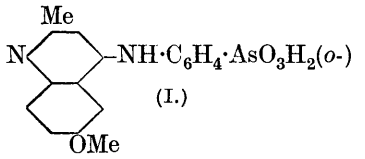
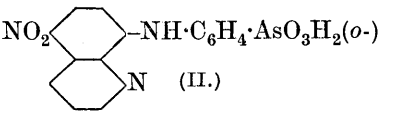
CCLXIV.—*Quinoline Compounds containing Arsenic. Part III. Synthesis of* o-5′-*Nitro*-8′-*quinolylaminophenylarsonic Acid,* 12-*Chloro*-10-*nitro*-5 : 12-*dihydroquinbenzarsazine, and* 10-*Nitroquinbenzarsazinic Acid.*

By Robert Henry Slater.

Part II of this series (Slater, this vol., p. 107) describes the synthesis of *o*-6′-methoxy-2′-methyl-4′-quinolylaminophenylarsonic acid (I) and its quinbenzarsazine derivatives. o-5′-*Nitro*-8′-*quinolylaminophenylarsonic acid* (II) and its corresponding derivatives have now been prepared. Efforts to effect the direct condensation of *o*-aminophenylarsonic acid with 8-bromo-5-nitroquinoline (prepared from 8-aminoquinoline by a modification of the method of Dikshoorn, *Rec. trav. chim.*, 1929, **48**, 550) were unsuccessful. When amyl alcohol and potassium carbonate were used either with or without the addition of traces of copper-bronze and iodine (compare Part II, *loc. cit.*, p. 110), only a small amount of what was probably impure *o*-5′-nitro-8′-quinolylaminophenylarsonic acid (II) was isolated, the main product being 5-nitro-8-hydroxyquinoline. When the reactants were heated together in the dry state, or in pyridine, they were either recovered unchanged or decomposed by prolonged heating. *o*-Bromophenylarsonic acid and 5-nitro-8-aminoquinoline, however, condense in presence of amyl alcohol to give small yields of the desired *o*-5′-nitro-8′-quinolylaminophenylarsonic acid (II) in a pure state. The otherwise rather inaccessible 5-nitro-8-aminoquinoline was conveniently prepared from 8-bromo-5-nitroquinoline



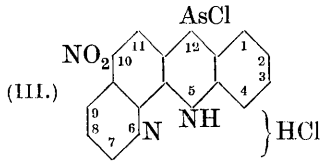
(I.)



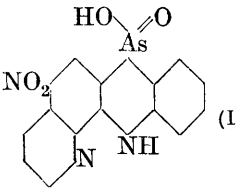
(II.)

by treatment with methyl-alcoholic ammonia. By reduction in boiling alcohol–hydrochloric acid solution by means of sulphur dioxide in presence of a trace of iodine, compound (II) was converted into the dark red *hydrochloride* of 12-*chloro*-10-*nitro*-5 : 12-*dihydroquinbenzarsazine* (III), which, on oxidation with hydrogen peroxide, gave 10-*nitroquinbenzarsazinic acid* (IV) (compare Part II, *loc. cit.*, p. 111). The sodium and potassium salts of this amphoteric acid show remarkable colour changes on dilution and addition of alkali: these colour reactions are similar to those described by Gibson and

Johnson (J., 1929, 1254, 1262) for certain nitrophenarsazinic acids in which the nitro-group occupies the same (meta-) position relative to the arsenic atom.

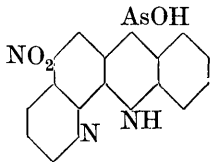


(III.)

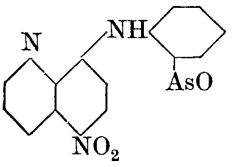


(IV.)

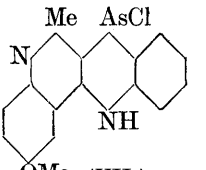
On treatment with 4 molecules of warm $N/10$-sodium hydroxide, the chlorine atoms in compound (III) are readily split off with production of an orange compound, which is presumably 10-*nitro*-12-*hydroxy*-5 : 12-*dihydroquinbenzarsazine* (V), m. p. 275—277° (decomp.). This compound is also formed when (III) is boiled with water for a few minutes; and (III) can be regenerated from it either (*a*) by the action of boiling hydrochloric acid, or (*b*) by oxidation with hydrogen peroxide in presence of acetic acid to compound (IV) and subsequent reduction in alcohol–hydrochloric acid with sulphur dioxide as described above. The fact that (V) can be oxidised to (IV) in presence of acetic acid appears to exclude the possibility that it possesses the arsenoxide structure (VI), since boiling acetic acid is itself unable to convert the open-ring arsonic acid (II) into the closed-ring arsazinic acid (IV).



(V.)



(VI.)



(VII.)

