Synthesis of 6-Hydroxy-1,4-dimethylisoquinoline and of Ethyl 7-Hydroxy-6-methoxy-1-methylisoquinoline-3-carboxylate

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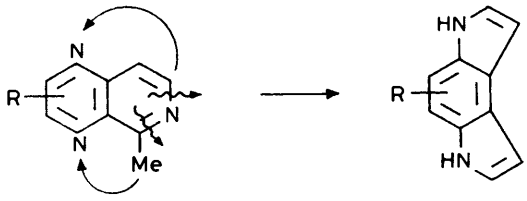
The syntheses of 6-methoxy- and 6-hydroxy-1,4-dimethylisoquinoline and of ethyl 7-hydroxy-6-methoxy-1-methylisoquinoline-3-carboxylate, key intermediates required for a synthetic approach[1] to the antitumour antibiotic CC-1065, are described.

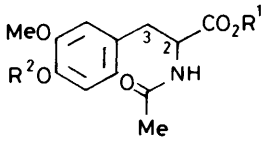
In our approach[1,2] to the synthesis of dihydrobenzo[1,2-*b*:-4,3-*b'*]dipyrroles, the heterocyclic unit found both in the highly potent antitumour antibiotic CC-1065[3] and also in the metabolites PDE-I and PDE-II,[4] which are phosphodiesterase inhibitors, an isoquinoline, with nitrogen substituents at C-5 and C-8, is transformed by opening of the pyridine ring followed by reclosures in an alternative sense, into the target tricyclic system (Scheme). The substituted isoquinolines needed for a



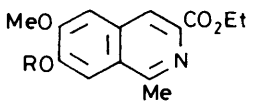
Scheme.

route to the natural materials required preparation of the title compounds, neither of which was known; we have now synthesized these and this work is described herein.

Synthesis of Ethyl 7-Hydroxy-6-methoxy-1-methylisoquinoline-3-carboxylate (**2b**).—Preparation of phenolic ester (**2b**)[5] proved to be straightforward using an unmodified Bischler-Napieralski route, despite doubts expressed[6] earlier.



(1)	R^1	R^2
a	H	H
b	Et	H
c	Et	CH_2Ph
d	Et	COPh

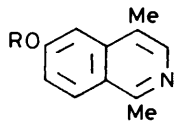


(2)	R	
a	H	3,4-dihydro-
b	H	
c	CH_2Ph	
d	COPh	
e	CH_2Ph	3,4-dihydro-
f	COPh	3,4-dihydro-

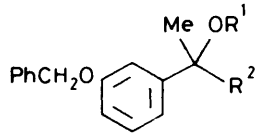
Condensation of vanillin with *N*-acetylglycine in acetic anhydride in the presence of sodium acetate gave an azlactone, reduction of which with sodium amalgam in alkaline solution, produced the amide acid (**1a**).[7] After esterification to produce the ester acetamide (**1b**), ring closure with hot phosphorus oxychloride, gave compound (**2a**), the regiochemistry of ring closure being confirmed by two aromatic singlet signals at δ 6.67 and 7.09 in the ^1H n.m.r. spectrum of the product. Dehydrogenation of compound (**2a**) with palladium in refluxing pyridine produced the required isoquinoline ester (**2b**).

The isoquinoline was protected before further use either by forming the benzoate (**2d**) from ester (**2b**) or by ring synthesis. Conversion of the acetamide (**1b**) into its benzyl ether (**1c**) or its benzoate (**1d**), followed by treatment with phosphorus oxychloride and polyphosphate ester respectively, gave compounds (**2e**) and (**2f**); palladium-catalysed dehydrogenation then produced the phenol-protected isoquinolines. In preparative terms however, especially on a larger scale, the ring synthesis producing the phenol itself was preferable.

Synthesis of 6-Hydroxy-1,4-dimethylisoquinoline (**3a**).—Although relatively few 4-methyl substituted isoquinolines have



(3)	R
a	H
b	CH_2Ph
c	Me



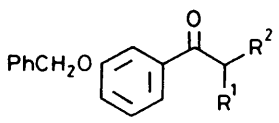
(4)	R^1	R^2
a	H	CH_2NHAc
b	$SiMe_3$	CN
c	H	CN
d	H	CH_2NH_2
e	Et	CH_2NHAc

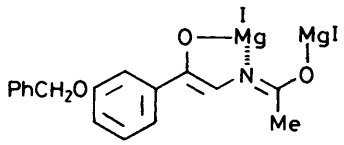
been reported,[8] this number does include 1,4-dimethylisoquinoline itself[8a,c-e] and we were, therefore, surprised when the synthesis of 6-hydroxy-1,4-dimethylisoquinoline (**3a**) proved not to be straightforward. No 4-methyl-, ring-A-oxygenated isoquinolines were known.

In order to avoid the need for a dehydrogenation,† our first approach aimed at the formation of the amide alcohol (**4a**), Pictet-Gams ring closure of which was expected to lead directly to the protected, fully aromatic isoquinoline (**3b**).

3-Benzyloxyacetophenone (**5a**) was monobrominated on the methyl group and nitrogen introduced *via* subsequent reaction with hexamine, to give the salt (**5b**), which on hydrolysis afforded the hydrochloride salt; this was then directly acetylated to produce (**5c**).

† Difficulties were reported[8d] in dehydrogenation of 3,4-dihydro-1,4-dimethylisoquinoline.

