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1,2-DIHYDROISOQUINOLINES—XVIII[1]
REARRANGEMENTS—IV

S. F. DYKE and R. G. KINSMAN

School of Chemistry and Chemical Engineering, Bath University, Bath, Somerset, England

and

DIHYDROISOQUINOLINE REARRANGEMENT—15[2]

J. KNABE and H. D. HOLTJE

Institut für Pharmazeutische Chemie der Universität des Saarlandes, Deutschland

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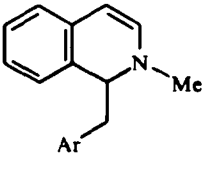
Abstract—When 1-allyl-2-methyl-1,2-dihydropapaverine is treated with hot, dilute mineral acid, rearrangement occurs to give, almost exclusively the 3-allyl-2-methyl-3,4-dihydropapaverinium salt. The previously reported rearrangement of 1-cinnamyl-2-methyl-6,7-dimethoxy-1,2-dihydroisoquinoline has been reexamined and the earlier result, that rearrangement occurs to yield the 3-cinnamyl-3,4-dihydroisoquinolinium salt, confirmed.

IT IS now well established[3–9] that when a 1-benzyl-1,2-dihydroisoquinoline (1) is treated with hot dilute mineral acids, rearrangement occurs to yield the 3-benzyl-3,4-dihydroisoquinolinium salt (2). The usual side-reactions that accompany this change are[5] (i) disproportionation of 1 to yield a mixture of the 1-benzyl-1,2,3,4-tetrahydroisoquinoline (3) and the corresponding aromatic quaternary salt (4, R = $ArCH_2$), (ii) elimination of the C_1-substituent to give 4 (R = H) and (iii) disproportionation of the



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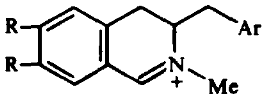

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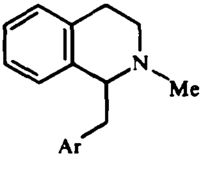

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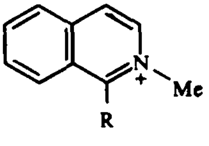

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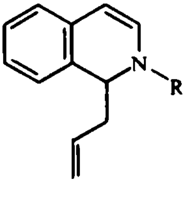
rearranged material (2). The extent of these competing reactions depends upon the nature of the substituents in the aromatic ring of the benzyl group. With substituents such as saturated alkyl or phenyl in place of the benzyl group of 1 only disproportionation[5] without rearrangement is observed. Although the benzyl migration has been shown[4] to be intermolecular, the precise mechanism of the transformation is still uncertain.

It has also been found[8, 10, 11] that a 1-allyl-1,2-dihydroisoquinoline (5, R = H or Me) rearranges to the 3-allyl-3,4-dihydroisoquinolinium salt (6, R = H or Me) in high yield when treated with hot dilute acids. This reaction, a suprafacial sigmotropic [3,3] shift, has been proven[10] to be intramolecular in nature.



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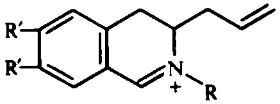

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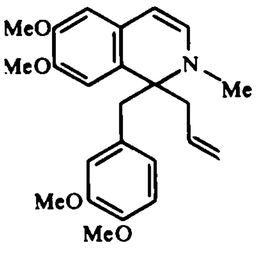
We now wish to describe our study with 1-allyl-2-methyl-1,2-dihydropapaverine (7), in which either the allyl or the benzyl group is free to migrate; we hoped in this way to gain some useful information concerning the comparative transition states in these two processes. The required base (7), which was easily prepared as a crystalline solid by the interaction of allyl magnesium bromide with papaverine methiodide, is an example[12] of a stable 1,2-dihydroisoquinoline. The C_3-proton resonates as a doublet at 5·85δ in the NMR spectrum and the C_4-proton, to which it is coupled, appears as a doublet at 4·90δ. When the chloroform solution of 7 is shaken with D_2O, the latter absorption disappears, and the absorption at 5·85δ collapses to a singlet, suggesting that in this neutral solution there is some tautomerism between the enamine form (7) and the imminium ion form. When the 1,2-dihydroisoquinoline (7) was treated with 2N HCl, under the conditions for the benzyl and allyl migrations described above, a quarternary



