The chloroform solution thus obtained was extracted with an equal volume of 1 *M* citric acid. The extract was made strongly alkaline and extracted with ether. The material extracted by the ether, after drying, was distilled, the part boiling at 190–195° (0.15 mm.) being collected. The recovery was 19 g. (60%). After conversion to the oxalate, the drug was re-examined by the 8-plate technique and showed the presence of 3% of the more basic inhomogeneity and 2% of the less basic inhomogeneity, which is within acceptable limits.

Reduction of 8-Nitroquinoline Derivatives. (a) **With Stannous Chloride.**—This method has been described in detail in a preceding paper.[5] If the aminoquinoline was a liquid, it was extracted with ether or chloroform. The material obtained on removal of the solvent was used directly.

(b) **With Iron and Acetic Acid.**—In the case of the reduction of 7-methyl-8-nitroquinoline by method (a), some nuclear chlorination occurred despite all precautions. Pure 7-methyl-8-aminoquinoline was obtained by use of iron and acetic acid.[26] A mixture of 10 g. of 7-methyl-8-nitroquinoline, 100 ml. of water, 5 ml. of glacial acetic acid, 1 ml. of dibutyl ether and 10 g. of iron filings was heated under reflux with stirring on the steam-bath for seventeen hours. The mixture was filtered, the filtrate was made basic and filtered again. The precipitate was washed once with acetone, and the combined aqueous filtrate and acetone washings were extracted three times with ether. The solid residue from the acetone wash was extracted three times with boiling acetone and filtered after each extraction. The material from the combined acetone and ether extracts, after drying, was distilled, the fraction boiling at 172–175° (22 mm.) being collected. The distillate was recrystallized from alcohol.

The properties of the various 8-aminoquinolines are given in Table II. In all cases R_8 is NH_2.

(26) Private communication from Dr. Walter Lauer of the University of Minnesota.

Summary

1. The synthesis of fifty-one analogs of Pamaquine (Plasmochin) has been described.

2. The synthesis of five new derivatives of 8-aminoquinoline has been described.

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[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Synthetic Antimalarials. 8-(5-Isopropylaminoamylamino)-6-methoxyquinoline (SN-13,276)[1] and Some Related Compounds[2]

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Clinical studies have indicated that SN-13,276 is a promising antimalarial.[2] The present paper describes the preparation of the drug and some of its close relatives.

In general the method of preparation follows that of Plasmochin. 8-Amino-6-methoxyquinoline is alkylated by means of 1-chloro-5-isopropylaminopentane hydrochloride, the drug is isolated as its monohydrochloride, converted to free base, and precipitated from alcohol as the monophosphate.

Demethylation of SN-13,276 by means of hydriodic acid[3] at 100° yields the corresponding quinolinol which was submitted for testing as its dihydriodide. Care must be taken not to overheat the reaction mixture during the removal of the methyl group; at temperatures above 100°, an excessive amount of the side-chain suffers cleavage from the nucleus.

The side-chain of SN-13,276 has been attached to 8-amino-5,6-dimethoxyquinoline, and to 8-amino - 5 - chloro - 6 - methoxyquinoline. The corresponding drugs separate nicely as monohydriodides.

The other relatives discussed are 8-(5-*t*-butylaminoamylamino) - 6 - methoxyquinoline and 8-(5-*t*-amylaminoamylamino) - 6 - methoxyquinoline.[4]

The preparation of the side-chain of these drugs is easily accomplished from dihydropyran. When dihydropyran is treated with aqueous acid, a vigorous reaction takes place and the dihydropyran dissolves. If this solution is brought to about *p*H 8.0 by means of isopropylamine and subjected to hydrogenation in the presence of Adams catalyst and a molar equivalent of isopropylamine, 5-isopropylamino-1-pentanol is produced and can be isolated as the hydrochloride. Thionyl chloride converts the hydrochloride practically quantitatively into 1-chloro-5-isopropylaminopentane hydrochloride, the compound necessary for the preparation of SN-13,276. Other amines can be substituted quite satisfactorily for isopropylamine in this synthesis.

