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A MECHANISM FOR THE REARRANGEMENT OF 1-BENZYL-1,2-DIHYDROISOQUINOLINES

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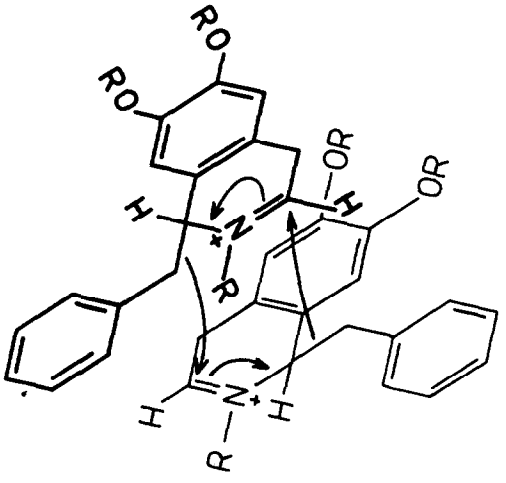
Since the original discovery[2)] that a benzyl group migrates from C_1 to C_3 when a 1-benzyl-1,2-dihydroisoquinoline is treated with mineral acids, a substantial amount of work has been reported with a series of 1-substituted-1,2-dihydroisoquinoline derivatives[3)]. Several proposals have been considered[4)] for the mechanism of the rearrangement, but until now no self-consistent theory has emerged.

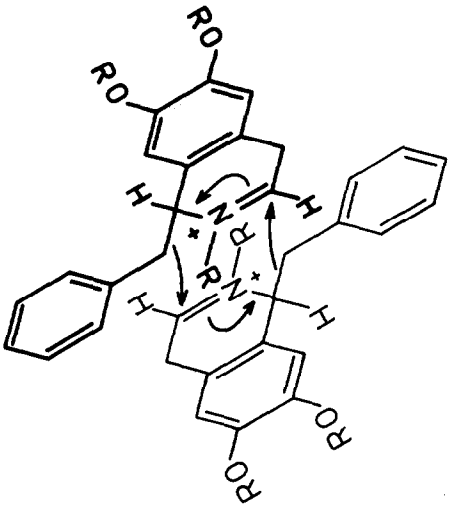
A satisfactory mechanism must take account of the following observations (a) the reaction is intermolecular[5)], (b) an increase in the size of the nitrogen substituent in the 1,2-dihydroisoquinoline results in a decrease in the yield of rearrangement product[6)], (c) substituents' effects[7),8)], and the failure[9)] of groups such as aryl and alkyl to migrate, indicate that the $C_1^{\delta+}$ - $CH_2^{\delta-}$ - Ar bond is polarised as indicated, (d) the yield of the rearrangement product, as compared with the yields of materials from the competing elimination and disproportionation reactions, depends strongly upon the concentration of the enamine[10)] (a decrease in enamine concentration results in a decrease in the yield of the rearrangement product) and (e) the rearrangement involves initial protonation of the enamine at C_4 to form a 1,4-dihydroisoquinolinium ion.

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

The observation (b) above seems to exclude the separation of the benzyl group as an ion or radical, but it is compatible with an exchange mechanism. Moreover, the fact that the reaction takes place in an aqueous solution is hardly compatible with the formation of free ions or radicals. In a complex of two molecules which exchange benzyl groups, the C_1 atom of one molecule should lie opposite to the C_3 atom of the second molecule, and vice-versa. Additionally, each of the migrating benzyl groups should be orientated towards its receptor molecule. There are two possible transition states, (1) and (2), which meet these requirements. Both transition states allow for an exchange of benzyl groups and the movement of



(1)



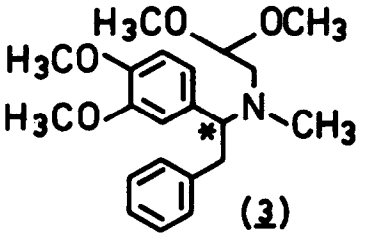
(2)

double bonds to occur in a cyclic, synchronous manner. In (1) both molecules of the 1,4-dihydroisoquinolinium ion that make up the transition state must possess the same configuration at C_1, whereas the transition state (2) requires the partners to have opposite configurations.

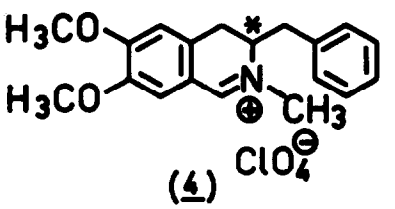
If the rearrangement does occur by a bimolecular exchange mechanism, the rearrangement of an optically active 1-benzyl-1,2-dihydroisoquinoline (chiral centre at C_1) should proceed with the generation of a new optically active centre at C_3 - i.e., optical activity should be retained. We have now found that when an optically active sample of (3)[11] is subjected to the conditions of the rearrangement, the 3-benzyl-3,4-dihydroisoquinolinium salt (4) formed is optically active.

The configuration and optical purity of this product are not yet certain.

This result shows that the rearrangement of the 1-benzyl-1,2-dihydroisoquinoline derived from (3), and of optically active (C_1) 1-benzyl-1,2-dihydroisoquinolines in general, occurs via the transition state (1). The transition state (2) may be involved in the rearrangement of racemic 1-benzyl-1,2-dihydroisoquinolines, and this point is being investigated.

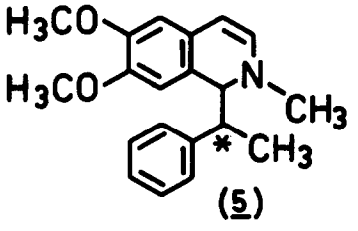


(3)

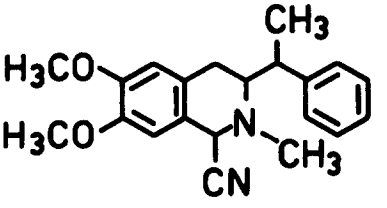


(4)

The rearrangement of an optically active sample of (5) was previously[4] reported to yield an optically inactive pseudocyanide (6), but a bimolecular exchange reaction involving either transition state (1) or (2) would require some retention of optical activity. A re-examination of this reaction[12] has revealed that the perchlorate derived from (6) is optically active. Probably the observed zero rotation in (6) is due to a fortuitous compensation from the three chiral centres present.



(5)



(6)

Further experiments designed to define more precisely the nature of the transition state of this unique rearrangement reaction, are in progress.

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11) It has been established (e.g., D.W. Brown, S.F. Dyke and M. Sainsbury, Tetrahedron 25, 1o1 (1969).) that aminoacetals of type (3) are converted into 1-substituted-1,2-dihydroisoquinolines under these conditions.

12) S.F. Dyke and R.G. Kinsman, unpublished work.