3. The preparation and properties reported in the literature for 3-chloro-8-aminoquinoline are corrected.

4. The methods used for the preparation of each quinoline nucleus are indicated.

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[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Synthetic Antimalarials. Some Derivatives of 8-Aminoquinoline[1]

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Plasmochin (pamaquine), 8-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline, and its derivatives have been the subject of an immense amount of research because of the reported curative action of Plasmochin on vivax malaria[2] when the drug is administered with quinine at approximately the maximum tolerated dosage level. The high toxicity of Plasmochin which is reputedly greater for non-Caucasian races, has prompted an intensive search for a better drug which will possess the curative action of plasmochin and be less toxic.

The present paper describes the preparation and properties of a number of plasmochin derivatives which were prepared with the above end in view.[3] The pharmacology of these drugs will be found elsewhere.[2]

N-Alkyl derivatives of 8-aminoquinoline are prepared by treating 8-aminoquinoline with a suitable alkylating agent, usually an alkyl halide. The desired compounds have a methoxyl group in the 6-position, and it has proved impossible in our laboratories and elsewhere[4] to use the Bucherer reaction to introduce a desired side chain in place of the hydroxyl group of a 6-methoxy-8-quinolinol, although the reaction is successful when applied to 8-quinolinol. Reductive alkylation has also proved impossible thus far. Alkylation, therefore, remains the only useful method of preparing the desired compounds.

In our work, alkylation was carried out by one of three general procedures as shown in Table I.

Method I consisted essentially in heating together two moles of the appropriate 8-aminoquinoline, one mole of the proper 1-halo-x-alkyl (or dialkyl) aminoalkane hydrohalide, and a small amount of water at successively higher temperatures until the mixture was eventually heated under reflux for several hours (about 100–105° inside t.). The resulting melt was poured into excess hydrochloric acid and the precipitated hydrochloride of the nucleus was removed by filtration and washed with cold water. The resulting filtrate was brought to about pH 5 by the addition of sodium acetate, and extracted with ether to remove the remainder of the nucleus. The extracted solution was made strongly basic by the addition of concentrated sodium hydroxide solution and again extracted with ether. The ether was then removed from the combined extracts by distillation, and the residue was distilled in high vacuum.[5] Method II was essentially that described by Rohrman and Shonle,[6] and method III was a variation of this procedure according to which Cellosolve (ethyleneglycol monoethyl ether) and water were used in place of alcohol, and some sodium acetate was added as buffer.

By far the majority of the drugs were submitted as salts; in a few cases where crystalline salts could not be obtained the compounds were submitted as a salt in an aqueous-alcoholic solution.

Table I lists the compounds prepared with the exception of SN-13,276 and some closely related compounds.[3] Those bases for which no carbon and hydrogen analyses are given were analyzed as salts, and the analytical data appear in the experimental part. The free bases are heavy, high-boiling oils which are very susceptible to air oxidation and are difficult to keep in a state of analytical purity; for this reason it was customary to purify salts for analysis.

Procedures are given for the preparation of intermediates only when the methods used are new or represent a substantial improvement over methods to be found in the literature.

Of these intermediates, only 5,6-dimethoxy-8-aminoquinoline deserves special mention here. This compound was prepared by a four-step process from veratrole. Nitration of veratrole in acetic acid produced 4,5-dinitroveratrole in one step. This substance in methanol was subjected to ammonolysis in a standard hydrogenation bomb. The resulting aminonitroveratrole was obtained from the ammonolysis by crystallization and after drying was used in a Skraup synthesis. The secret of the success of this Skraup reaction is

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

(2) A Survey of Antimalarial Drugs 1941–1945, F. Y. Wiselogle, Editor, Survey Office Monograph, in press. The term curative is used to designate that the drug prevents the relapses which occur in the absence of an additional infection and which are characteristic of vivax malaria.

(3) See also Drake *et al.*, THIS JOURNAL, **68**, 1529 (1946).

(4) Dr. R. C. Elderfield, Columbia University, private communication.

(5) For an alternate procedure which makes possible a cleaner separation of nucleus see ref. 3.

(6) Rohrman and Shonle, THIS JOURNAL, **66**, 1640 (1940).

a *very* short reaction time[7] (less than four minutes). Our early experiments with this Skraup reaction by all of the known modifications were uniformly unsuccessful until a very short reaction time was employed.

The resulting 5,6-dimethoxy-8-nitroquinoline was reduced by means of stannous chloride, and the aminoquinoline was isolated by filtration from the reduction mixture after the latter had been made strongly alkaline to dissolve tin salts. One crystallization from alcohol sufficed to yield a product which was satisfactory for use in alkylation processes. The over-all yield from 4,5-dinitroveratrole was 16–19%.

It should be emphasized that the ease of purification of 8-aminoquinoline drugs is influenced in large measure by the purity of the starting materials. The 6-methoxy-8-aminoquinoline[8] used in our work was purified by distillation under nitrogen at about 50 microns pressure followed by crystallization from methanol (0.4 ml. methanol/g. base). 6-Methoxy-8-aminoquinoline purified by distillation only contains some very easily oxidizable substance which is the cause of the rapid discoloration of the product when exposed to air. A distilled product, recrystallized from methanol several times, will remain colorless even in the open air for a relatively long period of time. One crystallization after distillation removes the bulk of the unknown contaminant and yields a product which is quite satisfactory. The homogeneity of 8-amino-6-methoxyquinoline so purified is about 98%.[9]

It will be noted that the yields given in Table I are rather low. These figures should not be considered to represent the optimum yields obtainable in any case; it should be remembered that the object of our work was to prepare for screening a large number of pure drugs in the shortest possible time. It seems likely in the light of our accumulated experience that the majority if not all of these yields could be raised to 50–70% by proper attention to detail.

Experimental[10]

8-(5-Aminoamylamino)-6-methoxyquinoline Diphosphate (SN-3851-5).[11]—6-Methoxy-8-(5-phthalimidoamylamino)-quinoline was prepared from 8-amino-6-methoxyquinoline and N-(5-bromoamyl)-phthalimide[11a,12] by method II (nucleus:phthalimide = 2:1). Unreacted nucleus was removed by distillation in vacuum, and the residue was subjected to hydrolysis in a large excess of boiling concentrated hydrochloric acid overnight. The solution was concentrated in vacuum and made strongly alkaline with concentrated sodium hydroxide. A dark brown oil separated and was separated from the aqueous layer. The oil was dissolved in methanol and a small amount of gummy product was removed by filtration. The filtrate was brought to an apparent *p*H of 4.1 by means of 85% phosphoric acid whereupon the salt separated as a yellow-brown precipitate. The phosphate was recrystallized from an ethanol–water solution (2.5:1) with use of decolorizing carbon. The diphosphate, which melted at 207–209°, was obtained in 22% over-all yield (based on one-half the amount of nucleus used). The estimated inhomogeneity[9] was 16 ± 5%. *Anal.* Calcd. for $C_{18}H_{21}N_3O\cdot 2H_3PO_4$: C, 39.56; H, 5.98. Found: C, 39.64, 39.50; H, 5.91, 5.92.

