CCCCXXVII.—*Attempts to find New Antimalarials. Part VII. Quinoline Compounds having in the 4-Position a Side Chain containing Two or More Nitrogen Atoms.*

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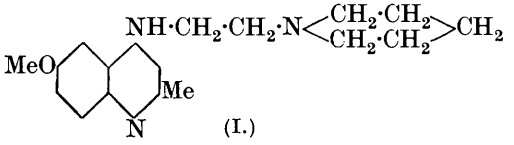
IN a previous paper (Kermack and Smith, J., 1930, 1356), certain quinoline derivatives were described in which a piperazino- or a piperidino-group is attached to the nucleus in the 4-position. It was thought desirable to prepare a series of analogous compounds having a side chain of more complex structure.

To this end piperidine was condensed with phthalo-β-bromoethylimide to yield *phthalo-β-piperidinoethylimide*, from which the phthalyl group was removed by means of hydrazine hydrate (Ing and Manske, J., 1926, 2348) to form β-piperidinoethylamine.

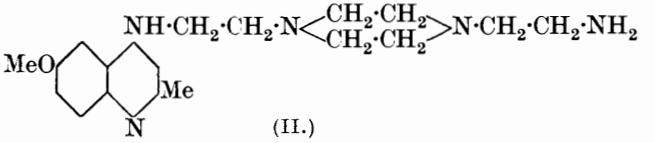
4-Chloro-6-methoxy-2-methylquinoline and β-piperidinoethylamine reacted only with difficulty, but a solid base (I) was ultimately obtained from the product of the reaction at 110—120° in presence of copper–bronze.



(I.)

As 4-β-*piperidinoethylamino*-6-*methoxy*-2-*methylquinoline* (I) had no antimalarial action, an attempt was made to prepare a homologous compound in which a chain of three carbon atoms would separate the two nitrogen atoms. From α-piperidinobutan-γ-one (Mannich and Wolfgang, *Arch. Pharm.*, 1927, **265**, 589), the *oxime* was pre-

pared, and this was reduced with zinc dust and acetic acid. α-Piperidino-γ-aminobutane was obtained, which gave a *dipicrate*,



(II.)

monohydrochloride and *dihydrochloride* as crystalline solids, but all attempts to condense it with either 4-chloro- or 4-bromo-6-methoxy-2-methylquinoline were unsuccessful. The only evidence of reaction was the formation of halogen ions and the development of fluorescence, but considerable quantities of unchanged material were always recovered and no new base could be isolated.

When α-piperidinobutan-γ-one hydrochloride in chloroform solution is treated with chloroacetyl chloride (but not acetyl chloride) a *compound*, $C_{18}H_{32}ON_2,2HCl$, is obtained in good yield. The chloroacetyl chloride acts apparently as a dehydrating agent and the structure (III) or (IV) can be assigned to the product (compare Descude, *Ann. Chim. Phys.*, 1903, **29**, 494).

(III.) $HCl,C_5H_{10}N\cdot CH_2\cdot CH_2\cdot CMe{:}CH\cdot CO\cdot CH_2\cdot CH_2\cdot NC_5H_{10},HCl$

(IV.) $HCl,C_5H_{10}N\cdot CH_2\cdot CH_2\cdot CMe{:}CAc\cdot CH_2\cdot NC_5H_{10},HCl$

Piperazine was condensed with phthalobromoethylimide, and from the reaction mixture two compounds were isolated, phthalo-β-piperazinoethylimide and 1 : 4-*di*-(β-*phthalimidoethyl*)*piperazine*.

The corresponding bases were obtained from these two compounds, from the first by acid or alkaline hydrolysis and from the second by the method of Ing and Manske (*loc. cit.*). β-Piperazinoethylamine, a non-crystallising oil, forms a *dipicrate*, but on account of the small yield was not condensed with 4-bromo-6-methoxy-2-methylquinoline. The second base is identical with 1 : 4-di-(β-aminoethyl)piperazine, prepared by Franchimont and Kramer (*Rec. trav. chim.*, 1912, **31**, 40) by the reduction of piperazine-1 : 4-diacetonitrile. Treatment of this base with alcoholic sodium hydroxide yields the corresponding iso*nitrile*.

