Phenol Oxidation. Part IV.[1] Synthesis and Novel Ring-opening of Spirocyclic Dienones related to the Benzylisoquinoline Alkaloid Cularine

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1.2.3.4-Tetrahydro-1-(4-hydroxy-3-methoxybenzyl)-7-methoxy-*N*-methylisoquinolin-8-ol was oxidatively coupled with potassium ferricyanide to give a mixture of diastereoisomeric dienones. Treatment of the mixture with hydrochloric acid in glacial acetic acid gave a product tentatively identified as 1-(4.6-dihydroxy-3-methoxybenzyl)-1.2.3.4-tetrahydro-7-methoxy-*N*-methylisoquinolin-8-ol. whereas treatment of the dienones with hydrogen chloride in methanol gave 1.2.3.4-tetrahydro-7-methoxy-*N*-methyl-1-(3.4.6-trimethoxybenzyl)-isoquinolin-8-ol, whose structure was confirmed by unambiguous synthesis. Two essentially different mechanisms for the formation of the latter product were differentiated by carrying out the ring opening in ethanol instead of methanol: the product was then 1-(4.6-diethoxy-3-methoxybenzyl)-1.2.3.4-tetrahydro-7-methoxy-*N*-methylisoquinolin-8-ol.

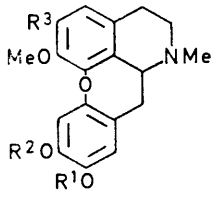
A BIOGENETICALLY modelled synthesis of the benzylisoquinoline alkaloid cularine (1a) was recently accomplished in Cardiff,[1,2] and also in Japan;[3] in both cases this was achieved by oxidative coupling of the phenolic precursor (2a) followed by methylation. We[4] and Kametani[3,5] also attempted to synthesise cularine *via* acid-catalysed rearrangement of the dienones (3a), which were prepared by oxidative coupling of the phenolic precursor (2b), and might also be implicated in the biosynthesis of cularine (1a). The acid-catalysed rearrangement of an analogous dienone (3b) to the cularine analogue (1b) had been described previously.[6] However in these laboratories[4] attempted rearrangement of the diastereoisomers (3a) in dry methanolic hydrogen chloride gave the 1-benzyltetrahydroisoquinoline (2d), whereas by treatment with concentrated sulphuric acid Kametani[5] obtained the aporphine (4). Both results were unexpected, especially the latter as it effectively involves a deoxygenation, but the structures of both products (2d) and (4) were confirmed by independent syntheses.[4,5] We now describe in full the synthesis and ring opening of the dienones (3a), and present evidence for the mechanism of the unusual ring opening to give the benzyltetrahydroisoquinoline (2d) in methanolic hydrochloric acid.

Our synthesis of the tetrahydroisoquinoline (2b) differed from that employed by Kametani,[3] and was closely analogous to that used earlier[1,2] for the isomer (2a). Thus 8-benzyloxy-7-methoxyisoquinoline was converted with benzoyl chloride and potassium cyanide into the Reissert compound (5).[1,2,4] Treatment of the anion of the latter with 4-benzyloxy-3-methoxybenzyl chloride followed by alkaline hydrolysis then gave the benzylisoquinoline (6a), which was converted into the *N*-methyl

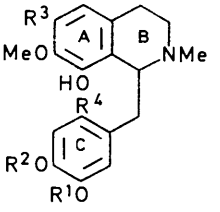
[1] Part III, A. H. Jackson, G. W. Stewart, G. A. Charnock, and J. A. Martin, *J.C.S. Perkin I*, 1974, 1911.
[2] A. H. Jackson and G. W. Stewart, *Chem. Comm.*, 1971, 149.
[3] T. Kametani, K. Fukumoto, and M. Fugihara, *Chem. Comm.*, 1971, 352; *Bio-organic Chem.*, 1971, **1**, 40.
[4] A. H. Jackson and G. W. Stewart, *Tetrahedron Letters*, 1971, 4941.
[5] T. Kametani, K. Fukumoto, and M. Fujihara, *J.C.S. Perkin I*, 1972, 394.
[6] T. Kametani, T. Kikuchi, and K. Fukumoto, *Chem. Comm.*, 1967, 546.

tetrahydro-derivative (7a) by methylation and reduction with borohydride. Treatment with concentrated hydrochloric acid under nitrogen in refluxing ethanol afforded the dihydric phenol (2b) almost quantitatively. This was oxidised with potassium ferricyanaide in a two-phase system (chloroform–aqueous 8% ammonium acetate) for 3 h at 20 °C. After preparative t.l.c. the dienones (3a) were obtained in 10% yield, and were fully characterised by n.m.r. and mass spectrometry as well as by elemental analysis.

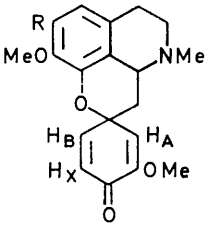
In the n.m.r. spectrum of (3a) one of the methoxy-groups showed two absorption bands, and the signals due to H_A and H_X each appeared as a double doublet rather



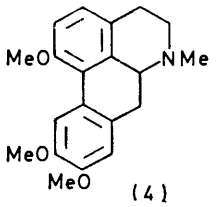
(1) a; $R^1 = R^2 = Me, R^3 = H$
b; $R^1 = Me, R^2 = H, R^3 = OMe$
c; $R^1 = R^3 = H, R^2 = Me$



(2) a; $R^1 = R^3 = R^4 = H, R^2 = Me$
b; $R^1 = Me, R^2 = R^3 = R^4 = H$
c; $R^1 = Me, R^2 = R^3 = H, R^4 = OH$
d; $R^1 = R^2 = Me, R^3 = H, R^4 = OMe$
e; $R^1 = Et, R^2 = Me, R^3 = H, R^4 = OEt$
f; $R^1 = Me, R^2 = Et, R^3 = H, R^4 = OEt$
g; $R^1 = R^2 = Et, R^3 = H, R^4 = OEt$



(3) a; R = H
b; R = OMe



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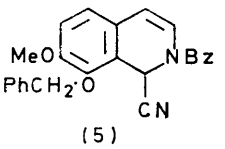

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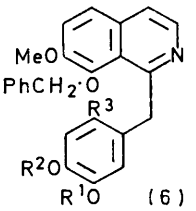
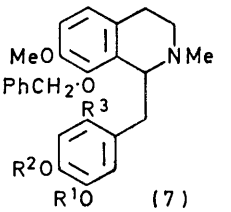


(6)

a; $R^1 = Me, R^2 = CH_2Ph, R^3 = H$
b; $R^1 = R^2 = Me, R^3 = OMe$
c; $R^1 = Et, R^2 = Me, R^3 = OEt$
d; $R^1 = Me, R^2 = Et, R^3 = OEt$



(7)

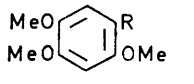
than a doublet.[7] This indicated that the product was as expected, a mixture of diastereoisomers, in agreement with the results of Kametani.[3,5]

In principle the rearrangement of the dienones (3a) could afford four isomers of the cularine type, two from migration of the CH_2 group of the pyran ring, and two from migration of the oxygen atom. The latter seemed more likely since an oxygen function is expected to have a greater migratory aptitude than an alkyl group. Indeed these predictions were encouraged by Kametani's report that the dienone (3b) was rearranged [6] by concentrated hydrochloric acid in glacial acetic acid to the cularine analogue (1b).

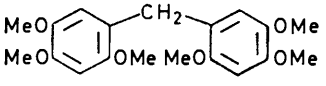
Accordingly the mixture of dienones (3a) was dissolved, under nitrogen, in glacial acetic acid containing a few drops of concentrated hydrochloric acid. After 18 h, work-up afforded a pale brown oil, the n.m.r. spectrum of which differed markedly both in the aromatic and methylene proton regions from that of authentic cularine. This product was assigned [4] the structure (2c).

The dienone rearrangement was next attempted in dry methanol with hydrogen chloride gas, conditions previously used [8] to give a methyl ether directly. Thus it was hoped that the dienones (3a) would be transformed either into cularine (1a) or into an isomer. The product, however, again showed a distinctly different n.m.r. spectrum from that of cularine; it also exhibited a bathochromic shift in the u.v. on addition of base, and a positive iron(III) chloride reaction, indicating the presence of a phenolic hydroxy-group. It was tentatively identified as the 1-benzyltetrahydroisoquinoline (2d) and this was confirmed by the unambiguous synthesis described below.

The trimethoxybenzaldehyde (8a) was prepared from



(8) a; R = CHO
b; R = CH_2·OH
c; R = CH_2Br



(9)

1,2,4-triacetoxybenzene [9] by hydrolysis and *O*-methylation followed by Vilsmeier–Haack formylation with

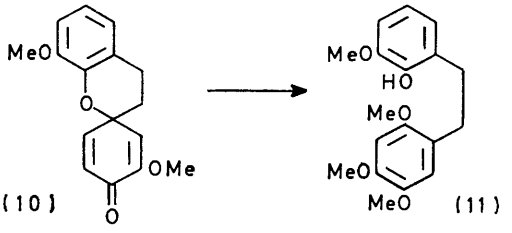
[7] *Cf.* A. R. Battersby, T. H. Brown, and J. H. Clements, *J. Chem. Soc.*, 1965, 4550.

