[Contribution from the Noyes Chemical Laboratory,
University of Illinois]

THE SYNTHESIS AND REDUCTION OF BIS(DIMETHYLAMINOMETHYL)ACETIC ACID AND α-DIMETHYLAMINOMETHYLACRYLIC ACID

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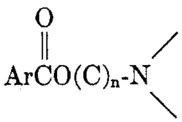
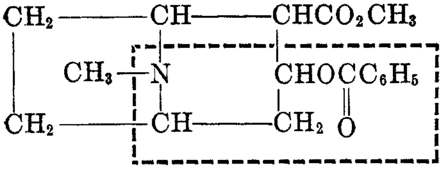
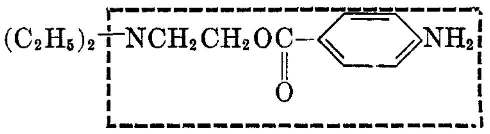
A great many compounds which manifest local anesthetic activity have been shown to contain  $\mathrm{Ar\overset{\overset{O}{\|}}{C}O(C)_n\text{-}N}\begin{smallmatrix}/\\ \backslash\end{smallmatrix}$ as the basic anesthesiophoric group (1). Cocaine (I) and procaine (II) are well known examples. The activity of a compound containing such an anesthesiophore is roughly a function of the aromatic acid with which the parent aminoalkanol is esterified, the alkanol group bearing the amino-nitrogen, and the substituents on the nitrogen atom (1). An interesting modification of the parent aminoalkanol which has received no attention (2) is represented in 2,2-bis(dimethylaminomethyl)ethanol (III), in which the β-carbon atom bears two dialkylaminomethyl groups. This paper describes the synthesis of III and several of its derivatives.



I



II

The proposed synthesis of III involved the reduction of bis(dimethylaminomethyl)acetic acid (IV) with lithium aluminum hydride. The required intermediate was reported by Mannich and Kather to be available in 35% yield by the condensation of malonic acid with formaldehyde and dimethylamine (3). A reinvestigation of this reaction has indicated that the reaction is more complicated than originally described. Mannich reported that the condensation afforded the hydrochloride of IV in 35% yield. We have obtained, in addition to IV, the hydrochloride of α-dimethylaminomethylacrylic acid (V), presumably formed by the elimination of a molecule of dimethylamine from IV (3, 4). Mannich records the melting point of bis(dimethylaminomethyl)acetic acid (IV) as 139°; in our hands, treatment of IV·HCl with either silver oxide or Amberlite IR-4B resin furnished a product melting at 82–83° which gave satisfactory analytical data, and could be reconverted to IV·HCl by treatment with hydro-

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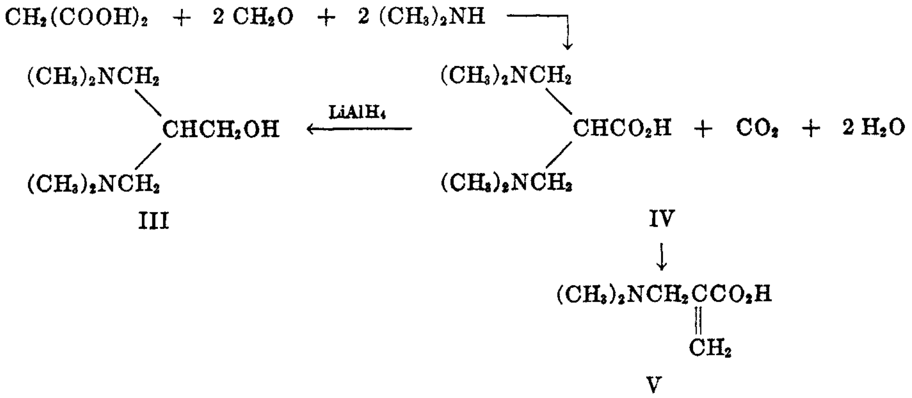
chloric acid. Since Mannich and Kather did not describe the method of effecting the conversion of IV·HCl to IV, the discrepancy in melting points is difficult to explain. One possible explanation involves the assumption that these workers prepared their "free amino acid" by neutralizing the corresponding hydrochloride with a strong base such as sodium hydroxide. Since it would be difficult by such a procedure to attain the exact isoelectric point, it is possible that their "free amino acid" was contaminated with substantial amounts of either the much higher-melting hydrochloride or sodium salt of IV.



