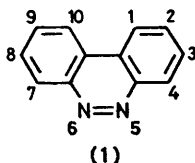


## Benzo[*c*]cinnolines. Part 3.<sup>1</sup> Halogenation Studies. N.M.R. Spectroscopic Study of Benzo[*c*]cinnoline and its Monobromo-derivatives

By John W. Barton and David J. Lapham, School of Chemistry, The University, Bristol BS8 1TS

Electrophilic bromination and chlorination of benzo[*c*]cinnoline in sulphuric acid give mixtures of 1- and 4-halogenobenzo[*c*]cinnolines, then 1,4-dihalogenobenzo[*c*]cinnolines. The <sup>1</sup>H n.m.r. spectra of the monobromobenzo[*c*]cinnolines have been analysed and previous assignments made for the parent benzo[*c*]cinnoline are corrected.

ELECTROPHILIC substitution of benzo[*c*]cinnoline (1) has been well investigated only in the case of nitration in sulphuric acid. Some early studies gave conflicting results,<sup>2</sup> but it is now established that at temperatures



in the range 0–100 °C, 1- and 4-nitrobenzo[*c*]cinnolines are formed in the ratio of ~4 : 1.<sup>3-5</sup> This agrees well with molecular-orbital theory which predicts an order of reactivity of 1 > 4 > 3 > 2 for a mono-protonated

minate benzo[*c*]cinnoline under less acidic conditions, with bromine-silver acetate in acetic acid, gave only starting material.

The only previous report on chlorination of benzo[*c*]cinnoline is of the formation of the octachloro-derivative with an excess of chlorine in the presence of aluminium chloride,<sup>8</sup> no reaction conditions being given. Chlorination in sulphuric acid under the same reaction conditions which were used for the bromination gave very similar results, except that here the ratio of the 1- to the 4-chloro-derivative was *ca.* 3.3 : 1. The isomer ratio in both reactions varied somewhat between individual runs, probably due to the heterogeneous nature of the reaction mixtures. Thus these halogenations parallel the nitration of benzo[*c*]cinnoline in sulphuric acid, the

<sup>1</sup>H N.m.r. spectra of halogenobenzo[*c*]cinnolines

Compound	Chemical shifts (τ)							Coupling constants (Hz)					
	H <sup>1,10</sup>		H <sup>4,7</sup>		H <sup>2,3,8,9</sup>			J <sub>1,2</sub>	J <sub>1,3</sub>	J <sub>2,3</sub>	J <sub>2,4</sub>	J <sub>3,4</sub>	
	H <sup>1</sup>	H <sup>2</sup>	H <sup>3</sup>	H <sup>4</sup>	H <sup>7</sup>	H <sup>8,9</sup>	H <sup>10</sup>						
Benzo[ <i>c</i> ]cinnoline	1.57m		1.36m		2.18m								
1-Bromo-		1.85dd	2.32t	1.28dd	1.25m	2.09m	0.11m						
2-Bromo-	1.37d		2.06dd	1.57dd	1.32m	2.12m	1.53m		2.25				
3-Bromo-	1.64d	2.10dd		1.19d	1.32m	2.12m	1.55m	7.13			2.25		
4-Bromo-	1.57dd	2.34t	1.91dd		1.31m	2.11m	1.53m	7.50	1.88	7.50			
1,4-Dibromo-		2.07m	2.07m		1.24m	2.07m	0.08m						
1-Chloro-		2.12dd	2.27t	1.36dd	1.34m	2.18m	0.37m			7.50	2.25	7.50	
2-Chloro-	1.46d		2.19m	1.28d	1.21m	2.19m	1.53m		3.00				8.63
3-Chloro-	1.65d	2.16m		1.34d	1.29m	2.16m	1.57m	8.75			2.63		
4-Chloro-	1.59dd	2.18t	2.12m		1.28m	2.12m	1.55m	9.00	2.25	9.00			
1,4-Dichloro-		1.98m	1.98m		0.97m	1.98m	0.11m						

d = Doublet; dd = doublet of doublets; t = triplet; m = multiplet.