[8] A. H. Jackson and J. A. Martin, *J. Chem. Soc.* (*C*), 1966, 2222.

[9] E. B. Vliet, *Org. Synth.*, Coll. Vol. I, 1932, 310.

dimethylformamide–phosphoryl chloride.[10] Conversion into the crystalline trimethoxybenzyl alchohol (8b) was best achieved by catalytic reduction in dry benzene in the presence of sodium hydrogen carbonate, owing to the sensitivity [7,11] of compounds of this type to acid-catalysed self condensation to give diphenylmethanes, *e.g.* (9). The corresponding bromide (8c), which was unstable, was prepared by treatment of the alcohol with phosphorous tribromide in benzene containing sodium hydrogen carbonate, and was condensed with the anion of the Reissert compound (5), prepared as before. Alkaline hydrolysis of the intermediate gave the benzylisoquinoline (6b), treatment of which with methyl fluorosulphate gave the crude *N*-methyl fluorosulphate.[12] This was reduced with sodium borohydride in aqueous methanol and afforded the crystalline *N*-methyltetrahydroisoquinoline (7b). The benzyl group was removed with concentrated hydrochloric acid in refluxing ethanol. The product (2d) was identical with that from the ring-opening reaction.

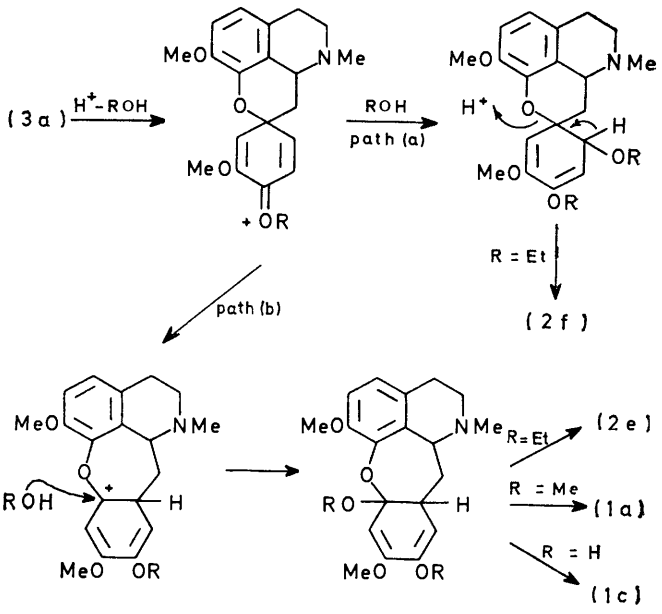
Since our original report [4] of the abnormal ring opening of the dienones (3a) to give the isoquinoline (2d) the analogous transformation of the dienone (10), with methanolic hydrogen chloride, into the phenol (11) has been described.[13]



In principle two essentially different mechanisms may operate in the methanolic acid-catalysed conversion of the dienones (3a) into the phenol (2d) (see Scheme 1). Both involve initial formation of an oxonium derivative which then undergoes addition of alcohol followed by opening of the spiro-ether ring [path (a)], or alkyl migration, followed by alcohol addition and opening of the ether ring [path (b)]. Route (b) might also be expected to give rise to cularine, or to a demethylcularine.

The two possible benzylisoquinolines (2f and e) formed by path (a) and (b) (Scheme 1), respectively, would be expected to differ in the orientation of their ring C substituents if ethanol were used as solvent rather than methanol. Consequently we considered that, if these isomers could be differentiated, preferably quantitatively, it should be possible to decide which of the two paths is operating.

Accordingly the diastereoisomeric mixture of dienones (3a) was treated with dry hydrogen chloride in ethanol. The reaction was slower than in methanol and t.l.c. showed the formation of a major and a minor product (see later). Although the former gave no molecular ion on electron impact, the field-ionisation mass spectrum showed molecular ions at *m/e* 401 and 415 together with fragment ions at *m/e* 192 and 209 and 223. This revealed



SCHEME 1

that the major product was a mixture of the 1-benzylisoquinoline (2e or f) together with *ca.* 50% of the triethoxy-homologue (2 g), and that the methoxy-group of ring C had been exchanged by the solvent, not that of ring A.

It was correctly anticipated at this juncture that the formation of the triethoxy-homologue (2g) would not affect the essential discrimination between the isomers (2e and f). The unambiguous synthesis of these two isomers, however, was necessary, and the approach to these compounds was again based on the Reissert compound (5). Condensation of the anion of (5) with the bromides (12a and b) followed by *N*-methylation, reduction of ring B, and removal of the benzyl groups was expected to give (2f and e), respectively. The unstable bromide (12b), prepared by the route vanillin ⟶ (13a) ⟶ (13b) ⟶ (13c) ⟶ (12b), was condensed with the anion of (5) as described above. Hydrolysis of the intermediate with alcoholic sodium hydroxide then yielded the isoquinoline (6c). The methiodide of the latter was reduced with sodium borohydride in aqueous methanol to the relatively stable tetrahydroisoquinoline (7c). Debenzylation to the less stable phenolic tetrahydroisoquinoline (2e) was postponed until completion of the synthesis of the isomer (2f).

The synthesis of the benzyl bromide (12a) proved less straightforward than that of (12b). Catalytic hydrogenaton of 2,4-dinitroanisole over palladised charco al at 20 atm gave 2,4-diaminoanisole (75%), but treatment of this with isopentyl nitrite or sodium nitrite and subsequent heating in water gave no phenolic products.

[10] D. E. Hall and A. H. Jackson, unpublished work (D. E. Hall, MSc. Thesis, Liverpool, 1964).
[11] T. R. Govindachari, K. Nagarajan, and P. C. Parthasaranthy, *J. Chem. Soc.*, 1958, 912.
[12] M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott, and M. C. Whiting, *Chem. Comm.*, 1968, 1533.
[13] A. M. Choudhury, *J.C.S. Perkin I*, 1974, 132.

Nitration of 1,3-diethoxybenzene gave only the 4,6-dinitro-derivative under a variety of conditions (*e.g.* nitric acid, silver nitrate in acetonitrile, or nitric acid in acetic anhydride). The use of stoicheiometric proportions of nitrating agent resulted in mixtures of starting material, mononitro-, and dinitro-derivatives. Hence a subsequently removable or potentially convertible blocking or deactivating group was necessary to ensure mononitration. β-Resorcylic acid (14a) appeared a suitable starting material in this respect as the carboxy-group would effectively block one of the positions of nitration and moreover should, at a subsequent stage, be easily convertible into a bromomethyl group. Accordingly β-resorcylic acid was nitrated, and gave 2,4-dihydroxy-5-nitrobenzoic acid in 50% yield, but attempts to form the diethyl ether of this compound, either with ethyl iodide or with diethyl sulphate and alkali, failed, perhaps because of the insolubility of the compound and hence the difficulty of forming the required anions. However, ethylation of the hydroxy-groups of β-resorcylic acid itself was achieved with diethyl sulphate, giving the diether (14b), but a considerable amount of a monoethoxy product (14c or d) was also obtained. This mixture proved difficult to separate without recourse to chromatography, and nitration gave the two corresponding nitro-compounds which were also difficult to separate. Consequently the mixture of products (14b) and (14c or d) was treated with ethanol and sulphuric acid to give a mixture of esters, which on washing with cold sodium hydroxide to remove phenols gave substantially pure ethyl 2,4-diethoxybenzoate (15a). Nitration of (15a) was best achieved by careful addition of nitric acid to a cooled solution in acetic anhydride. Above *ca.* 10 °C the reaction was very vigorous, if not explosive, but the desired ethyl 2,4-diethoxy-5-nitrobenzoate (15b) was obtained in 50—60% yield and was smoothly hydrogenated over palladised charcoal to the amine (15c) (89%). Conversion of the corresponding diazonium salt into the phenol (15d) proved difficult, but was finally achieved by adding an aqueous solution of the salt to a boiling saturated solution of copper sulphate. The product proved to contain, besides the phenol (15d), 2,4-diethoxy-5-hydroxybenzoic acid (15e), and ethyl 2,4-diethoxy-3-hydroxybenzoate (the last presumably formed from a minor product of the original nitration).

These three products were difficult to separate so the mixture was heated to reflux with dimethyl sulphate in sodium hydroxide solution. Ether formation was accompanied by complete ester hydrolysis so that the product was predominantly 2,4-diethoxy-5-methoxybenzoic acid (15f).

Reduction of the carboxy-group in (15f) with lithium aluminium hydride gave the corresponding alcohol (65%), which was easily purified by chromatography and converted with phosphorous tribromide into the required bromide (12a). By a series of reactions analogous to those described for the bromide (12b), the bromide (12a) was coupled with the Reissert compound (5) to give 8-benzyloxy-1-(2,4-diethoxy-5-methoxybenzyl)-7-methoxyisoquinoline (6d) which, as before, was converted into its methiodide and reduced to the 1,2,3,4-tetrahydroisoquinoline (7d).

