Cyclic Amidines. Part II. Derivatives of 2-Amino-4-hydroxyquinoline.*

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Ethyl cyanoacetate when heated with an arylammonium arenesulphonate affords a derivative of 2-amino-4-hydroxyquinoline; with an α-substituted ethyl cyanoacetate the corresponding 3-substituted quinolines are obtained.

2-AMINO-4-HYDROXYQUINOLINE has hitherto been obtained from ethyl α-cyano-α-*o*-nitrobenzoylacetate by reduction and from ethyl α-cyano-α-*o*-phthalimidobenzoylacetate by hydrolysis (Gabriel, *Ber.*, 1918, **51**, 1500); in these reactions, cyclisation apparently involves the addition of an intermediately formed primary amino-group to the cyano-group. The inaccessibility of the necessary derivatives of ethyl cyanoacetate limits the general application of this method.

For the synthesis of the quinoline ring with a hydroxyl group in the 4-position there are a number of methods which involve, in the cyclising stage, elimination of an alcohol from an alkoxyl fragment of an ester and hydrogen *ortho* to an amino-group attached to an aromatic nucleus; the best known examples are the Conrad–Limpach reaction (*Ber.*, 1887, **20**, 944) and the cyclisation of ethyl β-arylamino-α-ethoxycarbonylacrylates (Gould and Jacobs, *J. Amer. Chem. Soc.*, 1939, **61**, 2890). It appeared probable that an *N*-arylamidine formed from ethyl cyanoacetate and an arylamine would undergo an analogous cyclisation, to a 2-amino-4-hydroxyquinoline derivative.

In agreement, ethyl cyanoacetate and anilinium benzenesulphonate at 210° (1—2 hr.) yielded 2-amino-4-hydroxyquinolinium benzenesulphonate (II; R = X = Y = H, Z = $Ph{\cdot}SO_3$); and a salt of a substituted arylamine gave the appropriately substituted 2-amino-4-hydroxyquinoline. The positions of the substituents in the nine examples given in the

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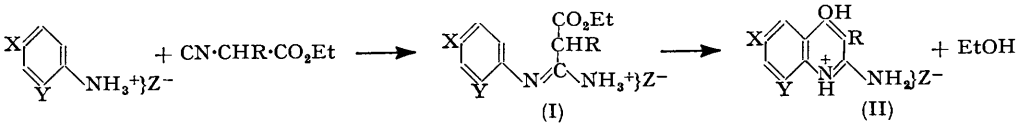
Experimental section follow from the orientation of the arylamines employed. The production of derivatives of 2-amino-4-hydroxyquinoline having a substituent in the 3-position involved the use of an α-substituted ethyl cyanoacetate; six examples of this are described in the Experimental section. The benzenesulphonate of *p*-nitroaniline and ethyl cyanoacetate reacted violently and none of the desired product was isolated.



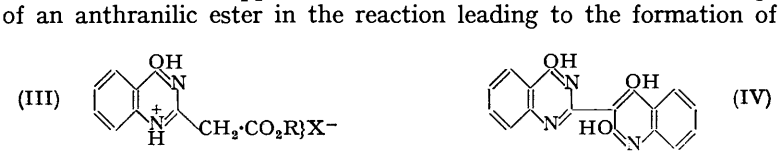
A number of side reactions involving loss of the ethoxycarbonyl group of the cyanoacetate occurred, since acetanilide, *N*-phenylacetamidine, α-cyanoacetanilide, and malondianilide were found amongst the by-products from the preparation of 2-amino-4-hydroxyquinoline. α-Cyanoacetanilide and α-*N*-phenylamidinoacetanilide were formed together with 2-amino-4-hydroxyquinoline when anilinium benzenesulphonate and ethyl cyanoacetate were heated together at 180° for 30 min. However, it appears unlikely that either of these anilides is the significant intermediate in the main reaction, since α-cyanoacetanilide when heated at 210° for an hour with anilinium benzenesulphonate afforded only 4% of 2-amino-4-hydroxyquinoline and 13% of α-*N*-phenylamidinoacetanilide; none of the quinoline was obtained when the benzenesulphonate of α-*N*-phenylamidinoacetanilide was heated.

α-*N*-Phenylamidinoacetanilide was also obtained by interaction of ethyl cyanoacetate and aniline in the presence of aluminium chloride (Oxley, Partridge, and Short, *J.*, 1947, 1110) and when the thio-imidic ester formed by interaction of ethyl cyanoacetate and thioglycollic acid in the presence of hydrogen chloride was heated with aniline. When the latter reaction was carried out at room temperature, α-ethoxycarbonyl-*N*-phenylacetamidine was isolated in small yield as its picrate (I; R = X = Y = H, Z = $C_6H_3O_7N_3$). This compound was not detected amongst the by-products of the reaction between ethyl cyanoacetate and anilinium benzenesulphonate.

ω-Cyanoacetophenone and anilinium benzenesulphonate afforded ω-*N*-phenylamidinoacetophenone (14%) and only 3% of 2-anilino-4-phenylquinoline. The formation of the latter presumably involved a secondary reaction of the intermediately formed 2-amino-4-phenylquinoline with the aniline salt analogous to that known to occur with *N*-phenylbenzamidine (Bernsthen, *Annalen*, 1877, **184**, 354).

