[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & COMPANY]

The Synthesis of 2,2-Dimethyl-3-(4-morpholinyl)-1-propanol and Analogous Amino Alcohols by the Mannich and Crossed Cannizzaro Reactions[1]

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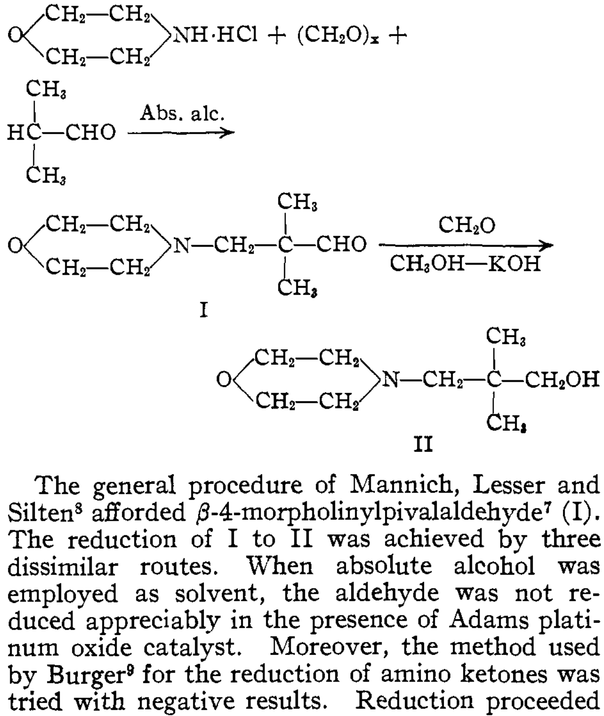
Certain esters of 3-diethylamino-2,2-dimethyl-1-propanol exhibit considerable physiological activity. Larocaine,[3] the *p*-aminobenzoate hydrochloride, has been introduced as a local anesthetic, whereas Synthropan,[4] the tropate phosphate, apparently has been well received in medicine as an antispasmodic. Several β,β-dimethyl-γ-4-morpholinylpropyl esters of substituted acetic acids[5] have been found to be antispasmodics of relatively low toxicity.[6]

In view of the recent disclosure by Wenner[7] that alcohols of the type $R_2NCH_2C(CH_3)_2CH_2OH$ can be prepared satisfactorily by hydrogenation of the corresponding Mannich bases, $R_2NCH_2C(CH_3)_2CHO$, under acidic conditions in the presence of Raney nickel catalyst, it appears of interest to report the experimental details of the Mannich–crossed Cannizzaro process developed for the preparation of 2,2-dimethyl-3-(4-morpholinyl)-1-propanol[5] and analogous amino alcohols.



The general procedure of Mannich, Lesser and Silten[8] afforded β-4-morpholinylpivalaldehyde[7] (I). The reduction of I to II was achieved by three dissimilar routes. When absolute alcohol was employed as solvent, the aldehyde was not reduced appreciably in the presence of Adams platinum oxide catalyst. Moreover, the method used by Burger[9] for the reduction of amino ketones was tried with negative results. Reduction proceeded rapidly and completely, however, with Adams catalyst in glacial acetic acid solution. 3-Diethylamino-2,2-dimethyl-1-propanol has been prepared by reduction of the corresponding aldehyde with 2% sodium amalgam in acetic acid solution,[8] but experimental details and the yields were not reported. A 52% yield of II was obtained by the application of this method.

Davidson and Bogert[10] and Davidson and Weiss[11] have shown that the action of aqueous methanolic alkali on a mixture of aromatic aldehyde and formaldehyde results in the almost complete reduction of the aromatic aldehyde to the corresponding alcohol. Apel and Tollens[12] have reported that isobutyraldehyde is converted into 2,2-dimethyl-1,3-propanediol with an excess of formaldehyde in the presence of lime. An extension of the crossed Cannizzaro reaction to I produced an 82.6% yield of pure II.

