[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Synthesis of 6-Methoxy-8-aminoquinoline Derivatives; Ethyleneimine Rearrangements in Attachment of Monoalkylaminoalkyl Side Chains[1]

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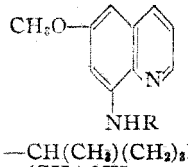
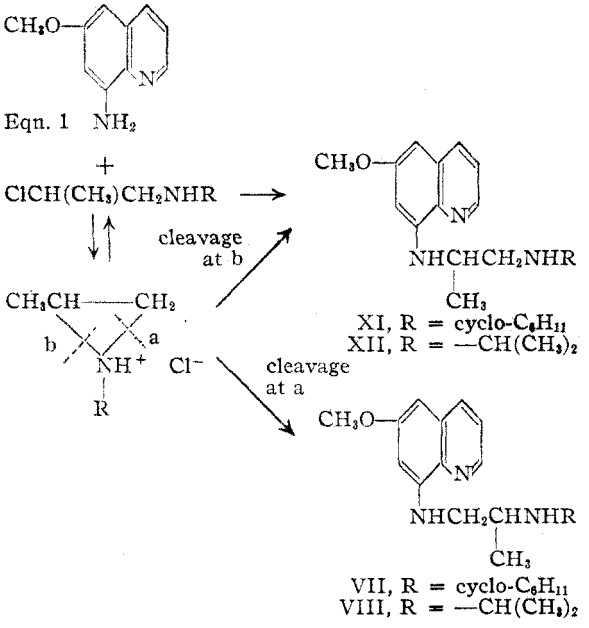
This paper describes the synthesis of a number of 6-methoxy-8-aminoquinoline derivatives[3] related to Plasmochin (I) but containing *primary* aminoalkyl (II and III) or *secondary* aminoalkyl side chains (IV-X) attached to the 8-amino group. Rearrangement is possible in the alkylation reactions through which VII, VIII, IX and X were prepared if ethyleneimines are formed as intermediates, as was proved to have occurred in two of the four cases by unequivocal syntheses of each of these compounds.

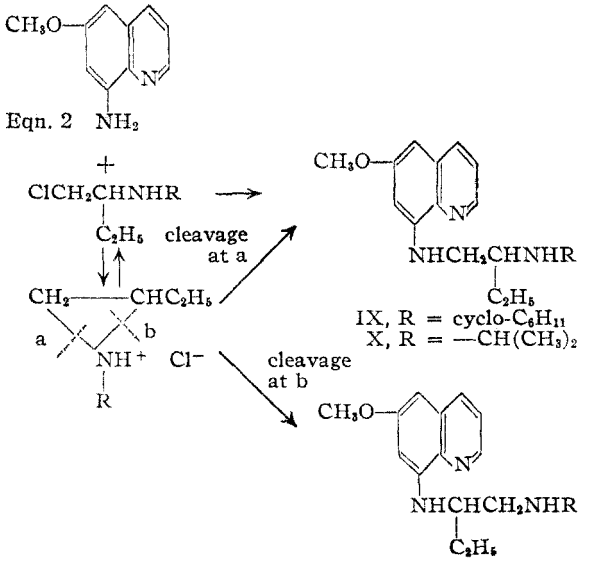
The *primary* aminoalkyl side chains in II and III were introduced by alkylation of 6-methoxy-8-aminoquinoline with phthalimidoalkyl halides, followed by removal of the phthalyl group as phthalhydrazide by treatment first with hydrazine hydrate then hydrochloric acid.[4] The primary amino group in II was converted to the isopropylamino group in the synthesis of IV by reductive alkylation with acetone in the presence of Adams platinum catalyst.



I, R = $-CH(CH_3)(CH_2)_3N(C_2H_5)_2$
II, R = $-(CH_2)_4NH_2$
III, R = $-CH_2CH(OH)CH_2NH_2$
IV, R = $-(CH_2)_4NHCH(CH_3)_2$
V, R = $-(CH_2)_2NHC_6H_{11}$-(cyclo)
VI, R = $-(CH_2)_2NHCH(CH_3)_2$

Secondary aminoalkyl side chains in V-X (Table II) were introduced by the alkylation of 6-methoxy-8-aminoquinoline with secondary aminoalkyl chloride hydrochlorides.[5] It is evident from the following equations that the alkylation reactions could proceed by direct displacement of the chlorine of the aminoalkyl chloride, as in an alkylation by a simple alkyl halide, or that an ethyleneimine might be formed as an intermediate. Either course would lead to the same product from an alkylaminoethyl chloride, as in the syntheses of V and VI by alkylation of 6-methoxy-8-aminoquinoline with cyclohexylaminoethyl chloride hydrochloride and isopropylaminoethyl chloride hydrochloride, respectively. The two paths could lead to the same or different products in cases where an intermediate ethyleneimine would have an unsymmetrical structure, ac-





(1) Part of 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 Massachusetts Institute of Technology.

(2) Abbott Laboratories Fellow, 1947-1948.

(3) Prepared as part of the antimalarial program sponsored by the Committee on Medical Research. The antimalarial activity in avian malaria of each of the compounds designated by an SN number in the Experimental Part is reported in "Antimalarial Drugs 1941-1945," Edwards Brothers, Ann Arbor, Michigan, 1946.

(4) By the procedure of Ing and Manske, *J. Chem. Soc.*, 2348 (1926). The preparation of II by this procedure has been described by Robinson and Tomlinson (ref. 18).

(5) By modifications of the method described by Rohrman and Shonle, THIS JOURNAL, **66**, 1642 (1944).

TABLE I

ALKYLAMINOALKYL CHLORIDE HYDROCHLORIDES

No.	Compound	Yield, %[b]	M. p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
1	Cyclo-$C_6H_{11}NHCH_2CH_2Cl\cdot HCl$[a,c]	91[d]	219.5–220[e]	$C_8H_{17}NCl_2$	48.5	48.4	8.65	8.60	7.07	7.08	35.8	35.8
2	$(CH_3)_2CHNHCH_2CH_2Cl\cdot HCl$[f]	82[g]	187.5–188[e]	$C_5H_{13}NCl_2$	38.0	38.0	8.29	8.37	8.86	8.81	44.9	44.8
3	Cyclo-$C_6H_{11}NHCH_2CH(CH_3)Cl\cdot HCl$[m,n]	43	220–222[o]	$C_9H_{19}NCl_2$								
4	$(CH_3)_2CHNHCH_2CH(CH_3)Cl\cdot HCl$[h]	37	184.5–185.5[i]	$C_6H_{15}NCl_2$	41.87	42.0	8.78	8.77	8.14	7.92	41.2	41.3
5	Cyclo-$C_6H_{11}NHCH(C_2H_5)CH_2Cl\cdot HCl$[j]	77	155–156[k]	$C_{10}H_{21}NCl_2$	53.09	53.23	9.36	9.32	6.19	6.05	31.4	31.4
6	$(CH_3)_2CHNHCH(C_2H_5)CH_2Cl\cdot HCl$[j]	90	115.5–117[l]	$C_7H_{17}NCl_2$	45.17	44.93	9.21	9.22	7.52	7.32	38.1	38.2

