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1,2-DIHYDROISOQUINOLINES—XIX[1]
REARRANGEMENT V

R. G. KINSMAN, S. F. DYKE and J. MEAD
School of Chemistry and Chemical Engineering, University of Bath, Bath, Somerset, England

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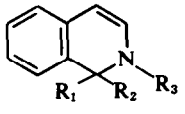
Abstract—1-Allyl-2, 3-dimethyl-1, 2-dihydroisoquinoline does not rearrange to 3-allyl-2, 3-dimethyl-3, 4-dihydroisoquinolinium chloride when treated with dilute hydrochloric acid, but the introduction of a C_1-Me or a C_6-OMe substituent enables a reaction to proceed. A rationalisation is provided for these observations.

It has been found[2] that when a 1-benzyl-1,2-dihydroisoquinoline (**1a**) is treated with hot dilute mineral acids, rearrangement occurs to yield the 3-benzyl-3, 4-dihydroisoquinolinium ion (**2a**). It is believed[3] that the reaction proceeds by a bimolecular



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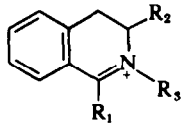


2

a: $R_1 = H$; $R_2 = CH_2Ar$; $R_3 = Me$
b: $R_1 = R_3 = H$; $R_2 = CH_2—CH=CH_2$
c: $R_1 = H$; $R_2 = CH_2—CH=CH_2$; $R_3 = Me$

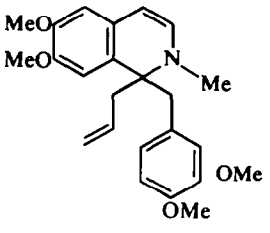
exchange mechanism which might occur in a concerted manner. It has also been shown[4] that a 1-allyl-1, 2-dihydroisoquinoline (**1b** or **1c**) rearranges to the 3-allyl-3, 4-dihydroisoquinolinium derivative **2b** or **2c**, respectively, when similarly treated with mineral acids. This latter reaction, which has been proved[4a] to be intramolecular in nature, is an example of a suprafacial sigmatropic [3,3] shift analogous to the Claisen and Cope rearrangements.

When 1-allyl-2-methyl-1,2-dihydropapaverine (**3**) was[1] treated with dilute HCl, rearrangement again occurred, to give 3 - allyl - 2 - methyl - 3, 4 - dihydropapaverinium chloride (**4**), thus demonstrating that the allyl group migrates more readily than the 3,4-dimethoxybenzyl group in this case.

It has been found by Knabe *et al*[5] that when a 3-alkyl-1-benzyl-1, 2-dihydroisoquinoline such as **5** is reacted in hot dilute HCl, no rearrangement occurred. The only product that was isolated was the isoquinolinium salt **6** formed, in low yield, by elimination of the C_1-benzyl group.

It was of interest to us to discover whether the same limitation applied to the more facile allyl migration, especially since elimination of a C_1-allyl group had not previously been observed.

1-Allyl-2, 3-dimethyl-1, 2-dihydroisoquinoline **7a**, which was readily formed by the addition of allyl



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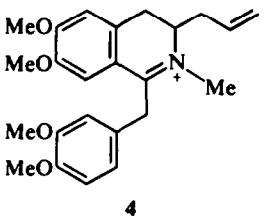

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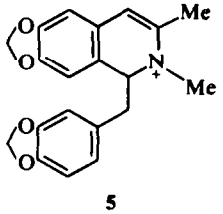

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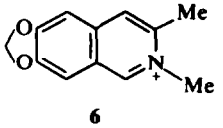

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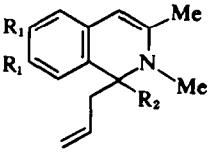

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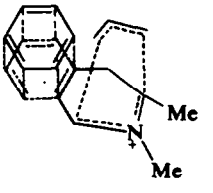
a: $R_1 = R_2 = H$
b: $R_1 = H$; $R_2 = Me$
c: $R_1 = OMe$; $R_2 = H$



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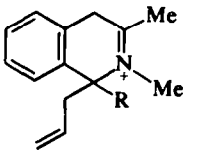

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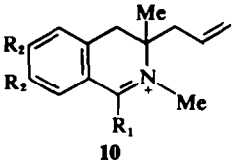
a: R = H
b: R = Me



