stein[19] or variations thereof. The results are summarized in Table I.

TABLE I

PREPARATION OF 5,6-DIMETHOXY-8-NITROQUINOLINE

	Run number 1	2	3	4[a]
4-Amino-5-nitroveratrole, mole	0.18	0.42	0.70	0.18
Acrolein, mole	.30	.63	0.80	.23
H_3AsO_4, moles	.36	.80	1.4	.36
85% H_3PO_4, ml.	175	400	750	200
Temperature, °C.	100 ± 2	95–100	96–98	100 ± 2
Time of addn. of acrolein, min.	40	45	45	30
Time of heating, min.	30	15	30	30
Yield, %[b]	40	37.7	36	40

[a] Acrolein acetal was substituted for acrolein. [b] After recrystallization from ethyl acetate.

B. **From 6-Methoxy-8-nitroquinoline.**—To a mixture of 408 g. of 6-methoxy-8-nitroquinoline, 152 g. of calcium carbonate, 8 g. of iron filings, 2 l. of chloroform and 400 ml. of water was added 400 ml. of bromine. The mixture was heated under reflux with stirring for 6 hr. and then allowed to stand at room temperature for 15 hr. The solid which separated was collected and pressed dry. Additional amounts of crude material, the total yield of which was 580 g., were obtained from the mother liquors. After recrystallization from benzene, 351 g. (62%) of 5-bromo-6-methoxy-8-nitroquinoline, m.p. 204–205°, was obtained. Concentration of the benzene mother liquor gave 135 g. of a mixture of product and unreacted starting material, m.p. 148–195°, which could not be separated easily into its components but which gave more bromo compound on recycling.

To 3000 ml. of anhydrous methanol in a 3-necked flask was added 46 g. of sodium. When the sodium had dissolved, the flask was fitted with a stirrer and reflux condenser and 700 ml. of pyridine and 568 g. of 5-bromo-6-methoxy-8-nitroquinoline were added. After refluxing with stirring for 96 hr., the mixture was poured into 30 l. of water. The crude product (460 g.), m.p. 116–120°, was recrystallized from methanol with decolorizing carbon giving 290 g. (62%) of 5,6-dimethoxy-8-nitroquinoline, m.p. 128–129°. An additional 86 g. of material, m.p. 116–121°, was obtained from the mother liquor.

5,6-Dimethoxy-8-aminoquinoline.—The previously described reduction of 5,6-dimethoxy-8-nitroquinoline has given erratic results.[17] Further study of the reaction has resulted in the following consistent and reliable procedure.

A mixture of 640 g. of stannous chloride dihydrate (analytical reagent grade) and 700 ml. of hydrochloric acid (sp. gr. 1.19) in a 5-l. 3-necked flask equipped with an efficient Hershberg stirrer, pentane thermometer and dropping funnel was chilled to 0° in an ice–salt-bath. In a separate flask, with cooling, a solution of 165.5 g. of 5,6-dimethoxy-8-nitroquinoline in 700 ml. of hydrochloric acid (sp. gr. 1.19) was prepared and chilled to 10°. After addition of 20 g. of granulated tin to the reducing solution stirring was started and the solution of the nitroquinoline was added dropwise with strong cooling at such a rate that the temperature never exceeded 10°. After the addition was complete the mixture was stirred for one hour at 10° and for 3 hr. at room temperature. The canary-yellow suspension was diluted with 2.5 l. of warm water which resulted in partial solution of the solid and a sharp color change of the remainder to scarlet. An excess (about 3 l.) of 8 *M* sodium hydroxide solution was added dropwise to the red suspension with stirring during which the temperature was kept below 20° to prevent occlusion of the stannic chloride complex. If excess alkali sufficient to redissolve the precipitated tin salts is not added, filtration of the amine is very slow with consequent large losses by air oxidation. The greenish-yellow amine was collected and washed thoroughly with water. The crude yield was 94%. Recrystallization from heptane with carbon gave 78% of yellow needles, m.p. 147.5–148°.

