744. *Cinnolines. Part XXXII.* Further Experiments on the Effects of Heterocyclic Nuclei as Substituents in the Widman–Stoermer Synthesis.*

By A. J. NUNN and K. SCHOFIELD.

A number of 4-aryl-3-pyridyl- and -quinolyl-cinnolines have been synthesised by the Widman–Stoermer method. A *p*-methoxyphenyl group at the potential cinnoline $C_{(4)}$-position renders cinnoline formation very rapid and independent of pH, provided the latter is not so high as to endanger the stability of the diazonium salt. In contrast the formation of 4-phenyl-3-pyridyl- and -quinolyl-cinnoline depends considerably on the pH, and yields decrease rapidly with increasing acid concentration. In the diazotisation of 1-*o*-aminophenyl-1-phenyl-2-2′-quinolylethylene in hydrochloric acid, but not in sulphuric acid, it is possible that the Pschorr cyclisation competes with cinnoline formation.

Related observations on the preparation of 4-heteroarylcinnolines are described.

It was shown earlier (Schofield, *J.*, 1949, 2408) that the ethylenes (I; $R = C_6H_4 \cdot OMe$-*p*, $R'' = H$, $R' = 2\text{-}C_5H_4N$ and $2\text{-}C_9H_6N$) gave on diazotisation high yields of 4-*p*-methoxyphenyl-3-2′-pyridyl- and -3-2′-quinolyl-cinnoline (as II) respectively. In contrast (I; $R = Ph$; $R' = 2\text{-}C_5H_4N$, $R'' = H$) gave only a poor yield of 4-phenyl-3-2′-pyridylcinnoline (as picrate), whilst (I; $R = Ph$; $R' = 2\text{-}C_9H_6N$, $R'' = H$) gave tars. Similarly, (I; $R = 2\text{-}C_5H_4N$, $R' = R'' = H$) provided a poor yield of 4-2′-pyridylcinnoline. It was suggested that ethylenes of the type (I), containing basic heterocyclic substituents, offered an interesting means of studying the effect of pH on the Widman–Stoermer synthesis. Further, the cinnolines produced would be of interest in themselves, being related (cf. III) on the one hand to numerous substances such as the phenanthrolines which are capable of chelating with metals, and on the other to pyridylquinolines possessing spasmolytic pro-

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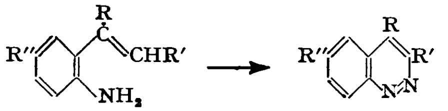
* Part XXXI, *J.*, 1953, 1811.

perties (Coates, Cook, Heilbron, Hey, Lambert, and Lewis, *J.*, 1943, 401). For these reasons we have extended the earlier work.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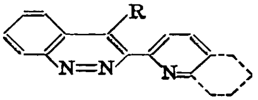
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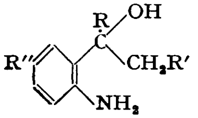

(IV)

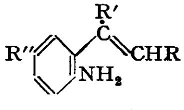
Recently (*J.*, 1952, 589) we described a number of alcohols of the types (IV; R = Aryl, R′ = 2-C_5H_4N or 2-C_9H_6N; and R = 2-, 3-, and 4-C_5H_4N), and these have now been dehydrated to the ethylenes (I). The ethylenes were diazotised under a variety of conditions.

EXPERIMENTAL

Unless described in the present paper the alcohols and ethylenes used were prepared by Schofield (*loc. cit.*) or Nunn and Schofield (*loc. cit.*; *J.*, 1953, 716). Diazotisations were effected at 0° with aqueous sodium nitrite (5%). Ethereal extracts were dried with anhydrous Na_2SO_4.

Ethylenes.—The appropriate alcohol and sulphuric acid were heated at 95°. The solution was basified and the product was isolated with ether. Details are tabulated.

