

## Mass Spectral and NMR Studies of some Cinnolines

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Fragmentation upon electron impact of cinnoline (1) occurs with the consecutive loss of  $N_2$  and  $C_2H_2$ . Fragmentation of 4,4'-dicinnolyl (2) and 4-styrylcinnoline (4) gives a series of ions leading to the "dibenzoladderene" ion (3) and the 1-phenylbenzodibutylene ion (5) respectively. Fragmentation of 4-styrylquinoline (6) also leads to 5, but of more interest is the loss of H· during ring rearrangement to give the highly resonance stabilized 3-styrylbenzocyclopentadieneonecimine ion (7) which then loses  $N$ ·. Fragmentation of various other substituted cinnolines follow different pathways: 4-methylcinnoline (8) apparently fragments through the "1,2-diazatropylium" ion (9); nitrocinnolines fragment with initial loss of the nitro substituent; aminocinnolines fragment with initial loss of  $N_2$ ; and 4-cinnolone (17) fragments with the consecutive loss of two HCN's and CO.

The NMR spectra of cinnolines generally show the following order of deshielding: 3-proton > 8-proton > 4-proton. The spectra of cinnolinium chloride (18) is interpreted in terms of protonation at *N*-1 of 1, and the spectrum of 17 is interpreted in terms of strong intermolecular hydrogen bonding.

As part of a systematic investigation into the carcinogenic activity of *p*-dimethylanilineazo dyes of various nitrogen heterocycles, all of the amino isomers of cinnoline (1) were desired. Except for the 3-amino- (2) and 4-amino- (3) isomers, preparation of the aminocinnolines require long, arduous routes (4,5). Therefore, alternative routes, which preferably would involve common intermediates, were sought. The most promising alternative for preparing the 5-amino- and 8-amino- isomers was through reduction of the respective nitro derivatives, prepared by nitration of 1 (6,7). The difficulty is that, except for 3-nitrocinnoline (2), reduction of nitrocinnolines does not give good yields of aminocinnolines (6,8). Even at that, the alternative appeared so attractive that 5-nitro- and 8-nitrocinnoline were prepared and reduced in an attempt to improve the yields of 5-amino- and 8-aminocinnoline.

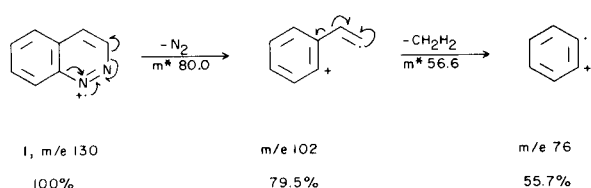
Catalytic hydrogenation of 5-nitro- and 8-nitrocinnoline to 5-amino- and 8-aminocinnoline was successful on a semi-micro scale; but of more immediate interest, were mass spectral and NMR studies of 3-amino-, 4-amino-, 5-amino- and 8-aminocinnoline and the various reaction intermediates leading to them.

## MASS SPECTRAL STUDY

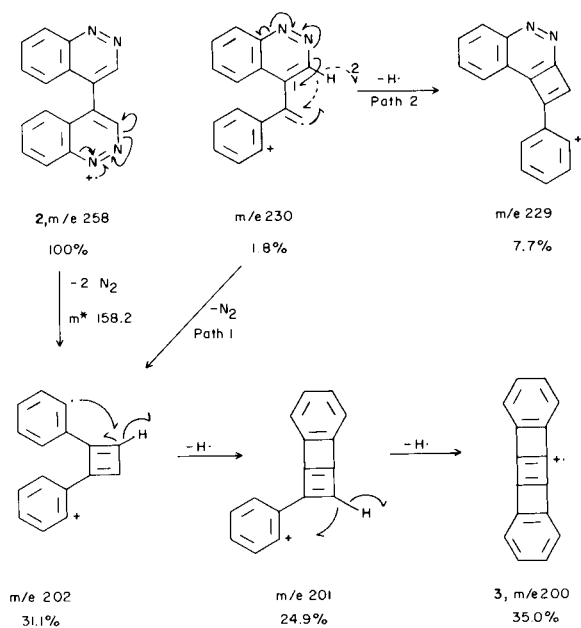
Although there have been several recent mass spectral studies on related nitrogen heterocycles such as quinolines (9), isoquinolines (9), quinazolines (10), naphthyridines (11), phenazines (12), 1,2,4-triazines (13), pyridazines (14), phthalazines (14), and benzo[*c*]cinnolines (15), no report has yet been made on the mass spectra of cinnolines.

Fragmentation of cinnoline (1), Scheme I, proceeds with the initial loss of  $N_2$  in correspondence with the initial fragmentation of 1,2,4-triazine (13), pyridazine (14), phthalazine (14), and benzo[*c*]cinnoline (15) which also contain adjacent nitrogen atoms. However, initial fragmentation of 1 contrasts with the initial fragmentation of phthalazine (14) in that no HCN is lost through an alternate pathway, thus indicating preference for the existence of 1 in the *-N=N-* form. In addition to the major peaks represented in Scheme I for 1, as well as for the other schemes to follow, other significant peaks, with relative abundances, are included in Table I. Representation of the major peaks is made on the basis of easily

