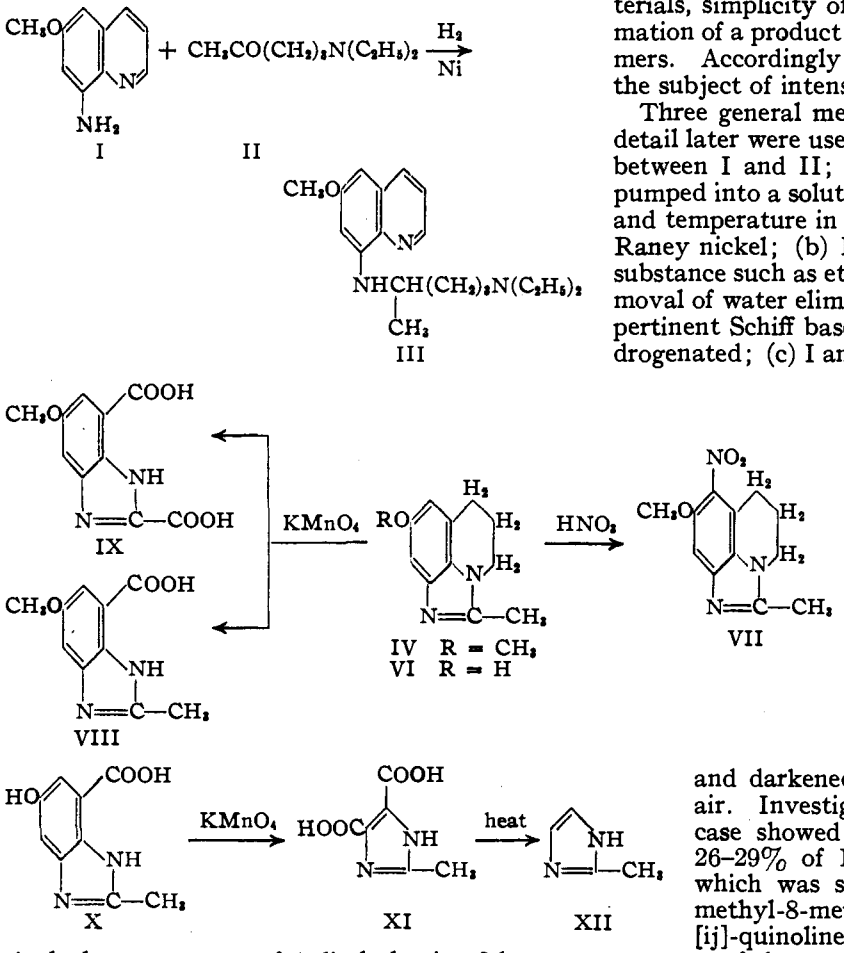
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY AND THE RESEARCH LABORATORIES OF SHARPLES CHEMICALS, INC.]

A Study of the Synthesis of Plasmochin by the Reductive Amination Method with Raney Nickel[1]

BY ROBERT C. ELDERFIELD, FRANK J. KREYSA, JAMES H. DUNN AND DAVID D. HUMPHREYS

Commercial Plasmochin (6-methoxy-8-[4-diethylamino-1-methylbutylamino]-quinoline) (III) as commonly manufactured contains significant amounts of an isomeric substance[2] to which the name Isoplasmochin and the tentative structure of 6-methoxy-8-(3-diethylamino-1-ethylpropylamino)-quinoline have been given.[2] The source of this isomer apparently may be found in the relatively large amounts of 1-diethylamino-3-bromopentane with which commercial 1-diethylamino-4-bromopentane, the intermediate for Plasmochin, is contaminated. Pure 1-diethylamino-4-bromopentane, from which pure Plasmochin may be prepared, can be made by the action of thionyl bromide on the corresponding alcohol[2,3] rather than by the action of hydrobromic acid on the alcohol as has been the commercial practice.



The use of the reductive amination reaction involving 6-methoxy-8-aminoquinoline and 1-diethylaminopentanone-4 (I–III) for the synthesis of Plasmochin presents attractive possibilities from the viewpoint of relatively accessible materials, simplicity of operation and potential formation of a product which should be free from isomers. Accordingly the reactions I–III have been the subject of intensive investigation.