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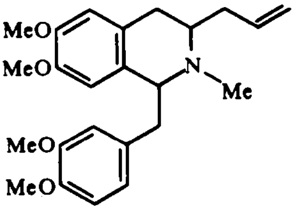

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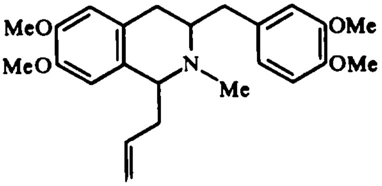

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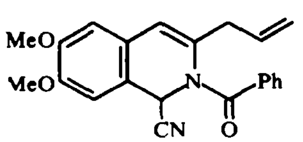
salt was formed, the UV spectrum of which was indicative of a 3,4-dihydroisoquinolinium salt. Reduction of this product with $NaBH_4$ gave a 1,2,3,4-tetrahydroisoquinoline $C_{24}H_{31}NO_4$ so that both the 3,4-dimethoxybenzyl and the allyl groups are still present. The tetrahydroisoquinoline is therefore either **8** or **9**, or possibly a mixture of these two compounds. The NMR spectrum of this reduced rearrangement product included a one proton singlet as 6·15δ (C_8–H) and a three proton singlet at 3·65δ (C_7–OMe), as expected[13–15] for a 2-methyl-1-benzyl-1,2,3,4-tetrahydroisoquinoline. These upfield shifts are not observed in 2-methyl-3-benzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline. This observation suggests that the reduced rearrangement product is **8**, rather than **9**. An authentic sample of the latter compound was easily prepared by addition of allyl magnesium bromide to **2** (R = OMe; Ar = 3,4-$(OMe)_2$ C_6H_3), itself prepared[3] by rearranging 2-methyl-1,2-dihydropapaverine. The compound **9** was found not to be identical with the reduced rearrangement product. In the NMR spectrum the singlets for C_8–H and C_7–OMe protons absorb in the expected positions.

Attempts have been made to synthesise **8**, but without success. In the first approach it was hoped that the readily available[8, 10] 3-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**6**, R = H; R^1 = OMe) could be dehydrogenated to the 3-allylisoquinoline, which could then be alkylated with 3,4-dimethoxybenzyl bromide via the Reissert[16] compound **10**. However, when **6**, (R = H, R^1 = OMe) was heated with 5% Pd/C in decalin, the only product that could be isolated (60% yield) was a new, dimeric base $C_{28}H_{30}N_2O_4$, the NMR spectrum of which revealed that dimerization had occurred via the two allyl side-chains to yield **11**. When **6**, (R = H, R^1 = OMe) was heated in decalin in the absence of a catalyst, a 20% yield of 6,7-dimethoxyisoquinoline was obtained; presumably the reaction is a concerted one as indicated in **12**. In another attempt to prepare **8**, the 3,4-dihydroisoquinoline (**6**, R = H; R^1 = OMe) was treated with PhCOCl and KCN under the conditions of the Reissert reaction and the expected product (**13**, R = H) was obtained in 70% yield. Alkylation with 3,4-dimethoxybenzyl chloride in the presence of NaH/DMF gave **13**, (R = 3,4-$(OMe)_2$ $C_6H_3CH_2$) in 50% yield. Whilst attempts were being made to remove the cyano and benzoyl groups from this product, the paper on "dihydro Reissert" compounds[17] appeared, but we were still unable to remove these groupings. The treatment with phosphoric acid recommended by Shamma and Jones caused charring, presumably as



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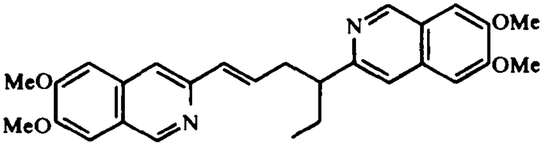

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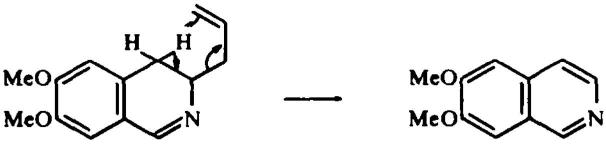

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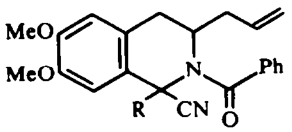
a result of the interaction of H_3PO_4 with the allyl group. The structure of **13** is secure, however, from the mass spectral data (Experimental).



