Seven-membered N-Heterocycles. XIV.[1] Syntheses of 6,7,8,9-Tetrahydro-5H-pyrido[2,3-d]azepines

Hiroshi Yamamoto,* Heizan Kawamoto, Shiro Morosawa, and Akira Yokoo
Department of Chemistry, Okayama University, Tsushima, Okayama 700, Japan

A variety of the title pyrido-azepines (5, 6) were synthesized by utilizing diethyl hexahydro-4-oxo-1H-azepine-1,5-dicarboxylate (2d) as the starting material. The structures of these new heterocyclic compounds are established by spectroscopic methods.

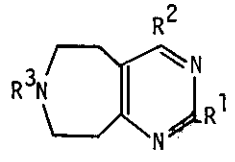
2,3,6,7-Δ^4-Tetrahydro-1H-azepines fuzed with various heterocycles have been actively synthesized in recent years mainly because of their pharmacological usefulness.[2] We have reported[1,3] the syntheses of a variety of substituted 6,7,8,9-tetrahydro-5H-pyrimido[4,5-d]azepines (1) by the condensation of N-substituted perhydro-4-oxo-azepine-5-carboxylate (e.g. 2c)[3,4] with various formamidine derivatives. The unusual rearrangement of 1 to 7H-pyrrolo[2,3-d]-pyrimidines[1] and the interesting stepwise dehydrogenation of 1 to the fully unsaturated 7H-pyrimido[4,5-d]azepines[5] have also been observed. These results prompted us to prepare the hitherto unreported Δ^4-tetrahydro-1H-azepines fuzed with a variously substituted pyridine ring (the simplest π-deficient N-heteroaromatic compound[6]) mainly for the purpose of a mechanistic study of above reactions as well as investigations of potential pharmacological activities of these compounds.

Model studies for the pyridine ring formation using readily available N-

substituted ethyl piperid-4-one-3-carboxylate (2a,b)[7-9] to synthesize several hitherto unknown 5,6,7,8-tetrahydro-1,6-naphthyridine derivatives were encouraging. Thus, on simply heating with ammonium hydroxide in ethanol, the β-keto esters 2a and 2b, which exist mostly as the enol forms (2'; by nmr),[10] were first converted into the enamino ester compounds 3a (bp 190°/0.4 mmHg, 50% yield) and 3b (mp 54-55°, 87%),[11,12] respectively, which in turn were led to the 1,6-naphthyridines 4a (mp 183°, 54%) and 4b (mp 194-195°, 56%), respectively, upon refluxing with diethyl malonate and sodium ethoxide in absolute ethanol according to the method of Prelog et al with a slight modification.[13]

The starting materials (2c,d)[3,4,10] for the preparation of the corresponding pyrido-azepines are now made more conveniently in increased yields by modifying the previous method.[14,15] Although the enamino ester 3d was isolated as a rather unstable colourless solid,[12] mp 75-76°, in 76% yield upon treatment of 2d with ethanolic ammonia at 60° in a sealed tube, the benzyl compound 3c could not be isolated due to facile decomposition when the same method was used for 2c.[16] The 6,7,8,9-tetrahydro-5H-pyrido[2,3-d]azepine (5a, mp 204°) was then best obtained upon refluxing 3d with diethyl malonate and sodium ethoxide either in dimethoxyethane containing HMPA (40-45% yield) or in absolute ethanol (30-40%). Heating 4a, 4b, and 5a with 2 N hydrochloric acid afforded 4c (mp 273-275°, 91%), 4d (mp 276-277°, 88%), and 5b (mp 260°, 88%), respectively.

Refluxing 5a with an excess phosphorous oxychloride in the presence of $PhNEt_2$ for 3 hr predominantly gave the 2,4-dichloropyrido-azepine (6a), mp 194-195°, in 50% yield. Without using the catalyst in the above replacement reaction, a mixture of 6a (35%) and the monochloro compound (5c, mp 174-175°, 19%) was produced. The latter was gradually converted to 6a on prolonged heating with $POCl_3$, thus showing the reaction to proceed stepwise. The com-



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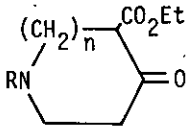
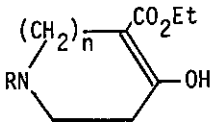
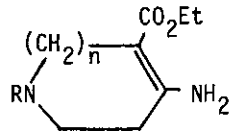


