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THE THERMAL UNCATALYSED CYCLISATION OF N-CYCLOHEXYL-o-NITROANILINE: THE QUESTION OF A NITRENE VERSUS AN ACI-NITRO MECHANISM

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We have reported[1] that N-cyclohexyl-o-nitroaniline (1) can be made to cyclise reductively with ferrous oxalate but also without a reducing agent simply by heating to give the pentamethylenebenzimidazole (5) in which ring expansion has occurred. For this and similar uncatalysed thermal cyclisations of nitrocompounds we propose route a based on some circumstantial evidence as set out. This path hinges on the formation of an aci-tautomer (2) which by loss of water gives the spiro-N-oxide (3). Its deoxygenation brought about by the reaction temperature (ca. 200°) is followed by rearrangement of (4) to produce the benzimidazole (5).

Abramovitch and Davis[2] put forward an alternative explanation in which the nitrocompound (1) by analogy with the pyrolysis of aryl azides yields a nitrene intermediate (6) on heating which by insertion (7) followed by dehydrogenation and rearrangement as shown (route b), furnishes the product (5). Subsequently, however, the possibility of an aci-nitro mechanism was conceded[3] for those cases in which such a tautomer could be formed and a deoxygenating agent was absent.

Smolinsky[4] and Feuer favour the aci-nitro mechanism for certain nitro-cyclisations in diphenyl ether and possibly even in the presence of ferrous oxalate.

We are now able to give further evidence in support of an aci-nitro mechanism (route a) for the thermal cyclisation of the title compound and to exclude the nitrene route.

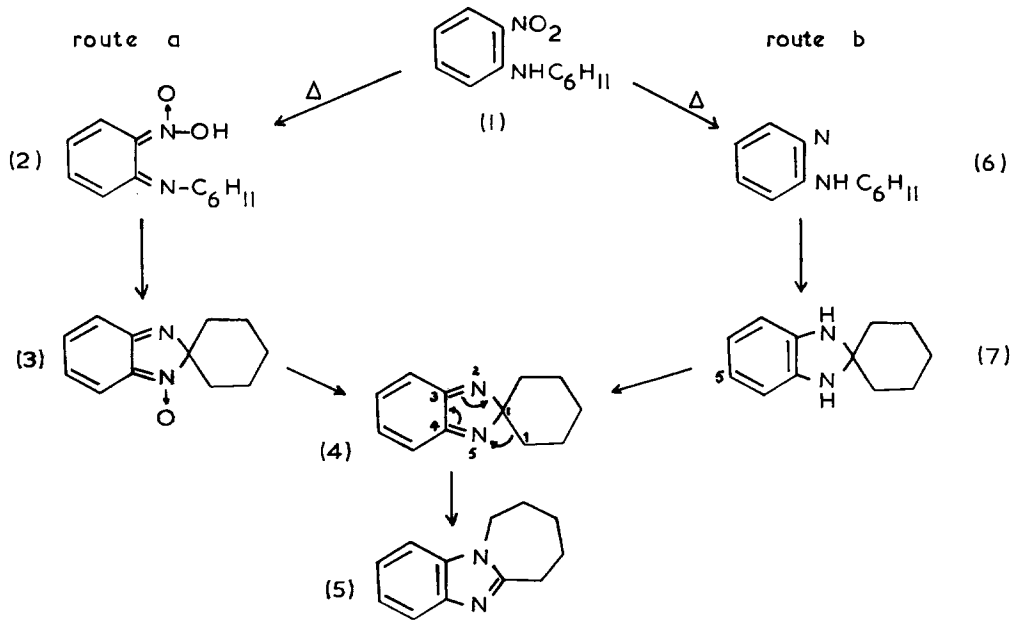
It was found that the dihydrospirobenzimidazole (7) available from o-phenylenediamine and cyclohexanone as described[5] did not rearrange on thermolysis according to route b (7→4→5) but broke up to give the starting materials used in its synthesis together with tar. Since the dihydro-compound (7) is a key intermediate formed by insertion in the nitrene route (route b) this mechanism is unlikely to operate. It could, however, be argued that the presence of a nitro-compound in the reaction mixture (e.g. 1) causes dehydrogenation of

the intermediate (7) to the isobenzimidazole (4) which is essential to form product (5). We, therefore, heated the 5-nitrodihydrobenzimidazole (*cf.* 7) under the conditions of the reactions and also added a nitrocompound to the previous reaction mixture but this still did not yield a benzimidazole.

