Benzoylation of (II) according to Schotten–Baumann yielded a monobenzoate, m. p. 123–124°. *Anal.* Calcd. for $C_{25}H_{32}O_3$: mol. wt., 380. Found: mol. wt., 370.

**3-(4-Hydroxyphenyl)-4-(4-hydroxycyclohexyl)-hexane** (III).—The benzene filtrate from the preparation of (II) was evaporated to one third of the original volume and cooled to 15°. The solid which crystallized melted at 125–126°, yield 130 mg. Three crystallizations from benzene and petroleum ether (2:1) yielded a product that melted at 132–133°. The melting point could be raised to 144–145° by further crystallization from aqueous methanol and drying under reduced pressure at 100°.

*Anal.* Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.12, 78.52; H, 9.60, 9.70.[8]

*dl*-**Dihydrodiethylstilbestrol.**—The reduction of the dimethyl ether of *trans*-diethylstilbestrol with Raney nickel catalyst led to the dimethyl ether of *dl*-dihydrodiethylstilbestrol. Demethylation of this ether according to the method of Bernstein and Wallis[9] yielded *dl*-dihydrodiethylstilbestrol[10] which melted at 126–129°. *Anal.* Calcd. for $C_{18}H_{22}O_2$: mol. wt., 270. Found: mol. wt., 263.

*meso*-**Hexestrol.**—The monomethyl ether of *meso*-hexestrol[11] was isolated in 13% yield from the reduction products of the monomethyl ether of *trans*-diethylstilbestrol (0.036 mole) in 100 cc. of methanol with 3 g. of Raney nickel at 210° (265 atm.).

*Anal.* Calcd. for $C_{19}H_{24}O_2$: C, 80.26; H, 8.51. Found: C, 80.16; H, 8.51.[8]

The remaining reduction products were crystallized from methanol and melted at 74–76°. When this mixture was demethylated according to the method of Bernstein and Wallis,[9] it gave a 60% yield of *meso*-hexestrol, m. p. 184–185°, mixed melting point with an authentic specimen (m. p. 186°) 184–186°.

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[9] Bernstein and Wallis, This Journal, **62**, 2871 (1940).

[10] Wessely and Welleba, *Ber.*, **74B**, 777 (1941).

[11] Foldi and Demjen, *ibid.*, **74B**, 930 (1941).

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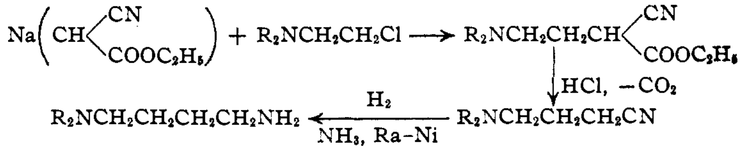
## Some Dialkylaminoalkylamines

BY WOLFGANG HUBER, R. O. CLINTON, W. BOEHME AND MARY JACKMAN

The synthesis of 4-dialkylaminobutylamines usually involves the preparation of a 4-dialkylaminobutyronitrile *via* the intermediate 4-chloro- or bromobutyronitrile.[1] The over-all yields by this method are usually quite low. In the present work a new synthesis for this type of compound has been developed, based upon a modification of the method of Magidson and Strukov.[2]



$$\mathrm{Na}\left(\mathrm{CH}\begin{matrix}\mathrm{CN}\\ \mathrm{COOC_2H_5}\end{matrix}\right) + \mathrm{R_2NCH_2CH_2Cl} \longrightarrow \mathrm{R_2NCH_2CH_2CH}\begin{matrix}\mathrm{CN}\\ \mathrm{COOC_2H_5}\end{matrix}$$

$$\downarrow \mathrm{HCl},\ -\mathrm{CO_2}$$

$$\mathrm{R_2NCH_2CH_2CH_2CH_2NH_2} \xleftarrow[\mathrm{NH_3,\ Ra{-}Ni}]{\mathrm{H_2}} \mathrm{R_2NCH_2CH_2CH_2CN}$$

It was possible by this method markedly to increase the yield of 4-diethylaminobutylamine; in the case of the dimethyl homolog the method does not appear to offer distinct advantages over the usual synthesis.