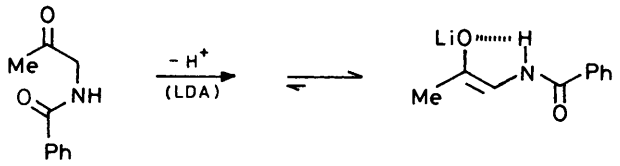




(6)

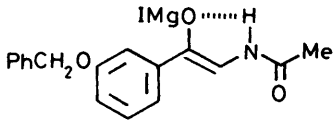
(5)	R^1	R^2
a	H	H
b	$(C_6H_{12}N_4)^+$ Br^-	H
c	NHAc	H
d	NHAc	Me

Although it was hoped that on treatment of the acetamide (**5c**) with 2 mol equiv. of methylmagnesium bromide, carbonyl addition, as well as the expected initial *N*-deprotonation, could be achieved, only starting material was recovered. Further, when iodomethane was added before aqueous work-up, a *C*-methylated derivative (**5d**) was obtained. Two explanations for these observations present themselves: in the first, one may envisage formation of the intramolecularly chelated magnesium enolate (**6**), which cannot now undergo carbonyl addition but which could be expected to *C*-methylate with iodomethane. An alternative view is based on the recent report[9] that, with the closely analogous keto amide (**7**), lithium di-isopropylamide effects a kinetic *N*-deprotonation; since, however, the *C*-deprotonated, intramolecularly hydrogen bond-stabilised, lithium enolate (**8**) is favoured thermody-



(7) (8)

namically, it is subsequently formed. This would explain the *C*-alkylation noted in the present iodomethane reaction, where the comparable species would be (**9**).

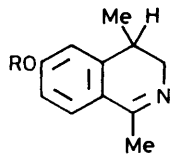


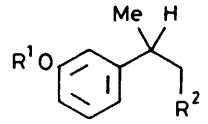
(9)

The use of excess of methyl-lithium with the keto amide (**5c**) did give the desired amide alcohol (**4a**), but, at best, as a 1:1 mixture with starting ketone. The amide alcohol could, however, be obtained by an alternative sequence involving reaction of the original ketone (**5a**) with trimethylsilyl cyanide to form the protected cyanohydrin (**4b**), aqueous acidic hydrolysis, to remove the silicon, followed by reduction with borane-THF complex, and finally acetylation then gave the amide alcohol (**4a**).

Ring closure of compound (**4a**) could not be achieved using the conditions normally employed for the Pictet–Gams variation of the Bischler–Napieralski isoquinoline synthesis, phosphorus oxychloride, polyphosphate ester, or phosphorus pentaoxide in hot decalin, giving complex mixtures of products. The alcohol (**4a**) was converted into the ether (**4e**) with ethanolic hydrogen chloride but attempts to ring close (**4e**) were unsuccessful. Isoquinoline ring closures of 2-acylamino-1-aryl-ethanols are known[10,8f] to involve dihydro-oxazoles, formed by interaction of amide and benzylic alcohol ether functions. It may be that non-productive sequences lead from the expected dihydro-oxazole in the present instance.

Abandoning the notion of avoiding a dehydrogenation stage, a synthesis of dihydroisoquinoline (**10a**) was developed. Condensation of 3-benzyloxybenzaldehyde with nitromethane





(10)	R
a	CH_2Ph
b	Me

(11)	R^1	R^2
a	CH_2Ph	NO_2
b	CH_2Ph	NH_2
c	CH_2Ph	NHAc
d	Me	NO_2
e	Me	NH_2
f	Me	NHAc

followed by conjugate addition of a methyl group using dimethylcopperlithium produced (**11a**). Nitro group reduction, acetylation, and phosphorus oxychloride ring-closure then gave (**10a**). All attempts to effect dehydrogenation of this benzyl-protected dihydroisoquinoline failed, the usual result being the production of complex mixtures of coloured materials. The sequence was repeated starting with 3-methoxybenzaldehyde, generating comparable intermediates (**11d—f**) then (**10b**). Dehydrogenation, with diphenyl disulphide, was now straightforward, and the isoquinoline (**3c**) was obtained. The latter when heated with 48% hydrobromic acid was converted into the target 6-hydroxy-1,4-dimethylisoquinoline (**3a**).

Experimental

General.—M.p.s were determined on a Kofler hot-stage microscope and are uncorrected. Wet organic solutions/extracts were dried with anhydrous $MgSO_4$, Na_2SO_4, or K_2CO_3 and evaporated at *ca.* 20 mmHg and *ca.* 40—70 °C using a rotary evaporator. Unless otherwise stated, u.v./vis. spectra were measured in ethanol using a Shimadzu UV/VIS 260 instrument; i.r. spectra were measured using Pye-Unicam SP3-200 or Perkin Elmer 1710 FT spectrometers; ^1H n.m.r. spectra of deuteriochloroform solutions, with TMS as internal standard, were measured on Perkin-Elmer R12B (60 MHz), Perkin-Elmer R34 (220 MHz), Varian SC 300 (300 MHz), or Varian XL 300 (300 MHz) spectrometers. Mass spectra were determined by the electron impact method on an AEI MS 30 instrument coupled to a DS 55 data system. For i.r. spectra, only clearly distinguished and unambiguously assignable absorptions are given. Only ions of > 10% of base peak are given for mass spectra, except where a less intense ion is of importance for structure assignment.

