507. *Cinnolines. Part XXIII. Some Derivatives of* 5-, 7-, *and* 8-*Nitro*-4-*hydroxycinnoline.* 4-*Hydroxy*-7-*acetylcinnoline.*

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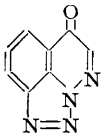
5- and 7-*Nitro*-4-*hydroxycinnoline* are described. Various derivatives have been prepared from these and from the 8-nitro-compound, and some from the derived amines. 4-*Hydroxy*-7-*acetylcinnoline* is converted by a Schmidt reaction into 7-*acetamido*-4-*hydroxycinnoline*. The ready displacement, by hydroxylamine, of the 4-phenoxy-group in a cinnoline derivative is reported.

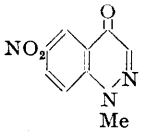
UNDER certain conditions 4-hydroxycinnoline yields on nitration, besides the major product, 6-nitro-4-hydroxycinnoline, a small amount of an unidentified mononitro-compound, m. p. 276—277° (Schofield and Simpson, *J.*, 1945, 512). In view of this, and of the potential therapeutic interest of derivatives of *Bz*-aminocinnolines (Keneford, Lourie, *et al.*, *Nature*, 1948, **161**, 603) we have prepared the various compounds described in this paper.

Recently (Schofield and Theobald, this vol., p. 796) we described a method of obtaining 6-nitro- and 4-nitro-2-aminoacetophenone, and these compounds, on diazotisation, readily provided 5-, m. p. 304—305°, and 7-*nitro*-4-*hydroxycinnoline*, m. p. 295—296°, respectively. Each of these cinnolines depressed the m. p. of the above-mentioned isomer, m. p. 276—277°, which, it has been suggested (Schofield and Swain, this vol., p. 1367), is 3-nitro-4-hydroxycinnoline. In contrast to 8-nitro-4-hydroxycinnoline (Schofield and Simpson, *loc. cit.*; Simpson, *J.*, 1947, 237) the new compounds readily form *acetyl* derivatives under normal conditions. Reduction of 7- and 8-nitro-4-hydroxycinnoline (the latter being now readily available; Schofield and Theobald, *loc. cit.*) gave 7- and 8-*amino*-4-*hydroxycinnoline*, both of which yielded *diacetyl* derivatives. On diazotisation 8-amino-4-hydroxycinnoline behaved similarly to 8-amino-4-hydroxyquinaldine (Halcrow and Kermack, *J.*, 1945, 415), giving 1 : 8-*azo*-1 : 4-*dihydrocinnol*-4-*one* (I). 4-*Chloro*-5-*nitro*-, 4-*chloro*-7-*nitro*-, and 4-*chloro*-8-*nitro*-*cinnoline* (cf. Keneford,

Morley, and Simpson, *J.*, 1948, 1702) were obtained by standard means, the last, like 4-chloro-6-nitrocinnoline (Schofield and Simpson, *loc. cit.*), being rapidly hydrolysed when kept. Keneford, Morley, and Simpson (*loc. cit.*), by the action of phenol and ammonium carbonate on 4-chloro-8-nitrocinnoline, obtained a mixture of 8-nitro-4-phenoxycinnoline and 8-nitro-4-aminocinnoline, but the course of this reaction is apparently sensitive to small changes in the conditions, for in a slightly modified experiment we obtained only the 4-phenoxy-compound. *7-Nitro-4-phenoxycinnoline* was prepared similarly. These phenoxy-derivatives gave the corresponding 8-nitro- and *7-nitro-4-aminocinnoline* on treatment with fused ammonium acetate, but reduction of these compounds to the diamines offered some difficulty. Finally, 4 : 8-*diaminocinnoline*, which gave a *diacetyl* derivative, was secured by using iron and aqueous ferrous sulphate (Hodgson and Hathway, *J.*, 1944, 538) as the reducing agent, but even under these mild conditions we could not produce the 4 : 7-diamine. The most that could be achieved was a mediocre yield of 4 : 7-*diacetamidocinnoline* by reductive acetylation of the nitro-compound.

