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The Chemistry of Lactim Ethers. IV.[1] Syntheses of 1,9- and 5,9-Diazasteroid Systems[2]

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The reaction of methyl valerolactim (**1**) with cyclic β-aminoester (**6**) afforded only 1,9-diazasteroid (**14**), whereas that of methyl valerothiolactim (**2**) with **6** led to the cyclic diamide (**12**) together with **14**. The latter reaction, followed by iodination and reduction, gave 5,9-diazasteroid (**17**).

Keywords——lactim ether; lactim thioether; β-aminoester; imine form; enamine form; 1,9-diazasteroid; 5,9-diazasteroid

In previous papers,[1,3] we reported an interesting annulation reaction of lactium ethers with cyclic β-aminosters which gave two kind of products, probably corresponding to the imine and the enamine forms.[3] On the other hand, the similar annulation of lactim thioethers with 1-ethoxycarbonylmethyl-1,2,3,4-tetrahydroisoquinoline (**3**) afforded only the imine-type products.[1] We have hitherto synthesized a number of diazasteroids[2] in view of their potential biological activities.[4] Therefore, we describe here the syntheses of 1,9- and 5,9-diazasteroid systems. The remarkable differences in chemical properties between methyl valerolactim (**1**) and methyl valerothiolactim (**2**) is particulary noteworthy.

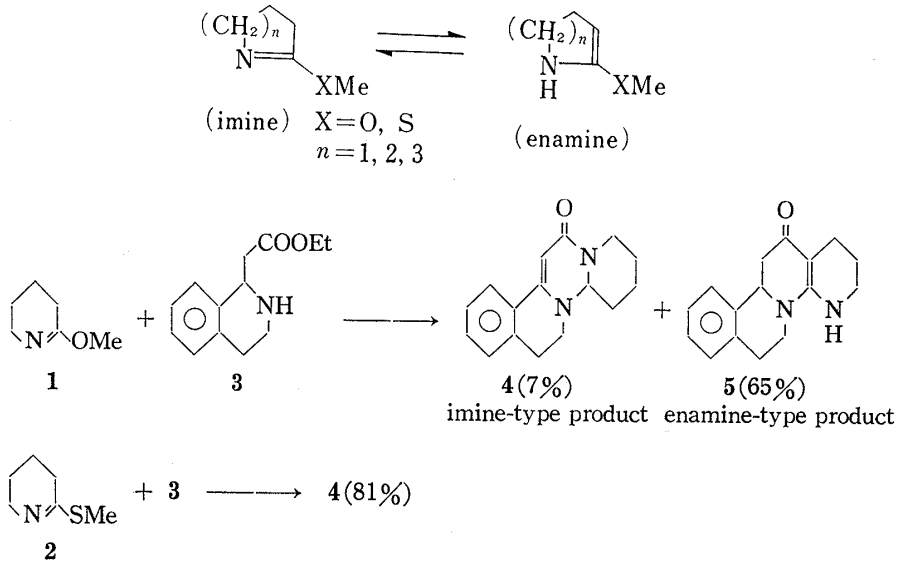

Chart 1

First, a cyclic β-aminoester (**6**)[5] suitable as a precusor of the steroidal C–D ring system was obtained by Bischler–Napieralski anunlation of the amide ester **7**, followed reduction. Bischler–Napieralski reaction of **7** was carried out with P_2O_5 as a condensing agent in CH_2Cl_2 at room temperature to give **8** in 67% yield. The IR spectrum of **8** showed absorptions of (NH), (CH_2COOEt), (NHC=CCOOEt), and (C=N) groups at 3350, 1740, 1670, and 1640 cm^{-1},

