chloro-2-phenylquinazoline (29.0 g., 0.12 mole) after distilling off the excess of the diaminopentane at reduced pressure, the condensation product, a thick yellow oil was distilled at very low pressure. A forerun of 2.5 g. (distilling up to 185° at 0.025–0.035 mm.) was separated, 37.2 g. (85.5% yield) of a thick yellow oil distilled (b. p. 187–188°) at 0.050–0.060 mm. On cooling a mass of crystals appeared radiating from the center, but it has not been possible to recrystallize the material for a melting point determination. A portion of this material was made into a phosphate which was identical with that from the preceding sample.

Dipicrate.—This derivative was prepared and recrystallized from absolute ethanol in bright yellow flakes, m. p. 163–163.5°.

Anal. Calcd. for $C_{35}H_{36}O_{14}N_{10}$: N, 17.06. Found: N, 17.31.[10]

4-(4'-Diethylamino-1'-methylbutylamino)-2-phenylquinazoline Diphosphate Monohydrate (SN 11,535-5-3).—A sample of each preparation of (VI) was made into the phosphate and the product isolated by the method used for the phosphate of (III). In each case after recrystallization from water–ethanol (1:7) the phosphate formed soft feathery crystals which showed slight shrinkage at 160–170° and melted at 221–224° (uncor., dec.). The phosphate recrystallized from water–ethanol (1:10) showed no change in melting point. From 9.6 g. (0.04 mole) of the aminophenylquinazoline (VI) a yield of 22.0 g. (95.3%) of diphosphate monohydrate was obtained.

Anal. Calcd. for $C_{23}H_{30}N_4 \cdot 2H_3PO_4 \cdot H_2O$: C, 47.90; H, 6.64; P, 10.75. Found: C, 47.39; H, 6.85; P, 10.67.[10]

Summary

4-(4'-Diethylamino-1'-methylbutylamino)-quinazoline (SN 11,534) and the corresponding 2-phenylquinazoline (SN 11,535) have been prepared for investigation as antimalarial drugs. The picrate and phosphate of each have been prepared.

The intermediate 4-chloro-2-phenylquinazoline and its picrate as well as the picrate of 4-chloroquinazoline have been made.

SOUTH HADLEY, MASS. RECEIVED APRIL 5, 1946

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

Quinazoline Derivatives.[1] II. Synthesis of 4-(4'-Diethylamino-1'-methylbutylamino)-6-methoxyquinazoline (SN 12,253)[2]

BY MARTHA E. SMITH, ELISE ELISBERG AND MARY L. SHERRILL

The possibility that 4-(4'-diethylamino-1'-methylbutylamino)-6-methoxyquinazoline (VIII) might possess antimalarial activity comparable to the analogous quinoline compound, plasmochin, but with less toxicity, led Magidson and Golovchenskaya[3] to undertake the synthesis of this compound and other analogous quinazolines with substituents in the 6-position. They prepared the nitro, amino and chloro derivatives but did not obtain the corresponding 6-methoxy compound because of the difficulty in preparing the intermediate 5-methoxyanthranilic acid (V). Although these investigators reported that these quinazoline derivatives showed little antimalarial activity as compared with analogous quinoline compounds, it seemed advisable to undertake the synthesis of the 6-methoxy compound.

To avoid the synthesis of 5-methoxyanthranilic acid (V), an attempt was made to prepare the 6-methoxy-4-quinazolone (VI) by nitration of the quinazolone,[3,4] alkaline reduction to 6-amino-4-quinazolone,[3] diazotization and introduction of the methoxyl group. This was very satisfactory through the diazotization[5] and the 4-quinazolone-6-diazonium fluoborate was isolated in almost quantitative yield. The replacement of the diazonium group by the methoxy group has given a mixture of compounds which has not yet been satisfactorily separated.

