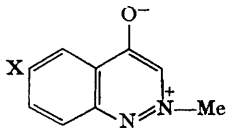
1084. *Cinnolines. Part V.*[1] *Methylation of Some Substituted Cinnolines.*

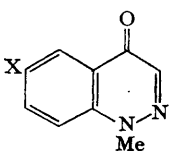
By D. E. Ames, R. F. Chapman, and (Miss) H. Z. Kucharska.

The action of methyl iodide on ethyl 6-chloro-4-hydroxycinnoline-3-carboxylate and 4-amino-, 4-methoxy-, and 4-phenoxy-cinnolines is examined and it is shown that methylation may occur at N-1 and/or N-2. Reduction of 3-hydroxy-4-phenylcinnoline and of 3-chlorocinnoline with lithium aluminium hydride gives 4-phenyl- and 3-chloro-1,4-dihydrocinnoline, respectively.

Methylation of 4-hydroxy- and 6-chloro-4-hydroxy-cinnolines has been shown[1,2] to occur predominantly at N-2 to give the anhydro-bases (I), only a small amount of the 1-methyl-4-cinnolone (II) being formed in each case. Methylation of ethyl 6-chloro-4-hydroxy-cinnoline-3-carboxylate (III) has now been examined to determine whether the presence of



(I)



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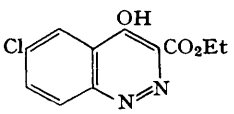

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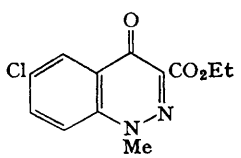
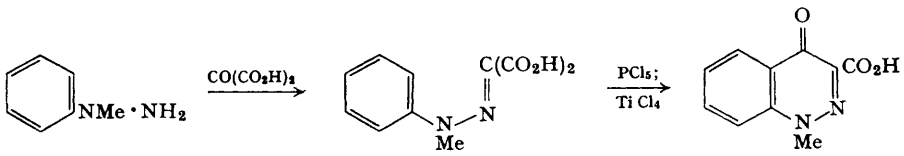


(IV)

the 3-substituent led to methylation at N-1. Treatment of compound (III) with sodium ethoxide and methyl iodide in ethanol gave a complex mixture from which the main product, ethyl 6-chloro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylate (IV) was isolated in 45% yield. The structure of this product was shown by hydrolysis and decarboxylation of the resulting acid to give 6-chloro-1-methyl-4-cinnolone (II; X = Cl). Further evidence was obtained by removal of the chlorine atom by hydrogenation, followed by hydrolysis to 1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylic acid (V), which was also synthesised by the following route:[3]



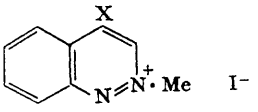
(V)

The quaternisation of 4-aminocinnoline with methyl iodide was examined by Atkinson and Taylor[4] who obtained an α-methiodide (and the α-methochloride) and also a β-methochloride. We have confirmed these results and also isolated the β-methiodide. Atkinson and Taylor advanced evidence indicating that quaternisation had occurred at N-1 and N-2 but did not assign definite structures to the salts. We have now found that alkaline hydrolysis of the α-methiodide gives the anhydro-base (I; X = H) in 54% yield while the β-methiodide gives 1-methyl-4-cinnolone (II; X = H) in 46% yield. In each case, none of the other isomer could be detected by chromatography. Thus, the α-methiodide must be 4-amino-2-

[1] Part IV, D. E. Ames, *J.*, 1964, 1763.
[2] D. E. Ames and H. Z. Kucharska, *J.*, 1963, 4924.
[3] Cf. H. J. Barber, K. Washbourne, W. R. Wragg, and E. Lunt, *J.*, 1961, 2828.
[4] C. M. Atkinson and A. Taylor, *J.*, 1955, 4236.

methylcinnolinium iodide (VI; X = NH_2) and the β-methiodide must be 4-amino-1-methylcinnolinium iodide (VII; X = NH_2).