respectively. This observation suggested that compound **8** was a tautomeric mixture of **8a** (imine) and **8b** (enamine). This view was confirmed by the PMR spectrum, which revealed the signals (quartets) of $-CH_2-$ of the ethylester group (**8a** and **8b**) at δ 4.34 and δ 4.20, respectively, as well as the signals of the vinyl proton and the amino proton of **8b** at δ 4.63 as singlet and δ 8.16 as broad singlet, respectively. The ratio of **8a** to **8b** was evaluated as about one to four by NMR analysis. On the other hand, the picrate of **8** (mp 124—126°) existed only in the imine form (**8a**) as judged from its IR spectrum (1720 and 1620 cm^{-1}). Next, the tautomeric mixture (**8a, b**) was reduced with $NaBH_4$ at pH 3—4 (maintained by continual addition of 20% HCl solution) to afford **6** in 70% yield. This product was characterized by spectroscopic analysis and gave satisfactory elemental analysis data.

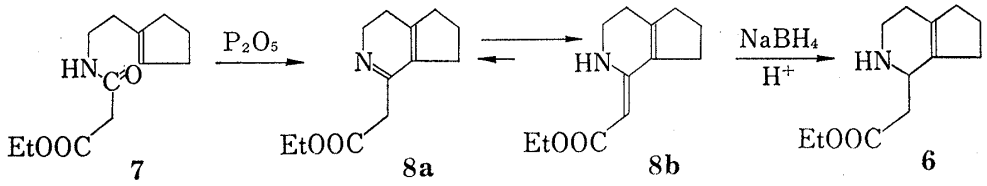

Chart 2

In the reaction of **1** and **2** with **6**, three products (**11**, **12**, and **14**) were expected on the basis of previous study,[1,3] as shown in Chart 3. In practice, the reaction of **1** with **6** in a sealed tube for 12 days at 100° provided only 1,9-diazasteroid (**14**) (mp 273—274°) in 20% yield (corresponding to the enamine form of **1**). This compound, **14**, gave appropriate MS [*m/e* 244 (M^+)] and elemental analysis (molecular formula $C_{15}H_{20}N_2O$) data. In the IR spectrum of **14**, a band due to NH of the 1-position (3140 cm^{-1}) and that attributable to C=O of the 6-position (1580 cm^{-1}) were observed. The UV spectrum showed absorptions at 308 nm (ε 16000) and 235 nm (ε 7000). In addition, dehydrogenation of **14** with $Hg(OAc)_2$ in 5% AcOH gave **15** (mp 256—258°) in 60% yield, and the PMR spectrum exhibited a singlet peak at δ 5.8, indicating the presence of a vinyl proton at the 7-position. Therefore, the structure (**14**) was unambiguously confirmed. On the other hand, attempted reduction of **14** with $LiAlH_4$ or $NaBH_4$ and catalytic hydrogenation of **14** with Pd/C or PtO_2 under various conditions both resulted in recovery of the starting material. Next, the reaction of **6** with **2** in a sealed tube at 110° afforded the unexpected product (**14**) in 9% yield and the cyclic diamide (**12**) (mp 210—213°) in 21% yield after alumina column chromatography. The spectra data for **12** [ν_{max}^{KBr} NH (3340 cm^{-1}) and C=O (1620 cm^{-1}); PMR δ ($CDCl_3$) 5.9 (NH, 1H, brs); CMR δ ($CDCl_3$)[6] 22.0, 24.0, 25.8, 26.1, 28.9, 33.4, 34.8, 35.6, 39.6, 41.0, 54.4, 134.4 (s), 138.2 (s), 172.4 (s), and 174.4 (s); MS *m/e* 262 (M^+)], and the elemental analysis data (molecular formula $C_{15}H_{22}N_2O_2$) supported the structure. Thus, the result that reaction with **2** preferentially gave the imine-type product (**12**) by addition of H_2O to **9** follwed by C–N bond cleavage is consistent with the previous report[3] (Chart 1). However, the other expected compound (**11**), corresponding to the imine form of **2**, was not obtained. Compound (**4**) shown in Chart 1 would be obtained by isomerization, *e.g.*, as in route **a**, induced by the presence of an aromatic ring in the β-aminoester such as **6**, the isomerization of **9** to **10** would be unable to proceed due to the lack of an aromatic moiety in **6**. A similar result has been reported in the reaction of 2-ethoxycarbonylmethylpiperdine (lacking an aromatic ring) with methyl caprolactim.[3] The chemical reactivities of **1** and **2** towards the cyclic β-aminoester (**6**) thus showed a marked difference, and because lactim ethers are known to react exclusively in the imine form,[7] the formation of **14** is an interesting result.

