Cyclic Amidines. Part III. 2-Acylamino-4-alkoxyquinolines.*

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The preparation of a number of 2-acylamino-4-alkoxyquinolines is described. 2 : 4-Dihydroxy- and 2-amino-4-hydroxy-quinoline afford the 3-bromo-derivatives on bromination. None of the compounds possessed useful biological activity.

THE ready availability of 2-amino-4-hydroxyquinoline (Part II *) prompted this investigation of the preparation of its ethers and acyl derivatives for biological study.

A considerable excess of diazomethane was required for the methylation of the hydroxyl group of 2-amino-4-hydroxyquinoline. Its silver or sodium salt with methyl iodide afforded only 5% of the desired product. However, homologous ethers were obtained in satisfactory yield by treatment of the silver salt with an alkyl halide or alkylene dihalide. Evidence for their being 4-alkoxyquinolines was provided by dealkylation. The product obtained by treatment of the silver salt with ethyl bromide afforded 2-amino-4-hydroxyquinoline on being boiled with aqueous hydrobromic acid; the corresponding *n*-butyl ether was

* Part II, *J.*, 1954, 3878.

converted as described below into 4-*n*-butoxy-2-hydroxyquinoline which furnished 2 : 4-dihydroxyquinoline when distilled with aqueous hydrobromic acid. An attempt to effect an alkoxyl interchange with 2-amino-4-butoxyquinoline in the manner described for other 4-alkoxyquinolines (Berinzaghi, Deulofeu, Labriola, and Muruzabal, *J. Amer. Chem. Soc.*, 1943, **65**, 1357) was unsuccessful.

2-Amino-4-methoxyquinoline was acylated in boiling benzene in the presence of triethylamine. The formation of 2-acetamido-4-methoxyquinoline both by acetylation and methylation served to confirm the constitution assigned to the product of acetylation of 2-amino-4-hydroxyquinoline.

2-Amino-4 : 8-dihydroxyquinoline, its 5-methyl homologue, and 2-amino-4 : 6-dihydroxyquinoline were obtained by demethylation of the corresponding 2-amino-4-hydroxy-6- or -8-methoxyquinolines. Interaction of ethyl cyanoacetate and *o*-hydroxyanilinium benzenesulphonate did not furnish 2-amino-4 : 8-dihydroxyquinoline; the products obtained were 2-methylbenzoxazole, *oo'*-dihydroxymalondianilide, and ammonium benzenesulphonate. The production of benzoxazoles from salts of *o*-hydroxyaniline and nitriles has been described by Hölljes and Wagner (*J. Org. Chem.*, 1944, **9**, 31) and we have observed the loss of the ethoxycarbonyl group in reactions of the foregoing type (Part II, *loc. cit.*).

On treatment with nitrous acid in solution in concentrated sulphuric acid, 2-amino-4-*n*-butoxyquinoline afforded 4-*n*-butoxy-2-hydroxyquinoline; in hydrochloric acid, the product contained also 4-*n*-butoxy-2-chloroquinoline.

