[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY, THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, AND THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

A Study of Plasmochin and the Occurrence of Rearrangements in the Preparation of Certain Plasmochin Analogs[1]

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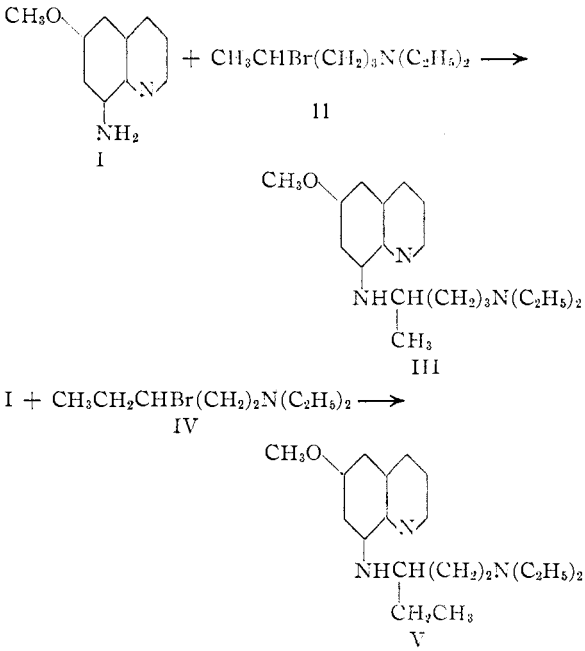
The antimalarial drug Plasmochin (Pamaquine) (III), is conventionally manufactured by condensation of 6-methoxy-8-aminoquinoline (I) with 1-diethylamino - 4 - bromopentane (Noval bromide) (II).[2] During the course of a systematic investigation of the homogeneity of various derivatives of 8-aminoquinoline by the countercurrent distribution technique[3,4] various samples of commercial Plasmochin of both domestic and foreign origin have been examined. These uniformly showed the presence of from 12 to 30% of inhomogeneity. By application of the countercurrent technique, it was possible to isolate the major component of commercial Plasmochin in pure state and to characterize it by means of its citrate, which melted at 125–127°. The major contaminant, for which we suggest the name "*iso*-Plasmochin," was also isolated in a pure state and formed a citrate which melted at 136–139°. The effect of this impurity on the antimalarial and pharmacological properties of Plasmochin, which does not appear to be serious, will be discussed elsewhere.[5]

At the time these observations were made, no details of the manufacture of either Noval bromide (II) or Plasmochin (III) were available. Subsequently, information was obtained from Germany[6] which threw considerable light on the origin and probable nature of *iso*-Plasmochin. The method by which Noval bromide is manufactured in Germany, and hence presumably in this country, consists of treating 1-diethylaminopentanol-4 with concentrated hydrobromic acid, a procedure almost certain to lead to the formation of greater or less amounts of 1-diethylamino-3-bromopentane (*iso*-Noval bromide) (IV). Indeed, the German manufacturers realized this, and their control specifications for Noval bromide to be used in the manufacture of Plasmochin tolerate the presence of up to 30% of the isobromide. *iso*-Plasmochin may then provisionally be assigned the structure of 6-methoxy-(3'-diethylamino - 1 - ethylpropylamino) - quinoline (V).



With this information at hand, the synthesis of *iso*-Plasmochin (V) was undertaken in order to establish on a firm basis the conclusions which had been drawn on the basis of the information received from Germany. 1-Diethylaminopentanol-3 was prepared by a modification of the procedure of Fourneau and Ramart-Lucas.[7] The alcohol was converted to *iso*-Noval chloride by the action of thionyl chloride in benzene. Homogeneity determinations[3,4] showed that the inhomogeneity present in the chloride was less than 3%. However, when *iso*-Noval chloride was coupled with I, a 24-plate countercurrent analysis of the resulting drug revealed the presence of two major components. Component A was present to the extent of 75–80%. Component B was present in the amount of 20–25%. No purification could be effected by redistillation of the base. From Component B a citrate was prepared which was identical (mixed m. p.) with the citrate of *iso*-Plasmochin (V). No crystalline salt of Component A was found.

Since the reaction time necessary to effect condensation between I and a dialkylamino chloride is

(1) The work described in this paper was done under contracts, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Columbia University, the Rockefeller Institute for Medical Research and the University of Minnesota.

(2) Schuleman, Schönhöfer and Wingler, various German Patents, *C. A.*, **24**, 3242 (1930); U. S. Patent 1,747,531 (Feb. 11, 1930).

(3) Craig, *J. Biol. Chem.*, **155**, 519 (1944).

(4) Craig, *et al.*, *ibid.*, **161**, 321 (1945).

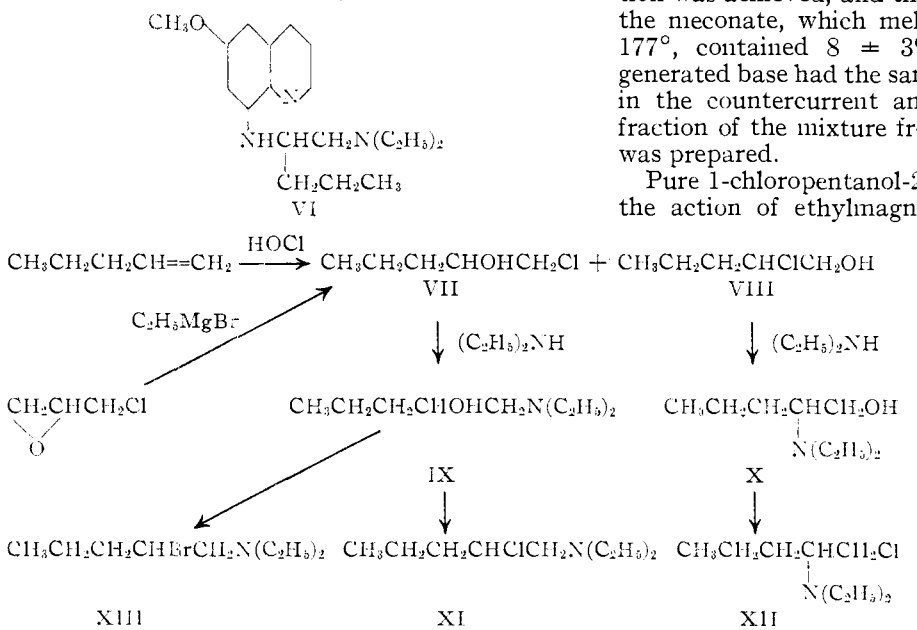
(5) Antimalarial Drugs 1941–1945, published by the Survey of Antimalarial Drugs, in press.