8-Amino-5-chloro-6-methoxyquinoline.[13]—One hundred and thirteen grams of acetic anhydride was added to 174 g. of 8-amino-6-methoxyquinoline in 260 ml. of acetic acid and the resulting solution was heated to boiling under reflux for ten minutes. One ml. of water was added, and the mixture was cooled and transferred to an 8-liter battery jar, whereupon an ice-cold solution of 71 g. of chlorine in 1.75 liter of acetic acid was added over a period of ten seconds to the vigorously stirred solution. 8-Acetamino-5-chloro-6-methoxyquinoline hydrochloride separated rapidly and the mixture became semi-solid. Water (4.35 liter) and concentrated ammonium hydroxide (170 ml.) were added and the slurry was stirred for a few minutes and filtered and sucked as dry as possible. The product was suspended in 870 ml. of hot water in an apparatus provided with a stirrer and a reflux condenser; the mixture was stirred and heated while 870 ml. of 1:1 hydrochloric acid was added through the condenser. Boiling and stirring were continued for fifty minutes, whereupon heating was discontinued and an ice-bath was placed about the flask while 520 ml. of ammonium hydroxide was added. The product was removed by filtration; it melted at 150–152°. The crude product was dissolved in about 4 liters of hot methanol, treated with decolorizing carbon, and allowed to crystallize. The yield was 125–135 g. (60–65%); m. p. 153–154°.

1-Bromo-6-methoxyhexane.[14,15]—A solution of 230 g. of sodium in 4.5 l. of *anhydrous* methanol was added over a five-hour period to a stirred refluxing solution of 2440 g. of hexamethylene bromide in 2.6 l. of *anhydrous* ether. The mixture was boiled under reflux for an additional three hours whereupon the condenser was adjusted for downward distillation and 4 liters of distillate was removed. The precipitated sodium bromide was removed by filtration and washed with 2 liters of dry ether. After the combined filtrate and washings had been washed with three 1.5-liter portions of water, the organic layer was dried and the product was obtained by fractional distillation. The following fractions were obtained: dimethoxyhexane, 520 g., b. p. <110° (30 mm.); bromomethoxyhexane, 920 g., b. p. 110–113° (30 mm.); hexamethylene bromide, 500 g., residue. The yield was 47% (based on the sodium used); the recovered 1,6-dimethoxyhexane was reconverted into hexamethylene bromide by adding it to hexamethylene glycol which was being converted to the dibromide in the usual way.[16]

1-Diethylamino-6-methoxyhexane.—A mixture of 640 g. of diethylamine and 390 g. of 1-bromo-6-methoxyhexane was heated under reflux and stirred for sixty-four hours. Excess diethylamine was then removed by distillation and the residue was poured into an excess of dilute hydrochloric acid. After unreacted 1-bromo-6-methoxyhexane and any other neutral products had been extracted from the aque-

(7) This important fact which makes the difference between success and failure was discovered in the laboratories of Columbia University. See R. C. Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946). Elderfield used 4-acetamino-5-nitroveratrole obtained by nitrating 4-acetaminoveratrole. The reaction works equally well with 4-amino-5-nitroveratrole.

(8) Purchased from the Winthrop Chemical Company.

(9) Determined by the counter-current extraction process. See Craig, *J. Biol. Chem.*, **155**, 519 (1944); Craig, *et al., ibid.*, **161**, 321 (1945). We should like to express our thanks to Dr. R. C. Elderfield for his kindness in having this determination carried out for us.

(10) Microanalyses by Miss Eleanor Werble of this Laboratory.

(11) (a) Baldwin, *J. Chem. Soc.*, 2959 (1929); (b) Beer, *J. Gen. Chem.* (U. S. S. R.), **9**, 2158 (1939); (c) Magidson and Bobyshev, *ibid.*, **8**, 899 (1938); (d) Tate and Vincent, *Parasitology*, **25**, 411 (1933).

(12) (a) A. Manasse, *Ber.*, **35**, 1367 (1902); (b) the substituted phthalimide was prepared according to "Org. Syn.," Coll. Vol. I, 119 (1941).

(13) R. Robinson and M. L. Tomlinson, *J. Chem. Soc.*, 1524 (1934).

(14) R. Dionneau, *Compt. rend.*, **145**, 127 (1907); *Ann. Chem. Phys.*, [9] **3**, 234 (1915).

(15) P. C. Mitter and S. Mukherjee, *J. Indian Chem. Soc.*, **19**, 303 (1942).

(16) "Org. Syn.," **20**, 24 (1940).

TABLE I

	Coupling product	SN	Procedure[a]	Isolated
1	8-(5-Aminoamylamino)-6-methoxyquinoline	3,851	HCl hydrolysis of crude phthalimido cpd.	As diphosphate
2	5-Chloro-8-(6-diethylaminohexylamino)-6-methoxyquinoline	13,694	III[c]	Directly as monohydrobromide and by molecular distn.
3	5-Chloro-8-(6-ethylaminohexylamino)-6-methoxyquinoline	13,695	III[c]	Directly as monohydrobromide
4	8-(6-Dibutylaminohexylamino)-6-methoxyquinoline	11,423	I	Vacuum distillation (twice)
5	8-(3-Dibutylaminopropylamino)-6-methoxyquinoline	2,026	I	Vacuum distillation (twice)
6	8-(10-Diethylaminodecylamino)-6-methoxyquinoline	12,892	II[d]	Molecular distillation (twice)
7	8-(11-Diethylaminohendecylamino)-6-methoxyquinoline	11,425	II[c]	Molecular distillation (twice)
8	8-(6-Diethylaminohexylamino)-5,6-dimethoxyquinoline	12,324	II	Molecular distillation (twice)
9	8-(6-Diethylaminohexylamino)-6-methoxyquinoline	11,191	I; II	Vacuum distillation (twice)
10	8-(3-Diethylaminopropylamino)-5,6-dimethoxyquinoline	11,889	II[d]	Vacuum distillation (twice)
11	8-(3-Diethylaminopropylamino)-6-methoxyquinoline	3,115	I	Vacuum distillation (twice)
12	8-(11-Di-*n*-hexylaminohendecylamino)-6-methoxyquinoline	12,449	I[e]	Molecular distillation (twice)
13	8-(6-Dimethylaminohexylamino)-6-methoxyquinoline	12,322	II[f]	Molecular distillation
14	8-(6-Di-*n*-octylaminohexylamino)-6-methoxyquinoline	11,424	I[g]	Vacuum distillation (twice)
15	8-(3-Di-*n*-octylaminopropylamino)-6-methoxyquinoline	11,422	I[g]	Vacuum distillation (twice)
16	8-(6-Isopropylmethylaminohexylamino)-6-methoxyquinoline	12,325	I[c]; II	Vacuum distillation (twice)
17	8-(6-Diethylaminohexylamino)-6-quinolinol	13,697	Demethoxylation of SN 11,191[c]	As dihydriodide
18	1-(4-Diethylamino-1-methylbutyl)-3-(6-methoxy-8-quinolyl)-urea	12,594	[c]	Crystallization

[a] Procedure I is condensation in aqueous medium; Procedure II is an alcoholic condensation; and Procedure III utilizes a sodium acetate-buffered cellosolve–water condensation medium. [c] Procedure described in the experimental part. [d] The extraction was made with ether. [e] After condensation, the mixture was immediately made alkaline and the extraction performed with chloroform. [f] Both ether and chloroform were used in the extraction. [g] The condensation mixture was immediately made alkaline and extracted due to insolubility of the product.

ous acid solution by means of ether, strong alkali was added to liberate the amine and the latter was extracted with ether. The product was obtained by distillation; yield, 350 g. (93%); b. p. 104–105° (15 mm.).

