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THE MECHANISM OF 1,4-METHYL MIGRATIONS IN THE FISCHER INDOLE REACTION

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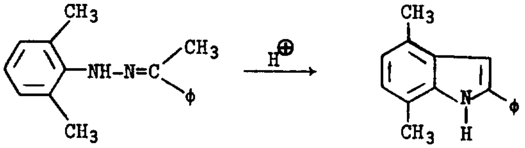
Fischer indole reactions of 2,6-dimethylphenylhydrazones normally result in 1,2-methyl migrations to give 4,7-dimethylindoles (e.g., eq. 1).[1] In 1959, however, Carlin and Moores[2] reported that rearrangement of a similarly substituted phenylhydrazone of cyclohexanone resulted in a 1,4-shift of the methyl group (eq. 2), and Fusco and Sannicolò recently reported a similar 1,4-methyl migration during rearrangement of a heterocyclic hydrazone of cyclohexanone.[3] The structures of the products of these reactions were established by independent syntheses by the Fischer indole reaction[2,3] - a procedure which might give rise to structural ambiguities. However, we have repeated the work of Carlin and Moores, and have found that the NMR spectra of the reaction products are in complete accord with their structural assignments.[4]



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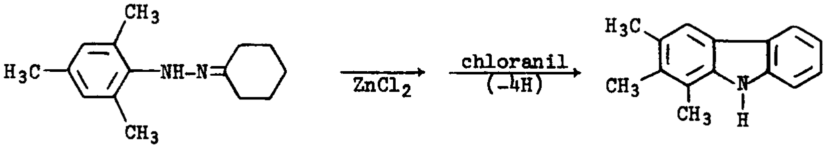
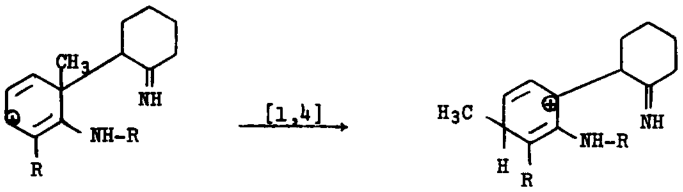


(2)

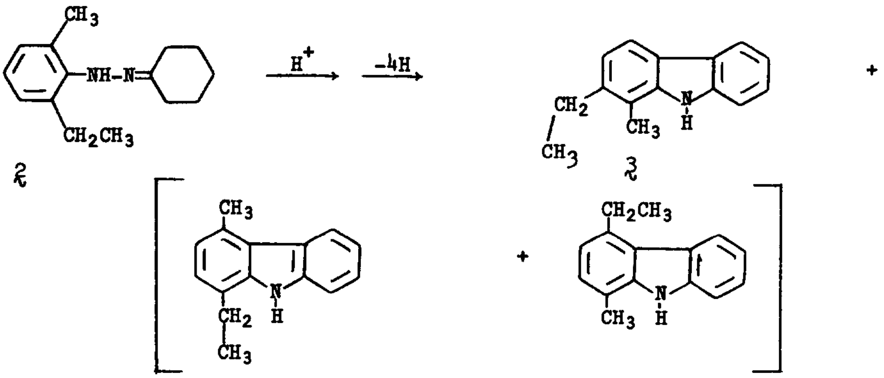
The previous workers proposed that these unusual rearrangements proceed by direct transannular [1,4] migrations of the methyl groups in intermediates such as **1**.[2,3] [1,4] Sigmatropic shifts of alkyl groups in carbonium ions are theoretically forbidden, and no other examples of such rearrangements are known, although [1,4] benzyl migrations in cyclohexadienyl carbonium ions have been reported.[5]

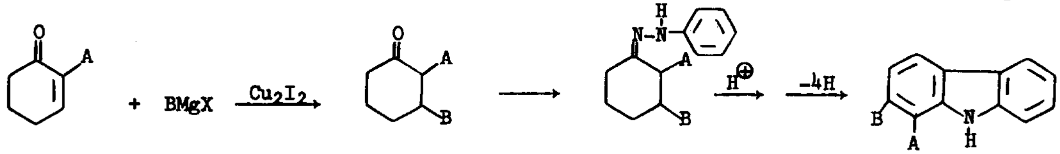
We now report evidence that the apparent [1,4] methyl migrations in Fischer indole rearrangements actually proceed by series of [1,2] shifts.



1

Rearrangement of cyclohexanone 2-ethyl-6-methylphenylhydrazone (2) in acetic acid, followed by dehydrogenation with chloranil, gives 2-ethyl-1-methyl carbazole (3), which was identified by comparison with a sample synthesized as shown below. In addition, a glpc fraction was obtained whose NMR spectrum was consistent with its formulation as a mixture of 1-ethyl-4-methylcarbazole and 4-ethyl-1-methylcarbazole, resulting from [1,2] migrations of methyl and ethyl groups, respectively. The cleavage products 1-methylcarbazole and 1-ethylcarbazole were also obtained.