Reduction of bis(dimethylaminomethyl)acetic acid with lithium aluminum hydride proceeded smoothly at room temperature to give the corresponding alcohol (III) in 76% yield. Direct addition of the powdered acid to a suspension of lithium aluminum hydride in ether was found to be the most efficient method of introduction. The solubility of IV in ether is too low to permit extraction in a reasonable time by the Soxlet technique. 2,2-Bis(dimethylaminomethyl)ethanol (III) was characterized as the dihydrochloride and benzoate dihydrochloride. These two derivatives have been submitted to the Eli Lilly Research Laboratories for pharmacological evaluation. The results of the tests will be reported elsewhere.

α-Dimethylaminomethylacrylic acid (V), m.p. 117.7–119.7°, was obtained in 86% yield by percolating an aqueous solution of its hydrochloride over a column of Amberlite IR-4B resin. Reduction of this unsaturated acid with lithium aluminum hydride did not furnish a homogeneous product.

EXPERIMENTAL[3]

Bis(dimethylaminomethyl)acetic acid dihydrochloride. To 50.5 g. (0.5 mole) of malonic acid was added, with cooling and efficient stirring, 150 g. (1.0 mole) of 30% aqueous dimethylamine. After the acid was completely dissolved, 75 g. (1 mole) of 37% formalin was added slowly and with vigorous stirring. After standing in the refrigerator for 18 hours, during which time carbon dioxide was evolved, the mixture was concentrated *in vacuo* over a steam-bath. The viscous residue was treated gradually with 90 ml. of concentrated hydrochloric acid, care being taken to maintain the temperature below 20°. The resulting

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[3] Melting points are corrected. C, H, and N analyses are by E. Davis, J. Fortney, and K. Pih; the Cl analysis is by the Clark Microanalytical Laboratory, Urbana, Illinois.

clear solution was evaporated to dryness *in vacuo* over a steam-bath and the white crystalline residue triturated with cold absolute ethanol. The insoluble bis(dimethylaminomethyl)-acetic acid dihydrochloride was collected and washed several times with cold absolute alcohol and acetone. Drying *in vacuo* over phosphorus pentoxide gave 30 g. (25%) of fluffy white crystals; m.p. 169–171°; lit. 169° (3).

α-Dimethylaminomethylacrylic acid hydrochloride. The alcoholic and acetone washings from IV·2HCl were combined and diluted to 2 l. with acetone. After standing two hours, slender needles of α-dimethylaminomethylacrylic acid hydrochloride had separated. Occasionally the product separated as an oil, but could be induced to crystallize by scratching. The product was collected after standing overnight in the refrigerator. Partial purification was effected by solution in the minimum of absolute alcohol followed by precipitation with dry ether. The air-dried material melted at 88–89°, but after drying 30 hours over phosphorus pentoxide at 60°, melted at 143–145°; yield 28 g. (35%). An analytical sample was prepared by recrystallization from ethanol-acetone; m.p. 143.9–145.7°.

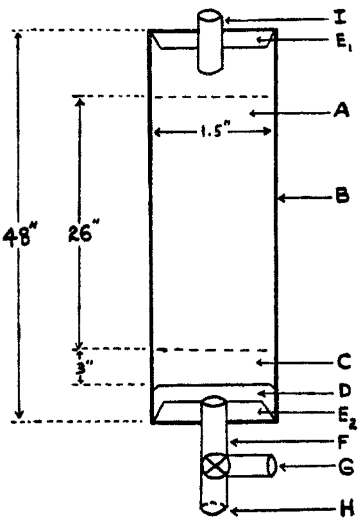

FIGURE 1. (A) Amberlite IR-4B, (B) Pyrex column, (C) quartz sand, (D) glass wool, (E_1, E_2) rubber stoppers, (F) T-tube with three-way stopcock, (G) backwash inlet, (H) effluent outlet, (I) backwash outlet.