1-Bromo-6-diethylaminohexane Hydrobromide.—To 154 g. of 1-diethylamino-6-methoxyhexane was added 855 ml. of constant boiling hydrobromic acid. The mixture was boiled for four hours, whereupon the excess of hydrobromic acid was removed under the vacuum of a good water pump. The residue was finally heated (bath t. 100–120°) for two hours under a pressure of less than a millimeter to remove the last of the moisture. The resulting light-brown solid weighed 256 g. (98%) and was used directly without further purification.

5-Chloro-8-(6-diethylaminohexylamino)-6-methoxyquinoline (SN-13,694).—A mixture of 522 g. of 8-amino-5-chloro-6-methoxyquinoline, 792 g. of 1-bromo-6-diethylaminohexane hydrobromide, 680 g. of sodium acetate trihydrate, 625 ml. of water, and 625 ml. of cellosolve was boiled under reflux for seventy-two hours; the temperature of the reactants was 112°. After the reaction was complete, the contents of the flask were poured into a large battery jar provided with a mechanical stirrer and diluted with 7.5 l. of water. The mixture was stirred for several hours and then filtered. After it had been dried at 80°, the solid weighed 787 g. and melted at 113–135°; it is a mixture of 8-amino-5-chloro-6-methoxyquinoline and 5-chloro-8-(6-diethylaminohexylamino)-6-methoxyquinoline monohydrobromide. This mixture will be referred to under 5-chloro-8-(6-diethylaminohexylamino)-6-methoxyquinoline monohydrobromide as solid "A."

The filtrate was made strongly alkaline and extracted with chloroform. The chloroform was removed by distillation and the more volatile constituents of the residue were removed by distillation at reduced pressure until the vapor temperature was about 80° (0.3 mm.). The remaining dark, viscous oil was again dissolved in chloroform (250 ml.) and diluted with petroleum ether; the amount of petroleum ether added was just short of the amount necessary to cause turbidity. The chloroform–petroleum ether mixture was allowed to flow by gravity through a large column of activated alumina (*ca.* 55 × 4.7 cm. inside dia.) and the resulting chromatograph was developed by means of a 1:1 chloroform–petroleum ether mixture. The lower, fluorescent band was fractionally eluted by more of the same mixture of solvents used for development. After removal of the solvent, the residue was distilled in a small Hickman molecular still under about four microns pressure (bath temp. 180°). Following a small fore-run, 42.4 g. (4.7%) of product was obtained, The base was not analyzed but was converted to salt for analysis.

5-Chloro-8-(6-diethylaminohexylamino)-6-methoxyquinoline Monohydrodide (SN-13,694-17).—The 42.4 g. of base mentioned directly above was mixed with 580 ml. of methanol and 26.2 g. of 57% hydriodic acid was added. While this solution was stirred and heated under reflux, 2.3 liters of dry ether was added slowly. After the mixture had been allowed to cool, the precipitated hydriodide

TABLE I (*Continued*)

	Yield, %	Dist. temp.[b] °C.	Press.	Analyses, % Calculated	Found
1	22 over-all	Not distilled			
2	24 total	180	4 microns		
3	6 over-all	Not distilled			
4	45	242- 5	0.4 mm.	C, 74.76 H, 10.19	C, 74.94 H, 9.80
5	49.7	206- 9	0.13 mm.		
6	22	180- 5	2-3 microns	C, 74.75 H, 10.20	C, 74.77, 75.09; H, 9.91, 9.95
7	27	175- 80	2-3 microns	C, 75.20 H, 10.27	C, 74.96, 75.24; H, 10.06, 10.00
8	30	170- 85	4 microns		
9	47; 38-46	180- 90	0.1 mm.		
10	51	188- 94	0.03 mm.		
11	35	170- 6	0.3 mm.		
12	37	200-210	1 micron	C, 77.51 H, 11.15 N, 8.22 methoxyl, 6.07	C, 77.42, 77.78; H, 10.54, 10.79; N, 8.31, 8.35; methoxyl, 5.91
13	46	160-200	5 microns		
14	38	277- 80	0.4 mm.	C, 77.21 H, 11.14	C, 77.32 H, 10.74
15	26.8	260- 5	0.05 mm.		
16	48, 38	185- 8	0.17 mm.		
17	20.8 over-all	Not distilled			
18	44	M. p. 130-136			

[b] Temperatures for molecular distillations are pot temperatures. The distillations were carried out in a Hickman still. In all cases where more than one distillation was made, the temperature is that of the final distillation.

was removed by filtration and recrystallized from methanol–ether. The yield was 40 g. (78%); m. p. 153–154°, estimated inhomogeneity[9] 2 ± 3%. *Anal.* Calcd. for $C_{20}H_{30}N_3OCl\cdot HI$: C, 48.85; H, 6.36. Found: C, 49.02, 48.94; H, 6.52, 6.66.

5-Chloro-8-(6-diethylaminohexylamino)-6-methoxyquinoline Monohydrobromide (SN-13,694-13).—The solid "A" referred to above was slurried with 3 liters of boiling methanol and the slurry was filtered hot. The 320 g. of solid thus obtained by filtration of the hot solution proved to be 8-amino-5-chloro-6-methoxyquinoline. Concentration of the methanol solution and cooling yielded a solid which after further fractional crystallization from methanol–ether weighed 220 g. and melted at 153–153.5°. *Anal.* Calcd. for $C_{20}H_{30}N_3OCl\cdot HBr$: C, 53.95; H, 7.02. Found: C, 53.94, 54.07; H, 6.85, 6.93.

1-Ethylamino-6-methoxyhexane.—A mixture of 97.5 g. of 1-bromo-6-methoxyhexane and 97 g. of a 70% aqueous solution of ethylamine was placed in a small hydrogenation bomb and heated at 50° for eighteen hours. The resulting solution was poured into excess dilute hydrochloric acid and neutral products were extracted by ether. The aqueous layer was then made strongly basic and extracted with ether. The combined ether extracts were distilled; after removal of the ether, 1-ethylamino-6-methoxyhexane distilled at 87–90° (2 mm.). The yield was 58 g. (73%); $n^{27}D$ 1.4269. A small quantity (11 g.) of a substance which boiled at 147–150° (2 mm.) was also obtained; it is probably N,N-di-(6-methoxyhexyl)-ethylamine, but was not further investigated.

1-Ethylamino-6-methoxyhexane was not analyzed as such; it was used in the preparation of 1-bromo-6-ethylaminohexane hydrobromide by the same method employed in the preparation of 1-bromo-6-diethylaminohexane hydrobromide (yield 85%). A satisfactory analysis of the drug (see directly below) in whose preparation the bromide-hydrobromide was used was considered sufficient proof of the composition of the side-chain.

