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QUINAZOLINES AND 1,4-BENZODIAZEPINES. XXXI. (1) NOVEL RING ENLARGEMENTS OF 1,2-DIHYDROQUINAZOLINE 3-OXIDES

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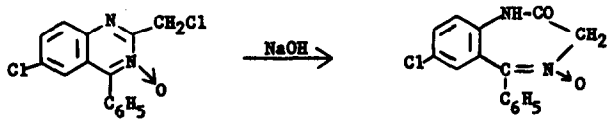
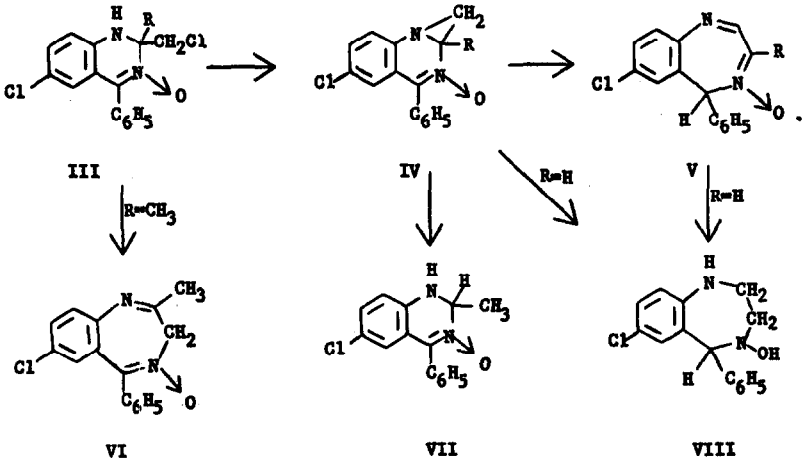
Recent work on the ring expansion of chloromethyldihydropyridines to azepines (2) prompts us to describe our studies of the ring expansion of 2-chloromethyl-1,2-dihydroquinazolines. The ring expansion of certain chloromethylquinazolines, e.g. I, to 1,4-benzodiazepine derivatives, e.g. II, on treatment with bases has been shown to proceed by addition across the 1,2-double bond of the quinazoline to form a 1,2-dihydroquinazoline as an unisolated intermediate (3). It therefore seemed likely that stable 1,2-dihydroquinazolines of type III (4) should react with base to form products analogous to II.



I II

However, the reaction of IIIa, m.p. 165-167°, (5) with potassium t-butoxide in tetrahydrofuran took a completely different course and gave compound IVa, m.p. 135-136°, which is a valence isomer of the unknown 2H-1,4-benzodiazepine ring system.

The infrared spectrum of IVa shows no band ascribable to an N-H, nor does the nmr spectrum reveal an exchangeable proton. The ultraviolet spectrum shows maxima at 224 (ε 16,000), 254 (ε 19,000), 308 (ε 8,000), 319 (ε 7,500), and 342 (infl.) mμ (ε 5,000). The nmr spectrum shows two doublets centered at δ = 2.65 ppm (J = 3 cps) and δ = 2.9 ppm (J = 4 cps) and a quartet at δ = 4.63 ppm. This spectrum is consistent with structure IVa if it is assumed that the geminal coupling constant for the methylene group is zero (6). In addition, the reduction of IVa resulted in two types of cleavage of the aziridine ring. Hydrogenation over Raney nickel gave the dihydroquinazoline N-oxide VII (4). Reduction with sodium borohydride in diglyme gave VIII (7).



a) R = H

b) R = CH_3

The 2H-benzodiazepine isomer IVa is thermally unstable, and was readily isomerized by a 1,5-hydrogen shift (8) in refluxing toluene solution to the 5H-benzodiazepine (Va), m.p. 157-158.5°, λ max. 239 (ε16,000), 285 (infl.) (ε4,400), 322 (ε7,400) and 350 (infl.) (ε4,800) mμ. The nmr spectrum shows no signals at high field indicating the disappearance of the methylene group. Reduction of VIa in the sodium borohydride in methanol also gave VIII.