The ease with which the chlorine atoms in (III) are hydrolysed by boiling water is of especial interest in view of the fact that the analogous 12-chloro-7-methoxy-11-methyl-5 : 12-dihydroquinbenzarsazine (VII; see Part II, p. 111) can be recrystallised unchanged from water. The chlorine atom in the simple chlorodihydrophenarsazines is highly labile (private communication from Prof. C. S. Gibson), so it is the chlorine atom in compound (VII) which appears to exhibit abnormally low reactivity; it is possible, however, that the reactivity of this chlorine atom may be influenced by the close proximity of the strongly polar quinoline nitrogen atom : in (III), these two atoms are much farther apart. This may have a bearing on the structure of these compounds, which, for convenience, have been formulated here as dihydroarsazine derivatives without

prejudice to the alternative arsazinium chloride formulation (compare Gibson and co-workers, J., 1929, 1238, *et seq.*; Kappelmeier, *Rec. trav. chim.*, 1931, **50**, 44).

The above quinoline compounds of arsenic 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 in malaria and trypanosomiasis. The results of these tests will be published later.

Experimental.

8-*Bromo*-5-*nitroquinoline*.—To a solution of 8-aminoquinoline (30 g.) in hydrobromic acid (150 c.c. of *d* 1·49 acid and 300 c.c. of water), crushed ice (400 g.) was added, and the cold stirred mixture diazotised with a solution of sodium nitrite (15 g.) in water (30 c.c.). The diazo-solution was added gradually to a solution of cuprous bromide (40 g.) in hydrobromic acid (400 c.c.; *d* 1·49) at 60—70°. After standing over-night at room temperature, the orange-red crystalline precipitate of the cuprous bromide salt of 8-bromoquinoline was filtered off, washed with water, added in small portions at a time to well-stirred sodium hydroxide solution (100 c.c. of 50%), and the liberated base extracted several times with ether. To the oil obtained after removal of the ether, nitric acid (50 c.c.; *d* 1·5) was carefully added so that the temperature did not rise above 80—90°, and then concentrated sulphuric acid (50 c.c.) was poured in. The reaction mixture was warmed on the water-bath for 1 hour, cooled, and added to water (4 litres); the copious, pale yellow precipitate of pure 8-bromo-5-nitroquinoline was filtered off, washed with water, and dried at 100°; m. p. 136—137°, yield 36—38 g.

Condensation of 8-*Bromo*-5-*nitroquinoline with* o-*Aminophenylarsonic Acid*.—8-Bromo-5-nitroquinoline (8·4 g.) and *o*-aminophenylarsonic acid (7·3 g.) were dissolved in dry amyl alcohol (50 c.c.), anhydrous potassium carbonate (6·3 g.) and traces of finely divided copper-bronze and iodine were added, and the mixture was kept at 140—150° for 8 hours. The products isolated were (*a*) about 1 g. of a dark reddish-brown solid, m. p. *ca.* 200°, which was difficult to purify [Found: As, 13·4. Calc. for $C_{15}H_{12}O_5N_3As$ (II): As, 19·3%]; (*b*) 5-nitro-8-hydroxyquinoline (2·5 g.), m. p. 172—173°; and (*c*) unchanged initial material. The same products were obtained when the reaction was carried out in the absence of traces of copper-bronze and iodine.

5-*Nitro*-8-*aminoquinoline*.—A mixture of 8-bromo-5-nitroquinoline (14 g.) and saturated methyl-alcoholic ammonia (100 c.c.) was heated in a sealed tube at 140° for 4 hours. After cooling, the contents of the tube were added to excess of water, and the orange-red pre-

cipitate was filtered off and dried at 100°. It crystallised from benzene (yield 9·2 g.) in fine orange needles, m. p. 196—197° (compare Dikshoorn, *Rec. trav. chim.*, 1929, **48**, 520).

o-5′-*Nitro*-8′-*quinolylaminophenylarsonic Acid* (II).—5-Nitro-8-aminoquinoline (6·3 g.) and *o*-bromophenylarsonic acid (9·4 g.) were dissolved in dry amyl alcohol (60 c.c.), and anhydrous potassium carbonate (6·3 g.) and traces of finely divided copper-bronze and iodine added. The mixture was kept at 140—150° for 10 hours, cooled, and the amyl alcohol removed by distillation in steam. The residual dark reddish-brown solution was filtered, and the solid residue (A) extracted several times with small amounts of boiling dilute sodium carbonate solution. The p_H of the combined filtrates was adjusted with hydrochloric acid to 3—4; the bright yellow *arsonic acid* thereby precipitated recrystallised from acetic acid (70%) in stellate clusters of fine, flat, yellow needles, m. p. 264—265° (decomp.); yield 3·2 g. (Found: As, 19·5. $C_{15}H_{12}O_5N_3As$ requires As, 19·3%). The solid residue (A) and the solid precipitated by water from the mother-liquors from the above crystallisation consisted chiefly of unchanged 5-nitro-8-aminoquinoline and *o*-bromophenylarsonic acid, respectively.

