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Reaction of Lactim Thioethers with 1-Carbethoxymethyl-1,2,3,4-tetrahydroisoquinoline[1]

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In order to examine the difference in chemical properties between lactim thioethers and lactim ethers, the reaction of lactim thioethers with 1-carbethoxymethyl-1,2,3,4-tetrahydroisoquinoline (**4**) was investigated.

Keywords——lactim thioethers; lactim ethers; 2-carbethoxymethyl piperidines; annulation; imine-type products; diazasteroid

In the previous paper,[1] we described an interesting annulation reaction of lactim ethers (**1′**, **2′**, and **3′**) with cyclic β-aminoesters such as 2-carbethoxymethyl piperidine derivatives, which gave two kinds of product probably attributable to the imine and enamine forms (Chart 1). These results prompted us to examine the similar cyclization of lactim thioethers (**1**, **2**, and **3**) with 1-carbethoxymethyl-1,2,3,4-tetrahydroisoquinoline (**4**) as a 2-carbethoxymethyl piperidine in order to compare the chemical behavior of lactim thioethers with that of lactim ethers. This note describes the results.

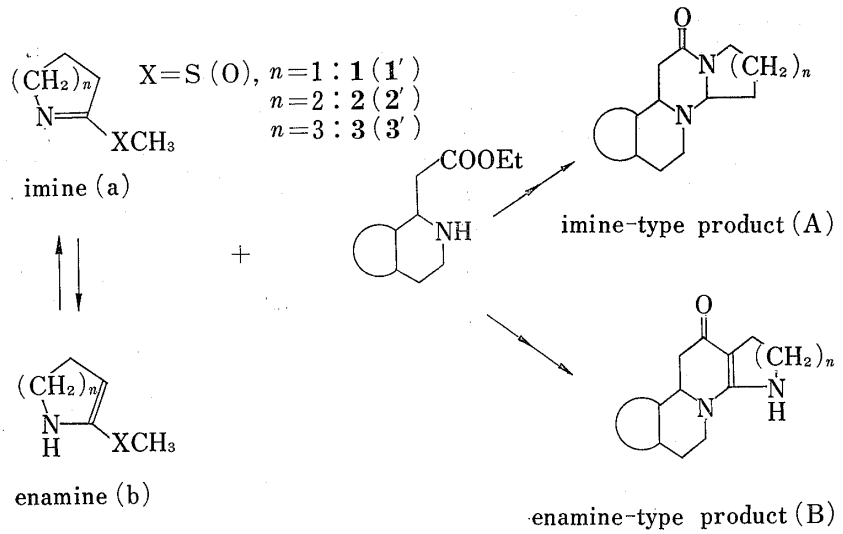

Chart 1

The reaction of **1** with **4** proceeded in a sealed tube at 100° for 48 hr to give only the imine-type product (**5**) (mp 195—196°) in 63.5% yield, the structure of which was characterized in terms of elemental composition and spectral data. In particular, the NMR spectrum of compound **5** showed a singlet at δ 5.65 indicative of the vinyl proton of a vinylogous amide group. Similarly, annulation of **1′** with **4** (100°, overnight) afforded **5** in 36.4% yield. The reduction

1) This paper forms Part III of "Chemistry of Lactim Ethers." Part II: H. Takahata, M. Ishikura, and T. Yamazaki, *Chem. Pharm. Bull.*, **28**, 220 (1980)

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of compound **5** with Adams' catalyst in AcOH furnished the 8,13-diazasteroid (**6**), previously prepared[3] by the reaction of **1'** with **4** followed by reduction with $NaBH_4$ after treatment with NaI.

Reaction of **2** with **4** (100°, 10 days) afforded exclusively the imine-type product (**7**)[4] in 81% yield. Interestingly, no enamine-type products could be obtained, though the reaction using methyl valerolactim (**2'**) gave the enamine-type product preferentially.[1] Similar annulation of **3** with **4** (100°, 14 days) also furnished the imine-type products **8**[4] and **9**[4] in 7.8% and 28.1% yields, respectively.