substrate.<sup>4</sup> In an attempt to compare electrophilic halogenation with the nitration reaction Corbett and Holt<sup>6</sup> found that bromine and iodine form molecular complexes with benzo[*c*]cinnoline in several solvents and only with bromine-silver sulphate in sulphuric acid was substitution achieved, giving rise to a mixture of a monobromobenzo[*c*]cinnoline, m.p. 199 °C, and a dibromobenzo[*c*]cinnoline, m.p. 193 °C. The monobromo-compound was identified as 1-bromobenzo[*c*]cinnoline and the dibromo-compound as 1,4- or 1,7-dibromobenzo[*c*]cinnoline; however, the former was later shown to be different from authentic 1-bromobenzo[*c*]cinnoline, m.p. 121–122 °C.<sup>7</sup>

Reinvestigation of the bromination reaction using a similar procedure has shown that at room temperature both 1- and 4-bromobenzo[*c*]cinnoline are formed in the ratio *ca.* 2.3 : 1. The dibromo-compound, formed in lesser amount, is shown by n.m.r. spectroscopy (below) to be 1,4-dibromobenzo[*c*]cinnoline. Attempts to bro-

lower 1- : 4-isomer ratios reflecting the different steric demands of the attacking electrophiles.

<sup>1</sup>H N.M.R. Spectroscopy of Benzo[*c*]cinnoline and its Halogeno-derivatives.—The 100 MHz <sup>1</sup>H n.m.r. spectra of benzo[*c*]cinnoline and its monobromo-derivatives have been measured in deuteriochloroform solution; chemical shifts from internal tetramethylsilane, assignments, and certain coupling constants are listed in the Table. The spectrum of the parent compound exhibits three multiplets at τ 1.36, 1.57, and 2.18 in the proton ratio 2 : 2 : 4. In the spectrum of 4-bromobenzo[*c*]cinnoline one proton of the lowest-field pair is missing, thus in benzo[*c*]cinnoline the pair at τ 1.36 may be assigned as H<sup>4,7</sup> and that at τ 1.57 as H<sup>1,10</sup>, the latter value showing close correspondence to that for the angular (H<sup>4,5</sup>) protons in phenanthrene.<sup>9</sup> These assignments for benzo[*c*]cinnoline have been assumed by some workers but are contrary to those previously made by Martin *et al.*<sup>10</sup> and by Kooti and Nixon.<sup>11</sup> In 4-bromo-

benzo[*c*]cinnoline the bromine atom exerts the usual effects resulting in the deshielding of H<sup>3</sup>, shielding of H<sup>2</sup>, and slight shielding of H<sup>1</sup>, thus in an expanded spectrum all the protons become separately assignable with the exception of H<sup>8</sup> and H<sup>9</sup>. The spectrum of 1-bromobenzo[*c*]cinnoline complements that of the 4-isomer as regards the assignments made for the parent compound, but in this case the proximity of the bromine atom to H<sup>10</sup> causes the latter to resonate at very low field ( $\tau$  0.11), the effect being similar to that observed for the corresponding proton (H<sup>6</sup>) in 4-bromophenanthrene.<sup>12</sup> The data concerning the monobromobenzo[*c*]cinnolines enables the structure of the dibromo-derivative from the bromination reaction to be assigned as 1,4-dibromobenzo[*c*]cinnoline. The spectrum of this compound shows three multiplets at  $\tau$  0.08, 1.24, and 2.07 having the proton ratio 1 : 1 : 4, *i.e.* as compared with benzo[*c*]cinnoline each of the low-field pairs has lost one proton, the compound must therefore be the 1,4- or the 1,7-isomer. The proton at lowest field is H<sup>10</sup>, showing the characteristic down-field shift due to the bromine atom at position 1. The other bromine atom must occupy the 4- rather than the 7-position, otherwise the single proton resonances would show as doublets rather than as multiplets. As the bromine atoms are *para* to each other they exert little or no effect on the chemical shifts of H<sup>2</sup> and H<sup>3</sup>, thus these make up the 4 H multiplet with H<sup>8</sup> and H<sup>9</sup>.

Apart from the smaller deshielding effect of chlorine compared with bromine the spectra of the chlorobenzo[*c*]cinnolines (see Table) were found to be closely similar to those of the corresponding bromo-derivatives.

#### EXPERIMENTAL

The n.m.r. spectra were recorded on a JEOL PS100 spectrometer.