Anal. Calc'd for $C_6H_{11}NO_2 \cdot HCl$: C, 43.51; H, 7.30; N, 8.46; Cl, 21.41.

Found: C, 43.56; H, 7.38; N, 8.68; Cl, 21.50.

Bis(dimethylaminomethyl)acetic acid (IV). This compound was prepared from the corresponding dihydrochloride by percolation over Amberlite IR-4B resin and by treatment with freshly-prepared silver oxide.

1. With Amberlite IR-4B resin. Optimum results were obtained when a Pyrex tube (Figure 1), packed with resin to a depth of 26 inches, was prepared for charging as follows. Dilute hydrochloric acid (1%) was passed through the column (downflow) until the effluent attained *p*H 2. Gas was evolved and the resin expanded considerably during this operation. The stopper, E_1, connected with a tube leading to a drain, was replaced and the resin classified by thorough backwashing (upflow) with distilled water. Sodium salts were then eluted with 40 to 50 l. of distilled water in a downflow operation. At no time during preparation of the resin was the liquid level allowed to fall below the resin level. The final effluent had *p*H 5.6–6.5.

A solution of 19.0 g. (0.08 mole) of bis(dimethylaminomethyl)acetic acid dihydrochloride in 1 l. of distilled water was fed slowly into the column in a downflow operation. After discarding the first 200 ml. of effluent, the free amino acid was eluted with 2 l. of water. The effluent was concentrated to a syrup *in vacuo* and after standing over phosphorus pentoxide, large crystals of the amino acid separated. These were purified by crystallization from a very small quantity of hot absolute ethanol; occasionally a small amount of ether was added to facilitate crystallization. There was obtained 10.2 g. (73%) of fine white crystals melting at 82–83°. The product is unstable and after several months storage at room temperature acquires a brown color.

2. With silver oxide. An aqueous suspension of a slight excess of freshly prepared silver oxide (5) was added to a solution of 41.7 g. (0.17 mole) of bis(dimethylaminomethyl)acetic acid dihydrochloride in 1 l. of water. The mixture was stirred thoroughly and then stored in the dark for 12 hours. The precipitated silver chloride was washed with 50 ml. of water and the basic filtrate and washings were concentrated to 800 ml. *in vacuo*. Following saturation with hydrogen sulfide, the solution was freed of silver sulfide by filtering through charcoal. The filtrate was further concentrated to 50 ml., clarified, and let stand over phosphorus pentoxide as described above. Crystallization from the minimum of hot absolute ethanol furnished 30.4 g. (88%) of bis(dimethylaminomethyl)acetic acid; m.p. 81–82°. A sample suitable for analysis was prepared by drying 11 hours at 55°; m.p. 82–83°.

Anal. Calc'd for $C_8H_{18}N_2O_2$: C, 55.15; H, 10.35; N, 16.10.

Found: C, 55.15; H, 10.33; N, 16.04.

α-Dimethylaminomethylacrylic acid (V). A solution of 60.0 g. (0.36 mole) of α-dimethylaminomethylacrylic acid hydrochloride in 900 ml. of distilled water was perfused through Amberlite IR-4B resin as described for IV. The light yellow effluent was decolorized with Norit and processed as previously described. The crude, hygroscopic product (40.4 g., 86%) was recrystallized from hot acetone to give material of m.p. 57–58°. After drying over phosphorus pentoxide, the melting point was 117.7–119.7°.

Anal. Calc'd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.85.

Found: C, 55.63; H, 8.42; N, 10.89.

2,2-Bis(dimethylaminomethyl)ethanol (III). Finely ground bis(dimethylaminomethyl)-acetic acid (10 g., 0.06 mole) was added gradually to a stirred suspension of 5.0 g. (0.13 mole) of lithium aluminum hydride in 500 ml. of absolute ether. A vigorous reaction accompanied each addition of the acid. The mixture was stirred for three hours and then sufficient wet ether was added to decompose the excess lithium aluminum hydride. About 20 ml. of water was added dropwise with stirring to decompose the alcoholate and the mixture was stirred another half-hour. The reaction mixture was filtered and the copious precipitate washed well with ether. The filtrate and washings were combined, dried over potassium hydroxide, and the ether removed. The light yellow oil remaining was fractionated *in vacuo*. The yield of material boiling at 61–66° at 8 mm., n_D^{20} 1.4469–1.4466, was 7 g. (76%).

