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THE MECHANISM OF THE REARRANGEMENT OF 1-BENZYL-1,2-DIHYDROISOQUINOLINES: SOME CRITICISMS ANSWERED

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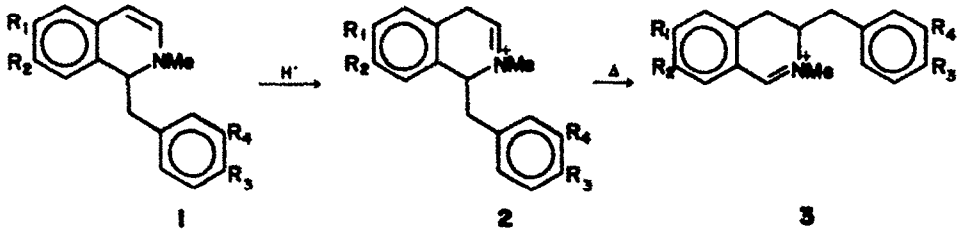
Abstract—The rearrangement of 2-methyl-1,2-dihydropapaverine (1a) to the corresponding 2-methyl-3-benzyl-3,4-dihydroisoquinolinium ion (3a) has been shown to be a second order rate process with an unusually high entropy of activation. These data, together with an analysis of the orbital symmetry requirements, have been shown to be consistent with the previously proposed double exchange mechanism for this reaction.

In previous publications[1-3] we have summarised the data available on the rearrangement that occurs when a 1 - benzyl - 1,2 - dihydroisoquinoline is treated with dilute mineral acid (eqn 1) and have listed the criteria that must be met when considering a mechanism for the reaction.

In particular it has been established that when an equimolar mixture of 1a and 1b,[4] or of 1c and 1d,[5] was rearranged all four possible 3 - benzyl - 3,4 - dihydroisoquinolinium ions of type 3 were obtained in equal amounts; i.e. the reaction is *completely intermolecular*. Furthermore, when an optically-active sample of 1e[5] or of 1e[3] was subjected to the rearrangement reaction conditions, the corresponding 3 - benzyl - 3,4 - dihydroisoquinoline derivatives were optically active. Additionally, the mixed migration of (+)-1e and (−)-1d gave an optically active mixture of the four rearrangement products.[3] Of great significance was the finding[3] that when optically active 4 was rearranged, the product 5 was also optically active (eqn 2).

A mechanism was proposed by us[1-3] that involved a bimolecular exchange process in which the transition state may be viewed as 6 for a four centre overlap or 7 if a six centre overlap is involved. We believe that this process may proceed in a concerted manner.

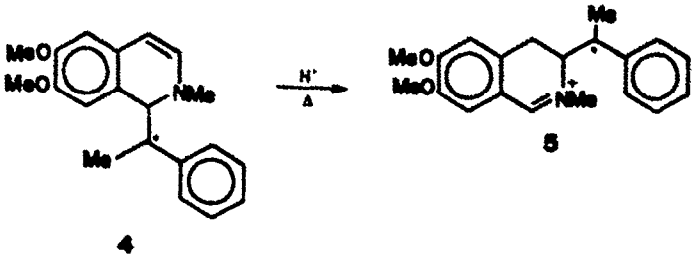
It was suggested[6] that the [1,3]-sigmatropic rearrangement reported by Baldwin and Walker[7] (eqn 3) might provide another example of a bimolecular exchange process. However, it has been reported recently[8] that this reaction is radical in character, although a CIDNP effect was not observed. Some



(1)

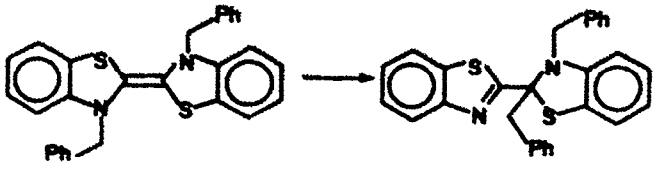
1 2 3

	R_1	R_2	R_3	R_4
(a)	OMe	OMe	OMe	OMe
(b)	OEt	OEt	OEt	OEt
(c)	OMe	OMe	OMe	H
(d)	O—CH_2	—O	OEt	H
(e)	OMe	OMe	H	H



(2)

4 5

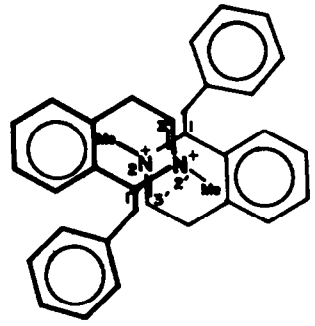


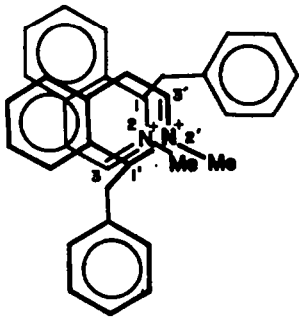
(3)

