[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Strongly Basic Derivatives of (+)- and (−)-1-Hydroxy-2-aminobutane[1]

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A number of optically active quaternary alkyl and guanidine bases related to 1-hydroxy-2-aminobutane has been prepared as potential resolving agents for unsubstituted amino acids. New ethers of colamine are also characterized.

Almost all of the numerous methods of resolution of amino acid enantiomorphs require the acylation of the DL-amino acid and deacylation of the derivative of one of the enantiomorphs. It may therefore be expected that simplified methods of resolution will be developed from optically active acids or bases functioning as salt components, solvents or sorbents if the resolving agent is a sufficiently strong acid or base to displace the corresponding group[3] in the amphionic amino acid. A few such methods using strong acids have been reported and may be found in the bibliography of a recent paper describing also the direct resolution of glutamic acid.[4] The present paper describes some new optically active bases prepared for their potential utility in meeting the stated objectives.

Success with butanolamine (1-hydroxy-2-aminobutane) in the resolution of unsubstituted glutamic acid[4] led to the preparation of a number of derivatives which might prove to be sufficiently basic for the resolution of "neutral" amino acids. Prior to the preparation of ethers of butanolamine several optically inactive ethers derived from colamine were synthesized in order to furnish orientation in the necessary conditions for reaction. Inasmuch as characterizations of a number of these compounds have not been found in the literature, constants are reported here.

A number of guanidine derivatives, from butanolamine and from other amines, was made because of the known basicity of guanidine[5] and its derivatives. Cyanamide was employed as the agent for guanidine formation with butanolamine. In the production of other guanidines, the methylisourea method of Kapfhammer and Müller[6] was applied. Werner reported that the reaction for preparation of this reagent was so highly exothermic that it could be performed conveniently only in test-tube size batches.[7] Conditions were found, however, for production of large laboratory quantities of methylisourea sulfate; these are described in the Experimental.

Experimental

Nitrogen was determined by the micro-Kjeldahl method.

(−)-**1-Hydroxy-2-dimethylaminobutane**.—This was prepared more satisfactorily by a variation of the Eschweiler–Clarke method[8] than by direct methylation in the presence of a number of bases. (−)-1-Hydroxybutane-2-ammonium hydrogen L-tartrate[4] (394 g., 1.53 moles) was treated directly with 90% formic acid (340 ml., 7 moles) and U.S.P. formalin solution (270 ml., containing 3.3–3.5 moles of formaldehyde). After overnight standing, the mixture was refluxed for 6 hr. and freed of formic acid with the aid of extra water and evaporation under reduced pressure. To the resulting sirup was added potassium hydroxide pellets (300 g., 5.3 moles) with cooling. The solid potassium tartrate was allowed to settle, so that the two liquid layers could be decanted and separated. The aqueous layer and the solid were extracted twice with ether, then all organic solutions were dried with potassium carbonate and fractionated through a 40-cm. Vigreux column to yield (−)-1-hydroxy-2-dimethylaminobutane, b.p. 61° (15 mm.), 163 g. (91%). Further description of the product appears under the preparation of the (+)-antipode.

(+)-1-**Hydroxybutane-2-dimethylammonium Hydrogen Oxalate**.—Mother liquors from (−)-1-hydroxybutane-2-ammonium hydrogen L-tartrate preparations, containing mostly the (+)amine, were combined and partially evaporated to yield 740 g. of impure amine salt after filtration. The filtrate was easily miscible with ether, a fact suggesting that all amine salt had been removed.

The Eschweiler–Clarke dimethylation was run as before, with this salt (740 g., 2.8 moles), 90% formic acid (630 ml., 13 moles), and U.S.P. formalin solution (500 ml., containing about 6.3 moles of formaldehyde). After liberation of free amine, the ether extracts of the aqueous phase were evaporated individually to permit comparison of the amounts of amine therein. The ether extraction had been reasonably complete, since the second extraction gave only 30 g. of amine compared with 90 g. for the first one. The combined amine samples were "flashed" away from inorganic residue by rapid non-fractionating vacuum distillation, then refractionated through a 60-cm. glass helix column to give a 97-g. fraction with an equivalent weight of 119 (theory 117) and a 109-g. fraction with an equivalent weight of 121. Another 40 g. was somewhat less pure. The total crude yield of 246 g. was 2.1 moles, 75%, b.p. 93° (73 mm.).