The reaction between **6** and **2** followed by iodination with NaI gave the iodide **16**, which without isolation, was reduced with $NaBH_4$ to produce the desired 5,9-diazasteroid (**17**) in 14% yield together with **14** in 9% yield. The elemental analysis (molecular formula $C_{15}H_{22}N_2O$) and MS spectrum [*m/e* 246 (M^+)] were consistent with the 5,9-diazasteroid structure. Com-

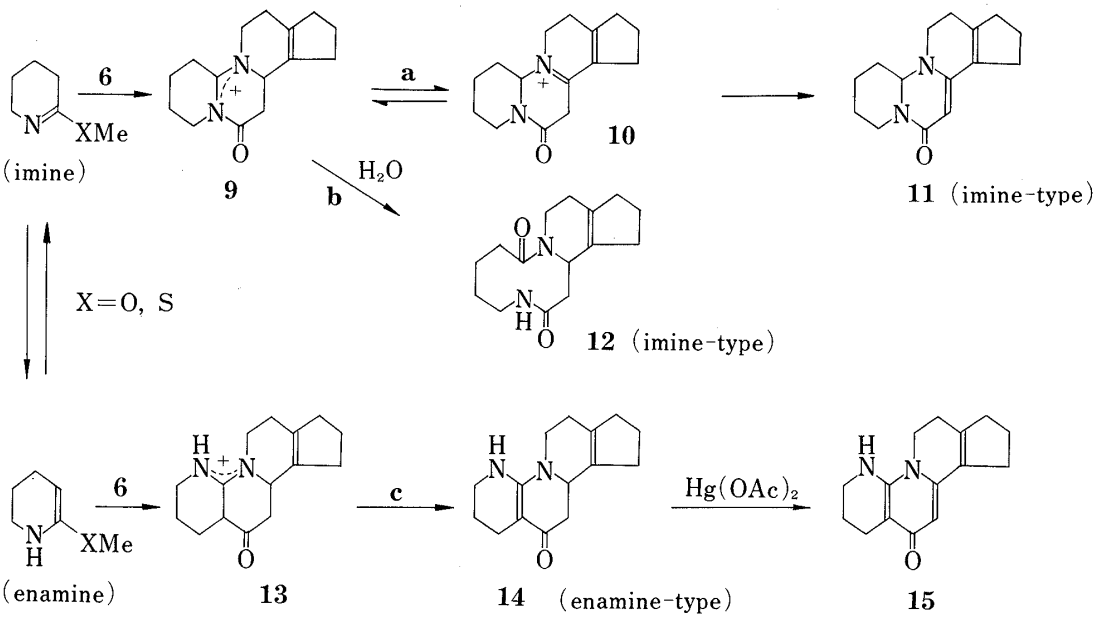

Chart 3

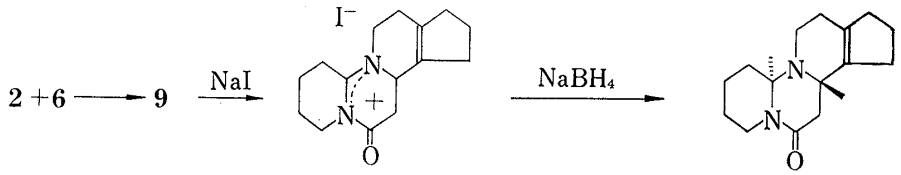

Chart 4

pound **17** did not show the Bohlmann band in the IR spectrum and exhibited a broad doublet at δ 4.8 in the PMR spectrum, indicating the 8-H to be *cis* to the adjacent nitrogen lone pair.[8] These spectral data support the view that the relation of C_8–H to C_{10}–H is *anti*.[9]

It was similarly confirmed that **1** had enamine character, whereas **2** preferentially showed imine character in these synthses of diazasteroids. The synthsis of medium-cyclic diamides related to **12** by using lactim thioethers is in progress.