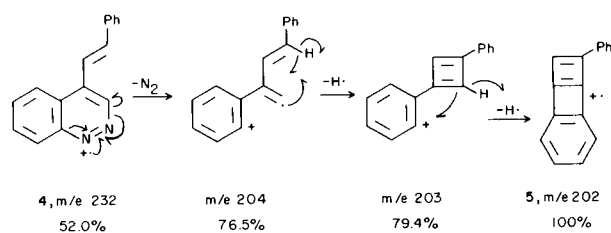
SCHEME I



SCHEME II



SCHEME III



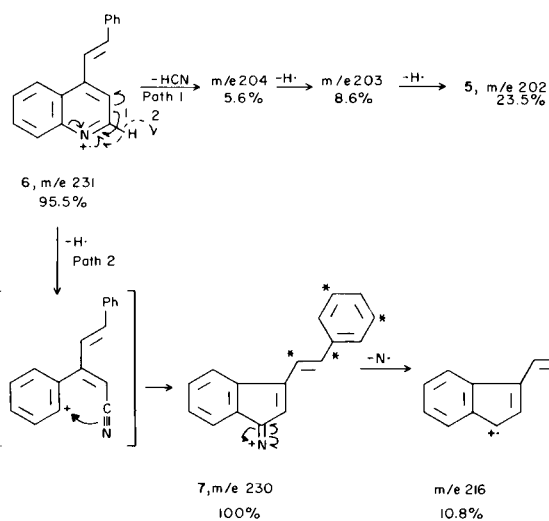
visualized electron shifts, as represented in the usual manner by a double-headed arrow for the shift of two electrons and by a "fishhook" arrow for the shift of one electron. The structures may not be strictly correct, or all inclusive, but they are used only as guides by which the various transitions may be visualized. "Meta-stable" peaks ( $m^*$ ), when observed, are recorded in the various schemes and are calculated values since the observed values could only be estimated to be in close proximity to the calculated values.

Fragmentation of 4,4'-dicinnolyl (2), Scheme II, pro-

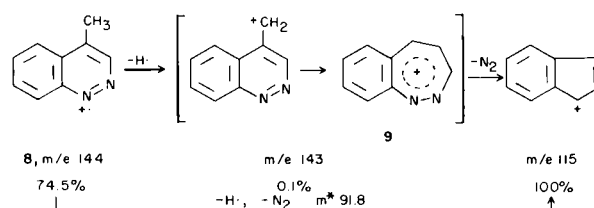
ceeds with the loss of two  $N_2$ 's as indicated by a "meta-stable" peak at  $m/e$  158.2. The transition probably occurs as two consecutive, fast reactions since a peak at  $m/e$  229 ( $P - N_2 - H\cdot$ ) is indicative of a  $m/e$  230 ( $-N_2$ ) intermediate. This is also substantiated by a  $m/e$  230 peak which is too large to be accountable only to the isotope peak of  $m/e$  229. Observation of a "meta-stable" peak for two consecutive, fast reactions has been made before (12, and references therein). Assignment of the "dibenzoladderene" ion (3) to the  $m/e$  200 peak is supported by a recent report (16) predicting un-ionized 3 to be stable. Additional verification of 3 as a very stable ion is provided by the appearance of peaks at  $m/e$  201<sup>2+</sup>,  $m/e$  202<sup>3+</sup>, and  $m/e$  200<sup>3+</sup>. Triply charged ions apparently are unusual and have only recently been reported (17) in the mass spectrum of triptycene. Finally, transitions of the type postulated for 2 are also observed in the mass spectrum of 4-styrylcinnoline (4).

Fragmentation of 4, Scheme III, proceeds in a manner reminiscent of 2. The most interesting feature of the spectrum is that the 1-phenylbenzodibutylene ion (5) at  $m/e$  202 is the base peak, thus indicating the facility of formation and stability of 5. Peaks were also observed at  $m/e$  204<sup>2+</sup> and at  $m/e$  203<sup>2+</sup> and  $m/e$  202<sup>3+</sup> in the spectrum of 4-styrylquinoline (6) (18), to follow.

SCHEME IV



SCHEME V



As a final confirmation of the transitions postulated for **2** and **4**, the mass spectrum of **6** was run with the expectation that its fragmentation, Scheme IV, would be analogous with the fragmentation of **4**. As it turned out, the ion series leading to **5** was observed, thus confirming the transitions previously postulated. But, more interesting was the loss of H $\cdot$  from the parent peak to give the base peak at  $m/e$  230. The  $m/e$  230 peak is visualized as arising from a ring rearrangement in which the loss of H $\cdot$  from the 2-position of the parent peak occurs simultaneously with a ring opening to give an acyclic nitrile, which then ring closes to the 3-styrylbenzocyclopentadieneoneimine ion (**7**). A similar transition has been postulated for phenazine (**12**). In retrospect, formation of **7** seems very much favored since formal resonance structures can be written to place the positive charge on the nitrogen and all carbons except those marked by asterisks, so as to give 14 principal resonance structures (66 if all the benzenoid contributions are considered). The structure of **7** is further supported by its fragmentation with the unusual loss of N $\cdot$  to  $m/e$  216. The loss of N $\cdot$  from **7** is reasonable from the point of view of electron shifts and parallels the loss of O $\cdot$  from aromatic *N*-oxides (**19**).

