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The Chemistry of Lactim Ethers. II.¹⁾ Reaction of Lactim Ethers with 2-Carbethoxymethyl Piperidines

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Annulation reactions of methyl valelolactim (2) and methyl caprolactim (3) with cyclic β -aminoesters, such as 2-carbethoxymethyl piperidine derivatives (4 or 5), often gave two kinds of products apparently arising from the imine and enamine forms of 2 and 3. These chemical properties were consistent with NMR observations of lactim ethers in CD₃OD solution.

Keywords—lactim ethers; 2-carbethoxymethyl piperidines; imine-enamine tautomeric equilibrium; annulation; imine type product; enamine type product

The application of lactams to the synthesis of heterocyclic systems depends on the activation of their amide function. The conversion of carboxylic amides to imino ethers has thus provided a new application.³⁾ Similarly, the conversion of lactams into lactim ethers offers greater scope for the use of lactams in organic synthesis.⁴⁾

The phenominon of imine-enamine tautomeric equilibrium in O-ethyl valerolactim is reflected in its IR and NMR spectra, and its pK_a . Therefore, it is of interest to examine the phenominon of imine-enamine tautomeric equilibrium in the lactim ethers (1), (2), and (3) in relation to their reactivities. We now report these results in details.

The phenominon of the tautomeric equilibrium (imine ⇒ enamine) was observed by studying the interaction of lactim ethers with deuteromethanol through NMR spectroscopy as follows.

$$(CH_2)_n$$

$$OMe$$

$$imine (a) \qquad enamine (b)$$

$$1: n=1 \text{ methyl butyrolactim}$$

$$2: n=2 \text{ methyl valerolactim}$$

$$3: n=3 \text{ methyl caprolactim}$$

$$Chart 1$$

$$(CH_2)_n$$

$$OMe$$

$$imine-type product$$

$$(CH_2)_n$$

$$(CH_2)_$$

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V.G. Granik, B.M. Pyatin, J.V. Persianova, N.P. Kostyuchenko, R.G. Glushkov, and Y.N. Shinker, Tetrahedron, 26, 4367 (1970).

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²⁾ Location: 2630, Sugitani, Toyama 930-10, Japan.

When solutions of lactim ethers (1), (2), and (3) in CD_3OD were kept 20°, the signals from protons in 3 positions gradually decreased and after two weeks they achieved $\sim 0\%$, $\sim 70\%$, and $\sim 30\%$ exchanges, as monitored in terms of the integral values, respectively (see "Experimental").

Based on these data, two types of chemical behavior of lactim ethers are expected, proceeding from the imine and enamine forms. In fact, reactions using lactim ethers are known to proceed exclusively in the imine form,⁴⁾ whereas the only known example of enamine-type reaction is the reaction with isocyanates.⁶⁾ Here we investigated annulation reactions of lactim ethers with cyclic β -aminoesters such as 2-carboxymethyl piperidine derivatives (4) and (5), which furnished products apparently attributable to both the imine and enamine forms.

Previously, we reported the synthesis of the 8,13-diazasteroid (6) by the reaction of 1-carbethoxymethyl 1,2,3,4-tetrahydroisoquinoline (4) with 1, which gave only the product resulting from the imine form. On the other hand, the reaction of 4 with 2 at 100° for 12 days in a sealed tube afforded compound (7) by the enamine-type reaction and compound (8) by the imine-type reaction in 65% and 7% yields, respectively, after chromatographic separation. The structure of 7 was characterized as its dehydrogenation product (9) derived by treatment with mercuric acetate. The NMR spectrum of 9 showed a singlet due to the vinyl proton at δ 5.03. In addition, compound (7) was allowed to react with acetic anhydride to give the N-acetylated product (10). The NMR spectrum of compound (8) showed a singlet at δ 5.3 indicative of the vinyl proton of a vinylogous amide group. A similar annulation reaction employing 2-carbethoxymethyl piperidine (5) furnished only compound (11) by an enamine-type reaction in 54% yield; its structure was confirmed by dehydrogenation, as in the case of 7.

