Found: 72.18, 72.24. Because of its hygroscopic nature, the elementary analyses were not satisfactory.

The yield of 1-di-*n*-butylamino-3-methylaminopropane, boiling at 102–103° (6 mm.), was 64%; d^{25}_{18} 0.8206, $n^{21}D$ 1.4480.

Anal. Calcd. for $C_{12}H_{28}N_2$: C, 71.93; H, 14.09. Found: C, 71.85; H, 13.89.

Summary

1-Di-*n*-butylamino-2-methylaminoethane was prepared in 63% over-all yield starting with di-*n*-butylaminoethanol. 1-Diethylamino- and 1-di-*n*-butylamino-3-methylaminopropane were prepared in 38% over-all yields starting with diethyl- and di-*n*-butylamine. The classical method of alkylating methylaniline and hydrolyzing the *p*-nitroso derivative was used. Much higher yields were obtained by hydrolysis by the sodium bisulfite than by the better known sodium hydroxide method.

NEW BRUNSWICK, NEW JERSEY RECEIVED APRIL 5, 1946

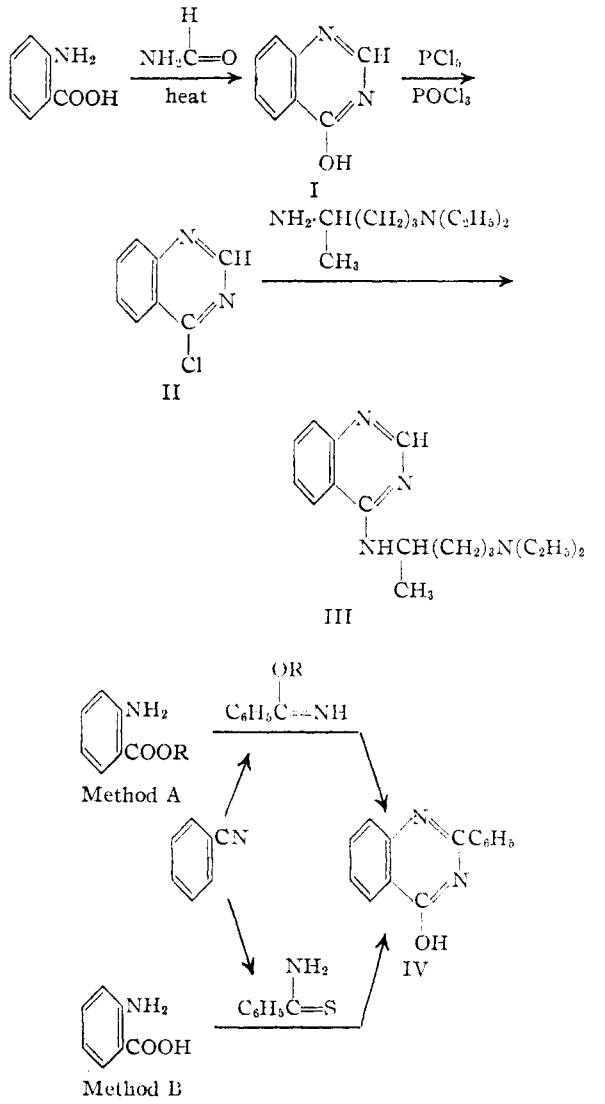
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF MOUNT HOLYOKE COLLEGE]

Quinazoline Derivatives.[1] I. The Synthesis of 4-(4′-Diethylamino-1′-methylbutylamino)-quinazoline (SN 11,534) and the Corresponding 2-Phenylquinazoline (SN 11,535)[2]

BY MARGARET M. ENDICOTT, EMILY WICK, MARIE L. MERCURY AND MARY L. SHERRILL

The investigation of quinazoline derivatives with an alkyl diamine side chain as potential antimalarial drugs was based in part on the similarity of quinazoline (benzopyrimidine) to quinoline (benzopyridine). The two compounds are very similar in reactivity, the heterocyclic ring in each having aromatic properties. The quinazolone nucleus has been found in certain alkaloids[3] and quinazoline derivatives have been reported as pharmaceuticals which affect blood pressure,[4] produce local anesthesia[4] and are active toward blood parasites.[5]

The synthesis of the two dialkylaminoalkylaminoquinazolines reported in this paper required the preparation from anthranilic acid of 4-quinazolone (I), 4-chloroquinazoline (II) and the condensation of the latter with 1-diethylamino-4-aminopentane to give the aminoquinazoline (III) as indicated in the chart. The 2-phenylquinazolone (IV) was prepared by two methods, the second being more satisfactory. Methyl or ethyl anthranilate was condensed with the corresponding alkyl imidobenzoate (Method A) and anthranilic acid with thiobenzamide (Method B). Subsequent reactions for the preparation of 2-phenyl-4-chloroquinazoline (V) and 4-(4′-diethylamino-1′-methylbutylamino) - 2 - phenylquinazoline (VI) were analogous to those for II and III.