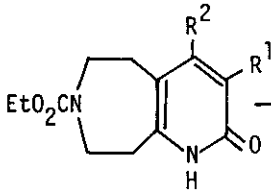


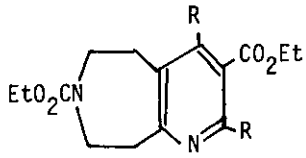
2	n	R	2'
a:	1	CH_2Ph	(100%)[a]
b:	1	CO_2Et	(100%)[a]
c:	2	CH_2Ph	(35%)[a]
d:	2	CO_2Et	(20%)[a]



3	n'	R
a:	1	CH_2Ph
b:	1	CO_2Et
[c:	2	CH_2Ph]
d:	2	CO_2Et

(n=2)

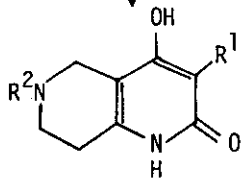




5	R^1	R^2
a:	CO_2Et	OH
b:	H	OH
c:	CO_2Et	Cl
d:	H	Cl
e:	CO_2Et	H
f:	H	H

6	R
a:	Cl
b:	H

(n=1)



4	R^1	R^2
a:	CO_2Et	CH_2Ph
b:	CO_2Et	CO_2Et
c:	H	CH_2Ph
d:	H	CO_2Et

SCHEME I

a) See Ref. 10.

pound 5b was similarly chlorinated with boiling $POCl_3$, giving the 4-chloro-2-pyridone (5d, mp 194°, 22%) as the only isolable product even in the presence of the catalyst; prolonged heating resulted in the gradual decomposition of the products, affording a large amount of an intractable tar.

The lability of the chlorine atom in 5c, 5d, and 6a was demonstrated by the facile hydrogenation over Pd-C to give the compounds 5e (mp 152-153°, 70%), 5f (mp 178-179°, 89%), and 6b (mp 64-65°, 67%) respectively.

The structures of these fuzed pyridines 4a-d, 5a-f, and 6a,b were assigned on the basis of elementary analyses[11] and the spectral data shown in Table. The uv absorption maxima of compounds 4a-d and 5a-f, which resembled closely those of similar 4-hydroxy-2-pyridones,[17] supported the 2-pyridone structure (rather than the 2,4-dihydroxy form) as shown in Scheme 1. A strong hypsochromic shift (ca 40 nm) of the long wavelength absorption maxima of 6a and 6b from those of 5a, 5c, and 5e indicated the absence of the 2-pyridone form in 6.[18] The nmr spectrum of 6b showed two doublets due to the aromatic ring protons at δ 8.90 and 8.00 (1H each, J=2 Hz), while that of 5e showed only a singlet at δ 8.00 (1H), thus making the signal at δ 8.90 (of 6b) assignable to H-2. This is in conformity with the known values of a structurally similar compound such as ethyl nicotinate, of which signals from H-2 and H-4 appear at δ 9.20 and 8.20 (J=2 Hz), respectively.[19] Other assignments of the nmr signals illustrated in Table were made by carefully comparing signals of each compounds with those of structurally related pyrido-azepines obtained presently and also with those of the tetrahydropyrimido-azepines 1.[1,3,5]

These tetrahydro-pyrido-azepines 5 and 6 thus synthesized easily from readily available starting material are considered to be of interest especially with regard to their chemical reactivities, which are currently under investigation.