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[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF COLUMBIA UNIVERSITY AND THE UNIVERSITY OF MICHIGAN]

Further Syntheses of Primaquine Analogs[1]

BY ROBERT C. ELDERFIELD,[2] ELIZABETH F. CLAFLIN, HOLLY E. MERTEL, ORVILLE L. MCCURDY, RICHARD T. MITCH, CHARLES D. VER NOOY, BRUCE H. WARK AND IRIS M. WEMPEN

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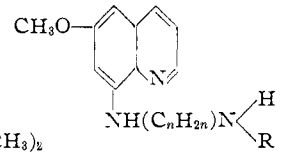
Synthesis of five analogs of primaquine in which the carbon skeleton of the side chain is branched in positions other than at the 1-carbon atom is presented. Preparation of the requisite phthalimido bromides is described.

Derivatives of 6-methoxy-8-(ω-dialkyl- or monoalkylaminoalkylamino)-quinoline previously have been described as effective agents against the exoerythrocytic forms of *Plasmodium vivax*.[3] However, derivatives of 6-methoxy-8-aminoquinoline typified by the general formula I are not as common.



I, R = H
II, R = $CH(CH_3)_2$

For the most part, such compounds have been characterized by a straight carbon chain in the fragment C_nH_{2n}.[4] Notable exceptions to this generalization are found in the drug, primaquine, and its analogs[5] in which the C_nH_{2n} fragment of I is branched at the 1-carbon atom. As far as we are aware, there are no instances of the synthesis of drugs of the type of I on record in which the branching of the C_nH_{2n} fragment occurs other than at the 1-carbon atom. Elderfield, Pitt and Wempen[6] reported the synthesis of a number of ω-isopropylaminoalkylamino bromides suitable for condensation with 6-methoxy-8-aminoquinoline with formation of compounds of the type of II. In this series of amino bromides the total number of carbon atoms in the fragment C_nH_{2n} was limited to 5 or 6

(1) The work here reported was done in part under National Institutes of Health Grant RG-195 to Columbia University and in part under contracts DA-49-007-MD-64 and DA-49-007-MD-334 between the Medical Research and Development Board, Department of the Army and Columbia University and the University of Michigan, respectively.

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(3) F. Y. Wiselogle, "Survey of Antimalarial Drugs," Edwards Bros., Ann Arbor, Mich., 1946.

(4) R. C. Elderfield, *et al.*, THIS JOURNAL, **68**, 1568 (1946), and references given therein.

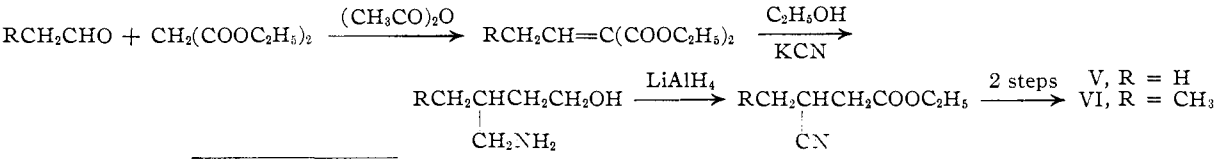
(5) R. C. Elderfield, *et al.*, *ibid.*, **77**, 4816 (1955).

(6) R. C. Elderfield, B. M. Pitt and I. M. Wempen, *ibid.*, **72**, 1334 (1950).

and the number of carbon atoms in the straight chain of C_nH_{2n} was fixed at 4 or 5 for reasons previously set forth. Since the previous publication,[6] evidence has been overwhelming that a terminal primary amino group as typified by primaquine[7] is much to be preferred to a terminal isopropylamino group, as typified by isopentaquine, in this particular type of antimalarial.

