1003. *Cinnolines. Part VI.*[1] *Tautomerism and Alkylation of 4-Hydroxycinnoline*

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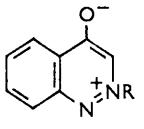
The tautomerism of 4-hydroxy- and 4-mercapto-cinnolines is re-examined by study of the ultraviolet spectra of these compounds and their *O*-, *S*-, and *N*-methyl derivatives. 4-Hydroxycinnolines usually undergo predominantly 2-alkylation giving anhydro-base (I), with little, if any, 1-alkylation to give 1-alkyl-4-cinnolone (II). These results are attributed to the dominance of steric factors in the alkylation reaction, particularly since 3-substituted 4-hydroxycinnolines give only 1-alkyl-4-cinnolone even when the 3-substituent is electron-donating.

An effective process for bromination of 4-hydroxycinnoline is described and the resulting 3-bromo-4-hydroxycinnoline is alkylated to give 1-alkyl-3-bromo-4-cinnolone. Catalytic hydrogenation then provides 1-alkyl-4-cinnolone much more efficiently than by direct alkylation of 4-hydroxycinnoline. The cyanoethylation of 3- and 4-hydroxycinnolines is discussed.

Alkylation of 4-hydroxycinnolines [2-4] gives mainly the anhydro-base (I), which apparently shows resonance effects like the analogous sydnones,[5] while the 1-alkyl-4-cinnolone (II) is obtained in lower yield, if at all. Alternative routes to the inaccessible 1-alkyl-4-cinnolones have therefore been sought. Methylation of ethyl 6-chloro-4-hydroxycinnoline-3-carboxylate gives the 1-methylcinnolone (III; X = Cl, R = Et) as the only isolated product, presumably because of the steric and electronic effects of the 3-ethoxycarbonyl group.[1] Decarboxylation of the corresponding acid (III; X = Cl, R = H) gave the cinnolone in only 25% yield. Attempts to decarboxylate the acid (III; X = R = H) by heating failed but both acids have now been decarboxylated by heating with strong sulphuric acid (yields 54 and 39%, respectively). Despite this improvement, the route is tedious and gives low overall yields of 1-alkyl-4-cinnolone.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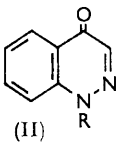
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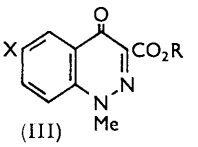
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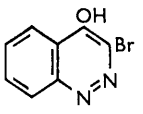
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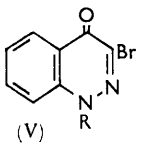
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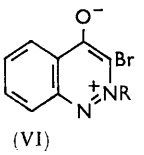
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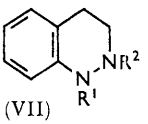
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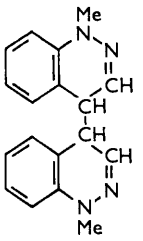
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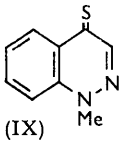
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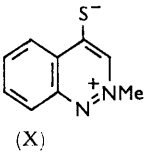
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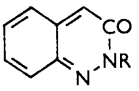
(XI)

The alkylation of 3-bromo-4-hydroxycinnoline was next examined in the hope that the steric effect of the 3-substituent group would also lead to 1-alkylation, although, in this

[1] Part V, D. E. Ames, R. F. Chapman, and H. Z. Kucharska, *J.*, 1964, 5659.
[2] D. E. Ames and H. Z. Kucharska, *J.*, 1963, 4924.
[3] D. E. Ames and H. Z. Kucharska, *J.*, 1964, 283.
[4] D. E. Ames, *J.*, 1964, 1763.
[5] E. Lunt and T. L. Threlfall, *Chem. and Ind.*, 1964, 1805.

case, electronic effects might be expected to increase the electron density at N-2. 3-Bromo-4-hydroxycinnoline has been prepared by cyclisation of diazotised *o*-amino-ω-halogeno-acetophenone [6] and, in low yield, by bromination of 4-hydroxycinnoline in acetic acid.[7] This bromination is presumably impeded by protonation of the cinnoline as hydrogen bromide is formed and we have now found that bromination can be effected almost quantitatively by addition of bromine to an *alkaline* solution of 4-hydroxycinnoline.

Methylation of the bromo-compound (IV) with methyl iodide in presence of sodium ethoxide gave only one product which was identified as 3-bromo-1-methyl-4-cinnolone (V; R = Me) by catalytic hydrogenation in presence of base to give 1-methyl-4-cinnolone (II; R = Me). Similar results were obtained on condensation of 3-bromo-4-hydroxycinnoline (IV) with ethyl, propyl, isopropyl, and benzyl halides. The structures of the 1-alkyl-3-bromo-4-cinnolones obtained were shown by hydrogenation to the corresponding 1-alkyl-4-cinnolone (II). In each case, these were quite different from the isomeric anhydro-bases (I) and also from the 4-alkoxycinnolines which were formed by action of sodium alkoxide on 4-chloro-cinnoline.[8] Alkylation of 4-hydroxycinnoline with the same halides gave anhydro-bases (I) and 1-alkyl-4-cinnolones (II) but the yield of the latter was small especially for the larger alkyl groups. Benzylation was reported [3] to give only anhydro-base (I; R = CH_2Ph) but 1-benzyl-4-cinnolone (II; R = CH_2Ph) has now been isolated in extremely small yield (0·4%). The structures of the anhydro-bases were established by reduction with zinc dust and aqueous ethanolic ammonia to give *o*-aminoacetophenone, indicating the presence of a 2-alkyl group (1-alkyl-4-cinnolones give *o*-alkylaminoacetophenone).[2,3]

The 1-alkyl-4-cinnolones were brominated in acetic acid containing ammonium or potassium acetate to give the 1-alkyl-3-bromo-4-cinnolones (V; R = Me or Et) already described. Under similar conditions, anhydro-bases (I; R = Me or Et) also gave bromo-derivatives which are regarded as 3-bromo-compounds; these darkened on keeping and were reduced to the parent anhydro-base by heating with potassium iodide in acetic acid. This ready reduction of the bromo-anhydro-bases (VI) is presumably due to the proximity of the positive charge on N-2, since, under the same conditions, the 1-alkyl-3-bromo-4-cinnolones were not reduced.