The *O*-benzyl groups were removed from the two isomers (7c and d) by heating to reflux with hydrochloric acid in dioxan. Both products (2c and f) were obtained as oils which proved to be inseparable either by t.l.c. or by g.l.c. of the trimethylsilyl ethers. The u.v. and mass spectra showed no significant differences, but the i.r. spectra exhibited several differences in the fingerprint region. However a more useful distinction was possible from their n.m.r. spectra in deuteriochloroform. Apart from minor differences in the aromatic region, in the deuteriochloroform region, τ 5.4—6.5 (OCH_2), and the region τ 8.4—8.6 ($OCH_2{\cdot}CH_3$ triplets), the singlets from the methoxy-groups in rings A and C of the isomer (2e) coincided at τ 6.14, whereas in the spectrum of the other isomer (2f) they were separated at τ 6.14 and 6.23. Presumably the change in methoxy-environment in ring C is

(12)

a; $R^1 = R^3 = Et$, $R^2 = Me$
b; $R^1 = R^2 = Et$, $R^3 = Me$

(13)

a; R = H
b; R = CHO
c; $R = CH_2{\cdot}OH$

(14)

a; $R^1 = R^2 = H$
b; $R^1 = R^2 = Et$
c; $R^1 = Et$, $R^2 = H$
d; $R^1 = H$, $R^2 = Et$

(15)

a; $R^1 = Et$, $R^2 = H$
b; $R^1 = Et$, $R^2 = NO_2$
c; $R^1 = Et$, $R^2 = NH_2$
d; $R^1 = Et$, $R^2 = OH$
e; $R^1 = H$, $R^2 = OH$
f; $R^1 = H$, $R^2 = OMe$

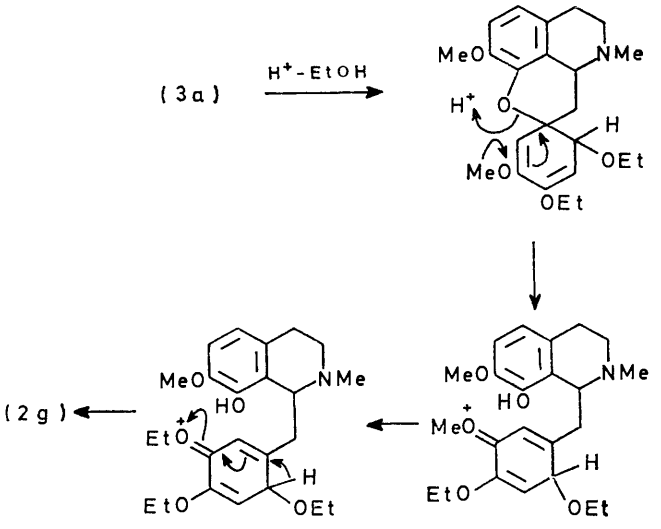
Comparison of n.m.r. data (τ values) of the 1-benzyltetrahydroisoquinolines (2e and f) with those of the product of ring opening by ethanolic hydrogen chloride of the dienones (3a) *

	(2e)		(2f)		Product from dienone (3a)	
	A	B	A	B	A	B
$OCH_2{\cdot}CH_3$	5.97 (q)	6.15 (m)	5.91 (q)	6.15 (m)	5.93 (q)	6.15 (m)
	5.98 (q)		5.98 (q)		6.00 (q)	
OCH_3	6.14 (C-7)	6.64	6.14 (C-7)	6.64	6.15	6.63
	6.14 (C-4′)	6.28	6.23 (C-5′)	6.38	6.24	6.38

* A, in deuteriochloroform; B, in deuteriochloroform (0.4 ml) + benzene (0.2 ml).

responsible for this difference. By the use of a mixture of deuteriochloroform and benzene it was possible to cause a shift of the signal due to the methoxy-groups in ring A of either isomer from τ 6.14 to 6.64, whereas the ring C methoxy-resonances for each isomer moved to a lesser but different extent. A mixture of the synthetic isomers in deuteriochloroform–benzene thus displayed two distinct singlets, at τ 6.28 (2e) and 6.38 (2f) due to the ring C methoxy-groups, whereas both ring A methoxy-signals coincided at τ 6.64.

A fresh sample of the dienone mixture (3a) was prepared and treated with hydrochloric acid in ethanol and the product was worked up as before. The i.r. spectrum differed from those of both synthetic isomers (2e and f) as expected owing to the contribution from the triethoxy-homologue (2g). However similarities were observed with the 1-(2,4-diethoxy-5-methoxybenzyl) isomer (2f). The amount of the triethoxy-homologue (2g) present was estimated as 70% both by g.l.c. of the trimethylsilyl ether derivative and by integration of the n.m.r. signals. The presence of a singlet at τ 6.24 in the n.m.r. spectrum in deuteriochloroform clearly indicated the presence of



SCHEME 2

(2f); moreover, when the spectra was run in deuteriochloroform–benzene, only one ring C methoxy-group singlet was observed, at τ 6.38, thus confirming the presence of (2f) and the absence of the isomer (2e).

The evidence for the mechanism of the ring opening of (3a) therefore points unambiguously to path (a) in Scheme 1, in which ring opening of the spiro-ether takes place without migration of the alkyl group. The concomitant formation of the triethoxy-homologue when the reaction is carried out in ethanol was shown not to take place *via* either of the isomers (2e and f); it may have arisen *via* either of the two pathways in Scheme 2.

The ring opening reaction in either ethanol or methanol afforded a second, very minor product. The mass spectrum was similar to that of cularine [14] and showed a molecular ion at *m/e* 327, corresponding to a demethylcularine. Accurate mass measurements confirmed the molecular formula as $C_{19}H_{21}NO_4$ and an ion at *m/e* 175 is typical of the cularine type.[15] The presence of a molecular ion in electron impact spectra is strong evidence for a four-ring structure. It is possible that this minor product was the demethylcularine (1c), but attempts to methylate the compound with diazomethane gave only a very small amount of product, which differed in t.l.c. characteristics from cularine; its n.m.r. spectrum, obtained by accumulation, proved uninterpretable.

The unusual mass spectral behaviour of the mixture of dienones (3a) in showing an ion at $M + 2$ is discussed in our preliminary communication.[4]

EXPERIMENTAL

U.v. and i.r. spectra were determined with Unicam SP 800 and SP 200 instruments, respectively. N.m.r. spectra were determined, for the most part, with a Perkin-Elmer R14 instrument at 100 MHz for solutions in deuteriochloroform unless otherwise stated. Mass spectra were measured with a Varian CH5-D double-focusing spectrometer, by use of a Varian 620i computer and a Statos 21 fast printer. Thin and preparative layer chromatography were carried out with Merck Kieselgel SF 254; spots were located by treatment with iodine unless stated otherwise. ' Petrol ' refers to light petroleum (b.p. 40—60°).

8-Benzyloxy-1-(4-benzyloxy-3-methoxybenzyl)-7-methoxyisoquinoline (6a).—A 50% oil dispersion of sodium hydride (0.53 g) was washed free of the oil with petrol (2 × 10 ml) and dimethylformamide (DMF) (25 ml) (dried over Linde type 4A molecular sieve) was added. The resulting slurry was stirred under dry, oxygen-free nitrogen and cooled in an ice–salt bath at −6 °C. 2-Benzoyl-8-benzyloxy-1,2-dihydro-7-methoxyisoquinoline-1-carbonitrile [1] (3.96 g) in DMF (915 ml) was added over 10 min and the solution was stirred for a further 5 min. 4-Benzyloxy-3-methoxybenzyl chloride (2.9 g) in DMF (15 ml) was then added dropwise over 30 min. The solution was stirred for a further 2 h at 0 °C and left to warm slowly to 20 °C (*ca.* 1 h). Ethanol (3 ml) was added to destroy any sodium hydride and the DMF was then removed under vacuum. The product was extracted into benzene (250 ml) and washed with water (2 × 150 ml). Removal of the benzene under vacuum gave an oil (7.1 g) which on t.l.c. (10% ether–benzene) showed a major component with the same R_F value as the starting Reissert compound, but an n.m.r. spectrum of this crude intermediate clearly showed the incorporation of the benzyl group.

The oil (7.1 g) was dissolved in ethanol (150 ml), sodium hydroxide (50 g) in water (50 ml) was added, and the mixture was boiled under nitrogen for 2½ h. On cooling, the aqueous alkaline phase separated from the organic layer, which was decanted off. Water (200 ml) was added to the alkaline phase, and this was extracted with benzene (250 ml). The organic extracts were combined and evaporated under vacuum. The resulting oil was redissolved in benzene

[14] T. Kametani, S. Shibuya, C. Kibayashi, and S. Sasaki, *Tetrahedron Letters*, 1966, 3215.