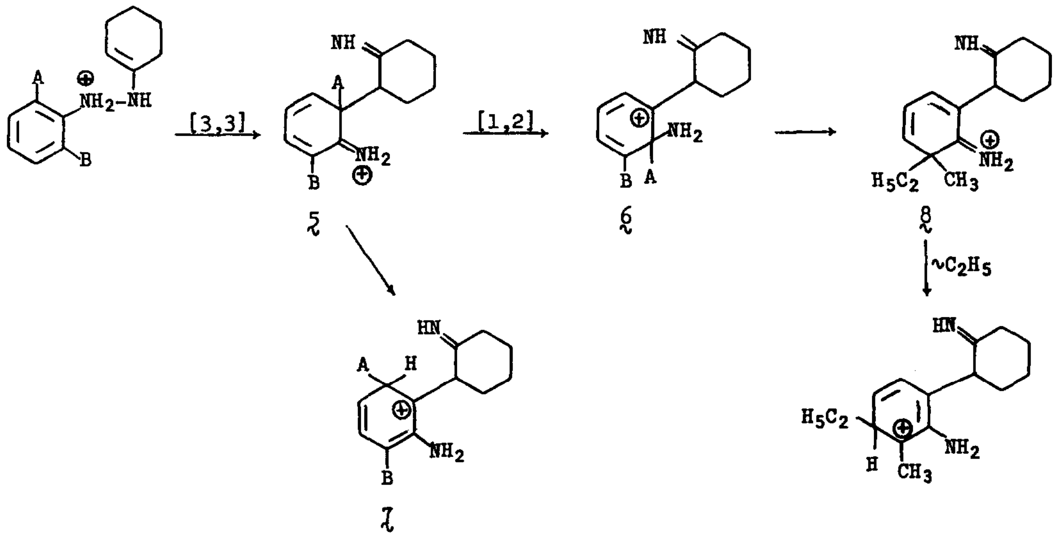
3, $A=CH_3$, $B=C_2H_5$

4, $A=C_2H_5$, $B=CH_3$

Most significantly, no trace of the 1,4-methyl migration product, 2-methyl-1-ethylcarbazole (4) could be detected, although 4 was synthesized as shown above and was found to be readily detectable by glpc analysis of the product mixture in amounts less than 1% that of 3.

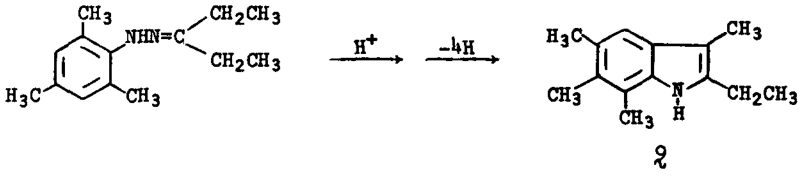
Formation of 3 by rearrangement of 2 might be explained as due to a direct [1,4] ethyl migration. However, this mechanism offers no obvious explanation for the absence of any [1,4] methyl migration. It also requires the assumption that attack at the aromatic ring to form intermediate 5[6] should take place much more rapidly at the ethylated carbon than at the methylated carbon, in contradiction to what would be expected on steric grounds.

The observed results can be accounted for by a series of [1,2] shifts of either ethyl or methyl groups to give ion 8, in which the ethyl group should migrate in preference to a methyl group.[7] An apparent [1,4] ethyl migration would therefore result from attack at either the ethylated or methylated carbon of 8.

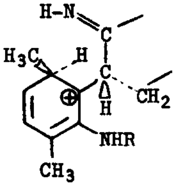


Two questions remain to be considered: why the substituent in 5 should migrate to the imino carbon to give 6 when 7, which would be obtained by migration to the vinyl carbon, would be expected to be much more stable,[8] and why "1,4" migrations are observed in reactions of cyclohexanone phenylhydrazones, but not those of other ketones.

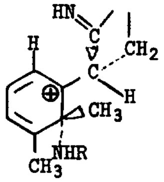
We have found that rearrangement of the 2,4,6-trimethylphenylhydrazone of diethyl ketone gives (after dehydrogenation) carbazole 9 as the only isolated rearrangement product. Thus, the presence of a cyclohexane ring is unnecessary for "1,4" migration. What does seem to be necessary is that the aromatic ring be attacked by a secondary, rather than a primary, carbon of the intermediate enehydrazine. Migration of a methyl group to the vinyl carbon would



then give an intermediate, 7a, which has strong steric repulsions in all conformations. In contrast, migration of the methyl group to the imino carbon would give 6a, which can adopt



7a



6a

a much less crowded conformation.

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References

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2) R.B. Carlin and M.S. Moores, J. Am. Chem. Soc., 81, 1259 (1959); 84, 4107 (1962).

3) R. Fusco and F. Sannicolò, Tetrahedron Letters, 3351 (1975).

4) E.g., The NMR spectrum of 1,2,3-trimethylcarbazole shows methyl singlets at δ 2.26, 2.30, and 2.38 ppm, while that of 1,3,4-trimethylcarbazole, which would be formed by a 1,2-methyl shift, shows singlets at δ 2.33, 2.36, and 2.69 (methyl at C-4).

5) B. Miller and M.R. Saidi, J. Am. Chem. Soc., 98, 2227 (1976); see also A.L.J. Beckwith, W.B. Renfrow, A. Renfrow, and J.K. Teubner, Tetrahedron Letters, 3463 (1968).

6) We assume that the monoprotonated intermediate rearranges, although the evidence for this is scanty. See R. Robinson, Chem. Revs., 63, 373 (1963).

7) The best models for rearrangement of 8 appear to be acid catalyzed rearrangements of cyclohexadienones, in which an ethyl group migrates ca. 55 times as rapidly as a methyl group. [J.N. Marx, J.C. Argyle, and L.R. Norman, J. Am. Chem. Soc., 96, 2121 (1974)].

8) J. Hine and N.W. Flachskam, J. Am. Chem. Soc., 95, 1179 (1973) showed that vinyl ethers, halides, and sulfides are appreciably more stable than isomers in which the heteroatoms are bonded to sp^3 carbons. This should also be true of enamines.