In view of the accessibility of 3-bromo-4-hydroxycinnoline, alkylation and reduction provide an efficient route to 1-alkyl-4-cinnolones (II) and this has facilitated further study of these compounds. The reduction of 1-methyl-4-cinnolone with lithium aluminium hydride gives 1,2,3,4-tetrahydro-1-methylcinnoline (VII; R^1 = Me, R^2 = H) as the main product [2] but re-examination has now shown that a non-distillable product, m. p. 160—162°, is also formed. On the basis of the high melting point, and analytical and spectroscopic data (see Experimental section), this product is tentatively formulated as 1,1′,4,4′-tetrahydro-1,1′-dimethyl-4,4′-bicinnolyl (VIII). Reductive coupling of this type is involved in reduction of 4-chlorocinnoline to 4,4′-bicinnolyl.[9]

Reduction of 1-ethyl-4-cinnolone with lithium aluminium hydride gave 1-ethyl-1,2,3,4-tetrahydrocinnoline (VII; R^1 = Et, R^2 = H). This product showed a rather different boiling point from that obtained by action of diethylzinc on benzenediazonium chloride or phenylazoethane and assigned this structure without further evidence or characterisation.[10] Treatment of base (VII; R^1 = Et, R^2 = H) with picric acid in boiling methanol effected oxidation to 1-ethylcinnolinium picrate, isomeric with the known 2-ethylcinnolinium salt.[3] The acetyl derivative of 2-ethyl-1,2,3,4-tetrahydrocinnoline was also reduced with lithium aluminium hydride to give 1,2-diethyl-1,2,3,4-tetrahydrocinnoline (VII; R^1 = R^2 = Et), apparently the first 1,2-dialkyl derivative of this base to be reported.

Ultraviolet spectra of alkylation products derived from 4-hydroxycinnoline and related compounds have now been determined (Table 1). Both 1-alkyl-4-cinnolones (II) and the

[6] K. Schofield and J. C. E. Simpson, *J.*, 1948, 1170.
[7] K. Schofield and J. Swain, *J.*, 1950, 384.
[8] K. Schofield and J. C. E. Simpson, *J.*, 1945, 512, 520.
[9] J. S. Morley, *J.*, 1951, 1971; D. E. Ames and H. Z. Kucharska, *J.*, 1962, 1509.
[10] M. M. Tichwinsky, *J. Russ. Phys. Chem. Soc.*, 1904, **36**, 1052.

TABLE 1

Ultraviolet spectra of substituted cinnolines (in ethanol)

Compound	$\lambda_{max.}$ mμ	($\varepsilon_{max.}$)	$\lambda_{max.}$ mμ	($\varepsilon_{max.}$)	$\lambda_{max.}$ mμ	($\varepsilon_{max.}$)	$\lambda_{max.}$ mμ	($\varepsilon_{max.}$)
1-Methyl-4-cinnolone	209	(29,600)	234	(10,200)	284	(2100)	341	(12,600)
			240	(10,300)	296	(2300)	360	(10,900)
			254	(6900)				
			263	(5300)				
1-Ethyl-4-cinnolone	211	(32,000)	234	(11,700)	284	(2900)	345	(13,400)
			240	(12,100)	296	(3000)	*358*	(11,300)
			255	(8000)				
			263	(6200)				
1-Propyl-4-cinnolone	211	(30,500)	*234*	(12,100)	285	(2900)	344	(13,400)
			240	(12,400)	296	(3100)	*360*	(11,400)
			254	(7900)				
			262	(6300)				
1-Isopropyl-4-cinnolone	211	(31,600)	*234*	(11,800)	285	(3000)	344	(13,400)
			240	(12,300)	296	(3300)	*359*	(12,500)
			254	(8400)				
			263	(6700)				
1-Benzyl-4-cinnolone	209	(36,000)	238	(11,800)	283	(3000)	343	(14,500)
			254	(9000)	294	(2900)	*358*	(12,400)
			265	(6100)				
1-2′-Bromoethyl-4-cinnolone	211	(27,300)	*236*	(11,900)	284	(2600)	346	(13,300)
			241	(12,500)	294	(2400)		
			255	(8200)				
			263	(6700)				
1-2′-Cyanoethyl-4-cinnolone	210	(31,000)	*234*	(11,400)	283	(2700)	344	(12,800)
			240	(11,800)	292	(2400)		
			255	(8200)				
			263	(6600)				
1-2′-Carboxyethyl-4-cinnolone	210	(30,700)	*235*	(12,200)	285	(2700)	346	(13,800)
			240	(12,300)	296	(2700)		
			254	(8100)				
			263	(6300)				
6-Chloro-1-methyl-4-cinnolone	214	(32,500)	243	(16,700)	289	(4700)	352	(12,400)
					301	(6300)	361	(11,700)
							370	(12,100)
1-Vinyl-4-cinnolone	219	(23,000)	251	(17,500)	—	—	360	(12,300)
			287	(2400)				
3-Bromo-1-methyl-4-cinnolone	213	(24,000)	*238*	(10,900)	289	(4100)	350	(12,800)
			247	(13,200)	301	(4600)	357	(12,100)
			257	(9500)			367	(10,800)
			265	(7400)				
1,4-Dihydro-1-methyl-4-oxocinnoline-3-carboxylic acid, ethyl ester	212	(29,500)	237	(9700)	—	—	*315*	(7200)
			259	(6300)			344	(13,300)
6-Chloro-1,4-dihydro-1-methyl-4-oxocinnoline-3-carboxylic acid, ethyl ester	217	(34,800)	251	(11,600)	—	—	317	(8600)
							350	(13,900)
Anhydro-bases:								
(I; R = Me)	212	(32,500)	254	(8100)	—	—	352	(12,400)
	221	(16,200)	*267*	(4600)			369	(12,800)
			279	(3000)				
(I; R = Et)	213	(34,600)	253	(8900)	—	—	351	(12,600)
	221	(17,700)	*266*	(4800)			369	(13,000)
			279	(3000)				
(I; R = n-C_3H_7)	215	(36,600)	254	(9800)	—	—	351	(13,300)
			268	(5300)			368	(13,700)
			280	(3000)				
(I; R = iso-C_3H_7)	214	(36,600)	253	(10,200)	—	—	350	(13,900)
			267	(5500)			367	(14,200)
			280	(3000)				
(I; R = CH_2·Ph)	210	(34,900)	255	(9900)	—	—	353	(12,600)
			281	(3100)				
			295	(2300)				
(I; R = $[CH_2]_2$·OH)	214	(30,600)	255	(9600)	—	—	353	(12,800)
			267	(5000)			370	(13,100)
			280	(2800)				

TABLE 1 (*Continued*)

