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THERMAL REARRANGEMENT OF CONDENSED DIHYDRODIAZEPINONES (1)

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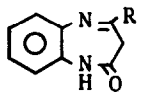
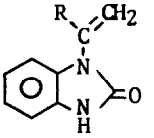
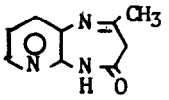
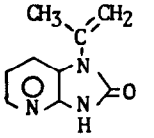
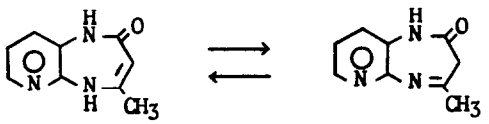
The condensation of o-phenylenediamine with ethyl acetoacetate in boiling xylene has recently been shown to yield 2,3-dihydro-4-methyl-1H-1,5-benzodiazepin-2-one (I, R = CH_3) as the major product, together with a small but variable quantity of N-isopropenylbenzimidazolone (II, R = CH_3) (2,3). A rather implausible multi-step sequence was suggested to explain the formation of the rearranged product (2). We have observed a similarly rearranged by-product formed in variable yield and accompanying the diazepinone derivative from the reaction of 2,3-diaminopyridine with ethyl acetoacetate in boiling xylene. In this instance, however, the unsymmetrical character of the heteroaromatic diamine provides an opportunity for the formation of two theoretically possible diazepine derivatives (III and IV), as well as two possible imidazolones (V and VI). An understanding of the structural relationship of the imidazolone by-product to the diazepinone which it accompanied has provided insight into the origin of the rearrangement product.

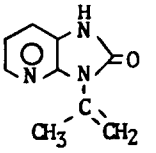
I 

II 

III 

V 

IV 

VI 

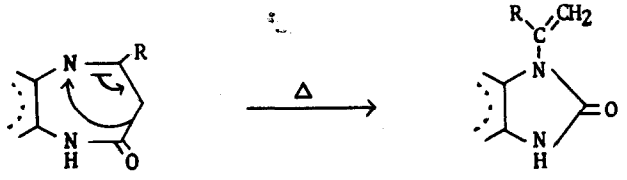
Reaction of 2,3-diaminopyridine with ethyl acetoacetate in boiling xylene was recently reported by us to give 3,5-dihydro-2-methyl-4H-pyrido[2,3-b][1,4]diazepin-4-one (III) (4,5). The white crystalline by-product from this reaction, with m.p. 180-183°, was found to be isomeric with the diazepinone product and appeared to be an isopropenylimidazolone on the basis of spectral considerations: $\lambda_{max.}^{ethanol}$ 227 and 293 mμ (ε 6,100 and 11,800, respectively): $\lambda_{max.}^{KCl}$ 2.90 (N-H), 3.22 (=CH_2), 5.82 (strong amide carbonyl), 6.06 (C=C), 6.90 and 7.20 (C-CH_3) μ; NMR (60 mc): 3H quartet 137 cps (J = 4 cps, methyl split by two vinyl protons), 1H vinyl quartet 315 cps (J = 3 cps), 1H vinyl quartet 323 cps (J = 5 cps), series of three 1H quartets 416-484 cps (pyridine ring protons). This material was shown to be the 1,3-dihydro-1-isopropenyl-2H-imidazo[4,5-b]pyridin-2-one (V) by hydrogenation of the olefinic double bond in the presence of palladium-charcoal and comparison of the resulting 1-isopropyl compound (m.p. 179-181°) with an authentic sample of 1,3-dihydro-3-isopropyl-2H-imidazo[4,5-b]pyridin-2-one (m.p. 159.5-160.5°), prepared by treating 3-amino-2-isopropylaminopyridine with phosgene. A mixture of the two isopropyl compounds resulted in a depressed melting point and comparison of the ultraviolet, infrared, and nuclear magnetic resonance spectra, although similar in general detail, revealed significant differences.

