[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MOUNT HOLYOKE COLLEGE]

Synthesis of 1-Diethylamino-5-aminohexane[1]

BY ELEANOR P. ANDERSON, JEAN V. CRAWFORD AND MARY L. SHERRILL

The synthesis of 1-diethylamino-5-aminohexane (X) was undertaken to make available a homolog of 1-diethylamino-4-aminopentane (Noval diamine) which by condensation with aromatic nuclei might produce compounds with antimalarial activity.

The diamine (X) was obtained by the reduction[2] of the oxime (IX) of 1-diethylaminohexan-2-one (VIII) prepared by the action of diethylamine on 6-bromohexan-2-one (V). The ketone (V) was synthesized from trimethylene glycol by two series of reactions (A and B), the second method proving to be the more satisfactory. In method A the intermediate compounds were 3-ethoxypropan-1-ol (I),[3,4] 1-bromo-3-ethoxypropane (II),[5] ethyl 2-aceto-5-ethoxyvalerate (III) and 6-ethoxyhexan-2-one (IV). In method B, the intermediates were 1,3-dibromopropane (VI),[6] 2-methyl-3-carbethoxy-5,6-dihydropyran (VII)[7,8] which by hydrolysis with hydrobromic acid gave the bromo ketone (V) rather than the acetobutyl alcohol.[7,8,9]

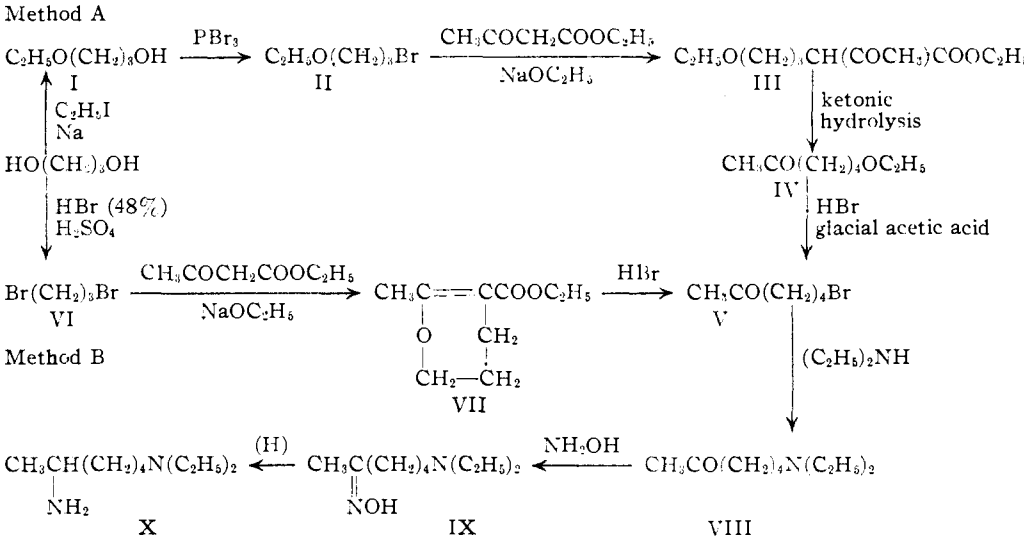
Experimental[10,11]

3-Ethoxypropan-1-ol (I).—A 65% yield (124 g.) of 3-ethoxypropan-1-ol (b. p. 162–163° at 760 mm., 69–70° at 22 mm., 59–60° at 12 mm.) was obtained from 1.8 moles (42 g.) of sodium, 2 moles (318 g.) of ethyl iodide and 4 moles (300 g.) of trimethylene glycol.

1-Bromo-3-ethoxypropane (II).—By treating 136 g. (1.3 moles) of I with 115 g. (0.43 mole) of phosphorus tribromide,[5] a yield of 162 g. (75%) of ethoxypropyl bromide (II) (b. p. 151–152° at 760 mm., 63–65° at 33 mm., 46–48° at 13 mm.) was obtained.

