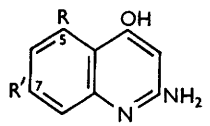
120. *Cyclic Amidines. Part VI.* 5- and 7-Substituted 2-Amino-4-hydroxyquinolines.*

By R. Hardman and M. W. Partridge.

The formation of 5- and 7-substituted 2-amino-4-hydroxyquinolines by the interaction of ethyl cyanoacetate and the benzenesulphonates of *meta*-substituted arylamines has been examined. From these salts of *m*-toluidine and of *m*-chloroaniline, both isomerides were produced, whereas the salts of *m*-anisidine and of *m*-aminophenol gave only 7-substituted aminohydroxyquinolines.

In Part II [1] we described the production of 2-amino-4-hydroxyquinolines by interaction of ethyl cyanoacetate or an α-substituted ethyl cyanoacetate with an arylammonium arenesulphonate. We have now examined the reaction between *meta*-substituted arylammonium benzenesulphonates and ethyl cyanoacetate in which either a 5- or a 7-substituted quinoline can be formed. By this reaction, the benzenesulphonates of *m*-toluidine and *m*-chloroaniline furnished both isomerides (I; R = Me or Cl, R′ = H and R′ = Me or Cl, R = H), the major component of the mixture, as shown by orientation, being the 7-substituted quinoline. From *m*-aminophenol and *m*-anisidine salts, only 7-substituted quinolines (I; R′ = OH or OMe, R = H) were formed.



(I)

Degradations of 2-amino-4-hydroxyquinoline and its derivatives were studied as models for the orientation of its 5- and 7-substituted derivatives. Its hydrolysis to 2 : 4-dihydroxyquinoline was effected in only moderate yield by potash fusion. Oxidation by permanganate furnished a mixture from which 4-hydroxyquinazoline and 2 : 4-dihydroxyquinazoline were isolated. The formation of the quinazoline ring apparently involved an initial oxidative fission of the 3 : 4-bond of the quinoline, followed by a recyclisation of the resulting aminodicarboxylic acid; in agreement, oxalylanthranilic acid, previously recognised as an oxidation product of 4-hydroxyquinoline,[2] was also isolated from the oxidation products. The heterocyclic ring exhibited a resistance to reduction similar to that reported for other 4-hydroxyquinolines; [3] the product of reduction with Raney alloy and alkali [4] was evidently 2-amino-5 : 6 : 7 : 8-tetrahydro-4-hydroxyquinoline.

3-Bromo-2 : 4-dihydroxyquinoline readily afforded 2 : 4-dihydroxyquinoline on reduction with Raney alloy and alkali,[5] but with 2 : 4-dichloroquinolines the yields of reduction products were low. In the latter cases, halogen was removed by tin and hydrochloric acid.[6]

Peroxide oxidation of quinisatin oxime, produced by treatment of 2-amino-4-hydroxyquinoline with nitrous acid,[1] was unsatisfactory, since it gave only 2 : 4-dihydroxy-3-nitroquinoline. No recognisable product was obtained when degradation of this oxime *via* a Beckmann transformation was attempted.

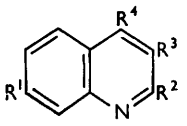
For orientation 2-amino-4-hydroxy-7-methylquinoline (I; R′ = Me, R = H) was brominated to its 3-bromo-derivative (II; R^1 = Me, R^2 = NH_2, R^3 = Br, R^4 = OH) which with nitrous acid furnished the bromodihydroxyquinoline (II; R^1 = Me, R^2 = R^4 = OH, R^3 = Br); removal of the bromine by reduction with Raney alloy [5] gave the dihydroxyquinoline (II; R^1 = Me, R^2 = R^4 = OH, R^3 = H), and the dichloroquinoline (II; R^1 = Me, R^2 = R^4 = Cl, R^3 = H), obtained by interaction of this

* Part V, *J.*, 1957, 2888.

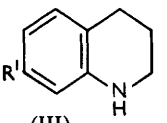
[1] Hardman and Partridge, *J.*, 1954, 3878.
[2] Kretschy, *Monatsh.*, 1883, **4**, 156; 1884, **5**, 16.
[3] Cavallito and Haskell, *J. Amer. Chem. Soc.*, 1944, **66**, 1166.
[4] Cf. Papa, Schwenk, and Breiger, *J. Org. Chem.*, 1949, **14**, 366.
[5] Cf. Schwenk, Papa, and Ginsberg, *Ind. Eng. Chem. Anal.*, 1943, **15**, 576.
[6] Gabriel and Thieme, *Ber.*, 1919, **52**, 1079.

dihydroxyquinoline and phosphorus oxychloride, was reduced to 1 : 2 : 3 : 4-tetrahydro-7-methylquinoline (III; R^1 = Me). This was characterised by comparison of its benzoyl derivative, hydrochloride, and picrate with authentic specimens. The second methylquinoline formed from *m*-toluidine was therefore the 5-methyl derivative.

