

767. *Heterocyclic Compounds of Nitrogen. Part IX.¹ The Preparation of Some Cinnoline Derivatives.*

By J. MALCOLM BRUCE and P. KNOWLES.

The preparation and proton magnetic resonance spectra of 6,7-dimethoxy-4-methyl- and 6,7-dimethoxy-cinnoline, and a synthesis of decahydro-cinnoline are described.

TREATMENT of 2-amino-4,5-dimethoxyacetophenone with methyl-lithium gave the corresponding tertiary alcohol from which 6,7-dimethoxy-4-methylcinnoline was obtained by successive dehydration and diazotisation. Reduction ² of 6,7-dimethoxy-4-cinnolone with lithium aluminium hydride, followed by oxidation of the product with mercuric oxide gave 6,7-dimethoxycinnoline.

The proton magnetic resonance spectrum of 6,7-dimethoxy-4-methylcinnoline contains a singlet at τ 1.02 which is assigned to the 3-proton by analogy with the spectra of other 4-substituted cinnolines,^{1,3} and because the spectrum of 6,7-dimethoxycinnoline contains a doublet ($J = 6$ c./sec.) in this region. The benzenoid protons of the latter compound give resonances at τ 2.24 and 3.01, the former masking one component of the major doublet

¹ Part VIII, Bruce, Knowles, and Besford, preceding Paper.

² Cf. Atkinson and Sharpe, *J.*, 1959, 2858.

³ Besford, Allen, and Bruce, *J.*, 1963, 2867.

($J = 6$ c./sec.) arising from the 4-proton. The other component, at $\tau 2.34$, is an unsymmetrical doublet ($J = 0.5$ c./sec.) with the smaller band at highest field indicating long-range coupling with a proton giving a resonance at lower field, probably that at position 8 since for quinoline $J_{48} \sim 1$ c./sec., but J_{45} has not been observed. However, the band at $\tau 2.24$ could not be resolved, possibly because it contains appreciable contributions from resonances due to the 4-proton, but if it is due to the 8-proton it follows⁵ that the resonances from the corresponding proton in cinnolines unsubstituted in the benzenoid ring should occur at about $\tau 1.7$, and a multiplet of intensity equivalent to one proton has been observed^{1,3} in this region for several such cinnolines.

Addition of diethyl azodicarboxylate to 1-vinylcyclohexene proceeded normally⁶ to give diethyl 1,2,3,5,6,7,8,8a-octahydrocinnoline-1,2-dicarboxylate, the proton magnetic resonance spectrum of which contained a multiplet centred at $\tau 4.60$ attributable to a single vinylic proton; the corresponding proton in the Diels-Alder adduct⁷ from maleic anhydride and 1-vinylcyclohexene gives a band centred at 4.55. Hydrolysis⁸ or dehydrogenation⁸ of the octahydrocinnoline did not proceed cleanly, but hydrogenation followed by hydrolysis gave decahydrocinnoline.

EXPERIMENTAL

Solutions in organic media were washed with water and dried with magnesium sulphate. Sublimation and bulb-to-bulb distillation temperatures are those of the heating bath. M. p.s are corrected. Infrared spectra were determined with a Unicam S.P. 200 spectrometer, and proton magnetic resonance spectra with a Varian A-60 spectrometer. Tetramethylsilane was used as an internal standard.

2-(2-Amino-4,5-dimethoxyphenyl)propan-2-ol.—2-Amino-4,5-dimethoxyacetophenone⁹ (0.89 g.) in tetrahydrofuran (50 c.c.) was added during 3 hr. to a mixture of ethereal methyl-lithium (20 c.c.; 0.88 mole/l.) and tetrahydrofuran (100 c.c.) stirred under nitrogen at room temperature, and stirring was continued for 1 hr. more. The mixture was cooled in ice, water (5 c.c.) was added, and solvent (150 c.c.) then removed under reduced pressure (water-pump). Extraction of the residue with benzene, sublimation of the soluble material at $110^\circ/0.01$ mm., and crystallisation of the sublimate from benzene-light petroleum (b. p. $60-80^\circ$) gave the *alcohol* (0.4 g.) as needles, m. p. $116-117^\circ$ (Found: C, 61.9; H, 7.9; N, 6.6. $C_{11}H_{17}NO_3$ requires C, 62.6; H, 8.2; N, 6.6%). ν_{\max} (Nujol) 3300 and 3360 cm^{-1} ; τ (12% in CDCl_3) 3.30 (6-H), 3.78 (3-H), 6.21 [(OMe)₂ + NH₂ + OH, reduced to (OMe)₂ by addition of D₂O], and 8.40 (CMe₂).

