 136–139°, after drying under high vacuum. The crude product was recrystallized twice from isopropyl alcohol to large pale yellow, transparent crystals; 43 g.; m.p. 142–143°; infrared (mull), 5.89 μ (–C=N– stretch.); n.m.r. (deuteriochloroform) (τ), $-CH_2$ (5.17), CH_3–N (6.60), $-CH_3$ (7.23), $-C(CH_3)_2$ (8.32); ratios of band areas, 2:3:3:6.

Anal. Calcd. for $C_7H_{14}INO$: C, 32.95; H, 5.53; I, 49.75; N, 5.49. Found: C, 33.20; H, 5.41; I, 50.05; N, 5.34.

Hydrogen Iodide Salt of the Ester of Acetic Acid and 2-Hydroxymethyl-2-methylaminopropane (IIa).—A solution of 10.2 g. (0.04 mole) of Ia in 6 ml. of water was heated at 80° for 2 hr. After removal of the water under reduced pressure, a yellow viscous liquid remained, which would not crystallize; methylene chloride was added and then removed under vacuum. Yellow crystals formed and were dried under high vacuum. The crude product, 10.7 g. (98.3%), was recrystallized from ethyl acetate yielding large colorless triclinic crystals, m.p. 189.5–191.0°. Titration showed the compound to be 99.9% pure salt; infrared (mull), 5.70 μ (C=O stretch.); n.m.r. (deuteriochloroform) (τ), $-CH_2$– (5.77), CH_3–N (7.34), CH_3–C=O (7.72), $-C(CH_3)_2$ (8.43); acidic H, 1.77; ratios of band areas, 2:3:3:6 (acidic H band too broad to integrate).

Anal. Calcd. for $C_7H_{16}INO_2$: C, 30.78; H, 5.91; I, 46.47; N, 5.13. Found: C, 30.96; H, 5.91; I, 46.39; N, 5.20.

2-Methylamino-2-acetoxymethylpropane (IIIa).—A total of 36 g. of 26% sodium methoxide in methanol was added slowly to a solution of 44 g. (0.173 mole) of Ia in 50 ml. of methanol with continuous stirring to a permanent phenolphthalein end point. A few drops of water were added whenever the phenolphthalein end point color lingered before the equivalence point was reached. The addition of water caused the pink color to disappear immediately. Finally when a constant pink color was attained, the solvent was removed under reduced pressure. A viscous liquid with a strong amine odor along with considerable white solid (sodium iodide) remained as a residue. The amine ester was extracted repeatedly with small amounts of ether totalling 500 ml. It was difficult to separate the salt because of its appreciable solubility in the amine ester. The recovered salt weighed 23 g. (26 g., theoretical). The ether extracts were combined, dried, and evaporated to 100 ml. The remaining ether was removed under reduced pressure leaving 19.5 g. of a pale yellow liquid (85%) with a characteristic amine odor. Distillation at 72–73° through a Vigreux microcolumn gave 16 g. of colorless liquid; n^{25}D 1.4317; infrared (smear), 3.54 ($-N-CH_3$), 2.99 (N–H), 5.73 (C=O), 8.08 μ (C–O); n.m.r. (deuteriochloroform) (τ), $-CH_2$– (6.09), N–CH_3 (7.69), CH_3C=O (7.93), $-C(CH_3)_2$ (8.94); ratio of band areas, 2:3:3:6.

Anal. Calcd. for $C_7H_{15}NO_2$: C, 57.90; H, 10.41; N, 9.64. Found: C, 57.82; H, 10.35; N, 9.58.