4-*Aryl*-3-*heteroarylcinnolines.*—(1) 4-p-*Methoxyphenyl*-3-2′-*pyridylcinnoline.* (*a*) The appropriate ethylene was diazotised in 2N-hydrochloric acid, and the solution was immediately made up to 100 c.c. with hydrochloric acid of various concentrations. Diazonium tests were negative after about 10 min. After 4 days at room temperature the solutions were neutralised with sodium carbonate and the precipitate was recrystallised from methanol until the m. p. was that of the pure cinnoline (157—158°). In each case the yield of crude cinnoline, m. p. 154—156°, was quantitative.



	Alcohol,	H_2SO_4		Time,	Ethylene (I),
	g.	Concn.	c.c.	hr.	g.
R = 2-C_5H_4N; R′ = *p*-C_6H_4Me; R″ = H	2	50% v/v	32	1	2 [1]
R = 2-C_9H_6N; R′ = *p*-C_6H_4Me; R″ = H	0·5	,,	8	0·5	0·5 [2]
R = 2-C_5H_4N; R′ = Ph; R″ = Cl	2	Conc.	,,	,,	1·9 [1]
R = 2-C_9H_6N; R′ = Ph; R″ = Cl	1	,,	4	1	0·89 [3]
R = 3-C_5H_4N; R′ = *p*-MeO·C_6H_4; R″ = H	0·5	20% v/v	10	,,	0·48 [1]
R = Me; R′ = 2-C_5H_4N; R″ = H	2	Conc.	8	0·5	1·84 [1]
R = R″ = H; R′ = 3-C_5H_4N	,,	,,	,,	0·75	1·94 [4]
R = Me; R′ = 3-C_5H_4N; R″ = H	,,	,,	,,	0·5	1·72 [1]
R = R″ = H; R′ = 4-C_5H_4N	0·24	,,	1	,,	0·22 [1]
R = R″ = H; R′ = 2-C_4H_3S	0·5	20% v/v	10	1	0·48 [1]

[1] Yellow oil. [2] Yellow prisms, m. p. 161—162° (Found: C, 84·9; H, 5·6. $C_{24}H_{20}N_2$ requires C, 85·7; H, 6·0%), from ethanol. [3] Yellow prisms, m. p. 147—148° (Found: C, 76·6; H, 4·7. $C_{23}H_{17}N_2Cl$ requires C, 77·4; H, 4·8%), from aqueous ethanol. [4] The ethylene was a yellow oil. Its *picrate* formed yellow needles, m. p. 125—126° (Found: C, 52·9; H, 3·8. $C_{13}H_{12}N_2,C_6H_3O_7N_3$ requires C, 53·6; H, 3·6%), from aqueous methanol.

(*b*) With the same ethylene the diazotisation was effected in acid of various concentrations. The crude products (88—91%) had m. p. 155—158°. Careful repetition of the diazotisation under the original conditions (Schofield, *loc. cit.*) realised a yield of 80·1% of the cinnoline.

(2) 4-p-*Methoxyphenyl*-3-2′-*quinolylcinnoline.* The diazotisations were carried out as in (*b*) above (see Table). Diazonium ions could no longer be detected after about 45 min. The products tabulated below had the m. p. (151—152°) of pure 4-*p*-methoxyphenyl-3-2′-quinolylcinnoline (Schofield, *loc. cit.*), except for the first (m. p. 144—148°), and the last (m. p. 157—158°) which appeared to be a polymorphic form (yellow needles instead of the usual plates; mixed m. p. 150—152°).

(3) 4-*Phenyl*-3-2′-*pyridylcinnoline.* The corresponding amine was diazotised by method (*b*) above (see Table). Yields are not quoted since the products were not crystallised. The first had m. p. 141—143°, and the second, 118—120°. In a further experiment the ethylene (6 g.) was diazotised in hydrochloric acid (0·2N; 250 c.c.). After 5 days at room temperature basification gave a solid (4·25 g.; m. p. 139—141°). Passage in benzene over alumina provided

pale yellow crystals of 4-*phenyl*-3-2′-*pyridylcinnoline*, m. p. 145—146° (Found : C, 79·8; H, 4·5. $C_{19}H_{13}N_3$ requires C, 80·5; H, 4·6%).

