Tetrahedron. Vol. 26, pp. 5265–5274. Pergamon Press 1970. Printed in Great Britain

1,2-DIHYDROISOQUINOLINES—XV[1]

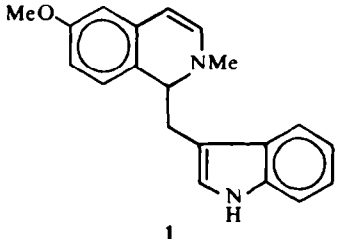
REARRANGEMENT III

M. SAINSBURY, S. F. DYKE,* D. W. BROWN and R. G. KINSMAN
School of Chemistry and Chemical Engineering, Bath University of Technology, Bath, Somerset, England

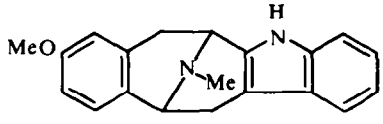
(*Received in the UK* 18 *June* 1970; *Accepted for publication* 14 *July* 1970)

Abstract—The acid-catalysed rearrangement of a 1-allyl-1,2-dihydroisoquinoline into a 3-allyl-3,4-dihydroisoquinolinium salt has been shown to occur in an intramolecular process. The rearrangement of a 1-propargyl-1,2-dihydroisoquinoline into a 3-allenyl-3,4-dihydroisoquinolinium salt is also described.

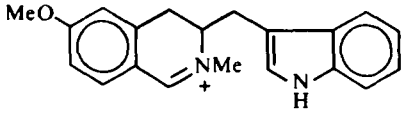
IN PART VIII of this series[2] we summarised the literature concerning the intermolecular migration of a benzyl group from C_1 to C_3 of 1,2-dihydroisoquinoline derivatives, and we found that the two reactions, rearrangement and pavine formation, occur concurrently under all of the sets of conditions that we examined. It is interesting to note[3] that compounds of the type **1** undergo pavine-type cyclisation to **2** so readily that to achieve rearrangement to **3**, an excess of acid has to be avoided. Knabe and Holtje[4] have found that



1



2

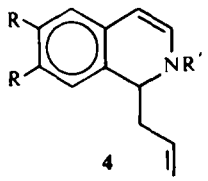


3

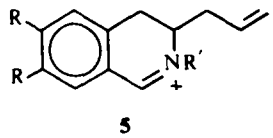
1-cinnimyl-1,2-dihydroisoquinolines will rearrange, but that, as expected, the 1-styryl derivatives undergo disproportionation without rearrangement.

We[2] have reported that 1-allyl-2-methyl-1,2-dihydroisoquinoline (**4**, R = H, R^1 = Me), formed by the addition of allyl magnesium bromide to isoquinoline methiodide, can be rearranged to the 3-allyl-3,4-dihydroisoquinolinium salt (**5**, R = H, R^1 = Me) in good yield. Knabe and Holtje[5] have also briefly described an allyl migration in **4** (R = OMe, R^1 = Me) to give high yields of **5** (R = OMe, R^1 = Me). In a discussion of the chemistry of benzylaminoacetaldehyde dimethyl acetals we[6] reported that when **6** (R = H) was treated with dilute HCl, it was transformed into the 3-allyl-3,4-dihydroisoquinolinium salt (**5**, R = OMe, R^1 = H) in almost quantitative

* To whom correspondence should be addressed.

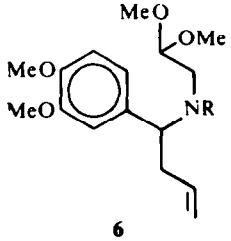


4

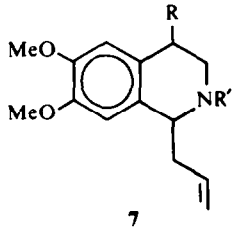


5

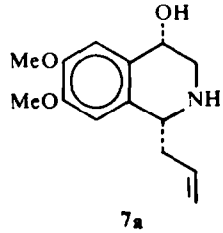
yield. Since we have now been able to isolate the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (7, R = OH, R^1 = H), and since compounds of this type are easily dehydrated by acids, it is clear that



6



7

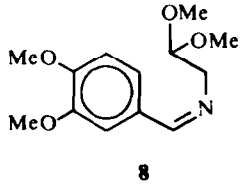


7a

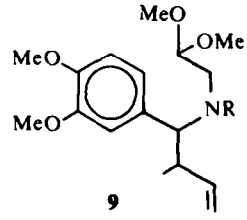
the reaction proceeded via the 1,2-dihydroisoquinoline (4, R = OMe, R^1 = H). The NMR spectrum of 7 (R = OH, R^1 = H) can be interpreted in terms of a diastereomorphic mixture, the two components being present in nearly equal amounts. Crystallisation from acetone gave one pure isomer, and from the chemical shift positions of the C_5 and C_8 H atoms, it is concluded that it is the isomer shown as **7a**, on the basis of the reported[7] NMR data for the 1-methyl-4-hydroxy-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines.