Attempts to produce a 3 : 3-disubstituted dihydroquinoline derivative from a disubstituted ethyl cyanoacetate and a salt of an arylamine were unsuccessful; the ethoxycarbonyl group was lost and a derivative of *N*-phenylacetamidine was obtained. Thus ethyl α-benzyl-α-cyano-β-phenylpropionate with anilinium benzenesulphonate or *p*-methoxyanilinium benzenesulphonate furnished 1 : 3-diphenyl-2-*N*-phenylamidinopropane and 2-*N*-*p*-methoxyphenylamidino-1 : 3-diphenylpropane respectively.

It appeared reasonable to suppose that the aniline salt could with advantage be replaced by a salt of an anthranilic ester in the reaction leading to the formation of 2-amino-4-



hydroxyquinoline. However, the products isolated after interaction of ethyl cyanoacetate and the benzenesulphonate of ethyl anthranilate at 140° were 2-ethoxycarbonylmethyl-4-hydroxyquinazolinium benzenesulphonate (III; R = Et, X = Ph·SO_3) and a feebly basic, alkali-soluble compound to which the constitution (IV) is tentatively assigned. With the toluene-*p*-sulphonate of methyl anthranilate, ester exchange occurred, and (III; R = Me, X = *p*-$C_6H_4Me·SO_3$) was formed; at 210° the products were 4-hydroxy-2-methylquinazolinium benzenesulphonate and the compound (IV). The formation of this 2-methylquinazoline salt is readily accounted for since both the alkoxycarbonylmethylquinazolines (III; R = Et and Me, X = Ph·SO_3 and *p*-$C_6H_4Me·SO_3$) in boiling acetic acid afforded

4-hydroxy-2-methylquinazoline. The compound (IV) was also obtained together with 4-hydroxy-2-methylquinazoline when (III; R = Me, X = *p*-$C_6H_4Me{\cdot}SO_3$) was heated with methyl anthranilate. Vigorous treatment of (IV) with phosphorus oxychloride yielded a dichloro-compound $C_{17}H_9ON_3Cl_2$ which was soluble in aqueous alkalis.

Experimental

The following *benzenesulphonates* were prepared: 2 : 4-*dimethylanilinium*, needles, m. p. 194—195°, from *iso*propanol (Found: C, 59·9; H, 6·1. $C_{14}H_{17}O_3NS$ requires C, 60·2; H, 6·1%); o-*ethoxycarbonylanilinium*, needles (from *iso*propanol), m. p. 164° (Found: C, 55·8; H, 5·4. $C_{15}H_{17}O_5NS$ requires C, 55·7; H, 5·3%); o-*methoxyanilinium*, needles, m. p. 206°, from ethanol (Found: C, 55·6; H, 5·3. $C_{13}H_{15}O_4NS$ requires C, 55·5; H, 5·4%); 2-*methoxy-5-methylanilinium*, prisms, m. p. 202—203°, from *iso*propanol (Found: C, 57·0; H, 5·5. $C_{14}H_{17}O_4NS$ requires C, 56·9; H, 5·8%); p-*nitroanilinium*, yellow plates (from ethyl acetate), m. p. 239° (decomp.) (Found: N, 9·7. $C_{12}H_{12}O_5N_2S$ requires N, 9·5%).

2-*Amino-4-hydroxyquinoline*.—(i) Ethyl cyanoacetate (11·3 g.) and anilinium toluene-*p*-sulphonate (26·5 g., 1 mol.) were heated together at 210° for 75 min. To a solution of the cooled melt in water (40 c.c.) and ethanol (20 c.c.), saturated sodium carbonate solution (50 c.c.) was added and the mixture was shaken thoroughly with chloroform (20 c.c.). The crude product [6·45 g.; m. p. 275—280° (decomp.)] which separated overnight crystallised from aqueous ethanol or water and had m. p. 301—302° (decomp.), undepressed on admixture with an authentic specimen (Gabriel, *Ber.*, 1918, **51**, 1500); the yield was 5 g. (31%) (Found: N, 17·5. Calc. for $C_9H_8ON_2$: N, 17·5%). The *picrate* separated from ethanol as yellow needles, m. p. 258—259° (decomp.) (Found: N, 18·0. $C_{15}H_{11}O_8N_5$ requires N, 18·0%). 2-*Amino-4-hydroxyquinolinium benzenesulphonate* (34%) crystallised when the reaction mixture from ethyl cyanoacetate and anilinium benzenesulphonate was digested with chloroform and occurred as needles, m. p. 248—249°, from water (Found: N, 8·5. $C_{15}H_{14}O_4N_2S$ requires N, 8·8%); its *sulphate* crystallised from water as prisms, m. p. 247—248° [Found: C, 51·4; H, 4·4. $(C_9H_8ON_2)_2H_2SO_4$ requires C, 51·6; H, 4·3%].

The same yield was obtained when the heating was prolonged to 2 hr. or continued for 30 min. at 245°. From experiments in which the period of heating at 210° was 5 to 12 hr. and at 180°, 2 to 5 hr., 20—25% yields of 2-amino-4-hydroxyquinoline were obtained. Change in the quantity of anilinium benzenesulphonate to 0·5 or 2 mols. led to a decrease in the yield to 19%.