The methylation of 6-nitro-4-hydroxycinnoline (Schofield and Simpson, *loc. cit.*) is of interest in that it provides both 6-nitro-1-methyl-1 : 4-dihydrocinnol-4-one (II) and the methyl


(I.)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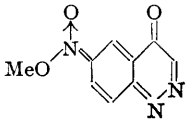
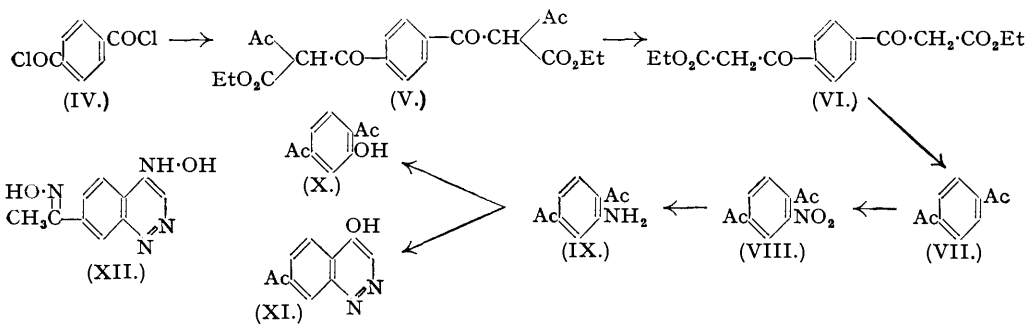

(III.)

nitronate (III). In contrast, 8-nitro-4-hydroxycinnoline, for which the same formal possibilities exist, gave only 8-*nitro*-1-*methyl*-1 : 4-*dihydrocinnol*-4-*one* (possibly because nitronate formation here would involve the less stable *o*-quinonoid form). As was to be expected, 5- and 7-nitro-4-hydroxycinnoline behaved similarly, giving respectively 5- and 7-*nitro*-1-*methyl*-1 : 4-*dihydrocinnol*-4-*one*.

When our work began, 4-nitro-2-aminoacetophenone was not available and the diazotisation of 2-amino-1 : 4-diacetylbenzene (IX), combined with obvious standard conversions, appeared to offer the easiest means of access to derivatives of 7-aminocinnoline. 2-Amino-1 : 4-diacetylbenzene has been described by Ruggli and Gassenmeier (*Helv. Chim. Acta*, 1939, **22**, 496) and by Christensen, Graham, and Griffith (*J. Amer. Chem. Soc.*, 1945, **67**, 2001), and was prepared from terephthaloyl chloride (IV) in the stages shown below. In the step (VI) ⟶ (VII) the


(IV.) (V.) (VI.) (X.) (XII.) (XI.) (IX.) (VIII.) (VII.)

Swiss authors obtained only a 10—15% yield. We raised this to 75—80%, and by using the method of Kermack and Smith (*J.*, 1929, 814) have reduced the conversion (V) ⟶ (VII) to a one-stage process with an overall yield of 55—60%. Nitration of (VII) gave 60% of (VIII), m. p. 63°, in agreement with the figure given by Christensen and his co-workers (*loc. cit.*) (Ruggli and Gassenmeier, *loc. cit.*, give m. p. 46°). Diazotisation of 2-amino-1 : 4-diacetylbenzene gave either 2-*hydroxy*-1 : 4-*diacetylbenzene* (X) or 4-*hydroxy*-7-*acetylcinnoline* (XI), depending on whether the reaction was effected in dilute or concentrated acid solution (cf. Schofield and Simpson, *J.*, 1948, 1170).

The *oxime* of 4-hydroxy-7-acetylcinnoline was unaffected by hydrochloric–acetic acid mixture, but was converted by sulphuric acid into a compound, m. p. 276—277° (not analysed), yielding an *acetyl* derivative, m. p. 191°, which analysed satisfactorily for 7-acetamido-4-acetoxycinnoline, but which, in view of the preparation described above, must be regarded as of doubtful nature (it may be 4-acetoxycinnoline-7-carboxymethylamide). However, a

Schmidt rearrangement of 4-hydroxy-7-acetylcinnoline readily provided *7-acetamido-4-hydroxycinnoline*, identified by hydrolysis to the free amine identical with that described above.

