Seven-membered N-Heterocycles. XV.[1]

Ethyl 2-Phenyl-7H-pyrimido[4,5-d]azepine-7-carboxylate

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The title azepine (6) was derived from the 6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepine (2) via 6,7-dihydro-5H-derivative (3a) by the stepwise dehydrogenation. The 8,9-dihydro-7H-pyrimido-azepine (4a) was also prepared. The structures are discussed on the basis of uv, ir, and nmr spectra.

Azepine derivatives and those fuzed with aromatic rings are of interest in view of their expected antiaromatic character, and they have been synthesized mainly by ring expansion or valence bond isomerization.[2] The thermal and chemical lability of these azepine rings has generally prevented the synthetic approach involving dehydrogenation of their partially (or fully saturated) precursors, because such reactions usually require rather drastic conditions.

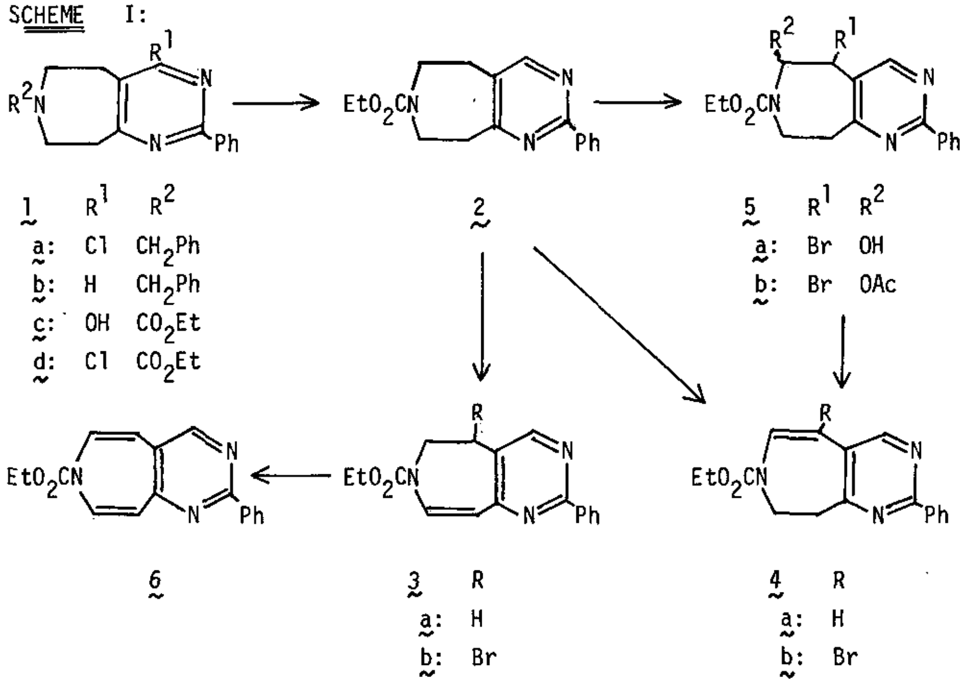
We wish to report here the first successful result, to our knowledge, of dehydrogenation of 2,3,6,7-Δ^4-tetrahydro-1H-azepine fused with π-deficient pyrimidine ring to provide a fully unsaturated azepine derivative.

In order to systematically explore dehydrogenation reaction of the tetra-hydro-azepine ring, several 2-phenyl-6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]-azepines (1b-d, 2) were presently prepared in good yields[3] according to the usual method previously described for other pyrimido-azepines.[4,5] Structures of these new azepines were assigned on the basis of elementary analyses and spectral data, which closely resembled those of the known pyrimido-azepines;[4,5] the assignment of the nmr signals of 2 is shown in Table.