2-*t*-Butyl-4,4-dimethyl-Δ^2-oxazoline.—To 66.8 g. (0.75 mole) of freshly distilled 2-amino-2-methyl-1-propanol, 76.6 g. (0.75 mole) of molten pivalic acid was added slowly with stirring and cooling to control the exothermic formation of amine salt. After refluxing for an hour, the temperature dropped from 168° to a constant temperature of 154°. On distillation through a 9-in. Vigreux column, the fraction boiling at 95–112° at atmospheric pressure was collected in 200 ml. of hexane, with water separating as the lower phase. The water layer was extracted twice with 40-ml. quantities of hexane. A total of 27 ml. of water, the theoretical amount, remained. The hexane extracts were combined, dried over sodium hydroxide pellets, and distilled at atmospheric pressure until the vapor temperature rose to 135°. The residue, pale yellow in color and characterized by a pleasant medicinal odor, weighed 79.8 g. (69%). Titration showed it to be 98.0% pure oxazoline; n^{25}D 1.4196; infrared (smear), 6.02 μ (–C=N– stretch); n.m.r. (deuteriochloroform) (τ), $-CH_2$– (6.14), $-C(CH_3)_2$ (8.77), $-C(CH_3)_3$ (8.81); ratios of band areas, 2:6:9.

Anal. Calcd. for $C_9H_{17}NO$: C, 69.62; H, 11.04; N, 9.02. Found: C, 69.69; H, 11.19; N, 8.89.

3,4,4-Trimethyl-2-*t*-butyl-Δ^2-oxazolinium Iodide (Ib).—To 31.0 g. (0.20 mole) of 2-*t*-butyl-4,4-dimethyl-Δ^2-oxazoline dissolved in 90 ml. of nitromethane, 42.6 g. (0.30 mole) of iodomethane was added with stirring followed by heating at 70° for 4 hr.; the resulting red solution was cooled to room temperature and diluted with 600 ml. of ether. A total of 44.0 g. (74.4%) of crude IIb, m.p. 184–188°, was obtained. Nine grams of crude material was recrystallized from a solution of 25 ml. of isopropyl alcohol and 20 ml. of ethyl acetate, giving 5.5 g. of large, pale yellow triclinic crystals, m.p. 189–191°. Infrared (mull), 5.97 μ (–C=N stretch.); n.m.r. (deuteriochloroform) (τ), $-CH_2$– (5.08), –N–CH_3 (6.48), $-C(CH_3)_2$ (8.29), $-C(CH_3)_3$ (8.46); ratios of band areas, 2:3:6:9.

Anal. Calcd. for $C_{10}H_{20}INO$: C, 40.42; N, 4.71; I, 42.70. Found: C, 40.24; N, 4.63: I, 42.93.

Hydrogen Iodide Salt of the Ester of 2-Hydroxymethyl-2-methylaminopropane and Pivalic Acid (IIb).—Five and a half grams (0.185 mole) of Ib in 3.0 ml. of water was heated with stirring at 92° for 3 hr. The water was removed under reduced pressure leaving 4.9 g. of a yellow crystalline solid; recrystallization from chloroform–ether yielded white needles, m.p. 187°. A second recrystallization from ethyl acetate yielded long, transparent needles, m.p. 188–189.5°. Titration showed the recrystallized material to be practically pure; infrared (mull), 3.73 (N–H), 5.75 (C=O), 8.60 μ (C–O); n.m.r. (deuteriochloroform) (τ), $-CH_2$– (5.78), N–CH_3 (7.33), $-C(CH_3)_2$– (8.44), $-C(CH_3)_3$ (8.73); ratios of band areas, 2:3:6:9.

Anal. Calcd. for $C_{10}H_{22}INO_2$: C, 38.10; H, 7.04; N, 4.44; I, 40.26. Found: C, 38.12; H, 7.15; N, 4.44; I, 39.98.

2-Hydroxymethyl-2-methylaminopropane Ester of Pivalic Acid (IIIb).—Forty-one grams of Ib was dissolved in 30 ml. of water and heated at 90° for 2 hr. About 26.0 g. of 26% sodium methoxide in methanol was required to neutralize the reaction solution at room temperature to a phenolphthalein end point. The solution was extracted four times with 30-ml. portions of ether. The extracts were combined, washed once with water, dried with anhydrous sodium sulfate, and evaporated under partial vacuum, followed by high vacuum. A mobile yellow liquid remained with a characteristic light amine odor; 19.9 g. (77.2%); $n^{26.5}$D 1.4230. On redistillation, the pure ester was colorless; b.p. 72–73° (5 mm.); $n^{26.5}$D 1.4320; 99.5% pure IIIb by titration; infrared (smear), 2.98 (N–H), 3.57 (N–CH_3), 5.77 (C=O), 8.66 μ (C–O); n.m.r. (deuteriochloroform) (τ), $-CH_2$– (6.16), N–CH_3 (7.73), $-C(CH_3)_3$ (8.82), $-C(CH_3)_2$ (8.97); ratios of band areas, 2:3:9:6.