[a] Survey number SN 15,288; see ref. 3 for significance. [b] Of material with the melting point tabulated unless otherwise noted. [c] Thionyl chloride added during two hours and the mixture heated under reflux for two hours. [d] M. p. 212–212.5° (uncor.). [e] Recrystallized from ethanol. [f] Heated under reflux for one and one-half hours. [g] M. p. 176–177° (uncor.). [h] The mixture was allowed to stand overnight at room temperature after the thionyl chloride was added. [i] Recrystallized from ethanol and from chloroform. [j] Heated under reflux for half an hour. [k] Recrystallized from ethanol–ether and from carbon tetrachloride–petroleum ether. The m. p. tabulated was observed on rapid heating. Slow heating produced softening at this temperature and decomposition at 238–240°. [l] Recrystallized from ethanol–ethyl acetate and from ethyl acetate. [m] Described by Hancock, Hardy, Heyl, Wright and Cope, THIS JOURNAL, **66**, 1751 (1944). [n] Heated under reflux for one and one-half hours. [o] Recrystallized from ethanol; m. p. uncor.

cording to the point at which it opened in the alkylation.[6]

Displacement reactions of tertiary aminoethyl halides have been established as proceeding through intermediate quaternary ethyleneimmonium salts in a number of instances.[7] Ross[8] has shown that one unsymmetrical quaternary ethyleneimmonium salt reacted by cleavage under basic conditions between the nitrogen and the least substituted carbon atom (corresponding to cleavage at point *a* in the tertiary ethyleneimines represented as intermediates in equations 1 and 2). In other cases intermediate quaternary ethyleneimmonium salts apparently cleaved between the nitrogen and the most highly substituted carbon atom (as at point *b* in equations 1 and 2),[9] while in still other cases similar unsymmetrical quaternary ethyleneimmonium intermediates cleaved at both positions to give mixtures of isomeric products.[10] More recently secondary ethyleneimines have been shown to rupture preferentially but not exclusively at the primary carbon atom in reactions with amines, catalyzed by ammonium chloride.[11]

The alkylation reactions in which VII-X were prepared differ from others studied earlier in that the alkylating agents are secondary aminoalkyl chlorides, and the possible intermediates would be tertiary ethyleneimines or their hydrochlorides. Independent syntheses of VII-X by methods noted below established their structures, which correspond to cleavage of the ethyleneimines between the nitrogen and the least substituted carbon atom (point *a*, equations 1 and 2). Another possibility in the synthesis of IX and X, in which rearrangement did not occur, is direct displacement of the chlorine without intervention of a cyclic intermediate. It should be noted that yields of VII-X were not high, and the presence of isomers (derivable by cleavage of the intermediates at point *b*) in the solutions from which they were isolated is not excluded.

The secondary aminoalkyl chloride hydrochlorides with which 6-methoxy-8-aminoquinoline was alkylated in the syntheses of V-X were prepared from the corresponding aminoalcohol hydrochlorides and thionyl chloride (Table I). Evidence that rearrangement did not occur in the preparation of the chlorides was obtained for the last four compounds in Table I, which could have isomeric structures if the ethyleneimmonium chlorides formulated in equations 1 and 2 were formed as intermediates. These four compounds were heated with an excess of aqueous silver nitrate, which converted them to nitric acid salts of alkylaminoalcohols (any intermediate nitric acid esters which may have been formed were hydrolyzed under the reaction conditions). The alkylaminoalcohols which were obtained when the solutions were made basic were proved to be identical with the original alkylaminoalcohols from which the chlorides were prepared by a direct comparison of physical properties and of the hydrochlorides, which were prepared as solid derivatives. Rearrangement under the acidic conditions of these transformations is unlikely, and formation of the original alkylaminoalcohols of two structural types (two primary and two secondary alcohols) makes it very improbable that ethyleneimmonium salts were intermediates in the reaction with silver nitrate, for the cyclic imines which would be of the same structural type in all four cases would have to undergo

(6) The alkylaminoalkyl chlorides were used as hydrochlorides, which would be less susceptible to the rearrangement than the corresponding bases. In alcohol solution containing 6-methoxy-8-aminoquinoline, however, an equilibrium would be set up in which all of the basic species present would be present as bases and salts in amounts dependent upon their concentrations, basic strengths and solubilities of their hydrochlorides. Presence of the hydrogen chloride is not shown in the equations except in the ethyleneimmonium salts, which would be formed as a first step in self alkylation regardless of whether subsequent cleavage at a or b occurred in the salt or the corresponding base.

(7) (a) Bergmann, Fruton, Golumbic, Stahmann and Stein, *J. Org. Chem.*, **11**, 518–591 (1946); (b) Bartlett, Ross, Swain and Davis, THIS JOURNAL, **69**, 2971–2982 (1947).

(8) Ross, *ibid.*, **69**, 2982 (1947).

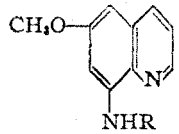
(9) Kerwin, Ullyot, Fuson and Birkle, *ibid.*, **69**, 2961 (1947).

(10) Elderfield, *et al.*, *ibid.*, **68**, 1516 (1946); Schultz, Robb and Sprague, *ibid.*, **69**, 188, 2454 (1947).

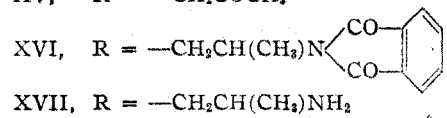
(11) Clapp, *ibid.*, **70**, 184 (1948).

two different types of cleavage to lead to these products.

Two of the possible alkylation products of equation 1 were prepared by first adding 6-methoxy-8-aminoquinoline to 1-nitro-1-propene to give 6-methoxy-8-(2-nitroisopropylamino)-quinoline (XIII).[12] XIII was reductively al-