The chloroform solution of by-products of the reaction was evaporated to dryness and distilled in steam to remove ethylaniline. Acetanilide was extracted from the residue by means of light petroleum, and the remaining insoluble bases when fractionally crystallised as their picrates from ethanol afforded 2-amino-4-hydroxyquinolinium picrate and *N*-phenylacetamidinium picrate, m. p. and mixed m. p. 191—192° (Found: C, 46·6; H, 3·3; N, 19·1. Calc. for $C_{14}H_{13}O_7N_5$: C, 46·3; H, 3·6; N, 19·3%). Non-basic by-products were isolated by extraction of the basic by-products from a further quantity of the chloroform solution with dilute hydrochloric acid, adsorption of the mixed non-basic materials on a charcoal column, and fractional elution with methanol; in this way malondianilide, m. p. and mixed m. p. 224—225° (Found: C, 71·0; H, 4·9; N, 10·8. Calc. for $C_{15}H_{14}O_2N_2$: C, 70·9; H, 5·5; N, 11·0%), and α-cyanoacetanilide, m. p. and mixed m. p. 198—199° (Found: C, 67·6; H, 4·9; N, 17·5. Calc. for $C_9H_8ON_2$: C, 67·5; H, 5·0; N, 17·5%), were obtained.

(ii) An aqueous-ethanolic solution of the melt obtained when anilinium benzenesulphonate (25·1 g.) and ethyl cyanoacetate (11·3 g., 1 mol.) were heated together at 180° for 30 min. deposited α-cyanoacetanilide (1·3 g., 8%), m. p. and mixed m. p. 199—200°. The mother-liquor, after concentration, afforded on the addition of sodium hydroxide, crude α-*N*-*phenylamidinoacetanilide* (1·9 g., 15%), which had m. p. and mixed m. p. 176·5—177° (decomp.) (see below) after crystallisation from ethanol. Neutralisation of the alkaline mother-liquor furnished 2-amino-4-hydroxyquinoline (0·8 g., 5%), m. p. and mixed m. p. 297—299° (decomp.). In addition aniline (5·9 g., 63%) was recovered.

(iii) α-Cyanoacetanilide (3·2 g.) and anilinium benzenesulphonate (5 g., 1 mol.) were heated together at 210° for 1 hr. On being worked up in the usual manner, 2-amino-4-hydroxyquinoline (0·12 g., 4%), m. p. and mixed m. p. 300—301° (decomp.), was isolated. In addition a water-insoluble, basic fraction was obtained; from this by extraction with lactic acid and basification, there was isolated α-*N*-phenylamidinoacetanilide (0·65 g., 13%), m. p. and mixed m. p. 175—177° (decomp.) after crystallisation from benzene.

Quinisatin Oxime.—2-Amino-4-hydroxyquinoline (5 g.), dissolved in concentrated sulphuric acid (20 c.c.), was treated during 20 min. at 0° with sodium nitrite (5 g.). Next day the viscous mixture was poured on crushed ice (150 g.), and the precipitate was recrystallised from aqueous acetic acid [yield, 5·5 g., 88%; orange prisms, m. p. 209—210° (decomp.)] (Found: C, 56·6; H, 3·3. Calc. for $C_9H_6O_3N_2$: C, 56·8; H, 3·2%). Baeyer and Homolka (*Ber.*, 1883, **16**, 2216) record the m. p. as 208° (decomp.). This compound is an extremely sensitive reagent for ferrous iron; a visible blue colour is obtained at a dilution of 1 in $2·5 \times 10^7$.

2-*Amino*-4-*hydroxy*-6-*methylquinoline.*—The cooled melt obtained by heating *p*-toluidinium benzenesulphonate and ethyl cyanoacetate (1 mol.) together for 1 hr. at 210° furnished, on digestion with chloroform, crude 2-*amino*-4-*hydroxy*-6-*methylquinolinium benzenesulphonate* (39%), m. p. 260—265° (decomp.), which on recrystallisation from water (charcoal) gave needles, m. p. 283—287° (decomp.) (Found: N, 8·8. $C_{16}H_{16}O_4N_2S$ requires N, 8·4%). A solution of this salt in aqueous ethanol afforded, on the addition of ammonia, the *base* which crystallised as needles, m. p. 341—342° (decomp.), from aqueous ethanol (Found: C, 68·8; H, 5·6; N, 16·0. $C_{10}H_{10}ON_2$ requires C, 68·9; H, 5·8; N, 16·1%). Its *picrate* separated as aggregates of yellow needles, m. p. 274—275° (decomp.), from ethanol (Found: N, 17·5. $C_{16}H_{13}O_8N_5$ requires N, 17·4%).