From the reaction product obtained by heating 1 : 4-di-(β-aminoethyl)piperazine and 4-bromo-6-methoxy-2-methylquinoline, two bases were isolated: (1) 4-(4′-β-aminoethylpiperazinoethylamino)-6-methoxy-2-methylquinoline (II), a non-crystallising oil, forming a *picrate*, a chloroplatinate, and an extremely hygroscopic hydrochloride; (2) a by-product, which is apparently formed from two molecules of the bromoquinoline derivative and one molecule of the piperazino-base and is obtained in better yield if an excess of 4-bromo-6-methoxy-2-methylquinoline is used. The formula

$C_{30}H_{38}O_2N_6,4HCl,5H_2O$ is given to it with reserve, especially as regards the amount of water of crystallisation.

4-Piperazino-6-methoxy-2-methylquinoline (Kermack and Smith, *loc. cit.*) was treated with chloroacetyl chloride to yield 4-(4′-chloroacetylpiperazino)-6-methoxy-2-methylquinoline, with the intention of subsequently replacing the chlorine atom by a basic group. The halogen atom, however, appears to be relatively inactive, as treatment with aqueous or alcoholic ammonia in the cold did not have the desired result.

EXPERIMENTAL.

Phthalo-β-piperidinoethylimide.—A solution of piperidine (6·8 g.) and phthalobromoethylimide (10 g.) in dry toluene (15 c.c.) was refluxed in presence of anhydrous potassium carbonate (11 g.) for 4 hours. The yellow solution was filtered hot, and the residue of potassium bromide washed with toluene. The filtrate, after concentration, deposited large, pale yellow prisms of *phthalo-β-piperidinoethylimide* (yield, 70%), m. p. 91° after recrystallisation from alcohol (Found : N, 11·1. $C_{15}H_{18}O_2N_2$ requires N, 11·1%).

This base is extremely soluble in acetone and chloroform, very soluble in alcohol and benzene, soluble in ether, and sparingly soluble in water. It is also soluble in acetic and dilute mineral acids, and in concentrated sulphuric acid it exhibits a green fluorescence in the arc light.

β-*Piperidinoethylamine.*—Phthalo-β-piperidinoethylimide (7·7 g.) was hydrolysed with hydrazine hydrate (3 g. of a 50% solution) by Ing and Manske's method (*loc. cit.*). The filtrate from the insoluble phthalylhydrazide was diluted with water, and the alcohol distilled off. The solution was made strongly alkaline with sodium hydroxide and the oily base which separated was taken up with ethyl acetate. After this solvent had been removed by distillation, the base, which had a strong ammoniacal odour, remained as a brown viscous oil which decomposed when heated in a vacuum. The *picrate* crystallised from hot water in yellow, serrated, fern-like prisms, m. p. 225° (decomp.) (Found : N, 19·2. $C_7H_{16}N_2,C_6H_3O_7N_3$ requires N, 19·6%).

The base absorbs moisture and carbon dioxide very readily from the air. It is very soluble in acetone, alcohol, chloroform, ethyl acetate, and water, sparingly soluble in benzene and ether, and soluble in mineral acids and acetic acid. It exhibits a fluorescence in the arc light which varies from bluish-green in neutral solvents to blue in some acids. No fluorescence is observable in hydrochloric and nitric acid solutions. The base gives a greenish-yellow insoluble precipitate with phosphomolybdic acid, a white precipitate (decomposes on boiling) with silicotungstic acid, no

precipitate with platinic chloride, a brown precipitate (soluble when hot) with auric chloride, and with mercuric chloride a white precipitate soluble in hydrochloric acid or when hot. The last salt on exposure to sunlight becomes pink and then lilac.