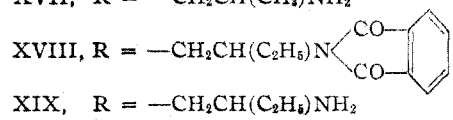


XIII, R = $-CH(CH_3)CH_2NO_2$
XIV, R = $-CH_2CHOHCH_3$
XV, R = $-CH_2COCH_3$



XVI, R = $-CH_2CH(CH_3)N$(CO)$_2$C$_6$H$_4$

XVII, R = $-CH_2CH(CH_3)NH_2$



XVIII, R = $-CH_2CH(C_2H_5)N$(CO)$_2$C$_6$H$_4$

XIX, R = $-CH_2CH(C_2H_5)NH_2$

kylated with cyclohexanone and with acetone in the presence of Adams platinum catalyst[13] to give XI and XII, which were isolated as the dihydrochlorides. The dihydrochlorides and dipicrates of XI and XII differed in m.p. and showed depressions in mixed m.p. with the corresponding derivatives prepared from the alkylation products (equation 1), which accordingly could be assumed to be the isomers VII and VIII. Attempts to prepare known samples of VII and VIII by a similar procedure beginning with the addition of 6-methoxy-8-aminoquinoline to 2-nitro-1-propene were unsuccessful, for a pure crystalline addition product could not be isolated. Attempts to utilize 6-methoxy-8-(2-hydroxypropylamino)-quinoline (XIV) or 6-methoxy-8-acetonylaminoquinoline (XV) as intermediates in the synthesis of VII and VIII also were unsuccessful. XIV was prepared from 6-methoxy-8-aminoquinoline and propylene oxide, but could not be oxidized to XV under the conditions which were investigated. XV was obtained in very low yield by alkylation of 6-methoxy-8-aminoquinoline with bromoacetone, and could be converted to a crystalline semicarbazone and phenylhydrazone, which by reduction might have been converted to 6-methoxy-8-(2-aminopropylamino)-quinoline (XVII). The low yield in the preparation of XV led to abandonment of this route in favor of successful syntheses of VII and VIII through XVII as an intermediate which began with 2-phthalimido-1-propanol, prepared from phthalic anhydride and 2-amino-1-propanol. Reaction of this compound with phosphorus pentabromide yielded 2-phthalimido-1-bromopropane, which with 6-methoxy-8-aminoquinoline gave 6-methoxy-8-(2-phthalimidopropylamino)-quinoline (XVI). Removal of the phthalyl group in XVI[14] yielded 6-methoxy-8-(2-aminopropylamino)-quinoline (XVII). Reductive alkylation of XVII with cyclohexanone and with acetone gave samples of VII and VIII of known structure, which were proved to be identical with the alkylation products (equation 1) by comparison of the m.p. and mixed m.p. of the dihydrochlorides and dipicrates, and of the free base in the case of VII (a crystalline solid).

Similar syntheses which gave samples of IX and of X of known structure utilized as intermediates 2-amino-1-butanol, 2-phthalimido-1-butanol and 2-phthalimido-1-bromobutane, which with 6-methoxy-8-aminoquinoline yielded 6-methoxy-8-(2-phthalimidobutylamino)-quinoline (XVIII). Removal of the phthalyl group in XVIII gave 6-methoxy-8-(2-aminobutylamino)-quinoline XIX, which was reductively alkylated with cyclohexanone and with acetone to give IX and X. These samples of IX and X yielded dihydrochlorides and dipicrates which were identical (m.p. and mixed m.p.) with corresponding derivatives prepared from the products obtained from alkylation according to equation 2, and the crystalline samples of IX from the two sources were identical.

Difficulty was encountered in some instances in obtaining hydrochlorides with constant melting or decomposition points in this series (VII-X) and although their mixed melting points indicated the identities noted, comparison of the crystalline bases (VII and IX) and the picrates of VII-X obtained by the two methods of synthesis furnished more satisfactory proofs of identity.

Experimental[14]

6-Methoxy-8-(4-aminobutylamino)-quinoline Dihydrochloride Hemihydrate (II, SN 3, 883).—4-Bromobutylphthalimide[15] was prepared from tetramethylene dibromide[16] and potassium phthalimide[17] and recrystallized from ligroin; yield 48%, m.p. 78–79°. A mixture of 60.0 g. of 6-methoxy-8-aminoquinoline and 97.0 g. of 4-bromobutylphthalimide was heated in a bath at 120–125° for six hours. The temperature of the reaction mixture was observed and heating was discontinued in the early stages if necessary to avoid a rapid spontaneous rise in temperature. After cooling, the mixture was heated under reflux with 350 ml. of ethanol to dissolve oily material, cooled and filtered. The orange hydrobromide was converted to the free base by shaking with methylene chloride and a dilute solution of potassium carbonate. The extract was washed with sodium chloride solution, filtered through sodium sulfate and concentrated. Crystallization of the residue from ethanol gave 55.0 g. (43%) of light yellow prisms, m.p. 92–94°. Several recrystalliza-

(12) Analogous to the addition of aniline to nitroethylene to give N-(2-nitroethyl)-aniline reported by Wieland and Sakellarios, *Ber.*, **52**, 903 (1919).

(13) Emerson and Uraneck, This Journal, **63**, 749 (1941), have reported the reductive alkylation of nitromethane with ketones to give secondary amines

(14) Melting points are corrected and boiling points are uncorrected. We are indebted to Mr. S. M. Nagy, Mr. Philip H. Towle, Mrs. Louise W. Spencer and Mrs. C. K. Fitz for analyses.

(15) Gabriel and Maas, *Ber.*, **32**, 1269 (1899).

(16) Wilson, *J. Chem. Soc.*, 50 (1945).

(17) By the procedure described for preparing β-bromoethylphthalimide in "Organic Syntheses," Coll. Vol. I, second ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 119.

tions from ethanol gave an analytical sample of 6-methoxy-8-(4-phthalimidobutylamino)-quinoline, m.p. 94–94.5°.

Anal. Calcd. for $C_{22}H_{21}O_3N_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.2; H, 5.73; N, 11.1.

The hydrobromide of 6-methoxy-8-(4-phthalimidobutylamino)-quinoline melted at 210–211° (dec.) after several crystallizations from ethanol. Robinson and Tomlinson[18] report m.p. 196–198° (dec.).

Anal. Calcd. for $C_{22}H_{21}O_3N_3 \cdot HBr$: N, 9.21; Br, 17.51. Found: N, 9.08; Br. 17.6.

A solution of 55.0 g. of 6-methoxy-8-(4-phthalimidobutylamino)-quinoline and 10.0 g. of 85% hydrazine hydrate in 500 ml. of ethanol was heated under reflux for two hours. The solvent was removed under reduced pressure and the residue was heated on a steam-bath with 200 ml. of 4.0 *N* hydrochloric acid for one hour. The mixture was cooled, filtered to remove phthalhydrazide, and the filtrate was concentrated under reduced pressure. Crystallization of the residue from ethanol yielded 41.9 g. (87%) of II, m.p. 209–211° (dec.). An analytical sample purified by several crystallizations from ethanol had m.p. 213–214° (dec.) (ref. 18 reports m.p. 208° (dec.)).

Anal. Calcd. for $C_{14}H_{19}ON_3 \cdot 2HCl \cdot 0.5H_2O$: C, 51.38; H, 6.78; N, 12.84; Cl, 21.66; H_2O, 2.75. Found: C, 51.2; H, 6.48; N, 12.7; Cl, 21.6; H_2O, 2.59 (by loss in weight on drying at 1 mm. and 110°).

6-Methoxy-8-(4-isopropylaminobutylamino)-quinoline Dihydrochloride (IV, SN 13,275).—The above dihydrochloride hemihydrate (II) (19.6 g.) was converted to the free base by shaking with ether and a dilute solution of potassium carbonate. The ether solution was dried over sodium sulfate, the ether was distilled and the residual oil was dissolved in 60 ml. of ethanol. Acetone (5 ml.) was added and the solution was added to the platinum catalyst prepared by hydrogenating 1.5 g. of platinum oxide in ethanol. Hydrogenation began rapidly at atmospheric pressure and became very slow after about thirty minutes; 78% of the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration and 70 ml. of 1.96 *N* ethanolic hydrogen chloride was added to the filtrate. After concentration, the filtrate was diluted with ether and yielded 15.5 g. (72%) of IV, m.p. 185–187° (dec.). An analytical sample was crystallized several times from ethanol–ether; m.p. 189–190° (dec.).