Compound	$\lambda_{max.}$ mμ	($\varepsilon_{max.}$)	$\lambda_{max.}$ mμ	($\varepsilon_{max.}$)	$\lambda_{max.}$ mμ	($\varepsilon_{max.}$)	$\lambda_{max.}$ mμ	($\varepsilon_{max.}$)
(I; R = $[CH_2]_2$·OAc)	215	(31,600)	254	(8000)	—	—	353	(11,700)
			267	(4300)			369	(11,900)
(I; R = $[CH_2]_3$·OH)	214	(34,100)	254	(9800)	—	—	353	(11,700)
			267	(5100)			370	(13,200)
			279	(3200)				
6-Chloro-4-hydroxy-2-methylcinnolinium hydroxide, anhydrobase	215 *228*	(30,200) (14,800)	259	(10,800)	—	—	357 373	(13,100) (14,000)
4-Hydroxycinnoline			228	(10,200)	282	(2800)	336	(12,600)
			236	(11,000)	292	(3000)	352	(11,700)
			251	(8400)				
			260	(6300)				
4-Methoxycinnoline			226	(39,700)	*284*	(5200)	317	(4500)
					292	(5600)		
1,2,3,4-Tetrahydro-2-methyl-3-oxocinnoline	206	(15,500)	*253*	(4000)				
2-Benzyl-1,2,3,4-tetrahydro-3-oxocinnoline	206	(25,500)						
2-Methyl-3-cinnolone	*209*	(12,500)	230	(49,700)	290	(1250)	403	(3200)
					301	(1500)		
					314	(1200)		
2-Benzyl-3-cinnolone	208	(20,700)	232	(49,900)	303	(2400)	402	(3400)
					317	(2000)	413	(3400)
2-2′-Cyanoethyl-3-cinnolone			232	(48,600)	303	(850)	402	(1700)
					316	(700)		—

isomeric anhydro-bases (I) show maxima at about 210 mμ (ε *ca.* 30,000) and also an intense band in the region 340—370 mμ (ε *ca.* 12,000) usually with two maxima. The 1-alkyl-4-cinnolones show a band at about 240 mμ (ε *ca.* 12,000), with subsidiary maxima or inflections at about 235, 255, and 263 mμ, and also a very characteristic pair of weaker bands at about 285 and 295 mμ (ε *ca.* 3000).

The isomeric anhydro-bases (I) of 2-alkyl-4-hydroxycinnolinium hydroxides, however, show a strong band at about 255 mμ (ε *ca.* 10,000) with inflections or sidebands at longer wavelengths (usually about 267 and 279 mμ) and show a minimum in the region 290—300 mμ.

In both series, the presence of a 6-chloro-group results in some loss of the fine structure, but the main bands are still present. A 3-ethoxycarbonyl group, in conjugation with the cinnolone system, however, changes the spectrum considerably and the bands at 285, 295 mμ are not observed.

In view of these observations, it is possible to distinguish compounds of the two series, especially on the basis of the bands at 285, 295 mμ in the spectra of 1-alkyl-4-cinnolones. The tautomerism of 4-hydroxycinnoline was examined by Hearn, Morton, and Simpson [11] by comparison of the spectra of 4-hydroxy- and 4-methoxy-cinnoline with the spectrum of " 1-methyl-4-cinnolone." The latter product was, in fact, the anhydro-base of 2-methyl-4-hydroxycinnolinium hydroxide [2] and the spectra have therefore been re-examined, together with that of the true 1-methyl-4-cinnolone. The spectrum of 4-hydroxycinnoline resembles those of the *N*-alkyl compounds and differs considerably from that of 4-methoxycinnoline (Figure 1). Since the 4-hydroxycinnoline spectrum shows the bands at about 285 and 295 mμ characteristic of 1-methyl-4-cinnolones, it appears that tautomerism involves protonation at N-1 rather than N-2. This contrast with the alkylation of cinnoline and 4-hydroxycinnoline predominantly at N-2 [3] is presumably due to the reversibility of protonation leading to the most stable structure irrespective of steric factors.

Similarly, when Albert and Barlin [12] examined the tautomerism of 4-mercaptocinnoline, the anhydro-base (I; R = Me), m. p. 165°, was regarded as 1-methyl-4-cinnolone [2] so that the product, m. p. 182°, obtained by action of phosphorus pentasulphide on this compound,

[11] J. M. Hearn, R. A. Morton, and J. C. E. Simpson, *J.*, 1951, 3318.
[12] A. Albert and G. B. Barlin, *J.*, 1962, 3129.

was formulated as 1-methylcinnoline-4-thione (IX). This product is therefore the anhydro-base of 4-mercapto-2-methylcinnolinium hydroxide (X). The isomeric 1-methylcinnoline-4-thione (IX), m. p. 143°, has now been prepared by action of phosphorus pentasulphide on 1-methyl-4-cinnolone, m. p. 114°.* In contrast with the *N*-methylation of 4-hydroxycinnoline, 4-mercaptocinnoline seems to undergo only *S*-methylation, with

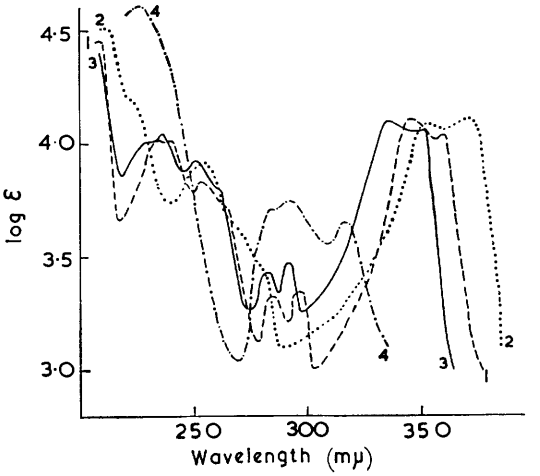

FIGURE 1. Derivatives of 4-hydroxycinnoline. 1, 1-Methyl-4-cinnolone. 2, Anhydro-base of 4-hydroxycinnolinium hydroxide. 3, 4-Hydroxycinnoline. 4, 4-Methoxycinnoline

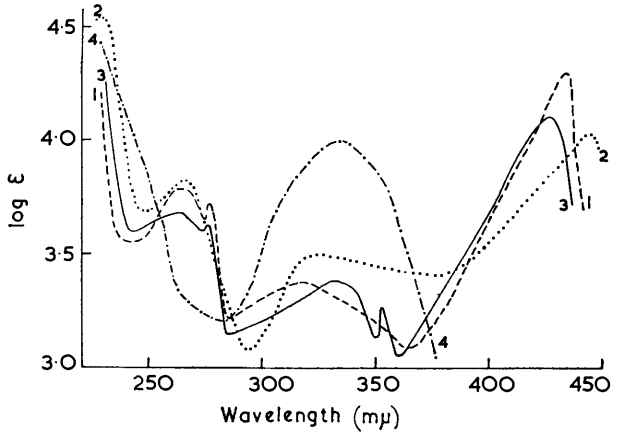

FIGURE 2. Derivatives of 4-mercaptocinnoline. 1, 1-Methylcinnoline-4-thione. 2, Anhydro-base of 4-mercapto-2-methylcinnolinium hydroxide. 3, 4-Mercaptocinnoline. 4, 4-Methylthiocinnoline

methyl iodide in presence of alkali, to give 4-methylthiocinnoline.[12,13] The ultraviolet spectra again show that tautomerism of 4-mercaptocinnoline leads to *N*-protonated form, since the spectrum resembles that of the *N*-alkyl derivatives rather than that of 4-methylthiocinnoline (Figure 2). The spectra of the *N*-methyl compounds, (IX) and (X), are too similar to provide any definite indication of the position of protonation.

