

1,2-DIHYDROISOQUINOLINES—XX¹

REARRANGEMENTS—VI

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Abstract—A mechanism is proposed for the rearrangement of 1-benzyl-1,2-dihydroisoquinolines into 3-benzyl-3,4-dihydroisoquinolines involving a bimolecular exchange reaction. Two transition states are considered, and it is believed that both can be involved, depending upon the precise nature of the starting enamine

Since the original discovery² that the benzyl group migrates from C₁ to C₃ when a 1-benzyl-1,2-dihydroisoquinoline is treated with hot, dilute mineral acid, a substantial amount of work has been reported with a series of 1-substituted-1,2-dihydroisoquinoline derivatives.³ Several proposals have been considered⁴ for the mechanism of the benzyl rearrangement, based largely upon yields of products under essentially standard conditions,⁵ but until now no self-consistent theory has emerged.

A satisfactory mechanism must take account of the following observations: (a) the reaction is intermolecular;⁶ (b) an increase in the size of the nitrogen-substituent in the 1,2-dihydroisoquinoline results in a decrease in the yield of rearrangement product;⁶ (c) the effects of substituents^{7,8} and the failure of groups such as aryl or alkyl to migrate⁹ indicate that the C^α-CH:Ar bond polarisation promotes migration; (d) the yield of rearrangement product, as compared with the yields of materials from the competing elimination and disproportionation reactions, depends strongly upon the concentration of the enamine¹⁰ (a decrease in enamine concentration results in a decrease in the yield of rearrangement product) and (e) the rearrangement involves initial protonation of the enamine at C₁ to form a 1,4-dihydroisoquinolinium ion.

The intermolecular character of the reaction can be interpreted in two ways: (i) separation of the migrating benzyl group as an ion or radical and migration to a second molecule that itself loses a benzyl group, or has already lost one, or (ii) a bimolecular exchange reaction in the course of which two molecules exchange their benzyl groups, such a process would probably occur in a concerted manner.

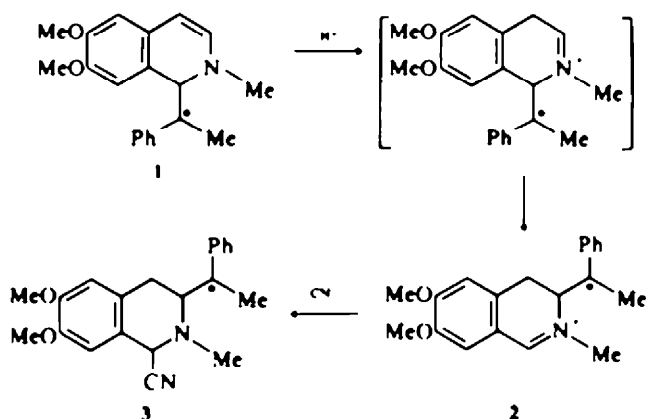
Whereas the reported⁶ observation that racemisation occurs when an optically active sample of 1 is rearranged is compatible with the formation of ions during the reaction, it is difficult to explain the observed effect of size of the nitrogen substituent on this basis. The fact that the observed migration reactions occur in dilute aqueous mineral acid is hardly in accord with the production of free

ions, and so it was decided to re-investigate the migration reaction of 1, particularly since the pseudocyanide 3 of the 3-benzyl-3,4-dihydroisoquinolinium ion 2, upon which the optical measurements were made previously,⁴ contains three chiral centres. It is possible that the observed zero rotation in 3 may be fortuitous.

As in the previous study,⁴ the (+)-isomer of 1 was prepared and subjected to the conditions of the rearrangement. The course of the reaction was followed by making polarimetric measurements. The original rotation of (+) 1-85° (for 25 ml of a solution in 2N HCl) fell to +0.70° after 48 hr heating under reflux, and this was unchanged after a further 12 hr heating. The rate of change of optical activity was approximately second order. An aliquot (25 ml) of the resultant solution was cooled, basified with NaHCO₃ and extracted with ether to give a small amount of an unidentified base ($\alpha = -0.10^\circ$, measured for 25 ml of 2N HCl solution). The aqueous liquor from this extraction was found to be optically active. The pseudocyanide 3 was obtained from this aqueous solution in the usual way and, as previously reported,⁴ it is optically inactive. However, the 3,4-dihydroisoquinolinium salt 2 that was regenerated from 3 with HCl/ethanol was found to be optically active ($\alpha = +0.80^\circ$ for 25 ml solution in 2N HCl). It was not possible to obtain 2 in an analytically pure condition so it was reduced with NaBH₄ to yield the 3-(α -phenylethyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline, $[\alpha]_D^{20} = -4.0^\circ$ (5.5% in CHCl₃).

Thus, it has been demonstrated that the rearrangement of the optically active 1,2-dihydroisoquinoline 1 occurs with retention of optical activity, at least to some extent.

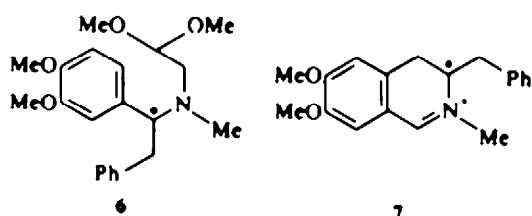
In order to explain the facts that the rearrangement is intermolecular, and also proceeds with retention of optical activity, it was proposed^{11,12} that two 1-benzyl-1,4-dihydroisoquinolinium ions could form a four-centre overlap transition state 4. Independently Knabe and Dorr arrived at essentially the same conclusion,^{10,11} but they preferred a transition state 5 resulting from a 6-centre overlap of two 1-benzyl-1,4-dihydroisoquinolinium ions. It is envisaged that in a complex of two molecules