N-(2-Aminoethyl)-di-*n*-hexylamine and 2-amino-4-morpholinobutane have been prepared by the Ing and Manske modification of the Gabriel method from N-(2-chloroethyl)-di-*n*-hexylamine and 2-chloro-4-morpholinobutane, respectively.

### Experimental[3]

**Ethyl 2-Cyano-4-diethylaminobutyrate.**—A mixture of 120 g. of ethyl sodiocyanoacetate[4] (84% pure) and 250 ml. of distilled ethyl cyanoacetate (the ester acts as a solvent) was heated with stirring on the steam-bath and treated during one hour with a solution of 83.4 g. of 2-chlorotriethylamine in 250 ml. of dry benzene. When the addition of the halogen compound was complete, the mixture was heated and stirred for an additional one and one-half hours. After cooling, the sodium chloride precipitate was removed by filtration and washed with benzene until the filtrate ran colorless. The filtrate was evaporated at 55° and 12 mm., and the residual yellow oil was fractionated *in vacuo*, yielding 109.3 g. (68.7%) of colorless product, b. p. 125–127° at 3 mm.

*Anal.* Calcd. for $C_{11}H_{20}O_2N_2$: C, 62.26; H, 9.43; N, 13.20; neut. equiv., 212. Found: C, 62.38; H, 9.45; N, 13.15; neut. equiv., 214.

**4-Diethylaminobutyronitrile.**—A mixture of 127 g. of the above ester and 300 ml. of 10% aqueous hydrochloric acid was stirred at room temperature for two hours. Excess hydrochloric acid was removed at 40° and 12 mm. and the oily residue was evaporated *in vacuo* four times with 300-ml. portions of water to remove the hydrogen chloride insofar as possible. The crude 2-cyano-4-diethylaminobutyric acid hydrochloride (often crystalline) was then immersed in a bath preheated to 150° and, when carbon dioxide evolution had begun, the temperature was raised to 160° and held at this point for two hours. The cooled residue was covered with ether and treated with concentrated aqueous potassium carbonate solution. After separation of the ether layer, the aqueous layer was further extracted twice with ether, and the combined ethereal extracts were dried over anhydrous potassium carbonate. After removal of the ether the residual oil was fractionated *in vacuo*, yielding 70.1 g. (83%) of colorless product, b. p. 89–89.5° at 9 mm. (lit.[5] b. p. 101–103° at 21 mm.).

The **picrate** had m. p. 68–68.5° (lit.[5] m.p. 69–70°). The reduction of the nitrile to **4-diethylaminobutylamine** has been previously reported.[6]

**Ethyl 2-Cyano-3-dimethylaminobutyrate.**—Prepared from 2-dimethylaminoethyl chloride (obtained in 68% yield from 2-dimethylaminoethanol and thionyl chloride) and ethyl sodiocyanoacetate in 39% yield, the pure compound had b. p. 106° at 12 mm.

*Anal.* Calcd. for $C_9H_{16}O_2N_2$: C, 58.69; H, 8.69; N, 15.12. Found: C, 58.76; H, 8.47; N, 15.52.

Hydrolysis and decarboxylation gave a 64% yield of **4-dimethylaminobutyronitrile**, b. p. 44–47° at 1.5 mm. The **picrate** had m. p. 119–120° (lit.[10] m. p. 120°). The nitrile was also prepared in 39% yield from alcoholic dimethylamine and 4-chlorobutyronitrile. Reduction of the nitrile by the procedure of Huber[6] gave a 58% yield of **4-dimethylaminobutylamine**, b. p. 74–75° at 45 mm. The **chloroaurate** had m. p. 175° (lit.[10] m. p. 175°).

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[1] *Cf.* (a) Strukov, *Khim. Farm. Prom.*, 332 (1933); *Chem. Abs.*, **28**, 3714 (1934)); (b) Utermohlen and Hamilton, This Journal, **63**, 156 (1941); (c) Keil, *Z. physiol. Chem.*, **171**, 242 (1927).

[2] Magidson and Strukov, *Arch. Pharm.*, **271**, 359 (1933).