Cyanoethylation of 3- and 4-hydroxycinnolines has also been examined. Addition of acrylonitrile to 3-hydroxycinnoline in presence of benzyltrimethylammonium hydroxide gave *N*-alkylation product (XI; R = $[CH_2]_2$·CN), the ultraviolet spectrum of which corresponded closely with that of the *N*-methyl compound (XI; R = Me).[2] Similar addition of acrylonitrile to 4-hydroxycinnoline gave an adduct, m. p. 192—194°, in 78%

* *Note added in proof.*—G. B. Barlin, *J.*, 1965, 2260, has recently prepared these two compounds and formulated them similarly.

[13] R. N. Castle, H. Ward, N. White, and K. Adachi, *J. Org. Chem.*, 1960, **25**, 570.

yield; no isomeric product could be isolated. This adduct is regarded as the 1-alkylation product, 1-cyanoethyl-4-cinnolone (II; R = $[CH_2]_2$·CN) on the basis of the following evidence: first, the ultraviolet spectrum closely resembles those of 1-methyl- and 1-ethyl-4-cinnolones and shows maxima at 283 and 292 mμ, already described as characteristic of these compounds; secondly, no *o*-aminoacetophenone could be isolated by reduction with zinc and acetic acid; thirdly, hydrolysis of the adduct under acidic conditions gave the corresponding acid (II; R = $[CH_2]_2$·CO_2H), the spectrum of which again resembled that of a 1-alkyl-4-cinnolone—the acid did not give *o*-aminoacetophenone on reduction; finally, cyanoethylation of 3-bromo-4-hydroxycinnoline under similar conditions yielded 3-bromo-1-2′-cyanoethyl-4-cinnolone, which was also obtained by bromination of 1-2′-cyanoethyl-4-cinnolone. Since alkylation of 3-bromo-4-hydroxycinnolines gives only 1-alkyl-3-bromo-4-cinnolones, the cyanoethylation product must be the 1-alkyl derivative.

Unsuccessful attempts were made to prepare the nitrile (II; R = $[CH_2]_2$·CN), or its isomer (I; R = $[CH_2]_2$·CN), or the corresponding acids, by another route. Condensation of 4-hydroxycinnoline with ethylene dibromide in presence of sodium ethoxide gave mainly dialkylation products and also a small amount of 1-2′-bromoethyl-4-cinnolone (II; R = $[CH_2]_2$·Br). This was identified by the characteristic ultraviolet spectrum of a 1-alkyl-4-cinnolone and also by catalytic hydrogenation in presence of base to give 1-ethyl-4-cinnolone.[3] Treatment of the bromoethyl compound with sodium or potassium cyanide in various solvents failed to give any nitrile and only 1-vinyl-4-cinnolone (II; R = CH:CH_2) could be isolated. This gave 1-ethyl-4-cinnolone on catalytic reduction.

Alkylation of 4-hydroxycinnoline with 2-bromoethanol in presence of sodium ethoxide furnished the anhydro-base (I; R = $[CH_2]_2$·OH), the structure of which was indicated by the spectrum and by reduction to *o*-aminoacetophenone. Attempts to convert this product into the bromide (I; R = $[CH_2]_2$·Br) failed since hydrogen bromide in acetic acid gave an *O*-acetate (I; R = $[CH_2]_2$·OAc) while hydrogen bromide in acetic acid–sulphuric acid apparently yielded the anhydro-base of 2-2′-acetoxyethyl-3-bromo-4-hydroxycinnolinium hydroxide (VI; R = $[CH_2]_2$·OAc). This was reduced to the *O*-acetate by catalytic-hydrogenation.

Condensation of 4-hydroxycinnoline with 3-bromopropanol also gave only the anhydro-base (I; R = $[CH_2]_3$·OH), identified in the same way as the lower homologue. Attempts to oxidise it to the corresponding acid were unsuccessful.

With a considerable number of alkylation products from various cinnolines now identified, it is of interest to consider the alkylation of cinnolines and especially of 4-hydroxy cinnolines. The results are summarised in Table 2. The 4-hydroxycinnolines were all alkylated in alkaline media so that 1-alkyl-4-cinnolone (II) and/or anhydro-base (I) were isolated. The yields obtained vary considerably but two generalisations may be made: first, small alkylating groups give two or three times as much 2- as 1-alkylation product (both in the cases of 4-hydroxy- and of 6-chloro-4-hydroxy-cinnoline); secondly, for larger alkylating groups, 4-hydroxycinnoline gives little, if any, 1-alkyl-4-cinnolone. Thus alkylation occurs preferentially at N-2, approach to which is less sterically hindered than to N-1, especially for large alkyl groups.

The presence of a bulky 3-substituent in a 4-hydroxycinnoline leads to complete, or almost complete, alkylation at N-1. This occurs not only with a 3-ethoxycarbonyl group but also with a 3-bromo-group, which might be expected to reduce the electron density at N-1 more than that at N-2 and so favour alkylation at N-2. These results indicate clearly that the position of alkylation of 4-hydroxycinnolines is controlled by steric factors, rather than by the electron density at N-1 or N-2.

The striking exception to this generalisation is the case of cyanoethylation which gives only 1-cyanoethyl-4-cinnolone. This result is attributed to the reversibility of the base-catalysed cyanoethylation leading to formation of the most stable product, 1-alkyl-4-cinnolone, despite the steric factors favouring N-2 (cf. protonation in tautomerism of 4-hydroxycinnoline already discussed).

TABLE 2

Alkylation of cinnolines

Cinnoline	Alkylating agents	1-Alkyl (%)	2-Alkyl (%)	Ref.
4-Hydroxy-	Me_2SO_4–KOH	13	42	2
	MeI–NaOEt	11	31	2
	Et_2SO_4–KOH	17	34	3
	EtI–NaOEt	6	18	*a*
	n-C_3H_7Br–NaOEt	11	65	*b*
	iso-C_3H_7Br–NaOEt	7	54	*b*
	$Ph{\cdot}CH_2{\cdot}Cl$–NaOEt	0·4	76	3
	$HO{\cdot}(CH_2)_2{\cdot}Br$–NaOEt	—	30	*b*
	$HO{\cdot}(CH_2)_3{\cdot}Br$–NaOEt	—	20	*b*
	$CH_2{:}CH{\cdot}CN$–Triton B	78	—	*b*
	$Br{\cdot}(CH_2)_2{\cdot}Br$–NaOEt	5	—	*c*
6-Chloro-4-hydroxy-	Me_2SO_4–NaOH	20	46	4
	MeI–NaOEt	17	53	4
3-Bromo-4-hydroxy-	MeI–NaOEt	47	—	*b*
	EtI–NaOEt	53	—	*b*
	n-C_3H_7Br–NaOEt	33	—	*b*
	iso-C_3H_7Br–NaOEt	37	—	*b*
	$Ph{\cdot}CH_2{\cdot}Br$–NaOEt	50	—	*b*
	$CH_2{:}CH{\cdot}CN$–Triton B	53	—	*b*
6-Chloro-3-ethoxycarbonyl-4-hydroxy-	MeI–NaOEt	46	—	1
Cinnoline	MeI	—	78	3
	EtI	—	55	3
4-Acetamido-	MeI	13	37	*b*
4-Amino-	MeI	13	28	1
4-Methoxy-	MeI	10	62	1
4-Phenoxy-	MeI	—	30	1
6-Chloro-4-phenoxy-	MeI	—	11	4

a, Unpublished work. *b*, Experimental section. *c*, No other products were isolated from a complex mixture of dialkylation products.