Quaternisation of 4-phenoxycinnoline with methyl iodide involves methylation at N-2, since hydrolysis with hydrobromic acid yields only the anhydro-base of 2-methyl-4-hydroxycinnolinium hydroxide (I; X = H) and no 1-methyl-4-cinnolone. Treatment of 4-methoxycinnoline with methyl iodide in ethanol, however, gave 4-methoxy-2-methylcinnolinium iodide (VI; X = OMe) as the main product, but fractional crystallisation also gave a small, amount of 1-methyl-4-cinnolone. The structure of the quaternary salt was established by hydrolysis with hydrobromic acid, and by heating at 160°; in each case the anhydro-base (I; X = H) was obtained.



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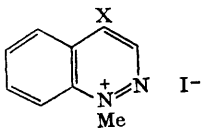
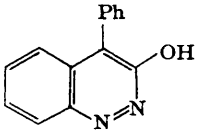


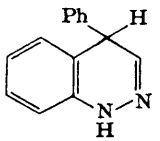
(VII)

These results, with those obtained previously,[1,2,5] show that the reactive centre of cinnoline is at N-2 but that, in substituted cinnolines, electronic and steric effects of substituent groups may lead to reaction at N-1 and/or N-2.

It has been shown previously[6] that reduction of 3-hydroxycinnoline with lithium aluminium hydride gives 1,2,3,4-tetrahydrocinnoline, whereas 4-hydroxycinnoline gives this base and some cinnoline. The reduction of various hydroxy-phenylcinnolines with lithium aluminium hydride has been described by Atkinson and Sharpe[7] who did not isolate the reduction products but oxidised them with mercuric oxide to obtain phenylcinnolines. The reduction of 3-hydroxy-4-phenylcinnoline (VIII) with lithium aluminium hydride has now been found to give 1,4-dihydro-4-phenylcinnoline (IX). This compound was long regarded



(VIII)



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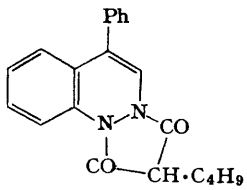

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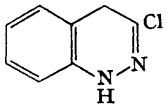

(XI)

as the 1,2-dihydro-derivative but structure (IX) was recently indicated by a study of the nuclear magnetic resonance spectrum.[8] The dihydro-compound (IX) condensed with diethyl butylmalonate in the presence of sodium ethoxide to give the butylmalonyl derivative (X), analogous to the drug, phenylbutazone. Formation of this cyclic product is presumably due to rearrangement of compound (IX) to the 1,2-dihydro-isomer under the drastic reaction conditions (as in the preparation of the corresponding phthaloyl derivative[8]).

Reduction of 3-chlorocinnoline with lithium aluminium hydride also gave the 1,4-dihydro-derivative (XI). This structure was indicated by catalytic hydrogenolysis in the presence of a base to give 1,4-dihydrocinnoline (which was also obtained similarly from 3-chlorocinnoline). The resistance of the chloro-compound to hydrogenolysis by excess of lithium aluminium hydride is surprising, especially since 4-chlorocinnoline is reduced to 4,4'-bicinnolyl.[6]

[5] D. E. Ames and H. Z. Kucharska, *J.*, 1964, 283.
[6] D. E. Ames and H. Z. Kucharska, *J.*, 1962, 1509.
[7] C. M. Atkinson and C. J. Sharpe, *J.*, 1959, 2858.
[8] L. S. Besford, G. Allen, and J. M. Bruce, *J.*, 1963, 2867.

Experimental

Ethyl 6-Chloro-4-hydroxycinnoline-3-carboxylate.—6-Chloro-4-hydroxycinnoline-3-carboxylic acid[3] (10 g.), ethereal boron trifluoride (20 c.c.; 45%), and ethanol (300 c.c.) were refluxed until all the solid had dissolved (12 hr.). The *ester* (9·4 g.), which separated on cooling, had m. p. 228—230° (from ethanol) (Found: C, 52·5; H, 3·8; N, 11·2; Cl, 14·2. $C_{11}H_9ClN_2O_3$ requires C, 52·3; H, 3·6; N, 11·1; Cl, 14·0%).

