CCCIII.—*Derivatives of 4-Methyl-, 4:6-, 4:7-, and 4:8-Dimethyl-2-hydroxyquinolines.*

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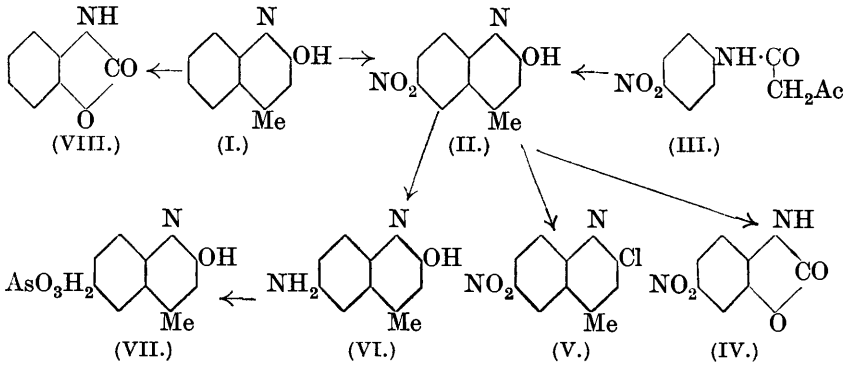
THE substance plasmoquine recently introduced into medicine as a valuable drug for the treatment of malaria has stimulated work in this field of inquiry (Barger and Robinson and collaborators, J., 1929, 2947; this vol., p. 1356; Slater, this vol., p. 1209). In the present investigation certain 2-hydroxyquinolines were taken as

starting points, the object in view being partly the preparation of aminotetrahydroquinolines for biological examination in malaria. Although this object has not yet been realised, an account is given of the work completed.

On nitration 2-hydroxy-4-methylquinoline (I) yields 6-*nitro*-2-*hydroxy*-4-*methylquinoline* (II), the constitution of which follows from its synthesis from *p*-nitroacetoacetanilide (III) by Ewins and King's modification (J., 1913, **103**, 104) of Knorr's method (*Ber.*, 1884, **17**, 542); the conversion is difficult on account of hydrolysis



to *p*-nitroaniline (compare acetoacet-α-naphthalide; Gibson, Hariharan, Menon, and Simonsen, J., 1926, 2249).

Oxidation of 2-hydroxy-4-methylquinoline and 6-nitro-2-hydroxy-4-methylquinoline with hot neutral aqueous potassium permanganate (compare Kaufmann and de Petherd, *Ber.*, 1917, **50**, 336) yields benzoxazolone (VIII) and its 5-nitro-derivative (IV) respectively. Hence the oxidation of derivatives of 4-methylcarbostyril follows a novel course, since only derivatives of anthranilic acid (Kaufmann and de Petherd, *loc. cit.*) and of indole (D.R.-P. 292394) have been obtained from other carbostyrils.

When 6-nitro-2-hydroxy-4-methylquinoline (II) is reduced with stannous chloride and hydrochloric acid, 6-*amino*-2-*hydroxy*-4-*methylquinoline* (VI) is obtained. Attempts to prepare the tetrahydro-derivative of this by the action of sodium and alcohol on the base or on (II) have not been successful. (The same applies to the other nitro- and amino-derivatives described.) Even the action of platinum oxide and hydrogen on 2-*chloro*-6-*nitro*-4-*methylquinoline* (V; Späth, *Ber.*, 1924, **57**, 1243) failed to produce the desired compound, although chloroquinolines are suitable materials for the preparation of aminotetrahydroquinolines (compare Gibson, Hariharan, Menon, and Simonsen, *loc. cit.*).

