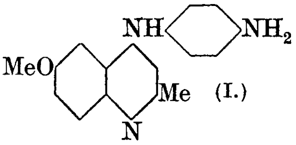
CLII.—*Quinoline Compounds containing Arsenic. Part I. Synthesis of 6-Methoxyquinoline Derivatives of Aminophenylarsinic Acids.*

By ROBERT HENRY SLATER.

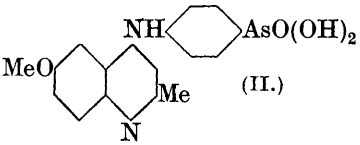
THE chemotherapeutic activity in malaria of certain 6-methoxyquinoline compounds, such as quinine and plasmoquine (compare Barger and Robinson, J., 1929, 2947), and of arsenic (particularly in chronic cases where quinine has only a slight curative action) would seem to indicate that a highly efficient anti-malarial might be produced by the combination of a 6-methoxyquinoline derivative with an arsenic compound.

For the synthesis of compounds of this type, 4-chloro-6-methoxy-2-methylquinoline, easily accessible (Conrad and Limpach, *Ber.*, 1888, **21**, 1651) and containing labile halogen, appeared to be a suitable initial material. The first method investigated, namely, direct condensation with *o*- or *p*-aminophenylarsinic acid, was unsuccessful, whether the two substances were heated together (*a*) in the dry state, (*b*) in presence of quinoline, or (*c*) in boiling amyl alcohol to which anhydrous potassium carbonate and a trace of copper powder and cuprous iodide had been added (compare Burton and Gibson, J., 1926, 459; Wintersteiner and Lieb, *Ber.*, 1928, **61**, 1126).

When, however, 4-chloro-6-methoxy-2-methylquinoline was heated with an excess of *p*-phenylenediamine, 4-p-*aminoanilino*-6-*methoxy*-2-*methylquinoline* (I) was produced. This base was converted into p-6′-*methoxy*-2′-*methyl*-4′-*quinolylaminophenylarsinic acid* (II) by means of the Bart reaction, uniform yields being obtained when the solid diazo-compound was employed.



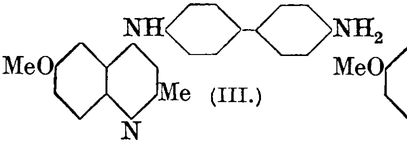
(I.)

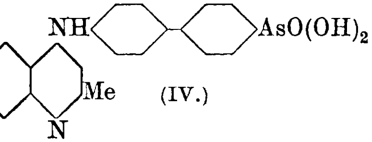


(II.)

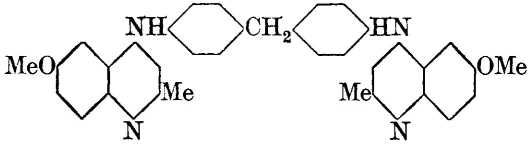
By a similar series of reactions 4-m-*aminoanilino*-6-*methoxy*-2-*methylquinoline* and m-6′-*methoxy*-2′-*methyl*-4′-*quinolylaminophenylarsinic acid* were obtained.

4-Chloro-6-methoxy-2-methylquinoline and benzidine condensed readily when heated together, with formation of 4-*benzidino*-6-*methoxy*-2-*methylquinoline* (III). This base was readily converted into 4′-6″-*methoxy*-2″-*methyl*-4″-*quinolylaminodiphenylylarsinic acid* (IV) by means of the Bart reaction.


(III.)


(IV.)

pp′-Diaminodiphenylmethane and 4-chloro-6-methoxy-2-methylquinoline condensed slowly when heated together. pp′-*Di*-6′-*methoxy*-2′-*methyl*-4′-*quinolyldiaminodiphenylmethane* (V) was the only product even when a large excess of *pp*′-diaminodiphenylmethane was present.

(V.)


