tion was extracted twice more with 50-cc. portions of ether. The combined ether extracts were dried over magnesium sulfate and the ether was removed on the steam cone. Excess diamine was distilled under reduced pressure; 8.3 g. was collected at 81–82° (14 mm.) and 5.5 g. at 45–48° (0.5 mm.). The residue began to crystallize even before all the diamine had distilled so it was purified by recrystallization rather than by distillation. After treating with 3 g. of decolorizing charcoal in 200 cc. of boiling benzene, the benzene solution was concentrated to about 40 cc. and 300 cc. of low-boiling petroleum ether was added with stirring. The mixture was cooled and the light tan crystalline product was collected in a filter; 24.5 g. (82%), m. p. 113–119°. This product was recrystallized twice from Skellysolve B (b. p. 60–68°), yielding 20.0 g of white plates, m. p. 122–123°.

Anal. Calcd. for $C_{20}H_{31}N_3$: C, 76.63; H, 9.97. Found: C, 76.74; H, 9.99.

4-Hydroxy-1,5-naphthyridine.—In view of the parallel preparation reported concurrently by Hauser,[16] only the properties of our products will be described. **3-Aminopyridine** was prepared from (a) nicotinamide by the Hofmann method,[17] (b) nicotinamide and ethyl nicotinate by the Curtius method[18] and (c) 3-bromopyridine by amination.[19] The last method was found to be the most satisfactory. Vacuum distillation was found to be greatly superior to recrystallization as a means of purifying crude 3-aminopyridine. Ethyl β-(3-pyridylamino)-α-carbethoxyacrylate was isolated as white microneedles, m. p. 63–65°

(16) Hauser, THIS JOURNAL, **68**, 1317 (1946).

(17) Pollak, *Monatsh.*, **16**, 54 (1895).

(18) Curtius and Mohr, *Ber.*, **31**, 2493 (1898).

(19) Maier-Bode, *ibid.*, **69**, 1534 (1936).

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.07; H, 6.10. Found: C, 59.23; H, 6.27.

Cyclization at high dilution yielded tan powdery **3-carbethoxy-4-hydroxy-1,5-naphthyridine** (79%), m. p. 268°, dec., softening from 250°. **4-Hydroxy-1,5-naphthyridine-3-carboxylic acid,** obtained by hydrolysis in 85% yield, sublimed without melting at about 315°, losing carbon dioxide, to yield a sublimate of **4-hydroxy-1,5-naphthyridine.** The latter also sublimed without melting, but with no decomposition, at about 300–305°. These properties agree very well with the observations of Klisiecki and Sucharda.[11]

Anal. Calcd. for $C_8H_6ON_2$: C, 65.74; H, 4.14. Found: C, 65.53; H, 4.32.

Summary

A general method for the preparation of 4-hydroxyquinolines has been developed. This synthesis is illustrated by the conversion of *m*-chloroaniline, *p*-anisidine, and 3,4-dimethylaniline to 4-hydroxyquinoline derivatives and of 3-aminopyridine to 4-hydroxy-1,5-naphthyridine. The aromatic amines were condensed with ethoxymethylenemalonic ester and the resulting carbethoxyanilinoacrylates cyclized by heating in a high-boiling solvent to produce 4-hydroxyquinoline-3-carboxylic acid esters. Saponification yielded the corresponding acids which were converted readily to the desired 4-hydroxyquinolines by decarboxylation.

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[CONTRIBUTION FROM THE LABORATORIES OF THE UNIVERSITY OF MARYLAND]

Synthetic Antimalarials. The Preparation of Certain 4-Aminoquinolines[1]

BY NATHAN L. DRAKE, HUGH J. CREECH, JOHN A. GARMAN, STUART T. HAYWOOD, RICHARD M. PECK, JOHN O. VAN HOOK AND EDWARD WALTON

Prior to 1942 little attention had been given in this country to quinolines bearing dialkylaminoalkylamino groups in the 4-position as possible antimalarials. A number of members of this class of compounds, however, had been prepared by the Germans[2,3] and by the Russians.[4] Some members of this class have been described recently in the American literature[5] and reported active.

The present paper describes the preparation of a number of substituted 4-aminoquinolines. These compounds fall into two well-defined groups. Those found in Part I of the experimental part are 4-(4-diethylamino-1-methylbutylamino)-quinolines variously substituted in the nucleus; those described in Part II are 7-chloro-4-(dialkylaminoalkylamino)-quinolines[6] with the exception of one 7-chloro-4-aminoalkylaminoquinoline. The present communication deals only with the chemistry of the drugs; their activity and pharmacology will be reported elsewhere.[7]

Substituted 4-aminoquinolines are conveniently synthesized by reaction of an appropriately substituted 4-chloroquinoline with a primary amine. It was found that the conditions necesssary for condensation vary widely as a function of substitution. 4-Chloroquinolines bearing a substituent in the 2 or 3-position require longer times and higher temperatures for complete reaction than do 4-chloroquinolines bearing their other substituents only in the benzene ring. In a few cases

(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 the University of Maryland.

(2) H. Andersag, S. Breitner and H. Jung, German Patent 683,692 (Oct. 26, 1939); *C. A.*, **36**, 4973 (1942).

(3) H. Andersag, S. Breitner and H. Jung, U. S. Patent 2,233,970 (March 4, 1941); *C. A.*, **35**, 3771 (1941).