We[6] pointed out that the allyl migration reaction can be viewed as an example of a suprafacial sigmatropic [3,3] reaction, analogous to the Cope reaction, and as such may occur in a concerted manner under thermal conditions. In this paper we describe some experiments which show conclusively that the rearrangement of a 1-allyl-1,2-dihydroisoquinoline to the 3-allyl-3,4-dihydroisoquinolinium salt occurs by an intramolecular process. Some of this work has appeared in a preliminary form.[8, 9]

The substituted benzylaminoacetal (9, R = H) was prepared by the addition of crotyl magnesium bromide to the imine 8. Rearrangements of crotyl to methallyl



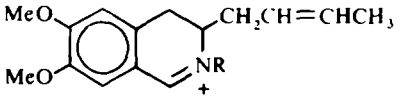
8



9

groupings in Grignard reactions are well known.[10, 11] The structure of 9 (R = H) follows from the NMR spectrum, which lacks absorption attributable to a $CH_3-\overset{|}{C}=C\diagup\diagdown$ grouping. Two doublets in the region 0·72–1·06δ indicate that 9 (R = H) is a mixture of two diastereomorphs in the ratio of 2:1. The major component

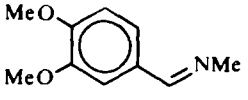
was obtained pure by crystallisation of the mixture from acetone; its NMR spectrum exhibits a three proton doublet (J = 7·0 Hz) at 1·28δ and a three proton multiplet at 5·0–6·3δ. This pure diastereomorph, and the mixture of diastereomorphs were separately treated with dilute HCl when the same product was isolated in each case in yields of 96%. The NMR spectrum of this product indicates clearly that it is a 3-crotyl-3,4-dihydroisoquinoline (**10**, R = H), and we believe that the crotyl group has the *trans* geometry. Simultaneous irradiation of the methyl and methylene groups flanking the double bond permitted an estimate to be made of the coupling constant (15 Hz) between the olefinic protons, but the pattern in the olefinic region was not clearly defined. For an intramolecular rearrangement, the *cis*-crotyl product would also be expected, but it is possible that isomerisation to the more stable *trans* geometry occurs under the conditions of the reaction. Similar results were obtained when **9** (R = Me), prepared by reacting **9** (R = H) with methyl iodide, was treated with mineral acid. The product was shown to be **10** (R = Me) by the usual spectroscopic



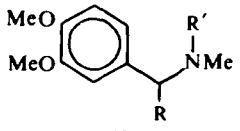
10

methods, but again some ambiguity concerning the geometry of the crotyl group remains. However, in both cases, the high yield of the 3-crotyl product with no detectable amounts of 3-methallyl-3,4-dihydroisoquinolinium salts, points strongly in favour of an intramolecular rearrangement.

A mixed migration experiment was next attempted, using equimolecular amounts of **6** (R = Me) and **9** (R = H). Only two products were formed, which were separated and shown to be identical with authentic samples of **5** (R = OMe, R^1 = Me) and **10** (R = H). The mass spectra of all four pure compounds (**5**, R = OMe, R^1 = H; **5**, R = OMe, R^1 = Me; **10**, R = H and **10**, R = Me), obtained by separately rearranging **6** (R = H; R = Me), **9** (R = H and R = Me), respectively, were compared with the spectra of the two products isolated from the mixed migration experiment. No evidence of crossed migrations was found. Considerable difficulty was experienced in preparing a sample of **6** (R = Me) free from the secondary amine **6** (R = H), and ultimately it was obtained from the Schiff base **11**. Addition of allyl magnesium bromide gave the expected secondary amine (**12**, R = $CH_2CH{=}CH_2$, R^1 = H) which was then alkylated with bromoacetal.

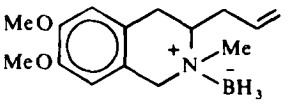


11

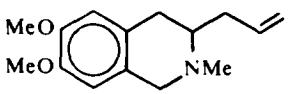


12

When **5** (R = OMe, R^1 = Me) was reduced with aqueous ethanolic $NaBH_4$ the product was the amine borane (**13**) and not the expected 1,2,3,4-tetrahydroisoquinoline (**14**). Although boranes of this type have been encountered before,[12] they were previously obtained with THF as the solvent.



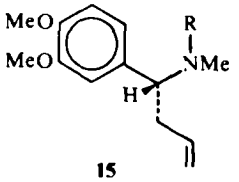
13



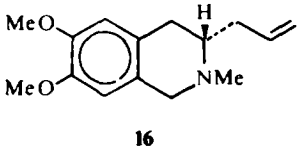
14

The required product (**14**) was obtained by hydrolysing **13** with 6N HCl.

Conclusive evidence for the intramolecular nature of the allyl migration reaction has now been provided by a study of the optically active benzylamine (**15**, R = H). The racemate (**12**, R = $CH_2CH{=}CH_2$, R^1 = H) was resolved with dibenzoyltartaric acid, and the isomer with $[\alpha]_D^{20}$ + 23·9° was found to have a very similar ORD curve (positive Cotton effect) to that[13] of *R*-αphenyl-β-phenylethylamine of known absolute configuration. Treatment of **15** (R = H) with glycidol gave **15** (R = CH_2 CHOH CH_2OH) which was converted to the aldehyde **15** (R = CH_2 CHO) with

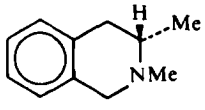


15



16

$NaIO_4$, and this, without isolation, was reacted with HCl under the conditions used previously. The product quaternary salt was reduced with $NaBH_4$, and the resulting tertiary base (**16**) had $[\alpha]_D^{20}$ + 35·0°. Resolution of a sample of **14**, obtained in the usual way from **6** (R = Me), with dibenzoyltartaric acid gave **16** with $[\alpha]_D^{20}$ + 36·9° so that the conversion of **15** (R = H) into **16** was accomplished with essentially 100% retention of optical activity. That the product possesses the *S*-configuration expressed in **16** was established by showing that the ORD curves of it and *S*-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**17**) are very similar (plain positive). The required sample of **17** was prepared by the application of the Bischler–Napieralski reaction, followed by

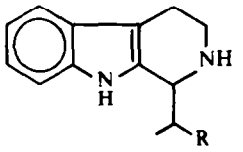


17

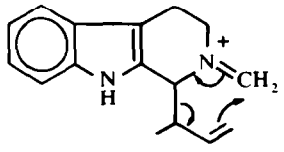
quaternisation and reduction, to (+)-amphetamine of known absolute configuration.