Anal. Calcd. for $C_{17}H_{25}ON_3 \cdot 2HCl$: C, 56.66; H, 7.55; N, 11.66; Cl, 19.68. Found: C, 56.6; H, 7.62; N, 11.6; Cl, 19.7.

6-Methoxy-8-(3-amino-2-hydroxypropylamino)-quinoline (III, SN 12,943).—A mixture of 174 g. of 6-methoxy-8-aminoquinoline, 120 g. of 3-chloro-2-hydroxypropylphthalimide[19] and 300 ml. of *n*-butanol was heated under reflux for sixty-eight hours. The mixture was cooled and poured into 800 ml. of water containing 1.2 moles of hydrochloric acid, with stirring. The suspension was stirred with 500 ml. of benzene for thirty minutes, the benzene was decanted, and the process was repeated with 200 ml. of benzene. The mixed hydrochlorides were collected by filtering the aqueous suspension, dried, and converted to the free bases by dissolving in 1200 ml. of boiling ethanol and 130 ml. of pyridine. After cooling overnight the solids were separated by filtration and redissolved in 500 ml. of boiling ethanol and 100 ml. of pyridine. The hot solution was filtered and 400 ml. of hot water was added slowly. On cooling, 54 g. (29%) of 6-methoxy-8-(3-phthalimido-2-hydroxypropylamino)-quinoline separated, m.p. after recrystallization from 700 ml. of ethanol 142–143°.

Anal. Calcd. for $C_{21}H_{19}O_4N_3$: C, 66.83; H, 5.07; N, 11.13. Found: C, 66.8; H, 5.1; N, 11.1.

A solution of 46 g. of 6-methoxy-(3-phthalimido-2-hydroxypropylamino)-quinoline and 8.5 ml. of hydrazine hydrate in 460 ml. of ethanol was heated under reflux for ninety minutes. The ethanol was removed under reduced pressure and the residue heated under reflux for fifteen minutes with 420 ml. of water containing 0.3 mole of hydrochloric acid. After cooling and separating phthalhydrazide by filtration, 400 ml. of 1.0 *N* sodium hydroxide was added. After cooling for one hour the crystalline product was separated; yield of III 29 g. (92%), m.p. after recrystallization from 750 ml. of boiling ethanol 157–158°.

Anal. Calcd. for $C_{13}H_{17}O_2N_3$: C, 63.13; H, 6.93; N, 16.99. Found: C, 62.9; H, 6.9; N, 17.1.

The hydrochloride was prepared from III and after recrystallization from ethanol–ether had m.p. 189–190°.

Anal. Calcd. for $C_{13}H_{17}O_2N_3 \cdot 2HCl$: C, 48.76; H, 5.98. Found: C, 48.5; H, 6.4.

Alkylaminoalkyl Chloride Hydrochlorides.—The following general procedure was used in preparing the compounds listed in Table I. The aminoalcohol[20] (0.3–1.0 mole) was dissolved in dry alcohol-free chloroform (750 ml. per mole) and placed in a three-necked flask fitted with a stirrer, reflux condenser and gas delivery tube dipping beneath the surface of the liquid. The solution was stirred and saturated with dry hydrogen chloride. The gas delivery tube was replaced with a dropping funnel and thionyl chloride (2.0 to 3.0 molar equivalents) was added with stirring and cooling. The solution was heated under reflux or allowed to stand as stated in the footnotes, the solvent and excess thionyl chloride were removed under reduced pressure, and the residue was crystallized to constant melting point from the solvent noted.

Evidence confirming the structures of the last four alkylaminoalkyl chloride hydrochlorides listed in Table I was obtained by converting them into the corresponding aminoalcohols in the following manner. 1-Isopropylamino-2-chloropropane hydrochloride (9.3 g., 0.056 mole), 39.2 g. (0.23 mole) of silver nitrate and 100 ml. of water were heated under reflux for eighteen hours. The mixture was filtered and the silver chloride (15.6 g., 97.5%) was washed with water. Saturated sodium chloride solution was added to the combined filtrate and washings until no more silver chloride precipitated. After filtering and washing the silver chloride with water, the combined filtrate and washings were made basic with sodium hydroxide and extracted with ether. The extracts were dried over magnesium sulfate and treated with dry hydrogen chloride in acetone to convert the aminoalcohol into its hydrochloride. On concentration 4.8 g. of 1-isopropylamino-2-propanol hydrochloride separated, m.p. 143.5–145°. The m.p. of this sample was not depressed on mixture with a known sample prepared from the aminoalcohol[20b] and hydrogen chloride in acetone and purified by crystallization to constant m.p. from acetone and acetone–methylene chloride; m.p. 144.5–146.5°.

Anal. Calcd. for $C_6H_{16}ONCl$: C, 46.90; H, 10.50; N, 9.12; Cl, 23.08. Found: C, 46.80; H, 10.57; N, 8.81; Cl, 23.2.

By a similar procedure 1-cyclohexylamino-2-chloropropane hydrochloride (20 g.) was converted to 1-cyclohexylamino-2-propanol (11.4 g., 77%), b.p. 125° (20 mm.), which solidified on cooling and was identified as the hydrochloride, m.p. and mixed m.p. with a known sample[20b] 162.5–164°. Likewise 2-isopropylamino-1-chlorobutane hydrochloride (20.6 g.) yielded 10.3 g. (68%) of 2-isopropylamino-1-butanol, b.p. 88° (20 mm.), m.p. 43–46°. This aminoalcohol was converted to the hydrochloride as a solid derivative, m.p. 99.5–101°. Its m.p. was not depressed on mixture with a known sample prepared from 2-isopropylamino-1-butanol[20c] and hydrogen chloride in acetone and recrystallized from acetone; m.p. 100–101.5°.

Anal. Calcd. for $C_7H_{18}ONCl$: C, 50.14; H, 10.82; N, 8.35; Cl, 21.15. Found: C, 50.28; H, 10.58; N, 8.29; Cl, 21.2.

On treatment with silver nitrate under similar conditions 2-cyclohexylamino-1-chlorobutane hydrochloride

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

(19) Gabriel and Ohle, *Ber.*, **50**, 820 (1917).

(20) (a) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942); (b) **66**, 1454 (1944); (c) Hancock and Cope, *ibid.*, **66**, 1738 (1944).