5-Methoxyanthranilic acid (V) has been successfully obtained through a series of reactions reported by Mason[6] and Heilbron and co-workers,[7] as indicated in the chart. This compound was tranformed into 6-methoxy-4-(4'-diethylamino-1'-methylbutylamino)-quinazoline (VIII) by the methods given for analogous compounds in the preceding paper.[8]

Experimental[9]

Di-(3-aldehydo-4-nitro)-phenyl Carbonate (I).—Fifty-four grams (0.2 mole) of di-(3-aldehydo)-phenyl carbonate (m. p. 127–128°)[10] was nitrated[6] with nitric acid (sp. gr. 1.5) in concentrated sulfuric acid at −2–+3°. The reaction product was precipitated with ice, filtered, washed free of acid, finally washed with ethanol and dried. The yield was 70 g. (97%) of cream colored crystals (m. p. 195–196°) which on recrystallization from glacial acetic acid or xylene melted at 197–198° (recorded value, 194–198°).[6]

5-Hydroxy-2-nitrobenzaldehyde (II).[6]—The crude aldehydonitrophenyl carbonate (I) (72.9 g., 0.2 mole) was refluxed with 2 *M* sodium hydroxide solution and the hydroxynitrobenzaldehyde precipitated with acetic acid. The yield was 65 g. (97%) of glistening tan crystals (m. p. 164–167°). Recrystallized from ethanol–water, the compound melted at 163–166° (recorded value 166°).[6]

5-Methoxy-2-nitrobenzaldehyde (III).[7]—The crude (II) (59.0 g., 0.35 mole) was methylated with 151 g. (1.2 mole)

(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) Bogert and Geiger, THIS JOURNAL, **34**, 524 (1912).

(5) Starkey, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 225.

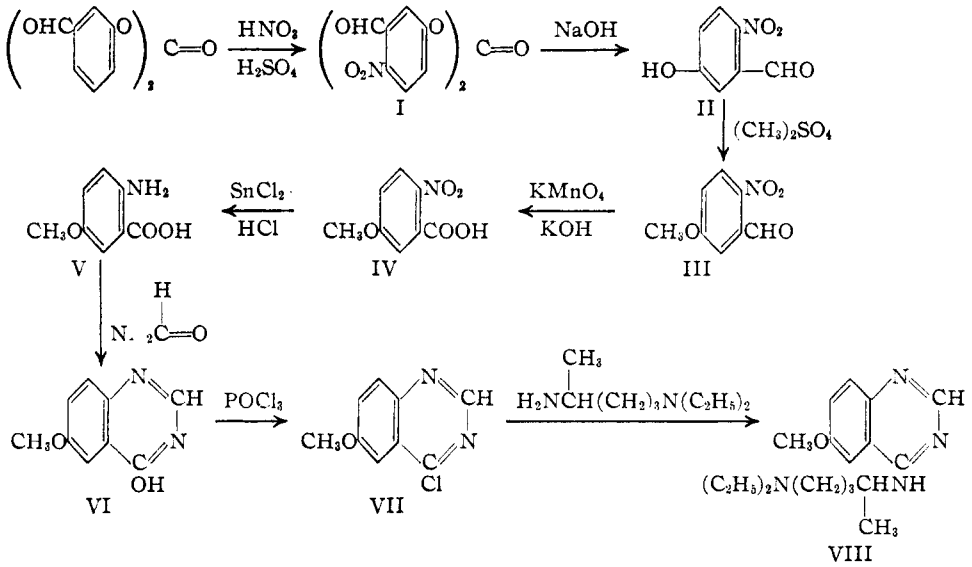
(6) Mason, *J. Chem. Soc.*, **127**, 1197 (1925).

(7) Heilbron, Kitchen, Parkes and Sutton, *ibid.*, **127**, 2173 (1925).

(8) Sherrill and co-workers, THIS JOURNAL, **68**, 1299 (1946).

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

(10) This compound was obtained through the courtesy of the Heyden Chemical Co.



of dimethyl sulfate in 2 *M* sodium hydroxide solution at 60°. The yield was 56 g. (87%) of glistening tan crystals (m. p. 82–83.5°) which recrystallized from ethanol melted at 83–83.5° (recorded value 83–84°).[6]

5-Methoxy-2-nitrobenzoic Acid (IV).[7,11]—To crude methoxynitrobenzaldehyde (III) (18.1 g., 0.1 mole) 1 liter of *M* potassium permanganate (10.5 g., 0.067 mole) in 350 ml. water, was added dropwise with stirring (one and one-half hours). The warm reaction mixture was filtered, the solution was acidified with 3 *M* sulfuric acid, saturated with sodium chloride and filtered immediately, washed and dried in the dark. The yield was 16.5 g. (83.7%) of pale yellow crystals (m. p. 130–131°, recorded value 132–133°).[7] The residue from an ether extract of the filtrate, recrystallized from water, yielded 2.5 g. (m. p. 130–131°) making the total yield 95%.