The amine was combined with oxalic acid dihydrate (265 g., 2.1 moles) and crystallized from 420 ml. of 95% ethanol to yield 142 g. of pure (+)-1-hydroxybutane-2-dimethylammonium hydrogen oxalate. Further fractional crystallization brought the total yield to 174 g., 0.84 mole, m.p. 117°. The original dimethylated amine had consisted of 82% (+)antipode by calculation; the yield was thus 49%; $[\alpha]^{26}D$ +20.6 ± 0.5° (1.6% in water).

Anal. Calcd. for $C_8H_{17}O_5N$: N, 6.75; neut. equiv., 207. Found: N, 6.64; neut. equiv., 205.

All subsequent fractions, regardless of recrystallization, had rotations of +9 to +10° (corresponding to 56% racemic and 44% optically active salt).

(+)-**1-Hydroxy-2-dimethylaminobutane**.—The amine was liberated by potassium hydroxide with the aid of two ether extractions from the hydrogen oxalate (155 g., 0.75 mole) in a slurry with 100 ml. of water. After being dried with potassium carbonate, the product was distilled under reduced pressure to give 85 g. (96%) of pure (+)-1-hydroxy-2-dimethylaminobutane, b.p. 92° (68 mm.), d^{30} 0.8805, $n^{17.5}D$ 1.4460, $[\alpha]^{30}D$ +5.2 ± 0.1° (10% in water).

Anal. Calcd. for $C_6H_{15}ON$: neut. equiv., 117.2. Found: neut. equiv., 119.

(+)-(α-**Ethylcholine Iodide**).—Hygroscopic, bipyramidal

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(2) To whom inquiries should be addressed.

(3) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publ. Corp., New York, N. Y., 1943, p. 75.

(4) F. H. Radke, R. B. Fearing and S. W. Fox, THIS JOURNAL, **76**, 2801 (1954).

(5) N. F. Hall and M. R. Sprinkle, *ibid.*, **54**, 3469 (1932).

(6) J. Kapfhammer and H. Müller, *Z. physiol. Chem.*, **225**, 1 (1934).

(7) E. A. Werner, *J. Chem. Soc.*, **105**, 927 (1914).

(8) H. T. Clarke, H. B. Gillespie and S. Z. Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

prisms recrystallized from dry acetone; m.p. 228°, $[\alpha]^{28.5}D$ +4.4 ± 0.2°, (4% in water).

Anal. Calcd. for $C_7H_{18}ONI$: N, 5.4; I, 49.0. Found: N, 5.3; I, 48.7.

Dialkylaminoethyl Ethers. 1-Amyloxy-2-diethylaminoethane.—Redistilled β-diethylaminoethanol (88 g., 0.75 mole) and sodium (17.2 g., 0.75 mole) were mixed in 200 g. of molten trioxane, stirred and heated under reflux with air passing through the condenser, this cooling being sufficient to condense trioxane without freezing it. When a clear solution was obtained, *n*-amyl bromide (73 g., 0.48 mole) was added dropwise with more stirring and reflux for a total of 4 hr. of heating. Excess sodium alcoholate was used to avoid formation of quaternary salt.

About 300 ml. of Skelly D was added, and the mixture was stirred and cooled. Most of the trioxane crystallized, so that the petroleum ether could be decanted. The process was repeated with fresh Skelly D. A titration on each petroleum ether extract of the trioxane showed that two extractions were sufficient. The combined solutions were washed with water, removing a little trioxane and inorganic content. Fractionation then gave some unreacted β-diethylaminoethanol, and a pure fraction of β-diethylaminoethyl amyl ether; 45 g. (50% from amyl bromide), b.p. 102° (16 mm.), d^{29} 0.812, $n^{26.5}D$ 1.4254.

Anal. Calcd. for $C_{11}H_{25}ON$: neut. equiv., 187.1. Found: neut. equiv., 187.5.