TABLE II

6-METHOXY-8-AMINOQUINOLINE DERIVATIVES PREPARED BY ALKYLATION WITH ALKYLAMINOALKYL CHLORIDE HYDROCHLORIDES

Alkylating agent No.[a]	Moles	6-Methoxy-8-aminoquinoline, moles	Formula of product	Survey number[b]	Yield, %[c]	M. p., °C.
1	0.22	0.20	V	SN 13,705	12	229–229.5 (dec.)[h]
2	.11	.10[l]	VI	SN 13,704	20	228.5–229 (dec.)[h]
3	.17	.16	VII	SN 13,707[e]	20[f]	229–230 (dec.)[h]
4	.10	.10	VIII	SN 13,706[d]	18	232.5–233.5 (dec.)[h]
5	.16	.16[k]	IX	SN 13,709	14[g]	208–209 (dec.)[h]
6	.134	.134	X	SN 13,708	16	177–179[i,j]

[a] Identified by these numbers in column 1, Table I. [b] Number by which the compound is designated in ref. 3. [c] Designated as XI in ref. 3 but the correct structure is VII. [d] Designated as XII in ref. 3 but the correct structure is VIII. [e] Yield of analytically pure material crystallized to constant m. p. Yields of fairly pure products were considerably higher. [f] Yield of the free base, distilled at 0.03 mm. and a bath temperature of 180–200° and recrystallized from ethanol–water; m. p. 93–94°. *Anal.* Calcd. for $C_{19}H_{27}ON_3$: C, 72.81; H, 8.69; N, 13.41. Found: C, 73.15; H, 8.66; N, 13.3. [g] Eight per cent. was isolated as the free base, distilled at 0.03–0.04 mm. and a bath temperature of 170–185° and recrystallized from ethanol–water; m. p. 62–63°. *Anal.* Calcd. for $C_{20}H_{29}ON_3$: C, 73.35; H, 8.93; N, 12.83. Found: C, 73.50; H, 8.89; N, 12.7. The remainder (6%) was isolated as the dihydrochloride. [h] Recrystallized from absolute ethanol. [i] Recrystallized from absolute ethanol–ether. [j] Dried at 60° and 1 mm. overnight. Analysis indicated that the salt was a hemihydrate. Drying at 118° and 1 mm. caused partial loss of hydrogen chloride. [k] The reactants were heated in 40 ml. of refluxing *n*-butanol for sixty-eight hours. [l] The period of reflux was forty-seven hours.

(13.35 g.) yielded 7.4 g. (73%) of 2-cyclohexylamino-1-butanol, b.p. 128–129° (25 mm.). The hydrochloride was prepared as a derivative, m.p. 158.5-160.5°. The m.p. of this sample was not depressed on mixture with a known sample prepared from 2-cyclohexylamino-1-butanol[20c] and hydrogen chloride in acetone–ethanol and recrystallized from methylene chloride–acetone and ethanol–ether; m.p. 161–162°.

Anal. Calcd. for $C_{10}H_{22}ONCl$: C, 57.81; H, 10.68; N, 6.75; Cl, 17.07. Found: C, 57.97; H, 10.49; N, 6.57; Cl, 17.0.

Alkylation of 6-Methoxy-8-aminoquinoline with Alkylaminoalkyl Chloride Hydrochlorides.—The 6-methoxy-8-aminoquinoline derivatives V-X listed in Table II were prepared by the procedure described by Rohrmann and Shonle,[5] modified as described below and in the foot notes. Absolute ethanol solutions of the reactants were heated under reflux for sixty to sixty-seven hours, after which the ethanol was removed under reduced pressure. Water was added to the residue, which was made strongly basic with 20% sodium hydroxide, in some cases saturated with potassium carbonate,[21] and extracted with ether or methylene chloride.[22] The extracts were dried over magnesium sulfate, concentrated, and the residue was distilled in a short-path modified Hickmann molecular-type pot still. In each case 6-methoxy-8-aminoquinoline was separated as a low boiling fraction. V, VII and IX distilled as higher boiling fractions, VII and IX under conditions noted in the footnotes and V at 0.015 mm. and a bath temperature of 155–180°. V was converted to the dihydrochloride and purified by recrystallization, while VII and IX were purified by the methods described in the footnotes. In the distillation of VI, VIII and X, decomposition began after removal of the 6-methoxy-8-aminoquinoline, so the undistilled residues were dissolved in ethanol and hydrochloric acid was added to convert the products to dihydrochlorides, which were purified by recrystallization.

Dipicrates (Table III) were prepared from VII, VIII, IX and X prepared by alkylation (Table II) in order to obtain additional crystalline derivatives for comparison with dipicrates of these compounds obtained from the unequivocal syntheses described below. The bases and picric acid (2.2 molar equivalents) in absolute ethanol were heated to the reflux temperature. The dipicrates separated on cooling, and were purified by recrystallization to constant m.p. from the solvents noted in Table III.

(21) There was some evidence that the bases were partially converted to carbonates in the presence of potassium carbonate, which was omitted in later preparations.

(22) In the preparation of V, 6-methoxy-8-aminoquinoline was separated from the more basic product by preparing a solution of the crude product in 500 ml. of water and 200 ml. of ethanol, adding concd. hydrochloric acid until the solution was acid to congo red, then sodium acetate until the solution was slightly basic to congo red, and extracting with eight 100-ml. portions of ether. See Elderfield, *et al.* THIS JOURNAL, **68**, 1521 (1946).

Synthetic Proofs of Structure

6-Methoxy-8-(2-nitroisopropylamino)-quinoline (XIII).—A solution of 3.5 g. of freshly distilled 1-nitro-1-propene[23] in 50 ml. of ether was added to 7 g. of 6-methoxy-8-aminoquinoline dissolved in 50 ml. of ether, and the solution was heated under reflux for twenty-four hours. The ether was removed under reduced pressure; the residue crystallized on cooling and scratching. Crystallization from 40 ml. of absolute ethanol gave 7.5 g. (72%) of light yellow needles, m.p. 84–85°.

Anal. Calcd. for $C_{13}H_{15}O_3N_3$: C, 59.76; H, 5.79; N, 16.08. Found: C, 60.03; H, 6.01; N, 16.15.

6-Methoxy-8-(2-cyclohexylaminoisopropylamino)-quinoline Dihydrochloride (XI).—A solution of 1 g. of XIII and 0.75 g. of cyclohexanone in 15 ml. of ethanol was added to the platinum catalyst prepared by reducing 0.1 g. of platinum oxide in 5 ml. of ethanol, and the mixture was shaken with hydrogen. After twenty-two hours hydrogen absorption stopped at 98% of the theoretical value. The catalyst was separated and ethanolic hydrogen chloride added to the filtrate, which was concentrated and diluted with ether. One recrystallization of the yellow product from absolute ethanol gave 0.6 g. (40%) of XI; m.p. 207.5–208.5° (dec.), which was raised to a constant m.p. of 210–211° (dec.) by two recrystallizations from absolute ethanol.

Anal. Calcd. for $C_{19}H_{27}ON_3 \cdot 2HCl$: C, 59.06; H, 7.57; N, 10.88; Cl, 18.35. Found: C, 59.19; H, 7.44; N, 11.09; Cl, 18.35.

A mixed m.p. of XI with the product of alkylation (VII, equation 1; Table II, m.p. 226–228° (dec.)) was depressed to 196–200° (dec.).

XI was heated with 2.2 equivalents of picric acid in ethanol and converted to the dipicrate, which was recrystallized from 95% ethanol to a constant m.p. of 171.5–172.5° (dec.).

Anal. Calcd. for $C_{31}H_{33}O_{15}N_9$: N, 16.34. Found: N, 16.38.

A mixed m.p. of XI dipicrate with the dipicrate of the

(23) Schmidt and Rutz, *Ber.*, **61**, 2146 (1928).