(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 those compounds to which Survey Numbers have been assigned will be tabulated in a forthcoming monograph.

(3) Asahina, Manske, Robinson, *J. Chem. Soc.*, 1708 (1927).

(4) Paal and Busch, *Ber.*, **22**, 2683 (1889); Gabriel and Colman, German Patent 161,401, *Chem. Zentr.*, **76**, II, 182 (1905); British Patent 346,118, *Chem. Zentr.*, **102**, II, 87 (1931); Maffei, German Patent 525,653, *C. A.*, **25**, 4664 (1931).

(5) I. G. Farbenind. A. G. British Patents 287,179, 288,159, *C. A.*, **23**, 396 (1929); British Patent 330,583, *Chem. Zentr.*, **101**, II, 1773 (1930).

Experimental[6]

4-Qninazolone (I).—Anthranilic acid (137.1 g., 1.0 mole) was heated with excess of formamide (75.6 g.) for four hours at 120–125°.[7] The product was filtered and recrystallized from ethanol. The yield was 131.5 g. (90%) m. p. 215.5–216.5°.

4-Chloroquinazoline (II).—4-Quinazolone (14.6 g., 0.1 mole), phosphorus pentachloride (30 g., 0.14 mole) and phosphorus oxychloride (120 ml.) were refluxed for two hours at 115–118°.[8] The phosphorus oxychloride was removed by distillation at reduced pressure. The residue was extracted three times with ether. The undissolved material mixed with ether was poured into ice and water, and several ether extracts made. The ether extracts were freed from acid with sodium bicarbonate and dried. The product from the ether extract was recrystallized from hexane forming needle rosets, m. p. 96.5–97.5°, the yield was 8.3 g. (62.5%), 3.0 g. of 4-quinazolone being recovered. *Anal.* Calcd for $C_8H_5N_2Cl$: Cl, 21.54. Found: Cl, 21.46.

Picrate.—The chloroquinazoline formed this derivative[9] in an alcohol–ether solution. On recrystallization from absolute ethanol it formed yellow needles, m. p. 170–170.5°.

Anal. Calcd. for $C_{14}H_8O_7N_5Cl$: N, 17.78. Found: N, 17.50.[10]

4-(4′-Diethylamino-1′-methylbutylamino)-quinazoline (SN 11,534)[2] (III).—4-Chloroquinazoline (8.2 g., 0.05 mole) and 17.4 g. (0.10 mole) of 1-diethylamino-4-aminopentane (b. p. 80–81° at 11 mm., purified through the dithiocarbamate)[11] were refluxed in benzene[12,13,14] two to three hours and left overnight. After the benzene was distilled, the residual gum was treated with a saturated solution of potassium hydroxide and the mixture extracted with ether. The ether extracts were dried over solid potassium hydroxide and the ether distilled. The residual oil was heated at 150° at 18–20 mm., until the excess 1-diethylamino-4-aminopentane was removed. The solid residue recrystallized from hexane formed soft, white crystals, m. p. 101–101.5°. The yield was 13.7 g. (98–99%). This compound is soluble in ether, benzene, hot ligroin (90–95°) and hot hexane.

Anal. Calcd. for $C_{17}H_{28}N_4$: C, 71.29; H, 9.15; neut. equiv., 143.2. Found C, 71.66; H, 9.48[15]; neut. equiv., 143.6.[16]

Picrate.—This derivative formed readily[9] and was recrystallized from absolute ethanol in yellow crystals, m. p. 186.5–187.5°.

Anal. Calcd. for $C_{23}H_{29}O_7N_7$: N, 19.00. Found: N, 19.10.

4-(4′-Diethylamino-1′-methylbutylamino)-quinazoline Diphosphate Monohydrate (SN 11,534-5-3).—The method, a modification of that used for the 4-aminoquinolines,[14] was to add 85% phosphoric acid (9.1 g., 0.08 mole) to a suspension of the aminoquinazoline (11.5 g., 0.04 mole) in 40 ml. of water. To the cooled solution 300 ml. of dioxane was added and the phosphate separated, on standing, as a mixture of gum and crystalline solid. After removal of the water-dioxane layer, the phosphate gum, cooled in an ice-bath, became a mass of fine powdery crystals. The phosphate crystallized slowly from a water–ethanol (1:1) solution; the yield was 18.5 g. (95%), m. p. 138–140° (uncor.). On recrystallization from water–ethanol (1:3) the phosphate formed feathery crystals, m. p. 141–142° with dec. at 145°. The phosphate is very soluble in water and methanol, insoluble in other organic solvents.