Thus, the sample of *R*-**15** (R = H) is converted in a stereospecific manner into a 3-allylisoquinoline derivative which has the *S*-configuration, as required[14] for an intramolecular rearrangement reaction.

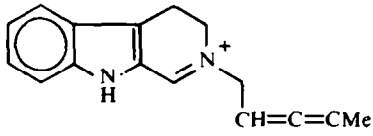
It has been reported[15] that when **18** (R = —CH=CH_2) is treated with formaldehyde, the product is **20**; the reaction presumably involves **19** as an intermediate. We have now demonstrated an analogous reaction in the isoquinoline series; when **22** is reacted with formaldehyde in glacial acetic acid, an 82% yield of **23**, isolated as the pseudocyanide, is formed. The structure of the product follows from its mass and NMR spectral data. Winterfeldt and Franzischka[15] also described the rearrangement, under similar conditions, of **18** (R = —C≡CH) to the allene derivative **21**.



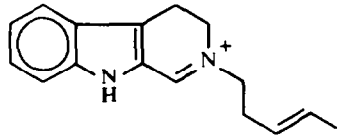
18



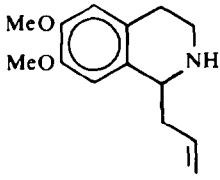
19



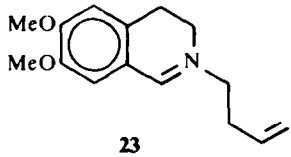
21



20

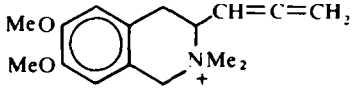


22



23

We have examined the reaction in which a 1-propargyl-1,2-dihydroisoquinoline was treated with mineral acid. Propargyl magnesium bromide was added to the imine (**11**) to yield the secondary amine (**12**, R = CH_2 C≡CH, R^1 = H), the structure of which follows from its mass spectrum and the characteristic NMR spectrum. Reaction of this acetylenic amine with glycidol yielded **12** (R = CH_2 C≡CH, R^1 = CH_2 CH(OH) CH_2 OH), which was oxidised with $NaIO_4$ to **12** (R = CH_2 C≡CH, R^1 = CH_2 CHO) and this aldehyde was treated with dilute HCl under the conditions used for the allyl migrations experiments. A 46% yield of a 3,4-dihydroisoquinolinium salt was isolated, but since it proved to be unstable it was characterised as **24** by reduction with $NaBH_4$ to the tertiary base and conversion to the methiodide. IR band



24

at 1970 cm^{-1} indicated the presence of an allene system in the molecule, and the NMR spectrum was found to be entirely compatible with structure **24**. Catalytic hydrogenation of the tertiary base formed by reduction of the rearrangement product with $NaBH_4$, yielded 2-methyl-3-n-propyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline, identical with an authentic sample prepared by catalytic hydrogenation of **14**. The formation of a 3-allenyl-3,4-dihydroisoquinoline from a 1-propargyl-1,2-dihydroisoquinoline suggests that an intramolecular process operates in this rearrangement also.

EXPERIMENTAL

All m.ps are uncorrected, UV spectra were recorded in 95% EtOH soln and IR spectra were measured as nujol mulls. NMR spectra were recorded using a Varian A-60 spectrometer and chemical shifts are

measured in ppm, downfield from TMS as internal standard. GLC analyses were carried out using a Pye 104 gas chromatograph.

1-*Allyl-6,7-dimethoxy-4-hydroxy-1,2,3,4-tetrahydroisoquinoline* (7; R = OH, R' = H). N-[4-(3,4-dimethoxyphenyl)butenyl] aminoacetaldehyde dimethylacetal hydrochloride (3·3 g) was dissolved in a mixture of conc HCl (25 ml) and crushed ice (25 g). After standing at RT overnight, the colourless soln was cooled to 0° and basified with 2N NaOH. The base was extracted with $CHCl_3$, dried and evaporated to give a gum, which, on trituration with acetone, gave 7 (R = OH, R' = H) as colourless prisms (1·55 g; 61%) m.p. 118–120°; ν_{max} cm^{-1}, 3330, 3120, 1645; NMR ($CDCl_3$) ppm, 6·98 s [0·4] (C_5—H of minor diastereomer), 6·91 s [0·6] (C_5—H of major diastereomer), 6·73 [0·6] (C_8—H, major isomer) 6·60 s [0·4] (C_8—H, minor isomer), 6·2–4·9 c [3] (—CH=CH_2), 4·45 m [1] (—CH(OH)), 3·9 s [6] (2 × —OCH_3), 3·9 m [1] (Ar—CH(—N<), 3·3–2·3 c [4] (CH_2—CH=CH_2 and —CH(OH)—CH_2—N<), 2·85 s [2] (>NH and —CH OH; removed by deuteration).

Recrystallization from acetone yielded only one diastereoisomorph (7a; 0·5 g) m.p. 124–125°; NMR ($CDCl_3$) ppm, 6·88 s [1] (C_5—H), 6·73 s [1] (C_8—H). (Found: C, 67·6; H, 7·8; N, 5·6. $C_{14}H_{19}NO_3$ requires: C, 67·5; H, 7·7; N, 5·6%).

Acid treatment of 7a. The base (249 mg, 0·001 mol) was dissolved in 6N HCl (15 ml) and heated at 100° for 1 hr. On cooling, the soln was diluted with water (20 ml) and basified with NH_4OH aq. Extraction with ether gave, after removal of solvent, a lemon oil (220 mg) 95%, the IR, UV and NMR spectra of which were identical with 3-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline.