TABLE II (*Continued*)

Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
$C_{18}H_{27}ON_3Cl_2$	58.06	58.09	7.31	7.78	11.29	11.23	19.05	19.07
$C_{15}H_{23}ON_3Cl_2$	54.2	54.4	6.98	6.95	12.7	12.6	21.3	21.3
$C_{19}H_{29}ON_3Cl_2 \cdot 0.5H_2O$	57.72	57.74	7.88	7.64	10.63	10.93	17.94	18.07
$C_{16}H_{25}ON_3Cl_2$	55.48	55.3	7.28	7.66	12.13	11.8	20.48	20.32
$C_{20}H_{31}ON_3Cl_2$	59.99	60.12	7.81	7.90	10.50	10.5	17.7	17.3
$C_{17}H_{27}ON_3Cl_2 \cdot 0.5H_2O$	55.28	55.6	7.64	7.72	11.38	11.2	19.20	19.4

TABLE III

DIPICRATES OF 6-METHOXY-8-AMINOQUINOLINE DERIVATIVES PREPARED BY ALKYLATION

Dipicrate of:	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
VII	186–186.5 (dec.)[a]	$C_{21}H_{23}O_{15}N_9$	48.25	48.16	4.31	4.36
VIII	188.5–189 (dec.)[a]	$C_{28}H_{29}O_{15}N_9$	45.97	45.86	4.00	4.31
IX	164.5–165[a]	$C_{21}H_{23}O_{15}N_9$	48.92	48.63	4.49	4.49
X	140.5–141[b]	$C_{28}H_{31}O_{15}N_9$	46.71	46.71	4.19	4.48

[a] Recrystallized from a mixture of two parts of absolute ethanol and one part of acetone. [b] Recrystallized from a mixture of four parts of absolute ethanol and one part of acetone.

alkylation product (VII, equation 1; Table III, m.p. 186–186.5° (dec.)) was depressed to 162–162.5° (dec.).

6-Methoxy-8-(2-isopropylaminoisopropylamino)-quinoline Dihydrochloride (XII).—Hydrogenation of a solution of 1 g. of XIII and 0.45 g. of acetone in 15 ml. of ethanol in the presence of 100 mg. of prereduced platinum oxide required twenty-two hours, and 96.5% of hydrogen was absorbed. The product was isolated in the same manner as XI and recrystallized from ethanol; yield 0.45 g. (35%), m.p. 217.5–218.5° (dec.).

Anal. Calcd. for $C_{16}H_{28}ON_3 \cdot 2HCl$: C, 55.48; H, 7.28; N, 12.13; Cl, 20.48. Found: C, 55.56; H, 7.41; N, 12.10; Cl, 20.60.

A mixed m.p. of XII with the product obtained by alkylation (VIII, equation 1; Table II, m.p. 239–240° (dec.)) was depressed to 207–207.5° (dec.).

XII was converted to the dipicrate, which was recrystallized from 2:1 ethanol–acetone; m.p. 184–185° (dec.).

Anal. Calcd. for $C_{28}H_{29}O_{15}N_9$: C, 45.97; H, 4.00. Found: C, 46.09; H, 4.12.

A mixed m.p. of XII dipicrate with the dipicrate of the alkylation product (VIII, equation 1; Table III, m.p. 188.5–189° (dec.)) was depressed to 169–170° (dec.).

6-Methoxy-8-(2-hydroxypropylamino)-quinoline (XIV).—Propylene oxide (7 g.) was added to a solution of 17.4 g. of 6-methoxy-8-aminoquinoline in 50 ml. of dioxane and 10 ml. of water. The solution was heated under reflux for twenty-four hours, concentrated under reduced pressure, and the residue distilled from a Hickmann molecular-type pot still. 6-Methoxy-8-aminoquinoline (12.5 g.) distilled at a bath temperature of 110–130° (0.02–0.025 mm.), followed by XIV as a very viscous orange oil (6.8 g., 29%) at a bath temperature of 130–145° (0.02–0.025 mm.).

Anal. Calcd. for $C_{12}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found: C, 67.21; H, 6.97; N, 12.01.

Attempts to oxidize XIV to XV with chromic acid in acetic acid, potassium permanganate in acetone, cyclohexanone and aluminum isopropoxide in benzene, and benzophenone and potassium *t*-butoxide in benzene were unsuccessful.

6-Methoxy-8-acetonylaminoquinoline (XV).—A solution of 34.8 g. of 6-methoxy-8-aminoquinoline and 13.7 g. of bromoacetone in 250 ml. of ether was heated under reflux for a total of forty-four hours and filtered at intervals to remove insoluble salts (principally 6-methoxy-8-aminoquinoline hydrobromide). The ether filtrate was concentrated under reduced pressure. Semicarbazide hydrochloride (5 g.) and sodium acetate (10 g.) were added to a solution of the residue in 75 ml. of ethanol, followed by water to the point of turbidity (50 ml.). The mixture was boiled for ten minutes, cooled, and the solid which separated was recrystallized to constant melting point from benzene–petroleum ether to yield 3.0 g. of XV semicarbazone, m.p. 171.5–173.5°.

Anal. Calcd. for $C_{14}H_{17}O_2N_5$: C, 58.52; H, 5.97; N, 24.38. Found: C, 58.65; H, 5.99; N, 24.09.

XV semicarbazone (1 g.) was hydrolyzed by heating on a steam-bath with 20 ml. of 3 *N* hydrochloric acid for thirty minutes. The solution was cooled, made alkaline with potassium carbonate, and extracted with methylene chloride. The XV in the extract was purified by crystallization from methylene chloride–ether and ether; m.p. 92.5–93.5°.

Anal. Calcd. for $C_{12}H_{14}O_2N_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.85; H, 6.16; N, 12.23.

XV (0.1 g.) was converted to the phenylhydrazone as an additional derivative, which was purified by four crystallizations from ethanol–water; yield 0.055 g., m.p. 133.5–135°.

Anal. Calcd. for $C_{18}H_{18}ON_4$: C, 71.23; H, 6.29; N, 17.49. Found: C, 71.40; H, 6.50; N, 17.54.

6-Methoxy-8-(2-phthalimidopropylamino)-quinoline (XVI).—XVI was prepared and isolated by the procedure described for 6-methoxy-8-(4-phthalimidobutylamino)-quinoline, from 19 g. of 2-phthalimido-1-bromopropane[24] and 13.6 g. of 6-methoxy-8-aminoquinoline, which were heated in a nitrogen atmosphere at 145–150° for six hours. The product crystallized from ethanol as light yellow needles; yield 5.35 g. (21%), m.p. 142–144°. An analytical sample recrystallized twice from ethanol had a constant m.p. of 145–145.5°.

Anal. Calcd. for $C_{21}H_{19}O_3N_3$: C, 69.79; H, 5.30; N, 11.63. Found: C, 69.48; H, 5.33; N, 11.76.

