A Ready Synthesis of Dihydrobenzimidazoles

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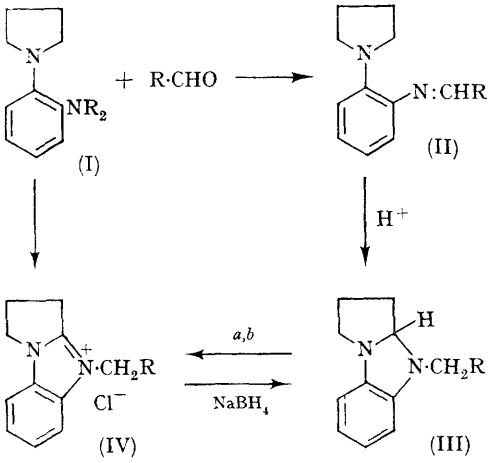
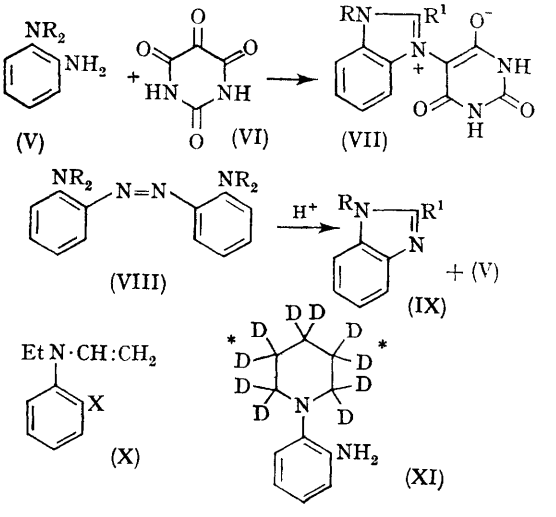
WHILST studying *o*-substituted tertiary anilines, we have prepared a series of anils (II) and explored their reactions. Rather surprisingly these compounds cyclise rapidly at ambient temperatures in the presence of a trace of acid to give almost quantitative yields of the corresponding dihydrobenzimidazoles (III).† Indeed, if attempts to prepare the anils (II) under acidic conditions are made, the dihydrobenzimidazoles are formed directly. Furthermore if the anil-forming reaction is performed in carbon tetrachloride solution under reflux with a soluble acid catalyst (*e.g.*, trifluoroacetic acid), the benzimidazolium salts (IV) may be isolated. El'tsov and his co-workers[1] have observed that dihydrobenzimidazoles are oxidised to the aromatic system, with elimination of hydride ions by carbon tetrachloride. Similarly, if the amine (I) hydrochloride and a suitable aldehyde are heated under reflux in acetone solution the corresponding benzimidazolium salt (IV) is again formed, acetone being reduced to 2-propanol. These benzimidazolium salts are readily reconverted to their dihydro-analogues with sodium borohydride.



R = Ph, $PhNO_2$ (*o*-, *m*-, and *p*-), $C_6H_3{\cdot}Cl_2$(3.4-), $C_6H_5{\cdot}CH{=}CH$, 2-, 3- and 4-pyridyl, 2-thienyl and 2-benzimidazolyl. *a* = CCl_4; *b* = acetone.

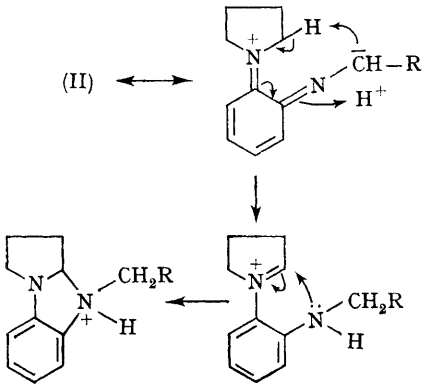
This ready cyclisation has analogies in the literature. Thus, Clark-Lewis and his co-workers[2] have shown that the reaction of alloxan (VI) and *o*-aminodiethylaniline (V; R = Et) (preferably but not essentially under acid-catalysis) gives the barbituryl benzimidazolium salt (VII; R = Et, R^1 = Me). We have extended this reaction to a series of cyclic bases [(V); $R_2 = (CH_2)_4$; $(CH_2)_5$; $(CH_2)_6$ or $(CH_2)_2{\cdot}O{\cdot}(CH_2)_2$] to give the corresponding salts (VII).



Price[3] has observed that the azo-compounds (VIII; R = Me) give the benzimidazole (IX; R = Me, R^1 = H) and the amine (V; R = Me) with either acid or hydrated cobalt chloride. Likewise we have found that the azo-compound [(VIII); $R_2 = (CH_2)_5$] with acid produces the corresponding benzimidazole [(IX); R + R^1 = $(CH_2)_4$] and the amine [(V); $R_2 = (CH_2)_5$].

Clark-Lewis has postulated a mechanism for the formation of barbituryl derivatives (VII) by way of a radical process in which he suggests that the key intermediate is the enamine (X). This mechanism is, however, not consistent with our work. Thus, when *N*-(*o*-aminophenyl) perdeuteriopiperidine (XI) was treated with alloxan in the usual way, no loss of deuterium from the β-position of the piperidine ring [starred in (XI)] was observed in the benzimidazolium salt produced. Furthermore, when the anil (II; R = $C_6H_4{\cdot}NO_2$-*p*) was cyclised in MeOD solution with DCl in D_2O as catalyst, no D was incorporated in the pyrrolidine ring or the

† All the compounds reported show satisfactory elementary analyses, infrared and n.m.r. spectra.



benzylic methylene group of the product. We thus conclude that the cyclisation is intramolecular in character, and suggest the mechanism indicated on the left.

In the reactions with alloxan, the alloxan itself can perform the role of acid-catalyst and oxidant in accordance with its known properties.

It is remarkable that while the anils of the substituted pyrrolidine (I) cyclise readily, those derived from the piperidine analogues are unchanged by acid treatment even after prolonged heating. The scope and mechanism of these reactions are under further investigation.

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[1] E. V. El'tsov, *J. Org. Chem.* (*U.S.S.R.*), 1965, **1**, 1121, and references cited therein.
[2] J. W. Clark-Lewis, J. A. Edgar, J. S. Shannon, and M. J. Thompson, *Austral. J. Chem.*, 1965, **18**, 907, and references cited therein.
[3] R. Price, *J. Chem. Soc.* (*A*), 1967, 521.