The hydrogen oxalate, m.p. 85–86°. *Anal.* Calcd. for $C_{13}H_{27}O_5N$: neut. equiv., 277; N, 5.05. Found: neut. equiv., 275; N, 4.98.

The ethiodide, m.p. 108°. *Anal.* Calcd. for $C_{13}H_{30}ONI$: I, 37.0; N, 4.09. Found: I, 36.8; N, 4.16.

1-Allyloxy-2-diethylaminoethane.—β-Diethylaminoethanol (46 g., 0.4 mole), sodium (9.2 g., 0.4 mole), and allyl bromide (42 g., 0.35 mole) were used in a preparation similar to the previous one. The crude, dried amine was treated with sodium to remove unreacted aminoalcohol which would otherwise be difficult to fractionate from the product. Fractionation then gave 27 g. of amine (50% from allyl bromide), b.p. 67° (15 mm.), $n^{28}D$ 1.4337.

Anal. Calcd. for $C_9H_{19}ON$: neut. equiv., 157. Found: neut. equiv., 158.

The ethiodide, when recrystallized from acetone, had m.p. 90–90.5°. *Anal.* Calcd. for $C_{11}H_{24}ONI$: I, 40.6; N, 4.48. Found: I, 40.8; N, 4.52.

1-Benzyloxy-2-diethylaminoethane.—One change was made in this synthesis with sodium (17.2 g., 0.75 mole), β-diethylaminoethanol (88 g., 0.75 mole) and benzyl chloride (63 g., 0.5 mole). After the first 4 hr. of reflux most of the trioxane was fractionated directly from the reaction flask to concentrate the reagents; the temperature of the reaction mixture reached 173° during this distillation. After removal of trioxane, water (200 ml.) was added to the cooled flask, and stirred to dissolve solid residue. The resulting two layers were separated and the top phase extracted again with water. All aqueous solutions were extracted with ether. The combined and potassium carbonate-dried organic solution was fractionated at the water-pump up to 134°, when the product began coming over steadily; then a Hyvac pump was used, and the amine distilled at 97–100° (0.5 mm.), d^{29}_4 0.930, 92 g. (89% from benzyl chloride).

Anal. Calcd. for $C_{13}H_{21}ON$: neut. equiv., 207. Found: neut. equiv., 207.

The ethiodide m.p. 103–103.5°; Clemo and Perkin[9] reported 105°. *Anal.* Calcd. for $C_{15}H_{26}ONI$: I, 35.0; N, 3.86. Found: I, 35.2; N, 3.98.

The hydrogen oxalate m.p. 102.5–103°. *Anal.* Calcd. for $C_{15}H_{23}O_5N$: neut. equiv., 297; N, 4.72. Found: neut. equiv., 296; N, 4.76.

Optically Active Ethers of 1-Hydroxy-2-dimethylaminobutane. (−)-1-Benzyloxy-2-dimethylaminobutane.—(−)-1-Hydroxy-2-dimethylaminobutane (41 g., 0.35 mole) and sodium (8 g., 0.35 mole) were allowed to reflux in 250 g. of trioxane. Almost immediately sodium derivative precipitated voluminously to interfere with further reaction with sodium. Trioxane, although a good solvent for the sodium derivative of the ethanol analog, was unsuitable for the dimethylaminobutanol. The addition of an equal volume of dioxane, however, dissolved enough solid to permit ready completion of the reaction. After the sodium had dissolved, benzyl chloride (38 g., 0.3 mole) was added dropwise and the liquid was refluxed for 6 hr. The solvents were then distilled off until the pot temperature reached 155°. The remainder was stirred with 100 ml. of water and separated in a separatory funnel. The top layer was extracted with 40 ml. of water containing a little potassium hydroxide. It was then dried with potassium hydroxide pellets and fractionated to yield 45.5 g., 0.22 mole (73%, b.p. 136° (17 mm.) or 117° (4 mm.)), $n^{28}D$ 1.4936, d^{28} 0.9279, $[\alpha]^{28}D$ −4.85 ± < 0.1° (3% in absolute ethanol).