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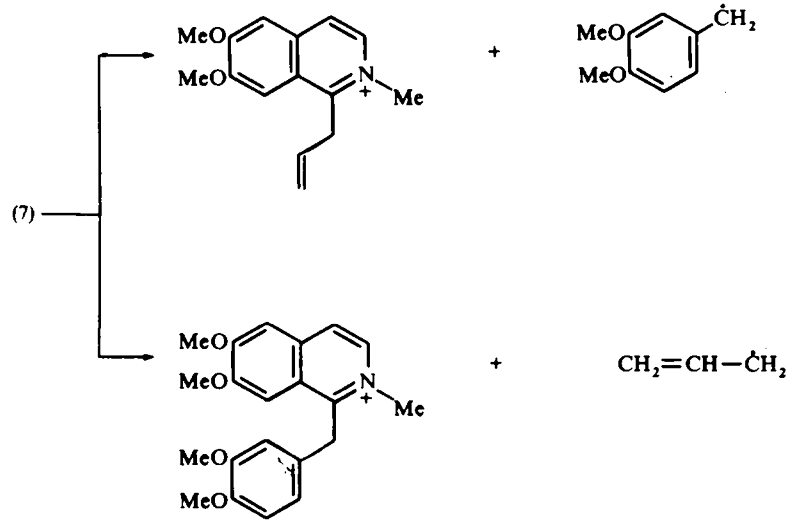
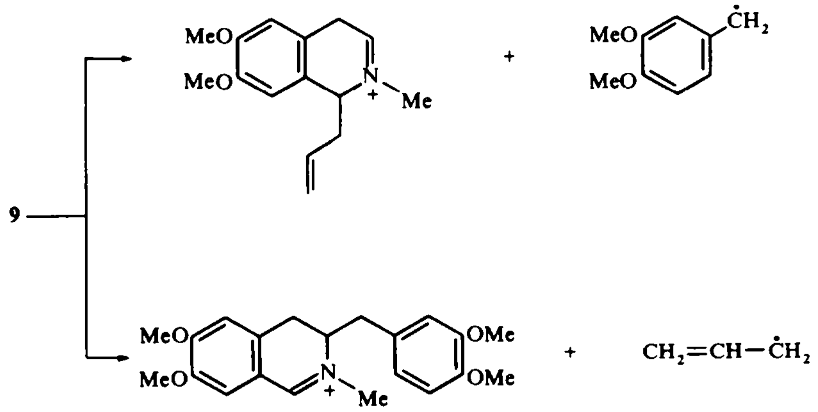
Although we have shown above that the reduced rearrangement product is **8** and not **9**, it is possible that a small amount of benzyl migration could have occurred, and we investigated this point. Unfortunately it proved to be impossible to separate, by TLC or by GLC, synthetic mixtures of **9** and the reduced rearrangement product. In the NMR spectra of **8** and **9** the most easily distinguishable features are the chemical shift values of the C_8-protons, $6{\cdot}1\delta$ in **8** and $6{\cdot}5\delta$ in **9**, and of the C_7-methoxyl groups, $3{\cdot}65\delta$ in **8** and $3{\cdot}8\delta$ in **9**. In the NMR spectrum of the reduced rearrangement product, to which varying amounts of **9** were added, it was not possible to detect less than 10% of added **9**; the NMR spectrum of the reduced rearrangement product itself did not exhibit a resonance at $6{\cdot}5\delta$.

The mass spectrum of **7** was easily interpreted to indicate, as a first step in the fragmentation, a competition between loss of the C_1-allyl group and loss of the C_1-benzyl group; in both cases the aromatic isoquinolinium salt is formed, but from the relative intensities of the peaks at *m/e* 246 and *m/e* 356, the benzyl loss :allyl loss is favoured in the ratio of 8 :1. With compound **9**, however, there is not only competition between the loss of benzyl *vs* loss of allyl, but also competition between the formation of a 1,4-dihydroisoquinolinium ion and the more stable 3,4-dihydroisoquinolinium ion:

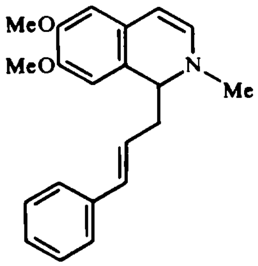




The ratio of intensities of the peaks at *m/e* 246 and *m/e* 356 now favours benzyl loss only to the extent of 5:3. On this basis, the allyl loss from **8** should be very small indeed in comparison to the benzyl loss, since it involves the loss of the less favoured radical from the less favoured site.