(4) E. P. Hal'perin, *Med. Parisitol. Parasitic Diseases* (U.S.S.R.), **9**, 44 (1940); *C. A.*, **36**, 1674 (1942); O. J. Magidson and M. V. Rubstov, *J. Gen. Chem.* (U.S.S.R.), **7**, 1896 (1937); *C. A.*, **32**, 564 (1938).

(5) Steck, Hallock and Holland, THIS JOURNAL, **68**, 129, 132 (1946).

(6) 7-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (SN-7618) is omitted from this group. It will form the subject of a separate communication; *cf.* Drake, *et al.*, THIS JOURNAL, **68**, 1214 (1946).

(7) Synthetic Antimalarials 1941–1945. Published by the Survey of Antimalarial Drugs, in press. The various drugs will be assigned the same SN numbers in the monograph by which they were identified in the Survey Office. These same SN numbers will also be used to identify the drugs in our paper.

where conditions promoting condensation were found to be so severe as to be impractical, phenol added to the reaction mixture in molar quantity equivalent to the quinoline reduces the necessary temperature and time sufficiently to make the condensations practical.

In general the condensations were carried out without other solvent than an excess of side-chain; in all cases the nucleus was completely soluble in the side-chain at the temperature necessary for reaction. The ratio of side-chain to nucleus was usually 2.2:1.

The temperature and time of reaction necessary were found to vary widely. Condensations were carried out in a flask provided with a stirrer and a thermometer *in the reaction mixture*. The flask was heated in an oil-bath whose temperature was followed carefully and compared at short intervals with that of the reaction mixture. Heating was begun slowly and the temperatures of mixture and bath followed closely. The ΔT between mixture and oil-bath remains relatively constant as bath temperature is raised slowly until the reaction rate becomes appreciable. At that point ΔT decreases rapidly and becomes negative owing to the exothermic nature of the reaction. It is frequently found necessary to remove the heating bath and to cool the mixture by means of a cold oil-bath in order to prevent the reaction from getting out of hand. As might be expected, those side-chains having no branches adjacent to the primary amino group react most vigorously and at the lowest temperatures.

The reaction was considered to be complete when a small portion of the mixture dissolved in 5% nitric acid remained clear upon the addition of sodium acetate solution.[8]

After the coupling was substantially complete, the mixture was made strongly alkaline with excess concentrated sodium hydroxide and extracted with ether; after removal of the ether, the residue was distilled.[9] After removal of the side-chain by distillation, the product was collected and, if possible, recrystallized. In many instances the bases were heavy oils which did not crystallize; these were converted directly to salts for submission for testing. The distillations were carried out in modified von Braun flasks with *wide* tubes (10–30 mm) under pressures ranging from 0.5 mm. to a few microns. Phosphates (usually diphosphates) proved to be the most satisfactory salts of those 4-aminoquinolines which we have studied.

The nuclei, and some of the side chains used were obtained from other laboratories which were coöperating in the malaria program. In the interests of speed and efficiency it was deemed desirable to concentrate the actual drug preparation in one laboratory as far as possible. We should like to express our thanks to all these groups for their wholehearted and unselfish coöperation. The sources of the various intermediates are acknowledged in the experimental part in so far as the record permits.

Table I gives pertinent data about the drugs prepared. In order to avoid repetition we have chosen to describe the preparation of only a few compounds *in detail*. These substances have been selected with the object of presenting as many different modifications of the general preparative scheme as possible. Considered in conjunction with Table I, these preparations make the picture reasonably complete.

Experimental

Part I

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-carbostyril (SN-10,568).—A mixture of 51 g. of 4,7-dichlorocarbostyril[10] and 83 g. of 1-diethylamino-4-aminopentane was stirred and heated at about 175°; the reaction was extremely exothermic. The reaction mixture was dissolved in aqueous acetic acid, made basic, and extracted with benzene. Concentration of the benzene yielded 22 g. of solid.

An attempt to obtain a phosphate from water–dioxane mixtures yielded a product which after recrystallization corresponded in per cent. composition to no simple phosphate. The base was therefore regenerated and recrystallized twice from benzene; 6.7 g. of product were obtained; *anal.* (see Table I).

Mixture of 2-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline Diphosphate Trihydrate and 4-Chloro-2-(4-diethylamino-1-methylbutylamino)-quinoline Diphosphate Trihydrate (SN-10,963–5).—The base from which this drug was prepared was a mixture. It was prepared in the usual way from 2,4-dichloroquinoline.[11] Instead of one product, two were obtained; these bases could not be crystallized or separated satisfactorily by distillation. A phosphate was prepared from the fraction which boiled at 200–210° (1 mm.). No further attempt at separation of the apparent isomers was made inasmuch as preliminary tests in avian malaria of the substance submitted were not encouraging. The above base (19.8 g.) was dissolved in a solution of 14 g. of 85% phosphoric acid in 45 ml. of water. Dioxane was added to turbidity (100 ml.), and the mixture was seeded and allowed to stand for several hours, whereupon an additional 100 ml. of dioxane was added. After standing overnight the salt was removed by filtration, washed with 80% aqueous dioxane and redissolved in a small amount of water. This aqueous solution was added slowly with seeding to 250 ml. of 2-propanol. The product was removed by filtration and washed with 2-propanol. The yield of salt[12] was 48%; m. p. 95–99°. *Anal.* Calcd. for $C_{18}H_{26}N_3Cl\cdot 2H_3PO_4\cdot 3H_2O$: P, 10.87. Found: P, 10.93.