5-Chloro-8-(6-ethylaminohexylamino)-6-methoxyquinoline Monohydrobromide (SN-13,695-13).—A mixture of 153 g. of 8-amino-5-chloro-6-methoxyquinoline, 212 g. of 1-bromo-6-ethylaminohexane hydrobromide, 200 g. of sodium acetate trihydrate, 183 ml. of water, and 183 g. of cellosolve was heated under reflux for seventy-five hours. The mixture was diluted with 2.2 liters of water and stirred mechanically overnight. The solid, after filtration and drying, weighed 180 g.; there was no isolable product in the filtrate. The solid was slurried with 900 ml. of boiling methanol and filtered hot. The residue from the filtration consisted of 79 g. of 8-amino-5-chloro-6-methoxyquinoline; on cooling, the filtrate deposited 53 g. of substance which melted at 171–172°. Three recrystallizations of this product from methanol (decolorizing carbon used) raised the melting point of the yellow crystals to 175–176°. The yield was 18 g. (6%). *Anal.* Calcd. for $C_{18}H_{26}N_3OCl\cdot HBr$: C, 51.90; H, 6.48; N, 10.08; methoxyl, 7.44. Found: C, 51.90, 51.51; H, 6.36, 6.23; N, 9.89, 9.76; methoxyl, 7.31, 7.36.

1-Di-*n*-butylamino-6-methoxyhexane.—A mixture of 128 g. of di-*n*-butylamine and 64 g. of 1-bromo-6-methoxyhexane was stirred and heated at 100° for forty hours. The product was worked up as described under 1-diethylamino-6-methoxyhexane. The yield was 52 g. (65%) of a product which boiled at 158–160° (16 mm.).

1-Bromo-6-di-*n*-butylaminohexane Hydrobromide.—This compound was prepared from a mixture of 24.3 g. of

1-di-*n*-butylamino-6-methoxyhexane and 183 ml. of constant-boiling hydrobromic acid in the usual way; yield, 36 g. (96%).

8-(6-Di-*n*-butylaminohexylamino)-6-methoxyquinoline Diphosphate (SN-11,423-5).—An aqueous solution of this salt was prepared by dissolving 17.3 g. of twice-distilled 8-(6-di-*n*-butylaminohexylamino)-6-methoxyquinoline (see Table I) in 10.35 g. of 85% phosphoric acid and 42 ml. of water. This solution (*p*H 2.86) was submitted for testing inasmuch as we were unable to obtain a crystalline salt.

1-Chloro-3-di-*n*-butylaminopropane.[17,18]—A mixture of 31.5 g. of trimethylene chlorobromide[19] and 56.8 g. of di-*n*-butylamine was heated and stirred at 75° (bath temp.) for eight hours. Aqueous alkali was added in excess and the mixture was extracted with benzene. The product was obtained by distillation of the combined benzene extracts. The yield was 31 g. (75.5%); b. p. 70–80° (1 mm.). This product was used directly in the preparation of SN-2026.

8-(3-Di-*n*-butylaminopropylamino)-6-methoxyquinoline Triphosphate (SN-2026-5).—SN-2026 (22.8 g.) was dissolved in a mixture of 15.25 g. of 85% phosphoric acid[20] and 93 ml. of water. To this solution were added 46 ml. of methanol and 228 ml. of 2-propanol. The mixture was allowed to stand overnight in a refrigerator and the product was separated by filtration and washed with 2-propanol and ether. The yellow crystals of the triphosphate (15.7 g., 37%) melted at 164–165°. *Anal.* Calcd. for $C_{21}H_{33}N_3O\cdot 3H_3PO_4$: C, 39.56; H, 6.64; P, 14.58. Found: C, 40.95, 40.22; H, 6.91, 6.64; P, 14.83, 14.77.

1-Bromo-10-cyclohexoxydecane.—A boiling hot solution of sodium cyclohexoxide, prepared by boiling 1 kg. of purified cyclohexanol with 18.2 g. of sodium, was added to 750 g. of decamethylene bromide. After the mixture had been stirred and boiled under reflux for four and one-half hours, the suspension was filtered, and the filtrate was fractionally distilled. Cyclohexanol (795 g.), and decamethylene bromide (435 g.) were recovered as lower-boiling fractions; the desired product (225 g.) was obtained as a fraction which boiled at 132–138° (0.15 mm.); n_D 1.4772. The yield was 67% based on unrecovered decamethylene bromide.

1-Cyclohexoxy-10-diethylaminodecane.—A mixture of 225 g. of 1-bromo-10-cyclohexoxydecane, 156 g. of diethylamine, and 300 ml. of benzene was boiled under reflux for fifteen hours. After the mixture had cooled, the precipitated diethylamine hydrobromide (93 g.) was removed by filtration and washed with benzene. The combined filtrate and washings were fractionally distilled under nitrogen. One hundred and seventy-one grams of 1-cyclohexoxy-10-diethylaminodecane, which boiled at 172–177° (0.5 mm.), was obtained (78%).

1-Bromo-10-diethylaminodecane Hydrobromide.—A mixture of 171 g. of 1-cyclohexoxy-10-diethylaminodecane and 650 ml. of 47% hydrobromic acid was boiled under reflux for four hours. The cyclohexyl bromide formed was removed at intervals by means of a conventional water trap; 65 ml. of the calculated 68 ml. of cyclohexyl bromide was obtained. Excess hydrobromic acid was removed by distillation in vacuum, and the residue was finally dried in a lyophile at 85–90° under a vacuum of about 0.2 mm. The weight of the crystalline residue was 200 g. (98%). Neither this product nor the one directly preceding were analyzed; the analysis of SN-12,892, the drug prepared from 1-bromo-10-diethylaminodecane hydrobromide, was considered sufficient evidence of their composition.

8-(10-Diethylaminodecylamino)-6-methoxyquinoline Diphosphate (SN-12,892-5).—An alcoholic solution, prepared by dissolving 39.2 g. of 8-(10-diethylaminodecylamino)-6-methoxyquinoline in 23.5 g. of 85% phosphoric acid and diluting the mixture to 500 ml. with 80% ethanol, was submitted for testing; the apparent *p*H of the mixture was 4.2. We were unable to obtain a suitable solid salt of SN-12,892.

11-Diethylaminohendecanoic Acid, Butyl Ester.—A mixture of 191 g. of 11-bromohendecanoic acid,[21] m. p. 50°, 213 g. of diethylamine, and 500 ml. of benzene was boiled under reflux and stirred for thirteen hours. After the diethylamine hydrobromide had been removed from the cooled solution by filtration and washed with benzene, the combined filtrate and washings were concentrated *in vacuo*, and 70 ml. of hydrochloric acid and 10 g. of *p*-toluenesulfonic acid were added. One liter of benzene and 273 ml. of *n*-butanol were added and the mixture was boiled under reflux through a conventional water trap. Refluxing was continued until no more water was removed. The cooled solution was washed with potassium carbonate solution until the washings were basic, and then with water until the washings were neutral. The benzene solution was fractionally distilled under nitrogen; the yield of ester was 195 g. (87%); the product boiled at 148–149° (2 mm.).