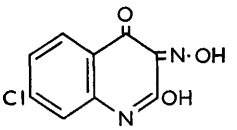
2-Amino-4-hydroxy-7-methoxyquinoline (I; R′ = MeO, R = H) with phosphorus oxychloride yielded a chloro-compound (II; R^1 = MeO, R^2 = NH_2, R^3 = H, R^4 = Cl), the amino-group of which was replaced by hydroxyl on treatment with nitrous acid. This chlorohydroxyquinoline (II; R^1 = MeO, R^2 = OH, R^3 = H, R^4 = Cl) was converted *via* the dichloroquinoline (II; R^1 = MeO, R^2 = R^4 = Cl, R^3 = H) into 1 : 2 : 3 : 4-tetrahydro-7-methoxyquinoline (III; R^1 = MeO) which afforded a benzoyl derivative, a hydrochloride, and a picrate identical with those derived from authentic 7-methoxyquinoline.



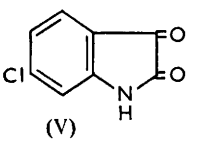
(II)



(III)



(IV)



(V)

The orientation of the hydroxyquinoline prepared from *m*-aminophenol (I; R′ = OH, R = H) followed from that of its orientated homologue (I; R′ = OMe, R = H), since the product of demethylation of the latter furnished a base, hydrochloride, and picrate identical with those derived from the former. The identical orientation of the quinolines produced from *m*-anisidine and *m*-aminophenol was confirmed by demethylation of 2-amino-4-chloro-7-methoxyquinoline (II; R^1 = MeO, R^2 = NH_2, R^3 = H, R^4 = Cl) to the same chlorohydroxyquinoline (II; R^1 = OH, R^2 = NH_2, R^3 = H, R^4 = Cl) as was formed when the aminodihydroxyquinoline (I; R′ = OH, R = H) was treated with phosphorus oxychloride. Further, hydrolysis of this chlorohydroxyquinoline (II; R^1 = OH, R^2 = NH_2, R^3 = H, R^4 = Cl) furnished the original dihydroxyquinoline (I; R′ = OH, R = H). The chlorohydroxyquinoline (II; R^1 = OH, R^2 = NH_2, R^3 = H, R^4 = Cl) could not be converted into the dichloroquinoline (II; R^1 = R^4 = Cl, R^2 = NH_2, R^3 = H) for comparison with the compound formed by interaction of 2-amino-7-chloro-4-hydroxyquinoline (I; R′ = Cl, R = H) and phosphorus oxychloride.

2-Amino-7-chloro-4-hydroxyquinoline (I; R′ = Cl, R = H) with nitrous acid gave 7-chloro-3 : 4-dihydro-2-hydroxy-3-hydroxyimino-4-oxoquinoline (IV), which on being boiled with sulphuric acid yielded 6-chloroisatin (V). Analogous conversions of quinoline derivatives into isatin derivatives have been previously reported.[7] This isatin derivative was smoothly oxidised by hydrogen peroxide to 4-chloroanthranilic acid and the latter by deamination gave 4-chlorobenzoic acid. The isomeric aminochlorohydroxyquinoline derived from *m*-chloroanilinium benzenesulphonate and ethyl cyanoacetate was accordingly the 5-chloro-derivative.

Most of the quinoline derivatives described in this communication were examined for amœbacidal activity; none was observed.

Experimental

Oxidation of 2-Amino-4-hydroxyquinoline.—(i) 2-Amino-4-hydroxyquinoline (4 g.) in a solution of potassium hydroxide (2·8 g.) in water (270 ml.) was treated at room temperature during 4 days with N-potassium permanganate (600 ml.). The suspension was filtered, concentrated, and neutralised with sulphuric acid. Amphoteric material was extracted from the precipitate with aqueous sodium hydroxide and reprecipitated; this on recrystallisation from ethanol gave 4-hydroxyquinazoline (1·0 g., 27%), m. p. and mixed m. p. 219—220° [Found: C, 65·8; H, 4·4; N, 19·2%; *M* (ebullioscopic), 140. Calc. for $C_8H_6ON_2$: C, 65·8; H, 4·1; N,

[7] Lahey, Lamberton, and Price, *Austral. J. Sci. Res.*, 1950, *A*, **3**, 155.

19·2%; *M*, 146]; its picrate had m. p. and mixed m. p. 207—208°. The mother-liquor from the isolation of the amphoteric material, after completion of the removal of manganese dioxide, concentration, and acidification, furnished hydrated oxalylanthranilic acid (0·5 g., 10%), m. p. and mixed m. p. 195—196° (decomp.).

(ii) Water-soluble material obtained from an oxidation at 85—90° for 30 min., on being boiled for 90 min. with concentrated hydrochloric acid, gave as a water-soluble fraction 4-hydroxyquinazoline (0·5 g., 14%), m. p. and mixed m. p. 219—220°, and as a water-insoluble fraction, purified by sublimation *in vacuo*, 2 : 4-dihydroxyquinazoline (0·6 g., 15%), plates, m. p. and mixed m. p. 355° (decomp.) (from ethyl acetate) (Found: C, 59·8; H, 3·7; N, 17·0. Calc. for $C_8H_6O_2N_2$: C, 59·3; H, 3·7; N, 17·3%), $\lambda_{max.}$ (in EtOH) 217 (ε 40,000), 310 mμ (ε 3400); authentic 2 : 4-dihydroxyquinazoline had $\lambda_{max.}$ 217 (ε 42,600), 310 mμ (ε 3600); the 3-methyl derivative had m. p. and mixed m. p. 229—232°.