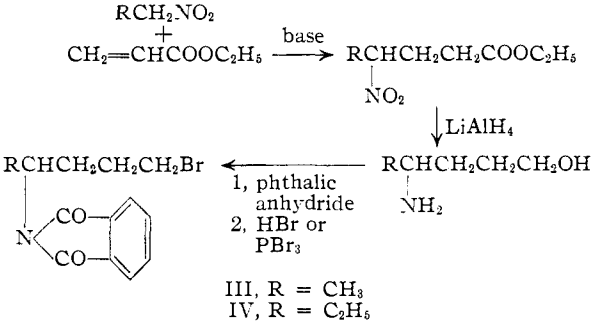
In an accompanying paper,[5] we present the synthesis of a number of analogs of primaquine in which branching of the C_nH_{2n} fragment occurs exclusively at the 1-carbon atom. In the present communication we wish to present the synthesis of certain analogs of primaquine in which the branching of the carbon chain in C_nH_{2n} occurs at positions other than at the 1-carbon atom.

With the restrictions previously imposed,[6] ten such isomers are possible, of which we now present the synthesis of five, namely, 6-methoxy-8-(5-amino-3-methylamylamino)-quinoline (CN-1106)[8]; 6-methoxy-8-(4-amino-4-methylbutylamino)-quinoline (CN-1115), 6-methoxy-8-(4-amino-4-ethylbutylamino)-quinoline (CN-1111), 6-methoxy-8-(4-amino-3-methylbutylamino)-quinoline (CN-1120) and 6-methoxy-8-(4-amino-3-ethylbutylamino)-quinoline (CN-1121). Synthesis of the remaining members of the series will be reported in a later paper.



The ultimate step in the synthesis of all of these drugs involves condensation of an appropriate ω-phthalimido bromide with 6-methoxy-8-aminoquinoline.[5] The problem thus resolves itself into development of suitable syntheses of the requisite ω-phthalimido bromides. The phthalimido bromide required for CN-1106 already has been described.[6]

Synthesis of the phthalimido bromides (III and IV) required for CN-1115 and CN-1111 is represented by the sequence



Michael condensation of nitroethane or 1-nitropropane with ethyl acrylate occurred readily according to Kloetzel[9] or according to Bruson.[10] Details of the relative advantages of the two methods are given in the Experimental part. Reduction of the nitro esters to the amino alcohols with lithium aluminum hydride proceeded smoothly. The method of Amundsen and Nelson[11] proved to be of great value in avoiding cyclization of the amino alcohols during the work-up of the reaction mixtures. The amino alcohols were obtained as very hygroscopic oils for which, in general, it was impossible to obtain satisfactory analytical data. However, they were entirely satisfactory for use in the subsequent steps in the syntheses.

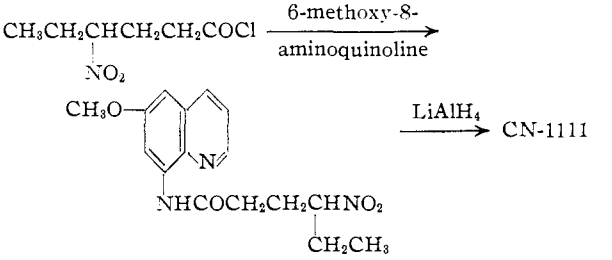
The preparation of phthalimido alcohols from amino alcohols has been described previously.[12,13] In our experience they were obtained as viscous oils with no difficulty except for slight contamination with phthalic anhydride which was difficult to remove and did not interfere with subsequent operations. The phthalimido bromides were prepared from the alcohols with hydrobromic acid, although, as indicated below, phosphorus tribromide may be a superior reagent.

The route employed for synthesis of the phthalimido bromides (V and VI) required for CN-1120 and CN-1121 is shown in the following sequence up to the amino alcohol stage. From there on the reactions are identical to those described above except that phosphorus tribromide appears to be the reagent of choice for the preparation of the bromides.

Condensation of acetaldehyde or propionaldehyde with diethyl malonate gave the alkylidene malonates.[14] Simultaneous cleavage of one carbethoxyl group from and addition of hydrogen cyanide to the alkylidene malonates[15] resulted in the formation of the cyano esters which were in turn reduced with lithium aluminum hydride to the amino alcohols.