4-Chloro-7-acetylcinnoline was obtained by standard means and converted into *4-phenoxy-7-acetylcinnoline*. Treatment of the latter with fused ammonium acetate, a reagent which converts the 4-phenoxy-compound into the 4-aminocinnoline in good yield in other cases (present paper and Part XVII, *J.*, 1948, 358), gave no useful result. 4-Phenoxy-7-acetylcinnoline reacted in an unexpected fashion with hydroxylamine, giving *4-hydroxylamino-7-acetylcinnoline oxime* (XII), as indicated by the fact that phenol was liberated during the reaction and by analysis of the product. Other examples of this ready nucleophilic substitution are being examined. The oxime (XII) was re-arranged by hydrogen chloride in acetic acid–anhydride mixture to *4-hydroxylamino-7-acetamidocinnoline* (or 4-hydroxylaminocinnoline-7-carboxymethylamide).

Experimental.

M.p.s are uncorrected. Diazotisations were effected at 0°.

5- and 7-Nitro-4-hydroxycinnoline.—6-Nitro-2-aminoacetophenone (0·8 g.) in acetic acid (8 c.c.) and sulphuric acid (4 c.c.; *ca.* 30N.) was diazotised with powdered sodium nitrite (4 g.), the solution set aside for 24 hours at room temperature, heated for ½ hour at 95°, and then diluted with water, and the product collected (0·59 g.). *5-Nitro-4-hydroxycinnoline* separated from alcohol in colourless needles, m. p. 304—305° (Found: C, 50·7; H, 2·8. $C_8H_5O_3N_3$ requires C, 50·3; H, 2·6%). The *acetyl* derivative crystallised in colourless leaflets, m. p. 185—186°, from dilute alcohol (Found: C, 50·7; H, 2·9. $C_{10}H_7O_4N_3$ requires C, 51·5; H, 3·0%).

In the same way 4-nitro-2-aminoacetophenone (1·5 g.) gave *7-nitro-4-hydroxycinnoline* (1·2 g.), forming pale yellow needles, m. p. 295—296°, from alcohol (Found: C, 50·1; H, 2·3%). The *acetyl* derivative separated from dilute alcohol and had m. p. 140—141° (Found: C, 52·1; H, 3·2%).

7- and 8-Amino-4-hydroxycinnoline.—7-Nitro-4-hydroxycinnoline (0·2 g.), acetic acid (2 c.c.), water (1 c.c.), and iron powder (0·14 g.) were boiled together for 1 hour, the mixture was filtered hot, the iron cake was washed with boiling water (50 c.c.), and the combined filtrate and washings were cooled in ice. *7-Amino-4-hydroxycinnoline* (0·18 g.) formed fawn-coloured needles, m. p. 276—277°, from dilute alcohol (Found: C, 60·7; H, 5·3. $C_8H_7ON_3$ requires C, 59·6; H, 4·4%). Boiling acetic anhydride converted this into *7-acetamido-4-acetoxycinnoline*, which gave very small colourless needles, m. p. >330°, from dilute alcohol (Found: C, 58·8; H, 4·6. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·5%).

Obtained by the same method, in similar yield, *8-amino-4-hydroxycinnoline* formed lustreless yellow needles, m. p. 290—291°, from dilute acetic acid (Found: C, 59·0; H, 4·1%). *8-Acetamido-4-acetoxycinnoline* separated in tan needles, m. p. 282—283°, from dilute ethanol (Found: C, 59·3; H, 4·5%). Diazotisation of the blood-red solution of 8-amino-4-hydroxycinnoline (0·06 g.) in hydrochloric acid (2 c.c.; 2N.) with aqueous sodium nitrite (10%) gave an immediate white precipitate. Collected after 2 hours at 0° (0·05 g.), this gave buff-coloured leaflets of 1 : 8-*azo*-1 : 4-*dihydrocinnol-4-one*, m. p. 159—160° (decomp.), from dilute ethanol (Found: C, 56·0; H, 2·4. $C_8H_4ON_4$ requires C, 55·8; H, 2·3%).

4-Chlorocinnoline Derivatives.—The 4-hydroxy-compound (1 part by wt.) and phosphorus oxychloride (2 vols.) were heated for ¼ hour at 95°, and the mixture was decomposed with ice, neutralised with sodium acetate, and extracted with chloroform. In this way 5-nitro-4-hydroxycinnoline (0·1 g.) gave *4-chloro-5-nitrocinnoline* (0·08 g.), which formed lemon-yellow crystals, m. p. 170—171°, from ether–ligroin (b. p. 40—60°) (Found: C, 46·3; H, 2·5. $C_8H_4O_2N_3Cl$ requires C, 45·8; H, 1·9%). *4-Chloro-7-nitrocinnoline*, formed in similar yield, gave pale yellow needles (from the same solvent), m. p. 148—149° (Found: C, 45·8; H, 2·1%). 4-Chloro-8-nitrocinnoline gave golden leaflets, m. p. 167—169°, which were quickly hydrolysed when kept.