The alkylation of 8-amino-6-methoxyquinoline by 1 - chloro - 5 - isopropylaminopentane hydrochloride takes place smoothly. The quinoline (2 moles), the chloride-hydrochloride (1 mole), and a small amount of water are stirred at 80° for twenty hours (internal t.) and then at 103–104° for four hours. The melt is poured into a small amount of water and brought to about *p*H 5.0 by means of alkali and sodium acetate. Extraction of the hot solution with benzene or toluene removes excess nucleus. When the extracted

(1) See Antimalarial Drugs, 1941–1945, F. Y. Wiselogle, Editor, in press. The survey number (SN) identifies the drug in the Survey Office and in the monograph.

(2) This work was done under a contract recommended by the Committee on Medical Research between the Office of Scientific Research and Development and the University of Maryland.

(3) See Drake, *et al.*, THIS JOURNAL, **68**, 1536 (1946), for a similar demethoxylation of SN-11,191.

(4) Survey numbers will not be assigned to any more drugs, at least at present. Some of the compounds in the present paper will be given with the U. M. numbers by which they will be identified to the pharmacologists who test them.

solution is cooled, the monohydrochloride of SN-13,276 separates as a gray solid. For purification, the filtered hydrochloride is converted by means of excess sodium hydroxide to free base, extracted with ether and, after removal of the ether by distillation, precipitated from ethanol solution as monophosphate.

Experimental

1-Chloro-5-isopropylaminopentane Hydrochloride.—A mixture of 84 ml. of concentrated hydrochloric acid and 1 liter of distilled water was placed in a 2-liter beaker fitted with an efficient glass stirrer and was cooled to 0–5° in an ice-bath. The ice-bath was removed and 336 g. (4.0 moles) of dihydropyran[5] was added in one portion. The resulting mixture was stirred until it became homogeneous, allowed to stand for ten minutes, and then cooled in an ice-bath to 10–15°. Isopropylamine was then added slowly with cooling until the *p*H of the mixture was 8.0; about 59.5 g. (81.6 ml.) of amine was required. An additional 236 g. (4.0 moles) of isopropylamine was then added to the cold solution while the temperature was held below 20°. The mixture was transferred to a hydrogenation bomb and hydrogenated at 25° under about 3000 p.s.i. initial pressure in the presence of Adams catalyst. About three hours were necessary for the hydrogenation. Temperature and pressure seem to have little effect on the yield; the hydrogenation proceeds quite smoothly at room temperature.

When the reductive alkylamination was complete, the charge was removed from the bomb and filtered free from catalyst. Solid sodium hydroxide (60 g.) was added to make the mixture strongly basic, and excess isopropylamine was removed by distillation until the vapor temperature was 95–100°. When the alkali was added, two phases appeared. After the distillation was complete, the lower aqueous phase was separated from the organic layer and 1 liter of petroleum ether (90–100°) was added to the aqueous phase. The addition of petroleum ether caused the separation of some additional aminoalcohol as a third layer. The *wet* aminoalcohol is practically insoluble in petroleum ether; the *dry* aminoalcohol is completely soluble in warm petroleum ether in the concentrations used. The upper layer (or upper two layers if a total of three is present) was separated, added to the original organic layer, and mixed with an additional 3 liters of petroleum ether. The resulting two-phase system was dried by refluxing the water–petroleum ether azeotrope through a suitable water trap. When the solution was dry, the second liquid phase had disappeared and a clear petroleum ether solution containing some suspended inorganic matter had resulted. The aminoalcohol may crystallize slowly from the dry petroleum ether solution if the latter is allowed to stand for some time.

The solution was filtered and transferred to a 5 liter three-necked flask fitted with an *efficient* stirrer, a drying tube, and a gas inlet tube which did not dip below the surface. The flask was cooled in an ice-bath and dry hydrogen chloride was blown slowly over the surface of the liquid until the mixture was just acid. An appreciable excess of hydrogen chloride causes the precipitated hydrochloride to become gummy. The suspension of hydrochloride was filtered by suction and the product was dried to constant weight at 60°. The yield was 513 g. (71%). The crude hydrochloride was found to be satisfactory for the next step; recrystallization from a 1:10 alcohol–acetone mixture yielded a product which melted at 97.7–98.4°. *Anal.* Calcd. for $C_8H_{19}NO\cdot HCl$: Cl, 19.50. Found: Cl, 19.29, 19.28 (Volhard).