Simplification of the synthesis has been accomplished by combining the Mannich and crossed Cannizzaro reactions to form a practical unit process. Satisfactory yields of II are obtained without isolation of the aldehyde intermediate (I) when formalin, methanol and potassium hydroxide are added directly to the Mannich reaction mixture.

Since a variety of other secondary amine hydrochlorides can be used in place of morpholine hydrochloride, the process constitutes a convenient and economical method for the preparation of 3-dialkylamino-2,2-dimethyl-1-propanols and their heterocyclic analogs.

Experimental[13]

β-4-Morpholinylpivalaldehyde.—By following the exact procedure described for the preparation of the diethylamino analog,[8] 740 g. (6 moles) of morpholine hydrochloride[14] provided 889 g. (an 85% yield) of product, distilling as a colorless oil, b.p. 89–90° at 3 mm.: n^{20}_D 1.4597. *Anal.* Calcd. for $C_9H_{17}NO_2$: N, 8.18. Found: N, 8.06.

The following derivatives were prepared by conventional procedures:

β-4-Morpholinylpivalaldehyde Hydrochloride: dec. 182.5–183.5° (from absolute alcohol–ether); lit.[7] 166°, obtained from material for which no analysis is reported. *Anal.* Calcd. for $C_9H_{17}NO_2 \cdot HCl$: N, 6.74. Found: N, 6.94.

β-4-Morpholinylpivalaldoxime hydrochloride: dec. 175.5° (needles from absolute alcohol–ether). *Anal.* Calcd. for $C_9H_{18}N_2O_2 \cdot HCl$: N, 12.58. Found: N, 12.41.

β-4-Morpholinylpivalaldehyde semicarbazone: m.p. 172.5–173.5° (colorless needles from water). *Anal.* Calcd. for $C_{10}H_{20}N_4O_2$: N, 24.55. Found: N, 24.20.

2,2-Dimethyl-3-(4-morpholinyl)-1-propanol.[7] **A. By Catalytic Reduction.**—A solution of 34.2 g. (0.2 mole) of β-4-morpholinylpivalaldehyde in 100 ml. of glacial acetic acid was shaken with 0.2 g. of Adams catalyst under a hydrogen gage pressure of 3 atmospheres. In 55 minutes the theoretical quantity of hydrogen was taken up. Four similar runs were made. Catalyst was removed from the

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[3] Mannich, U. S. Patent 1,889,678 (1932).

[4] Guggenheim, U. S. Patent 1,932,341 (1933); Blankart, U. S. Patent 1,987,546 (1935).

[5] Cheney and Bywater, THIS JOURNAL, **64**, 970 (1942).

[6] Rowe, *J. Am. Pharm. Assoc.*, Scientific Ed., **31**, 57 (1942); Chase, Lehman and Yonkman, *J. Pharmacol.*, **81**, 174 (1944).

[7] Wenner, *J. Org. Chem.*, **15**, 301 (1950); U. S. Patent 2,477,842 (1949).

[8] Mannich, Lesser and Silten, *Ber.*, **65**, 378 (1932).

[9] Burger, THIS JOURNAL, **60**, 1536 (1938).

[10] Davidson and Bogert, *ibid.*, **57**, 905 (1935).

[11] Davidson and Weiss, *Org. Syntheses*, **18**, 79 (1938).

[12] Apel and Tollens, *Ber.*, **27**, 1088 (1894); *Ann.*, **289**, 38 (1896).

[13] All melting points are corrected.

