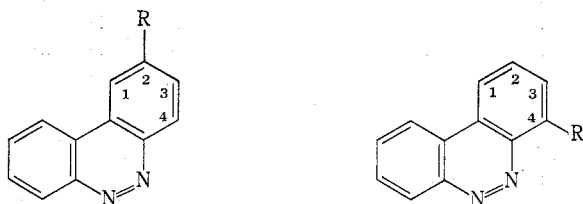


BENZO[c]CINNOLINE DERIVATIVES.*

III.† ALKOXYBENZO[c]CINNOLINES

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Dialkylaminobenzo[c]cinnolines have been prepared from chlorobenzo[c]cinnolines through nucleophilic displacement reactions with dimethylamine and diethylamine, respectively;^{1,2} and it has now been shown that 2- and 4-chlorobenzo[c]cinnoline may be easily converted into the corresponding alkoxy compounds (I-IV) through reactions with the appropriate sodium alkoxides.



- | | |
|-------------------------------|------------------------------|
| (I) R = OEt | (II) R = OEt |
| (III) R = OMe | (IV) R = OMe |
| (V) R = NMe ₂ | (VI) R = NMe ₂ |
| (VII) R = NEt ₂ | (VIII) R = NEt ₂ |
| (IX) R = Me | (X) R = Me |
| (XI) R = CO ₂ Et | (XII) R = CO ₂ Et |
| (XIII) R = CO ₂ Me | (XIV) R = CO ₂ Me |

The two chlorobenzo[c]cinnolines were found to react smoothly with sodium ethoxide in ethanol at reflux temperature; and the reaction of 4-chlorobenzo[c]cinnoline with sodium methoxide in methanol also proceeded satisfactorily under equivalent conditions. The reaction of 2-chlorobenzo[c]cinnoline with sodium methoxide in methanol, however, proved to be extremely slow; but, when toluene was employed as solvent and the reaction temperature raised to 100°, the methoxy compound was formed in virtually quantitative yield within a reasonable time.

Following the preparation of the alkoxy derivatives (I-IV), a comparison of the n.m.r. spectral characteristics of the compounds with those of other 2- and 4-substituted benzo[c]cinnolines was carried out in order to confirm that only normal

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¹ Lewis, G. E., and Reiss, J. A., *Aust. J. Chem.*, 1967, **20**, 1451.

² Lewis, G. E., and Reiss, J. A., *Aust. J. Chem.*, 1967, **20**, 2217.

nucleophilic substitution had taken place. The n.m.r. spectral details of the 2- and 4-dimethylamino compounds (V and VI) and of the 2- and 4-diethylamino compounds (VII and VIII) were already available from previous work;^{2,3} and studies were extended to the methyl derivatives (IX and X),⁴ the ethoxycarbonyl compounds (XI and XII), and the methoxycarbonyl compounds (XIII and XIV). The preparation of methyl benzo[c]cinnoline-2-carboxylate (XIII) has been previously described;^{5,6} and the other three esters required were prepared through esterification of the known⁶ benzo[c]cinnoline-carboxylic acids.

TABLE 1
N.M.R. SPECTRA OF 2- AND 4-SUBSTITUTED BENZO[c]CINNOLINES IN CDCl₃

Com- pound	Methyl Protons (τ)	Proton Count	Methylene Protons $\ddagger$ (τ)	Proton Count	Ring Protons $\S$ (τ)	Proton Count
(I)	8.51†	3	5.80	2	1.33-2.75	7
(II)	8.37†	3	5.63	2	1.25-2.93	7
(III)	6.07*	3	—	—	1.35-2.72	7
(IV)	5.90*	3	—	—	1.25-2.94	7
(V)	6.90*	6	—	—	1.38-2.92	7
(VI)	6.65*	6	—	—	1.30-3.02	7
(VII)	8.74†	6	6.47	4	1.43-2.93	7
(VIII)	8.71†	6	6.27	4	1.38-3.06	7
(IX)	7.48*	3	—	—	1.33-2.53	7
(X)	6.98*	3	—	—	1.32-2.48	7
(XI)	8.55†	3	5.53	2	0.80-2.21	7
(XII)	8.55†	3	5.44	2	1.27-2.35	7
(XIII)	6.05*	3	—	—	0.85-2.56	7
(XIV)	5.98*	3	—	—	1.32-2.40	7

* Singlet. † Triplet (J 7 c/s). ‡ Quartets (J 7 c/s). § Multiplets.