The other alkylations of cinnolines (Table 2) were carried out in organic solvents so that quaternary salts were formed initially. These were either separated into 1- and 2-alkylation products or hydrolysed to cinnolones (II) or anhydro-bases (I). The yields of identified products are given in Table 2. In these quaternisations, alkylation appears to occur exclusively at the more accessible N-2 except when electron-donating groups (NH_2, OMe, or NHAc) in the 4-position increase the electron density at N-1.

EXPERIMENTAL

Evaporations were carried out under reduced pressure; light petroleum refers to the fraction, b. p. 60—80°.

Decarboxylation of Cinnolone-3-carboxylic Acids.—6-Chloro-1-methyl-4-cinnolone-3-carboxylic acid [1] (2·5 g.) in a mixture of concentrated sulphuric acid (30 c.c.) and water (10 c.c.) was heated at 185—195° (internal temperature) for 60 hr. The cooled solution was poured into water, basified, and extracted repeatedly with chloroform. The extracts were washed with water, dried (Na_2SO_4), and evaporated to give 6-chloro-1-methyl-4-cinnolone (1·1 g.), m. p. and mixed m. p.[1] 155—157°, from benzene–light petroleum. Acidification of the aqueous layer and extraction with chloroform gave unchanged acid (0·2 g.).

1-Methyl-4-cinnolone-3-carboxylic acid [1] (2·0 g.) in a mixture of concentrated sulphuric acid (40 c.c.) and water (10 c.c.) was heated at 185—195° for 22 hr. to give, on isolation in a similar manner, 1-methyl-4-cinnolone (0·60 g.), m. p. and mixed m. p.[2] 111—114°.

3-Bromo-4-hydroxycinnoline.—Bromine (8·0 c.c.) was added dropwise to a solution of 4-hydroxycinnoline (8·0 g.) in 5N-potassium hydroxide (200 c.c.). The solution was left at room temperature for 1·5 hr., poured into water containing an excess of acetic acid, and filtered to give 3-bromo-4-hydroxycinnoline (11·9 g., 96%), m. p. 272—273°. Recrystallisation from ethanol furnished product, m. p. and mixed m. p.[7] 272—275°.

1-Alkyl-3-bromo-4-cinnolones.—Sodium (1 g.) was dissolved in ethanol (50 c.c.) and 3-bromo-4-hydroxycinnoline (3 g.) in ethanol (150 c.c.) was added. After addition of methyl iodide (10 c.c.), the mixture was refluxed for 2 hr. and poured into water (1 l.). Isolation with chloroform and crystallisation from benzene gave *3-bromo-1-methyl-4-cinnolone* (1·5 g., 47%), m. p.

198—200° (Found: C, 45·5; H, 2·9; N, 11·9; Br, 34·4. $C_9H_7BrN_2O$ requires C, 45·2; H, 3·0; N, 11·7; Br, 33·4%).

The following compounds were prepared similarly by use of alkyl bromides: *3-bromo-1-ethyl-4-cinnolone* (53%), m. p. 175—176°, from benzene (Found: C, 47·4; H, 3·7; N, 11·0; Br, 30·8. $C_{10}H_9BrN_2O$ requires C, 47·5; H, 3·6; N, 11·1; Br, 31·6%); *3-bromo-1-propyl-4-cinnolone* (33%), m. p. 92—94°, from benzene–light petroleum (Found: C, 49·3; H, 4·3; N, 10·5; Br, 29·7. $C_{11}H_{11}BrN_2O$ requires C, 49·5; H, 4·2; N, 10·5; Br, 30·0%); *3-bromo-1-isopropyl-4-cinnolone* (37%), m. p. 138—140°, from benzene–light petroleum (Found: C, 49·5; H, 4·1; N, 10·4; Br, 29·3%); and *1-benzyl-3-bromo-4-cinnolone* (50%), m. p. 182—183°, from benzene (Found: C, 57·5; H, 3·5; N, 8·8; Br, 25·5. $C_{15}H_{11}BrN_2O$ requires C, 57·2; H, 3·5; N, 8·9; Br, 25·4%).

Bromination of 1-Methyl-4-cinnolone.—The cinnolone (0·1 g.) in acetic acid (5 c.c.) containing potassium acetate (0·5 g.) was treated with bromine (0·1 c.c.) and the mixture was heated at 100° for 3 hr. Evaporation, addition of water, filtration, and recrystallisation from benzene gave 3-bromo-1-methyl-4-cinnolone (40 mg.), m. p. and mixed m. p. 195—197°. Similarly 1-ethyl-4-cinnolone was converted into the 3-bromo-derivative, m. p. and mixed m. p. 173—175°.

1-Alkyl-4-cinnolones.—(*a*) *From 1-alkyl-3-bromo-4-cinnolones.* 3-Bromo-1-methyl-4-cinnolone (1·6 g.) in ethanol (100 c.c.) was hydrogenated in presence of triethylamine (10 c.c.) and 10% palladised charcoal (0·4 g.). After 30 min., absorption became very slow and hydrogenation was stopped. The solution was filtered at the b. p., concentrated to small volume, and poured into water. Isolation with chloroform gave 1-methyl-4-cinnolone (0·9 g., 84%, *i.e.*, 39% overall from 4-hydroxycinnoline), m. p. and mixed m. p. 112—114°, from benzene–light petroleum.

The following compounds were obtained similarly: 1-ethyl-4-cinnolone (82%), m. p. and mixed m. p.[3] 85—87°; 1-propyl-4-cinnolone (66%), m. p. and mixed m. p. 81—83°; 1-isopropyl-4-cinnolone (82%), m. p. and mixed m. p. 98—100°; and *1-benzyl-4-cinnolone* (72%), m. p. 125—126°, from benzene–light petroleum (Found: C, 76·1; H, 5·2; N, 12·1. $C_{15}H_{12}N_2O$ requires C, 76·3; H, 5·1; N, 11·9%).

(*b*) *From 4-hydroxycinnoline.* Sodium (2 g.) was dissolved in ethanol (200 c.c.), and 4-hydroxycinnoline (5 g.) added. After addition of isopropyl bromide (15 c.c.) the mixture was refluxed for 3 hr. and poured into water. Isolation with chloroform and crystallisation from benzene–light petroleum gave the *anhydro-base* of *4-hydroxy-2-isopropylcinnolinium hydroxide*, m. p. 120—121° (Found: C, 69·9; H, 6·6; N, 14·7. $C_{11}H_{12}N_2O$ requires C, 70·2; H, 6·4; N, 14·9%). Chromatography of the mother-liquors in benzene on alumina and elution with benzene–chloroform (2 : 1) gave more anhydro-base (total: 2·4 g., 54%) and, in the first part of the eluate, *1-isopropyl-4-cinnolone* (0·31 g., 7%), m. p. 98—100° (Found: C, 70·0; H, 6·6; N, 14·6%).