Three general methods which are described in detail later were used in carrying out the reaction between I and II; *viz.*, (A) the ketone, II, was pumped into a solution of I at a specified pressure and temperature in the presence of hydrogen and Raney nickel; (b) I and II were refluxed with a substance such as ethylbenzene for azeotropic removal of water eliminated in the formation of the pertinent Schiff base and the latter was then hydrogenated; (c) I and II were heated with stirring in the presence of a dehydrating agent such as magnesium methoxide and the resulting crude product was hydrogenated. Although several variations of the above procedures were investigated, the high boiling products from all runs were roughly similar in composition. On fractionation, the material boiling in the Plasmochin range consisted of a yellow semi-solid which melted at about 104–109° and darkened rapidly on exposure to the air. Investigation of this in a typical case showed the presence of 4–5% of I, 26–29% of III and 50% of a substance which was subsequently shown to be 2-methyl-8-methoxy-5,6-dihydro-4-imidazo-[ij]-quinoline (IV). Material from other runs was of the same general composition.

After IV had been chemically identified, the substance was described by Price and Herbrandson[4] and by Barber and Wragg.[5] Although compounds of the type of IV have been previously reported[4,6] from the reaction of 8-amino-derivatives of 1,2,3,4-tetrahydroquinoline with acetic acid

(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 and Sharples Chemicals, Inc. A preliminary note on this material has already appeared, THIS JOURNAL, **69**, 186 (1947).

(2) Elderfield, *et al.*, *ibid.*, **68**, 1516 (1946).

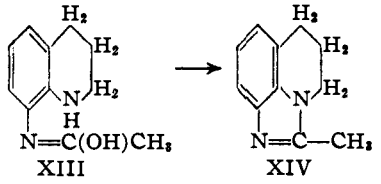
(3) Elderfield, *et al.*, *ibid.*, 1579 (1946).

(4) Price and Herbrandson, *ibid.*, **68**, 910 (1946).

(5) Barber and Wragg, *J. Chem. Soc.*, 610 (1946).

(6) Hazlewood, Hughes and Lions, *Proc. Roy. Soc. N. S. Wales*, **71** 467 (1937–1938).

under mild dehydrating conditions in accordance with XIII–XIV it seemed improbable that such a reaction would occur when a ketone was substituted for acetic acid. In the latter case rupture of



a carbon–carbon linkage under relatively mild conditions must occur. Therefore, prior to the appearance of Price and Herbrandson's note,[4] the constitution of IV was established by a study of its chemical reactions.

The presence of the methoxyl group was shown by its cleavage to the corresponding phenol VI. Attempted oxidation with 35% nitric acid resulted in the formation of a mononitro derivative for which the most likely structure is VII by analogy with the behavior of other quinoline compounds on nitration. Oxidation of IV with potassium permanganate in pyridine resulted in cleavage of the reduced pyridine ring with the formation of 2-methyl-5-methoxybenzimidazole-7-carboxylic acid (VIII) as the major product together with a small amount of 5-methoxybenzimidazole-2,7-dicarboxylic acid (IX). Attempted decarboxylation of the acid, VIII, did not lead to the isolation of any definite compound. However, when 2-methyl-5-hydroxybenzimidazole-7-carboxylic acid (X), obtained from VIII by cleavage of the ether, was oxidized further with potassium permanganate, 2-methylimidazole-4,5-dicarboxylic acid (XI) was obtained. XI, on decarboxylation, gave 2-methylimidazole XII. The identities of XI and XII were established by comparison with known samples synthesized by the methods of Fargher and Pyman[7] and Dedichen,[8] respectively.

On the basis of the above degradation. the structure IV must be assigned to the major product arising from the reductive amination reaction with I and II. This was confirmed by comparison of the substance with a sample prepared by known methods.[4,6]

It is obvious that the elements of N,N-diethylpropylamine must have been eliminated during the course of the formation of the imidazole from I and II. Therefore the solvent removed from the crude hydrogenation reaction mixture was examined. From this it was indeed possible to isolate the above amine which was identified by comparison with a sample synthesized by known methods. Thus, the at first seemingly unlikely formation of the imidazole IV from I and II has been definitely confirmed. A further study of the formation of such imidazoles is reported in the succeeding paper.

(7) Fargher and Pyman, *J. Chem. Soc.*, **115**, 229 (1919).

(8) Dedichen, *Ber.*, **39**, 1838 (1906).

