Tetrahedron. Vol. 31, pp. 449 to 454 Pergamon Press 1975. Printed in Great Britain

1,2-DIHYDROISOQUINOLINES—XX[1]

REARRANGEMENTS—VI

R. G. KINSMAN, A. W. C. WHITE and S. F. DYKE*
School of Chemistry, University of Bath, Claverton Down, Bath BA2 7AY, Avon England

(*Received in the UK* 18 *July* 1974; *Accepted for publication* 14 *October* 1974)

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 discovery[2] that the benzyl group migrates from C_1 to C_3 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 considered[4] for the mechanism of the benzyl rearrangement, based largely upon yields of products under essentially standard conditions,[7] but until now no self-consistent theory has emerged.

A satisfactory mechanism must take account of the following observations: (a) the reaction is intermolecular;[5] (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 migrate[9] indicate that the $C_1^{\delta+}$–$^{\delta-}CH_2Ar$ 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 enamine[10] (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 C_4 to form a 1,4-dihydroisoquinolinium ion.

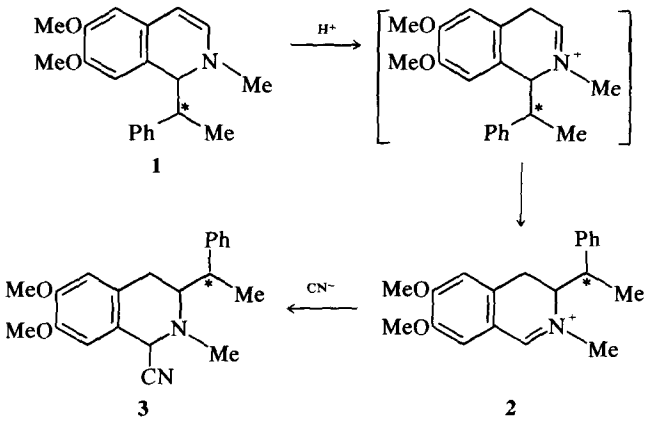
The intermolecular character of the reaction can be interpreted in two ways: (i) separation of the migrating benzyl group as an ion or radical and migration to a second molecule that itself loses a benzyl group, or has already lost one, or (ii) a bimolecular exchange reaction in the course of which two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

Whereas the reported[4] 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 2NHCl) 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 $NaHCO_3$ and extracted with ether to give a small amount of an unidentified base ($\alpha = -0{\cdot}10°$; measured for 25 ml of 2NHCl 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* ($\alpha = +0{\cdot}80°$ for 25 ml solution in 2NHCl). It was not possible to obtain **2** in an analytically pure condition so it was reduced with $NaBH_4$ to yield the 3 - (α - phenylethyl) - 2 - methyl - 1,2,3,4 - tetrahydroisoquinoline, $[\alpha]_D^{20} = -4{\cdot}0°$ (5·5% in $CHCl_3$).

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 *inter*molecular, 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,[10,13] 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

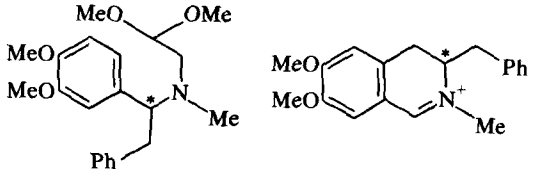


1 2 3

which exchange benzyl groups, the C_1-atom of one molecule should lie opposite to the C_3-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 found[10] that when an optically active sample of **6** is subjected to the conditions of the rearrangement[14] 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 observed[5] 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