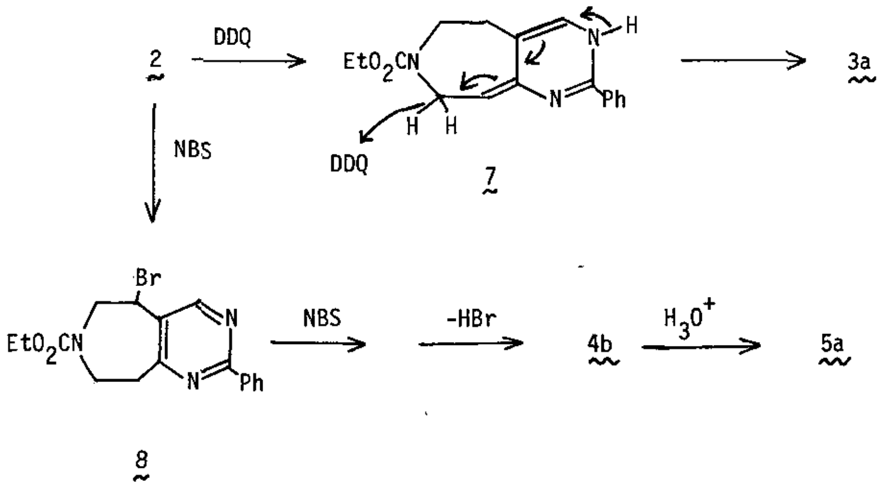
Attempts to accomplish dehydrogenation of the tetrahydro compounds 1a-d with Pd-C in boiling decalin or with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in boiling dioxane were unsuccessful; in all cases complex reaction mixture were formed, from which no products were isolated. Heating 2 with 10% Pd-C, however, produced a chromatographically separable mixture (on silica gel) of two different dihydro-pyrimido-azepines 3a (mp 116°, 10%) and 4a (oil, 5%) besides a large amount of recovered 2 (50%). A strong bathochromic shift (ca 50-60 nm) of the uv absorption maxima of these products from that of 2 suggested the presence of an additional double bond in the azepine ring. This was supported by the elementary analyses and ir and mass spectra (Table). The location of the double bond was assigned by the close comparison of the nmr signals from H(or H_2)-5 and -9 of the products 3a and 4a with those of 2;[6] see Table for the spectral assignment. The action of DDQ on 2 in boiling dioxane in contrast afforded a 35% yield of the 6,7-dihydro-5*H*-pyrimido-azepine 3a as a predominant product without giving the 8,9-dihydro derivative 4a; the most probable reason for this result will be discussed below.

The latter compound 4a on the other hand was more efficiently synthesized from 2 first by brominating with NBS (*N*-bromosuccinimide, 2 equiv. in wet CCl_4), followed by reduction (zinc powder in acetic acid, 60°C) of the resulting 5a (mp 110-113°) in a 50% overall yield. This bromohydrin 5a which gradually decomposes on standing even at 0° readily gave a relatively stable acetyl derivative 5b (mp 91-93°) with Ac_2O/pyridine. Another unstable bromo compound 4b (mp 89-90°), a likely intermediate for the formation of 5a, could be isolated in a low yield (15%) upon treatment of 2 with NBS in dry CCl_4 and was confirmed

SCHEME I:



SCHEME II:



to produce 5a in wet CCl_4 in the presence of a catalytic amount of acid such as benzoic acid.

Further prolonged heating of the dihydrocompounds 3a and 4a with DDQ in dioxane to introduce another double bond in the azepine ring has so far resulted in gradual decomposition, giving no isolable products. Compounds 5a, 5b, and 4b also readily decomposed under the similar conditions. However, the 7H-pyrimido-azepine 6 (orange prisms, mp 104°) was successfully synthesized by converting 3a into the unstable mono-bromo compound 3b (mp 122-123°) (NBS in dry CCl_4), which in turn was dehydrobrominated with DBU (1,8-diazabicyclo[5.4.0]-7-undecene) in benzene (50% overall yield).

Structures of these pyrimido-azepines 3b, 4b, 5a, 5b, and 6 were determined on the evidence of their spectral data (see Table) and supported by elementary analyses. Uv spectrum of 6 which resembles those of 3H-benz[d]azepines[7] had a weak absorption at a long wavelength charactristic of 1H-azepine ring system.[2,7] It is worth noting that the nmr signals from azepine ring protons and H-4 of the dihydro compounds 3a, 3b, and 4a shifted up-field (ca 0.5 ppm) when the azepine ring was led to the fully unsaturated structure as in 6.

Scheme II illustrates a probable reaction pathway for the formation of the dihydro-azepines 3a and 4b from 2. The C-9 methylene group of 2 (which is α- and γ- to the pyrimidine ring nitrogens) is expected to be more acidic than that of C-5.[8] Thus the dehydrogenation reaction of 2 is supposed to proceed through the abstruction of a hydride ion at C-8 of a tautomer 7 and analogous to the mechanism proposed for dehydrogenation of cyclic ketones via more rapidly formed enol.[9] Bromination of 4,5-dimethylpyrimidines with NBS has been known to give 5-bromomethyl-4-methylpyrimidines.[10] This would account for the preferable bromination of 2 with NBS at the 5-position, initially yielding 8, which was probably converted into 5a via 4b.