Since the empirical formula of the imidazole IV is the same as that of 6-methoxy-8-ethylaminoquinoline (XV) and since formation of the latter was conceivable by a transethylation during the reaction of I and II, we have prepared XV which has not been reported previously. Ethylation of 6-methoxy - 8 - (*p*-toluenesulfonylamino)-quinoline according to the general method of Gawron and Spoerri[9] for the amination of aminoquinoxalines followed by hydrolysis of the tosyl group readily yielded XV.

Experimental[10,11]

Reaction of 6-Methoxy-8-aminoquinoline with 1-Diethylaminopentanone-4 in the Presence of Nickel and Hydrogen.—Three general methods have been used.

Procedure A.—A 2-gallon hydrogenation autoclave was charged with 800 ml. of methanol, 60 g. of Raney nickel and 348 g. (2 moles) of 6-methoxy-8-aminoquinoline (I). After heating to 130° at 600 lb. hydrogen pressure, 628 g. (4 moles) of 1-diethylaminopentanone-4 (II) was pumped in. A pressure drop of about 150 lb. took place over about two and one-half hours. The reaction mixture, after filtration from the catalyst was distilled up to a temperature of 135° (1 mm.) for removal of excess amino ketone and alcohol derived from it by reduction. An intermediate fraction (about 200 g.) consisting of unreacted 6-methoxy-8-aminoquinoline, and probably some of its tetrahydro-derivative, followed. The so-called "Plasmochin fraction"[11] (96 g.) was collected at 182–194° (1 mm.). It consisted of a mush of crystalline material in an oil which rapidly discolored on exposure to the air. The residue in the flask was a hard brittle resin and was not investigated further. The 182–194° fraction was redistilled under nitrogen and examined spectrographically in the ultraviolet using a Beckman quartz spectrophotometer. The curves obtained are shown in Figs. 1 and 2 in which it has been necessary to depart from the conventional manner of plotting to secure the information desired.[12]

At 390 mμ neither the pure imidazole, IV, nor 6-methoxy-8-aminoquinoline (I) has an appreciable extinction coefficient. The amount of Plasmochin (III) present calculated by the extinction coefficient at this wave length is 29%. At about 360 mμ, 6-methoxy-8-aminoquinoline and Plasmochin have the same extinction coefficient whereas the imidazole, IV, has a coefficient of O. Calculations at this wave length indicate a total of 34% 8-aminoquinolines, assuming Plasmochin and 6-methoxy-8-aminoquinoline to be the only 8-aminoquinolines present. At 295 mμ the imidazole, IV, has a sharp maximum. By correcting for the absorption of the 8-aminoquinolines at this wave length, calculations show the presence of about 50% of the imidazole on the assumption that no other compound present absorbs at this wave length.

Colorimetric analysis of the crude reaction product substantiated the above results. Direct coupling of the material with diazotized sulfanilic acid indicated a total of 30% 8-aminoquinolines in terms of Plasmochin. Direct diazotization and coupling indicated the presence of about 4% of 6-methoxy-8-aminoquinoline. The difference is about 26% of Plasmochin.

That there is still another substance or substances present in the crude reaction product is indicated by the fact that the absorption curve is falling at 320 to 330 mμ whereas at these wave lengths the pure imidazole, IV, has an extinction coefficient of zero while the curves for the 8-

(9) Gawron and Spoerri, THIS JOURNAL, **67**, 514 (1945).

(10) All melting points are corrected.

(11) The microanalyses reported in this paper were done by Miss Lois May of the Columbia laboratories.

(12) We wish to acknowledge our indebtedness to Dr. Bernard Brodie of the Goldwater Memorial Hospital for carrying out the spectrographic and colorimetric analyses here reported and for permission to incorporate them in this paper.

