REACTION OF LACTIM ETHERS WITH CARBOETHOXYMETHYL PIPERIDINES A SYNTHESIS OF 1,9-DIAZASTEROID

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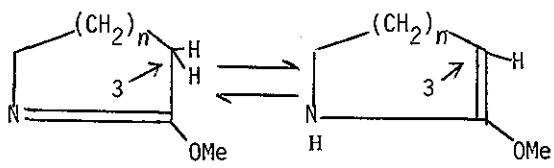
Imine-enamine tautomerization was observed in methyl valelolactim (2) and methyl caprolactim (3), whereas rarely in methyl butyrolactim (1) on NMR. The evidence for the tautomerization was elucidated also by the chemical behaviors of the lactim ethers towards cyclic β-aminoesters such as, 2-carboethoxymethyl piperidine derivatives, which often gave two kinds of products probably resulted from both the imine and the enamine forms. This was applied to a synthesis of the 1,9-diazasteroid.

Lactim ethers have widely been employed as activated lactims for the syntheses of heterocyclic systems.[1,2] Granik et al suggested the presence of imine-enamine tautomeric equilibrium in O-ethylvalerolactim in alcoholic solution.[3] Therefore, we examined the existence of the tautomeric equilibrium (imine $\rightleftharpoons$ enamine) of lactim ethers (1), (2) and (3) in CD_3OD (NMR spectra).

As given in table I, (1) is shown to exist only in its imine form, whereas



(1) n=1 methyl butyrolactim
(2) n=2 methyl valerolactim
(3) n=3 methyl caprolactim

(imine) (enamine)

(2) and (3) in both imine and enamine forms. Actually, all examples using (1)are known to react exclusively in the imine form and the reactions employing (2) and (3) also proceeded in the imine fashion in spite of the coexistence of the enamine form.[4]

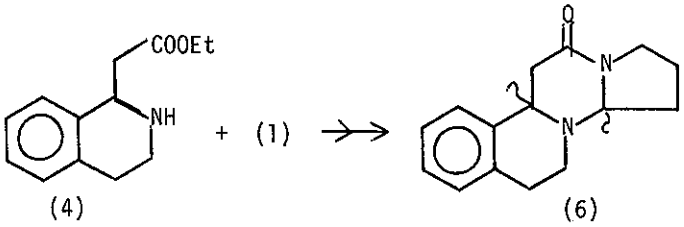
Table I*

	(1)	(2)	(3)
a)	2.5	2.2	2.4
b)	~0%	~65%	~10%

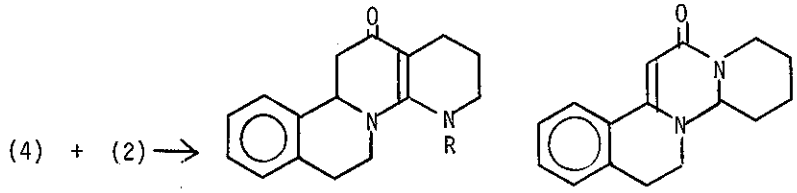
a) Chemical shift of 3-hydrogens (δ) ppm
b) Decrease (%) in integral values of 3-hydrogens on the deuteration after 9 days on NMR

* Solutions of (1),(2) and (3) in 15% (w/v) CD_3OD were kept at room temperature for 9 days, respectively[3]

On the other hand, we found that lactims (2) and (3) reacted with 2-carboethoxymethyl piperidines (4) and (5) to furnish the products attributed to both enamine and imine forms. Previously one of the authers (T.Y.) reported the sythesis of 8,13-diazasteroid (6) by the reaction of 1-carboethoxymethyl-1,2,3,4-tetrahydroisoquinoline (4) with (1), which actually reacted in the imine form.[5] The annelation reaction of (2) with (4) (at 100°C for 10 days) gave the compound (7) in the enamine fashion and compound (8) in the imine fashion in 65% yield and 7% yield, respectively. The structure of (7) is characterized as its dehydrogenation product (9) derived from mercuric acetate oxidation or its acetate (10). Similiar reaction using (3) afforded (11) (1.2%), (12) (44%) and (13)[6](13%), which showed the

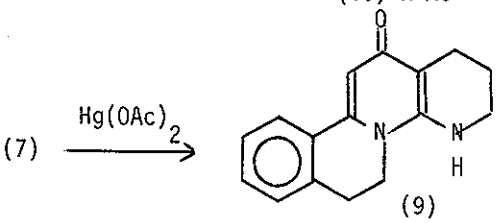


(4) (6)

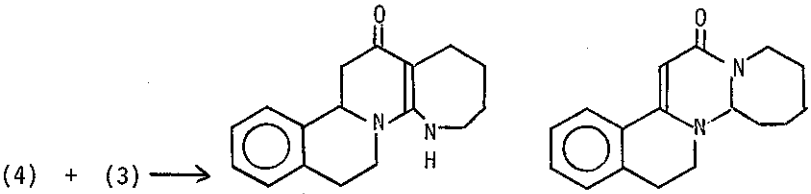


(7) R=H
(10) R=Ac

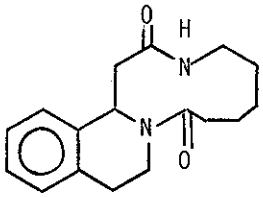
(8)



