373. *Cinnolines. Part XXXI.* The Nature of the $C_{(3)}$-Position. Some Experiments with 3-Substituted Cinnolines.*

By E. J. Alford and K. Schofield.

The structure of 3-hydroxycinnoline was proved by its conversion into 3-chloro- and its formation from 3-bromo-cinnoline. Methylation of 3-hydroxycinnoline under acidic conditions, or with ethereal diazomethane, gave 2 : 3-dihydro-3-keto-2-methylcinnoline which was reduced to the 1 : 2 : 3 : 4-tetrahydro-3-keto-derivative, and also to oxindole and methylamine.

4-Methylcinnoline reacted readily with chloral, and 3-methylcinnoline methiodide gave in small yield a derivative with *p*-dimethylaminobenzaldehyde.

3-Aminocinnoline was obtained from 3-chloro- and 3-bromo-cinnoline. pK_a and ultra-violet absorption spectra determinations are presented which indicate that 3-hydroxycinnoline exhibits lactam–lactim tautomerism, and that $N_{(2)}$ is the basic centre in 3-aminocinnoline.

We have previously described the synthesis of 3-hydroxy-,† 3-methyl-, 3-chloro-, and 3-bromo-cinnoline (*J.*, 1952, 2102; 1953, 609), and now record preliminary experiments with these compounds, bearing on the interplay between $N_{(2)}$ and $C_{(3)}$ in cinnoline derivatives.

(A) 3-*Hydroxycinnoline.*—This compound gave with phosphorus oxychloride a small yield of 3-chlorocinnoline. Although the hydroxy-compound readily formed a benzoate (Alford and Schofield, *loc. cit.*), we were unable to obtain an acetate. pK_a values for 3-hydroxycinnoline (8·64) and 3-hydroxyquinoline (8·07) were determined in water at 20°.

With methyl sulphate and a deficiency of sodium hydroxide, 3-hydroxycinnoline gave the bright yellow 2 : 3-dihydro-3-keto-2-methylcinnoline (I). This was also formed from 3-hydroxycinnoline and ethereal diazomethane, a reagent which was without effect on the more feebly acidic 4-hydroxycinnoline, but converted 3-hydroxy- into 3-methoxy-quinoline. 2 : 3-Dihydro-3-keto-2-methylcinnoline was decomposed to a tar by alkali. Neber, Knöller, Herbst, and Trissler (*Annalen*, 1929, **471**, 127) reduced 3-hydroxycinnoline with red phosphorus and hydriodic acid to ammonia and oxindole, and (I) similarly gave methylamine and oxindole. Milder reduction of (I) provided a pale yellow tetrahydro-compound, presumably (II). 2 : 3-Dihydro-3-keto-2-methylcinnoline appeared to give a methiodide but this could not be purified.

The tar formed when 3-hydroxycinnoline was treated with methyl sulphate and excess of alkali yielded a small amount of an orange product. The high m. p. of this substance excluded its formulation as 3-methoxycinnoline and it is tentatively regarded as (III).

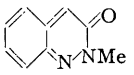
Although 3-hydroxy- gave 3-amino-quinoline in a Bucherer reaction, 3-hydroxycinnoline was unchanged by this process.

(B) 3-*Methylcinnoline.*—Unlike 4-methylcinnoline, which provided (IV), the 3-methyl isomer did not react with chloral in pyridine. It did, however, readily form a methiodide, which reacted with *p*-dimethylaminobenzaldehyde to give a small yield of the deeply coloured styryl compound (V). No product could be isolated from reactions between the

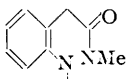
* Part XXX, *J.*, 1953, 609. † The term "3-hydroxycinnoline" is used throughout without implications for the fine structure of the compound.

methiodide and *p*-dimethylaminobenzaldehyde under the conditions used by Brooker and White (*J. Amer. Chem. Soc.*, 1951, **73**, 1094).

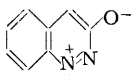
(C) 3-*Halogenocinnolines.*—3-Bromocinnoline reacted with methanolic sodium methoxide at 110—120° to give 3-methoxycinnoline, isolated as its picrate. In a similar experiment in undried methanol, the sodium salt of 3-hydroxycinnoline was obtained in good yield. Several attempts to convert 3-bromo- and 3-chloro- into 3-hydroxy-cinnoline by Maier-Bode's method (*Ber.*, 1936, **69**, 1534) gave only traces of the desired product.