[3] All melting points and boiling points are uncorrected. The microanalyses were made by the Misses Esther Bass, Alice Rainey and Patricia Curran.

[4] Prepared by the method of Thorpe, *J. Chem. Soc.*, **77**, 923 (1900). The crude sodium salt obtained usually analyzed 83-90% pure. The chief impurities are ethyl cyanoacetate and ethanol.

[5] Whitmore, *et al.*, This Journal, **66**, 725 (1944).

[6] Huber, *ibid.*, **66**, 876 (1944).

**N-(2-Chloroethyl)-di-*n*-hexylamine.**—A solution of 89.6 g. of 2-di-*n*-hexylaminoethanol,[7] b. p. 110–114° at 2.5 mm., in 400 ml. of dry chloroform was treated during one-half hour with a solution of 47.6 g. of purified thionyl chloride in 100 ml. of dry chloroform. The mixture was stirred mechanically and cooled in an ice-bath during the addition. The resulting mixture was allowed to stand in the ice-bath for one hour, heated gently under reflux for one hour and then taken to dryness *in vacuo*. A viscous brown residue of the hydrochloride resulted, which could not be obtained crystalline. The crude yield was quantitative. The hydrochloride was converted to the base in the usual manner. The **isothiouronium picrate**[8] formed tiny light yellow prisms, m. p. 174–176°.

*Anal.* Calcd. for $C_{21}H_{36}O_7N_6S$: N. 16.27. Found: N, 16.40.

**N-(2-Phthalimidoethyl)-di-*n*-hexylamine.**—A mixture of 85 g. of crude N-(2-chloroethyl)-di-*n*-hexylamine, 65.1 g. of potassium phthalimide and 500 ml. of dry toluene was refluxed for twenty-four hours. The resulting mixture was filtered and the precipitate was washed well with hot toluene. After removal of the toluene *in vacuo* there was obtained 115.1 g. of crude non-crystalline product. The **picrate** had m. p. 100–101°.

*Anal.* Calcd. for $C_{28}H_{37}O_9N_5$: N, 11.92. Found: N, 11.63.

**N-(2-Aminoethyl)-di-*n*-hexylamine.**—A mixture of 100 g. of the preceding crude phthalimido compound, 16.5 g. of 85% hydrazine hydrate and 750 ml. of alcohol was refluxed for one and one-half hours. The precipitate was filtered and the filtrate taken to dryness *in vacuo*. The combined residue and precipitate were dissolved in 100 ml. of water, made strongly acidic with 6 *N* hydrochloric acid and filtered; the amine was liberated from the filtrate with base. The dark brown oil was taken up in ether, the ethereal solution dried and the ether removed *in vacuo*. After fractionation *in vacuo* there was obtained 54.6 g. (85.8% based on the crude phthalimido compound) of colorless oil, b. p. 100–103° at 2.5 mm. The pure amine had b. p. 108° at 3 mm., $n^{20}D$ 1.4539. The amine was insoluble in 5% hydrochloric acid.

*Anal.* Calcd. for $C_{14}H_{32}N_2$: C, 73.61; H, 14.12; N, 12.27. Found: C, 73.49; H, 13.88; N, 12.17.

The **dithiocarbamate hydrate** formed small prisms from alcohol, m. p. 118–119°.

*Anal.* Calcd. for $C_{15}H_{32}N_2S_2 \cdot H_2O$: N, 8.68. Found: N, 8.56.

**2-Amino-4-morpholinobutane.**—This amine was prepared from 2-hydroxy-4-morpholinobutane[7] in a manner analogous to that used in making the above compound. The intermediate **2-chloro-4-morpholinobutane** hydrochloride (95.5% yield) formed leaflets from absolute alcohol–ethyl acetate, m. p. 197°.

*Anal.* Calcd. for $C_8H_{17}ONCl_2$: C, 44.87; H, 8.00; N, 6.54. Found: C, 44.94; H, 7.85; N, 6.78.

The free base was condensed with potassium phthalimide at 180–190° for three and one-half hours without a solvent. **2-Phthalimido-4-morpholinobutane** (97.8% yield) formed slender white needles from dilute alcohol, m. p. 69–70°.