Anal. Calcd. for $C_{13}H_{21}ON$: neut. equiv., 207.3. Found: neut. equiv., 208.

(−)-1-Benzyloxy-2-dimethylaminobutane Hydrogen Oxalate.—In order to check whether any racemization had occurred during this procedure, a sample of the amine (1.45 g., 6.98 millimoles) was combined with oxalic acid (880 mg., 6.98 millimoles) in 76% ethanol and read immediately in the polarimeter. The specific rotation was calculated as −14.1° for this hydrogen oxalate. When the pure hydrogen oxalate was prepared in isoamyl alcohol and precipitated with ether, then recrystallized from alcohol–ether, the crystals obtained had m.p. 81.5–82°, $[\alpha]^{28}D$ −14.5 ± < 0.1° (76% ethanol).

Anal. Calcd. for $C_{15}H_{23}O_5N$: neut. equiv., 297; N, 4.71. Found: neut. equiv., 294; N, 4.77.

Inasmuch as the purified hydrogen oxalate had practically the same rotation as that calculated from the unpurified mixture, it is believed that the distillate was optically pure even before hydrogen oxalate formation; therefore the preparation itself did not involve any extensive racemization.

The benzyl bromide addition product was recrystallized from alcohol–ether, m.p. 124°, $[\alpha]^{24}D$ +4.5 ± 0.1° (5.5% in 95% ethanol).

Anal. Calcd. for $C_{20}H_{28}ONBr$: Br, 21.1; N, 3.7. Found: Br, 20.9; N, 3.6.

The methiodide was recrystallized from ethanol and acetone, m.p. 141–142°. An analysis was performed on the enantiomorph.

(+)-1-Benzyloxy-2-dimethylaminobutane Methiodide.—This was obtained from the (+)-amine and methyl iodide, then recrystallized from butanol and acetone; m.p. 142.5–143°, $[\alpha]^{27}D$ +11.9 ± 0.5° (1.5% in water); the rotation reading remained unchanged after ten hours.

Anal. Calcd. for $C_{14}H_{24}ONI$: N, 4.0; I, 36.4. Found: N, 3.9; I, 36.3.

(−)-1-*p*-Chlorobenzyloxy-2-dimethylaminobutane.—(−)-1-Hydroxy-2-dimethylaminobutane (33 g., 0.28 mole) was dissolved in 500 ml. of xylene. Sodium (6.5 g., 0.28 mole) was added, and dissolved with stirring and reflux, to a clear solution, thus demonstrating the superiority of xylene as a solvent in this case. A purified sample of Eastman Kodak Co. practical *p*-chlorobenzyl chloride (40.2 g., 0.25 mole) was dissolved in a small amount of xylene and added dropwise to the above stirred, refluxing solution. After 6 hr. of reflux, most of the solvent was removed by fractionation which required another 8 hr. of heating. Titrations indicated that only a negligible amount of amine codistilled.

At the end of this period, 90 ml. of water was added and the mixture was stirred. The organic layer was washed once more with 60 ml. of water, during which operation addition of hexane was necessary for good separation. Fractionation yielded 50.5 g., 0.207 mole (83%), based on *p*-chlorobenzyl chloride), b.p. 127° (1 mm.), d^{25} 1.0256, $n^{28}D$ 1.5058, $[\alpha]^{28}D$ −4.5 ± 0.2° (5% in absolute ethanol).

Anal. Calcd. for $C_{13}H_{20}ONCl$: neut. equiv., 242. Found: neut. equiv., 244.

The methiodide was crystallized from alcohol, m.p. 158°, $[\alpha]^{27}D$ −11.1 ± 0.2° (7% in 75% ethanol).

Anal. Calcd. for $C_{14}H_{23}ONClI$: I, 33.2; N, 3.66. Found: I, 33.4; N, 3.65.

The benzyl bromide addition product was recrystallized from dry acetone, m.p. 122.5, $[\alpha]^{26}D$ +6.65 ± 0.2° (4% in 95% ethanol).

