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., $n^{20}\mathrm{D}$ 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., $n^{20}\mathrm{D}$ 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)].

overnight the precipitated 6-chloro-9-(4-diethylaminobutylamino)-2-methoxyacridine dihydrochloride[1] was filtered and washed with acetone; a yield of 40.0 g. (81.6%) of bright yellow crystals was obtained, m. p. 265° (dec.) (Magidson and Grigorovskiĭ reported 246–248°).

Anal. Calcd. for $C_{22}H_{28}ClN_3O \cdot 2HCl \cdot 2H_2O$: N, 8.49; Cl, 14.36; H_2O, 7.3. Found: N, 8.35; Cl, 13.98; H_2O, 7.7.

The free base was prepared from an aqueous solution of 5.0 g. of the dihydrochloride in 50 cc. of water by addition of 28% ammonium hydroxide until alkaline to litmus. After extracting with benzene and removal of the solvent, the crude base (4.1 g.) was recrystallized twice from benzene; 6-chloro-9-(4-diethylaminobutylamino)-2-methoxyacridine was obtained as bright yellow crystals, m. p. 79.5–80.5° (Magidson and Grigorovskiĭ reported 76–78° for the pentahydrate). A sample dried *in vacuo* over phosphorus pentoxide at 56° for two hours was found to be anhydrous (m. p. 79.5–80.5°).

Anal. Calcd. for $C_{22}H_{28}ClN_3O$: C, 68.39; H, 7.26; N, 10.88. Found: C, 68.19; H, 7.34; N, 10.67.

6-Chloro-9-(4-dimethylaminobutylamino)-2-methoxyacridine Dihydrochloride.—A mixture of 23.9 g. (0.20 mole) of 4-dimethylaminobutylamine,[5] 55.6 g. (0.20 mole) of 6,9-dichloro-2-methoxyacridine and 75.0 g. (0.80 mole) of phenol was heated at an inside temperature of 100–105° for two and one-half hours (initial exothermic reaction caused a temperature rise to 124°). The amber melt was poured into 800 cc. of acetone containing 75 cc. of concentrated hydrochloric acid, was stirred with cooling and filtered. The orange solid was slurried three times with acetone, and then recrystallized three times from methanol–acetone with charcoaling. A yield of 68 g. (80%) of bright yellow crystals was obtained, m. p. 240–244° (dec.).

Anal. Calcd. for $C_{20}H_{24}ClN_3O \cdot 2HCl$; C, 55.74; H, 6.03; N, 9.75. Found: C, 55.46; H, 6.27; N, 9.96.

7-Chloro-4-(1-methyl-3-morpholinopropylamino)-quinoline.—A mixture of 19.8 g. (0.10 mole) of 4,7-dichloroquinoline,[7] 32.0 g. (0.20 mole) of 2-amino-4-morpholinobutane,[5] and 0.1 g. of sodium iodide was heated with stirring to 160° (bath temperature); a vigorous exothermic reaction ensued with the inside temperature rising to 194°. The reaction mixture was then cooled to room temperature (total heating period ten to fifteen minutes). The viscous melt was poured into cold 10% hydrochloric acid with stirring and the acidic solution, after buffering with sodium acetate to congo red (neutral), was extracted exhaustively with ether. The aqueous layer was then made strongly alkaline with cold 30% sodium hydroxide solution and extracted several times with ether. On chilling, 23.0 g. of crystals, m. p. 141–144°, was obtained. Concentration of the mother liquor yielded another 5.0 g. (total yield 88%). A sample was recrystallized three times from benzene for analysis, m. p. 141–144°.

Anal. Calcd. for $C_{17}H_{22}ClN_3O$: C, 63.85; H, 6.88; N, 13.16. Found: C, 63.96; H, 6.87; N, 13.26.

The crystalline **diphosphate** was prepared by mixing a methanolic solution of the base with an equimolecular amount of 85% phosphoric acid.

Anal. Calcd. for $C_{17}H_{22}ClN_3O \cdot 2H_3PO_4$:[8] base, 62.0; acid, 38.0. Found: base, 62.7; acid, 38.2.

7-Chloro-4-(2-di-*n*-hexylaminoethylamino)-quinoline.—A mixture of 19.8 g. (0.10 mole) of 4,7-dichloroquinoline,[7] 45.8 g. (0.20 mole) of 2-di-*n*-hexylaminoethylamine,[5] and 0.1 g. of sodium iodide was heated at an inside temperature of 158–165° for one hour. The condensate was isolated as the dihydrochloride in the same manner as above; for purification, the free base was liberated and distilled. It came over as a yellow, very viscous oil (b. p. 187–191° at 22 μ and bath temperature of 220–225°), which solidified on cooling. A sample for analysis was recrystallized from petroleum ether, m. p. 55–57°.

Anal. Calcd. for $C_{23}H_{36}ClN_3$: C, 70.90; H, 9.25; N, 10.79. Found: C, 71.21; H, 9.35; N, 11.28.

The crystalline **diphosphate** was prepared by mixing a methanolic solution of the base with an equimolecular amount of 85% phosphoric acid.

Anal. Calcd. for $C_{23}H_{36}ClN_3 \cdot 2H_3PO_4$[8]: base, 66.5; acid, 33.5. Found: base, 67.2; acid, 34.1.

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(7) U. S. Patent 2,233,930.

(8) **The phosphates reported in this paper crystallized as hydrates. Analytical data are reported on an anhydrous basis.**

The Metalation of Isopropylbenzene, Condensations by Sodium. XXIX

BY AVERY A. MORTON, JOHN T. MASSENGALE AND MALCOLM L. BROWN

Over a period of a number of years, the action of amylsodium on isopropylbenzene has been observed on several occasions. It has been the intention to submit this compound and others to an extensive series of tests but the work has been so delayed that it is thought desirable to publish these results as they are.

The position at which amylsodium attacks isopropylbenzene is largely para and some ortho to the isopropyl group. The yield is good if the hydrocarbon is made the solvent and the reaction mixture is allowed to stand overnight, and is fair if isopropylbenzene is added to amylsodium and the mixture is heated.

The inactivity of the tertiary hydrogen atom may at first seem peculiar since bromination shows activity at this position and since the frequent use of phenylisopropylpotassium has created an impression that the metal should be attached at that position. The difference between bromination and metalation is, however, a clear one for the product of the former reaction has a carbonium ion and that of the latter reaction has a carbanion ion. Hence, it is reasonable to suppose that the hydrogen atom most readily attacked in one instance will be least readily attacked in the other. The position taken by the metal ion is in agreement also with the general repression of activity toward acid–salt interchange which accompanies the introduction of methyl groups into a hydrocarbo acid. In this instance the acidity of the side chain[1] in cumene is much less than that of toluene because of the two additional methyl groups. As the acidity in the side chain is repressed that in the ring becomes apparent.

Experimental

Amylsodium was prepared in the usual manner from 15.5 g. of amyl chloride and 10 g. of sodium sand at −6 to −11° in isopropylbenzene as a solvent. The mixture was allowed to warm and stand overnight before carbonation. The aqueous solution of the sodium salts[2] was then acidified and extracted with benzene. Distillation of the acids gave a fraction which boiled at 128–142° (3 mm.) and partially solidified. The purified cuminic acid amounted to 6 g. and melted at 116.2–116.5°. The recorded value is

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(1) Morton, *Chem. Rev.*, **35**, 1 (1944).

(2) Morton, Davidson and Hakan, THIS JOURNAL, **64**, 2242 (1942).