Anal. Calcd., for $C_9H_7ON_2Cl$: C, 55.55; H, 3.63; Cl, 18.22. Found: C, 55.37; H, 3.64; Cl, 17.83.[17]

Picrate.—This derivative crystallized from absolute ethanol in yellow crystals (m. p. 210–210.5°), and recrystallization gave no change in melting point. *Anal.* Calcd., for $C_{15}H_{10}O_8N_5Cl$: N, 16.53. Found: N, 16.20.[16]

4-(4'-Diethylamino-1'-methylbutylamino)-6-methoxyquinazoline (SN 12,253) (VIII).—4-Chloro-6-methoxyquinazoline (18.9 g., 0.097 mole) was refluxed with 1-diethylamino-4-aminopentane (30.8 g., 0.195 mole) in 275 ml. of benzene for seven hours at 115–120° and finally for half an hour at 135–140°, when a crystalline solid separated. The cooled mixture was treated with saturated potassium hydroxide solution, the benzene layer was separated and the alkaline layer extracted with ether. The benzene–ether extract, dried over solid potassium hydroxide, was concentrated under reduced pressure. The crystalline amine was filtered, washed with ether and dried. The yield was 25.6 g. (83%). Recrystallization from ethanol–water was unsatisfactory, the product separated as an oil. A 10.0 g. sample was recrystallized from 5 l. of petroleum ether (35–70°) and 7.0 g. of the amine (VIII), m. p. 151.5–152°, was recovered. A second recrystallization did not change the melting point. The amine was insoluble in boiling water, soluble in ethanol and acetone, slightly soluble in petroleum ether. It was completely soluble in dilute hydrochloric acid and 85% phosphoric acid.

Anal. Calcd., for $C_{18}H_{28}ON_4$: C, 68.31; H, 8.91; neut. equiv., 158.2. Found: C, 68.15; H, 8.90[16]; neut. equiv., 158.6.[18]

(17) Analysis by Lois May, Microanalytical Laboratory, Columbia University.

(18) Electrometric titration by Kathleen Tiftickjian, Mount Holyoke College.

Picrate.—This derivative, recrystallized from absolute ethanol, formed powdery yellow crystals, m. p. 138.5–140° (dec.) which did not change melting point on a second crystallization.

Anal. Calcd. for $C_{24}H_{31}O_8N_7$: N, 17.99. Found: N, 18.05.[16]

4-(4'-Diethylamino-1'-methylbutylamino)-6-methoxyquinazoline Diphosphate Monohydrate (SN 12,253-5-3).—The aminomethoxyquinazoline (VIII) (0.5 g., 0.002 mole) was suspended in 2.5 ml. of water and 85% phosphoric acid (0.4 g., 0.004 mole) was added. After the addition of absolute ethanol to cloudiness, fine white crystals gradually separated. These were filtered and washed with ethanol. The phosphate was recrystallized by dissolving it in water and adding absolute ethanol. After twelve hours the phosphate was filtered, washed with ethanol and dried. The yield was 0.7 g. (78%) of a diphosphate, m. p. 207.5–208.5° (uncor.). A second crystallization gave fine needles, m. p. 218–219°, which showed no change in melting point on repeated recrystallizations. Similar treatment of a larger sample of the amine (12.0 g., 0.038 mole) gave 14.5 g. (75% yield) of the diphosphate, m. p. 219–220° (dec.).

Anal. Calcd., for $C_{18}H_{28}ON_4 \cdot 2H_3PO_4 \cdot H_2O$: P, 11.67. Found: P, 11.56.[16]

Summary

6-Methoxy-4-quinazolone, 6-methoxy-4-chloroquinazoline, 4-(4'-diethylamino-1'-methylbutylamino)-quinazoline and the corresponding diphosphate have been prepared. Picrate derivatives of these compounds have also been made.