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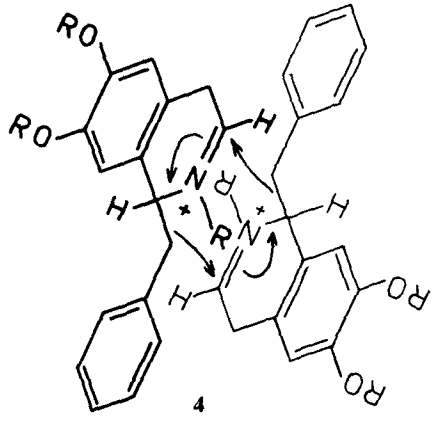
(−)−**8b**. It is assumed that the configurations of (+)−**8a** and (+)−**8b** are the same. If transition state **5** is involved, then when a mixture of these two compounds is subjected to the rearrangement conditions, the products should be **9a** and **9b** (both optically active), with none of the 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_3 considerably reduces the competing ring-closure reactions leading to pavinanes[10,15,16] and isopavines.[17] The molecular weights of the possible products **9a–9d** are sufficiently different from each other



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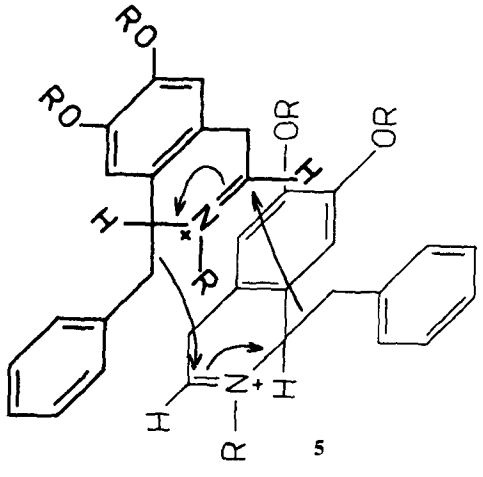

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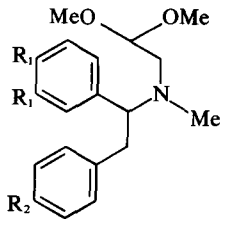
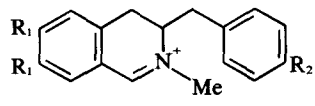


8a: $R_1 = R_2 = OMe$
8b: $R_1 + R_1 = CH_2O_2$; $R_2 = OEt$
8c: $R_1 = OMe$; $R_2 = OEt$
8d: $R_1 + R_1 = CH_2O_2$; $R_2 = OMe$



9a: $R_1 = R_2 = OMe$
9b: $R_1 + R_1 = CH_2O_2$; $R_2 = OEt$
9c: $R_1 = OMe$; $R_2 = OEt$
9d: $R_1 + R_1 = CH_2O_2$; $R_2 = OMe$

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,[18] 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 characterised 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.

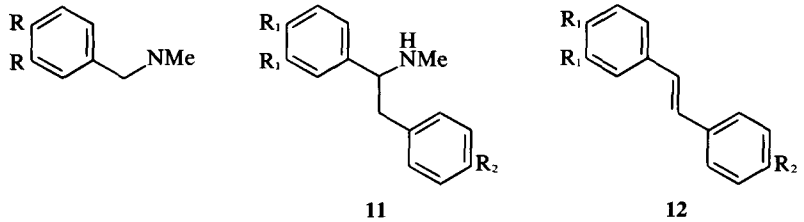
Synthetic mixtures of the pseudocyanides were used to develop the quantitative mass spectral analysis used later (Experimental). It was established that equimolecular mixtures of the pseudocyanides of **9a** + **9b**, and of **9c** + **9d** did not undergo thermal disproportionation in the mass spectrometer. The spectrum of each mixture was found to be the summation of the spectra of the components. An equimolecular 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 dibenzolytartaric acids. Alkylation of these two amines with bromacetal in DMF at 100° proceeded in greater than 90% yields to give (+) – **8a** ($[\alpha]_D^{20} + 95°$) and (−) – **8b** ($[\alpha]_D^{20} - 102°$). 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 causes[19] disproportionation).

When a sample of (+) – **8a** was rearranged, the product **9a**, characterised as the 1,2,3,4-tetrahydroisoquinoline, had $[\alpha]_D^{20} + 76°$, 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 equimolecular 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.