Next, a similar reaction of 4 with 3 gave 13 (1.2%), 14 (44%), and 15 (13%), which were fully characterized spectroscopically and by elemental analyses. In the case of the hydrated

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product (15), its IR spectrum exhibited strong bands at 1590 and 1620 cm⁻¹, while the NMR spectrum showed a broad singlet at δ 8.1 due to the amide group, and the MS spectrum gave a parent peak at m/e 286. The annulation of 3 with 5 gave 16 (26%) and 17 (13%), which gave appropriate spectra.

Thus, the differences in the three lactim ethers detected in CD₃OD solution were reflected in the chemical behavior. It was found that reaction using methyl valerolactim (2) preferentially gave enamine-type products.

Formation of these compounds can be explained by the mechanism depicted in Chart 5. The initial nucleophilic attack of the secondary amine of the β -aminoester (4) or (5) at the 2-position of each lactim ether is expected to yield the amidine intermediate (18),8) which can then isomerize to 19.9 Subsequently, 18 and 19 may undergo ring closure by acylation to give immonium intermediates (20) and (21), respectively, which lead to the final products. Another possible pathway involves acylation at the 1-position of the imine form (2a) or (3a) and the 3-position of the enamine form (2b) or (3b) to afford the intermediates (22) and (23), followed by ring closure to give the same intermediates (20) and (21), respectively. Compounds (8) and (14) would presumably be obtained by way of isomerization of the immonium intermediate (20) to the iminium intermediate (24) induced by the presence of an aromatic ring, as in Chart 4.10 On the other hand, addition of H₂O to 20, followed by C-N bond cleavage would give the cyclic diamides (15) and (17).

Next, the reaction of the β -aminoester (4) with 2 in the presence of triethylamine as a base gave 7 (21%), 8 (14%), and the cyclic diamide (26) (19%). Compound (16) had strong bands at 3340 and 1640 cm⁻¹ in the IR spectrum, together with a signal at δ 7.7—8.3 in the NMR spectrum ascribable to the amide group, and gave a satisfactory elemental composition. The same reaction employing 3 furnished 14 (52%) and the cyclic diamide (15) (6%), but no enamine-type product. Though the effect of the base on this reaction is equivocal, the products of imine-type reaction were preferentially obtained compared to the reaction in the absence of the base.

Lactim ether (27) and (28) having one electron-withdrawing substituent at the 3-position may favor the enamine-type tautomers (27b) and (28b) more than the unsubstituted lactim ethers (2) and (3). The IR spectrum of a 3-cyanolactim ether such as 27 shows two bands at 2180 and 2260 cm⁻¹ due to conjugated and unconjugated cyano groups, respectively, and that of 28 has similar bands at 2200 and 2250 cm⁻¹. However, the reaction of 27 with

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4 gave unexpectedly only the imine-type compound (29) (26%), which was characterized spectroscopically and by elemental analysis, with recovery of the starting material (26%). Similarly, the reaction of 28 with 4 afforded compound (30) (32%) and the starting material (20%). The reason for the absence of enamine-type products may be that the nucleophilicity of the 3-position of lactim ethers (27 and 28) is depressed by the enaminonitrile system.

Chart 5

Chart 6

Experimental¹¹⁾

The NMR Spectra of Lactim Ethers (1), (2), and (3)—Lactim ethers were prepared by the method of Peterson *et al.*¹²⁾ The NMR spectra of lactim ethers were measured in 15% (w/v) CHCl₃ solution and assigned as shown in Table I.