Monoquinolyl derivatives also have not yet been obtained from *o*-tolidine or *o*-dianisidine and 4-chloro-6-methoxy-2-methylquinoline. Attempts are being made to condense these bases and various aminophenylarsinic acids with 4-bromo-6-methoxy-2-methylquinoline (which contains a more reactive halogen atom).

Several of the substances now described exhibit a remarkable tendency to form gels when warm dilute aqueous solutions of their salts are cooled, and most of them give brilliant colorations, ranging from red to purple, when they are added under suitable conditions to a dilute aqueous solution of iodine in potassium iodide. These reactions will be more fully described elsewhere.

The above quinolylarsinic acids and some of the intermediate compounds are being tested by the Joint Committee on Chemotherapy formed by the Medical Research Council and the Department of Scientific and Industrial Research in respect of their chemotherapeutic actions. The results of these tests will be published later.

EXPERIMENTAL.

4-p-*Aminoanilino*-6-*methoxy*-2-*methylquinoline* (I).—A mixture of 4-chloro-6-methoxy-2-methylquinoline (10·4 g.) and *p*-phenylenediamine (9 g.), heated at 130—140°/15 mm. during 20 minutes, became dark brown and almost completely solid. A solution of the product in the minimum amount of hot dilute hydrochloric acid (5%) was filtered, cooled, and added to twice its volume of concentrated hydrochloric acid (*d* 1·19). From the pale green, crystalline hydrochloride (13·5 g.) which separated, the free *base* was liberated by aqueous ammonia. It crystallised from aqueous alcohol (50%) in large, thick, light brown, rectangular plates, melting with loss of water at 215° (Found: C, 68·5; H, 6·2. $C_{17}H_{17}ON_3,H_2O$ requires C, 68·7; H, 6·4%). The base is soluble in ethyl alcohol, methyl alcohol, and acetic acid, but much less soluble in benzene and light petroleum. A dilute alcoholic or acetic acid solution does not give a coloration with *N*/1000-iodine. The hydrochloride separates in fine, white, prismatic needles when hydrochloric acid is added to an alcoholic solution of the base.

The *acetyl* derivative, prepared by means of boiling acetic anhydride, crystallised from aqueous alcohol (20% alcohol) in large, pale yellow rhombohedra which contained water of crystallisation. After dehydration at 150° the compound has m. p. 240° (Found: C, 71·2; H, 5·7; N, 12·8. $C_{19}H_{19}O_2N_3$ requires C, 71·0; H, 6·0; N, 13·1%). It is soluble in alcohol and acetic acid, but practically insoluble in benzene and light petroleum. A warm dilute acetic acid solution (2%) sets to a firm jelly on cooling. A dilute acetic acid solution gives with *N*/1000-iodine a brilliant blue coloration, which disappears on warming and reappears on cooling. A dilute alcoholic solution behaves similarly, but fresh iodine solution has to be added to the cooled solution in order to restore the blue colour. A blue coloration is also produced when a dilute aqueous solution of potassium iodide is added to a mixture of an acetic acid solution of the acetyl compound and bromine water. Hydrochloric acid precipitates the hydrochloride from an alcoholic solution in yellow feathery needles which are sparingly soluble in water.