6-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (SN-11,046).—A mixture of 19.8 g. of 4,6-dichloroquinoline[13] and 34.8 g. of 1-diethylamino-4-aminopentane was stirred and heated at 155–160° for five hours and at 160–170° for two and one-half hours. The reaction mixture was taken up in aqueous acetic acid and the solution filtered. Alternately, the acetic acid solution may be extracted with ether. The filtered or extracted solution was made strongly alkaline with sodium hydroxide and extracted with ether. The product was obtained from the

(8) Care must be exercised in applying this test; the salts of certain drugs are relatively sparingly soluble in dilute acid.

(9) Many other methods of operation are possible, *cf.* Drake, *et al.*, THIS JOURNAL, **68**, 1214 (1946), and refs. 2 and 3.

(10) Supplied by Dr. R. E. Lutz, University of Virginia, see THIS JOURNAL, **68**, 1288 (1946).

(11) Supplied by Dr. R. C. Elderfield, Columbia University.

(12) This preparation is included because it illustrates a method which was successful in a very troublesome case.

(13) Supplied by Dr. D. S. Tarbell, University of Rochester, Rochester, N. Y.

TABLE I

No.	Product	SN	Reaction Temp.,[a] °C.	Reaction Time, hr.	Method[b]
1	7-Chloro-4-(4-diethylamino-1-methylbutylamino)-carbostyril	10,568	180[d]	9	[e]
2	4-(7-Chloro-4-quinolylamino)-1-diethylamino-2-butanol	10,960	120–138	2.3	II
3	2,2′-[3-(7-Chloro-4-quinolylamino)-propylimino]-diethanol	10,562	95–105	6.5	I
4	3-(7-Chloro-4-quinolylamino)-1-diethylamino-2-propanol	8,137	137–140	0.8	
			135	3	II
5	4-(3-Aminopropylamino)-7-chloroquinoline	11,438	120–125	1.5	
			140–145	1	II[h]
6	7-Chloro-4-(3-diethylaminocyclohexylamino)-quinoline	12,107	130–140	14	I
7	7-Chloro-4-(4-diethylaminocyclohexylamino)-quinoline	12,108	140–150	4	
		14,477	150–165	3	II[i,k]
8	7-Chloro-4-[3-(2-diethylaminoethoxy)-propylamino]-quinoline	10,962	130–140	1	
			140–150	0.5	II[k,o]
9	7-Chloro-4-(6-diethylaminohexylamino)-quinoline	9,776	145	4	II
10	7-Chloro-4-(5-diethylamino-1-methylamylamino)-quinoline	10,961	170–180	6	II
11	2-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline plus 4-chloro-2-(4-diethylamino-1-methylbutylamino)-quinoline	10,963	150	6	I
12	6-Chloro-4-(4-diethylamino)-1-methylbutylamino)-quinoline	11,046	155–160	5	
			160–170	2.5	I[e]
13	8-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline	11,407	158–162	1.5	
			167–173	3	II[k]
14	7-Chloro-4-(4-diethylamino-1-methylbutylamino)-2-phenylquinoline	10,556	165–175	15	II
15	7-Chloro-4-(4-diethylamino-1-methylbutylamino)-3-phenylquinoline	10,555	155	1	
			183–187	4.5	III[e]
16	7-Chloro-4-(3-diethylaminopropylamino)-quinoline	9,584	135	1.5	
			130	1	I
17	4-(4-Diethylamino-1-methylbutylamino)-2,3-dimethylquinoline	10,447	175	13	
			200[d]	11	III
18	4-(4-Diethylamino-1-methylbutylamino)-7-methoxyquinoline	11,421	160–170	1	
			170–180	2	II
19	4-(4-Diethylamino-1-methylbutylamino)-8-methoxyquinoline	10,661	165–175[m]	2	II[k]
20	4-(4-Diethylamino-1-methylbutylamino)-6-methoxy-2-phenylquinoline	1,905	200	8	I[n]
21	4-(4-Diethylamino-1-methylbutylamino)-7-methoxy-2-phenylquinoline	10,549	161–166	12	III
22	4-(4-Diethylamino-1-methylbutylamino)-6-phenoxyquinoline	10,889	175–180	7	II[p]
23	4-(4-Diethylamino-1-methylbutylamino)-7-phenoxyquinoline	10,663	175	8	[e]
24	4-(4-Diethylamino-1-methylbutylamino)-2-phenylquinoline	10,552	165–185	14	II[e]
25	7-Chloro-4-(4-diethylamino-1-methylbutylamino)-8-quinolinol	12,268	100	1.5	
			130–140	3.5	
			145–155	3	[e]

[a] Temperature of the reaction mixture unless otherwise indicated. [b] An example of each method is described in the Experimental Part. The chief differences are: I, the reaction mixture is taken up in acetic acid; II, the reaction mixture is treated directly with alkali; III, phenol is used in the condensation. [d] Bath temperature. [e] Procedure described in the Experimental Part. [h] The solid separating directly from the neutralized reaction mixture (acetyl compound) was hydrolyzed in refluxing 20% HCl for seven hours. [i] This compound could be separated by repeated fractional crystallizations from ethanol or acetone, into *cis* and *trans* forms. The relative proportion of the two depended to a large extent on variations in the side chain caused by different conditions during catalytic reduction of the benzenoid amine. [k] The product separated from the ether extract. [m] Temperature rose briefly to 215° due to heat of reaction. [n] Extracted with benzene. [o] Nucleus supplied by another laboratory.[22] [p] Nucleus supplied by another laboratory.[16]

dried ether solution by distillation. The yield was 24.4 g.; b. p. 180–185° (0.1 mm.). The base was crystallized from benzene–Skellysolve F (petroleum ether 30–60°), yield 15.1 g. (48.8%); m. p. 71–73°; *anal.*, see Table I.