2-(2-Amino-4,5-dimethoxyphenyl)prop-2-ene.—The foregoing experiment was repeated on six-times the scale, but the product obtained by extraction with benzene was distilled (bulb-to-bulb, $160^\circ/0.5$ mm.), and the distillate heated at 180° (bath) with a small crystal of ammonium chloride until evolution of water had ceased (15 min.). The residue was chromatographed on silica gel (60×4 cm., 60–120 B.S.S.) using 3 : 1 ether : benzene as eluent, and the first fraction distilled (bulb-to-bulb, $110^\circ/0.01$ mm.) to give the olefin (2.7 g.) as a pale yellow oil (Found: C, 68.0; H, 7.7; N, 7.7. $C_{11}H_{15}NO_2$ requires C, 68.2; H, 7.8; N, 7.3%). ν_{\max} (liquid film) 1625, 3320, and 3400 cm^{-1} ; τ (18% in CCl_4) 3.46 (6-H), 3.85 (3-H), 4.81, 5.01 (multiplets, =CH₂), 6.31 [(OMe)₂], 6.48 (NH₂, removed by addition of D₂O), 7.98 (multiplet, CMe).

6,7-Dimethoxy-4-methylcinnoline.—The foregoing olefin (190 mg.) in aqueous 15% hydrochloric acid (1 c.c.) was diazotised at -5° with aqueous 15% sodium nitrite, and then made strongly alkaline with solid sodium hydroxide. The precipitate was extracted with benzene and sublimed at $135^\circ/0.005$ mm., and the sublimate was chromatographed on alumina (15×1.2 cm., grade H), the column being eluted first with 3 : 1 ether : benzene to remove an oil, and then with 9 : 1 ether : ethanol to give the *cinnoline* which by further sublimation was obtained as yellow crystals (85 mg.), m. p. $180-182^\circ$ (Found: C, 65.5; H, 6.3; N, 13.2. $C_{11}H_{12}N_2O_2$

⁴ Paterson and Bigam, *Canad. J. Chem.*, 1963, **41**, 1841, and references therein.

⁵ Cf. Diehl, *Helv. Chim. Acta*, 1961, **44**, 829.

⁶ Diels and Alder, *Annalen*, 1926, **450**, 237. Cf. Gillis and Beck, *J. Org. Chem.*, 1962, **27**, 1947; Franzus and Surridge, *ibid.*, p. 1951, and references therein.

⁷ Cook and Lawrence, *J.*, 1938, 58.

⁸ Cf. Alder and Nicklas, *Annalen*, 1954, **585**, 81.

⁹ Simpson, *J.*, 1946, 94.

requires C, 65.5; H, 6.0; N, 13.7%; ν_{\max} (Nujol) 1625 cm^{-1} ; τ (10% in CDCl_3) 1.02 (3-H), 2.29 (8-H), 2.98 (5-H), 5.91 [(OMe)₂], and 7.42 (4-Me).

6,7-Dimethoxycinnoline.—6,7-Dimethoxy-4-cinnolone¹ (2.8 g.) lithium aluminium hydride (1.4 g.), and tetrahydrofuran (200 c.c.) were refluxed for 15 hr., most of the solvent was removed, and benzene (150 c.c.) was added to the residue. The mixture was decomposed with methanol (8 c.c.) followed by water (8 c.c.), and the benzene phase removed and combined with benzene extracts of the aqueous phase. Removal of the solvent and distillation (bulb-to-bulb, 180°/1 mm.) of the residue gave an oil (1 g.) which was refluxed for 48 hr. with red mercuric oxide (7 g.) in dry benzene (100 c.c.). The benzene phase was separated centrifugally, and the solvent removed. Sublimation of the residue at 130°/0.01 mm., and crystallisation of the sublimate from cyclohexane gave the *cinnoline* (260 mg.) as yellow crystals, m. p. 123–124.5° unchanged by two further sublimations (Found: C, 63.2; H, 5.2; N, 14.8. $\text{C}_{10}\text{H}_8\text{N}_2\text{O}_2$ requires C, 63.1; H, 5.3; N, 14.8%); ν_{\max} (Nujol) 1625 cm^{-1} ; τ (15% in CDCl_3) 0.83 (doublet, $J = 6$ c./sec.; 3-H), 2.24 (8-H + part of 4-H), 2.29 ("quartet," $J_1 = 6$ c./sec., $J_2 = 0.5$ c./sec., the components at 2.24 being obscured; 4-H), 3.01 (5-H), 5.88, and 5.93 [(OMe)₂].