2-*Amino*-5 : 6 : 7 : 8-*tetrahydro*-4-*hydroxyquinoline*.—A solution of 2-amino-4-hydroxyquinoline (12 g.) in 10% aqueous sodium hydroxide (360 ml.) was treated at 85° during 7 hr. with Raney alloy (51 g.), stirred for a further 2 hr., and filtered. The precipitate obtained by neutralisation was freed from 2-amino-4-hydroxyquinoline by the addition of chloroform to a methanol solution and then gave the *tetrahydroquinoline* (6 g., 49%) as prisms, m. p. 335—336° (decomp.), from aqueous ethanol (Found: N, 16·9. $C_9H_{12}ON_2$ requires N, 17·1%). This compound was insoluble in aqueous sodium carbonate, soluble in aqueous sodium hydroxide, and gave a ferric colour similar to that of 2-amino-4-hydroxyquinoline, but on pyrolysis evolved ammonia less readily. Its *picrate*, needles from aqueous ethanol, had m. p. 252° (decomp.) (Found: C, 45·8; H, 4·1; N, 17·5. $C_{15}H_{15}O_8N_5$ requires C, 45·8; H, 3·8; N, 17·8%); the *hydrochloride* formed prisms, m. p. 244—246° (decomp.), from hydrochloric acid (Found: C, 53·7; H, 6·2. $C_9H_{13}ON_2Cl$ requires C, 53·8; H, 6·5%). With nitrous acid, it gave 3 : 4 : 5 : 6 : 7 : 8-*hexahydro*-2-*hydroxy*-3-*hydroxyimino*-4-*oxoquinoline* as purple prisms, m. p. above 400° (from dimethylformamide) (Found: C, 55·6; H, 4·7; N, 14·9. $C_9H_{10}O_3N_2$ requires C, 55·7; H, 5·2; N, 14·4%); this compound did not give a positive Liebermann's test. The *acetyl derivative*, plates, m. p. 137°, from aqueous ethanol (Found: C, 63·9; H, 6·9. $C_{11}H_{14}O_2N_2$ requires C, 64·1; H, 6·8%), was soluble in aqueous alkalis. Under Schotten–Baumann conditions, it formed an alkali-insoluble *dibenzoyl derivative* [prisms, m. p. 158—159°, from ethanol (Found: C, 74·6; H, 5·7; N, 7·8. $C_{23}H_{20}O_3N_2$ requires C, 74·2; H, 5·4; N, 7·5%)].

2-Amino-4-hydroxyquinoline was apparently unaffected on treatment with benzoyl chloride under Schotten–Baumann conditions, but on being warmed with benzoyl chloride gave a *monobenzoyl derivative hydrochloride* (50%), prisms, m. p. 191—192° (from methanol–benzene) (Found: C, 64·0; H, 4·5; N, 9·1. $C_{16}H_{13}O_2N_2Cl$ requires C, 63·9; H, 4·4; N, 9·3%); the free (N- or O-)*benzoyl derivative* formed prisms, m. p. 121—123°, from benzene–light petroleum (Found: C, 72·7; H, 4·7; N, 10·2. $C_{16}H_{12}O_2N_2$ requires C, 72·7; H, 4·6; N, 10·6%). This compound readily formed 2-amino-4-hydroxyquinoline with aqueous alkali.

3-*Bromo*-2 : 4-*dichloroquinoline*.—3-Bromo-2 : 4-dihydroxyquinoline [8] when boiled with phosphorus oxychloride for 6 hr. furnished the 2 : 4-*dichloroquinoline* (87%), needles (from ethanol), m. p. 95°, b. p. 157—158°/1·5 mm. (Found: C, 39·4; H, 1·6; halogen, 54·5. $C_9H_4NCl_2Br$ requires C, 39·0; H, 1·5; halogen, 54·5%).

2 : 4-*Dihydroxyquinoline*.—(i) 3-Bromo-2 : 4-dihydroxyquinoline (20·6 g.) in 10% aqueous sodium hydroxide (600 ml.) was heated at 90° with Raney alloy [5] (75 g.) during 2½ hr., stirring was continued for a further 1 hr., and the mixture was filtered. On acidification, the filtrate yielded 2 : 4-dihydroxyquinoline (10·6 g., 77%) which was identified as its monoacetate, m. p. and mixed m. p. 214—215°. This reduction could not be effected with sodium and ethanol, or sodium and *iso*pentyl alcohol.

(ii) 2-Amino-4-hydroxyquinoline was fused at 250—290° with potassium hydroxide for 3 hr.; the acid-insoluble fraction recovered from the melt gave 2 : 4-dihydroxyquinoline (37%), which was characterised as its monoacetate. This hydrolysis could not be effected with potassium hydroxide in water or in ethylene glycol.

1 : 2 : 3 : 4-*Tetrahydroquinoline*.—(i) Quinoline on being reduced with Raney alloy [4,5] gave its 1 : 2 : 3 : 4-tetrahydro-derivative (87%) which was characterised as its picrate,[9] m. p. 141·5—143·5°, and its benzoyl derivative,[10] m. p. 76°.

