The Children's Cancer Research Foundation and the Departments of Biological Chemistry and Pathology, Harvard Medical School at The Children's Hospital Medical Center

Synthesis and Tautomeric Behavior of Dihydropyrido[2,3-*b*][1,4]diazepinones (1)

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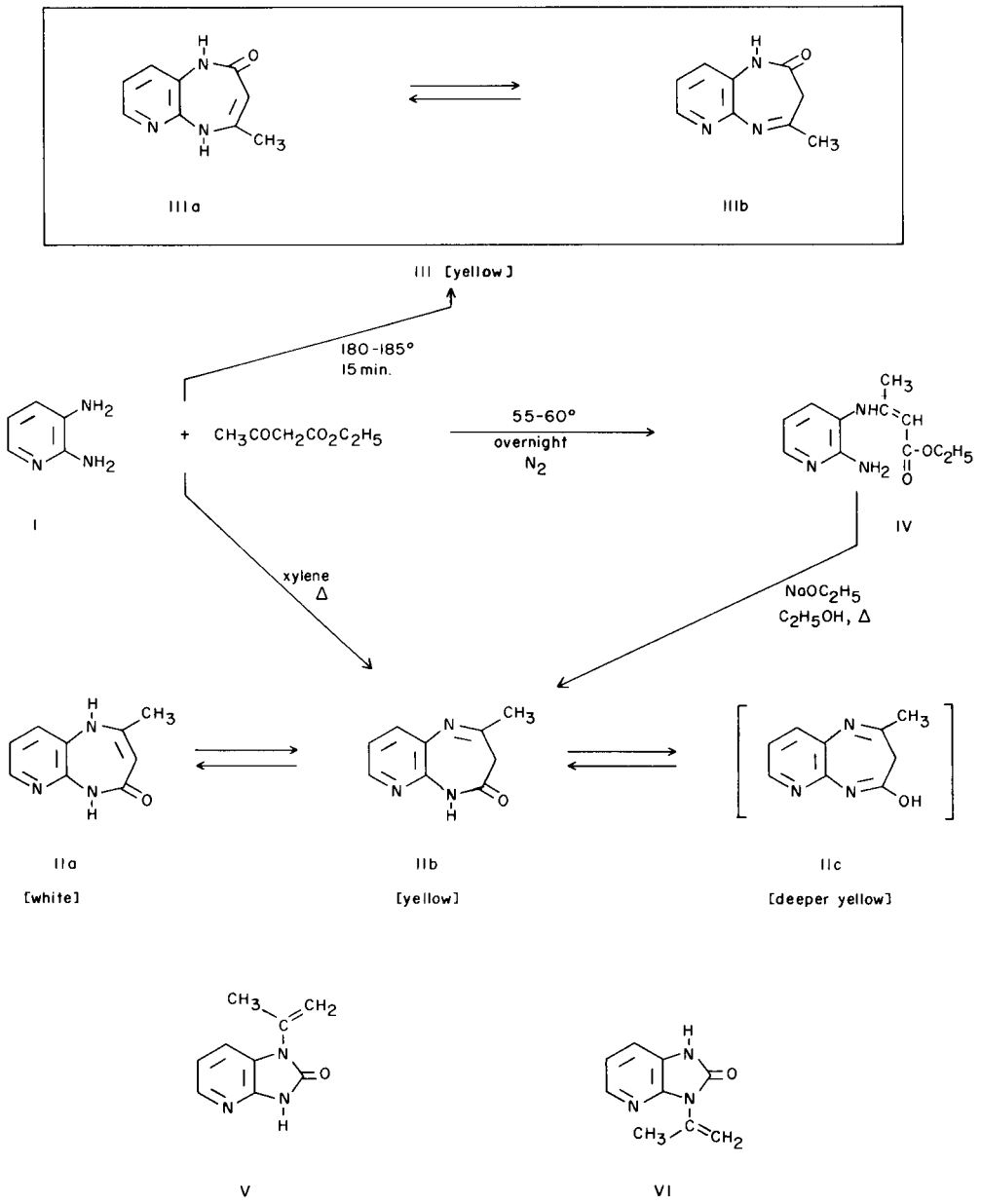
Sir:

Condensation of the unsymmetrical, heteroaromatic diamine 2,3-diaminopyridine (I) with ethyl acetoacetate can theoretically give two isomeric dihydropyrido[2,3-*b*]-[1,4]diazepinones, II and III. We have found that different reaction conditions result in the preferential formation of one or the other isomer. We wish now to report on the preparation and characterization of the two diazepine derivatives and on the remarkable tautomeric nature of one



V

VI

of these compounds. Compounds II and III belong to an essentially uncharacterized heterocyclic ring system; the only literature reference on derivatives of the pyrido[2,3-*b*]-[1,4]diazepine system, a communication by Barchet and Merz (2), fails to give experimental details or any evidence in support of the structure assignment.

Treatment of I with ethyl acetoacetate in boiling xylene for 8 hours, with azeotropic removal of water, afforded II as the major product. A companion product, 1,3-dihydro-1-isopropenyl-2*H*-imidazo[4,5-*b*]pyridin-2-one (V), was invariably present in small yield (3). The identity of the major product as II is based upon accumulated physical and chemical evidence (*vide infra*) and alternate synthesis from ethyl 3-(2-amino-3-pyridylamino)crotonate (IV).

Compound IV, m.p. 117-120°, was formed in 62% yield when a mixture of I and ethyl acetoacetate was maintained under nitrogen at 55-60° overnight in the absence of solvent. *Anal.* Calcd. for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 19.00. Found: C, 59.62; H, 6.83; N, 18.84. The n.m.r. spectrum (4) of IV was consistent with an enamine structure, rather than an anil. Alkylation was shown to have occurred at the more basic 3-amino group of I, as one would expect, by diazotization, basicity, and n.m.r. studies on IV (5). Cyclization of IV by means of sodium ethoxide in boiling ethanol for 5 hours afforded the dihydrodiazepinone II, identical in all respects with the material obtained from the reaction of I with ethyl acetoacetate in boiling xylene.

The existence of 2 isolable, interconvertible tautomeric forms of II is worthy of special note since we are unaware of any previous report on the isolation of a pair of easily interconvertible carbon-to-nitrogen triad prototropic tautomers, each capable of stable, independent existence under ordinary conditions (6). A third tautomeric form of II appears also to exist but is demonstrable only in solution.

Crystallization of the crude yellow diazepinone from cyclohexane produced white needles. *Anal.* Calcd. for $C_9H_9N_3O$: C, 61.69; H, 5.19; N, 23.99. Found: C, 61.48; H, 5.25; N, 23.80. On heating or prolonged standing at room temperature, or upon dissolution in various solvents (e.g., pyridine, dimethyl sulfoxide), the white material reverted to yellow in color; recrystallization of the yellow material from cyclohexane returned leuco compound (7). On melting point determination, the white crystals turned yellow in the range of 128-134° before melting at 187-189°. The yellow modification, which melted sharply at 187-189°, could be produced quantitatively by maintaining the leuco compound at 130-140° for 30 minutes under nitrogen. *Anal.* Found: C, 61.53; H, 5.23; N, 24.12.

The leuco tautomer has been assigned structure IIa, 1,5-dihydro-2-methyl-4*H*-pyrido[2,3-*b*][1,4]diazepin-4-one, in which the double bond in the diazepine ring is not in conjugation with the pyridine nucleus. An instantaneous ultraviolet absorption spectrum of IIa showed λ max (ethanol), mμ (ε) 229 (15,000), 251 (6,800), and 296 (6,100). The highest wavelength absorption of IIa, at 296 mμ, is consistent with an unconjugated pyridinediamine chromophore; this assignment is further supported by the absence of color in IIa and by examination of molecular models (Dreiding type), which show the carbonyl group and the carbon-carbon double bond to be significantly out of the plane of the heteroaromatic ring. The yellow tautomer, 3,5-dihydro-2-methyl-4*H*-pyrido[2,3-*b*][1,4]-diazepin-4-one (IIb), the structure of which is supported by n.m.r. evidence, showed λ max (ethanol), mμ (ε) 232 (16,100), 252 (8,300), and 314 (3,300). In *p*H 1 solution, both IIa and IIb exhibited the same u.v. absorption spectrum, with maxima at 256 and 336 mμ (ε, 5,600 and 5,500, respectively). Each tautomer exhibited a characteristic infrared spectrum, with amide type carbonyl absorption (5.98 μ for IIa *vs.* 6.02 μ for IIb). A mixture melting point of IIa and IIb was undepressed; both samples showed identical behavior on thin layer chromatography.