The conversion of 5-isopropylamino-1-pentanol hydrochloride to the corresponding chloride-hydrochloride by means of thionyl chloride proceeded smoothly. To an ice-cold suspension of 1448 g. (8.0 moles) of 5-isopropylamino-1-pentanol hydrochloride in 8 l. of petroleum ether (90–100°) contained in a three-necked flask fitted with a stirrer, a dropping funnel, and a reflux condenser connected to a gas-absorption trap, was added 1056 g. (8.8 moles) of *pure* thionyl chloride over a period of two hours. The hydrochloride became dark colored and pasty as the reaction proceeded. After addition of the thionyl chloride was complete, the mixture was warmed to 50° for an hour and then boiled under reflux for six hours. The reflux condenser was then replaced by a condenser set for downward distillation, and 500 ml. of petroleum ether was distilled to remove excess thionyl chloride. The mixture was allowed to cool to room temperature and was filtered; the product was dried to constant weight *in vacuo*. The yield was 1545 g. (97%); the product melted at 112–120°. Recrystallization from acetone–ether yielded a product which melted at 125–126°. *Anal.* Calcd. for $C_8H_{18}NCl\cdot HCl$: Cl^-, 17.71. Found: Cl^-, 17.68, 17.54 (Volhard).

8-(5-Isopropylaminoamylamino)-6-methoxyquinoline Monophosphate (SN-13,276-5).—A 250-ml., three-necked flask fitted with a mechanical stirrer, a reflux condenser, and a thermometer extending into the reaction mixture, was charged with 69.6 g. (0.40 mole) of 8-amino-6-methoxyquinoline, 40.0 g. (0.20 mole) of 5-chloro-1-isopropylaminopentane hydrochloride, and 50 ml. of water. The mixture was stirred and heated at 80° for twenty hours and then at 103° for four hours (temp. of reactants).

The melt was poured into 200 ml. of water, and enough concentrated sodium hydroxide solution was added to bring the *p*H of the mixture to about 4.5; solid sodium acetate trihydrate was then added until the *p*H was 5.0. The mixture, which contained a considerable amount of solid and semi-solid at this point, was heated to 65° and extracted at that temperature with four 200-ml. portions of benzene to remove excess nucleus. The combined benzene extracts were washed with one 20-ml. portion of hot water, and the aqueous layer was separated and added to the main portion. The dried benzene extracts yielded 35 g. of 8-amino-6-methoxyquinoline when they were distilled.

The combined aqueous portions were allowed to cool, whereupon the monohydrochloride of the base separated. The light-gray solid was separated by filtration, pressed as dry as possible on the funnel, and then dissolved in 200 ml. of water at 50°. A solution of 10 g. of sodium hydroxide in 20 ml. of water was added, the strongly alkaline mixture was cooled to 25°, and extracted with four 150-ml. portions of ether. A small amount of black emulsion appeared between the layers while the first extraction was being carried out; the emulsion layer was removed and filtered by suction and the filtrate was returned to the aqueous layer for further extraction. A very thin layer of black tar remained on the filter paper. The ether extracts were combined, washed with three 50-ml. portions of water, and dried over anhydrous magnesium sulfate. The ether was then removed from the filtered dry solution by distillation on a steam-bath; the residue weighed 59 g. A small aliquot was dissolved in excess 0.1 *N* hydrochloric acid and back-titrated to about *p*H 6.8 with standard alkali; from this titration the amount of base in the residue was calculated.

The base was next dissolved in 550 ml. of 95% ethanol in a flask provided with a stirrer, a reflux condenser, and a funnel for addition of acid. The mixture was stirred and boiled under reflux while a solution of 17.0 g. (0.147 mole) of 85% phosphoric acid in 30 ml. of 95% ethanol was added over a period of about five minutes. Pale yellow crystals of the monophosphate soon appeared; the mixture was heated under reflux for fifteen minutes and then allowed to cool with stirring for an hour. After the mixture had been finally cooled with stirring in an ice-bath for two hours, it was filtered. The yellow crystals were washed with 50 ml. of ice-cold 95% alcohol and finally dried in a vacuum oven at 50°. They weighed 56.0 g. and melted at 189–189.5°. The yield was 70% based on either side chain or nucleus. *Anal.* Calcd. for $C_{18}H_{27}N_3O\cdot H_3PO_4$: C, 54.13; H, 7.58. Found: C, 53.89, 53.82; H, 7.74, 7.93.