Fragmentation of 4-methylcinnoline (**8**), Scheme V, shows a "meta-stable" peak at  $m/e$  91.8 for the transition  $m/e$  144 to  $m/e$  115 (P-H $\cdot$ -N $_2$ ), but essentially no  $m/e$  143 (P-H $\cdot$ ) is observed; therefore, two consecutive, fast reactions must be occurring (*cf.* **2**). No attempt has been made to account for the structures by electron movement. Instead, analogy is made with the methyl-substituted quinolines (**9**), isoquinolines (**9**), naphthyridines (**11**), and phthalazines (**14**). Accordingly, the formation of  $m/e$  115 is postulated to go through the "1,2-diazatropylium" ion (**9**),  $m/e$  143, which then loses N $_2$ . The alternative, involving the initial loss of N $_2$ , seems less likely since the resulting  $m/e$  116 ion would be expected to be stable (*cf.* the postulated  $m/e$  117 ion from 4-methyl-1,5-naphthyridine (**11**)), and all of  $m/e$  116 is accountable to the isotope peak of  $m/e$  115. Such an unstable "1,2-diazatropylium" ion (**9**) contrasts with the stable "2,3-diazatropylium" ion observed in the fragmentation of 4-methylphthalazine (**14**).

Initial fragmentation of 3-nitrocinnoline (**10**), 5-nitrocinnoline (**11**) and 8-nitrocinnoline (**12**) (Table I) occurs in the usual manner with cleavage of the nitro group and loss of NO $_2$  $\cdot$  and to a lesser extent NO. Further fragmentation of the  $m/e$  145 ion (P-NO) of **10**, **11**, and **12** occurs with the consecutive loss of N $_2$  (or CO) and CO (or N $_2$ ) to give ions at  $m/e$  117 and  $m/e$  89. Further fragmentation of the  $m/e$  129 ion (P-NO $_2$  $\cdot$ ) of **10** occurs with the consecutive loss of two HCN's to give ions at  $m/e$  102 and  $m/e$  75 and contrasts with the further

fragmentation of **11** and **12** which occurs with the consecutive loss of N $_2$  and C $_2$ H $_2$  to give ions at  $m/e$  101 and  $m/e$  75. In addition, the  $m/e$  129 ion of **10** and **12** loses C $_4$ H $_3$  $\cdot$  to give an ion at  $m/e$  78. Finally, no *peri*-effects of the type observed with 5-nitroquinazoline (**10**) and 1-nitronaphthalene (**20**) were observed in **11**, but a *peri*-effect apparently accounts for the small parent and P-NO $_2$  peaks of **12**.

In contrast with the nitrocinnolines which initially lose the nitro substituent, fragmentation of 3-aminocinnoline (**13**), 4-amino-cinnoline (**14**), 5-aminocinnoline (**15**), and 8-aminocinnoline (**16**) (Table I) occurs with the initial loss of N $_2$  to give an  $m/e$  117 ion which then loses HCN and H $\cdot$  to give ions at  $m/e$  90 and  $m/e$  89, respectively. Except for **13**, the  $m/e$  117 ion also fragments with the consecutive loss of H $\cdot$  and HCN to give ions at  $m/e$  116 and  $m/e$  89. In addition, **14** fragments by an alternate pathway with an initial loss of HCN to give an  $m/e$  118 ion. Finally, the spectra of **15** and **16** are essentially identical.

The last mass spectrum to be considered is that of 4-cinnolone (**17**). Fragmentation of **17** (Table I) occurs with the consecutive loss of two HCN's, CO, and H $\cdot$  to give ions at  $m/e$  119,  $m/e$  92,  $m/e$  64, and  $m/e$  63. In addition, **17** fragments by an alternate pathway with an initial loss of H $\cdot$ , analogous with 4-quinazolone (**10**), to give an  $m/e$  145 ion. However, fragmentation of **17** contrasts with 4-quinazolone (**10**) and 1-phthalazone (**14**) both of which fragment with the initial loss of CO.

TABLE I

## Mass Spectra of Some Cinnolines (a)

1	131 (10.0), 130 (100), 103 (7.2), 102 (79.5), 76 (55.7), 75 (15.0), 74 (13.5), 63 (13.1), 52 (14.4), 51 (23.2), 50 (36.0), 39 (12.2). m* -- 32.9 (76 $\rightarrow$ 50).
2(b)	259 (19.8), 258 (100), 230 (1.8), 229 (7.7), 215 (2.7), 203 (8.5), 202 (31.1), 201 (24.9), 200 (35.0), 176 (8.8), 175 (6.7), 150 (5.8), 126 (5.9), 101 (11.7), 100.5 (2.7), 100 (12.4), 88 (16.1), 87 (7.8), 76 (7.3), 75 (18.6), 74 (10.9), 67.3 (0.1), 66.7 (0.1), 63 (7.8), 51 (11.3), 50 (9.7).
4	233 (12.7), 232 (52.0), 205 (13.7), 204 (76.5), 203 (79.4), 202 (100), 201 (17.6), 200 (12.7), 189 (5.6), 178 (5.6), 176 (8.4), 152 (5.6), 151 (7.4), 150 (7.7), 135 (13.3), 130 (9.8), 128 (5.3), 126 (5.3), 121 (5.3), 119 (6.0), 115 (14.7), 107 (7.7), 106 (11.2), 105 (12.3), 104 (5.6), 103 (6.7), 102 (24.6), 101.5 (4.2), 101 (25.3), 100 (22.1), 94 (5.6), 92 (6.3), 91 (11.2), 89 (7.6), 88 (13.0), 87 (7.0), 85