The phthalimido bromides condensed readily with 6-methoxy-8-aminoquinoline to yield the drugs.

Prior to the successful synthesis of CN-1111 and CN-1115 an alternate route to CN-1111 was explored as



The reactions were carried through successfully up

(7) References 5–8 in ref. 5.

(8) The prefix CN identifies a drug in the files of Columbia University or the University of Michigan.

(9) M. C. Kloetzel, THIS JOURNAL, **70**, 3571 (1948).

(10) H. A. Bruson, U. S. Patent 2,342,119.

(11) L. H. Amundsen and L. S. Nelson, THIS JOURNAL, **73**, 242 (1951).

(12) R. Robinson and H. Suginome, *J. Chem. Soc.*, 304 (1932).

(13) F. Garelli and G. Racciu, *Atti accad. sci. Torino, Classe sci. fis., mat. nat.*, **69**, 358 (1934); *C. A.*, **29**, 6223 (1935).

(14) W. S. Fones, *Org. Syntheses*, **32**, 54 (1952).

(15) J. Bredt and J. Kallen, *Ann.*, **293**, 338 (1896).

to the acylaminoquinoline. Although reduction of this was not attempted in view of the successful synthesis outlined above, there seems to be no reason to doubt that it would proceed as anticipated.

Experimental[16,17]

6-Methoxy-8-(4-amino-4-methylbutylamino)-quinoline (CN-1115). A. Ethyl γ-Nitrovalerate.—This was prepared in good yield from nitroethane and ethyl acrylate according to Kloetzel[9] with triethylamine as catalyst. Alternately the method of Bruson[10] using Triton B as catalyst was used. Substitution of an aqueous solution of choline for Triton B gave poorer yields. In comparison, Kloetzel's method gave a somewhat more consistent yield of the nitro ester with but little attention during the several days required for the reaction; Bruson's method furnished the ester in shorter time but required care as to reaction conditions.

B. **4-Amino-1-pentanol.**—In a 3-liter flask equipped with a mercury sealed stirrer, a dropping funnel, two Hoffman condensers and a nitrogen inlet tube was placed 57 g. of lithium aluminum hydride which had been ground under nitrogen. After flushing the system with nitrogen, 500 ml. of absolute ether was added and the mixture was stirred for several hours until most of the hydride had dissolved. A solution of 75 g. of ethyl γ-nitrovalerate in 400 ml. of absolute ether then was added dropwise with stirring. In order to avoid fires it was necessary to keep the stopcock of the funnel carefully greased and to avoid caking of solids on the walls of the flask. During the course of the reduction the ether entrained by the escaping hydrogen was replaced continuously (300–800 ml. in various runs). The mixture was stirred for several hours and allowed to stand overnight. Forty-five ml. of water was added dropwise with vigorous stirring to decompose excess lithium aluminum hydride followed by 35–40 ml. of 20% sodium hydroxide solution and 50 ml. of water. After filtering from suspended solids, the greenish one-phase ether solution was distilled through a two-foot Vigreux column and the residue (27.5 g.) was distilled under reduced pressure yielding 20.0 g. (45%) of colorless, oily, very hygroscopic liquid, b.p. 73° (1.1 mm.). Redistillation from barium oxide gave analytically pure material, b.p. 67–68° (0.2 mm.).

Anal. Calcd. for $C_5H_{13}NO$: C, 58.3; H, 12.6; N, 13.6. Found: C, 58.5; H, 12.3; N, 13.6.

C. **4-Phthalimido-1-pentanol.**—To a solution of 100 g. of finely powdered phthalic anhydride in 600 ml. of boiling carbon tetrachloride was added dropwise a solution of 68 g. of 4-amino-1-pentanol and the mixture was refluxed for 2 hr. A thick gummy mass separated as the amino alcohol was added. After distillation of the solvent at atmospheric pressure, the phthalamic acid was converted to the phthalimide by heating to 160° under water-pump vacuum for one hour. Vacuum distillation of the residue gave 121 g. (79%) of thick viscous yellow liquid, b.p. about 127° (0.03 mm.).