11-Diethylamino-1-hendecanol.—The above butyl ester was reduced by the Bouveault–Blanc method.[22] The yield of product was 50%; b. p. 135–136° (0.5 mm.); $n^{24}D$ 1.4587. The alcohol was redistilled through a 2-ft. column with controlled take-off; the boiling range of the fraction accepted as product was 103–105° (0.04 mm.); $n^{21}D$ 1.4596. A comparison of the two refractive indexes indicates that little change in composition was effected by the second distillation (recovery 86%). Analysis showed the compound to be slightly impure, but it was not deemed worthwhile to subject it to further purification. It was, therefore, converted to the corresponding bromide-hydrobromide and used for alkylation. The composition of the drug SN-11,425 was considered sufficient evidence of the composition of the intermediates for our purpose. *Anal.* Calcd. for $C_{15}H_{33}NO$: C, 74.1; H, 13.58; N, 5.76. Found: C, 72.21, 72.36; H, 13.36, 13.40; N, 6.04, 5.39, 5.26 (Dumas).

1-Bromo-11-diethylaminohendecane Hydrobromide.—Dry hydrogen bromide was passed rapidly through 63.5 g. of 11-diethylamino-1-hendecanol which was stirred and heated at 100° until the liquid was saturated (one hour). The temperature of the mixture was then raised to 135° and a slow stream of hydrogen bromide was passed through the mixture for an additional five hours. Water and excess hydrogen bromide were removed by distillation in vacuum, and the residue was finally dried by heating it at 100° under about 50 microns pressure for some time. The residue weighed 101 g. (100%). It was used as described directly below.

8-(11-Diethylaminohendecylamino)-6-methoxyquinoline (SN-11,425).[23]—A mixture of 101 g. of 1-bromo-11-diethylaminohendecane hydrobromide, 41.2 g. of 8-amino-6-methoxyquinoline and 250 ml. of absolute ethanol was refluxed for sixty-five hours, poured into 800 ml. of ice-water, and made strongly alkaline.[6] The organic products were extracted with chloroform. After the chloroform extracts had been washed and dried, they were distilled in a von Braun flask with *wide* tubes until a vapor temperature of about 105° (4 microns) was reached (bath temp., 156°). The residue was transferred to a Hickman molecular still and distilled at 3–4 microns pressure. After a small fore-run, the fraction which distilled when the bath temperature was 150–180° was collected; there was a considerable amount of high-boiling residue left in the still-pot. The product was subjected to a second "molecular distillation"; the portion accepted distilled at a rate of about 5 drops/minute when the bath temperature was held at 170-

(17) A. Marxer, *Helv. Chim. Acta*, **24**, 209E (1941).

(18) F. F. Blicke and C. Otsuki, THIS JOURNAL, **63**, 2345 (1941).

(19) Prepared in 77% yield according to directions of J. B. Cloke, *et al.*, THIS JOURNAL, **53**, 2791 (1931). This product is available commercially.

(20) This quantity of phosphoric acid represents an acid–base ratio of only 2:1. A diphosphate was expected.

(21) Prepared from undecylenic acid according to Ashton and Smith, *J. Chem. Soc.*, 435 (1934).

(22) "Org. Syn.," Coll. Vol. II, 372 (1943).

(23) (a) Soc. des usines chimiques Rhone-Poulenc, French Patent 769,263 (Aug. 23, 1934); (b) Bovet and Demanche, *Ann. Inst. Pasteur*, **51**, 528 (1933); (c) Magidson, *et al.*, *Arch. Pharm.*, **273**, 320 (1935); (d) Fourneau, *et al.*, *Ann. Inst. Pasteur*, **50**, 731 (1933); (e) Altman, *Rec. trav. chim.*, **57**, 941 (1938); (f) Krichevskii, *et al.*, *J. Microbiol. Epidemiol. Immunobiol.* (U. S. S. R.), **14**, 642 (1935).

180° (pressure 2–3 microns). The yield was 26 g. (27%); $n^{28}D$ 1.4942. *Anal.* See Table I.

8-(11-Diethylaminohendecylamino)-6-methoxyquinoline Diphosphate (SN-11,425-5).—An alcoholic solution, whose apparent *p*H was 4.0, was made by dissolving 24.0 g. of base in 13.8 g. of 85% phosphoric acid and diluting the mixture to 250 ml. with 80% ethanol. This solution was submitted for testing; we were unable to obtain a satisfactory solid salt. The estimated inhomogeneity[9] was 15 ± 5%.

4,5-Dinitroveratrole.[24]—To a well-stirred solution of 483 g. of veratrole in 1450 ml. of acetic acid cooled to 15° was added, over a one-hour period, 683 g. of concentrated nitric acid (sp. gr. 1.05). The temperature of the mixture was held below 40° by cooling and proper regulation of the rate of addition of the acid. When the acid had all been added considerable mononitroveratrole had separated. Stirring was continued and 2127 ml. of fuming nitric acid (sp. gr. 1.50) was added over a period of an hour while the temperature of the solution was held below 30°. As the nitration proceeded the mononitroveratrole dissolved and, when all the acid had been added, the solution was clear. The nitration mixture was allowed to stand for two hours and was then poured into a large volume of cold water. The precipitated nitro compound was filtered, washed with water until free from acid, and recrystallized directly from ethanol. The yield was 690 g. (87%) m. p. 129.5–130.5°.

4-Amino-5-nitroveratrole.[25]—A mixture of 159 g. of 4,5-dinitroveratrole and 1 liter of methanol which had been saturated with ammonia at 0° was placed in a 1700 ml. hydrogenation bomb[26] provided with a pressure gage and a thermocouple. The bomb was placed in the rocker-heater assembly whose heating jacket had been pre-heated to about 500° (dull red just visible in the dark interior of the heating jacket) so that the time-lag in raising the temperature of the bomb's contents to the proper point was as short as possible. With the jacket heater on high, the bomb was shaken until the thermocouple recorded a temperature of 125°, when the heater was turned off. The temperature rose to about 150° within twenty minutes after heating was started; after five minutes of heating at this temperature, the rocker was stopped and the bomb was removed from the jacket and cooled quickly under the tap. The bomb was opened and the charge removed and cooled in an ice-bath. The product (91–102 g.) was removed by filtration and was pure enough to be used directly in the Skraup reaction; yield, 66–74%; m. p. 170–171°.

The yield in this preparation was found to be much influenced by time of heating. It was found necessary to bring the temperature of the mixture to 150° as rapidly as possible and to hold it at that level for no longer than five minutes. Other methods of operation resulted in *much* reduced yields. It was found to be unprofitable to attempt to work up the filtrates for a second crop of amine. The product obtained from the ammonolysis is pure enough for all ordinary purposes.

5,6-Dimethoxy-8-nitroquinoline.[27]—Glycerol (177 ml.) which had been previously dried by heating for fifteen minutes to a temperature such that copious fumes were evolved was added hot to a mixture of 60 g. of 4-amino-5-nitroveratrole and 34.5 g. of arsenic pentoxide contained in a 3-liter round-bottomed flask. The contents of the flask were mixed by shaking and 90 ml. of concentrated sulfuric acid was added cautiously around the sides of the flask. A vigorous reaction started immediately and was allowed to proceed for three minutes whereupon the mixture was immediately poured into 1.4 liter of cold water. The acid solution was filtered through a mat of diatomaceous earth, cooled, and made strongly alkaline; during the neutralization of the acid the temperature of the mixture was not allowed to exceed 30°. Crude 5,6-dimethoxy-8-nitroquinoline was obtained by filtration, dissolved in warm 10% hydrochloric acid, filtered, and reprecipitated by the addition of ammonia solution. After filtration, the product was dissolved in 500 ml. of alcohol, treated with decolorizing carbon, filtered, and caused to crystallize by the addition of 150 ml. of water. The yield was 25.5 g. (36%); m. p. 127.5–129° with sintering at 118°.