The following quinoline derivatives were prepared in a similar manner from equimolecular quantities of ethyl cyanoacetate and the benzenesulphonate of the appropriate arylamine:

2-*Amino*-4-*hydroxy*-8-*methylquinoline*. *Benzenesulphonate* (34%), prisms, m. p. 295—296° (decomp.), from aqueous *iso*propanol (Found: C, 58·1; H, 4·9; N, 8·4. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9; N, 8·4%); *base*, needles, m. p. 308—311° (decomp.), from aqueous ethanol (Found: loss at 150°/vac., 18·7. Found, on dried material: C, 69·3; H, 5·8; N, 15·8. $C_{10}H_{10}ON_2,2H_2O$ requires H_2O, 17·1. $C_{10}H_{10}ON_2$ requires C, 69·0; H, 5·8; N, 16·1%); *picrate*, yellow rosettes, m. p. 240—241° (decomp.), from aqueous ethanol (Found: N, 17·0. $C_{16}H_{13}O_8N_5$ requires N, 17·4%).

2-*Amino*-4-*hydroxy*-6 : 8-*dimethylquinoline*. *Benzenesulphonate* (39%), needles, m. p. 309—312° (decomp.), from aqueous ethanol (Found: C, 59·3; H, 5·1; N, 7·7. $C_{17}H_{18}O_4N_2S$ requires C, 59·0; H, 5·2; N, 8·1%); *base*, plates, m. p. 317—321° (decomp.) after sintering at 300—311°, from ethanol (Found, on dried material: N, 14·7. $C_{11}H_{12}ON_2$ requires N, 14·9%); *picrate*, yellow needles, m. p. 261—262° (decomp.), from aqueous ethanol (Found: N, 16·7. $C_{17}H_{15}O_8N_5$ requires N, 16·8%).

2-*Amino*-4-*hydroxy*-6-*methoxyquinoline*. *Benzenesulphonate* (29%), plates, m. p. 297—298·5° (decomp.), from aqueous ethanol (Found: C, 55·2; H, 4·6; N, 7·6. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·6; N, 8·0%); *base*, prisms, m. p. 293—295° (decomp.), from *n*-butanol–benzene (Found: C, 62·9; H, 4·8; N, 14·6. $C_{10}H_{10}O_2N_2$ requires C, 63·1; H, 5·3; N, 14·7%); *picrate*, yellow needles, m. p. 266—267° (decomp.), from aqueous ethanol (Found: N, 16·3. $C_{16}H_{13}O_9N_5$ requires N, 16·7%).

2-*Amino*-4-*hydroxy*-8-*methoxyquinoline*. *Benzenesulphonate* (28%), needles, m. p. 301—302° (decomp.), from water (Found, on material dried at 150°/vac.: C, 55·1; H, 4·9; N, 7·7. $C_{16}H_{16}O_5N_2S$ requires C, 55·2; H, 4·6; N, 8·0%); *base*, needles (from aqueous ethanol), m. p. 313·5—315° (decomp.) (Found: loss at 150°/vac., 9·1. Found, on dried material: C, 63·0; H, 5·6; N, 15·1. $C_{10}H_{10}O_2N_2,H_2O$ requires H_2O, 8·7. $C_{10}H_{10}O_2N_2$ requires C, 63·1; H, 5·3; N, 14·7%); *picrate*, orange prisms, m. p. 251—251·5° (decomp.), from ethanol (Found: N, 16·4. $C_{16}H_{13}O_9N_5$ requires N, 16·7%).

2-*Amino*-4-*hydroxy*-8-*methoxy*-5-*methylquinoline*. *Benzenesulphonate* (47%), needles, m. p. 312—313° (decomp.), from aqueous ethanol (Found: C, 56·7; H, 4·8; N, 7·8. $C_{17}H_{18}O_5N_2S$ requires C, 56·4; H, 5·0; N, 7·7%); *base*, needles, m. p. 266—268·5° (decomp.), from aqueous ethanol (Found: C, 64·9; H, 6·0; N, 13·5. $C_{11}H_{12}O_2N_2$ requires C, 64·7; H, 5·9; N, 13·7%); *picrate*, yellow needles, m. p. 239—240° (decomp.), from aqueous ethanol (Found: N, 16·0. $C_{17}H_{15}O_9N_5$ requires N, 16·2%).

2-*Amino*-4 : 6-*dihydroxyquinoline.*—Equimolecular quantities of *p*-hydroxyanilinium benzenesulphonate and ethyl cyanoacetate were heated together at 210° for 1 hr. The *base*, isolated in the manner described for 2-amino-4-hydroxyquinoline, crystallised from aqueous ethanol as needles (17%), m. p. 348—349° (decomp.) (Found: loss at 100°/vac., 13·3. Found, on dried material: C, 61·0; H, 4·7; N, 15·7. $C_9H_8O_2N_2,1·5H_2O$ requires H_2O, 13·3. $C_9H_8O_2N_2$ requires C, 61·4; H, 4·6; N, 15·9%). Its *picrate* crystallised as yellow needles, m. p. 280—281° (decomp.), from aqueous ethanol (Found: N, 17·3. $C_{15}H_{11}O_9N_5$ requires N, 17·3%).

The following quinoline derivatives were prepared in a similar manner from the benzenesulphonate of the appropriate arylamine and ethyl cyanoacetate.

2-*Amino*-6-*chloro*-4-*hydroxyquinoline* (21%), needles, m. p. 358—361° (decomp.) from aqueous ethanol (Found : C, 55·4; H, 3·7; N, 14·6. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6; N, 14·4%); *picrate*, aggregates of yellow needles, m. p. 282—285° (decomp.), from ethanol (Found : N, 16·6. $C_{15}H_{10}O_8N_5Cl$ requires N, 16·5%).