Anal. Calcd. for $C_{13}H_{15}NO_3$: N, 6.0. Found: N, 5.9.

The phthalimido alcohol also was prepared in yields of 75–98% when glacial acetic acid was the solvent.

D. **1-Bromo-4-phthalimidopentane.**—A solution of 121 g. of 4-phthalimido-1-pentanol in 300 ml. of 48% hydrobromic acid was warmed on the steam-bath for 2 hr. during which an oily layer separated. After cooling, the organic layer was separated and the aqueous layer was extracted several times with benzene. The combined organic layer and benzene extracts were dried over anhydrous potassium carbonate and, after removal of the solvent, the residue was distilled under reduced pressure yielding 60 g. (39%) of very viscous pale yellow oil, b.p. 137° (0.06 mm.), $n^{26}D$ 1.5658. Although not analytically pure, the material was pure enough for subsequent steps.

Anal. Calcd. for $C_{13}H_{14}BrNO_2$: C, 52.7; H, 4.7. Found: C, 53.9; H, 4.8.

E. **CN-1115.**—The above phthalimido bromide was condensed with 6-methoxy-8-aminoquinoline by the method given in the preceding paper[5] using a phosphate buffer (*p*H 8.3). Hydrolysis of the phthalimido group was done without purification of the intermediate. The crude drug in ether was extracted with 2 *M* phosphate buffer (*p*H 5.88) for removal of unreacted 6-methoxy-8-aminoquinoline which remained in the ether. The buffer extracts were made basic and extracted with ether. From the ether extracts on addition of phosphoric acid 86% (based on phthalimido bromide) of crude drug phosphate was obtained. After one recrystallization from methanol containing a little phosphoric acid, material, m.p. 163–169°, was obtained. As has been noted previously with phosphates of 8-aminoquinoline drugs, this was mainly the diphosphate with a small amount of triphosphate being present. Recrystallization apparently resulted in some disproportionation between the two salts with resultant increase in the melting point range (168–175°). The once-recrystallized material contained 46.6% of phosphoric acid which corresponds to 2.16 moles of acid per mole of drug base. The drug base was homogeneous by the Craig counter-current method.

Anal. Calcd. for $C_{13}H_{21}N_3O \cdot 2.16H_3PO_4$: C, 37.1; H, 5.8; P, 14.8. Found: C, 37.1; H, 6.1; P, 14.7.

6-Methoxy-8-(4-amino-4-ethylbutylamino)-quinoline (CN-1111). A. Ethyl γ-Nitrohexanoate.—Condensation of 1-nitropropane with ethyl acrylate as above gave 72% of material, b.p. 93° (1–2 mm.).

B. **4-Amino-1-hexanol.**—Reduction of the above ester as in the preceding case gave 60% of hygroscopic oil, b.p. 88–93° (1–2 mm.), $n^{25}D$ 1.4607.

C. **4-Phthalimido-1-hexanol.**—To a suspension of 257 g. of finely ground phthalic anhydride in 700 ml. of glacial acetic acid 203 g. of 4-amino-1-hexanol was added in a thin stream. The mixture was stirred under reflux and allowed to cool overnight. After removal of the acetic acid at the water-pump, the residue was distilled under reduced pressure yielding 386 g. (90%) of pale yellow viscous oil, b.p. 170° (0.04 mm.).

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.9. Found: C, 67.5; H, 7.1.

D. **1-Bromo-4-phthalimidohexane.**—Treatment of the above phthalimido alcohol with hydrobromic acid as in the preceding case gave 32% of viscous yellow oil, b.p. 156° (0.1 mm.), which was used directly.

E. **CN-1112.**—Condensation of the phthalimido bromide with 6-methoxy-8-aminoquinoline was done by the buffer method. The phthalimido intermediate crystallized after removal of the ether. A small sample was recrystallized from ethanol and melted at 130–131°.

