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A SYNTHETIC APPROACH TO NEW 1,4-BENZODIAZEPINE DERIVATIVES

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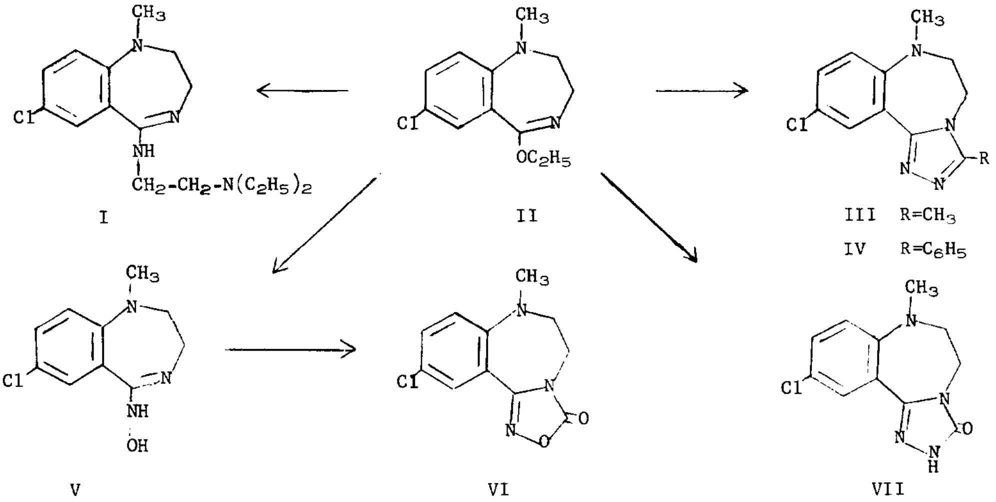
A recent publication by Meguro and Kuwada[1] prompts us to report some of our results in this area. In particular we have studied the utility of electrophilic amide derivatives for the preparation of 1,4-benzodiazepines with heterocyclic systems fused to the "a" and the "d" faces of the benzodiazepine system.

An electrophilic center at C-5 was created by alkylation of 7-chloro-1,2,3,4-tetrahydro-1-methyl-5H-1,4-benzodiazepin-5-one[2,3], mp 183-185°, with triethyloxonium fluoroborate[4] to give 7-chloro-5-ethoxy-2,3-dihydro-1H-1,4-benzodiazepine (II), mp 38.5-39°. This compound (II) readily condensed with amines to give amidines. Thus reaction of II with N,N-diethylethylenediamine in refluxing benzene gave 7-chloro-5-[[2-(diethylamino)ethyl]amino]-2,3-dihydro-1-methyl-1H-1,4-benzodiazepine (I) which was isolated as its dihydrochloride salt, mp 253-255°.