[14] Knorr, *Ann.*, **301**, 4 (1898).

combined suspensions by filtration through a hardened filter paper. After being cooled in ice the filtrate was slowly treated with a solution of 550 g. of sodium hydroxide in 550 g. of water. The resulting mass was extracted with 1 liter of ether in two portions, then diluted with 800 ml. of water and extracted with 1 liter of ether in four portions. Combined extracts were washed with water and dried over anhydrous potassium carbonate. Distillation from a modified Claisen flask gave 159.7 g. (92% yield) of colorless oil, b.p. 96-97° at 2 mm.; $n^{20}D$ 1.4648. *Anal.* Calcd. for $C_9H_{19}NO_2$: N, 8.09. Found: N, 8.11.

B. **By Sodium Amalgam Reduction.**—To a well-stirred solution of 51.5 g. (0.3 mole) of β-4-morpholinylpivalaldehyde in 200 ml. of glacial acetic acid was added portionwise the sodium amalgam prepared from 2 kg. of mercury and 40 g. of sodium. Before addition was complete, 100 ml. of dioxane and 100 ml. of glacial acetic acid were introduced to thin down the reaction mixture. After all of the sodium amalgam had been added the thick mass was stirred for half an hour and then diluted with 200 ml. of water to dissolve the sodium acetate. The reaction mixture was cooled in ice, rendered strongly alkaline with a solution of 400 g. of potassium hydroxide in 400 ml. of water and extracted with 1 liter of ether in four portions. The ethereal extracts were combined, washed with water and dried over anhydrous sodium sulfate. Distillation gave 27.4 g. (52.7% yield) of colorless product, b.p. 96-97° at 2 mm.; $n^{20}D$ 1.4647.

C. **By the Crossed Cannizzaro Reaction.**[11]—Three hundred and thirty-five grams of potassium hydroxide (85% KOH) (5.1 moles) and 500 ml. of methanol were stirred in a 2-liter flask until nearly all of the alkali had dissolved. The flask was cooled in a water-bath until the internal temperature had dropped to 60°, whereupon a mixture of 343 g. (2 moles) of β-4-morpholinylpivalaldehyde, 200 ml. (*ca.* 2.6 moles) of formalin and 200 ml. of methanol was added at such a rate that the internal temperature did not exceed 70°. The stirred mixture was heated at 65-70° for four hours, during which time a brown color developed. Finally, the mixture was refluxed at 80-85° for one hour. Methanol was distilled from the stirred product (wax-bath) until the internal temperature reached 104°. Upon cooling in an ice-bath, 250 ml. of ether and 200 ml. of water were added to the well-stirred mixture. Subsequent to the separation of the ether layer the aqueous phase was extracted with three 200-ml. portions of ether. Combined ether extracts were washed with a saturated solution prepared from 100 g. of sodium bisulfite and dried over anhydrous potassium carbonate. Following removal of the ether, distillation from a modified Claisen flask yielded 286.2 g. (82.6%) of colorless 2,2-dimethyl-3-(4-morpholinyl)-1-propanol, b.p. 101-102° at 2.5 mm.; $n^{20}D$ 1.4648. Only partial conversion to the alcohol was obtained when one mole of β-4-morpholinylpivalaldehyde was subjected to the crossed Cannizzaro reaction in accordance with the milder procedure of Davidson and Bogert[10] for the preparation of aromatic alcohols.

