TABLE I

4-DIETHYLAMINO-1-METHYLBUTYLAMINOQUINOLINES

No.	Survey[a] Number	Position of substituent	Hours heated	Boiling range °C.	Mm.	Yield, %	M. p. of dipicrate, °C.	Analyses,[b] % C	H
1	11,532	2	13	157–159	0.2	57	164.5–165.5	75.84	9.72
2	11,528	5	72	*ca.* 194	.2	29	171.7–173.3	75.64	9.66
3	11,529	6	44	174–176.5	.2	37	.....	76.06	9.32
4	11,530	7	40	173–175	.15	50	169.0–169.8	75.84	9.78
5[c]	11,531	8	40	153–154.5	.2	54	148 –150	...	..

[a] The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. The antimalarial activities of drugs so listed will be tabulated in a forthcoming monograph. [b] Analyses by Dr. W. R. Vaughan. Calcd. for all substances: C, 76.05; H, 9.16. [c] Prepared previously, *C. A.*, **29**, 6249 (1935); German Patent 615,184 (1935), and footnote 3.

Salts of this base with most common acids were hygroscopic. An oxalate was prepared, probably a mixture of salts, and sent elsewhere for determination of per cent. base present;[12] found, 64.5.

8-(4'-Diethylaminocyclohexylamino)-quinoline Monohydrochloride (SN-14,065-4).—This base was prepared from 8-quinolinol (0.63 mole) and 4-diethylaminocyclohexylamine[11] (0.29 mole) in order to convert a maximum of the latter reagent into the drug. The yield of yellow oil, b. p. 195–198° (0.7 mm.), was 31%.

Anal. Calcd. for $C_{19}H_{27}N_3$: C, 76.72; H, 9.15. Found: C, 76.92; H, 9.50.

By adding a standard dry ether solution of hydrochloric acid gradually to the above base in the same solvent, two hydrochlorides, decomposing at 291–294° and 251.7–252.2°, respectively, were obtained, the former precipitating first. The diamine used to produce the drug base was thought to be a mixture of *cis* and *trans* forms, the latter predominating. The lower melting salt was produced in sufficient quantity for purification and analysis.

(12) Analysis by courtesy of Dr. R. C. Elderfield, whose help also in furnishing intermediates and with advice is gratefully acknowledged.

Anal. Calcd. for $C_{19}H_{27}N_3 \cdot HCl$: C, 68.34; H, 8.45. Found: C, 68.79, 68.63; H, 8.89, 8.81.

8-[3-[4-(3'-Aminopropyl)-1-piperazinyl]-propylamine]-quinoline Tetrahydrochloride Dihydrate (SN-14,066-4-3).—This substance was prepared using 8-quinolinol and 1,4-piperazinebispropylamine[11] in 40% yield. The product and excess of amine were salted out of the reaction mixture with sodium hydroxide, dried and fractionated *in vacuo*. The base boiled about 245° (0.4 mm.) with excessive foaming. The oily base in alcohol gave a solid hydrochloride with concentrated hydrochloric acid, which was recrystallized from alcohol–water and melted at 274.4–276.2° dec.

Anal. Calcd. for $C_{19}H_{29}N_5 \cdot 4HCl \cdot 2H_2O$: C, 44.80; H, 7.32; Cl, 27.84. Found: C, 44.75, 44.86; H, 7.90, 7.98; Cl, 27.63, 27.75.

Summary

1. Five isomeric 4-diethylamino-1-methylbutylaminoquinolines have been prepared, one of them having been characterized previously.

2. Five N-substituted 8-aminoquinolines, otherwise unsubstituted, have been synthesized.

HANOVER, N. H. RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

8-[3-(3'-Aminopropylamino)-propylamino]-6-methoxyquinoline[1]

BY L. W. KISSINGER,[2] ISAIAH VON[3] AND MARVIN CARMACK

Robinson and co-workers[4,5,6] described the preparation of a substance designated as R-63 which showed high activity against *Plasmodium relictum* in canaries. From their method of preparation of R-63 one might expect the product to be 8-[3-(3'-aminopropylamino)-propylamino]-6-methoxyquinoline (formula III below), but alternative syntheses designed to produce this same structure led to products with low antimalarial activity.

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

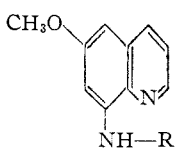
(2) Present address: Naval Ordnance Laboratory, Washington, D. C.

(3) Present address: Calco Chemical Division, American Cyanamid Company, Bound Brook, New Jersey.

(4) Robinson and Tomlinson, *J. Chem. Soc.*, 1524 (1934).

(5) Quin and Robinson, *ibid.*, 555 (1943).

(6) Glen and Robinson, *ibid.*, 557 (1943).