p-*6′-Methoxy-2′-methyl-4′-quinolylaminophenylarsinic Acid* (II).—A mixture of 4-*p*-aminoanilino-6-methoxy-2-methylquinoline (5·6 g.) and hydrochloric acid (9 c.c.; *d* 1·19) was cooled to − 5° and diazotised (sodium nitrite, 1·6 g.; water, 7 c.c.) below 0°. After an hour, the mixture was neutralised at 0° with 5*N*-sodium hydroxide, and sodium arsenite solution (a mixture of arsenious oxide, 3 g., in 5*N*-sodium hydroxide solution, 6 c.c.; sodium carbonate, 6 g., in water, 18 c.c.; and 10% copper sulphate solution, 0·6 c.c., to which was added sufficient aqueous ammonia to give the soluble complex salt) added. The whole was kept at room temperature for 16 hours and then warmed gently on the water-bath until evolution of nitrogen ceased. After filtration, the solid residue was extracted thrice with small quantities of aqueous sodium hydroxide (5%). The hydrogen-ion concentration of the combined filtrates was adjusted with hydrochloric acid to p_H 7·5; the *arsinic acid* was then quantitatively precipitated as a white gelatinous solid. This was collected and repeatedly dissolved in dilute sodium hydroxide solution and reprecipitated at its isoelectric point (p_H 7·5) with nitric acid; the stellate clusters of fine, white, prismatic needles obtained were washed with water (yield, 0·5—3·2 g.). The acid was unmelted at 307° (Found: N, 7·6; As, 19·4. $C_{17}H_{17}O_4N_2As$ requires N, 7·2; As 19·3%).

A more uniform yield was obtained by the following method. A well-stirred mixture of 4-*p*-aminoanilino-6-methoxy-2-methylquinoline (5·6 g.) and glacial acetic acid (30 c.c.) was cooled to 10°, sodium nitrite (1·6 g.) added gradually, and the clear reddish-brown solution poured into dry ether (150 c.c.). The solid orange diazonium compound, which separated, was collected, washed with dry ether, and added to the sodium arsenite mixture (as used above). After standing over-night, the reaction product was worked up and the arsinic acid isolated as in the last experiment (yield, 2·6 g.).

The arsinic acid is practically insoluble in water and the usual organic solvents. It dissolves readily in dilute sodium and ammonium hydroxide solutions and in moderately concentrated hydrochloric acid. No satisfactory explanation can be advanced of the curious phenomenon that the acid is precipitated from a solution of its sodium salt in a crystalline form by nitric acid (*vide supra*) and, under exactly similar conditions, in a gelatinous form by hydrochloric acid. A colloidal solution of the arsinic acid in dilute acetic acid gives a purple coloration with *N*/1000-iodine.

The sodium salt is precipitated in colourless plates when concentrated sodium hydroxide solution is added to a solution of the arsinic acid in dilute alkali. The following salts are precipitable from an aqueous solution of the ammonium salt: magnesium salt, white, gelatinous, insoluble in hot water; barium salt, white, gelatinous, soluble in hot water, crystallises on cooling in fine slender needles; calcium salt, white, gelatinous, less soluble in hot water; silver salt, pale yellow, curdy, insoluble in hot water; mercuric salt, white, curdy, insoluble in hot water.

4-m-*Aminoanilino*-6-*methoxy*-2-*methylquinoline*.—A mixture of 4-chloro-6-methoxy-2-methylquinoline (10·4 g.) and *m*-phenylenediamine (10 g.) was heated at 140°/20 mm. for 1½ hours, the almost solid product dissolved in hot dilute hydrochloric acid (5%), and the filtered solution rendered alkaline with aqueous ammonia. The base obtained crystallised from aqueous alcohol (20% alcohol) in long, pale brown, rectangular, prismatic needles (10 g.), m. p. 230—231° (Found: C, 73·4; H, 6·2; N, 14·7. $C_{17}H_{17}ON_3$ requires C, 73·1; H, 6·1; N, 15·0%).

4-m-*Aminoanilino*-6-*methoxy*-2-*methylquinoline* is readily soluble in ethyl alcohol, methyl alcohol, and acetic acid, but sparingly soluble in benzene and light petroleum. A dilute alcoholic or acetic acid solution gives with *N*/1000-iodine a faint red coloration, which slowly deepens. The addition of hydrochloric acid to an alcoholic solution of the base gives a white gelatinous precipitate of the hydrochloride.