The mass spectrum of the reduced rearrangement product shows a ratio of benzyl loss:allyl loss of 110:1. A detailed study of the mass spectra of mixtures of the reduced rearrangement product with various amounts of **9** added suggests that, in the reduced rearrangement product obtained from **7**, there is, if any, a maximum of 4 ± 1% of **9** present. In an effort to increase the proportion of benzyl to allyl migration, the reaction of **7** with HCl was carried out at lower temperatures, but although migration was observed even at −30° (where 7 days was required for completion), the product was not detectably different from that obtained at 100°.

Thus, we have demonstrated that, in a 1-substituted-1,2-dihydroisoquinoline where it is possible for either a benzyl group or an allyl group to migrate, the latter does so with practically complete exclusion of the former, and it was rather intriguing to learn[18] that in compound **14**, where the C_1 substituent can migrate either as a vinylogous benzyl group to yield **15**, or as a substituted allyl group,[19] to give **16** or **17** the former process only was observed. In the light of the above work with **7**, it was decided to investigate the reaction of **14** further. The rearrangement product,[18] which has now been obtained in 80% yield, was reduced to a 1,2,3,4-tetrahydroisoquinoline with $NaBH_4$. The NMR spectrum of the olefinic region of this base contains multiple



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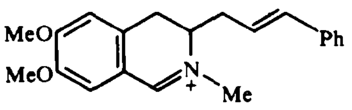

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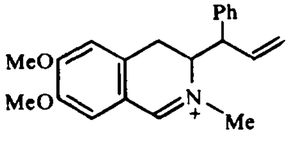

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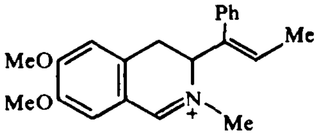

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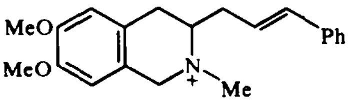

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signals attributable to TWO protons only, in accord with structure **18**, derived from **15**. The reduction product from **16** should exhibit absorption due to three olefinic protons, whereas the spectrum of the tetrahydroisoquinoline expected from **17** should exhibit absorptions due to a $=CH—CH_3$ group; none were found. Conclusive evidence in support of structure **15** was provided by ozonolysis of **18**; benzaldehyde (42% yield) was the only non-basic carbonyl compound found in the oxidation products.

EXPERIMENTAL

Mp's are uncorrected. UV spectra were recorded for 95% EtOH solns and IR spectra for nujol mulls or liquid films. NMR spectra were measured using a Varian A60 spectrometer; chemical shifts are expressed as ppm downfield from TMS as internal standard.

1-Allyl-2-methyl-1,2-dihydropapaverine (**7**). Papaverine methiodide (48·3 g; 0·10 mole) was suspended in dry THF (200 ml) and allyl magnesium bromide (0·25 mole) in ether (250 ml) was added slowly. After evaporation of the ether, the residual soln was heated under reflux for 3 hr. To the cooled soln was added 20% NH_4Cl aq (200 ml) and the aqueous phase was separated and extracted with ether (3 × 200 ml). The combined ether and THF solns were washed with 20% NH_4Cl aq, dried and evaporated to yield a yellow oil which crystallized from EtOH as lemon needles (28·2 g; 71%) m.p. 108–110°. λ_{max}nm (ε_{max}) 205 (51,000): 256 (10,800); 285 (3,700); 345 (7,900). ν_{max}cm^{-1} 3050; 1640; 1630; 920 NMR ($CDCl_3$) contains 5·85d [1] $J = 8$ Hz, (collapsing to a singlet with D_2O)(C_3—$\underline{H}$): 4·9d [1] $J = 8$ Hz (removed by D_2O) (C_4—$\underline{H}$): 6·2–4·8 m [3] ($—\underline{CH}=\underline{CH}_2$). (Found: C, 73·1; H, 7·3; N, 3·7. $C_{24}H_{19}NO_4$ requires: C, 72·9; H, 7·4; N, 3·5%).