I. R = $-CH_2CH_2CH_2-NH_2$

II. R = $-CH_2CH_2CH_2-NH-CH_2CH_2CN$

III. R = $-CH_2CH_2CH_2-NH-CH_2CH_2CH_2-NH_2$

IV. R = $-CH_2CH_2CH_2-NH-CH_2CH_2CONH_2$

Since the identity of the active component of R-63 appeared to be still an open question, it seemed of interest to prepare the compound III by a different method and to investigate further its toxicity and antimalarial activity against different organisms. The present paper describes the preparation of the compound III by a two-step procedure involving the addition of 8-(3-aminopropylamino)-6-methoxyquinoline (I) to acrylonitrile to form the amino nitrile, II, which was then hydrogenated to the amine, III. The final drug was characterized as the non-hygroscopic crystalline trihydrochloride and was sub-

mitted for antimalarial tests under the Survey Number 5652.[7,8,9] The results of these tests will be reported elsewhere.

The starting material, 8-(3-aminopropylamino)-6-methoxyquinoline (I), was prepared from γ-phthalimidopropyl chloride and 6-methoxy-8-aminoquinoline. Similar procedures have been described by Baldwin[10] and by Magidson and Bobyshev.[11] The addition of I to acrylonitrile took place when equivalent amounts of the amine and nitrile were agitated with aqueous potassium hydroxide at room temperature. The product, II, was separated from unreacted starting amine through its alcohol-insoluble picrate. The amino nitrile, II, was recovered in nearly pure condition from the picrate by decomposition of the salt with aqueous diethanolamine and extraction with benzene.

The hydrogenation of the amino nitrile to the desired amine, III, was carried out over Raney nickel in a mixture of alcohol and anhydrous ammonia. The product was isolated as the red trihydrochloride, m. p. 232–233° (cor., dec.).

Attempts were also made to effect the addition of I to acrylonitrile in hot alcoholic potassium hydroxide. There was evidence of hydrolysis (ammonia was evolved) and the reaction product, analyzed as the dipicrate, had a formula which agreed with that of the nitrile plus one mole of water; it seems probable that this product was the amino amide, IV, resulting from partial hydrolysis of the intermediate nitrile, II.

Experimental

8-(3-Aminopropylamino)-6-methoxyquinoline (I).[10,11]—γ-(N-Phthalimido)-propyl chloride was prepared from phthalimide and trimethylenechlorobromide in the presence of potassium carbonate by a procedure similar to that of Ing and Manske[12] for the preparation of the corresponding bromide.

A mixture of 70 g. (0.40 mole) of 6-methoxy-8-aminoquinoline and 100 g. (0.45 mole) of γ-(N-phthalimido)-propyl chloride in a round-bottomed flask was heated with frequent stirring in an oil-bath at 120–130° for twelve and one-half hours. Then 400 ml. of alcohol and 39 ml. (0.45 mole) of concentrated hydrochloric acid were added and the mixture heated under reflux for five to ten minutes. The mixture was cooled to room temperature and the yellow crystalline hydrochloride was filtered and washed with alcohol. The hydrochloride was triturated with 5% sodium carbonate to liberate the solid amino phthalimide compound, which was then washed with water by decantation and recrystallized twice from 500–600-ml. volumes of alcohol. The pure 8-(3-phthalimidopropylamino)-6-methoxyquinoline melted at 101–102° (reported m. p. 101–102°,[10] m. p. 102–103°[11]); yield, 49.0 g. (34%).

The cleavage of the phthalimide derivative to form the free base, I, was carried out with hydrazine hydrate according to the procedure of Baldwin.[10] The amine was purified by recrystallization of its dihydrochloride from methanol. The average yield of salt, m. p. 244–246° (in bath preheated to 230°), was 60% of the theoretical.

8-[3-(2′-Cyanoethylamino)-propylamino]-6-methoxyquinoline (II).—Twenty-five and one-half grams (0.084 mole) of 8-(3-aminopropylamino)-6-methoxyquinoline dihydrochloride dissolved in 190 ml. of water was treated with 12.8 g. (0.23 mole) of potassium hydroxide, with cooling, then with 4.2 g. (0.08 mole) of acrylonitrile. The suspension was agitated mechanically for two hours at room temperature and then allowed to stand for four hours. The mixture was extracted with benzene to remove the addition product, and the benzene extracts were added, after being washed with water, to a refluxing solution of 56 g. of picric acid in 200 ml. of 95% alcohol. It was helpful to seed the solutions with crystals from previous runs when possible. The heating under reflux was continued for one-half hour, after which the mixture stood for two days. The product, consisting of 55.0 g. of heavy red crystals of the picrate, melted at 176–177°. A recrystallization from 95% alcohol yielded 48.3 g. of heavy red needles, m. p. 177–179°. In some runs the product melted at this temperature without recrystallization; when this happened the recrystallization was omitted. Under these conditions of purification the picrate of the starting amine, I, was shown to be soluble.