Ethyl 2-Aceto-5-ethoxyvalerate (III).—This compound was prepared by condensing 1 mole of sodio-acetoacetic ester[12] with 1 mole (167 g.) of ethoxypropyl bromide. A yield of 153 g. (70% of crude ester, distilling at 145–158° at 25–27 mm., was obtained. Redistillation of this gave 110 g. (51%) of the ester (III), b. p. 139–141° at 12 mm.

6-Ethoxyhexan-2-one (IV).—Hydrolysis and decarboxylation[13] of 108 g. (0.50 mole) of the ester (III) gave 43 g. (60% yield) of the ethoxyhexanone (IV), b. p. 90–92° at 13 mm. When the crude ester (III) was used 50 g. (35%) of (IV) was obtained from 1 mole of the ethoxypropyl bromide (II). The **2,4-dinitrophenylhydrazone** of the above ketone crystallized from ethanol in deep orange needles, m. p. 63.3–63.8°.



Anal. Calcd. for $C_{14}H_{30}O_5N_4$: C, 51.85; H, 6.22. Found: C, 52.11; H, 6.17.

2-Methyl-3-carbethoxy-5,6-dihydropyran. (VII).—In the preparation of this compound, the proportions of reactants used by Perkin[7] (2 moles of sodium and of acetoacetic ester to 1 mole of trimethylene bromide)[6] and by Lipp[8] (1 mole of each reactant) have been tried. In the first case the yield of the pyran (VII) was 65% and a large excess of acetoacetic ester was recovered; in the second

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Mount Holyoke College.

(2) Suter and Moffett, THIS JOURNAL, **56**, 487 (1934); Lycan, Puntambeker and Marvel, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 318.

(3) Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 367 (1939).

(4) Noyes, *Am. Chem. J.*, **19**, 766 (1897).

(5) Harrison and Diehl, "Organic Syntheses," Vol. 23, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 32.

(6) Kamm and Marvel, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 30.

(7) Perkin, *Ber.*, **16**, 208, 1787 (1883); *J. Chem. Soc.*, **51**, 702 (1887); Colman and Perkin, *ibid.*, **55**, 354 (1889).

(8) Lipp, *Ber.*, **18**, 3277 (1885); *Ann.*, **289**, 181 (1896).

(9) Buchman and Richardson, THIS JOURNAL, **67**, 398 (1945).

(10) All melting points are corrected.

(11) All analyses, unless otherwise indicated, were made by Lois May, Microanalytical Laboratory, Columbia University.

(12) Marvel and Hager, "Organic Syntheses," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 248.

(13) Johnson and Hager, *ibid.*, p. 351.

case the yield was 35%, with a large recovery of trimethylene bromide.

These results indicated that an excess of sodium ethoxide was necessary for the cyclization to the pyran and better results have been obtained from 2 moles of sodium (46 g.), 1 mole (130 g.) of acetoacetic ester and 1 mole (202 g.) of trimethylene bromide. The usual procedure[12] was modified by a longer period of heating (twenty-two hours at 80–85°) and by a somewhat different treatment of the reaction product. When the alcohol solution and washings (decanted from the sodium bromide) were concentrated at reduced pressure, an additional quantity of sodium bromide precipitated. This was filtered, washed with ether and the ether added to the filtrate. After the removal of the ether an 80% yield of the pyran (136 g., distilling at 110–115° at 15–16 mm.) was obtained from 1 mole of (VI).

This pyran, without further purification, gave a 70% yield of the bromohexanone (V), or a 56% yield based on (VI), as compared with those obtained with the proportions of reactants of previous investigators,[7,8] 32% in the first case, 22% in the second.

For determinations of physical constants and for analysis the pyran was redistilled: b. p. 104–105° at 10 mm., 120–121° at 27 mm., 216.6° at 760 mm. (Cottrell apparatus); $n^{20}D$ 1.4780; d^{20}_4, 1.0564. The reported values[7] are 225–226° at 760 mm.; $n^{24.5}D$ 1.4772; d^{20}_{20} 1.0647.