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

Quinazoline Derivatives.[1] III. The Synthesis of 4-(3'-Diethylaminopropoxy)-6-chloroquinazoline (SN 12,254)[2]

BY MARGARET M. ENDICOTT, BETTY W. ALDEN AND MARY L. SHERRILL

The investigation of 4-(3'-diethylaminopropoxy)-6-chloroquinazoline (IV) for antimalarial activity seemed advisable although previous investigators[3] had tested two dialkylaminoalkylamino-6-chloroquinazolines for such activity. The 5-chloroanthranilic acid (I) necessary for these syntheses had been made from *m*-nitrobenzaldehyde through a series of reactions. The preparation of (I) through the action of sulfuryl chloride on anthranilic acid[4] was more direct and the compound, due to its greater basicity, was readily separated from the side product, 3,5-dichloroanthranilic acid. The 6-chloro-4-quinazolone (II) and 4,6-dichloroquinazoline (III) were obtained by methods for analogous compounds.[3,5] Although 4-alkoxyquinazolines had been prepared[6,7] alkylaminoalkoxy derivatives had not been reported. 4-(3'-Diethylaminopropoxy)-6-chloroquinazoline (IV) has been obtained from (III) with sodium 3-diethylaminopropoxide in an excess of the aminopropanol.

(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) The Survey Number designated SN, identifies a drug in the records of the Survey of Antimalarial Drugs. The antimalarial activities of these compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(3) Magidson and Golovchenskaya, *J. Gen. Chem.* (U. S. S. R.), **8**, 1797 (1938).

(4) Eller and Klemm, *Ber.*, **55B**, 217 (1922).

Experimental[8]

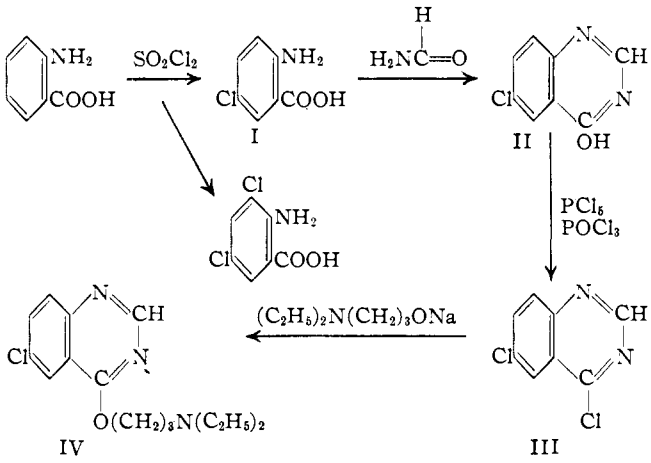
5-Chloroanthranilic Acid (2-Amino-5-chlorobenzoic Acid) (I).—Anthranilic acid (40.0 g., 0.3 mole) was added in small portions with shaking to a mixture of well-cooled sulfuryl chloride (52.8 g., 0.39 mole) and ether (600 ml.) in a flask, fitted with a reflux condenser and an addition tube. After the removal of ether and sulfuryl chloride at reduced pressure, the residue was treated with water and the mixture of acids was filtered by suction, digested for two hours at 60° with 800 ml. of 8% hydrochloric acid and again filtered. The 5-chloro-anthranilic acid, precipitated from the filtrate by neutralization partially with sodium hydroxide (6 *M*), finally with saturated sodium acetate solution, was filtered, dissolved in hot 95% ethanol and

(5) Sherrill and co-workers, THIS JOURNAL, **68**, 1301 (1946).

(6) Bogert and May, *ibid.*, **31**, 509 (1909).

(7) Lange and Sheibley, *ibid.*, **53**, 3867 (1931).

(8) All melting points are corrected unless otherwise indicated.



hot water added to cloudiness. The yield of acid (I) was 25 g. (49%, m. p. 204–205°). The yield of the crude 3,5-dichloroanthranilic acid (m. p. 216–219°) was 14 g. (22%).

6-Chloro-4-quinazolone (II).—The crystallized acid (I) (17.2 g., 0.1 mole) and formamide (17.2 g., 0.4 mole) were heated for one hour at 130–140° for three hours at 160–165°. The light tan crystals were filtered, washed with ethanol-benzene (1:1) and dried *in vacuo*. The yield was 17.5 g. (m. p. 261–263°). Recrystallized from 50% acetic acid the chloroquinazolone formed long plate-like needles, m. p. 262.5–263.5°.

Picrate.—This derivative of (II) crystallized from absolute ethanol in yellow needles, m. p. 199.5–200°.

