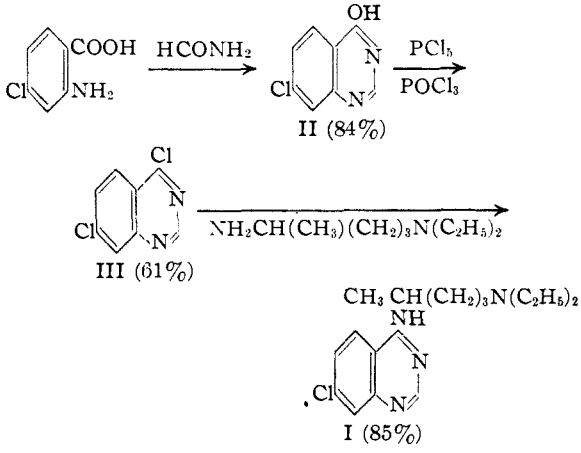
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

4-(4'-Diethylamino-1'-methylbutylamino)-7-chloroquinazoline[1]

BY CHARLES C. PRICE, NELSON J. LEONARD AND DAVID Y. CURTIN

A number of 4-dialkylaminoalkylaminoquinazolines, both unsubstituted and substituted in the 6-position, have been prepared and tested for antimalarial activity by Magidson and Golovchinskaya.[1a] They were found to be less toxic than the corresponding quinolines but had no antimalarial activity. In spite of these results, the reported antimalarial properties of 4-(4'-diethylamino - 1' - methylbutylamino) - 7 - chloroquinoline[2] have suggested the desirability of preparing and testing the quinazoline analog (I).

The method of preparation is that which has been used generally for the preparation of 4-aminoquinazolines. 4-Chloroanthranilic acid, which had been prepared by the reaction of 2,4-dichlorobenzoic acid with ammonia in an autoclave,[3] was converted to 7-chloro-4-quinazolone (II) by heating with formamide. This compound reacted with phosphorus pentachloride and phosphorus oxychloride to give 4,7-dichloroquinazoline (III) which, on treatment with 4-amino-1-diethylaminopentane, yielded the desired product (I).



This drug, SN-12,100,[4] was found to have activity as a suppressive for avian malaria equivalent or slightly superior to quinine.

(1) The work reported in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

(1a) Magidson and Golovchinskaya, *J. Gen. Chem.* (U. S. S. R.), **8**, 1797 (1938).

(2) Andersag, Breitner and Jung, German Patent 683,692 (1939); *C. A.*, **36**, 4973 (1942).

(3) German Patent 244,207; *Chem. Zentr.*, **83**, I, 867 (1912).

(4) The Survey Number, designated SN, identifies a drug listed under that number 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.

Experimental[5]

4-Chloroanthranilic acid was obtained from R. A. Bauman and D. M. Burness of this Laboratory, who prepared it according to the directions in a German patent[3] by treatment of 2,4-dichlorobenzoic acid with 30% ammonia and a catalytic amount of copper in an autoclave at 120° for fifty hours.

7-Chloro-4-quinazolone.—Thirty grams (0.17 mole) of 4-chloroanthranilic acid (m. p. 231–232° with decomposition) was heated with 18 g. (0.40 mole) of formamide in an oil-bath at 130° for forty-five minutes and then at 175° for one hour and fifteen minutes. After the flask had cooled, the solid residue was ground with 50 cc. of water and the suspension was filtered. The light brown solid which was collected weighed 25 g. (84%). It sintered at 250° and melted at 253–254° and was used in the next reaction without further purification. It was purified for analysis by recrystallization, with decolorization by activated charcoal, from an ethanol–water and also an ethanol–benzene mixture. The purified compound was a white crystalline solid, m. p. 252–254°.