[8] Hardman and Partridge, *J.*, 1955, 510.
[9] Ishii, *J. Pharm. Soc. Japan*, 1952, **72**, 1317.
[10] Hoffmann and Königs, *Ber.*, 1883, **16**, 727.

(ii) 2 : 4-Dichloroquinoline, reduced in the same way,[4,5] yielded quinoline (4%), 1 : 2 : 3 : 4-tetrahydroquinoline (22%), and unchanged dichloro-compound (44%). When the reduction was effected in the presence of ethanol, in addition to the tetrahydroquinoline (16%), another base, probably 4-ethoxyquinoline, was recovered as its *picrate*, m. p. 195° (Found: C, 51·0; H, 3·4; N, 13·9. $C_{17}H_{14}O_8N_4$ requires C, 50·8; H, 3·5; N, 13·9%). Reduction with tin and hydrochloric acid [6] led to 1 : 2 : 3 : 4-tetrahydroquinoline (74%) and quinoline (4%).

(iii) 3-Bromo-2 : 4-dichloroquinoline by the same method [6] of reduction gave 1 : 2 : 3 : 4-tetrahydroquinoline (52%) and quinoline (3%), whereas, with Raney alloy,[4,5] the products were 2 : 4-dichloroquinoline [11] (12%), m. p. and mixed m. p. 67°, and quinoline (2%).

2-Amino-4-chloroquinoline.—2-Amino-4-hydroxyquinoline (6·4 g.) was refluxed for 8 hr. with phosphorus oxychloride (40 ml.). After removal of the excess of phosphorus oxychloride *in vacuo*, the solid, phosphorus-containing residue was boiled with water for 1 hr. and basified with sodium hydroxide. The gelatinous *chloroquinoline* after being collected in chloroform crystallised from benzene–light petroleum as prisms, m. p. 136° (4·4 g., 62%) (Found: N, 15·3; Cl, 19·9. $C_9H_7N_2Cl$ requires N, 15·7; Cl, 19·9%); it gave a *hydrochloride*, needles, m. p. 207—208°, from hydrochloric acid (Found: N, 12·9. $C_9H_8N_2Cl_2$ requires N, 13·0%), *benzenesulphonate*, prisms, m. p. 168°, from aqueous propan-2-ol (Found: C, 52·5; H, 4·5; N, 7·5. $C_{15}H_{13}O_3N_2ClS,0{\cdot}5H_2O$ requires C, 52·1; H, 4·1; N, 8·1%), and *picrate*, prisms, m. p. 279—280° (decomp.), from glacial acetic acid (Found: C, 44·4; H, 2·6; N, 16·9; Cl, 8·9. $C_{15}H_{10}O_7N_5Cl$ requires C, 44·2; H, 2·5; N, 17·2; Cl, 8·7%). The chloroquinoline was stable to hydriodic acid and to aqueous alkali but gave 2-amino-4-hydroxyquinoline on being boiled with potassium hydroxide in ethylene glycol. When refluxed for 20 hr. with sodium propoxide in propan-1-ol, it furnished 2-amino-4-*n*-propoxyquinoline [8] (78%).

The following *benzenesulphonates* were prepared: m-*chloroanilinium*, plates, m. p. 203°, from propan-2-ol (Found: N, 4·8. $C_{12}H_{12}O_3NClS$ requires N, 4·9%); m-*hydroxyanilinium*, prisms, m. p. 187·5—188°, from methanol–ethyl acetate (Found: C, 54·1; H, 4·8. $C_{12}H_{13}O_4NS$ requires C, 53·9; H, 4·9%); m-*methoxyanilinium*, needles, m. p. 173·5—174·5°, from propan-2-ol (Found: C, 55·7; H, 5·3. $C_{13}H_{15}O_4NS$ requires C, 55·5; H, 5·4%); m-*methylanilinium*, plates, m. p. 170°, from propan-2-ol (Found: C, 59·0; H, 5·9. $C_{13}H_{15}O_3NS$ requires C, 58·9; H, 5·7%).

2-Amino-4-hydroxy-5- and -7-methylquinoline.—Ethyl cyanoacetate (22·6 g.) and *m*-methylanilinium benzenesulphonate (53 g., 1 mol.) were heated together at 210° for 1 hr. A solution of the chloroform-insoluble fraction of the product in 50% aqueous ethanol deposited the *7-methylquinolinium benzenesulphonate* (17·6 g., 27%) as elongated prisms, m. p. 289—291° (decomp.) (Found: C, 57·9; H, 4·8; N, 8·3. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9; N, 8·4%). The free *base* occurred as solvated needles (from aqueous ethanol), m. p. 331° (decomp.) (Found: C, 69·4; H, 5·3; N, 15·8. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%); its *picrate*, needles from propan-2-ol, had m. p. 275—276° (decomp.) (Found: N, 17·1. $C_{16}H_{13}O_8N_5$ requires N, 17·4%).