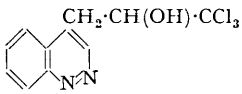
(I)



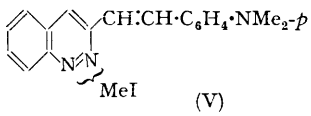
(II)



(III)



(IV)



(V)

It was shown by Schofield and Swain (*J.*, 1950, 384) that 3-bromo-4-chlorocinnolines were converted by phosphorus oxychloride into 3 : 4-dichlorocinnolines, more rapidly at 95° than at 135°. We now find 3-bromocinnoline, on the basis of carbon analyses, to behave similarly, though more slowly.

3-Bromocinnoline was reduced to cinnoline by hydrazine in alkaline medium with a palladium catalyst (Busch and Weber, *J. pr. Chem.*, 1936, **146**, 1).

3-Bromo- and 3-chloro-cinnoline reacted with ammonia under pressure in the presence of copper sulphate (Maier-Bode, *loc. cit.*) to give 3-aminocinnoline. The chloro-compound requires a higher reaction temperature than the bromo-compound.

(D) 3-*Aminocinnoline.*—In contrast to 3-aminoquinoline, the cinnoline is yellow, and its yellowish-green aqueous solution exhibited greenish-blue fluorescence, to be compared with the violet fluorescence of the quinoline derivative. 3-Aminocinnoline readily formed an acetyl derivative. 3-Aminoquinoline is readily diazotised, and the diazonium solution forms a deep red azo-compound with α-naphthol (Mills and Watson, 1910, **97**, 741), but in a similar test 3-aminocinnoline gave merely a reddish-brown solution. This reaction requires rigorous examination, but it seems that 3-aminocinnoline does not readily form a diazonium salt, if it does so at all.

pK_a values for 3-aminocinnoline (3·63) and 3-aminoquinoline (4·96) were determined in water. The value for 3-aminoquinoline confirms that given by Albert, Goldacre, and Phillips (*J.*, 1948, 2240).

Experimental

Extracts were dried with anhydrous sodium sulphate.

(A) *Replacement of Hydroxy- by Chloro-group.*—3-Hydroxycinnoline (0·5 g.) and phosphorus oxychloride (10 c.c.) were refluxed together for 8 hr. The mixture was decomposed with ice and sodium hydroxide, and extracted with ether. The extract yielded 3-chlorocinnoline (0·05 g.), m. p. 90—91°, alone and mixed with an authentic specimen (Alford and Schofield, *loc. cit.*).

Methylation.—(i) 3-Hydroxycinnoline (5 g.), water (25 c.c.), and half of a solution of sodium hydroxide (1·5 g.) in water (40 c.c.) were stirred at 95° and treated during 10 min. with methyl sulphate (4·5 c.c.), and the other half of the alkali solution was then added dropwise. After being stirred at the same temperature for 20 min. more, the product was extracted with chloroform. Concentration provided a solid (5·05 g.; m. p. 125—130°) which separated from acetone as golden-yellow plates (3·0 g.) of 2 : 3-*dihydro*-3-*keto*-2-*methylcinnoline*, m. p. 135·5—136·5° (Found: C, 67·1; H, 5·4. $C_9H_8ON_2$ requires C, 67·5; H, 5·0%). The aqueous solution of the compound exhibited a powerful green fluorescence. With hot alkali the substance formed a tar, and a deep green colour developed.

(ii) An experiment on the same scale with 2N-alkali (40 c.c.) and methyl sulphate (6 c.c.) gave a dark solution and much tar. Treatment of the tar with hot acetone left undissolved a yellow solid (0·17 g.), which was recrystallised from alcohol and from chloroform–ligroin; it formed

orange plates of the *anhydro*-salt (III), m. p. 280—283°, of 3-hydroxy-1-methylcinnolinium hydroxide (Found: C, 68·8; H, 4·9. $C_9H_8ON_2$ requires C, 67·5; H, 5·9%).

(iii) 3-Hydroxycinnoline (0·5 g.) dissolved with effervescence during ½ hr. in an ethereal solution of diazomethane (from 1 c.c. of methylnitrosourethane). Filtration and evaporation gave glistening yellow plates (0·27 g.) of 2 : 3-dihydro-3-keto-2-methylcinnoline, m. p. 132—134°, after crystallisation from benzene. More of this product was obtained from the ethereal mother-liquor.