(6) Private communication from Dr. K. C. Blanchard, OSRD Intelligence Representative in Germany.

(7) Fourneau and Ramart-Lucas, *Bull. soc. chim.*, [4] **25**, 364 (1919).

much longer than that required by a corresponding bromide, a similar experiment was carried out using I and *iso*-Noval bromide (IV) prepared from the alcohol and thionyl bromide. Unfortunately, it was not possible to check the homogeneity of the diethylaminobromopentane because of the strong tendency of this substance to undergo self-condensation under the conditions of the homogeneity test. However, when coupled with I under conditions relatively mild as compared with those required for coupling the analogous chloride, a reasonable yield of drug base was obtained. The drug base showed the presence of 7 ± 3% inhomogeneity, and, on conversion to the citrate, furnished a salt melting at 137–139° which was identical with that prepared from *iso*-Plasmochin. From these data it is obvious that some rearrangement has occurred during the coupling of I with *iso*-Noval chloride, and that the extent of rearrangement is markedly less when *iso*-Noval bromide is used.

In the attempted preparation of another derivative of 8-aminoquinoline, 6-methoxy-8-(2′-diethylamino - 1′ - *n* - propylethylamino)-quinoline (VI), a more striking case of rearrangement has been found. The requisite side chain, 1-diethylamino-2-*n*-propyl-2-chloro-(or bromo)-ethane was prepared by various routes. The first synthesis involved addition of hypochlorous acid to pentene-1.[8] As indicated below, this reaction led to a



mixture of 1-chloro-2-hydroxypentane (VII) and 1-hydroxy-2-chloropentane (VIII), presumably in the proportion of about 9:1. This mixture was allowed to react with diethylamine, yielding a mixture of 1-diethylamino-2-hydroxypentane (IX) and 1-hydroxy-2-diethylaminopentane (X), as evidenced by countercurrent distribution determinations run on the mixture of aminocarbinols. In any event, the mixture of carbinols (IX and X) thus obtained was converted to a mixture of 1-diethylamino-2-chloropentane (XI) and 1-chloro-2-diethylaminopentane (XII) by the action of thionyl chloride. It was not possible to check the homogeneity of the aminochloride at this point, again because of the tendency of the latter substances to undergo self-condensation under the conditions of the determination. The mixed aminochlorides (XI and XII) were condensed with I, yielding a drug which gave analytical figures corresponding to the expected VI. However, when subjected to countercurrent analysis, this drug was found to be a mixture of three constituents in the relative amounts of 2, 66 and 32%. The inhomogeneity in the amino alcohol, on the reasonable assumption that no rearrangements occurred during preparation of the chloride, accounts only partially for the relative amounts of impurities showing up in the final drug. In view of the discrepancies between the composition of the mixture of aminoalcohols (IX and X) and that of the final drug (VI), it appeared likely that drastic rearrangements had occurred during the synthesis of the latter. From the mixture of isomers obtained in the condensation reaction, a meconate was prepared. By recrystallization of this salt considerable purification was achieved, and the base regenerated from the meconate, which melted constantly at 176–177°, contained 8 ± 3% impurity. This regenerated base had the same distribution constant in the countercurrent analysis as did the 66% fraction of the mixture from which the meconate was prepared.

Pure 1-chloropentanol-2 (VII) was prepared by the action of ethylmagnesium bromide on epichlorohydrin, a modification of the method of Magrane and Cottle.[9] This on reaction with diethylamine gave 1-diethylaminopentanol-2 (IX), which showed the presence of 4 ± 2% impurity. From this we conclude that the formation of the mixture of chlorohydrins VII and VIII from pentene-1 was due to addition of hypochlorous acid in two modes rather than to isomerization to X, possibly through formation of an ethylene oxide, during reaction of VII with diethylamine. From the pure aminocarbinol, IX, both the chloride (XI) and bromide (XIII) were prepared by the action of the respective thionyl halides. Both of the halides were then coupled

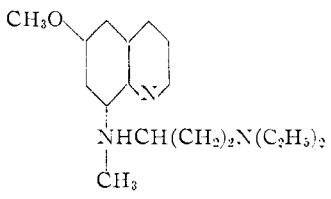
(8) Clavis, Ryden and Marvel, THIS JOURNAL, **59**, 707 (1937).

(9) Magrane and Cottle, *ibid.*, **64**, 484 (1942).

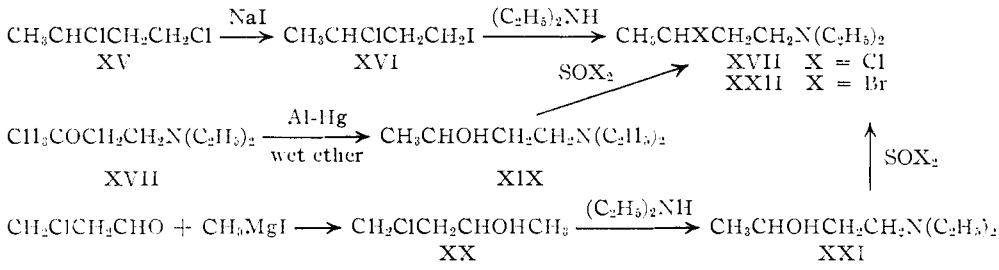
with I. The product prepared from the aminobromide (XIII) showed the presence of three components in the amounts of 7, 66 and 27% and that from the aminochloride (XI) showed the same three components in the amounts of 3, 63 and 34%. The distribution constants for these three substances were identical with those corresponding to the three components in the product prepared from the mixture of aminochlorides IX and X.