Similarly *n*-propyl bromide gave the *anhydro-base* of *4-hydroxy-2-propylcinnolinium hydroxide* (65%), m. p. 115—116° (Found: C, 69·4; H, 6·7; N, 14·7%) and *1-propyl-4-cinnolone* (11%), m. p. 81—83° (Found: C, 70·2; H, 6·5; N, 14·8%).

4-Hydroxycinnoline (14·6 g.) was condensed with benzyl chloride as described.[3] Recrystallisation from ethyl acetate gave the anhydro-base of 2-benzyl-4-hydroxycinnolinium hydroxide (18·0 g., 76%). The mother-liquors were evaporated and the residue in benzene–light petroleum (1 : 1) was applied to a 10 × ¾ in. column of alumina. The first portion of eluate was evaporated and the residue crystallised from light petroleum to give 1-benzyl-4-cinnolone (100 mg., 0·4%), m. p. 122—124°, undepressed by admixture with the sample prepared *via* the bromo-compound.

Reduction of Anhydro-bases with Zinc and Ammonia Solution.—The anhydro-base of 4-hydroxy-2-propylcinnolinium hydroxide (1·0 g.), zinc dust (3 g.), and ethanol (50 c.c.) were refluxed gently and aqueous ammonia (10 c.c., *d* 0·88) was added gradually. The mixture was refluxed for 6 hr., filtered, evaporated to small volume, and poured into water. After repeated extractions with ethyl acetate, the organic layers were extracted with 2N-hydrochloric acid. Basification and isolation with ethyl acetate gave a sticky solid which was triturated with light petroleum (100 c.c.). A little anhydro-base was filtered off; the filtrate was evaporated and the residue treated with phenylhydrazine in aqueous acetic acid. The mixture was left overnight and the crystals were collected and recrystallised from aqueous ethanol to give *o*-aminoacetophenone phenylhydrazone, m. p. and mixed m. p. 104—106°.

The 2-isopropyl compound gave the same result.

4-Alkoxycinnolines.—4-Chlorocinnoline [8] (1·8 g.) was added to a solution of potassium hydroxide (2 g.) in benzyl alcohol (25 c.c.) and xylene (20 c.c.) from which water had been removed by azeotropic distillation. The mixture was left at room temperature for 48 hr. and poured into water. Isolation with chloroform gave a sticky solid which was triturated with ether and recrystallised from light petroleum–benzene to give *4-benzyloxycinnoline* (1·7 g.), m. p. 104—106° (Found: C, 76·1; H, 5·6; N, 11·9. $C_{15}H_{12}N_2O$ requires C, 76·3; H, 5·1; N, 11·9%). The following compounds were prepared similarly by dissolving sodium in the appropriate alcohol and adding 4-chlorocinnoline: *4-propoxycinnoline*, m. p. 49—50°, from benzene–light petroleum (Found: C, 69·9; H, 6·4; N, 14·7. $C_{11}H_{12}N_2O$ requires C, 70·2; H, 6·4; N, 14·9%); and *4-isopropoxycinnoline*, m. p. 100—101°, from benzene–light petroleum (Found: C, 70·2; H, 6·5; N, 15·0%).

Bromination of Anhydro-bases.—The anhydro-base of 2-ethyl-4-hydroxycinnolinium hydroxide (1 g.) and ammonium acetate (1·5 g.) in acetic acid (20 c.c.) were stirred at 100° while bromine (0·32 c.c.) in acetic acid (5 c.c.) was added dropwise. The mixture was stirred at 100° for 1 hr., cooled, and poured into water; the solution was made *slightly* alkaline and extracted three times with chloroform. Evaporation furnished the *anhydro-base* of *3-bromo-2-ethyl-4-hydroxycinnolinium hydroxide* (0·8 g.) as yellow needles, m. p. 132—133°, from benzene (Found: C, 47·9; H, 3·8; N, 10·8; Br, 31·6. $C_{10}H_9BrN_2O$ requires C, 47·5; H, 3·6; N, 11·1; Br, 31·6%). The *2-methyl analogue*, prepared similarly, had m. p. 161—163° (Found: C, 45·4; H, 3·1; N, 11·8; Br, 33·3. $C_9H_7BrN_2O$ requires C, 45·2; H, 3·0; N, 11·7; Br, 33·4%).

A solution of the 2-ethyl compound (0·58 g.) and potassium iodide (2 g.) in acetic acid (15 c.c.) was refluxed for 4 hr. The mixture was poured into water and basified; isolation with chloroform gave the anhydro-base of 2-ethyl-4-hydroxycinnolinium hydroxide (0·26 g.), m. p. and mixed m. p. 138—140°. The 2-methyl anhydro-base was obtained by similar debromination of its 3-bromo-derivative but 3-bromo-1-ethyl- and 3-bromo-1-methyl-4-cinnolone were each recovered unchanged after similar treatment with potassium iodide in acetic acid.

Reduction of 1-Methyl-4-cinnolone with Lithium Aluminium Hydride.—The cinnolone (2·5 g.) in benzene (100 c.c.) was added to lithium aluminium hydride (1·5 g.) in ether (100 c.c.) and the mixture was refluxed for 3 hr. and left overnight. After addition of 5N-sodium hydroxide (5 c.c.), the mixture was refluxed for 1 hr. and filtered, the solid being washed repeatedly with ethyl acetate. The combined filtrates were extracted five times with 2N-hydrochloric acid; basification of the extracts and isolation with ethyl acetate gave a viscous oil. Distillation yielded 1,2,3,4-tetrahydro-1-methylcinnoline (1·0 g.), b. p. 75—80°/0·5 mm. The residue in benzene (100 c.c.) was applied to a 3 × ¾ in. column of alumina; elution with benzene gave 1-methyl-4-cinnolone, m. p. and mixed m. p. 114—116°; elution with ethyl acetate then gave yellow crystals, tentatively formulated as *1,1′,4,4′-tetrahydro-1,1′-dimethyl-4,4′-bicinnolyl*, m. p. 160—162° (Found: C, 73·2; H, 6·2; N, 19·4. $C_{18}H_{18}N_4$ requires C, 73·5; H, 6·3; N, 19·3%); $\nu_{max.}$ 1600, 1575, and 1488 cm.$^{-1}$; $\lambda_{max.}$ 306 mμ (ε 12,700) in ethanol.