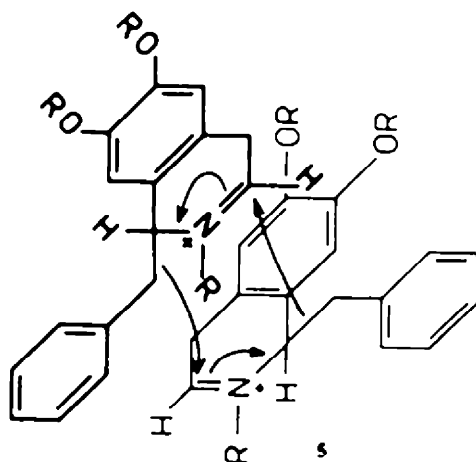
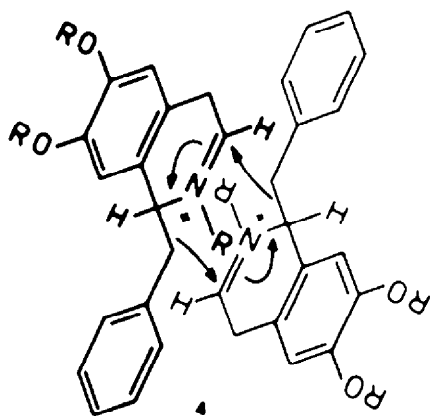
which exchange benzyl groups, the C_1 -atom of one molecule should lie opposite to the C_1 -atom of the second molecule, and *vice versa*: in addition each of the migrating benzyl groups must be orientated towards its receptor molecule. The two possible transition complexes 4 and 5 meet these requirements, and allow for an exchange of benzyl groups and the rearrangement of double bonds to occur in a cyclic, synchronous manner. In 4 the participating molecules must have opposite configurations at C_1 , whereas the transition complex 5 requires the partners to have the same configuration.

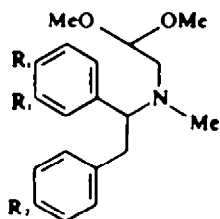
It has been found¹⁰ that when an optically active sample of 6 is subjected to the conditions of the rearrangement¹⁴ the 3-benzyl-3,4-dihydroisoquinolinium salt 7 formed is optically active. The configuration and optical purity of the product are not known, but the result does show that optically active 1-benzyl-1,2-dihydroisoquinolines (chiral centre at C_1) can rearrange through the 6-centre transition state 5, which of course could also be involved in the rearrangement of racemic compounds. The previously observed⁷ crossed migrations of racemic compounds is also explicable in terms of this same transition. However, it is possible that the alternative transition state 4 may be involved in the rearrangement of racemic 1-benzyl-1,2-dihydroisoquinolines, and we investigated this point.

The compounds selected for study were (+)-8a and

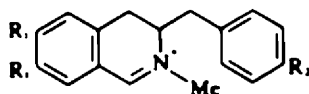


(-)-8b. It is assumed that the configurations of (+)-8a and (+)-8b are the same. If transition state 5 is involved, then when a mixture of these two compounds is subjected to the rearrangement conditions, the products should be 9a and 9b (both optically active), with none of the cross-over products 9c and 9d. If, however, transition state 4 is involved in the rearrangement of (+)-8a and (-)-8b, the products should be only 9c and 9d (both optically active) with none of the products 9a and 9b—provided of course that the two transition states are of unequal energies. The compounds 8a and 8b were expected to rearrange at similar rates, with the 4'-alkoxy group facilitating the rearrangement and suppressing the competing elimination reactions. The absence of an alkoxy group at C_1 considerably reduces the competing ring-closure reactions leading to pavinanes^{10,11,16} and isopavines.¹⁷ The molecular weights of the possible products 9a-9d are sufficiently different from each other





- 8a** $R_1 = R_2 = \text{OMe}$
8b $R_1 = R_2 = \text{CH}_3\text{O}$; $R_3 = \text{OEt}$
8c $R_1 = \text{OMe}$; $R_2 = \text{OEt}$
8d $R_1 = R_2 = \text{CH}_3\text{O}$; $R_3 = \text{OMe}$



- 9a** $R_1 = R_2 = \text{OMe}$
9b $R_1 = R_2 = \text{CH}_3\text{O}$; $R_3 = \text{OEt}$
9c $R_1 = \text{OMe}$; $R_2 = \text{OEt}$
9d $R_1 = R_2 = \text{CH}_3\text{O}$; $R_3 = \text{OMe}$

for analysis of the reaction mixture to be possible by mass spectrometry.

Samples of (racemic) **8a–8d** were prepared by the addition of *p*-methoxy- and *p*-ethoxybenzyl magnesium chlorides to **10a** and **10b**, followed by treatment of the secondary amines **11a–11d** with bromoacetal in DMF at 100°. When the alkylation reactions were performed at higher temperatures elimination occurred to yield stilbenes **12**. In view of the ease with which benzylbenzylamines can now be prepared through the α -aminonitrile route,¹⁰ it is possible that a simple synthesis of stilbenes can be developed. This is being investigated.

Each of the benzylaminoacetals **8a–8d** was separately rearranged under identical conditions (which were used throughout) and the products **9a–9d** were characterized as the pseudocyanides and as the 3-benzyl-1,2,3,4-tetrahydroisoquinolines; the yields (35–40%) were unusually low for rearrangement reactions of this type. A careful examination of the tarry residues revealed the presence of 10% or more of the stilbenes **12** already noted above.