[15] M. Ohashi, J. M. Wilson, H. Budzikiewicz, M. Shamma, W. A. Slusarchyk, and C. Djerassi, *J. Amer. Chem. Soc.*, 1963, **85**, 2807.

(400 ml) and washed with water (2 × 300 ml). Removal of the solvent under vacuum gave a brown oil (4.3 g, 88%) which on t.l.c. (10% ether–benzene) showed minor impurities. This oil crystallised from benzene–petrol giving pale buff crystals (3.4 g, 69%); a sample was recrystallised from benzene–di-isopropyl ether giving the *1-benzylisoquinoline* (6a) as pale cream crystals, m.p. 109—110°, τ 1.62 (1 H, d, *J* 6 Hz, ArH), 2.4—2.8 (13 H, m, ArH), 3.3—3.6 (3 H, m, ArH), 4.96, 5.03, and 5.18 (6 H, 3s, 3 × $ArCH_2$), and 6.09 and 6.40 (6 H, 2s, s × OMe) (Found: C, 78.5; H, 6.3; N, 3.0. $C_{32}H_{29}NO_4$ requires C, 78.2; H, 5.9; N, 2.8%).

8-Benzyloxy-1-(4-benzyloxy-3-methoxybenzyl)-7-methoxy-N-methylisoquinolinium Iodide [*Methiodide of* (6a)].—(a) *With methyl iodide in solution.* The foregoing 1-benzylisoquinoline (400 mg) was dissolved in absolute ethanol (6 ml) and ether (5 ml) and methyl iodide (5 ml) was added. After 2 h t.l.c. (10% ether–benzene) showed the presence of unchanged 1-benzylisoquinoline together with a base-line component presumed to be the methiodide. The flask was stoppered and left at 20 °C for 2 days; t.l.c. then showed no further reaction. Methyl iodide (5 ml) was added and the solution was heated under reflux for 3 h; t.l.c. then revealed only a trace of starting material. The solvent was removed under vacuum leaving an oil which crystallised and was recrystallised from benzene–ethyl acetate, giving the methiodide as fluffy yellow crystals (250 mg, 49%), m.p. 131—133°. A satisfactory elemental analysis was not obtained.

(b) *With neat methyl iodide.* The foregoing 1-benzylisoquinoline (1 g) was dissolved in methyl iodide (15 ml) and left under nitrogen for 18 h. The 1-benzylisoquinolinium methiodide formed as a bright yellow precipitate and was filtered off and dried in a vacuum desiccator (yield 1.0 g, 78%). T.l.c. (10% ether–benzene) showed only the base-line component, and since recrystallisation lowered the yield considerably this product was used without further purification.

8-Benzyloxy-1-(4-benzyloxy-3-methoxybenzyl)-1,2,3,4-tetrahydro-7-methoxy-N-methylisoquinoline (7a).—(a) *By hydrogenation.* The foregoing methiodide (400 mg) in absolute ethanol (25 ml) was hydrogenated over platinum oxide (100 mg) at 20 °C and 1 atm. After 5 h no uptake of hydrogen had been observed and t.l.c. (methanol) confirmed that only the polar methiodide was present.

(b) *With sodium borohydride.* The foregoing methiodide (500 mg; not recrystallised) was dissolved in hot methanol (30 ml) and water (1 ml) was added. The solution was heated under reflux and sodium borohydride (1 g) was added during 1½ h. The reaction was monitored by t.l.c. (methanol); 10 min after the final portion of sodium borohydride had been added no base-line starting material remained and the product showed only a trace of impurity at higher R_F. The solvent was removed under vacuum, and ice was added to decompose the boron complex. The product was extracted into benzene (100 ml) and the solvent removed under vacuum leaving an oil (417 mg) which crystallised. The product was recrystallised from light petroleum (b.p. 60—80°) giving the *tetrahydroisoquinoline* (7a) as crystals (317 mg, 79%), m.p. 88—89°, τ (CCl_4) 2.5—3.0 (10 H, ArH), 3.3—3.6 (5 H, ArH), 4.97 (2 H, ABq, *J* 11 Hz, OCH_2Ph), 5.08 (2 H, $ArOCH_2Ph$), 6.22 and 6.42 (6 H, 2s, 2 × ArO*Me*), 6.6—7.7 (6 H, m, 3 × CH_2), and 7.86 (3 H, s, NMe) (Found: C, 77.8; H, 7.3; N, 2.6. $C_{33}H_{35}NO_4$ requires C, 77.8; H, 6.9; N, 2.7%).

1,2,3,4-Tetrahydro-1-(4-hydroxy-3-methoxybenzyl)-7-methoxy-N-methylisoquinolin-8-ol (2b).—The foregoing tetrahydroisoquinoline (600 mg) in ethanol (15 ml) was treated, under nitrogen, with concentrated hydrochloric acid (15 ml) and the solution heated under reflux for 1 h. The mixture was diluted with water (70 ml) and extracted with ether (2 × 60 ml); after basification with sodium hydrogen carbonate, the phenolic product was extracted into chloroform (3 × 80 ml) and dried ($MgSO_4$). The solvent was removed under vacuum giving the phenolic tetrahydroisoquinoline (2b) as pale cream crystals (370 mg, 96%). T.l.c. in 5% methanol–chloroform showed only minor impurities and coupling experiments were conducted on this material without further purification. The product could, however, be recrystallised from ether–petrol giving the *diphenol* (2b) as crystals, m.p. 58—59°, τ 3.2—3.5 (5 H, m, ArH), 4.0br (2 H, s, 2 × ArOH), 5.75—5.93 (1 H, m, ArC*H*N), 6.16 and 6.23 (6 H, 2s, 2 × ArOMe), 6.6—7.7 (m, 3 × CH_2), and 7.6 (NMe) (Found: C, 69.1; H, 7.1; N, 4.2. $C_{19}H_{23}NO_4$ requires C, 69.3; H, 7.0; N, 4.25%).

Phenol Coupling Reactions of the Diphenol (2b).—The foregoing phenolic tetrahydroisoquinoline (407 mg) was dissolved in chloroform (250 ml) and 8% ammonium acetate (100 ml) was added followed by potassium ferricyanide (1.3 g) in 8% ammonium acetate (150 ml). The two-phase system was shaken gently at 20 °C and samples were withdrawn every hour, tested for free phenol with iron(III) chloride reagent, and also subjected to t.l.c. in 20% methanol–chloroform. After 3 h both tests showed that all starting phenol had been used up. (In some experiments, however, reaction was complete only after 18 h.) The solution was basified with ammonium hydroxide and the chloroform layer collected. The aqueous phase was re-extracted with chloroform (250 ml) and the combined organic layers were dried ($MgSO_4$) and filtered. The solvent was removed under vacuum giving a crystalline solid (343 mg). T.l.c. in 20% methanol–chloroform showed four major components, the one with the highest R_F giving an orange colouration with 2,4-dinitrophenylhydrazine spray reagent. The product was chromatographed on alumina (grade III; 10 g; 11 cm × 1.3 cm column) in 10% chloroform–benzene and the eluate was tested for ketone by spotting a sample onto a silica t.l.c. plate presprayed with 2,4-dinitrophenylhydrazine reagent. On warming, the fractions containing the dienone gave an orange colouration. These were combined and the solvent was removed under vacuum giving the dienones (3a) as a pale brown oil (46 mg, 11.5%) which later crystallised. It was possible to recrystallise the dienones (3a) from ether–petrol giving colourless crystals, m.p. 119—122°, $\nu_{max.}$ ($CHCl_3$) 1 622, 1 649, and 1 680 cm^{-1}, $\lambda_{max.}$ 213, 234, and 282 nm, τ 2.82 (dd, *J* 10 and 3 Hz, H_B), 3.03 (dd, *J* 10 and 3 Hz, H_B), 3.25 (ABq, *J* 8 Hz, ArH in ring A), 3.70 (d, *J* 10 Hz, H_X), 3.74 (d, *J* 10 Hz, H_X), 3.97 (d, *J* 3 Hz, H_A), 4.14 (d, *J* 3 Hz, H_A), 6.18 (s, 2 × OMe), 6.28 (s, OMe), 6.34 (s, OMe), 6.4—7.4 (m, $ArCH_2CH_2N$ + ArC*H*N), 7.59 (s, NMe), and 7.6—8.0 (m, $NCH{\cdot}CH_2$) (Found: C, 69.7; H, 6.9; N, 4.0%; M^+, 327.1470 ± 0.0017. Calc. for $C_{19}H_{21}NO_4$: C, 69.7; H, 6.5; N, 4.3%; *M*, 327.1470).

Rearrangement of the Dienones (3a).—(a) *With concentrated hydrochloric acid in glacial acetic acid.* The mixture of dienones (41 mg) was dissolved in glacial acetic acid (10 ml) under nitrogen, and concentrated hydrochloric acid (4 drops) was added. The solution was left at 20 °C for 18 h, then concentrated under vacuum, diluted with water (30 ml), and basified with solid sodium hydrogen carbonate. The product was extracted with chloroform (3 × 40 ml). Removal of the solvent under vacuum gave an oil (45 mg). T.l.c.