The distribution constants, defined as the concentration in the organic phase divided by the concentration in the aqueous buffer phase, of the various 6-methoxy-8-diethylaminoalkylamino quinolines encountered in this study, are tabulated in Table IV. Since the distribution constants at a comparable *p*H represent characteristic physical constants, a method is provided by which the coupled quinoline bases may be compared even when it is not possible to prepare characteristic salts. Further, by using this constant, the various components of the base may be directly compared without preparation of a salt. This possesses the advantage of eliminating any uncertainty that might arise because of loss of, or confusion of identity of one or more components of the mixture during the preparation or recrystallization of the salts. It is impossible at present to assign definite structures to any of these substances except Plasmochin and possibly *iso*-Plasmochin.

The synthesis of 6-methoxy-(3′-diethylamino-1-methylpropylamino) - quinoline (XIV) likewise presents an opportunity for rearrangement. The first preparation of XIV furnished a substance which showed the presence of 20% inhomogeneity in the countercurrent analysis, and rearrangement was suspected. However, this turned out not to be the case, and the inhomogeneity was shown to have its origin in impure 1-diethylamino-3-chlorobutane (XVII) used in the synthesis. Since the impurities in XVII apparently have not been recognized before and since they apparently can be detected only by the countercurrent distribution method, the details of the synthesis are given in full.



XIII



The synthesis of the aminochloride (XVII) was accomplished by three methods, The product obtained using the method described by Hass and Huffman,[10] showed the presence of 8 ± 2% impurity. The second method involved reduction of 1-diethylaminobutanone-3 (XVIII)[11,12] to 1-diethylaminobutanol-3 (XIX) and replacement of the hydroxyl group in the latter by chlorine. The reduction of XVIII catalytically led to extensive cleavage. However, use of aluminum amalgam and moist ether gave good yields of the aminocarbinol. A sample of XVII prepared in this manner showed the presence of 17% impurity despite the fact that the melting point of the aminochloride hydrochloride agreed with that reported in the literature and with that of the hydrochloride prepared by either of the two alternate methods. The third synthesis of XVII involved the preparation of 1-chlorobutanol-3 (XX) from methylmagnesium iodide and β-chloropropionaldehyde. Condensation of XX with diethylamine gave the aminocarbinol (XXI) from which both XVII and 1-diethylamino-3-bromobutane (XXII) were prepared by the action of the appropriate thionyl halide. As thus prepared, the aminochloride (XVII) was of satisfactory purity and when coupled with 5,6-dimethoxy-8-aminoquinoline as well as with 6-methoxy-8-aminoquinoline (I), led to drugs also of satisfactory purity. It was not possible to determine the purity of the aminobromide (XXII), since the compound apparently underwent self-condensation during the determination. However, the drug prepared from XXII and I was of good purity.

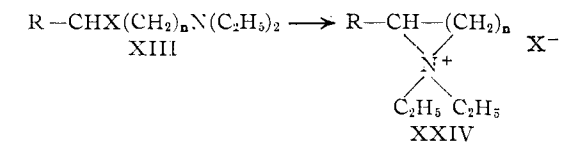
At this time it is not possible to present a complete explanation for the observed experimental facts on the synthesis of compounds of the Plasmochin type. On reaction of alkyl halides with amines, the alkylated amine generally possesses the expected structure. The presence of an amino group in the halides under consideration affords the basis for a possible explanation for the rearrangements noted. If the aminohalides are formulated by a general formula, XXIII, and if

(10) Hass and Huffman, THIS JOURNAL, **63**, 1233 (1941).

(11) Robinson, *J. Chem. Soc.*, 53 (1937).

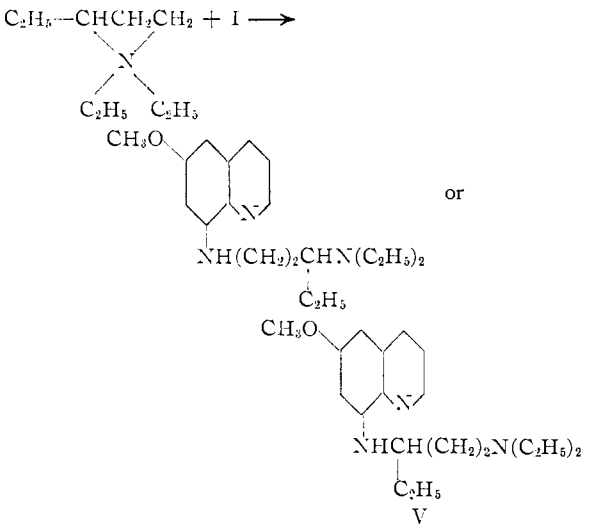
(12) Tuda, Hukusima and Oguri, *J. Pharm. Soc. Japan*, **61**, 69 (1941); *C. A.*, **36**, 3154 (1942).

the possibility of the formation of cyclic quaternary imines (XXIV) is recognized, then a preliminary basis for rationalizing the experimental facts may be postulated.



XIII XXIV

In the cases where $n = 3$ or 4, the cyclic imine would be a pyrrolidinium or piperidinium salt and as such would be expected to be stable. This is indicated by the failure to secure any condensation product of I and either 1,1-diethyl-2-methylpyrrolidinium chloride or bromide. However, in the cases were $n = 1$ or 2, the cyclic imine would be in ethylene imine or propylene imine with a comparatively large amount of strain. The latter type compounds should be good alkylating agents. In the special case of 1-diethylamino-3-bromopentane (IV), the course of the alkylation of I could then take either of two routes.



