[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, RESEARCH DIVISION, CIBA PHARMACEUTICAL PRODUCTS, INC.]

β-Dimethylaminoethylamine and Dimethylaminoacetonitrile

BY ROBERT A. TURNER

Only in recent years has β-dimethylaminoethylamine been mentioned in the chemical literature. Amundsen and Krantz[1] prepared the diamine from β-dimethylaminoethyl bromide hydrobromide and alcoholic ammonia. The yield was very small, and no physical constants for the diamine were recorded. Later the diamine was obtained by the reduction of dimethylaminoacetonitrile (dimethylglycinonitrile) with sodium and absolute alcohol.[2] Although no yield was stated, the boiling point of the anhydrous diamine was found to be 107°, and many derivatives were prepared.

In connection with other investigations being carried on in this laboratory a large quantity of β-dimethylaminoethylamine was required. It was prepared by hydrogenation of dimethylaminoacetonitrile over Raney nickel. Although this nitrile has been known for some time,[3,4,5,6] the methods of preparation [3,4] have been unsatisfactory. Nowhere has any yield been reported, and the only physical constant known is the boiling point (137°).[5,6] The nitrile has been prepared in yields of 73 to 83% of the theoretical by a method which differs from the methods of previous investigators. An alkaline solution of hydroxymethyldimethylamine was allowed to react with hydrocyanic acid at room temperature. The nitrile was isolated from the aqueous medium by extraction with benzene or chloroform. It could not be distilled directly, for it was miscible with water and formed an azeotrope with water whose composition was approximately 50% of each component.

After the extractant was distilled, the nitrile distilled at 137°. Finally, a residue remained which sublimed easily into the distilling column, and which was identified as dimethylaminoacetamide, a new compound.

The nitrile, purified by contact with Raney nickel for several days and by subsequent redistillation, was hydrogenated readily at 60 to 80° under high pressure. Fractionation of the filtered hydrogenation product gave β-dimethylaminoethylamine (47%), followed by a considerable quantity (20%) of another amine which proved to be the secondary amine that would be expected to accompany the primary amine as a hydrogenation product, *viz.*, bis-(β-dimethylaminoethyl)-amine.

Experimental

Dimethylaminoacetonitrile.—Into a three-necked flask set in a bath with cold water in circulation was introduced 1320 g. (7.34 moles) of 25% aqueous dimethylamine solution. To the vigorously stirred solution was added 660 g. (8.14 moles) of 37% aqueous formaldehyde solution at such a rate that the temperature did not exceed 25°. Under the same temperature control 396 g. (7.75 moles) of 96% sodium cyanide was added, followed after one hour by 610 cc. (7.10 moles) of concentrated hydrochloric acid. After the solution had stood fifteen hours, it was extracted continuously with either chloroform or thiophene-free benzene. The non-aqueous solution was dried and distilled through a Vigreux column. After distillation of the solvent the fraction which distilled at 130–139° was retained and redistilled. The yield of nitrile which distilled at 134–137° (uncor.) was 450 to 515 g. (73–83%). A pure sample of dimethylaminoacetonitrile gave these constants: d^{25} 0.8634; n^{25}_{D} 1.4095; *MR* 24.35 (calcd.), 24.11 (obs.).

When all of the nitrile had distilled, 10–20 g. of a brown residue remained which sublimed easily. After a few recrystallizations from benzene–petroleum ether the melting point became constant at 94–95° and was not depressed when the substance was mixed with dimethylaminoacetamide, described below.

The **partition coefficients** of the nitrile in benzene–water and chloroform–water mixtures were determined by titration of the aqueous phase with hydrochloric acid, and were found to be 1.15 and 4.96, respectively. (The values for the coefficients express the ratio of the solubility in the organic phase to that in the aqueous phase.)