(20% methanol–chloroform) showed a single component with R_F 0.3 [dienones (3a) R_F 0.6], τ 3.12 (1 H, d, J 2 Hz, ArH), 3.34 (2 H, ABq, J 9 Hz, ArH), 3.37 (1 H, d, J 2 Hz, ArH), 4.05 (2 H, s, 2 × OH), 5.8—6.0 (1 H, m, ArC*H*N), 6.14 and 6.23 (6 H, 2s, 2 × OMe), 6.6—7.3 (6 H, m, 3 × CH_2), and 7.62 (3 H, s, NMe). On this evidence, and in the light of the other rearrangements of the dienones (3a) described below, this product was assigned the structure (2c).

(b) *With hydrogen chloride in dry methanol.* The dienones (20 mg) were dissolved in dry methanol (20 ml), the solution was saturated with dry hydrogen chloride (for *ca.* 1 h), and the mixture was left at 20 °C for a further 1 h. The methanol was removed under vacuum, sodium hydrogen carbonate solution was added to neutralise residual acid, and the product was extracted into chloroform (3 × 75 ml). Removal of the solvent under vacuum gave an oil (20 mg). T.l.c. (20% methanol–chloroform) showed that there was one major component, R_F 0.4, with two minor impurities of higher R_F. The product, in ethanol, showed $\lambda_{max.}$ 216, 231, and 285 (stirred in alkali to 293) nm, τ 3.22 (1 H, s, ArH), 3.34 (2 H, ABq, J 10 Hz, 2 × ArH), 3.48 (1 H, s, ArH), 5.8—5.95 (1 H, m, ArC*H*·N), 6.14 (6 H, s, 2 × OMe), 6.19 (3 H, s, OMe), 6.23 (3 H, s, OMe), 6.5—7.5 (6 H, m, 3 × CH_2), and 7.66 (3 H, s, NMe), and gave a green colouration with iron(III) chloride. It was therefore assigned structure (2d) and this was confirmed by the synthesis described later.

(c) *With concentrated sulphuric acid in dry methanol.* The dienones (40 mg) in dry methanol (25 ml) were treated with concentrated sulphuric acid (0.2 ml) and kept at 20 °C under nitrogen for 18 h. T.l.c. (20% methanol–chloroform) then showed that all the dienone had reacted and that a single new product had been formed. The solution was diluted with water (50 ml), basified with sodium hydrogen carbonate, and extracted with chloroform (2 × 100 ml). Evaporation of the extract under vacuum afforded an oil (30 mg), which gave a positive iron(III) chloride reaction; its n.m.r. spectrum was identical with that of the product from (b).

(d) *With hydrogen chloride in dry ethanol.* A solution of dienones (15 mg) in ethanol (3 ml) was saturated with dry hydrogen chloride and left at 20 °C for 1 h. The solvent was then evaporated off, and the residue treated with 2M-sodium hydrogen carbonate (*ca.* 10 ml) and extracted with chloroform (10 ml). Work-up as above afforded an oily mixture of the 1-(diethoxymethoxybenzyl)tetrahydroisoquinoline (2e or f) and 1-(2,4,5-triethoxybenzyl)tetrahydroisoquinoline (2 g), τ 3.20, 3.28, 3.35, and 3.49 (4s, ArH), 5.93 and 6.00 (2q, J 8 Hz, OCH_2), 6.15 (s, OCH_3), 6.24 (s, O*C*H_3), 6.5—7.5 (m, CH_2 and CH), 7.56 (s, NCH_3), and 8.60 (m, OCH_2·CH_3), *m/e* (electron impact) 192 (100%); (field ionisation) 415 [7%, M^+ (2 g)], 401 [7%, M^+ (2f)], 223 [28, $(EtO)_3C_6H_2CH_2^+$], 209 [13, $(EtO)_2(MeO)C_6H_2CH_2^+$], and 192 (100) (M − 1-substituent). The 1-(diethoxymethoxybenzyl)isoquinoline was shown to have structure (2f) by spectral comparisons with synthetic specimens of (2e and f) described below.

T.l.c. showed a trace of a third component which was isolated by preparative t.l.c. in methanol–chloroform (1 : 9); the mass spectrum showed a molecular ion at *m/e* 327 corresponding to a demethylcularine (Found: M^+, 327.147. Calc. for $C_{19}H_{21}NO_4$: M, 327.146). Methylation with diazomethane gave a product whose n.m.r. spectrum (run by accumulation) was insufficiently well resolved to be interpreted.

(e) Treatment of the dienone with trifluoroacetic acid or hydrogen fluoride led to mixtures of products. No reaction occurred on passage through a column of acidic alumina in chloroform solution.

1,2,4-*Trimethoxybenzene.*—1,2,4-Triacetoxybenzene [9] (110 g) in methanol (250 ml) was stirred, under nitrogen, and sodium hydroxide (60 g) in water (60 ml) was added. The mixture was heated nearly to boiling on a water-bath and dimethyl sulphate (210 g) was run in portions with sodium hydroxide (60 g) in water (60 ml) at such a rate that the solution kept gently boiling and also became acidic from time to time during the addition. The solution was then basified with sodium hydroxide (25 g) in water (30 ml), cooled, poured into water (1 500 ml), and extracted with ether (3 × 300 ml). The extracts were dried ($MgSO_4$), filtered, and evaporated under vacuum. The remaining oil was distilled under vacuum yielding 1,2,4-trimethoxybenzene as an oil (71 g, 97%), b.p. 146° at 25 mmHg (lit.,[16] 154° at 42 mmHg).

2,4,5-*Trimethoxybenzaldehyde* (with Mr. D. E. Hall).—Phosphoryl chloride (26 g) was added slowly with stirring to DMF (65 ml) cooled in an ice-bath. 1,2,4-Trimethoxybenzene (23 g) in DMF (65 ml) was then added with continued stirring and cooling. The mixture was then warmed at 40 °C for 1 h, and poured into water (650 ml). The resulting solution was basified with 10% sodium hydroxide, and the product crystallised out. This was recrystallised from water giving feathery needles (21.8 g, 81%), m.p. 114° (lit.,[16] 114°) of the aldehyde.

2,4,5-*Trimethoxybenzyl Alcohol.*—A solution of 2,4,5-trimethoxybenzaldehyde (1 g) in dry benzene (100 ml) containing sodium hydrogen carbonate (1 g) and platinum oxide (100 mg) was shaken at 20 °C under hydrogen at 1 atm. After uptake had ceased (*ca.* 2 h) the solution was filtered and evaporated under vacuum leaving crystals (1 g) of 2,4,5-trimethoxybenzyl alcohol, m.p. 70° (lit.,[17] 70—71°), τ 3.13 (1 H, s, ArH), 3.48 (1 H, s, ArH), 5.39 (2 H, s, ArCH_2O), 6.12 (3 H, s, OMe), and 6.17 (6 H, s, OMe).

Attempts to prepare this alcohol by reduction of the aldehyde with borohydride followed by acidification with dilute hydrochloric acid led to bis-(2,4,5-trimethoxyphenyl)-methane (75%), m.p. 98—110° (lit.,[11] 102°), τ 3.31 (2 H) and 3.44 (2 H) (ArH), 6.12 (6 H), 6.19 (6 H), and 6.25 (6 H) (OMe), and 6.16 (2 H, $ArCH_2Ar$), *m/e* 346 (M^+) and 181 [$(MeO)_3C_6H_2CH_2^+$].

2,4,5-*Trimethoxybenzyl Bromide.*—Phosphorus tribromide (6 ml) was added to a stirred slurry of sodium hydrogen carbonate (12 g) in dry benzene (160 ml), and 2,4,5-trimethoxybenzyl alcohol (1 g) in dry benzene (40 ml) was added over 5 min. The solution was stirred for a further 10 min, then poured onto crushed ice, and the benzene layer was collected and washed with water (2 × 50 ml). The solvent was removed under vacuum below 40 °C and a deep blue colouration developed as the solution became concentrated. 2,4,5-Trimethoxybenzyl bromide was obtained as a deep blue crystalline compound (1.4 g), τ 3.17 and 3.52 (2 H, 2s, 2 × ArH), 5.44 (2 H, s, ArCH_2Br), 6.12 (6 H, s, 2 × OMe), and 6.18 (3 H, s, OMe). Attempts to recrystallise this product from dry solvents gave only a dark blue oil which did not solidify on removal of the solvent; it was assumed that decomposition was occurring and the blue crystalline material was used without further purification.

8-*Benzyloxy*-1,2,3,4-*tetrahydro*-7-*methoxy*-2-*methyl*-1-(2,4,5-*trimethoxybenzyl*)*isoquinoline* (7b).—Sodium hydride

[16] A. H. Jackson, Ph.D. Thesis, Cambridge, 1954.
[17] J. Harley-Mason and A. H. Jackson, *J. Chem. Soc.*, 1954, 1165.