(4) 4-*Phenyl*-3-2′-*quinolylcinnoline.* In the experiments tabulated the appropriate amine was diazotised in sulphuric acid of various concentrations. 4-*Phenyl*-3-2′-*quinolylcinnoline* formed yellow prisms, m. p. 162—163° (Found : C, 83·4; H, 4·8. $C_{23}H_{15}N_3$ requires C, 82·9; H, 4·5%), from aqueous ethanol. The products tabulated had m. p.s 157—160°, 152—154° and 162—163°.

In other experiments the ethylene (0·5 g.) was diazotised in hydrochloric acid of various concentrations (25 c.c. total volume), and after 3 weeks at room temperature the solutions were processed as usual. The mixtures obtained were treated with picric acid in ethanol with the following results (acid concn., colour of picrates, m. p.) : 0·2N, orange-yellow, 157—162°; 2N, orange-yellow, 157—162°; 5N, red, 157—162°; 8N, pale yellow, 192—195°. The first mixture yielded as the more soluble component a *picrate* which formed red needles, m. p. 94—95° (Found : C, 65·1; H, 3·7; N, 11·6. $C_{23}H_{15}N,C_6H_3O_7N_3$ requires C, 65·2; H, 3·4; N, 10·5%), from ethanol. [1 : 1-Diphenyl-2-2′-quinolylethylene (Ziegler and Zeiser, *Annalen*, 1931, **485**, 174) gave a *picrate* which crystallised from methanol as yellow plates, m. p. 215—216° (Found : C, 64·4; H, 3·6; N, 10·2. $C_{23}H_{17}N,C_6H_3O_7N_3$ requires C, 64·9; H, 3·8; N, 10·4%).] The fourth product (0·45 g.) was slightly impure 4-*phenyl*-3-2′-*quinolylcinnoline picrate*, which on recrystallisation from ethanol gave yellow prisms, m. p. 219—220° (Found : C, 62·0; H, 3·2; N, 14·7. $C_{23}H_{15}N_3,C_6H_3O_7N_3$ requires C, 61·9; H, 3·2; N, 14·9%).

Cinnoline	Wt. of ethylene (g.)	Normality of acid [1]	Approx. time after which coupling ceased	Product (g.)
1(*a*)	1·92	0·2	10 min.	1·67
	1·81	0·4	,,	1·54
	1·88	2·0	,,	1·58
	,,	5·0	,,	1·63
	1·91	9—10	,,	1·43
1(*b*)	1·96	0·2	10—15 min.	1·43
	,,	2·0	15 min.	1·49
	,,	5·0	20 ,,	,,
	1·98	8·0	25 ,,	1·51
	,,	11—12	30 ,,	1·49
2	0·5	0·2	—	0·25
	,,	2·0	—	0·38
	,,	0·5	—	0·44
	,,	8·0	—	,,
	,,	11—12	—	0·42
3	0·25	0·2	20 hr.	—
	,,	0·4	,,	—
	,,	5·0	—	Tar
	,,	8·0	5 days	,,
4	0·5	0·2	21 days	0·18
	3·0	0·4	,,	0·15
	0·5	1·0	,,	0·01

[1] The total volume of acid in experiments (1*a*) and (1*b*) was always 100 c.c., in experiments (2) 25 c.c., in (3) 12 c.c., and in (4) 25, 150, and 25 c.c.

3-2′-*Pyridyl*-4-p-*tolylcinnoline.* The ethylene (2 g.) was diazotised in 2N-hydrochloric acid (84 c.c.), and after 11 days at room temperature the product was isolated as usual. Crystallisation from benzene–light petroleum (b. p. 60—80°) gave substantially pure material (1·5 g.; m. p. 164—165°), but this was green. Passage in benzene over alumina gave 3-2′-*pyridyl*-4-p-*tolylcinnoline*, m. p. 164—165° (Found : C, 80·3; H, 5·4. $C_{20}H_{15}N_3$ requires C, 80·8; H, 5·1%), which formed yellow needles from aqueous ethanol.