Synthetic mixtures of the pseudocyanides were used to develop the quantitative mass spectral analysis used later (Experimental). It was established that equimolar mixtures of the pseudocyanides of **9a + 9b**, and of **9c + 9d** did not undergo thermal disproportionation in the mass spectrometer. The spectrum of each mixture was found to be the summation of the spectra of the components. An equimolar mixture of the racemates **8a** and **8b** were subjected to the rearrangement conditions, and the

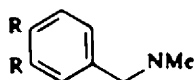
3,4-dihydroisoquinolinium salt fraction, obtained in 40% yield, was shown by mass spectrometry of the derived pseudocyanides to consist of similar amounts of all four compounds **9a–9d**. This established that the enamines **8a** and **8b** were reacting at comparable rates in the rearrangement reaction.

Samples of (-)-**11a** and (-)-**11b** were obtained by resolving with the two dibenzoyltartaric acids. Alkylation of these two amines with bromoacetal in DMF at 100° proceeded in greater than 90% yields to give (+)-**8a** ($[\alpha]_D^{20} + 95^\circ$) and (-)-**8b** ($[\alpha]_D^{20} - 102^\circ$). No racemisation occurred when **11a** was heated in DMF at 100° for 12 hr, thus suggesting a high degree of retention of optical activity in the alkylation reaction. (The alternative approach—resolution of racemic 1-benzyl-1,2-dihydroisoquinolines with optically active acids causes¹¹ disproportionation).

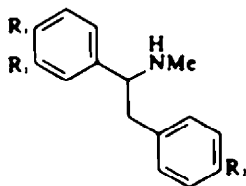
When a sample of (+)-**8a** was rearranged, the product **9a**, characterized as the 1,2,3,4-tetrahydroisoquinoline, had $[\alpha]_D^{20} + 76^\circ$, a value not affected by the duration of the acid treatment, thereby demonstrating the retention of optical activity during the migration. The optical purity and absolute configuration of this reduced rearrangement product are unknown.

A mixture of equimolar amounts of (+)-**8a** and (-)-**8b** were rearranged under the standard conditions, and the products analysed as before. All four possible products **9a–9d** were found to be present in the optically active mixture in similar amounts, thus showing that the rearrangement reaction cannot be proceeding exclusively through either transition state 4 or 5. The results are compatible with the participation of both transition states 4 and 5, which must be of comparable energies.

¹⁰It is interesting to note that racemic **8a** rearranged four times as fast as (+)-**8a** under identical conditions.

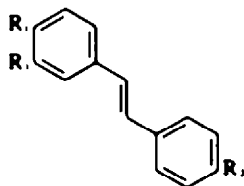


- 10a** $R = \text{OMe}$
10b $2R = \text{CH}_3\text{O}$



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- a** $R_1 = R_2 = \text{OMe}$
b $2R_1 = \text{CH}_3\text{O}$; $R_2 = \text{OEt}$
c $R_1 = \text{OMe}$; $R_2 = \text{OEt}$
d $2R_1 = \text{CH}_3\text{O}$; $R_2 = \text{OMe}$



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EXPERIMENTAL

Mps are uncorrected UV spectra are reported in nm for solns in 95% EtOH and IR spectra in cm^{-1} for nujol mull or liquid film except where noted. NMR spectra were measured on solns in CDCl₃, using a Varian A60 spectrometer, chemical shifts are expressed in ppm downfield of TMS as internal standard. Mass spectra were measured on an AFI MS12 and relative peak intensities are quoted as a percentage of the base peak.

(-)-1- α -Phenylethyl-6,7-dimethoxyisoquinoline methiodide (-)-1- α -Phenylethyl-6,7-dimethoxyisoquinoline was prepared by the method of Knabe and Powilleit,¹ and obtained from MeOH as colourless prisms, mp 120–1° (lit.¹ 120–2°) with $[\alpha]_D^{20} = 58^{\circ}$ (1.5% in EtOH) (lit.¹ 62°). The base (6.0 g) in nitromethane (60 ml) and acetone (2 ml) was treated with MeI (5 ml) and the mixture warmed in a sealed flask at 75° for 6 hr. The orange red soln was evaporated to dryness and the residue dissolved in acetone (20 ml). This acetone soln was added dropwise to a rapidly stirred volume (500 ml) of dry ether and the precipitated methiodide was separated by filtration (6.0 g, 68%), mp 135–8° ($[\alpha]_D^{20} = 102^{\circ}$ (2% in CHCl₃)). NMR: 8.8 d and 8.4 d (J = 7 Hz) (Ar-CH=CH-N), 7.8 s [1] and 7.2 s [1] (C₆H and C₄H), 7.25 s [5] (benzyl aromatic protons), 5.55 q [1] (J = 6 Hz) (C-CH₂-CH₂), 4.7 s [3] (N-CH₂), 4.0 s [3] and 3.6 s [3] (2 × -OCH₂), 2.1 d [3] (J = 6 Hz) (C-CH₂-CH₂). Neither the methiodide nor the methoperchlorate could be crystallised in a satisfactory manner.

(+)-1- α -Phenylethyl-6,7-dimethoxy-2-methyl-1,2-dihydroisoquinoline. LAH (0.5 g) was added portionwise to a stirred suspension of the above methiodide (1.2 g) in dry ether (25 ml), under a protective atmosphere of N₂. The mixture was stirred at room temp for 1 hr and then decomposed by the dropwise addition of a saturated soln of sodium potassium tartrate (50 ml). After separation, the aqueous phase was extracted with ether (3 × 25 ml), and the combined ether layers were washed with water, dried and evaporated to give a pale yellow gum which could not be crystallised (0.8 g), λ_{max} 210, 334, ν_{max} 2800, 1630, 760, 705. NMR indicates a mixture of two diastereomers in similar proportions, 7.3–6.7 complex [5] (benzyl aromatic protons), 6.45 and 6.40 two s [1] (C₆H), 5.97 and 5.95 two d [1] (J = 7 Hz) (Ar-CH=CH-), 5.90 and 5.75 two s [1] (C₆H), 5.1 d [1] (J = 7 Hz) (Ar-CH=CH-), 4.2 complex [1] (C₆H), 3.77 and 3.74 two s [3] (C₄-OCH₂), 3.55 and 3.45 two s [3] (C₄-OCH₂), 2.85 and 2.55 two s [3] (N-CH₂), 1.25 and 1.05 two d [3] (J = 7 Hz) (C-CH₂-CH₂). $[\alpha]_D^{20} + 92.5^{\circ}$ (2% in 2N HCl). Mass *m/e* (%): 309 (10) (M⁺), 308 (0.1), 204 (100).