The recovery of pure amino nitrile, II, from the picrate was carried out as follows. The red picrate (75 g., m. p. 177–179°) was warmed with a solution of 150 g. of diethanolamine in 150 ml. of water for one hour at a temperature of 85°. The solution was cooled and extracted with four portions of benzene, from which the free base, II, was recovered as 22.3 g. of viscous oil suitable for use in the next step. A specimen of the base was converted into the dihydrochloride with dry hydrogen chloride in absolute alcohol. The crude orange-red solid, m. p. 213–214° (dec.), was recrystallized once from absolute alcohol; m. p. 217–218°, unchanged by further recrystallizations.

Anal. Calcd. for $C_{16}H_{20}N_4O \cdot 2HCl$: C, 53.47; H, 5.91; N, 15.49; Cl, 19.38; neut. equiv., 179. Found[13]: C, 53.63, 53.71; H, 6.03, 5.83; N, 15.61, 15.48; Cl, 19.30, 19.60; neut. equiv., 183.

The phosphate salt of the amino nitrile, II, was prepared with an excess of 85% phosphoric acid in absolute alcohol; m. p. 181–182° (dec.) unchanged after one recrystallization from alcohol.

8-[3-(3′-Aminopropylamino)-propylamino]-6-methoxyquinoline (III).—Twenty-two and one-half grams of the liquid amino nitrile, II, as recovered directly from the picrate, was hydrogenated over Raney nickel at 70° and an initial pressure of 2000 lb. per sq. in. in the presence of 20 ml. of absolute alcohol and 50 ml. of liquid ammonia. From the mixture, freed of catalyst and solvent, 21.4 g. of liquid product was isolated. The amine was purified by distillation from a pot type molecular still at 0.25 mm. and a bath temperature of 200–210°. A small first portion, somewhat discolored as the result of spattering, and a main portion of pale yellow oil weighing 11.5 g. were collected. The latter fraction was dissolved in 450 ml. of absolute alcohol and converted into 14.9 g. of trihydrochloride consisting of fine orange-yellow crystals, m. p. 232–233° (cor., dec.); the solid was only slightly soluble in alcohol. A mixed melting point determination by Dr. Harry S. Mosher[7,8] with a specimen of R-120[9] prepared by him,[8] m. p. 232°, showed no depression.

Anal. Calcd. for $C_{16}H_{24}N_4O \cdot 3HCl$: C, 48.31; H, 6.84; N, 14.09; Cl, 26.74. Found[13]: C, 47.69, 47.65; H, 7.19, 7.19; N, 14.07, 14.13; Cl, 26.54, 26.74.

A sample of the free base, III, was treated with an excess of picric acid in absolute alcohol, forming an orange picrate, m. p. 167–168° after several recrystallizations from absolute alcohol. The picrate did not show a depression of melting point when mixed with a sample of the picrate pre-

(7) After our work had been started we learned that Dr. Harry S. Mosher was in the process of investigating R-63, R-120,[9] and other related compounds. Dr. Mosher very kindly furnished us with data on his work and made a comparison of our hydrochloride of III with his sample of R-120[8]; he reported that the two specimens showed no depression of mixed melting point.

(8) H. S. Mosher, THIS JOURNAL, **68**, 1565 (1946).

(9) Crum and Robinson, *J. Chem. Soc.*, 561 (1943).

(10) Baldwin, *ibid.*, 2959 (1929).

(11) Magidson and Bobyshev, *J. Gen. Chem.* (U. S. S. R.), **8**, 899 (1938); *Chem. Zentr.*, **110**, I, 4953 (1939).

(12) Ing and Manske, *J. Chem. Soc.*, 2348 (1926).

(13) Analyses by Dr. Carl Tiedcke, Laboratory of Microchemistry, New York, N. Y.

pared by Dr. Mosher[8] from the product of the reaction of trimethylenediamine and 8-(3-chloropropylamino)-6-methoxyquinoline.

The small forerun obtained in the molecular distillation of III, as described above, was redistilled; 1.2 g. of distillate was converted into 1.1 g. of solid hydrochloride salt, m. p. 224–225°. Elementary analyses suggested that this solid was a mixture of approximately 30% of III trihydrochloride and 70% of 6-methoxy-8-aminoquinoline monohydrochloride. Recrystallization of the mixture from hot alcohol gave the latter compound in nearly pure state, m. p. 226–227°, not depressed by mixture with an authentic sample.