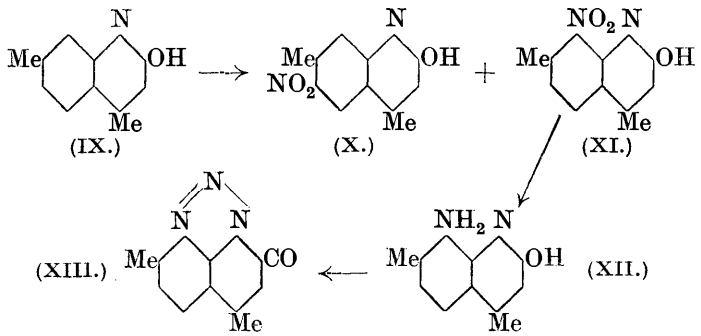
When 6-amino-2-hydroxy-4-methylquinoline is submitted to the

Bart–Schmidt reaction, 2-*hydroxy*-4-*methylquinoline*-6-*arsinic acid* (VII) is obtained.

2-Hydroxy-4 : 6-dimethylquinoline on nitration furnishes a mono-nitro-compound. This is presumably the 3-*nitro*-derivative, because the base obtainable from the 8-nitro-compound by reduction would give with nitrous acid a diazoimide incapable of coupling with alkaline β-naphthol, whereas the base actually obtained from the nitro-compound diazotises normally. Furthermore, carbostyril is nitrated fully to give 3 : 6 : 8-trinitrocarbostyril (Kaufmann and de Petherd, *loc. cit.*), and as the 6-position in 2-hydroxy-4 : 6-dimethylquinoline is occupied, the 3-position is the only one available.

3-*Amino*-2-*hydroxy*-4 : 6-*dimethylquinoline* failed to furnish an arsinic acid.

2-Hydroxy-4 : 7-dimethylquinoline (IX) gives on nitration a mixture of the 6-*nitro*- and the 8-*nitro*-derivative (X and XI) The latter on reduction yields 8-*amino*-2-*hydroxy*-4 : 7-*dimethylquinoline* (XII) : from this on treatment with nitrous acid an insoluble diazoimide (XIII) is obtained which does not couple with sodium β-naphthoxide. On oxidation the two nitro-derivatives give 5-nitro- and 3-*nitro*-4-*methylbenzoxazolone* respectively.



6-*Amino*-2-*hydroxy*-4 : 7-*dimethylquinoline* gives 2-*hydroxy*-4 : 7-*dimethylquinoline*-6-*arsinic acid* normally but in poor yield.

2-Hydroxy-4 : 8-dimethylquinoline on nitration gives only one nitro-compound, presumably the 6-*nitro*-derivative, which yields 5-*nitro*-3-*methylbenzoxazolone* on oxidation. With phosphorus pentachloride, 6-nitro-2-hydroxy-4 : 8-dimethylquinoline furnishes 2-*chloro*-6-*nitro*-4 : 8-*dimethylquinoline*, and on reduction it gives 6-*amino*-2-*hydroxy*-4 : 8-*dimethylquinoline* : from this, in the Bart–Schmidt reaction, 2-*hydroxy*-4 : 8-*dimethylquinoline*-6-*arsinic acid* is obtained.

Biological Examination.—The results of tests made with the preceding quinoline-6-arsinic acids on mice infected with *T. equi-*

perdum are in the following table, the symbols having the usual significance :

Quinolinearsinic acid.		*T*.	*C*.	*C*/*T*.
2-Hydroxy-4-methyl	(*o*)	>5·0	>2·0	—
	(*i*)	0·5	0·5	1·0
2-Hydroxy-4 : 7-dimethyl	(*o*)	5·0	2·0	1/2·5
	(*i*)	0·5	0·5	1·0
2-Hydroxy-4 : 8-dimethyl	(*o*)	>5·0	2·0	>1/2·5
	(*i*)	0·25	>0·25	—

EXPERIMENTAL.