N-Acetyl-β-(4-hydroxy-3-methoxyphenyl)alanine Ethyl Ester (**1b**).—Dry hydrogen chloride was bubbled vigorously into a solution of the amide acid (**1a**)[5] (28 g) in dry ethanol (300 ml) for 5 min after which the mixture was refluxed for 0.5 h. It was then evaporated, diluted with water, made basic with sodium hydrogen carbonate, and extracted with ethyl acetate. Evaporation of the extract gave the *ester* (**1b**) as a brown gum (23 g, 74%), m.p. 105—107 °C (from EtOH–H_2O); $\nu_{max.}$(Nujol) 3 347, 1 738, and 1 657 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.08 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.76 (3 H, s, CH_3CO), 2.80 (2 H, m, CH_2CH), 3.70

(3 H, s, CH_3O), 4.02 (2 H, q, *J* 7 Hz, CH_3CH_2), 4.37 (1 H, m, CH_2CHN), 6.59 (1 H, d, *J* 7 Hz, ArH), 6.67 (1 H, d, NH), 6.78 (1 H, s, ArH), 8.29 (1 H, d, *J* 7 Hz, ArH), and 8.80 (1 H, s, OH); *m/z* 281 ($M^{+\cdot}$, 10%), 222 (95), 177 (23), 166 (26), 150 (26), and 137 (100) (Found: C, 60.1; H, 6.9; N, 4.9%; *M*, 281.1270. $C_{14}H_{19}NO_5$ requires C, 59.8; H, 6.8; N, 5.0%; *M*, 281.1263).

Ethyl 3,4-Dihydro-7-hydroxy-6-methoxy-1-methylisoquinoline-3-carboxylate (**2a**).—Freshly distilled phosphorus oxychloride (90 g) was added to a solution of the amide ester (**1b**) (30 g) in dry chloroform (300 ml) and the mixture refluxed for 20 h. Solvent was then removed by evaporation under reduced pressure, and ice–water added. The mixture was then basified with sodium hydrogen carbonate and extracted with chloroform. After drying, evaporation of the extract gave the *dihydroisoquinoline* (**2a**) as a pale yellow semicrystalline, air-sensitive solid (20 g, 71%), which was utilised without further purification.

Ethyl 7-Hydroxy-6-methoxy-1-methylisoquinoline-3-carboxylate (**2b**).—A solution of the dihydroisoquinoline (**2a**) (20 g) in pyridine (150 ml) was heated at reflux with palladium–charcoal (10%) for a total of 48 h. Initially 1 g of catalyst was added and thereafter further portions (0.5 g) were added after each 12 h period. The reaction mixture was cooled, filtered through a pad of Celite and evaporated under reduced pressure to give the *isoquinoline* (**2b**) (19 g, *ca.* 100%), as a crystalline solid, m.p. 253—255 °C (from EtOH); $\nu_{max.}$(film) 3 583 and 1 718 cm^{-1}; δ_H[$(CD_3)_2SO$] 1.30 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.72 (3 H, s, 1-CH_3), 3.40 (1 H, br s, OH), 3.91 (3 H, s, CH_3O), 4.31 (2 H, q, *J* 7 Hz, CH_3CH_2), 7.43 (1 H, s, ArH), 7.54 (1 H, s, ArH), and 8.29 (1 H, s, 4-H); *m/z* 261 ($M^{+\cdot}$, 37%), 216 (12), 189 (100), and 146 (33) (Found: C, 64.3; H, 5.9; N, 5.3. $C_{14}H_{15}NO_4$ requires C, 64.4; H, 5.7; N, 5.4%).

Ethyl 7-Benzoyloxy-6-methoxy-1-methylisoquinoline-3-carboxylate (**2d**).—(a) *By benzoylation of* (**2b**). A solution of the phenol (**2b**) (19 g) in pyridine (150 ml) was treated with benzoyl chloride (12 g) at 5 °C. After 3 h at room temperature a precipitate of pyridine hydrochloride had formed. The mixture was taken almost to dryness under reduced pressure and added to ice–water; it was extracted with ethyl acetate. The organic phase was extracted with hydrochloric acid (3M; 4 × 200 ml), and the aqueous extracts were made basic with sodium hydrogen carbonate; the product was then extracted with ethyl acetate. Evaporation of the dried extract under reduced pressure gave the *benzoate* (**2d**) (15 g, 56%) as a pale yellow crystalline solid, m.p. 147—150 °C; $\nu_{max.}$(Nujol) 1 735 and 1 700 cm^{-1}; δ_H 1.45 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.94 (3 H, s, 1-CH_3), 3.94 (3 H, s, CH_3O), 4.51 (2 H, q, *J* 7 Hz, CH_3CH_2), 7.33 (1 H, s, ArH), 7.56 (2 H, m, ArH), 7.70 (1 H, m, ArH), 7.96 (1 H, s, ArH), 8.28 (2 H, d, *J* 8 Hz, ArH), and 8.41 (1 H, s, 4-H); *m/z* 365 ($M^{+\cdot}$, 2%), 320 (1), 293 (7), 243 (1), and 105 (100) (Found: C, 69.1; H, 5.4; N, 3.7. $C_{21}H_{19}NO_5$ requires C, 69.0; H, 5.2; N, 3.8%).