Bromination of 2-amino-4-hydroxyquinoline in glacial acetic acid furnished a monobromo-derivative which on treatment with nitrous acid gave the same bromo-2 : 4-dihydroxyquinoline, m. p. 232—233° (decomp.), as was obtained by a similar bromination of 2 : 4-dihydroxyquinoline. The same monobromo-derivative, together with a dibromo-derivative, was formed when the bromination was carried out in formic acid (98—100%). It appeared likely that monobromination would occur in the 3-position in both cases. If the 3-position were free in the 2-amino-bromo-4-hydroxyquinoline, interaction with nitrous acid would, by analogy with the behaviour of 2-amino-4-hydroxyquinoline (Gabriel, *Ber.*, 1918, **51**, 1500) and 2 : 4-dihydroxyquinoline (Baeyer and Homolka, *Ber.*, 1883, **16**, 2216), afford a 3 : 4-dihydro-3-hydroxyiminoquinoline. Further, nitration of 2 : 4-dihydroxyquinoline (Gabriel, *loc. cit.*), and bromination of 4-hydroxyquinoline (Riegel, Lappin, Albisetti, Adelson, Dodson, Ginger, and Baker, *J. Amer. Chem. Soc.*, 1946, **68**, 1229; Schofield and Swan, *J.*, 1950, 384) and 2-hydroxylepidine (Knorr, *Annalen*, 1886, **236**, 69), result in the entry of the substituent in the 3-position. Meyer and Heimann (*Compt. rend.*, 1936, **203**, 264) state that 3-bromo-2 : 4-dihydroxyquinoline, prepared by bromination of 2 : 4-dihydroxyquinoline in formic acid (100%), has m. p. 281° and that its orientation can be proved by oxidation with potassium permanganate to 3-bromo-2 : 4-dihydroxyquinolinic acid; no confirmatory analytical data are provided. We find that the behaviour of 2 : 4-dihydroxyquinoline on oxidation with potassium permanganate is similar to that of 4-hydroxyquinoline (Friedländer and Ostermaier, *Ber.*, 1882, **15**, 332); isatin is produced in both cases. The bromo-2 : 4-dihydroxyquinoline, m. p. 232—233° (decomp.), prepared by us, similarly afforded isatin. Accordingly, we believe the bromine to occupy the 3-position in this bromo-2 : 4-dihydroxyquinoline and hence also in the 2-amino-bromo-4-hydroxyquinoline.

Many of the compounds described in this communication were weakly spasmolytic when tested against acetylcholine and histamine but the effect was much less than that of known antagonists; the most active was 2-benzamido-4-methoxyquinoline. Some amœbicidal activity was exhibited *in vitro* by 2-amino-4-propoxyquinoline and its homologues but was not retained *in vivo*.

Experimental

2-Amino-4-methoxyquinoline.—A solution of 2-amino-4-hydroxyquinoline (16 g.) in methanol (400 c.c.) was treated at 3° with nine successive quantities of a wet ethereal solution (130 ml.) of diazomethane each prepared from nitrosomethylurea (14 g., 120 mols.) during 6 hr. After 3 days, the solvent was evaporated under reduced pressure, and, after removal of unchanged

2-amino-4-hydroxyquinoline (1 g., 6%) by extraction of the residue with sodium hydroxide, *2-amino-4-methoxyquinoline* was obtained as plates (12·3 g., 71%), m. p. 195—196°, by crystallisation of the alkali-insoluble material from benzene (Found: C, 68·6; H, 5·8; N, 16·2. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·8; N, 16·1%). Its *benzenesulphonate* separated from *iso*propyl alcohol in prisms, m. p. 203—204° (Found: C, 58·0; H, 4·9; N, 8·3. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9; N, 8·4%). The yield in this preparation fell markedly with any decrease in the quantity of diazomethane.

2-Amino-4-ethoxyquinoline.—A suspension of the silver salt [prepared from 2-amino-4-hydroxyquinoline (12 g.), sodium (2·3 g., 1·3 g.-atoms), and silver nitrate (17 g., 1·3 mol.)] in aqueous ethanol (250 ml.) was boiled with ethyl bromide (22 g., 2·7 mols.), added gradually during 18 hr. The suspension was filtered, and the crude base, obtained by evaporation of the filtrate and treatment of the residue with sodium hydroxide, afforded the *benzenesulphonate* on the addition of aqueous-ethanolic benzenesulphonic acid; it formed needles (9·8 g., 38%), m. p. 229°, from *iso*propyl alcohol (Found: C, 59·1; H, 5·2; N, 8·0. $C_{17}H_{18}O_4N_2S$ requires C, 59·0; H, 5·2; N, 8·1%). *2-Amino-4-ethoxyquinoline* crystallised from benzene as plates, m. p. 164—165° (Found; C, 70·6; H, 6·1; N, 14·7. $C_{11}H_{12}ON_2$ requires C, 70·2; H, 6·4; N, 14·9%). A solution of 2-amino-4-ethoxyquinoline (3 g.) in aqueous hydrobromic acid (48%; 30 ml.) was boiled for 3 hr., distilled to remove most of the acid, and made alkaline to Titan-yellow with aqueous sodium hydroxide; the clear solution, on being neutralised with hydrochloric acid, afforded 2-amino-4-hydroxyquinoline (2·2 g., 86%), which, after recrystallisation from water, had m. p. and mixed m. p. 300—302° (decomp.). Its picrate had m. p. 263—265° (decomp.), undepressed by an authentic specimen (Part II, *loc. cit.*).