Anal. Calcd. for $C_{20}H_{27}ONClBr$: Br, 19.4; N, 3.40. Found: Br, 19.5; N, 3.33.

(+)-1-Butoxy-2-dimethylaminobutane.—(−)-1-Hydroxy-2-dimethylaminobutane (41 g., 0.35 mole) and sodium (8.0 g., 0.35 mole) reacted together in about 350 ml. of 1:1 di-

(9) G. R. Clemo and W. H. Perkin, Jr., *J. Chem. Soc.*, **121**, 642 (1922).

oxane–trioxane. After 5 hr. of reflux the sodium had dissolved, and *n*-butyl bromide (32.2 ml., 0.3 mole) was added dropwise. After reflux for 8 hr., most of the solvent was fractionated from the product and sodium chloride; the latter was then extracted with water in two portions. The organic layer, after drying with potassium hydroxide pellets, was fractionated through a 60-cm. glass helix column to give 26.5 g. of pure product (52%); b.p. 87.5° (17 mm.), d^{28} 0.8155, $n^{29}D$ 1.4218, $[\alpha]^{29}D$ +0.47 ± 0.1° (8% in absolute ethanol).

Anal. Calcd. for $C_{10}H_{23}ON$: neut. equiv., 173. Found: neut. equiv., 172.

(+)-1-Butoxy-2-dimethylaminobutane Hydrogen Oxalate.—In view of the low rotation, the hydrogen oxalate was again used to check for racemization as before; that from the distillate without recrystallization had $[\alpha]^{28}D$ −8.0 ± 0.1° (9% in 76% ethanol). The pure hydrogen oxalate was recrystallized from ethanol with ether, m.p. 77–78°, $[\alpha]^{28}D$ −7.9 ± 0.1° (76% ethanol). Evidently no racemization had occurred in the preparation.

Anal. Calcd. for $C_{12}H_{25}O_5N$: neut. equiv., 263; N, 5.3. Found: neut. equiv., 262; N, 5.3.

(+)-1-Butoxy-2-dimethylaminobutane Methiodide.—Extremely hygroscopic crystals were produced from ethanol–ether, m.p. 110–112°, $[\alpha]^{28}D$ −10.4 ± 0.2° (6.5% in 95% ethanol). After drying over phosphorus pentoxide in a vacuum desiccator, the material was yet somewhat pasty and moist.

Anal. Calcd. for $C_{11}H_{26}ONI$: N, 4.4; I, 40.3. Found: N, 4.3; I, 40.9.

(−)-1-*o*-Chlorobenzyloxy-2-dimethylaminobutane.—Sodium (8 g., 0.35 mole) was dissolved in a solution of (−)-1-hydroxy-2-dimethylaminobutane (41 g., 0.35 mole) in 700 ml. of 1:1 dioxane–trioxane. After several hours of stirring and reflux, the sodium was dissolved; the stirred mixture was treated dropwise with Eastman Kodak Co. reagent grade *o*-chlorobenzyl chloride (48.3 g., 0.3 mole). After 6 hr. of reflux, the solvent was partially distilled off, thus furthering the reaction. After 5 more hours of reflux, more solvent was distilled off, and 100 ml. of water was added and stirred to dissolve sodium chloride. Separation of layers gave a top organic layer, the density of which was near to that of water, so that a second extraction with water required addition of Skelly B to facilitate separation of layers. Fractionation through a 20-cm. Vigreux column gave 55 g., 0.228 mole, of amine (76% based on the *o*-chlorobenzyl chloride) b.p. 122–127° (<1 mm.), $n^{30}D$ 1.5050, d^{24} 1.0199, $[\alpha]^{26}D$ −3.40 ± 0.1° (10% in absolute ethanol).

Anal. Calcd. for $C_{13}H_{20}ONCl$: neut. equiv., 241.5. Found: neut. equiv., 241.

(−)-1-*o*-Chlorobenzyloxy-2-dimethylaminobutane Hydrogen Oxalate.—The possibility of racemization was again checked by preparation of the hydrogen oxalate which had m.p. 103° and $[\alpha]^{25}D$ −10.8 ± 0.1° (10% in 79% ethanol). That prepared directly in solution from the distillate had $[\alpha]^{26}D$ −10.4 ± 0.1° (10% in 79% ethanol). Thus very little, if any, racemization took place during the reaction.