V

A similar situation would obviously obtain in the case of the reaction of I with the halide derived from the aminocarbinol (IX).

The formation of pure products of the condensation of the aminohalides of XVII and XXII with I with the apparent absence of rearrangement products is difficult to explain on the basis of existing data. A possible explanation lies in the assumption of a different behavior of the postulated intermediate cyclic imines derived from XVII and from IV when the imines act as alkylating agents. The experimental basis for this explanation of the observed facts is under investigation at present.

In the course of this study we have had occasion to investigate in detail the experimental conditions required for successful condensation of an 8-aminoquinoline and a side chain of the general type of Noval bromide (II). These observations also apply to coupling of 8-aminoquinolines with other types of aminohalides. 1-Diethylamino-4-bromopentane hydrobromide is stable to heat. In basic solution a pyrrolidinium bromide, the type of XXIV, is readily produced, and this on heating results in the formation of a mixture of diethylaminopentenes.[13] Neither 1,1-diethyl-2-methylpyrrolidinium chloride nor bromide yields Plasmochin under the standard experimental conditions used. All of the aminohalides used in the present study are strong bases and therefore not readily decomposed at *p*H's below 5.5–6. However, intramolecular alkylation does proceed in this *p*H range and even at a *p*H as low as 4.5, although the rate of the reaction is much slower in the more acidic ranges.

In order to accomplish selective alkylation of an 8-aminoquinoline, it therefore is necessary to select a *p*H range in which the desired alkylation will take place with a minimum of intramolecular reaction of the aminoalkyl halide. This problem was complicated by the fact that the nitrogen of the 8-aminoquinoline must be present as the free base, rather than as a salt in order for successful alkylation by the alkyl halide to occur. The observed pK_a values for Plasmochin,[14] namely, pK_{a_1} 3.46 due to the quinoline nitrogen, pK_{a_2} 10.2 due to the tertiary terminal nitrogen and the observation that the third nitrogen gains a proton in 5 *N* sulfuric acid, furnish an indication of the difficulties encountered in coupling an 8-aminoquinoline with an alkylamino halide which can undergo either inter- or intramolecular condensation itself. The 8-amino group of such a quinoline is relatively reactive in basic solution as indicated by the ease with which a side chain such as β-diethylaminoethyl chloride reacts while no reaction occurs in acidic solution. While pK_a values indicate that a *p*H above 4 would be satisfactory for maintaining 6-methoxy-8-aminoquinoline in the form of the base, titration with a *p*H meter indicates that an appreciable percentage of the substance exists as a salt below *p*H 4.8–5.0.

The choice of the optimum *p*H for the coupling reaction was therefore a compromise between the high *p*H desired to increase 8-aminoquinoline reactivity and low *p*H necessary to prevent inter- or intramolecular condensation of the alkylamino halide. The most desirable *p*H appears to be in the range of 4.8–5.2. This was obtained by any one of the procedures given in the present paper or by procedures C or D of the succeeding paper.[15] Procedure C with its more drastic heating conditions was successful only with the more stable types of side chains. The use of sodium acetate in the preparation of Plasmochin resulted in very low yields. However, the substitution of either excess nucleus or citric acid-sodium phosphate as a buffer according to the availability of the nucleus,

(13) Kharasch and Fuchs, *J. Org. Chem.*, **9**, 359 (1944).

(14) Private communication from Drs. K. C. Blanchard and Logan Irvin.

(15) Elderfield, *et al.*, THIS JOURNAL, **68**, 1524 (1946).

gave good results with Plasmochin type side chains.

Experimental[16,17]

1-Diethylamino-4-bromopentane Hydrobromide.—1-Diethylaminopentanol-4, prepared by reduction of 1-diethylaminopentanone-2 over Raney nickel, was converted to the bromide by the procedure used elsewhere.[18] After recrystallization from alcohol–ether, the bromide hydrobromide melted at 94–94.5°.

Anal. Calcd. for $C_9H_{21}Br_2N$: C, 35.6; H, 6.9. Found: C, 35.9; H, 7.0.

When heated at 280° for thirty minutes, the bromide hydrobromide showed no signs of gross decomposition.

1,1-Diethyl-2-methylpyrrolidinium Bromide.—To a 10% solution of pure 1-diethylamino-4-bromopentane hydrobromide was added an excess of cold 40% sodium hydroxide solution. The free bromo-amine was rapidly extracted with ether. The filtered ether solution was allowed to stand overnight. The pyrrolidinium bromide which had separated was filtered off and recrystallized from acetone. It melted at 269–271°.

Anal. Calcd. for $C_9H_{20}BrN$: C, 48.7; H, 9.0. Found: C, 49.1; H, 9.2.

1,1-Diethyl-2-methylpyrrolidinium Chloride.—Pure distilled 1-diethylamino-4-chloropentane, prepared from the alcohol and thionyl chloride and boiling at 63–66° (6 mm.) was warmed on the steam-bath until solid. The chloride was recrystallized from acetone and melted at 283–285°.

Anal. Calcd. for $C_9H_{20}ClN$: C, 60.9; H, 11.3. Found: C, 60.7; H, 11.1.

Neither the pyrrolidinium bromide nor chloride yielded any Plasmochin when treated with I according to Procedure B described below.