TABLE Spectral Data for Some of the Pyrimido-azepines

Compd.	^{1}H-Nmr: δ -Values a) for					Uv(EtOH) λ$_{max}$ nm (log ε)	Ir (CHCl$_3$) ν cm.$^{-1}$	Mass m/e(%)
	Ph-2	H-4	H-5 (H-9)	H-6 (H-8)	EtO$_2$C-7			
2	7.45m b) 8.35m c)	8.50s	2.9m c) (3.3m) c)	3.6m c) (3.6m) c)	1.30t b,d) 4.25q c,d)	261(4.38)	1680	297(M^+, 100)
3a	7.5m b) 8.5m c)	8.47s	3.0m c) (6.01d) e)	4.1m c) (7.56d) e)	1.37t b,d) 4.35q c,d)	268(4.50) 316(4.29)	1720 1625	295(M^+, 100)
3b	7.5m b) 8.5m c)	8.60s	5.05m (6.04d) e)	3.49d f) 5.45d d) (7.50d) e)	1.39t b,d) 4.40q c,d)	277(4.48) 317(4.00)	1710 1610	375(M^+, 10) 373(M^+, 10) 294(100)
4a	7.5m b) 8.5m c)	8.59s	5.58d e) (3.3m) c)	7.26d e) (4.1m) c)	1.36t b,d) 4.32q c,d)	325(4.40)	1720 1635	295(M^+, 100)
4b	7.6m b) 8.5m c)	9.06s	—— (3.3m) c)	7.86s (4.0m) c)	1.38t b,d) 4.30q b,d)	265(4.35) 338(4.50)		375(M^+, 100) 373(M^+, 100)
5a	7.5m b) 8.5m c)	8.72s	5.30d g) (3.4m) c)	6.31d g) 5.50s h) (3.6m) c)	1.30t b,d) 4.24q c,d)	267(4.35)	3480 1660	393(M^+, 37) 391(M^+, 37) 313(62) 312(60)
5b	7.5m b) 8.5m c)	8.58s	5.30d g) (3.4m) c)	7.20d g) 1.98s i) (3.6m) c)	1.36t b,d) 4.35q c,d)		1740 1700	435(M^+, 4) 433(M^+, 4) 295(100)
6	7.6m b) 8.5m c)	8.05s	5.22d e) (5.50d) e)	6.29d e) (6.70d) e)	1.28t b,d) 4.28q c,d)	224(4.46) 276(4.64) 336(4.00) 425(3.23)	1710 1675 1615	293(M^+, 88) 265(25) 221(50) 220(100) 194(17) 193(25)

a) 60M Hz in CDCl$_3$, ppm from TMS; the coupling was confirmed by double resonance. b) 3H. c) 2H. d) J=7 Hz. e) J=10 Hz. f) J=14 Hz. g) J=4 Hz. h) For $\underline{H}$O-6. i) For $C\underline{H}_3CO_2$-6.

Since the 7H-pyrimido-azepine 6 and its derivatives are now relatively easily available, further investigations of thermal and chemical liability of these azepines are in progress.

REFERENCES AND NOTES

1 Part XIV. H. Yamamoto, H. Kawamoto, S. Morosawa, and A. Yokoo, Heterocycles, 1979, 10, preceding paper.

2 e.g. See L. Paquette, "Nonbenzenoid Aromatics I", ed. J. P. Snyder, Academic Press New York, 1969, pp. 249-294.

3 Compound 2 was made according to the following scheme: 1a[5] → 1b (mp 123-124° in 50% yield with H_2/Pd-C in Et_3N/C_6H_6-MeOH) → 2 (mp 89°, 55% with $ClCO_2Et$) or 1c (mp 205°, 70% from diethyl hexahydro-4-oxo-1H-azepine-1,5-dicarbonate[1] and benzamidine) → 1d (mp 109°, 80% with $POCl_3$) → 2 (73% yield with H_2/Pd-C in Na_2CO_3-EtOH).

4 H. Yamamoto, M. Nakata, S. Morosawa, and A. Yokoo, Bull. Chem. Soc. Japan, 1971, 44, 153.

5 H. Yamamoto, H. Kawamoto, S. Morosawa, and A. Yokoo, Bull. Chem. Soc. Japan, 1977, 50, 453.

6 The H_2-5 signals of these tetrahydro-pyrimido-azepines without substituent at 4-position appear at higher field (ca 0.4 ppm) compared with those from H_2-9, see ref. 4 and 5.

7 I. Takeuchi, I. Ozawa, Y. Hamada, H. Masuda, and M. Hirota, Chem. Lett., 1976, 519, and references cited therein.

8 4-Methyl group of pyrimidines is generally more acidic than 5-methyl group; see W. Pfleiderer and H. Mosthaf, Chem. Ber., 1957, 90, 728.

9 See H. O. House, "Modern Synthetic Reactions", 2nd Ed, Benjamin, California, 1972, pp. 37-44, and references cited therein.

10 e.g. See D. J. Brown, "The Pyrimidines", Interscience, New York, 1962, p.131.

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