Acid treatment of 1. The base (1.08 g) was dissolved in 2N HCl (40 ml) and the rotation of the soln was measured. The soln was heated under reflux and its rotation was measured from time to time, the values obtained are shown below.

Time elapsed (hr)	Rotation (°+)
0	1.85
1	1.57
2	1.45
6	1.20
24	0.85
48	0.70
60	0.70

An aliquot (25 ml) of the soln was basified with NaHCO₃ and extracted with ether (3 × 10 ml). The combined ether layers were washed with water then extracted with 2N HCl (1 × 10 ml, 2 × 5 ml), the combined acid extracts were diluted with 2N HCl to 25 ml, and the soln was found to have a rotation of -0.10°. This

soln was re-basified and extracted with ether (3 × 10 ml) to give a yellow gum (90 mg) which has not been identified. The aqueous basic soln from the mixture (diluted by the addition of the water back-wash) was found to have a rotation of +0.60°. It was treated with KCN (0.5 g) and the cloudy mixture was extracted with ether (5 × 10 ml), the aqueous phase now becoming inactive. The pseudocyanide 3 was obtained by evaporation of the combined, dried ether layers as a colourless gum (0.39 g, 71%). This material was also optically inactive, λ_{max} 208, 250, 293, 318, 378; NMR is complex, indicating a mixture of diastereomers, and includes 4.7 s [1] (Ar-CH-CN), 4.3 complex [1] (-CH₂-CH-CH-). Crystallisation from ether (small yield) gave colourless prisms, mp 172 (soften), 175–9° (lit.¹ 160–2°). Mass *m/e* (%): 336 (10) (M⁺), 309 (6), 308 (8), 231 (100), 206 (10), 204 (17).

The inactive 3 was dissolved in conc HCl/EtOH (1:1) and heated on a steam-bath for 2 hr. The yellow soln was evaporated to dryness and dissolved in 2N HCl (25 ml), this soln being optically active, with a rotation of -0.80°. Compound 2 was obtained as a yellow gummy solid (0.39 g, 65% based on the isoquinoline methiodide) $[\alpha]_D^{20} + 28^{\circ}$ (6.2% in EtOH), ν_{max} 1640, λ_{max} 207, 255, 317, 377, NMR includes 9.8 s [1] (Ar-CH=N), 7.7–6.6 complex [7] (aromatic protons), 4.15, 4.00, 3.95 and 3.90

four s [9] (N-CH₂ and 2 × -OCH₂ from diastereo mixture), 1.40 and 1.30 two d [3] (J = 7 Hz) (CH-CH-CH₂). Mass *m/e* (%): 310 (1) (M⁺), 309 (1), 308 (2), 206 (100), 204 (10). A crystalline salt (iodide or perchlorate) could not be obtained.

Reduction of 2 with sodium borohydride. Compound 2 (0.39 g) in EtOH (10 ml) was treated with NaBH₄ (0.3 g) for 2 min at room temp (yellow colour was discharged in 30 sec). The mixture was carefully acidified with conc HCl (5 ml) and heated on a steam-bath for 5 min. The resulting colourless soln was diluted with water (50 ml) and washed with ether, then basified with NH₄OH and extracted with ether (3 × 20 ml) to give, after removal of the solvent, a colourless gum (0.34 g, 97%), ν_{max} 2800, 755, 705, λ_{max} 209, 230, 286. NMR indicates a mixture of diastereomers, and includes: 7.25 and 7.23 two s [5] (benzyl aromatic protons), 6.52 s [1], 6.48 and 6.36 two s [1] (C₆H and C₄H), 3.78 s [3], 3.75 and 3.70 two s [3] (2 × -OCH₂), 2.35 s [3] (N-CH₂), 1.37 and 1.25 two d [3] (J = 6 Hz) (CH-CH-CH₂). Mass *m/e* (%): 310 (0.2) (M⁺), 206 (100), 204 (5) $[\alpha]_D^{20} + 4^{\circ}$ (5.2% in CHCl₃).

The methiodide was prepared in acetone at room temp and recrystallised from EtOH as lemon plates, mp 237–8°. NMR includes: 7.4 [5] (benzyl aromatic protons), 6.8 [1] and 6.7 [1] (C₆H and C₄H), 3.9 [6] and 3.8 [3] (2 × -OCH₂ and N-CH₂), 2.7 [3] (N-CH₂), 1.6 [3] (J = 7 Hz) (CH-CH-CH₂). Mass *m/e* (%): 326 (0.03) (M⁺), 206 (100), 204 (6) $[\alpha]_D^{20} + 1.6^{\circ}$ (2% in CHCl₃). Found: C, 55.9, H, 6.7, N, 3.0, 1.27.8. C₁₈H₁₈NO₂ requires: C, 55.6, H, 6.2, N, 3.1, 1.28.0%.

The racemic amines (11b–d). These were prepared by Grignard reaction in the usual manner and purified by either vacuum distillation (11a and c), or recrystallisation of the hydrochloride salts (11b and d).

