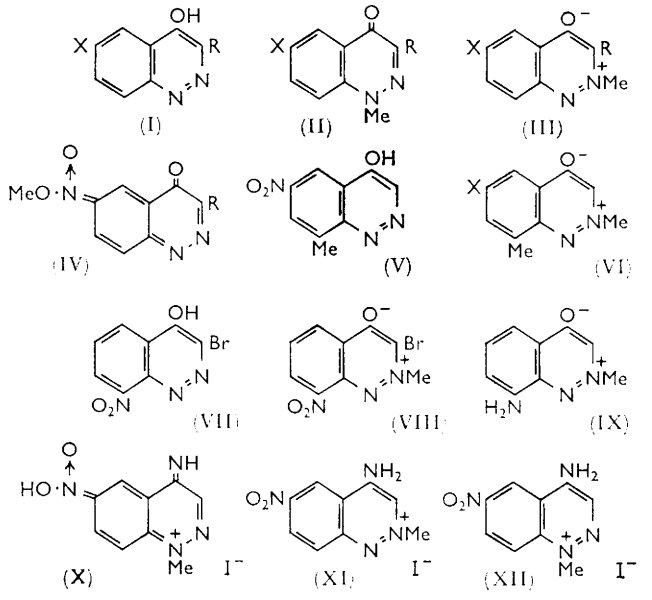
Cinnolines. Part IX.[1] Methylation of Substituted Cinnolines

By D. E. Ames and R. F. Chapman, Chemistry Department, Chelsea College of Science and Technology, Manresa Road, London S.W.3

Methylation of 4-hydroxy-6-nitro- and of 4-hydroxy-3-methyl-6-nitro-cinnolines gives the N-1 and N-2 methyl derivatives not the *O*-methylnitronate. It is shown that 4-hydroxy-8-methyl-6-nitrocinnoline and 3-bromo-4-hydroxy-8-nitrocinnoline are methylated only at N-2 while 4-hydroxy-3-nitrocinnoline reacts only at N-1. Quaternisation of 4-amino-6-nitrocinnoline and of 4-methylthiocinnoline with methyl iodide yields a mixture of the corresponding 1- and 2-methylcinnolinium salts.

In Part VIII [1] it was shown that the two products obtained by methylation of 4-hydroxy-6-nitrocinnoline (I; R = H, X = NO_2) are 1-methyl-6-nitro-4-cinnolone (II; R = H, X = NO_2) and the anhydro-base (III; R = H, X = NO_2) of 4-hydroxy-2-methyl-6-nitrocinnolinium hydroxide. The latter structure, which was indicated by the stability of the product to acid hydrolysis and by spectroscopic evidence, has now been confirmed by degradation. The anhydro-base (III; R = H, X = NO_2) was reduced catalytically to the amine (III; R = H, X = NH_2) which, on diazotisation and treatment with cuprous chloride, gave the known [2] anhydro-base (III; R = H, X = Cl) of 6-chloro-4-hydroxy-2-methylcinnolinium hydroxide. Reduction



of the cinnolone (II; R = H, X = NO_2) also gave the corresponding amine (II; R = H, X = NH_2); diazotisation and reduction with hypophosphorous acid produced 1-methyl-4-cinnolone (II; R = X = H).

The methylation of 4-hydroxy-3-methyl-6-nitrocinnoline (I; R = Me, X = NO_2) was described by Simpson and his co-workers [3] who obtained two products which were formulated as the cinnolone (II; R = Me, X = NO_2) and the methyl nitronate (IV; R = Me). The structure assigned to the cinnolone has now been confirmed by reduction to the corresponding amine (II; R = Me, X = NH_2) followed by diazotisation and reduction with hypophosphorous acid to give 1,3-dimethyl-4-cinnolone [1] (II; R = Me, X = H). The second product, however, must be the anhydro-base (III; R = Me, X = NO_2), not the methyl nitronate, since similar transformations give the anhydro-base [1] (III; R = Me, X = H) of 4-hydroxy-2,3-dimethylcinnolinium hydroxide.