The reaction of the methyl analog IIIb, m.p. 157-159° with base was more complex. Thin layer chromatography of the reaction mixture obtained by treating IIIb with potassium t-butoxide in ether indicated that three products were present. The product of highest Rf was the 5H-benzodiazepine, Vb, m.p. 169-170°, λ max. 236 (ε17,800), 280 (ε4,400) and 324 (ε6,800) mμ. Its nmr spectrum showed a singlet at δ = 2.17 ppm for the methyl group and no other high field signals. The product of second highest Rf was the 2H-benzodiazepine isomer IVb and was too unstable to be isolated in pure form since it was converted to Vb, on standing at room temperature or slight warming. Apparently the 1,5-hydrogen shift becomes extraordinarily facile when the aziridine ring bears a methyl group in this position[1].

The third product was the 3H-benzodiazepine VI, m.p. 164-166° (dec.) which could be obtained in good yield by treatment of IIIb with sodium hydroxide in ethanol. Here at last was a product formed by a path analogous to that known for the chloromethyl-quinazolines. Its infrared spectrum shows no bands in the 3600-3300 cm^{-1} region. The nmr spectrum shows no exchangeable protons, a singlet at δ = 2.5 ppm due to the methyl

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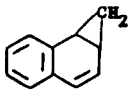
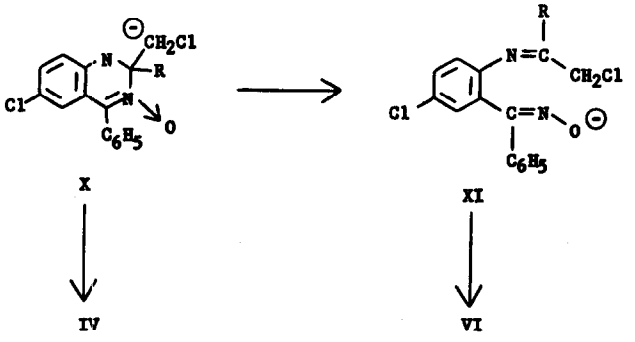
1. For instance, the hydrocarbon IX undergoes an analogous transformation only when heated to 260° (8b).



IX

group and another singlet at δ = 4.44 ppm due to the methylene group. Reduction of the 1,2-double bond with sodium borohydride gave 7-chloro-2,3-dihydro-2-methyl-5-phenyl-1H-1,4-benzodiazepine 4-oxide, m.p. 200-202.5°, λ max. 240 (ε 26,000), 265 (ε 17,500), 305 (ε 9,500) and 380 mμ (ε 4,200) (6). The nmr spectrum shows a doublet at δ = 1.33 ppm (J = 6 cps) due to the 2-methyl group. Oxidation with manganese dioxide re-introduced the 1,2-double bond to reform VI.

The formation of these benzodiazepines may be explained as follows. Base abstracts the proton at position 1 to give the anion X which may displace chloride to form product IV, or it may isomerize to the valence tautomeric anion XI depending on solvent and the substitution at position 2. Anion XI will then eject chloride ion to form the 3H-benzodiazepine VI.



Thus derivatives of three of the five possible tautomeric forms of the basic 1,4-benzodiazepine nucleus have been obtained. Significantly, there appear to be distinct energy barriers between the tautomeric forms. These energy barriers may be related to the fact that intermediates would involve an 8-π-electron system in the seven-membered ring if it were planar. The chemistry of these products will be described in detail in due course.

REFERENCES

(1) Paper XXX. M. Müller and P. Zeller, Helv. Chim. Acta., in press.

(2) R. F. Child and A. W. Johnson, Chem. Comm., 95 (1965).

(3) A. Stempel, E. Reeder and L. H. Sternbach, J. Org. Chem., 30, 4267 (1965).

(4) These compounds were prepared by the method described by G. F. Field, W. J. Zally and L. H. Sternbach, J. Org. Chem., 30, 3957 (1965).

(5) All compounds gave satisfactory elemental analyses.

(6) See K. L. Williamson, C. A. Langford and C. R. Nicholson, J. Am. Chem. Soc., 86, 762 (1964).

(7) W. Metlesics, G. Silverman and L. H. Sternbach, J. Org. Chem., 28, 2459 (1963).

(8) See, for example (a) A. P. TerBorg and H. Kloosterziel, Rec. trav. chim., 82, 1189 (1963); or (b) E. Miller, H. Fricke and H. Kessler, Tetra. Let. 1525 (1964).