CLXXVI.—*Attempts to find New Antimalarials. Part V. Some Piperidino- and Piperazino-derivatives of Quinoline.*

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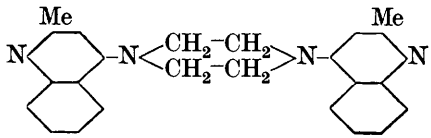
4-CHLORO-2-METHYLQUINOLINE and its derivatives, which are readily obtained by the treatment with phosphoryl chloride and phosphorus pentachloride, of the corresponding 4-hydroxy-2-methylquinolines, prepared according to the method of Conrad and Limpach (*Ber.*, 1887, **20**, 947) by the condensation of ethyl acetoacetate with the requisite derivatives of aniline, condense readily with various primary and secondary amines. For instance, 4-piperidino-2-methylquinoline and 4-piperidino-6-methoxy-2-methylquinoline were obtained from piperidine and 4-chloro-2-methylquinoline and 4-chloro-6-methoxy-2-methylquinoline, respectively, at 180°.

When 4-chloro-2-methylquinoline was heated at 140° with a considerable excess of piperazine hexahydrate for 2—3 hours, a white solid separated, from which *4-piperazino-2-methylquinoline* was

(I.) 

isolated, besides a small quantity of *1 : 4-di-2′-methyl-4′-quinolylpiperazine* (I). When relatively less piperazine was used, a corre-

spondingly larger quantity of (I) was formed. Under similar conditions 4-chloro-6-methoxy-2-methylquinoline condensed with piperazine hydrate with the formation of *4-piperazino-6-methoxy-2-methylquinoline* and 1 : 4-*di*-6′-*methoxy*-2′-*methyl*-4′-*quinolylpiperazine*.

The preparation of mono-*N*-substituted derivatives of piperazine usually presents considerable difficulty, and, with the simpler reactive halides, the disubstituted compound is usually obtained exclusively, or in preponderating amount (compare Moore, Boyle, and Thorn, J., 1929, 39). *p*-Chloronitrobenzene is said to yield the monosubstituted derivative readily; it is therefore of some interest that 4-chloro-2-methylquinoline and its derivatives can without difficulty be made to react with piperazine so as to yield monosubstituted products.

Certain of the above compounds have been tested in respect of their antimalarial action, and the results of these biological experiments will be published elsewhere. As in other papers of this series, the numbers, given in parentheses, after certain compounds are to facilitate reference to the biological tests.

EXPERIMENTAL.

4-Piperidino-2-methylquinoline(Km. 10).—Equimolecular quantities of piperidine (2·5 g.) and 4-chloro-2-methylquinoline (5·3 g.) were heated together at 180° under reflux for 3—4 hours. The purple solid which separated was extracted with dilute hydrochloric acid (3%), and the solution made alkaline with caustic soda. The dark red oil which separated was subjected to steam distillation to remove any excess of piperidine or chloroquinaldine. The residue was dissolved in ether, dried over potassium carbonate, and recovered as a dark oil. This, on distillation in a vacuum, gave a somewhat viscous, light yellow oil, b. p. 207°/12 mm., which would not crystallise. The *picrate*, obtained by means of a cold saturated solution of picric acid in benzene, crystallised from alcohol in yellow needles, m. p. 182° (Found : N, 15·4. $C_{15}H_{18}N_2,C_6H_3O_7N_3$ requires N, 15·4%).

The *chloroaurate*, obtained by mixing a solution of the hydrochloride, containing an excess of hydrochloric acid, with an aqueous solution of gold chloride, separated as a yellow-brown precipitate, insoluble in hot water, but easily soluble in alcohol, from which it crystallised in dark red, almost rectangular, rhombic plates, m. p. 174° (Found : Cl, 24·9. $C_{15}H_{19}N_2AuCl_4$ requires Cl, 25·1%).

4-Piperidino-2-methylquinoline is fairly readily soluble in acids, although concentrated nitric acid, when added to a solution of the hydrochloride, precipitates yellow needles, m. p. 192° (decomp.), presumably the nitrate, which is sparingly soluble in cold, and rather

more soluble in hot water. The hydrochloride could not be obtained as a solid by passing dry hydrogen chloride into a benzene solution of the base. The base is somewhat soluble in most organic solvents, but is sparingly soluble in cold water. Its solution in concentrated sulphuric acid exhibits a very faint bluish fluorescence when illuminated by the arc lamp. Very little darkening of the solution is observed on warming (compare the behaviour of the methoxy-derivative).