Anal. Calcd. for $C_8H_5ClN_2O$: C, 53.20; H, 2.79; N, 15.52. Found: C, 53.08; H, 2.86; N, 14.63, 14.82, 15.33.*

4,7-Dichloroquinazoline.—7-Chloro-4-quinazolone (25.5 g.) was heated under reflux for three hours with 50 g. of phosphorus pentachloride and 200 cc. of phosphorus oxychloride. The solid dissolved after one hour. The phosphorus oxychloride was removed under reduced pressure at 80°. Benzene (200 cc.) was added and an insoluble white solid removed by filtration. The filtrate containing the dichloroquinazoline was evaporated to dryness. The crystalline residue was dissolved in boiling petroleum ether (b. p. 90–110°), decolorized with activated charcoal and filtered. On cooling, the product separated as white needles (17 g., 61%) melting at 132–134°. The compound was purified for analysis by further crystallization from petroleum ether and melted at 135–136°.

Anal. Calcd. for $C_8H_4Cl_2N_2$: C, 48.26; H, 2.02; N, 14.07. Found: C, 48.52; H, 2.03; N, 13.93.

4-(4'-Diethylamino-1'-methylbutylamino)-7-chloroquinazoline.—4-Amino-1-diethylaminopentane was purified by preparation of the dithiocarbamate followed by decomposition with concentrated hydrochloric acid and distillation.[6] The purified diamine (25 g., 0.16 mole, n^{28}D 1.4428) was added to 17.1 g. (0.085 mole) of 4,7-dichloroquinazoline dissolved in benzene which had been previously distilled from phosphorus pentoxide. The benzene solution was heated under reflux for three hours. Then 50 cc. of 20% aqueous sodium hydroxide was added and the benzene layer separated. The water layer was washed with three 20-cc. portions of benzene. The solvent was removed by distillation from the combined benzene layers and 40 cc. of acetone was added to the oily residue. Carbon disulfide (7 cc., 8 g., 0.10 mole) was added and the solution stirred and allowed to stand for fifteen minutes. The precipitate of the dithiocarbamate of unreacted 4-amino-1-diethylaminopentane, which had begun to appear almost immediately, was removed by filtration and washed with 20 cc. of acetone. More carbon disulfide (3 cc.) was added

(5) All melting points are corrected. The microanalyses were carried out by Miss Theta Spoor and Miss Lillian Hruda. All nitrogen analyses were made by the method of Dumas which, however, was found to be unsatisfactory in some cases. Those nitrogen analyses which are followed by an asterisk were made by the method of Dumas modified by the use in the combustion tube of a special platinum catalyst.

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

to the combined filtrates. Again the solution was allowed to stand and again the dithiocarbamate was removed and washed with acetone. The filtrate was evaporated to dryness on a steam cone under reduced pressure. The quinazoline remained as a slightly oily, light yellow solid. After being ground once with petroleum ether (b. p. 90–110°) it was collected in a filter. The yield of the crude quinazoline was 23.1 g. (85%) and it melted at 108–111°. It was further purified by recrystallization from 200 cc. of petroleum ether and decolorization with activated charcoal to give 17.7 g. (65%) of white crystals, m. p. 118–119°.

When it was dried at 20° over paraffin, it melted at 120–121°. The analysis indicated that water was present.

Anal. Calcd. for $C_{17}H_{25}ClN_4 \cdot 1.77H_2O$: C, 57.87; H, 8.15 Found: C, 57.88; H, 8.11.

A second sample was therefore prepared and analyzed after drying at 70° over phosphorus pentoxide and paraffin under reduced pressure. This sample melted at 115–116°.

Anal. Calcd. for $C_{17}H_{25}ClN_4$: C, 63.62; H, 7.85; N, 17.46. Found: C, 63.68; H, 7.56; N, 16.62, 17.66.*

The *dipicrate* was prepared and recrystallized from ethanol. It melted with decomposition at 205–206°.

Anal. Calcd. for $C_{17}H_{25}ClN_4 \cdot 2C_6H_3N_3O_7$: C, 44.70; H, 4.01. Found: C, 44.95; H, 4.22.

Summary

4 - (4′ - Diethylamino - 1′ - methylbutylamino)-7-chloroquinazoline has been prepared readily in good yield from 2,4-dichlorobenzoic acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Quinazolines. III. Syntheses of 4-Alkylaminoquinazolines[1]

BY BERT E. CHRISTENSEN, BRUCE GRAHAM AND ARTHUR J. TOMISEK

The introduction of alkylamino side chains to quinolines has resulted in the synthesis of several valuable drugs. A natural extension of this work has been to study the effect of similar substituents on other heterocyclic ring systems.