The following ethers and their salts were prepared in a similar manner:

2-Amino-4-n-propoxyquinoline, needles, m. p. 142—142·5°, from benzene (Found: C, 71·3; H, 7·4; N, 13·6. $C_{12}H_{14}ON_2$ requires C, 71·3; H, 7·0; N, 13·9%); yield 65%. *Benzenesulphonate*, prisms, m. p. 191·5—192·5°, from ethanol (Found: C, 60·1; H, 5·9; N, 7·9. $C_{18}H_{20}O_4N_2S$ requires C, 60·0; H, 5·6; N, 7·8%).

2-Amino-4-isopropoxyquinoline, prisms (61%), m. p. 140°, from benzene (Found: C, 70·9; H, 6·8; N, 13·7%). *Benzenesulphonate*, prisms, m. p. 212°, from ethanol (Found: C, 60·2; H, 5·7; N, 7·8%).

2-Amino-4-n-butoxyquinoline, needles (46%), m. p. 167—169°, from light petroleum (b. p. 100—120°) (Found: C, 71·9; H, 7·2; N, 13·2. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·5; N, 13·0%). *Benzenesulphonate*, prisms, m. p. 175—176°, from ethanol (Found: C, 60·9; H, 6·1; N, 7·7. $C_{19}H_{22}O_4N_2S$ requires C, 61·0; H, 5·9; N, 7·5%). *Nitrate*, needles, m. p. 172—173°, from *iso*propyl alcohol (Found: C, 56·0; H, 6·4; N, 15·1. $C_{13}H_{17}O_4N_3$ requires C, 55·9; H, 6·1; N, 15·1%).

2-Amino-4-n-pentyloxyquinoline, needles (74%), m. p. 141—142°, from benzene (Found C, 72·8; H, 7·6; N, 12·2. $C_{14}H_{18}ON_2$ requires C, 73·0; H, 7·9; N, 12·2%). *Benzenesulphonate*, needles, m. p. 166·5—167°, from ethanol (Found: C, 61·9; H, 6·1; N, 7·3. $C_{20}H_{24}O_4N_2S$ requires C, 61·8; H, 6·2; N, 7·2%).

2-Amino-4-1'-methylbutoxyquinoline, needles (37%), m. p. 101—102°, from *cyclo*hexanol (Found: C, 72·7; H, 7·9; N, 12·3. $C_{14}H_{18}ON_2$ requires C, 73·0; H, 7·9; N, 12·2%). *Benzenesulphonate*, cubes, m. p. 191—191·5°, from *iso*propyl alcohol (Found: C, 62·2; H, 5·9; N, 7·4. $C_{20}H_{24}O_4N_2S$ requires C, 61·8; H, 6·2; N, 7·2%).

2-Amino-4-n-octyloxyquinoline, needles (63%), m. p. 128—129°, from *cyclo*hexanol (Found: C, 75·0; H, 9·1; N, 10·4. $C_{17}H_{24}ON_2$ requires C, 75·0; H, 8·9; N, 10·3%). *Benzenesulphonate*, needles, m. p. 145—146°, from *iso*propyl alcohol (Found: C, 64·3; H, 7·1; N, 6·5. $C_{23}H_{30}O_4N_2S$ requires C, 64·2; H, 7·0; N, 6·5%).