(140 mg; 50% oil dispersion) was washed free of oil with petrol and immediately suspended in dry DMF (10 ml). The stirred suspension was cooled in an ice–salt bath at −6 °C and the flask was flushed with pure dry nitrogen. The Reissert compound (5) (1 g) in DMF (10 ml) was added dropwise over 10 min and the solution stirred for a further 5 min; 2,4,5-trimethoxybenzyl bromide (1 g) in dry DMF (10 ml) was then added over 30 min, the temperature being maintained at −6 °C. The red colouration of the anion diminished as the bromide was added, and after stirring for 1 h at 0 °C and 1 h at 20 °C ethanol (2—3 ml) was added to destroy any excess of sodium hydride. Removal of the solvent under vacuum gave an oil which was extracted into benzene (100 ml). The extract was washed with water (3 × 50 ml) to remove the last traces of DMF and evaporated under vacuum. The remaining oil was dissolved in ethanol (40 ml) and heated under reflux for 2½ h with sodium hydroxide (12 g) in water (12 ml) under nitrogen. On cooling, the alcoholic layer was decanted from a solid cake of sodium hydroxide which was washed with benzene (50 ml) and the organic solutions were combined and evaporated under vacuum. The residual oil was extracted into benzene (150 ml); the extract was washed with water (100 ml) and evaporated under vacuum giving an oil (1.5 g) which crystallised from benzene–di-isopropyl ether.

The crude trimethoxybenzylisoquinoline (1 g) was dissolved in carbon tetrachloride (50 ml) and treated with methyl fluorosulphate [12] (0.5 ml). The solution was shaken at 20 °C for 1 h. After a few minutes it became yellow, and later a dark brown gummy solid and green oil were formed. The carbon tetrachloride solution was decanted off and the remaining oil was dissolved in methanol (60 ml) and water (1 ml). The solution was heated under reflux and sodium borohydride (2 g) was added in portions over 30 min. After 1 h the methanol was removed under vacuum leaving a yellow solid boron complex. This was decomposed with crushed ice and the product was extracted into benzene (100 ml). Removal of the benzene under vacuum left an oil which on t.l.c. (20% ether–benzene) showed three components and some base-line material. The product was chromatographed on alumina (grade III) in benzene and fractions containing the major component were combined. Removal of the solvent under vacuum again afforded an oil which was crystallised from petrol giving the N-*methyltetrahydroisoquinoline* (7b) as crystals (150 mg), m.p. 67—68°, τ 2.5—2.8 (5 H, m, ArH), 3.24 (2 H, m, ArH), 3.42 (1 H, s, ArH), 3.61 (1 H, s, ArH), 4.93 (2 H, ABq, *J* 12 Hz, 8-ArC*H*$_2$), 5.8—6.0 (1 H, m, ArC*H*N), 6.20 (6 H, s, 2 × OMe), 6.39 (6 H, s, 2 × OMe), 6.5—7.5 (6 H, m, 3 × CH$_2$), and 7.79 (3 H, s, NMe) (Found: C, 72.5; H, 7.3; N, 3.2. $C_{28}H_{33}NO_5$ requires C, 72.5; H, 7.2; N, 3.0%).

1,2,3,4-*Tetrahydro*-7-*methoxy*-N-*methyl*-1-(2,4,5-*trimethoxybenzyl*)*isoquinolin*-8-*ol* (2d).—The tetrahydroisoquinoline (7b) (700 mg) was dissolved in absolute ethanol (16 ml) and boiled under nitrogen with concentrated hydrochloric acid (16 ml) for 1 h. After cooling the solution was diluted with water (100 ml) and the aqueous phase was washed with ether (2 × 60 ml), basified with sodium hydrogen carbonate, and extracted with chloroform (3 × 60 ml). Evaporation of the extract under vacuum gave an oil (380 mg) which on t.l.c. (20% methanol–chloroform) showed two major components. These were separated by chromatography on alumina (grade III) in 20% chloroform–benzene and the upper component was isolated as an oil (135 mg) which was crystallised from ether–petrol giving the *phenolic tetrahydroisoquinoline* (2d) as crystals (90 mg, 16%), m.p. 98—99° (Found: C, 67.1; H, 7.3; N, 3.5. $C_{21}H_{27}NO_5$ requires C, 67.5; H, 7.3; N, 3.75%), identical [n.m.r. ($CDCl_3$), i.r., and u.v. spectra] with the methanol–hydrochloric acid rearrangement product of the dienones (3a).

2-*Methoxyhydroquinone*.—Vanillin (3.05 g) in M-sodium hydroxide (18 ml) was treated with 6% hydrogen peroxide (12.5 ml) dropwise. The solution turned dark red and an exothermic reaction began. After stirring at 40—45 °C for 2 h, the mixture was poured into saturated aqueous sodium hydrogen carbonate (40 ml) and extracted with ether (3 × 50 ml). The extracts were washed with saturated aqueous sodium sulphate (3 × 50 ml) and water (2 × 50 ml), dried, and evaporated to yield an oil. Distillation then gave an oil (2 g, 73%), b.p. 185—187° at 28 mmHg, which solidified m.p. 79—81° (lit.,[18] 87°), τ 1.55 and 2.55 (2 H, 2s, OH), 3.30 (1 H, d, *J* 11 Hz, 6-H), 3.54 (1 H, d, *J* 3 Hz, 3-H), 3.72 (1 H, dd, *J* 11 and 3 Hz, 5-H), and 6.26 (3 H, s, OMe).

2,5-*Diethoxyanisole* (13a).—2-Methoxyhydroquinone (14 g), ethyl iodide (34.4 g), and potassium carbonate (27.6 g) were heated to reflux in acetone (200 ml), under nitrogen. The solution was boiled for 18 h, then filtered and evaporated. The residue was taken up in ether (400 ml); the solution was washed with water (200 ml), M-sodium hydroxide (3 × 150 ml), and water (2 × 100 ml), dried, and evaporated to give a solid (8.5 g, 50%). T.l.c. showed one component, 2,5-diethoxyanisole (13a), m.p. 37—38° (lit.,[19] 42—43°), $\lambda_{max.}$ 230 (ε 7 550) and 286 nm (3 850) (Found: C, 67.1; H, 8.1. Calc. for $C_{11}H_{16}O_3$: C, 67.3; H, 8.2%), which was used without further purification.

2,5-*Diethoxy*-4-*methoxybenzaldehyde* (13b).—Freshly distilled phosphoryl chloride (1.9 g) was added to DMF (4.8 g) with cooling in ice. 2,5-Diethoxyanisole (1.98 g) in DMF (10 ml) was then added dropwise; the solution was stirred at 40 °C for 1.5 h and then poured into water (50 ml). The resulting solution was made alkaline with aqueous 10% sodium hydroxide and cooled, yielding needles. Filtration and recrystallisation from ethanol–water gave the benzaldehyde (13b) (1.8 g, 80%), m.p. 107—108° (lit.,[20] 111°), τ −0.35 (1 H, s, CHO), 2.68 (1 H, s, 6-H), 3.49 (1 H, s, 3-H), 5.86 and 5.91 (4 H, 2q, *J* 8 Hz, 2 × C*H*$_2$Me), 6.06 (3 H, s, OMe), and 8.55 and 8.58 (6 H, 2t, *J* 8 Hz, 2 × CH$_2$*Me*), $\nu_{max.}$ 1 655 cm^{-1} (CHO), $\lambda_{max.}$ 236 (ε 9 650), 273 (6 440), and 342 nm (5 310) (Found: C, 64.1; H, 7.0. Calc. for $C_{12}H_{16}O_4$: C, 64.3; H, 7.2%).

2,5-*Diethoxy*-4-*methoxybenzyl Alcohol* (13c).—2,5-Diethoxy-4-methoxybenzaldehyde (2.27 g), platinum oxide (100 mg), and sodium hydrogen carbonate (2 g) were suspended in dry benzene (100 ml). The mixture was then stirred at 20 °C under 1 atm of hydrogen until uptake ceased and filtered through Celite; the filtrate was evaporated to give the *benzyl alcohol* (13c) as a yellow solid (2.05 g, 88%), affording prisms, m.p. 77—78° (from ethanol–water), τ 3.09 (1 H, s, 6-H), 3.49 (1 H, s, 3-H), 5.39 (2 H, s, C*H*$_2$OH), 6.00 (4 H, q, *J* 8 Hz, C*H*$_2$Me), 6.17 (3 H, s, OMe), 7.21 (1 H, s, OH), and 8.62 (6 H, t, *J* 8 Hz, 2 × CH$_2$*Me*), $\nu_{max.}$ 3 370 cm^{-1} (OH), $\lambda_{max.}$ 232 (ε 8 180) and 287 nm (6 070) (Found: C, 63.8; H, 8.0. $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%).

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[20] A. T. Shulgin, *J. Medicin. Chem.*, 1968, **11**, 186.

