The Mechanism of the Acid-catalysed Conversion of Anils into Benzimidazoles and Quinoxalines: a New Ring-expansion of Nitrogen Heterocycles

By R. K. GRANTHAM and O. METH-COHN*

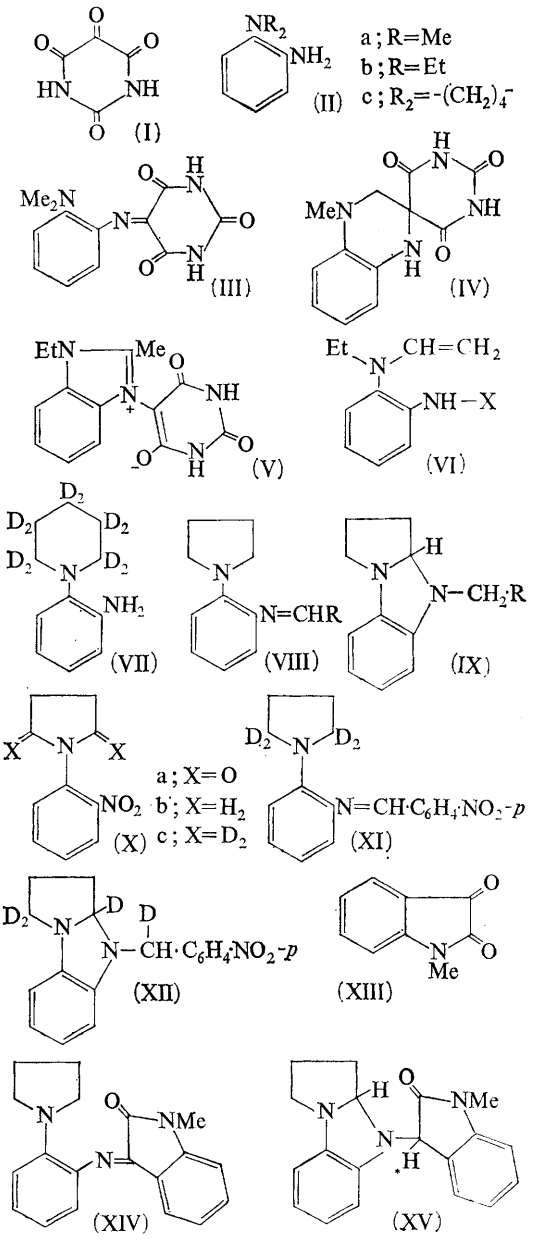
(*Department of Chemistry and Applied Chemistry, University of Salford, Salford 5, Lancs.*)

IN 1951, King and Clark-Lewis[1] demonstrated that the product from the action of alloxan (I) on *o*-aminodimethylaniline (IIa) was not the anil (III) but the spiroquinoxaline (IV), while *p*-aminodimethylaniline gave the expected anil. Clark-Lewis and his co-workers[2] later showed that the diethylaniline (IIb) gave not the quinoxaline but the benzimidazolium barbiturate (V). To account for these products they proposed[3] several homolytic mechanisms alternative to the primary formation of the anil (III) as an intermediate, but which indicated, in the case of the diethylaniline

(IIb) the intermediacy of the enamine (VI). We have recently shown[4] that this mechanism is untenable by use of the deuteriated aniline derivative (VII) in which no loss of deuterium occurred from the β-position, on benzimidazolium salt formation. Furthermore, we have shown[4] that anils of the general type (VIII) are rapidly cyclised with acid to dihydrobenzimidazoles (IX), with no incorporation of deuterium when the reaction is conducted in deuteriomethanol with deuterium chloride in deuterium oxide catalyst. We now present positive evidence for intramolecular proton transfer as proposed earlier, and demonstrate that in the alloxan reaction, the anil is first formed and is subsequently converted into the dihydrobenzimidazole, which may then be further converted into either the benzimidazolium salt or the spiroquinoxaline.