6-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline Diphosphate Dihydrate (SN-11,046-5).—To a solution of 12.8 g. of base in 9.2 g. of 85% phosphoric acid and 50 ml. of water were added 25 ml. of methanol and 140 ml. of 2-propanol. After the mixture had stood in the ice-box for three days, the crystals were removed by filtration and washed with 2-propanol and ether. The yield of salt was 17.5 g. (79.5%); m. p. 152.4–154.0°. *Anal.* Calcd. for $C_{18}H_{29}N_3Cl\cdot 2H_3PO_4\cdot 2H_2O$: P, 11.21; moisture, 6.52. Found: P, 11.42; moisture, 6.26 (at 100°, no vacuum).

8-Chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline Diphosphate Trihydrate (SN-11,407-5).—To a solution of 7.25 g. of base (prepared in the usual way from 4,8-dichloroquinoline[13]) in 5.24 g. of 85% phosphoric acid and 29 ml. of water were added 15 ml. of methanol and 57 ml. of 2-propanol. After the mixture had stood in an ice-box for two days, the solid was removed by filtration and washed with 2-propanol and ether. A second crop of crystals was obtained from the filtrate. The yield of salt was 11.1 g. (86%); m. p. 119.5–120.8° with previous sintering at 116°. This material was heated under reflux in boiling ethanol for eight hours, cooled and filtered. It weighed 10.7 g., and melted at 121.4–122.1°. *Anal.* Calcd. for $C_{18}H_{28}N_3Cl\cdot 2H_3PO_4\cdot 3H_2O$: P, 10.87; moisture, 9.48. Found: P, 10.83; moisture 10.0 (100°, no vacuum).

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-2-phenylquinoline Diphosphate (SN-10,556-5).—The base of SN-10,556 was prepared in the usual way from 4,7-dichloro-2-phenylquinoline.[14] A solution of 25.6 g. of base in 70 ml. of water containing 14.92 g. of 85% phosphoric acid was warmed with Darco and filtered. After the addition of 35 ml. of methanol to the filtrate, 2-propanol was added to turbidity. The salt was allowed to crystallize overnight in a refrigerator, and was then removed by filtration and recrystallized from warm water and 2-propanol as before; yield 18.9 g. (46.5%); m. p. 248–252°. *Anal.* Calcd. for $C_{24}H_{30}N_3Cl\cdot 2H_3PO_4$: P, 10.5. Found: P, 10.9, 11.0.

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-3-phenylquinoline (SN-10,555).[2,3]—A mixture of 25 g. of 4,7-dichloro-3-phenylquinoline,[14] 8.6 g. of phenol and 31.8 g. of 1-diethylamino-4-aminopentane was stirred and heated at 155° for one hour and at 185° for four and one-half hours. Aqueous acetic acid was added and any un-

(14) Supplied by Dr. R. C. Elderfield, Columbia University, see THIS JOURNAL, **68**, 1276 (1946).

TABLE I (*Continued*)

No.	B. p. °C.	Mm.	M. p., °C.[c]	Yield, %	Composition, % Calculated	Found
1	Not dist.		223.1–225.0	11	C, 64.4 H, 7.81	C, 64.38 H, 7.40
2	xS sidechain dist. in vac., residue accepted as product			Isolated as salt		
3	Not dist.[f]		110.5–111.4[g]	63	C, 59.35 H, 6.85	C, 61.27, 61.21 H, 6.64, 6.59
4	212–218	0.1	118.9–119.9	64		
5	195–200	0.3	87.8–89.8[h]	44	C, 61.20 H, 5.97 N, 17.83	C, 60.91, 60.73 H, 6.03, 5.90 N, 17.74, 17.37
6	215–220	0.5		83		
7	Not dist.		147–149	81		
8	Not dist.		91–92[i]	49	C, 64.37 H, 7.80	C, 63.84 H, 7.32
9	250–251	0.5	67–69[i]	90[l]		
10	235–238	0.5	80.5–82.0	72	C, 68.3 H, 8.45	C, 67.6, 68.0 H, 8.42, 8.19
11	200–210	0.5		52		
12	180–185	0.1	71–73	49	C, 67.6 H, 8.19	C, 66.16 H, 7.73
13	Not dist.		122.9–123.5	36	C, 67.6 H, 8.19	C, 68.58 H, 7.96
14	235–245	0.001		80		
15	225–231	0.1		44		
16	210–218	0.5	73–74	83		
17	185–190	0.5		58		
18	230–240	0.5	101.0–101.7	77[l]	C, 72.35 H, 9.26 methoxyl, 9.85	C, 71.70, 72.05 H, 8.71, 8.83 methoxyl, 9.61, 9.90
19	220	0.5	138.3–139.7	35	C, 72.35 H, 9.26 methoxyl, 9.85	C, 71.67 H, 8.77 methoxyl, 9.35
20	245	0.5		53		
21	238–242	0.2		53		
22	245–249	0.5	109.5–110.5[i]	61[l]	C, 76.36 H, 8.28	C, 76.56, 75.86 H, 8.42, 8.69
23	Not dist.		102–104	30	C, 76.36 H, 8.28	C, 76.0 H, 7.9
24	225–250	0.5		85		
25	Not dist.		115–128	28		

[c] Melting points are corrected. [f] Product crystallized on washing after separation from neutralized acetic acid solution. [g] Recrystallized from (1) alcohol–water; (2) alcohol–ether. [i] Recrystallized from benzene–petroleum ether. [l] Before recrystallization.

reacted nucleus was removed by extracting the suspension with ether. The aqueous acid phase was then made strongly basic and again extracted with ether. The product was obtained from the ether solution by distillation. The fraction collected boiled at 225–230° (0.1 mm.) and weighed 15.9 g. (44.1%). The base could not be recrystallized successfully; it was converted to the salt for analysis.