2-*Amino*-8-*chloro*-4-*hydroxyquinoline* (8%), hygroscopic needles, m. p. 321—323° (decomp.) from aqueous ethanol (Found : loss at 150°/vac., 8·5. Found, on dried material : C, 55·4; H, 3·5; N, 14·2. $C_9H_7ON_2Cl,H_2O$ requires H_2O, 8·5. $C_9H_7ON_2Cl$ requires C, 55·5; H, 3·6; N, 14·4%); *benzenesulphonate*, needles, m. p. 295—296° (decomp.), from water (Found : loss at 150°/vac., 7·3. Found, on dried material : C, 50·9; H, 3·8; N, 8·2. $C_{15}H_{13}O_4N_2ClS,1·5H_2O$ requires H_2O, 7·1. $C_{15}H_{13}O_4N_2ClS$ requires C, 51·0; H, 3·7; N, 7·9%); *picrate*, yellow needles, m. p. 233—235° (decomp.), from aqueous ethanol (Found : N, 16·8. $C_{15}H_{10}O_8N_5Cl$ requires N, 16·5%).

2-*Amino*-3-n-*butyl*-4-*hydroxyquinoline*.—Ethyl 2-cyanohexanoate (8·5 g.) and anilinium toluene-*p*-sulphonate (14 g., 1 mol.) reacted slightly exothermically when heated together at 210° for 2 hr. The crude *toluene*-p-*sulphonate* (10·5 g., 54%), m. p. 220—222°, which separated from a solution of the melt in aqueous ethanol was obtained as prisms, m. p. 227—229°, on recrystallisation from water (Found : C, 61·6; H, 6·7; N, 6·9. $C_{20}H_{24}O_4N_2S$ requires C, 61·8; H, 7·2; N, 6·2%). 2-*Amino*-3-n-*butyl*-4-*hydroxyquinoline* crystallised as elongated prisms, m. p. 237—238° (decomp.), from aqueous ethanol (Found : C, 72·2; H, 7·2; N, 13·2. $C_{13}H_{16}ON_2$ requires C, 72·2; H, 7·4; N, 13·0%).

2-*Amino*-3-n-*butyl*-4-*hydroxy*-6-*methoxyquinoline*.—Equimolecular quantities of *p*-methoxyanilinium benzenesulphonate and ethyl 2-cyanohexanoate were heated together at 210° for 2 hr.; the cooled melt, on digestion with chloroform, afforded crude 2-*amino*-3-n-*butyl*-4-*hydroxy*-6-*methoxyquinolinium benzenesulphonate* (45%), m. p. 205—208°, which on recrystallisation from aqueous ethanol separated as needles, m. p. 218—219° (Found : C, 59·4; H, 5·8; N, 6·8. $C_{20}H_{24}O_5N_2S$ requires C, 59·4; H, 6·0; N, 6·9%). Decomposition of this salt in aqueous-ethanolic solution by the addition of ammonia furnished the *base* which crystallised from ethanol as needles, m. p. 233—235° (decomp.) (Found : C, 68·2; H, 6·9; N, 11·5. $C_{14}H_{18}O_2N_2$ requires C, 68·3; H, 7·4; N, 11·4%). The *picrate* separated as needles, m. p. 229—230·5° (decomp.), from ethanol (Found : N, 15·0. $C_{20}H_{21}O_9N_5$ requires N, 14·7%).

The following quinoline derivatives were prepared in a similar manner from equimolecular quantities of the named arylammonium benzenesulphonate and the named substituted ethyl cyanoacetate :

2-*Amino*-3-*benzyl*-4-*hydroxyquinoline* (53%), from anilinium benzenesulphonate and ethyl α-cyano-β-phenylpropionate; elongated plates, m. p. 298·5—300·5° (decomp.), from aqueous ethanol (Found : C, 76·8; H, 5·1; N, 11·2. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%); *benzenesulphonate*, prisms, m. p. 239—240°, from ethanol (Found : C, 64·6; H, 5·0; N, 6·5. $C_{22}H_{20}O_4N_2S$ requires C, 64·7; H, 4·9; N, 6·9%); *picrate*, yellow needles, m. p. 238·5—239° (decomp.), from *iso*propanol (Found : N, 14·4. $C_{22}H_{17}O_8N_5$ requires N, 14·6%).

2-*Amino*-3-*benzyl*-4-*hydroxy*-6-*methoxyquinoline* (47%), from *p*-methoxyanilinium benzenesulphonate and ethyl α-cyano-β-phenylpropionate; needles, m. p. 303—304° (decomp.), from aqueous ethanol (Found : C, 72·8; H, 5·7; N, 10·1. $C_{17}H_{16}O_2N_2$ requires C, 72·8; H, 5·8; N, 10·0%); *benzenesulphonate*, elongated prisms, m. p. 263—264° (decomp.), from aqueous ethanol (Found : C, 62·7; H, 5·0; N, 5·9. $C_{23}H_{22}O_5N_2S$ requires C, 63·0; H, 5·1; N, 6·4%); *picrate*, yellow prisms, m. p. 270—271° (decomp.), from aqueous acetic acid (Found : C, 60·9; H, 4·6; N, 12·2. $C_{23}H_{19}O_9N_5,C_2H_4O_2$ requires C, 60·5; H, 4·1; N, 12·3%).