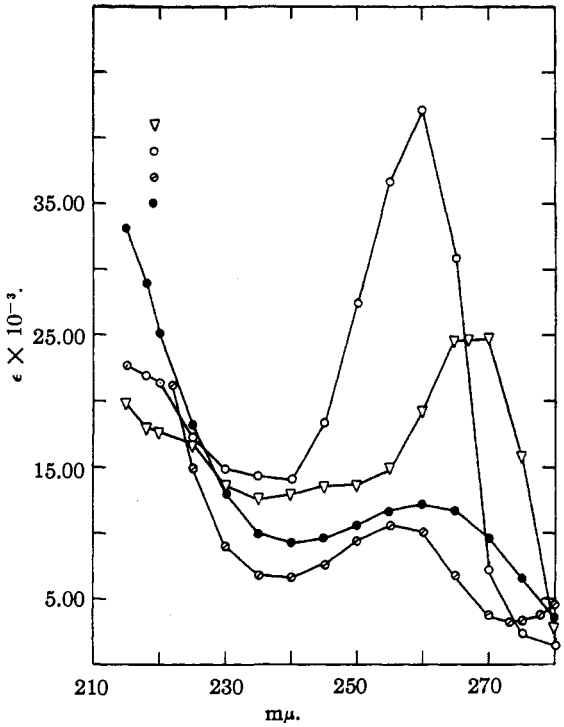


Fig. 1.—Ultraviolet absorption spectra: ▽, Plasmochin; O, 6-methoxy-8-aminoquinoline; ⊙, pure imidazole, IV; ●, twice distilled plasmochin fraction; solvent, heptane; concentration, 10 γ per ml.

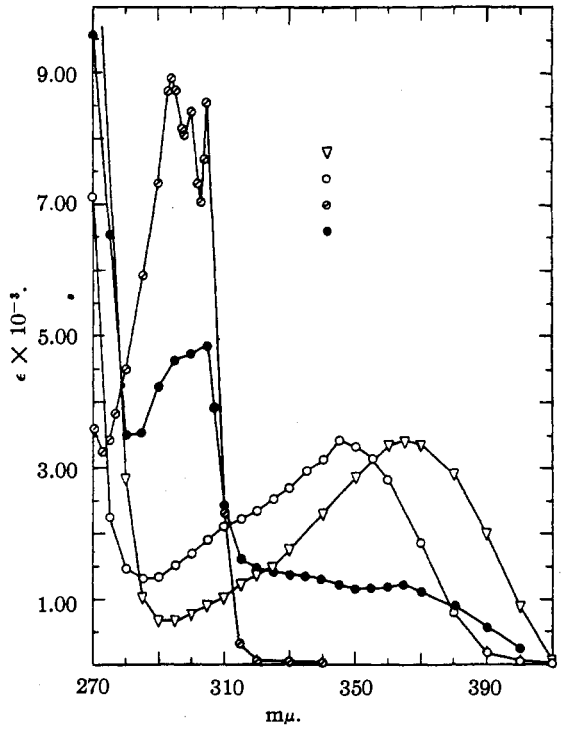


Fig. 2.—Ultraviolet absorption spectra: ▽, Plasmochin; O, 6-methoxy-8-aminoquinoline; ⊙, pure imidazole, IV; ●, twice distilled plasmochin fraction; solvent, heptane; concentration, 100 γ per ml.

aminoquinolines are rising. No attempt was made to isolate other substances which may have been present.

Procedure B.—A 2-gallon autoclave was charged with 348 g. (2 moles) of 6-methoxy-8-aminoquinoline, 60 g. of Raney nickel and a solution of magnesium methylate prepared by dissolving 24 g. of magnesium turnings in 1600 ml. of boiling absolute methanol. At 130° and 780 lb. hydrogen pressure, 628 g. (4 moles) of 1-diethylaminopentanone-4 was pumped in. The temperature was raised to 150° where a pressure drop of 250 lb. was noted. After cooling, water was added to the reaction mixture and the magnesium hydroxide was filtered off with considerable difficulty and some loss of material. Distillation of the product gave a "Plasmochin fraction" of 83 g. which was of the same character as that obtained above.

Procedure C.—The Schiff base (see below) prepared by refluxing 174 g. (1 mole) of 6-methoxy-8-aminoquinoline and 314 g. (2 moles) of 1-diethylaminopentanone-4 with 200 ml. of ethylbenzene for seventy-two hours was reduced at 90–95° and 600 lb. hydrogen pressure with 40 g. of Raney nickel for two and one-half hours. After working up as before 40 g. of a "Plasmochin fraction" having the same characteristics as that described above was obtained.

Several runs by each of the above procedures were made. Temperature limits were from 95 to 180°. In all of the runs the product was essentially the same.

Isolation of N,N-Diethylpropylamine from the Products of the Above Reaction.—The Dry Ice traps in the apparatus in which the crude product from a run similar to that given under Procedure A was distilled contained 30 ml. of liquid. This was fractionated through a small Podbielniak column. The carefully purified material boiled at 111.9–112.2°.

Anal. Calcd. for $C_7H_{17}N$: C, 73.0; H, 14.9; neutral equiv., 115. Found: C, 73.2; H, 15.1; neutral equiv., 115.7.