(b) *By dehydrogenation of* (**2f**). A solution of the dihydroisoquinoline (**2f**) (2 g) in dry toluene (100 ml) was heated at reflux with palladium–charcoal (10%) (100 mg) for 36 h, further portions (100 mg) of catalyst being added after each 12 h interval. The cooled mixture was filtered through Celite and evaporated to give the isoquinoline (**2d**) (1.7 g, 85%) as a brown crystalline solid.

N-*Acetyl*-β-(4-*benzyloxy*-3-*methoxyphenyl*)*alanine Ethyl Ester* (**1c**).—A mixture of the phenol (**1b**) (0.77 g), benzyl chloride (0.89 g), potassium carbonate (0.49 g), and sodium iodide (10 mg) was heated at reflux in ethanol (50 ml) for 2.5 h. The mixture was filtered and evaporated under reduced pressure to give a residue which was partitioned between water and ethyl acetate; the organic phase was then separated, dried, and evaporated to give a pale orange gum. Purification of this by chromatography over silica, eluting with toluene–ethyl acetate (5:1), gave the *benzyl ether* (**1c**) as white crystals (0.65 g, 65%), m.p. 157—160 °C; $\nu_{max.}$(Nujol) 1 640, 1 740, and 3 260 cm^{-1}; δ_H 1.21 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.96 (3 H, CH_3CON), 3.15 (2 H, d, *J* 7 Hz, CH_2CH), 3.85 (3 H, s, CH_3O), 4.25 (2 H, q, *J* 7 Hz, CH_3CH_2), 4.95 (1 H, m, CH_2CH], 5.12 (2 H, s, $PhCH_2O$), 6.10 (1 H, br, NH), 6.45—6.85 (3 H, m, ArH), and 7.4 (5 H, m, ArH); *m/z* 371 ($M^{+\cdot}$, 4%), 312 (22), and 91 (100) (Found: C, 67.8; H, 7.0; N, 4.0. $C_{21}H_{25}NO_5$ requires C, 67.9; H, 6.7; N, 3.8%).

N-*Acetyl*-β-(4-*benzoyloxy*-3-*methoxyphenyl*)*alanine Ethyl Ester* (**1d**).—A solution of the phenol (**1b**) (2 g) in pyridine (30 ml) was treated with benzoyl chloride (1 g) at room temperature for 4 h. The mixture was poured onto ice and extracted with ethyl acetate. The organic phase was washed with dilute HCl, dried, and evaporated to give a brown gum which was purified by chromatography over silica, eluting with toluene–ethyl acetate to give the *benzoate* (**1d**) (1.8 g, 66%) as a white crystalline solid, m.p. 118—119 °C (from EtOH); δ_H 1.21 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.95 (3 H, s, CH_3CON), 3.12 (2 H, d, *J* 7 Hz, CH_2CH), 3.74 (3 H, s, CH_3O), 4.15 (2 H, q, *J* 7 Hz, CH_3CH_2), 4.85 (1 H, m, CH_2CH), 6.17 (1 H, br, NH), and 6.15—8.17 (8 H, ArH); *m/z* 385 ($M^{+\cdot}$, 1%), 326 (14), and 105 (100) (Found: C, 65.8; H, 6.1; N, 3.5. $C_{21}H_{23}NO_6$ requires C, 65.45; H, 6.0; N, 3.6%).

Ethyl 7-Benzyloxy-3,4-dihydro-6-methoxy-1-methylisoquinoline-3-carboxylate (**2e**).—A solution of the amide (**1c**) (1 g) in phosphorus oxychloride (10 ml) was heated at reflux for 3 h. The phosphorus oxychloride was removed by evaporation under reduced pressure and ice–water added; the residue was then made basic with sodium hydrogen carbonate and extracted with ethyl acetate. The dried organic layer was evaporated under reduced pressure to give a brown gum which was purified by chromatography over silica, eluting with toluene–ethyl acetate (5:1) to give the dihydroisoquinoline (**2e**) (0.62 g 65%) as pale yellow crystals, m.p. 162—163 °C (from EtOH); $\nu_{max.}$(Nujol) 1 725 cm^{-1}; δ_H 1.15 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.16 (3 H, d, *J* 2 Hz, 1-CH_3), 2.88 (2 H, d, *J* 8 Hz, CH_2CH), 3.96 (3 H, s, CH_3O), 4.18 (1 H, d, *J* 8 Hz, CH_2CH), 4.28 (2 H, q, *J* 7 Hz, CH_3CH_2), 5.18 (2 H, s, $PhCH_2O$), 6.76 (1 H, s, ArH), 7.06 (1 H, s, ArH), and 7.43 (5 H, m, ArH); *m/z* 353 ($M^{+\cdot}$, 2%), 280 (29), 262 (4), 189 (14), 188 (10), 160 (8), and 91 (100) (Found: C, 71.4; H, 6.75; N, 3.8. $C_{21}H_{23}NO_4$ requires C, 71.4; H, 6.5; N, 4.0%).