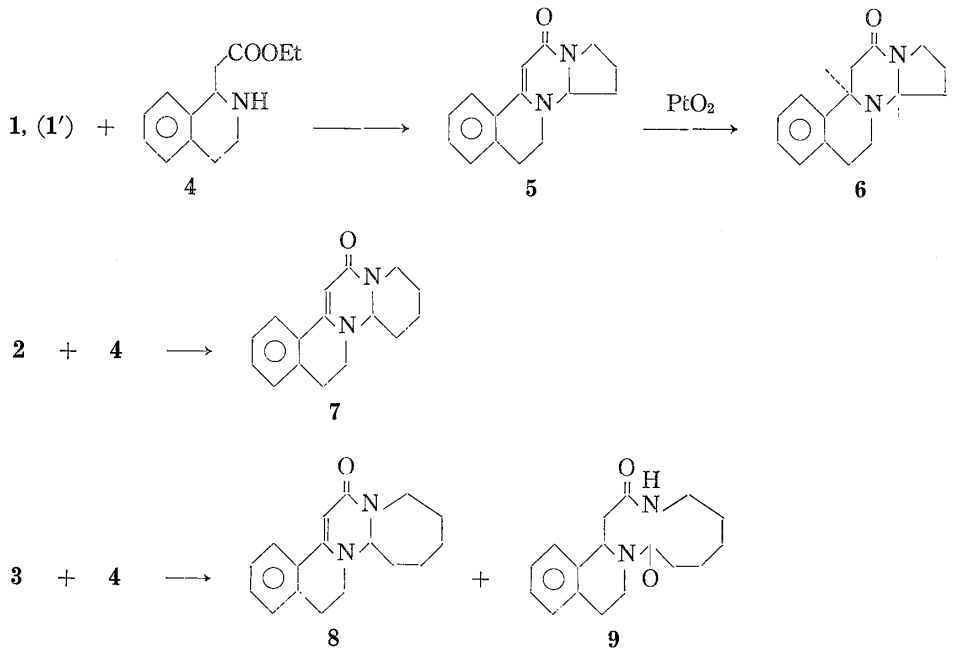

Chart 2

In conclusion, the results here presented indicate that the chemical features of lactim thioethers that differ from those of lactim ethers can be attributed to their imine forms (a).[5] We are currently studying the synthesis of 1,9- and 5,9-diazasteroids by utilizing the characteristic differences in chemical properties between **2** and **2'**. These results will be reported in due course.

Experimental[6]

Preparation of Lactim Thioethers (1, 2, and 3)——A suspension of thiolactam in dry ether was treated with excess CH_3I at room temperature for 2 hr. After completion of addition, the reaction mixture was stirred overnight. The mixture was concentrated *in vacuo* to leave a mass, which was neutralized with 10% K_2CO_3 solution. The mixture was extracted with ether. The extract was dried over anhyd. $MgSO_4$ and concentrated *in vacuo* to give an oil, which was distilled under reduced pressure to give **1**, bp 98° (25

3) T. Koizumi, Y. Yanagawa, E. Yoshii, and T. Yamazaki, *Chem. Pharm. Bull.*, **26**, 1308 (1978).
4) These compounds (**7**, **8**, and **9**) were identical with the samples[1] prepared previously (IR and NMR data and chromatographic behavior).
5) It has been reported that treatment of **1** with arylisocyanates gave the enamine-type products, whereas **2** and **3** gave the imine-type products. U. Kraatz, *Ann. Chem.*, **1976**, 412.
6) Melting points are uncorrected. IR spectra were obtained with a Hitachi 215 spectrophotometer and NMR spectra with a JEOL C-60H spectrometer using TMS as an internal standard. UV spectra were taken with a Hitachi EPS-2T spectrometer. MS spectra were measured with a JEOL 01SG spectrometer.

mmHg), lit.[7] bp 167—169°, **2**, bp 75° (13 mmHg), lit.[8] bp 71—79° (13 mmHg), or **3**, bp 98—100° (25 mmHg), lit.[9] bp 100.5—101.5° (21 mmHg).

8,13-Diazagona-1,3,5(10),9(11)-tetraen-12-one (5)——a) A mixture of **1** (1.05 g, 9.14 mmol) and **4** (1 g, 4.57 mmol) was kept in a sealed tube at 100° for 48 hr. The reaction mixture was purified by column chromatography on silica gel, eluted with $CHCl_3$–MeOH (30: 1), to give **5** (696 mg, 63.5%), mp 195—196° (recrystallized from benzene). IR ν_{max}^{KBr} cm^{-1}: 1620. NMR ($CDCl_3$) δ: 5.65 (1H, s, C<u>H</u>=C). UV λ_{max}^{EtOH} nm (ε): 251 (18000), 346 (8000). MS *m/e*: 240 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.37. Found: C, 75.06; H, 6.48; N, 11.37.

b) A mixture of **1'** (0.90 g, 9.14 mmol) and **4** (1 g, 4.67 mmol) was heated in a sealed tube at 100° overnight. In the manner described for a) the reaction mixture afforded **4** (400 mg, 36.4%), which was identical with the above sample (IR and NMR data and TLC).

8,13-Diazagona-1,3,5(10)trien-12-one (6)——Compound **5** (500 mg, 2.08 mmol) was hydrogenated over PtO_2 (100 mg) in AcOH (50 ml) at room temperature under a preseure of 4 atmospheres. The mixture was then filtered to remove the catalyst and the solvent was evaporated off *in vacuo*, giving an oil, which was neutralized with saturated $NaHCO_3$ solution. The mixture was extracted with CH_2Cl_2. The extract was dried over anhyd. $MgSO_4$ and concentrated *in vacuo* to afford **6** (309 mg, 61.4%), mp 191—193°. lit.[3] 197°, which was identical with the sample[3] prepared previously as regards spectral data.

Reaction of 2 with 4——A mixture of **2** (1.18 g, 9.14 mmol) and **4** (1g, 4.57 mmol) was kept in a sealed tube at 120° for 12 days. The reaction mixture was purified by column chromatography on silica gel, eluted with $CHCl_3$–MeOH (30: 1), to give **7** (940 mg, 81.1%), mp 166°[4].

Reaction of 3 with 4——A mixture of **3** (1.13 g, 9.14 mmol) and **4** (1 g, 4.67 mmol) was kept in a sealed tube at 100° for 14 days. The reaction mixture was separated by column chromatography on silica gel, eluted with $CHCl_3$–MeOH (30: 1), to afford **8** (95 mg, 7.8%) and **9** (365 mg, 28.1%). **8**,[4] mp 160—162°. **9**,[4] mp 140—145°.

7) S. Huenig and F. Mueller, *Ann. Chem.*, **651**, 89 (1962).
8) A.G. Agfa, *CA.*, **56**, 6827 i. *Brit.*, 814375.
9) J. Korosi, *J. Pract. Chem.*, **23**, 212 (1964).