Details of the integrated n.m.r. spectra and assignments are summarized in Table 1; and it can be seen that there are characteristic variations in the τ values of the methyl (or methylene) protons of the substituent groups, according to the positions of attachment of the substituent to the benzo[c]cinnoline nucleus. The τ value for the methyl protons of a methyl, of a dimethylamino, or of a methoxycarbonyl substituent, is considerably lower when the substituent is attached to the 4-position than when it is attached to the 2-position; and the τ value for the methylene protons of a diethylamino or of an ethoxycarbonyl substituent is likewise distinctly lower when the substituent is attached to the 4-position. The lower τ value associated with each instance of 4-substitution is obviously due to the closer proximity of the substituent to the electron-attracting nitrogen atom of the central ring of the benzo[c]cinnoline nucleus. The magnitude of the change in τ value (attending the change from 2- to 4-substitution) is also seen to decrease with increasing

³ Lewis, G. E., and Reiss, J. A., *Aust. J. Chem.*, 1968, **21**, 1043.

⁴ Badger, G. M., Drewer, R. J., and Lewis, G. E., *Aust. J. Chem.*, 1963, **16**, 1042.

⁵ Badger, G. M., Drewer, R. J., and Lewis, G. E., *Aust. J. Chem.*, 1964, **17**, 1036.

⁶ Jerchel, D., and Fischer, H., *Liebigs Ann.*, 1954, **590**, 216.

distance of the protons from the aromatic nucleus. The difference between the spectra of the two methoxy compounds (III and IV), and the difference between the spectra of the two ethoxy compounds (I and II), are in overall agreement with the foregoing observations, the closest quantitative comparisons being with the spectral differences between the two dimethylamino compounds and those between the two diethylamino compounds respectively.

It is clear from these correlations that the products from the reactions of the chlorobenzo[c]cinnolines with sodium methoxide and sodium ethoxide are normal nucleophilic substitution products. Anomalous substitution (such as that found to occur in the reaction of 2-chlorobenzo[c]cinnoline with lithium dimethylamide³) obviously does not take place in these reactions.

Experimental

Materials

The chlorobenzo[c]cinnolines and the benzo[c]cinnoline-carboxylic acids used in the reactions described below were prepared by previously recorded methods.⁵ Methyl benzo[c]cinnoline-2-carboxylate (XIII) was available from earlier work,⁵ as were 2- and 4-methylbenzo[c]cinnoline (IX and X).⁴

Alkoxybenzo[c]cinnolines (I-IV)

2-Chlorobenzo[c]cinnoline (65 mg) was heated at 100° for 12 hr in a mixture of sodium methoxide (c. 400 mg), methanol (c. 300 mg), and toluene (5 ml). The reaction mixture was then shaken with water and extracted with chloroform several times. The combined chloroform-toluene extract was washed with water and dried (MgSO₄); and the solvent was removed. 2-Methoxybenzo[c]cinnoline (66 mg; 100%) remained; and this formed cream-coloured needles, m.p. 147-148°, when recrystallized from chloroform-light petroleum (Found: C, 72.5; H, 4.9; N, 13.3; mol. wt. (mass spectrum), 210. C₁₃H₁₀N₂O requires C, 74.3; H, 4.8; N, 13.3%; mol. wt., 210).