The amine was definitely identified by mixed melting points of the hydrochloride and methiodide with an authentic sample synthesized as below.

N,N-Diethyl-*n*-propylamine has been described as the chloroplatinate by LeBel[13] but the base has not been described. It was therefore synthesized by the general method described by Caspe[14] for the preparation of the corresponding isopropyl compound.

A mixture of 50 g. of glycerol, 123 g. of *n*-propyl bromide and 95 g. of diethylamine was heated under reflux for sixty hours. The melt was dissolved in 50 ml. of water and the solution was made strongly alkaline with 200 ml. of 50% potassium hydroxide solution, the temperature being kept below 25°. The amine layer was separated and the aqueous layer was repeatedly extracted with ether. The combined amine and ether layers were dried over potassium hydroxide and fractionated yielding 58 g. (50%) of the amine.

Anal. Calcd. for $C_7H_{17}N$: C, 73.0; H, 14.9. Found: C, 73.1; H, 14.7.

N,N-Diethyl-*n*-propylamine hydrochloride formed hygroscopic white needles from ethyl acetate and melted at 205.5–206.5°.

Anal. Calcd. for $C_7H_{17}N\cdot HCl$: C, 55.4; H, 12.0. Found: C, 55.5; H, 12.2.

N,N-Diethyl-*n*-propylamine methiodide formed hygroscopic plates from isopropanol or acetone and melted at 243–244°.

Anal. Calcd. for $C_7H_{17}N\cdot CH_3I$: C, 37.4; H, 7.8. Found: C, 37.6; H, 8.1.

Isolation of 2-methyl-8-methoxy-5,6-dihydro-4-imidazo-[ij]-quinoline, IV, from the "Plasmochin fraction."—The crystalline mush of twice distilled "Plasmochin fraction" obtained by any of the above procedures was washed with cold heptane and the insoluble crystalline material was

(13) LeBel, *Compt. rend.*, **125**, 351 (1897).

(14) Caspe, THIS JOURNAL, **54**, 4457 (1932).

further recrystallized from heptane yielding plates which melted at 119.5–120°.

Anal. Calcd. for $C_{12}H_{14}ON_2$: C, 71.3; H, 7.0; N, 13.9; OCH_3, 15.3. Found: C, 71.2; H, 6.8; N, 14.0; OCH_3, 15.0.

The hydrochloride of the imidazole formed hygroscopic needles from absolute alcohol–carbon tetrachloride (1:1) which melted at 233–233.5°.

Anal. Calcd. for $C_{12}H_{14}ON_2 \cdot HCl$: C, 60.4; H, 6.3; N, 11.7; Cl, 14.9. Found: C, 60.1; H, 6.2; N, 11.7; Cl, 14.8.

The hydrobromide, from absolute alcohol, was hygroscopic and melted at 242°.

Anal. Calcd. for $C_{12}H_{14}ON \cdot HBr$: C, 50.9; H, 5.3; N, 9.9; Br, 28.2. Found: C, 51.0; H, 5.4; N, 9.7; Br, 28.1.

The picrate, from alcohol or dioxane, softened at 243° and decomposed at 248–253°.

Anal. Calcd. for $C_{18}H_{17}O_8N_5$: C, 50.1; H, 4.0. Found: C, 50.2; H, 4.0.

The methiodide, from methanol, darkened at 280° and decomposed at 285–290°.

Anal. Calcd. for $C_{12}H_{14}ON_2 \cdot CH_3I$: C, 45.4; H, 5.0. Found: C, 45.4; H, 4.9.

The *p*-toluenesulfonic acid salt, from isopropyl ether, alcohol or carbon tetrachloride, melted at 139.5–140.5°.

Anal. Calcd. for $C_{19}H_{22}N_2O_4S$: C, 60.9; H, 5.9; N, 7.5. Found: C, 61.1; H, 5.7; N, 7.4.

The imidazole was identified by mixed melting points of the base and the above derivatives with samples prepared according to the known method of Hazlewood, Hughes and Lions.[6]

Perbromide of the Imidazole, IV.—To a solution of 0.2 g. of the imidazole in 10 ml. of carbon tetrachloride, 5 ml. of a 5% solution of bromine in carbon tetrachloride was added dropwise. Orange crystals separated but no evolution of hydrogen bromide occurred. After recrystallization from methanol, the substance darkened at 265° and decomposed about 285°.