N-Methyl- α -(4'-methoxybenzyl)-3,4-dimethoxybenzylamine (11a), mp 63–5°, NMR: 7.3–6.6 complex [7] (aromatic H), 3.85 s [6] (2 × OCH₂), 3.75 s [3] (OCH₂), 3.54 t [1] (J = 6 Hz) (Ar-CH-CH₂-Ar), 2.85 d [2] (J = 6 Hz) (Ar-CH-CH₂-Ar), 2.23 s [3] (N-CH₂), 1.9 broad s [1] (removed by D₂O) (N-H), ν_{max} 3315, 2790, 1614, 1517, 1253, 1176, 1025, λ_{max} (c) 228 (20,800), 279 (4800), mass *m/e* (%): 301 (c): 11 (M⁺), 180 (100) (Found: C, 71.6, H, 7.6, N, 4.7. C₁₆H₁₇NO₃ requires: C, 71.7, H, 7.7, N, 4.7%).

N-Methyl- α -(4'-ethoxybenzyl)-3,4-methylenedioxybenzylamine (11b), mp 63–4°. NMR: 7.0–6.6 complex [7] (aromatic H), 5.87 s [2] (O-CH₂-O), 3.92 q [2] (J = 7 Hz) (OCH₂CH₂), 3.46 t [1] (J = 6 Hz) (Ar-CH-CH₂-Ar), 2.8–2.5 complex [2] (Ar-CH-CH₂-Ar), 2.1 s [3] (N-CH₂), 1.36 t [3] (J = 7 Hz)

OCH_2CH_3), ν_{max} , 3300, 2790, 1609, 1510, 1238, 1175, 1040, λ_{max} (e) 228 (12,300), 285 (4,900) Hydrochloride salt, mp 235–6°. Mass *m/e* (%) 299 (5) (M^+ -HCl), 269 (6), 164 (100) (Found: C, 64.5, H, 6.6, N, 4.1, Cl, 10.40 $\text{C}_{16}\text{H}_{17}\text{NO}_2\text{HCl}$ requires: C, 64.4, H, 6.6, N, 4.2, Cl, 10.6%)

N-Methyl- α -(4'-ethoxybenzyl)-3,4-dimethoxybenzylamine (11c), mp 89–90°; NMR 7.2–6.7 complex [7] (aromatic H), 4.01 q [2] ($J = 7$ Hz) (OCH_2CH_3), 3.88 s [6] ($2 \times \text{OCH}_3$), 3.7 m [1] ($\text{Ar}-\text{CH}-\text{CH}_2-\text{Ar}$), 2.86 d [2] ($J = 7$ Hz) ($\text{Ar}-\text{CH}-\text{CH}_2-\text{Ar}$), 2.25 s [3] ($\text{N}-\text{CH}_3$), 1.5 broad s [1] (removed by D_2O) ($\text{N}-\text{H}$), 1.41 t [3] ($J = 7$ Hz) (OCH_2CH_3), ν_{max} , 3300, 2790, 1610, 1510, 1248, 1130, 1031, λ_{max} (e) 230 (18,000), 280 (3,240); mass *m/e* (%) 315 (1) (M^+), 314 (5), 285 (6), 180 (100) (Found: C, 72.5, H, 8.1, N, 4.3 $\text{C}_{17}\text{H}_{19}\text{NO}_2$, requires: C, 72.4, H, 8.0, N, 4.4%)

N-Methyl- α -(4'-methoxybenzyl)-3,4-methylenedioxybenzylamine (11d), NMR 7.2–6.5 complex [7] (aromatic H), 5.91 s [2] ($\text{O}-\text{CH}_2-\text{O}$), 3.75 s [3] (OCH_3), 3.55 t [1] ($J = 6.5$ Hz) ($\text{Ar}-\text{CH}_2-\text{CH}_2-\text{Ar}$), 2.8 d [2] ($J = 6.5$ Hz) ($\text{Ar}-\text{CH}-\text{CH}_2-\text{Ar}$), 2.18 s [3] ($\text{N}-\text{CH}_3$), 1.78 s [1] (removed by D_2O) ($\text{N}-\text{H}$), ν_{max} , 3320, 2790, 1611, 1512, 1485, 1250, 1178, 1040; λ_{max} (e) 228 (11,600), 286 (4,800) Hydrochloride salt, mp 234–5°, mass *m/e* (%) 285 (1) (M^+ -HCl), 255 (3), 164 (100) (Found: C, 63.6, H, 6.2, N, 4.2, Cl, 10.7 $\text{C}_{17}\text{H}_{17}\text{NO}_2\text{HCl}$ requires: C, 63.4, H, 6.2, N, 4.4, Cl, 11.0%)

Alkylation of 11a-d with bromoacetal to form 8a-d Three additions of bromoacetal (1.0 g each) were made at 12 hr intervals to a mixture of the appropriate amine (11, 1.2 g), K_2CO_3 (0.6 g) and dry DMF (20 ml) maintained at 100° under N_2 . The heating was continued for a further 24 hr, then the reaction was cooled, diluted with water (120 ml) and extracted with benzene (4 \times 50 ml). The combined organic phase was washed with water (5 \times 20 ml) and evaporated *in vacuo* to afford a yellow gum which was dissolved in ether (50 ml) and extracted into ice-cold 2N H_2SO_4 (3 \times 15 ml). The acid extracts were basified with NaHCO_3 , extracted with ether (3 \times 25 ml), dried (MgSO_4) and evaporated to yield the acetal (90–95%) as a yellow oil