4-β-*Piperidinoethylamino*-6-*methoxy*-2-*methylquinoline* (I).—β-Piperidinoethylamine (2·6 g.) and 4-chloro-6-methoxy-2-methylquinoline (4·2 g.) were kept at 110—120° for 10 hours in presence of a trace of copper–bronze. An extract of the product in boiling water was filtered hot and made alkaline with sodium hydroxide. The oily base which separated solidified on standing. When it was recrystallised from aqueous alcohol, the *hydrate* of 4-β-*piperidinoethylamino*-6-*methoxy*-2-*methylquinoline* separated as light yellow needles, m. p. 73° (Found : loss of water, 10·4. $C_{18}H_{25}ON_3,2H_2O$ requires loss, 10·7%). The crystals when dried in a vacuum desiccator yielded the anhydrous base, m. p. 140—141° (Found : N, 14·1. $C_{18}H_{25}ON_3$ requires N, 14·0%).

This base is extremely soluble in chloroform and readily soluble in alcohol and acetone, but only sparingly soluble in benzene, ether, and water. It is readily soluble in all the common acids to form strongly fluorescing solutions varying from violet in organic acids to bluish-violet in mineral acids, the phenomenon being more marked in dilute solution. In neutral solution the base exhibits a violet fluorescence observable only in the arc light.

α-*Piperidinobutan*-γ-*oneoxime*.—The hydrochloride of α-piperidinobutan-γ-one (19·2 g.), obtained from the condensation of piperidine hydrochloride, acetone, and trioxymethylene by Mannich and Wolfgang's method (*loc. cit.*), was heated on the water-bath with an equivalent of hydroxylamine hydrochloride (7 g.) and a slight excess of sodium hydroxide in 20 c.c. of water for 2—3 hours. Carbon dioxide was then bubbled through the cooled solution until a dense white crystalline precipitate appeared. (If an excess of gas is passed through, the precipitate redissolves.) The *oxime*, recrystallised from alcohol, separated as monoclinic prisms, m. p. 91—92° (Found : N, 16·9. $C_9H_{18}ON_2$ requires N, 16·5%). It is extremely soluble in chloroform, very soluble in acetone, and sparingly soluble in alcohol, benzene, and water, but dissolves readily in these solvents when hot. It is soluble in all the common acids, forming colourless solutions. Its solution in moderately concentrated nitric acid becomes pale green when warmed and nitrogen peroxide is evolved.

α-*Piperidino*-γ-*aminobutane*.—To a boiling solution of the preceding oxime (10 g.) or its hydrochloride (12·4 g.) in 30 c.c. of glacial acetic acid and 150 c.c. of alcohol, zinc dust (8 g.) was added during 20 minutes, and the solution refluxed for 7—8 hours. The yellow-

green solution was then filtered, the solid washed with alcohol, and the filtrate and washings evaporated to dryness on the water-bath. The residue, after being made strongly alkaline with sodium hydroxide, was extracted repeatedly with amyl alcohol. When this extract was distilled α-piperidino-γ-aminobutane was obtained in poor yield as a clear, almost colourless oil with a strong ammoniacal odour; b. p. 106—110°/12 mm. When the amyl-alcoholic solution was extracted with dilute hydrochloric acid (10%), and the aqueous extract evaporated to dryness, both the *monohydrochloride* and the *dihydrochloride* were obtained. After recrystallisation from aqueous alcohol, these salts had m. p. 210° and 241° respectively (Found : Cl, 18·4. $C_9H_{20}N_2$,HCl requires Cl, 18·4%. Found : Cl, 30·2; N, 12·1. $C_9H_{20}N_2$,2HCl requires Cl, 31·0; N, 12·2%). The *dipicrate* crystallised from hot water in sheaves of pale yellow needles, m. p. 241—242° (decomp.) (Found : N, 18·3. $C_9H_{20}N_2$,$2C_6H_3O_7N_3$ requires N, 18·2%).

α-Piperidino-γ-aminobutane is a relatively strong base which absorbs carbon dioxide from the air with avidity. It is soluble in water and alcohol, but is very sparingly soluble in most other organic solvents. It is very readily soluble in most acids, including dilute acetic, hydrochloric, sulphuric and nitric acids.

1 : 4-*Di*-(β-*phthalimidoethyl*)*piperazine*.—When piperazine hexahydrate (9·7 g.; 1 mol.) and phthalobromoethylimide (25·4 g.; 2 mols.) were heated together at 140° for 1—2 hours, the *dihydrobromide* of 1 : 4-*di*-(β-*phthalimidoethyl*)*piperazine* separated in good yield. This sparingly soluble salt crystallised from hot water in almost colourless blades, m. p. 300° (Found : Br, 26·9. $C_{24}H_{24}O_4N_4$,2HBr requires Br, 27·3%).