Anal. Calcd. for $C_{12}H_{14}Br_2ON_2$: C, 39.8; H, 3.9. Found: C, 39.8; H, 3.8.

2-Methyl-7(?)-nitro-8-methoxy-5,6-dihydro-4-imidazo[ij]quinoline.—The imidazole, IV, was unattacked when oxidation with 35% nitric acid was attempted. Rather a mononitro derivative was formed during the working up of the reaction mixture.

A solution of 1 g. of the imidazole in 10 ml. of 35% nitric acid was boiled under reflux for five hours. The mixture was transferred to an evaporating dish and 10 ml. of 70% nitric acid was added. It was then evaporated to dryness on the steam-bath after which 10 ml. of water was added and the evaporation was repeated. After triturating with 5 ml. of ice water the crystalline nitro compound was collected and recrystallized from ethyl acetate or alcohol. The substance is soluble in aqueous acid (*p*H 3) and is reprecipitated at *p*H 10. It melted at 238–240° (dec.). Assignment of the nitro group to the 7-position is preferred although the 9-position cannot be excluded.

Anal. Calcd. for $C_{12}H_{13}O_3N_3$: C, 58.3; H, 5.3. Found: C, 58.3; H, 5.2.

2-Methyl-8-hydroxy-5,6-dihydro-4-imidazo[ij]-quinoline.—A solution of 5 g. of the imidazole, IV, in 75 ml. of 48% hydrobromic acid was refluxed for ten hours. On refrigeration a crystalline precipitate separated. This was dissolved in 75 ml. of warm water (*p*H 4) and the solution was adjusted to *p*H 10 with sodium hydroxide during which the hydroxy compound first precipitated and then dissolved. The filtered alkaline solution was saturated with carbon dioxide and the precipitate was recrystallized from isopropanol. It darkened at 285° and decomposed at 295–305° (copper block).

Anal. Calcd. for $C_{11}H_{12}ON_2$: C, 70.2; H, 6.4. Found: C, 70.2; H, 6.4.

Oxidation of the Imidazole, IV, with Potassium Permanganate.—To a boiling well-stirred solution of 6 g. of the imidazole, IV, in 900 ml. of 33% aqueous pyridine was added 1200 ml. of 3% aqueous potassium permanganate solution over two hours. The mixture was boiled and stirred for an additional hour. After cooling, the manganese dioxide was filtered and extracted by boiling it with 500 ml. of 10% aqueous pyridine for half an hour. The combined filtrates from the manganese dioxide were evaporated to dryness on the steam-bath. The residue was dissolved in 200 ml. of warm water (*p*H 10) and the *p*H of the filtered solution was adjusted to 5–6 with hydrochloric acid. After refrigerating, the precipitate was collected and recrystallized from dioxane, water or alcohol. The yield was 70%. On air drying 2-methyl-5-methoxybenzimidazole-7-carboxylic acid was thus obtained as the dihydrate which darkened at 295° and decomposed at 300–305°.

Anal. Calcd. for $C_{10}H_{10}O_3N_2 \cdot 2H_2O$: C, 49.6; H, 5.8; N, 11.6. Found: C, 49.8; H, 5.7; N, 11.6.

On drying at 175° and 15 mm. over calcium chloride for one hour the substance lost 14.72% of water; calcd. 14.87%. The anhydrous acid decomposed at 295–305°.

Anal. Calcd. for $C_{10}H_{10}O_3N_2$: C, 58.3; H, 4.9; N, 13.6. Found: C, 58.5; H, 4.7; N, 13.6.

The aqueous filtrate from the above acid at *p*H 5–6 was acidified to *p*H 2 with hydrochloric acid. After refrigerating, the precipitate was purified by acidification of its hot filtered solution in 10% sodium hydroxide with hydrochloric acid and finally by recrystallization from glacial acetic acid. The yield of 5-methoxybenzimidazole-2,7-dicarboxylic acid monohydrate which darkened about 270° and decomposed at 290–295° was 0.1 g. The air-dried acid, for which analytical figures are given, lost 7.1% of water on drying at 175° and 15 mm. over calcium chloride; calcd. 7.1%.

Anal. Calcd. for $C_{10}H_8O_5N_2 \cdot H_2O$: C, 47.3; H, 4.0; N, 11.0. Found: C, 47.3; H, 4.0; N, 11.3.