Ethyl 6-Chloro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylate.—The ester (6 g.), in boiling ethanol (200 c.c.) was added to hot sodium ethoxide solution (from sodium, 3 g., and ethanol, 75 c.c.). Methyl iodide (40 c.c.) was added during 20 min. and the mixture was refluxed for 3 hr. Evaporation under reduced pressure and addition of acetic acid (50 c.c.) and then water (250 c.c.) gave the *cinnolone* (2·8 g.), m. p. 180—181°, from ethanol (Found: C, 54·5; H, 4·4; N, 10·8; Cl, 13·4. $C_{12}H_{11}ClN_2O_3$ requires C, 54·0; H, 4·2; N, 10·5; Cl, 13·3%).

6-Chloro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylic Acid.—The ester (1·5 g.) and potassium hydroxide (3 g.) in water (30 c.c.) were heated under reflux for 2 hr. Acidification of the filtered solution gave the *acid* (1·3 g.), m. p. 280—282° (decomp.) (from 2-ethoxyethanol) (Found: C, 50·4; H, 3·1; N, 11·6; Cl, 14·9. $C_{10}H_7ClN_2O_3$ requires C, 50·3; H, 3·0; N, 11·7; Cl, 14·9%). The acid (0·5 g.) was heated at 260° for 1 hr.; extensive decomposition and some sublimation occurred. Extraction with benzene (charcoal), evaporation, and recrystallisation from benzene–light petroleum (b. p. 60—80°) gave 6-chloro-1-methyl-4-cinnolone[1] (0·1 g.), m. p. and mixed m. p. 155—157°.

1,4-Dihydro-1-methyl-4-oxocinnoline-3-carboxylic Acid.—(*a*) Ethyl 6-chloro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylate (2·8 g.) in ethanol (200 c.c.) was hydrogenated in the presence of triethylamine (15 c.c.) and palladised charcoal (0·5 g.) (10%), 340 c.c. being taken up in 45 min. The solution was filtered hot, concentrated under reduced pressure, poured into water, and extracted with ethyl acetate. Evaporation and crystallisation from benzene–light petroleum (b. p. 60—80°) gave *ethyl 1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylate* (1·7 g.), m. p. 123—125° (Found: C, 62·0; H, 5·1; N, 12·0. $C_{12}H_{12}N_2O_3$ requires C, 62·1; H, 5·2; N, 12·1%).

This product (1·7 g.) and sodium hydroxide (5 g.) in water (50 c.c.) were refluxed for 1 hr. Acidification gave the acid (1·3 g.), m. p. and mixed m. p. 244—246°.

(*b*) A solution of the sodium salt of mesoxalic acid (1 g.) in 2N-hydrochloric acid (10 c.c.) was warmed on a steam-bath for 5 min. with *N*-methyl-*N*-phenylhydrazine (1·3 g.). The *hydrazone* (0·8 g.) separated on cooling and formed yellow needles, m. p. 103° (with decarboxylation), from ethyl acetate–light petroleum (b. p. 60—80°) (Found: C, 53·6; H, 4·8; N, 12·9. $C_{10}H_{10}N_2O_4$ requires C, 54·1; H, 4·5; N, 12·6%).

Phosphorus pentachloride (17 g.) was added to the hydrazone (8·5 g.) in chloroform (230 c.c.) and the mixture refluxed for 1·5 hr. and then evaporated under reduced pressure. The residue in nitrobenzene (70 c.c.) was stirred at 20° while titanium tetrachloride (5 c.c.) was added. After the mixture had been heated at 95° for 2 hr., water (250 c.c.) was added, and nitrobenzene was removed by steam-distillation; the residue was basified with 2N-sodium hydroxide and the filtered solution was acidified to give *1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylic acid* (0·5 g.), needles, m. p. 242—243° (decomp.), from benzene (Found: C, 59·7; H, 4·1; N, 14·1. $C_{10}H_8N_2O_3$ requires C, 58·8; H, 4·0; N, 13·7%).