The *base* was obtained from a solution of its hydrobromide in boiling pyridine on cooling, separating as very small, short needles, m. p. 240° (Found : N, 12·8. $C_{24}H_{24}O_4N_4$ requires N, 12·9%), insoluble in water and acetone. It can be recrystallised from hot benzene and hot alcohol, but not readily from chloroform, in which it is very soluble. It is readily soluble in acetic and sulphuric acids, but it is only soluble in hydrochloric and nitric acids when hot.

1 : 4-*Di*-(β-*aminoethyl*)*piperazine*.—1 : 4-Di-(β-phthalimidoethyl)-piperazine (8·6 g.) was hydrolysed with hydrazine hydrate (4 g. of a 50% solution). A hydrochloric acid solution of the product was concentrated on the water-bath; the *tetrahydrochloride*, which crystallised on cooling, was recrystallised from hot aqueous alcohol and obtained in rhombohedra, m. p. 295° (decomp.) (Found : Cl, 43·0; N, 17·5. $C_8H_{20}N_4$,4HCl requires Cl, 44·6; N, 17·6%).

It was extremely difficult to isolate the base by the above method

owing to the poor yield and to the ease with which the base absorbs moisture and carbon dioxide. Accordingly recourse was made to the method of Franchimont and Kramer (*loc. cit.*). The base, b. p. 250—270°, thus obtained, however, would not crystallise: Franchimont and Kramer state that it solidifies spontaneously and give the m. p. of the hydrate as 68° (decomp.).

Phthalo-β-piperazinoethylimide.—When phthalobromoethylimide (10 g.; 1 mol.) was condensed with piperazine hexahydrate (16 g.; 4 mols.) for 2 hours at 140—150°, the yield of the dihydrobromide of 1 : 4-di-(β-phthalimidoethyl)piperazine (isolated as already described) was 2·4 g., *i.e.*, notwithstanding the excess of piperazine, 25% of the imide had reacted to form the diphthalimidoethyl compound. The filtrate from the insoluble dihydrobromide was made strongly alkaline with sodium hydroxide solution (45%), and the thick oil which separated was extracted with amyl alcohol at least three times. The alcoholic solution was dried over anhydrous potassium carbonate, and the amyl alcohol distilled off almost completely at the ordinary pressure; the last traces were removed in a vacuum on the water-bath. The extremely deliquescent residue consisted of phthalo-β-piperazinoethylimide. The picrate crystallised from hot water in very long, slender, rectangular prisms, m. p. 265° (decomp.). The *dihydrobromide*, precipitated on addition of hydrobromic acid to a moderately concentrated solution of the base in alcohol, crystallised from aqueous alcohol in slender, white prisms, m. p. 243° (decomp.) (Found: Br, 38·0; N, 10·3. $C_{14}H_{17}O_2N_3$,2HBr requires Br, 38·0; N, 10·0%).

The base is readily soluble in water, moderately easily soluble in alcohol, and sparingly soluble in benzene, acetone, ether, and chloroform. It is readily soluble in acetic and mineral acids. Its solution in concentrated sulphuric acid exhibits a green fluorescence in the arc light.

β-Piperazinoethylamine.—(1) Phthalo-β-piperazinoethylimide was treated with hot concentrated caustic soda solution, and the liberated β-piperazinoethylamine extracted with ethyl acetate; the aqueous liquid on acidification deposited phthalic acid. (2) The imide was refluxed with concentrated hydrochloric acid for 1 hour, the solution made alkaline with caustic soda, and the base extracted with amyl alcohol or ethyl acetate.

The *dipicrate*, obtained by mixing alcoholic solutions of the base and picric acid, crystallised from hot water in well-formed tetragonal prisms, m. p. 290° (Found: C, 37·0; H, 3·3; N, 21·0. $C_6H_{15}N_3$,2$C_6H_3O_7N_3$ requires C, 36·8; H, 3·6; N, 21·4%).

