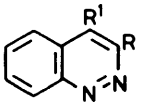
Cinnolines. Part 1. Widman-Stoermer Reactions of Functionalised 2-Phenylbut-2-enes to give Cinnolinecarbaldehydes

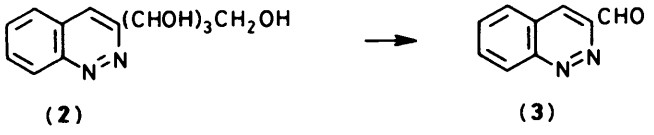
John W. Barton* and Neil D. Pearson
School of Chemistry, The University, Cantock's Close, Bristol, BS8 1TS

Diazotisation of a mixture of the *E*- and *Z*-isomers of 2-(2-aminophenyl)but-2-ene-1,4-diol gives 4-(hydroxymethyl)cinnoline-3-carbaldehyde, by spontaneous oxidation of the presumed intermediate, 3,4-bis(hydroxymethyl)cinnoline. Further oxidation of the reaction product gives cinnoline-3,4-dicarbaldehyde. Cyclisation reactions of other 2-(2-aminophenyl)but-2-ene derivatives, leading to quinolines and a benzisoxazine, are described.

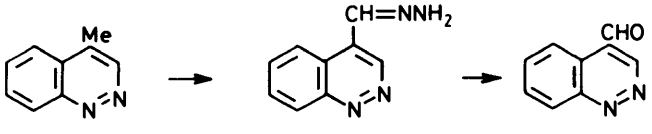
ortho-Dialdehydes are key intermediates in certain ring annelations[1,2] and for the construction of various fused-ring heterocycles. In order to apply such reactions to the cinnoline system we have investigated the synthesis of cinnoline-3,4-dicarbaldehyde (**1**), a compound previously undescribed. The corresponding 3- and 4-monocarbaldehydes (**3**) and (**6**) are known, although they are not readily accessible. The former has been obtained by intramolecular cyclisations of aldose osazones under basic conditions with subsequent oxidative cleavage of the stereoisomeric tetrols (**2**),[3] and the latter by indirect oxidation of 4-methylcinnoline (**4**) *via* the hydrazone (**5**).[4]



(**1**) R = R^1 = CHO
(**7**) R = R^1 = Me
(**8**) R = Me, R^1 = CHO
(**9**) R = Me, R^1 = CH_2SePh
(**10**) R = Me, R^1 = $CH(OAc)_2$

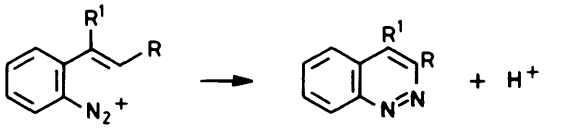


(**2**) (**3**)



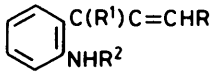
(**4**) (**5**) (**6**)

We first attempted to obtain cinnoline-3,4-dicarbaldehyde (**1**) by the oxidation of the known 3,4-dimethylcinnoline (**7**),[5] but this only served to confirm an earlier report[6] that the 3-methyl group of this compound is extremely resistant to oxidation. Oxidation of (**7**) with benzeneseleninic anhydride[7] gave approximately equal amounts of 3-methylcinnoline-4-carbaldehyde (**8**) and 3-methyl-4-(selenophenylmethyl)-cinnoline (**9**). The use of an excess of oxidant only reduced the yields obtained, no oxidation of the 3-methyl group being observed. Similarly, oxidation of compound (**7**) with manganese(III) acetate,[8] followed by hydrolysis of the 4-diacetoxymethyl-3-methylcinnoline (**10**) formed, gave the aldehyde (**8**) (43%). The use of more oxidant again failed to give the required product.



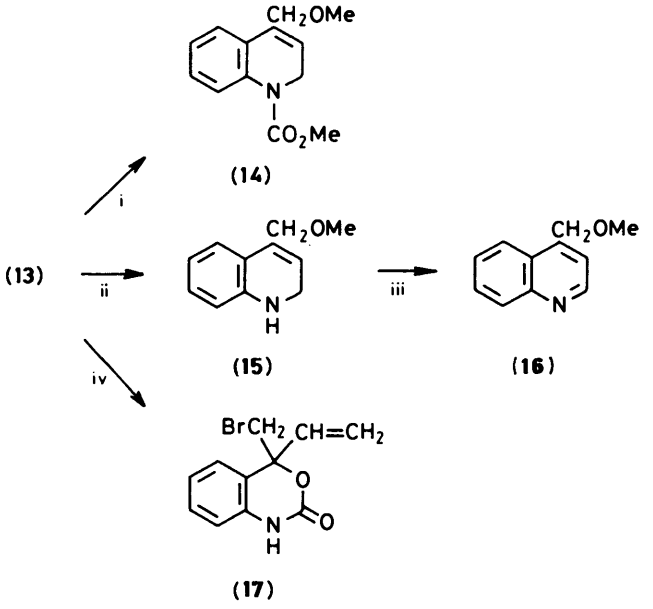
Scheme 1.