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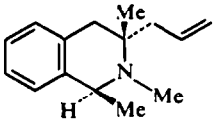
a: $R_1 = R_2 = H$
b: $R_1 = Me$; $R_2 = H$
c: $R_1 = H$; $R_2 = OMe$

magnesium bromide to 2,3-dimethylisoquinolinium iodide, formed a stable crystalline perchlorate. Spectroscopic data (UV, IR and NMR) indicated that this salt exists in the immonium structure **8a** required for the thermal rearrangement. When the base **7a** was treated with dilute HCl, even under reflux for a prolonged period, no reaction, rearrangement or elimination, was observed; the starting enamine was recovered in practically quantitative yield upon basification and solvent extraction.

An examination of the transition state **9** for the rearrangement demonstrates clearly that there should be no steric barrier to the migration reaction. A comparison of the stabilising factors acting upon the immonium systems present in the starting material **8a** and in the hoped-for product **10a** indicates that the former is thermodynamically preferred; hyperconjugative stabilisation from five hydrogen atoms α to C_3 (in **8a**) is greater[6] than the stabilisation afforded by conjugation with a phenyl ring (in **10a**). It might thus be anticipated that **10a** should rearrange to **8a** on heating, but unfortunately we have been unable to test this hypothesis since a sample of **10a** could not be prepared. It should be possible, however, to redress the stability balance, and still demonstrate thermodynamic control in the reaction, by examining the behaviour of 1-allyl-1, 2, 3-trimethyl-1, 2-dihydroisoquinoline (**7b**) in acid solution, where the stabilising effects of the C_1-Me and C_3-Me substituents effectively cancel. The rearrangement should then occur as readily as in 1-allyl-2-methyl-1,2-dihydroisoquinoline itself.

The required 1 - allyl - 1, 2, 3 - trimethyl - 1, 2 - dihydroisoquinoline (**7b**) was obtained as an unstable oil by the interaction of 1,2,3-trimethylisoquinolinium iodide and allyl magnesium bromide. Treatment of **7b** with dilute HCl under the usual conditions readily yielded the 3,4-dihydroisoquinolinium ion (**10b**). Reduction of **10b** with $NaBH_4$ gave the corresponding 1,2,3,4-tetrahydroisoquinoline in an overall yield of 75% from 1,2,3-trimethylisoquinolinium iodide. An analysis of the NMR spectrum of this base indicates that it is a mixture of the two diastereomers (**11** and **12**), each possessing the equatorial C_1-Me group (doublet absorptions at 1·35 and 1·33δ for the C_1-Me protons and singlets at 1·20 and 0·80δ for the C_3-Me protons).



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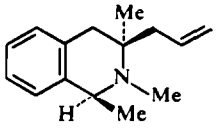

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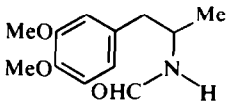
It is possible[7] that the additional stabilisation, in the 3,4-dihydroisoquinolinium ion, afforded by a C_6-OMe group might be sufficient for the migration of an allyl group from C_1 to C_3 in a 3-methyl-1, 2-dihydroisoquinoline to be observed. 3-Methyl-6, 7-dimethoxy-3, 4-dihydroisoquinoline was obtained by treating the formamide **13** with PCl_5 in benzene at room temperature. This modification[8] of the Bischler-Napieralski reaction gave much higher yields than those previously reported[9] for this reaction. Catalytic dehydrogenation, quaternisation, and reaction with allyl magnesium bromide in the usual way, gave the required enamine (**7c**) as an



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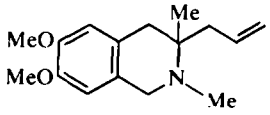

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unstable oil. This was treated with dilute HCl for 3 h at 100°. A mixture of the protonated starting material (**7c**) and the 3,4-dihydroisoquinolinium ion (**10c**) was obtained (as indicated by the UV spectrum). The ratio of these components was not altered by further heating (15 h). The reaction mixture was separated and shown to consist of the enamine (**7c**) and the product **10c** (isolated as the pseudocyanide) in the ratio of 2:1. The rearrangement product was characterised as the 1,2,3,4-tetrahydroisoquinoline (**14**).