When 1,1-diethyl-2-methylpyrrolidinium chloride was heated at 250–270° for fifteen minutes, decomposition occurred. The product was taken up in the minimum amount of water, the solution was made strongly alkaline and the organic layer was separated and distilled, the fraction boiling at 84–90° (25 mm.) being collected. Calcd.: neut. equiv., 141. Found: 141. The material is reported to be a mixture of unsaturated tertiary amines, predominantly 1-diethylaminopentene-4.[13]

1-Diethylaminopentanol-3.—Although this compound has been prepared by Fourneau and Ramart-Lucas[7] and Hromatka,[19] the following procedure was found to be more satisfactory. A mixture of 12.5 g. of 1-chloropentanol-3[7] and 25 g. of redistilled diethylamine was heated in a sealed tube at 100° for nine hours. Ether was added to the reaction mixture, and the diethylamine hydrochloride which precipitated was filtered off and washed thoroughly with dry ether. The combined ether filtrates were extracted with 20 ml. of hydrochloric acid (sp. gr. 1.19) and the acid extract was diluted successively first with 50 ml. of water and then with 20 ml. of water. This acid solution was made just alkaline with solid potassium hydroxide and then saturated with potassium carbonate. The precipitated potassium chloride was filtered off by suction and thoroughly washed with ether. The ether layer was separated from the filtrate and the aqueous layer was extracted once more with ether. The combined ether solutions were dried with potassium carbonate, after which the ether and excess diethylamine were removed by distillation. The product was then distilled under reduced pressure, the fraction boiling at 93–94° (18 mm.) being collected. The yield was 12 g., or 77%. Fourneau and Ramart-Lucas[7] report the base boiling at 76° (13 mm.). Calcd.: neut. equiv., 159. Found: 160. The benzoate hydrochloride melted at 105–106° after recrystallization from acetone. It is reported as melting at 106–107°.[7]

1-Diethylamino-3-chloropentane.—To a solution of 27.7 g. of 1-diethylaminopentanol-3 in 110 ml. of dry benzene contained in a three-necked flask equipped with a sealed stirrer, dropping funnel and a reflux condenser protected by a calcium chloride tube, was added a solution of 23 g. of thionyl chloride distilled from quinoline and linseed oil in 75 ml. of dry benzene over a period of two and one-half hours while keeping the mixture thoroughly chilled in an ice-bath. The mixture was stirred with cooling for an additional ninety minutes and then at room temperature for sixty minutes, and finally refluxed for thirty minutes. The benzene was removed under reduced pressure, leaving a dark viscous residue which crystallized on cooling. A small portion of this hydrochloride was withdrawn for purification, and the remainder was treated with excess 20% potassium hydroxide solution. After saturating the aqueous solution with potassium carbonate, the amine was extracted with ether. The ether extracts were dried with potassium carbonate, and the product distilled under reduced pressure. The chloroamine distilled completely at 85.5–87° (18 mm.). The yield was 22.6 g. of a colorless liquid.

Anal. Calcd. for $C_9H_{20}ClN$: C, 60.8; H, 11.3; neut. equiv., 178. Found: C, 60.5; H, 11.3; neut. equiv., 180.

When examined in a benzene phosphate buffer at *p*H 6.28, the inhomogeneity was 3%.

1-Diethylamino-3-bromopentane, IV.—This was prepared as was the corresponding chloride using thionyl bromide.[18] The free base boiled at 90–92° (18 mm.). It polymerized readily on standing and a determination of its homogeneity was not possible for this reason.

Anal. Calcd. for $C_9H_{20}BrN$: C, 48.6; H, 9.0. Found: C, 48.1; H, 9.2.

1-Diethylaminopentanol-2 and 2-Diethylaminopentanol-1.—Pentene-1, prepared from allyl bromide and ethylmagnesium bromide,[20] was converted into a mixture of 1-chloropentanol-2 and 2-chloropentanol-1 according to Glavis, Ryden and Marvel.[3] The mixed chlorohydrins were heated with diethylamine at 110–120° for twelve hours according to the procedure given in an accompanying paper.[18] The mixed aminoalcohols (yield 52%) were collected at 74–78° (10 mm.). Countercurrent distribution in a benzene–phosphate buffer (*p*H 7.10) system showed the presence of 10% inhomogeneity. The mixed aminocarbinols were accordingly shaken with equal volumes of benzene and phosphate buffer (*p*H 6.7) which left pure 1-diethylaminopentanol-2 in the buffer layer from which it was recovered by addition of alkali and extraction with ether.

Anal. Calcd. for $C_9H_{21}ON$: C, 67.9; H, 13.2. Found: C, 68.2; H, 13.4.

1-Chloropentanol-2, VII.—Magrane and Cottle[9] obtained a 70–80% yield of IX by reaction of equimolar amounts of diethylmagnesium and epichlorohydrin and report that substitution of ethylmagnesium bromide for diethylmagnesium results in only a 10–15% yield. We have now found that if 1 mole of the more convenient ethylmagnesium bromide is used per 2 moles of epichlorohydrin, the yield of VII based on ethylmagnesium bromide is 70–80%. The chlorohydrin boiled at 80° (28 mm.), $n^{20}D$ 1.4425. Magrane and Cottle[9] report $n^{20}D$ 1.4422.

1-Diethylamino-2-bromo- and 2-Chloropentane.—VII was converted to 1-diethylaminopentanol-2 (IX) [inhomogeneity 4 ± 2% in a benzene–phosphate buffer (*p*H 7.10) system] by the above procedure. The alcohol was in turn converted to the bromide and chloride by use of the appropriate thionyl halides in dry benzene.[18] Neither the bromide hydrobromide or chloride hydrochloride could be crystallized. They were used as obtained for condensation with I.

1-Diethylaminobutanol-3, XIX. (a) **From 1-Diethylaminobutanone-3.**—A solution of 50 g. of 1-diethylaminobutanone-3[11,12] in 50 ml. of ether was added to 7 g. of aluminum foil, which had been sanded bright and swirled with 2% mercuric chloride solution and washed with alcohol and ether, in 150 ml. of ether. The mixture was refluxed with occasional addition of 2-ml. portions of water

(16) All melting points are corrected.

(17) Microanalyses by Miss Lois May and D. Rigakos.

(18) Elderfield, *et al.*, THIS JOURNAL, **68**, 1579 (1946).

(19) Hromatka, *Ber.*, **75**, 379 (1942).

(20) Kirrman, *Bull. soc. chim.*, [4] **39**, 988 (1926).