2,5-*Diethoxy*-4-*methoxybenzyl Bromide* (12b).—Freshly distilled phosphorus tribromide (15 ml) was added to sodium hydrogen carbonate (30 g) in dry benzene (330 ml). 2,5-Diethoxy-4-methoxybenzyl alcohol (13c) (2.5 g) in benzene (50 ml) was then added over 5 min to the stirred solution at 20 °C and the resulting mixture was stirred for 10 min. The solution was then poured onto ice (50 ml) and the benzene layer separated, washed with water (2 × 150 ml), and evaporated to yield the bromide (12b) as an unstable blue solid (2.86 g, 90%), m.p. 61—66°, τ 3.25 (1 H, s, 6-H), 3.45 (1 H, s, 3-H), 6.02 (6 H, m, CH_2), 6.16 (3 H, s, OMe), and 8.60 and 8.68 (6 H, 2t, *J* 8 Hz, CH_2Me), $\lambda_{max.}$ 226 (ε 9 280) and 287 nm (5 780).

8-*Benzyloxy*-1-(2,5-*diethoxy*-4-*methoxybenzyl*)-7-*methoxyisoquinoline* (6c).—Sodium hydride (0.4 g; 50% suspension in oil) was washed with petrol (2 × 20 ml) and suspended in dry DMF (20 ml). The nitrile (5) (2 g) in DMF (20 ml) was added dropwise to the stirred suspension at −5 °C. A deep red colouration, indicative of a Reissert anion, was observed. The benzyl bromide (12b) (2.2 g) in DMF (20 ml) was then added at −5 °C over 0.5 h and the resulting solution was stirred at 0 °C for 1 h and at 20 °C for 1 h. Ethanol was then added dropwise to destroy the excess of sodium hydride and the solvent was removed. The resulting solid was extracted with benzene (100 ml); the extracts were washed with water (2 × 75 ml) and evaporated under vacuum. The residue was taken up in ethanol (80 ml) and sodium hydroxide (24 g) in water (24 ml) was added. The resulting solution was heated to reflux for 2 h, then cooled, and the ethanol layer was separated. The aqueous layer was extracted with benzene (50 ml) and the organic extracts were combined and evaporated. The residue was dissolved in benzene (150 ml); the solution was washed with water (2 × 100 ml), dried, and evaporated to give the isoquinoline (6c) as an oil (1.8 g, 76%), τ 1.67 (1 H, d, *J* 7 Hz, 3-H), 2.65 (8 H, m, ArH), 3.60 (1 H, s, ring c 6-H), 3.70 (1 H, s, ring c 3-H), 5.10 (2 H, s, $PhCH_2O$), 5.16 (2 H, s, $ArCH_2$·C), 6.10 (4 H, m, 2 × CH_2Me), 6.12 and 6.20 (6 H, 2s, 2 × OMe), and 8.78 and 8.89 (6 H, 2t, *J* 8 Hz, 2 × CH_2Me), $\lambda_{max.}$ 208 (ε 31 000), 234 (36 000), 285 (7 670), 292 (7 960), and 347 nm (5 020); *picrate*, needles, m.p. 167—169° (from ethanol) (Found: C, 59.5; H, 4.8; N, 7.5. $C_{35}H_{34}N_4O_{12}$ requires C, 59.8; H, 4.8; N, 7.9%).

8-*Benzyloxy*-1-(2,5-*diethoxy*-4-*methoxybenzyl*)-1,2,3,4-*tetrahydro*-7-*methoxy*-2-*methylisoquinoline* (7c).—The isoquinoline (6c) (1 g) was heated to reflux in methyl iodide (20 ml) for 8 h. Cooling and filtration gave the methiodide as a yellow solid (1 g, 70%), m.p. 166—168°, $\lambda_{max.}$ 212 (ε 52 800), 257 (42 600), 289 (11 100), and 395 nm (5 450). This salt (100 mg) in methanol (7 ml) and water (7 drops) was heated under reflux, and sodium borohydride (180 mg), was added in portions. The solution was then held at reflux for 0.5 h; the solvent was removed and ice added. The resulting mixture was extracted with chloroform (2 × 30 ml); the extracts were dried and evaporated to yield an oil. Preparative t.l.c. (petrol–ether, 1 : 4) gave the tetrahydroisoquinoline (7c) as an oily solid (50 mg, 70%), m.p. 58—60°, τ 2.66 (5 H, s, OCH_2Ph), 3.16, 3.34, and 3.54 (4 H, 3s, ArH), 4.94 (2 H, ABq, *J* 11 Hz, OCH_2Ph), 6.14 (4 H, m, 2 × CH_2-Me), 6.19 and 6.22 (6 H, 2s, 2 × OMe), 7.66 (3 H, s, NMe), and 8.69 and 8.71 (6 H, 2t, *J* 7 Hz, 2 × CH_2Me), $\lambda_{max.}$ 215, 229, and 286 nm.

Ethyl 2,4-*Diethoxybenzoate* (15a).—To diethyl sulphate (120 ml) in sodium hydroxide (40 g) and water (90 ml) was slowly added β-resorcylic acid (30 g) in ethanol (100 ml). An exothermic reaction ensued and after a further addition of sodium hydroxide (20 g) in water (20 ml) the solution was heated to reflux overnight. The resulting solution was poured into water (200 ml), acidified with 6M-hydrochloric acid, and extracted with chloroform (3 × 80 ml). The extracts were dried and evaporated. The residue was dissolved in ethanol (250 ml) and concentrated sulphuric acid (20 ml) added. The solution was heated to reflux for 3 h, poured into water (1 l), and extracted with chloroform (3 × 300 ml). The extracts were washed with dilute aqueous sodium hydrogen carbonate (3 × 500 ml) and water (2 × 500 ml), dried, and evaporated to yield an oil. Distillation then gave *ethyl* 2,4-*diethoxybenzoate* (15a) (30 g, 51%), b.p. 120° at 1 mmHg, τ 2.08 (1 H, d, *J* 10 Hz, 6-H), 3.50 (2 H, m, 3- and 5-H), 5.63 (2 H, q, *J* 8 Hz, CO_2CH_2Me), 5.90 (4 H, q, *J* 8 Hz, 2 × OCH_2Me), and 8.60 (9 H, m, 3 × Me), $\nu_{max.}$ 1 720 cm^{-1} (CO_2Et), $\lambda_{max.}$ 217, 257, and 293 nm (Found: C, 65.5; H, 7.3. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%).

Ethyl 2,4-*Diethoxy*-5-*nitrobenzoate* (15b).—The foregoing ester (10 g) in acetic anhydride (50 ml) was treated dropwise with concentrated nitric acid (10 ml), with the temperature kept below 40 °C. The mixture was stirred at 0 °C for 0.5 h and then at 20 °C for a further 0.5 h. The solution was poured into water (80 ml) and filtered to yield a solid. Recrystallisation from ethanol then gave the *ester* (15b) (5.5 g, 46%) as needles, m.p. 134—135°, τ 1.35 (1 H, s, 6-H), 3.40 (1 H, s, 3-H), 5.61 (2 H, q, *J* 8 Hz, CO_2CH_2Me), 5.76 (4 H, q, *J* 8 Hz, 2 × OCH_2Me), and 8.57 (9 H, m, Me), $\nu_{max.}$ 1 695 cm^{-1} (CO_2Et), $\lambda_{max.}$ 213 (ε 12 300), 245 (13 500), 279 (6 700), and 323 nm (4 300) (Found: C, 55.1; H, 6.2; N, 5.1. $C_{13}H_{17}NO_6$ requires C, 55.1; H, 6.05; N, 4.95%).

Ethyl 5-*Amino*-2,4-*diethoxybenzoate* (15c).—The ester (15b) (0.58 g) in ethanol (100 ml) and 10% palladium–charcoal (100 mg) were shaken with hydrogen at 20° and 1 atm until uptake ceased. The resulting mixture was filtered through Celite and the solvent removed to yield a solid. Recrystallisation from petrol (b.p. 60—80°) gave the *aminobenzoate* (15c) as pale grey needles (0.5 g, 87%), m.p. 110—110.5°, τ 2.74 (1 H, s, 6-H), 3.53 (1 H, s, 3-H), 5.67 (2 H, q, *J* 8 Hz, CO_2CH_2Me), 5.94 (4 H, m, 2 × OCH_2Me), 6.38 (2 H, s, NH_2), and 8.64 (9 H, m, 3 × Me), $\nu_{max.}$ (Nujol) 3 370, 3 450 (NH_2), and 1 670 cm^{-1} (CO_2Et), $\lambda_{max.}$ 215 (ε 22 800), 230 (32 000), 261 (12 200), and 323 nm (7 580) (Found: C, 61.4; H, 7.5; N, 6.1. $C_{13}H_{19}NO_4$ requires C, 61.6; H, 7.6; N, 5.6%).