In the methylation of 6-nitro-4-hydroxy-8-methylcinnoline (V), the steric effects of the 8-substituent impede 1-methylation, so that only one product is obtained. This is formulated as the anhydro-base (VI; X = NO_2) of 4-hydroxy-2,8-dimethyl-6-nitrocinnolinium hydroxide, since reduction and deamination give the anhydro-base (VI; X = H) of 4-hydroxy-2,8-dimethylcinnolinium hydroxide.

4-Hydroxy-3-nitrocinnoline was methylated by Baumgarten [4] who isolated only one product which was tentatively assigned the cinnolone structure (II; R = NO_2, X = H). This view has been verified by catalytic reduction of the product to the amine (II; R = NH_2, X = H). The latter was also prepared by hydrogenation of 6-chloro-1-methyl-3-nitro-4-cinnolone.[1] Treatment of the amino-cinnolone (II; R = NH_2, X = H) with nitrous acid gave 3-hydoxy-1-methyl-4-cinnolone (II; R = OH, X = H); this is apparently the first *N*-methyl derivative of the unknown 3,4-dihydroxycinnoline to be described. 3,4-Dimethoxycinnoline 1-oxide has, however, been prepared.[5]

It was of interest to examine the methylation of 3-bromo-4-hydroxy-8-nitrocinnoline (VIII) in which there is some steric hindrance to attack at N-1 and N-2. As in the case of 3-bromo-4-hydroxy-8-methylcinnoline,[1] methylation occurred at N-2, the product being the anhydro-base (VIII) which was identified by reduction to amine (IX); this, on diazotisation and further reduction, gave the anhydro-base (III; R = X = H) of 4-hydroxy-2-methylcinnolinium hydroxide.

The quaternisation of 4-aminocinnolines has been studied by Simpson [6] and by Atkinson and Taylor [7] who showed that, in general, two salts are formed and that these involve reaction at N-1 and N-2. The

[1] Part VIII, D. E. Ames, R. F. Chapman, and D. Waite, *J. Chem. Soc.* (*C*), 1966, 470.
[2] D. E. Ames, *J. Chem. Soc.*, 1964, 1763.
[3] J. R. Keneford, J. S. Morley, J. C. E. Simpson, and P. H. Wright, *J. Chem. Soc.*, 1950, 1104.
[4] H. E. Baumgarten, *J. Amer. Chem. Soc.*, 1955, **77**, 5109.
[5] M. Ogata, H. Kano, and K. Tori, *Chem. and Pharm. Bull.* (*Japan*), 1963, **12**, 1527.
[6] J. C. E. Simpson, *J. Chem. Soc.*, 1947, 1653.
[7] C. M. Atkinson and A. Taylor, *J. Chem. Soc.*, 1955, 4236.

methiodides of 4-aminocinnoline [8] and 4-amino-6-chlorocinnoline [2] have previously been identified by conversion into the corresponding 1-methyl-4-cinnolones or 2-methyl anhydro-bases. Quaternisation of 4-amino-6-nitrocinnoline has now been re-examined. This compound was prepared by Keneford, Schofield, and Simpson [9] from 4-hydroxy-6-nitrocinnoline by conversion through the 4-chloro-derivative into 6-nitro-4-phenoxycinnoline which was fused with ammonium acetate. It has now been found that nitration of 4-aminocinnoline gives the 6-nitro-derivative in good yield; this route avoids preparation of the very unstable 4-chloro-6-nitrocinnoline.