(iv) 3-Hydroxyquinoline (0·5 g.) similarly dissolved during ¼ hr. in ethereal diazomethane. Next morning the solution was evaporated, leaving 3-methoxyquinoline (0·57 g.) as a dark oil. *3-Methoxyquinoline picrate*, prepared from alcoholic solutions of the components, crystallised from dioxan as orange prisms, m. p. 220—222° (Found: C, 50·0; H, 3·3. $C_{10}H_9ON,C_6H_3O_7N_3$ requires C, 49·5; H, 3·1%).

Reduction of 2 : 3-*Dihydro*-3-*keto*-2-*methylcinnoline*.—(i) The keto-derivative (1 g.), alcohol (20 c.c.), and zinc dust (5 g.) were refluxed together during the addition of aqueous ammonia (15 c.c.; *d* 0·88) in portions (2·5 c.c.) during ¾ hr. After refluxing for a total of 1 hr., the initial green fluorescence had disappeared, and the colourless solution was refluxed for 5 hr. more and then evaporated to dryness *in vacuo*. The residue crystallised from benzene–ligroin as light yellow crystals (0·44 g.). Pure 1 : 2 : 3 : 4-*tetrahydro*-3-*keto*-2-*methylcinnoline*, m. p. 91—92·5° (Found: C, 66·2; H, 6·1; N, 17·7. $C_9H_{10}ON_2$ requires C, 66·6; H, 6·2; N, 17·3%), was colourless.

(ii) The dihydroketo-derivative (1 g.), red phosphorus (1 g.), and hydriodic acid (10 c.c.; *d* 1·65—1·70) were refluxed together for 8 hr. After cooling and filtration, colourless needles separated. Water was added to dissolve these, and the solution was filtered, neutralised with sodium hydroxide, and extracted with ether. The residue (0·45 g.) from the extract was recrystallised from water, and then from benzene–ligroin (b. p. 100—120°), and finally from ligroin, giving colourless needles of oxindole, m. p. 125—126·5° (Found: C, 72·6; H, 5·45. Calc. for C_8H_7ON: C, 72·2; H, 5·3%), identical with a specimen similarly obtained from 3-hydroxycinnoline (Neber *et al.*, *loc. cit.*).

To the neutral aqueous reaction solution remaining after ether-extraction was added 4N-sodium hydroxide (20 c.c.) and water (20 c.c.), and the resulting solution was distilled into hydrochloric acid (80 c.c.; 4N) until only a small amount of the original remained. The acid solution was evaporated, leaving a solid residue (0·37 g.). A portion (0·2 g.) of this, acetic acid (5 c.c.), phthalic anhydride (0·2 g.), and anhydrous sodium acetate were refluxed together for 1 hr. The hot solution was filtered and evaporated, giving colourless needles of *N*-methylphthalimide (0·13 g.), m. p. 133—135 (unchanged by crystallisation from acetic acid and vacuum-sublimation) (Found: C, 67·6; H, 4·5. Calc. for $C_9H_7O_2N$: C, 67·1; N, 4·4%), identical with an authentic specimen. The remainder of the residue was treated with picric acid in hot water and gave methylamine picrate, yellow prisms, m. p. 208—212° (decomp.), from ethyl acetate, identical with an authentic specimen.

Conversion of 3-*Hydroxy- into* 3-*Amino-quinoline*.—3-Hydroxyquinoline (0·5 g.), saturated ammonium sulphite solution (7 c.c.), and aqueous ammonia (7 c.c.; *d* 0·88) were heated for 8 hr. at 130—140°. Sodium hydroxide was added, and the mixture extracted with ether. Removal of the solvent gave crude 3-aminoquinoline (0·05 g.), m. p. after crystallisation from toluene, 80—83°.

(B) 4-(3 : 3 : 3-*Trichloro*-2-*hydroxypropyl*)*cinnoline*.—4-Methylcinnoline (2 g.), pyridine (5 c.c.), and chloral (2·2 g.) were heated at 95° for 2 hr. When poured into water, the solution gave an oil which quickly solidified, giving 3·85 g. of product. 4-(3 : 3 : 3-*Trichloro*-2-*hydroxypropyl*)*cinnoline* separated from ethanol as glistening silver leaflets, m. p. 165—166° (decomp.) (Found: C, 45·5; H, 3·0. $C_{11}H_9ON_2Cl_3$ requires C, 45·3; H, 3·1%).