Derivatives of 2-Hydroxy-4-methylquinoline.—*6-Nitro-2-hydroxy-4-methylquinoline* (II). To a solution of 2-hydroxy-4-methylquinoline (10·6 g.) in concentrated sulphuric acid (50 c.c.) at 0° was added with mechanical stirring a mixture of nitric acid (*d* 1·42; 4·9 c.c.) and concentrated sulphuric acid (5·0 c.c.); after standing for 2 hours at room temperature, the mixture was poured into ice-water. The *nitro*-compound, obtained in theoretical yield, was insoluble in alcohol and water, and sparingly soluble in glacial acetic acid (charcoal), from which it crystallised in minute colourless rods, m. p. 340° (decomp.) (Found in material dried at 100°: N, 13·8. $C_{10}H_8O_3N_2$ requires N, 13·7%).

The same substance (mixed m. p.) was obtained by adding 1 g. of *p*-nitroacetoacetanilide (D.R.-P. 246286) very slowly to concentrated sulphuric acid (1 c.c.), heating the mixture on the water-bath for 10 minutes, and pouring it into water.

Oxidation of 6-nitro-2-hydroxy-4-methylquinoline. A solution and suspension of 2 g. of the nitro-compound in boiling water (2 l.) was treated with mechanical stirring with 1% potassium permanganate solution (300 c.c.). After 2 hours, the manganese dioxide was removed, the solution concentrated to about 40 c.c., and hydrochloric acid added until the reaction was acid to Congo-paper. The 5-nitrobenzoxazolone obtained crystallised from water (charcoal) in long, fine, pale yellow needles (0·3 g.), m. p. 242° (Found in material dried at 100°: N, 15·8. Calc.: N, 15·6%).

This compound is identical with a specimen prepared from *o*-aminophenol by conversion into benzoxazolone and subsequent nitration according to Mr. F. J. Paxon, who used nitric acid (*d* 1·42) in sulphuric acid at 0° (private communication). Chelmicki (*J. pr. Chem.*, 1890, **42**, 441) gives m. p. 241°, whereas Bender (*Ber.*, 1886, **19**, 2271) and Hewitt and King (J., 1926, 823) record m. p. 256° and 255° respectively. Samples of 5-nitrobenzoxazolone prepared by the last two methods and also by the action of carbonyl chloride on 5-nitro-2-aminophenol were found to melt, alone or mixed, at 242°.

2-Chloro-6-nitro-4-methylquinoline (V) was prepared by refluxing

6-nitro-2-hydroxy-4-methylquinoline (6·0 g.) with phosphorus pentachloride (16·2 g.) and phosphorus oxychloride (8 c.c.) for 1 hour at 160°. After basification, the chloro-compound was obtained partly by filtration and partly by extraction with benzene. It crystallised from benzene in long, pale brown, prismatic needles, m. p. 207° (Found in dried material: N, 12·5; Cl, 16·2. $C_{10}H_7O_2N_2Cl$ requires N, 12·6; Cl, 15·9%). It was fairly readily soluble in benzene and chloroform, sparingly soluble in ether and absolute alcohol, crystallising in colourless needles from the latter, but insoluble in boiling water.

6-*Amino*-2-*hydroxy*-4-*methylquinoline* (VI) was prepared by heating the corresponding nitro-derivative (6·12 g.) with stannous chloride (20·34 g.) in concentrated hydrochloric acid (60 c.c.) on the water-bath for ½ hour. The stannichloride obtained, after removal of tin by hydrogen sulphide, gave the base in 63·5% yield. This crystallised from water or alcohol, in which it was very sparingly soluble, in pale yellow needles, m. p. 315° (Found: N, 16·2. $C_{10}H_{10}ON_2$ requires N, 16·1%). The *hydrochloride* crystallised from 2*N*-hydrochloric acid, in which it was moderately easily soluble, in colourless needles, which did not melt at 310° (Found: N, 13·4; Cl, 16·7. $C_{10}H_{10}ON_2,HCl$ requires N, 13·3; Cl, 16·9%). It was soluble in hot water, giving a solution faintly acid to Congo-red. The *acetamido*-derivative crystallised from dilute alcohol in colourless needles, m. p. 314° (Found: N, 13·0. $C_{12}H_{12}O_2N_2$ requires N, 12·9%).

