343. *Cinnolines. Part IV.*[1] *Quaternisation of 4-Amino-6-chloro- and 6-Chloro-4-phenoxy-cinnoline.*

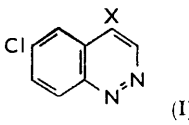
By D. E. Ames.

The work of Simpson [2] on the quaternisation of 4-amino-6-chlorocinnoline has been re-examined, and alkylation is shown to occur at N-1 and N-2 on the basis of revised structures for the methylation products of 6-chloro-4-hydroxycinnoline. 6-Chloro-4-phenoxycinnoline, however, appears to form a methiodide only by reaction at N-2.

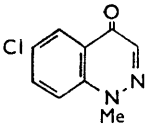
Evidence that the basic centre of cinnoline in quaternisation reactions is at N-2 has been described previously.[1] The basic centre of substituted cinnolines has generally been considered to be at N-1, largely because of the high reactivity of the methyl group in quaternary salts of 4-methylcinnoline.[1,3] One of the few cases in which more substantial evidence is available is 4-amino-6-chlorocinnoline (I; X = NH_2); the results which led Simpson [2] to conclude that the position of quaternary salt formation of this substance is N-1 have now been re-examined.

Simpson [2] described the methylation of 6-chloro-4-hydroxycinnoline (I; X = OH) with dimethyl sulphate and alkali; the crude product had m. p. 180—200° but only a substance with m. p. 221—222° was isolated, and this was assigned the expected structure (II) without experimental support. This methylation has now been found to give two products, m. p.s 220—224° (yield *ca.* 50%) and 160—162° (*ca.* 20%), readily separated by recrystallisation from benzene and chromatography on alumina. Similar results were obtained by methylation of 6-chloro-4-hydroxycinnoline with sodium ethoxide–ethanol–methyl iodide.

The high-melting compound is now considered to be the anhydro-base (III; X = Cl) of 6-chloro-4-hydroxy-2-methylcinnolinium hydroxide because catalytic hydrogenation in the presence of a base gives the anhydro-base (III; X = H) described previously;[4] also, reduction with zinc and acetic acid, followed by treatment with toluene-*p*-sulphonyl chloride and catalytic hydrogenation, yields 2-toluene-*p*-sulphonamidoacetophenone (IV).



(I)



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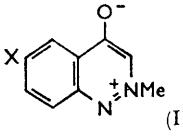

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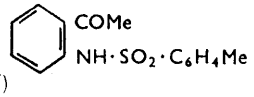
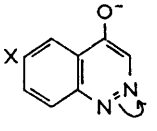
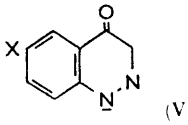


(IV)



(V)



(VI)

The low-melting methylation product is regarded as the true 6-chloro-1-methyl-4-cinnolone (II) since catalytic hydrogenation in the presence of triethylamine provides 1-methyl-4-cinnolone which had previously been reduced to *o*-methylaminoacetophenone.[4]

Simpson [2] stated that alkylation in 4-hydroxycinnolines occurs at N-1 because *N*-alkylation of any hydroxylated nitrogenous heterocyclic ring involves triad or pentad prototropy, irrespective of basicity. The predominant formation of the anhydro-base

[1] Part III, Ames and Kucharska, *J.*, 1964, 283.
[2] Simpson, *J.*, 1947, 1653.
[3] Atkinson and Taylor, *J.*, 1955, 4236.
[4] Ames and Kucharska, *J.*, 1963, 4924.

(III) by alkylation at N-2 is presumably due to reaction through the ion (V), rather than its isomer (VI), under the strongly basic conditions involved; possibly the reactivity of N-2 results from a tendency of the N=N bond to polarise as shown in (V).

Quaternisation of 4-amino-6-chlorocinnoline (I; X = NH_2) with methyl iodide was next re-examined. In agreement with the observations of Simpson,[2] alkaline hydrolysis of the quaternary salt furnished two products, m. p.s 220 and 160°. Simpson isolated (II), m. p. 160°, which he referred to as " product X," and recorded that it was isomeric with the second product but did not examine its structure. On the basis of the erroneous structure (II) for the anhydro-base (III; X = Cl), m. p. 220°, Simpson inferred that quaternisation had occurred at N-1. The present results indicate that quaternisation of 4-amino-6-chlorocinnoline must take place at both N-1 and N-2 to give a mixture of salts, since both methyl derivatives (II) and (III; X = Cl) are obtained on hydrolysis. This conclusion agrees with the work of Atkinson and Taylor [3] who obtained two series of quaternary salts from a number of 4-aminocinnolines.