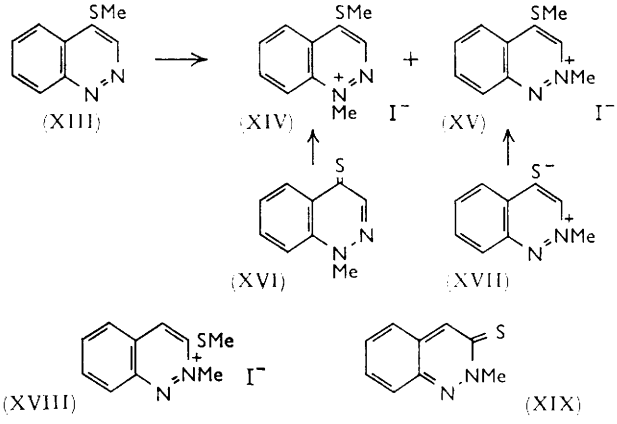
Atkinson and Taylor [7] showed that two salts (designated α- and β-methiodides) were formed by quaternisation of 4-amino-6-nitrocinnoline with methyl iodide. They considered that the task of assigning structures to these salts was complicated by possibilities of tautomerism involving the hetero-ring and the 6-nitro group. They excluded the possibility that one salt arose by methylation at the 4-amino group by preparation of the hydrochloride of 4-methylamino-6-nitrocinnoline, which differed from both α- and β-methochlorides.

The red α-methiodide was found by these workers to have an ultraviolet spectrum almost identical with that of the compound then regarded as the methyl nitronate (IV; R = H). They therefore formulated the α-salt as the 1-methiodide of an *aci*-nitro-form (X). Since the alleged methyl nitronate has been shown above to be actually the anhydro-base (III; R = H, X = NO_2) of 4-hydroxy-2-methyl-6-nitrocinnolinium hydroxide, this spectroscopic evidence clearly suggests that the α-salt is formed by quaternisation at N-2 and has structure (XI). This conclusion has now been confirmed by treatment of the α-methiodide with nitrous acid, to give the anhydro-base (III; R = H, X = NO_2).

In the case of the β-methiodide, Atkinson and Taylor found that hydrolysis with water or alkali yielded ammonia and 1-methyl-6-nitro-4-cinnolone (II; R = H, X = NO_2). We have hydrolysed the mixture of quaternisation products to obtain this cinnolone; the anhydro-base was again formed from the α-isomer in the mother-liquors by subsequent treatment with nitrous acid. Thus, the degradative evidence clearly indicates that the β-methiodide is 4-amino-1-methyl-6-nitrocinnolinium iodide (XII), and this is consistent with the formulation of the α-isomer, the exclusion of 4-substitution, and the absence of any evidence indicating tautomerism involving the 6-nitro group.

Quaternisation of 4-methylthiocinnoline (XIII) gives a mixture of two quaternary salts. The major product (59%) must be 2-methyl-4-methylthiocinnolinium iodide (XV), since it was also formed by action of methyl iodide on the anhydro-base (XVII) of 4-mercapto-2-methylcinnolinium hydroxide. Similarly, the minor product (13%) must be 1-methyl-4-methylthiocinnolinium iodide (XIV), since it was obtained by heating 1-methylcinnoline-4-thione (XVI) with methyl iodide. Fry, Kendall, and Morgan [10] were similarly able to ascertain the site of quaternisation of 4-methylthioquinazoline by showing that its quaternary salt was identical with that from 1-methylquinazoline-4-thione.

2-Methyl-3-methylthiocinnolinium iodide (XVIII) was prepared by treating 2-methylcinnoline-3-thione with methyl iodide. This thione (XIX) was obtained by the action of phosphorus pentasulphide on 2-methyl-3-cinnolone. Attempts to prepare 3-methylthiocinnoline and its 1-methiodide have, however, been unsuccessful.



EXPERIMENTAL

Evaporations were carried out under reduced pressure. Light petroleum refers to the fraction of b. p. 60—80°. Ultraviolet spectra were measured on a Perkin-Elmer 137 spectrophotometer.