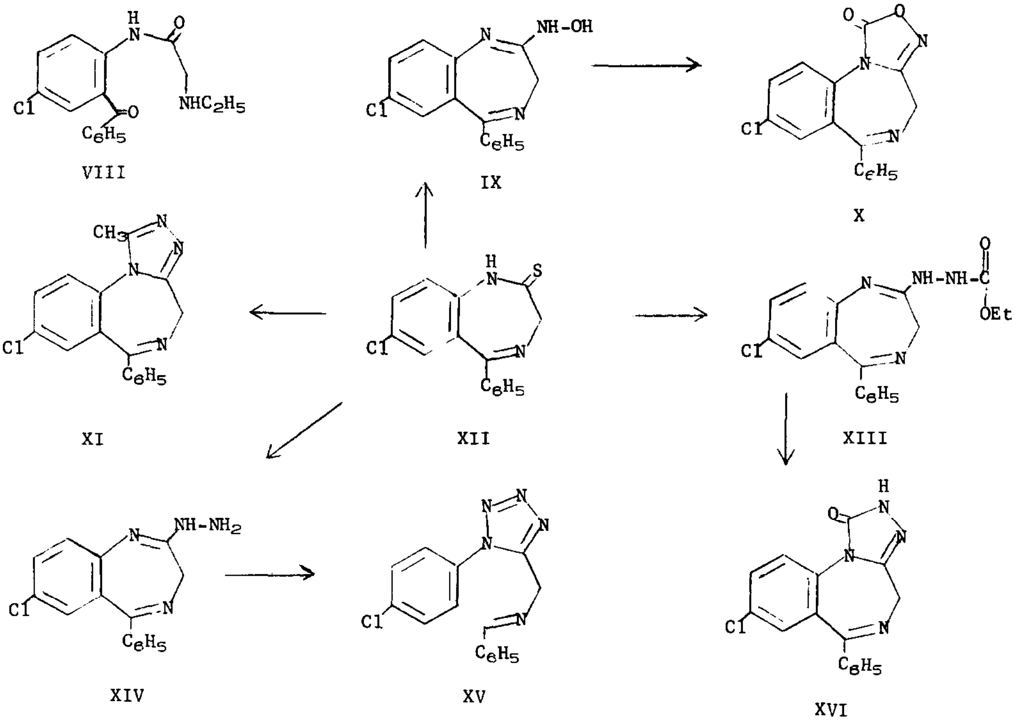
Addition of hydroxyl amine to II in refluxing ethanol gave 7-chloro-2,3-dihydro-5-(hydroxyamino)-1-methyl-1H-1,4-benzodiazepine (V), mp 186.5-189°; which was condensed with carbonyldiimidazole in refluxing THF to give 10-chloro-6,7-dihydro-7-methyl-3H,5H-[1,2,4]oxadiazolo-[4,3-d][1,4]benzodiazepin-3-one (VI), mp 190-191°. The reaction of II with acid hydrazides proceeded with concomitant cyclodehydration to give s-triazolo[4,3-d][1,4]benzodiazepines. Thus condensation of II with acetic acid and benzoic acid hydrazides gave 10-chloro-6,7-dihydro-3,7-dimethyl-5H-s-triazolo[4,3-d][1,4]benzodiazepine (III), mp 185-186.5°, and 10-chloro-6,7-dihydro-7-methyl-3-phenyl-5H-s-triazolo[4,3-d][1,4]benzodiazepine (IV), mp 207.5-208.5°, respectively. Similarly the reaction of II with ethyl carbazate gave 10-chloro-2,5,6,7-tetrahydro-7-methyl-3H-s-triazolo[4,3-d][1,4]benzodiazepin-3-one (VII), mp 259-262°.

Chart 1



An attempt to create an electrophilic center at C-2 of the 1,4-benzodiazepine system by alkylating 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one[5] with triethyloxonium fluoroborate gave 2'-benzoyl-4'-chloro-2-(ethylamino)acetanilide (VIII), mp 71.5-72.5°, ir (Nujol) 3350, 3180 (NH), 1695, 1640 cm^{-1} (C=O); which was the result of initial alkylation at N-4 followed by hydrolysis of the resulting iminium salt during the aqueous work up. 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazpine-2-thione (XII)[6] could, however, be utilized for the desired nucleophilic additions at C-2 of the 1,4-benzodiazepine system. Thus reaction of XII with hydroxylamine in methanol gave 7-chloro-2-(hydroxyamino)-5-phenyl-3H-1,4-benzodiazepine (IX), mp 126-130°, which was condensed with phosgene in the presence of triethylamine to give 8-chloro-6-phenyl-1H,4H[1,2,4] oxadiazolo[4,3-a][1,4]benzodiazepin-1-one (X), mp 191-192°. In a similar manner compound XII reacted with hydrazine hydrate in methanol to give 7-chloro-2-hydrazino-5-phenyl-3H-1,4-benzodiazepine (XIV), mp 217.5-219°[1]. A mixture of XIV and 2N hydrochloric acid reacted with sodium nitrite at -5° to give 8-chloro-6-phenyl-4H-tetrazolo[1,5-a][1,4]benzodiazepine (XV), mp 181-182°. Condensation of XII with ethyl carbazate gave 3-(7-chloro-5-phenyl-3H-1,4-benzodiazepin-2-yl)carbazic acid ethyl ester (XIII), mp 198-199° dec, which was cyclized thermally at 197-207° to afford 8-chloro-2,4-dihydro-6-phenyl-1H-s-triazolo[4,3-a][1,4]benzodiazepin-1-one (XVI), mp 255-256°. The reaction of thiolactam XII with acid hydrazides gave s-triazolo[4,3-a][1,4] benzodiazepines directly. Thus acetic acid hydrazide condensed with XII in refluxing 1-butanol to give 8-chloro-1-methyl-6-phenyl-4H-s-triazolo[4,3-a][1,4]benzodiazepine (XI), mp 228-228.5°. This compound was the progenitor of a new series of highly active CNS depressant compounds which is currently undergoing extensive clinical evaluation.[7,8]