The quaternisation of 6-chloro-4-phenoxycinnoline (I; X = OPh) with methyl iodide was also examined. Hydrolysis of the crude quaternary salt with hydrobromic acid cleaved the ether group and gave the anhydro-base (III; X = Cl). A small amount of 6-chloro-4-phenoxycinnoline was recovered but no 6-chloro-1-methyl-4-cinnolone could be detected by chromatography. Thus, quaternisation of 6-chloro-4-phenoxycinnoline seems to occur entirely, or almost entirely, at N-2 as with cinnoline itself.[1] The application of these methods to the determination of the basic centre in other substituted cinnolines is being examined.

Experimental

Evaporations were carried out under reduced pressure. Light petroleum had b. p. 60—80°.

Methylation of 6-Chloro-4-hydroxycinnoline.—(*a*) *With dimethyl sulphate.* The hydroxycinnoline [5] (2·4 g.) was dissolved in water (25 c.c.) and half of a solution of sodium hydroxide (2·5 g.) in water (40 c.c.). The solution was warmed to 75° and dimethyl sulphate (4 c.c.) was added, the mixture being kept at 70—80° for 20 min. with occasional shaking. After addition of the other half of the alkali, the mixture was warmed at 70—80° for 20 min., poured into water (200 c.c.), and extracted five times with chloroform. Evaporation of the dried (Na_2SO_4) extracts, and recrystallisation from benzene (200 c.c.), gave very pale yellow needles (1·2 g.), m. p. 220—224°, of the anhydro-base of 6-chloro-4-hydroxy-2-methylcinnolinium hydroxide (lit.,[2] m. p. 221—222°, after previous shrinking, but regarded as 6-chloro-1-methyl-4-cinnolone).

Chromatography of the mother-liquors on an 8 in. column of alumina and elution with benzene then benzene–chloroform (4 : 1) gave 6-chloro-1-methyl-4-cinnolone (0·5 g.), needles, m. p. 160—162° (from benzene–light petroleum) (Found: C, 55·5; H, 3·7; N, 14·3. $C_9H_7ClN_2O$ requires C, 55·5; H, 3·6; N, 14·4%). The m. p. was depressed to 115—125° on admixture with 6-chloro-4-methoxycinnoline (m. p. 169—170°).[2]

(*b*) *With sodium ethoxide and methyl iodide.* Sodium (1·0 g.) was dissolved in ethanol (100 c.c.), 6-chloro-4-hydroxycinnoline (3·0 g.) and methyl iodide (10 c.c.) were added, and the mixture was heated to the b. p. and set aside for 3 days. After addition of water (400 c.c.), the mixture was extracted with chloroform and the products were isolated as in (*a*). The anhydro-base (III; X = Cl) (1·70 g.), m. p. and mixed m. p. 220—224°, and 6-chloro-1-methyl-4-cinnolone (0·55 g.), m. p. and mixed m. p. 160—162°, were obtained.

Reduction of the Anhydro-base of 6-Chloro-4-hydroxy-2-methylcinnolinium Hydroxide.—(*a*) *Catalytic hydrogenation.* The anhydro-base (0·2 g.), triethylamine (5 c.c.), and 10% palladised charcoal (0·1 g.), in ethanol (50 c.c.), were hydrogenated. After a period of induction (10 min.), absorption was rapid (25 c.c. in 10 min.) and then became very slow, and the hydrogenation was stopped. The filtered solution was poured into water (150 c.c.) and extracted with ethyl acetate. Evaporation of the extract and recrystallisation of the residue from benzene–light petroleum and from ethyl acetate gave the anhydro-base of 4-hydroxy-2-methylcinnolinium hydroxide, m. p. and mixed m. p.[4] 164—166°.

[5] Barber, Washbourn, Wragg, and Lunt, *J.*, 1961, 2828.