The **azeotrope** which the nitrile forms with water was studied by distilling mixtures of these substances and titrating the distillates with hydrochloric acid. A solution of 15 cc. of the nitrile in 25 cc. of water was distilled through a column. Almost all of the solution distilled at 96.6°. When a solution of 25 cc. of the nitrile in 15 cc. of water was heated, about three-fourths distilled at 96.6°, and then the temperature rose sharply to 136.5°. In each case the composition of the distillate which had passed over at 96.6° was 46.6% nitrile.

Dimethylaminoacetonitrile hydrochloride, prepared from concentrated hydrochloric acid, crystallized from solution as needles upon the addition of acetone; m. p. 152–152.5°.

Anal. Calcd. for $C_4H_9N_2Cl$: HCl, 30.24. Found: HCl, 30.15.

The **picrate,** recrystallized from acetone–ethanol, melted at 171.5–172.5°.[7]

Anal. Calcd. for $C_{10}H_{11}O_7N_5$: N, 22.36. Found: N, 22.64.

Dimethylaminoacetamide.—Three and four-tenths grams (0.04 mole) of dimethylaminoacetonitrile, cooled to $-15°$, was mixed with 15 cc. of equally cold, concentrated sulfuric acid. After the solution had stood at room temperature for eighty-five hours, it was poured upon ice and made alkaline by about 45 cc. of concentrated ammonium hydroxide. The solution was saturated with salt and extracted copiously with chloroform. The combined extracts, dried over magnesium sulfate, were evaporated to dryness. The residue weighed 3.10 g. (76%) and had a m. p. of 95.0–95.8°, unchanged by further purification.

Anal. Calcd. for $C_4H_{10}ON_2$: C, 47.03; H, 9.87; N, 27.43. Found: C, 46.81; H, 9.73; N, 27.31.

β-Dimethylaminoethylamine.—Into a Parr hydrogenation bomb were introduced 126 g. (1.50 moles) of dimethylaminoacetonitrile[8] and 30 g. of Raney nickel. The theoreti-

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[1] Amundsen and Krantz, THIS JOURNAL, **63**, 305 (1941).

[2] Baltzly, Buck and Ide, *ibid.*, **64**, 2232 (1942).

[3] Eschweiler, *Ann.*, **279**, 44 (1884).

[4] Henry, *Rec. trav. chim.*, **24**, 173 (1905).

[5] Von Braun, *Ber.*, **40**, 3936 (1907).

[6] Luten, *J. Org. Chem.*, **3**, 588 (1939).

[7] The melting point given by Thomson and Stevens, *J. Chem. Soc.*, 2609 (1932), is 168–169°.

[8] The sample of nitrile for this experiment was isolated by extraction with thiophene-free benzene (see above). When chloroform was used as extractant, the nitrile had to be distilled from Raney nickel before hydrogenation, else the absorption of hydrogen was slow or failed to take place.

cal quantity of hydrogen at an average pressure of 1000 lb. per sq. in. was absorbed in three hours at 78°. After filtration of the catalyst the brown reaction product was fractionally distilled. The first fraction, dimethylaminoethylamine, distilled at 105–108° and weighed 62 g. (47%). It fumed on exposure to air.

The **phenylthiourea** melted at 82.6–83.0°; reported,[3] 83.0–83.5°.

bis-(β-Dimethylaminoethyl)-amine.—After the distillation of dimethylaminoethylamine the second fraction, which distilled at 198° as a light yellow, hygroscopic liquid, weighed 24 g. (20%). After drying over potassium hydroxide and redistilling, the product was clear and colorless; d^{25} 0.8283; n^{25}_D 1.4406; *MR* 50.74 (calcd.), 50.62 (obs.).

Anal. Calcd. for $C_8H_{21}N_3$: C, 60.32; H, 13.29; N, 26.38. Found: C, 59.60; H, 13.52; N, 26.66.

The **phenylthiourea**, prepared with phenyl isothiocyanate in benzene solution, melted at 113.6–114.0°.

Anal. Calcd. for $C_{15}H_{26}SN_4$: C, 61.18; H, 8.90. Found: C, 61.15; H, 8.87.