On being concentrated, the aqueous ethanolic mother-liquor furnished the *benzenesulphonate* (19·6 g., 15%) of the 5-methyl isomer, which crystallised from propan-2-ol as prisms, m. p. 274—275° (decomp.) (Found: C, 57·8; H, 4·7; N, 8·5. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9; N, 8·4%). *2-Amino-4-hydroxy-5-methylquinoline* crystallised as solvated needles, m. p. 283—284° (decomp.), from aqueous ethanol (Found: C, 69·1; H, 5·4; N, 15·8. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%); its *picrate*, needles, m. p. 258—259° (decomp.), crystallised from aqueous ethanol (Found: C, 48·1; H, 3·7; N, 17·4. $C_{16}H_{13}O_8N_5$ requires C, 47·7; H, 3·3; N, 17·4%).

2-Amino-3-bromo-4-hydroxy-7-methylquinoline.—2-Amino-4-hydroxy-7-methylquinoline (19·6 g.), treated in boiling glacial acetic acid (300 ml.) with bromine (18 g.), gave the *3-bromo-hydrobromide* (36·5 g., 97%), which crystallised from glacial acetic acid as needles, m. p. 221—222° (decomp.) (Found: C, 35·8; H, 3·5. $C_{10}H_{10}ON_2Br_2$ requires C, 36·0; H, 3·0%). The *base* crystallised from aqueous ethanol as needles, m. p. 285° (decomp.) (Found: C, 47·8; H, 3·6; N, 10·8. $C_{10}H_9ON_2Br$ requires C, 47·3; H, 3·6; N, 11·0%); its *picrate*, needles from aqueous ethanol, had m. p. 238—239° (decomp.) (Found: N, 14·5. $C_{16}H_{12}O_8N_5Br$ requires N, 14·5%).

3-Bromo-2 : 4-dihydroxy-7-methylquinoline.—Sodium nitrite (24 g.) was gradually stirred into a solution of 2-amino-3-bromo-4-hydroxy-7-methylquinoline (25 g.) in concentrated sulphuric acid (63 ml.) at 0°. Next day, the paste was treated with crushed ice, and the

[11] Friedländer and Weinberg, *Ber.*, 1882, **15**, 2679.

precipitate was collected. Crystallisation of the ethanol-soluble fraction from glacial acetic acid gave the 2 : 4-*dihydroxy-derivative* (14·4 g., 57%) as plates, m. p. 254—255° (decomp.) (Found: C, 47·0; H, 3·2; N, 5·4. $C_{10}H_8O_2NBr$ requires C, 47·1; H, 3·2; N, 5·5%). On acetylation with acetic anhydride and a trace of pyridine, this dihydroxyquinoline gave a *monoacetate*, needles, m. p. 242° (decomp.) (from ethanol) (Found: C, 48·9; H, 3·6; N, 4·6. $C_{12}H_{10}O_3NBr$ requires C, 48·7; H, 3·4; N, 4·7%).

2 : 4-*Dihydroxy-7-methylquinoline* was obtained (89%) by reduction of the foregoing 3-bromoquinoline (10·4 g.) in 10% aqueous sodium hydroxide (300 ml.) with Raney alloy (38 g.) at 90° and crystallised from glacial acetic acid as prisms, m. p. above 400° (Found: C, 68·7; H, 5·3; N, 7·9. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·2; N, 8·0%). Its *monoacetate*, needles from ethanol, had m. p. 229—230° (decomp.) (Found: C, 66·0; H, 4·8; N, 6·5. $C_{12}H_{11}O_3N$ requires C, 66·4; H, 5·1; N, 6·5%).

2 : 4-*Dichloro-7-methylquinoline* was produced (6·4 g.) when the dihydroxymethylquinoline (5·5 g.) was boiled with phosphorus oxychloride (25 ml.) for 7 hr. and the mixture was worked up in the usual way; it formed needles, m. p. 107—108°, from methanol (Found: N, 6·7; Cl, 34·1. $C_{10}H_7NCl_2$ requires N, 6·6; Cl, 33·4%).

1 : 2 : 3 : 4-*Tetrahydro-7-methylquinoline* was obtained (73%) from the foregoing 2 : 4-dichloroquinoline by reduction with tin and hydrochloric acid [6] and characterised by comparison of its benzoyl derivative, m. p. 77—78°, its hydrochloride, m. p. 204—205°, and its picrate, m. p. 156°, with authentic specimens. For this comparison, 7-methylquinoline (12 g.) in ethanol (300 ml.) and 10% aqueous sodium hydroxide (300 ml.) was reduced at the b. p. during 4 hr. with Raney alloy (35 g.). The tetrahydro-derivative (78%) furnished a picrate, m. p. 154—155° (decomp.), previously reported [12] to have m. p. 153—154°. The hydrochloride, prisms, m. p. 204—205°, from methanol–ethyl acetate, was prepared from the picrate (Found: C, 65·6; H, 7·8; N, 7·6. Calc. for $C_{10}H_{14}NCl$: C, 65·4; H, 7·7; N, 7·6%); the benzoyl derivative, prepared from the hydrochloride, crystallised from light petroleum as prisms, m. p. 77—78° (Found: C, 81·2; H, 6·9; N, 5·5. Calc. for $C_{17}H_{17}ON$: C, 81·2; H, 6·8; N, 5·6%). Previously reported [12] values for these m. p.s are 175° and 70—72° respectively. The 7-methylquinoline was authenticated [13] as its picrate, m. p. 242°, and styphnate, m. p. 242°.