2-*Hydroxy*-4-*methylquinoline*-6-*arsinic acid* (VII) was prepared by the Bart–Schmidt reaction from the corresponding aminoquinoline (yield, 18%). It crystallised from 2*N*-acetic acid, in which it was sparingly soluble, in colourless needles containing $1H_2O$, which did not melt at 320° (Found in air-dried material: loss at 100°, 6·2. $C_{10}H_{10}O_4NAs,H_2O$ requires H_2O, 6·0%. Found in dried material: As, 26·5; N, 5·2. $C_{10}H_{10}O_4NAs$ requires As, 26·5; N, 4·9%). The arsinic acid is very sparingly soluble in boiling water and almost insoluble in hot alcohol. The magnesium and calcium salts are micro-crystalline and the barium salt forms long fine needles.

Derivatives of 2-*Hydroxy*-4 : 6-*dimethylquinoline*.—The following compounds were prepared by the methods described above. 3-*Nitro*-2-*hydroxy*-4 : 6-*dimethylquinoline* (21·0 g.) was prepared from 2-hydroxy-4 : 6-dimethylquinoline (20·8 g.). It crystallised from glacial acetic acid, in which it was moderately easily soluble, in prismatic needles, m. p. 294° (Found: N, 13·0. $C_{11}H_{10}O_3N_2$ requires N, 12·8%). It was very sparingly soluble in alcohol and insoluble in boiling water.

2-*Chloro*-3-*nitro*-4 : 6-*dimethylquinoline* (yield, 32·4%) crystallised

from benzene, in which it was readily soluble, in yellow rectangular plates, m. p. 157° (Found in material dried at 100° : N, 11·8; Cl, 15·1. $C_{11}H_9O_2N_2Cl$ requires N, 11·8; Cl, 15·1%). It was readily soluble in chloroform and ether, moderately easily soluble in alcohol, and almost insoluble in boiling water.

3-*Amino*-2-*hydroxy*-4 : 6-*dimethylquinoline* (yield, 45·1%) crystallised from 50% alcohol in colourless square plates, m. p. 264° (Found : N, 14·6. $C_{11}H_{12}ON_2$ requires N, 14·9%), sparingly soluble in alcohol and water. The *hydrochloride* crystallised from 2*N*-hydrochloric acid in long yellow needles, m. p. 240° (Found : N, 11·8; Cl, 15·5. $C_{11}H_{12}ON_2,HCl$ requires N, 12·4; Cl, 15·8%) : it dissociated in water, the base being precipitated. The *acetamido*-derivative crystallised from 2*N*-acetic acid in thick prisms, m. p. 270° (decomp.) (Found : N, 12·2. $C_{13}H_{14}O_2N_2$ requires N, 12·2%).

Derivatives of 2-*Hydroxy*-4 : 7-*dimethylquinoline*.—The nitration of 2-hydroxy-4 : 7-dimethylquinoline (31·2 g.) yielded a mixture of 6-nitro- (14·4 g.) and 8-nitro-2-hydroxy-4 : 7-dimethylquinoline (8·7 g.).

6-*Nitro*-2-*hydroxy*-4 : 7-*dimethylquinoline* (X) crystallised from glacial acetic acid (charcoal), in which it was very sparingly soluble, in colourless, elongated, rhomboidal leaflets, darkening from *ca.* 280° with partial decomposition (Found : N, 12·7. $C_{11}H_{10}O_3N_2$ requires N, 12·8%). It was insoluble in alcohol and boiling water. On oxidation with 1% permanganate solution, 5-nitro-4-methylbenzoxazolone (0·3 g. from 2 g.), m. p. 233°, was obtained as fine, pale yellow needles, very sparingly soluble in hot water (Found : N, 14·9. Calc. : N, 14·4%). Benda and Sievers (U.S.P. 1539798) give m. p. 227—228°.

8-*Nitro*-2-*hydroxy*-4 : 7-*dimethylquinoline* (XI) crystallised from a mixture of equal parts of alcohol and glacial acetic acid (charcoal) in large, yellow, rectangular plates, m. p. 226° (Found : N, 12·5%). It was readily soluble in hot acetic acid but only sparingly soluble in alcohol.