7- and 8-Nitro-4-phenoxycinnoline.—4-Chloro-7-nitrocinnoline (0·6 g.), phenol (5 g.), and ammonium carbonate (2 g.) were gently warmed together; the reaction was allowed to subside and completed by heating for ½ hour at 95°. The product (0·82 g.), isolated by pouring the solution into dilute sodium hydroxide solution, gave pale yellow needles of *7-nitro-4-phenoxycinnoline*, m. p. 172—173°, on crystallisation from benzene–ligroin (b. p. 40—60°) (Found: C, 62·9; H, 3·2. $C_{14}H_9O_3N_3$ requires C, 62·9; H, 3·4%). 8-Nitro-4-hydroxycinnoline (0·5 g.) and phosphorus oxychloride (5 c.c.) were heated for ½ hour at 95°, ligroin (b. p. 40—60°) was added, and the precipitate, after being washed several times by decantation with ligroin, was treated as above, giving a product (0·77 g.), which provided pale yellow needles of 8-nitro-4-phenoxycinnoline, m. p. 166—167°, from benzene (Found: C, 63·0; H, 3·7%).

7- and 8-Nitro-4-aminocinnoline.—7-Nitro-4-phenoxycinnoline (0·65 g.) was added with stirring to ammonium acetate (5 g.) at 140° (internal temperature), the mixture maintained for ¼ hour at this temperature, and the amine (0·45 g.) isolated by dilution and addition of an excess of aqueous ammonia. Crystallisation from dilute ethanol gave yellow leaflets of *7-nitro-4-aminocinnoline*, m. p. 300—301° (decomp.) (Found: C, 48·7; H, 3·6. $C_8H_6O_2N_4,\frac{1}{2}H_2O$ requires C, 48·2; H, 3·5%).

A 5-minutes reaction gave a similar yield of 8-nitro-4-aminocinnoline, which separated from the same solvent in fine yellow needles, m. p. 235—236° (decomp.) (Found: C, 47·0; H, 3·85. Calc. for $C_8H_6O_2N_4,H_2O$: C, 46·1; H, 3·9%) [Keneford *et al.*, *loc. cit.*, give m. p. 242—243° (decomp.). The difference may be due to the degrees of hydration].

4 : 7-Diacetamidocinnoline.—7-Nitro-4-aminocinnoline (0·06 g.), acetic anhydride (2 c.c.), zinc dust (0·1 g.), and sodium acetate (0·02 g.) were warmed at 95° for ½ hour with frequent shaking. Addition of water (10 c.c.), filtration whilst hot, and addition of an excess of aqueous ammonia gave a product (0·02 g.), which formed very small colourless needles of 4 : 7-*diacetamidocinnoline*, m. p.

(300°) 312° (decomp.), on crystallisation from dilute ethanol (Found: C, 54·4; H, 5·9. $C_{12}H_{12}O_2N_4,H_2O$ requires C, 54·9; H, 5·4%).

4 : 8-*Diaminocinnoline*.—8-Nitro-4-aminocinnoline (0·1 g.), iron powder (0·2 g.), water (10 c.c.), and ferrous sulphate (0·02 g.) were heated under reflux for 1 hour, the mixture was made alkaline with aqueous ammonia and filtered whilst hot. The iron residues were washed with hot water, and the combined filtrate and washings extracted with chloroform. Removal of the dried (Na_2CO_3) solvent and one crystallisation of the crude material (0·08 g.) from ether–ligroin (b. p. 40—60°) gave a product (0·04 g.), m. p. 163—166°. Pure 4 : 8-*diaminocinnoline* was a buff-coloured solid, m. p. 167—168° (Found: C, 56·0; H, 4·8. $C_8H_8N_4,\frac{2}{3}H_2O$ requires C, 55·8; H, 5·5%). Acetic anhydride converted this into 4 : 8-*diacetamidocinnoline*, m. p. 299—300°, which formed pale greenish-yellow needles from dilute alcohol (Found: C, 59·1; H, 5·1. $C_{12}H_{12}O_2N_4$ requires C, 59·0; H, 4·95%).