Chart 2



A sample of the monohydrobromide salt of XI was dissolved in 95% ethanol and allowed to crystallize slowly at ambient temperature. The crystals were shown by x-ray crystallographic analysis to be the hemihydrobromide ethanol solvate. The crystals are triclinic, space group $P\bar{1}$, with cell dimensions $\underline{a}$=7.54Å, $\underline{b}$=14.62Å, $\underline{c}$=17.61Å, α=94.2°, β=92.5°, γ=100.9°. The symmetry independent unit contains two molecules of XI, two ethanols, and one HBr. Final results of a three-dimensional x-ray analysis (R=0.059) show that one of the molecules is protonated at N-2 of the triazole ring. Both the protonated and the unprotonated molecules have the same conformation (shown below for the protonated molecule). The protonated triazole nitrogen forms a strong hydrogen bond (N···O distance of 2.66Å) to one of the ethanol oxygens. The ethanols are hydrogen-bonded to the Br ion.

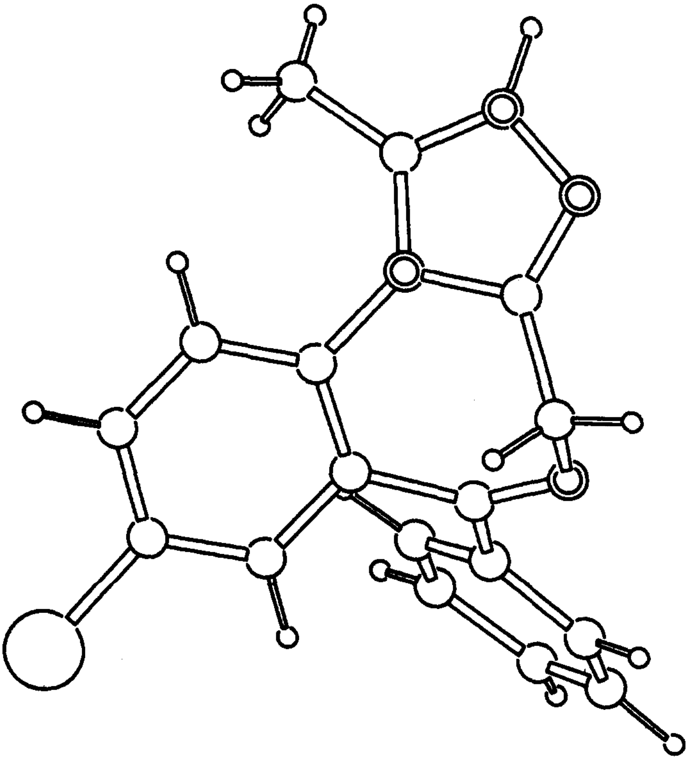


Figure. Computer drawing XI from x-ray results for the protonated molecule (see text).

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7. The authors wish to acknowledge the able technical assistance of Mr. J. Robert Greene.
8. A complete report of this work will be published elsewhere.