(*b*) *With zinc and acetic acid.* A mixture of the anhydro-base (1·2 g.), zinc dust (3 g.), and acetic acid (30 c.c.) containing concentrated hydrochloric acid (1 drop) was refluxed for 4·5 hr., more zinc dust (1 g.) being added after 3 hr. The solid was collected and washed with ethyl acetate, and the filtrates were poured into 5N-sodium hydroxide and extracted with ethyl acetate. Evaporation and distillation gave a red oil (0·3 g.), b. p. 115—120°/0·5 mm. This, in benzene (20 c.c.), was treated with pyridine (5 c.c.) and toluene-*p*-sulphonyl chloride (1 g.) at room temperature overnight. Addition of dilute hydrochloric acid, isolation with ethyl acetate, and recrystallisation from ethanol gave a sulphonamide (0·3 g.), m. p. 140—155°, which appeared to be a mixture, presumably owing to partial hydrogenolysis of the chloro-group during reduction. It was hydrogenated in ethanol (100 c.c.) containing triethylamine (0·5 c.c.), in the presence of 10% palladised charcoal (0·2 g.), until absorption ceased. Evaporation of the filtered solution afforded a solid which was washed with water and recrystallised from ethanol, to give 2-toluene-*p*-sulphonamidoacetophenone, m. p. and mixed m. p. 146—148° (lit.,[6] m. p. 148°).

Reduction of 6-*Chloro*-1-*methyl*-4-*cinnolone.*—The cinnolone (0·5 g.; m. p. 160—162°) and triethylamine (1 c.c.), in ethanol (50 c.c.), were hydrogenated with 10% palladised charcoal (0·5 g.). Absorption became slow when 60 c.c. had been taken up, and hydrogenation was stopped and the filtered solution poured into water. Isolation with ethyl acetate, and recrystallisation from light petroleum, gave 1-methyl-4-cinnolone, m. p. and mixed m. p.[4] 114—116°.

Hydrolysis of 4-*Amino*-6-*chlorocinnoline Methiodide.*—4-Amino-6-chlorocinnoline was quaternised with methyl iodide as described by Simpson,[2] and the methiodide (1·1 g.), in water (40 c.c.), was treated with 2N-sodium hydroxide (25 c.c.) and left at room temperature overnight. After addition of sodium hydroxide (5 g.), the solution was refluxed for 1·5 hr., diluted with water (100 c.c.), and extracted four times with chloroform. Evaporation of the extracts and recrystallisation from benzene gave the anhydro-base of 6-chloro-4-hydroxy-2-methylcinnoliniúm hydroxide, m. p. and mixed m. p. 220—224°. On chromatography of the mother-liquors on a 6 in. column of alumina, elution with benzene–chloroform (4 : 1) gave 6-chloro-1-methyl-4-cinnolone (Simpson's " substance X "[2]), m. p. and mixed m. p. 158—160°.

Hydrolysis of 6-*Chloro*-4-*phenoxycinnoline Methiodide.*—6-Chloro-4-phenoxycinnoline[7] (1·0 g.), ethanol (20 c.c.), and methyl iodide (20 c.c.), were refluxed (bath 90°) for 4 hr. The solution was evaporated to dryness and the residue boiled under reflux for 6 hr. with hydrobromic acid (30 c.c.; 48%). After addition of water (100 c.c.) and repeated extraction with chloroform, the extracts were washed with 2N-sodium hydroxide and water, dried (Na_2SO_4), and evaporated. Recrystallisation of the residue from benzene–light petroleum gave the anhydro-base of 6-chloro-4-hydroxy-2-methylcinnolinium hydroxide, m. p. and mixed m. p. 220—223°. Chromatography in benzene on a 6 in. column of alumina (elution with benzene) furnished 6-chloro-4-phenoxycinnoline, m. p. and mixed m. p. 127—129°. Elution with benzene–chloroform (1 : 1) gave more anhydro-base, m. p. and mixed m. p. 218—220° (total yield 80 mg.). No 6-chloro-1-methyl-4-cinnolone could be isolated from the eluate.

In another experiment, the crude quaternary salt was recrystallised from ethanol–ether. 6-*Chloro*-2-*methyl*-4-*phenoxycinnolinium iodide* formed bright red prisms, m. p. 200° (decomp.) (Found: C, 45·3; H, 3·0; N, 7·4. $C_{15}H_{12}ClIN_2O$ requires C, 45·2; H, 3·0; N, 7·0%).

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[6] Elson, Gibson, and Johnson, *J.*, 1930, 1131.
[7] Keneford and Simpson, *J.*, 1947, 920.