**1-Bromobenzo[*c*]cinnoline.**—A solution of 1-aminobenzo[*c*]cinnoline<sup>5</sup> (0.5 g) in 47% hydrobromic acid (2 ml) and water (5 ml) was diazotised at 0–5 °C with sodium nitrite (0.175 g) in water (1 ml). The resulting yellow suspension was added with stirring to a solution of cuprous bromide (2.5 g) in 47% hydrobromic acid (5 ml) at 0 °C. After 10 min the reaction mixture was heated to 80–90 °C on a water-bath and then cooled, diluted, and filtered. The solids were extracted with benzene, using dilute aqueous ammonia to dissolve the precipitated copper salts. Evaporation of the dried benzene extracts and sublimation of the residue at 140–150 °C (bath)/15 Torr gave 1-bromobenzo[*c*]cinnoline (0.5 g, 75%), pale yellow needles, m.p. 121–122 °C, from methanol (Found: C, 55.3; H, 2.7; Br, 30.9; N, 10.7. C<sub>12</sub>H<sub>7</sub>BrN<sub>2</sub> requires C, 55.6; H, 2.7; Br, 30.9; N, 10.8%). 2-Bromobenzo[*c*]cinnoline<sup>5</sup> and 4-bromobenzo[*c*]cinnoline<sup>1</sup> were prepared by stannous chloride reduction of their 6-oxides as previously described.

**4-Bromo-2,2'-dinitrobiphenyl.**—Copper bronze (78 g) was added in portions to a stirred solution of 2-bromonitrobenzene (87 g) and 2,5-dibromonitrobenzene (60.75 g) in boiling *NN*-dimethylformamide (280 ml) during 20 min. After a further 20 min the reaction mixture was cooled to 70 °C and filtered, using acetone to extract the solid residue. The filtrate and extracts were poured into water and the resulting oily precipitate crystallised first from acetic acid

and then from ethanol in fractions, giving 4-bromo-2,2'-dinitrobiphenyl (28.6 g, 41%), m.p. 141–145 °C. After further crystallisation it formed pale yellow prisms, m.p. 146–147 °C (lit.,<sup>13</sup> m.p. 120–124 °C) (Found: C, 44.7; H, 2.25; Br, 25.3; N, 8.7. C<sub>12</sub>H<sub>7</sub>N<sub>2</sub>BrO<sub>4</sub> requires C, 44.6; H, 2.2; Br, 24.8; N, 8.7%). Further crops gave 2,2'-dinitrobiphenyl and mixed material.

**3-Bromobenzo[*c*]cinnoline.**—4-Bromo-2,2'-dinitrobiphenyl was reduced, using hydrazine hydrate and Raney nickel, by the method of Moore and Furst,<sup>14</sup> giving 3-bromobenzo[*c*]cinnoline in 81% yield. It formed pale yellow needles, m.p. 194–195 °C (lit.,<sup>6</sup> m.p. 191 °C), from methanol.

**Bromination of Benzo[*c*]cinnoline.**—Bromine (3.5 g) in carbon tetrachloride (20 ml) was added dropwise to a rapidly stirred solution of benzo[*c*]cinnoline (3.6 g) and silver sulphate (3.4 g) in concentrated sulphuric acid (40 ml) at room temperature. After 2 h, the reaction mixture was filtered, poured into ice-water (250 ml), and then steam-distilled briefly to remove carbon tetrachloride. Next day the precipitate was collected and crystallised from methanol to give 1,4-dibromobenzo[*c*]cinnoline as bright yellow needles (0.15 g, 3%), m.p. 196–198 °C (Found: C, 42.55; H, 1.9; Br, 46.9; N, 8.1. C<sub>12</sub>H<sub>6</sub>Br<sub>2</sub>N<sub>2</sub> requires C, 42.6; H, 1.8; Br, 47.3; N, 8.3%). The filtrate was neutralised with aqueous ammonia to a final volume of *ca.* 500 ml and then cooled. The precipitated solid was collected, washed, dried, and chromatographed on an alumina column in benzene–chloroform (4 : 1), the fractions being monitored by t.l.c. First eluted was a trace of 1,4-dibromobenzo[*c*]cinnoline, followed by 4-bromobenzo[*c*]cinnoline (0.85 g, 21%) as yellow needles (from methanol), m.p. and mixed m.p. 199–200 °C. The later fractions gave 1-bromobenzo[*c*]cinnoline (2.09 g, 49%), m.p. and mixed m.p. 121–122 °C (from methanol), and starting material (0.75 g).