It was therefore decided to introduce side-chain functionality before formation of the pyridazine ring and to use the Widman-Stoermer ring closure[9] of a suitably substituted 2-(2-aminophenyl)but-2-ene as the ring formation step (Scheme 1). It had been shown previously[10,11] that the polarisation effects of R and R′ must result in a negative charge on the β-carbon atom of the ethylenic side-chain, hence this reaction has mainly been used to make alkyl and aryl substituted cinnolines.[10] The modification of these substituents to hydroxymethyl or alkoxymethyl groups appeared to be appropriate, thus allylic bromination followed by bromide displacement from a suitably protected 2-(2-aminophenyl)but-2-ene (**11**) was attempted.



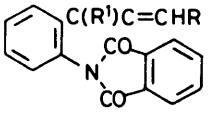
(**11**) R = R^1 = Me, R^2 = H
(**12**) R = R^1 = Me, R^2 = CO_2Me
(**13**) R = R^1 = CH_2Br, R^2 = CO_2Me

The amine (**11**) was protected as its methyl carbamate (**12**) and converted into 1,4-dibromo-2-(2-methoxycarbonylaminophenyl)but-2-ene (**13**), some (*E*)-1,1,4-tribromo-2-(2-methoxycarbonylaminophenyl)but-2-ene being formed as a by-product. The dibrominated material was obtained as a mixture of the *E*- and *Z*-isomers in the ratio of 9:1, but separation of these was not attempted as both should lead to the same cyclisation product. Displacement of the allylic bromine atoms in (**13**) was attempted (Scheme 2). With sodium methoxide in methanol intramolecular cyclisation gave 1-methoxycarbonyl-4-methoxymethyl-1,2-dihydroquinoline (**14**), while in the presence of water, loss of the carbamate group occurred. Formation of the dihydroquinoline (**15**) could be demonstrated by ^{1}H n.m.r. spectroscopy but stirring a chloroform solution of the reaction product in air gave the fully aromatised 4-methoxymethylquinoline (**16**). When non-basic hydrolysis to the 1,4-diols was attempted, using silver trifluoroacetate under phase-transfer conditions, intramolecular cyclisation took place *via* the alternative tertiary carbonium ion intermediate to give the dihydrobenzoxazinone (**17**).



Scheme 2. *Reagents:* i, NaOMe, MeOH; ii, NaOH, aq. MeOH; iii, Air; iv, CF_3CO_2Ag, $Bu_4^+NBr^-$, benzene/H_2O.

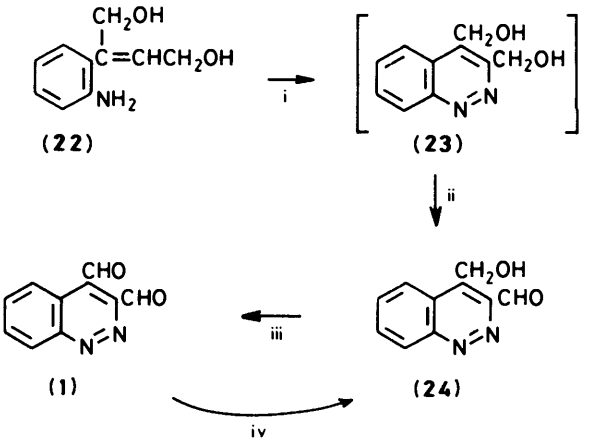
As a completely protected amino function appeared to be necessary, the phthalimide derivatives (**18**) were prepared and dibrominated to give (**19**). The latter were found to be difficult to separate from tribrominated impurities, thus the crude mixture was used. Attempted displacement of the allylic bromines with sodium methoxide in methanol removed the protecting group, but reaction with acetate anion under phase-transfer conditions gave 1,4-diacetoxy-2-(2-phthalimidophenyl)but-2-ene (**20**), with an *E*- to *Z*-ratio of 4 : 1. Hydrolysis in 90% methanol containing a catalytic quantity of hydrochloric acid gave the mixture of diols (**21**); further deprotection by means of 0.2M methanolic hydrazine gave the amino diols (**22**), in high overall yield from (**20**).



(**18**) R = R^1 = Me
(**19**) R = R^1 = CH_2Br
(**20**) R = R^1 = CH_2OAc
(**21**) R = R^1 = CH_2OH

Diazotisation of the isomer mixture (**22**) at 5 °C, gave, after 40 h at that temperature, 4-(hydroxymethyl)cinnoline-3-carbaldehyde (**24**) in a crude yield of 75%, presumably produced by aerobic oxidation of the initially formed 3,4-bis(hydroxymethyl)cinnoline (**23**) (Scheme 3). Although the aldehyde (**24**) was not stable to column chromatography and could not be purified by recrystallisation, oxidation of the crude cyclisation product with pyridinium dichromate gave cinnoline-3,4-dicarbaldehyde (**1**) in 16% yield based on the amine (**22**). On reduction with sodium borohydride the dicarbaldehyde (**1**) gave the aldehyde (**24**) as a pure crystalline compound, identical by ^1H n.m.r. with the crude cyclisation product, the orientation being shown by n.O.e. difference experiments, thus confirming its structure.