Anhydro-base of 6-Amino-4-hydroxy-2-methylcinnolinium Hydroxide (III; R = H, X = NH_2).—(*a*) The anhydro-base of 4-hydroxy-2-methyl-6-nitrocinnolinium hydroxide [1] (0·5 g.) in ethanol (75 c.c.) was hydrogenated in the presence of palladised charcoal (0·2 g.; 5%). After hydrogen (160 c.c.) had been taken up during 20 min., the filtered solution was evaporated. Recrystallisation from ethanol gave the *amino-compound* (0·3 g.), m. p. >360° (Found: C, 61·1; H, 5·4; N, 23·8. $C_9H_9N_3O$ requires C, 61·7; H, 5·2; N, 24·0%), $\lambda_{max.}$ 217, 254, 272, 344, and 408 mμ (ε 18,500, 19,600, 16,200, 7000, and 15,200), $\nu_{max.}$ 1630, 1670, 3210, and 3390 $cm.^{-1}$.

(*b*) A solution of stannous chloride (6·0 g.) in acetic anhydride (5 c.c.) and acetic acid (20 c.c.) was saturated with hydrogen chloride.[11] This solution was added during 10 min. to the nitro-compound (0·5 g.) in acetic acid (2·5 c.c.), the temperature being maintained at 20—25°. The mixture was left for 10 min. with occasional stirring, poured on to ice, and basified with 10N-sodium hydroxide. Filtration and recrystallisation from ethanol gave the amino-compound (0·2 g.); the infrared spectrum was identical with that of the previous sample.

Anhydro-base of 6-Chloro-4-hydroxy-2-methylcinnolinium Hydroxide (III; R = H, X = Cl).—The amino-compound (0·5 g.) in concentrated hydrochloric acid (5 c.c.) was

[8] D. E. Ames, R. F. Chapman, and H. Z. Kucharska, *J. Chem. Soc.*, 1964, 5659.
[9] J. R. Keneford, K. Schofield, and J. C. E. Simpson, *J. Chem. Soc.*, 1948, 358.
[10] D. J. Fry, J. D. Kendall, and A. J. Morgan, *J. Chem. Soc.*, 1960, 5062.
[11] A. Albert and W. H. Linnell, *J. Chem. Soc.*, 1936, 1614.

diazotised with sodium nitrite (0·2 g.) in water (2 c.c.) at 0°. The mixture was poured into a freshly prepared solution of cuprous chloride (from cupric sulphate hydrate, 0·75 g.) in concentrated hydrochloric acid (3 c.c.) at 0°. After 2 hr., the solution was heated to 80° and allowed to cool. Basification, and isolation with chloroform, gave the chloro-compound (0·25 g.), m. p. and mixed m. p.[2] 220—222°.

6-*Amino*-1-*methyl*-4-*cinnolone* (II; R = H; X = NH_2). —1-Methyl-6-nitro-4-cinnolone (600 mg.) in ethanol (50 c.c.) was hydrogenated with palladised charcoal (0·2 g.; 5%) until absorption ceased (30 min.). Evaporation of the filtered solution and recrystallisation of the residue from ethyl acetate–light petroleum gave the *amine* (370 mg.) m. p. 209—211° (Found: C, 61·7; H, 5·4; N, 24·0%), $\lambda_{max.}$ 213, 255, 312, and 395 mμ (ε 12,900, 21,000, 5900, and 8900).

The amine (350 mg.) in concentrated hydrochloric acid (3 c.c.) was treated with sodium nitrite (150 mg.) in water (2 c.c.) at 0°, and hypophosphorous acid (2 c.c.; 50%) was added. The solution was kept at 0° overnight, and basified; isolation with chloroform and recrystallisation from benzene–light petroleum afforded 1-methyl-4-cinnolone [12] (150 mg.), m. p. and mixed m. p. 113—115°.