*Anal.* Calcd. for $C_{16}H_{20}O_3N_2$: N, 9.72. Found: N, 9.81.

Hydrolysis of the phthalimido compound with hydrazine hydrate gave a 73.2% yield of the amine, b. p. 65° at 1 mm., $n^{20}D$ 1.4774. The amine repeatedly gave poor analyses, but could be characterized through the **dithiocarbamate alcoholate,** m. p. 148–149° (dec.) (from pyridine–alcohol).

*Anal.* Calcd. for $C_9H_{18}ON_2S_2 \cdot C_2H_5OH$: N, 9.99. Found: N, 10.19.

The dithiocarbamate decomposed when attempts were made to obtain it alcohol-free.

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[7] Obtained through the courtesy of the Carbide and Carbon Chemicals Corp., New York, N. Y.

[8] Shriner and Fuson, "Identification of Organic Compounds," 2nd ed., John Wiley and Sons, New York, N. Y., 1940, p. 159.

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## Preparation of Some Dialkylaminoalkylaminoacridines and Quinolines

BY WOLFGANG HUBER, R. K. BAIR AND S. C. LASKOWSKI

Magidson and Grigorovskiĭ[1] reported 6-chloro-9-(4-diethylaminobutylamino)-2-methoxyacridine to be one-third more active against *Plasmodium praecox* in siskins than its homolog quinacrine, 6-chloro-9-(4-diethylamino-1-methylbutylamino)-2-methoxyacridine. The antiplasmodial activity of 4-substituted quinolines also has been described in the literature.[2,3,4]

The new method of preparation for several dialkylaminoalkylamines, recently reported from these laboratories,[5] made it seem of interest to prepare some compounds similar to the above mentioned types for more detailed investigation of their antiplasmodial activity.

This report describes the condensation of 4-diethylaminobutylamine and 4-dimethylaminobutylamine with 6,9-dichloro-2-methoxyacridine, as well as the condensation of 2-amino-4-morpholinobutane and 2-di-*n*-hexylaminoethylamine with 4,7-dichloroquinoline. The condensations were carried out by heating the appropriate amine with the substituted chloroacridine or chloroquinoline with or without the use of a solvent, such as phenol. This procedure is a modification of the one described by Mietzsch and Mauss.[6] The antiplasmodial activity of these compounds will be reported at a later date.

### Experimental

All melting points and boiling points are uncorrected. The analyses were made by the Misses Alice Rainey and Patricia Curran and by Mr. George Bronell.

**6-Chloro-9-(4-diethylaminobutylamino)-2-methoxyacridine** Dihydrochloride.—To a mixture of 38 g. of phenol and 15 g. (0.10 mole) of 4-diethylaminobutylamine,[5] 28 g. (0.10 mole) of 6,9-dichloro-2-methoxyacridine was added with stirring in the course of five minutes. The inside temperature was then raised to and kept at 95–100° for one hour with continued stirring. The resulting homogenous amber melt was taken up with a mixture of 350 cc. of acetone and 35 cc. of 12 *N* hydrochloric acid. The mixture was thoroughly stirred until all lumps were broken and then cooled overnight. The crude product was filtered and washed with acetone until the filtrate became colorless; yield, 45.0 g.; m. p. 257–259° (dec.). For purification this material was dissolved in 90 cc. of distilled water and treated with charcoal; to the clear amber filtrate was added 15 cc. of 12 *N* hydrochloric acid. After cooling

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[1] O. Yu. Magidson and A. M. Grigorovskiĭ, *Ber.*, **69**, 396 (1936).

[2] O. Yu. Magidson and M. V. Rubtsov, *J. Gen. Chem.* (U.S.S.R.), **7**, 1896 (1937).

[3] W. F. Holcomb and C. S. Hamilton, THIS JOURNAL, **64**, 1309 (1942).

[4] E. P. Galperin, *Am. Rev. Soviet Med.*, **1**, 220 (1944).

[5] W. Huber, R. O. Clinton, W. Boehme and M. Jackman, THIS JOURNAL, **67**, 1618 (1945).

[6] German Patent 553,072 (1930) [*C. A.*, **26**, 4683 (1932)].