1-Ethyl-1,2,3,4-tetrahydrocinnoline.—1-Ethyl-4-cinnolone (1·6 g.) in benzene (50 c.c.) was added to lithium aluminium hydride (3 g.) in ether (100 c.c.), and the mixture was refluxed for 3 hr. Sodium hydroxide (3 g.) in water (10 c.c.) was added and, after the mixture had been refluxed for 1 hr., it was filtered and the solid was extracted repeatedly with ethyl acetate. The combined filtrates were extracted with 2N-hydrochloric acid; basification and isolation with ethyl acetate gave the base (0·8 g.), b. p. 80—85°/0·6 mm. (Found: C, 74·4; H, 8·5; N, 17·7. Calc. for $C_{10}H_{14}N_2$: C, 74·0; H, 8·7; N, 17·3%). The *hydrochloride* formed needles, m. p. 144—145°, from ether–ethanol (Found: C, 60·7; H, 7·7; N, 13·8. $C_{10}H_{15}ClN_2$ requires C, 60·4; H, 7·6; N, 14·1%).

Tichwinsky [10] gave b. p. 92—98°/17 mm. but did not characterise the material or confirm its structure.

1-Ethylcinnolinium Picrate.—1-Ethyl-1,2,3,4-tetrahydrocinnoline (0·6 g.) gave an oil on treatment with ethereal picric acid. After decantation of the ethereal layer, the oil was refluxed with methanolic picric acid (15 c.c., 2%) for 1 hr. Addition of ether and repeated recrystallisation of the product from ethanol (charcoal) gave the *quaternary salt*, m. p. 127—128° (Found: C, 49·2; H, 3·6; N, 17·9. $C_{16}H_{13}N_5O_7$ requires C, 49·6; H, 3·4; N, 18·1%).

1,2-Diethyl-1,2,3,4-tetrahydrocinnoline.—Acetylation (pyridine–acetic anhydride at room temperature) of 2-ethyl-1,2,3,4-tetrahydrocinnoline [3] gave *1-acetyl-2-ethyl-1,2,3,4-tetrahydrocinnoline*, m. p. 84—85°, from ethyl acetate–light petroleum (Found: C, 70·7; H, 8·2; N, 13·5.

$C_{12}H_{16}N_2O$ requires C, 70·6; H, 7·9; N, 13·7%). This (1 g.) in benzene (75 c.c.) was added to lithium aluminium hydride (1 g.) in ether (75 c.c.) and the mixture was refluxed for 3 hr. Isolated by the procedure described, the *base* (0·77 g.) had b. p. 72°/0·5 mm. (Found: C, 75·6; H, 9·9; N, 14·4. $C_{12}H_{18}N_2$ requires C, 75·7; H, 9·5; N, 14·7%).

1-*Benzyl*-1,2,3,4-*tetrahydrocinnoline*.—1-Benzyl-4-cinnolone (2·7 g.) in benzene (75 c.c.) was added dropwise to lithium aluminium hydride (2 g.) in ether (200 c.c.) and the mixture was refluxed for 6 hr. Isolated by the procedure described above, the *base* (1·0 g.) was obtained as a yellow oil, b. p. 150—154°/0·15 mm., which darkened on keeping (Found: C, 80·2; H, 7·1; N, 12·9. $C_{15}H_{16}N_2$ requires C, 80·3; H, 7·2; N, 12·5%).

1-*Methylcinnoline*-4-*thione*.—1-Methyl-4-cinnolone (0·5 g.) and phosphorus pentasulphide (1·0 g.) in benzene (50 c.c.) were refluxed for 30 min. The solution was evaporated, treated with water, and extracted with chloroform; the combined extracts were applied to a 4 × ¾ in. column of alumina which was eluted with more chloroform. Evaporation and crystallisation from benzene–light petroleum gave the *thione*, as red needles, m. p. 143—146° (Found: C, 60·8; H, 5·0; N, 16·1; S, 18·3. $C_9H_8N_2S$ requires C, 61·4; H, 4·6; N, 15·9; S, 18·2%).

Similar treatment of the anhydro-base of 4-hydroxy-2-methylcinnolinium hydroxide gave the anhydro-base of 4-mercapto-2-methylcinnolinium hydroxide, m. p. 182—184°. Albert and Barlin [12] give m. p. 182—184·5°, but formulate the compound as 1-methylcinnoline-4-thione.

Condensations with Acrylonitrile.—(*a*) 3-*Hydroxycinnoline*. A mixture of 3-hydroxycinnoline (2 g.), 1,2-dimethoxyethane (20 c.c.), acrylonitrile (4 c.c.), and benzyltrimethylammonium hydroxide (4 drops of 40% solution) was heated at 100° for 5 hr. After addition of ethyl acetate, the mixture was washed with water and evaporated; crystallisation of the residue from ethyl acetate gave 2-2′-*cyanoethyl*-3-*cinnolone* (1·5 g.) as amber plates, m. p. 161—163° (Found: C, 66·8; H, 4·5; N, 20·7. $C_{11}H_9N_3O$ requires C, 66·3; H, 4·6; N, 21·1%).

(*b*) 4-*Hydroxycinnoline*. The cinnoline (6 g.), 1,2-dimethoxyethane (120 c.c.), acrylonitrile (6 c.c.), and benzyltrimethylammonium hydroxide (1 c.c., 40%) were heated at 100° for 7 hr. After evaporation to dryness, and addition of sodium carbonate solution, the mixture was extracted repeatedly with chloroform. Evaporation, and crystallisation from ethyl acetate, gave 1-2′*cyanoethyl*-4-*cinnolone* (6·4 g.), m. p. 192—194° (Found: C, 66·3; H, 4·8; N, 21·1%). No other product could be isolated by chromatography of the mother-liquors in benzene on alumina.

Similarly 3-bromo-4-hydroxycinnoline was converted into 3-*bromo*-1-2′-*cyanoethyl*-4-*cinnolone*, m. p. 159—160° (Found: C, 47·2; H, 2·8; N, 15·0; Br, 29·9. $C_{11}H_8BrN_3O$ requires C, 47·5; H, 2·9; N, 15·1; Br, 28·8%). The same product, m. p. and mixed m. p. 158—160°, was obtained as follows: the adduct from 4-hydroxycinnoline (1 g.), ammonium acetate (1 g.), and acetic acid (10 c.c.) were heated at 100° and bromine (0·26 c.c.) in acetic acid (5 c.c.) was added gradually. The mixture was heated at 100° for 3 hr., cooled, filtered, and poured into sodium acetate solution. The bromo-nitrile (0·52 g.) was filtered off and crystallised from ethyl acetate.

Treatment of this bromo-compound with potassium iodide in acetic acid did not effect reduction (cf. 3-bromo-1-alkyl-4-cinnolones and contrast 3-bromo-anhydro-bases).