Ethyl 7-Benzoyloxy-3,4-dihydro-6-methoxy-1-methylisoquinoline-3-carboxylate (**2f**).—The acetamide (**1d**) (0.5 g) in dry chloroform (50 ml) was heated at reflux with polyphosphate ester (4 g) for 2 days. The solvent was evaporated under reduced pressure and the residue poured onto ice, made basic with potassium carbonate, and extracted with ethyl acetate. The organic phase was then extracted with HCl (3M), and the aqueous phase made basic with sodium hydrogen carbonate and product extracted into ethyl acetate. Work-up of the extract gave a brown oil which was further purified by chromatography over silica to produce the *dihydroisoquinoline* (**2f**) as a pale yellow gum (0.33 g, 70%), $\nu_{max.}$($CHCl_3$) 1 740 and 1 612 cm^{-1}; δ_H 1.26 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.35 (3 H, d, *J* 2 Hz, 1-CH_3), 2.93 (2 H, d, *J* 9 Hz, CH_2CH), 3.80 (3 H, s, CH_3O), 4.2 (3 H, m, CH_2CH, CH_3CH_2), 6.82 (1 H, s, ArH), 7.31 (1 H, s, ArH), and 7.45—8.2 (5 H, m, ArH); *m/z* 376 ($M^{+\cdot}$, 1%), 326 (2), 294 (37), and 105 (100) (Found: *M*, 367.1421. $C_{21}H_{21}NO_5$ requires 367.1419).

Ethyl 7-Benzyloxy-6-methoxy-1-methylisoquinoline-3-carboxylate (**2c**).—A solution of the dihydroisoquinoline (**2e**) (0.5

g) in dry toluene (50 ml) was heated at reflux in the presence of palladium–charcoal (10%; 100 mg) for 15 h. After cooling, the mixture was filtered through a plug of Celite and evaporated to give the *isoquinoline* (**2c**) (0.48 g, *ca.* 95%) as white crystals, m.p. 153—155 °C (from EtOH); $\nu_{max.}$(Nujol) 1 705 cm^{-1}; δ_H 1.54 (3 H, t, *J* 7 Hz, CH_3CH_2), 2.95 (3 H, s, 1-CH_3), 4.10 (3 H, s, CH_3O), 4.57 (2 H, q, *J* 7 Hz, CH_3CH_2), 5.39 (2 H, s, $PhCH_2O$), 7.15 (1 H, s, ArH), 7.4 (6 H, m, ArH), and 8.29 (1 H, s, ArH); *m/z* 351 ($M^{+\bullet}$, 5%), 279 (5), 260 (6), and 91 (100) (Found: C, 72.2; H, 6.1; N, 3.9. $C_{21}H_{21}NO_4$ requires C, 71.8; H, 6.0; N, 4.0%).

Hexaminium Salt (**5b**).—Hexamine (2.48 g) was added to a solution of bromomethyl 3-benzyloxyphenol ketone (5.37 g) in solution in chloroform–ether (1:1; 200 ml) at room temperature and the mixture stirred overnight. The precipitated *salt* (**5b**) (7.8 g, *ca.* 100%) had m.p. 109—110 °C (Found: C, 56.2; H, 5.6; Br, 18.3; N, 12.1. $C_{21}H_{25}BrN_4O_2$ requires C, 56.6; H, 5.6; Br, 18.0; N, 12.6%).

N-[2-(3-*Benzyloxyphenyl*)-2-*oxoethyl*]*acetamide* (**5c**).—The hexaminium salt (**5b**) (7.27 g) was hydrolysed when stirred in ethanol (80 ml) with HCl (12M; 16 ml) at room temperature for 6 h. Solvent and excess of acid were removed by evaporation under reduced pressure and the resultant hydrochloride salt utilised for acetylation without further purification.

The crude hydrochloride was suspended in water–ethanol (6:5; 100 ml), and the suspension cooled to 5 °C whilst acetic anhydride (3.52 g) was added with stirring. Solid sodium acetate was added gradually to bring the pH up to *ca.* 4.5, the temperature being kept below 10 °C. Most of the ethanol was evaporated under reduced pressures; the residue was then added to water and the product extracted into ethyl acetate; work-up of the extract gave the crude product as a brown oil (4 g, 85%), which afforded the *acetamide* (**5c**) as crystals (3.3 g) from methanol, m.p. 109—110 °C, $\nu_{max.}$(Nujol) 3 400 and 1 670 cm^{-1}; δ_H 2.05 (3 H, s, CH_3CO), 4.68 (2 H, d, *J* 5 Hz, CH_2NH), 5.03 (2 H, s, CH_2O), 6.55 (1 H, br s, NH), and 7.1—7.5 (9 H, m, ArH); *m/z* 283 ($M^{+\bullet}$, 6%), 211 (37), and 91 (100) (Found: C, 71.9; H, 6.2; N, 4.9. $C_{17}H_{17}NO_3$ requires C, 72.0; H, 6.0; N, 4.9%).