It has not been possible to obtain an n.m.r. spectrum of IIa due to the facile solvolytic conversion of IIa into IIb, even in deuteriochloroform. A time averaged spectrum of IIa in perdeuteriocyclohexane, in which the compound is barely soluble at room temperature, afforded only the spectrum of IIb, thus indicating that the existence of IIa is limited to the solid state. Dissolution of the leuco compound (IIa) in deuteriopyridine afforded a bright yellow solution, the n.m.r. spectrum of which was identical with that of IIb in the same solvent. Both samples showed resonance absorption signals at 137 c.p.s. (3 protons, $C\text{-}CH_3$), 194 c.p.s. (2 protons, $\text{-}CH_2\text{-}$), and 745 c.p.s. (broad, 1 proton, -NH-), as well as signals for the 3 pyridine ring protons.

The addition of 1 or 2 drops of deuterium oxide to a solution of IIa or IIb in deuteriopyridine intensified and deepened the yellow color and brought about a shift of the methylene peak from 194 c.p.s. to 115 c.p.s. This resulting n.m.r. spectrum would be consistent with the presence of a third tautomeric form of II in solution. Recovery of pure IIb from the n.m.r. sample established that the rearranged spectrum was not due to some decomposition product. The shift of the methylene signal from the downfield to the upfield side of the methyl peak may be accounted for by the formation of the enolic hydroxyl group in structure IIc, which would result in less deshielding of the methylene function as compared with the keto group of IIb (8).

In the absence of solvent, reaction of I with ethyl acetoacetate was found to yield the isomeric diazepine derivative (III), which was obtained as an inseparable tautomeric mixture of 1,3- and 1,5-dihydro-4-methyl-2*H*-pyrido-[2,3-*b*][1,4]diazepin-2-one. Compound III, m.p. 195-197°, resulted when a mixture of I and excess ethyl

acetoacetate was immersed for 15 minutes in a bath preheated to 185°. *Anal.* Found: C, 61.69; H, 5.01; N, 23.81. Also obtained from this reaction were small quantities of II and 1,3-dihydro-3-isopropenyl-2*H*-imidazo[4,5-*b*]-pyridin-2-one (VI) (3). Compound III showed λ max (ethanol), mμ (ε) 230 (15,700), 250 (8,600), and 310 (4,600). In contrast to II, III could not be obtained in a colorless modification. The n.m.r. spectrum of III (9) indicated the existence of 2 tautomeric forms in approximately a 3:1 ratio. The predominant tautomer, IIIa, was distinguished by the presence of the methyl group at 115 c.p.s., which appeared as a doublet (J~0.5 c.p.s.) as a result of spin-spin coupling with the adjacent vinyl proton. The vinyl proton appeared as a poorly resolved multiplet at 297 c.p.s (J~4 c.p.s.). Tautomer IIIb, to which the color of the mixture can probably be ascribed, was distinguished by resonance signals at 141 (singlet, C-CH_3) and 196 (singlet, -CH_2-) c.p.s., which spectrum is quite similar to that of IIb and of the corresponding dihydro-1,5-benzodiazepinone (8).

The mechanism of the cyclization reaction leading to II and III is presently under study, as is the extension of the scope of the reaction to include other β-ketoesters and other heteroaromatic *o*-diamines (10).

REFERENCES

(1) This investigation was supported in part by research grant C6516 and research career development award K3-CA-22, 151 from the National Cancer Institute, National Institutes of Health, U.S. Public Health Service.