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



10a: R = OMe
10b: 2R = CH_2O_2

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12

a: $R_1 = R_2 = OMe$
b: $2R_1 = CH_2O_2$; $R_2 = OEt$
c: $R_1 = OMe$; $R_2 = OEt$
d: $2R_1 = CH_2O_2$; $R_2 = OMe$

EXPERIMENTAL

M.ps 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 $CDCl_3$ using a Varian A60 spectrometer; chemical shifts are expressed in ppm downfield of TMS as internal standard. Mass spectra were measured on an AEI 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,[4] and obtained from MeOH as colourless prisms, mp 120 − 1° (lit[4] 120 − 2°) with $[\alpha]_D^{20}$ − 58° (1·5% in EtOH) (lit[4] − 62·7°). 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° (2% in $CHCl_3$). NMR: 8·8 *d* and 8·4 *d* (J = 7 Hz) (Ar-CH=CH-$\overset{+}{N}$), 7·8*s*[1] and 7·2*s*[1] (C_5-H and C_8-H), 7·25*s*[5] (benzyl aromatic protons), 5·55*q*[1] (J = 6 Hz) C-CH-CH_3), 4·7*s* [3] ($\overset{+}{N}$-CH_3), 4·0*s*[3] and 3·6*s*[3] (2×-OCH_3), 2·1*d*[3] (J = 6 Hz) (C-CH-CH_3). Neither the methiodide nor the methoperchlorate could be crystallised in a satisfactory manner.

(+) - 1 - α - *Phenylethyl* - 6,7 - *dimethoxy* - 2 - *methyl* - 1,2 - *dihydroisoquinoline* **1**. 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 N_2. 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] (C_5-H), 5·97 and 5·95 two *d*[1] (J = 7 Hz) (Ar-CH=CH-), 5·90 and 5·75 two *s*[1] (C_8-H), 5·1*d*[1] (J = 7 Hz) (Ar-CH=CH-), 4·2 complex [1] (C_1-H), 3·77 and 3·74 two *s*[3] (C_6-OCH_3), 3·55 and 3·45 two *s*[3] (C_7-OCH_3), 2·85 and 2·55 two *s*[3] (N-CH_3), 1·25 and 1·05 two *d*[3] (J = 7 Hz) (C-CH-CH_3). $[\alpha]_D^{20}$ + 92·5° (2% in 2 N HCl). Mass *m/e* (%), 309 (0·1) (M^+), 308 (0·1), 204 (100).

Acid treatment of **1**. The base **1** (0·8 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 $NaHCO_3$ 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] (-CH_2-CH-CH-). Crystallisation from ether (small yield) gave colourless prisms, mp 172 (soften), 175–9° (lit[4] 160–2°). Mass *m/e* (%), 336 (0·1) (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° (6·2% in EtOH); ν_{max} 1640; λ_{max} 207, 255, 317, 377; NMR includes 9·85*s*[1] (Ar-CH=$\overset{+}{N}$), 7·7–6·6 complex [7] (aromatic protons), 4·15, 4·00, 3·95 and 3·90 four *s*[9] ($\overset{+}{N}$-CH_3 and 2×-OCH_3 from diastereo mixture), 1·40 and 1·30 two *d*[3] (J = 7 Hz) (CH-CH-CH_3). 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 $NaBH_4$ (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 NH_4OH 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] (C_5-H and C_8-H), 3·78*s*[3], 3·75 and 3·70 two *s*[3] (2×-OCH_3), 2·35*s* [3] (N-CH_3), 1·37 and 1·25 two *d*[3] (J = 6 Hz) (CH-CH-CH_3). Mass *m/e* (%), 310 (0·2) (M^+-1), 206 (100), 204 (5). $[\alpha]_D^{20}$ − 4° (5·5% in $CHCl_3$).