2-*Amino-4-hydroxy-7-methoxyquinoline*.—The *benzenesulphonate* of this base separated from a chloroform solution of the product of interaction of *m*-methoxyanilinium benzenesulphonate and ethyl cyanoacetate (1 mol.) at 210° for 1 hr.; it afforded solvated prisms, m. p. 222°, from water (Found: C, 55·4; H, 4·2; N, 8·2. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·6; N, 8·0%); yield 39%. The *base*, prisms from aqueous ethanol, had m. p. 309—310° (decomp.) (Found: C, 62·8; H, 5·1; N, 14·4. $C_{10}H_{10}O_2N_2$ requires C, 63·2; H, 5·3; N, 14·7%). Its 3-*bromo-derivative*, prepared in the usual way, crystallised as needles, m. p. 283° (decomp.), from aqueous lactic acid (Found: C, 44·9; H, 3·7; N, 10·4. $C_{10}H_9O_2N_2Br$ requires C, 44·6; H, 3·4; N, 10·4%) and gave a *hydrobromide* as needles, m. p. 231—232° (decomp.), from glacial acetic acid (Found: C, 34·1; H, 3·1; N, 8·0. $C_{10}H_{10}O_2N_2Br_2$ requires C, 34·3; H, 2·9; N, 8·0%).

2-*Amino-4-chloro-7-methoxyquinoline*.—2-Amino-4-hydroxy-7-methoxyquinoline (30·5 g.) was boiled with phosphorus oxychloride (150 ml.) for 8 hr. The solid obtained by evaporation, when boiled for 90 min. with 25% aqueous hydrochloric acid (300 ml.), gave the *hydrochloride* which crystallised as solvated prisms, m. p. 210° (decomp.), from dilute hydrochloric acid (Found: C, 48·8; H, 4·3; N, 11·4; Cl, 28·2. $C_{10}H_{10}ON_2Cl_2$ requires C, 49·0; H, 4·1; N, 11·4; Cl, 28·9%). On basification, this salt furnished the *chloroquinoline* (28 g., 87%), prisms (from benzene), m. p. 200° (Found: C, 57·8; H, 4·3; N, 13·4; Cl, 16·7. $C_{10}H_9ON_2Cl$ requires C, 57·5; H, 4·4; N, 13·4; Cl, 17·0%). This compound could not be brought into reaction with aniline. Its *picrate*, dark red prisms from 2-ethoxyethanol, had m. p. 270° (decomp.) (Found: C, 43·7; H, 2·9; Cl, 7·6. $C_{16}H_{12}O_8N_5Cl$ requires C, 43·9; H, 2·8; Cl, 8·1%).

4-*Chloro-2-hydroxy-7-methoxyquinoline*.—The foregoing 2-amino-derivative (10 g.) in ice-cold, concentrated sulphuric acid (30 ml.) was treated with sodium nitrite (10 g.). Next day, the mixture, when added to crushed ice, furnished 4-*chloro-2-hydroxy-7-methoxyquinoline* (68%) which crystallised from ethanol as needles, m. p. 252° (Found: C, 57·3; H, 3·6; N, 6·6. $C_{10}H_8O_2NCl$ requires C, 57·3; H, 3·8; N, 6·7%).

2 : 4-*Dichloro-7-methoxyquinoline* was produced (95%) when 4-chloro-2-hydroxy-7-methoxyquinoline was boiled with phosphorus oxychloride for 16 hr.; it formed needles, m. p. 132—133°,

[12] von Braun, Gmelin, and Schultheiss, *Ber.*, 1923, **56**, 1338.
[13] Bradford, Elliott, and Rowe, *J.*, 1947, 437.

from ethanol (Found: C, 52·6; H, 3·1; Cl, 30·9. $C_{10}H_7ONCl_2$ requires C, 52·7; H, 3·1; Cl, 31·1%).

1 : 2 : 3 : 4-*Tetrahydro-7-methoxyquinoline.*—(i) 7-Methoxyquinoline (10·3 g.) was heated on a steam-bath for 21 hr. with tin (50 g.) and concentrated hydrochloric acid (130 ml.). Excess of alkali was added; the steam-volatile material, after isolation and fractionation, afforded 1 : 2 : 3 : 4-*tetrahydro-7-methoxyquinoline* (3·4 g., 32%), b. p. 127—128°/1·8 mm. (Found: C, 73·7; H, 7·9; N, 8·7. $C_{10}H_{13}ON$ requires C, 73·6; H, 8·0; N, 8·6%). Its *benzoyl derivative* crystallised from light petroleum (b. p. 40—60°) as prisms, m. p. 81—82° (Found: C, 76·4; H, 6·3; N, 5·4. $C_{17}H_{17}O_2N$ requires C, 76·4; H, 6·4; N, 5·2%), its *hydrochloride* as prisms, m. p. 181°, from methanol–ethyl acetate (Found: C, 60·2; H, 6·6. $C_{10}H_{14}ONCl$ requires C, 60·1; H, 7·1%), and its *picrate* as rods, m. p. 156° (decomp.), from ethanol (Found: C, 48·9; H, 4·2; N, 14·2. $C_{16}H_{16}O_8N_4$ requires C, 49·0; H, 4·1; N, 14·3%). The non-volatile material was collected in ether and recovered; its basic fraction, after being extracted with acid and reprecipitated, gave on fractional crystallisation from benzene–light petroleum a less-soluble *substance* as solvated prisms, m. p. 170—178° [Found: C, 74·8; H, 7·0; N, 8·1%; *M* (Rast), 657. $C_{40}H_{46}O_4N_4$ requires C, 74·3; H, 7·2; N, 8·7%; *M*, 646], and a more-soluble *substance* as prisms, m. p. 99—107° [Found: C, 74·5; H, 7·3; N, 8·2%; *M* (Rast), 326. $C_{20}H_{24}O_2N_2$ requires C, 74·0; H, 7·5; N, 8·6%; *M*, 324]. Both these compounds gave, after treatment with nitrous acid, a positive Liebermann's test.