The isomeric 3-isopropenylimidazolone (VI) was isolated as a by-product from the reaction of 2,3-diaminopyridine with ethyl acetoacetate at 185° for 15 minutes in the absence of solvent; this reaction has been shown to afford predominantly diazepinone IV, which exists as an inseparable mixture of the 1,3- and 1,5-dihydro tautomers (4). Compound VI [m.p. 136-136.5°; $\lambda_{max.}^{ethanol}$ 230 and 293 mμ (ε 5,500 and 12,000, respectively); $\lambda_{max.}^{KCl}$ 2.95 (N-H), 3.18 (=CH_2), 5.86 (strong amide carbonyl), 6.08 (C=C), 6.92 and 7.22 (C-CH_3) μ; NMR: 3H quartet 138 cps (J = 4 cps), 1H quartet 322 cps (J = 4 cps), series of three 1H quartets 410-485 cps, broad N-H peak 659 cps], upon reduction of the olefinic linkage, afforded 1,3-dihydro-3-isopropyl-2H-imidazo[4,5-b]pyridin-2-one, identical in all respects with the unambiguously synthesized material.

It was noted that, in the hot xylene reaction, the variability of yield of rearranged material was directly related to the severity and length of time of reflux: the longer the reaction time or the more vigorous the reflux, the greater the amount of isopropenyl compound formed. The possibility of a thermally induced transformation of dihydrodiazepinone into

isopropenylimidazolone, which this observation suggested, was further enhanced when it was found that III, prepared alternately from ethyl 3-(2-amino-3-pyridylamino)crotonate (4), was partially converted into V merely by boiling in xylene. Similarly, the reaction of 2,3-diaminopyridine with ethyl acetoacetate at 185°, which afforded mainly IV after 15 minutes, gave almost exclusively rearranged product (VI) when allowed to continue for 1.5 hours.

Eventually it was found that III was thermally rearranged smoothly into V, and IV into VI, by dry fusion at 185° for 1.5 hours. Dry fusion was similarly used to convert the following diazepinone derivatives into the corresponding imidazolones: I, R = CH_3; I, R = CF_3 (6); I, R = C_6H_5 (7); 3,5-dihydro-2-methyl-4H-pyrido[3,4-b][1,4]diazepin-4-one (8); and 1,3-dihydro-4-methyl-2H-pyrido[3,4-b][1,4]diazepin-2-one (8). The rearrangement, thus, appears to be general for condensed dihydrodiazepinones (9) and independent of the substituents on the diazepine ring, providing the endocyclic double bond exists as, or can be tautomerized into, an azomethine linkage. Although the mechanism of this rearrangement is not yet clear, the ease of the reaction, the high yield of rearranged product, and the apparent lack of influence of the substituent R suggest a possible concerted reaction:



Such a reaction pathway would be a unique example of a sigmatropic shift of order [1,3] from carbon to nitrogen, but, according to the Woodward-Hoffmann selection rules (10), would be permitted only if it proceeded with inversion of the carbonyl group. A thermal rearrangement involving a sigmatropic change from C-1 to C-3 was recently reported to proceed with inversion of configuration in the migrating group (11). In the present diazepinone to imidazolone interconversion, the inversion of the carbonyl carbon atom would not be observable, but might be additionally favored by participation of the π-orbital of the carbonyl group (10b).

In two instances, namely, with the isomeric diazepinones derived from 4,5-diaminopyrimidine and ethyl acetoacetate (12), a temperature of 210° was required to initiate the rearrangement. At this temperature, the reaction was complicated by dealkylation and

decomposition, with the resultant isolation of only unsubstituted 8-purinone in low yield.

We are continuing to explore the scope of this rearrangement and to apply these findings to the determination of ambiguous diazepinone structures arising from reactions of β-ketoesters with unsymmetrical diamines. We thank Dr. Roald Hoffmann, Department of Chemistry, Cornell University, for his helpful comments regarding the possible mechanism of reaction.

REFERENCES

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3. We have repeated the work of Davoll (reference 2) and have additionally confirmed these structures by means of nuclear magnetic resonance spectrometry; the results of these studies will be reported elsewhere.
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5. This compound exhibits the remarkable ability to exist in two stable, isolable tautomeric forms (reference 4). For the purposes of this report, only the 3,5-dihydro structure is given, since it is this form which is present at reaction temperatures.
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8. Unpublished results from these laboratories.
9. In addition to the diazepinones given in the text, we have tentatively identified 2-amino-6-methylthio-9-(1,1,1-trifluoro-2-propenyl)-8-purinone as a by-product accompanying the diazepinone from the reaction of 2,4,5-triamino-6-methylthiopyrimidine with ethyl trifluoroacetoacetate in boiling xylene (to be published); this product must have been formed by thermal rearrangement of the diazepinone during the course of the reaction.
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