Because of the similarity of the quinoline to the quinazoline nucleus Magidson and Golovchinskaya[2] synthesized several 4-alkylaminoquinazolines for antimalarial purposes. The possibility of utilizing quinazolines for this purpose was later recognized by Dewar.[3] Although the few quinazoline drugs which have been reported have been found to be relatively inactive as antimalarial agents, the coupling with other effective side chains appears worthy of investigation.

The exceptional reactivity of the 4-chloroquinazoline simplifies the coupling with the amines which proceeds without the catalysts and vigorous conditions sometimes required in related reactions with the 9-chloroacridines. The syntheses were carried out in a benzene solution whenever the solubility of the amines permitted.

Alcohol was chosen as the solvent for the condensations with amino alcohols. The activity of the 4-chloroquinazolines did not appear to cause any complications by reacting with the hydroxyl groups of the amino alcohols or with the solvent, though the reaction probably did proceed in part via the 4-ethoxyquinazoline.[4]

Since the presence of acid[4] is known to activate 4-substituted haloheterocycles, hydrogen chloride was added for purposes of activation as well as isolation of the insoluble hydrochlorides. Condensation of 4-chloroquinazoline with ethanolamine indicated that the presence of acid did increase the reaction rate.

On the other hand, an attempted synthesis of 4-(ω-hydroxyhexylamino)-7-chloroquinazoline under conditions considered suitable resulted in an incomplete reaction. The addition of equimolar amounts of solid sodium hydroxide to the reaction mixture led to satisfactory yields. The function of the base is not known and is being investigated further.

Experiments using additional acid were not attempted with 2-(2′-aminoethoxy)-ethanol and 2-methyl-2-amino-1,3-propanediol since these compounds gave satisfactory yields in the initial trials.

Experimental[5]

4,6-Dichloroquinazoline.—This compound was prepared according to the directions given by Price and Curtin for 4,7-dichloroquinazoline.[6] Sixty-one grams (0.34 mole) of 6-chloro-4-hydroxyquinazoline[2] gave 55 g. (82%) of 4,6-dichloroquinazoline, m. p. 148–153°. The yield by this procedure was much better than reported for the original synthesis[2] of the compound.

4-(1-Piperidyl)-quinazoline (SN 12496).—A solution containing 20.75 g. (0.24 mole) of piperidine in 50 cc. of dry benzene was added with stirring to a solution of 20 g. (0.12 mole) of 4-chloroquinazoline in 200 cc. of dry benzene. After the mixture had cooled the piperidine hydrochloride was removed by filtration. The filtrate and washings were concentrated and then distilled *in vacuo*, b. p. 139–140° (5 mm.). The yield was 22 g. (85%) of a colorless sirup. The hydrochloride was obtained by dissolving the sirup in warm absolute alcoholic hydrogen chloride solution, cooling and filtering. A second fraction was obtained by evaporating the filtrate *in vacuo*. Both fractions were analytically pure white crystals, m. p. (dec.) 230° (obtained by dropping on a hot block).

4-(1-Morpholinyl)-quinazoline.—Five and four-tenths grams (0.062 mole) of morpholine and 5.08 g. (0.031 mole) of 4-chloroquinazoline in benzene solution were allowed to react according to the above directions. Morpholine

(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 Oregon State College. The Survey Number (SN) identifies a drug in the records of the Survey of Antimalarial Drugs. Published with the approval of the Monographs Publication Committee, Oregon State College, as Research Paper No. 101, School of Science.

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

(3) Dewar, *J. Chem. Soc.*, 619 (1944).

(4) Tomisek and Christensen, THIS JOURNAL, **67**, 2112 (1945); Banks, *ibid.*, **66**, 1127 (1944).

(5) All melting points are corrected.

(6) C. C. Price and D. Y. Curtin, unpublished work.