N-Methyl-*N*-(4'-methoxybenzyl)-3,4-dimethoxybenzylaminoacetaldehyde dimethylacetal (8a), NMR, 7.15–6.65 complex [7] (aromatic H), 4.44 t [1] ($J = 5$ Hz) ($\text{CH}_2-\text{CH}(\text{OCH}_3)_2$), 3.84 s [6] and 3.72 s [3] ($3 \times \text{Ar}-\text{OCH}_3$), 3.31 s [6] ($\text{CH}-\text{OCH}_3$), 3.9–2.4 complex [5] (aliphatic H), 2.36 s [3] ($\text{N}-\text{CH}_3$), ν_{max} (CHCl_3), 1595, 1493, 1240, 1023, 1008, λ_{max} (e), 227 (18,300), 279 (4,500), mass *m/e* (%) 389 (< 1) (M^+), 358 (6), 271 (16), 268 (60), 252 (8), 180 (20), 87 (30), 75 (17), 47 (40) (M^+-1) = 388 2127 $\text{C}_{21}\text{H}_{25}\text{NO}_4$, requires 388 2124

N-Methyl-*N*-(α -(4'-ethoxybenzyl)-3,4-methylenedioxybenzyl)aminoacetaldehyde dimethylacetal (8b), NMR, 7.15–6.60 complex [7] (aromatic H), 5.91 s [2] ($\text{O}-\text{CH}_2-\text{O}$), 4.41 t [1] ($J = 5$ Hz) ($\text{CH}_2-\text{CH}(\text{OCH}_3)_2$), 3.95 q [2] ($J = 7$ Hz) (OCH_2CH_3), 3.32 s [6] ($\text{CH}-\text{OCH}_3$), 3.8–2.5 complex [5] (aliphatic H), 2.31 s [3] ($\text{N}-\text{CH}_3$), 1.34 t [3] ($J = 7$ Hz) (OCH_2CH_3), ν_{max} (CHCl_3), 1612, 1510, 1240, 1040, 1020, λ_{max} (e) 227 (14,900), 286 (5,400); mass *m/e* (%) 387 (< 1) (M^+), 252 (100), 236 (10), 164 (30), 135 (9), 75 (23)

N-Methyl-*N*-(α -(4'-ethoxybenzyl)-3,4-dimethoxybenzyl)aminoacetaldehyde dimethylacetal (8c), NMR, 7.1–6.6 complex [7] (aromatic H), 4.43 t [1] ($J = 5$ Hz) ($\text{CH}_2-\text{CH}(\text{OCH}_3)_2$), 3.95 q [2] ($J = 7$ Hz) (OCH_2CH_3), 3.84 s [6] ($2 \times \text{Ar}-\text{OCH}_3$), 3.32 s [6] ($\text{CH}_2\text{CH}(\text{OCH}_3)_2$), 3.9–2.4 complex [5] (aliphatic H), 2.36 s [3] ($\text{N}-\text{CH}_3$), 1.34 t [3] ($J = 7$ Hz) (OCH_2CH_3), ν_{max} (CHCl_3), 1594, 1492, 1242, 1020, 1006, λ_{max} (e), 227 (17,500), 280 (5,000), mass *m/e* (%) 403 (< 1) (M^+), 285 (18), 268 (100), 252 (10), 180 (15), 75 (12)

N-Methyl-*N*-(α -(4'-methoxybenzyl)-3,4-methylenedioxybenzyl)aminoacetaldehyde dimethylacetal (8d), NMR, 7.15–6.6 complex [7] (aromatic H), 5.92 s [2] ($\text{O}-\text{CH}_2-\text{O}$), 4.43 t [1] ($J = 5$ Hz) ($\text{CH}_2-\text{CH}(\text{OCH}_3)_2$), 3.75 s [3] ($\text{Ar}-\text{OCH}_3$), 3.33 s [6] ($\text{CH}_2-\text{CH}(\text{OCH}_3)_2$), 3.8–2.65 complex [5] (aliphatic H), 2.31

s [3] ($\text{N}-\text{CH}_3$), ν_{max} (CHCl_3), 1613, 1510, 1240, 1040, 1025, λ_{max} (e), 227 (14,400), 286 (5,400)

Isolation of trans-3,4,4'-trimethoxystilbene (12a) Alkylation of 11a with bromoacetal, K_2CO_3 and DMF, as above but at reflux temp for 24 hr, afforded the required 8a (56%), and from the non-basic fraction, the stilbene 12a (9%) as a colourless solid recrystallised from MeOH, mp 135° (lit¹³ 133–57, NMR, 7.5–6.8 complex [9] (7 aromatic H + 2 olefinic H), 3.93 s [3], 3.89 s [3] and 3.81 s [3] ($3 \times \text{OCH}_3$), ν_{max} , 1610, 1518, 1265, 1140, 1025, λ_{max} (e) 305 (12,400), 330 (16,000), 343 (11,400); mass *m/e* (%) 270 (100) (M^+) (Found: C, 75.2, H, 6.6 $\text{C}_{17}\text{H}_{17}\text{O}_3$, requires: C, 75.5, H, 6.7%) Irradiation of 12a with UV light afforded material, λ_{max} (e) 230 (10,700), 257 (8,300), 284 (6,400), mass *m/e* (%) 268 (55) (M^+), considered to be a phenanthrene

Resolution of amines 11a and b The amine 11a (7.2 g) and (-) dibenzoyltartaric acid (4.7 g) were dissolved in hot 95% EtOH (40 ml) and stood at RT for 20 hr. The precipitated diast. (NMR and Element analysis) was recrystallised from EtOH (8 times) until the liberated amine showed a constant specific rotation, $[\alpha]_D^{25} = 88.5^\circ$ (2% in EtOH), mp 76°. Similarly (-) - 11b was isolated from its racemate using (+) dibenzoyltartaric acid $[\alpha]_D^{25} = 98^\circ$ (2% in EtOH), mp 62°

Optically active acetals (+)-8a and (-)-8b The above optically active amines ((+)-11a and (-)-11b) were alkylated with bromoacetal under the standard conditions, to yield, (+)-8a (89%), $[\alpha]_D^{25} = 95^\circ$ (2% in EtOH) and (-)-8b (84%), $[\alpha]_D^{25} = 102^\circ$ (2% in EtOH), respectively