1:3-Bis-(2-aminoquinolyl-4-oxy)propane, prisms (49%), m. p. 256—258° (decomp.), from aqueous ethanol (Found: C, 70·1; H, 5·8; N, 15·2. $C_{21}H_{20}O_2N_4$ requires C, 70·0; H, 5·6; N, 15·5%). *Dibenzenesulphonate*, needles, m. p. 227·5—228·5° (decomp.), from ethanol (Found: loss at 110°/vac., 6·8; C, 57·8; H, 5·0; N, 7·7. $C_{33}H_{32}O_8N_4S_2,C_2H_6O$ requires C_2H_6O, 6·4; C, 58·1; H, 5·3; N, 7·7%).

2-Benzamido-4-methoxyquinoline.—Anhydrous 2-amino-4-methoxyquinoline (2·1 g.) was boiled for 5 hr. in benzene (50 ml.) with benzoyl chloride (2·1 g., 1·25 mols.) in the presence of triethylamine (3 g., 2·5 mols.). The suspension was evaporated to dryness and the residue, after crystallisation first from aqueous ethanol and then from ether, afforded the *benzoyl* derivative as prisms, m. p. 77—81° (1·4 g., 42%) (Found: N, 9·9. $C_{17}H_{14}O_2N_2$ requires N, 10·1%).

2-p-Anisamido-4-methoxyquinoline, prepared in a similar manner, crystallised from aqueous

ethanol as needles, m. p. 133—134°; yield 84% (Found: N, 9·1. $C_{18}H_{16}O_3N_2$ requires N, 9·1%). Unchanged 2-amino-4-methoxyquinoline was recovered when the acylation was attempted under Schotten–Baumann conditions.

4-Methoxy-2-piperonamidoquinoline occurred as needles (75%), m. p. 187·5°, when crystallised from ethanol (Found: C, 66·8; H, 4·3; N, 8·5. $C_{18}H_{14}O_4N_2$ requires C, 67·1; H, 4·4; N, 8·7%).

2-(3 : 4-*Dimethoxybenzamido*)-4-*methoxyquinoline* separated as needles (97%), m. p. 154°, from ethanol (Found: C, 67·5; H, 5·4; N, 8·6. $C_{19}H_{18}O_4N_2$ requires C, 67·4; H, 5·4; N, 8·3%).

2-Diphenylacetamido-4-methoxyquinoline was obtained as prisms (77%), m. p. 156—157°, from methanol (Found: C, 78·4; H, 5·1; N, 7·6. $C_{24}H_{20}O_2N_2$ requires C, 78·2; H, 5·5; N, 7·6%).

4-Methoxy-2-phenylacetamidoquinoline crystallised from ethanol as plates (66%), m. p. 245—246° (decomp.) (Found: C, 73·9; H, 5·6; N, 9·7. $C_{18}H_{16}O_2N_2$ requires C, 74·0; H, 5·5; N, 9·6%). When the acylation was effected in pyridine solution and in aqueous sodium hydroxide, the yields were 14% and 31% respectively.

2-Acetamido-4-hydroxyquinoline.—(i) Anhydrous 2-amino-4-hydroxyquinoline (4 g.) was boiled for 30 min. with acetic anhydride (5·5 g., 2 mols.) in glacial acetic acid (6 ml.) containing concentrated sulphuric acid (2 drops). The mixture was poured into water and the precipitated *acetyl* derivative crystallised as needles (3·7 g., 73%), m. p. 302—303° (decomp.), from dilute acetic acid (Found in material dried at 150°/vac.: C, 65·3; H, 5·1; N, 13·9. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0; N, 13·9%). This compound was soluble in aqueous sodium hydroxide and gave the same colour as does 2-amino-4-hydroxyquinoline with ferric chloride.