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-3-phenylquinoline Dihydriodide (SN-10,555–17).—To a solution of 15.65 g. of base in a mixture of 50 ml. of water, 50 ml. of ethanol, and 9.11 g. of 85% phosphoric acid was added a solution of 13.1 g. of potassium iodide in 150 ml. of water. The yellow hydriodide which formed was filtered (23 g.) and recrystallized from methanol. A composite from several experiments (23 g.) was stirred for five hours with warm water (50°) and again filtered and dried. The yield in this step was 21 g. (91% recovery); m. p. 263–273° dec. *Anal.* Calcd. for $C_{24}H_{30}N_3Cl\cdot 2HI$: C, 44.2; H, 4.95. Found: C, 44.11; H, 4.78.

4-(4-Diethylamino-1-methylbutylamino)-2,3-dimethylquinoline Diphosphate (SN-10,447–5).—To a solution of 25.7 g. of SN-10,447, prepared in the usual way from Noval diamine and 4-chloro-2,3-dimethylquinoline,[10] was added 18.5 g. of 85% phosphoric acid, 25 ml. of water, and 75 ml. of dioxane. The aqueous phase was decanted from the oil which separated and treated with additional dioxane. Crystallization occurred and the product was separated by filtration, washed with dioxane and ether and recrystallized from water–dioxane. The yield was 35 g. (83%); m. p. 223.5–225°. *Anal.* Calcd. for $C_{20}H_{31}N_3\cdot 2H_3PO_4$: P, 12.17. Found: P, 12.32, 11.95.

4-(4-Diethylamino-1-methylbutylamino)-7-methoxyquinoline Diphosphate (SN-11,421–5).—The base for this salt was prepared from 4-chloro-7-methoxyquinoline[15] in the usual way. To a solution of 6.68 g. of base in 4.88 g. of 85% phosphoric acid and 27 ml. of water were added 14 ml. of methanol and 50 ml. of 2-propanol. After the mixture had stood overnight in a refrigerator, 10.0 g. of salt which melted, after sintering at 170°, at 198–200° was obtained. This substance was heated under reflux in boiling ethanol for six hours and allowed to stand overnight. The salt was then filtered from the solution and dried; yield 9.4 g. (86.7%); m. p. 197.9–199.1°. *Anal.* Calcd. for $C_{19}H_{29}N_3\cdot 2H_3PO_4$: P, 12.1. Found: P, 11.9.

4-(4-Diethylamino-1-methylbutylamino)-8-methoxyquinoline Diphosphate Trihydrate (SN-10,661–5).—The base for this salt was prepared from 4-chloro-8-methoxyquinoline[15] in the usual way. To 10.2 g. of base in 7.47 g. of 85% phosphoric acid and 40 ml. of water were added 20 ml. of methanol and 83 ml. of 2-propanol. After the mixture had been cooled in a refrigerator overnight, the salt was removed by filtration and washed with 2-propanol and ether. For purification the crude salt was heated under reflux in boiling alcohol for eight hours, cooled and filtered. The yield was 14.7 g. (80%); m. p. 127.5–128.4°. *Anal.* Calcd. for $C_{19}H_{29}N_3\cdot 2H_3PO_4\cdot 3H_2O$: P, 10.95; moisture, 9.55. Found: P, 10.90; moisture, 9.80 (100°, no vacuum).

4-(4-Diethylamino-1-methylbutylamino)-6-methoxy-2-phenylquinoline Triphosphate (SN-1905–5).—The base

(15) Supplied by Dr. W. M. Lauer of the University of Minnesota, see THIS JOURNAL, **68**, 1268 (1946).

for this salt was prepared in the usual way from 4-chloro-6-methoxy-2-phenylquinoline.[14] A solution of 24 g. of the base (SN-1905) in 14.14 g. of 85% phosphoric acid and 96 ml. of water was prepared; methanol (48 ml.) was added and then enough 2-propanol to cause turbidity. After the mixture had cooled in a refrigerator for four hours, the salt was removed by filtration and washed with 2-propanol and ether. The yield was 20 g. (47.5%); m. p. 205.4–206.8°. *Anal.* Calcd. for $C_{25}H_{33}N_3O\cdot 3H_3PO_4$: P, 13.56. Found: P, 13.50, 13.41.

4-(4-Diethylamino-1-methylbutylamino)-7-methoxy-2-phenylquinoline Triphosphate (SN-10,549-5).—The base for this salt was prepared in the usual way from 4-chloro-7-methoxy-2-phenylquinoline.[14] The base (5.25 g.) was stirred thoroughly with a mixture of 4.54 g. of 85% phosphoric acid and 20 ml. of water. The solution was decanted from undissolved material, and to it were added 11 ml. of methanol and 52 ml. of 2-propanol; the mixture was then cooled for three hours. Filtration yielded 6.34 g. of salt; m. p. 194.5–197.5°. Recrystallization from water–methanol–2-propanol produced 5.65 g. of salt (62%) which melted at 195.0–197.5°. *Anal.* Calcd. for $C_{25}H_{33}N_3O\cdot 3H_3PO_4$: P, 13.56. Found: P, 13.21.