3-Methylcinnoline Methiodide.—When 3-methylcinnoline (1·25 g.) and methyl iodide (1·25 c.c.) were dissolved together in ethanol (8 c.c.), heat was evolved and the solution became red. After being refluxed for 2½ hr. and then cooled the mixture deposited orange leaflets (1·31 g.), m. p. 202—205·5° (decomp.). Concentration gave a second crop (0·73 g.), m. p. 147—149°. Recrystallisation from methanol gave red needles of *3-methylcinnoline methiodide*, m. p. 204—206·5° (decomp.) (Found: C, 41·75; H, 3·7. $C_{10}H_{11}N_2I$ requires C, 42·0; H, 3·9%). This was readily soluble in water, and addition of sodium hydroxide produced a transient blue colour which changed to green, and was followed by precipitation of amorphous green material which could not be crystallised.

The methiodide (0·36 g.) and *p*-dimethylaminobenzaldehyde (0·25 g.) were added to boiling acetic anhydride (25 c.c.), and the mixture was refluxed for 1¼ hr., then stored overnight; a

dark green crystalline product (0·07 g.), m. p. 330—335°, was collected. This separated as black crystals (with a green reflex), m. p. 353—355° (decomp.), from its deep blue solution in alcohol, and a further crystallisation produced a brownish powder, decomposing at about 370° and still impure (Found: C, 56·6; H, 5·2; N, 11·6. Calc. for $C_{19}H_{20}N_3I$: C, 54·7; H, 4·8; N, 10·1%). When the experiment was repeated with carefully purified reactants at 160° for 2 hr. the product (not recrystallised), m. p. 335—340° (decomp.), had a more satisfactory analysis (Found: C, 56·0; H, 4·8; N, 9·1%). The dark colour of the compound was destroyed by acids and alkalis.

(C, D) *Halogen Exchange.*—3-Bromocinnoline (0·2 g.) and phosphorus oxychloride (2 c.c.) were refluxed together for 2 hr. A clear green solution was formed with no obvious evolution of bromine. The product (0·16 g.; m. p. 91—92·5°), isolated in the usual way and crystallised once from light petroleum, had m. p. 92·5—93° (Found : C, 47·1; H, 2·3. Calc. for $C_8H_5N_2Br$: C, 45·9; H, 2·4. Calc. for $C_8H_5N_2Cl$: C, 58·35; H, 3·1%). From a similar experiment (with 3 c.c. of phosphorus oxychloride) carried out at 95°, the product (0·18 g.; m. p. 80—90°) after one crystallisation had m. p. 90—91° (Found : C, 49·2; H, 2·4%).

Reduction of 3-*Bromocinnoline.*—3-Bromocinnoline (0·25 g.), methanolic potassium hydroxide (3 c.c., 5%), palladised charcoal (0·15 g., 5%), and hydrazine hydrate (0·1 g., 90%) were refluxed for 2 hr. Water (3 c.c.) was then added and an oil extracted with ether. The picrate (0·24 g.; m. p. 185—190°) from this product crystallised from dioxan as orange prisms (0·15 g.), m. p. 191—194°, giving no m. p. depression with cinnoline picrate.

Conversion of Bromo- into Amino-group.—3-Bromocinnoline (0·5 g.), copper sulphate (0·06 g.), and aqueous ammonia (8 c.c.; *d* 0·88) were heated for 20 hr. at 130—140°. The mixture was warmed to remove ammonia, treated with water (5 c.c.) and 4N-sodium hydroxide (10 c.c.), and extracted with ether. The crude product (0·49 g.) was recrystallised from ethyl acetate, giving 3-*aminocinnoline* (0·37 g.), which when pure formed clusters of yellow needles, m. p. 165—166·5° (Found : C, 66·1; H, 5·2. $C_8H_7N_3$ requires C, 66·2; H, 4·9%), from ethyl acetate–ligroin (b. p. 60—80°). The same yield of amine was obtained from 3-chlorocinnoline only at 160—170°. The amine and acetic anhydride, when refluxed together for 5 min. and then poured into water, gave colourless crystals. Crystallisation from water provided silky needles of 3-*acetamidocinnoline*, m. p. 225—226° (Found : C, 64·6; H, 4·8. $C_{10}H_9ON_3$ requires C, 64·15; H, 4·85%).