D. **By the Mannich-Crossed Cannizzaro Reactions.**—Into a two-liter flask equipped with a reflux condenser, dropping funnel, thermometer (reaching nearly to bottom of flask) and efficient stirrer were placed 123.6 g. (1 mole) of morpholine hydrochloride, 86.5 g. (1.1 moles) of isobutyraldehyde (du Pont), 30 g. (1 equivalent) of paraformaldehyde and 90 ml. of absolute alcohol. After the suspension had been refluxed and stirred (water-bath) for two hours another 30 g. of paraformaldehyde was added and refluxing and stirring were continued for a further four hours. The oily reaction mixture was cooled in an ice-salt-bath and treated with a solution of 66 g. (1 mole) of 85% potassium hydroxide in 80 ml. of water (temperature rose to 8-10°). Then 100 ml. of formalin was added. Finally a warm milky suspension of 300 g. (4.6 moles) of 85% potassium hydroxide in 530 ml. of methanol was added slow enough to maintain the temperature below 60°. The stirred mixture was heated at an internal temperature of 65-70° for four hours, during which time a brown coloration developed, and then refluxed (80-85°) for one hour. Solvent was distilled with the aid of a wax-bath until the internal temperature reached 103°. Upon cooling in an ice-bath the stirred mixture was treated with 200 ml. of ether and 400 ml. of water. The ether layer was separated, and the dark brown aqueous layer was extracted with three 200-ml. portions of ether. Combined ether extracts were washed with a saturated solution of sodium bisulfite freshly prepared from 100 g. of the salt. Desiccation over anhydrous potassium carbonate followed by distillation from a modified Claisen flask yielded 110.6 g. (63.7%) of 2,2-dimethyl-3-(4-morpholinyl)-1-propanol, b.p. 101-102.5° at 2.5 mm.; $n^{20}D$ 1.4639.

β,β-Dimethyl-γ-4-morpholinylpropyl *p*-Nitrobenzoate and Its Hydrochloride.—Samples of the alcohols secured by the four different procedures all yielded the identical *p*-nitrobenzoate hydrochloride when treated with a 20% excess of *p*-nitrobenzoyl chloride in chloroform solution. After standing overnight at room temperature each reaction mixture was refluxed for two hours, cooled and filtered. Crystallization from methanol yielded ivory crystals, m.p. 204.5-205.5°; lit.[7] 192-194°. *Anal.* Calcd. for $C_{16}H_{22}N_2O_5\cdot HCl$: N, 7.81. Found: N, 7.70.

The addition of ammonium hydroxide to a warm aqueous solution of the hydrochloride precipitated the free ***p*-nitrobenzoate**; lemon yellow prisms, m.p. 97-98°, crystallized from methanol. *Anal.* Calcd. for $C_{16}H_{22}N_2O_5$: N, 8.80. Found: N, 8.69.

β,β-Dimethyl-γ-4-morpholinylpropyl *p*-Aminobenzoate Hydrochloride.—Catalytic reduction of an alcoholic solution of the corresponding nitrobenzoate hydrochloride by means of palladium-charcoal afforded pale pink crystals, m.p. 196.5-197.5°. *Anal.* Calcd. for $C_{16}H_{24}N_2O_3\cdot HCl$: N, 8.52. Found: N, 8.54.

β,β-Dimethyl-γ-4-morpholinylpropyl *p*-ethoxybenzoate hydrochloride, prepared by the procedure described for the *p*-nitrobenzoate salt, melted at 170-171° after recrystallization from alcohol. *Anal.* Calcd. for $C_{18}H_{26}NO_4\cdot HCl$: N, 3.91. Found: N, 3.98.

3-Diethylamino-2,2-dimethyl-1-propanol.[8]—One mole (109.6 g.) of diethylamine hydrochloride (Eastman Kodak Co.) was converted into the above alcohol by a combination of the Mannich and crossed Cannizzaro reactions as described in procedure D for the preparation of the morpholine analog. Fractionation gave 91.8 g. (57.6% yield) of colorless product, b.p. 100-103° at 24 mm.; $n^{20}D$ 1.4409. *Anal.* Calcd. for $C_9H_{20}NO$: N, 8.85. Found: N, 8.81.

The *p*-nitrobenzoate hydrochloride melted at 159-160°, in agreement with the literature.[7,8]

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Summary

The crossed Cannizzaro reaction has been found to constitute an excellent method for the reduction of α,α-disubstituted amino aldehydes.

A unit process involving a combination of the Mannich and crossed Cannizzaro reactions has been described which affords a direct and practical synthesis for a variety of 2,2-disubstituted amino alcohols analogous in constitution to 2,2-dimethyl-3-(4-morpholinyl)-1-propanol.

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