Reduction of the Anhydro-base of 4-*Hydroxy*-2,8-*dimethyl*-6-*nitrocinnolinium Hydroxide*.—This nitro-compound (1·0 g.) was hydrogenated in the manner described, to give the *anhydro-base* of 6-amino-4-hydroxy-2,8-dimethylcinnolinium hydroxide (VI; X = NH_2) (0·7 g.), m. p. >360° (from ethanol) (Found: C, 62·6; H, 5·8; N, 21·8. $C_{10}H_{11}N_3O$ requires C, 63·5; H, 5·9; N, 22·2%). This (0·5 g.), in concentrated hydrochloric acid (3 c.c.), was diazotised with sodium nitrite (0·2 g.) in water (2 c.c.) at 0°. Hypophosphorous acid (1·5 c.c.; 50%) was added, and the solution kept at 0° for 24 hr. Basification, isolation with chloroform, and recrystallisation from benzene yielded the anhydro-base (0·2 g.) of 4-hydroxy-2,8-dimethylcinnolinium hydroxide (VI; X = H), m. p. and mixed m. p.[1] 193—194°.

Methylation of 4-*Hydroxy*-3-*methyl*-6-*nitrocinnoline*.—A solution of the cinnoline (2·0 g.) in 0·3N-potassium hydroxide (40 c.c.) was stirred at 45° and treated with dimethyl sulphate (1·0 c.c.). After 10 min., the solid was collected and recrystallised from benzene and then from ethanol, to give the anhydro-base of 4-hydroxy-2,3-dimethyl-6-nitrocinnolinium hydroxide (III; R = Me, X = NO_2) (0·6 g., 29%), m. p. 176—177° (Found: C, 54·5; H, 4·4; N, 19·3. Calc. for $C_{10}H_9N_3O_3$: C, 54·8; H, 4·1; N, 19·2%), $\lambda_{max.}$ 260, 322, 336, and 410 mμ (ε 13,700, 3700, 4600, and 14,100) (lit.,[3] m. p. 161—162°; compound formulated as the methyl nitronate).

Concentration of the mother-liquors and recrystallisation from benzene afforded 1,3-dimethyl-6-nitro-4-cinnolone (II; R = Me, X = NO_2) (1·2 g., 59%), m. p. 181—182° (lit.,[3] 181—183°), $\lambda_{max.}$ 215, 238, 269, 277infl., 331, and 385 mμ (ε 13,800, 15,600, 8200, 6900, 1000, and 12,200). Keneford *et al.*,[3] who obtained the products in similar proportions, found that the cinnolone separated first.

Reduction of the Anhydro-base of 4-*Hydroxy*-2,3-*dimethyl*-6-*nitrocinnolinium Hydroxide*.—Catalytic reduction in the manner described gave the corresponding amine. The crude product (from 400 mg. of nitro-compound) was dissolved in concentrated hydrochloric acid (2 c.c.) and treated with sodium nitrite (200 mg.) in water (2 c.c.) at 0°, and hypophosphorous acid (2 c.c.; 50%) was added. The solution was kept at 0° overnight and basified; isolation with chloroform and recrystallisation from benzene–light petroleum gave the anhydro-base of 4-hydroxy-2,3-dimethylcinnolinium hydroxide (90 mg.), m. p. and mixed m. p. 155—157°.

Reduction of 1,3-*Dimethyl*-6-*nitro*-4-*cinnolone*.—The nitro-compound (1·0 g.) was hydrogenated catalytically as described, to give 6-*amino*-1,3-*dimethyl*-4-*cinnolone* (II; R = Me, X = NH_2) (0·6 g.), m. p. 240—242° (from ethanol) (Found: C, 63·2; H, 5·9; N, 21·6%). Diazotisation and reduction with hypophosphorous acid as in the previous example yielded 1,3-dimethyl-4-cinnolone (0·25 g.), m. p. and mixed m. p.[1] 136—138° (from benzene–light petroleum).