1-2′-*Carboxyethyl*-4-*cinnolone*.—A solution of the nitrile (5 g.) in concentrated hydrochloric acid (100 c.c.) was refluxed for 5 hr. and then evaporated to dryness. Addition of concentrated ammonium acetate solution gave a precipitate which was collected and crystallised from ethyl acetate. The *acid* (4·8 g.) had m. p. 171—172° (Found: C, 60·8; H, 4·5; N, 12·6. $C_{11}H_{10}N_2O_3$ requires C, 60·5; H, 4·6; N, 12·8%). The 3-*bromo-derivative*, prepared similarly, had m. p. 251—252° (Found: C, 44·7; H, 3·2; N, 9·6; Br, 28·0. $C_{11}H_9BrN_2O_3$ requires C, 44·5; H, 3·0; N, 9·4; Br, 27·0%).

Condensation of 4-*Hydroxycinnoline with Ethylene Dibromide*.—Sodium (1·5 g.) was dissolved in ethanol (250 c.c.) and the solution was refluxed while 4-hydroxycinnoline (10 g.) and ethylene dibromide (30 g.) were added successively. The mixture was left at room temperature for 5 days, poured into water (500 c.c.), and extracted repeatedly with chloroform. Evaporation gave a solid which was extracted with boiling benzene (200 c.c.); the extracts were applied to a 12 in. × ¾ in. column of alumina. Elution with benzene furnished 1-2′-*bromoethyl*-4-*cinnolone* (0·6 g.), m. p. 149—151°, from benzene–light petroleum (Found: C, 47·6; H, 3·7; N, 11·9. $C_{10}H_9BrN_2O$ requires C, 47·4; H, 3·6; N, 11·1%).

The cinnolone (0·5 g.) in ethanol (20 c.c.) was treated with sodium cyanide (2·0 g.) in water (10 c.c.) and the solution was refluxed for 5 hr. Addition of water, isolation with chloroform,

and crystallisation from benzene–light petroleum furnished 1-*vinyl*-4-*cinnolone* (0·32 g.), m. p. 110—112° (Found: C, 69·4; H, 4·4. $C_{10}H_8N_2O$ requires C, 69·8; H, 4·7%). This (0·25 g.) in ethanol (50 c.c.) was hydrogenated in presence of palladised charcoal (0·1 g., 10%). After absorption of 15 c.c. of hydrogen, reduction became very slow and the solution was filtered. Evaporation and crystallisation from light petroleum gave 1-ethyl-4-cinnolone, m. p. and mixed m. p. 85—87°.

Condensation of 4-*Hydroxycinnoline with* 2-*Bromoethanol*.—4-Hydroxycinnoline (2 g.) was added to a boiling solution of sodium ethoxide (from sodium, 0·5 g.) in ethanol (50 c.c.). After addition of 2-bromoethanol (2·5 c.c.), the mixture was refluxed for 2 hr. and left overnight. Water (5 c.c.) was added and the solution was evaporated to dryness and the residue extracted repeatedly with hot ethyl acetate. Concentration of the extracts gave the *anhydro-base* (1·79 g.), m. p. 171—172°, from ethyl acetate, of 4-hydroxy-2-2′-hydroxyethylcinnolinium hydroxide, from ethyl acetate (Found: C, 63·6; H, 5·3; N, 15·1. $C_{10}H_{10}N_2O_2$ requires C, 63·2; H, 5·3; N, 14·7%). No isomeric product could be isolated by chromatography of the mother-liquors in benzene on alumina.

Similarly 3-bromopropanol gave only the *anhydro-base*, m. p. 129—130°, from ethyl acetate, of 4-hydroxy-2-3′-hydroxypropylcinnolinium hydroxide (Found: C, 64·4; H, 5·7; N, 14·0. $C_{11}H_{12}N_2O_2$ requires C, 64·7; H, 5·9; N, 13·7%).

Both anhydro-bases were reduced with zinc dust and aqueous ethanolic ammonia, in the manner described above, to give *o*-aminoacetophenone (phenylhydrazone, m. p. and mixed m. p. 103—105°).

Anhydro-base of 2-2′-*Acetoxyethyl*-4-*hydroxycinnolinium Hydroxide*.—(*a*) The hydroxyethyl compound (0·6 g.) was dissolved in acetic acid (20 c.c.) and the solution at 70° was saturated with hydrogen bromide and then heated at 100° for 3·5 hr. Addition of water, basification with sodium hydrogen carbonate solution, and repeated extractions with chloroform, followed by evaporation of the extracts, gave the *anhydro-base* (0·25 g.), m. p. 122—123°, from benzene–light petroleum (Found: C, 62·1; H, 5·4; N, 12·0. $C_{12}H_{12}N_2O_3$ requires C, 62·1; H, 5·2; N, 12·0%).

(*b*) The hydroxyethyl compound (0·62 g.) was dissolved in hydrogen bromide in acetic acid (20 c.c., *d* 1·2) and concentrated sulphuric acid (2 c.c.) was added. The solution was left overnight at room temperature and then heated at 100° for 3 hr.; it was poured into water, basified, and extracted with chloroform. Evaporation and crystallisation from benzene–light petroleum gave the *anhydro-base* (0·6 g.), m. p. 137—139°, of 2-2′-acetoxyethyl-3-bromo-4-hydroxycinnolinium hydroxide (Found: C, 46·5; H, 3·1; N, 9·1; Br, 25·8. $C_{12}H_{11}BrN_2O_3$ requires C, 46·3; H, 3·5; N, 9·0; Br, 25·9%).

This product (0·28 g.) in ethanol (20 c.c.) was hydrogenated in presence of palladised charcoal (0·2 g., 10%) and sodium acetate (0·2 g.). The filtered solution was evaporated to dryness and the residue extracted with benzene. Evaporation and crystallisation from benzene–light petroleum gave the anhydro-base (0·15 g.), m. p. and mixed m. p. 123—124°, of 2-2′-acetoxyethyl-4-hydroxycinnolinium hydroxide (Found: C, 61·9; H, 5·4; N, 11·8%).

Quaternisation of 4-*Acetamidocinnoline*.—A solution of 4-acetamidocinnoline (1·0 g.) in ethanol (20 c.c.) and methyl iodide (5 c.c.) was refluxed for 30 min. and then evaporated. The residue in 2N-sodium hydroxide (100 c.c.) was refluxed for 3 hr. Isolation with chloroform, chromatography in benzene on alumina, and elution with benzene gave 1-methyl-4-cinnolone (0·11 g., 13%), m. p. and mixed m. p. 112—114°. Elution with benzene–chloroform (2 : 1) gave the anhydro-base (0·32 g., 37%), m. p. and mixed m. p. 162—164°, of 4-hydroxy-2-methylcinnolinium hydroxide.

In another experiment, the methiodide precipitated during refluxing was filtered off and recrystallised from ethanol to provide orange crystals of 4-*acetamido*-2-*methylcinnolinium iodide*, m. p. 248—250° (Found: C, 40·7; H, 3·9; N, 12·9. $C_{11}H_{12}IN_3O$ requires C, 40·1; H, 3·7; N, 12·8%). Hydrolysis of this salt in the manner described yielded only the anhydro-base, m. p. and mixed m. p. 160—163°.

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