Certain pertinent data follow: SN-13,276 boils at 165–

(5) Prepared by dehydrating tetrahydrofurfuryl alcohol over alumina at 330°. See "Org. Syn.," **23**, 25 (1943); the product used boiled at 87°.

170° (20 microns) (bath temp., 200–210°) and has $n^{25}D$ 1.5785. *Anal.* Calcd. for $C_{18}H_{27}N_3O$: C, 71.73; H, 9.02. Found: C, 72.13; H, 9.39.

The monohydrochloride melts at 152–153°, the dihydrochloride at 218–219° dec. with previous sintering at 216°. *Anal.* Calcd. for $C_{18}H_{27}N_3O \cdot HCl$: C, 63.98; H, 8.35. Found: C, 64.17, 64.44; H, 8.52, 8.25. Calcd. for $C_{18}H_{27}N_3O \cdot 2HCl$: C, 57.75; H, 7.80. Found: C, 57.94, 57.73; H, 7.75, 7.74.

The solubility of the dihydrochloride in water is 0.5 g./ml. at 10°, in ethanol, 0.017 g./ml. at 5°; the *p*H of a solution containing 3 g./25 ml. is 2.0.

The solubility of the monohydrochloride in water at 10° is 0.012 g./ml., in ethanol, 0.026 g./ml. at 5°. The *p*H of a saturated solution at 10° is 6.05.

8-(5-Isopropylaminoamylamino)-6-quinolinol Dihydriodide (UM-122-Q).—The removal of the methyl group from SN-13,276 and the formation of the dihydriodide of the product were carried out essentially as were the similar transformations of SN-11,191.[6] The over-all yield from 50.6 g. of SN-13,276 to the dihydriodide was 35 g. (38%); the product melted at 202–203.5°. *Anal.* Calcd. for $C_{17}H_{25}N_3O \cdot 2HI$: C, 37.61; H, 5.02. Found: C, 37.94, 37.77; H, 5.04, 5.42.

8-(5-Isopropylaminoamylamino)-5,6-dimethoxyquinoline Monohydriodide (UM-132-Q).—The preparation of the base for this salt from 8-amino-5,6-dimethoxyquinoline[6] and 5-chloro-1-isopropylaminopentane hydrochloride was so similar to the preparation of SN-13,276 that a detailed description is unnecessary. A few salient points, however, deserve mention. The monohydrochloride was too soluble to make direct isolation feasible; the base was therefore extracted from a strongly basic solution and distilled; it boiled at 157–160° (3 microns) (bath t. 210–215°). The monohydriodide was prepared by titrating 41.5 g. of base with hydrochloric acid to *p*H 6.0, and then adding a molar equivalent plus 10% excess of potassium iodide to the solution. The product separated cleanly and was recrystallized from about 400 ml. of water. Two recrystallizations gave 51 g. of product whose melting point was 154–155°. The over-all yield of salt was 45%. *Anal.* Calcd. for $C_{19}H_{29}N_3O_2 \cdot HI$: C, 49.7; H, 6.54. Found: C, 49.72, 49.47; H, 6.75, 6.58.

8-(5-Isopropylaminoamylamino)-5-chloro-6-methoxyquinoline Monohydriodide (UM-130-Q).—The preparation of the base for this salt from 8-amino-5-chloro-6-methoxyquinoline[6] and 5-chloro-1-isopropylaminopentane hydrochloride followed exactly that of UM-132-Q. Large volumes of ether were necessary to extract the base for the latter is relatively sparingly soluble. The base boiled at 180–195° (5 microns) (bath temp. 200–220°). The monohydriodide melted at 155–156° and was obtained in 16% yield. *Anal.* Calcd. for $C_{18}H_{26}N_3OCl \cdot HI$: C, 46.6; H, 5.87. Found: C, 46.66, 47.05; H, 6.24, 6.12.