(9)



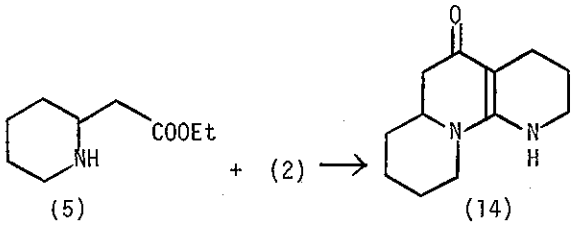
(11) (12)

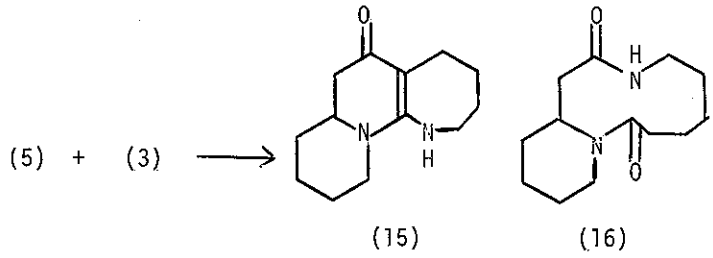


(13)

the spectral data as in Table II.

Furthermore, the same annelation of (2) with 2-carboethoxymethyl piperidine (5) proceeded smoothly to furnish only (14) in 54% yield , which that of (3) gave (15) in 26% yield and (16)[6] in 13% yield. Imine-enamine tautomerization in (2) and (3) was thus ascertained from the products mentioned above.





Next, a synthesis of the 1,9-diazasteroid was undertaken as an application of the annelation employing (2), which reacted with the compound (17)[7] as C-D ring segment to afford 1,9-diazagona-5(10),13-dien-6-one (18) as a sole product in 20% yield attributed to the enamine form.

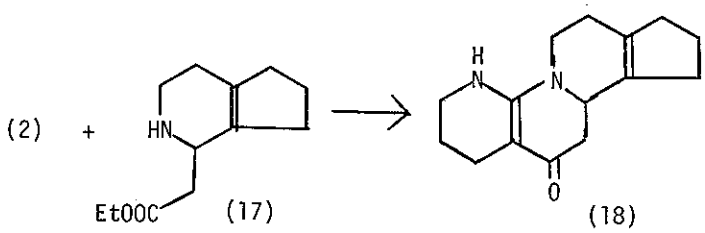


Table II[7]

Compd.	mp (°C)	IR (KBr) ν cm^{-1}	UV (EtOH) nm (ε)	NMR ($CDCl_3$) δ ppm
(7)	324	3240,1580	309 (19000)	
		1560	238 (10000)	
(8)	166	1620,1590	366	5.3 (s,CH=C)
		1550	252	
(9)	314	3160,1620	308	6.6 (s,CH=C)
		1580,1550	249	6.2 (NH)
(10)	141	1660,1640		2.2 (s,N-Ac)
		1590,1570		
(11)	300	3280,1570	316	
		1550,1490	240	
(12)	162	1620,1590	358 (5000)	5.4 (s,CH=C)
		1550	252 (10800)	
(13)	145	3380,1640		8.1 (NH)[a]
		1620,1550		
(14)	292	3240,1580	308 (17000)	
		1560,1500	239 (7200)	
(15)	247	3280,1580	318 (22000)	
		1560,1490	228 (8600)	
(16)	172	3300,1660		6.1 (NH)
		1610,1550		
(18)	274	3240,1580	308 (16000)	3.8 (C_8-H)[b]
		1560,1500	235 (7000)	

a) (DMSO-d_6) b) (CD_3OD)

REFERENCES AND NOTES

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2 a) D.Bormann, Chem. Ber, 1974, 107, 270.

b) B.M.Trost and R.A.Kunz, J. Am. Chem. Soc., 1975, 97, 7152.

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4 A sole example in enamine fashion. T.Kato and T.Sakamoto, Chem. Pharm. Bull. (Tokyo)., 1975, 23, 2629.

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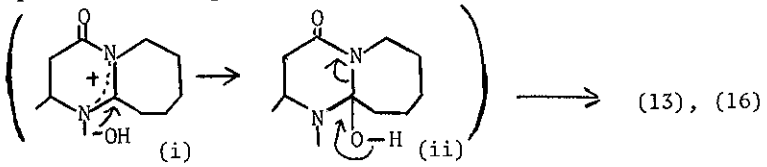
6 These products would presumably be formed as follows.



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8 Mass spectra of all compounds showed molecular ion peaks.

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