The 7-methoxyquinoline was characterised as its picrate, m. p. 234—235°, oxalate, m. p. 120°, and dichromate, m. p. 203°. Bradford, Elliott, and Rowe [13] record m. p. 229°, 126°, and 210° respectively for these salts.

(ii) 2 : 4-Dichloro-7-methoxyquinoline, reduced by the same method, furnished the same tetrahydromethoxyquinoline in 35% yield, the identity being confirmed by the m. p. and mixed m. p. of the benzoyl derivatives, hydrochlorides, and picrates.

2-*Amino*-4 : 7-*dihydroxyquinoline.*—(i) The product of interaction of *m*-hydroxyanilinium benzenesulphonate (53·4 g.) and ethyl cyanoacetate (22·6 g.) at 210° for 1 hr., on prolonged digestion with acetone, gave a solid which, after basification, removal of ethanol-soluble impurities, purification *via* its hydrochloride, and crystallisation from ethanol afforded 2-*amino*-4 : 7-*dihydroxyquinoline* (9·4 g., 27%) as solvated prisms, m. p. 400—401° (decomp.) (Found: C, 61·2; H, 4·5; N, 16·1. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·6; N, 15·9%). Its *hydrochloride* formed solvated needles, m. p. 297—298° (decomp.), from dilute hydrochloric acid (Found: C, 50·9; H, 4·6; N, 12·7. $C_9H_9O_2N_2Cl$ requires C, 50·9; H, 4·3; N, 13·2%) and its *picrate*, solvated prisms from aqueous ethanol, had m. p. 283° (decomp.) (Found: C, 44·6; H, 2·8. $C_{15}H_{11}O_9N_5$ requires C, 44·5; H, 2·7%).

(ii) 2-Amino-4-hydroxy-7-methoxyquinoline was boiled for 10 hr. with 55% hydriodic acid; from the reaction mixture there was recovered a base (91%), m. p. 400—401° (decomp.), which yielded a hydrochloride, m. p. 297—298° (decomp.), and a picrate, m. p. 283° (decomp.), all undepressed on appropriate admixture with the foregoing compounds.

2-Amino-4-chloro-7-hydroxyquinoline was obtained (97%) as its *hydrochloride* when 2-amino-4 : 7-dihydroxyquinoline was boiled with phosphorus oxychloride for 11 hr. and the mixture was worked up as described for the corresponding 7-methoxyquinoline; it crystallised as solvated prisms, m. p. 282—283° (decomp.), from dilute hydrochloric acid (Found: C, 47·1; H, 3·7; N, 12·3; Cl, 30·9. $C_9H_8ON_2Cl_2$ requires C, 46·8; H, 3·5; N, 12·1; Cl, 30·7%); the *base* formed solvated prisms, m. p. 226°, from aqueous ethanol (Found: N, 14·3; Cl, 17·5. $C_9H_7ON_2Cl$ requires N, 14·4; Cl, 18·2%), the *benzenesulphonate* prisms, m. p. 209—210°, from propan-2-ol (Found: C, 50·7; H, 3·6; N, 7·5; Cl, 10·1. $C_{15}H_{13}O_4N_2ClS$ requires C, 51·1; H, 3·7; N, 7·9; Cl, 10·1%), and the *picrate* prisms, m. p. 290—291° (decomp.), from aqueous ethanol (Found: N, 16·4; Cl, 8·4. $C_{15}H_{10}O_8N_5Cl$ requires N, 16·5; Cl, 8·4%).

The same base was obtained (*ca.* 100%) when 2-amino-4-chloro-7-methoxyquinoline was boiled with constant-boiling hydriodic acid for 8 hr. and the mixture was basified. The identity was confirmed by comparison of the hydrochlorides and picrates.

When 2-amino-4-chloro-7-hydroxyquinoline was boiled for 10 hr. with 20% potassium hydroxide in ethylene glycol, 2-amino-4 : 7-dihydroxyquinoline (57%) was produced.

2-*Amino*-5- *and* -7-*chloro*-4-*hydroxyquinoline.*—The cooled melt obtained after heating together *m*-chloroanilinium benzenesulphonate (129 g.) and ethyl cyanoacetate (51 g.) for 90 min. at 210° was digested with chloroform for 24 hr. 2-*Amino*-7-*chloro*-4-*hydroxyquinolinium benzenesulphonate* (35 g., 22%) which separated from the cold solution gave prisms, m. p.