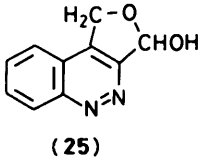
The aerobic oxidation of the diol (**23**) to the aldehyde (**24**) rather than 3-(hydroxymethyl)cinnoline-4-carbaldehyde is



Scheme 3. *Reagents:* i, $NaNO_2$, 2M HCl, 5 °C, 40 h; ii, Air; iii, $(C_5H_5\overset{+}{N})_2Cr_2O_7^{2-}$, CH_2Cl_2; iv, $NaBH_4$, aq. EtOH.

somewhat surprising when compared with the oxidation of the 4-methyl compound (**7**) to give the 4-carbaldehyde (**8**), and may be attributed to steric effects in the radical intermediates. A hydroxymethylene radical in the 4-position would have unfavourable interactions with the 3-(hydroxymethyl) substituent and also the *peri*-interaction with 5-H. This may be expected to cause the hydroxymethylene radical to twist out of the plane of the aromatic ring preventing any delocalisation. However, a hydroxymethylene radical in the 3-position would only have an unfavourable interaction on one side, thus allowing it to lie in the aromatic plane and be stabilised by delocalisation. This type of steric effect has been shown by ^1H n.m.r. to twist the nitro group in 2-methyl-1-nitronaphthalene out of the aromatic plane.[12] The greater stability of radical substituents in the β position is also apparent in the radical bromination of 1-(bromomethyl)-2-methylnaphthalene where dibromination gives 1-(bromomethyl)-2-(dibromomethyl)-naphthalene,[13] again presumably due to this effect.

The ^{13}C n.m.r. of (**1**) in $(CD_3)_2SO$ solution has the two highest resonances due to non-quaternary carbon atoms at 192.52 and 146.34 p.p.m., the latter being lower than expected for an aldehydic carbon. Similarly, the ^1H n.m.r. spectrum in $CDCl_3$ solution shows one resonance due to an aldehydic proton at 10.56 p.p.m. and one at a lower value of 9.56 p.p.m. These observations imply partial hydration of one of the aldehyde groups in solution, probably the one at the 3-position, giving rise to a time-averaged spectrum with lowering of the observed chemical shifts. In (**24**) the ^1H n.m.r. and the ^{13}C n.m.r. spectra again indicate partial hydration of the aldehyde group,



(**25**)

the corresponding resonances being observed at 9.56 and 149.12 p.p.m. respectively. The lowest observed ^1H and ^{13}C chemical shifts in the spectra of (**24**) are at 5.28 and 57.98 p.p.m. respectively, which are of the order expected for the hydroxymethyl group, although in this case the presence of the cyclic acetal (**25**) in the equilibrium cannot be discounted.

Experimental

Organic extracts were dried over magnesium sulphate. Flash chromatography was carried out on Merck Kieselgel 60, 230—

400 mesh. N.m.r. spectra were obtained on a JEOL JNM FX200 spectrometer. Samples were run as solutions in $CDCl_3$ at ambient temperature unless otherwise stated and chemical shifts are recorded as p.p.m. downfield from internal tetramethylsilane. In listing n.m.r. data, primed numbers are used to designate the ring carbons of substituted benzene rings. I.r. spectra were run as Nujol mulls unless otherwise stated. Mass spectra were obtained on an AEI MS902 instrument operated at 70 eV and a source temperature of 200 °C. The following starting materials were prepared by literature routes: 3,4-dimethylcinnoline (**7**)[5] and 2-(2-aminophenyl)but-2-ene (**11**).[5] The latter was obtained as a mixture of *E*- and *Z*-isomers and used as such.

3-*Methylcinnoline*-4-*carbaldehyde* (**8**).—(*a*) 3,4-Dimethylcinnoline (**7**) (1.00 g, 26.6 mmol) and manganese triacetate dihydrate (7.14 g, 26.6 mmol) in glacial acetic acid (150 ml) and acetic anhydride[8] (45.2 g) were heated to reflux for 15 min. Water (500 ml) was added and the resulting solution neutralised using 10% aqueous sodium carbonate. Continuous extraction with ether for 3 days gave crude 3-methylcinnoline-4-carbaldehyde (**8**) which was heated to reflux in 2M hydrochloric acid (250 ml) for 15 min to complete hydrolysis of any 3,3-diacetoxymethyl-4-methylcinnoline present. The mixture was extracted with ether (3 × 250 ml), and the extract dried and evaporated under reduced pressure to give the aldehyde (**8**) (0.45 g, 43%) as yellow prisms, m.p. 151—153 °C (from light petroleum) (lit.,[6] 143—145 °C); $\nu_{max.}$ 1 690 cm^{-1} (C=O); δ_H 10.96 (1 H, s, CHO-4 by n.O.e. difference experiments), 8.86—8.78 (1 H, m, 5-H by n.O.e. difference experiments), 8.64—8.57 (1 H, m, 8-H), 7.93—7.82 (2 H, m, 6- and 7-H), and 3.28 (3 H, s, 3-Me); *m/z* (%) 172(68, M^+), 144(2, $M - N_2$), 116(19, $M - N_2 - CO$), and 115(100, $M - N_2 - CHO$).