Acid treatment of racemic acetals (8a-d) The acetal (8) (1.0 mmole) in 6N HCl (10 ml, outgassed with N_2) was kept at 100° under N_2 in a stoppered tube for 1 hr. The mixture was cooled, diluted with water (10 ml) and washed with ether (3 \times 10 ml), then basified (NaHCO_3) and extracted with CHCl_3 (4 \times 10 ml). Removal of the CHCl_3 , *in vacuo*, afforded a gum which was leached with water at 35–40° (4 \times 5 ml). NaCN (25 mg) was added to the combined NaHCO_3 soln and water leachings and the white ppt extracted into ether (4 \times 15 ml). The ether extracts were washed with water (3 \times 10 ml), dried (MgSO_4) and evaporated to give the δ -cyanide derivatives of 9a-d in yields 25–30%

1-Cyano-6,7-dimethoxy-3-(4'-methoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (from 9a) Obtained as a colourless solid on intiruration with ether, mp 138–140°, NMR, 7.25–6.4 complex [6] (aromatic H), 4.83 s [0.2] and 4.72 s [0.8] ($\text{C}-\text{H}$ of diastereomers), 3.89 s [3], 3.85 s [3] and 3.79 s [3] ($3 \times \text{OCH}_3$), 3.7–3.0 complex [3] (aliphatic H), 2.75 s and 2.63 s [3] ($\text{N}-\text{CH}_3$, of diastereomers), 2.5 d [2] ($J = 7$ Hz) ($2 \times \text{C}-\text{H}$), ν_{max} , 2220, 1612, 1140, mass *m/e* (%) (low eV), 326 (25), 325 (100) (M^+-HCN), 231 (40), 206 (60) (Found: C, 71.3, H, 6.9, N, 7.8 $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_4$, requires: C, 71.6, H, 6.9, N, 8.0%)

1-Cyano-3-(4'-ethoxybenzyl)-2-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydroisoquinoline (from 9b) An off-white solid obtained on intiruration with ether, mp 90–4°, NMR, 7.3–6.45 complex [6] (aromatic H), 5.99 s and 5.94 s [2] ($\text{O}-\text{CH}_2-\text{O}$, diastereomers), 4.81 s [0.2] and 4.70 s [0.8] ($\text{C}-\text{H}$, diastereomers), 4.05 q [2] ($J = 7$ Hz) (OCH_2CH_3), 3.3–2.8 complex [3] (aliphatic H), 2.74 s and 2.62 s [3] ($\text{N}-\text{CH}_3$, diastereomers), 2.5 d [2] ($J = 6$ Hz) ($2 \times \text{C}-\text{H}$), 1.4 t [3] ($J = 7$ Hz) (OCH_2CH_3), ν_{max} , 2220, 1515, 1042, mass *m/e* (%) (low eV), 324 (30), 323 (100) (M^+-HCN), 215 (90) (Found: C, 71.5, H, 6.7, N, 8.4 $\text{C}_{21}\text{H}_{25}\text{N}_2\text{O}_4$, requires: C, 72.0, H, 6.3, N, 8.0%)

1-Cyano-3-(4'-ethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (from 9c), mp 99°, NMR, 7.2–6.5 complex [6] (aromatic H), 4.85 s [0.2] and 4.35 s [0.8] ($\text{C}-\text{H}$, diastereomers), 4.05 q [2] ($J = 7$ Hz) (OCH_2CH_3), 3.85 s [3] and 3.80 s [3] ($2 \times \text{OCH}_3$), 3.4–2.8 complex [3] (aliphatic H), 2.74 s and 2.63 s [3] ($\text{N}-\text{CH}_3$, diastereomers), 2.51 d [2] ($J = 6.5$ Hz) ($2 \times \text{C}-\text{H}$), 1.4 t [3] ($J = 7$ Hz) (OCH_2CH_3), ν_{max} , 2220, 1615, 1514, 1252, 1143, 1118, 799, mass *m/e* (%) (low eV) 340 (25), 339 (100)

(M⁺-HCN), 324 (20), 231 (20), 206 (100) (Found: C, 71.4, H, 7.2, N, 7.8. C₂₂H₂₀N₂O, requires: C, 71.2, H, 7.4, N, 7.9%)

1 - Cyano - 3 - (4' - methoxybenzyl) - 2 - methyl - 6,7 - methylenedioxy - 1,2,3,4 - tetrahydroisoquinoline (from 9d). Pale lemon crystals from ether, mp 94-5°. NMR, 7.3-6.4 complex [6] (aromatic H), 5.95 s and 5.91 s [2] (O-CH₂-O, diastereomers), 4.79 s [0.2] and 4.69 s [0.8] (C-H, diastereomers), 3.8 s [3] (OCH₃), 2.72 s and 2.62 s [3] (N-CH₂), 3.3-2.4 complex [5] (CH₂-CH-CH₂), ν_{\max} , 2220, 1615, 1516, 1247, 1040, 842, mass *m/e* (%) (low eV), 310 (27), 309 (100) (M⁺-HCN), 215 (30) (Found: C, 71.7, H, 5.8, N, 8.2. C₂₀H₁₈N₂O, requires: C, 71.4, H, 6.0, N, 8.3%)