Methylation of 4-*Hydroxy*-3-*nitrocinnoline*.—The cinnoline (0·5 g.) was dissolved in potassium hydroxide solution (60 c.c.; 1%) at 50°, and dimethyl sulphate (2 c.c.) was added. The precipitate was collected, washed with water, dried, and dissolved in benzene. The solution was applied to a column (15 × 2 cm.) of alumina; elution with benzene gave 1-methyl-3-nitro-4-cinnolone (0·35 g.), m. p. 231—233° (lit.,[4] 232—232·5°) (from benzene–light petroleum), $\lambda_{max.}$ 222, 238infl, 267infl, 340, and 355infl mμ (ε 14,000, 11,400, 3800, 12,600, and 10,400). No other product could be isolated.

3-*Amino*-1-*methyl*-4-*cinnolone* (II; R = NH_2, X = H).—6-Chloro-1-methyl-3-nitro-4-cinnolone [1] (0·25 g.) in ethanol (75 c.c.) containing triethylamine (5 c.c.) was hydrogenated with palladised charcoal (0·3 g.; 5%). After hydrogen (110 c.c.) had been taken up during 15 min., the filtered solution was poured into water. Isolation with chloroform furnished 3-*amino*-1-*methyl*-4-*cinnolone* (0·15 g.), m. p. 209—210° (from ethanol) (Found: C, 61·3; H, 5·3; N, 24·2. $C_9H_9N_3O$ requires C, 61·7; H, 5·2; N, 24·0%), $\lambda_{max.}$ 256, 299, and 390 mμ (ε 23,200, 2400, and 7100).

Hydrogenation of 1-methyl-3-nitro-4-cinnolone (300 mg.) in the manner described also gave the amino-cinnolone (180 mg.), m. p. and mixed m. p. 209—210°.

Diazotisation of 3-*Amino*-1-*methyl*-4-*cinnolone*.—(a) *In hydrobromic acid*. The amine (300 mg.) in hydrobromic acid (10 c.c.; 48%) was diazotised with sodium nitrite (150 mg.) in water (2 c.c.) at 0° and the solution was kept at 0° overnight. Basification and isolation with chloroform gave a solid which was partially insoluble in benzene. Recrystallisation of the insoluble fraction from ethanol gave 3-*hydroxy*-1-*methyl*-4-*cinnolone* (II; R = OH, X = H) (20 mg.), m. p. 218—219° (Found: C, 61·9; H, 4·8; N, 16·3. $C_9H_8N_2O_2$ requires C, 61·4; H, 4·6; N, 15·9%), $\lambda_{max.}$ 247, 286, 298, 367, and 386 mμ (ε 22,400, 2400, 1900, 11,900, and 10,900). Evaporation of the benzene extracts and recrystallisation from benzene–light petroleum yielded 3-bromo-1-methyl-4-cinnolone (150 mg.), m. p. and mixed m. p. 197—199°.

(b) *In sulphuric acid*. The amine (200 mg.) in 10N-sulphuric acid (10 c.c.) was diazotised at 0° with sodium nitrite (100 mg.) in water (2 c.c.). After 1 hr., the solution was warmed to 50°, and then allowed to cool. Aqueous ammonia (*d* 0·88) was added until the solution was faintly alkaline. When the mixture was left at room temperature for 24 hr., crystals separated; recrystallisation from ethanol gave 3-hydroxy-1-methyl-4-cinnolone (100 mg.), m. p. and mixed m. p. 218—219°.

3-*Bromo*-4-*hydroxy*-8-*nitrocinnoline*.—4-Hydroxy-8-nitrocinnoline (1·2 g.) in N-potassium hydroxide (25 c.c.) was stirred and treated with bromine (0·5 c.c.). After 30 min.,

[12] D. E. Ames and H. Z. Kucharska, *J. Chem. Soc.*, 1963, 4924.

the mixture was poured into dilute acetic acid, and the solid was collected and recrystallised from ethanol. The *bromo-compound* (VII) (1·5 g.) had m. p. 235—237° (Found: C, 35·5; H, 1·8; Br, 29·8; N, 16·0. $C_8H_4BrN_3O_3$ requires C, 35·6; H, 1·5; Br, 29·6; N, 15·6%), $\lambda_{max.}$ 227, 254, 285infl, 296infl, and 390 mμ (ε 18,900, 14,000, 13,200, 5900, 4900, and 11,300).