Replacement of Bromo- by Methoxy- and Hydroxy-groups.—3-Bromocinnoline (0·25 g.) and a solution of sodium (0·13 g.) in dry methanol (4 c.c.) were heated in a sealed tube for 17 hr. at 110—120°. The resultant solution was diluted with water and extracted with ether. From the extract, 3-methoxycinnoline was isolated as a pale yellow oil which slowly crystallised (0·24 g.; m. p. 40—42°) but was not purified. Its *picrate*, formed from alcoholic solution, crystallised from the same solvent as yellow prisms, m. p. 155—157·5° (Found : C, 46·9; H, 2·8. $C_9H_8ON_2$,$C_6H_3O_7N_3$ requires C, 46·3; H, 2·85%).

The reaction solution from an experiment on twice the above scale, but with undried methanol, on cooling deposited large yellow plates of the sodium salt, m. p. $>270°$, of 3-hydroxycinnoline. From the aqueous solution of this compound on acidification with dilute acetic acid, there separated yellow crystals (0·25 g.), m. p. 200—202°, of 3-hydroxycinnoline, identified by conversion into 3-benzoyloxycinnoline.

*Physical Determinations.**—pK_a values for 3-hydroxy-cinnoline and -quinoline were determined in 0·002M-aqueous solution at 20° ± 0·1°, by potentiometric titration with aqueous sodium hydroxide (0·11N), a glass electrode and a Cambridge pH meter being used. The blue fluorescence of dilute aqueous solutions of 3-hydroxyquinoline was diminished in intensity by the titration, but not extinguished. Values for 3-amino-cinnoline and -quinoline were determined similarly in M/90-aqueous solution, by titration with 0·91N-hydrochloric acid.

Ultra-violet absorption spectra were measured in the usual way by means of a Unicam Spectrophotometer, Model SP 500.

Discussion

There is much evidence that heterocyclic nitrogen compounds formally containing α- or γ-hydroxyl groups may exist predominantly as the keto-forms (Ewing and Steck, see Table; Elderfield, " Heterocyclic Compounds," Wiley and Sons, New York, 1952, Vol. 4, pp. 137, 439; Marshall and Walker, *J.*, 1951, 1004; Albert, " The Acridines," London, 1951, p. 326), though not necessarily so (Albert, *op. cit.*). The case of 3-hydroxycinnoline is interesting

* Full details will be found in the Ph.D. thesis of E. J. Alford, London, 1952.

from this point of view, an analogous example with both the nitrogen atom and the $-C(OH)-$ unit at β-positions in the bicyclic structure evidently not having been described before. We have now tried to establish that the phenolic structure (VI) is not adequate as a representation of 3-hydroxycinnoline, without attempting quantitative assessment of the importance of the lactam form.

Longuet-Higgins and Coulson's calculations (*J.*, 1949, 971) suggest that the structure (VI) would be more acidic than 3-hydroxyquinoline, itself a true phenol [the calculations are borne out in the case of 4- (Keneford, Morley, Simpson, and Wright, *J.*, 1949, 1356) and 8-hydroxycinnoline (Alford, Irving, Marsh, and Schofield, *J.*, 1952, 3009), compared with the quinoline analogues], but the reverse is actually the case. This suggests that lactam–lactim tautomerism is of significance in 3-hydroxycinnoline.

Consistent with this view are the absorption spectra of 3-hydroxycinnoline and 2 : 3-dihydro-3-keto-2-methylcinnoline. [The structure of the methyl compound is proved by its reduction to methylamine and oxindole, the latter probably arising from the cyclisation of an acyclic intermediate with extrusion of $N_{(2)}$, a type of elimination conclusively established in the similar case of the Fischer indole synthesis (Clusius and Weisser, *Helv. Chim. Acta*, 1952, **35**, 400).] The spectrum of 3-hydroxycinnoline in methanol differs only slightly from that in water (see Table), but in alkaline solution a hypsochromic shift occurs owing to ionisation of the compound. By contrast, the absorption in acid medium differs little from that in water. This recalls the behaviour of carbostyril and *iso*carbostyril (Ewing and Steck, *loc. cit.*) which, probably being weaker acids than 3-hydroxycinnoline, show no change even in alkaline solution. Thus the curves suggest the possibility of lactam–

Absorption spectra.