4-(4-Diethylamino-1-methylbutylamino)-7-phenoxyquinoline (SN-10,663).—A mixture of 51 g. of 4-chloro-7-phenoxyquinoline[16] and 69.6 g. of 1-diethylamino-4-aminopentane was stirred and heated at 175° for eight hours. Aqueous alkali was added and the mixture was extracted with benzene. The benzene extract was washed with water, concentrated as far as possible on a steam-bath, diluted with 500 ml. of Skellysolve F, and set aside to crystallize. The crystalline base was removed by filtration and dried. The yield was 61.5 g.; m. p. 96–108°. Recrystallization to constant melting point gave 22.5 g. of product (30%); m. p. 102–104°; *anal.*, see Table I.

4-(4-Diethylamino-1-methylbutylamino)-2-phenylquinoline (SN-10,552).[17]—A mixture of 49 g. of 4-chloro-2-phenylquinoline[14] and 63 g. of 1-diethylamino-4-aminopentane was stirred and heated at 170–190° for fourteen hours. Strong alkali was added and the mixture was extracted with ether. The ether was removed on a steam-bath and the product distilled. The yield was 62.7 g. (85%); b. p. 225–250° < 1 mm. The base did not crystallize; it was converted to salt for analysis.

4-(4-Diethylamino-1-methylbutylamino)-2-phenylquinoline Triphosphate (SN-10,552-5).—To a solution of 20.1 g. of the base, SN-10,552, in 78 ml. of water and 17.0 g. of 85% phosphoric acid were added 40 ml. of methanol and sufficient 2-propanol to cause turbidity. The turbid solution was seeded and cooled overnight in a refrigerator. After filtration and washing with 2-propanol and ether, the salt weighed 23.4 g.; it melted at 168-171°. After recrystallization from water–methanol–2-propanol, the product weighed 19.5 g. (56%); m. p. 174–176°. *Anal.* Calcd. for $C_{24}H_{31}N_3\cdot 3H_3PO_4$: P, 14.2. Found: P, 14.4, 14.5.

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-8-quinolinol (SN-12,268).—A mixture of 16.6 g. of 4,7-dichloro-8-methoxyquinoline[15] and 25.4 g. of 1-diethylamino-4-aminopentane was stirred and heated at 100° for one and one-half hours, at 135° for three and one-half hours, and at 150° for three hours. The mixture was dissolved in aqueous acetic acid and then brought to *p*H 8.0 with alkali. A gummy precipitate separated which was washed with water by decantation. The precipitate was dissolved in 350 ml. of benzene and dried by azeotropic distillation. When the dry solution was allowed to stand overnight in a refrigerator, a yellow-green solid separated; it was removed from the liquid by centrifugation and washed with benzene–petroleum ether. The yield was 6.9 g. (28%); m. p. 115–128°. Because of the broad melting range and difficulty of crystallization, the base was not analyzed. When it was later analyzed as diphosphate it was learned that the compound had been demethoxylated at some stage of the process.

7-Chloro-4-(4-diethylamino-1-methylbutylamino)-8-quinolinol Diphosphate (SN-12,268-5).—The base (6.9 g.) was dissolved in 27 ml. of water containing approximately the correct amount of phosphoric acid to form a diphosphate and the solution was treated with Darco and filtered. To the filtrate was added 14 ml. of methanol and 50 ml. of 2-propanol, and the mixture was allowed to stand in a refrigerator for a week; at the end of this time the separated oil had crystallized completely. The product weighed 5.4 g. and melted at 216–220°. It was heated under reflux in boiling alcohol and then recovered by filtration; it then weighed 5.3 g. and melted at 217.7–220°. Another recrystallization from water–methanol–2-propanol after treatment with Darco produced almost colorless crystals (4.5 g.) which melted at 219.7–221.6°. *Anal.* Calcd. for $C_{18}H_{26}N_3OCl\cdot 2H_3PO_4$: C, 40.6; H, 6.05; P, 11.63; methoxyl, none. Found: C, 40.37, 40.13; H, 5.91, 5.95; P, 11.84; methoxyl, none.

Part II

4-(7-Chloro-4-quinolylamino)-1-diethylamino-2-butanol Diphosphate (SN-10,960-5).—The base for this salt was prepared in the usual way from 1-diethylamino-4-amino-2-butanol.[18] The base from 56 g. of 4,7-dichloroquinoline was dissolved in 70.6 g. of 85% phosphoric acid in 392 ml. of water by warming. About 3600 ml. of methanol was added and the mixture was cooled in a refrigerator overnight. The product was filtered and washed with methanol and ether. The yield was 98 g. (67% over-all from the DCQ[19,20]; the product melted at 217-218°. *Anal.* Calcd. for $C_{17}H_{24}N_3OCl\ 2H_3PO_4$: P, 12.0. Found: P, 12.3, 12.3.

2,2'-[3-(7-chloro-4-quinoylamino)-propylimino]-diethanol Diphosphate (SN-10,562-5).—The base for this salt was prepared in the usual way; both the DCQ[20] and the side-chain[21] were supplied by other laboratories. To a solution of 6.48 g. of base in 4.62 g. of 85% phosphoric acid and 20 ml. of water were added 12 ml. of methanol and 5 ml. of 2-propanol. The crystalline salt was filtered and dried; the yield was 10.2 g. (98%); m. p. 199.4–201.2°. *Anal.* Calcd. for $C_{16}H_{22}N_3O_2Cl\cdot 2H_3PO_4$: P, 11.92. Found: P, 11.86.