When the pseudocyanide of **10c** was subjected to dilute HCl at 100° for 3 h *the same mixture* of **7c** and **10c** was obtained in the *same ratio* of 2:1. The enamine **7c** was isolated in 63% yield from this reaction mixture. Reduction of this sample of **7c** with $NaBH_4$ gave the corresponding 1-allyl-1, 2, 3, 4-tetrahydroisoquinoline, which was shown to be different from **14**. Clearly the long sought for "reverse migration" has occurred. The equilibrium constant of about 2 suggests a free energy difference of approximately 2 KJMole^{-1} in favour of the protonated 1-allyl-1, 2-dihydroisoquinoline form.

EXPERIMENTAL

M.ps 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. Mass spectra were measured on an AEI MS12 spectrometer and relative peak intensities are quoted as a percentage of the base peak.

1-Allyl-2, 3-dimethyl-1, 2-dihydroisoquinoline (**7a**). 3-Methylisoquinoline methiodide (14·4 g) was reacted with allyl magnesium bromide (50% excess) in dry THF at 50° for 2 h. The mixture was then cautiously treated with NH_4Cl soln, separated, and the aqueous phase extracted with ether. The combined organic layers were dried and evaporated to give **7a** as a colourless oil (8·3 g; 83%); λ_{max} nm, 206, 237, 336; ν_{max} cm^{-1}, 2800, 1640, 1620; NMR ($CDCl_3$) ppm, 6·8 complex [4] (aromatic protons), 6·1–4·6 complex [3] (–CH_2–CH=CH_2), 5·1 singlet [1] (considerably reduced by D_2O overnight) (Ar–CH=C–), 4·1 triplet [1] J = 6Hz) (Ar–CH–CH_2–), 2·8 singlet [3] (N–CH_3), 2·4–2·1 complex [2] (–CH–CH_2–CH=), 1·8 singlet [3] considerably reduced by D_2O overnight) (–CH=C–CH_3).

MS, M^+(*m/e* 199)(1%), M^+–1(6%), M^+–41(100%) (metastable 125·4).

The base formed a stable perchlorate salt, recrystallised from MeOH as colourless needles, mpt 102–103°; λ_{max} nm, 213; ν_{max} cm^{-1}, 1675, 1645, 1085 (broad); NMR (DMSO) ppm, includes, 4·3 singlet [2] (considerably reduced by D_2O overnight)($\overset{+}{N}$=C–CH_2–), 2·6 singlet [3] (considerably reduced by D_2O overnight) ($\overset{+}{N}$=C–CH_3). (Found: C, 56·5; H, 5·9; N, 4·8. $C_{14}H_{18}NClO_4$ requires: C, 56·1; H, 6·1; N, 4·7%).

Prolonged treatment (48 h at reflux) of the base **7a** with 2N HCl produced no rearrangement product. Basification and extraction of the reaction mixture yielded the starting base in near quantitative amount.

1-*Allyl*-1, 2, 3-*trimethyl*-1, 2-*dihydroisoquinoline* (**7b**) *and its acid treatment.* 1,3-Dimethylisoquinoline methiodide (1·0 g) was reacted with excess allyl magnesium bromide in ether at room temp overnight. The mixture was decomposed with NH_4Cl soln and worked-up for base product in the usual way, to give the title product as an unstable green oil; λ_{max} nm, 205, 237, 335. This base was dissolved in 2N HCl (10 ml), heated on a steam-bath for 3 h and allowed to cool. After basification with $NaHCO_3$ the soln was washed with ether and then treated with $NaBH_4$ (0·5 g), at room temp, overnight. The resultant mixture was acidified (HCl) and warmed with stirring for a few min, then rebasified and extracted with ether (3 × 10 ml). The combined extracts were dried and evaporated to give a lemon coloured oil (540 mg; 75%) which was purified by filtration of a soln in $CHCl_3$ through a column of alumina, evaporation and distillation under reduced pressure, to give a colourless oil bpt approx 150°/0·01 mm, λ_{max} nm, 208; ν_{max} cm^{-1}, 2800, 1600, 910; NMR ($CDCl_3$) ppm, 7·0 complex [4](aromatic protons), 6·3–4·5 complex [3] (–CH_2–C$\overset{1}{H}$=C$\overset{2}{H}_2$), 3·8–3·3 two overlapping quartets [1] (J = 6Hz) (C_1–H for **11** and **12**), 3·1–1·6 complex [4](Ar–CH_2–C–CH_2–), 2·35 and 2·30 two singlets [3] (N–CH_3 for **11** and **12**), 1·37 and 1·35 two doublets [3](J = 6Hz)(Ar–CH–CH_3), 1·2 singlet [40% of 3] (C_3–CH_3 for **11**), 0·80 singlet [60% of 3](C_3–CH_3 for **12**). MS, M^+(*m/e* 215)(0·2%), M^+–1(0·4%), M^+–15(7%), M^+–41(100%), M^+–43(7%), M^+–57(18%). (Found: C, 83·5; H, 9·9; N, 6·2. $C_{15}H_{21}N$ requires: C, 83·7; H, 9·8; N, 6·5%).