N-[4-(3,4-*Dimethoxyphenyl*)-3-*methyl-butenyl*]*aminoacetaldehyde dimethyl acetal* (9, R = H). N-[3,4-Dimethoxybenzylidene)aminoacetaldehyde dimethyl acetal (31·4 g) was dissolved in dry ether (50 ml) and crotyl magnesium bromide (0·2 mol) in ether (250 ml) was added slowly. After stirring for 0·5 hr at RT, the reaction mixture was heated under reflux for 1 hr and then cooled. Finally 20% NH_4Cl aq (250 ml) was added, to destroy the excess reagent, and the aqueous phase was separated and extracted with ether. The combined ether phase and extracts were re-extracted with ice cold 2N H_2SO_4 (1 × 200 ml, 3 × 50 ml). The acid extracts were washed with ether, basified with NH_4OH aq and extracted with ether (3 × 100 ml). The combined extracts were dried and evaporated to yield a lemon oil (26·4 g, 69%), distillation of which gave a fraction, b.p. 158–163°/0·2 mm (21·4 g, 56%) of 9, R = H). ν_{max} cm^{-1}, 3370, 3090, 1645, 915; NMR ($CDCl_3$) ppm, 6·9 s [1] and 6·8 s [2] (aromatic protons); 6·2–4·8 c [3] (—CH=CH_2); 4·4 t [1], J = 6 Hz (—CH_2—CH(OCH_3)$_2$); 3·9 s [3] and 3·85 s [3] (2 × Ar OCH_3); 3·6 c [1] (—CH—CH<); 3·32 s [3] and 3·30 s [3] (2 × —CH(OCH_3)$_2$); 2·6 d [2], J = 6 Hz (—CH_2—CH(OCH_3)$_2$); 2·4 c [1] (Ar—CH—CH<); 1·8 broad s [1], removed with D_2O, (>NH); 1·0 d [2], J = 7 Hz (>CH—CH_3), major diastereomer; 0·8 d [1], J = 7 Hz (>CH—CH_3, minor diastereomer). (Found: C, 66·3; H, 8·7; N, 4·9. $C_{17}H_{27}NO_4$ requires: C, 66·0; H, 8·8; N, 4·5%).

Monomethylation of this product with MeI (molar equiv) in acetone at RT over Na_2CO_3 gave 9 (R = CH_3) in 90% yield.

Treatment of a solution of 9 (R = H) in ether with HCl (g) gave a lemon solid, m.p. 128–130°; NMR ($CDCl_3$) ppm, 1·35 d [2], J = 7 Hz (>CH—CH_3, major isomer); 1·05 d [1], J = 7 Hz (>CH—CH_3, minor isomer). Two recrystallizations from acetone yielded a sample of the hydrochloride of the major diastereomorph (9, R = H) as colourless needles m.p. 134–135°. NMR ($CDCl_3$) ppm, 1·3 d [3], J = 7 Hz (>CH—CH_3).

Acid treatment of 9 (R = H). The mixed diastereomorphs of the secondary base (3·0 g) were dissolved in EtOH and conc HCl (1:1; 50 ml) and heated at 100° for 3 hr. The mixture was diluted with water (200 ml) and washed with ether (3 × 50 ml): basification of the aqueous phase with NH_4OH, followed by ether extraction, gave, after removal of the dried solvent, a yellow oil (2·4 g, 98%) of 10a. Al_2O_3, TLC (10% EtOH in $CHCl_3$) showed one spot R_f 0·55, GLC (5′ × ¼″ column of 5% SE 30 silicone rubber on 85–100 mesh Universal B) column temp 150°, N_2 flow rate 30 ml/min indicated one component retention time 2 min 40 sec; mol wt. (mass spec) 245; λ_{max} nm, 234, 285, 315—almost identical with UV spectrum of 6,7-dimethoxy-3,4-dihydroisoquinoline; ν_{max} cm^{-1}, 3030, 1630, 970; NMR ($CDCl_3$) ppm, 8·2 d [1], J = 3 Hz

(Ar—CH=N—); 6·8 s [1] and 6·65 s [1] aromatic protons); 5·9–5·2 c[2](—CH—CH=CH—CH_3); 3·85 s [6] (2 × —OCH_3); 3·6–2·1 c [5] (aliphatic protons); 1·8–1·5 c [3] (—CH=CH—CH_3). Simultaneous irradiation of methyl and methylene protons flanking the double bond of the crotyl side chain reveals the olefinic coupling constant to be approx 15 Hz.

The hydrochloride was prepared and recrystallized from acetone as pale yellow crystals m.p. 188–189°; ν_{max} cm^{-1}, 3030, 2520, 1650, 970. λ_{max} (ε) nm, 211 (9300), 248 (15,700), 313 (8100), 370 (6000). (Found: C, 63·3; H, 7·4; N, 5·1; Cl, 12·6. $C_{15}H_{20}NO_2Cl$ requires: C, 63·9; H, 7·2; N, 5·0; Cl, 12·6%). The pure diastereomorph of the secondary base **9** (R = H) was similarly treated with acid, and the product was identical in all respects to that obtained by acid treatment of the mixed diastereoisomorphs.

The base **10a** (2·95 g) was dissolved in aqueous EtOH and treated with $NaBH_4$ (3 g) and allowed to stand overnight at RT. The soln was evaporated to half bulk and treated with H_2O (50 ml) and ether (50 ml). The ether layer was separated, dried ($MgSO_4$) and the hydrochloride ppt'd with HCl (g). This salt was recrystallized from EtOH as lemon coloured needles (2·0 g, 59%) m.p. 211–212°; λ_{max} (ε) nm, 232 (5600), 287 (2900); ν_{max} cm^{-1}, 3040, 2740, 2620, 2540, 2505, 2460, 970. (Found: C, 63·2; H, 7·6; N, 5·0. $C_{15}H_{22}NO_2Cl$ requires: C, 63·5; H, 7·8; N, 4·9%).