3-2′-*Quinolyl*-4-p-*tolylcinnoline.* Diazotisation of the ethylene (0·25 g.) in hydrochloric acid (2N; 8 c.c.) gave in the usual way after 11 days a *product* which, crystallised from aqueous ethanol and benzene–ligroin (b. p. 60—80°), formed yellow needles (0·19 g.), m. p. 153—154° (Found : C, 82·6; H, 4·6. $C_{24}H_{17}N_3$ requires C, 82·95; H, 4·9%).

6-*Chloro*-4-*phenyl*-3-2′-*pyridylcinnoline.* The ethylene (1·9 g.) was diazotised in 0·4N-hydrochloric acid (84 c.c.). The *product* isolated after 15 days gave yellow prisms (1·05 g.), m. p. 143—144° (from aqueous ethanol) (Found : C, 71·7; H, 3·9. $C_{19}H_{12}N_3Cl$ requires C, 71·8; H, 3·8%).

6-*Chloro*-4-*phenyl*-3-2′-*quinolylcinnoline.* The ethylene (0·25 g.) was diazotised in 2N-sulphuric acid (8 c.c.), and gave after 6 weeks a *product* which on crystallisation from ethanol formed yellow needles (0·12 g.), m. p. 205—206° (Found : C, 74·4; H, 3·9. $C_{23}H_{14}N_3Cl$ requires C, 75·1; H, 3·8%). No product could be isolated from an experiment in 2N-hydrochloric acid.

4-p-*Methoxyphenyl*-3-3'-*pyridylcinnoline*. A diazonium solution from the ethylene (0·48 g.) and 2N-hydrochloric acid (20 c.c.) gave after 1 hour a solid which formed yellow needles (0·37 g.) of 4-p-*methoxyphenyl*-3-3'-*pyridylcinnoline*, m. p. 145—146° (Found : C, 76·5; H, 4·7. $C_{20}H_{15}ON_3$ requires C, 76·7; H, 4·8%), from aqueous ethanol.

4-*Heteroarylcinnolines*.—4-2'-*Pyridylcinnoline*. The ethylene (0·5 g.) was diazotised in 2N-hydrochloric acid (25 c.c.). The product, obtained by the usual method, was treated with picric acid in methanol. Recrystallisation from this solvent gave the picrate (0·43 g.), m. p. 196—199° (pure m. p. 201—203°; Schofield, *loc. cit.*), from which, by treatment with alkali and ether, was isolated the cinnoline (0·18 g.), m. p. 125—126°. The results of similar experiments in acid of different concentrations are recorded below.

3-*Methyl*-4-2'-*pyridylcinnoline*. The ethylene (0·22 g.), when diazotised in 0·2N-sulphuric acid (10 c.c.), gave after 4 days a product which from benzene–ligroin (b. p. 60—80°) provided pale yellow prisms (0·1 g.) of 3-*methyl*-4-2'-*pyridylcinnoline*, m. p. 155—156° (Found : C, 75·7; H, 5·0. $C_{14}H_{11}N_3$ requires C, 76·0; H, 5·0%). Experiments with N-sulphuric gave only tars.

4-3'-*Pyridylcinnoline*. In the usual way the ethylene (1·94 g.) in 0·4N-hydrochloric acid (84 c.c.) gave a solid after 11 days. This formed from benzene–light petroleum (b. p. 60—80°) yellow needles (0·95 g.) of 4-3'-*pyridylcinnoline*, m. p. 141—142° (Found : C, 75·5; H, 4·4; N, 20·4. $C_{13}H_9N_3$ requires C, 75·3; H, 4·4; N, 20·3%).