4-*Piperidino*-6-*methoxy*-2-*methylquinoline*(Km. 12).—When equimolecular quantities of 4-chloro-6-methoxy-2-methylquinoline (6·2 g.) and piperidine (2·5 g.) were heated together under the conditions adopted in the preparation of 4-piperidino-2-methylquinoline, and the purple solid formed was extracted and purified as above, a clear yellow, viscous oil was finally obtained, b. p. 220°/12 mm. The base, which could not be induced to crystallise, exhibited a strong greenish fluorescence, and in its properties closely resembled 4-piperidino-2-methylquinoline. With concentrated sulphuric acid, however, it gave a strong blue fluorescence which disappeared on dilution. On warming, the solution in concentrated acid developed an orange-brown colour, the blue fluorescence becoming less marked. The *picrate*, obtained as before, crystallised from alcohol in clusters of long yellow prisms, m. p. 191° (Found : N, 14·2. $C_{16}H_{20}ON_2,C_6H_3O_7N_3$ requires N, 14·4%).

The *chloroaurate*, obtained as above, crystallised from alcohol, in which it was readily soluble, in red rhombic plates, m. p. 156° (Found : Cl, 24·1. $C_{16}H_{27}ON_2AuCl_4$ requires Cl, 23·8%).

4-*Piperazino*-2-*methylquinoline*(Km. 13).—4-Chloro-2-methylquinoline and a large excess of piperazine hexahydrate (15 g.) were heated under reflux for 3—4 hours in an oil-bath at 140°. The white solid which separated was extracted with dilute hydrochloric acid (3%), and the solution filtered, leaving behind a small quantity of the white hydrochloride of the corresponding diquinolylpiperazine. The filtrate, when made alkaline with caustic soda, deposited a yellow oil, which slowly crystallised. On recrystallisation from hot water (in which solvent there is a marked tendency to supersaturation), large, yellow-brown, rhombic plates of the *hydrate* were obtained, m. p. 60°. These, on drying in a desiccator, lost 24·4% of their weight, corresponding to four molecules of water of crystallisation (24·1%), and yielded the anhydrous *base*, m. p. 103° (Found : C, 74·2; H, 7·5; N, 18·3. $C_{14}H_{17}N_3$ requires C, 74·0; H, 7·5; N, 18·5%).

This compound is very soluble in alcohol, in dilute mineral, and acetic acids, soluble in ether, but very slightly soluble in benzene and in cold water; it dissolves quite readily, however, in hot water. When treated with concentrated sulphuric acid in the cold, the base

dissolves only with difficulty, yielding a clear solution; this exhibits in the arc lamp a very faint blue fluorescence which disappears on dilution. Neither the solution in concentrated sulphuric acid nor that in concentrated nitric acid exhibits any characteristic colour changes on warming (compare the methoxy-derivative).

4-*Piperazino*-6-*methoxy*-2-*methylquinoline*(Km. 9).—4-Chloro-6-methoxy-2-methylquinoline (5 g.) was treated with piperazine hydrate (15 g.) under the same conditions as recorded in the preparation of 4-piperazino-2-methylquinoline. In this case, none of the corresponding diquinolylpiperazine was formed, the compound being obtained in a very pure form by diluting the condensation product with 3—4 times its volume of water and allowing the hot solution to stand; crystals of the *hydrate* soon separated as pink pyramids which, after recrystallisation from hot water, melted at 55°. These crystals, when dried in a desiccator, lost 17·9% of their weight, corresponding to three molecules of water of crystallisation (17·4%), and yielded the anhydrous *base*, m. p. 113° (Found: C, 69·7; H, 7·5; N, 16·0. $C_{15}H_{19}ON_3$ requires C, 70·0; H, 7·4; N, 16·3%).

This compound resembles 4-piperazino-2-methylquinoline in solubility. Its solution in cold concentrated sulphuric acid, however, exhibits a very strong greenish-blue fluorescence which disappears on dilution. When the concentrated acid solution is warmed, a reddish-brown colour develops and the fluorescence, although less marked, is retained. When treated with hot concentrated nitric acid, this compound develops a red colour.

