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SYNTHESES AND STRUCTURES OF 7-CHLORO-2-HYDRAZINO-5-PHENYL-3H-1,4-BENZODIAZEPINES AND SOME ISOMERIC 1,4,5-BENZOTRIAZOCINES

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During the course of synthetic studies on 1,4-benzodiazepine derivatives, we found that the treatment of 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine (I)[1] with hydrazine hydrate in methanol in the presence of an acid afforded 7-chloro-2-hydrazino-5-phenyl-3H-1,4-benzodiazepine (II), colorless prisms (from CH_2Cl_2-benzene), mp 170° (browning), 202-204° (decomp.), NMR ($CDCl_3$)[2]: δ = 4.18 (2H, s, $-CH_2-$), 4.94 (3H, broad, $-NHNH_2$). Compound II gave a positive ninhydrin test (yellowish-brown) and, when recrystallized from acetone, formed the isopropylidene derivative (III), mp 184.5-185.5°, NMR ($CDCl_3$) : δ = 2.04, 2.07 (each 3H, s, $(CH_3)_2$), 4.49 (2H, s, $-CH_2-$). In boiling methanol, compound II formed a bis-compound (IV), mp 253-254°, mol. wt. 536 (mass spectrum), while treatment of II with Raney nickel in boiling ethanol regenerated I. Acid hydrolysis of II and IV afforded the 1,4-benzodiazepin-2-one (V).

7-Chloro-2-hydrazino-5-phenyl-3H-1,4-benzodiazepine (II) was also prepared from both 1,4-benzodiazepine-2-thione (VI)[3] and 2-methylmercapto-1,4-benzodiazepine (VII)[3] by reaction with hydrazine hydrate.

Compound II was easily cyclized by treatment with ethyl orthoformate to 8-chloro-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (VIII), mp 226-227° (from Me_2CO-n-hexane), NMR ($CDCl_3$) : δ = 4.90 (2H, broad, $-CH_2-$), 8.61 (1H, s, proton on the triazole ring).

Similarly, starting with 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine 4-oxide (IX)[4], the following compounds were obtained: the 2-hydrazino derivative (X), mp 262-263° (decomp.), ninhydrin + (yellowish-brown), NMR

($CDCl_3$) : δ = 4.51 (2H, s, $-CH_2-$), ca. 5.60 (3H, very broad, $-NHNH_2$); the isopropylidene derivative (XI), mp 223-224°, NMR ($CDCl_3$) : δ = 2.06, 2.11 (each 3H, s, $(CH_3)_2$), 4.76 (2H, s, $-CH_2-$); 8-chloro-6-phenyl-4H-s-triazolo[4,3-a]-[1,4]benzodiazepine 5-oxide (XII), mp 267-268° (decomp.), NMR (DMSO-d_6) : δ = 5.38 (2H, s, $-CH_2-$), 9.30 (1H, s, proton on the triazole ring). Deoxygenation of XII with phosphorus trichloride or by catalytic hydrogenation over Raney nickel gave VIII, the structure of which was confirmed by the X-ray crystallographic analysis[5].