2-Methyl-5-hydroxybenzimidazole-7-carboxylic Acid.—A solution of 5 g. of the methoxy acid, VIII, in 50 ml. of 48% hydrobromic acid was refluxed for forty-five minutes at which time bumping caused by separated crystalline material necessitated stopping the reaction. After cooling, the hydroxy acid was filtered off and dissolved in 50 ml. of warm water (*p*H 2). The *p*H was adjusted to 5 with sodium hydroxide at which point the acid, X, precipitated. It was recrystallized from 900 ml. of boiling water yielding 3 g. of white needles which slowly decomposed without melting at 300–350° (copper block).

Anal. Calcd. for $C_9H_8O_3N_2$: C, 56.3; H, 4.2; N, 14.6. Found: C, 56.2; H, 4.0; N, 14.7.

Oxidation of the Acid, X, to 2-Methylimidazole-4,5-dicarboxylic Acid, XI.—To a stirred suspension of 1 g. of the acid, X, in 200 ml. of water cooled to 5° was added 80 ml. of 4% potassium permanganate solution during the course of one hour. Oxidation was prompt and the temperature was kept below 10° by external cooling. The mixture was then refrigerated for twelve hours and any unreacted permanganate was destroyed with methanol. The filtrate from the manganese dioxide was acidified to *p*H 2–3 with hydrochloric acid and then evaporated to dryness. The residue was dissolved in 40 ml. of 7% ammonium hydroxide solution, and the solution was treated with 0.1 g. of decolorizing carbon (Norit A) in the cold, filtered and evaporated to dryness. If too much Norit is used or if the solution is boiled at this point the ammonium salt of the acid is completely absorbed on the Norit. The solution of the residue in 10 ml. of warm water was acidified to *p*H 2–3 and the crystalline precipitate was collected and recrystallized several times from a small amount of water. The fine white needles decomposed at 275–285°. After drying at atmospheric pressure over calcium chloride, the acid still retained a molecule of water.

Anal. Calcd. for $C_6H_6N_2O_4 \cdot H_2O$: C, 38.3; H, 4.3. Found: C, 38.3; H, 4.0.

A sample of 2-methylimidazole-4,5-dicarboxylic acid monohydrate prepared according to Fargher and Pyman[7] by condensation of tartaric acid dinitrate with acetalde-

hyde, and recrystallized in the same manner decomposed at 275–285°.

The acid was decarboxylated by heating it over a small free flame according to Dedichen[8] and the resulting 2-methylimidazole was recrystallized from benzene. The latter compound prepared from the acid from both sources melted at 134–136° and the mixed melting point was not depressed. Dedichen[8] reports the m. p. of 2-methylimidazole as 139°.

6-Methoxy-8-(4-diethylamino-1-methylbutylideneamino)-quinoline.—The Schiff base was used by Barber and Wragg in the preparation of tetrahydropamaquine but neither the method of synthesis nor physical constants of the compound are given by the British workers. A mixture of 157 g. (1 mole) of 1-diethylaminopentanone-4, 87 g. (0.5 mole) of 6-methoxy-8-aminoquinoline and 150 ml. of ethylbenzene was refluxed for one hundred hours in an apparatus equipped with a liquid separator from which the condensed reflux of ethylbenzene was returned to the reaction flask after passing through anhydrous potassium carbonate for removal of water. The bulk of the solvent was distilled off at atmospheric pressure in an atmosphere of nitrogen and 80 g. of the amino-ketone was then removed at water pump vacuum followed by 45 g. of unreacted 6-methoxy-8-aminoquinoline boiling at 175–185° (4 mm.). The crude Schiff base (85 g.) then distilled at 230–240° (4 mm.). Redistillation yielded 55 g. (35%) of orange oil boiling at 184–186° (0.4 mm.).

Anal. Calcd. for $C_{19}H_{27}ON_3$: C, 72.8; H, 8.7. Found: C, 72.8; H, 8.5.

6-Methoxy-8-(*p*-toluenesulfonylamido)-quinoline.—A mixture of 17.5 g. of 6-methoxy-8-aminoquinoline, 19 g. of *p*-toluenesulfonyl chloride and 100 ml. of 10% sodium hydroxide was shaken at room temperature until the acid chloride was all gone. The sulfonamide was recrystallized from isopropanol and melted at 133.5°.

Anal. Calcd. for $C_{17}H_{16}O_3N_2S$: C, 62.2; H, 4.9. Found: C, 62.0; H, 4.8.