8-(5-*t*-Butylaminoamylamino)-6-methoxyquinoline Monohydrochloride (SN-13,473-4).—The 5-chloro-1-*t*-butylaminopentane hydrochloride necessary for this drug was prepared according to the method described for 5-chloro-1-isopropylaminopentane hydrochloride except that *t*-butylamine[7] was substituted for isopropylamine. The monohydrochloride of SN-13,473 is rather sparingly soluble and separated in good yield from the solution from which excess nucleus had been extracted by means of benzene. The salt was recrystallized from water for purification. The yield was 49% over-all; the salt melted at 168–169°. *Anal.* Calcd. for $C_{19}H_{29}N_3O \cdot HCl$: C, 64.8; H, 8.53. Found: C, 64.95, 64.69; H, 8.48, 8.39.

8-(5-*t*-Butylaminoamylamino)-6-methoxyquinoline (SN-13,473).—This base is a light yellow viscous oil which distills at 170° (3 microns) (bath 210–220°); $n^{25}D$ 1.5721. *Anal.* Calcd. for $C_{19}H_{29}N_3O$: C, 72.4; H, 9.21. Found: C, 72.41; H, 9.30.

5-*t*-Butylamino-1-pentanol and its Hydrochloride.—The hydrochloride of this aminoalcohol was prepared by the method described above. It is conveniently isolated as its hydrochloride which melts at 153–153.5°. *Anal.* Calcd. for $C_9H_{21}NO \cdot HCl$: C, 55.3; H, 11.25. Found: C, 55.06, 55.09; H, 11.36, 11.12.

The aminoalcohol boils at 230° under atmospheric pressure and melts at 62–63.5°. *Anal.* Calcd. for $C_9H_{21}NO$: C, 67.9; H, 13.21. Found: C, 68.05, 68.30; H, 13.58, 13.47.

1-Chloro-5-*t*-Butylaminopentane Hydrochloride.—This substance was prepared by the action of thionyl chloride on 5-*t*-butylamino-1-pentanol hydrochloride suspended in petroleum ether as described above. The substance melts at 125–127°. *Anal.* Calcd. for $C_9H_{20}NCl \cdot HCl$: C, 50.5; H, 9.82. Found: C, 50.73, 50.47; H, 9.90, 10.30.

8-(5-*t*-Amylaminoamylamino)-6-methoxyquinoline Monohydrochloride (UM-131-Q).—This hydrochloride was prepared from free base isolated by distillation at the end of a procedure substantially the same as that described above under UM-132-Q and UM-130-Q. The monohydrochloride separated while the distilled base was being titrated with hydrochloric acid. It was recrystallized from water for analysis. The base boiled at 198–205° (2 microns); $n^{25}D$ 1.5675. The monohydrochloride, dried in a vacuum oven at *ca.* 50°, is hydrated and has a melting point of 115–125°. This product contains 4.53% of moisture (determined by heating at 100° in vacuum). The moisture-free product melts at 138.5–140.5° after sintering at 136°. *Anal.* Calcd. for $C_{20}H_{31}N_3O \cdot HCl$: C, 65.63; H, 8.81. Found: C, 65.68, 65.60; H, 8.57, 8.67.

The composition of the hydrated substance corresponds closely to that of a monohydrate; moisture determined was 4.53%, that required, 4.69%.

Summary

1. The preparation and some of the properties of 8-(5-isopropylaminoamylamino)-6-methoxyquinoline (SN-13,276) are discussed.

2. The preparation of 8-(5-isopropylaminoamylamino) - 6 - quinolinol dihydriodide from SN-13,276 is described.

3. The preparation of some relatives of SN-13,276, *viz.*, 8-(5-isopropylamino)-5,6-dimethoxyquinoline monohydriodide, 8-(5-isopropylaminoamylamino) - 5 - chloro - 6 - methoxyquinoline monohydriodide, 8 - (5 - *t* - butylaminoamylamino) - 6 - methoxyquinoline (SN-13,473), and 8 - (5 - *t* - amylaminoamylamino) - 6 - methoxyquinoline, is described.

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(6) See Drake, *et al.*, THIS JOURNAL, **68**, 1536 (1946).

(7) See Campbell, Sommers and Campbell, *ibid.*, **68**, 140 (1946), also Karabinos and Serijan, *ibid.*, **67**, 1856 (1945). We carried out the hydrogenation at high pressure.