Anal. Calcd. for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 63.92; H, 11.36; N, 7.46.

Following the publication of Taylor's work,[3] one equivalent of sodium hydroxide was added to a 1 *M* solution of Ib in deuterium oxide. Reaction occurred immediately resulting in a lower (heavy water) layer and an oily upper layer. N.m.r. and infrared data showed that the oil contained no amide as described by Taylor,[3] but only IIIb. Similarly the lower layer contained no amide, but only a trace of unchanged Ib.

2-Phenyl-4,4-dimethyl-Δ^2-oxazoline.—To 61.0 g. (0.50 mole) of benzoic acid, 44.5 g. (0.50 mole) of freshly distilled 2-amino-2-methylpropane was added with stirring and cooling. After 2 hr. of refluxing during which time the temperature dropped from a maximum of 176° to a constant temperature of 156°, the equiv-

alent amount of water, 18 ml., was removed by distillation at atmospheric pressure through a 12-in. Vigreux column. The product was distilled through the same column at 10 mm. The main fraction of 69 g. (79%) was collected at 112–114°. Titration showed it to be 98.5% pure oxazoline. A second distillation under the same conditions yielded a main fraction of 99.5% pure oxazoline; $n^{25}D$ 1.5306 (lit.[6] $n^{17}D$ 1.5338 for a product made from tosylated amido alcohol); infrared (smear), 6.05 (–C=N), 3.25 (=C—H stretch.) 12.86 and 14.45 μ (aromatic C–H def., monosubst.); n.m.r. (deuteriochloroform) (τ), C_6H_5– (1.95–2.75), $-CH_2-$ (6.00), $-C(CH_3)_2$ (8.69); ratios of band areas, 2:6:5.

3,4,4-Trimethyl-2-phenyl-Δ²-oxazolinium Iodide (Ic).—A solution of 31.7 g. (0.22 mole) of iodomethane and 26.3 g. (0.15 mole) of 2-phenyl-4,4-dimethyl-Δ²-oxazoline in 80 ml. of nitromethane was heated at reflux for 3.5 hr. during which the refluxing temperature rose from 76 to 85° and the solution turned red. On cooling the solution, yellow crystals precipitated as soon as the temperature dropped to 70°. More crystals were obtained by adding a large amount of ether to the cooled mixture. A total of 47.0 g. (98.7%) of crude Ic was obtained, m.p. 193–194.5°. Recrystallization of 5 g. of Ic from 10 ml. of anhydrous methanol and 25 ml. of ethyl acetate yielded 3.2 g. of Ic, large colorless needles, m.p. 197–198°, 99.8% pure iodide salt by titration; infrared (mull), 6.06 (–C=N), 12.88 and 14.36 μ (aromatic C–H def., monosubst.); n.m.r. (deuteriochloroform) (τ), $-CH_2-$ (4.90), $N-CH_3$ (6.43), $-C(CH_3)_2$ (8.22), C_6H_5– (1.80–2.57); ratios of band areas, 2:3:6:5.

Anal. Calcd. for $C_{12}H_{16}INO$: N, 4.42; I, 40.01. Found: N, 4.25; I, 40.14.

Hydrogen Iodide Salt of 2-Methylamino-2-benzoxymethylpropane (IIc).—A solution of 31.7 g. (0.10 mole) of Ic in 50 ml. of water was heated with stirring at 75° for 1 hr. Light yellow crystals precipitated at once on cooling to room temperature. On drying under high vacuum, the crude solid weighed 29.4 g. (87.7%), m.p. 193–193.5°. Recrystallization from absolute methanol yielded colorless square plates, m.p. 193–193.5°; 99.5% pure by titration; infrared (mull), 5.77 (C=O), 14.26 μ (aromatic C–H def., monosubst.); n.m.r. (deuteriochloroform) (τ), C_6H_5– (1.92–2.73), $-CH_2-$ (5.54), $N-CH_3$ (7.30), $-C(CH_3)_2$ (8.38); ratios of band areas, 2:3:6:5.