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] (C_5-H and C_8-H), 3·9 [6] and 3·8 [3] (2×-OCH_3 and $\overset{+}{N}$-CH_3), 2·7 [3] ($\overset{+}{N}$-CH_3), 1·6 [3] (J = 7 Hz) (CH-CH-CH_3). Mass *m/e* (%), 326 (0·03) (M^+), 206 (100), 204 (6). $[\alpha]_D^{20}$ 1·6° (2% in $CHCl_3$) (Found: C, 55·9; H, 6·7; N, 3·0; I, 27·8. $C_{21}H_{28}NO_2I$ requires: C, 55·6; H, 6·2; N, 3·1; I, 28·0%).

The racemic amines (**11a–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×OCH_3), 3·75 *s*[3] (OCH_3), 3·54 *t*[1] (J = 6 Hz) (Ar-CH-CH_2-Ar), 2·85 *d*[2] (J = 6 Hz) (Ar-CH-CH_2-Ar), 2·23 *s*[3] (N-CH_3), 1·9 broad *s*[1] (removed by D_2O) (N-H); ν_{max} 3315, 2790, 1614, 1517, 1253, 1176, 1025; $\lambda_{max}(\epsilon)$ 228 (20,800), 279 (4800); mass *m/e* (%) 301 (< 1) (M^+), 180 (100) (Found: C, 71·6; H, 7·6; N, 4·7. $C_{18}H_{23}NO_3$ 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-CH_2-O), 3·92 *q*[2] (J = 7 Hz) (OCH_2CH_3), 3·46 *t*[1] (J = 6 Hz) (Ar-CH-CH_2-Ar), 2·8–2·5 complex [2] Ar-CH-CH_2-Ar), 2·1 *s*[3] (N-CH_3). 1·36 *t*[3] (J = 7 Hz)

OCH_2CH_3); ν_{max} 3300, 2790, 1609, 1510, 1238, 1175, 1040; λ_{max} (ϵ) 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 $C_{18}H_{21}NO_3HCl$ 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 × OCH_3), 3·7 *m*[1] (Ar–CH–CH_2–Ar), 2·86 *d*[2] (J = 7 Hz) (Ar–CH–CH_2–Ar), 2·25 *s*[3] (N-CH_3), 1·5 broad *s*[1] (removed by D_2O) (N-H), 1·41 *t*[3] (J = 7 Hz) (OCH_2CH_3); ν_{max} 3300, 2790, 1610, 1510, 1248, 1130, 1031; λ_{max} (ϵ) 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. $C_{19}H_{25}NO_3$ 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] (O–CH_2–O), 3·75 *s*[3] (OCH_3), 3·55 *t*[1] (J = 6·5 Hz) (Ar–CH_2–CH_2–Ar), 2·8 *d*[2] (J = 6·5 Hz) (Ar–CH–CH_2–Ar), 2·18 *s*[3] (N–CH_3), 1·78 *s*[1] (removed by D_2O) (N–H); ν_{max} 3320, 2790, 1611, 1512, 1485, 1250, 1178, 1040; λ_{max} (ϵ) 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. $C_{17}H_{19}NO_3HCl$ 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 × 50 ml). The combined organic phase was washed with water (5 × 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 × 15 ml), The acid extracts were basified with $NaHCO_3$, extracted with ether (3 × 25 ml), dried ($MgSO_4$) and evaported to yield the acetal (90–95%) as a yellow oil.