- (30.2), 79 (9.5), 78 (20.0), 77 (27.0), 76 (31.6), 75 (18.6), 74 (12.6), 67 (6.0), 65 (10.9), 64 (7.0), 63 (22.5), 62 (8.1), 52 (13.0), 51 (36.9), 50 (25.3).
- 6** 232 (17.8), 231 (95.5), 230 (100), 229 (6.9), 228 (7.4), 217 (2.0), 216 (10.8), 204 (5.6), 203 (8.6), 202 (23.5), 154 (9.8), 153 (7.6), 115.5 (4.9), 115 (6.4), 102 (7.6), 101.5 (4.5), 101 (19.3), 100 (6.1), 89 (10.6), 88 (6.4), 77 (7.4), 76 (8.1), 75 (6.7), 67.3 (0.1), 63 (6.2), 51 (9.9), 50 (8.2).
- 8** 145 (8.3), 144 (74.5), 143 (0.1), 116 (10.6), 115 (100), 89 (10.9), 75 (5.2), 63 (11.8), 62 (5.1), 57.5 (7.7), 51 (8.6), 50 (8.2).  
m\* - 68.9 (115 → 89).
- 10(c)** 176 (9.2, 10.3, 1.0), 175 (87.3, 100, 10.7), 145 **11**, (3.2, 24.4, 2.1), 129 (100, 48.0, 2.9), 117 (1.9, 5.6, **12(c)** 5.4), 102 (56.9, 7.2, 4.8), 101 (10.6, 34.0, 30.3), 90 (3.6, 15.9, 10.8), 89 (16.3, 38.0, 15.4), 78 (96.1, 0.8, 22.0), 75 (54.2, 84.4, 100), 63 (21.2, 35.2, 30.8), 51 (46.3, 21.2, 50.7), 50 (19.8, 14.0, 31.2).  
m\* (d) -95.1 (175 → 129; **10,11**), 80.7 (129 → 102; **10**), 79.1 (129 → 101; **11**), 55.7 (101 → 75; **11**), 55.2 (102 → 75; **10**), 47.2 (129 → 78; **10**), 44.6 (89 → 63; **11**), 33.4 (78 → 51; **10**), 25.5 (102 → 51; **10**).
- 13,14** 146 (10.5, 9.9, 10.1, 10.7), 145 (100, 100, 100, **15,16** 100), 118 (5.6, 9.2, 2.3, 2.7), 117 (40.6, 11.7, 10.4, 12.1), 116 (7.7, 12.5, 12.3, 14.5), 115 (1.5 8.7, 1.4, 1.0), 91 (3.7, 11.2, 8.5, 9.4), 90 (32.0, 39.9, 25.6, 25.6), 89 (34.2, 35.3, 26.6, 25.4), 65 (2.3, 7.6, 4.6, 5.0), 64 (4.6, 9.4, 6.7, 6.4), 63 (12.1, 11.7, 10.2, 10.8), 62 (5.6, 5.0, 4.6, 4.7), 58.5 (10.6, 6.1, 5.8, 6.2), 52 (3.9, 6.5, 4.8, 4.7), 51 (6.0, 8.2, 3.5, 3.4), 50 (7.0, 6.3, 3.2, 2.8).  
m\* (d) - 94.4 (145 → 117; **15,16**), 88.0 (90 → 89; **13, 15, 16**), 69.2 (117 → 90; **13, 15, 16**), 68.3 (116 → 89; **16**).
- 17** 147 (10.5), 146 (100), 145 (20.1), 119 (41.2), 118 (6.0), 92 (36.1), 91 (14.1), 90 (15.6), 89 (8.2), 65 (6.4), 64 (19.9), 63 (19.9), 62 (7.2), 52 (6.6), 51 (4.5), 50 (6.4).

(a) In general, only ions above m/e 50 with relative abundances (in parentheses) above 5% are recorded. The ions in italics are discussed in the text. (b) The direct inlet was used. (c) A strip recorder was used in place of the usual "visicorder". (d) The "meta-stable" ions are presented as: ion (transition; compound(s) observed).

#### NMR STUDY

The NMR spectra of cinnoline (**1**) (21,22), cinnolinium

salts (23,24), various substituted cinnolines (21, 25), and 4-cinnolone (17) (26,27) have been reported. In the current work an attempt has been made to make as complete an interpretation as possible of the NMR spectra of various substituted cinnolines (including the spectra of some cinnolines already reported) by using reasonable, first-order correlations. The working hypothesis for interpretation was: (1) that the 3-proton (adjacent to ring *N*-2) would be most deshielded (farthest downfield); (2) that the 8-proton (*peri* to ring *N*-1) would be next most deshielded; and (3) that the 4-proton (influenced by a resonance effect from ring *N*-1 and by a proximity effect from ring *N*-2) would be next most deshielded. Other useful correlations are distinction between the 6 cps coupling constant of the 3- and 4-protons in the nitrogen ring and the 8 cps *ortho* coupling constant in the carbocyclic ring and the 1 cps inter-ring coupling constant of the 4- and 8- protons (22,24). All NMR spectra are recorded in Table II, but only those peaks of special interest are discussed.