Anal. Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.65, 63.77; H, 8.50, 8.32.[14]

6-Bromohexan-2-one (IV).—(a) Thirty-six grams (0.025 mole) of ethoxyhexanone (IV) treated with hydrogen bromide in glacial acetic acid[3] gave 26 g. (58%) of the bromo ketone (V), b. p. 118–119° at 28 mm. (b) The pyran (VII) was hydrolyzed, decarboxylated and transformed into the bromohexanone (V) in one step. Hydrobromic acid (450 g., 48%) was added with stirring to 150 g. (0.88 mole) of the pyran and almost immediately carbon dioxide was evolved. The solution was stirred for four hours at room temperature and for a three-hour period during which it was refluxed. When the cooled solution was poured into 800 g. of ice and water, a dark heavy oil appeared. This was separated from the acid–water layer and the latter extracted with chloroform. The chloroform extracts were added to the oil and the solution, freed from acid with saturated sodium bicarbonate solution, was dried. After the chloroform was removed the bromo-ketone (V) was obtained in 70% yield (110 g.), b. p. 104–105° at 15 mm., 112–114° at 22 mm., 118–119° at 28 mm., $n^{20}D$ 1.4713. This compound (b. p. 214–215° at 720 mm. with dec.) was prepared previously from acetobutyl alcohol[7,8] but no yields were given.

The **2,4-dinitrophenylhydrazone** prepared from the bromo-ketone (a) proved to be identical with that prepared from (b). It crystallized from ethanol in pale orange needles, m. p. 80.5–81.5°.

Anal. Calcd. for $C_{12}H_{15}O_4N_4Br$: C, 40.12; H, 4.21. Found: C, 41.32; H, 4.40.

Semicarbazone.—This derivative crystallized from ethanol–water in white needles, m. p. 104–105°, but decomposed on standing so no analysis was made.

6-Diethylaminohexan-2-one (VIII).—A solution of 60 g. (0.33 mole) of the bromohexanone (V) in 75 ml., of benzene was added dropwise to diethylamine (48 g., 0.66 mole) in 75 ml., of benzene. The heat of reaction was sufficient to reflux the solution for some time. After twelve hours the benzene solution was decanted from the diethylamine hydrobromide, and the latter was washed with benzene. The benzene solution, in an equal volume of water, was cooled in ice and neutralized with dilute sulfuric acid. The benzene and any unreacted bromo-ketone were removed by ether extraction. The water layer, well cooled, was made strongly alkaline with solid potassium hydroxide, extracted with ether and the ether solution dried with sodium sulfate. After the ether and any excess diethylamine were removed, the diethylaminohexanone (VIII) was distilled at diminished pressure. The yield was 26 g. (86%), b. p. 112–114° at 19–20 mm.

Picrate.—This derivative crystallized from ethanol in yellow needles, m. p. 76–76.5°.

Anal. Calcd. for $C_{16}H_{24}O_8N_2$: C, 47.98; H, 6.04. Found: C, 47.57; H, 5.95.

The **2,4-dinitrophenylhydrazone** of the above ketone crystallized from ethanol as the hydrochloride in orange needles, m. p. 188–189°.

Anal. Calcd. for $C_{16}H_{25}O_4N_5Cl$: C, 49.55; H, 6.76. Found: C, 50.04; H, 6.99.

6-Diethylaminohexan-2-one Oxime (IX).—Hydroxylamine hydrochloride (6.3 g., 0.1 mole) was dissolved in 275 ml., of hot absolute ethanol and the solution cooled to room temperature. To this was added a solution of the amino hexanone (VIII) (17.1 g., 0.1 mole in 25 ml. of ethanol). If the solution was basic hydroxylamine hydrochloride was added in small portions until the solution was neutral. The mixture was left at least twelve hours, then the alcohol was removed at diminished pressure and the hydrochloride of (IX) separated in rosets of fine needles. The yield was the theoretical but the salt (app. m. p. 87–89°) was very hygroscopic so was kept in alcohol solution until just prior to transformation into the oxime.

The salt dissolved in water (0.1 mole in 40 ml.) was treated with 30% potassium hydroxide solution as long as an oil formed. The latter was separated, ether extracts of the water layer added to the oil, and the ether solution dried. After removal of the ether, 15 g. (90%) of the diethylaminohexanone oxime (IX), a thick viscous oil, b. p. 163–164° at 18 mm., was obtained.