(ii) When the aminoquinoline (4 g.) was boiled for 3 hr. with acetyl chloride (6·4 g., 3·3 mols.) in pyridine (60 ml.) containing piperidine (2 drops), the *hydrochloride* of the acetyl derivative was obtained; it formed needles, m. p. 315—317° (decomp.) (5·3 g., 89%), from water (Found: C, 55·7; H, 4·6. $C_{11}H_{11}O_2N_2Cl$ requires C, 55·4; H, 4·6%). A sample of the base, m. p. 302—303° (decomp.), recovered from the hydrochloride did not depress the m. p. of the foregoing base. Acetylation could not be effected either in the absence of sulphuric acid or by Chattaway's method (*J.*, 1931, 2495).

2-Acetamido-4-methoxyquinoline was prepared (i) in 93% yield by acetylation of the aminoquinoline in the presence of sulphuric acid and (ii) in 80% yield by methylation of 2-acetamido-4-hydroxyquinoline (0·55 g.) in methanol (40 ml.) with diazomethane obtained from nitrosomethylurea (7 g.); it formed plates, m. p. 250—251°, from ethanol (Found: N, 12·9. $C_{12}H_{12}O_2N_2$ requires N, 13·0%).

2-Amino-4 : 6-dimethoxyquinoline was prepared by treatment of 2-amino-4 : 6-dihydroxyquinoline with diazomethane and crystallised from benzene as plates, m. p. 188·5—189° (43%) (Found: C, 64·7; H, 5·8; N, 14·1. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%). From the mother-liquors 2-amino-4-hydroxy-6-methoxyquinoline, m. p. and mixed m. p. 293—295° (decomp.), was isolated in 32% yield.

2-Amino-4 : 6-dihydroxyquinolinium bromide (yield 92%) separated when 2-amino-4-hydroxy-6-methoxyquinoline was boiled for 7 hr. with hydrobromic acid; on recrystallisation from glacial acetic acid, this salt was obtained as needles, m. p. 280—281° (decomp.) (Found: C, 41·8; H, 3·8. $C_9H_9O_2N_2Br$ requires C, 42·0; H, 3·5%). The m. p. of the base prepared from the bromide was undepressed on admixture with an authentic specimen (Part II, *loc. cit.*).

2-Amino-4 : 8-dihydroxyquinoline, prepared in 95% yield by demethylation of the corresponding 8-methoxyquinoline with hydriodic acid, was isolated as its *hydrochloride* which crystallised as hygroscopic needles, m. p. 301—302° (decomp.), from dilute hydrochloric acid (Found, in material dried at 150°/vac.: N, 13·4. $C_9H_9O_2N_2Cl$ requires N, 13·2%). Its *picrate* crystallised from aqueous ethanol as yellow prisms, m. p. 253—255° (decomp.) (Found: C, 44·3; H, 3·0. $C_{15}H_{11}O_9N_5$ requires C, 44·4; H, 2·7%). This demethylation could not be effected with aqueous hydrobromic acid (48%) or with hydrobromic acid (55%) in glacial acetic acid.

2-Amino-4 : 8-dihydroxy-5-methylquinoline.—The 8-methoxyquinoline was boiled with hydriodic acid for 12 hr. and the solution was evaporated to dryness. On addition of hydrochloric acid to an aqueous extract of the residue the *hydrochloride* separated in 95% yield; it gave prisms, m. p. 333—334° (decomp.), from ethanol (Found: C, 53·2; H, 5·1. $C_{10}H_{11}O_2N_2Cl$ requires C, 53·0; H. 4·9%). Its *picrate* was obtained as yellow needles, m. p. 268° (decomp.), from aqueous ethanol (Found: C, 46·2; H, 3·1. $C_{16}H_{13}O_9N_5$ requires C, 45·8; H, 3·1%).