As would be expected, the spectrum of **1** fits the working hypothesis very well. The 3-proton gives a doublet ( $J = 6$ ) at  $\delta$  9.10 and is coupled with the doublet ( $J = 6$ ) of the 4-proton at  $\delta$  7.73. The 8-proton couples with the 7-proton so as to give a doublet ( $J = 8$ ) at  $\delta$  8.30. Each branch of the doublet is further split into an octet as a result of long-range *meta* coupling with the 6-proton, *para* coupling with the 5-proton, and inter-ring coupling ( $J = 1$ ) with the 4-proton (as seen in the further splitting of the doublet of the 4-proton).

The spectrum of cinnolinium chloride (**18**) (cinnoline hydrochloride) corresponds with cinnolinium perchlorate (23) in that both the 3- and 4-protons are more deshielded than in **1**. Direct comparison has not been attempted, but the conclusion reached for protonation on *N*-2 of **1** in cinnolinium perchlorate contrasts with the conclusion reached for the point of protonation in **18**. The 3-proton of **18** gives a doublet ( $J = 6$ ) at  $\delta$  9.27 and is coupled with the doublet ( $J = 6$ ) of the 4-proton at  $\delta$  8.80. Interpretation in terms of protonation on *N*-1 of **1** is based on the large increase in deshielding of the 4-proton and the shielding of the 8-proton of **18** relative to **1**. Protonation of *N*-1 of **1** would be expected to deshield the 4-proton by electron withdrawal through resonance and to shield the 8-proton through a space effect; whereas, protonation of *N*-2 of **1** would be expected to shift the 3-proton more than the 4-proton and to have no direct effect on the 8-proton.

The spectrum of 4-methylcinnoline (**8**) shows the shielding influence of an electron releasing group at the 4-position on the 3-proton with the chemical shift of the 3-proton moving from  $\delta$  9.10 in **1** to  $\delta$  8.96 in **8**. The 3-proton and the 4-methyl group at  $\delta$  2.53 split each other

TABLE II  
NMR Spectra of Some Cinnolines (a)

	3-	4-	5-	6-	7-	8-	Other Protons
1 (b)	9.10 (c) d (6)	7.73 dd (6,1)				8.30 (c) d (8)	5-, 6-, 7- <i>ca.</i> 7.57 m
18 (d)	9.27 d (6)	8.80 d (6)					5-, 6-, 7-, 8- <i>ca.</i> 8.02 m NH <sup>+</sup> (e)
8 (f)	8.96 (g) d (0.5)					8.30 m	5-, 6-, 7- <i>ca.</i> 7.68 4-CH <sub>3</sub> 2.53 d (0.5) (g)
19 (h)	9.85 s		8.50 m			8.73 m	6-, 7- <i>ca.</i> 7.93 m 4-CO <sub>2</sub> H (i)
4 (f)	9.30 s		7.97 m			8.32 m	9 H's <i>ca.</i> 7.35 m
10 (h)		9.23 d (1)	8.30 m			8.60 m	6-, 7- <i>ca.</i> 8.07 m
11 (f)	9.40 d (6)	8.80 dd (6,1)		8.83 d (8)	7.90 t (8)	8.62 dd (8,1)	
12 (f)	9.40 d (6)		7.20 d (5)				4-, 6-, 7- <i>ca.</i> 7.95 m
13 (h)		7.00 s				8.17 d (8)	5-, 6-, 7- <i>ca.</i> 7.53 m 3-NH <sub>2</sub> (j)
14 (h)	8.73 s						5-, 6- <i>ca.</i> 7.65 m 7-, 8- <i>ca.</i> 8.17 m 4-NH <sub>2</sub> 7.37 s
15 (h)	9.13 d (6)	8.25 d (6)		6.82 q (4)	7.52 d (4)	7.52 d (4)	5-NH <sub>2</sub> (k)
16 (f)	9.03 d (6)		7.55 d (6)		7.30 d (7)		4-, 6- <i>ca.</i> 6.85 m 8-NH <sub>2</sub> 5.38 s
17 (h)	7.65		7.97 (l) d (8)				6-, 7-, 8- <i>ca.</i> 7.40 m NH 13.40 s

(a) Chemical shifts ( $\delta$ ) are recorded as ppm downfield from TMS with the coupling constant(s) (J in cps) in parentheses. The abbreviations used are: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, and m = multiplet. All spectra gave satisfactory integration values for the indicated number of protons. The chemical shifts in italics are discussed in the text. (b) Ten percent carbon tetrachloride. (c) The literature values are 9.22 (carbon tetrachloride 21) and 9.28 (deuteriochloroform, 22) for the 3-proton and 8.53 (deuteriochloroform, 22) for the 8-proton. (d) Ten percent deuterium oxide. The water standard was converted to the TMS standard by adding  $\delta$  4.62. (e) This proton was not seen because of exchange with water in the solvent. (f) Ten percent deuteriochloroform. (g) The literature values are 8.95 (carbon tetrachloride, 21) and 9.35 (DMSO, 26) for the 3-proton and 2.51 (carbon tetrachloride, 21) for the methyl protons. (h) Ten percent DMSO-d<sub>6</sub>. (i) The acid proton was not seen, but the usual water peak of DMSO-d<sub>6</sub> shifted from  $\delta$  3.25 to  $\delta$  5.66. (j) Neither the amine protons nor the usual water peak of DMSO-d<sub>6</sub> was seen. (k) The amine protons were not seen, but the usual water peak of DMSO-d<sub>6</sub> shifted from  $\delta$  3.25 to  $\delta$  4.37. (l) The literature values in DMSO are 7.83 (26) and 7.88 (27) for the 3-proton and 8.11 (26) and 8.17 (27) for the 5-proton.