6,7-*Dimethoxy*-3-*methyl*-3,4-*dihydroisoquinoline.* Compound **13** (1·96 g) in dry benzene (50 ml) was added dropwise to a cooled (< 15°), stirred mixture of PCl_5 (3·92 g) in dry benzene (100 ml). The reaction was continued for 40 h at RT then water (250 ml) was added. The organic layer was separated and extracted with 2N HCl (3 × 50 ml); the combined aqueous layers were washed with ether (3 × 100 ml), basified with NH_4OH and extracted with $CHCl_3$. The chloroform soln was passed down a column of alumina and evaporated to give the required product as a yellow oil (1·55 g 86%), λ_{max} nm, 207, 231, 285, 314. ν_{max} cm^{-1}, 1620, NMR ($CDCl_3$) ppm, 8·25 doublet [1](J = 3Hz)(Ar–C$\overset{1}{H}$=N–), 6·9 and 6·7 two singlets [2](aromatic protons), 4·0–3·8 complex [1](–CH_2–CH–CH_3) 3·9 singlet [6](2x–OCH_3), 2·8–2·4 complex [2](Ar–CH_2–CH–), 1·4 doublet [3](J = 7Hz) (–CH–CH_3). MS, M^+ (*m/e* 205) M^+–15(92%).

6,7-*Dimethoxy*-3-*methylisoquinoline methiodide.* The above 3,4-dihydroisoquinoline (2 g) was dehydrogenated using 10% Pd/C (0·4 g) in tetralin (15 ml) at 200° for 3 h. The basic product was purified by passing a soln in $CHCl_3$ down an alumina column. The methiodide was formed in acetone and recrystallised from EtOH as off-white needles (1·7 g 53%) m.p. 212–214°, λ_{max} nm, 225 (sh), 254, 315, ν_{max} cm^{-1}, 1650, 1620, NMR (TFA) ppm, 9·3 singlet [1] ($\overset{+}{Ar}$–C$\overset{1}{H}$=N–), 8·1, 7·7 and 7·5 three singlets [3](C_4, C_5 and C_8 aromatic protons), 4·4 singlet [3](N–CH_3), 4·2 singlet [6](2x–OCH_3), 2·9 singlet [3](C–CH_3). The methoperchlorate was prepared and recrystallised from EtOH as pale yellow needles m.p. 256–257°. (Found: C, 49·4; H, 5·2; N, 4·2. $C_{13}H_{16}NO_6Cl$ requires: C, 49·2; H, 5·1; N, 4·4%).

1-*Allyl*-6, 7-*dimethoxy*-2, 3-*dimethyl*-1, 2-*dihydroisoquinoline* (**7c**) *and its treatment with acid.* 6,7-Dimethoxy-3-methylisoquinoline methiodide (1·0 g) in dry THF (100 ml) was treated with allyl magnesium bromide (100% excess) in ether; the ether was removed by evaporation and the soln stirred at RT overnight. The usual work-up procedure gave the required product (**7c**) as a green-brown oil (0·72 g, 96%), λ_{max} nm, 206, 237(sh), 334, ν_{max} cm^{-1}, 2840, 1635, 1620, NMR ($CDCl_3$) ppm, 6·50 and 6·48 two singlets [2](C_5 and C_8 aromatic protons), 6·1–4·7 complex [3](–CH_2–C$\overset{1}{H}$=C$\overset{2}{H}_2$), 5·2 singlet [1] (Ar–C$\overset{1}{H}$=C–CH_3)(reduced by D_2O overnight), 4·2 triplet [1](J = 6Hz)(Ar–C$\overset{1}{H}$–CH_2–), 3·85 singlet [6](2x–OCH_3), 3·0 singlet [3](N–CH_3), 2·6–2·2 complex [2] (–CH_2–CH=CH_2), 1·97 singlet [3](C–CH_3)(reduced by D_2O overnight). MS, M^+(*m/e* 261)(8%), M^+–1(18%), M^+–41(27%), M^+–42(56%), M^+–43(100%).