Anal. Calcd. for $C_{12}H_{18}INO_2$: N, 4.18; I, 37.86. Found: N, 4.16; I, 37.68.

2-Methylamino-2-benzoxymethylpropane (IIIc).—A solution of 28.7 g. (0.086 mole) of IIc in 100 ml. of methanol was slowly neutralized to a phenolphthalein end point with 18.0 g. of 26% sodium methoxide in methanol and with vigorous stirring. The methanol was removed under reduced pressure leaving a mixture of sodium iodide and an oily liquid with a strong benzoate odor. Sodium iodide was very soluble in the amine ester. The product was extracted repeatedly with small amounts of ether, which were combined and washed three times with a little water until the ether layer became clear. After drying over anhydrous sodium sulfate, the ether was removed under reduced pressure. Thirteen grams of liquid remained. A vacuum distillation produced three fractions. (a) Titration and infrared analysis showed it [2.1 g., b.p. 62–68° (10 mm.)] to be 2-hydroxymethyl-2-methylaminopropane, 40.2%, with the remainder consisting mainly of methyl benzoate. (b) Titration and infrared analysis showed only 0.9% of the free amine with the rest methyl benzoate [5.8 g., b.p. 72–78° (10 mm.)]. A second distillation at atmospheric pressure yielded a main fraction at 196–199°; $n^{25}D$ 1.5150 (lit. b.p. 199.5°). The infrared spectrum obtained was identical with that of Sadler for methyl benzoate. The n.m.r. spectrum showed in addition to the phenyl hydrogen absorption, a single peak for the methoxy group at 6.14 τ. (c) Titration showed that it [2.5 g., b.p. 110–116° (4 mm.)] contained 82% of IIIc. A second distillation yielded a main fraction, b.p. 100–101° (1 mm.); $n^{25}D$ 1.5074. Titration showed that it was 99.0% pure IIIc; infrared (smear), 2.99 (N–H), 3.56 ($N-CH_3$), 5.78 μ (C=O); n.m.r. (deuteriochloroform) (τ), C_6H_5– (1.93–2.66), $-CH_2-$ (5.90), $N-CH_3$ (7.70), $-C(CH_3)_2$ (8.84), N–H, 9.04; ratios of band areas, 2:3:6:1:5.

Anal. Calcd. for $C_{12}H_{17}NO$: N, 6.82. Found: N, 7.04.

N-Methyl-2-acetoxymethyl-2-benzenesulfonamidopropane (IV). Synthesized from IIIa.—A solution of 6.0 g. (0.035 mole) of benzenesulfonyl chloride in 15 ml. of ether was dropped slowly into 4.79 g. (0.03 mole) of IIIa dissolved in 15 ml. of absolute ether and 10 ml. of pyridine at 0 to 5° with continuous agitation. A white flocculent precipitate formed immediately. Stirring was continued for 0.5 hr. at 10°. The reaction mixture was poured into ice–water and extracted twice with 25-ml. portions of ether. The ether extracts were combined and washed repeatedly with dilute acid until all of the pyridine was removed. The ether solution was then washed with water to neutrality. The ether layer was dried overnight with anhydrous sodium sulfate and subsequently evaporated under vacuum. A total of 7.3 g. of a pale mobile liquid was obtained (78.7%). This was purified by molecular distillation. The infrared and n.m.r. spectra were identical with IV prepared from VI.

Anal. Calcd. for $C_{13}H_{19}NO_4S$: N, 4.91; S, 11.24. Found: N, 4.74; S, 11.42.

