Synthesis of 4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile and Related Compounds

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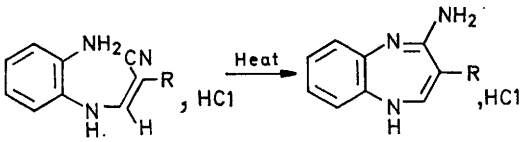
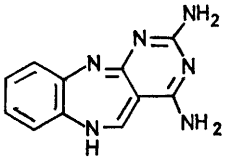
Summary In the presence of hydrochloric acid, *o*-*N*-(2,2-dicyanovinyl)aminoaniline is easily converted into 4-amino-1*H*,1,5-benzodiazepine-3-carbonitrile, which can be hydrolysed with various bases to other diazepine, triazepine, or benzimidazole derivatives.

IT has been reported that *o*-*N*-(2,2-dicyanovinyl)aminoaniline [free base of (Ia)], produced by reaction of *o*-phenylenediamine with ethoxymethylenemalonitrile, is easily converted into benzimidazole when heated.[1] In contrast to this finding, we now describe a new synthesis of the benzodiazepine (IIa) and related compounds from the hydrochloride (Ia)



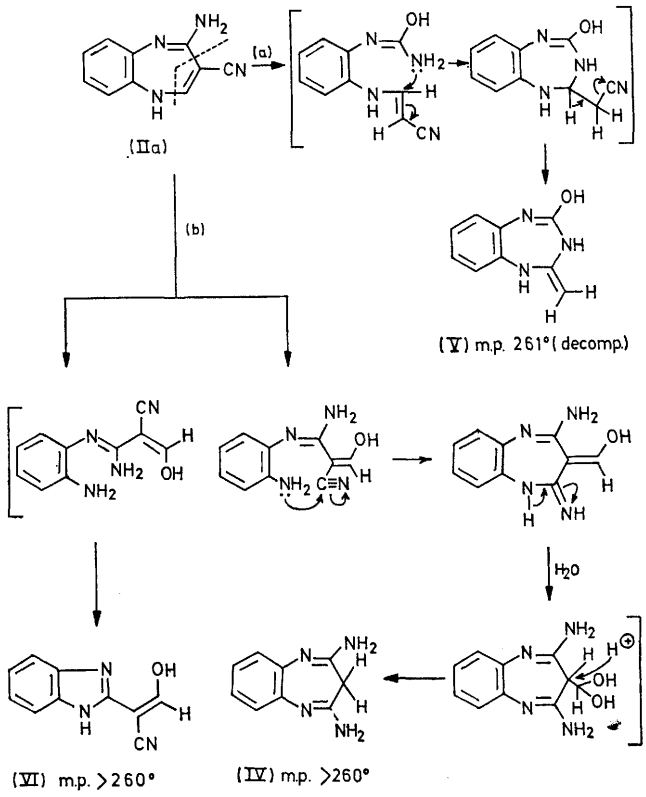
(Ia) R = CN (IIa) R = CN, m.p. 280° (decomp.)
(Ib) R = CO_2Et (IIb) R = CO_2Et, m.p. 230° (decomp.)



(III)

When the hydrochloride (Ia) was refluxed in ethanol for 2 h, orange needles were precipitated (80—90%), m.p. 280° (decomp.) (from H_2O). I.r., n.m.r., mass spectral, and elemental analytical data indicated that the product was the benzodiazepine (IIa).† The hydrochloride (IIb) was similarly synthesized from the ester (Ib), obtained from the reaction of *o*-phenylenediamine with ethyl ethoxymethylenecyanoacetate.

In an attempt to obtain a condensed benzodiazepine (III), addition of guanidine to a hot aqueous solution of (IIa) gave, instead of compound (III), the benzodiazepine (IV) (30%). A similar result was also obtained with methylguanidine. These findings showed that the reactions were hydrolytically catalysed by alkaline agents. Reaction of compound (IIa) (1 g) with NaOH (1·4 g) in water (50 ml) on a water-bath for 15 min gave compound (IV) (50%), while hydrolysis of compound (IIa) (1 g) with NaOH (0·45 g) in water (100 ml) afforded the benzodiazepine (V) (38%). In contrast, the benzimidazole (VI) (36%) was obtained by hydrolysis of (IIa) with concentrated aqueous ammonia or 2-aminopyrimidine.



SCHEME

We suggest the mechanism in the Scheme, involving cleavage of either a C–C bond (a) or a C–N bond (b) of the diazepine ring in (IIa). We assume that cleavage (b), followed by recyclization, would probably give (IV) and (VI), whereas cleavage (a) would give (V). Which cleavage occurs probably depends on the basicity of the base used.

(*Received*, 15*th February* 1973; *Com.* 210.)

† Satisfactory analytical data were obtained for all new compounds described.

[1] K. S. Sardesai and S. V. Sunthankar, *J. Sci. Ind. Res., India*, 1959, **B 18**, 158; P. H. Stahl, R. Barchet, and K. W. Merz, *Arzneim.-Forsch.*, 1968, **18**, 1214.