Anal. Calc'd for $C_8H_{20}N_2O$: C, 59.95; H, 12.58; N, 17.48.

Found: C, 60.10; H, 12.35; N, 17.32.

2,2-Bis(dimethylaminomethyl)ethyl benzoate dihydrochloride (VI). A solution of 0.9 g. of III in 15 ml. of benzene was treated with 1.5 ml. of benzoyl chloride. After the addition, the mixture was heated under reflux for 15 minutes. Cooling in an ice-bath caused the separation of a crystalline benzoate which was washed with benzene and then ether. Crystallization from the minimum of hot absolute ethanol gave 1.2 g. (72%) of shimmering white plates of pure 2,2-bis(dimethylaminomethyl)ethyl benzoate dihydrochloride; m.p. 245.2–247.2° dec.

Anal. Calc'd for $C_{15}H_{26}N_2O_2 \cdot 2HCl$: C, 53.41; H, 7.77; N, 8.31.

Found: C, 53.19; H, 8.00; N, 8.41.

2,2-Bis(dimethylaminomethyl)ethanol dihydrochloride (VII). A solution of 0.5 g. of III in 5 ml. of dry ether was treated with anhydrous hydrogen chloride until precipitation was complete. The product separated in a sticky condition but quickly crystallized when scratched. The crystalline mass (0.9 g., 93%) was washed well with ether and recrystallized from the minimum of absolute alcohol to give pure VII of m.p. 211.3–212.6°.

Anal. Calc'd for $C_8H_{20}N_2O \cdot 2HCl$: C, 41.24; H, 9.51; N, 12.01.
Found: C, 41.52; H, 9.71; N, 12.27.

Reduction of α-dimethylaminomethylacrylic acid. Compound V (10 g.) was treated with a suspension of lithium aluminum hydride in ether according to the procedure described for the reduction of IV. Distillation of the product furnished three fractions of uncertain identity. The combined yield of fractions 1 and 2 amounted to 6 g.

FRACTION	B.P., °C./0.2 MM.	n_D^{20}
1	47–52	1.4457
2	53–56	1.4397
3	140–153	polymeric

Anal. (Fraction 1). Calc'd for $C_6H_{13}NO$: C, 62.57; H, 11.37; N, 12.17.
Calc'd for $C_6H_{15}NO$: C, 61.49; H, 12.90; N, 11.95.
Found: C, 59.96; H, 12.00; N, 12.82.

Treatment of fraction 2 with benzoyl chloride furnished an extremely hydroscopic product which was separated into material of m.p. 128–129° and a very small amount of m.p. 240°. The analytical results obtained on the 128°-material correspond roughly to those calculated for a dihydro-benzoate hydrochloride.

Anal. Calc'd for $C_{13}H_{17}NO_2 \cdot HCl$: C, 61.05; H, 7.09; N, 5.48.
Calc'd for $C_{13}H_{19}NO_2 \cdot HCl$: C, 60.57; H, 7.84; N, 5.44.
Found: C, 60.42; H, 7.66; N, 5.84.

Treatment of fraction 2 with dry hydrogen chloride gave a very hydroscopic oil which could not be induced to crystallize.

SUMMARY

The reaction of malonic acid with formalin and dimethylamine has been shown to give α-dimethylaminomethylacrylic acid (V) in addition to the reported bis(dimethylaminomethyl)acetic acid (IV). The free amino acids were prepared conveniently and in a high state of purity by percolating solutions of their hydrochlorides over Amberlite IR-4B resin.

Reduction of IV with lithium aluminum hydride furnished 2,2-bis(dimethylaminomethyl)ethanol (III) in 76% yield. Compound III is of possible interest as an intermediate in the synthesis of compounds possessing local anesthetic activity.

URBANA, ILLINOIS

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