Anal. Calcd. for $C_{10}H_{22}ON_2$: C, 64.46; H, 11.91; neut. equiv., 186.3. Found: C, 65.18; H, 12.56; neut. equiv., 185.6, 186.9, 185.5.

Picrate.—This derivative crystallized from ethanol as a lemon yellow powder, m. p. 104–105°.

Anal. Calcd. for $C_{16}H_{25}O_8N_5$: C, 46.26; H, 6.07. Found: C, 47.00; H, 6.37.

1-Diethylamino-5-aminohexane (X).—The oxime (IX) (37.2 g., 0.2 mole, dissolved in 450 ml. of anhydrous butanol-1) was reduced with 32.2 g. (1.4 mole) of sodium.[2] The distillate was collected in excess hydrochloric acid. After the removal of the water–butanol at diminished pressure the hydrochloride of the diamine was treated with saturated sodium hydroxide solution until all the oil had separated. This was dried repeatedly with sodium hydroxide pellets and then distilled. The yield of 1-diethylamino-5-aminohexane (b. p. 105–106° at 16.5 mm.) was 24 g. (65%). The compound is very hygroscopic.

Anal. Calcd. for $C_{10}H_{24}N_2$: C, 69.71; H, 14.05; neut. equiv., 86.2. Found: C, 70.19; H, 14.68; neut. equiv., 85.23, 86.72, 86.12.

Picrate.—This derivative crystallized from absolute ethanol in powdery orange crystals, m. p. 91–92°.

Anal. Calcd. for $C_{16}H_{27}O_7N_5$: C, 47.87; H, 6.78. Found: C, 48.20; H, 7.13.

Dithiocarbamate.—This compound was prepared by the method of Jones.[15] Recrystallized from water–acetone, it formed white needles, m. p. 128–129° (dec.).

The 1-diethylamino-5-aminohexane was sent to another investigator[16] for attachment to an aromatic nucleus.

Summary

Ethyl 2-aceto-5-ethoxyvalerate (III) and 6-ethoxyhexan-2-one (IV) have been prepared by a series of reactions from trimethylene glycol. By a different series of reactions, 2-methyl-3-carbethoxy-5,6-dihydropyran (VII) has also been made. From both (IV) and (VII) 6-bromohexan-2-one (V) has been obtained, transformed into 6-

(14) Analysis made by the Arlington Laboratories, Fairfax, Virginia.

(15) Jones, *Ind. Eng. Chem., Anal. Ed.*, **16**, 431 (1944).

(16) Dr. N. L. Drake, University of Maryland.

diethylaminohexan-2-one (VIII), the correspondine oxime (IX) and the latter reduced to give the 1-diethylamino-5-aminohexane (X).

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Synthesis of Alicyclic Diamines[1]

BY L. C. BEHR, J. E. KIRBY, R. N. MACDONALD AND C. W. TODD

The superiority of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline[2] over quinacrine in the treatment of malaria prompted the preparation of other 7-chloroquinolines containing a basic side chain in the 4-position. The two amino groups in the quinacrine side chain are separated by an open chain of four carbon atoms. To our knowledge, analogous compounds in which the carbon atoms joining the two amino groups form elements of an alicyclic structure had not been tested as antimalarials. Accordingly, this work was undertaken to supply the requisite alicyclic diamines for the preparation of compounds of this type.[3]

It was found that N-substituted *p*-phenylenediamines and *p*-nitroanilines could be hydrogenated to substituted cyclohexanediamines using either ruthenium dioxide or cobalt-on-alumina as the catalyst. It is known that 1,4-disubstituted cyclohexanes may exist in *cis* and *trans* forms. Although in our work the geometric isomers of the diamines have not been separated, the final drug, 7-chloro-4-(4-diethylaminocyclohexylamino)-quinoline, prepared from samples of our N,N-diethyl-1,4-cyclohexanediamine obtained by reduction over ruthenium and over cobalt-on-alumina has been separated by Drake[3] into two isomeric forms of different melting points. The isolation of larger amounts of the high melting form from the drug prepared from the cobalt-reduced diamine indicates that reduction over cobalt-on-alumina at high temperatures (200–210°) favors the formation of the *trans* isomer, whereas reduction over ruthenium at lower temperatures (100–110°) favors the formation of the *cis* isomer of the diamine. This is in agreement with the studies of other investigators[4] on the isomeric forms of related compounds obtained by reduction over other hydrogenation catalysts.