N-[2-(3-*Benzyloxyphenyl*)-2-*hydroxypropyl*]*acetamide* (**4a**).—(*a*) A solution of methyl-lithium–lithium bromide (1.2M; 14 ml) was added to the ketone (**5c**) (1.2 g) in THF, under nitrogen at −78 °C and the mixture stirred at −78 °C for 2 h; during this period it became red. It was then added to water (10 ml) which was then saturated with sodium chloride and the organic layer separated. The aqueous phase was re-extracted with ethyl acetate and the combined, dried organic extracts evaporated to give a mixture (1.23 g) of starting ketone and product. These were separated by silica chromatography eluting with a gradient of toluene and ethyl acetate to give the ketone (**5c**) (0.54 g) and the *alcohol* (**4a**) (0.53 g, 39%), m.p. 120—121 °C; $\nu_{max.}$($CHCl_3$) 3 400, 3 350, and 1 640 cm^{-1}; δ_H 1.50 (3 H, s, CH_3COH), 1.90 (3 H, s, CH_3CO), 3.53 (2 H, q, *J* 10 Hz, CH_2N), 3.90 (1 H, s, OH), 5.05 (2 H, s, CH_2O), 6.00 (1 H, br, NH), and 6.90—7.50 (9 H, m, ArH); *m/z* 299 ($M^{+\bullet}$, 0.8%), 227 (20), 91 (100), and 73 (47) (Found: C, 72.5; H, 7.0; N, 4.4. $C_{18}H_{21}NO_3$ requires C, 72.3; H, 7.0; N, 4.7%). (*b*) The amino alcohol (**4d**) (300 mg) in ethyl acetate (10 ml) was treated with acetic anhydride (560 mg) at 80 °C for 5 min. The solvent was removed, the residue treated with aqueous potassium carbonate, and the product extracted into ethyl acetate to give the alcohol (**4a**) (324 mg, 90%), identical in all respects with material prepared as in (*a*) above.

N-[2-(3-*Benzyloxyphenyl*)-2-*ethoxypropyl*]*acetamide* (**4e**).—The alcohol (**4a**) (197 mg) was heated in refluxing ethanol in the presence of toluene-*p*-sulphonic acid (124 mg) for 10 h. The solvent was evaporated and the residue treated with aqueous potassium carbonate and ethyl acetate; evaporation of the dried organic phase gave the ether (**4e**) (197 mg, 91%) as an oil, $\nu_{max.}$($CHCl_3$) 3 440 and 1 665 cm^{-1}; δ_H 1.20 (3 H, t, *J* 7 Hz, CH_3CH_2), 1.57 (3 H, s, CH_3C), 2.01 (3 H, s, CH_3CON), 3.0—3.9 (2 H, m, CH_2N), 5.09 (2 H, s, CH_2O), and 6.8—7.4 (9 H, m, ArH); *m/z* 327 ($M^{+\bullet}$, 0.5%), 255 (43), and (91) 100 (Found: *M*, 327.1839. $C_{20}H_{25}NO_3$ requires *M*, 327.1834).

2-(3-*Benzyloxyphenyl*)-2-*trimethylsilyloxypropanenitrile* (**4b**) *and* 2-(3-*Benzyloxyphenyl*)-2-*hydroxypropanenitrile* (**4c**).—Cyanotrimethylsilane (1 ml) was added slowly to a mixture of the ketone (**5e**) (1.57 g) and zinc iodide (19 mg) with stirring at room temperature under nitrogen. After the mixture had been stirred for 3 h at 42 °C, it was added to cold HCl (1M) and the product extracted with ether. The ethereal layer was washed with water, dried, and evaporated to give the *cyano-silyl ether* (**4b**) (2.2 g, 95%) (Found: *M*, 325.1491. $C_{19}H_{23}NO_2Si$ requires *M*, 325.1498), which was utilised without purification for subsequent reactions. Hydrolysis of the cyano-silyl ether (2 g) was achieved by treatment with HCl (3M; 30 ml) at 60 °C for 3 h. The mixture was extracted with ether, and the extract dried and evaporated to afford the *cyanohydrin* (**4c**) (1.78 g) as a pale brown oil, δ_H 1.91 (3 H, s, CH_3C), 3.32 (1 H, br s, OH), 5.12 (2 H, s, CH_2O), and 6.9—7.5 (9 H, m, ArH); *m/z* 253 ($M^{+\bullet}$, 2%) 226 (28), and 91 (100) (Found: *M*, 253.1103. $C_{16}H_{15}NO_2$ requires *M*, 253.1103).

2-(3-*Benzyloxyphenyl*)-2-*hydroxypropanamine* (**4d**).—The cyano-silyl ether (**4b**) (1.7 g), prepared as above and dissolved in THF (10 ml), was reduced with borane–THF complex (1M; 5.2 ml) at room temperature for 15 h. After careful addition of 95% aqueous ethanol to destroy the excess of reagent, solvents were removed under reduced pressure and the residue partitioned between HCl (1M; 10 ml) and ether. The aqueous layer was made basic with potassium carbonate and the product extracted into chloroform; evaporation of the latter gave the *amine* (**4d**) (0.51 g, 38%) as a colourless oil, δ_H 1.44 (3 H, s, CH_3C), 2.0 (3 H, br, OH and NH), 2.71 and 3.02 (2 H, 2 × d, *J* 11 Hz, CH_2N), 5.01 (2 H, s, CH_2O), and 6.75—7.4 (9 H, m, ArH); *m/z* 257 ($M^{+\bullet}$; 3%), 229 (15), 228 (100), 227 (91), 226 (38), 212 (23), 149 (11), and 91 (35) (Found: *M*, 257.1419. $C_{16}H_{19}NO_2$ requires *M*, 257.1416).