Acid treatment of **9** (R = CH_3). The tertiary base (3·23 g, 0·01 mol) was heated with 6N HCl (25 ml), at 100° for 3 hr. After cooling, dilution with water (100 ml) and basification to pH 8 with $NaHCO_3$, the soln was washed with ether (3 × 25 ml). [A small amount of **10a** was obtained from the ether layers, indicating the presence of **9** (R = H) in the tertiary base.] The aqueous soln was treated with NaCN (0·5 g) and again extracted with ether (4 × 25 ml), to give, after removal of solvent, a colourless waxy solid (2·65 g, 93%), which when triturated with ether had m.p. 70–71°; λ_{max} (ε) nm, 238 (7800), 288 (3600), 315 (2300), 373 (2300); ν_{max} cm^{-1}, 2800, 2015, 965; NMR ($CDCl_3$) ppm, 6·70 s [1] and 6·63 s [1] (aromatic protons) 5·84–5·26 m [2] (—CH_2—CH=CH—CH_3), 4·73 s [1] (Ar—CH—CN), 3·8 s [6] (2 × —OCH_3), 3·3–2·3 m [5] (Ar—CH_2—CH—CH_2—) 2·6 s [3] (>N—CH_3), 1·7 c [3] (—CH=CH—CH_3). (Found: C, 70·8; H, 7·5; N, 10·0. $C_{17}H_{22}N_2O_2$ requires: C, 71·3; H, 7·7; N, 9·8%).

N-[4-(3,4-*Dimethoxyphenyl) butenyl*] *methylamine* (**12**, R = —$CH_2CH=CH_2$, R^1 = H). Procedure as for **9**, R = H), but using compound **11** (35·8 g, 0·2 mol) and allyl magnesium bromide (0·25 mol). After removal of ether solvent, a pale yellow oil was obtained (35·8 g), which was purified via the hydrochloride. The latter recrystallized from EtOH as colourless plates, m.p. 167–168°; ν_{max} cm^{-1}, 2800, 2710, 2440, 1645. (Found: C, 61·2; H, 7·8; N, 5·7. $C_{13}H_{20}NO_2Cl$ requires: C, 60·6; H, 7·8; N, 5·4%). The pure base was obtained from the hydrochloride as a colourless oil, λ_{max} (ε) nm, 231 (8200), 281 (2800); ν_{max} cm^{-1}, 3330, 2790, 1640; NMR ($CDCl_3$) ppm, 6·9 s [1] and 6·8 s [2] (aromatic protons); 6·1–4·8 c [3] (—CH_2—CH = CH_2), 3·82 s [3] and 3·78 s [3] (2 × OCH_3); 3·45 m [1] (Ar—CH—N<), 2·4 m [2] (>CH—CH_2—CH = CH_2); 2·2 s [3] (>N—CH_3), 1·4 broad s, removed by D_2O (>NH).

N-[4-(3,4-*Dimethoxyphenyl butenyl*]-N-*methyl aminoacetaldehyde dimethyl acetal* (**6**, R = CH_3). Bromacetal (5·72 g, 0·034 mol) and **12** (R = —CH_2—CH=CH_2, R^1 = H; 8·4 g, 0·034 mol) were heated at 120° for 2 hr with rapid stirring. The cooled mixture was dissolved in water (100 ml) and ether (50 ml); the aqueous layer was separated and extracted with ether (2 × 50 ml). The combined ether phase and extracts were dried ($MgSO_4$) and evaporated to yield a yellow oil (10·2 g, 87%) which was distilled under reduced pressure to give **6** (R = Me) as an oil (7·3 g, 61%), bp 130–133°/0·3 mm. This material was basically identical with previous sample of **6** (R = CH_3), but was free from **6** (R = H).

Attempted crossed migration experiment (**6**, R = CH_3; 1·00 g) and **9** (R = H; 1·00 g) were dissolved in 6N HCl (15 ml) and heated at 100° for 1 hr. On cooling, the soln was diluted with water (50 ml) and washed with Et_2O (3 × 10 ml). The soln was then basified with $NaHCO_3$ to pH 8 and extracted with ether (5 × 10 ml); after drying the combined extracts were evaporated to give a colourless oil (A) (0·75 g). The aqueous phase was treated with NaCN (0·5 g), extracted with ether (5 × 10 ml) and these extracts evaporated to give a lemon coloured waxy solid (B) (0·86 g).

The base A was shown to be identical with **10a** previously obtained (IR, NMR and mass spectra), rigorous TLC and GLC analysis did not detect that cross migration had occurred, whereas a synthetic mixture of **5a** (R = —OCH_3; 5%) and **10a** (95%) was easily analysed (GLC as before, retention times 1 min 55 sec and 2 min 40 sec respectively).

The pseudo cyanide (B) was similarly shown to be identical to the pseudo cyanide of **5** (R = OCH_3, R' = CH_3), this too was a single compound. GLC showed a single peak under a variety of conditions. Using the same column packing and flow rates as previously described, but at 200°, a peak with a retention time of

2 min 15 sec, identical to that of a pure sample was obtained. A mixture of the pseudo cyanide of **10** (R = CH_3; 5%) and the pseudo cyanide of **5** (R = OCH_3, R' = CH_3; 95%) was easily analysed by GLC showing retention times of 3 min 0 sec and 2 min 15 sec respectively at 200°. The mass spectra of B showed no peaks above *m/e* 245.