Experimental

Infrared spectra were determined on a Hitachi 215 or a Jasco IRA 1 spectrophotometer and are reported in units of cm^{-1}. Proton NMR spectra were determined in the indicated solvent on a JEOL C-60H or a Varian XL 200 instrument, and chemical shifts are reported in δ units downfield from internal Me_4Si. Carbon-13 NMR spectra were determined on a Varian XL 200. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were obtained on a JEOL 01SG spectrometer. Melting points were determined on a Yanaco MP apparatus and are uncorrected. Ultraviolet spectra were determined on a Hitachi EPS-2T spectrometer.

1-Ethoxycarbonylmethyl-3,4-dihydrocyclopenteno[*c*]pyridine (8)——A mixture of **7** (22 g) and P_2O_5 (10 g) in CH_2Cl_2 (50 ml) was stirred for 20 hr at room temperature under nitrogen. The resulting black mixture was poured into ice water. The mixture was made alkaline with sat. Na_2CO_3 solution, and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated to leave an oil, which was purified by column chromatography on silica gel with benzene: ethyl acetate (5: 1) as an eluant to give **8a, b** (13.5 g, 67%). IR ν_{max}^{neat}: 3350, 1730, 1670, 1640. PMR ($CDCl_3$): 1.3 (3H, t, J=7 Hz, $-CH_2\underline{CH_3}$), 4.2 and 4.34 (2H, q, J=7 Hz, $-\underline{CH_2}CH_3$), 4.5 (0.8H, s, C=CH), 8.0 (0.8H, brs, NH). MS *m/e*: 207 (M^+), 162, 135. The picrate of **8**: mp 124—126° (recrystallized from ethanol). IR ν_{max}^{KBr}: 1720, 1620. *Anal.* Calcd for $C_{18}H_{20}N_4O_9$: C, 49.54; H, 4.62; N, 12.84. Found: C, 49.46; H, 4.52; N, 12.96.

1-Ethoxycarbonylmethyl-1,2,3,4-tetrahydrocyclopenteno[*c*]pyridine (6)——$NaBH_4$ (8.3 g) was added in portions to a solution of **8a, b** (14.9 g) in 95% ethanol (50 ml) with stirring under ice cooling at pH 3—4 maintained by continual addition of 20% HCl solution). When the addition was complete, the reaction

mixture was stirred for 2 hr at room temperature, made alkaline with 10% Na_2CO_3 solution, and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated. The resulting oil was distilled to give **6** (9 g, 60%). bp 96—98°/0.2 mmHg. IR ν_{max}^{neat}: 3350, 1730. PMR ($CDCl_3$): 1.3 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 3.7 (1H, brs, NH), 4.2 (2H, q, J=7 Hz, $OC\underline{H_2}CH_3$). MS m/e: 209 (M^+), 122. *Anal.* Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.72; H, 9.20; N, 6.83.

1,9-Diazagona-5(10),13-dien-6-one (14)——A mixture of **1** (14 g) and **6** (14 g) was heated in a sealed tube at 100° for 14 days. The reaction precipitate was filtered off and washed with benzene to give **14** (3.2 g, 20%). mp 273—274° (Recrystallized from isopropanol). IR ν_{max}^{KBr}: 3240, 1580, 1560, 1500. PMR (CD_3OD): 1.6—2.7 (14H, m), 2.7—3.1 (1H, m), 3.1—4.2 (2H, m). UV λ_{max}^{EtOH} nm: 308 (ε 16000), 235 (ε 7000). MS m/e: 244 (M^+), 235. *Anal.* Calcd for $C_{15}H_{20}N_2O$: C, 73.73; H, 8.25; N, 11.47. Found: C, 73.92; H, 8.06: N, 11.33.