Summary

Dimethylaminoacetonitrile has been synthesized from dimethylamine solution in good yield. By catalytic hydrogenation of this nitrile dimethylaminoethylamine has been prepared.

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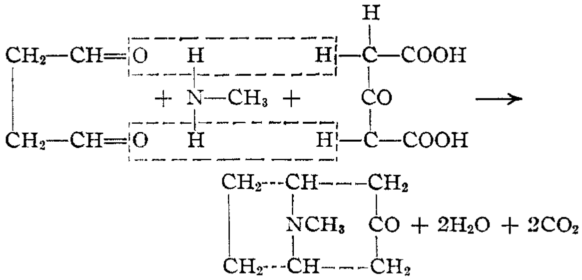
[Contribution from the Research Laboratories, School of Pharmacy, University of Maryland]

Tropanone and its Homologs

By LeRoy C. Keagle[1] and Walter H. Hartung

Robinson's synthesis of tropanone[1a] from acetone, methylamine and succinaldehyde, characterized by Willstätter as "von bewundernswerter Eleganz,"[2] stimulated speculation on the possible mechanism of synthesis of atropine and other products in plant tissue. The discussion, well summarized by Schopf,[3] raises among others the question whether certain natural intermediates, which may be expected to occur in living tissue, react spontaneously to give the precursors of natural products. If so, then those same intermediates brought together *in vitro*, under biological conditions of temperature, dilution and *p*H, should react to form those same precursors. These, by further biochemical processes in the plant, *e. g.*, by hydrogenation, decarboxylation, esterification, etc., are converted into the natural products.

Robinson's synthesis of tropanone does not meet biological conditions, for his reaction proceeded only in strongly alkaline solution. However, if, instead of acetone, acetonedicarboxylic acid is employed, the formation of tropanone proceeds smoothly according to the equation



The yields are highly satisfactory at high dilution and in neutral or nearly neutral solution.[3,4] Reduction of this ketone in the plant with subsequent esterification by tropic acid leads to atropine or, if the acid is optically active, to hyoscyamine.

Analogous syntheses have been postulated and demonstrated as possible and probable for other alkaloids, including those derived from quinoline, isoquinoline, pyridine, etc. (*cf.* ref. 3).

Such hypotheses are intriguing. Not only do the experimental results offered in their favor merit confirmation, but further questions naturally follow: First, may these postulated reactions be adapted practically for the synthetic preparation of natural products? Second, may the reaction be modified, *e. g.*, by employing other intermediates, for the synthesis of substances unknown in nature but with modified physiological properties? The results reported here give partial affirmative answers to both questions, with respect to tropanone and its homologs.

Not only have the experiments of Schöpf and Lehmann,[4] in their synthesis of tropanone under biological conditions, been substantially confirmed, but also the conditions of the condensation reaction may be appreciably modified to make it more practicable in the laboratory. The reaction also has been extended by substituting other primary amines for methylamine to obtain, in an analogous manner, higher homologs, with the larger alkyl groups attached to the nitrogen atom of the tropanone skeleton. Since tropanone may be easily reduced to tropanol, no difficulty is anticipated in preparing the N-homologs.

Of the necessary intermediates succinaldehyde is the most difficult to obtain. Saytzeff[5] reduced succinyl chloride with sodium amalgam, but his product was later shown to be γ-butyrolactone.[6] The dialdehyde was prepared in small yields

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[1] H. A. B. Dunning Fellow 1940–1943. Present address: Rutgers University, College of Pharmacy, Newark, N. J.

[1a] Robinson, *J. Chem. Soc.*, **111**, 762, 876 (1917).

[2] Winterstein–Trier, "Die Alkaloide," Gebrüder Borntraeger, Berlin, 1931, p. 295.

[3] Schöpf, *Angew. Chem.*, **50**, 779, 797 (1937).

[4] Schöpf and Lehmann, *Ann.*, **518**, 5 (1935).

[5] Saytzeff, *Ber.*, **6**, 1255 (1873); **13**, 1061 (1880).

[6] Fittig, *Ann.*, **208**, 112 (1881).