Anal. Calcd. for $C_{24}H_{25}NO_3$: C, 71.5; H, 6.2; N, 10.4. Found: C, 71.6; H, 6.1; N, 10.6.

The crude intermediate was hydrolyzed as before giving 28% (based on phthalimido bromide) of a mixture of phosphates, m.p. 144–147°, which contained 45% phosphoric acid. This corresponds to 2.33 moles of acid per mole of drug base. The drug base was homogeneous by the counter current method.

Anal. Calcd. for $C_{16}H_{23}N_3O \cdot 2.33H_3PO_4$: C, 38.5; H, 6.0; P, 14.4. Found: C, 38.4; H, 6.1; P, 14.3.

γ-Nitrohexanoic Acid.—A mixture of 39.2 g. of ethyl γ-nitrohexenoate and 80 ml. of 6 *N* hydrochloric acid was refluxed for 4 hr. After cooling, the solution was extracted with ether and the ether solution was shaken with sodium bicarbonate solution. After acidification the bicarbonate extracts again were extracted with ether. After drying and removal of the solvent 30 g. (85%) of the acid crystallized. After recrystallization from benzene–heptane it melted at 48–49°.

Anal. Calcd. for $C_6H_{11}NO_4$: C, 44.7; H, 6.9; N, 8.7; neut. equiv., 161. Found: C, 45.3; H, 7.1; N, 8.7; neut. equiv., 159.

6-Methoxy-8-(3-nitrohexanamido)-quinoline.—γ-Nitrohexanoyl chloride was prepared by dropwise addition of a solution of 30 g. of γ-nitrohexanoic acid in 50 ml. of dry benzene to 32.1 g. of thionyl chloride with stirring. After the addition was complete the mixture gradually was heated to reflux and held at this temperature until gas evolution ceased.

After removal of the solvent and excess thionyl chloride, the acid chloride (23 g. or 74%) was distilled, b.p. 104° (1.2 mm.), and used directly.

To a mixture of 10 g. of 6-methoxy-8-aminoquinoline, 30 ml. of dry chloroform and 5 g. of calcium carbonate in a flask equipped with a stirrer, dropping funnel and calcium chloride tube, a solution of 10.3 g. of γ-nitrohexanoyl chlo-

(16) All melting points are corrected for stem exposure and boiling points are uncorrected.

(17) Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y.

ride in 20 ml. of dry chloroform was added at such a rate that the temperature did not exceed room temperature. After stirring for 2 hr., the solids were filtered off and washed with chloroform. Ether was added to the filtrate to incipient precipitation and the mixture was refrigerated. Bright yellow needles, m.p. 156–160° dec., separated and a second crop of less pure material was obtained on further addition of ether to the mother liquor. After recrystallization from ethyl acetate–methanol the substance melted at 160–163° dec.

Anal. Calcd. for $C_{16}H_{19}N_3O_4 \cdot HCl$: C, 54.3; H, 5.7; N, 11.9. Found: C, 54.7; H, 5.9; N, 12.2.

6-Methoxy-8-(4-amino-3-methylbutylamino)-quinoline (CN-1120). A. Ethyl β-Cyanobutyrate.—Attempted preparation of ethyl β-cyanobutyrate by addition of hydrogen cyanide to ethyl crotonate gave low yields (14%). Kurtz[18] reports a 2% yield in this reaction. Accordingly, the following synthesis based on observations of Bredt and Kallen[15] and Koelsch and Stratton[19] was used. In a 5-liter three-necked flask equipped with a stirrer, dropping funnel and reflux condenser a solution of 238 g. of diethyl ethylidenemalonate[14] in 3 l. of absolute alcohol was heated to 60°. After rapid addition of a solution of 90 g. of potassium cyanide in 150 ml. of water the mixture was stirred at 60° for 10–15 hr. After filtering, 30 ml. of 10% hydrochloric acid was added to the filtrate and the suspended solids again were filtered off. After removal of the alcohol at reduced pressure the residue was taken up in water, and extracted with four 100-ml. portions of ether. After drying and removal of the solvent, distillation at reduced pressure gave 30–40% of ethyl β-cyanobutyrate, b.p. 102° (11 mm.), $n^{25}D$ 1.4201. Bredt and Kallen[15] report b.p. 105–106° (14 mm.).