6-Methoxy-8-(*p*-toluenesulfonylethylamido)-quinoline. To a stirred solution of 32.8 g. of the above tosyl compound in 350 ml. of absolute alcohol at 75–80° in a flask protected from atmospheric moisture was added a solution of 6.7 g. of potassium hydroxide in 150 ml. of absolute alcohol. After stirring the mixture for thirty minutes at 70–80° and then cooling, the crystalline potassium salt (90%) was filtered off and washed with absolute alcohol.

A stirred mixture of 18.3 g. of the above potassium salt, 8.3 g. of ethyl bromide (no reaction occurred when ethyl iodide was used) and 250 ml. of absolute alcohol was heated under reflux for twenty-four hours. After cooling the filtrate from the potassium bromide was evaporated to dryness. To the residue was added 250 ml. of 5% potassium hydroxide solution and this mixture was extracted with ether. After washing and drying the extract, evaporation of the ether left a yellow residue which was recrystallized from isopropanol or acetone. The substance melted at 125–126°.

Anal. Calcd. for $C_{19}H_{30}O_3NS$: C, 64.0; H, 5.7. Found: C, 64.0; H, 5.6.

6-Methoxy-8-ethylaminoquinoline.—A mixture of 1 g. of the above compound and 3 ml. of 96% sulfuric acid was heated with occasional stirring at 100° for ten minutes. After cooling and standing at room temperature for three hours, 20 ml. of 40% sodium hydroxide solution was added very cautiously. The mixture was extracted with benzene, yielding a yellow oil which gradually solidified. After recrystallization from *n*-heptane, the ethylaminoquinoline melted at 38–40°.

Anal. Calcd. for $C_{12}H_{14}ON_2$: C, 71.3; H, 7.0. Found: C, 71.0; H, 6.9.

Summary

1. Reductive amination of 1-diethylaminopentanone-4 with 6-methoxy-8-aminoquinoline with Raney nickel under various conditions leads to a mixture consisting of Plasmochin and 2-methyl-8-methoxy-5,6-dihydro-4-imidazo[ij]-quinoline as principal components.

2. A study of the oxidative degradation of 2-methyl-8-methoxy-5,6-dihydro-4-imidazo[ij]-quinoline has been made.

3. N,N-Diethylpropylamine and 6-methoxy-8-ethylaminoquinoline have been prepared.

NEW YORK 27, N. Y.
WYANDOTTE, MICH. RECEIVED MARCH 21, 1947

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

The Reaction of *o*-Phenylenediamine and of 8-Amino-1,2,3,4-tetrahydroquinoline Derivatives with Carbonyl Compounds

BY ROBERT C. ELDERFIELD AND FRANK J. KREYSA

In the preceding paper[1] a study of the reductive amination of 1-diethylamino-pentanone-4 with 6-methoxy-8-aminoquinoline has been described. The major product of the reaction was 2-methyl-8-methoxy-5,6-dihydro-4-imidazo[ij]quinoline (I) and N,N-diethyl-*n*-propylamine was isolated from the products of the reaction. Since the formation of I obviously involves cleavage of a carbon–carbon bond under relatively mild conditions the reaction conditions under which imidazoles of the general type of I are formed from ketones have been the subject of further investigation.

As pointed out by Hazlewood, Hughes and Lions[2] 8-amino-1,2,3,4-tetrahydroquinoline (II) can be regarded as a mono-N-alkyl-*o*-phenylenediamine and the same authors prepared imidazoles of the type of I by the action of acids on II under mild dehydrating conditions. Formation of the imidazole ring in this fashion is easily understood and obviously proceeds by intramolecular elimination of water from an enolic form of an N-acyl derivative of II (III) in accordance with the observations of Phillips[3] on the behavior of *o*-phenylenediamine itself under similar conditions. Whether the acyl derivatives of II involve the ring nitrogen or that of the primary amino group is irrelevant and cannot be stated with certainty at this time. As far as we are aware only three cases of the formation of a 2-substituted benzimidazole

(1) Elderfield, *et al.*, THIS JOURNAL, **70**, 40 (1948).

(2) Hazlewood, Hughes and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 467 (1937–1938).

(3) Phillips, *J. Chem. Soc.*, **173**, 2395 (1928); see also McCoy and Day, THIS JOURNAL, **65**, 2159 (1943).