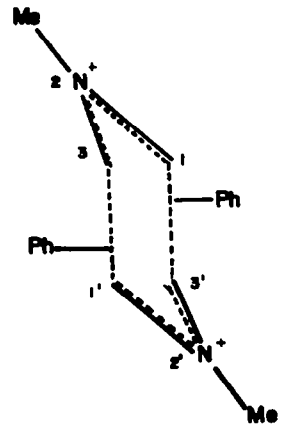
significance was attached to the finding that only partial cross-over was observed when mixtures with differently substituted rings were rearranged. Additionally, these authors,[8] in a reference to our work, censured our proposed mechanism by stating that "being an eight electrons suprafacial process, it violates the basic tenets of orbital symmetry. Furthermore, inspection of models indicates that such a mechanism involves simultaneous front side attacks at both sp^3 benzylic centres".

By considering models of the transition state in our proposed bimolecular exchange process it is quite clear that in such a highly ordered transition state a large, negative entropy of activation would be expected; furthermore, the reaction should be second order. We have now studied the kinetics of the rearrangement of 1a (obtained for the first time as a crystalline solid) at five temperatures between 30 and 70°.

The two dihydroisoquinolines 1a and 3a, separately or







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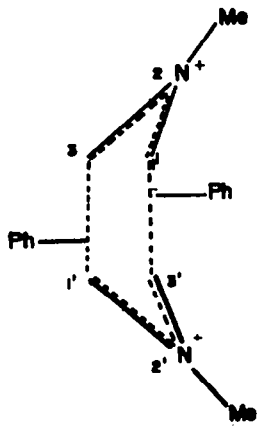

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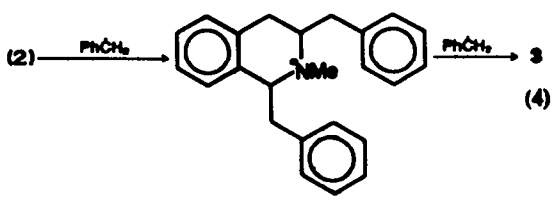
We considered several radical mechanisms, in one of which[9] the 1,4-dihydroisoquinolinium ion of type 2 was attacked by a benzyl radical to give 8, followed by elimination of the C_1-benzyl radical (eqn 4). Some asymmetric induction may be anticipated in such a process. However, we have been unable to detect an ESR signal or a CIDNP effect in any of our reactions, neither have we been able to detect any 1,3 - dibenzyl - 2 - methyl - 1,2,3,4 - tetrahydroisoquinoline derivatives. We found that the rearrangement of 1a is accompanied by the formation of the corresponding bibenzyl (0.2%) and 3,4-dimethoxytoluene (0.1%), presumably produced from minor, competing reactions involving homolytic and heterolytic cleavage respectively of the C_1-benzyl bond in 1a or 2a.



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(4)

in admixture, are reduced quantitatively at pH 8–9 with $NaBH_4$ to the corresponding 2 - methyl - 1,2,3,4 - tetrahydroisoquinolines, which can be separated by GLC. Analysis of a series of standard mixtures showed that the FID response to the two compounds was identical and that an accurate measure of the ratio could therefore be obtained by direct comparison of peak areas.

It was necessary for the reaction to be performed under an inert atmosphere and within certain limits of enamine and acid concentrations, in order to minimise competing reactions; the conditions selected were, an enamine concentration of 0.01 molar and 1 M-HCl (in 1:1 ethanol/water to facilitate rapid dissolution). Data were obtained from a reaction followed near 50°C and "trial-fitted" to the integrated rate equations corresponding to first, second and third order kinetics. Only with the appropriate $f(a-x)$ for second order kinetics was there a straight-line relationship. The best straight line, obtained by a "least-squares" treatment, assuming the error in time-measurement to be negligible, was followed with a correlation coefficient, r, of +0.997 (degree of confidence[10] < 0.1%).

The reaction was then examined at temperatures near 30°, 40°, 60° and 70°; in each case the data fit a second-order relationship with high correlation (Table 1). Using

Table 1.