272—273°, after recrystallisation from aqueous ethanol (Found: C, 51·2; H, 3·5; N, 7·3. $C_{15}H_{13}O_4N_2ClS$ requires C, 51·1; H, 3·7; N, 7·9%); the *base* formed rods, m. p. 348—349° (decomp.), from aqueous ethanol (Found: C, 55·9; H, 3·8. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6%), and the *picrate* prisms, m. p. 290—291° (decomp.), from aqueous ethanol (Found: N, 16·2. $C_{15}H_{10}O_8N_5Cl$ requires N, 16·5%). At 5°, the chloroform mother-liquor deposited *2-amino-5-chloro-4-hydroxyquinolinium benzenesulphonate* (7 g., 4%) which crystallised from aqueous ethanol as prisms, m. p. 280° (decomp.), depressed to 240—252° by the 7-isomer (Found: C, 51·3; H, 3·6; N, 8·3. $C_{15}H_{13}O_4N_2ClS$ requires C, 51·1; H, 3·7; N, 7·9%); this yielded the *base*, plates (from aqueous ethanol), m. p. 352—353° (decomp.), depressed to 310—313° (decomp.) by the 7-isomer (Found: C, 55·4; H, 3·7; N, 14·1. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6; N, 14·4%), and *picrate*, needles, m. p. 243—244° (decomp.), from aqueous ethanol (Found: C, 42·8; H, 2·8. $C_{15}H_{10}O_8N_5Cl$ requires C, 42·5; H, 2·4%).

7-Chloro-3 : 4-dihydro-2-hydroxy-3-hydroxyimino-4-oxoquinoline.—Sodium nitrite (5 g.) was gradually stirred into a solution of 2-amino-7-chloro-4-hydroxyquinoline (4·9 g.) in concentrated sulphuric acid (22 ml.) at 0°. Next day, the paste was mixed with ice. The glacial acetic acid-soluble fraction of the precipitated material afforded with sodium hydroxide a green sodium salt which, after decomposition with dilute hydrochloric acid and crystallisation from glacial acetic acid, gave the required *2-hydroxy-3-hydroxyimino-derivative* as green-yellow prisms, m. p. 233° (decomp.) (2·7 g., 48%) (Found: C, 48·1; H, 2·4; N, 12·3; Cl, 15·1. $C_9H_5O_3N_2Cl$ requires C, 48·1; H, 2·2; N, 12·5; Cl, 15·8%).

6-Chloroisatin.—The foregoing oxoquinoline (1·8 g.) when boiled with 30% sulphuric acid (70 ml.) for 1 hr. furnished 6-chloroisatin (1·1 g., 75%) which crystallised from dilute sulphuric acid as orange prisms, m. p. 256·5—258°; Senear *et al.*[14] record m. p. 258—259° (Found: C, 52·4; H, 2·4; N, 8·0. Calc. for $C_8H_4O_2NCl$: C, 52·9; H, 2·2; N, 7·7%). On oxidation with hydrogen peroxide,[15] this isatin gave 4-chloroanthranilic acid,[16] m. p. and mixed m. p. 236—237° (decomp.); reduction of the diazonium salt derived from this amine with hypophosphorous acid furnished *p*-chlorobenzoic acid, m. p. and mixed m. p. 242—243°.

2-Amino-4 : 7-dichloroquinoline was prepared (81%) as its *hydrochloride* from 2-amino-7-chloro-4-hydroxyquinoline and phosphorus oxychloride and formed needles, m. p. 246·5—247·5°, from dilute hydrochloric acid (Found: C, 43·5; H, 3·1; N, 11·5. $C_9H_7N_2Cl_3$ requires C, 43·3; H, 2·8; N, 11·2%); this afforded the *base*, needles, m. p. 201—202°, from benzene (Found: N, 13·5; Cl, 33·6. $C_9H_6N_2Cl_2$ requires N, 13·2; Cl, 33·3%), and *picrate*, needles, m. p. 285—286° (decomp.), from glacial acetic acid (Found: C, 40·8; H, 2·0; N, 15·5; Cl, 16·4. $C_{15}H_9O_7N_5Cl_2$ requires C, 40·7; H, 2·1; N, 15·8; Cl, 16·0%). The hydroxyl group in 2-amino-4-chloro-7-hydroxyquinoline was not attacked by phosphorus oxychloride, phosphorus pentachloride, and cetyltrimethylammonium bromide.[17]

The authors gratefully acknowledge their indebtedness to Mr. E. C. Wilmshurst and Miss M. E. Thompson, Boots Pure Drug Co., Ltd., for the biological tests.

THE UNIVERSITY, NOTTINGHAM. [*Received, August 13th*, 1957.]

[14] Senear, Sargent, Mead, and Koepfli, *J. Amer. Chem. Soc.*, 1946, **68**, 2695.
[15] Mayer and Schulze, *Ber.*, 1925, **58**, 1465.
[16] Cohn, *Monatsh.*, 1901, **22**, 473.
[17] Cairns and Kermack, *J.*, 1950, 1322.