4′-*Acetyl*-4-*piperazino*-2-*methylquinoline*.—4-Piperazino-2-methylquinoline was heated with acetic anhydride for 2—3 hours on the water-bath, the product warmed with water, and the solution made alkaline with caustic soda. The oily base obtained, which solidified, crystallised from hot water in large, brown, rhombic plates of the *hydrate*, m. p. 70°. When dried in a desiccator, these crystals lost 16·9% of their weight, equivalent to three molecules of water of hydration (16·7%), and yielded the anhydrous base, m. p. 122°.

This acetyl derivative resembles the parent base in solubility and in exhibiting a very faint blue fluorescence in concentrated sulphuric acid solution, by the arc light. In addition, its alcoholic solution exhibits a slight greenish fluorescence.

4′-*Acetyl*-4-*piperazino*-6-*methoxy*-2-*methylquinoline*(Km. 11).—This compound was prepared in a similar manner to the preceding one. The *hydrate* was obtained from hot water in light brown needles, m. p. 86°, which, when dried in a desiccator, lost 10·9% of their weight, equivalent to two molecules of water of crystallisation (10·7%), and yielded the anhydrous base, m. p. 154°.

Here again, the properties of this acetyl derivative resemble closely

those of the parent base. The distinctive colour reactions shown by 4-piperazino-6-methoxy-2-methylquinoline when warmed with concentrated nitric or sulphuric acid, as well as the fluorescences exhibited, were slightly more marked in this case. In addition, its solution in alcohol exhibits a slight greenish fluorescence.

1 : 4-*Di*-2′-*methyl*-4′-*quinolylpiperazine*(Km. 14).—4-Chloro-2-methylquinoline (3·5 g.) was condensed with piperazine hydrate (2 g.) under the same conditions as those adopted in the preparation of the monoquinolylpiperazines. The white solid which had separated after 2—3 hours was treated with cold hydrochloric acid (3%), which removed any unchanged materials, and was then dissolved in a large quantity of boiling water; when this solution was made alkaline with sodium hydroxide, the *base* was obtained as a voluminous white precipitate. It was practically insoluble in most organic solvents, but crystallised from hot pyridine in white rhombohedra, m. p. 314° (Found : C, 78·1; H, 6·7. $C_{24}H_{24}N_4$ requires C, 78·3; H, 6·5%).

This compound is fairly readily soluble in acetic and lactic acids, but forms sparingly soluble salts with dilute hydrochloric, nitric and sulphuric acids. It dissolves, however, in concentrated nitric acid to give a light yellow solution, which darkens only slightly on warming (compare the methoxy-derivative). With concentrated sulphuric acid, it yields a clear solution which exhibits a very faint violet fluorescence in the arc light. When warmed, this solution rapidly turns green, changing to greenish-brown and finally dirty brown.

1 : 4-*Di*-6′-*methoxy*-2′-*methyl*-4′-*quinolylpiperazine*(Km. 15).—This compound was obtained when 4-piperazino-6-methoxy-2-methylquinoline (2·5 g.) and 4-chloro-6-methoxy-2-methylquinoline (2 g.) were heated together at 140° for 2—3 hours, or when 4-chloro-6-methoxy-2-methylquinoline (4 g.) and piperazine hydrate (2 g.) were heated under the same conditions as in the preparation of the last compound. In either case, the base was obtained as a white solid when a hot aqueous solution of the buff-coloured hydrochloride was made alkaline with caustic soda, the hydrochloride being readily isolated from the reaction mixture on account of its insolubility. The *base* crystallised from hot pyridine in pink rhombohedra, m. p. 286° (Found : C, 72·5; H, 6·5. $C_{26}H_{28}O_2N_4$ requires C, 72·9; H, 6·5%).

In its sparing solubility in most solvents it resembles very closely 1 : 4-di-2′-methyl-4′-quinolylpiperazine, already described. When its solution in concentrated nitric acid is warmed, however, a dark red coloration quickly develops. Its pale yellow solution in concentrated sulphuric acid exhibits a strong green fluorescence which

disappears on warming, the solution becoming successively pale violet, dark violet, and finally reddish-purple.

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