6-Methoxy-8-(2-aminopropylamino)-quinoline Dihydrochloride (XVII).—A solution of 7 g. of XVI and 1.4 g. of 85% hydrazine hydrate in 150 ml. of absolute ethanol was heated under reflux for two hours and then concentrated under reduced pressure. The residue was heated on a steam-bath for one hour with 200 ml. of 2 *N* hydrochloric acid, cooled, and filtered to remove the phthalhydrazide, which was washed with water. The filtrate and washings were concentrated under reduced pressure, treated with dilute sodium hydroxide to liberate XVII as the free base, and extracted with methylene chloride. The extracts were washed with sodium chloride solution, dried over sodium sulfate, and concentrated. A solution of the residue in ethanol was made acid to congo red with hydrogen chloride in ethanol. XVII separated as bright orange crystals on cooling; yield 4.0 g. (68%), m.p. 230.5–233° (dec.). Two recrystallizations from absolute ethanol gave an analytical sample with a constant m.p. of 230.5–231.5° (dec.).

(24) Gabriel and Ohle, *Ber.*, **50**, 812 (1917).

Anal. Calcd. for $C_{19}H_{17}ON_3 \cdot 2HCl$: C, 51.32; H, 6.30; N, 13.81; Cl, 23.31. Found: C, 51.34; H, 6.41; N, 13.89; Cl, 22.85.

6-Methoxy-8-(2-cyclohexylaminopropylamino)-quinoline (VII).—One gram of XVII was converted to the free base by shaking with dilute sodium hydroxide and methylene chloride. The extract was dried, the solvent removed, and a solution of the residue and 1 ml. of cyclohexanone in 15 ml. of ethanol was shaken with hydrogen and 100 mg. of prereduced platinum oxide. The theoretical amount of hydrogen was absorbed in ten minutes, and then the rate decreased sharply. The catalyst was removed, the filtrate concentrated to a volume of 15 ml., and water was added slowly. VII separated as light brown needles; yield 0.66 g. (65%), m.p. 92–93°. Crystallization from ethanol–water after treatment with Darco gave 0.62 g. of VII as white needles, m.p. 93–93.5°, which was not depressed on mixture with a sample of VII melting at 93–94° prepared by alkylation (equation 1, Table II).

Anal. Calcd. for $C_{19}H_{27}ON_3$: C, 72.81; H, 8.69; N, 13.41. Found: C, 72.43; H, 8.41; N, 13.60.

The dihydrochloride of VII prepared in this way was recrystallized twice from absolute ethanol and dried to constant weight at 40° and 1 mm.; m.p. 229–230°; mixed m.p. with VII dihydrochloride prepared by the alkylation reaction (equation 1, m.p. 229–230° (dec.), Table II) was not depressed. A mixed m.p. with XI dihydrochloride (m.p. 210–211° (dec.)) was depressed to 200–201° (dec.). Analysis indicated that VII dihydrochloride was a hemihydrate.

Anal. Calcd. for $C_{19}H_{27}ON_3 \cdot 2HCl \cdot 0.5H_2O$: C, 57.72; H, 7.65. Found: C, 57.80; H, 7.61.

The dipicrate of VII from this source was recrystallized from 2:1 ethanol–acetone as bright orange crystals, m.p. 186–186.5° (dec.); mixed m.p. with the dipicrate of VII prepared by alkylation (equation 1; m.p.186–186.5° (dec.), Table III) was unchanged; mixed m.p. with XI dipicrate (m.p. 171.5–172.5° (dec.)) was depressed to 162–168.5° (dec.).

Anal. Calcd. for $C_{31}H_{33}O_{15}N_9$: C, 48.25; H, 4.31; N, 16.34. Found: C, 48.39; H, 4.52; N, 16.10.

6-Methoxy-8-(2-isopropylaminopropylamino)-quinoline Dihydrochloride (VIII).—One gram of XVII dihydrochloride was converted to the free base and reductively alkylated with acetone (1 ml.) in 15 ml. of absolute ethanol by the procedure described for VII. The theoretical amount of hydrogen was absorbed in one hundred minutes. VIII was isolated as the dihydrochloride in yellow needles, m.p. 234.5–235° (dec.); yield 0.9 g. (79%). A mixed m.p. with VIII dihydrochloride prepared by alkylation (equation 1; m.p. 232.5–233.5° (dec.), Table II) was 233–233.5° (dec.). A mixed m.p. with the isomeric XII dihydrochloride (m.p. 217.5–218.5° (dec.) was depressed to 205–207° (dec.)).

Anal. Calcd. for $C_{16}H_{23}ON_3 \cdot 2HCl$: C, 55.48; H, 7.28; N, 12.13; Cl, 20.48. Found: C, 55.11; H, 7.46; N, 12.37; Cl, 20.45.

The dipicrate prepared from this sample of VIII was recrystallized from 2:1 absolute ethanol–acetone and dried to constant weight at 40° and 1 mm.; m.p. and mixed m.p. with the dipicrate of VIII prepared by alkylation (equation 1; m.p. 188.5–189° (dec.), Table III) 188.5–189°.

Anal. Calcd. for $C_{28}H_{29}O_{15}N_9$: C, 45.97; H, 4.00; N, 17.23. Found: C, 46.23; H, 4.44; N, 17.04.

2-Phthalimido-1-hydroxybutane.—Phthalic anhydride (41.5 g.) was added in portions with cooling to a solution of 25 g. of 2-amino-1-butanol in 100 ml. of methanol. The methanol was removed by distillation and the residue was heated at 20 mm. in a bath at 180–200° until no more water distilled. Distillation of the residue gave 37 g. (60%) of 2-phthalimido-1-hydroxybutane as a very viscous straw-colored liquid, b.p. 155–159° (1 mm.); $n^{25}D$ 1.5613; d^{25}_4 1.2107. MD calcd. 57.18, found 58.66. A redistilled sample was analyzed; b.p. 180° (4 mm.); $n^{25}D$ 1.5617.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.78; H, 5.99; N, 6.48.

2-Phthalimido-1-bromobutane.—2-Phthalimido-1-hydroxybutane (45 g.) was added dropwise to 88.4 g. of phosphorus pentabromide, and after the addition the mixture was heated on a steam-bath until it became homogeneous. After cooling, 200 ml. of water was added, followed by potassium carbonate until the mixture was alkaline. The product was extracted with ether, dried over magnesium sulfate and distilled; yield 37 g. (64%), b.p. 159–162° (2 mm.). A redistilled sample of the viscous straw-colored liquid had b.p. 159–160° (2 mm.); $n^{25}D$ 1.5736.

Anal. Calcd. for $C_{12}H_{12}O_2NBr$: C, 51.08; H, 4.29; N, 4.97; Br, 28.33. Found: C, 51.05; H, 4.36; N, 4.97; Br, 28.16.

6-Methoxy-8-(2-phthalimidobutylamino)-quinoline (XVIII).—A mixture of 25 g. of 2-phthalimido-1-bromobutane and 17 g. of 6-methoxy-8-aminoquinoline was heated in a nitrogen atmosphere at 145–155° for twelve hours. The mixture was heated under reflux with 50 ml. of absolute ethanol, cooled, and filtered to remove 6-methoxy-8-aminoquinoline hydrobromide (11.3 g.). The filtrate was made acid to congo red with concd. hydrochloric acid and yielded a yellow crystalline salt (9.6 g.) which was converted to the free base (XVIII). After crystallization the yield of the yellow product was 6.9 g. (21%), m. p. 112–113°. Three recrystallizations from absolute ethanol gave an analytical sample with a constant m. p. of 113.5–114° (with previous softening).