		λ (mμ), $\log_{10}\varepsilon$				
	Solvent	Max.	Min.	Max.	Min.	Max.
3-Hydroxyquinoline	95% MeOH	—	262, 3·29	286, 3·33	300, 3·16	322, 3·59 333, 3·64
	95% EtOH *	234, 4·43	258, 3·43	270, 3·46 279, 3·46	300, 3·20	321, 3·63 336, 3·65
	0·01N-HCl *	240, 4·40	266, 2·72	315, 3·60	321, 3·56	345, 3·72
	0·01N-NaOH *	235, 4·32	—	—	303, 2·78	350, 3·73
3-Hydroxycinnoline	95% MeOH	—	—	300, 2·84 312, 2·76	321 325 2·6	400, 3·47
	H_2O	226, 4·67	292, 2·87	300, 2·93 312, 2·89	324, 2·58	394, 3·51
	0·01N-HCl	—	287, 2·82	300, 2·88	323, 2·56	398, 3·46
	0·01N-NaOH	—	—	—	314, 2·38	385, 3·62
2 : 3-Dihydro-3-keto-2-methylcinnoline	95% MeOH	—	285, 3·02	305, 3·12	329, 2·59	400, 3·51
	0·01N-HCl	—	286, 2·94	303, 3·06	326, 2·53	400, 3·50
	0·01N-NaOH	—	283, 2·90	303, 3·12	328, 2·58	395, 3·52
3-Chlorocinnoline	95% MeOH	—	255, 3·04	285, 3·33	308, 3·09	330, 3·43
	0·01N-HCl	—	260, 2·98	285, 3·28	308, 3·09	335, 3·42
	0·01N-NaOH	—	258, 3·07	285, 3·40	308, 3·22	338, 2·54
3-Aminocinnoline	95% MeOH	237, 4·59	—	—	312, 2·79	385, 3·43
	0·01N-HCl	235, 4·59	305, 2·79	310, 2·88 315, 2·83	320 340 2·68	405, 3·45
	0·01N-NaOH	233, 4·53	—	—	312, 2·60	372, 3·36

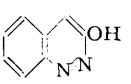
* See also Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181.

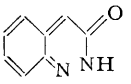
lactim tautomerism in 3-hydroxycinnoline, and the close similarity between the spectra of 3-hydroxycinnoline and 2 : 3-dihydro-3-keto-2-methylcinnoline reinforces this conclusion, although until 3-methoxycinnoline becomes available the evidence is not complete. The insignificant changes in the spectrum of the keto-derivative in passing from alkaline to acid medium are consistent with its structure. In contrast to those of 3-hydroxycinnoline, the curves for 8-hydroxycinnoline (Alford *et al.*, *loc. cit.*) and 3-hydroxyquinoline show appreciable differences depending on pH, as would be expected, both the phenolic and basic properties of these compounds being well developed.

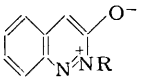
From the foregoing it is apparent that lactam–lactim tautomerism is possible in 3-

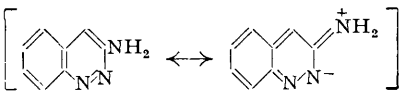
hydroxycinnoline, although owing to the particular structure of the lactam the acidic nature of the lactim is more developed than in such a substance as carbostyril. The lactam would be represented in classical terms by the *o*-quinonoid structure (VII) but, it being borne in mind that 2 : 3-naphthaquinone is unknown, a better representation of this and 2 : 3-dihydro-3-keto-2-methylcinnoline is probably (VIII; R = H or Me) (Huisgen, *Annalen*, 1948, **559**, 101).