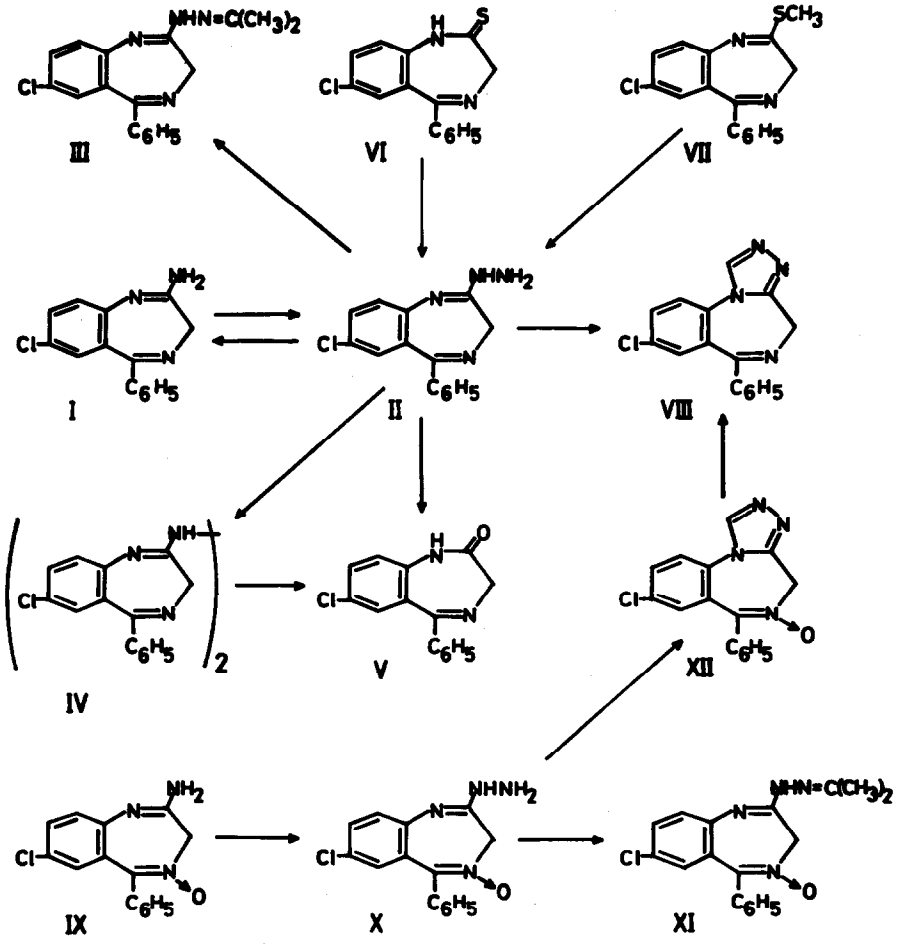

Chart 1

Derieg, et al.[6] stated that the treatment of 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide (XIII) with anhydrous hydrazine followed by hydrogenation over Raney nickel gave 7-chloro-2-hydrazino-5-phenyl-3H-1,4-benzodiazepine 4-oxide (X) and its deoxygenated compound (II), respectively. However, the melting points they described for these products differ from those we obtained for X and II by our synthetic routes (Chart 1). We therefore repeated their experiments and obtained, instead, the 8-membered ring 2-oxime (XIV), mp 232-235° (decomp.) and the deoxygenated compound (XV), mp 173-174° (decomp.). Acetylation of XIV gave the diacetyl derivative (XVI), mp 230-231°, which, after saponification, afforded the monoacetyl derivative (XVII), mp 225-226°. The melting points of the 1,4,5-benzotriazocines (XIV → XVII) were in agreement with those reported[6] for the alleged diazepines.

Compounds XIV and XV were not colored by ninhydrin reagent and did not form isopropylidene derivatives. The oximes (XIV and XVII) gave positive $FeCl_3$ (deep green) and NH_4SCN-$Fe(NO_3)_3$ tests[7] whereas XV and XVI were negative to these reagents. The IR spectrum of XVI showed bands at 1770 cm^{-1} (suggesting the presence of an acetoxyl) and at 1666 cm^{-1} (amide carbonyl). The band at 1770 cm^{-1} was absent in the IR spectrum of XVII.

The 100 MHz NMR spectrum of XIV in DMSO-d_6 showed the presence of an ABX coupling system attributable to the $-CH_2NH-$ grouping. On addition of D_2O or

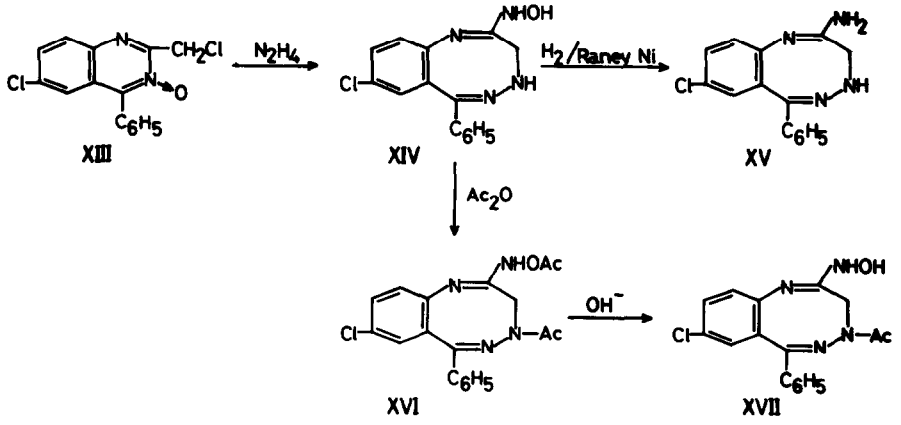

Chart 2

by irradiation of the NH proton (which appeared as a triplet, δ = 7.86, J = 3.5 Hz), the pair of unresolved quartets due to the methylene collapsed into a pair of doublets (δ = 3.39 and 3.84, J = 7.5 Hz). On irradiation of the methylene protons, the NH signal collapsed to a singlet. The same coupling system was observed with XV but not with XVI and XVII.

The above-mentioned chemical and physico-chemical data indicate that XIV is not a diazepine as proposed by Derieg et al.[6] but rather the isomeric cyclic amidoxime having an 8-membered 1,4,5-benzotriazocine ring. X-Ray analysis[5] of XVI established its structure as 2-acetoxyamino-4-acetyl-8-chloro-3,4-dihydro-6-phenyl-1,4,5-benzotriazocine[8]. The reactions from XIII are, therefore, as depicted in Chart 2.

Satisfactory elemental analyses were obtained for all crystalline compounds with melting points reported herein.

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6. M. E. Derieg, R. I. Fryer, L. H. Sternbach, J. Chem. Soc. 1968, (C), 1103.
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8. Both the N^1-C^2 and C^2-exo-N bonds were found to have double bond character by X-Ray analysis. For convenience, the formulae in Chart 2 are drawn with an endo-bouble bond.