4-(3-Aminopropylamino)-7-chloroquinoline Diphosphate (SN-11,438-5).—The base from which this salt was prepared was obtained in the usual way from 1-acetamino-3-aminopropane. The acetyl group was removed by acid hydrolysis (20% hydrochloric acid for seven hours) subsequent to the condensation.

Two molecular equivalents of 85% phosphoric acid were added dropwise to a stirred refluxing solution of 6.33 g. of base in 150 ml. of ethanol. After addition of the acid was complete, the mixture was stirred for one hour, cooled, and filtered. The product was washed with alcohol and dried in a vacuum oven at 40°. The yield was 12.65 g. (99%); m. p. 205.9–209.6° with previous sintering at 203°. *Anal.* Calcd. for $C_{12}H_{14}N_3Cl\cdot 2H_3PO_4\cdot C_2H_5OH$: P, 12.98; ethoxyl, 9.45. Found: P, 13.02, 12.93; ethoxyl, 2.57, 4.85, 3.46, 2.95.

For some unknown reason it was impossible to obtain consistent analyses for alkoxyl on this substance. It seems likely that the sample contained both alcohol *and* water of solvation equivalent to about 46 weight units.

1-Acetamino-3-aminopropane.—A mixture of 28 g. of 1,3-diaminopropane[22] and 33.3 g. of ethyl acetate was

(16) Supplied by Dr. B. Riegel, Northwestern University, see THIS JOURNAL, **68**, 1264 (1946).

(17) U. P. Basu and P. K. Das-Gupta, *J. Ind. Chem. Soc.*, **16**, 301 (1939); *C. A.*, **34**, 1021 (1940).

(18) Supplied by Dr. R. C. Elderfield, Columbia University, see THIS JOURNAL, **68**, 1291 (1946).

(19) 4,7-Dichloroquinoline, hereinafter called DCQ.

(20) The bulk of our DCQ was supplied by Dr. C. C. Price and his associates at the University of Illinois. Considerable quantities were also supplied by Dr. R. C. Elderfield and his associates at Columbia University and by Dr. Byron Riegel and his group at Northwestern University.

(21) Supplied by Dr. R. C. Elderfield, Columbia University, see THIS JOURNAL, **68**, 1291 (1946).

(22) Supplied by Dr. R. C. Elderfield, Columbia University.

heated in a sealed tube at 100° for twelve hours.[23] Distillation yielded 16 g. (36%) of product which boiled at 130–140° (2.5 mm.).

The same product was prepared in somewhat better yield and much more simply from β-acetaminopropionitrile. To 151 g. of β-aminopropionitrile[24] was added 440 g. of acetic anhydride with cooling. The mixture was heated under reflux for one-half hour, and then fractionated *in vacuo*. The yield was 104 g. (43%); b. p. 169–172° (15 mm.); there was a considerable solid residue. Ninety-nine grams of β-acetaminopropionitrile was reduced in the presence of Raney nickel at 60° (initial pressure 4000 p. s. i.). The product was recovered by fractional distillation. The yield was 45 g. (44%).

3-(7-Chloro-4-quinolylamino)-1-diethylamino-2-propanol Diphosphate (SN-8137-5).—The base for this salt was prepared in the usual manner from DCQ[20] and 3-amino-1-diethylamino-2-propanol.[25] The *p*H of a solution of 217 g. of base in 870 ml. of water containing an equimolar amount of phosphoric acid was adjusted at 3.38 by the addition of more phosphoric acid. The solution was filtered and 3.6 liters of methanol was added together with a small amount of seed. The solution was allowed to stand for about eighteen hours in a refrigerator and was then filtered; the salt was washed with cold methanol and then with ether. The yield was 270 g. (77%); m. p. 209–210.3°. *Anal.* Calcd. for $C_{16}H_{22}N_3OCl\cdot 2H_3PO_4$: P, 12.31. Found: P, 12.30, 12.40.

7-Chloro-4-(3-diethylaminocyclohexylamino)-quinoline Diphosphate (SN-12,107-5).—The base for this salt was prepared in the usual way from 3-diethylaminocyclohexylamine[26] and DCQ.[19] A solution was made of 12.6 g. of base in 20 ml. of water and 8.75 g. of 85% phosphoric acid. After ethanol was added to turbidity, the mixture was cooled overnight in a refrigerator and the crystals were removed by filtration. The yield was 14.6 g. (73%). The product (20.4 g.) was reconverted to base and recrystallized from benzene–petroleum ether (recovery 87%). The purified base was dissolved in 250 ml. of dioxane and two molecular equivalents of 85% phosphoric acid was added slowly while the mixture was stirred in the presence of seed crystals. A suspension of salt formed and was stirred for two hours at 100° and overnight at room temperature. After filtration and drying, the phosphate weighed 18 g.; m. p. 200–230° This product was heated under reflux with 300 ml. of a boiling mixture of ethanol–2-propanol (1:1) for two hours and allowed to stand overnight. After filtration and drying the salt weighed 17 g. (61% over-all). Analysis showed that the product contained 3% of moisture; the theoretical composition of the salt is calculated on this basis. *Anal.* Calcd. for $C_{19}H_{26}N_3Cl\cdot 2H_3PO_4$ + 3% H_2O: C, 41.9; H, 5.33; P, 11.38. Found: C, 41.62, 41.62; H, 5.62, 5.84; P, 11.55, 11.57; moisture, 2.96, 3.01.