This base resembles β-piperidinoethylamine very closely and like it is readily soluble in water (alkaline reaction), alcohol, chloro-

form, and ethyl acetate and very sparingly soluble in benzene and ether. It is readily soluble in dilute acetic and mineral acids. The solution in concentrated sulphuric acid becomes cherry-red when warmed.

4-(4′ - β - *Aminoethylpiperazinoethylamino*) - 6 - *methoxy* - 2 - *methylquinoline* (II).—4-Bromo-6-methoxy-2-methylquinoline (2·5 g.) was heated with a slight excess of 1 : 4-di-(β-aminoethyl)piperazine (2 g.) for 2 hours at 170°, and the brown viscous oil formed was extracted with boiling hydrochloric acid (10%). The extract, after being filtered from the tetrahydrochloride of the diquinolyl base (see below) which slowly separated, was made strongly alkaline with sodium hydroxide and extracted with amyl alcohol. Hydrogen chloride was passed through the amyl-alcoholic extract (dried over anhydrous potassium carbonate); a sticky solid was precipitated which could not be removed by filtration. The acid alcoholic solution was therefore extracted with water until it was almost colourless, and the aqueous solution was evaporated to dryness on the water-bath. The sticky residue was extracted with boiling alcohol, and the solution filtered. The small amount of dark-coloured precipitate which separated on cooling and was obviously impure was removed, and the filtrate reduced to 50 c.c. on the water-bath. The light sand-coloured precipitate, consisting of microscopic needles of the hydrochloride of 4-(4′-β-aminoethylpiperazinoethylamino)-6-methoxy-2-methylquinoline, m. p. 140—150° (decomp.), was filtered off as quickly as possible, washed with alcohol, and immediately put in a desiccator. No analysis of this salt was made owing to its extremely deliquescent nature. The chloroplatinate crystallised from hot water in yellow microscopic needles which darkened at 220° and melted at 273° (decomp.). The *picrate*, crystallised several times from boiling water, was obtained as microscopic yellow crystals, m. p. 175° (Found : C, 38·2; H, 3·6; N, 18·7. $C_{19}H_{29}ON_5,5C_6H_3O_7N_3,3H_2O$ requires C, 38·1; H, 3·2; N, 18·2%).

The base, obtained as a very dark coloured oil when a concentrated solution of the hydrochloride is made strongly alkaline with caustic soda, is readily soluble in ethyl alcohol, soluble in water and chloroform, sparingly soluble in acetone and ether, and insoluble in benzene. It is readily soluble in dilute acetic and hydrochloric acids. The solutions in concentrated sulphuric and nitric acids are dark brown and red respectively; on dilution with water they yield precipitates which dissolve on heating and are reprecipitated on cooling. In acetone the base exhibits a violet fluorescence, in all other neutral solvents a weak greenish fluorescence, and in acid solutions a strong blue fluorescence.

1 : 4-*Di*-(β-6′-*methoxy*-2′-*methyl*-4′-*quinolylaminoethyl*)*piperazine*. —1 : 4-Di-(β-aminoethyl)piperazine (3·4 g.) and 4-bromo-6-methoxy-2-methylquinoline (10 g.) were heated at 160° for 1—2 hours, and the clear, brown, glassy product extracted with boiling hydrochloric acid (10%). The filtered solution on cooling deposited a cream-white gelatinous *tetrahydrochloride*, which crystallised from hot water in white microscopic needles, m. p. above 310° (Found : Cl, 18·9; N, 11·4. $C_{30}H_{38}O_2N_6,4HCl,5H_2O$ requires Cl, 18·9; N, 11·2%). The base obtained from this by means of caustic soda was a buff-coloured sticky solid which darkened on exposure to the air and also when heated; it did not melt below 300°. The base is insoluble in benzene and ether, sparingly soluble in water and acetone, and soluble in chloroform, ethyl alcohol, and pyridine. It is sparingly soluble in dilute hydrochloric, sulphuric and nitric acids but readily dissolves on heating and is reprecipitated on cooling, except from nitric acid. It is more readily soluble in acetic acid. A violet fluorescence is exhibited by its solution in dilute hydrochloric acid. In all other solutions, alkaline, neutral and acid, it exhibits a greenish fluorescence observable in the arc light and in daylight in the case of the ethyl-alcoholic solution. The solutions in concentrated sulphuric and nitric acids are dark brown and yellow respectively; only the former exhibits a green fluorescence.