Reduction of **5** (R = OCH_3; R' = CH_3) with $NaBH_4$. The salt (500 mg) in EtOH (10 ml) was treated with $NaBH_4$ (500 mg) at room temp. After 2 hr the soln was diluted with water (50 ml) and extracted with ether (3 × 25 ml). After removal of the ether, the residue (an oil + needle-like crystals) was crystallised from a small volume of EtOH to yield colourless needles (170 mg) of **13** m.p. 137–138°; ν cm^{-1} 2380, 2330, 2290, 1640; λ_{max} mn(ε): 226(6000), 287(3300). M.W. (mass spec) 261. (Found: C, 69·5; H, 9·6; N, 6·0. $C_{15}H_{24}BNO_2$ requires: C, 69·0; H, 9·3; N, 5·4%).

The boron complex **13**, combined with the mother liquors from its crystallisation, was treated with conc HCl on a steam bath for ½ hr. After dilution, basification and extraction with ether, a colourless oil (420 mg) was isolated which was shown (UV, NMR, IR) to be identical with **14**.[6]

Resolution of N-[4-(3,4-*dimethoxyphenyl*)-*butenyl*]-*methylamine* (**12**; R = $-CH_2-CH=CH_2$, R' = H). The base (10·0 g) was dissolved in acetone (100 ml) containing (−) dibenzoyl tartaric acid (32·4 g) warmed to about 60°, cooled and left at 0° overnight. The colourless crystalline product (10·4 g) which had separated was collected and recrystallised from acetone ether (1 : 1) a total of six times, until a constant optical rotation of $[\alpha]_{20}^{D} = -78°$ (2% in EtOH) was obtained. The purified salt (3·5 g) was basified with $NaHCO_3$ and the liberated base was extracted into ether. Removal of the solvent gave **12** (R = $-CH_2-CH=CH_2$, R' = H) as a colourless oil (0·8 g) $[\alpha]_{20}^{D} = +23·9$ (8% in EtOH), ORD (in isooctane) shows plain (+)ve curve, with (+)ve Cotton effect at 285 nm. Comparison with ORD curve of *R*-(α)-phenyl-β-phenylethylamine [(+)ve plain curve, (+)ve Cotton effect at 269 nm] indicates that this compound has the *R* configuration e.g. **15** (R = H).

Isolation of **16** *after rearrangement.* The base **15** (R = H) (700 mg) and glycidol (300 mg) were heated together at 100° for 2 hr. On cooling, water (10 ml) and $CHCl_3$ (10 ml) were added, and the temp reduced to 0°. $NaIO_4$ (610 mg) in water (10 ml) was added slowly, and the pH was adjusted to 8 with NaOH aq. After stirring at RT for 3 hr, the $CHCl_3$ layer was separated and the aqueous phase extracted with $CHCl_3$ (3 × 5 ml). The combined $CHCl_3$ phase and extracts were re-extracted with 6N HCl (4 × 5 ml) and the acid extracts were heated at 100° for 1 hr, cooled, and diluted with water (50 ml). The soln was basified with $NaHCO_3$ and washed with ether (2 × 25 ml), then treated with $NaBH_4$ (500 mg) at RT for 1 hr. The resultant mixture was acidified with 2N HCl and heated at 100° for a few min, then cooled, basified and extracted with ether (4 × 25 ml) to give the corresponding 1,2,3,4-tetrahydrobase as a colourless oil (273 mg) $[\alpha]_{20}^{D} = +31·1°$. The base was passed down a column of alumina, eluting with $CHCl_3$, and the product was then crystallized from light petroleum (40–60°) as colourless plates (210 mg) m.p. 44–45°, $[\alpha]_{20}^{D} = +35·0°$. (Found: C, 72·6; H, 8·5; N, 5·6. $C_{15}H_{21}NO_2$ requires: C, 72·8; H, 8·6; N, 5·7%), ORD (isooctane) show plain (+)ve curve. Comparison with ORD curve of *S*-2,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (**17**), which is very similar, supports the configuration **16**. The specific rotation of this product compared with that of **16** prepared by the resolution of **14** indicates that at least 97% retention of configuration is maintained during rearrangement.

Resolution of **14**. The 3-allyl tetrahydroisoquinoline (2·47 g) and (−)-dibenzoyl tartaric acid (1·79 g) were dissolved in acetone (10 ml) and cooled to −30°. After standing overnight the solid product which had formed was collected and recrystallised from acetone a total of eight times. After basification with ammonia soln the free base, from this salt, was extracted into ether and, after removal of the solvent, was obtained as a colourless solid. Recrystallisation from light petroleum (40–60°) gave plates (179 mg) m.p. 45–46° $[\alpha]_{20}^{D} = +36·9°$.

S-2,3-*Dimethyl*-1,2,3,4-*tetrahydroisoquinoline* (**17**). (+)-*S*-Amphetamine (6·75 g) $[\alpha]_{D}^{20}$ +33·6° and formic acid (3·7 g) were heated together in an open flask for 3 hr at 180°. The resultant oil was dissolved in H_3PO_4 (s.g. 1·75; 30 ml) and P_2O_5 (50 g) added. The mixture was heated for 3 hr at 200–210° with occasional stirring. After cooling, the mixture was poured onto crushed ice (500 ml) and the aqueous soln was then washed with benzene (3 × 100 ml).