2-*Amino*-4-*hydroxy*-3-*phenylquinoline* (53%), from anilinium benzenesulphonate and ethyl α-cyanophenylacetate; needles, m. p. 345—349° (decomp.), from aqueous ethanol (Found : C, 76·3; H, 5·3; N, 11·4. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·1; N, 11·9%); *benzenesulphonate*, rosettes, m. p. 253—255° (decomp.), from *n*-butanol (Found : N, 7·1. $C_{21}H_{18}O_4N_2S$ requires N, 7·1%); *picrate*, yellow needles, m. p. 221—222·5° (decomp.), from aqueous ethanol (Found : loss at 110°/vac., 3·8. Found, on dried material : C, 54·6; H, 3·6; N, 14·9. $C_{21}H_{15}O_8N_5,H_2O$ requires H_2O, 3·7. $C_{21}H_{15}O_8N_5$ requires C, 54·2; H, 3·3; N, 15·1%).

2-*Amino*-4-*hydroxy*-6-*methoxy*-3-*phenylquinoline* (35%), from *p*-methoxyanilinium benzenesulphonate and ethyl α-cyanophenylacetate; prisms, m. p. 366—368° (decomp.), from aqueous acetic acid (Found : C, 71·8; H, 5·3. $C_{16}H_{14}O_2N_2$ requires C, 72·2; H, 5·3%); *benzenesulphonate*, needles, m. p. 246·5—247°, from *iso*propanol (Found : C, 61·9; H, 5·0; N, 6·4. $C_{22}H_{20}O_5N_2S$ requires C, 62·3; H, 4·8; N, 6·6%); *picrate*, yellow needles, m. p. 228—230° (decomp.), from ethanol (Found : C, 53·5; H, 3·4. $C_{22}H_{17}O_9N_5$ requires C, 53·3; H, 3·5%).

α-*Ethoxycarbonyl*-N-*phenylacetamidine*.—The crude thioimidic ester obtained when a mixture

of ethyl cyanoacetate (11·3 g.) and thioglycollic acid (13·8 g., 1·5 mols.) was saturated with dry hydrogen chloride and kept at 0° for 4 hr. was added to aniline (25 g., 2·7 mols.) in absolute alcohol (100 c.c.). After 3 days, basic material was liberated, collected in benzene, fractionated by extraction with acetate buffer (pH 4·5), liberated to chloroform, and recovered. Fractional crystallisation of the mixed picrates from *iso*propanol afforded *α-ethoxycarbonyl-N-phenylacetamidinium picrate* (0·7 g., 1·6%) as needles, m. p. 146—147° (Found: C, 47·1; H, 3·8; N, 16·2. $C_{17}H_{17}O_9N_5$ requires C, 46·9; H, 3·9; N, 16·1%).

α-N-*Phenylamidinoacetanilide*.—(i) The crude thioimidic ester prepared as in the foregoing experiment was heated with aniline (20 g., 2·1 mols.) on a steam-bath for 4 hr. Basic material was liberated and fractionated by successive fractional partitions between acetate buffer (pH 4·5) and first benzene and then ether. α-N-*Phenylamidinoacetanilide* (1·4 g., 11%) crystallised from methanol as prisms, m. p. 178—179° (decomp.) (Found: C, 71·0; H, 6·1; N, 16·7. $C_{15}H_{15}ON_3$ requires C, 71·1; H, 6·0; N, 16·6%).

(ii) To a mixture of aniline (9·3 g.) and ethyl cyanoacetate (11·3 g., 1 mol.), powdered aluminium chloride (13·4 g., 1 mol.) was gradually added at 130° and the mixture was kept at 130—140° for 30 min. A solution of the product in water furnished, on the addition of sodium hydroxide, α-*N*-phenylamidinoacetanilide (3·2 g., 26%), m. p. and mixed m. p. 178—179° (decomp.). Its *benzenesulphonate* crystallised as flat prisms, m. p. 174°, from ethyl acetate (Found: C, 61·0; H, 5·6; N, 10·4. $C_{21}H_{21}O_4N_3S$ requires C, 61·3; H, 5·2; N, 10·2%). This salt did not afford 2-amino-4-hydroxyquinoline on being heated at 210° for 30 min.