3-*Methyl*-4-3'-*pyridylcinnoline*. The appropriate amine (1·72 g.) in 0·2N-sulphuric acid (60 c.c.) gave, as above, a *product* (1·4 g., m. p. 192—193°) which formed yellow prisms (0·88 g.), m. p. 192—193° (from ethanol) (Found : C, 75·7; H, 4·9%).

4-4'-*Pyridylcinnoline picrate*. A black tar was isolated after 6 days from the diazotisation of 1-*o*-aminophenyl-1-4'-pyridylethylene (0·22 g.) in 2N-hydrochloric acid (10 c.c.). Treatment of the tar with ethanolic picric acid gave 4-4'-*pyridylcinnoline picrate* (0·1 g.), which formed yellow prisms, m. p. 276—278° (Found : C, 51·2; H, 2·95. $C_{13}H_9N_3,C_6H_3O_7N_3$ requires C, 52·3; H, 2·8%), from methanol.

4-2'-*Thienylcinnoline*. The ethylene (0·4 g.) in 0·4N-hydrochloric acid (21 c.c.) gave after 4 days a solid which was extracted with boiling ether. From the ether yellow prisms of 4-2'-*thienylcinnoline* (0·2 g.), m. p. 85—86° (Found : C, 67·4; H, 4·0; N, 13·2. $C_{12}H_8N_2S$ requires C, 67·9; H, 3·8; N, 13·2%), were obtained.

Miscellaneous Experiments.—4-p-*Hydroxyphenyl*-3-2'-*pyridylcinnoline*. 4-*p*-Methoxyphenyl-3-2'-pyridylcinnoline (1 g.) and hydrobromic acid (8 c.c.; *d* 1·5) were refluxed for 1 hr. and the cooled solution was basified. The product (0·86 g.) gave yellow prisms of 4-p-*hydroxyphenyl*-3-2'-*pyridylcinnoline*, m. p. 265—266° (Found : C, 76·1; H, 4·1. $C_{19}H_{13}ON_3$ requires C, 76·2; H, 4·4%), from ethanol.

Diazotisation of 2-o-*aminophenyl*-3-2'-*pyridylpropylene*. The alcohol gave in the usual way with concentrated sulphuric acid a yellow oil, which formed a *dipicrate*, yellow prisms, m. p. 174—175° (from methanol) [Found : C, 45·6; N, 2·9; N, 17·0. $C_{14}H_{14}N_2,(C_6H_3O_7N_3)_2$ requires C, 46·7; H, 3·0; N, 16·8%]. Diazotisation of the ethylene in sulphuric acid of various concentrations gave tars, but with 0·2N-acid traces of yellow crystals, m. p. 149—151°, were isolated

Experiments with 1-O-*aminophenyl*-1-p-*methoxyphenyl*-2-2'-*pyridylethylene*. When the ethylene was diazotised in hydrochloric acid (0·2N), and the solution was added immediately to sodium acetate, water, and copper powder, or to aqueous dimethylamine and sodium carbonate, only diminished yields of 4-*p*-methoxyphenyl-3-2'-pyridylcinnoline resulted. When the ethylene (1·85 g.) was rapidly diazotised in 2N-hydrochloric acid (40 c.c.) and copper powder (0·5 g.) was added immediately, shaking and warming then precipitated a green solid (2·48 g.), whilst much nitrogen was evolved. Recrystallisation of the solid from ethanol gave green prisms of a *complex*, m. p. 222—223° (Found : C, 53·8; H, 3·5. $C_{20}H_{15}ON_3Cl_2Cu$ requires C, 53·65; H, 3·4%). Boiled with aqueous ammonia (*d* 0·88) the solid liberated 4-*p*-methoxyphenyl-3-2'-pyridylcinnoline.