TABLE I

CONDENSATION OF 6-METHOXY-8-AMINOQUINOLINE WITH DIETHYLAMINOALKYL HALIDES

	SN[a]	Aminohalide	Method	Yield, %	B. p. °C.	Mm.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
1	971	$CH_3CHCl(CH_2)_3N(C_2H_5)_2$	B[b]	8–10	178–180	0.15	72.1	9.2	72.1	8.9
2	971	$CH_3CHBr(CH_2)_3N(C_2H_5)_2$[c]	B	45	187–189	.2				
3	971	$CH_3CHBr(CH_2)_3N(C_2H_5)_2$	B	45	185–187	.2				
4	13,431	$C_2H_5CHCl(CH_2)_2N(C_2H_5)_2$[d]	A	41	172–175	.2	72.4	9.2	72.2	9.0
5	13,431	$C_2H_5CHCl(CH_2)_2N(C_2H_5)_2$[e]	A	55	175–180	.3	72.4	9.2	72.6	9.0
6	13,431	$C_2H_5CHBr(CH_2)_2N(C_2H_5)_2$	B	50	172–174	.15				
7	13,526	$CH_3CHCl(CH_2)_2N(C_2H_5)_2$	A	56	165–170	.1	71.7	9.0	71.7	8.8
8	13,526	$CH_3CHBr(CH_2)_2N(C_2H_5)_2$	B	25[f]	170–175	.1	71.7	9.0	71.8	9.0
9	13,527[g]	$CH_3CHCl(CH_2)_2N(C_2H_5)_2$	A	48	180–185	.3	68.9	8.7	68.8	8.6
10		n-$C_3H_7CHClCH_2N(C_2H_5)_2$[h]	A	50	180–185	.3	72.4	9.2	72.3	9.3
11		n-$C_3H_7CHBrCH_2N(C_2H_5)_2$[i]	B	25	175–180	.2	72.4	9.2	72.0	9.2
12		n-$C_3H_7CHClCH_2N(C_2H_5)_2$[i]	A	40	175–180	.2	72.4	9.2	72.6	9.1

[a] The Survey Number, designated SN, identifies a drug in the files of the Survey of Antimalarial Drugs. The activities of these drugs will be tabulated in a forthcoming monograph. [b] Standard procedure modified by using 50% alcohol instead of water. [c] Commercial amino bromide hydrobromide used. [d] Inhomogeneity not more than 3%. [e] Inhomogeneity 8%. [f] Over-all yield for two steps: preparation of the bromide and condensation reaction. [g] 5,6-Dimethoxy-8-aminoquinoline used. [h] Prepared from approximately 9:1 mixture of 2-diethylaminopentanol-1 and 1-diethylaminopentanol-2. [i] Prepared from aminoalcohol showing 3 ± 2% inhomogeneity.

for fifty hours. The precipitate was filtered off and dissolved in sodium hydroxide solution. This alkaline solution was extracted with several portions of ether and the extracts were combined with the ether filtrate from the aluminum hydroxide. After drying and removal of the solvent, the aminocarbinol was distilled, giving 19.7 g. (40%) of material boiling at 72–75° (20 mm.).

Reduction of 1-diethylaminobutanone-3 by catalytic methods led exclusively to cleavage of the aminoketone.

(b) **From 1-Chlorobutanol-3.**—1-Chlorobutanol-3 (XX), prepared from methylmagnesium iodide and β-chloropropionaldehyde,[7,21] was heated with 3.5 equivalents of diethylamine in a sealed tube at 125–130° for sixteen hours. The diethylamine hydrochloride was filtered off and the aminocarbinol was distilled. The yield of material boiling at 82° (18 mm.) was 60%; $n^{25}D$ 1.4372. The substance is reported as boiling at 72–74° (18 mm.),[22] 72° (13 mm.),[7] and 68.5° (7 mm.).[12] The hydrochloride melted at 115–116°. It is reported as melting at 118–120°.[12]

Anal. Calcd. for $C_8H_{20}ClNO$: C, 52.9; H, 11.0. Found: C, 52.9; H, 11.0.

1-Diethylamino-3-chlorobutane. (a) **From 1-Diethylaminobutanol-3.**—The identical procedure was applied to the carbinol obtained by each of the two methods described above. To 24.5 g. of 1-diethylaminobutanol-3 in 50 ml. of anhydrous alcohol-free chloroform at −5° was added a solution of 60 g. of pure thionyl chloride in 100 ml. of cold anhydrous chloroform over a period of thirty minutes. The mixture was allowed to stand overnight in the refrigerator and then refluxed for an hour. Most of the solvent was removed under reduced pressure. Water was added to the residue and the mixture was made basic with cold potassium hydroxide solution and extracted with chloroform. After drying, the aminocarbinol was distilled, yielding 85–87% of material boiling at 70–72° (17 mm.). If the chloroform is not rigorously dried, the yield suffers. The hydrochloride melted at 80–82° after recrystallization from a mixture of acetone, butanol and ether. This melting point agrees with that reported by Hass and Huffman[11] and mixtures of the hydrochlorides prepared by the three methods showed no depression of melting point.

Countercurrent distribution analysis in a benzene-phosphate buffer system at pH 6.28 showed the presence of 17% impurity in the aminochloride originating from 1-diethylaminobutanone-2 and 2% in the material prepared via the Grignard reaction.

(b) **From 1-Iodo-3-chlorobutane.**—1,3-Dichlorobutane (XV) was prepared by heating 14 g. of 1,3-butylene glycol with 10 g. of zinc chloride and 52 ml. of hydrochloric acid (sp. gr. 1.19) in a sealed tube at 150° for eight hours. The dichloride was extracted with petroleum ether and a 49% yield of material boiling at 125–135° was obtained. This was converted to 1-diethylamino-3-chlorobutane exactly according to Hass and Huffman.[11] The material thus prepared contained 8 ± 2% impurity.