The preparation of 1-piperazinepropylamine and 1,4-piperazinebispropylamine by the reduction of the acrylonitrile adducts of piperazine for use as side chains in the preparation of other antimalarial drugs is also described.

(1) The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and E. I. du Pont de Nemours and Company.

(2) *Science*, **103**, 8 (1946).

(3) The coupling of these diamines with 4,7-dichloroquinoline was done by N. L. Drake, THIS JOURNAL, **68**, 1214 (1946).

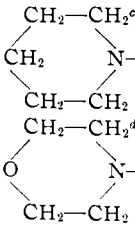
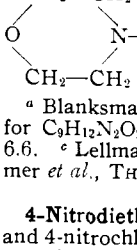
(4) Linstead, *et al.*, *ibid.*, **64**, 1985 (1942); Farkas, *Trans. Faraday Soc.*, **35**, 910 (1939).

Experimental

Preparation of Substituted Nitroanilines.—The N-substituted nitroanilines required in this work were prepared by the reaction of 4-nitrochlorobenzene with the appropriate amine in the absence of a solvent. A typical preparation is described below. The preparations of the other substituted nitroanilines are summarized in Table I.

TABLE I

SUBSTITUTED NITROANILINES X—C$_6$H$_4$—NO$_2$

X	Reaction temp., °C.	Time, hours	Yield, %	M. p., °C.
$(C_2H_5)_2N$—[5]	175	8	94	76
C_2H_5NH—[a]	160	5	75	96
$(CH_3)_2CHNH$—[b]	175	10	40	81–82
 [c]	145	3	83	103.5–104.5
 [d]	145	4	67	150–151

[a] Blanksma, *Rec. trav. chim.*, **21**, 271 (1902). [b] Calcd. for $C_9H_{12}N_2O_2$: C, 59.8; H, 6.7. Found: C, 59.8; H, 6.6. [c] Lellmann and Geller, *Ber.*, **21**, 2282 (1888). [d] Kremer *et al.*, THIS JOURNAL, **61**, 2552 (1939).

4-Nitrodiethylaniline.[5]—Diethylamine (100 g., 1.4 mole) and 4-nitrochlorobenzene (97.8 g., 0.6 mole) were heated in an agitated Parr bomb for eight hours at 175°. The contents of the bomb were then added to one liter of water. The precipitate was filtered, washed with water, dissolved in 200 ml. of 20% hydrochloric acid at 60°, and the solution filtered through sintered glass. The addition of ammonium hydroxide to the filtrate precipitated crude 4-nitrodiethylaniline (114 g., 94% yield), melting at 71–73°. Recrystallization from ethyl alcohol yielded the 4-nitrodiethylaniline (85 g.) as light yellow plates melting at 76°.

Preparation of Alicyclic Diamines.—The preparations of the alicyclic diamines are summarized in Table II. As typical examples, the reductions of 4-aminodiethylaniline to N,N-diethyl-1,4-cyclohexanediamine and of 4-nitroisopropylaniline to N-isopropyl-1,4-cyclohexanediamine are described below.

N,N-Diethyl-1,4-cyclohexanediamine.—4-Aminodiethylaniline (175 g., 1.07 mole) was reduced at 200° and 2000 to 2500 lb. sq. in. of hydrogen pressure in the presence of 17 g. of cobalt-on-alumina.[6] The theoretical amount of hydrogen was absorbed over three and one-half hours. The catalyst was then removed by filtration and the product distilled. There was obtained 126 g. (70% yield) of

(5) Holleman and de Mooy, *Rec. trav. chim.*, **35**, 32 (1915).

(6) This catalyst was prepared by treating a 1:1 cobalt-aluminum alloy with an amount of aqueous sodium hydroxide insufficient to dissolve the alumina formed.