Methylation of 3-*Bromo*-4-*hydroxy*-8-*nitrocinnoline*.—The cinnoline (1·4 g.) was dissolved in 0·05N-potassium hydroxide (40 c.c.) and treated with dimethyl sulphate (1·0 c.c.) at room temperature. The precipitate was collected after 15 min. and recrystallised from ethanol, to give the *anhydro-base* of 3-bromo-4-hydroxy-2-methyl-8-nitrocinnolinium hydroxide (VIII) (1·0 g., 68%), m. p. 209—211°, as yellow needles (Found: C, 38·8; H, 2·2; Br, 28·4; N, 14·7. $C_9H_6BrN_3O_3$ requires C, 38·1; H, 2·1; Br, 28·1; N, 14·8%), $\lambda_{max.}$ 259, 318infl, 332, 373infl, and 390 mμ (ε 8300, 4400, 6200, 10,600, and 13,300).

This product (0·9 g.) was hydrogenated in ethanol (100 c.c.) over palladised charcoal (0·3 g.; 5%), hydrogen (280 c.c.) being absorbed during 30 min. Evaporation of the filtered solution, and recrystallisation from ethanol, furnished the *anhydro-base* of 8-amino-4-hydroxy-2-methylcinnolinium hydroxide (IX) (0·4 g.) as yellow needles, m. p. 199—200° (Found: C, 62·2; H, 5·2; N, 23·8. $C_9H_9N_3O$ requires C, 61·7; H, 5·2; N, 24·0%). Sodium nitrite (0·15 g.) in water (2 c.c.) was added to this amine (0·35 g.) in concentrated hydrochloric acid (3 c.c.) at 0°, and hypophosphorous acid (2 c.c.; 50%) was added. The mixture was left at 0° overnight, basified, and extracted with chloroform; the extracts were evaporated and the residue was recrystallised from benzene–light petroleum, to give the anhydro-base of 4-hydroxy-2-methylcinnolinium hydroxide (0·17 g.), m. p. and mixed m. p. 162—164°.

4-*Amino*-6-*nitrocinnoline*.—Fuming nitric acid (1·0 c.c.) was added dropwise to a stirred solution of 4-amino-cinnoline (2·0 g.) in concentrated sulphuric acid (20 c.c.) at 0—5°. The mixture was kept at 0—5° for 2 hr. and poured on to ice; after basification with aqueous ammonia (*d* 0·88), the solid was filtered off. 4-Amino-6-nitrocinnoline (1·7 g.), obtained by recrystallisation from 2-methoxyethanol, had m. p. 289—291°, undepressed by admixture with material prepared as described by Keneford, Schofield, and Simpson.[9]

Quaternisation of 4-*Amino*-6-*nitrocinnoline*.—(*a*) The cinnoline (1·5 g.) and methyl iodide (10 c.c.) in ethanol (50 c.c.) were refluxed for 2 hr., and the mixture was evaporated. Repeated recrystallisation of the residue from water gave red needles of 4-*amino*-2-*methyl*-6-*nitrocinnolinium iodide* (XI), m. p. 218—222° (decomp.) [lit.,[7] 222°, for α-methiodide formulated as the 1-methiodide (X) of an *aci*-nitro-form]. The salt (0·6 g.) in sulphuric acid (20 c.c.; 40%) was treated with sodium nitrite (150 mg.) in water (3 c.c.) at 0°. After the solution had been left at room temperature for 1 hr., it was warmed to 60° and allowed to cool. Isolation with chloroform and recrystallisation from ethanol gave the anhydro-base of 4-hydroxy-2-methyl-6-nitrocinnolinium hydroxide (190 mg., 55%), m. p. and mixed m. p. 228—229°. No other product could be isolated.