Temperature (°C)	Rate constant (mol^{-1} sec^{-1})	Correlation coefficient
29.7	0.211	0.988
40.2	0.305	0.985
50.8	0.380	0.997
60.2	0.635	0.986
69.9	0.793	0.997

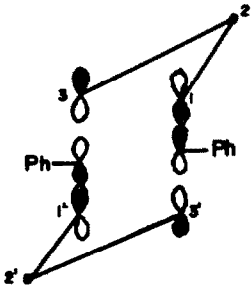
the rate constants obtained, a plot of log k against 1/T is found to be linear, with $r = -0.991$, a "t-factor" of 12.8 and a corresponding degree of confidence of 0.1%. From the slope of this plot, the Arrhenius activation energy, E, is found to be 28.9 kJ mol^{-1} and the enthalpy of activation, $\Delta H^{\ddagger}$, at the mean reaction temperature, has a value of 26.2 kJ mol^{-1}. The entropy of activation, derived using[11] the following equation:

$$\Delta S^{+}/2.303\,R = \log k - \log ek/h - \log T + \Delta H^{+}/2.303\,RT$$

is found to be -180 J K^{-1} mol^{-1} (-43 cal. $deg.^{-1}$ mol^{-1}).

The observed order of this intermolecular rearrangement suggests that the rate determining step is the interaction of two imminium ions 2a forming a bimolecular transition complex which breaks down to form two product ions 3a. Interaction of two large, like-charged, molecules would not be expected to be accompanied by a great change in solvation; thus the large negative entropy of activation must be attributed solely to loss of rotational and vibrational freedoms on formation of the transition complex.

There remains the criticism[6] that our proposed reaction violates the basic tenets of orbital symmetry. The benzyl migration reaction could be viewed as an extension of the Cope reaction, and the symmetry requirements could be examined in an analogous manner. Hereby the process could be envisaged as the exchange of two benzyl quasi-radicals between a pair of allyl quasi-radicals. Symmetry allowed transition states can be written through which inversion 9 or retention 10 of configuration at the benzylic centre would be predicted:



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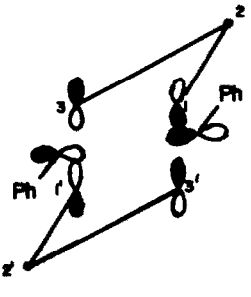

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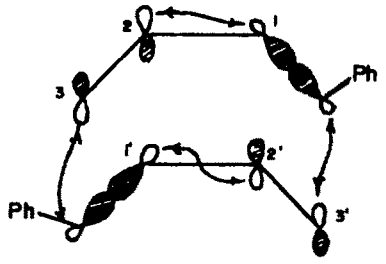
An alternative approach would treat the rearrangement as a pericyclic reaction in which the p orbitals that develop by the opening of the $C_1 - C_{benzyl}$ σ-bond interact with the p orbitals of the π systems. Accepting the stereochemical restriction that benzyl groups enter and leave at the same face of each allyl system, bonding interactions are possible between the σ HOMO orbitals of each benzyl group and the π LUMO orbitals of each other molecule, resulting in either inversion 11 or retention 12 of configuration at the benzylic carbon atom. The Woodward–Hoffmann rule for thermal pericyclic reactions state "A ground-state pericyclic change is symmetry allowed when the total number of $(4q+2)s$ and $(4r)a$ components is odd". For sigmatropic rearrangements this arises as a direct consequence of a reoccurring pattern of orbital symmetries throughout the continuously conjugated π system across which the sigma bond migrates. In our case, the proposed rearrangement mechanism involves the exchange of sigma bonds between two separate and isolated π systems whose orbital symmetries are in no way interdependant, and we maintain that the Woodward–Hoffmann rule (as stated above) was never formulated to include such a situation. It can be seen from 11 and 12 above, that if the two molecules become aligned with correctly related frontier orbital symmetries to "allow" the migration of one benzyl group then the relative orbital symmetries *must* be correct for the "allowed" migration of the second benzyl group.



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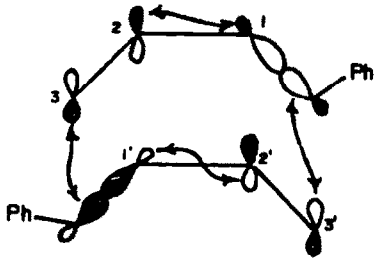

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We believe that the orbital symmetry analysis developed above, together with the kinetics data, strongly support our original concept of a concerted bimolecular exchange reaction for the rearrangement of a 1 - benzyl - 1,2 - dihydroisoquinoline into the 3 - benzyl - 3,4 - dihydroisoquinoline derivative. In particular the obvious alternative of a radical process of some kind now seems very much less likely.

EXPERIMENTAL

Mass spectra were obtained on an AEI MS12 and NMR were recorded with a Jeol PS100 spectrometer and are quoted as ppm downfield of tetramethylsilane as internal standard. GLC was carried out on a Pye 104 chromatograph with a recorder fitted with a disc and cam integrator; all analyses were performed on a 5 ft. column of SE 30 on chromasorb W at 250°.