Interaction of EthylCyanoacetate and o-Hydroxyanilinium Benzenesulphonate.—The nitrile

(22·6 g.) and the salt (53·4 g., 1 mol.) reacted exothermically when heated at 180° for 1 hr. Ammonium benzenesulphonate (23·4 g., 67%) remained undissolved when the cooled melt was extracted with chloroform. The chloroform extract on distillation afforded 2-methylbenzoxazole (6 g., 22%), b. p. 200—201° (Ladenburg, *Ber.*, 1876, **9**, 1524, records b. p. 200—201°). It was further characterised by conversion into *o*-hydroxyacetanilide, m. p. and mixed m. p. 209°. By crystallisation of the non-volatile residue from ethanol, *oo'-dihydroxymalondianilide* (4·8 g., 17%) was obtained as plates, m. p. 233·5—234·5° (decomp.) [Found: C, 63·1; H, 4·5; N, 9·8%; *M* (Rast), 266. $C_{15}H_{14}O_4N_2$ requires C, 62·9; H, 4·9; N, 9·8%; *M*, 286].

o-*Hydroxyanilinium benzenesulphonate*, needles from equal volumes of ethanol and ethyl acetate, had m. p. 237—238° (decomp.) (Found: N, 5·3. $C_{12}H_{13}O_4NS$ requires N, 5·2%).

Interaction of 2-Amino-4-n-butoxyquinoline and Nitrous Acid.—(i) A suspension of 2-amino-4-*n*-butoxyquinoline (6·5 g.) in concentrated hydrochloric acid was treated at 0° with sodium nitrite (4·1 g.); after being kept overnight at 0°, there was added further sodium nitrite (2 g.) and the mixture was warmed on a steam-bath for 10 min. The precipitate afforded 4-n-*butoxy-2-hydroxyquinoline*, m. p. 184—185° (5·1 g., 78%), as prisms on crystallisation from aqueous ethanol (Found: C, 72·0; H, 7·2; N, 6·7. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 7·0; N, 6·5%). 4-n-*Butoxy-2-chloroquinoline* (1·35 g., 19%), liberated from the mother-liquors, crystallised as prisms, m. p. 88—89°, from aqueous methanol (Found: C, 66·5; H, 6·3; N, 5·8; Cl, 14·6. $C_{13}H_{14}ONCl$ requires C, 66·3; H, 6·0; N, 6·0; Cl, 15·1%).

A solution of 4-*n*-butoxy-2-hydroxyquinoline (1 g.) in aqueous hydrobromic acid (48%; 30 ml.) was distilled at atmospheric pressure until 25 ml. of distillate, which contained butyl bromide, had been collected. The residue was made alkaline to Titan-yellow with aqueous sodium hydroxide, filtered, and neutralised with hydrochloric acid. The precipitated 2 : 4-dihydroxyquinoline (0·3 g.), m. p. 352—354° (decomp.), was characterised as its acetyl derivative, m. p. 213—214°, undepressed by an authentic specimen (Ashley, Perkin, and Robinson, *J.*, 1930, 382).

(ii) 2-Amino-4-*n*-butoxyquinoline (5 g.), dissolved in concentrated sulphuric acid (10 ml.) and treated with sodium nitrite in the usual way, furnished the 2-hydroxyquinoline (4 g., 80%), m. p. and mixed m. p. 184—185°.

2-Amino-3-bromo-4-hydroxyquinoline.—2-Amino-4-hydroxyquinoline (2 g.), dissolved in glacial acetic acid (32 ml.), was treated during 10 min. at the b. p. with bromine (2 g., 1 mol.) dissolved in glacial acetic acid (5 ml.); boiling was continued for 30 min. Next day, the *2-amino-3-bromo-4-hydroxyquinolinium bromide* (3·7 g., 93%) was collected; it formed needles, m. p. 249—252° (decomp.), unchanged after recrystallisation from glacial acetic acid (Found: N, 9·0. $C_9H_8ON_2Br_2$ requires N, 8·8%). The *base* crystallised from aqueous ethanol as rods, m. p. 280—281° (decomp.) (Found: N, 11·9. $C_9H_7ON_2Br$ requires N, 11·7%). Its *picrate* separated as yellow elongated prisms, m. p. 244—245° (decomp.), from ethanol (Found: N, 15·2. $C_{15}H_{10}O_8N_5Br$ requires N, 15·0%).