N - *Methyl* - N - (4′ - *methoxybenzyl*) - 3,4 - *dimethoxybenzyl*]*aminoacetaldehyde dimethylacetal* (**8a**), NMR, 7·15–6·65 complex [7] (aromatic H), 4·44 *t*[1] (J = 5 Hz) (CH_2–$CH(OCH_3)_2$), 3·84 *s*[6] and 3·72 *s*[3] (3 × Ar–OCH_3), 3·31 *s*[6] (CH–$(OCH_3)_2$), 3·9-2·4 complex [5] (aliphatic H), 2·36 *s*[3] (N-CH_3); ν_{max} ($CHCl_3$), 1595, 1493, 1240, 1023, 1008; λ_{max} (ϵ), 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. $C_{22}H_{30}NO_5$ 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] O–CH_2–O), 4·41 *t*[1] (J = 5 Hz) (CH_2–$CH(OCH_3)_2$), 3·95 *q*[2] (J = 7 Hz) (OCH_2CH_3), 3·32 *s*[6] (CH–$OCH_3)_2$), 3·8–2·5 complex [5] (aliphatic H), 2·31 *s* [3] (N–CH_3), 1·34 *t* [3] (J = 7 Hz) (–OCH_2CH_3): ν_{max} ($CHCl_3$), 1612, 1510, 1240, 1040, 1020; λ_{max} (ϵ) 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) CH_2–$CH(OCH_3)_2$), 3·95 *q*[2] (J = 7 Hz) (OCH_2CH_3), 3·84 *s*[6] (2 × Ar–OCH_3), 3·32 *s*[6] ($CH_2CH(OCH_3)_2$), 3·9–2·4 complex [5] (aliphatic H), 2·36 *s*[3] (N-CH_3), 1·34 *t*[3] (J = 7 Hz) (OCH_2CH_3); ν_{max} ($CHCl_3$) 1594, 1492, 1242, 1020, 1006; λ_{max} (ϵ), 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] (O–CH_2–O), 4·43 *t*[1] (J = 5 Hz) (CH_2–$CH(OCH_3)_2$), 3·75 *s*[3] (Ar–OCH_3), 3·33 *s*[6] (CH_2–$CH(OCH_3)_2$), 3·8–2·65 complex [5] (aliphatic H), 2·31 *s*[3] (N–CH_3); ν_{max} ($CHCl_3$), 1613, 1510, 1240, 1040, 1025; λ_{max} (ϵ), 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° (lit[20] 133–5°); 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 × OCH_3); ν_{max}, 1610, 1518, 1265, 1140, 1025; λ_{max} (ϵ) 305 (12,400), 330 (16,000), 343 (11,400); mass *m/e* (%), 270 (100) (M^+) (Found: C, 75·2; H, 6·6. $C_{17}H_{18}O_3$ requires: C, 75·5; H, 6·7%). Irradiation of **12a** with UV light afforded material, λ_{max} (ϵ) 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 disalt (NMR and Element analysis) was recrystallised from EtOH (8 times) until the liberated amine showed a constant specific rotation, $[\alpha]_D^{20}$ + 88·5° (2% in EtOH); mp 76°. Similarly (−) − **11b** was isolated from its racemate using (+) dibenzoyltartaric acid. $[\alpha]_D^{20}$ − 98° (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%), $[\alpha]_D^{20}$ + 95° (2% in EtOH) and (−) − **8b** (84%), $[\alpha]_D^{20}$ − 102° (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 × 10 ml), then basified ($NaHCO_3$) and extracted with $CHCl_3$ (4 × 10 ml). Removal of the $CHCl_3$, *in vacuo*, afforded a gum which was leached with water at 35–40° (4 × 5 ml). NaCN (25 mg) was added to the combined $NaHCO_3$ soln and water leachings and the white ppt extracted into ether (4 × 15 ml). The ether extracts were washed with water (3 × 10 ml), dried ($MgSO_4$) and evaporated to give the ψ-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 trituration 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] (C_1-H of diasteriomers), 3·89 *s*[3], 3·85 *s*[3] and 3·79 *s*[3] (3 × OCH_3), 3·7–3·0 complex [3] (aliphatic H), 2·75 *s* and 2·63 *s*[3] (N–CH_3 of diasteriomers), 2·5 *d*[2] (J = 7 Hz) (2 × C_4–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. $C_{21}H_{24}N_2O_3$ 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 trituration with