The *acetyl* derivative crystallises from aqueous alcohol (10% alcohol) in stout, pale yellow, prismatic needles, m. p. 269° (Found : C, 71·0; H, 6·1; N, 12·7. $C_{19}H_{19}O_2N_3$ requires C, 71·0; H, 6·0; N, 13·1%). It is slightly soluble in ethyl alcohol and acetic acid, but practically insoluble in benzene and light petroleum. A dilute alcoholic solution gives a deep blue coloration with *N*/1000-iodine and a dilute acetic acid solution gradually gives a brilliant purple coloration; these colours disappear on warming but reappear on cooling. The addition of water to a solution of the acetyl compound in concentrated hydrochloric acid produces a white gelatinous precipitate of the hydrochloride.

m-6′-*Methoxy*-2′-*methyl*-4′-*quinolylaminophenylarsinic Acid*.—This acid was obtained from 4-*m*-aminoanilino-6-methoxy-2-methylquinoline by the Bart reaction under practically the same conditions which were used in the first method of preparation of its *p*-isomeride (base, 5·6 g.; hydrochloric acid, 15 c.c. of *d* 1·14; sodium nitrite, 1·6 g., in water, 7 c.c.), but a slightly higher temperature (0—5°) was permitted. The reaction of the alkaline filtrate was adjusted with hydrochloric acid to p_H 5 and the *arsinic acid*, then quantitatively precipitated as a white gelatinous solid, was purified by several reprecipitations from solution in dilute aqueous sodium hydroxide at the above isoelectric point (p_H 5), washed with water, and dried (yield, 1·5 g.). It darkened at 280° but was unmelted at 300° (Found : As, 19·5. $C_{17}H_{17}O_4N_2As$ requires As, 19·3%).

This arsinic acid resembles the *p*-isomeride in solubility, but it is not precipitated in a crystalline form when nitric acid is added to an aqueous solution of its sodium salt; also, the colloidal solution in dilute acetic acid does not give a coloration with *N*/1000-iodine.

The sodium salt of the arsinic acid is readily precipitated as a crystalline mass when concentrated sodium hydroxide solution is added to its dilute alkali solution. The following salts are insoluble in cold water : magnesium salt, white, gelatinous, slightly soluble in hot water; calcium salt, pale yellow, gelatinous, less soluble in hot water; barium salt, white, gelatinous, soluble in hot water, gelatinous precipitate on cooling; silver salt and mercuric salt, pale yellow, curdy, insoluble in hot water.

4-*Benzidino*-6-*methoxy*-2-*methylquinoline* (III).—A mixture of 4-chloro-6-methoxy-2-methylquinoline (5·2 g.) and benzidine (7 g.) was heated at 160° during 15 minutes and the almost solid product was digested with excess of hot dilute hydrochloric acid (5%), which readily converted it into an insoluble yellow hydrochloride. This was extracted several times with small quantities of boiling dilute hydrochloric acid and then warmed with sodium hydroxide solution. The base (7·2 g.) liberated crystallised from toluene in fine, pale yellow, microscopic, rectangular prisms, m. p. 245° (Found: C, 77·8; H, 6·1; N, 11·5. $C_{23}H_{21}ON_3$ requires C, 77·7; H, 6·0; N, 11·8%).

4-*Benzidino*-6-*methoxy*-2-*methylquinoline* is soluble in acetic acid and boiling toluene, but sparingly soluble in ethyl and methyl alcohols, benzene and light petroleum. Its solution in warm dilute acetic acid sets to a gel on cooling. A dilute acetic acid solution of this base gives with *N*/1000-iodine a deep purple coloration; this disappears on warming but does not reappear on cooling.

The *acetyl* derivative crystallises from aqueous alcohol in stellate clusters of fine, yellow, rectangular, prismatic needles, m. p. 159—160° (Found: N, 9·7. $C_{25}H_{23}O_2N_3,2H_2O$ requires N, 9·7%). It is readily soluble in ethyl and methyl alcohols and in acetic acid, but it is only slightly soluble in benzene and practically insoluble in light petroleum. A solution in warm dilute acetic acid sets to a gel on cooling. A dilute alcoholic or acetic acid solution gives with *N*/1000-iodine a brilliant purple coloration which disappears on warming and reappears on cooling. This coloration is also produced when a dilute potassium iodide solution is added to a mixture of the acetic acid solution of the acetyl compound and bromine water. The addition of hydrochloric acid to an alcoholic solution of the base precipitates a crystalline hydrochloride sparingly soluble in water.