2-(3-*Benzyloxyphenyl*)-1-*nitropropane* (**11a**).—2-(3-Benzyloxyphenyl)-1-nitroethene[11] (6.0 g) in THF (100 ml) was added slowly to the suspension produced by adding cuprous iodide (5.8 g) to methyl-lithium–lithium bromide complex in ether (1.2M; 26 ml) at 0 °C. After being stirred for a further 1 h the mixture was poured into dilute aqueous ammonia saturated with ammonium chloride and the product extracted with ether; work-up of the latter gave a brown oil (7.5 g) from which the pure *nitropropane* (**11a**) (4.8 g, 75%) was obtained as a colourless oil by chromatography over silica eluting with hexane–toluene (1:1), δ_H 1.33 (3 H, d, *J* 8 Hz, CH_3CH), 3.6 (1 H, m, CH_3CH), 4.45 (2 H, m, CH_2NO_2), 4.99 (2 H, s, CH_2O), and 6.7—7.4 (9 H, m, ArH); *m/z* 271 ($M^{+\bullet}$, 8%) and 91 (100) (Found *M*, 271.1202. $C_{16}H_{17}NO_3$ requires 271.1208).

N-[2-(3-*Benzyloxyphenyl*)*propyl*]*acetamide* (**11c**).—The nitropropane (**11a**) (0.91 g) in THF (10 ml) was added slowly to a solution of lithium aluminium hydride (0.37 g) in THF (10 ml) at room temperature and the mixture heated at 60 °C for 1 h. Cautious addition of a little water to decompose the excess of reagent, and then sodium hydroxide solution (50%), to dissolve the inorganic solids, was followed by separation of the organic layer. The aqueous layer was further extracted with ether, and the organic extracts were combined, dried, and evaporated to produce the amine (**1b**) as a somewhat unstable green oil. This

was immediately converted, in an exothermic reaction, into the corresponding acetamide by treatment with acetic anhydride (1.5 g). The acetylation was completed by heating the mixture at 90 °C for 20 min. Dilute aqueous sodium hydroxide was added at 0 °C and the mixture extracted with ether; work-up of the extract gave a crude yellow-brown oil (0.75 g) which was, purified by chromatography over silica to give the *acetamide* (**11c**) (0.47 g, 49%) as a colourless oil, $\nu_{max.}$(film) 3 300 and 1 650 cm^{-1}; δ_H 1.25 (3 H, d, *J* 7 Hz, CH_3CH), 1.85 (3 H, s, CH_3CON), 2.6—3.9 (3 H, m, CH_2CH), 5.02 (2 H, s, CH_2O), 5.5 (1 H, br, NH), and 6.6—7.6 (9 H, m, ArH); *m/z* 283 ($M^{+\bullet}$, 4%), 224 (45), and 91 (100) (Found: *M*, 283.1571. $C_{18}H_{21}NO_2$ requires *M*, 283.1572).

6-*Benzyloxy*-3,4-*dihydro*-1,4-*dimethylisoquinoline* (**10a**).—Phosphorus oxychloride (3 ml) was added to a solution of the acetamide (**11c**) (1.8 g) in dry toluene (40 ml) and the mixture heated at 110 °C for 2.5 h. Addition of ice–water and then sodium hydroxide, followed by separation of the toluene layer and further extraction of the aqueous phase with ethyl acetate gave combined organic extracts which were dried and evaporated to give the *dihydroisoquinoline* (**10a**) (1.6 g, 95%) as a pale brown gum, $\nu_{max.}$(film) 1 630 cm^{-1}; $\lambda_{max.}$ 215 and 270 nm, $\lambda_{max.}$(EtOH–H^+) 235 and 321 nm; δ_H 1.19 (3 H, d, *J* 7 Hz, CH_3CH), 3.34 (3 H, s, 1-CH_3), 2.8, 3.4, and 3.7 (3 × 1 H, m, CH_2CH), 5.10 (2 H, s, CH_2O), 6.9 (2 H, s + d, 5-H and 7-H), and 7.5 (6 H, m, ArH); *m/z* 265 ($M^{+\bullet}$, 52%), 174 (70), and 91 (100) (Found: *M*, 265.1469. $C_{18}H_{19}NO$ requires *M*, 265.1467).

2-(3-*Methoxyphenyl*)-1-*nitropropane* (**11d**).—A solution of 2-(3-methoxyphenyl)-1-nitroethene[11] (6.0 g) in THF (120 ml) was added dropwise over 40 min to the pale yellow suspension produced by adding cuprous iodide (8.23 g) to methyl-lithium–lithium bromide complex in ether (1.5M; 29 ml) at 0 °C. After being stirred for a further 1.5 h at 0 °C, the mixture was poured into aqueous ammonia saturated with ammonium chloride and the resulting blue solution extracted with ether; the extract, after drying and evaporation, gave an oil (5.73 g) from which the *nitropropane* (**11d**) (4.24 g, 76%) was obtained as a colourless oil by chromatography over silica eluting with hexane–toluene (1:1); δ_H 1.33 (3 H, d, *J* 7 Hz, CH_3CH), 3.57 (1 H, m, CH_2CH), 3.76 (3 H, s, CH_3O), 4.45 (2 H, m, CH_2CH), 6.75 (3 H, m, ArH), and 7.23 (1 H, t, *J* 6 Hz, ArH); *m/z* 195 ($M^{+\bullet}$, 24%), 149 (23), 148 (100), 146 (14), 135 (12), 134 (20), 121 (88), 108 (16), 105 (15), 103 (14), 92 (11), 91 (53), and 77 (30) (Found: *M*, 195.0898. $C_{10}H_{13}NO_3$ requires *M*, 195.0895).