Condensation of the Aminohalides with I.—Two general procedures have been used. Procedure A is substantially that of Rohrmann and Shonle[15,23].

Procedure B is based on information received from Germany.[6] A well-stirred mixture of 1 mole of aminobromide hydrobromide, 2 moles of I and 300 ml. of water was heated continuously for six hours at 45–50°, for one hour at 60°, for one hour at 70° and finally for five hours at 90–100°. The mixture was then diluted with 600 ml. of hot water and then made acid to congo red with hydrochloric acid. After stirring and chilling thoroughly in ice, the precipitated mixture of the hydrochloride and hydrobromide of I was filtered off and washed thoroughly with water. The filtrate was buffered until neutral to congo red with sodium acetate and extracted with ether to complete the removal of I. The aqueous solution from this ether extraction was made strongly alkaline and heated at 80° for five hours to complete cyclization of any II present. The drug base was then extracted from the cooled solution with ether and distilled at least twice at a pressure of not more than 0.3 mm. under a nitrogen atmosphere.

The results of the various condensations are summarized in Table I. Analyses given are for the free bases.

Salts were prepared by adding an alcoholic solution of the appropriate acid to an ethereal solution of the base. The salts were recrystallized from acetone.[24] The properties of the salts so prepared are summarized in Table II. The experiment numbers refer to the corresponding ones in Table I.

In Table III are summarized the data on the homogeneity of the bases listed in Table I. The various column headings refer to the general procedure of Craig.[4] Concentrations were determined using a Beckman quartz spectrophotometer and were based on the absorption at the wave length indicated in column 5.

In Table IV are listed the distribution constants for the various condensation products. These were all determined

(21) Backer and Bolt, *Rec. trav. chim.*, **54**, 68 (1935).

(22) French Patent 795,597, March 17, 1936.

(23) Rohrmann and Shonle, THIS JOURNAL, **66**, 1640, 1643 (1944).

(24) We wish to acknowledge our indebtedness to Drs. C. R. Hauser and George Coleman for a supply of meconic acid.

TABLE II

SALTS PREPARED FROM FREE BASES LISTED IN TABLES I AND III

	Identification of component (Table III)	Salt	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
1	Major	Citrate	125–127 dec.			[a]	
2	70%	Citrate	125–127 dec.			[a]	
	30%	Citrate	136–139 dec.	59.2	7.3	59.0	7.2
3	Sole	Citrate	125–127 dec.	59.2	7.3	59.0	7.5
4	20–25%	[b]					
	75–80%	Citrate	136–137 dec.	59.2	7.3	59.1	7.2
5	60–65%	[b]					
	35–40%	[c]					
6	Major	Citrate	136–139 dec.	59.2	7.3	59.0	7.3
7	Major	Dimeconate	169–171 dec.	54.8	5.0	54.6	5.2
8	Major	Dimeconate	169–171 dec.	54.8	5.0		
9	Major	Dimeconate	100–103 dec.	54.6	5.7[f]	54.4	5.9
10	Combined	Dimeconate[g]	175–178 dec.	55.4	5.2	[h]	
11	Combined	Dimeconate	175–178 dec.	55.4	5.2	55.6	5.4
12	No salt prepared						

[a] Not analyzed, but showed no depression in mixed m. p. with citrate from pure Plasmochin base. [b] No solid salt could be found. [c] Not characterized. [d] Magidson and Bobyshev [*J. Gen. Chem.* (*U.S.S.R.*), **8**, 889 (1938)] report the dimeconate melting at 145° dec. However, since their alkylamino bromide was prepared by the action of hydrobromic acid, it appears probable that they were dealing with a mixture which would account for the lower m. p. for the dimeconate reported by them. [e] Mixed m. p. with dimeconate from run 7 showed no depression. [f] The calculated values are for the dimeconate containing one isopropanol of crystallization. Attempts to remove this prior to analysis resulted in partial decomposition of the salt. [g] Base regenerated from the dimeconate showed 8±3% inhomogeneity. The identity of this base was not established. [h] Showed no depression in m. p. when mixed with dimeconate from run 11.

TABLE III

INHOMOGENEITY DETERMINATIONS ON FREE BASES LISTED IN TABLE I

	Inhomogeneity, %	Organic solvent	Aqueous buffer system	*p*H of buffer	Wave length used for analysis in mμ	Concn., mg./ml.	Plates
1	3±2	Cyclohexane	Phosphate	5.1	370	1	8
2	30	Cyclohexane	Phosphate	5.1	370	1	8
3	4±2	Cyclohexane	Phosphate	5.1	370	1	24
4	20-25	Isopropyl ether	Citrate	4.36	365	10	24
5	35-40	Isopropyl ether	Citrate	4.36	365	1	24
6	7±3	Isopropyl ether	Citrate	4.85	365	1	24
7	4±2	Cyclohexane	Citrate	5.12	370	0.5	8
8	4±2	Cyclohexane	Phosphate	5.12	370	.66	8
9	5±2	Cyclohexane	Citrate	4.84	390	.33	8
10	2-66-32	Isopropyl ether	Citrate	4.10	365	1	24
11	7-66-27	Isopropyl ether	Citrate	4.13	365	1	24
12	3-63-34	Isopropyl ether	Citrate	4.10	365	1	24

TABLE IV

DISTRIBUTION CONSTANTS OF THE BASES

Compound	Source	*p*H	*k*
Plasmochin	Pure	4.30	0.031
SN 13,431	Expt. 6 (Table I)	4.34	0.195
?	Major fraction, Expt. 4 (Table II)	4.35	0.71
?	66% fraction, Expt. 10 (Table II)	4.35	2.42
?	66% fraction, Expt. 10 (Table II)	4.10	0.91
?	32% fraction, Expt. 10 (Table II)	4.10	3.25

in an isopropyl ether-citrate buffer system at the *p*H indicated. Because of uncertainty of structures of many of the bases, it is not possible to give them a definite formula at this time.