Diethyl 1,2,3,5,6,7,8,8a-Octahydrocinnoline-1,2-dicarboxylate.—Diethyl azodicarboxylate (10.4 g.) in dry benzene (50 c.c.) was added during 1 hr. to 1-vinylcyclohexene^{7,10} (6.4 g.) in dry benzene (50 c.c.), the mixture left at room temperature for 48 hr., and the solvent removed. The residue was heated at 110°/0.1 mm. to remove a little diethyl hydrazine-1,2-dicarboxylate (m. p. and mixed m. p. 130–130.5°), and then distilled to give the *octahydrocinnoline* (12 g.) as an oil, b. p. 126°/0.1 mm. (Found: C, 59.4; H, 7.8; N, 9.8. $\text{C}_{14}\text{H}_{22}\text{N}_2\text{O}_4$ requires C, 59.6; H, 7.9; N, 9.9%); ν_{\max} (liquid film) 1700 cm^{-1} ; τ (16% in CCl_4) multiplet centred at 4.60 (4-H), quartets centred at 5.85 and 5.87 [$J = 7$ c./sec., (OCH₂)₂], and a triplet at 8.74 ($J = 7$ c./sec., Me₂) superimposed on broad resonances due to the skeletal protons [cf. 1,2,3,5,6,7,8,8a-octahydronaphthalene-1,2-dicarboxylic anhydride, m. p. 51.5–52.5° (lit.,⁷ 52–53°), which had τ (12% in CCl_4) multiplet centred at 4.55 (4-H)].

Diethyl Decahydrocinnoline-1,2-dicarboxylate.—The foregoing olefin (7.4 g.) in ethanol (200 c.c.) was hydrogenated at normal temperature and pressure over Adams catalyst (200 mg.), and the product twice distilled to give the *decahydrocinnoline* as an oil (6.6 g.), b. p. 129–130°/0.1 mm. (Found: C, 59.1; H, 8.2; N, 10.2. $\text{C}_{14}\text{H}_{24}\text{N}_2\text{O}_4$ requires C, 59.3; H, 8.5; N, 9.9%); ν_{\max} (liquid film) 1705 cm^{-1} , and τ (15% in CCl_4) quartets centred at 5.87 and 5.93 [$J = 7$ c./sec. (OCH₂)₂], and triplets at 8.75 and 8.79 ($J = 7$ c./sec., Me₂) superimposed on broad resonances due to the skeletal protons.

Decahydrocinnoline.—The foregoing ester (6.7 g.) was refluxed for 4 hr. with freshly distilled 48% hydrobromic acid (35 c.c.), the acid removed by distillation under reduced pressure, and the residue dissolved in aqueous 20% sodium hydroxide (20 c.c.). Solid sodium hydroxide was added until two layers formed, the mixture extracted with benzene, and the extract was washed with water, and dried (MgSO₄). The solvent was removed, and the residue twice distilled to give *decahydrocinnoline* (2.4 g.) as an almost colourless oil, b. p. 104–105°/6.5 mm., which rapidly darkened in air (Found: C, 68.1; H, 11.2; N, 19.9. $\text{C}_8\text{H}_{14}\text{N}_2$ requires C, 68.3; H, 11.5; N, 20.0%); ν_{\max} (liquid film) 3250 cm^{-1} . Treatment with phthalic anhydride in refluxing pyridine gave a *phthaloyl derivative* which, after distillation (bulb-to-bulb, 160°/0.01 mm.) and crystallisation from ethanol, had m. p. 119–119.5°; ν_{\max} (Nujol) 1600, 1635, and 1645 cm^{-1} (Found: C, 71.1; H, 6.7; N, 10.6. $\text{C}_{16}\text{H}_{18}\text{N}_2\text{O}_2$ requires C, 71.1; H, 6.7; N, 10.7%). Reaction with benzoyl chloride in pyridine at 20°, distillation (bulb-to-bulb, 200°/0.01 mm.) of the product, and crystallisation of the distillate from ethanol gave a *dibenzoyl derivative* which had m. p. 164–168° unchanged by recrystallisation; ν_{\max} (Nujol) 1655 and 1665 cm^{-1} (Found: C, 75.4; H, 6.9; N, 8.2. $\text{C}_{22}\text{H}_{24}\text{N}_2\text{O}_2$ requires C, 75.6; H, 6.9; N, 8.1%).

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DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MANCHESTER.

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¹⁰ Ohloff, Farnow, and Schade, *Chem. Ber.*, 1956, **89**, 1549.