Quaternisation of 4-Aminocinnoline.—4-Aminocinnoline (6·5 g.) was quaternised with methyl iodide as described by Atkinson and Taylor[4] and two products were separated by fractional crystallisation from ethanol: α-methiodide (4-amino-2-methylcinnolinium iodide) (3·6 g.), m. p. 256—258° (lit.,[4] 258°); and β-methiodide (*4-amino-1-methylcinnolinium iodide*) (1·7 g.), m. p. 206—208° (Found: C, 36·4; H, 3·7; I, 44·6; N, 14·7. $C_9H_{10}IN_3$ requires C, 37·6; H, 3·5; I, 44·2; N, 14·6%). The corresponding methochlorides had m. p.s 258—260° and 286—288° (lit.,[4] 261° and 291°).

Hydrolysis of 4-Aminocinnoline Methiodides.—(*a*) *α-Methiodide.* The salt (1·0 g.) was heated under reflux with 2N-sodium hydroxide (100 c.c.) for 3 hr., the solution turning yellow, brown, then blue. The cooled mixture was extracted repeatedly with chloroform and the extracts were washed, dried, and evaporated. Crystallisation from benzene gave the anhydro-base of 2-methyl-4-hydroxycinnolinium hydroxide, m. p. and mixed m. p.[2] 164—166°. Chromatography of the mother liquors in benzene on a column of alumina and elution with benzene gave more product (total, 0·30 g., 54%), but no 1-methyl-4-cinnolone could be detected.

(*b*) *β-Methiodide.* Hydrolysis was carried out similarly and gave 1-methyl-4-cinnolone

(46%), m. p. and mixed m. p.[2] 114—116°. None of the isomer could be detected by chromatography.

Quaternisation of 4-Phenoxycinnoline.—4-Phenoxycinnoline (1·3 g.), ethanol (25 c.c.), and methyl iodide (7 c.c.) were refluxed for 2 hr. After evaporation under reduced pressure, the crude methiodide and hydrobromic acid (15 c.c.; 48%) were refluxed for 13 hr. Addition of water, basification, extraction with chloroform, and evaporation gave the anhydro-base of 2-methyl-4-hydroxycinnolinium hydroxide (0·28 g.) which was purified as before. No 1-methyl-4-cinnolone could be detected.

2-Methyl-4-phenoxycinnolinium picrate, m. p. 124—126°, from ether–ethanol, was obtained from the crude methiodide and ethanolic picric acid (Found: C, 52·7; H, 3·6; N, 15·2. $C_{21}H_{15}N_5O_8,0{\cdot}5H_2O$ requires C, 53·1; H, 3·4; N, 14·8%).

Quaternisation of 4-Methoxycinnoline.—The cinnoline (3·5 g.), ethanol (150 c.c.), and methyl iodide (40 c.c.) were heated under reflux for 3 hr. and left overnight. *4-Methoxy-2-methylcinnolinium iodide* (4·1 g.) separated as orange needles which were recrystallised from ethanol (Found: C, 39·6; H, 3·7; I, 41·0; N, 9·3. $C_{10}H_{11}IN_2O$ requires C, 39·7; H, 3·7; I, 42·0; N, 9·3%). These melted with decomposition at about 130°, became colourless and resolidified, finally melting at 164—166°. When the salt (1·0 g.) was heated at 150—160° for 1 hr. to effect this decomposition, chromatography of the product again gave only the anhydro-base of 2-methyl-4-hydroxycinnolinium hydroxide (0·25 g.), m. p. and mixed m. p. 163—165°.

The same product (0·20 g.), m. p. and mixed m. p. 164—166°, was obtained by boiling the methiodide (0·7 g.) with hydrobromic acid (30 c.c.; 48%) for 6 hr. and isolating as in the previous hydrolysis.

4-Methoxy-2-methylcinnolinium picrate, m. p. 190—192°, from ethanol, was obtained from the methiodide and ethanolic picric acid (Found: C, 48·1; H, 3·7; N, 17·7. $C_{16}H_{13}N_5O_8$ requires C, 47·6; H, 3·2; N, 17·4%).