5-, 7-, *and* 8-*Nitro*-1-*methyl*-1 : 4-*dihydrocinnol*-4-*one*.—In each case the 4-hydroxy-compound (0·2 g.) in warm 2% potassium hydroxide solution (3·65 c.c.) was treated at 50°, with stirring, with methyl sulphate (0·1 c.c.), and the substantially pure product collected after 2 minutes (0·16—0·17 g.). 5-*Nitro*-1-*methyl*-1 : 4-*dihydrocinnol*-4-*one* gave pale yellow leaflets, m. p. 188—189°, from ethanol (Found: C, 52·4; H, 3·4. $C_9H_7O_3N_3$ requires C, 52·7; H, 3·4%). From the same solvent 7-*nitro*-1-*methyl*-1 : 4-*dihydrocinnol*-4-*one* formed pale orange leaflets, m. p. 238° (Found: C, 53·1; H, 3·5%), whilst 8-*nitro*-1-*methyl*-1 : 4-*dihydrocinnol*-4-*one* separated in yellow needles, m. p. 243—244° (Found: C, 53·0; H, 3·5%).

p-*Diacetylbenzene*.—(i) (V) ⟶ (VII). Terephthaloyldiacetoacetic ester (V) (10 g.; obtained in 70% yield from runs using 100 g. of terephthalic acid, by the method of Berend and Herms, *J. pr. Chem.*, 1906, **74**, 133), alcohol (100 c.c.), and concentrated sulphuric acid (5 c.c.) were heated under reflux for 14 hours, water was added (100 c.c.), the solution concentrated to its original volume and then boiled under reflux for 8 hours more. The crude ketone was triturated with 3% sodium hydroxide solution, washed with water, and dried: yield, 2·5 g. (60%); m. p. 113—114° (Berend and Herms, *loc. cit.*, give m. p. 114°).

(ii) (V) ⟶ (VI) ⟶ (VII). 5 G. of (V) were warmed and stirred at 60° with alcoholic ammonia (25 g. of a mixture made from 11·4 c.c. of ammonia, *d* 0·88, and 93 c.c. of ethanol) until dissolution was complete. After acidification the product was collected and crystallised from ethanol; yield, 3·10 g.; m. p. 70°.

2·7 G. of (VI) were heated under reflux for 6 hours with 10% sulphuric acid (25 c.c.), the mixture was cooled, and the product collected, washed with water, and purified as in (i) above; yield, 1·09 g.; m. p. 113—114°.

2-*Hydroxy*-1 : 4-*diacetylbenzene*.—2-Amino-1 : 4-diacetylbenzene (0·2 g.) in 4N-hydrochloric acid 10 c.c.) was diazotised with aqueous sodium nitrite (10%), and the solution heated on the steam-bath until it no longer showed coupling properties. The product (0·11 g.) gave colourless needles of 2-*hydroxy*-1 : 4-*diacetylbenzene*, m. p. 74—75°, from dilute alcohol (Found: C, 67·1; H, 5·1. $C_{10}H_{10}O_3$ requires C, 67·4; H, 5·6%).

4-*Hydroxy*-7-*acetylcinnoline*.—The amine (3 g.) in concentrated hydrochloric acid (75 c.c.) was diazotised with aqueous sodium nitrite (10%), concentrated hydrochloric acid (300 c.c.) added, and the solution set aside for 3 days at room temperature and then heated at 75° until coupling properties disappeared. Concentration to a small volume and neutralisation with sodium acetate precipitated the product (1·5 g.), which crystallised from alcohol in pale yellow prisms of 4-*hydroxy*-7-*acetylcinnoline*, m. p. 242—243° (Found: C, 63·0; H, 4·2. $C_{10}H_8O_2N_2$ requires C, 63·8; H, 4·3%).

The cinnoline (1 g.), alcohol (20 c.c.), hydroxylamine hydrochloride (0·37 g.), sodium acetate (0·44 g.), and water (10 c.c.), when boiled under reflux for 1 hour, gave the substantially pure *oxime* (0·64 g.), which separated from alcohol as a buff-coloured solid, m. p. 294—295° (Found: C, 59·0; H, 4·3. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4%).