Reaction of 8-(3-Aminopropylamino)-6-methoxyquinoline (I) and Acrylonitrile in 95% Ethanol.—Two grams (0.0066 mole) of 8-(3-aminopropylamino)-6-methoxyquinoline dihydrochloride and 1 g. (0.019 mole) of potassium hydroxide were dissolved in 25 ml. of 95% alcohol, 0.33 g. (0.0062 mole) of acrylonitrile was added, and the mixture was boiled under reflux for two hours. The odor of ammonia was detected. The mixture was cooled, 150 ml. of water was added, and the product extracted with chloroform. Addition of the chloroform extracts to a solution of picric acid in absolute alcohol resulted in the formation of 4.0 g. of a yellow picrate, m. p. 196–197° (dec.) with preliminary darkening at 185°. Several recrystallizations from alcohol raised the melting point only to 197–198° (dec.) with preliminary darkening at 185°.

Anal. Calcd. for $C_{16}H_{22}N_4O_2 \cdot 2C_6H_3N_3O_7$: C, 44.22; H, 3.71; N, 18.42. Found[13]: C, 44.42, 44.14; H, 3.86, 3.83; N, 18.30, 18.49. Picric acid determination: calcd., 60.3; found, 60.9.

A portion of the dipicrate was reconverted into the base and then to the hydrochloride, but the latter proved to be too hygroscopic to isolate in pure condition.

An attempt to add the base I to acrylonitrile in absolute alcohol, using potassium hydroxide as catalyst, yielded only a small amount of the product IV, and most of the starting amine was recovered unchanged.

Summary

8-[3-(3'-Aminopropylamino)-propylamino]-6-methoxyquinoline was prepared by a new procedure for tests of its antimalarial activity. The compound appears to be the same as Robinson's R-120.

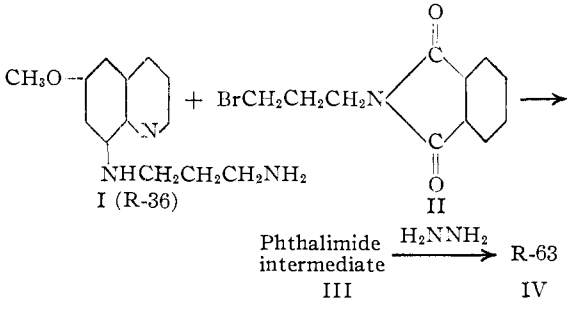
PHILADELPHIA, PENNSYLVANIA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Heterocyclic Basic Compounds. VIII. 8-[3-(3'-Aminopropylamino)-propylamino]-6-methoxyquinoline

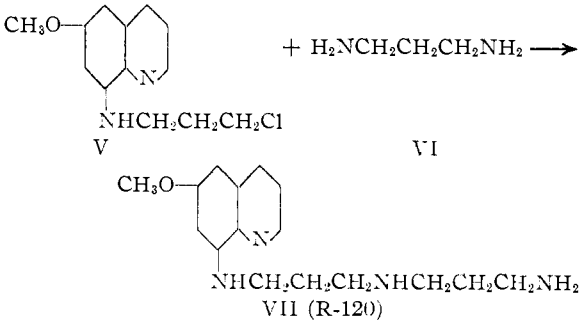
BY HARRY S. MOSHER

One of the most active antimalarial substances reported by Robinson and co-workers in their extensive studies is R-63.[1] This material, whose structure has not been definitely established, was prepared by the following indicated series of reactions



which would be expected to produce the compound whose structure is indicated by formula VII. This compound (VII), which has since been prepared by Crum and Robinson[2] according to the procedure indicated below, was assigned the number R-120. It was completely different in chemical properties and antimalarial activity from R-63.

We have repeated the synthesis of R-120 (VII) essentially as reported and obtained an 80% yield of distilled base and a 45% yield of re-



crystallized, non-hygroscopic trihydrochloride monohydrate melting with bubbling at 232° (reported by Crum and Robinson,[2] 225° dec.). Kissinger, Von and Carmack[3] have prepared 8-[3-(3'-aminopropylamino)-propylamino]-6-methoxyquinoline hydrochloride (R-120) by a completely independent method and the melting point of the above product was undepressed when mixed with the material kindly furnished by Dr. Carmack.

We have also repeated the Robinson synthesis of R-63 (IV). From the reaction of R-36 (I) with N-3-bromopropylphthalimide (II), after a tedious fractional crystallization, there were obtained unreacted starting materials and two different crystalline products; one of these, m. p. 215–216° (obtained in 19% yield), analyzed for, and corresponded to, the expected phthalimide intermediate (III).[1b] This phthalimide inter-

(1) (a) Robinson and Tomlinson, *J. Chem. Soc.*, 1524 (1943); (b) Quin and Robinson, *ibid.*, 555 (1943); (c) Glen and Robinson, *ibid.*, 557 (1934).

(2) Crum and Robinson, *ibid.*, 561 (1943).

(3) Kissinger, Von and Carmack, THIS JOURNAL, **68**, 1563 (1946).