Anal. Calcd. for $C_{15}H_{22}O_5NCl$: neut. equiv., 331; N, 4.23. Found: neut. equiv., 329; N, 4.15.

The methiodide was recrystallized from alcohol, m.p. 167½°, $\alpha^{25}D$ −8.8 ± 0.2° (2.5% in 80% ethanol).

Anal. Calcd. for $C_{14}H_{23}ONClI$: I, 33.2; N, 3.66. Found: I, 33.5; N, 3.64.

The benzyl bromide addition product was recrystallized from alcohol–ether, m.p. 124°, $\alpha^{24}D$ +4.54 ± 0.1° (5.5% in 95% ethanol).

Anal. Calcd. for $C_{20}H_{27}ONClBr$: Br, 19.3; N, 3.4. Found: Br, 19.2; N, 3.3.

Guanidines. (+)-Di-(1-hydroxybutane-2-guanidinium) Sulfate.—This was made by a variation of the procedure of Paden and McLean[10] by using sulfuric acid (8 g., 0.16 equivalent) in 50 ml. of 95% ethanol, (−)-1-hydroxy-2-aminobutane[4] (16 g., 0.18 mole), and Eastman reagent grade cyanamide (10 g., almost 0.25 mole). The slight excess of hydroxyaminobutane over sulfuric acid provided a desirably high *p*H. Drying of the resulting sirup by co-distillation of moisture with 25 ml. of isoamyl alcohol at 70 mm. pressure gave crystals weighing (after absolute alcohol–ether wash) 19 g. (60%), m.p. 138–141°. Recrystallization from water-alcohol gave 14.5 g. (50%) m.p. 183–184°, $[\alpha]^{28.5}D$ +33.1 ± 0.2° (2% in water).

Anal. Calcd. for $C_{10}H_{28}O_6N_6S$: S, 8.93; N, 23.5. Found: S, 8.90; N, 23.5.

O-Methylisourea Hydrogen Sulfate.—In one variation of the method developed here, urea (60 g., 1.0 mole) was shaken gradually into dimethyl sulfate (126 g., 1.0 mole) maintained at 110–115°, with stirring. The monomethyl sulfate salt of methylisourea was produced as an oil. Liberation (with calcium hydroxide) of free methylisourea base was not convenient at this point because the highly soluble calcium methylsulfate interfered with distillation.

An amount of sulfuric acid calculated to displace methylsulfuric acid was dissolved in ether (slowly with cooling) and added to the oil from the reaction, along with about the same volume of acetone. When the mixture was cooled and shaken so as to distribute the initial seeds, 58 g. (35%), of methylisourea bisulfate was obtained, after washing with acetone; m.p. 115–118°, lit. 119–120°.[11] The acetone condensed to dark red compounds in the acid solution, but did not affect the yield, as shown by comparison with other methods.

In the preparation on a larger scale, urea (300 g., 5 moles) and dimethyl sulfate (630 g., 5 moles) were placed in a flask, covered with a layer of cyclohexane and heated cautiously. At 80°, the reagents under the cyclohexane were not completely miscible but reacted satisfactorily when stirred. Previously 105° had been claimed as necessary for this reaction.[12] The refluxing cyclohexane prevented the temperature from rising much above 80°; no external heating was necessary. After less than an hour the three phases became two (cyclohexane was always immiscible), and soon the temperature dropped, no longer sustained by an exothermic reaction. The reaction was not self-sustaining below 75°. An unsuccessful attempt was made to crystallize the normal sulfate, by adding the proper amount of sulfuric acid. To prepare the hydrogen sulfate, an excess of sulfuric acid was added slowly, the mixture was very cautiously extracted three times with ether (heat was produced when the first portion of ether was added). Finally, addition of an equal volume of butanol-1 and cooling gave good crystals of the hydrogen sulfate, which was washed with butanol and finally with acetone, 249 g. (29%).