(*b*) 3,4-Dimethylcinnoline (**7**) (1.00 g, 6.3 mmol) and benzeneseleninic anhydride (0.80 g, 2.2 mmol) in dry chlorobenzene (100 ml) were heated to reflux under nitrogen for 30 min. The mixture was evaporated to dryness under reduced pressure and the product purified by flash chromatography using ethyl acetate–light petroleum (1:1) as eluant to give 3-methylcinnoline-4-carbaldehyde (**8**) (0.30 g, 28%) as yellow prisms, m.p. 151—153 °C (from light petroleum). Further elution gave 3-*methyl*-4-(*selenophenylmethyl*)*cinnoline* (**9**) (0.60 g, 30%) as tan needles, m.p. 109—110 °C (from ethyl acetate–light petroleum) (Found: C, 61.4; H, 4.6; N, 9.1. $C_{16}H_{14}N_2Se$ requires C, 61.4; H, 4.55; N, 8.9%); δ_H 8.47—8.42 (1 H, dd, *J* 8.5 and 0.6 Hz, 8-H), 7.80—7.74 (1 H, m, 5-H by n.O.e. difference experiments), 7.71—7.55 (2 H, m, 6- and 7-H), 7.42—7.38 (2 H, *o*-protons by n.O.e. difference experiments), 7.33—7.14 (3 H, m, *m*-and *p*-H), 4.43 (2 H, m, *J* 11.5 Hz, CH_2Se by n.O.e. difference experiments), and 2.80 (3 H, s, 3-Me); *m/z* (%) [317(2.0), 316(10), 315(9), 314(50), 312(25), 311(9), 310(9), 308(1) M^+], 209(17), 158(20), 157(78), 129(29), 127(45), and 77(21).

(E)- *and* (Z)-2-(2-*Methoxycarbonylaminophenyl*)*but*-2-*ene* (**12**).—The amine mixture (**11**) (1.00 g, 6.8 mmol), methyl chloroformate (2.56 g, 27.0 mmol), and anhydrous potassium carbonate (5.63 g, 40.8 mmol) in dry acetone (15 ml) were heated to reflux for 16 h. Filtration, evaporation to dryness under reduced pressure and purification by flash chromatography using light petroleum and ethyl acetate (10:1) as eluant gave a mixture of the *E*- and *Z*-butene (**12**) (0.58 g, 45%) as a colourless oil (Found: M^+, 205.1119. $C_{12}H_{15}NO_2$ requires *M*, 205.1103); $\nu_{max.}$liquid film) 3 420(NH), 3 060, 3 020, 2 960, 2 920, 2 860, 1 735(C=O), 1 520, 1 220, and 755 cm^{-1}; δ_H(*E*-butene) 8.11 (1 H, d, *J* 8.3 Hz, 3-H), 7.31—7.20 (1 H, m, 5′-H by n.O.e. difference experiments), 7.09—7.00 (2 H, m, 4′- and 6′-H), 6.79 (1 H, br s, NH), 5.75 (1 H, qq, *J* 6.8 and 1.6 Hz, olefinic H), 3.76 (3 H, s, CO_2Me), 1.95 (3 H, dq, *J* 1.5 and 1.6 Hz, 1-Me), and 1.41 (3 H, dq, *J* 6.8 and 1.5 Hz, 4-Me of *E*-isomer from n.O.e. difference experiments), (*Z*-butene) 8.06—8.00 (1 H, m, 3′-H), 7.28—7.19 (1 H, m, 5′-H), 7.07—6.96 (2 H, m, 4′- and 6′-H), 6.88 (1 H, br s, NH), 5.51 (1 H, qq, *J* 6.8 and 1.5 Hz, olefinic H), 3.76 (3 H, s, CO_2Me), 1.92 (3 H, dq, *J* 1.5 and 1.1 Hz, 1-Me), and 1.80 (3 H, dq, *J* 6.8 and 1.1 Hz, 4-Me of *Z*-isomer by n.O.e. difference experiments); *m/z* (%) 205(27, M^+), 146(100, $M - CO_2Me$), and 131(24).