(*b*) In a similar experiment, the crude quaternisation product was refluxed with water (50 c.c.) for 8 hr. Isolation with chloroform and recrystallisation from benzene–light petroleum gave 1-methyl-6-nitro-4-cinnolone (0·25 g., 17%), m. p. and mixed m. p. 182—183°.

Evaporation of the aqueous layer and diazotisation of the residue as in (*a*) gave the anhydro-base of 2-methyl-4-hydroxy-6-nitrocinnolinium hydroxide (0·43 g., 29%), m. p. and mixed m. p. 226—228°.

Methylation of the Anhydro-base of 4-*Mercapto*-2-*methylcinnolinium Hydroxide*.—The anhydro-base [13] (60 mg.) in benzene (5 c.c.) and methyl iodide (0·5 c.c.) were refluxed for 10 min. The precipitate was collected and recrystallised from ethanol, to give orange 2-*methyl*-4-*methylthiocinnolinium iodide* (XV) (100 mg.), m. p. 214—216° (decomp.) (Found: C, 37·7; H, 3·5; I, 40·0; N, 8·7; S, 10·3. $C_{10}H_{11}IN_2S$ requires C, 37·7; H, 3·5; I, 39·9; N, 8·8; S, 10·1%).

Methylation of 1-methylcinnoline-4-thione [13] in the same manner yielded 1-*methyl*-4-*methylthiocinnolinium iodide* (XIV), orange prisms, m. p. 191—193° (decomp.) (from ethanol) (Found: C, 37·8; H, 3·5; I, 40·1; N, 8·8; S, 10·1%).

Quaternisation of 4-*Methylthiocinnoline*.—The cinnoline (350 mg.), benzene (10 c.c.), and methyl iodide (1 c.c.) were refluxed for 30 min. Orange crystals, which separated on cooling, were collected and recrystallised from ethanol, to yield 2-methyl-4-methylthiocinnolinium iodide (370 mg., 59%), m. p. and mixed m. p. 214—216° (decomp.). Concentration of the mother-liquors furnished material which, on recrystallisation from ethanol, gave 1-methyl-4-methylthiocinnolinium iodide (80 mg., 13%), m. p. and mixed m. p. 190—192° (decomp.).

2-*Methylcinnoline*-3-*thione* (XIX).—2-Methyl-3-cinnolone [12] (0·5 g.), phosphorus pentasulphide (4 g.), and benzene (50 c.c.) were refluxed for 30 min. After the solution had been evaporated, water was added and the products were extracted with chloroform. This solution was applied to a column (30 × 2 cm.) of alumina. Elution with chloroform afforded 2-*methylcinnoline*-3-*thione* (0·2 g.), m. p. 184—186° (Found: C, 61·4; H, 4·6; N, 15·6; S, 18·1. $C_9H_8N_2S$ requires C, 61·4; H, 4·6; N, 15·9; S, 18·2%), $\lambda_{max.}$ 224, 255infl, 277, 320, 329, and 433 mμ (ε 20,000, 12,000, 22,700, 15,200, 15,800, and 2100).

Methylation of 2-*Methylcinnoline*-3-*thione*.—A solution of the thione (60 mg.) in benzene (10 c.c.) and methyl iodide (1 c.c.) was refluxed for 15 min. Filtration and recrystallisation from ethanol yielded 2-*methyl*-3-*methylthiocinnolinium iodide* (XVIII) (100 mg.), m. p. 195—197° (decomp.) (Found: C, 38·0; H, 3·5; I, 40·2; N, 8·8; S, 10·0%).

We are grateful to Dr. J. F. McGhie for helpful discussions, and to the S.R.C. for the award of a research studentship (to R. F. C.).

[6/878 *Received, July 12th,* 1966]

[13] D. E. Ames, R. F. Chapman, H. Z. Kucharska, and D. Waite, *J. Chem. Soc.*, 1965, 5391.