The typical 30% yield was not due to difficulty of isolation inasmuch as the product was highly insoluble in butanol and acetone and crystallized easily. All other conditions tried, with higher temperatures and addition of reagents gradually in both possible orders, gave the same yield (30–35%). Methylisourea hydrogen sulfate (327 g.) from several preparations was recrystallized from one liter of methanol by addition of 2.5 liters of ether, yield 274 g., m.p. 119°.

Methylisourea Sulfate.—Methylisourea hydrogen sulfate (192 g., 1.12 equivalents) was dissolved in water and cooled by an ice-bath. The hydrogen sulfate ion was neutralized in an ice-bath by addition of 572 ml. of 1.95 *N* barium hydroxide solution at 60°. Centrifugation gave a clear solution. Evaporation of water under reduced pressure was aided by addition of butanol. After addition of acetone the crystals were filtered and washed with acetone, yielding 119 g., m.p. 159–160°. Recrystallization from 200 ml. of water by addition of 800 ml. of acetone yielded 96 g. of pure salt (70%), m.p. 171–172°.

Anal. Calcd. for $C_4H_{14}O_6N_4S$: S, 13.0; N, 22.7. Found: S, 12.9; N, 22.6.

Although many other salts of methylisourea have been described, the normal sulfate seems not to have been previously reported.

***n*-Butylguanidine Sulfate.**—Methylisourea sulfate (6.15 g., 50 meq.) and *n*-butylamine (3.65 g., 50 meq.) were combined in 30 ml. of water. Titrations on small aliquots showed that after 5 min. of reflux the reaction was 88% complete. After 0.5 hr. the solution was evaporated to

(10) J. H. Paden and A. F. McLean, U. S. Patent 2,425,341 (1947); *C. A.*, **41**, 7414 (1947).

(11) W. L. Hughes, Jr., J. A. Saroff and A. L. Carney, THIS JOURNAL, **71**, 2476 (1949).

(12) P. A. Ongley, *Trans. Proc. Roy. Soc. New Zealand*, **77**, 10 (1948).

near-dryness under reduced pressure to yield a white solid. Addition of 25 ml. of absolute ethanol, then evaporation to about 20 ml. and addition of 20 ml. of isoamyl alcohol gave 4.0 g. (50%) of product, which was washed with ether, m.p. 210–211°. A melting point of 206° was reported by Davis and Elderfield.[13]

Morpholinecarboxamidine Sulfate.—Methylisourea sulfate (6.15 g., 50 meq.) and morpholine (7.5 g., 86 meq.) were mixed in 30 ml. of 50% methanol. After standing at 25–30° for 36 hours, 3.3 g. of prisms separated. The solution was evaporated and ethanol was added to yield 3.0 g., total 6.3 g. (70%), m.p. 306° dec.

Anal. Calcd for $C_{10}H_{24}O_6N_6S$: S, 9.00; N, 23.6. Found: S, 9.02; N, 23.0.

***d*-Bornylguanidine Sulfate.**—When this compound was first prepared with stoichiometric quantities under conditions similar to those for butylguanidine sulfate, the reaction was about 75% complete in 12 hours, but the precipitate contained some *d*-bornylamine sulfate, as indicated by titration to an alizarin yellow end-point, and confirmed by a low nitrogen content. It proved difficult to remove this impurity, so the reaction was repeated, this time with excess methylisourea as follows: *d*-bornylamine (3.5 g., 22.8 meq.) in 30 ml. of methanol was treated with methylisourea sulfate (4.07 g., 33 meq.), and enough barium hydroxide solution to remove the 10 excess meq. of sulfate ion. After a brief warming, the solution was filtered from barium sulfate and concentrated. Cooling yielded 1.5 g. of precipitate which, after recrystallization from 90% methanol, gave no titration to the alizarin yellow end-point, m.p. 326–330° dec., $[\alpha]^{28}D$ +21.4 ± 0.6° (3.5% in 50% ethanol).

Anal. Calcd. for $C_{20}H_{44}O_4N_6S$: S, 6.5; N, 17.2. Found: S, 6.4; N, 17.1.