TABLE III

## Substituent Effects of Some Cinnolines (a)

	$\Delta 3$	$\Delta 4$	$\Delta 5$ (b)	$\Delta 6$ (b)	$\Delta 7$ (b)	$\Delta 8$
<b>18</b>	0.17	1.07				
<b>8</b>	-0.14					
<b>19</b>	0.48		0.93			0.43
<b>4</b>	0.20		0.40			0.02
<b>10</b>		1.50	0.73			0.30
<b>11</b>	0.30	1.07		1.26	0.33	0.32
<b>12</b>	0.30		-0.37 (c)			
<b>13</b>		-0.73				-0.13
<b>14</b>	-0.37					
<b>15</b>	0.03 (c)	0.52 (c)		-0.75	-0.05	-0.05
<b>16</b>	-0.07		-0.02		-0.27	
<b>17</b>	-1.45		+0.40			

(a) Substituent effects are recorded as changes in chemical shifts ( $\Delta \delta$ ) so that  $-\Delta \delta$  means shielding and  $+\Delta \delta$  means deshielding. (b) The change in the chemical shift is based on the change from the 5-, 6-, and 7- proton multiplet at *ca.* 7.57 in **1**. (c) Apparent anomaly.

into doublets ( $J = 0.5$ ), and the 8-proton gives a multiplet at  $\delta$  8.30.

The spectra of 4-carboxy-(**19**) and 4-styryl- (**4**) cinnoline were similar in nature with an electron withdrawing group in the 4-position deshielding (relative to **1**) both the 3- and 5-protons. The carboxy group was a stronger electron withdrawing group than the styryl group; and accordingly, the 3-proton at  $\delta$  9.58 and the 5-proton at  $\delta$  8.50 in **19** were farther downfield than were the 3-proton at  $\delta$  9.30 and the 5-proton at  $\delta$  7.97 in **4**. The 8-proton gives a multiplet at  $\delta$  8.73 for **19** and at  $\delta$  8.32 for **4**. The 8-proton was assigned the chemical shift next farthest downfield from the 3-proton as a matter of form, and it may be that assignment of the 5- and 8-protons should be reversed for either one or both compounds.

The spectra of 3-nitrocinnoline (**10**), 5-nitrocinnoline (**11**) and 8-nitrocinnoline (**12**) were similar in that the electron withdrawing nitro group tends to pull all chemical shifts downfield relative to **1**. The spectrum of **10** shows the 4-proton shifted downfield to  $\delta$  9.23 by the adjacent nitro group and split into a doublet ( $J = 1$ ) by the 8-proton. The 5- and 8- protons appear as multiplets at  $\delta$  8.30 and  $\delta$  8.60 respectively. The spectrum of **11** shows the 3-proton split into a doublet ( $J = 6$ ) at  $\delta$  9.40 and coupled with the doublet ( $J = 6$ ) of the 4-proton at  $\delta$  8.80. The doublet of the 4-proton is split into a second pair of doublets ( $J = 1$ ) by the doublet of doublets ( $J_{78} = 8, J_{48} = 1$ )

of the 8-proton at  $\delta$  8.62. The 6-proton at  $\delta$  8.83 is split into a doublet ( $J = 8$ ) by the 7-proton, and the 7-proton is split equivalently by the 6- and 8- protons and appears as a triplet ( $J_{67} = J_{78} = 8$ ) at  $\delta$  7.90. The spectrum of **12** shows the 3-proton as a doublet ( $J = 6$ ) at  $\delta$  9.40. Another doublet ( $J = 5$ ) at  $\delta$  7.20 had been tentatively assigned to the 5-proton because it is not (a) the 4-proton which should be coupled with the 3-proton, (b) the 7-proton which should be downfield, or (c) the 6-proton which should be a multiplet. Still, the assignment is tenuous, principally because of the small *ortho* coupling constant.

The spectra of 3-aminocinnoline (**13**), 4-aminocinnoline (**14**), 5-aminocinnoline (**15**) and 8-aminocinnoline (**16**) were similar in that the electron donating amine group tends to push all chemical shifts upfield relative to **1**. The spectrum of **13** shows the 4-proton as a singlet at  $\delta$  7.00 and the 8-proton as a doublet ( $J = 8$ ) at  $\delta$  8.17. The spectrum of **14** shows the 3-proton as a singlet at  $\delta$  8.73 and the amine protons as a singlet at  $\delta$  7.37. The spectrum of **15** shows the 3- and 4- protons as doublets ( $J = 6$ ) at  $\delta$  9.13 and  $\delta$  8.25, respectively. Assignment of the 6-, 7-, and 8- protons is made in terms of a "deceptively simple" ABX pattern (28) in which  $\delta 7 = \delta 8$  and  $J_{68} \sim 0$ . Accordingly, the 7- and 8-protons appear as a doublet ( $J = 4$ ) at  $\delta$  7.52, and the 6-proton appears as a quartet ( $J = 4$ ) at  $\delta$  6.82. An alternate, first-order interpretation in which the doublet at  $\delta$  7.52 is assigned to "accidentally

equivalent" 6- and 8- protons and the quartet at  $\delta$  6.82 is assigned to the 7-proton seems less likely because (a) the *ortho* coupling constants should be larger and (b) the 6-proton adjacent to the amine group, should be farthest upfield. The spectrum of **16** shows a doublet ( $J = 6$ ) for the 3-proton at  $\delta$  9.03, a doublet ( $J = 6$ ) for the 5-proton at  $\delta$  7.55, a doublet ( $J = 7$ ) for the 7-proton at  $\delta$  7.30, and a singlet for the amine protons at  $\delta$  5.38.