TABLE Spectral Data for the 1,6-Naphthyridines and the Pyrido-azepines

Compd.	^{1}H-Nmr: δ-Values[a] for H-2 (H-4)	H-3	H_2-5 (H_2-9)	H_2-6,8 (H_2-7)	EtO_2-7 (EtO_2-6)	Uv (EtOH) λ_{max}^{nm} (log ε)	Ir ($CHCl_3$) ν $cm.^{-1}$
4a	13.6m[b] (12.4m)[e]	1.38t[c] 4.40q[c]	3.43s[f] (2.8m)	(2.8m)	(3.73s)[d] (7.32s)[d]	225(4.46) 318(3.99)	3400-2300 1660-1630
4b	13.7m[b] (12.5m)[e]	1.41t[c] 4.41q[c]	4.37s[f,g] (2.7t)	(3.7t)[g]	(1.29t)[c] (4.18q)[c]	289(3.82) 313(3.68)	3400-2300 1710,1660,1640
4c	h)	6.73s	4.70s[f] (3.5m)	(4.2m)	(4.60s)[d] (7.55s)[d]	286(3.85)	3600-2300 1650-1610
4d	h)	6.72s	4.70s[f,g] (3.0t)	(4.0t)[g]	(1.43t)[c] (4.40q)[c]	285(3.80)	3400-2300 1675,1605
5a	13.8m[b] (12.7m)[e]	1.42t[c] 4.42q[c]	2.8m (3.0m)	3.6m	1.28t[c] 4.17q[c]	227(4.32) 323(4.00)	3400-2300 1690,1650,1630
5b	h)	6.66s	3.0m (3.2m)	3.8m	1.35t[c] 4.30q[c]	242(3.76) 288(3.90)	3400-2300 1680,1640
5c	13.6m[b] (——)	1.38t[c] 4.45q[c]	2.9m (3.1m)	3.6m 3.6m	1.28t[c] 4.19q[c]	237(3.76) 326(4.05)	3400-2300 1725,1685,1640
5d	10.0m[b] (——)	6.54s	2.9m (3.1m)	3.6m	1.26t[c] 4.16q[c]	238(3.83) 318(8.91)	3400-2300 1680,1640
5e	(8.00s)	1.33t[c] 4.33q[c]	2.8m (3.1m)	3.6m	1.28t[c] 4.19q[c]	242(3.91) 345(4.03)	3400-2300 1725,1680,1640
5f	(7.28d)[i]	6.31d[i]	2.8m (3.0m)	3.6m	1.24t[c] 4.17q[c]	235(4.02) 315(3.94)	3200-2300 1680, 1645
6a	—— (——)	1.40t[c] 4.45q[c]	3.1m (3.2m)	3.6m	1.29t[c] 4.18q[c]	280(3.70)	1730,1685
6b	8.90d[j] (8.00d)[j]	1.40t[c] 4.39q[c]	3.0m (3.2m)	3.6m	1.29t[c] 4.18q[c]	285(3.79)	1715,1685

a) 60 M Hz in $CDCl_3$ except for 4c, 4d, and 5b (in CF_3CO_2H), ppm from TMS.

b) For H-1. c) For $CH_3CH_2O_2C$; the coupling was confirmed by double resonance, J=7 Hz. d) For $C_6H_5CH_2$-6. e) For HO-4. f) For H_2-8. g) J=6 Hz. h) Overlapped with the solvent signal at δ ca. 11. i) J=9 Hz. j) J=2 Hz.

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10 The enol percentage in equilibrium of 2 and 2' in CCl_4 are indicated in parentheses.

11 Satisfactory figures of the elementary analyses have been obtained for all new compounds reported in this communication.

12 The enamino structures of 3 were established by ir and nmr spectra.

13 V. Prelog and S. Szpilvogel, Helv. Chem. Acta, 1945, 28, 1968, and references cited therein for the preparation of 2,3-cycloalkanopyridines.

14 The preparation of 2c was carried out under N_2 at below -60° for a longer period (6-7 hr) using 1.5 equiv. of $BF_3 \cdot OEt_2$ and 1.6 equiv. of freshly prepared ethyl diazoacetate. Thus 57 g (0.3 mol) of 1-benzylpiperid-4-one

yielded constantly 53 g (56%) of 2c (HCl salt) as colourless, stable leaflets (from EtOH), mp 168° dec. (lit.[4] mp 164.5° dec., 34%).

15 The ethoxycarbonyl compound 2d formerly prepared by the ring expansion of piperid-4-one-1-carboxylate (30% yield)[4] is now made in 70-80% yield upon refluxing 2c with an excess ethyl chlorocarbonate in dry benzene.

16 The six-membered enamino esters 2a and 2b were apparently much more stable than the seven-membered compounds 2c and 2d, which appeared to affect the yield of the products 4 and 5; a systematic examination of the reactivities with regard to the ring size are under consideration.

17 e.g. See ref. 6, p. 96 and 386.

18 For review, see J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, "The Tautomerism of Heterocycles", Academic Press, New York, 1976, pp. 71-213.

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