***cis* and *trans*-7-Chloro-4-(4-diethylaminocyclohexylamino)-quinoline** (SN-12,108 and SN-14,477).—These substances, SN-12,108 and SN-14,477 were prepared from DCQ[19] and various samples of 4-diethylaminocyclohexylamine.[26] In keeping with the possibility of the existence of two stereoisomeric forms of the amine, two modifications of the drug were obtained. These forms can be separated by a tedious fractional crystallization. The lower-melting form, SN-12,108, has been tentatively assigned the *cis* configuration; this form of the base melts at 157.8–159° with previous sintering at 156.6°. The higher-melting form, SN-14,477, has been tentatively assigned the *trans* configuration; this form of the base melts at 223–225.5° after previous sintering at 210°. *Anal.* Calcd. for $C_{19}H_{26}N_3Cl$: C, 68.75; H, 7.90. Found: SN-12,108, C, 68.24, 68.29; H, 7.70, 7.74; SN-14,477, C, 68.13, 68.30; H, 7.75, 7.46.

A diphosphate was prepared from a sample of base whose melting point was 147–149°. To a stirred solution of 23.3 g. of base in 300 ml. of refluxing 2-propanol was added dropwise 16.1 g. of 85% phosphoric acid. The mixture was heated under reflux for two hours, cooled and filtered. After it had been washed and dried, the phosphate weighed 35 g. (94.5%), and melted at 226.2–228.0° with previous sintering at 222.5°. *Anal.* Calcd. for $C_{19}H_{26}N_3Cl\cdot 2H_3PO_4$: C, 43.2; H, 6.11; P, 11.73. Found: C, 42.6, 42.8; H, 5.91, 5.89; P, 11.74, 11.84.

7-Chloro-4-(6-diethylaminohexylamino)-quinoline Diphosphate (SN-9776-5).—The base for this salt was prepared from 1-diethylamino-6-aminohexane[27] and DCQ[19] in the usual way. A solution of 16.5 g. of base in 250 ml. of ethanol was boiled under reflux with stirring, and 11.42 g. of 85% phosphoric acid was added dropwise. The mixture was allowed to boil under reflux overnight and was then cooled. The crude salt was removed by filtration (24.5 g., m. p. 152–157°) and dissolved in a small amount of water. Alcohol was added to turbidity and the mixture was set aside to cool during crystallization. The yield was 22.2 g. (85%); m. p. 200.2–201.9°. The salt has two transition points; it softens and resolidifies at 150° and at 180°. *Anal.* Calcd. for $C_{19}H_{28}N_3Cl\cdot 2H_3PO_4$: P, 11.70. Found: P, 11.7.

7-Chloro-4-(5-diethylamino-1-methylamylamino)-quinoline Diphosphate (SN-10,961-5).—The base for this salt was prepared in the usual way from DCQ[19] and 1-diethylamino-5-aminohexane.[26] To a solution of 12.1 g. of once recrystallized base (two recrystallizations are necessary to produce base of analytical purity) in a mixture of 8.36 g. of 85% phosphoric acid and 48 ml. of water were added 24 ml. of methanol and 150 ml. of 2-propanol. Crystallization was allowed to proceed in a refrigerator for three days, whereupon the salt was removed by filtration and washed with 2-propanol and ether. The yield was 15 g. (78%); m. p. 188.8–190.8°. *Anal.* Calcd. for $C_{19}H_{28}N_3Cl\cdot 2H_3PO_4$: P, 11.7. Found: P, 12.3%.

7-Chloro-4-(3-diethylaminopropylamino)-quinoline Diphosphate (SN-9584-5).—The base for this salt was prepared in the usual way from DCQ[19] and 3-diethylaminopropylamine.[29] The base (362 g.) was dissolved in 1.5 liters of water containing 286 g. of 85% phosphoric acid. Methanol (750 ml.) and 2-propanol (3 l.) were added and the product was allowed to crystallize in a refrigerator. The yield was 591 g. (98%); m. p. 232.5–234.5°. *Anal.* Calcd. for $C_{16}H_{22}N_3Cl\cdot 2H_3PO_4$: C, 39.39; H, 5.79; P, 12.70. Found: C, 39.58; H, 5.42; P, 12.71.

Summary

1. The preparation of 4-aminoquinolines from 4-chloroquinolines is discussed.

2. Twenty-five 4-aminoquinolines and the majority of the corresponding salts are described.

3. The preparation of certain necessary intermediates is described.

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(23) S. R. Aspinall, THIS JOURNAL, **62**, 2160 (1940).

(24) F. C. Whitmore, H. S. Mosher, *et al.*, *ibid.*, **66**, 725 (1944).

(25) Supplied by Dr. C. C. Price, University of Illinois, see *ibid.*, **68**, in press (1946).

(26) Supplied by Dr. C. W. Todd, du Pont Experimental Station, Wilmington, Delaware, *ibid.*, **68**, 1296 (1946).

(27) O. J. Magidson and A. M. Grigorowsky, *Ber.*, **69B**, 396 (1936).

(28) Supplied by Dr. Mary Sherrill, Mount Holyoke College, see THIS JOURNAL, **68**, 1294 (1946).

(29) Supplied by Dr. Homer Adkins, University of Wisconsin.