The oxime (1 g.) was added gradually to sulphuric acid (5 c.c.; 85%) and stirred over a small flame until dissolved. After the mixture had been poured into water, the product was crystallised from alcohol, giving a brown solid, m. p. 281—282°. Treatment with boiling acetic anhydride gave a *product*, m. p. 191—192° (Found: C, 58·2; H, 4·2. $C_{12}H_{11}O_3N_3$ requires C, 58·8; H, 4·5%).

7-*Acetamido*-4-*hydroxycinnoline*.—4-Hydroxy-7-acetylcinnoline (0·1 g.), concentrated sulphuric acid (2 c.c.), and chloroform (10 c.c.) were stirred together at room temperature and then treated with sodium azide (0·1 g.). Stirring was continued for 3 hours with occasional replenishment of the chloroform. Finally the chloroform was allowed to evaporate completely, the residue diluted with ice and neutralised with sodium acetate, and the product collected (0·07 g.). 7-*Acetamido*-4-*hydroxycinnoline* separated from alcohol in colourless crystals, m. p. >330° (Found: C, 58·2; H, 5·2. $C_{10}H_9O_2N_3$ requires C, 59·1; H, 4·4%). The acetamido-compound (0·06 g.) was heated under reflux with hydrochloric acid (2 c.c.; 5N.) for 1 hour, and the solution cooled and neutralised with sodium acetate. When kept, the solution deposited 7-amino-4-hydroxycinnoline (0·03 g.) identical with that described above.

4-*Chloro*-7-*acetylcinnoline*.—4-Hydroxy-7-acetylcinnoline (0·2 g.) and phosphorus oxychloride (2 c.c.) were heated for 10 minutes at 95°, and the solution was decomposed with ice, neutralised with sodium acetate, and extracted with ether. Concentration of the extract, after it had been washed with dilute sodium carbonate solution and dried (Na_2SO_4), gave a pale yellow solid (0·18 g.). 4-*Chloro*-7-*acetylcinnoline* formed pale yellow needles, m. p. 147—148°, from ether–ligroin (b. p. 40—60°) (Found: C, 57·6; H, 3·6. $C_{10}H_7ON_2Cl$ requires C, 58·4; H, 3·5%).

4-*Phenoxy*-7-*acetylcinnoline*.—The chloro-compound (0·2 g.) gave the desired product (0·15 g.) in the usual way. From ether–ligroin (b. p. 40—60°) 4-*phenoxy*-7-*acetylcinnoline* formed colourless leaflets, m. p. 141—142° (Found: C, 70·9; H, 4·5. $C_{16}H_{12}O_2N_2,\frac{1}{2}H_2O$ requires C, 70·3; H, 4·8%).

4-*Hydroxylamino*-7-*acetylcinnoline Oxime*.—The phenoxy-compound (0·1 g.), hydroxylamine hydrochloride (0·03 g.), sodium acetate (0·05 g.), alcohol (5 c.c.), and water (5 c.c.) were warmed for a few minutes on the steam-bath, the solution was set aside for 24 hours at room temperature, and the product collected (0·09 g.). 4-*Hydroxylamino*-7-*acetylcinnoline oxime* gave pale yellow crystals, m. p.

264—265° (decomp.), from alcohol (Found : C, 54·8; H, 4·8. $C_{10}H_{10}O_2N_4$ requires C, 55·0; H, 4·6%). The oximation mother-liquor was treated with an excess of sodium carbonate, saturated with carbon dioxide, and steam-distilled. Extraction of the distillate with ether, removal of the ether after drying (Na_2SO_4), and treatment of the residue, in acetic acid, with bromine water gave tribromophenol, m. p. 91—93°, alone and mixed with an authentic specimen.

4-*Hydroxylamino*-7-*acetamidocinnoline*.—A solution of the oxime (0·1 g.) in acetic acid (5 c.c.) and acetic anhydride (2·5 c.c.) was saturated with hydrogen chloride and set aside for 1 day at room temperature, and the product collected (0·07 g.). Crystallisation from alcohol gave pale yellow needles of 4-*hydroxylamino*-7-*acetamidocinnoline*, m. p. 229—230° (Found : C, 55·6; H, 4·9. $C_{10}H_{10}O_2N_4$ requires C, 55·05; H, 4·6%).

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