Anal. Calcd. for $C_{22}H_{21}O_3N_3$: C, 70.38; H, 5.64; N, 11.19. Found: C, 70.31; H, 5.70; N, 11.25.

6-Methoxy-8-(2-aminobutylamino)-quinoline Dihydrochloride (XIX).—The procedure described for preparing XVII was used to convert 7.5 g. of XVIII to XIX; yield 5.0 g. (78%), m. p. 231–232° (dec.). After one recrystallization from absolute ethanol an analytical sample had a constant m. p. of 235–235.5° (dec.).

Anal. Calcd. for $C_{14}H_{19}ON_3 \cdot 2HCl$: C, 52.84; H, 6.65; N, 13.20; Cl, 22.28. Found: C, 52.86; H, 6.94; N, 13.39; Cl, 22.13.

6-Methoxy-8-(2-cyclohexylaminobutylamino)-quinoline (IX).—The reductive alkylation procedure described for preparing VII was applied to XIX (1 g.) and 1 ml. of cyclohexanone; hydrogenation was complete in fifteen minutes. IX was isolated as silky-white needles by crystallization from ethanol–water; yield 0.6 g. (58%), m. p. 61–61.5°. Recrystallization from ethanol–water raised the m. p. to 62–62.5°; mixed m. p. with IX prepared by alkylation (equation 2; Table II, m. p. 62–63°) was not depressed.

Anal. Calcd. for $C_{20}H_{29}ON_3$: C, 73.35; H, 8.93; N, 12.83. Found: C, 73.41; H, 8.95; N, 13.22.

The dihydrochloride of this sample of IX, recrystallized from absolute ethanol and dried to constant weight at 70° and 1 mm. had a constant m. p. and mixed m. p. with IX dihydrochloride prepared by alkylation (equation 2; Table II, m. p. 208–209° (dec.)) of 208–209° (dec.).

Anal. Calcd. for $C_{20}H_{29}ON_3 \cdot 2HCl$: C, 59.99; H, 7.81; N, 10.50. Found: C, 59.78; H, 7.92; N, 10.52.

The dipicrate of this sample of IX had a constant m. p. of 165–166° after one recrystallization from 2:1 ethanol–acetone and a mixed m. p. with IX dipicrate derived from the alkylation product (equation 2; m. p. 164–165°, Table III) was not depressed.

Anal. Calcd. for $C_{32}H_{35}O_{15}N_9$: C, 48.92; H, 4.49. Found: C, 48.63; H, 4.46.

6-Methoxy-8-(2-isopropylaminobutylamino)-quinoline Dihydrochloride (X).—One gram of XIX was reductively alkylated with acetone during two hours by the procedure described for preparing VIII. X was obtained in a yield of 0.8 g. (70%), m. p. 161.5–166° (with previous softening). Three recrystallizations from ethanol gave an analytical sample with a constant m. p. of 171–171.5° (with previous softening). The salt lost weight on drying

and appeared to be a hydrate; a sample dried at 40° and 1 mm. analyzed correctly for a hemihydrate.

Anal. Calcd. for $C_{17}H_{25}ON_3 \cdot 2HCl \cdot 0.5H_2O$: C, 55.28; H, 7.64; N, 11.38; Cl, 19.20. Found: C, 55.76; H, 7.36; N, 11.66; Cl, 19.12.

A mixed m. p. of this sample of X with X prepared by alkylation (equation 2; Table II, m. p. 177–179°) was 172–173°.

The dipicrate prepared from this sample of X, recrystallized from 4:1 ethanol–acetone and dried at 70° and 1 mm. had a m. p. of 137–138° (with previous softening) and was not depressed on mixture with X dipicrate prepared from the alkylation product (equation 2; Table III, m. p. 140.5–141°).

Anal. Calcd. for $C_{29}H_{31}O_{15}N_9$: C, 46.71; H, 4.19. Found: C, 46.76; H, 4.44.

Summary

A number of derivatives of 6-methoxy-8-aminoquinoline have been prepared which are substituted on the 8-amino group by primary or secondary aminoalkyl side chains. A rearrangement proceeding through a tertiary ethyleneimine intermediate has been observed to occur in the alkylation of 6-methoxy-8-aminoquinoline with 1-alkylamino-2-chloropropane hydrochlorides (equation 1). 6-Methoxy-8-(alkylaminoalkylamino)-quinolines of known structure have been synthesized by first attaching primary aminoalkyl side chains to the 8-amino group through intermediate phthalimido compounds, and then reductively alkylating the primary aliphatic amino group with acetone and with cyclohexanone in the presence of Adams platinum catalyst and hydrogen. A 6-methoxy-8-(nitroalkylamino)-quinoline also has been reductively alkylated with these ketones under the same conditions.

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The Adsorption of Water Vapor on Activated Charcoal

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There will be presented in the papers that follow a method for measuring pore size distribution of charcoal which assumes that water on charcoal is held by capillary condensation. The main support for this assumption is that the pronounced hysteresis in the adsorption isotherm can best be accounted for by explanations based on the capillary condensation theory.[2,3,4,5] The results reported in this paper of studies of the changes in the density of adsorbed water with change in relative pressure and of the changes in the dimensions of an activated charcoal during adsorption and desorption lend further support to this theory.

I. Linear Expansion of Charcoal

The change in length of charcoal rods as water and also various other vapors are adsorbed has been studied by numerous investigators.[6] In most of these investigations, which will be discussed later, relatively large carbon rods were employed whereas in the present work an activated gas mask adsorbent was used.

This charcoal, N-19, was prepared from hardwood sawdust, zinc chloride activated, extruded as rods 1/16 inch diameter, calcined at 600°, washed and calcined at 850°. It had an ash content of 0.2%, an apparent density of 0.48, a particle density of 0.80, a carbon density (by helium) of 2.09 and a surface area of 1300–1700 sq. m./g.

Determination of Linear Expansion of Charcoal.—The principal part of the apparatus for measuring the linear expansion of charcoal during adsorption and desorption is shown in Fig. 1. The inner tube A is filled with the extruded charcoal rods, 2–5 mm. long and 1.6 mm. diameter, placed end to end. The ends of each granule were squared off with emery cloth before being placed in the tube. B is a short piece of wire with squared-off ends placed on top of the charcoal column. Changes in length of the column during adsorption and desorption were observed by following with a cathetometer the movement of the upper edge of the wire with respect to a reference mark on the inner tube. The length of the charcoal column was 960 mm. and its weight was 0.920 g.

The tube assembly, which was weighed at intervals to determine the water content, was attached to an apparatus similar to that shown in Fig. 4 for the necessary evacuation of the sample, adsorption, desorption, measurement of the relative vapor pressure, etc. The charcoal column was thermostated at 24.4° with a water-cooled jacket.

Fig. 1.—Apparatus for measuring linear expansion of charcoal.

Results

The per cent. change in length of the charcoal column as a function of the relative pressure is shown in Fig. 2. It will be observed that, starting with dry char, as the humidity is increased the charcoal first contracts and then at $p/p_0 \sim 0.68$ begins to expand

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