4′-6″-*Methoxy*-2″-*methyl*-4″-*quinolylaminodiphenylylarsinic Acid* (IV).—A well-stirred mixture of the preceding benzidino-compound (3·5 g.), hydrochloric acid (5·7 c.c. of *d* 1·19), and water (15 c.c.) was cooled to 5°, and a saturated solution of sodium nitrite (0·8 g.) added gradually below 8°. After 1 hour, the diazo-mixture was carefully neutralised at 5° with aqueous sodium hydroxide (5*N*), and sodium arsenite solution (a mixture of arsenious oxide, 2 g., in 5*N*-sodium hydroxide solution, 4 c.c.; sodium carbonate, 4 g., in water, 12 c.c.; and 10% copper sulphate solution, 0·4 c.c., to which was added sufficient aqueous ammonia to give the soluble complex salt) added. After remaining at room temperature over-night, the mixture was warmed gently on the water-bath until evolution of nitrogen ceased. After the addition of *N*-sodium hydroxide (10 c.c.) the liquid was filtered, and the residue extracted thrice with warm dilute sodium hydroxide solution. The reaction of the combined filtrates was adjusted with hydrochloric acid in the cold to p_H 7; the *arsinic acid* then completely precipitated was purified by several precipitations (at p_H 7) from its solution in dilute alkali with hydrochloric acid and obtained in pale yellow needles (radially arranged) which, when washed free from sodium chloride, were converted into a gelatinous solid (yield, 2·2 g.). The acid darkened at 290° but was unmelted at 300° (Found : As, 16·0. $C_{23}H_{21}O_4N_2As$ requires As, 16·15%).

This arsinic acid is practically insoluble in water and in the usual organic solvents, readily soluble in dilute sodium and ammonium hydroxide solutions, but only slightly soluble in hydrochloric acid. A colloidal solution in dilute acetic acid gives with *N*/1000-iodine a dark red coloration which changes to purple on the addition of hydrochloric acid. The crystalline sodium salt is readily produced in the usual way. The magnesium, calcium, and barium salts are white and gelatinous, the silver salt is pale yellow and gelatinous, and the mercuric salt pale yellow and curdy : all are insoluble in water.

pp′-*Di-6′-methoxy-2′-methyl-4′-quinolyldiaminodiphenylmethane* (V).—*pp*′-Diaminodiphenylmethane (7·5 g.) was heated to 130°, and to the melt were added 4-chloro-6-methoxy-2-methylquinoline (5·2 g.) and a trace of finely divided copper-bronze. After 3 hours' heating, the mixture, which had almost completely solidified, was digested with hot dilute hydrochloric acid (5%) and the residual, sparingly soluble, pale yellow hydrochloride (4·5 g.) was treated with warm aqueous sodium hydroxide solution. The *base* thus liberated crystallised from hot alcohol in small, pale brown, rectangular, prismatic needles, m. p. 144° (decomp.) (Found : C, 77·3 ; H, 6·0 ; N, 10·2. $C_{35}H_{32}O_2N_4$ requires C, 77·7 ; H, 6·0 ; N, 10·4%). It is soluble in ethyl alcohol and acetic acid, but only sparingly soluble in benzene and light petroleum. A dilute alcoholic or acetic acid solution gives with *N*/1000-iodine a deep purple coloration, which disappears on warming but reappears on cooling. The addition of hydrochloric acid to an alcoholic solution of the base precipitates the hydrochloride in fine, yellow, rectangular, prismatic needles.

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ROYAL COLLEGE OF PHYSICIANS' LABORATORY,
EDINBURGH.
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