2-Hydroxymethyl-2-benzenesulfonamidopropane (V).—To 25.6 g. (0.40 mole) of 2-amino-2-hydroxymethylpropane, dissolved in 10 ml. of 10% aqueous sodium hydroxide, 77.7 g. (0.44 mole) of benzenesulfonyl chloride was added dropwise over a period of 0.5 hr. with vigorous stirring, keeping the reaction temperature at 50°. Simultaneously with the benzenesulfonyl chloride, 190 ml. of 10% aqueous sodium hydroxide was added dropwise, maintaining a pH of 10. A white flocculent precipitate appeared after about half of the benzenesulfonyl chloride had been added. Stirring was continued for another 2 hr. at about 45–50°. The solution was cooled to room temperature and neutralized. The crude, white product was filtered by suction, washed repeatedly with water, and then dried to a constant weight of 81 g. (88%) under high vacuum over phosphorus pentoxide. Recrystallization of 80 g. of crude product from 150 ml. of isopropyl alcohol gave 57 g. of crystalline material, m.p. 119.5–121°; infrared (mull), 2.84 (O–H), 3.18 (N–H), 7.59 (SO_2 sym. stretch.), 8.71 (SO_2 asym. stretch.), 13.28, 13.98 μ (aromatic C–H def., monosubst.); n.m.r. (deuteriochloroform) (τ), C_6H_5– (2.00–2.76), N–H (4.69), $-CH_2-$ (6.50, 6.61 (doublet), –OH (7.22, 7.32, 7.42 triplet), $-C(CH_3)_2$ (8.90); ratios of band areas, 5:1:2:1:6.

Anal. Calcd. for $C_{10}H_{15}NO_3S$: N, 6.14; S, 13.99. Found: N, 6.30; S, 13.80.

N-Methyl-2-hydroxymethyl-2-benzenesulfonamidopropane (VI).—A total of 6.87 g. (0.03 mole) of V was dissolved in a solution of 0.70 g. of metallic sodium in 30 ml. of absolute methanol. The methanol was removed completely under reduced pressure leaving behind the sodium salt of the sulfonamide derivative as a white solid to which 70 ml. of dry benzene was added, followed by 4.2 g. (0.03 mole) of dimethyl sulfate. After 11 hr. of refluxing under anhydrous conditions, the major part of the solid went into solution. On cooling to room temperature, the white solid remaining was filtered from the benzene solution and dried to a constant weight of 4.02 g. It was soluble in water and the solution gave no precipitate on acidification. The benzene filtrate was washed once with 2.5% aqueous sodium hydroxide which, upon acidification, yielded no precipitate. The benzene, after drying over anhydrous sodium sulfate, was removed under reduced pressure followed by removal of the excess dimethyl sulfate under high vacuum. The residue was a mobile oil weighing 6.5 g. (89%); infrared (smear), 2.82 (O–H), 7.58 (SO_2 sym. stretch.), 13.24, 13.85 μ (aromatic C–H def., monosubst.); n.m.r. (deuteriochloroform) (τ), C_6H_5– (2.07–2.56), –OH (6.28), $N-CH_3$ (7.02), OCH_3 (7.29), $-C(CH_3)_2$ (8.78); ratios of band areas, 5:1:3:2:6.

Conversion of VI to IV.—A solution of 1.2 g. of acetyl chloride in 5 ml. of ether was added dropwise with stirring at 10° to 2.43 g. (0.01 mole) of VI dissolved in 10 ml. of pyridine and 30 ml. of absolute ether. Pyridine hydrochloride precipitated as a white solid. After standing at room temperature for 5 hr., the mixture was poured with vigorous stirring into ice–water. The ether layer was separated, washed a few times with acidified water until all of the pyridine was removed, then with water to neutrality, and dried over anhydrous sodium sulfate. After removal of the ether under reduced pressure, the product was dried under high vacuum to a constant weight of 3.0 g. (96.0%). It was purified by molecular distillation; infrared (smear), 3.53 ($N-CH_3$), 5.74 (C=O), 7.56 (SO_2 sym. stretch.), 8.12 (C–O), 8.73 (SO_2 asym. stretch.), 13.26, 13.86 μ (C–H def., monosubst.); n.m.r. (deuteriochloroform) (τ), C_6H_5– (2.22–2.63), $-CH_2-$ (5.93), $N-CH_3$ (7.13), CH_3CO- (8.15); $-C(CH_3)_2$ (8.70); ratios of band areas, 5:2:3:3:6.

Anal. Calcd. for $C_{13}H_{19}NO_4S$: N, 4.91; S, 11.24; Found: N, 4.65; S, 11.51.

Acknowledgment.—The authors wish to thank Dr. E. R. Malinowski for his assistance in the interpretation of the n.m.r. data.