**2-Chlorobenzo[*c*]cinnoline,** yellow needles (from ethanol) m.p. 213–214 °C (lit.,<sup>15</sup> m.p. 215.5–216 °C) was obtained in 41% yield by a Sandmeyer reaction of the corresponding amine,<sup>5</sup> using a procedure similar to that described above for the 1-bromo-derivative.

**3-Chlorobenzo[*c*]cinnoline** was prepared by methods analogous to those outlined above for the 3-bromo-derivative. A crossed Ullmann reaction between 2-chloronitrobenzene and 2,5-dichloronitrobenzene gave 4-chloro-2,2'-dinitrobiphenyl, pale yellow needles (from ethanol), m.p. 130–131 °C (Found: C, 51.4; H, 2.5; Cl, 13.25; N, 9.7. C<sub>12</sub>H<sub>7</sub>N<sub>2</sub>O<sub>4</sub> requires C, 51.7; H, 2.5; Cl, 12.75; N, 10.05%), in 56% yield and this was reduced to 3-chlorobenzo[*c*]cinnoline, dull yellow needles (from ethanol), m.p. 189–190 °C (lit.,<sup>15</sup> m.p. 189.5–190.5 °C), in 61.5% yield.

**Chlorination of Benzo[*c*]cinnoline.**—This was carried out as for the bromination (above). In a typical run benzo[*c*]cinnoline (3.6 g) gave 1,4-dichlorobenzo[*c*]cinnoline (0.28 g, 6%), yellow needles (from ethanol), m.p. 203–204 °C (Found: C, 57.6; H, 2.4; N, 11.2. C<sub>12</sub>H<sub>6</sub>Cl<sub>2</sub>N<sub>2</sub> requires C, 57.8; H, 2.4; N, 11.2%), 4-chlorobenzo[*c*]cinnoline (0.58 g, 15%), yellow needles (from ethanol), m.p. 190–191 °C (lit.,<sup>15</sup> m.p. 190–191 °C), 1-chlorobenzo[*c*]cinnoline (1.9 g, 50%), yellow needles (from ethanol), m.p. 144–145 °C (lit.,<sup>15</sup> m.p. 145–146 °C), and recovered starting material (0.4 g).

We thank the S.R.C. for a studentship (to D. J. L.).

[8/1440 Received, 3rd August, 1978]

## REFERENCES

- <sup>1</sup> Part 2, J. W. Barton and J. F. Thomas, *J. Chem. Soc.*, 1964, 1265.
- <sup>2</sup> J. C. Arcos, M. Arcos, and J. A. Miller, *J. Org. Chem.*, 1956, **21**, 651.
- <sup>3</sup> W. T. Smith and P. R. Ruby, *J. Amer. Chem. Soc.*, 1954, **76**, 5807.
- <sup>4</sup> J. F. Corbett, P. F. Holt, and M. L. Vickery, *J. Chem. Soc.*, 1962, 949.
- <sup>5</sup> J. W. Barton and M. A. Cockett, *J. Chem. Soc.*, 1962, 2454.
- <sup>6</sup> J. F. Corbett and P. F. Holt, *J. Chem. Soc.*, 1961, 5029.
- <sup>7</sup> P. F. Holt and R. Oakland, *J. Chem. Soc.*, 1966, 1306.
- <sup>8</sup> J. A. McBride, *J.C.S. Chem. Comm.*, 1972, 1219.
- <sup>9</sup> H. J. Bernstein, W. G. Schneider, and J. A. Pople, *Proc. Roy. Soc.*, 1956, **236A**, 515.
- <sup>10</sup> R. H. Martin, N. Defay, F. Geerts-Evrard, and D. Bogaert-Verhoogen, *Tetrahedron*, 1966, **22**, Suppl. 8, Part I, 181.
- <sup>11</sup> M. Kooti and J. F. Nixon, *J. Organometallic Chem.*, 1976, **105**, 217.
- <sup>12</sup> F. M. Beringer, L. L. Chang, A. N. Fenster, and R. R. Rossi, *Tetrahedron*, 1969, **25**, 4339.
- <sup>13</sup> B.P. 1,091,403 (1964) (*Chem. Abs.*, 1964, **64**, P5008c).
- <sup>14</sup> R. E. Moore and A. Furst, *J. Org. Chem.*, 1958, **23**, 1504.
- <sup>15</sup> G. M. Badger, R. J. Drewer, and G. E. Lewis, *Austral. J. Chem.*, 1964, **17**, 1036.