8-Amino-5,6-dimethoxyquinoline.[28]—This substance was prepared in 90% yield by reduction of 5,6-dimethoxy-8-nitroquinoline with stannous chloride. The product obtained melted at 149.5–150.5°.

8-(6-Diethylaminohexylamino)-5,6-dimethoxyquinoline Dihydriodide (SN-12,324-17).—A solution of SN-12,324 (26.6 g.) and 33.3 g. of 57% hydriodic acid in 150 ml. of methanol was prepared. The salt was precipitated as a red oil by the addition of 450 ml. of dry ether. Scratching and seeding finally induced crystallization; 32.4 g. of crude salt (71%) was obtained. The crude salt was dissolved in 140 ml. of ethanol and reprecipitated by addition of 390 ml. of dry ether. This product (31.1 g.) melted at 137–144°; it was twice recrystallized from dry alcohol. The recrystallized product (25.8 g., 56.6%) melted at 161–163°, estimated inhomogeneity[9] 15%+. *Anal.* Calcd. for $C_{21}H_{33}N_3O_2 \cdot 2HI$: C, 40.99; H, 5.73. Found: C, 41.01, 40.90; H, 5.30, 5.35.

8-(6-Diethylaminohexylamino)-6-methoxyquinoline Diphosphate (SN-11,191-5).[29]—To 40 g. of SN-11,191 were added 28.1 g. of 85% phosphoric acid, 160 ml. of water, 80 ml. of methanol, and 3 liters of 2-propanol. The mixture was heated until clear, cooled until cloudy, seeded, and cooled in a refrigerator overnight. The crude product was recrystallized twice by dissolving it in water (2 ml./g. of salt) and adding 2-propanol (120 ml./g. of salt). The yield was 41.5 g. (65%); m. p. 109–111°, estimated inhomogeneity[9] <2%. *Anal.* Calcd. for $C_{20}H_{31}N_3O \cdot 2H_3PO_4$: C, 45.71; H, 7.10; P, 11.79. Found: C, 45.56; H, 6.75; P, 11.88.

1-Chloro-3-diethylaminopropane.[30]—This compound was prepared essentially according to the method of Marxer. The yield was 60%; b. p. 40–46° (6 mm.).

8-(3-Diethylaminopropylamino)-5,6-dimethoxyquinoline Dihydriodide (SN-11,889-17).[31]—This salt, first thrown out of a dioxane–2-propanol–water solution was recrystallized from methanol–ether. The product melted at 175–176.5°.[32] *Anal.* Calcd. for $C_{18}H_{27}N_3O_2 \cdot 2HI$: C, 37.71; H, 5.10. Found: C, 38.05, 37.98; H, 5.02, 4.83.

8-(3-Diethylaminopropylamino)-6-methoxyquinoline Diphosphate (SN-3115-5).[33]—This salt was separated from

(24) For other preparative methods see: Moureu, *Compt. rend.*, **125**, 31 (1897); *Bull. soc. chim.*, [3] **15**, 646 (1896); Merck, *Ann.*, **108**, 60 (1858); Brüggemann, *J. prakt. Chem.*, [2] **53**, 252 (1851); Tiemann and Matsomoto, *Ber.*, **9**, 939 (1876); Heinisch, *Monatsh.*, **15**, 233 (1894); Rossin, *ibid.*, **12**, 491 (1891); Robinson, *J. Chem. Soc.*, **109**, 1087 (1916); Harding, *ibid.*, **105**, 2795 (1914); Gibson, *et al.*, *ibid.*, **111**, 81 (1917); A. H. Parijs, Thesis, Leyden (1928); H. Vermeulen, *Rec. trav. chim.*, **48**, 969 (1929); C. Kuroda and T. Matsukuma, *Sci. Papers Inst. Phys. Chem. Research* (Tokyo), **18**, 51 (1932); T. Kaku and H. Ri, *J. Pharm. Soc. Japan*, **57**, 1015 (in German, 289) (1937); B. K. Nandi, *Current Sci.*, **9**, 118 (1940); Bogert and Frisch, *J. Org. Chem.*, **8**, 331 (1943).

(25) See ref. 23, A. H. Parijs, and Bogert and Frisch; Jones and Robinson, *J. Chem. Soc.*, **111**, 914 (1917); Simonsen and Rau, *ibid.*, **113**, 27 (1918); A. H. Parijs, *Rec. trav. chim.*, **49**, 45 (1930).

(26) Standard Aminco apparatus.

(27) F. Schönhöfer, German Patent 531,083 (Feb. 18, 1930). The method employed in our laboratories is a modification of one devised in the Columbia laboratories; see Elderfield, *et al.*, THIS JOURNAL.

(28) See Elderfield, *et al.*, THIS JOURNAL, **68**, 1584 (1946).

(29) See ref. 23c, d, e, f.

(30) (a) Slotta and Behnisch, *Ber.*, **68B**, 754 (1935); (b) Magidson, *et al.*, *J. Applied Chem.*, U. S. S. R., **9**, 304 (1936); (c) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933); (d) Dorf, Russian Patent, 36,414 (May 31, 1934); see also ref. 17.

(31) Schönhöfer and Andersag, U. S. Patent, 1,938,047 (Dec. 5, 1933); German Patent 536,447 (Mar. 13, 1930); British Patent, 354,352 (May 2, 1930).

(32) See Elderfield, *et al.*, THIS JOURNAL, **68**, 1524 (1946).

(33) The base, SN-3115, has been reported many times: (a) Sergent, *et al.*, *Ann. Inst. Past.*, **47**, 57 (1931); (b) Dubovskaya and Rotenberg, *Z. Microbiol. Epidemiol. Immunitätsforsh.* (U. S. S. R.), **18**, 233 (1937); (c) Fourneau, *et al.*, *Ann. Inst. Pasteur*, **46**, 514, 534 (1931); (d) Strukov, Russian Patent 39,105 (Oct. 31, 1934); (e) British Patent 267,169 (1927); (f) German Patent, 486,079,

water–methanol–2-propanol. After recrystallization and drying it melted at 169–171°, estimated inhomogeneity[9] <4%, yield 74%. *Anal.* Calcd. for $C_{17}H_{25}N_3O\cdot 2H_3PO_4$: C, 42.24; H, 6.46; P, 12.82. Found: C, 42.11; H, 6.31; P, 12.91.

10-Hendecene-1-ol.—This substance was prepared by reduction of the ethyl ester of undecylenic acid.[22] The yield was 85%.

10-Hendecene-1-ol Acetate.[34]—10-Hendecene-1-ol was esterified with acetic acid; benzene was added to the mixture and the water formed was removed with benzene as the azeotrope. The product boiled at 74° (0.025 mm.); the yield was 88%.