Interaction of ω-Cyanoacetophenone and Anilinium Benzenesulphonate.—ω-Cyanoacetophenone (14·5 g.) and anilinium benzenesulphonate (25·1 g., 1 mol.) were heated together at 210° for 1 hr. From the solid obtained by the addition of sodium hydroxide to an aqueous-ethanolic solution of the melt, basic material was extracted with aqueous lactic acid and reprecipitated. The precipitate furnished from benzene ω-*N*-phenylamidinoacetophenone ((3·3 g., 14%), m. p. 162°, undepressed on admixture with a specimen prepared according to Krishnamurti's method (*J.*, 1928, 415) (Found: N, 11·9. Calc. for $C_{15}H_{14}ON_2$: N, 11·8%) [*picrate*, yellow prisms, m. p. 147—148° (decomp.), from *iso*propanol (Found: N, 15·4. $C_{21}H_{17}O_8N_5$ requires N, 15·0%)]. When shaken with dilute hydrochloric acid, the benzene mother-liquor yielded a resin from which 2-*anilino*-4-*phenylquinoline* (0·45 g., 3%) was recovered and crystallised as pale yellow needles, m. p. 190°, from aqueous ethanol [Found: C, 85·4; H, 5·4; N, 9·4%; *M* (Rast), 294. $C_{21}H_{16}N_2$ requires C, 85·1; H, 5·4; N, 9·5%; *M*, 296]. The *picrate* crystallised from methanol in aggregates of needles, m. p. 240—241·5° (decomp.) (Found: C, 61·6; H, 3·5; N, 13·5. $C_{27}H_{19}O_7N_5$ requires C, 61·7; H, 3·6; N, 13·3%).

1 : 3-*Diphenyl*-2-N-*phenylamidinopropane*.—Ethyl α-benzyl-α-cyano-β-phenylpropionate (7·6 g.) and anilinium benzenesulphonate (9·4 g., 1 mol.) were heated together at 210° for 3 hr. The gum remaining on evaporation of a chloroform extract of the cooled melt was washed thoroughly with ether and basified with ammonia in ethanolic solution. The crude basic material, after purification *via* its lactate, afforded 1 : 3-*diphenyl*-2-N-*phenylamidinopropane* (2 g., 17%) as needles, m. p. 176—177·5°, on crystallisation from *cyclo*hexane (Found: C, 83·9; H, 6·9; N, 8·8. $C_{22}H_{22}N_2$ requires C, 84·0; H, 7·0; N, 8·9%). Its *picrate* crystallised in clusters of needles, m. p. 171—172°, from aqueous acetic acid (Found: N, 13·0. $C_{28}H_{25}O_7N_5$ requires N, 12·9%).

2-N-p-*Methoxyphenylamidino*-1 : 3-*diphenylpropane*.—The melt obtained when ethyl α-benzyl-α-cyano-β-phenylpropionate (7·6 g.) and *p*-methoxyanilinium benzenesulphonate (10·5 g., 1 mol.) were heated together at 210° for 2 hr. was worked up as described for the foregoing compound. 2-N-p-*Methoxyphenylamidino*-1 : 3-*diphenylpropane* (1·1 g., 9%) crystallised as needles, m. p. 135—135·5°, from *cyclo*hexane (Found: C, 80·5; H, 7·0; N, 7·9. $C_{23}H_{24}ON_2$ requires C, 80·2; H, 7·0; N, 8·1%).

Interaction of Ethyl Cyanoacetate and 2-Alkoxycarbonylanilinium Salts.—(i) Ethyl cyanoacetate (5·7 g.) and *o*-ethoxycarbonylanilinium benzenesulphonate (16·2 g., 1 mol.) were heated together at 140° for 2 hr. The material which crystallised from an ethanolic extract of the melt afforded 2-*ethoxycarbonylmethyl*-4-*hydroxyquinazolinium benzenesulphonate* (3·7 g., 19%) as rods, m. p. 205—206° (decomp.), on recrystallisation from ethanol (Found: C, 55·3; H, 4·6; N, 7·2. $C_{18}H_{18}O_6N_2S$ requires C, 55·4; H, 4·7; N, 7·2%). The *base*, liberated by sodium hydrogen carbonate, crystallised from benzene as rods, m. p. 163—164° (decomp.) (Found: C, 62·4; H, 5·1; N, 12·3. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2; N, 12·1%). The material insoluble in alcohol furnished 2-(2 : 4-*dihydroxy*-3-*quinolinyl*)-4-*hydroxyquinazoline* (4·7 g., 31%) as needles, m. p. 353—355° (slight decomp.), when crystallised from glacial acetic acid (Found: C, 66·8; H, 3·8; N, 13·9. C_1-$H_{11}O_3N_3$ requires C, 66·9; H, 3·6; N, 13·8%). Light absorption

in N/50-sodium hydroxide, $\lambda_{max.}$ 221 mμ (ε 53,900), inflection at 230 mμ (ε 47,800), $\lambda_{max.}$ 285 (ε 17,000), $\lambda_{max.}$ 304 (ε 18,000).

(ii) Repetition of the foregoing experiment but with ethyl cyanoacetate and *o*-methoxycarbonylanilinium toluene-*p*-sulphonate afforded *4-hydroxy-2-methoxycarbonylmethylquinazolinium toluene*-p-*sulphonate* (17%) which was crystallised from glacial acetic acid and then from ethanol as prisms, m. p. 221—223° (decomp.) (Found: C, 55·2, 55·4; H, 4·9, 4·7; N, 7·1. $C_{18}H_{18}O_6N_2S$ requires C, 55·4; H, 4·7; N, 7·2%). The corresponding *base* crystallised from benzene as needles, m. p. 184—185° (decomp.) (Found: C, 60·6; H, 4·7; N, 12·9. $C_{11}H_{10}O_3N_2$ requires C, 60·5; H, 4·6; N, 12·8%). The acetic acid mother-liquor slowly deposited 4-hydroxy-2-methylquinazolinium toluene-*p*-sulphonate, m. p. and mixed m. p. 276—277° (decomp.) (see below).