(E)- *and* (Z)-1,4-*Dibromo*-2-(2-*methoxycarbonylaminophenyl*)*but*-2-*ene* (**13**).—*E*- and *Z*-Butene (**12**) (0.20 g, 9.8 mmol), *N*-bromosuccinimide (0.35 g, 20 mmol), and dibenzoyl peroxide (0.04 g, 0.16 mmol) in carbon tetrachloride (10 ml) were heated to reflux for 6 h. The solution was filtered when cold and evaporated under reduced pressure. Purification by flash chromatography using ethyl acetate–light petroleum (9:1) as eluant gave first (E)-1,1,4-*tribromo*-2-(2-*methoxycarbonylaminophenyl*)*but*-2-*ene* (0.04 g, 9%) as an unstable colourless oil (Found: M^+, 440.8407. $C_{12}H_{12}{}^{79}Br_2{}^{81}BrN$ requires *M*, 440.8397); $\nu_{max.}$(liquid film) 3 430(NH), 1 740(C=O), and 1 220 cm^{-1}; δ_H 7.92 (1 H, d, *J* 6.0 Hz, 3′-H), 7.47—7.38 (1 H, m, 5′-H), 7.14—7.04 (2 H, m, 4′- and 6′-H), 6.62 (1 H, d, *J* 11.0 Hz, olefinic H from n.O.e. difference experiments), 5.59 (1 H, br s, NH), 5.70 (1 H, d, $CHBr_2$ *E*-stereochemistry from n.O.e. difference experiments), 4.18 (2 H, s, CH_2Br), and 3.77 (3 H, s, CO_2Me); *m/z* (%) 443 (2, M^+), 441(2, M^+), 362(12), 224(54), 222(55), and 143(100). Further elution gave 1,4-*bromo*-2(2-*methoxycarbonylaminophenyl*)*but*-2-*ene* (**13**) (0.26 g, 74%) as an unstable colourless oil containing both the *E*- and *Z*-isomers (9:1) (Found: M^+, 362.9301. $C_{12}H_{13}{}^{79}Br^{81}BrN$ requires *M*, 362.9292); $\nu_{max.}$(liquid film) 3 420(NH), 1 730(C=O), 1 230, and 760 cm^{-1}; δ_H 8.05—8.00 (1 H, m, 3′-H), 7.44—7.35 (1 H, m, 5′-H), 7.18—7.06 (2 H, m, 4′- and 6′-H), 6.72 (1 H, m, 5′-H), 6.68 (1 H, br s, NH) 6.32 (1 H, t, *J* 8.0 Hz, H of *E*-isomer from n.O.e. difference experiments), 5.96 (1 H, t, *J* 8.5 Hz, H of *Z*-isomer from n.O.e. difference experiments), 4.26 (2 H, s, CH_2Br of *Z*-isomer), 4.18 (2 H, s, CH_2Br of *E*-isomer), 4.18 (2 H, d, CH_2Br of *Z*-isomer), 3.77 (3 H, s, CO_2Me), and 3.68 (2 H, d, CH_2Br of *E*-isomer); *m/z* (%) 365(1, M^+), 363(2, M^+), 361(1, M^+), 284(15, $M - Br$), 282(15, $M - Br$), 203(16, $M - Br_2$), and 144(100).

1-(*Methoxycarbonyl*)-4-(*methoxymethyl*)-1,2-*dihydroquinoline* (**14**).—Sodium methoxide (0.20 g, 3.7 mmol) in methanol (5 ml) was added to the dibromides (**13**) (0.20 g, 0.55 mmol) in methanol (10 ml) cooled to 0 °C. The solution was heated to reflux for 16 h and neutralised with 2M hydrochloric acid. The mixture was evaporated to low volume under reduced pressure, extracted with ether (3 × 20 ml) and the extract dried and evaporated under reduced pressure to give the crude product (0.12 g, 93%). Purification of this by flash chromatography using light petroleum–ethyl acetate (2:1) as eluant, gave the *title compound* (**14**) (0.10 g, 78%) as a colourless oil which discoloured with time (Found: M^+, 233.1061. $C_{13}H_{15}NO_3$ requires *M*, 233.1052); $\nu_{max.}$(liquid film) 1 700, 1 600, 1 230, and 1 100 cm^{-1}; δ_H 7.56 (1 H, dd, *J* 7.5 and 1.5 Hz, 8-H), 7.35 (1 H, dd, *J* 7.5 and 1.5 Hz, 5-H), 7.24 (1 H, dt, *J* 7.5 and 1.5 Hz, 6-H), 7.11 (1 H, dt, *J* 7.5 and 1.5 Hz, 7-H), 6.06 (1 H, dt, *J* 4.4 and 0.8 Hz, H), 4.40 (2 H, dt, *J* 4.4 and 0.8 Hz, CH_2), 4.27 (2 H, dt, *J* 1.0 and 0.8 Hz, CH_2OMe), 3.77 (3 H, s, CO_2Me), and 3.38 (3 H, s, CH_2OMe); *m/z* (%) 233(94, M^+), 232(47), 218(67, $M - Me$), 188(100), 151(74), 144(73), 130(50), 86(67), and 84(97).

4-*Methoxymethylquinoline* (**16**).—The dibromide (**13**) (0.40 g, 1.1 mmol), sodium hydroxide (0.10 g, 2.5 mmol) in methanol (7 ml), and water (8 ml) were heated to reflux for 16 h. The solution was evaporated to low volume under reduced pressure and neutralised with 2M hydrochloric acid. The mixture was

extracted with ether (3 × 20 ml) and the extract dried and evaporated to dryness under reduced pressure to give a mixture containing 4-methoxymethylquinoline (**16**) and, by ^{1}H n.m.r. evidence, 4-*methoxymethyl*-1,2-*dihydroquinoline* (**15**); the mixture when stirred in chloroform (10 ml) for 24 h no longer contained (**15**); δ_H (from 90 MHz spectrum of initial product mixture) 8.10—6.42 (4 H, m, ArH), 5.76 (1 H, m, olefinic H), 4.23 (2 H, m, CH_2OMe), 4.17 (2 H, m, CH_2), 4.10 (1 H, br s, NH), and 3.42 (3 H, s, Me). Purification by flash chromatography using light petroleum–ethyl acetate (2:1) as eluant gave 4-methoxymethylquinoline (**16**) (0.08 g, 42%) as a colourless oil, b.p. 140—145 °C/6 mmHg (lit.,[14] 142—145 °C/6 mmHg) (Found: M^+, 173.0831. $C_{11}H_{11}NO$ requires M, 173.0841); δ_H 8.92 (1 H, m, 8-H), 8.28 (1 H, d, J 8.4 Hz, 4-H), 8.00 (1 H, d, 3-H), 7.79 (1 H, dd, J 7.7 and 1.5 Hz, 5-H), 7.67—7.57 (2 H, m, 6- and 7-H), 4.98 (2 H, d, J 1.0 Hz, CH_2), and 3.56 (3 H, s, Me); m/z (%) 173(60, M^+), 160(44), 144(88), 143(96), 130(100), and 115(56).