Anal. Calcd. for $C_{17}H_{26}N_4 \cdot 2H_3PO_4 \cdot H_2O$: C, 40.79; H, 6.85; P, 12.38. Found: C, 40.81; H, 6.88;[17] P, 12.44.[18]

2-Phenyl-4-quinazolone (IV): Method A.—The methyl and ethyl esters of anthranilic acid were prepared in 70–75% yields.[19] The methyl and ethyl imidobenzoates were prepared from benzonitrile, the corresponding alcohol and hydrogen chloride according to the method of Derby.[20] The yield of methyl imidobenzoate (b. p. 109–110° at 27 mm.) was 75–80%, that of the ethyl imidobenzoate (b. p. 108–110° at 13.5 mm.) was 65–70%.

Methyl or ethyl anthranilate (0.2 mole) was heated with a slight excess (0.22 mole) of the corresponding alkyl imidobenzoate[21] for two hours at 210–220°. The solid product which separated on cooling was filtered, washed with methanol and dried. The crude 2-phenyl-4-quinazolone (m. p. 226–230° uncor.) was obtained in 30–40% yield.

(Method B).—Thiobenzamide (m. p. 116–117°) was obtained in 90–98% yield by the Gabriel method.[22] Thiobenzamide (27.2 g., 0.2 mole) and anthranilic acid (27.4 g., 0.2 mole) were heated[23] for two hours at 135–160°. The crude product was dissolved in hot cyclohexanone and the 2-phenyl-4-quinazolone separated in white feathery needles, m. p. 232.5–235.5°, the yield being 22 g. (50%). Recrystallization from cyclohexanone or 95% ethanol gave needles m. p. 235–236°.

4-Chloro-2-phenylquinazoline (V).—This was prepared and isolated by the method given for (II) the only difference being that a reaction temperature of 125–130° was necessary. From 11.1 g. (0.05 mole) of (IV) 9.1 g. (76.8%) of crude product (m. p. 122–123°) was obtained. This recrystallized from ligroin (90–95°) formed white crystals in rosets, m. p. 124–124.5°. It is very soluble in ether and benzene, and fairly soluble in boiling hexane. It is more soluble in cold ligroin than is 2-phenyl-4-quinazolone so traces of the latter can be removed by fractional crystallization.

Anal. Calcd. for $C_{14}H_9N_2Cl$: C, 69.86; H, 3.77; Cl, 14.73. Found: C, 70.08; H, 3.95;[10] Cl, 14.56, 14.88.[18]

Picrate.—This derivative crystallized slowly from alcohol–ether solution of the reagents and on recrystallization from 95% ethanol formed fine yellow needles, m. p. 191–192°.

Anal. Calcd. for $C_{20}H_{12}O_7N_5Cl$: N, 14.90. Found: N, 15.33.[10]

4-(4′-Diethylamino-1′-methylbutylamino)-2-phenylquinazoline (SN 11,535)[2] (VI).—In a trial preparation, the chlorophenylquinazoline (9.6 g., 0.04 mole) was refluxed with purified 1-diethylamino-4-aminopentane in 180 ml. of anhydrous benzene for six to seven hours. The reaction mixture was treated as in the case of III, but the product was a gum containing semicrystalline material. It was impossible to crystallize this from any organic solvent and it was converted into a phosphate.

In a repeated preparation using a larger sample of 4-

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

(7) Niementowski, *J. prakt. Chem.*, (2) **51**, 566 (1895).

(8) Gabriel and Stelzner, *Ber.*, **29**, 1314 (1896); Gabriel and Colman, *ibid.*, **37**, 3643 (1904); Bogert and May, THIS JOURNAL, **31**, 509 (1909); I. G. Farbenind. A. G., U. S. Patent 1,880,447, *C. A.*, **27**, 998 (1933).

(9) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, New York, N. Y., 1940, p. 149.

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

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

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

(13) Winthrop Chemical Co., U. S. Patent 2,233,970.

(14) "Coupling of Amines with 4-Chloroquinolines," N. L. Drake, R. C. Elderfield, C. S. Hamilton, Private Communication, Oct. 16, 1944.

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

(16) Electrometric titration by Elizabeth Sackmann, Mount Holyoke College.

(17) Analysis by F. Marx, Microanalytical Laboratory, Columbia University.

(18) Analysis by Jean Moore, Mount Holyoke College.

(19) E. Erdmann and H. Erdmann, *Ber.*, **32**, 1215 (1899).

(20) Derby, *Am. Chem. J.*, **39**, 442 (1908).

(21) Finger and Schupp, *J. prakt. Chem.*, (2) **74**, 154 (1906).

(22) Gabriel and Heymann, *Ber.*, **23**, 158 (1890).

(23) Pawlewski, *ibid.*, **36**, 2884 (1903); v. Walther, *J. prakt. Chem.*, (2) **67**, 460 (1903).

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.