Midwest Research Institute

A New Heterocyclic Ring System. Pyrimido[4,5-b]diazepine (1)

Wayne H. Nyberg, C. Wayne Noell and C. C. Cheng

Sir:

Although 1H-1,5-benzodiazepine has been known since the beginning of this century (2), the corresponding pyrimido[4,5-b]diazepine (I), which is closely related to purines and pteridines (3), has not yet been synthesized. Chatterjee, Trites and Modest in 1959 (4) claimed the synthesis of several compounds of this type, but each product was reported as a hydrate. These compounds were later found by the same authors to be substituted but uncyclized pyrimidines (5).

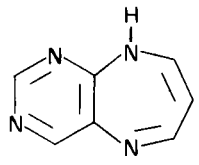
We now wish to report the first compound synthesized in the pyrimido[4,5-b]diazepine series: A mixture of 5.5 g. (0.050 mole) of 4,5-diaminopyrimidine (6) and 9.75 g. (0.075 mole) of ethyl acetoacetate in 400 ml. of xylene was refluxed for 5 hr. with stirring, during which time the color of the suspension gradually changed from light gray to yellow. The reaction mixture was cooled, the yellow solid filtered and washed repeatedly with hot ethanol to give 3.35 g. (38.1% yield) of analytically pure 4-methyl-2-oxo-1,2-dihydropyrimido[4,5-b]diazepine (II), m.p. 250-252° dec., λ max (*p*H 1) 284 mμ (ε, 9,200); λ max (*p*H 11) 240 (ε, 9,900); 310 mμ (ε, 3,700); λ max (ethanol) 229 (ε, 14,100); 254 (ε, 9,600); 306 mμ (ε, 3,000).

Anal. Calcd. for $C_8H_8N_4O$: C, 54.5; H, 4.57; N, 31.8. Found: C, 54.7; H, 4.80; N, 31.5.

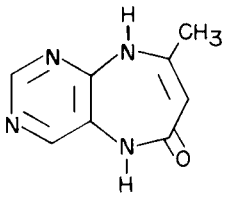
The product was also obtained, in lower yield, in refluxing xylene containing a small amount of sodium hydroxide.

Compound II was undoubtedly cyclized through the intermediate IV, which was in turn formed by the condensation of the ester moiety of ethyl acetoacetate and the amino group at the 5-position of the pyrimidine ring (7), with the elimination of one molecule of ethanol. The possibility of formation of an alternate condensation product V, which eventually should yield the isomeric diazepine III on cyclization, has been ruled out by the following evidence: Paper chromatographic measurements for the product in three solvent systems gave only one spot (8). Elementary analysis of an off-white solid (C, 49.6; H, 5.16; N, 29.1), m.p. 221-225° dec., isolated from the ethanol washings, unquestionably indicated that the intermediate was IV (calcd. for $C_8H_{10}N_4O_2$: C, 49.5; H, 5.18; N, 28.9) rather than V (calcd. for $C_{10}H_{14}N_4O_2$: C, 54.0; H, 6.35; N, 25.2).

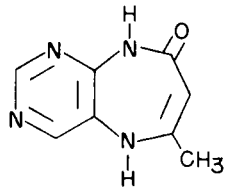
The structure of the cyclized compound II was further confirmed by means of nuclear magnetic resonance studies (9). The methyl protons appeared at δ = 1.87 ppm and a single peak for ring -CH=C= was noted at δ = 4.58 ppm. Two single sharp peaks for ring -CH=N- hydrogens were observed at δ = 8.03 and 8.30 ppm, respectively. A broad N-H



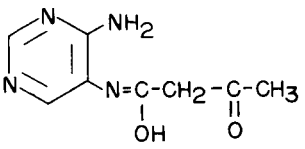
I



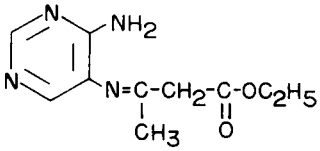
II



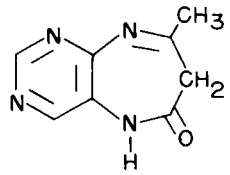
III



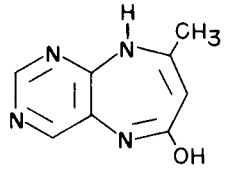
IV



V



VI



VII

absorption is indistinctly split into two peaks, separated from each other about 0.2 ppm). The integral spectra showed protons in the proportions of 3:1:1:1:2 (the proportions being given in the order of increasing chemical shift). The calculation of integral spectra and peak positions clearly show the presence of one CH_3-, three -CH=, and two -NH- protons, which is in complete agreement with structure II assigned for the product. The n.m.r. information also indicates that the product in dimethylsulfoxide is actually in the form of II and not in other tautomeric forms (such as VI and VII).

The scope of cyclization and preparation of other pyrimido[4,5-b]diazepines are currently under active investigation.

REFERENCES

(1) This investigation was supported by the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Public Health Service, Contract PH-43-65-94.

(2) J. Thiele and G. Steimmig, *Ber.*, 40, 955 (1907).

(3) The transformation of purines to pteridines, of pteridines to purines, of 1,4-benzodiazepines to quinazolines, etc., have been reported. See, for example, (a) W. S. McNutt, *J. Biol. Chem.*, 210, 511 (1954); (b) A. Albert, *Biochem. J.*, 65, 124 (1957); (c) W. Pfleiderer, *Ber.*, 92, 2468 (1959); (d) W. S. McNutt, *J. Am. Chem. Soc.*, 83, 2303 (1961); (e) L. H. Sternbach, E. Reeder, A. Stempel and A. I. Rachlin, *J. Org. Chem.*, 29, 332 (1964); (f) W. S. McNutt and S. P. Damle, *J. Biol. Chem.*, 239, 4272 (1964).

(4) S. Chatterjee, D. H. Trites and E. J. Modest, *Abstr. Papers* 136th Meeting, American Chemical Society, Atlantic City, September 1959, 34-0.

(5) S. Chatterjee, D. H. Trites and E. J. Modest, *Nature*, 203, 970 (1964).

(6a) O. Isay, *Ber.*, 39, 255 (1906); (b) D. J. Brown, *J. Appl. Chem.*, 2, 239 (1952).

(7) For the relative basicity and the reactivity of 4-amino and 5-amino groups in a pyrimidine ring system, see (a) D. J. Brown, "Pyrimidines", Interscience Publishers, Inc., New York, N. Y., 1962, p. 324; (b) G. W. Kenner and A. Todd, in R. C. Elderfield's "Heterocyclic Compounds", John Wiley and Sons, Inc., New York, N. Y., 1957, Vol. 6, p. 307.

(8) Rf values of the product in the following three systems (all measured at 25° on Whatman No. 1 paper, descending) are 0.65, 0.81 and 0.60, respectively: (a) 5% ammonium bicarbonate, (b) methanol-formic acid-water, 15:3:1 (v/v), (c) butanol saturated with 2N aqueous ammonia.

(9) The spectrum was run on a Varian A-60 high resolution n.m.r. spectrometer. The compound was dissolved in d_6-DMSO. The positions of all peaks are referred to the d_5-DMSO peak (which occurs in d_6-DMSO as a minor impurity). These are in turn corrected to the chemical shift of d_5-DMSO peak (δ = 2.52 ppm) in $CDCl_3$, with reference to tetramethylsilane. The authors thank Dr. James J. Downs of our Institute for n.m.r. discussions.

Received March 16, 1965 Kansas City, Missouri 64110