4-(*Bromomethyl*)-4-*vinyl*-1,4-*dihydro*-2H-3,1-*benzoxazin*-2-*one* (**17**).—The dibromide (**13**) (0.20 g, 0.56 mmol) in benzene (6 ml) was added to silver trifluoroacetate (0.26 g, 1.16 mmol) and tetramethylammonium bromide (0.01 g, 0.03 mmol) in water (8 ml) and stirred vigorously for 16 h in the dark. The benzene layer was separated, dried and evaporated under reduced pressure and the residue purified by flash chromatography using light petroleum–ethyl acetate (1:1) as eluant to give the *cyclic carbamate* (**17**) (0.10 g, 58%) as a colourless oil (Found: M^+, 266.9891. $C_{11}H_{10}{}^{79}BrNO_2$ requires M, 266.9894); $\nu_{max.}$ 3 420(NH), 3 100, 3 000, 2 940, 1 720, 1 600, 1 500, and 1 360 cm^{-1}; δ_H 9.56 (1 H, br s, NH), 7.35—7.27 (1 H, m, ArH), 7.14—7.10 (2 H, m, ArH), 6.96—6.93 (1 H, m, ArH), 6.04 (1 H, dd, J 10.6 and 17.0 Hz, olefinic H), 5.39 (1 H, dd, J 10.6 and 0.3 Hz, olefinic H), 5.33 (1 H, dd, J 17.0 and 0.3 Hz, olefinic H), and 3.90 and 3.80 (2 H, ABq, J 7.6 Hz, CH_2Br); δ_C 151.86(s), 135.88(d), 134.80(s), 129.72(d), 124.64(d), 123.32(d), 119.61(s), 118.43(t), 115.06(d), 84.72(s), and 36.74(t); m/z (%) 269(5, M^+), 267(5, M^+), 175(12), and 174(100).

(E)- *and* (Z)-2-(2-*Phthalimidophenyl*)*but*-2-*ene* (**18**).—The amines (**11**) (4.08 g, 27.8 mmol), phthalic anhydride (4.20 g, 28.4 mmol), and triethylamine (8 ml) in toluene (250 ml)[15] were heated to reflux for 16 h. Evaporation under reduced pressure gave the mixed *E*- and *Z*-*phthalimides* (**18**) (6.08 g, 80%) as white needles (from methanol) (Found: C, 77.7; H, 5.45; N, 4.8. $C_{18}H_{15}NO_2$ requires C, 78.0; H, 5.45; N, 5.0%); $\nu_{max.}$ 1 780, 1 765, 1 740, 1 710, 1 610, 770, and 755 cm^{-1}; δ_H 7.97 (4 H, m, ArH), 7.51—7.20 (4 H, m, ArH), 5.44 (1 H, qq, J 6.8 and 1.5 Hz, olefinic H of *E*-isomer), 5.36 (1 H, qq, J 6.9 and 1.5 Hz, olefinic H of *Z*-isomer), 195 (3 H, dq, J 1.5 and 1.6 Hz, Me of *Z*-isomer), 1.88 (3 H, dq, J 1.5 and 1.2 Hz, Me of *E*-isomer), 1.52 (3 H, dq, Me of *E*-isomer), and 1.34 (3 H, dq, Me of *Z*-isomer); m/z (%) 277(100, M^+), 262(65, M − Me), 247(37, M − 2 × Me), 234(60), and 133(86).

(E)- *and* (Z)-1,4-*Diacetoxy*-2-(2-*phthalimidophenyl*)*but*-2-*ene* (**20**).—The butene mixture (**18**) (4.00 g, 14.4 mmol) and *N*-bromosuccinimide (5.40 g, 30.3 mmol) in carbon tetrachloride (200 ml) were heated to reflux over a 150 W light bulb for 16 h. The mixture was filtered whilst ice-cold and evaporated under reduced pressure to give a mixture containing (*E*)- and (*Z*)-1,4-*dibromo*-2-(2-*phthalimidophenyl*)*but*-2-*ene* (**19**) (from ^{1}H n.m.r. evidence). The crude mixture was dissolved in dry acetonitrile (200 ml), 18-crown-6 ether (0.50 g, 1.9 mmol) and potassium acetate (9.00 g, 91.7 mmol) were added, and the mixture was stirred vigorously at room temperature for 16 h. This was filtered, and the filtrate evaporated under reduced pressure. The residue was dissolved in methylene dichloride (200 ml) and the solution washed with saturated aqueous potassium chloride (2 × 100 ml), dried, and evaporated under reduced pressure and the product purified by flash chromatography using light petroleum–ethyl acetate (4:1) as eluant to give the *title compound* (**20**) (2.44 g, 43%) as white needles (from ethyl acetate), (*E*- to *Z*-ratio of 1:4) (Found: C, 67.1; H, 4.85; N, 3.3. $C_{22}H_{19}NO_6$ requires C, 67.2; H, 4.85; N, 3.6%); $\nu_{max.}$ 1 770, 1 730, 1 600, 770, and 760 cm^{-1}; δ_H 7.97—7.74 (4 H, m, ArH), 7.54—7.24 (4 H, m, ArH), 5.80 (1 H, t, J 7.1 Hz, olefinic H of *Z*-isomer), 5.73 (1 H, t, J 7.1 Hz, olefinic H of *E*-isomer), 4.82 (2 H, s, CH_2 of *E*-isomer), 4.74 (2 H, s, CH_2 of *Z*-isomer), 4.60 (2 H, d, CH_2 of *E*-isomer), 4.38 (2 H, d, CH_2 of *Z*-isomer), 2.00 (3 H, s, Me of *Z*-isomer), 1.89 (3 H, s, Me of *E*-isomer), 1.82 (3 H, s, Me of *Z*-isomer), and 1.75 (3 H, s, Me of *E*-isomer); m/z (%) 393(0.2, M^+), 333(10, M − HCO_2CH_3), 291(100), 262(24), and 133(24).