Acid treatment of **7**

(a) The above base (1·00 g) was dissolved in 2N HCl (25 ml), stirred at 100° for 0·5 hr, and then cooled. The initial purple colour changed through green to yellow. After basification to pH 8 with $NaHCO_3$, the soln was washed with ether and then $NaBH_4$ (0·5 g) was added portionwise. The mixture was stirred at RT overnight and then extracted with ether. From the combined extracts was obtained a lemon oil (1·01 g; 100%). TLC using Al_2O_3 or SiO_2 under widely differing conditions exhibited only one component; λ_{max}nm; 208; 230 (sh): 285 (1,2,3,4-tetrahydroisoquinoline chromophore); NMR ($CDCl_3$) contains: 6·7 m [3] (aromatic protons of 3,4-dimethoxybenzyl group); 6·55 s [1] (C_5—$\underline{H}$); 6·1 s [1] (C_8—$\underline{H}$); 6·3–4·8 m [3] ($\underline{CH}=\underline{CH}_2$): 3·8 [9] (3 × $OC\underline{H}_3$): 3·6 s [3] (C_7—$OC\underline{H}_3$): 2·3 s [3] ($N—\underline{CH}_3$). The methiodide was obtained from acetone as colourless prisms m.p. 204–205° (Found: C, 56·0; H, 6·3; N, 2·7. $C_{25}H_{34}NO_4I$ requires; C, 55·7; H, 6·4; N, 2·6%).

(b) *To a cooled* (−50°) *suspension of* **7** (200 *mg*) in EtOH (1 ml) was added conc HCl (1 ml) also precooled to −50°. The temp of the mixture was allowed to rise to the required reaction temp, and the course of reaction followed by UV spectroscopy. Time taken (temp): 1·0 hr (20°); 1·5 hr (4°); 7 days (−30°). In each case normal work-up gave the tetrahydroisoquinoline (85–100%) indistinguishable (NMR and mass spectra) from the rearrangement product described above.

1-*Allyl-2-methyl-3-(3′,4′-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**9**). A soln of allyl magnesium bromide (0·1 mole) in ether (100 ml) was added slowly to a suspension of 3-(3′,4′-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline methiodide (4·85 g; 0·01 mole) in the THF (200 ml) and the mixture was stirred at RT over-night. After the usual work-up procedure, the product, which was purified by filtration through an alumina column, was obtained as a lemon yellow oil (2·7 g; 68 %). λ_{max}nm 205, 230, 286 (1,2,3,4-tetrahydroisoquinoline chromophore); NMR ($CDCl_3$ included 6·75 m [3] (aromatic protons of the 3,4-dimethoxybenzyl group); 6·6 s [1] (C_5—$\underline{H}$); 6·5 s [1] (C_8—$\underline{H}$); 6·3–4·8 m [3] (—C$\underline{H}$=C$\underline{H}_2$); 3·8 m [12] (4 × $OC\underline{H}_3$); 2·4 s [3] ($NC\underline{H}_3$). The methiodide crystallized from acetone as colourless needles containing one molecule of solvent m.p. 192–196°. (Found: C, 56·4; H, 6·3; N, 2·5. $C_{25}H_{34}NO_4I \cdot CH_3COCH_3$ requires: C, 56·3; H, 6·7; N, 2·4%).

Attempted dehydrogenation of 3-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**6**, R = H: R^1 = OMe). A mixture of **6** (R = H; R^1 = OMe; 2·0 g), decalin (15 ml) and 5% Pd/C (0·4 g) was heated under reflux for 3 hr, then cooled, diluted with benzene (50 ml), filtered through keiselguhr and extracted with 2N H_2SO_4 (3 × 10 ml). The combined extracts were washed with ether, basified with NH_3 and extracted with ether. The ether soln was evaporated to leave a yellow oil (1·7 g), which was chromatographed over alumina and eluted with $CHCl_3$. The main fraction (1·2 g) crystallized on standing to yield the dimer (**11**), characterized as the di-methiodide, m.p. 204–206° NMR (CF_3CO_2H) includes: 9·4 s [1] and 9·3 s [1] (C_1—$\underline{H}$ and C_1^1—$\underline{H}$); 8·3 s [1] and 8·15 s [1] (C_4—$\underline{H}$ and C_4^1—$\underline{H}$); 7·75 s [2] and 7·6 s [2] (C_5—$\underline{H}$, C_8—$\underline{H}$, C_5^1—$\underline{H}$ and C_8^1—$\underline{H}$); 6·86 m [2] (—C$\underline{H}$=C$\underline{H}$—); 4·5 s [3] and 4·45 s [3] (2 × N—$C\underline{H}_3$); 4·25 s [6] and 4·20 s [6] (4 × $OC\underline{H}_3$); 4·1 m [1] $\left({}^{\mathrm{C}\diagdown}_{\mathrm{C}\diagup}\mathrm{C\underline{H}}\text{—}\mathrm{C}\right)$; 3·2 m [2] $\left({}^{\diagdown}_{\diagup}\mathrm{CH}\text{—}\mathrm{C\underline{H}_2}\text{—}\mathrm{CH_3}\right)$; 1·2 t [3] J = 15 Hz (—CH_2—$C\underline{H}_3$). (Found: C, 48·5; H, 5·3; N, 3·8; I, 34·0. $C_{30}H_{36}N_2O_4I_2$ requires: C, 48·5; H, 4·9; N, 3·8; I, 34·2%).