3-*Nitro*-4-*methylbenzoxazolone* (0·3 g.) was obtained on oxidation of the above nitro-compound (2 g., 0·7 g. of which was recovered unchanged). It crystallised from 95% alcohol in brown, boat-shaped plates, m. p. 236° with previous softening (Found : N, 14·8. $C_8H_6O_4N_2$ requires N, 14·4%), very sparingly soluble in water.

2-*Chloro*-6-*nitro*-4 : 7-*dimethylquinoline* crystallised from absolute alcohol, in which it was very sparingly soluble, in long, colourless, silky needles, m. p. 164° (Found in material dried at 100° : N, 11·4; Cl, 15·1. $C_{11}H_9O_2N_2Cl$ requires N, 11·8; Cl, 15·1%). It was readily soluble in benzene (crystallising in plates) and chloroform, but sparingly soluble in ether.

6-*Amino*-2-*hydroxy*-4:7-*dimethylquinoline* (45% yield) crystallised from absolute alcohol in yellow rectangular prisms, which blackened at about 320° (Found: N, 14·9. $C_{11}H_{12}ON_2$ requires N, 14·9%). It was moderately easily soluble in alcohol, giving a blue fluorescent solution, but insoluble in boiling water. The *hydrochloride* crystallised from 2*N*-hydrochloric acid in long, colourless, rectangular prismatic needles, which became yellow on drying at 100° and did not melt at 320°. It was soluble in cold water, giving a solution faintly acid to Congo-paper (Found: N, 12·5; Cl, 15·8. $C_{11}H_{12}ON_2$,HCl requires N, 12·4; Cl, 15·8%). The *acetamido*-derivative crystallised from boiling water (containing two drops of acetic acid), in which it was very sparingly soluble, in long colourless needles, unmelted at 320° (Found: N, 12·0. $C_{13}H_{14}O_2N_2$ requires N, 12·2%).

2-*Hydroxy*-4:7-*dimethylquinoline*-6-*arsinic acid*, prepared by the Bart–Schmidt reaction from the above amino-compound (yield, 4·1%), crystallised from 50% acetic acid in colourless boat-shaped needles, unmelted at 320° (Found: As, 25·6; N, 4·7. $C_{11}H_{12}O_4NAs$ requires As, 25·2; N, 4·7%). It was moderately easily soluble in boiling water, less soluble in acetic acid, and insoluble in alcohol. The magnesium salt crystallised in hair-like needles, the calcium salt in fine needles (in stronger solutions it tended to gelatinise), and the barium salt in minute rods.

2-*Chloro*-8-*nitro*-4:7-*dimethylquinoline* crystallised from 95% alcohol in colourless prismatic needles, m. p. 156° (Found: N, 12·1; Cl, 15·0. $C_{11}H_9O_2N_2Cl$ requires N, 11·8; Cl, 15·1%). It was very soluble in benzene and chloroform, sparingly soluble in ether, and insoluble in water.

8-*Amino*-2-*hydroxy*-4:7-*dimethylquinoline* (XII) (50·5% yield) crystallised from 95% alcohol in colourless, elongated, rhomboidal plates, m. p. 255° (Found: N, 15·2. $C_{11}H_{12}ON_2$ requires N, 14·9%), insoluble in water. The *hydrochloride* crystallised from 2*N*-hydrochloric acid in colourless hydrated needles, m. p. 257° (efferv.) (Found in air-dried material: loss at 100°, 21·0.

$$C_{11}H_{12}ON_2,HCl,H_2O$$

requires HCl + H_2O, 22·1%): it dissociated on addition of water. The *acetamido*-derivative crystallised from 95% alcohol in broad irregular plates containing $2H_2O$, m. p. 266° (Found in air-dried material: loss at 100°, 13·7. $C_{13}H_{14}O_2N_2,2H_2O$ requires H_2O, 13·5%. Found in dried material: N, 12·0. $C_{13}H_{14}O_2N_2$ requires N, 12·2%).