The aqueous soln was then basified with $NaHCO_3$ and extracted with benzene (3 × 100 ml); removal of the dried solvent affording a yellow oil, λ_{max} 257 nm ν_{max} cm^{-1}, 1630, which was dissolved in acetone (30 ml) and treated with MeI (5 ml). Yellow needles soon formed; these were collected and crystallised from acetone (6·92 g; 48%) m.p. 155–156°; NMR (CF_3CO_2H) ppm 9·1 broad s [1] ($C_1-\underline{H}$); 8·1–7·4 m [4] (aromatic protons); 4·4 m [1] ($-CH_2-\underset{|}{\overset{|}{C}}H-CH_3$); 4·0 s [3] ($\underset{|}{\overset{|}{\overset{+}{N}}}-CH_3$); 3·8–2·8 c [2] ($Ar-CH_2-\underset{|}{\overset{|}{C}}H-$); 1·45 d

This salt (4·62 g) was dissolved in EtOH (25 ml) and $NaBH_4$ (2·0 g) added slowly. Water was then added, and the reaction mixture extracted with ether; removal of the dried solvent afforded a colourless oil (2·05 g, 79%), purified as the hydrochloride: colourless needles, m.p. 216–217° (EtOH). (Found: C, 66·9; H, 8·1; N, 7·1. $C_{11}H_{16}NCl$ requires: C, 66·8; H, 8·2; N, 7·1%). The pure base, liberated from the hydrochloride salt, was a colourless liquid. λ_{max} (ε) nm, 267 (500), 274 (500), ν_{max} cm^{-1}, 2800, 1380; NMR ($CDCl_3$) ppm 7·1 s [4] (aromatic protons; 3·8 d [1], J = 15 Hz and 3·55 d [1], J = 15 Hz (Ar—CH_2—N<); 3·0–2·5 c [3] (Ar—CH_2—$\underset{|}{CH}$—N<); 2·4 s [3] (>N—CH_3); 1·15 d [3], J = 7 Hz (>$\underset{|}{CH}$—CH_3), $[\alpha]_{20}^{D}$ = +89·8° (10% in EtOH); ORD plain (+)ve curve with (+)ve Cotton effect at 278 nm.

Preparation of **23**. 1-Allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (250 mg) in glacial AcOH (2·0 ml) and 40% HCHO soln (1·0 ml) was heated at 100° for 2 hr. After the addition of water (50 ml) and basification, the soln was washed with ether (3 × 10 ml). KCN (0·5 g) was then added and the cloudy suspension which formed was extracted with ether (3 × 10 ml). Removal of solvent from the combined dried extracts yielded a colourless solid (207 mg), which was recrystallised from benzene/petrol (40–60°), m.p. 78–79°; λ_{max} (ε) nm, 238 (6300), 288 (2800), 293 (2800), 316 (2200), 372 (2100); ν_{max} cm^{-1}, 2210, 1645; NMR ($CDCl_3$) ppm, 6·85 s [1] and 6·80 s [1] (aromatic protons), 6·2–4·9 c [3] (—$\underset{|}{CH_2}$—$\underset{|}{CH}$=CH_2). 4·8 s [1] (Ar—$\underset{|}{CH}$—CN), 3·9 s [6] (2 × —OCH_3), 3·2–2·2 c [8] (Ar—CH_2—CH_2—N—CH_2—CH_2—). (Found: C, 71·0; H, 7·4; N, 10·4. $C_{16}H_{20}N_2O_2$ requires: C, 70·6; H, 7·4; N, 10·3%).

N-methyl-1-(3,4-dimethoxy)phenylbut-3-ynamine (**12**, R = —CH_2—C≡CH, R′ = H). A soln of propargyl magnesium bromide (from 40 g propargyl bromide) in ether (240 ml) was added slowly to a soln of N-methylveratraldehyde imine (36 g) in ether (50 ml) at 0°. After stirring for 2 hr the reaction was heated at reflux for a further 30 min. The Grignard complex was then cautiously decomposed with 20% NH_4Cl aq, diluted with water (1 l) and the organic phase separated. After extraction with ether (5 × 50 ml) the combined ether layers were dried and evaporated to leave a brown oil (30 g), this was dissolved in benzene and the soln saturated with HCl. The solid which formed was collected and recrystallised from EtOH as colourless needles m.p. 222–224°; ν_{max} cm^{-1}, 3200, 2840, 2700–2200, 1610. (Found: C, 60·9; H, 7·1; N, 5·5. $C_{13}H_{18}NO_2Cl$ requires: C, 61·1; H, 7·1; N, 5·5%).

After basification with ammonia soln the corresponding base **12** (R = CH_2—C≡CH, R′ = H) was obtained as a pale brown oil (21 g) 46% which solidified on standing, and was recrystallised from 60–80° light petroleum as colourless needles m.p. 71°. Mass *m/e* 219 (m+) [3%], 180 [100%]; ν_{max} cm^{-1}, 3600–3200, 2820, 2780, 2100; NMR ($CDCl_3$) ppm, 7·0–6·9 broad s [3] (aromatic protons), 3·9 s [6] (2 × —OCH_3), 3·7 t [1], J = 7 Hz (Ar—$\underset{|}{CH}$—CH_2—), 2·5, m [2] (—$\underset{|}{CH}$—CH_2—C≡CH), 2·3 s [3] (—$\underset{|}{N}$—CH_3), 2·0 t [1], J = 2·5 Hz (—CH_2—C≡$\underline{CH}$), 1·9 s [1] (—$\underset{|}{N}$—$\underline{H}$) removed by deuteration.

Rearrangement of **12** (R = CH_2—C≡CH, R′ = H). The above compound (4·8 g) was heated with glycidol (1·5 g) at 100° for 2 hr. Chloroform (40 ml) and water (40 ml) were introduced, the mixture cooled to 0°, and sodium metaperiodate (5·0 g) in water (30 ml) was then slowly added. The reaction mixture was basified with NaOH (pH 8) and vigorously stirred for 3 hr. The chloroform layer was then separated and the aqueous phase extracted with chloroform, the chloroform layer and extracts were combined and re-extracted with 6N HCl (3 × 50 ml). The acid extracts were heated at 100° for 1 hr, cooled, diluted with water (250 ml), washed with ether (3 × 30 ml) and finally basified with $NaHCO_3$ aq. $NaBH_4$ (8 g) in small amounts was added to the aqueous soln and, after the reaction had ceased, the tertiary base formed was collected into ether. Removal of the ether afforded a brown oil (2·0 g) λ_{max} (ε) nm, 287 (1850); ν_{max} cm^{-1}, 1955, 1615, 1515; NMR ($CDCl_3$) ppm 6·6 s [1] and 6·55 s [1] (aromatic protons), 5·1 m [1] —$\underline{CH}$=C=$\underline{CH_2}$) 4·8–4·6 m [2] (—$\underset{|}{CH}$=C=$\underline{CH_2}$), 3·85 s [6] (2 × $O\underline{CH_3}$), 3·7 q [2], J = 2 Hz (Ar—CH_2—N<), 3·0–2·6 m [3] (Ar—CH_2—$\underset{|}{CH}$—), 2·45 s [3] (—$\underset{|}{N}$$\underline{CH_3}$).