Reaction of 4-*methylcinnoline with* p-*nitrosodimethylaniline*. 4-Methylcinnoline (4 g.), *p*-nitrosodimethylaniline (8 g.), anhydrous sodium carbonate (0·5 g.), and ethanol (270 c.c.) were refluxed for 7 hr. Filtration and concentration gave the *anil* (2·2 g.) which formed red leaflets, m. p. 196—197° (Found : C, 73·3; H, 6·1; N, 21·2. $C_{17}H_{16}N_4$ requires C, 73·9; H, 5·8; N, 20·3%), from ethanol. The anil was not hydrolysed by 40% hydrochloric acid.

1-o-*Methoxyphenyl*-1-*phenyl*-2-2'-*quinolylethylene*. *o*-Methoxybenzophenone (3 g.) in ether

(50 c.c.) was added dropwise during 10 min. to 2-quinolylmethyl-lithium [from quinaldine (6·1 g.)] in ether (100 c.c.). The mixture was refluxed for 1 hr. and then stirred for 4 hr. at room temperature. In the usual way the product was isolated as a brown oil which crystallised when rubbed with ether. The solid (3·4 g.) when crystallised from ether or aqueous methanol gave solvated prisms, m. p. 104—106° (with bubbling, after preliminary softening), which upon being dried (60°/0·5 mm.) provided prisms of 1-o-*methoxyphenyl*-1-*phenyl*-2-*quinolylethanol*, m.p. 122·5—123·5° (Found: C, 81·0; H, 5·8; N, 4·0. $C_{24}H_{21}O_2N$ requires C, 81·1; H, 5·9; N, 3·9%). This (0·2 g.), when heated for 2 hr. at 95° with 20% sulphuric acid (5 c.c.), gave a suspension of yellow needles. Basification and ether-extraction yielded the ethylene as a crisp froth (0·18 g.). The *picrate* formed thin yellow prisms, m. p. 209—211° (after subliming slightly at 197°) (Found: C, 63·9; H, 4·2; N, 9·7. $C_{24}H_{19}ON,C_6H_3O_7N_3$ requires C, 63·6; H, 3·9; N, 9·9%), from ethanol.

DISCUSSION

The main results of the above experiments are tabulated below. Clearly, the cyclisation of diazotised 1-*o*-aminophenyl-1-*p*-methoxyphenyl-2-2′-pyridyl- and -2-2′-quinolyl-ethylene to the corresponding cinnolines proceeds efficiently regardless of pH except that in the second case there is a decrease in yield in very dilute acid, where presumably the stability of the diazonium salt is endangered. These results are readily understood in terms of the following representation of the reaction (V ⟶ VI ⟶ VII). Although the electron demand of the pyridyl and quinolyl groups must increase with acid concentration, the *p*-methoxyphenyl group is so powerfully electron-releasing that it is able over the whole pH range examined to satisfy the electronic demands of the Widman–Stoermer reaction (*a* and *b* in V), as well as of the pyridinium and quinolinium groups (*c*). The velocities of these cyclisations are high, and greatly exceed those in cases where R in (V) is other than methoxyl. [If 1-*o*-aminophenyl-1-*p*-methoxyphenyl-2-2′-pyridylethylene possessed the *cis*-configuration it might have been possible to convert in into (VIII), but a number of experiments with this aim gave only the cinnoline, so rapid was the cyclisation.] Data on the formation of 3-2′-pyridyl- and 3-2′-quinolyl-4-*p*-tolylcinnoline are limited but, so far as they go, consistent with what is said above. The yields are lower than with the methoxyl compounds, presumably because the slower cyclisation gives greater opportunities for alternative decompositions of the diazonium salts to occur.