Evaporation of the mother liquors from separation of the methiodide, followed by extraction with benzene, evaporation, and crystallisation from benzene–light petroleum (b. p. 60—80°) gave white crystals of 1-methyl-4-cinnolone (0·35 g.), m. p. and mixed m. p. 114—116°.

Reduction of 3-Hydroxy-4-phenylcinnoline.—3-Hydroxy-4-phenylcinnoline[9] (1·4 g.) was placed in a Soxhlet apparatus and extracted into a refluxing suspension of lithium aluminium hydride (3 g.) in 1,2-dimethoxyethane (150 c.c.); refluxing was continued for 7 hr. Ether (200 c.c.) and 5N-sodium hydroxide (5 c.c.) were added and the mixture was left overnight. The solid was collected and washed with hot ethyl acetate, the filtrate being extracted with 2N-hydrochloric acid. Basification and isolation with ethyl acetate gave 1,4-dihydro-4-phenylcinnoline (0·4 g.), b. p. 120°/0·3 mm., m. p. and mixed m. p. 112—114° (lit.,[10] 115—116°), after recrystallisation from light petroleum (b. p. 60—80°).

Diethyl butylmalonate (5 g.) and dihydro-compound (5 g.) were added to sodium ethoxide (from sodium, 0·58 g.) in ethanol (15 c.c.). The mixture was distilled slowly and the residue heated at 150° for 12 hr. Addition of water and acidification gave the *malonyl derivative* (4·2 g.) as yellow needles, m. p. 160—161°, from ethanol (Found: C, 76·0; H, 6·0; N, 9·0. $C_{21}H_{20}N_2O_2$ requires C, 75·9; H, 6·1; N, 8·4%).

Reduction of 3-Chlorocinnoline with Lithium Aluminium Hydride.—3-Chlorocinnoline[11] (1 g.) in benzene (50 c.c.) was added to lithium aluminium hydride (1 g.) in ether (120 c.c.) and the mixture was refluxed for 5·5 hr. After addition of 5N-sodium hydroxide (5 c.c.), the mixture was left overnight; the solid was collected and washed with hot ethyl acetate. Evaporation of the combined filtrates and recrystallisation from benzene (charcoal) gave *3-chloro-1,4-dihydrocinnoline* (0·45 g.), colourless needles, m. p. 114—116° (Found: C, 57·4; H, 4·3; Cl, 21·0; N, 16·8. $C_8H_7ClN_2$ requires C, 57·7; H, 4·3; Cl, 21·3; N, 16·8%).

Catalytic Reduction of 3-Chloro-1,4-dihydrocinnoline.—The chloro-compound (1·5 g.) in ethanol (100 c.c.) was hydrogenated in presence of triethylamine (1·5 g.) and palladised charcoal (0·5 g.; 10%) until absorption ceased. After evaporation of the filtered solution, sodium hydrogen carbonate solution was added; isolation with ethyl acetate and recrystallisation from light petroleum (b. p. 60—80°) afforded 1,4-dihydrocinnoline (0·77 g.), m. p. and mixed m. p.[8,12] 78—80°. Similar hydrogenation of 3-chlorocinnoline also gave 1,4-dihydrocinnoline (55%).

[9] H. E. Baumgarten and P. L. Creger, *J. Amer. Chem. Soc.*, 1960, **82**, 4634.
[10] P. W. Neber, G. Knoller, K. Herbst, and A. Trissler, *Annalen*, 1929, **471**, 113.
[11] E. J. Alford and K. Schofield, *J.*, 1953, 1811.
[12] M. Busch and A. Rast, *Ber.*, 1897, **30**, 521.

Addition of the base to ethereal picric acid gave 1,4-*dihydrocinnoline picrate*, m. p. 117° (decomp.) (Found: C, 46·4; H, 3·0; N, 18·8. $C_{14}H_{11}N_5O_7$ requires C, 46·5; H, 3·1; N, 19·4%). Recrystallisation from benzene–ethanol resulted in oxidation[5] to cinnoline picrate, m. p. and mixed m. p. 188—189°.

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