Compound **7c** (0·61 g) was heated under reflux with 2N HCl (100 ml) and the reaction monitored by UV spectroscopy. An equilibrium mixture was achieved in 3 h (unchanged by a further 15 h reaction). The soln was washed with ether, basified with $NaHCO_3$ and extracted with ether (3 × 50 ml) to give recovered **7c** (0·33 g, 54%). The aqueous soln was treated with NaCN and extracted with ether, giving the pseudocyanide of **10c** (0·19 g, 28%) as a pink oil, λ_{max} nm, 213, 235(sh), 289, 318, NMR ($CDCl_3$) ppm, 6·8 singlet [1](C_8–H), 6·6 singlet [1](C_5–H), 6·1–4·9 complex [3](–CH_2–C$\overset{1}{H}$=C$\overset{2}{H}_2$), 4·8 singlet [1](Ar–C$\overset{1}{H}$–CN), 3·9 singlet [6](2x–OCH_3), 2·8–2·2 complex [4] (–CH_2–CH=CH_2 and Ar–CH_2–C–), 2·56 singlet [3] (N–CH_3), 1·2 and 1·1 two singlets [3](–C–CH_3, two diasteriomers present). MS, M^+ (*m/e* 286)(4%), M^+–26(7%), M^+–40(41%), M^+–41(100%).

The pseudocyanide of **10c** (0·60 g) was heated under reflux with 2N HCl (100 ml). Within 3 h an equilibrium mixture had been achieved containing a similar ratio (UV) of 1,2-dihydro- to 3,4-dihydro-, isoquinoline products to that found in the above "forward" reaction. The solution was worked-up as before to give **7c** (0·33 g, 61%) and recovered pseudocyanide (0·20 g, 33%).

3-*Allyl*-6, 7-*dimethoxy*-2, 3-*dimethyl*-1, 2, 3, 4-*tetrahydroisoquinoline* (**14**). The pseudocyanide of **10c** (0·18 g) was reduced with $NaBH_4$ in EtOH at RT overnight, to give **14** as a colourless oil (0·15 g). The methiodide was formed in acetone and recrystallised from EtOH as colourless microprisms m.p. 218–219°, ν_{max} cm^{-1}, 1640, NMR(DMSO) ppm, 6·86 and 6·78 two singlets [2] (aromatic protons), 6·3–5·0 complex [3](–CH_2–C$\overset{1}{H}$=C$\overset{2}{H}_2$), 4·6 broad singlet [2](Ar–CH_2–$\overset{+}{N}$), 3·75 singlet [6] (2x–OH_3), 3·1 singlet [6](2x.$\overset{+}{N}$–CH_3), 3·2–2·4 complex [4](–CH_2–C–CH_2–), 1·4 broad singlet [3](–C–CH_3).

1-*Allyl*-6, 7-*dimethoxy*-2, 3-*dimethyl*-1, 2, 3, 4-*tetrahydroisoquinoline.* Compound **7c** recovered from the "reverse" migration reaction was reduced with $NaBH_4$ in EtOH, the methiodide salt prepared and recrystallised from EtOH as lemon platelets m.p. 220–222°, ν_{max} cm^{-1}, 1640, (fiingerprint region showed considerable differences

compared with methiodide of **14**). NMR(DMSO) ppm, 6·92 and 6·82 two singlets [2](aromatic protons), 6·3–5·1 complex [3](–CH_2–CH=CH_2), 4·9 complex [1](Ar–CH–$\overset{+}{N}$), 4·0 complex [1](–CH_2–CH–CH_3), 3·74 and 3·68 two singlets [6](2x–OCH_3), 3·2 and 2·7 two singlets [6](2x$\overset{+}{N}$–CH_3), 3·1–2·6 complex [4](Ar–CH_2–CH and –CH–CH_2–CH=), 1·45 doublet [3](J = 6Hz) (–$CH(CH_3)$).

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