(E)- *and* (Z)-2-(2-*Phthalimidophenyl*)*but*-2-*ene*-1,4-*diol* (**21**).—The diacetate (**20**) (2.50 g, 6.4 mmol) was dissolved in 90% methanol (500 ml) and concentrated hydrochloric acid (0.4 ml) was added dropwise with stirring. The solution was then heated to reflux for 16 h and neutralised with 10% aqueous sodium carbonate. The mixture was evaporated to low volume, extracted with methylene dichloride (4 × 100 ml), and the extract dried; the residue was purified by flash chromatography using ether–acetone (4:1) as eluant to give the *diol* (**21**) (1.75 g, 89%) as white plates (from ethyl acetate and light petroleum) (*E*- to *Z*- ratio of 1:4) (Found: C, 69.8; H, 4.9; N, 4.4. $C_{18}H_{15}NO_4$ requires C, 69.9; H, 4.9; N, 4.5%); $\nu_{max.}$ 3 580, 1 780, 1 760, 1 735, 1 710, and 1 380 cm^{-1}; δ_H 7.91—7.73 (4 H, m, ArH), 7.55—7.24 (4 H, m, ArH), 5.84 (1 H, t, J 7.4 Hz, olefinic H of *Z*-isomer), 5.64 (1 H, t, J 6.8 Hz, olefinic H of *E*-isomer), 4.38 (2 H, s, CH_2 of *E*-isomer), 4.20 (2 H, s, CH_2 of *Z*-isomer), 4.05 (2 H, d, CH_2 of *E*-isomer), 3.87 (2 H, d, CH_2 of *Z*-isomer), and 2.78 (2 H, br s, 2 × OH); m/z (%) 308(0.5, M − 1), 292(13), 291(72, M − H_2O), 263(59), 262(65), and 133(100).

(E)- *and* (Z)-2-(2-*Aminophenyl*)*but*-2-*ene*-1,4-*diol* (**22**).—The phthalimides (**21**) (0.90 g, 2.9 mmol) and hydrazine hydrate (0.45 g, 9.0 mmol) in methanol (12 ml) were stirred vigorously at room temperature for 16 h. The solution was filtered and the residual solids washed with chloroform (10 ml). The combined filtrate were evaporated under reduced pressure and the residue purified by flash chromatography using chloroform–methanol (14:1) as eluant to give (E)- and (Z)-2-(2-*aminophenyl*)*but*-2-*ene*-1,4-*diol* (**22**) (0.48 g, 92%) as a yellow oil which rapidly discoloured with time (Found: M^+, 179.0940. $C_{10}H_{13}NO_2$ requires M, 179.0946); $\nu_{max.}$(liquid film) 3 350 br, 3 020, 2 935, 2 885, 1 620, 1 580, 1 495, and 1 450 cm^{-1}; δ_H 7.13—7.02 (4 H, m, ArH), 6.02 (1 H, t, J 7.1 Hz, olefinic H of *Z*-isomer), 5.85 (1 H, t, J 6.8 Hz, olefinic H of *E*-isomer), 4.33 (2 H, s, CH_2 of *E*-isomer), 4.27 (2 H, d, CH_2 of *E*-isomer), 4.17 (2 H, s, CH_2 of *Z*-isomer), 3.91 (4 H, br s, NH_2 and 2 × OH), and 3.87 (2 H, d, CH_2 of *Z*-isomer); m/z (%) 179(28, M^+), 161(12, M − H_2O), 160(20), 144(34), 130(100), 118(37), and 117(25).

