87. *Cinnolines. Part XVII. A Simple Method for the Preparation of 4-Aminocinnolines.*

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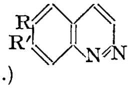
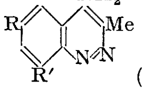
4-Aminocinnolines are readily prepared in good yield by reaction between molten ammonium acetate and the corresponding phenoxy-compounds.

Various problems connected with our studies in the cinnoline field made it necessary to devise a simple, general, and, if possible, inexpensive method for preparing 4-aminocinnolines. Initial experiments in this direction were carried out with 4-chlorocinnoline (I; R = R′ = H, R″ = Cl), and the experience gained in attempting to condense this substance directly with dialkylaminoalkylamines (Simpson and Schofield, *Nature*, 1946, **157**, 439; Keneford and Simpson, *J.*, 1947, 917) indicated that high-temperature reactions would be unlikely to be successful. Treatment of (I; R = R′ = H, R″ = Cl) with aqueous-alcoholic ammonia under pressure at 100—120° gave unchanged material and a *substance*, m. p. 237°, which from analysis appeared to be a hydrated aminohydroxycinnoline. The failure of the highly labile 4-chlorocinnoline (examples of the reactivity of this compound are given in the Experimental) to react completely under these conditions is in line with recent findings regarding the stability under mild alkaline conditions of chloro-heterocyclic compounds possessing an iminochloride, or



(I.)



(II.)

vinylogous iminochloride, structure (cf. Dobson and Kermack, *J.*, 1946, 150; Curd and Rose, *J.*, 1946, 363; Tomisek and Christensen, *J. Amer. Chem. Soc.*, 1945, **67**, 2112). The chloro-compound did not react with liquid ammonia at atmospheric pressure or with potassium phthalimide in boiling methyl ethyl ketone in presence of potassium carbonate.

On the other hand, 4-chlorocinnolines in general are readily converted into 4-phenoxycinnolines, which are likewise reactive (see Experimental), and which, further, also condense smoothly with dialkylaminoalkylamines (Keneford and Simpson, *loc. cit.*). The conversion of 4-chloroquinaldines into 4-aminoquinaldines by means of ammonia and phenol at 180° has been described by Backeberg and Marais (*J.*, 1942, 381), and G.P. 708,116 (*Chem. Abs.*, 1943, **37**, 5084) claims the conversion of 4-alkoxy- into 4-amino-quinolines by reaction with ammonium salts and ammonia. It therefore seemed worth while to investigate the reaction between an ammonium salt and 4-phenoxycinnolines, and it was found that, on addition of the latter to molten ammonium acetate, rapid reaction occurred with production of the corresponding 4-aminocinnolines. In this way 4-*amino-* (I; $R = R' = H$, $R'' = NH_2$), 6-*chloro*-4-*amino-* (I; $R = Cl$, $R' = H$, $R'' = NH_2$), 7-*chloro*-4-*amino-* (I; $R = H$, $R' = Cl$, $R'' = NH_2$), and 6-*nitro*-4-*amino-cinnoline* (I; $R = NO_2$, $R' = H$, $R'' = NH_2$), and also 6-*nitro-* (II; $R = NO_2$, $R' = H$) and 8-*nitro*-4-*amino*-3-*methylcinnoline* (II; $R = H$, $R' = NO_2$) were readily prepared. The amines had marked basic properties, but could be precipitated from acid solution by ammonia; they were readily acetylated. Formation of the nitroamines was accompanied by some hydrolysis of the phenoxy- to the hydroxy-compound.

We have also found that this method of preparation of amino-compounds from reactive chloro-compounds can be applied to the quinazoline and quinoline series; examples of these applications will be published in due course.

EXPERIMENTAL.

(M. ps. are uncorrected.)

Reaction of 4-*Chlorocinnoline with Ammonia.*—The chloro-compound (1 g.) was heated with alcohol (4 c.c.) and ammonia solution (4 c.c., *d* 0·88) in a sealed tube at 100° for 2½ hours. Concentration of the solution under reduced pressure gave a solid which, recrystallised from alcohol, yielded light coppery needles of the *product*, m. p. 238—239° (Found : C, 55·35; H, 4·85; N, 24·5. $C_8H_7ON_3,\frac{2}{3}H_2O$ requires C, 55·5; H, 4·8; N, 24·3%). Addition of sodium hydroxide to the filtrates and extraction with ether gave unchanged 4-chlorocinnoline, identified by its positive Beilstein reaction and by recrystallisation from hot water, which converted it into 4-hydroxycinnoline, m. p. and mixed m. p. 230°. Unchanged chlorocinnoline was still present after the reaction time had been increased to 8 hours. In another experiment, the temperature was raised from 20° to 120° during 2¼ hours; at this point the product was worked up, and yielded unchanged chloro-compound as sole isolable product [identified as 4-acetoxycinnoline, m. p. and mixed m. p. 124—126° (*J.*, 1945, 512), by short refluxing with acetic anhydride].

Reactions of 4-*Phenoxycinnoline.*—(*a*) The compound (50 mg.) was refluxed for 5 hours in alcohol (0·6 c.c.). Evaporation of the solvent and digestion with ether left crude 4-hydroxycinnoline, m. p. 212—216°, not depressed by admixture with authentic material.

(*b*) The compound (50 mg.) was refluxed for ¾ hour with acetic anhydride (0·5 c.c.). Removal of solvent under reduced pressure and crystallisation from alcohol gave 4-acetoxycinnoline, m. p. 122—124° (124—126° when mixed with an authentic sample).