The spectrum of 4-cinnolone (**17**) has been recorded before (26,27); and except for small differences in chemical shifts, the spectrum reported here is identical with the best reported spectrum (27). However, in contrast with the report (27) that no NH proton is observed because of proton exchange with water in DMSO, the NH proton has been observed as a singlet at  $\delta$  13.40. The presence of the very much deshielded NH proton is taken as evidence for very strong intermolecular hydrogen bonding between the NH proton and the carbonyl group of a second molecule of **17**. In support of this conclusion is the infrared spectrum of **17** which shows the NH stretch as a series of diffuse bands (reminiscent of the OH stretch of carboxylic acids) at  $3240\text{ cm}^{-1}$ ,  $3090\text{ cm}^{-1}$  and  $2920\text{ cm}^{-1}$  and the carbonyl stretch as a broad, diffuse band at  $1570\text{ cm}^{-1}$ . The appearance of the carbonyl stretch at such a low frequency indicates a great deal of single bond CO character and substantiates the strong intermolecular hydrogen bonding between CO and NH.

The substituent effects of cinnolines relative to **1** are tabulated in Table III for convenience. The chemical shifts generally decrease for electron releasing substituents and increase for electron withdrawing substituents, but anomalies occur with the 5-proton of **12** and the 3- and 4- protons of **15**.

## EXPERIMENTAL

Melting points were determined with a Fisher-Johns block and are uncorrected. Boiling points are also uncorrected. Infrared spectra were determined with a Beckman IR-8 spectrometer and are recorded in  $\text{cm}^{-1}$  as absorption maxima of strong (s) and medium (m) intensity. Nuclear magnetic resonance spectra were determined with a Varian HA-60 spectrometer. Mass spectra were determined with a Hitachi Perkin-Elmer RMU-6E mass spectrometer with an ionizing potential of 70 eV and an inlet temperature (up to  $230^\circ$ ) sufficient to obtain enough vapor pressure ( $2.5 \cdot 9 \times 10^{-7}\text{ mm.}$ ) for a spectrum.

### Preparation of Cinnoline (**1**) and 4,4'-Dicinnolyl (**2**).

1. 2-(*o*-Aminophenyl)propene was prepared from methyl anthranilate by the method of Jacobs, *et al.*, (29) as a yellow oil, b.p.  $75^\circ$  (2.5 mm.) [*lit.* (29) b.p.  $83.5\text{--}87.5^\circ$  (1.2 mm.)].

2. 4-Methylcinnoline (**8**) was prepared by the method of Jacobs, *et al.*, (29) and Atkinson and Simpson (30) with the following exceptions: the diazotized amine was not diluted, the reaction was considered complete after giving a negative  $\beta$ -naphthol test (*ca.* 18 hours), and a simple benzene extraction was made

after basification. Recrystallization from hexane gave **8** as orange needles, m.p.  $73\text{--}74^\circ$  [*lit.* (29) m.p.  $72.5\text{--}74^\circ$ ].

3. 4-Styrylcinnoline (**4**) was prepared by the method of Jacobs, *et al.*, (29) and Morley (6) as yellow needles, m.p.  $123\text{--}124^\circ$  (methanol) [*lit.* (29) m.p.  $113\text{--}118^\circ$ ; *lit.* (6) m.p.  $120\text{--}123^\circ$ ], infrared (potassium bromide)  $960\text{ s cm}^{-1}$  (*trans* alkene).

*Anal.* Calcd. for  $\text{C}_{16}\text{H}_{12}\text{N}_2$ : C, 82.75; H, 5.21; N, 12.07. Found: C, 82.71; H, 5.02; N, 12.20.

4. 4-Carboxycinnoline (**19**) was prepared by the method of Jacobs, *et al.*, (29) and Morley (6) except for the adaptation of Campbell *et al.*, (31) in using a 1:1 mixture of acetone:water as the solvent to give **19** as tan flakes m.p.  $212^\circ$  (dec.) [*lit.* (32) m.p.  $196^\circ$  (dec.)].

5. Cinnoline (**1**) and 4,4'-dicinnolyl (**2**) were prepared by the method of Jacobs, *et al.*, (29) and Morley (6) except extraction with ether left **2** as a brown, ether insoluble solid, m.p.  $235\text{--}239^\circ$  [*lit.* (6) m.p.  $237\text{--}238^\circ$ ].