4-(4′-*Chloroacetylpiperazino*)-6-*methoxy*-2-*methylquinoline*.—When a slight excess of chloroacetyl chloride (1·3 g.) was added drop by drop to a solution of 4-piperazino-6-methoxy-2-methylquinoline (3 g.) in chloroform (15 c.c.), the solution darkened and became very hot. A yellow solid began to separate on cooling and after 1 hour this was collected, washed with chloroform, and crystallised from hot water, the *hydrochloride* of 4-(4′-chloroacetylpiperazino)-6-methoxy-2-methylquinoline being obtained as pale yellow, slender prisms, m. p. 256° (decomp.) (Found : free Cl, 10·0; total Cl, 19·8. $C_{17}H_{20}O_2N_3Cl,HCl$ requires free Cl, 9·6; total Cl, 19·2%). The base was obtained from it as a sticky solid. The *picrate* was not very stable and separated from hot water as a yellow powder, m. p. 155—160° (Found : N, 16·1. $C_{17}H_{20}O_2N_3Cl,2C_6H_3O_7N_3$ requires N, 15·9%).

The base is sparingly soluble in most solvents, but is more readily soluble in alcohol. It is soluble in dilute acetic acid, but its hydrochloride, sulphate and nitrate are only soluble in hot water, from which they separate on cooling. The solution in concentrated nitric acid is brownish-red, and that in concentrated sulphuric acid yellow with a strong greenish-blue fluorescence.

1 : 4-*Di*-(β-iso*cyanoethyl*)*piperazine*.—In the course of a prepar-

ation of 1 : 4-di-(β-aminoethyl)piperazine by a modification of Franchimont and Kramer's method (*loc. cit.*) in which an attempt was made to extract the base with chloroform from the strongly alkaline alcoholic solution, sodium chloride separated when the mixture, which had become warm, was shaken. The salt was removed, the filtrate evaporated to dryness, and the solid residue extracted two or three times with boiling alcohol. From the hot filtered extract, 1 : 4-*di*-(β-iso*cyanoethyl*)*piperazine* separated in stellate clumps of colourless needles, m. p. 280° (Found : N, 29·0. $C_{10}H_{16}N_4$ requires N, 29·2%).

The *dihydrochloride* separated from a hot aqueous-alcoholic solution of the base, on addition of concentrated hydrochloric acid, as colourless needles, m. p. 277° (decomp.) (Found : Cl, 27·1. $C_{10}H_{16}N_4$,2HCl requires Cl, 26·8%).

The base is readily soluble in water, sparingly soluble in most organic solvents, and easily soluble in dilute acetic and mineral acids. It dissolves in moderately concentrated sulphuric acid with effervescence, giving a solution which on warming develops a greenish fluorescence visible in the arc light.

αη-Dipiperidino-γ-keto-ε-methyl-Δ^{δ}*-heptene* (III) [or *αε-Dipiperidino-β-acetyl-γ-methyl-*Δ^{β}*-pentene* (IV)].—The hydrochloride of α-piperidinobutan-γ-one (2 g.) was refluxed with chloroacetyl chloride (1·2 g.) in chloroform for 1 hour. The white crystalline solid that separated on dilution with acetone was collected after 1 hour, washed with acetone, and recrystallised from chloroform–acetone; a *dihydrochloride* then separated in plates and prisms, m. p. 182° (Found : C, 59·2; H, 8·8; N, 7·7; Cl, 19·3. $C_{18}H_{32}ON_2$,2HCl requires C, 59·1; H, 8·8; N, 7·7; Cl, 19·4%), soluble in water, alcohol, and chloroform but insoluble in benzene, ether, and acetone. The salt dissolved with effervescence in concentrated sulphuric acid, hydrogen chloride being evolved. It was rapidly attacked by concentrated nitric acid on warming, brown fumes being evolved. An aqueous solution decolorised bromine water.

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