Anal. Calcd. for $C_7H_{11}NO_2$: N, 9.9. Found: N, 9.7.

B. **4-Amino-3-methylbutanol.**—To a suspension of 32.6 g. of lithium aluminum hydride in 500 ml. of absolute ether cooled in an ice-bath was added over one hour a solution of 72 g. of ethyl β-cyanobutyrate with vigorous stirring. After stirring for an additional 1.5 hr., 20 ml. of ethyl acetate was added followed by 34 ml. of water, 25 ml. of 20% sodium hydroxide solution and 118 ml. of water successively. After stirring for 30 min. the white solid was filtered. After drying over anhydrous sodium sulfate, removal of the ether left 47–65% of crude material, b.p. 63–65° (0.2 mm.), $n^{25}D$ 1.4594.

For characterization the derivative with phenyl isothiocyanate, m.p. 108.5–109°, was prepared.

Anal. Calcd. for $C_{12}H_{18}N_2OS$: C, 60.5; H, 7.6; N, 11.7. Found: C, 60.2; H, 7.5; N, 11.8.

C. **1-Bromo-3-methyl-4-phthalimidobutane.**—Phthalic anhydride (42 g.) and 4-amino-3-methylbutanol (28.7 g.) were mixed and stirred in a round-bottom flask. The mixture became quite thick and was cooled in ice from time to time. The slightly brown paste was heated gently over the free flame of a micro burner for 20 min. to drive off water and cooled to room temperature. To the residue 27 g. of phosphorus tribromide was added in small portions with swirling. The liquid became very hot and hydrogen bromide was evolved. After cooling spontaneously to room temperature the mixture was poured onto ice and stirred until solidification was complete. Recrystallization from 95% ethanol gave 61 g. (72.6%) of material, m.p. 72–73°. Further recrystallization gave an analytical sample, m.p. 74.6–75°.

Anal. Calcd. for $C_{13}H_{14}BrNO_2$: C, 52.7; H, 4.8; N, 4.7. Found: C, 52.6; H, 4.8; N, 4.6.

D. **6-Methoxy-8-(4-phthalimido-3-methylbutylamino)-quinoline.**—This was prepared by direct fusion of 110.4 g. of redistilled 6-methoxy-8-aminoquinoline with 94 g. of the above bromophthalimide under nitrogen at 90–100° for one hour followed by 80–90° for 18 hr. The solid melt was broken up and extracted by boiling for 30 min. with three 200-ml. portions of benzene. The combined filtered benzene extracts were treated with decolorizing carbon and taken to dryness under reduced pressure. The residual yellow solid was recrystallized from 95% ethanol yielding 77 g. (62.3%) of material. After a second recrystallization it melted at 116.5–118°.

Anal. Calcd. for $C_{23}H_{23}N_3O_3$: C, 70.9; H, 6.0; N, 10.8. Found: C, 71.2; H, 5.8; N, 10.7.

E. **CN-1120.**—Hydrolysis of the phthalimido group in the above compound and conversion of the drug base to the phosphate as in the preceding cases gave 89% of the bright orange diphosphate, m.p. 181–182°, after recrystallization from absolute ethanol.

Anal. Calcd. for $C_{15}H_{21}N_3O \cdot 2H_3PO_4$: C, 39.6; H, 6.0; N, 9.2; P, 13.6. Found: C, 40.2; H, 6.3; N, 9.1; P, 13.5.