6,7-Dimethoxyisoquinoline from **6** (R = H; R^1 = OMe). The base **6** (R = H; R^1 = OMe; 0·5 g) in decalin (10 ml) was heated under reflux for 15 hr, then cooled and worked up for bases as above. The brown oil obtained was reacted with MeI and the resulting buff solid was crystallized from $EtOH/H_2O$ to yield 6,7-dimethoxyisoquinoline methiodide as a near-white powder, (0·14 g; 20%) m.p. 220° (dec), identical (IR and NMR) with an authentic sample.

1-*(3′,4′-Dimethoxybenzyl)-1-cyano-2-benzoyl-3-allyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**13**, R = 3,4-*dimethoxybenzyl*). Benzoyl chloride (11·6 ml: 0·065 mole) was added dropwise (1 hr) to a vigorously stirred mixture of 3-allyl-6,7-dimethoxy-3,4-dihydroisoquinoline (11·6 g: 0·05 mole) in CH_2Cl_2 (100 ml) and KCN (10 g: 0·15 mole) in water (40 ml). After stirring for a further 1 hr, the organic layer was separated and washed successively with water, 10% HCl, water, 5% NaOH and water. The dried CH_2Cl_2 soln was then evaporated to leave a yellow gum that was crystallized from EtOH to give **13** (R = H) as a waxy solid (12·7 g: 70%). A soln of **13** (R = H: 4·16 g: 0·0125 mole) in DMF (25 ml) was added dropwise to a suspension of NaH (0·3 g: 0·0125 mole) in DMF at 0°, with an atmosphere of N_2 maintained throughout. The deep red soln was stirred at 0° whilst a soln of 3,4-dimethoxybenzyl chloride (2·3 g: 0·012 mole) in DMF (10 ml) was added during 0·5 hr. The colour was slowly discharged. After warming to RT during 0·5 hr the mixture was treated with EtOH (5 ml) and water (20 ml), then concentrated to half volume. Benzene and water were added, the layers separated, the aqueous phase extracted with benzene and the combined organic soln was evaporated to leave a gum which crystallized from EtOH as colourless crystals of **13** (R = $3,4(OMe)_2C_6H_3CH_2$: 2·8 g: 48%) m.p. 169–170°. (Found: C, 72·9: H, 6·4; N, 4·9. $C_{31}H_{32}N_2O_5$ requires: C, 72·6: H, 6·3: N, 5·4%). Mass spectrum: *m/e* (relative abundance %) 512 (3·7), 485 (0·6), 444 (0·2), 361 (2·5), 256 (0·3), 215 (1·1), 151 (9·3), 105 (100), 77 (13): metastables at 407: 254·4: 56·5 and 30·6 were observed for the transitions *m/e* 485 → 444: *m/e* 512 → 361: *m/e* 361 → 105 and *m/e* 105 → 77 respectively.

2-*Methyl-3-cinnamyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline* (**18**). The 3,4-dihydroisoquinolinium salt[18] **15** (1·5 g) in MeOH was reduced with $NaBH_4$ and the product, isolated as its perchlorate, crystallized from $MeOH/Et_2O$ as colourless needles (1·4 g: 90%) m.p. 88–90°. (Found: C, 59·0: H, 6·1: N, 3·3. $C_{21}H_{26}NO_6Cl$ requires: C, 59·5: H, 6·2: N, 3·3%).

Ozonolysis of **18**. A soln of **18** (0·75 g) in 0·1N H_3PO_4 (15 ml) and water (30 ml) was ozonized at 0°. Extraction of the mixture with ether followed by evaporation of the dried extract left a residue of benzaldehyde, characterised as its 2,4-dinitrophenylhydrazone (0·28 g: 42%).

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