2 - *Methyl* - 1,2 - *dihydropapaverine* 1a. Papaverine methiodide was suspended in dry ether and reduced with 100% excess lithium aluminium hydride at room temp. for 1 hr. The customary work-up involving decomposition of the excess hydride with aqueous sodium potassium tartrate solution was found to cause some further reduction to the 2 - methyl - 1,2,3,4 - tetrahydroisoquinoline; this was avoided by effecting the hydride decomposition by slow addition of excess acetone. Tartrate solution (15%) was then added and the organic phase was

separated, dried and evaporated to yield the required enamine as a white solid which recrystallised from ethanol as colourless needles, m.p. 122°(d). NMR ($CDCl_3$), 6.9–6.4 c [4] (aromatic H), 5.95 s [1] (C_6–H), 6.1 d [1] ($J = 7$ Hz)(C_4–H), 5.3 d [1] ($J = 7$ Hz)(C_3–H), 3.9 s [6] and 3.8 s [3] (3x–OCH_3), 3.6 s [3] (C_7–OCH_3), 2.95 s [3] (N–CH_3), 2.9 c [2] (Ar–CH_2–). Mass: *m/e* (%) 355(0.3)(M^+), 354(0.3), 204(100), 151(2.9). GLC showed only one peak.

2 - *Methyl* - 1,2,3,4 - *tetrahydropapaverine.* Papaverine methiodide was dissolved in 90% aqueous ethanol and reduced with $NaBH_4$ at room temp. for 1 hr. The mixture was acidified with conc. HCl and warmed until effervescence ceased to decompose N-boranes and excess reducing agent. The resulting solution was evaporated to dryness and the residue shaken with a 1:1 mixture of water and 10% chloroform in ether. The aqueous was discarded and the remaining solution was washed with water, dried and evaporated to give a white solid which recrystallised from ether as fine colourless needles, m.p. 116–117°. NMR ($CDCl_3$), 6.85–6.55 c [4] (aromatic H), 6.1 s [1] (C_8–H), 3.84 s [6] and 3.77 s [3] (3x–OCH_3), 3.56 s [3] (C_7–OCH_3), 4.0–3.5 m [1] (–CH–CH_2–), 3.3–2.5 c [6] (–CH_2–CH_2– and CH–CH_2–), 2.55 s [3] (N–CH_3). Mass *m/e* (%), 357 (0.1)(M^+), 356(0.4), 206(100), 204(3.7), 151(8.0). GLC showed one peak at 3 min 40 sec.

6,7 - *Dimethoxy* - 3 - (3',4' - *dimethoxybenzyl*) - 2 - *methyl* - 1,2,3,4 - *tetrahydroisoquinoline.* 2 - Methyl - 1,2 - dihydropapaverine was rearranged by heating in dil. HCl for 1 hr on a steam bath. The yellow solution was basified with $NaHCO_3$, washed with ether and reduced with $NaBH_4$. The excess reagent and N-boranes were decomposed and the base extracted, as in the previous preparation, to give an oil which dissolved in ether and deposited at 0° as a colourless amorphous powder, m.p. 100–101°. NMR ($CDCl_3$), 6.9–6.5 c [5] (aromatic H), 3.88 s [6], 3.85 s [3] and 3.82 s [3] (4x–OCH_3), 4.0–3.4 c [3] (Ar–CH_2–N–CH–), 3.2–2.2 c [4] (–CH_2–CH–CH_2–), 2.55 s [3] (N–CH_3). Mass: *m/e* (%), 357(0.1)(M^+), 356(0.2), 355(0.3), 354(0.6), 206(100), 204(4.9), 151 (2.8). GLC showed one peak at 5 min 20 sec.

Measurement of rearrangement kinetics. An accurately weighed sample (about 90 mg) of 2 - methyl - 1,2 - dihydropapaverine was placed in the reaction tube and 25 ml of a 1:1 mixture of 2 M aqueous HCl and ethanol was added. The vessel was shaken in a thermostated bath and samples of 1–2 ml were removed onto solid $NaHCO_3$ (250 mg), solid $NaBH_4$ (100 mg) was added and the tube walls were washed down with ethanol (10 ml). After standing at room temperature for one hour, the mixtures were evaporated to dryness on a steam-bath. The residues were dissolved in 2N HCl_{aq} (10 ml), heated on a steam-bath for 10 min and cooled. The solutions were basified with NaOH (10 ml, 5 M), diluted to 30 ml with water and extracted with chloroform (2 ml). The organic phase was separated, then concentrated by evaporation and analysed by GLC. The sampling times and reaction temperatures were as below (Table 2).

Table 2.

Temperature (°C)	Sampling times (min)
29.7	10, 20, 30, 45, 60, 90
40.2	5, 10, 15, 20, 25, 30, 40, 50, 60
50.8	10, 20, 30, 45, 60, 90
60.2	5, 10, 15, 20, 25, 30, 35, 40
69.9	5, 10, 15, 20, 25, 30

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