3-Bromo-2 : 4-dihydroxyquinoline.—(i) The crude product which separated when 2-amino-3-bromo-4-hydroxyquinoline (12 g.) was dissolved in concentrated sulphuric acid (25 ml.), treated with sodium nitrite (12 g., 3·5 mols.) at 0° during 20 min., allowed to warm to room temperature, and poured on crushed ice furnished *3-bromo-2 : 4-dihydroxyquinoline* as plates, m. p. 231—232° (decomp.), on crystallisation from glacial acetic acid (Found: C, 44·8; H, 3·1; N, 5·7; Br, 33·0. $C_9H_6O_2NBr$ requires C, 45·0; H, 2·5; N, 5·8; Br, 33·3%); yield 10 g. (83%). Its *monoacetate* crystallised as needles, m. p. 228—229° (decomp.), from methanol (Found: C, 46·6; H, 3·2. $C_{11}H_8O_3NBr$ requires C, 46·8; H, 2·8%).

(ii) 2 : 4-Dihydroxyquinoline (1 g.), treated with bromine (1 g., 1 mol.) in the manner described for 2-amino-3-bromo-4-hydroxyquinoline, yielded 3-bromo-2 : 4-dihydroxyquinoline (1·35 g., 90%), m. p. and mixed m. p. 232—233° (decomp.) (Found: N, 5·6. Calc. for $C_9H_6O_2NBr$: N, 5·8%). The acetate prepared from this material had m. p. and mixed m. p. 228—229° (decomp.).

(iii) 2 : 4-Dihydroxyquinoline (2 g.), dissolved in formic acid (98—100%; 30 ml.), was treated with a solution of bromine (2 g., 1 mol.) in formic acid (12 ml.) as described for 2-amino-3-bromo-4-hydroxyquinoline. By fractional crystallisation of the crude product (2·65 g.; m. p. 180—190°) from methanol, there were obtained 3-bromo-2 : 4-dihydroxyquinoline, m. p. and mixed m. p. 232—234° (decomp.) (Found: N, 5·5; Br, 33·6. Calc. for $C_9H_6O_2NBr$: N, 5·8; Br, 33·3%), and a *dibromo-2 : 4-dihydroxyquinoline*, needles, m. p. 276—278° (decomp.), from methanol (Found: C, 34·1; H, 1·9; N, 4·3; Br, 51·2. $C_9H_5O_2NBr_2$ requires C. 33·9; H, 1·6; N, 4·4; Br, 50·2%). The *acetate* of the dibromo-derivative crystallised as needles,

m. p. 254° (decomp.), from glacial acetic acid (Found: N, 4·0; Br, 45·0. $C_{11}H_7O_3NBr_2$ requires N, 3·9; Br, 44·3%).

Oxidation of 2 : 4-*Dihydroxyquinoline.*—2 : 4-Dihydroxyquinoline (5 g.), dissolved in aqueous sodium hydroxide (10%, 50 ml.), was treated at 80—85° with saturated aqueous potassium permanganate (200 ml.). The filtrate from the manganese dioxide was adjusted to pH 6 and unchanged 2 : 4-dihydroxyquinoline (1·45 g.) was removed; the methanol-soluble fraction of the water-soluble material, when warmed in acid solution, furnished isatin (1·85 g., 41%), m. p. and mixed m. p. 200—201°.

Oxidation of 3-*Bromo*-2 : 4-*dihydroxyquinoline.*—3-Bromo-2 : 4-dihydroxyquinoline (6 g.), oxidised with saturated aqueous potassium permanganate (300 ml.) in alkaline solution as described in the foregoing experiment, afforded crude isatin (1·2 g., 33%) which after two recrystallisations from ethanol had m. p. and mixed m. p. 199—200°.

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