Acid treatment of (-)-8a The acetal (+)-8a (580 mg) in 6N HCl (15 ml) was treated under the described migration conditions and afforded the expected 3 - benzyl - ϕ - cyanide (168 mg, 31%). To this was added EtOH (10 ml) and NaBH₄ (80 mg) and the reaction heated under reflux for 1 hr. The solvent was removed, water (10 ml) added and the product extracted into ether (3 \times 10 ml). The solvent was evaporated and the residue warmed with 2N HCl (30 ml) (to decompose N-horane complex), then basified (NaHCO₃) and extracted with CHCl₃ (3 \times 20 ml) to yield (+)-6,7 - dimethoxy - 3 - (4' - methoxybenzyl) - 2 - methyl - 1,2,3,4 - tetrahydroisoquinoline as a pale yellow oil (129 mg); $[\alpha]_D^{25} + 76^\circ$ (2% in EtOH). NMR, 7.15-6.45 complex [6] (aromatic H), 3.85-3.70 complex [11] (3 \times OCH₃ and 2 \times C-H), 3.49 s [3] (N-CH₂), 3.4-2.35 complex [5] (Ar-CH₂-CH-CH₂-Ar), λ_{\max} (e), 288 (5600), mass *m/e* (%), 327 (M⁺), 206 (70), 205 (20) Perchlorate salt (from EtOH) mp 124-6°; mass *m/e* (%) 326 (2), 205 (100), 204 (90). Attempts to test the optical purity of the tetrahydroisoquinoline by further resolution using dibenzoyltartaric acid were unsuccessful.

TLC of ϕ -cyanide and tetrahydroisoquinoline derivatives of 9a-d No TLC separation of the ϕ -cyanides of 9a-d could be achieved using a range of solvent systems on either alumina or silica. The corresponding tetrahydroisoquinoline derivatives were prepared, as above.

It was found that TLC on alumina (eluted with 4 \times C₆H₆, then 2 \times C₆H₆/CHCl₃, 7:1) showed *R_f* 0.60 (slightly separated) for the 9a and 9c derivatives and *R_f* 0.65 (slightly separated) for those from 9b and 9d.

Mixed migration reactions

(i) **Racemic** A mixture of 8a (0.1 mmole) and 8b (0.1 mmole) was treated with hot 6N HCl (2 ml, outgassed with N₂) then reacted and worked-up as in the previous rearrangements. A mixture of ϕ -cyanides was obtained (18 mg, 26%); mass *m/e* (low eV) 339, 325, 323, 309, ratio of peak heights 1.2:0.9:1.0:1.0. A duplicate reaction yielded 20.5 mg (29%) with ratio of peak heights 1.1:0.9:1.0:0.9.

The mass spectrum (low eV) of an equimolar mixture of the four-cyanide derivatives of 9a-d showed, on duplicates, ratios of the corresponding peaks 1.2:1.1:1.1:1.0 and 1.2:1.1:1.0:0.9.

A sample of the ϕ -cyanides from the mixed reaction was treated with NaBH₄ in EtOH and worked up as above. TLC confirmed the presence of the four 3 - benzyl - 1,2,3,4 - tetrahydroisoquinolines.

(ii) **Optically active** A mixture of (+)-8a (0.1 mmole) and (-)-8b (0.1 mmole) was treated as above and the ϕ -cyanides were isolated (17.5 mg, 25% and 20 mg, 28.5%), mass *m/e* (low eV) 339, 325, 323, 309 in ratios 1.3:1.0:1.0:0.9 and 1.4:1.1:1.0:1.1. All four tetrahydroisoquinolines were again detected after treatment with NaBH₄.

Isolation of stilbenes 12a-d Acid treatment of the acetals 8a-d, separately, under the usual conditions produced some material

that was soluble in neither the acid medium nor ether. This was treated with charcoal in MeOH, filtered and evaporated and the residues recrystallised from MeOH. The stilbenes so isolated were considered to have been present in much greater amounts than those quoted for the pure products.

trans - 3,4,4' - Trimethoxystilbene (12a), (2%), mp 135°, spectra as previously reported.

trans - 4' - Ethoxy - 3,4 - methylenedioxy stilbene (12b), (10%), mp 141-2°; NMR, 7.48-6.75 complex [9] (7 \times aromatic H plus 2 \times olefinic H), 5.95 s [2] (O-CH₂-O), 4.03 q [2] (J = 6.5 Hz) (O-CH₂-CH₃), 1.42 t [3] (J = 6.5 Hz) (O-CH₂-CH₃); λ_{\max} (e) 295 (23,200), 307 (24,100), 334 (31,700), 348 (23,200); mass *m/e* (%), 268 (100) (M⁺), 239 (12), 238 (11), metastables 214.6, 213.2. After exposure to UV, λ_{\max} 255, 289, 300 (sh).

trans - 4' - Ethoxy - 3,4 - dimethoxystilbene (12c), (5%), mp 138-9°; NMR, 7.45-6.8 complex [9] (7 \times aromatic H plus 2 \times olefinic H), 4.04 q [2] (J = 6.5 Hz) (O-CH₂-CH₃), 3.92 s [3] and 3.87 s [3] (2 \times OCH₃), 1.40 t [3] (J = 6.5 Hz) (O-CH₂-CH₃); ν_{\max} , 1516, 1249, 1136, 969; λ_{\max} (e), 294 (20,600), 305 (24,400), 320 (28,300), 332 (31,000), 345 (22,500); mass *m/e* (%), 284 (100) (M⁺), 269 (19), 255 (22), metastables 254.5, 229 (Found: C, 75.7, H, 7.4. C₁₈H₂₀O, requires: C, 76.0, H, 7.1%). After exposure to UV, λ_{\max} 258, 286, 300 (sh).

trans - 4' - Methoxy - 3,4 - methylenedioxy stilbene (12d), (8%), mp 143-3.5°, ν_{\max} 1513, 1257, 1180, 959, 935; λ_{\max} (e), 295 (20,000), 306 (20,600), 334 (30,100), 347 (21,000); mass *m/e* (%), 254 (100) (M⁺), 239 (23), metastable 225, after exposure to UV, λ_{\max} 255, 295.

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