(2) R. Barchet and K. W. Merz, *Tetrahedron Letters*, 2239 (1964). The authors mention the reaction of 2,3-diaminopyridine with ethyl benzoylacetate and ethyl 3-nicotinoylacetate and, avoiding the question of alternate possibilities of cyclization, arbitrarily assign to the products structure IIa, in which the 2-methyl group is replaced by phenyl and 3-pyridyl, respectively.

(3) The identity of this material, as established by alternate synthesis, and the nature of its origin in the reaction mixture will be discussed in a subsequent report.

(4) N.m.r. spectra were obtained by means of a Varian A-60 spectrometer, equipped with a variable temperature controller, with tetramethylsilane as the internal reference; the solvent was anhydrous deuteriopyridine, stored over Linde 4A molecular sieves. The time averaged spectrum, where indicated, was obtained by means of a Japan Electron Optics Laboratory Company JRA-1 Spectrum Accumulator.

(5a) Diazotation of IV in dilute acid afforded an unstable diazonium intermediate which readily eliminated nitrogen gas and which failed to couple with α-naphthol. This behavior is consistent with that of 2-aminopyridine and its derivatives, which, on diazotization, readily give α-pyridones, whereas 3-aminopyridines behave like aniline and afford diazonium intermediates which are stabilized by aromatic resonance and which couple with α-naphthol to give deep red colored arylazo adducts; (b) Comparison of the *p*H values of equimolar solutions (0.03 *M*) of 2-aminopyridine, 3-aminopyridine, I, and IV, determined in 50% aqueous ethanol solution, showed IV (*p*H 8.1), with an expected reduced basicity due to the vinylogous amide function at position 3, to be of the same order of basicity as 2-aminopyridine (*p*H 8.5); had this alkylation occurred at the 2-amino group, the remaining free amino function at position 3 would have been expected to have imparted a basicity closer to that of 3-aminopyridine (*p*H 9.5) and I (*p*H 9.4); (c) The broad 2 proton signal at 385 c.ps. in the n.m.r. spectrum of IV occurred in the signal range which we associate with an amino group at position 2 of pyridine. Based on a study of a selected number of aminopyridines, it has been found that, in deuteriopyridine, a 2-amino function commonly is found downfield of 300 c.p.s., whereas a 3-amino group is located upfield of this value (unpublished observations in these laboratories).

(6) We know of only one other mention in the literature of stable, easily interconvertible tautomers: R. C. Fuson, W. D. Emmons, and G. W. Parshall [*J. Am. Chem. Soc.*, 76, 5466 (1954)] characterized the keto and enol tautomers of 6-*t*-butyl-4-keto-1-cyclohexenyl duryl ketone, the tautomeric forms of which could be produced by proper selection of crystallizing solvent. We thank Professor Ernest I. Becker of the University of Massachusetts at Boston for bringing this reference to our attention.

(7) The imino tautomer IIb is considerably less soluble than the enamine IIa: prolonged boiling of IIb with cyclohexane was necessary to effect solution, from which IIa was obtained upon cooling. This observation parallels the solubility behavior noted by Fuson, Emmons, and Parshall for their enol tautomer in petroleum ether; the keto form was recovered from the resulting petroleum ether solution (reference 6).

(8) In connection with this project, we prepared the corresponding dihydro-1,5-benzodiazepine *via* condensation of *o*-phenylenediamine with ethyl acetoacetate according to the procedure originally described by W. A. Sexton [*J. Chem. Soc.*, 303 (1942)]; the correct structure assignment of this product was made by J. Davoll [*J. Chem. Soc.*, 308 (1960)]. On examination of the n.m.r. spectrum and other physical properties, we observed tautomeric behavior of the benzodiazepine derivative similar to that of compound II. The existence of tautomeric forms of the dihydro-1,5-benzodiazepinone has not been previously recognized.

(9) The n.m.r. spectrum of III was obtained at 70°.

(10) We thank Dr. Kurt L. Loening, Director of Nomenclature, Chemical Abstracts Service, for assistance in ascribing correct nomenclature to the bicyclic pyrido derivatives described herein.

Received July 11, 1967 Boston, Massachusetts 02115