This material was characterised as **24**, colourless plates m.p. 212–213° (EtOH); mass *m/e* 260 (m+) [83·5%], 215 [78%], 206 [100%]; λ_{max} (ε) nm, 287 (2400), ν_{max} cm^{-1}, 1970, 1615, 1520; NMR (CF_3CO_2H) ppm 6·9 s [1] and 6·85 s [1] (aromatic protons), 5·6–5·0 m [3] (—$\underset{|}{CH}$=C=$\underline{CH_2}$), 4·8–4·6 m [2] (Ar—CH_2—$\overset{+}{\underset{|}{N}}$—),

4·4–4·2m[1](Ar—CH_2—CH—), 3·95s[6](2 × OCH_3), 3·4s[3](—$\overset{+}{N}$—CH_3), 3·4–3·2m[2](Ar—CH_2—CH—)
3·1 s [3] (—$\overset{+}{N}$—CH_3). (Found: C, 49·7; H, 5·9; N, 3·4. $C_{16}H_{22}NO_2I$ requires: C, 49·7; H, 5·7; N, 3·6%).

6,7-*Dimethoxy*-2-*methyl*-3-*n*-*propyl*-1,2,3,4-*tetrahydroisoquinoline*. The tertiary base from the rearrangement product, formed in the previous experiment, was hydrogenated at 5 atm pressure in acetone soln using 5% Pd–C as catalyst. After 15 hr at room temp the 3-n-propyl-tetrahydroisoquinoline was obtained as a colourless oil. This material was identical in all respects with a specimen prepared by the hydrogenation of **14** under the same conditions. Further characterisation was achieved by direct comparison of methiodides of the two samples; the methiodide was obtained as a colourless crystalline solid m.p. 246–247°; mass *m/e* 264 (m+) [0·06%], 206 [100%], λ_{max} (ε) nm, 287 (2100); ν_{max} cm^{-1}, 2845, 1615, 1520; NMR (CF_3CO_2H) ppm, 6·95 s [1] and 6·9 s [1] (aromatic protons), 4·65 m [2] (Ar—CH_2—$\overset{+}{N}$—), 4·0 s [6] (2 × —OCH_3), 4·0–3·5 m [1] (Ar—CH_2—CH—), 3·4 s [3] (—$\overset{+}{N}$—CH_3), 3·15 s [3] (—$\overset{+}{N}$—CH_3), 3·5–2·8 m [2] (Ar—CH_2—CH—), 2·2–0·8 m [7] (—CH—CH_2—CH_2—CH_3). (Found: C, 49·2; H, 6·6; N, 3·4; I, 32·1 $C_{16}H_{26}NO_2I$ requires: C, 49·1; H, 6·6; N, 3·6; I, 32·5%).

Acknowledgements—We wish to thank Mr. F. L. Hall, an undergraduate of this department, for the work on the acetylenic compounds, and Dr. A. Rosen, Pharmacy Department, Chelsea College of Science and Technology, for recording the ORD curves.

REFERENCES

[1] Part XIV: M. Sainsbury, D. W. Brown, S. F. Dyke, R. D. J. Clipperton and W. R. Tonkyn, *Tetrahedron* **26**, 2239 (1970)
[2] M. Sainsbury, D. W. Brown, S. F. Dyke, R. G. Kinsman and B. J. Moon, *Ibid.* **24**, 6695 (1968)
[3] H. Zinnes, F. R. Zuleski and J. Shavel, *J. Org. Chem.* **33**, 3605 (1968)
[4] J. Knabe and H.-D. Holtje, *Tetrahedron Letters* 2107 (1969)
[5] J. Knabe and H.-D. Holtje, *Ibid.* 433 (1969)
[6] D. W. Brown, S. F. Dyke and M. Sainsbury, *Tetrahedron* **25**, 101 (1969)
[7] G. Grethe, M. Uskokovic, T. Williams and A. Brossi, *Helv. Chim. Acta* **50**, 2397 (1967)
[8] D. W. Brown, S. F. Dyke, R. G. Kinsman and M. Sainsbury, *Autumn Meeting Chem. Soc. Keele* Abstract F11, Sept. (1968)
[9] D. W. Brown, S. F. Dyke, R. G. Kinsman and M. Sainsbury, *Tetrahedron Letters* 1731 (1969)
[10] M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances* p. 1155. Constable, London
[11] G. M. Whitesides, J. E. Norlander and J. D. Roberts, *Disc. Farad. Soc.* No. 34, 185 (1962)
[12] S. Yamada and S. Ikegami, *Chem. Pharm. Bull.* **14**, 1382 (1966)
[13] A. La Mana, V. Ghishlandi, P. M. Scopes and R. J. Swan, *Farm Ed. Sci.* **20**, 842 (1965)
[14] R. K. Hill and N. W. Gilman, *Chem. Commun.* 619 (1967)
[15] E. Winterfeldt and W. Franzischka, *Chem. Ber.* **100**, 3801 (1967)