Since the azido-cyclohexyl aniline (1; $NO_2 = N_3$) which would be the ideal source to generate the required nitrene is synthetically unavailable, other potential nitrene precursors were investigated. On the basis that deoxygenation of nitro-compounds with trialkyl phosphites often gives products similar to those obtained by decomposition of the corresponding azides[6] cyclisation of the *o*-nitrocyclohexylaniline (1) with trialkyl phosphite was attempted but gave only the amine (1; $NO_2 = NH_2$) and the phosphoramidate (1; $NO_2 = NH.P(O).(OR)_2$). Thermolysis of the *N*-methylazide (8; $R = N_3$) or deoxygenation of the nitro-compound (8; $R = NO_2$) with trimethyl phosphite gave in both cases predominantly *N*-cyclohexylbenzimidazole (9). The intermediate nitrene thus prefers insertion into the methyl group rather than into the cyclohexyl substituent which would have produced the *N*-methyl-dihydrocompound (10) via the *N*-methylspirocompound. Uncatalysed heating of the nitro-compound (8; $R = NO_2$) could not, of course, lead to formation of an *aci*-tautomer and gave only tars.

A key intermediate in our scheme is the spiro-isobenzimidazole (4) since it is formed directly from the *aci*-nitro-form (*cf.* route *a*). We have recently described[5b] its preparation by oxidation of the dihydrobenzimidazole (7). It was found that heating the isobenzimidazole (4) under the conditions of the nitro-cyclisation reaction gave the ring expanded benzimidazole (5) in a similar yield (*ca.* 30%) to that obtained from the nitro-compound (1). In hot solvents (e.g. dichlorobenzene) the transformation into (5) was less efficient (*ca.* 20%). This 1,5-sigmatropic rearrangement is thermally allowed and it was in fact found that irradiation of the isobenzimidazole (4) does not yield any of the product (5) but results in decomposition of the spiro-compound to give mainly phenylenediamine. The thermal isomerisations described by Klosterziel[7] for spirocyclopentadienes and especially rearrangements reported for two iso-imidazoles are closely analogous to our own observation; the two examples referred to include a benzyl shift[8] (11 12) and an interesting ring expansion[9] of a postulated iso-imidazole intermediate to give an imidazobenzisoquinoline.

The reaction path (*a*) appears to have precedents in the mechanism described by Carstens et al.[10] for the cyclisation of certain nitroso-uracils (13) which by oxidation and in some


route a
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Δ
Δ
(1)
(2)
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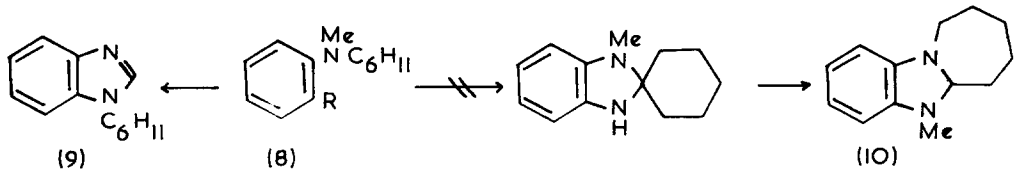
(7)


(8)
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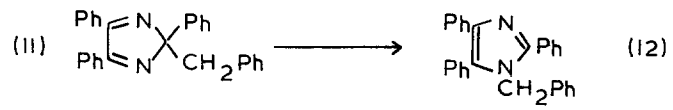
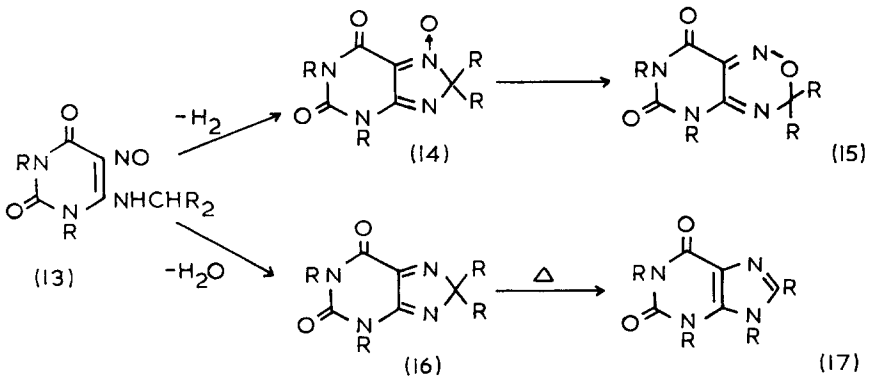

(11)
(12)


-H2
-H2O
Δ
(13)
(14)
(15)
(16)
(17)

cases by dehydration give xanthine-N-oxides (14) or xanthines (16) respectively. Some of the xanthines (16) can also be made to rearrange sigmatropically on heating to produce the 7,8-disubstituted xanthines (17). The resemblance of this reaction to ours is, however, incomplete since the intermediate N-oxide (14) isomerises readily to an oxadiazine (15) and the reaction is not applicable to aromatic nitroso compounds[10b].

We feel that the different behaviour of the nitrene precursors quoted above from that of the nitro-compound (1) together with the failure of the dihydrobenzimidazole (7) to give the benzimidazoles (5) is evidence against nitrene participation as shown in route b. The aci-nitro route on the other hand (route a) is thus supported by the negative nitrene evidence. The sigmatropic transformation of the spiro compound (4) is, of course, common to both mechanisms. It is a fair assumption that the thermal cyclisation of other o-substituted nitro-compounds capable of forming an aci-tautomer proceeds by a pathway analogous to route a.

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