5-Methoxyanthranilic Acid (2-Amino-5-methoxybenzoic Acid) (V).—Previous investigators[7,11] had reported the preparation of this acid but gave no yields nor details of isolation. The latter was the chief difficulty encountered and the following procedure proved satisfactory in repeated preparations.

To stannous chloride (98.5 g., 0.45 mole), dissolved in 100 ml. of concentrated hydrochloric acid, methoxynitrobenzoic acid (IV) was added all at once with stirring.[12,13] The mixture was heated slightly and the temperature rose quickly to 80° as the solid dissolved. After stirring for fifteen minutes, 50 ml. of concentrated hydrochloric acid was added and the solution was cooled in an ice-bath and stirred for twenty minutes. The precipitated complex stannic double salt was separated on a sintered glass funnel, washed with concentrated acid and drained thoroughly. The solid was stirred with portions of sodium carbonate (10%) until it dissolved and the mixture was alkaline, whereupon a grayish precipitate appeared and was removed on a sintered glass funnel.

The red filtrate, cooled in a freezing mixture, was treated with glacial acetic acid until a colloidal precipitate appeared then acetic acid (50%) was added dropwise until the solution had a *p*H of 4. The solid suddenly coagulated and precipitated in fine fluorescent needles which were filtered immediately. The yield was 7.1 g., m. p. 147–149°. A little excess of acetic acid produced only a slight precipitate so the solution was extracted ten times with ether (2 l.). The fluorescent ether solution was distilled, the last traces of ether and moisture being removed at reduced pressure. The residue, dried *in vacuo* over solid potassium hydroxide, consisted of silvery gray crystals (m. p. 149–150.5°, recorded value 149°).[11] The total yield of 5-methoxyanthranilic acid was 14 g. (83%).

A reduction of the methoxynitrobenzoic acid with ferrous sulfate and ammonia[14,15] gave a 35% yield of the methoxyanthranilic acid and the isolation was more difficult than in the acid reduction.

6-Methoxy-4-quinazolone (VI).—A mixture of the methoxyanthranilic acid (4.2 g., 0.025 mole) and formamide (4.5 g., 0.10 mole) was heated at 125–150° for five hours. The crystalline product was filtered, washed with small portions of water and dried. The yield was 4.1 g. (93%) m. p. 242–244° (uncor.). The compound, very insoluble in cold water, soluble in alcohol, insoluble in ether, ligroin and benzene, was recrystallized from boiling water forming fine white needles (m. p. 248–249°) which showed no change in melting point on a second crystallization.

Anal. Calcd. for $C_9H_8O_2N_2$: C, 61.34; H, 4.56; N, 15.90. Found: C, 61.58; H, 4.98; N, 15.94.[16]

Picrate.—This derivative recrystallized from absolute ethanol in yellow needles (m. p. 231.5–232°) which darkened on standing.

Anal. Calcd., for $C_{15}H_{11}O_9N_5$: N, 17.28. Found: N, 17.15.[16]

4-Chloro-6-methoxyquinazoline (VII).—The methoxyquinazolone (8.8 g., 0.05 mole) was refluxed with phosphorus oxychloride (60 ml., 0.65 mole) for four hours at 115–120°. Toluene (50 ml.) was added and the excess phosphorus oxychloride and toluene were removed at diminished pressure. The residue was treated with chloroform and ice, followed by a small amount of saturated sodium carbonate solution. The residue from the dried chloroform extract was a pale yellow solid melting at 104–180°, indicative of incomplete chlorination.

The residue was then treated with 60 ml. of phosphorus oxychloride and the process repeated and 6.8 g. (70% yield) of light tan solid was obtained. The two-stage chlorination was necessary for it was found that, even with longer heating and a greater concentration of the oxychloride in the first stage, the product was not completely chlorinated. The 4-chloro-6-methoxyquinazoline (VII) recrystallized from ligroin (b. p. 72–75°) formed pale yellow needles (m. p. 107.5–108°) which showed no change in melting point on a second crystallization.

(11) Pschorr, *Ann.*, **391**, 28 (1912).
(12) R. C. Elderfield, "Organic Syntheses."
(13) Ullmann and Dootson, *Ber.*, **51**, 20 (1918).
(14) Jacobs and Heidelberger, THIS JOURNAL, **39**, 1435 (1919).
(15) R. C. Elderfield, private communication.
(16) Analysis by the Arlington Laboratories, Fairfax, Va.

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.

SOUTH HADLEY, MASS. RECEIVED APRIL 5, 1946

[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.

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

(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).

(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.