ether, mp 90–4°, NMR, 7·3–6·45 complex [6] (aromatic H), 5·99 *s* and 5·94 *s*[2] (O–CH_2–O, diastereomers), 4·81 *s* [0·2] and 4·70 *s*[0·8] (C_1–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] (N-CH_3 diastereomers), 2·5 *d*[2] (J = 6 Hz) (2 × C_4–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. $C_{21}H_{22}N_2O_3$ 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 4·75 *s*[0·8] (C_1–H, diastereomers), 4·05 *q*[2] (J = 7 Hz) (OCH_2CH_3), 3·85 *s*[3] and 3·80 *s*[3] (2 × OCH_3), 3·4–2·8 complex [3] (aliphatic H), 2·74 *s* and 2·63 *s* [3] (N–CH_3, diastereomers), 2·51 *d* [2] (J = 6·5 Hz) (2 × C_4–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. $C_{22}H_{26}N_2O_3$ 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–CH_2–O, diasteromers), 4·79 *s* [0·2] and 4·69 *s*[0·8] (C_1–H, diastereomers), 3·8 *s*[3] (OCH_3), 2·72 *s* and 2·62 *s* [3] (N-CH_3), 3·3–2·4 complex [5] CH_2–CH–CH_2); 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. $C_{20}H_{20}N_2O_3$ 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 - ψ - cyanide (168 mg, 31%). To this was added EtOH (10 ml) and $NaBH_4$ (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 × 10 ml). The solvent was evaporated and the residue warmed with 2N HCl (30 ml) (to decompose N-borane complex), then basified ($NaHCO_3$) and extracted with $CHCl_3$ (3 × 20 ml) to yield (+) - 6,7 - dimethoxy - 3 - (4' - methoxybenzyl) - 2 - methyl - 1,2,3,4 - tetrahydroisoquinoline as a pale yellow oil (129 mg); $[\alpha]_D^{21}$ + 76° (2% in EtOH). NMR, 7·15–6·45 complex [6] (aromatic H), 3·85–3·70 complex [11] (3 × OCH_3 and 2 × C_1–H), 3·49 *s*[3] (N-CH_3); 3·4–2·35 complex [5] (Ar–CH_2–CH–CH_2–Ar); λ_{max} (ϵ), 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 ψ-cyanide and tetrahydroisoquinoline derivatives of **9a–d**. No TLC separation of the ψ-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 × C_6H_6 then 2 × C_6H_6/$CHCl_3$ 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 N_2) then reacted and worked-up as in the previous rearrangements. A mixture of ψ-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 ψ-cyanides from the mixed reaction was treated with $NaBH_4$ 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 ψ-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 $NaBH_4$.

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 - *methylenedioxystilbene* (**12b**), (10%), mp 141–2°; NMR, 7·48–6·75 complex [9] (7 × aromatic H plus 2 × olefinic H), 5·95 *s*[2] (O–CH_2–O), 4·03 *q*[2] (J = 6·5 Hz) (O–CH_2CH_3), 1·42 *t*[3] (J = 6·5 Hz) (O–CH_2–CH_3); λ_{max} (ϵ) 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 × aromatic H plus 2 × olefinic H), 4·04 *q*[2] (J = 6·5 Hz) (O–CH_2CH_3), 3·92 *s*[3] and 3·87 *s*[3] (2 × OCH_3), 1·40 *t*[3] (J = 6·5 Hz) (O–CH_2CH_3); ν_{max}, 1516, 1249, 1136, 969; λ_{max} (ϵ), 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. $C_{18}H_{20}O_3$ requires: C, 76·0; H, 7·1%). After exposure to UV; λ_{max}, 258, 286, 300 (sh).

trans - 4' - *Methoxy* - 3,4 - *methylenedioxystilbene* (**12d**), (8%), mp 143–3·5°; ν_{max} 1513, 1257, 1180, 959, 935; λ_{max} (ϵ), 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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