11-Di-*n*-hexylaminohendecan-1-ol.—Air and dry hydrogen bromide were passed through a solution of 53 g. of 10-hendecene-1-ol-acetate in 530 ml. of benzene until the solution was saturated.[34b] The resulting solution of 11-bromohendecan-1-ol acetate was washed with three 500-ml. portions of water and then dried by distilling off the benzene–water azeotrope. Di-*n*-hexylamine (140 g.) was added and the mixture was boiled under reflux and stirred for twenty hours. The di-*n*-hexylamine hydrobromide filtered from the cooled solution weighed 45 g. (68%). The benzene was removed from the filtrate by distillation *in vacuo* and 160 g. of 50% sodium hydroxide solution and 200 ml. of ethanol were added. After the mixture had been boiled under reflux for six hours and cooled, the aqueous layer was separated and discarded, and 500 ml. of ether was added. The ethereal solution was washed with water and then fractionally distilled under nitrogen. The yield was 50 g. (56%); b. p. 165–184° (0.025 mm.).

1-Bromo-11-di-*n*-hexylaminohendecane.—Dry hydrogen bromide was blown rapidly through 28 g. of 11-di-*n*-hexylaminohendecan-1-ol contained in a flask heated in an oil-bath whose temperature was 95°. After the amino-alcohol was saturated with hydrogen bromide, the temperature of the oil-bath was raised to 140° and a slow stream of hydrogen bromide was passed through the solution for three hours. The mixture was washed into a separatory funnel by means of 500 ml. of benzene; the benzene solution was then shaken with successive portions of 10% sodium carbonate solution until the aqueous layer was basic and then with water until the washings were neutral. The benzene solution was dried, the solvent was removed in vacuum and the residue was condensed with 8-amino-6-methoxyquinoline.

8-(11-Di-*n*-hexylaminohendecylamino)-6-methoxyquinoline Diphosphate (SN-12,449-5).—A solution of 10.03 g. of SN-12,449 (see Table I) in 4.52 g. of 85% phosphoric acid and enough ethanol to make 50 ml. of solution was submitted for testing. We were unable to obtain a crystalline salt of this substance.

1-Dimethylamino-6-methoxyhexane.[35]—A mixture of 48.5 g. of 1-bromo-6-methoxyhexane and 102 g. of 33% aqueous dimethylamine was shaken and heated at 100° for three and one-half hours in a small hydrogenation bomb and then poured into 83 ml. of hydrochloric acid. The acid solution was extracted with ether and then saturated with sodium hydroxide and extracted again. Fractional distillation of the ether extracts of the basic solution yielded 31 g. (78%) of product; b. p. 78° (11 mm.). *Anal.* Calcd. for $C_9H_{21}NO$: mol. wt., 159.3. Found: neutral equivalent, 158.7, 158.1.

1-Bromo-6-dimethylaminohexane Hydrobromide.[36]—A solution of 63 g. of 1-dimethylamino-6-methoxyhexane in 415 ml. of 47% hydrobromic acid was boiled under reflux for three hours. Excess hydrobromic acid was removed by distillation *in vacuo* and the residue was finally dried by heating at 120° (bath temp.) under 1 mm. pressure. The yield was practically quantitative; the product was used directly in the preparation of SN-12,322.

8-(6-Dimethylaminohexylamino)-6-methoxyquinoline Dihydriodide (SN-12,322-17).—SN-12,322, prepared in the same manner as SN-11,191 (46 g.) in hot absolute alcohol was neutralized with 68.7 g. of 57% hydriodic acid and the salt was thrown out by the addition of 300 ml. of dry ether. The crude salt melted at 178–180°. Recrystallization from methanol–ether yielded 55 g. (64%) of salt; m. p. 180–182°, estimated inhomogeneity[9] 3 ± 2%. *Anal.* calcd. for $C_{18}H_{27}N_3O\cdot 2HI$: C, 38.8; H, 5.25. Found: C, 38.63, 38.75; H, 4.99, 5.09.

1-Di-*n*-octylamino-6-methoxyhexane.—A mixture of 138 g. of di-*n*-octylamine and 53 g. of 1-bromo-6-methoxy hexane was stirred and heated at 100° for forty hours and then made basic and extracted with ether. The product was obtained by fractional distillation; yield 61 g. (63%); b. p. 190° (0.4 mm.).

1-Bromo-6-di-*n*-octylaminohexane Hydrobromide.—A mixture of 35.6 g. of 1-di-*n*-octylamino-6-methoxyhexane and 183 ml. of 47% hydrobromic acid was converted as previously described to a dry mass which was used directly in the preparation of SN-11,424.

8-(6-Di-*n*-octylaminohexylamino)-6-methoxyquinoline Diphosphate (SN-11,424-5).—A solution of 34.7 g. of SN-11,424 (see Table I), 161 g. of 85% phosphoric acid, and 49 g. of 95% ethanol was prepared and submitted for testing. We were unable to obtain a satisfactory solid salt of this base.

3-Di-*n*-octylamino-1-propanol.—A mixture of 101 g. of di-*n*-octylamine and 19 g. of trimethylene chlorohydrin was stirred and heated at 130° (bath temp.) for sixteen hours. Alkali was added, the mixture was extracted with benzene, and the product was obtained by distillation. The yield was 19.5 g. (32.4%); b. p. 145–152° (0.025 mm.).

1-Bromo-3-di-*n*-octylaminopropane Hydrobromide.—A mixture of 15 g. of 3-di-*n*-octylamino-1-propanol and 84.4 g. of 47% hydrobromic acid was boiled under reflux for sixteen hours. On cooling, the upper layer of the two-phase system solidified. The excess hydrobromic acid was decanted from the solid and the latter was used directly in the preparation of SN-11,422.

8-(3-Di-*n*-octylaminopropylamino)-6-methoxyquinoline Triphosphate (SN-11,422-5).—A mixture of 11.22 g. of SN-11,422 (see Table I), 50 ml. of water, and 8.65 g. of 85% phosphoric acid was warmed slightly to dissolve the salt and 63 ml. of methanol and 200 ml. of 2-propanol were added. The salt was allowed to crystallize in a refrigerator overnight. The yield was 9.7 g. (52.3%); m. p. 186.5–187.5°. *Anal.* Calcd. for $C_{29}H_{49}N_3O\cdot 3H_3PO_4$: C, 46.45; H, 7.80; P, 12.40. Found: C, 46.54; H, 7.63; P, 12.20.

1-Isopropylmethylamino-6-methoxyhexane.—A mixture of 56 g. of isopropylmethylamine[37] and 68 g. of 1-bromo-6-methoxyhexane was stirred and heated at 40–60° for twenty hours. The mixture was added to a slight excess of dilute hydrochloric acid, and unreacted 1-bromo-6-methoxyhexane was extracted with ether. The extracted solution was made strongly basic and again extracted with ether. The product was obtained by fractional distillation of the dried basic extracts. The yield was 54 g. (83%); b. p. 107–110° (13 mm.).

1-Bromo-6-isopropylmethylaminohexane Hydrobromide.—A mixture of 54 g. of 1-isopropylmethylamino-6-methoxyhexane and 300 ml. of 49% hydrobromic acid was boiled under reflux for four hours, converted into dry salt, and used directly in the preparation of SN-12,325 (see directly below).