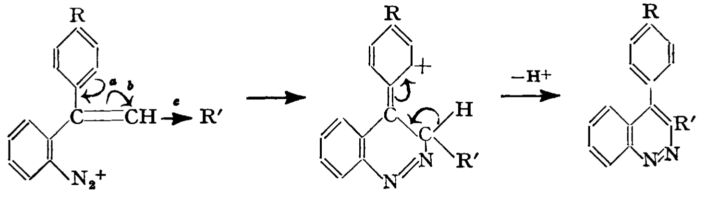
	Yield (%) in hydrochloric acid					
Cinnoline	0·2N	0·4N	N	2N	5N	8N
4-*p*-Methoxyphenyl-3-2′-pyridyl-	83·9	81·9	—	81·0	81·7	80·1
4-*p*-Methoxyphenyl-3-2′-quinolyl-	48·0	—	—	73·0	85·0	85·0
3-2′-Pyridyl-4-*p*-tolyl-	—	—	—	72·2	—	—
3-2′-Quinolyl-4-*p*-tolyl-	—	—	—	60·0	—	—
4-Phenyl-3-2′-pyridyl-	49·7	←		Tars		→
4-Phenyl-3-2′-quinolyl-	34·9 *	5·0 *	1·9 *	—	—	—
6-Chloro-4-phenyl-3-2′-pyridyl-	—	53·3	—	—	—	—
6-Chloro-4-phenyl-3-2′-quinolyl-	—	46·6 *	—	—	—	—
4-*p*-Methoxyphenyl-3-3′-pyridyl-	—	—	—	74·0	—	—
4-2′-Pyridyl-	2·5	—	16·1 *	34·1	Tar	—
3-Methyl-4-2′-pyridyl-	43·2 *	—	—	Tar	—	—
4-3′-Pyridyl-	—	46·0	—	—	—	—
3-Methyl-4-3′-pyridyl-	77·3 *	Tar	—	Tar	—	—
4-4′-Pyridyl-	—	—	—	20·4	—	—

* Experiments in sulphuric acid.

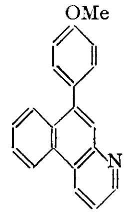
The diazotisation of 1-*o*-aminophenyl-1-phenyl-2-2′-quinolylethylene in hydrochloric acid is complicated, and is discussed below. However, the same reaction in sulphuric acid, and the diazotisations of 1-*o*-aminophenyl-1-phenyl-2-2′-pyridylethylene (in hydrochloric acid) show the expected features. Except in the most dilute acid the cinnolines could not be isolated, tars being formed. Even in dilute acid the yields were low, and the reactions were slow. These examples are in great contrast to the almost instantaneous formation of 3 : 4-diphenylcinnoline from 1-*o*-aminophenyl-1 : 2-diphenylethylene (Simpson, *J.*, 1943, 447), where the discouraging effect of the basic heterocyclic nucleus is absent. The presence of a chlorine atom, in two examples tabulated above, appears to benefit the cyclisation, perhaps because it stabilises the diazonium group, so compensating for the slow cyclisation.

It appears unlikely that 4-methyl-3-2′-pyridylcinnoline could be obtained from 2-*o*-aminophenyl-3-2′-pyridylpropylene in any circumstances.

In the formation of 4-pyridylcinnolines it would be expected that a 3-pyridyl group at the potential cinnoline $C_{(4)}$-position would retard the cyclisation less than either a 2- or 4-pyridyl group. The effect of protonisation of the pyridyl group would not make itself felt so strongly from the 3-pyridyl position as from the other positions, tautomeric transmission of charge not being possible in the first case. The evidence is not extensive, but it is clear that 4-3′-pyridylcinnoline is more readily formed than are the 2′- and the 4′-isomer. In the case of 1-*o*-aminophenyl-1-2′-pyridylethylene, it is evidently again necessary to balance the opposing factors of diazonium group stability and minimum protonisation of the pyridyl group to produce the optimum yield of cinnoline. A methyl group at the potential $C_{(3)}$-position assists the Widman–Stoermer cyclisation in these cases.