Cinnoline-3,4-*dicarbaldehyde* (**1**).—Sodium nitrite (0.47 g, 7.1 mmol) in water (10 ml) was added dropwise to a cooled solution of the amines (**22**) (1.17 g, 6.5 mmol) in 2M hydrochloric acid (25 ml, 1.83 g, 50 mmol) at such a rate that the temperature remained at 0—5 °C. The mixture was stirred for 40 h at this temperature, after which it was neutralised with 10% aqueous sodium carbonate and extracted with chloroform (5 × 50 ml). Work-up of the extract gave crude 4-*hydroxymethylcinnoline*-3-*carbaldehyde* (**24**) (0.93 g, 75%) as an unstable brown solid; δ_H 9.38 (1 H, br s, CHO from n.O.e. difference experiments), 8.53—8.47 (1 H, m, 5-H), 8.07—8.02 (1 H, m, 8-H from n.O.e. difference experiments), 7.88—7.77 (2 H, m, 6- and 7-H), 5.28 (2 H, br s,

4-CH_2 from n.O.e. difference experiments), and 3.68 (1 H, br s, OH). This solid was immediately dissolved in dry methylene dichloride (15 ml) and added to a rapidly stirred suspension of pyridinium dichromate (2.75 g, 7.3 mmol) in dry methylene dichloride (15 ml); the mixture was then stirred at room temperature for 16 h. After this, ether (30 ml) was added and the solids were filtered off and washed with ether (3 × 50 ml); the filtrate and washings were combined and evaporated under reduced pressure. Purification of the residue by flash chromatography using ethyl acetate–light petroleum (3:2) as eluant gave *cinnoline*-3,4-*dicarbaldehyde* (**1**) (0.19 g, 16%) as yellow needles, m.p. 144—145 °C (from light petroleum) which discoloured with time (Found: M^+, 186.0412. $C_{10}H_6N_2O_2$ requires M, 186.0429); $\nu_{max.}$($CHBr_3$) 1 685 and 1 680 cm^{-1}; δ_H 10.56 (1 H, s, 4-CHO), 9.56 (1 H, s, 3-CHO), 9.09—9.01 (1 H, m, 5-H), 8.76—8.68 (1 H, m, 8-H), and 8.06—7.96 (2 H, m, 6- and 7-H); δ_C[$(CD_3)_2SO$] 192.52(d), 151.74(s), 146.34(d), 134.62(d), 131.69(s), 131.27(d), 130.75(d), 123.82(d), 122.75(s), and 120.89(s); *m/z* (%) 186(10, M^+), 158(100), 129(6), 102(37), and 101(19).

4-*Hydroxymethylcinnoline*-3-*carbaldehyde* (**24**).—The dicarbaldehyde (**1**) (20 mg, 0.108 mmol) and sodium borohydride (10 mg, 0.264 mmol) in 50% ethanol (5 ml) were heated to reflux for 30 min after which the mixture was poured into water (50 ml) and extracted with chloroform (2 × 50 ml). Evaporation of the extract under reduced pressure gave the *title compound* (**24**) (0.018 g, 89%) as white needles, m.p. 153—154 °C (from light petroleum) which discoloured rapidly with time (Found: M^+, 188.0601. $C_{10}H_8N_2O_2$ requires M, 188.0586); $\nu_{max.}$ 3 300br s, 2 920, 2 860, 1 575, and 1 700 cm^{-1}; δ_H 9.38 (1 H, s, CHO), 8.53—8.47 (1 H, m, 5-H), 8.07—8.02 (1 H, m, 8-H), 7.88—7.77 (2 H, m, 6- and 7-H), 5.28 (2 H, s, 4-CH_2), and 3.68 (1 H, br s, OH); δ_C[$(CD_3)_2SO$] 149.12(s), 142.64(d), 134.52(s), 131.04(d), 130.61(d), 130.43(s), 129.39(d), 123.50(s), 123.34(d), and 57.98(t); *m/z* (%) 188(6, M^+), 160(100), 158(88), 131(47), and 102(88).

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References

1 J. D. Loudon and A. D. B. Sloan, *J. Chem. Soc.*, 1962, 3262.
2 A. Mallouli and Y. Lepage, *Synthesis*, 1980, 689.
3 H. J. Haas and A. Seeliger, *Chem. Ber.*, 1973, **96**(9), 2427.
4 R. N. Castle and M. Onda, *J. Org. Chem.*, 1961, **26**, 4465.
5 D. I. Haddlesey, P. Mayor, and S. S. Szinai, *J. Chem. Soc.*, 1964, 5269.
6 D. E. Ames and D. Bull, *Tetrahedron*, 1981, **37**, 2489.
7 D. H. R. Barton, R. A. H. F. Hui, D. J. Lester, and S. V. Ley, *Tetrahedron Lett.*, 1979, **35**, 3331.
8 K. Kurosawa, T. Takamura, Y. Ueno, J. F. W. McOmie, and N. D. Pearson, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 1914.
9 O. Widman, *Chem. Ber.*, 1883, **17**, 722.
10 M. H. Palmer and E. R. R. Russell, *J. Chem. Soc. C*, 1968, 2621.
11 R. Stoermer and O. Gaus, *Chem. Ber.*, 1912, **45**, 3104.
12 P. R. Wells and P. G. E. Alcorn, *Aust. J. Chem.*, 1963, **16**, 1108.
13 G. W. Gribble, E. J. Holubowitch, and M. C. Venuti, *Tetrahedron Lett.*, 1977, **33**, 2857.
14 M. Ikeda, S. Matsugashita, F. Tabusa, and Y. Takamura, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1166.
15 A. K. Bose, F. Greer, and C. C. Price, *J. Org. Chem.*, 1958, **23**, 1335.

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