8-(6-Isopropylmethylaminohexylamino)-6-methoxyquinoline (SN-12,325).—A mixture of 97.5 g. of 8-amino-6-methoxyquinoline, 89 g. of 1-bromo-6-isopropylmethylaminohexane hydrobromide, and 70 ml. of water was stirred and heated at 48° for five hours, at 60° for one hour, at 71° for one hour and at 104° for six hours (bath temperatures). The reaction mixture was added to 700 ml. of water containing 70 ml. of concentrated hydrochloric

488,945 (1924); (g) Magidson, *et al.*, *Arch. Pharm.*, **272**, 74 (1934); (h) Kritschewski and Sternberg, *Z. Immunitats*, **80**, 438 (1933); (i) Magidson, *et al.*, *Khim Farm. Prom.*, 9 (1933). See also 23c, d. e, f, and 30b, c.

(34) (a) Chuit, *et al.*, *Helv. Chim. Acta*, **9**, 1074 (1926); (b) Ashton and Smith, *J. Chem. Soc.*, 1308 (1934).

(35) Clarke, *J. Chem. Soc.*, **103**, 1704 (1913).

(36) Littman and Marvel, THIS JOURNAL, **52**, 287 (1930).

(37) Prepared by a method similar to that described by Cope and Hancock, THIS JOURNAL, **66**, 1738 (1944).

acid. The acid solution was heated until clear and then cooled to 15°. Precipitated 8-amino-6-methoxyquinoline hydrochloride was removed by filtration and washed with two 140-ml. portions of ice-water. The combined filtrate and washings were buffered with sodium acetate until neutral to congo paper, and then extracted with ether to remove any unalkylated nucleus remaining. The extracted solution was made strongly basic with potassium hydroxide, saturated with potassium carbonate, and extracted again with ether. After the ether had been removed from the extracts on a steam-bath, the residue was distilled and redistilled *in vacuo* under nitrogen from a modified von Braun flask. After the second distillation the product weighed 44 g. (48%); b. p. 185–188° (0.17 mm.).

8-(6-Isopropylmethylaminohexylamino)-6-methoxyquinoline Dihydriodide (SN-12,325-17).—To a solution of 61.6 g. of SN-12,325 in 100 ml. of ethanol was added 84 g. of 57% hydriodic acid. The hot solution was diluted with 400 ml. of ethanol and 300 ml. of ether and cooled overnight. The solid was removed by filtration and recrystallized twice from 400-ml. portions of ethanol. After it had been dried *in vacuo* at 70°, the product weighed 37 g. (47%); m. p. 135–138°, estimated inhomogeneity[9] 4.5 ± 3%. *Anal.* Calcd. for $C_{20}H_{31}N_3O\cdot 2HI\cdot XH_2O$ (the solid contained 1.10% of moisture by analysis): C, 40.57; H, 5.76. Found: C, 40.58, 40.46; H, 5.54, 5.65.

8-(6-Diethylaminohexylamino)-6-quinolinol Dihydriodide (SN-13,697-17).—A mixture of 85 g. of SN-11,191 and 1 liter of freshly-distilled 57% hydriodic acid was stirred and heated at 100° (inside t.) for eleven and one-half hours while a slow stream of carbon dioxide was bubbled through the mixture to sweep out the methyl iodide formed. Excess hydriodic acid was then removed by distillation under nitrogen *in vacuo;* the temperature of the mixture was not allowed to rise above 100° during the evaporation. The residue was washed into a separatory funnel by means of 1200 ml. of distilled water and neutralized with sodium bicarbonate. The alkaline solution was extracted with one 150-ml. portion and two 50-ml. portions of chloroform. The chloroform was removed from the combined extracts by distillation *in vacuo* under nitrogen; the temperature of the mixture was not allowed to rise above 100°.

The residue so obtained was dissolved in 900 ml. of absolute ethanol, and 105 g. of 57% hydriodic acid was added. The salt was precipitated by portion-wise addition of 1.2 liters of dry ether; it was necessary to add seed and to scratch the mass frequently in order to promote crystallization. The crude product weighed 86 g. (58%) and melted at 149–152°. It was recrystallized five times with use of decolorizing carbon in the first recrystallization; for recrystallization the product was dissolved in ethanol and thrown out by the addition of ether. The yield of purified salt was 30.8 g. (20.8% over-all from SN-11,191); m. p. 161–163°, estimated inhomogeneity[9] <5%. The substance was dried overnight *in vacuo* at 80° prior to analysis. *Anal.* Calcd. for $C_{19}H_{29}N_3O\cdot 2HI$: C, 40.0; H, 5.47; methoxyl, none. Found: C, 39.69, 39.80; H, 5.75, 5.55; methoxyl, none.

1-(4-Diethylamino-1-methylbutyl)-3-(6-methoxy-8-quinolyl)-urea (SN-12,594).—Phosgene (150 g.) was absorbed in an ice-cold solution of 37 g. of 8-amino-6-methoxyquinoline (m. p. 49.3–50.1°). About one-third of the solvent was removed by distillation. A slight vacuum was maintained in the apparatus to cause any phosgene evolved to bubble through an alkali-toluene absorption trap, and the operation was conducted in a good hood. The suspension was cooled and 74 g. of Noval Diamine was added while the contents of the flask were swirled about and cooled. While the mixture stood overnight, crystallization occurred and 86 g. of crude product was obtained. The impure base was dissolved in acetic acid, precipitated by alkali, and then recrystallized from benzene. The yield was 33.4 g. (44%); m. p. 130–136°. An additional 11.5 g. of product was obtained by diluting the original benzene filtrate with petroleum ether. The base was converted to salt for analysis (see directly below).

1-(4-Diethylamino-1-methylbutyl)-3-(6-methoxy-8-quinolyl)-urea Monophosphate (SN-12,594-5).—To 16.7 g. of SN-12,594 dissolved in 370 ml. of ethanol was added 5.3 g. of 85% phosphoric acid. The salt crystallized readily from the solution. The yield was 19.6 g. (92%); m. p. 205.0–205.5°. *Anal.* Calcd. for $C_{20}H_{30}N_4O_2\cdot H_3PO_4$: C, 52.6; H, 7.28; N, 12.29; P, 6.80; methoxyl, 6.80. Found: C, 51.97, 52.13; H, 6.94, 7.08; N, 12.60, 12.32; P, 7.10, 6.84; methoxyl, 6.59, 6.67.

Summary

1. The preparation of eleven 8-dialkylaminoalkylamino-6-methoxy-quinolines is described.

2. The preparation of 8-(5-aminoamylamino)-6-methoxyquinoline is described.

3. The preparation of two 8-dialkylaminoalkylamino-5,6-dimethoxyquinolines is described.

4. The preparations of one 8-dialkylaminoalkylamino-5-chloro-6-methoxyquinoline and one 8-monoalkylaminoalkylamino-6-methoxyquinoline are described.

5. The preparation of 8-(6-diethylaminohexylamino)-6-quinolinol from SN-11,191 is described.

6. The preparation of one 1-dialkylaminoalkyl-3-(6-methoxy-8-quinolyl)-urea is described.

7. The preparation of the intermediates necessary for the synthesis of the above quinolines is described.

8. Crystalline salts of the quinolines prepared have been obtained in all but a few cases.

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