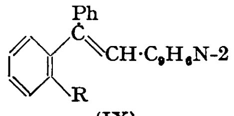
(V) (VI) (VII)



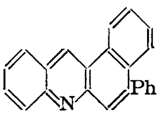
(VIII)

As stated above, and described in the Experimental section, the diazotisation of 1-*o*-aminophenyl-1-phenyl-2-2′-quinolylethylene in hydrochloric acid is complicated. In dilute acid a small amount of the cinnoline was formed, together with a quantity of another compound which was isolated as its red picrate. Surprisingly, the yield of the cinnoline increased with acid concentration until in 8N-hydrochloric acid it could be isolated (as its picrate) in 52% yield. We can offer no explanation for the relatively large yield of the cinnoline in such circumstances, but the occurrence of a second reaction, with its possible effect upon the isolation of the cinnoline, makes it impossible to decide whether the yield of the latter really decreases with increasing acid concentration though this seems unlikely.

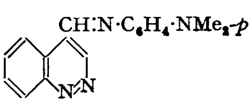
For the base corresponding to the red picrate the structures (IX; R = H), (IX; R = OH), and (X) require consideration. The first of these was eliminated by direct comparison of the red picrate with 1 : 1-diphenyl-2-2′-quinolylethylene picrate. 1-*o*-Methoxyphenyl-1-phenyl-2-2′-quinolylethylene was prepared from the corresponding alcohol, but an attempt to demethylate it with sodium (Prey, *Ber.*, 1943, **76**, 156) failed, and in any case analytical figures favour the expression (X). The latter can only be accepted tentatively. The m. p. (94—95°) of the red picrate is surprisingly low, and the formation of (X) would imply cyclisation into a pyridine ring under conditions not particularly favourable to the Pschorr reaction. However, the work of Hey and Osbond (*J.*, 1949, 3164) shows that such cyclisation is not impossible, and the case is of sufficient theoretical interest to merit further examination.



(IX)



(X)



(XI)

Attempts to prepare cinnoline-4-aldehyde, a possible source of 4-4′-pyridylcinnoline, failed because of our inability to hydrolyse (XI), prepared from 4-methylcinnoline and *p*-nitrosodimethylaniline. Similarly, we were unable to isolate a homogeneous product on oxidising 4-methylcinnoline with selenium dioxide, or hydrolysing 4-(3 : 3 : 3-trichloro-2-hydroxypropyl)cinnoline (Alford and Schofield, *J.*, 1953, 1811).

Experiments on the chelating ability of some of the new cinnolines will be described by Dr. H. Irving. The bacteriostatic properties of a number of the compounds are tabulated below. The figures represent the concentrations in mg./100 c.c. which prevented visible growth in Hedley Wright broth overnight at 37°. None of the compounds in the table had any action upon *P. berghei* or *T. equiperdum in vivo*. The first three compounds listed showed 1/20,000th, 1/10,000th, and 1/5,000th respectively of the spasmolytic action of atropine.

Cinnoline	Hæmolytic *Streptococcus*	*Staph. aureus*	*B. coli*	Approx. solubility (mg./100 c.c.)
4-*p*-Methoxyphenyl-3-2′-pyridyl-	0·3 [1]	>Sat. [2]	>Sat.	5
4-Phenyl-3-2′-pyridyl-	0·1 [1]	1·25 [1]	,,	5
4-*p*-Methoxyphenyl-3-2′-quinolyl-	1·25 [1]	>Sat.	>Sat.	2·5
6-Chloro-4-phenyl-3-2′-quinolyl-	5 [1]	,,	,,	5
4-3′-Pyridyl-	50	>50	>50	—
3-Methyl-4-3′-pyridyl-	>20	>20	>20	—

[1] The figures are approximate because of low solubility. [2] The sign > indicates lack of inhibition in saturated solution at pH 7·5, the figure representing the solubility.

We are indebted to Dr. F. Hawking of the National Institute of Medical Research, who arranged the bacteriostatic tests, and to Professor J. H. Burn, F.R.S., for the spasmolytic results. We are grateful to the Chemical Society, Imperial Chemical Industries Limited, and the Council of University College, Exeter, for financial support.

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