Ethyl 2,4-*Diethoxy*-5-*hydroxybenzoate* (15d).—The amino-ester (15c) (500 mg) in water (70 ml) and concentrated sulphuric acid (8 ml) was treated with an excess of sodium nitrite solution and stirred at 20 °C for 0.5 h. The mixture was then poured slowly into a boiling solution of copper sulphate (50 g) in water (50 ml). The mixture was boiled for 15 min and cooled. Extraction with methylene chloride (3 × 50 ml) and removal of solvent gave an oil. This was then taken up in M-sodium hydroxide, which was washed with chloroform until no further product was extracted, and the pH of the aqueous solution was adjusted to 7.5. Extraction with ether (3 × 50 ml), drying, and removal of solvent then yielded the *hydroxybenzoate* (15d) (137 mg, 28%), m.p. 74.5—75.4°, τ 2.55 and 3.47 (2 H, 2s, ArH), 5.68 (2 H, q, *J* 8 Hz, CO_2CH_2Me), 5.90 (4 H, m, 2 × OCH_2Me), and 8.60 (9 H, m, 3 × Me), M^+ 254 (55%), $\nu_{max.}$ 3 420 (OH) and 1 690 cm^{-1} (CO_2Et), $\lambda_{max.}$ 222 (ε 17 500), 257 (9 250), 300 (4 420), and 307 nm (4 420) (Found: C, 61.4; H, 7.0. $C_{13}H_{18}O_5$ requires C, 61.4; H, 7.1%).

Further adjustment of the aqueous solution to pH 2 and a further extraction with ether (3 × 50 ml) yielded 2,4-diethoxy-5-hydroxybenzoic acid (15e) (47 mg, 10%), τ 2.32

and 3.46 (2 H, 2s, ArH), 5.80 (4 H, m, 2 × CH_2), and 8.50 (6 H, m, 2 × Me), $\nu_{max.}$ 3 330 (OH) and 1 720 cm^{-1} (CO_2H), $\lambda_{max.}$ 208 (ε 11 800), 222 (12 700), 256 (7 600) and 309 nm (4 510).

2,4-*Diethoxy-5-methoxybenzoic Acid* (15f).—Dimethyl sulphate (1 ml) in sodium hydroxide (0.15 g) and water (2 ml) was added to the two products [ester (15a) and acid (15e)] of the above reaction (100 mg) in methanol (1 ml). The mixture was heated to reflux for 4 min after further addition of sodium hydroxide (0.05 g) in water (0.5 ml), and the solution was then poured into water (10 ml) and extracted with ether (3 × 10 ml). The extracts were dried and the solvent was removed to yield mainly 2,4-*diethoxy-5-methoxybenzoic acid* (15f) (90 mg, 88%), m.p. 120—121°, τ 3.43 and 3.51 (2 H, 2s, ArH), 5.95 (4 H, m, 2 × CH_2), 6.15 (3 H, s, OMe), and 8.59 (6 H, m, 2 × Me), $\nu_{max.}$ 3 320 (OH) and 1 725 cm^{-1} (CO_2H), $\lambda_{max.}$ 222 (ε 21 600), 256 (9 120), and 306 nm (4 560) (Found: C, 59.4; H, 6.6. $C_{12}H_{16}O_5$ requires C, 59.9; H, 6.7%). A trace of the 3-methoxy-isomer was also observed, but not separated.

2,4-*Diethoxy-5-methoxybenzyl Alcohol*.—The acid (15f) (100 mg) in dry ether (20 ml) was treated with lithium aluminium hydride (100 mg) and the mixture was heated to reflux for 0.5 h. The excess of lithium aluminium hydride was destroyed with ethanol containing 5% water and the solution was filtered, dried, and evaporated. Preparative t.l.c. (methylene chloride) gave 2,4-*diethoxy-5-methoxybenzyl alcohol* (42 mg, 45%), m.p. 46—47°, τ 3.16 and 3.56 (2 H, 2s, 3- and 6-H), 5.43 (2 H, s, CH_2·OH), 6.00 (4 H, q, *J* 8 Hz, 2 × CH_2Me), 6.25 (3 H, s, OMe), 7.20 (1 H, s, OH), and 8.62 and 8.66 (6 H, 2t, *J* 8 Hz, 2 × Me), $\nu_{max.}$ 3 400 cm^{-1} (OH), $\lambda_{max.}$ 208 (ε 13 300), 227 (6 990), and 277 nm (2 880) (Found: C, 63.7; H, 8.0. $C_{12}H_{18}O_4$ requires C, 63.7; H, 8.0%).

2,4-*Diethoxy-5-methoxybenzyl Bromide* (12a).—The foregoing benzyl alcohol was treated with phosphorus tribromide, as described in the preparation of the isomeric bromide (12b), to give the benzyl bromide (12a) (570 mg, 76%), m.p. 88—90°, τ 3.45 (2 H, s, 2 × ArH), 6.00 (9 H, m, OCH_2, OMe, and CH_2Br), and 8.60 (6 H, m, Me), $\lambda_{max.}$ 212 (ε 18 300), 277 (12 500), and 288 nm (6 280).

8-*Benzyloxy*-1-(2,4-*diethoxy-5-methoxybenzyl*)-7-*methoxyisoquinoline* (6d).—The bromide (12a) (0.5 g) was coupled with the anion from the nitrile (5) (0.6 g) as described in the preparation of the isomeric isoquinoline (6c) to give the *isoquinoline* (6d) (0.53 g, 75%), τ 1.60 (1 H, d, *J* 7 Hz, 3-H), 2.52 (8 H, m, 8 × ArH), 3.53 and 3.65 (2 H, 2s, 2 × ArH), 5.03 and 5.13 (4 H, 2s, 2 × $ArCH_2$), 6.02 (4 H, m, 2 × OCH_2-Me), 6.05 and 6.40 (6 H, 2s, 2 × OMe), and 8.65 (6 H, m, 2 × OCH_2Me), $\lambda_{max.}$ 347, 291, 235, and 218 nm; *picrate*, m.p. 162—164° (Found: C, 59.4; H, 4.8; N, 8.4. $C_{35}H_{34}N_5O_{12}$ requires C, 59.8; H, 4.8; N, 7.9%).

8-*Benzyloxy*-1-(2,4-*diethoxy-5-methoxybenzyl*)-1,2,3,4-*tetrahydro-7-methoxy-2-methylisoquinoline* (7d).—The methiodide of the isoquinoline (6d) was prepared as described for the isomer (6c); treatment with sodium borohydride as described in the formation of (7c) gave the tetrahydroisoquinoline (7d), τ 2.70, 3.16, and 3.53 (m, ArH), 4.90 (m, CCH_2Ar), 5.35 (s, OCH_2Ph), 6.0 (m, OCH_2Me), 6.12 and 6.41 (2s, 2 × OMe), 6.7—7.7 (m, CH_2CH_2 and CH), 7.76 (s, NMe), and 8.65 (m, CH_2Me), $\lambda_{max.}$ 288, 230, and 214 nm.

1-(2,4-*Diethoxy-5-methoxybenzyl*)-1,2,3,4-*tetrahydro-7-methoxy-2-methylisoquinoline-8-ol* (2f).—The tetrahydroisoquinoline (7d) (80 mg) in dioxan (8 ml) and concentrated hydrochloric acid was heated to reflux for 2 h, and poured into water (100 ml). The resulting solution was extracted with ether (3 × 40 ml) and the aqueous solution was neutralised with sodium hydrogen carbonate and re-extracted with chloroform (3 × 30 ml). Removal of solvent after drying of these second extracts, followed by preparative t.l.c. (ethyl acetate–methanol, 9 : 1) gave the product as a light yellow oil, R_F 0.28, $\lambda_{max.}$ 206 (ε 15 500), 228 (4 000), and 285 nm (2 500), $\nu_{max.}$ 3 580 cm^{-1} (OH), τ 3.21(s), 3.45(s), and 3.30 (ABq *J* 9 Hz) (ArH), 5.91(q) and 5.98(q) (*J* 7 Hz, OCH_2), 6.14 and 6.23 (OMe), 6.5—7.6 (m, CH_2 and CH), 7.61 (NMe), and 8.56(t) and 8.60(t) (*J* 7 Hz, OCH_2·CH_3).

1-(2,5-*Diethoxy-4-methoxybenzyl*)-1,2,3,4-*tetrahydro-7-methoxy-2-methylisoquinolin-8-ol* (2e).—This product was prepared from the 8-benzyloxy-compound (7c) as described for (2f), and was again isolated as a yellow oil, R_F 0.28, $\lambda_{max.}$ 206 (ε 14 300), 228 (6 670), and 285 nm (2 450), $\nu_{max.}$ 3 580 cm^{-1} (OH), τ 3.18(s), 3.48(s), and 3.32(ABq, *J* 9 Hz) (ArH), 5.97(q) and 5.98(q) (*J* 7 Hz, OCH_2), 6.14(s) and 6.14(s) (OMe), 6.5—7.6(m, CH_2 and CH), 7.61(s, NMe), and 8.58(t) and 8.60(t) (*J* 7 Hz, OCH_2CH_3).

Compounds (2e and f) were obtained pure (one spot on t.l.c.) but they were unstable oils, prepared in very small amounts and this precluded elemental analysis. However their spectroscopic properties were fully in accord with those expected.

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