was the hydrazo compound and not the expected amine.

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.1; H, 5.21. Calcd. for $C_{18}H_{17}N_3O_3$: C, 66.84; H, 5.30. Found: C, 66.92; H, 5.56.

Summary

1. The preparation of several new 5-amino- 8-(ω-dialkylaminoalkylamino)-quinolines is described.

2. Attempts to prepare 5-hydroxyplasmochin and 5-acetoxyplasmochin are described.

NOTRE DAME, INDIANA RECEIVED APRIL 5, 1946

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DARTMOUTH COLLEGE]

Some N-Substituted Aminoquinolines[1]

BY ELDEN B. HARTSHORN AND SPENCER L. BAIRD, JR.

With the finding that 8-(4-diethylamino-1-methylbutylamino)-quinoline possessed significant antimalarial activity[2] interest was awakened in derivatives of quinoline containing only aliphatic polyamine side chains with no other substituents. The present paper records the synthesis of several of these substances. The compounds prepared fall into two general groups: namely, those in which the conventional Plasmochin side chain has been attached in the 2-, 5-, 6-, 7- and 8-positions of quinoline, and those compounds derived from 8-aminoquinoline in which other side chains have been introduced.

With one exception all of the substances here reported were prepared by the method of Chelintsev and Dubinin.[3]

Experimental

Intermediates.—2-Chloroquinoline was prepared from N-methyl-2-quinolone (38%)[4] and reaction of the latter with phosphorus oxychloride (70%); m. p. 35–37°; literature, 37–38°.

5-Quinolinol was obtained by stannous chloride reduction of 5-nitroquinoline and a reverse Bucherer[5] reaction on the amine (47%), m. p. 224° dec.

6- and 7-quinolinols resulted from Skraup[6] reactions on technical 4- and 3-anisidines (54, 44%), the methoxyquinolines then being cleaved with constant boiling hydrobromic acid (80–90%). The products melted 190–193° and 238–240°, respectively;[7] literature, 193° and 235–238°, respectively.

Commercial 1-diethylamino-4-aminopentane was purified by the method of Jones.[8] 1-Diethylamino-3-aminopropane and 1-diethylamino-6-aminohexane were from the Universities of Wisconsin and Columbia, respectively.

The Bucherer Reaction.[3]—This synthesis was carried out by boiling a solution of 0.28 mole of a polyamine, such as 1-diethylamino-4-aminopentane, in 100 ml. of water in which 0.2 mole of sulfur dioxide had been dissolved, with 0.1 mole of the quinolinol for thirty or more hours under a pressure exceeding that of the atmosphere by 10 cm. of mercury. Generally the quinolinol dissolved at the boiling point of the mixture and a layer of insoluble oil formed on the surface of the solution as the reaction proceeded. When the separated oil no longer increased in volume, sodium hydroxide (20+ g.) was added, and the mixture subjected to steam distillation to remove excess of the reagent amine. The remaining insoluble, non-volatile oil was then extracted with ether, the ethereal solution was dried over anhydrous potassium carbonate, and the oil distilled *in vacuo* under nitrogen. In general, the yellow oils, so obtained, darkened in air and were therefore at once transformed into suitable salts.

Quinolines with the Plasmochin Side Chain as the Only Substituent.—The above method was used to prepare the four quinolines having the Plasmochin side chain in the 5-, 6-, 7- and 8-positions, respectively. The corresponding 2-derivative was necessarily prepared in another manner.[9] Details pertinent to these (4-diethylamino-1-methylbutylamino)-quinolines are given in Table I.

Before finding that citric acid formed satisfactory salts with many bases of this type, the above oils were stored in hydrochloric acid solution. Later, a solid monocitrate of no. 5 was prepared; yellow powder, m. p. 107–108°.

Anal. Calcd. for $C_{18}H_{27}N_3 \cdot C_6H_8O_7$: C, 60.36; H, 7.39; N, 8.30. Found: C, 60.06; H, 7.08; N, 8.89.

Other N-Substituted 8-Aminoquinolines.—The following drug bases were prepared by the standard Bucherer procedure outlined above, slight modifications of the procedure being made in some cases.

8-(3-Diethylaminopropylamino)-quinoline Monocitrate (SN-13,457).—The base was obtained in 41% and 58% yields (1.0 mole of 8-quinolinol used in second run), as a yellow oil, b. p. 156–159° (0.5 mm.). The yellow citrate turned white upon drying *in vacuo* and then decomposed at 94.3–95.0°.

Anal.[10] Calcd. for $C_{16}H_{23}N_3 \cdot C_6H_8O_7 \cdot {}^1/_2C_2H_5OH$: C, 58.47; H, 7.24; N, 8.81. Found: C, 58.43; H, 6.98; N, 8.67, 8.80.

8-(6′-Diethylaminohexylamino)-quinoline Monocitrate (SN-13,458).—The yellow oily base was prepared in 33% yield using 8-quinolinol (0.43 mole) rather than 1-diethylamino-6-aminohexane (0.2 mole) in excess. It boiled at 172.5–175° (0.3 mm.). The monocitrate, a pale yellow powder, melted at 91.4–92.5° dec.

Anal.[10] Calcd. for $C_{19}H_{29}N_3 \cdot C_6H_8O_7$: C, 61.08; H, 7.59; N, 8.55. Found: C, 61.30; H, 7.80; N, 8.42.

8-[3-(4′-Diethylamino-1′-methylbutylamino)-propylamino]-quinoline (SN-14,064).—Since the excess of 1-diethylamino-4-(3′-aminopropyl)-aminopentane[11] was non-volatile with steam, the reaction mixture was saturated with sodium hydroxide, extracted with ether and the drug obtained by fractional distillation of the dried ether solution. It boiled at 200–210° (0.4 mm.) when redistilled in a Hickman still. The yield was 30%.

Anal. Calcd. for $C_{21}H_{34}N_4$: C, 73.64; H, 10.00. Found: C, 73.31; H, 10.31.

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(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 Dartmouth College.

(2) Antimalarial Drugs 1941–1945, published by the Survey of Antimalarial Drugs, in press.

(3) *C. A.*, **35**, 3641 (1941).

(4) Perkin and Robinson, *J. Chem. Soc.*, **103**, 1977 (1913).

(5) Kogan and Nikolaeva. *C. A.*, **32**, 7031 (1938).

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

(7) Mr. R. G. Nelb prepared the 6- and 7-quinolinols. Dr. W. R. Vaughan investigated ring closures to produce 7-quinolinol and prepared some N-methylquinolone.

(8) Jones, *Ind. Eng. Chem., Anal. Ed.*, **16**, 431 (1944).

(9) Bachmann and Cooper, *J. Org. Chem.*, **9**, 309 (1944).

(10) Analyses by courtesy of Dr. Byron Riegel.

(11) Kindly furnished by Dr. J. E. Kirby of du Pont.

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.

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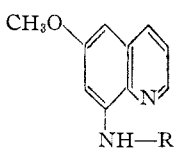
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

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.



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-

(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).