6-*Nitro*-4-*phenoxycinnoline.*—Application to 4-chloro-6-nitrocinnoline of the phenoxylation method previously described (*J.*, 1947, 917) gave much 6-nitro-4-hydroxycinnoline and only a poor yield of phenoxy-compound; the following conditions were therefore used. 6-Nitro-4-hydroxycinnoline (15 g.), phosphorus pentachloride (20 g.), and phosphorus oxychloride (45 c.c.) were heated on the steam-bath for 1 hour. The mixture was cooled, ligroin (b. p. 40—60°) was added, and the heavy granular solid washed several times by decantation with more ligroin (b. p. 40—60°). Phenol (50 g.) was immediately added, followed by powdered ammonium carbonate (20 g.). The mixture was warmed very slightly to start the reaction and then left for 10 minutes, after which it was heated on the steam-bath for ½ hour. (If the mixture developed an acid reaction—indicated by the appearance of a deep red colour—a little more ammonium carbonate was added until the mass acquired a brown colour; failure to do this resulted in extensive hydrolysis to the hydroxycinnoline.) The mass was then poured into dilute aqueous sodium hydroxide and the oily solid collected. This was suspended in warm water, sodium hydroxide was added until the solution reacted alkaline to litmus, and the granular solid was filtered off, washed, and purified by digestion with hot alcohol (150 c.c.), yielding 6-*nitro*-4-*phenoxycinnoline* (65% yield), m. p. 190—191°. The substance formed yellow blades from alcohol, and silky yellow needles from benzene (Found : C, 63·0; H, 3·6. $C_{14}H_9O_3N_3$ requires C, 62·9; H, 3·4%).

Preparation of 4-*Aminocinnolines.*—The phenoxy-compound (1 part) was added in one portion to ammonium acetate (6 parts) which had been heated to *ca.* 180° (bath temp.) and then allowed to cool to 160°. The temperature was raised during 5 minutes to *ca.* 210° or until a reaction set in (smell of phenol), and maintained at 210—220° until completion of the reaction (usually about 10 minutes; this was in general easily ascertained by the formation of a clear yellow or brown solution). When cold, the melt was diluted with water, the solid collected, and the filtrate basified with ammonia and filtered, and the two crops of solid were combined and digested with a little 30—40% aqueous acetic acid. Filtration and basification gave the amine, which usually separated in almost pure condition.

4-*Aminocinnoline* (yield, 85%) separated from water in pale yellow leaflets, m. p. 212—213° (Found : C, 65·5; H, 5·1; N, 29·2. $C_8H_7N_3$ requires C, 66·2; H, 4·9; N, 28·9%), and as a hydrate, m. p. 152—154°; each form when refluxed with acetic anhydride gave 4-*acetamidocinnoline*, which formed fine lustrous needles, m. p. 272—273°, from alcohol (Found : C, 64·6; H, 4·9; N, 22·5. $C_{10}H_9ON_3$ requires C, 64·15; H, 4·9; N, 22·45%). 6-*Chloro*-4-*aminocinnoline* (85% yield) crystallised from alcohol in small, faintly yellow parallelepipeds, m. p. 277—278° (Found : C, 50·5; H, 3·75; N, 22·4. $C_8H_6N_3Cl,\frac{1}{2}H_2O$ requires C, 50·9; H, 3·75; N, 22·3%). 7-*Chloro*-4-*aminocinnoline* (yield, 95%), pale yellow rods from alcohol, had m. p. 209—210° (Found : C, 51·5; H, 3·8; N, 22·5. $C_8H_6N_3Cl,\frac{1}{2}H_2O$ requires C, 50·9; H, 3·75; N, 22·3%). 6-*Nitro*-4-*aminocinnoline* (yield, 75%) crystallised from a large volume of water in bright yellow needles, m. p. 288—289° (decomp.) (sometimes in small brown prisms) (Found : C, 48·75; H, 3·45; N, 28·4. $C_8H_6O_2N_4,\frac{1}{2}H_2O$ requires C, 48·2; H, 3·5; N, 28·15%); the *acetyl* derivative, m. p. 232—233°, formed ochre-coloured brittle prisms from ethyl acetate (Found : C, 51·9; H, 3·5; N, 24·0. $C_{10}H_8O_3N_4$ requires C, 51·7; H, 3·45; N, 24·1%). 6-*Nitro*-4-*amino*-3-*methylcinnoline* formed small rust-coloured needles from alcohol, decomposing at 320° without melting (Found : C, 52·85; H, 4·45; N, 27·0. $C_9H_8O_2N_4$ requires C, 52·9; H, 4·0; N, 27·45%). The yield of amine was only 55%, but 40% of 6-nitro-4-hydroxy-3-methylcinnoline was recovered. 8-*Nitro*-4-*amino*-3-*methylcinnoline* (yield, 45%, together with 55% of recovered hydroxycinnoline) crystallised from alcohol in orange hair-like needles, m. p. 283—285° (decomp.) (Found : C, 52·75; H, 4·1; N, 27·3. $C_9H_8O_2N_4$ requires C, 52·9; H, 4·0; N, 27·45%); the *acetyl* derivative, m. p. 177—178°, separated from alcohol in yellow striated plates (Found : C, 54·1; H, 4·15. $C_{11}H_{10}O_3N_4$ requires C, 53·65; H, 4·1%).

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