Derivatives of 2-*Hydroxy*-4:8-*dimethylquinoline*.—6-*Nitro*-2-*hydroxy*-4:8-*dimethylquinoline* (81% yield) crystallised from glacial acetic acid, in which it was sparingly soluble, in colourless needles,

m. p. 310° (decomp.) (Found : N, 13·0. $C_{11}H_{10}O_3N_2$ requires N, 12·8%). It was insoluble in boiling water or alcohol.

5-*Nitro*-3-*methylbenzoxazolone*, obtained on oxidation of the above nitroquinoline (0·2 g. from 2 g.), crystallised from water, in which it was very sparingly soluble, in long, pale yellow needles, m. p. 249° (Found : N, 14·4. $C_8H_6O_4N_2$ requires N, 14·4%).

2-*Chloro*-6-*nitro*-4 : 8-*dimethylquinoline* (31% yield) crystallised from benzene in pale yellow needles, m. p. 195° (Found : N, 12·1; Cl, 15·3. $C_{11}H_9O_2N_2Cl$ requires N, 11·8; Cl, 15·1%). It was readily soluble in benzene and chloroform but sparingly soluble in alcohol and ether.

6-*Amino*-2-*hydroxy*-4 : 8-*dimethylquinoline* (54·4% yield) crystallised from water (1 part in 100 parts, boiling) in long, pale yellow, rectangular plates, m. p. 288° (Found : N, 15·1. $C_{11}H_{12}ON_2$ requires N, 14·9%). It was moderately easily soluble in absolute alcohol, the solution showing a blue fluorescence. The *hydrochloride* crystallised from 2*N*-hydrochloric acid, in which it was moderately easily soluble, in yellow needles, unmelted at 320° (Found : N, 12·8; Cl, 15·6. $C_{11}H_{12}ON_2,HCl$ requires N, 12·4; Cl, 15·8%). It was soluble in water, giving a solution faintly acid to Congo-paper, and diazotised normally. The *acetamido*-derivative crystallised from dilute alcohol in square plates, unmelted at 320° (Found : N, 12·1. $C_{13}H_{14}O_2N_2$ requires N, 12·2%).

2-*Hydroxy*-4 : 8-*dimethylquinoline*-6-*arsinic acid*, obtained from the corresponding amino-compound by the Bart–Schmidt reaction (yield, 9·6%), crystallised from 16% hydrochloric acid (charcoal) in colourless, hexagonal, prismatic needles containing $\frac{1}{4}H_2O$ not lost at 120°, and did not melt at 305° (Found in material dried at 120° : loss, 0·86; As, 24·3, 24·3; N, 4·6. $C_{11}H_{12}O_4NAs,\frac{1}{4}H_2O$ requires H_2O, 1·4; As, 24·5; N, 4·6%). It was insoluble in water and acetic acid. The magnesium and barium salts crystallised in needles, but the calcium salt was amorphous.

Oxidation of 2-*Hydroxy*-4-*methylquinoline. Isolation of Benzoxazolone.*—The hydroxymethylquinoline (6 g.), after treatment by the method of oxidation described on p. 2349, gave 3·8 g. of unchanged material, m. p. 224°. The solution, on further concentration, acidification, and extraction with ether, yielded an oil which soon crystallised. After five recrystallisations from water (charcoal), this was obtained in long, colourless, silky, rectangular plates, m. p. 142° (dried at 100°) with previous softening from 138°, either alone or mixed with a synthetic specimen of benzoxazolone. The air-dried material contained $1H_2O$ and had m. p. 98° (compare Young and Dunstan, J., 1908, **93**, 1056) (Found : loss in air-dried material in a vacuum desiccator over sulphuric acid, 11·8. Calc. :

H_2O, 11·8%. Found in dried material: C, 62·2; H, 4·0; N, 10·5. Calc.: C, 62·2; H, 3·7; N, 10·4%).

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