1,9-Diazagona-5(10),7,13-trien-6-one (15)——A mixture of **14** (500 mg) and $Hg(OAc)_2$ (2.6 g) in 5% CH_3COOH solution (30 ml) was heated with stirring at 100° for 1 hr. The precipitate was filtered off and H_2S gas bubbled through the filtrate. The resulting precipitate was filtered off and the filtrate was neutralized with 10% Na_2CO_3 solution. The mixture was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$), and evaporated to dryness to give **15** (300 mg, 60%). mp 256—258° (Recrystallized from isopropanol–benzene). IR ν_{max}^{KBr}: 3250, 1690, 1630, 1580. PMR (CD_3OD): 1.6—2.2 (4H, m), 2.3—2.8 (8H, m), 3.8 (2H, t, J=6 Hz), 5.8 (1H, s, C=CH). UV λ_{max}^{EtOH} nm: 249 (ε 48000), 310 (ε 6000). MS m/e: 242 (M^+), 241, 240. *Anal.* Calcd for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.62; H, 7.48; N, 11.71.

5,9-Diaza 5,10-seco-13-gonene-6,10-dione (12)——A mixture of **2** (1.65 g) and **6** (1.34 g) was heated in a sealed tube at 100° for 10 days. The resulting precipitate was collected by filtration, and washed with $CHCl_3$ to give **14** (141 mg, 9%). The filtrate was concentrated *in vacuo* to leave an oil, which was purified by column chromatography on alumina with $CHCl_3$: methanol (30: 1) as an eluant to afford **12** (344 mg, 20.5 %). mp 210—213° (Recrystallized from ethyl acetate–isopropylether). IR ν_{max}^{KBr}: 3340, 1620, 1540. PMR ($CDCl_3$): 5.9 (1H, NH). CMR ($CDCl_3$):[6] 22.0, 24.0, 25.8, 26.1, 28.9, 33.4, 34.8, 35.6, 39.6, 41.0, 54.4, 134.4(s), 138.2(s), 172.4(s), 174.4(s). MS m/e: 262 (M^+). *Anal.* Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45; N, 10.68. Found: C, 68.96; H, 8.48; N, 10.39.

5,9-Diaza-13-gonen-6-one (17)——A mixture of **2** (2.22 g) and **6** (1.8 g) was heated in a sealed tube at 100° for 14 days. A precipitate was collected by filtration, and washed with $CHCl_3$ to affords **14** (196 mg, 9.3%). The filtrate and the washing were combined, and 5% HCl solution (6 ml) was added. Insoluble material was removed by filtration. Next, sat. NaI solution was added to the filtrate until no further white precipitate appeared. The mixture was concentrated *in vacuo* to give a viscous oil, to which was added methanol (50 ml). $NaBH_4$ (1.0 g) was added in portions to the solution with ice-cooling and the reaction mixture was stirred overnight. Next, excess $NaBH_4$ in the reaction mixture was decomposed with 10% AcOH solution and the mixture was taken to pH 5. The mixture was then made alkaline with sat. $NaHCO_3$, and extracted with ethyl acetate. The extract was dried ($MgSO_4$), and concentrated *in vacuo* to give a yellow oil, which was purified by column chromatography with $CHCl_3$: methanol (100: 1) as an eluant to afford **17** (300 mg, 14%) as white plates. mp 95—96° (Recrystallized from isopropylether–*n*-hexane). IR ν_{max}^{KBr}: 1640. PMR ($CDCl_3$): 3.70 (1H, brd, C_{10}–H), 4.80 (1H, brd, C_8–H). MS m/e: 246 (M^+). *Anal.* Calcd for $C_{15}H_{22}N_2O$: C, 73.13; H, 9.00; N, 11.37. Found: C, 72.96; H, 8.78; N,11.50.

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References and Notes

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