6-Methoxy-8-(4-amino-3-ethylbutylamino)-quinoline (CN-1121). A. Ethyl β-Cyanovalerate.—This was prepared as in the preceding case except that diethyl propylidenemalonate, b.p. 95–98° (5 mm.), 116–117° (13 mm.), $n^{25}D$ 1.4409, was substituted for the ethylidenemalonate. The yield of material, b.p. 82–83° (2.2 mm.), $n^{25}D$ 1.4269, was 45–48%.

B. **4-Amino-3-ethylbutanol.**—Reduction of the above compound as in the preceding case gave 84–93% of the amino alcohol as a colorless hygroscopic liquid, b.p. 75–76° (0.05 mm.), $n^{25}D$ 1.4629. For characterization a neutral oxalate, m.p. 175–175.5°, was prepared.

Anal. Calcd. for $C_{14}H_{32}N_2O_6$: C, 51.8; H, 9.9. Found: C, 51.6; H, 10.2.

C. **6-Methoxy-8-(4-phthalimido-3-ethylbutylamino)-quinoline.**—3-Ethyl-4-phthalimidobutanol, b.p. 163–166° (0.05 mm.), was prepared in 85–88% yield as in the preceding case and was used directly for the preparation of 1-bromo-3-ethyl-4-phthalimidobutane by the phosphorus tribromide method described above. The yield of phthalimido bromide, b.p. 164–166° (0.1 mm.), was 83–89%. This was condensed with 6-methoxy-8-aminoquinoline by the direct fusion method. The crude product was taken up in hot absolute ethanol and chilled in solid carbon dioxide. On filtering, the crystalline material liquefied at room temperature. Several repetitions of this treatment gave crystalline material (72%), m.p. 85–89°, after washing with petroleum ether. Further recrystallization from methanol raised the m.p. to 89–90°.

Anal. Calcd. for $C_{24}H_{25}N_3O_3$: C, 71.4; H, 6.2; N, 10.4. Found: C, 71.6; H, 6.3; N, 10.7.

D. **CN-1121.**—The above substance was hydrolyzed and the drug converted to the diphosphate (70%) as before. Recrystallization from absolute ethanol gave orange-yellow needles, m.p. 105–106°.

Anal. Calcd. for $C_{16}H_{23}N_3O \cdot 2H_3PO_4$: C, 40.9; H, 6.2; N, 8.9; P, 13.2. Found: C, 40.9; H, 6.0; N, 8.6; P, 12.9.

6-Methoxy-8-(5-amino-3-methylamino)-quinoline (CN-1106).—1-Bromo-3-methyl-5-phthalimidopentane[6] (220 g.) and redistilled 6-methoxy-8-aminoquinoline (108.2 g.) were heated in 200 ml. of ethanol and 1400 ml. of phosphate buffer (*p*H 8.1) at 75–80° under nitrogen for 76 hr. The crude condensation product was hydrolyzed directly with 70 g. of hydrazine hydrate in 2 l. of ethanol. After working up as previously described, the ether solution of the drug base was extracted five times with phosphate buffer (*p*H 5.85). The drug base liberated from the buffer extracts was converted to the diphosphate in ether. On refluxing with methanol and cooling, 111 g. (34%) of diphosphate, m.p. 158–160°, crystallized. Recrystallization from 96% methanol gave material, m.p. 162–164°. Although the carbon and hydrogen figures agreed well with those demanded by a diphosphate, the phosphorus figure was low. Further, countercurrent analysis showed the presence of some 15% of impurity.

Therefore, 120 g. of phosphate (from a pooled batch) was converted to the free base and extracted into ether. The ether solution was washed six times with phosphate buffer (*p*H 6.4). From the buffer washes the drug was liberated and converted to the diphosphate as usual. After recrystallization as before 97 g., m.p. 162–165°, of material of satisfactory homogeneity was obtained.

Anal. Calcd. for $C_{16}H_{23}N_3O \cdot 2H_3PO_4$: C, 40.9; H, 6.2; P, 13.2. Found: C, 40.8; H, 6.3; P, 13.2.

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