(iii) The benzenesulphonate (32·3 g.) and ethyl cyanoacetate (11·3 g., 1 mol.) were brought into reaction at 210° for 1 hr.; the reaction was strongly exothermic and the melt gradually solidified during the heating. An aqueous extract of the cooled melt deposited on concentration 4-hydroxy-2-methylquinazolinium benzenesulphonate (4·6 g., 14%), m. p. 243—244°; after recrystallisation from aqueous *iso*propanol this had m. p. 245—245·5°, undepressed on admixture with an authentic specimen (see below). The base had m. p. and mixed m. p. 240·5—241° (Found: N, 17·4. Calc. for $C_9H_8ON_2$: N, 17·5%), and its picrate m. p. and mixed m. p. 210—211° (decomp.). The water-insoluble fraction of the melt was extracted with sodium hydroxide and the material precipitated by carbon dioxide furnished on crystallisation from acetic acid 2-(2 : 4-dihydroxy-3-quinolinyl)-4-hydroxyquinazoline, m. p. and mixed m. p. 353—355° (slight decomp.) (6·2 g., 40%).

2-(2 : 4-*Dihydroxy*-3-*quinolinyl*)-4-*hydroxyquinazoline*.—4-Hydroxy-2-methoxycarbonylmethylquinazolinium toluene-*p*-sulphonate (16·2 g.) and methyl anthranilate (6·2 g., 1 mol.) were heated together at 180—200° for 2 hr. 4-Hydroxy-2-methylquinazolinium toluene-*p*-sulphonate was extracted from the product with glacial acetic acid; the insoluble material, after recrystallisation from glacial acetic acid, afforded 2-(2 : 4-dihydroxy-3-quinolinyl)-4-hydroxyquinazoline, m. p. and mixed m. p. 353—355° (slight decomp.) (6·1 g., 50%) (Found: C, 67·0; H, 3·4; N, 13·5. Calc. for $C_{17}H_{11}O_3N_3$: C, 66·9; H, 3·6; N, 13·8). Light absorption in N/50-sodium hydroxide: $\lambda_{max.}$ 220 mμ (ε 53,500), inflection at 230 mμ (ε 47,700), $\lambda_{max.}$ 285 mμ (ε 16,700), $\lambda_{max.}$ 305 mμ (ε 17,500). This compound was soluble in aqueous sodium hydroxide and insoluble in aqueous sodium carbonate and mineral acids.

The foregoing compound (1 g.) was boiled with phosphorus oxychloride (4 c.c.) for 4 hr. and poured into water. Recrystallisation of the solid which separated from aqueous ethanol and from benzene afforded the *dichloro*-derivative as prisms, m. p. 260·5—261·5° (decomp.) (0·62 g., 55%). This compound was readily soluble in cold aqueous sodium hydroxide [Found: C, 59·5; H, 3·0; N, 12·3; Cl, 21·2%; *M* (Rast), 351. $C_{17}H_9ON_3Cl_2$ requires C, 59·7; H, 2·6; N, 12·3; Cl, 20·8%; *M*, 342]. The same compound was obtained when the period of boiling was 14 hr. Unchanged starting material was recovered when an attempt was made to bring about the reaction with a mixture of phosphorus pentachloride and phosphorus oxychloride and when acetylation was attempted under a variety of conditions.

4-Hydroxy-2-methylquinazoline.—(i) A solution of 2-ethoxycarbonylmethyl-4-hydroxyquinazolinium benzenesulphonate (1 g.) in glacial acetic acid was boiled for 1 hr.; the crystals which separated on cooling yielded on treatment with sodium hydrogen carbonate in aqueous solution 4-hydroxy-2-methylquinazoline, m. p. 240—241°, undepressed on admixture with a specimen prepared by Bogert's method (*J. Amer. Chem. Soc.*, 1900, **22**, 129); the *benzenesulphonate* formed needles, m. p. 245—245·5°, from *iso*propanol (Found: N, 9·0. $C_{15}H_{14}O_4N_2S$ requires N, 8·8%), the *toluene*-p-*sulphonate*, prisms, m. p. 276—277° (decomp.), from glacial acetic acid (Found: C, 57·8; H, 5·3. $C_{16}H_{16}O_4N_2S$ requires C, 57·8; H, 4·9%), and the *picrate* yellow needles, m. p. 210—211°, from water (Found: N, 17·9. $C_{15}H_{11}O_8N_5$ requires N, 18·0%).

(ii) 4-Hydroxy-2-methoxycarbonylmethylquinazolinium toluene-*p*-sulphonate (1 g.) was boiled in glacial acetic acid for 30 min.; the crude material which separated on cooling (0·7 g., 82%; m. p. 255—260°) after recrystallisation from glacial acetic acid had m. p. 276—277° (decomp.), undepressed by 4-hydroxy-2-methylquinazolinium toluene-*p*-sulphonate. The identity of these compounds was confirmed by a comparison of samples of the base.

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