Ether soluble **1** gave a yellow oil, b.p.  $103\text{--}107^\circ$  (1.2 mm.) [*lit.* (6) b.p.  $114^\circ$  (0.35 mm.)], infrared (neat) - same as *lit.* (33), which solidified on standing to give a yellow solid, m.p.  $33\text{--}36^\circ$  [*lit.* (29) m.p.  $37\text{--}38^\circ$ ; *lit.* (6) m.p.  $40\text{--}41^\circ$ ].

Cinnolinium chloride (**18**) was precipitated from an ethereal solution of **1** with ethereal hydrogen chloride prepared in the manner described by Matuszak and Matuszak (34).

### Preparation of 5-Aminocinnoline (**15**) and 8-Aminocinnoline (**16**).

1. Nitration of cinnoline (**1**) followed the method of Morley (6) and Moodie, *et al.*, (7) to give 8-nitrocinnoline (**12**), m.p.  $132\text{--}134^\circ$  [*lit.* (6) m.p.  $133\text{--}134^\circ$ ], and crude 5-nitrocinnoline (**11**) which was chromatographed on alumina (benzene eluent) to give pure **11**, m.p.  $150^\circ$  [*lit.* (6) m.p.  $151\text{--}152^\circ$ ].

#### 2. Hydrogenation of 5-Nitrocinnoline (**11**).

A mixture of 0.25 g. (0.0015 mole), **11**, 25 ml. absolute ethanol, and 0.05 g. 10% palladium on charcoal was hydrogenated in a Burgess-Parr apparatus at 15 p.s.i. for 30 minutes. The catalyst was filtered-off, the ethanol was evaporated, and the resulting residue was extracted with benzene and placed on an alumina column. Elution with ether gave a first fraction (0.1 g.) of a mixture (by NMR) of **11** and an unidentified product and a second fraction (0.05 g.) of 5-aminocinnoline (**15**), m.p.  $155\text{--}158^\circ$  [*lit.* (4) m.p.  $160\text{--}161^\circ$ ].

#### 3. Hydrogenation of 8-Nitrocinnoline (**12**).

A mixture of 0.5 g. (0.003 mole), **12**, 50 ml. absolute ethanol, and 0.1 g. 10% palladium on charcoal was hydrogenated as above. The residue was extracted with benzene and chromatographed on alumina (benzene eluent) to give 0.18 g. of yellow solid, m.p.  $70^\circ$ , which was recrystallized from 1:1 benzene:hexane to give a first crop (0.08 g.) of yellow solid, m.p.  $72^\circ$ , and a second crop (0.04 g.) of yellow solid, m.p.  $92^\circ$ . The NMR spectra of both crops were identical; therefore, it was concluded that both crops were 8-aminocinnoline (**16**) [*lit.* (5) m.p.  $89\text{--}92^\circ$ ].

### Preparation of 3-Nitrocinnoline (**10**) and 3-Aminocinnoline (**13**).

These compounds were prepared by the method of Baumgarten, *et al.*, (2) to give **10** m.p.  $195\text{--}202^\circ$  [*lit.* (2) m.p.  $204\text{--}205^\circ$ ], and **13**, m.p.  $165\text{--}166^\circ$  [*lit.* (2) m.p.  $165\text{--}166^\circ$ ]. Great difficulty was encountered both in preparing nitroformaldehyde *o*-formylphenylhydrazones from the ethylene acetal of *o*-nitrobenzaldehyde and then in converting it to **10**.

### Preparation of 4-Aminocinnoline (**14**).

1. Preparation of 4-cinnolone (**17**) was patterned after the

adaptation of Keneford and Simpson (35) on the method of Leonard and Boyd (36). A stirred solution of 27 g. (0.2 mole) of *o*-aminoacetophenone (Eastman Practical) in 250 ml. of concentrated hydrochloric acid was cooled to 0° in a dry ice-acetone bath and held there for 15 minutes during the dropwise addition of 40 ml. of 5 *M* sodium nitrite solution (0.2 mole). After an additional 30 minutes of cooling, the solution was allowed to warm to room temperature during 1 hour and was then heated on an oil bath at 55° until it gave a negative  $\beta$ -naphthol test (ca. 24 hours). The mixture, which contained a heavy suspension, was cooled in an ice bath and filtered to give a yellow-orange solid which, when neutralized with a 10% sodium carbonate solution and dried, gave 20.0 g. of **17** as tan flakes, m.p. 235-236°. Recrystallization of **17** from ethanol gave pale tan flakes, m.p. 241-242° [*lit.* (36) m.p. 236°], infrared (potassium bromide) 3240 m, 3090 m, and 2920 m cm<sup>-1</sup> (NH) and 1570 s cm<sup>-1</sup> (C=O) [*lit.* (37) in potassium bromide 3222 m and 3190 s cm<sup>-1</sup> (NH) and 1610 s cm<sup>-1</sup> (C=O)].

An additional 1.7 g. of **17** was isolated by evaporating the orange acid filtrate to dryness and treating as before to give a total yield of 21.7 g. (74%) of **17**.

2. Preparation of 4-aminocinnoline (**14**) from 4-cinnolone (**17**), with 4-chloro- and 4-phenoxy-cinnoline prepared as intermediates by the method of Keneford and Simpson (35), followed the method of Keneford, *et al.*, (3) with the adaptations used by Barber, *et al.*, (38) in preparing 6-nitro-4-aminocinnoline to give **14** as tan flakes m.p. 217° (ethanol) [*lit.* (3) m.p. 212-213°].

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Received July 2, 1968

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