The only experiment which requires detailed comment is Experiment 4. The distilled drug base was examined in a 24-plate system and the presence of two components is clearly indicated by the curve of Fig. 1. The drug base was redistilled and again examined in a 24-plate system. By reference to Fig. 1, it is apparent that no purification was achieved. The material (4.2 mg.) in tube 4 was extracted into isopropyl ether and, after removal of the solvent, treated with 2.8 mg. of citric acid in acetone. On seeding with the citrate of the major impurity of commercial Plasmochin, the citrate crystallized. It melted at 136–139° (hot-stage) and did not depress the melting point of the citrate of Plasmochin impurity. The base present in tube 13 could not be converted into a citrate.

Fractionation of Plasmochin.—An amount of commercial Plasmochin hydriodide corresponding to 100 mg. of free base was treated with 3 ml. of water and 10 ml. of ether. After addition of excess 10% sodium hydroxide solution, the base was extracted quantitatively with ether. The oily drug base, after removal of the ether, was subjected to a 19-plate distribution,[4] using cyclohexane and 2 molar phosphate buffer at *p*H 5.32. The curve for this distribution is shown in Fig. 2.

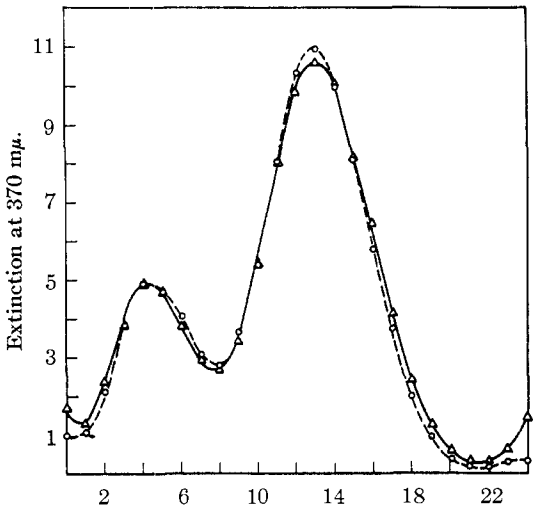


Fig. 1.—Fractionation of iso-plasmochin from iso-noval chloride isopropyl ether–citrate buffer: *p*H 4.34; Δ, before redistillation; O, after redistillation.

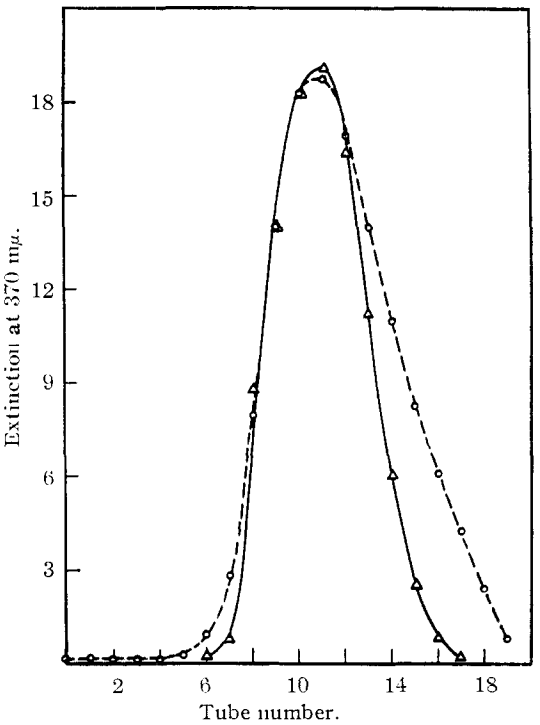


Fig. 2.—Distribution of plasmochin–cyclohexane–phosphate buffer, *p*H 5.32.

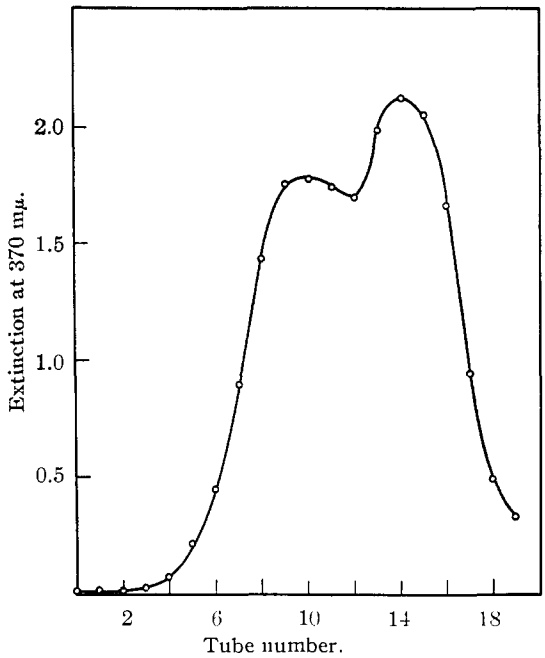


Fig. 3.—Plasmochin fractionation: redistribution of fractions 15–19 from Fig. 2.

Examination of the base found in tubes 15 to 19 revealed different partition coefficients in each. Further, these partition coefficients were different from those of the base in tubes 7 to 13. The latter tubes contained most of the total base and this material was homogeneous. The material in tubes 15 to 19 was therefore combined and subjected to a second 19-plate distribution using cyclohexane and 2 molar phosphate buffer at *p*H 5.00. The curve for this distribution is shown in Fig. 3. The base found in tubes 14 to 18 was converted to the citrate, which melted at 136–139° (hot stage).

Summary

1. Commercial Plasmochin has been shown to be a mixture of which the major component presumably has the structure conventionally assigned to it. The second component is presumably 6-methoxy-8-(3′-diethylamino-1′-ethylpropylamino)-quinoline.

2. The occurrence of rearrangements in the preparation of certain drugs of the 8-aminoquinoline group has been noted and a possible explanation for the observed facts has been indicated.

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