The arsonic acid is practically insoluble in water and in the usual neutral organic solvents, but is readily soluble in a mixture of alcohol and hydrochloric acid and moderately soluble in acetic acid. It dissolves readily in dilute sodium and ammonium hydroxides to give orange-coloured solutions, and in mineral acids to give yellow solutions; the arsonic acid is reprecipitated from the acid solutions on dilution with water. Its acetic acid solution gives a brown precipitate with *N*/1000-iodine. The arsonic acid is not converted into the arsazinic acid (IV) by hydrochloric acid even on prolonged boiling (compare Gibson and Johnson, J., 1927, 2501).

The sodium salt is very slowly precipitated in orange rectangular plates when concentrated sodium hydroxide solution is added to a solution of the arsonic acid in dilute alkali. The ammonium salt is slowly precipitated in sheaves of fine, orange, sharp-pointed needles in a similar way. The following salts are precipitable from an aqueous solution of the ammonium salt: calcium salt, bright yellow, gelatinous, insoluble in hot water; barium salt, bright yellow, crystalline, slightly soluble in hot water, sheaves of fine needles on cooling. The addition of magnesium sulphate solution causes the orange solution of the ammonium salt of the arsonic acid to become orange-red, but no precipitate is formed in the cold; the gelatinous orange magnesium salt is, however, precipitated on boiling. The following salts are precipitated in an amorphous condition and are insoluble in hot water: zinc salt, reddish-brown; silver salt, blood-

red, soluble in ammonium hydroxide solution to give an orange solution; lead and mercuric salts, bright red; ferric salt, dark brown; copper, nickel, and cobalt salts, vermilion.

12-*Chloro*-10-*nitro*-5 : 12-*dihydroquinbenzarsazine Hydrochloride* (III).—*o*-5′-Nitro-8′-quinolylaminophenylarsonic acid (II; 2·5 g.) was dissolved in a mixture of alcohol (20 c.c.) and hydrochloric acid (15 c.c.; *d* 1·19), and a small crystal of iodine added. The clear reddish-brown solution was gently boiled, and sulphur dioxide bubbled through. In a few minutes the *quinarsazine hydrochloride* crystallised in stellate clusters of dark red feathery needles, which turned yellowish-brown at about 200° and melted at 258—260° (decomp.) (Found : N, 9·9; Cl, 16·8; As, 18·5. $C_{15}H_{10}O_2N_3Cl_2As$ requires N, 10·2; Cl, 17·3; As 18·3%). Yield, 2·4 g.

10-*Nitroquinbenzarsazinic Acid* (IV).—Finely powdered 12-chloro-10-nitro-5 : 12-dihydroquinbenzarsazine hydrochloride (2 g.) was boiled in acetic acid (10 c.c.) for a few minutes, cooled rapidly, and hydrogen peroxide (20 c.c.; 10-vol.) added. No reaction appeared to take place in the cold, but when warmed, the fine red suspension was gradually converted into a bright yellow compound, and the mixture was kept on the water-bath for 15 minutes to complete the oxidation. When cold, the yellow solid was filtered off (1·7 g.); it crystallised from much acetic acid in clusters of fine, small, yellow needles, which darkened slightly at about 300° but were unmolten at 310° (Found : As, 20·4. $C_{15}H_{10}O_4N_3As$ requires As, 20·2%).

The *arsazinic acid* is practically insoluble in water and in the usual neutral organic solvents, but slightly soluble in acetic acid. It dissolves readily in dilute sodium or potassium hydroxide solution to give a bright yellow solution, which changes to red and then to a brilliant purple on the addition of concentrated caustic alkali; this change is reversible on dilution. In ammonium hydroxide solutions the corresponding colours are orange and bright red. In acetic acid solution, the arsazinic acid gives a dark brown precipitate with *N*/1000-iodine. The acid is readily soluble in sulphuric and nitric acids (yellow solutions), but is reprecipitated on dilution with water. It is slightly soluble in hydrochloric acid. On reduction in boiling alcohol–hydrochloric acid with sulphur dioxide it is converted into the dark red chlorodihydroquinbenzarsazine hydrochloride (III).

The gelatinous, purple potassium salt is precipitated from concentrated alkali solution, and the purple sodium and the orange ammonium salt can be precipitated (the latter very slowly) in the same way. The following salts are precipitable from an aqueous solution of the ammonium salt : magnesium salt, yellow, gelatinous,

slightly soluble in hot water, crystallises on cooling in long, sharp-pointed needles; the barium and calcium salts are yellow, gelatinous, soluble in hot water, and crystallise on cooling in sheaves of rectangular prismatic needles and clusters of fine, small needles, respectively. The following are insoluble in hot water: silver salt, violet, amorphous, soluble in ammonium hydroxide to a red solution; mercuric salt, bright red, amorphous; lead salt, yellow, gelatinous, changes to red in boiling water and remains red on cooling; cupric salt, deep brick-red, amorphous; ferric salt, orange, gelatinous; zinc salt, red, gelatinous; nickel salt, brown, gelatinous; cobalt salt, reddish-brown, gelatinous.

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