For the preparation of each of the other alkoxybenzo[c]cinnolines, the appropriate chlorobenzo[c]cinnoline (quantity indicated below) was dissolved in a mixture of the required sodium alkoxide (c. 400 mg) and the corresponding alcohol (5 ml); and the reaction mixture was heated under reflux for 9-12 hr. The working-up procedure was essentially similar to that described above, except that in the case of the 4-ethoxy compound the chloroform extract was chromatographed on a column of neutral alumina before removal of the solvent. 4-Chlorobenzo[c]cinnoline (60 mg) after treatment for 12 hr with sodium methoxide-methanol gave 4-methoxybenzo[c]cinnoline (51 mg; 85%) which was obtained as yellow prisms, m.p. 179-180°, following recrystallization from chloroform-light petroleum (Found: C, 73.6; H, 4.9; N, 13.2; mol. wt. (mass spectrum), 210. C₁₃H₁₀N₂O requires C, 74.3; H, 4.8; N, 13.3%; mol. wt., 210). 2-Chlorobenzo[c]cinnoline (69 mg) after treatment for 9 hr with sodium ethoxide-ethanol gave 2-ethoxybenzo[c]cinnoline (57 mg; 80%) which was obtained as cream-coloured needles, m.p. 149.5-150°, following recrystallization from chloroform-pentane (Found: C, 75.2; H, 5.3; N, 12.7; mol. wt. (mass spectrum), 224. C₁₄H₁₂N₂O requires C, 75.0; H, 5.4; N, 12.5%; mol. wt., 224). 4-Chlorobenzo[c]cinnoline (51 mg) after treatment for 9 hr with sodium ethoxide-ethanol gave 4-ethoxybenzo[c]cinnoline (53 mg; 96%) which was obtained as pale yellow prisms, m.p. 145.5-146.5°, following recrystallization from chloroform-light petroleum (Found: C, 75.2; H, 5.4; N, 12.5; mol. wt. (mass spectrum), 224. C₁₄H₁₂N₂O requires C, 75.0; H, 5.4; N, 12.5%; mol. wt., 224).

Alkoxy carbonylbenzo[c]cinnolines (XI, XII, XIV)

In each case the appropriate benzo[c]cinnoline-carboxylic acid (80 mg) was dissolved in the necessary alcohol (30 ml) containing hydrogen chloride, and the solution was boiled under reflux for 18 hr. After addition of water to the reaction mixture, the ester was extracted with chloro-

form; and, following chromatography of the extract on a short column of neutral alumina, the solvent was removed. The residual ester was then recrystallized from chloroform-pentane and finally dried (over P_2O_5) at $60^\circ/0.05$ mm. Benzo[c]cinnoline-2-carboxylic acid and ethanol-hydrogen chloride gave *ethyl benzo[c]cinnoline-2-carboxylate* (95% yield), which formed golden yellow needles, m.p. $107.5-108^\circ$ (Found: N, 11.5; mol. wt. (mass spectrum), 252. $C_{15}H_{12}N_2O_2$ requires N, 11.1%; mol. wt., 252). Benzo[c]cinnoline-4-carboxylic acid and ethanol-hydrogen chloride gave *ethyl benzo[c]cinnoline-4-carboxylate* (95% yield), which formed green-yellow needles, m.p. $131-132^\circ$ (Found: C, 71.2; H, 4.7; N, 11.1; mol. wt. (mass spectrum), 252. $C_{15}H_{12}N_2O_2$ requires C, 71.4; H, 4.8; N, 11.1%; mol. wt., 252). Benzo[c]cinnoline-4-carboxylic acid and methanol-hydrogen chloride gave *methyl benzo[c]cinnoline-4-carboxylate* (91% yield), which formed yellow prisms, m.p. $121.5-122.5^\circ$ (Found: C, 70.3; H, 4.5; N, 11.8; mol. wt. (mass spectrum), 238. $C_{14}H_{10}N_2O_2$ requires C, 70.6; H, 4.2; N, 11.8%; mol. wt., 238).

Spectra

The n.m.r. spectra were measured in deuteriochloroform solutions with a Varian DP60 spectrometer. Mass spectral measurements were made with an Hitachi Perkin-Elmer RMU-6D spectrometer.

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