Anal. Calcd., for $C_{14}H_8O_8N_5Cl$: N, 17.09. Found: N, 16.45.[9]

4,6-Dichloroquinazoline (III).—A mixture of the crude (II) (10.8 g., 0.06 mole), phosphorus pentachloride (12.7 g., 0.61 mole), and 72 ml. of phosphorus oxychloride was refluxed for five hours at 125–130°. After removal of the phosphorus oxychloride,[5] the solid was treated with chloroform (400 ml.), the last traces of solid being dissolved in 20 ml. of 3 *N* sodium hydroxide. The residue from the chloroform extract, recrystallized from ligroin (90–120°) gave 11.8 g. (90% yield) of feathery crystals (m. p. 154–155°).

Picrate.—This derivative crystallized from absolute ethanol in yellow needles, m. p. 172–172.5°.

Anal. Calcd., for $C_{14}H_7O_7N_5Cl_2$: N, 16.36. Found: N, 15.74.[9]

4-Ethoxy-6-chloroquinazoline.—This compound was prepared to test the reactivity of (III) prior to the preparation of (IV). To sodium (0.5 g., 0.2 mole) in 200 ml. of absolute ethanol, the dichloroquinazoline (III) (4.0 g., 0.02 mole) was added in small portions and refluxed for half an hour. After filtration the alcohol was distilled at reduced pressure. The residue recrystallized from 50% ethanol gave 3.7 g. (86% yield) of 4-ethoxy-6-chloroquinazoline, white needles, m. p. 104.5–105°.

Anal. Calcd., for $C_{10}H_9ON_2Cl$: C, 57.55; H, 4.35; Cl, 16.94. Found: C, 57.48; H, 4.44; Cl, 17.04.[9]

4-(3′-Diethylaminopropoxy)-6-chloroquinazoline (SN 12,254)[2] (IV).—Sodium (1.0 g., 0.043 mole) was added to 26.2 g. (0.2 mole) of 3-diethylaminopropanol (Eastman Kodak Co., b. p. 91–93° at 23 mm.) and refluxed until the sodium dissolved. To this cooled solution was added 4,6-dichloroquinazoline (8.0 g., 0.04 mole) which dissolved with evolution of heat. After twelve hours the solution was decanted into cold water. From the emulsion a yellow oil separated in six hours which was extracted with chloroform and dried. The chloroform was removed at reduced pressure and the oil heated for some time, 120° at 13–20 mm. On distillation the residue gave 4.2 g. (35% yield) of pale yellow oil (b. p. 195–200° at 3.5–4 mm. pressure) which was made into a phosphate.

Similar treatment of 29.9 g. (0.15 mole of (III) with 3.7 g. (0.16 mole) of sodium and 70 g. (0.53 mole) of diethylaminopropanol gave 22 g. (50% yield) of oil distilling at 150–155° at 0.080–0.090 mm.). Redistillation of this gave 19.7 g. (44% yield) of thick pale yellow oil (b. p. 155–156° at 0.064–0.066 mm.).

4-(3′-Diethylaminopropoxy)-6-chloroquinazoline Phosphate (SN 12,254-5).—To a suspension of 19.7 g. (0.066 mole) of the yellow oil (III) in 20 ml. of water, cooled in an ice-bath, 7.1 g., of 85% phosphoric acid (0.075 mole) was added. After the addition of absolute ethanol (300 ml.) the phosphate crystallized slowly, the yield was 26 g. (80%), m. p. 186.5–187.5° (uncor.). After slow recrystallization from water by the addition of alcohol, the compound melted at 193.5–195° (dec.) and there was no change in melting point on further recrystallization.

Anal. Calcd., for $C_{15}H_{20}ON_3Cl \cdot H_3PO_4$: C, 45.99; H, 5.92; P, 7.91. Found C, 46.03; H, 5.97;[10] P, 7.99.[9]

Summary

4-(3′-Diethylaminopropoxy)-6-chloroquinazoline and its monophosphate have been prepared. 4-Ethoxy-6-chloroquinazoline, the picrates of 6-chloroquinazolone and 4,6-dichloroquinazoline have also been prepared.

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(9) Analysis made by the Arlington Laboratories, Fairfax, Va.

(10) Analysis by Lathrope Baker, Microanalytical Laboratory, Columbia University.