N-[2-(3-*Methoxyphenyl*)*propyl*]*acetamide* (**11f**).—Palladium–charcoal (10%; 0.2 g) followed by ammonium formate (0.76 g) were added to a stirred solution of the nitropropane (**11d**) (0.53 g) in dry methanol (10 ml) under nitrogen added and the mixture was stirred at room temperature for 10 h. After removal of the catalyst by filtration through Celite, the solvent was evaporated and the residue partitioned between water and chloroform. The organic extract was separated, dried, and evaporated to give the amine (0.38 g), chromatographically pure, which was immediately acetylated with acetic anhydride (1 g) at room temperature for 1 h. The acetylation mixture was poured into ice-cold aqueous potassium carbonate and the product extracted with ether to give crude material purified by chromatography over silica (ethyl acetate) to give the *acetamide* (**11f**) (0.4 g, 71%), as a colourless gum, $\nu_{max.}$(film) 3 280 and 1 650 cm^{-1}; δ_H 1.50 (3 H, d, CH_3CH), 1.90 (3 H, s, CH_3CON), 2.9, 3.2, and 3.6 (3 × 1 H, ms, CH_2CH), 3.80 (3 H, s, CH_3O), 5.47 (1 H, br s, NH), 6.8 (3 H, m, ArH), and 7.26 (1 H, t, *J* 7 Hz, ArH); *m/z* 207 ($M^{+\bullet}$, 4%), 149 (12), 148 (100), 135 (32), 105 (12), and 72 (12) (Found: *M*, 207.1264. $C_{12}H_{17}NO_2$ requires *M*, 207.1259).

3,4-*Dihydro*-6-*methoxy*-1,4-*dimethylisoquinoline* (**10b**).—A solution of the acetamide (**11f**) (0.81 g) and freshly distilled phosphorus oxychloride (2.4 g) in dry toluene (25 ml) was heated at reflux for 20 h under nitrogen. The solvent was evaporated and the residual oil partitioned between ethyl acetate and aqueous sodium hydroxide (2M). After separation and further extraction of the aqueous phase, the organic extracts were dried and evaporated to give the *dihydroisoquinoline* (**10b**) (0.73 g, *ca.* 100%) chromatographically pure, as an oil, δ_H 1.24 (3 H, d, *J* 6 Hz, CH_3CH), 2.35 (3 H, t, *J* 3 Hz, 1-CH_3), 2.1—3.8 (3 H, m, CH_2CH), 3.80 (3 H, s, CH_3O), 6.6—6.9 (2 H, m, ArH), and 7.39 (1 H, d, *J* 8 Hz, ArH); *m/z* 189 ($M^{+\bullet}$, 51%), 188 (67), 175 (19), 174 (75), 149 (12), 148 (16), 131 (12), 94 (100), and 77 (10) (Found *M*, 189.1154. $C_{12}H_{15}NO$ requires *M*, 189.1154).

6-*Methoxy*-1,4-*dimethylisoquinoline* (**3c**).—A solution of the dihydroisoquinoline (**10b**) (0.7 g) and diphenyl disulphide (0.97 g) in tetralin (10 ml) was heated at 200 °C for 20 h. The cooled mixture was diluted with ethyl acetate and extracted with HCl (2M). Basification of the aqueous extract and re-extraction with ethyl acetate gave, after drying and evaporation of the extract, the *isoquinoline* (**3c**) (0.49 g, 70%) as a chromatographically pure gum, $\lambda_{max.}$ 245 and 310 nm; $\lambda_{max.}$(EtOH–H^+) 245 and 310 nm; δ_H 2.53 (3 H, s, 4-CH_3), 2.88 (3 H, s, 1-CH_3), 3.97 (3 H, s, CH_3O), 7.1—7.3 (2 H, m, ArH), 8.06 (1 H, d, *J* 7 Hz, 8-H), and 8.20 (1 H, s, 3-H); *m/z* 187 ($M^{+\bullet}$, 100%) and 173 (12) (Found: *M*, 187.0995. $C_{12}H_{13}NO$ requires *M*, 187.0997).

6-*Hydroxy*-1,4-*dimethylisoquinoline* (**3a**).—The ether (**3c**) (107 mg) was heated at reflux in hydrobromic acid (48%; 1.5 ml) for 24 h. The mixture was cooled, diluted with water (10 ml), made basic with potassium carbonate, and the product extracted with chloroform–ethanol (4:1), to give, after evaporation of the extract, an off-white solid which was recrystallised from toluene–ethanol (5:1) to give the *phenol* (**3a**) (73 mg, 74%), m.p. 244—247 °C decomp.; $\lambda_{max.}$ 234, 299, and 366 nm (log ε 4.59, 3.70, and 2.85); $\lambda_{max.}$(EtOH–NaOH) 251, 300, 312, and 341 nm (log ε 4.60, 3.66, 3.91, and 3.66); δ_H(CD_3OD) 2.45 (3 H, s, 4-CH_3), 2.79 (3 H, s, 1-CH_3), 7.18 (1 H, s, 5-H), 7.23 (1 H, d, *J* 7 Hz, 7-H), 7.95 (1 H, s, 3-H), and 8.12 (1 H, d, *J* 7 Hz, 8-H); *m/z* 173 ($M^{+\bullet}$, 100%) and 172 (33) (Found: C, 76.7; H, 6.6; N, 7.95. $C_{11}H_{11}NO$ requires C, 76.3; H, 6.4; N, 8.2%).

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