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AMES, IOWA

(13) T. L. Davis and R. S. Elderfield, THIS JOURNAL, **54**, 1499 (1932).

[CONTRIBUTION FROM THE JET PROPULSION LABORATORY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

Rate of Addition of the Nitrate Ion to the Ethylene Oxide Ring[1]

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The rate of addition of the nitrate ion to several oxides has been measured under neutral and acidic conditions in aqueous solution. A rapid method for determining the rate of the uncatalyzed reaction was developed. The nucleophilic tendency of the nitrate ion is discussed in terms of Swain's rate correlation equation. Acid-catalyzed rate constants determined in solutions of high salt concentration gave a prediction of yield data under conditions favorable for synthesis of nitric esters

Previous investigators[3,4] observed that the nitrate ion adds to the ethylene oxide ring in aqueous solution; however, no reasonably accurate rate data were obtained by them. Part of the difficulty was caused by the slow rate of addition of the nitrate ion as compared with the competing hydrolytic reaction. For this investigation, conditions were chosen which made it possible to determine the rate of addition of the nitrate ion to several oxides in both neutral and acid solutions. Moreover, rough rate measurements were made with ions even more weakly nucleophilic than the nitrate ion.

The major reactions occurring in aqueous solution when an unsymmetrical oxide reacts with the nitrate ion are[5]

$$\text{RCH}\!-\!\text{CH}_2 + \text{HOH} \xrightarrow{k_1} \text{RCHOHCH}_2\text{OH} \quad \text{(A)}$$
$$\text{O}$$

$$\text{RCH}\!-\!\text{CH}_2 + \text{HOH} \xrightarrow[(\text{H}^+_3\text{O})]{k_2} \text{RCHOHCH}_2\text{OH} \quad \text{(B)}$$
$$\text{O}$$

$$\text{RCH}\!-\!\text{CH}_2 + \text{NO}_3^- + \text{HOH} \xrightarrow{k_3} \begin{cases} \text{RCHOHCH}_2\text{ONO}_2 + \text{OH}^- \\ \text{RCHONO}_2\text{CH}_2\text{OH} + \text{OH}^- \end{cases} \quad \text{(C)}$$
$$\text{O}$$

$$\text{RCH}\!-\!\text{CH}_2 + \text{NO}_3^- + \text{H}_3^+\text{O} \xrightarrow{k_4} \begin{cases} \text{RCHOHCH}_2\text{ONO}_2 + \text{H}_2\text{O} \\ \text{RCHONO}_2\text{CH}_2\text{OH} + \text{H}_2\text{O} \end{cases} \quad \text{(D)}$$
$$\text{O}$$

Under the conditions used to obtain the kinetic data, the primary nitric ester was formed predominantly, except for propylene oxide where a mixture of the two isomers was produced.[5,6]

The fractional rate of oxide disappearance is

$$-\text{d(E)/(E)d}t = k_1(\text{HOH})^2 + k_2(\text{HOH})(\text{H}_3^+\text{O}) + k_3(\text{NO}_3^-)(\text{HOH}) + k_4(\text{NO}_3^-)(\text{H}_3^+\text{O}) \quad (1)$$

where (E) = concentration of oxide (moles liter), (HOH) = concentration of water (moles liter), (NO_3^-) = concentration of nitrate ion (moles/liter), and (H_3^+O) = concentration of hydronium ion (moles/liter). In equation 1 third-order rate constants are employed since they are believed to be consistent with the over-all kinetics of each reaction. Some of the values of k_1 and k_2 for the oxides studied had already been determined.[3] It was then necessary to choose conditions whereby the individual values of k_3 and k_4 for various oxides could be determined.

Experimental

Materials.—Reagent-grade sodium salts of the various ions tested were used without further purification. Epibromohydrin was obtained from Eastman Kodak Co., and epichlorohydrin and allyl glycidyl ether from Shell Chemical Co. Glycidol was prepared by the reaction of glycerol α-monochlorohydrin and alcoholic sodium ethoxide as described by Rider and Hill.[7] All of the oxides were distilled under vacuum through a 1-foot column filled with Podbielniak "Heli-pak" random packing.

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