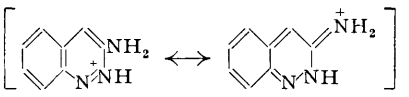
These observations, clearly indicating interaction between $N_{(2)}$ and a 3-substituent, raised our interest in 3-methylcinnoline. Formerly, reactivity in methyl groups in heterocyclic molecules was believed to depend on the existence of the elements of structure ·N:CMe· and ·N:C·C:CMe· (Sidgwick, " Organic Chemistry of Nitrogen," Oxford, 1937, p. 558). For this reason the ability of 4-methylcinnoline ethiodide to react with *p*-dimethylaminobenzaldehyde (Atkinson and Simpson, *J.*, 1947, 808) has been held to prove that in 4-methylcinnoline $N_{(1)}$ is the basic centre. 4-Methylcinnoline itself condenses with benzaldehyde in the presence of zinc chloride (Jacobs, Winstein, Henderson, and Spaeth, *J. Amer. Chem. Soc.*, 1946, **68**, 1310). Recently, however, Erlenmeyer, Brumann, and Sorkin (*Helv. Chim. Acta*, 1948, **31**, 1978) condensed 3-methyl*iso*quinoline with benzaldehyde, and Brooker and White (*loc. cit.*) condensed 3-methyl*iso*quinoline methiodide with *p*-dimethylaminobenzaldehyde, though reactivity was much less pronounced than in the 1-methyl series. Apparently a methyl group adjacent to a ring nitrogen will always be activated to some extent, considerably if the nitrogen–carbon link possesses a high degree of double-bond character. Our experiments demonstrate the lower reactivity of the 3- than of the 4-methyl group in cinnolines, but stress the need for caution in deducing the site of quaternisation from such reactivity in quaternary salts (the yields of products obtained from 3- and 4-methylcinnoline methiodides and *p*-dimethylaminobenzaldehyde were similar), and raise the interesting possibility that 3-methylcinnoline may quaternise on $N_{(2)}$. We are investigating this.


(VI)


(VII)


(VIII)


(IX)


(X)

The conversion of 3-hydroxy- into 3-chloro-cinnoline, and of 3-bromo- into 3-hydroxycinnoline, completes the proof of the structure of the latter product obtained by Bossel's method (Alford and Schofield, *loc. cit.*), which previously depended on its reduction to oxindole (Neber *et al.*, *loc. cit.*). Such conversions and the similar formation of 3-aminocinnoline are not, however, sufficient to reveal activation in the 3-halogen atoms. 3-Bromoquinoline has been aminated similarly (Kuhn and Westphal, *Ber.*, 1940, **73**, 1105). The formation of cinnoline by hydrazine reduction of 3-bromocinnoline indicates some degree of activation, for the more normally " aromatic " halogen compounds behave differently, 3-bromopyridine, for example, giving 3 : 3′-dipyridyl (Busch and Weber, *loc. cit.*). The absorption spectrum of 3-chlorocinnoline generally resembles that of cinnoline (Hearn, Morton, and Simpson, *J.*, 1951, 3318), modified slightly by the auxochromic chlorine atom. It is not surprising that the spectrum of such a weak base is so slightly modified in 0·01N-acid solution. More interesting is the fact that absorption falls to zero between 380 and 390 mμ and the characteristic, broad, long-wave-length maximum due to the ·N:N· group, already weak in cinnoline itself, disappears in this case.

The failure of 3-aminocinnoline to form a diazonium salt in dilute acid suggests the existence of resonance interaction between the amino-group and $N_{(2)}$ (IX) (Angyal and Angyal, *J.*, 1952, 1461), and this is in line with pK_a determinations and absorption spectra. The figures quoted above show that whilst 3-aminoquinoline and quinoline are almost identical in basic strength (Albert *et al.*, *loc. cit.*), 3-aminocinnoline is more basic by about

one pK unit than cinnoline (pK_a, 2·70). Although the base strengthening is smaller in this case than with 4-aminocinnoline and related compounds where it has been attributed to " additional ionic resonance " (Albert *et al.*, *loc. cit.*), yet the fact that the effect exists suggests that the cation of 3-aminocinnoline must be represented by (X), $N_{(2)}$ acting as the basic centre and permitting stabilisation by resonance as shown. The low degree of base strengthening in this case can be attributed to the incursion of an *o*-quinonoid form. The absorption spectra of 3-aminocinnoline (see Table) support the view that the proton in the cation is accepted by a ring-nitrogen atom, there being a bathochromic shift in acid solution. A hypsochromic shift of the broad, long-wave-length maximum occurs in alkali, as with the aminoquinolines (Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397). It is clearly desirable to decide the position of quaternisation of 3-aminocinnoline.

The authors are indebted to the Council of University College, Exeter, and to Imperial Chemical Industries Limited for financial support. They thank Dr. H. Irving and Mrs. Rossotti for most of the absorption spectra.

WASHINGTON SINGER LABORATORIES,
PRINCE OF WALES ROAD, EXETER.

[*Received, January 19th*, 1953.]