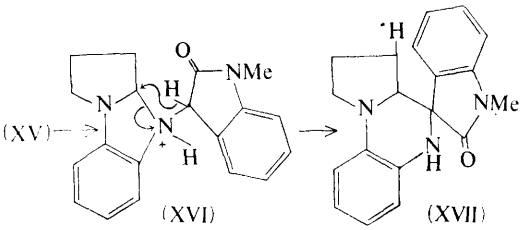
N-(*o*-Nitrophenyl)succinimide (Xa) is readily reduced in good yield to *N*-(*o*-nitrophenyl)pyrrolidine (Xb) with diborane (generated *in situ* by the dropwise addition of boron trifluoride etherate to a solution of the nitro-compound (Xa) and sodium borohydride in diglyme). With sodium borodeuteride, the deuteriated analogue (Xc) is produced. Reduction of the nitro-group and reaction of the resulting amine with *p*-nitrobenzaldehyde gave the deuteriated anil (XI), which on cyclisation gave a product (XII) in which one deuteron had been transferred to the benzylic position. N.m.r. spectroscopy showed a broadened, single-proton resonance at τ 5·59, thus supporting the proposed intramolecular mechanism.

Because of the acidity of alloxan (I) (resulting in auto-catalysis of the cyclisation) and the insolubility of the products formed from it with the amines (II) we considered other possible model systems for mechanistic study. *N*-Methylisatin (XIII) was found to be an ideal system. Four solutions containing equimolar quantities (0·005 M) of this ketone and the amine (IIc) in ethanol (20 ml.) were prepared. The first solution was allowed to stand for five days, with the slow formation of the deep violet anil (XIV); m.p. 159—160°; i.r. ν_{max} (Nujol), 1705 cm.$^{-1}$ (amide CO); n.m.r. ($CDCl_3$), τ 8·20 (quintet, $CH_2{\cdot}CH_2$), 6·73 (s, N–Me), 6·2 (tr, $CH_2{\cdot}N{\cdot}CH_2$), 2·5—3·4 (aromatic protons). The remaining solutions were treated respectively with 0·05 ml., 0·15 ml., and one mole of conc. hydrochloric acid. In each the transient violet colour of the anil was observed, and from the straw-coloured solution a white crystalline mass was precipitated. The product from the second solution was the dihydrobenzimidazole (XV), m.p. 148—150° (decomp.); i.r. ν_{max} (Nujol) 1700 cm.$^{-1}$ (amide CO); n.m.r. ($CDCl_3$), τ 8·15 (br, $CH_2{\cdot}CH_2$), 6·80 (s, N–Me), 6·85 (br, $CH_2{\cdot}N$), 4·98 (s, H*), 4·90 (tr, N.CH·N), 2·5—4·0 (aromatic protons).



From the third solution an isomer of the dihydrobenzimidazole (XV) was isolated, characterised by spectroscopy as the spiroquinoxaline (XVII), m.p. 215°; i.r. ν_{max} (Nujol) 3270 (NH), 1690 cm.$^{-1}$ (amide CO); n.m.r. ($CDCl_3$), τ 9·15

(complex, H*), 8·2 (complex, CH_2·CH), 6·77 (s, NMe), 6·59 (tr, CH_2·N), 6·23 (quartet, CH), 2·5—3·6 (aromatic protons and NH). The spiro-structure was confirmed by the appearance of a complex, single-proton high-field resonance (τ 9·15) due to one of the pyrrolidine ring protons [starred in (XVII)] being held in the shielding cone of the oxindolyl aromatic ring. This compound



was also produced when either the anil (XIV) or the dihydrobenzimidazole (XV) were treated with acid, or when the latter compound was heated briefly in ethanol. Finally, from the fourth solution was obtained the hydrochloride of the quinoxaline (XVII); m.p. 218° (decomp.).

The fact that the dimethylaniline (IIa) gave the spiro-compound (IV) while the diethyl analogue (IIb) gave the benzimidazolium salt (V) points to the greater hydride lability of the 2-proton of the dihydrobenzimidazole intermediate in the latter case. The formation of the quinoxaline requires the presence of an acidic proton at the rearrangement site (starred in XV) of the dihydrobenzimidazole and is rationalised as shown below [(XV) → (XVII)], being analogous to a Stevens rearrangement.

(*Received, March 4th*, 1968; *Com.* 272.)

[1] F. E. King and J. W. Clark-Lewis, *J. Chem. Soc.*, **1951**, 3080.
[2] J. W. Clark-Lewis, J. A. Edgar, J. S. Shannon, and M. J. Thompson, *Austral. J. Chem.*, **1964**, **17**, 877.
[3] J. W. Clark-Lewis, J. A. Edgar, J. S. Shannon, and M. J. Thompson, *Austral. J. Chem.*, **1965**, **18**, 907.
[4] M. A. Naqui and O. Meth-Cohn, *Chem. Comm.*, **1967**, **1157**.