Table I. NMR Chemical Shifts (δ) of Lactim Ethers (1, 2, and 3)

Compd. No.			
1	1.7—2.2 (2H, C ₄ -4)	2.2—2.7 (2H, C ₃ –H)	3.4—3.9 (5H, C ₅ –H and –OCH ₃)
2	$1.3-1.9$ (4H, $C_{4.5}-H$)	$1.9-2.4$ (2H, C_3-H)	3.3—3.8 (5H, C_6 –H and $-OCH_3$)
3	1.2—2.0 (6H, C _{4,5,6} –H)	$2.2-2.6$ (2H, C_3-H)	3.2—3.7 (5H, C ₇ –H and –OCH ₃)

After solutions of 1, 2, and 3 in CD₃OD had been kept at 20° for 14 days, the integral values of the signals from protons in the 3-position were decreased by -0%, -70%, and -30% from the starting NMR spectra.¹³)

1,2,3,4,6,7,11b,12-Octahydro-13H-isoquino[2,1-a][1,8]naphthylidin-13-one (7) and 1,2,3,4,4a,6,7,13 Octahydroisoquino[1,2-f]pyrido[2,1-b]pyrimidin-13-one (8)—A mixture of 4^7) (2 g, 0.9 mol) and 2 (2 g, 1.8 mol) was kept in a sealed tube at 100° for 12 days. The precipitate was filtered off, washed with benzene, and dried in vacuo to give 7 (1.5 g, 65%) as white plates on recrystallization from methanol, mp 322—324°. The filtrate was concentrated in vacuo to leave an oil, which was purified through an alumina column, eluting with benzene-ethanol (50:1), to give 8 (170 mg, 7.3%) as colorless needles on recrystallization from benzene, mp 164—166°, 7, IR v_{\max}^{KBr} cm⁻¹: 3240, 1580, 1560, 1500; UV $\lambda_{\max}^{\text{RioH}}$ nm (ε): 309 (19000), 238 (10000). MS m/e: 254 (M+), 253, 250. Anal. Calcd for $C_{16}H_{18}H_2O$: C, 75.59; H, 7.09; N, 11.02. Found: C, 75.31; H, 6.98; N, 11.27. 8, IR $_{\max}^{\text{KBr}}$ cm⁻¹: 1620, 1590, 1550. NMR (CDCl₃) δ : 1.9—3.7 (12H, m), 4.4—4.9 (2H, m), 5.3 (1H, s, -C=CH), 7.0—7.8 (4H, m, aromatic protons). UV $\lambda_{\max}^{\text{RioH}}$ nm (ε): 366 (8100), 252 (23000). MS m/e: 254 (M+), 253, 198, 170. Anal. Calcd for $C_{16}H_{18}N_2O$: C, 75.59; H, 7.09; N, 11.02. Found: C, 75.34; H, 7.05; N, 10.94.

1,2,3,4,6,7-Hexahydro-13H-isoquino[2,1-a][1,8]naphthylidin-13-one (9)——A solution of 7 (140 mg, 0.55 mmol) and Hg(OAc)₂ (700 mg, 2.2 mmol) in 5% acetic acid (10 ml) was heated with stirring at 85—90° for 3 hr. The precipitated metcurous acetate was filtered off after cooling, then hydrogen sulfide was passed into the filtrate and the mercuric sulfide which separated was filtered off. The filtrate was made basic with 20% Na₂CO₃ solution and extracted with CHCl₃, and the extract was dried over anhyd. MgSO₄ then concentrated to give colorless masses, which were purified by column chromatography (alumina, benzene–EtOH, 50: 1), giving 9 (60 mg, 43%) as colorless needles on recrystallization from methanol–acetone, mp 312—314°. IR $r_{\rm max}^{\rm KBT}$ cm⁻¹: 3160, 1620, 1580, 1550. NMR (CD₃OD) δ : 6.6 (1H, s, -C=CH), 7.0—7.7 (4H, m, aromatic protons). UV $\lambda_{\rm max}^{\rm EtOH}$ nm (ε): 249 (29000), 308 (9200). MS m/e: 252 (M⁺). Anal. Calcd for C₁₆H₁₆N₂O: C, 76.16; H, 6.39; N, 11.10;. Found: C, 76.21; H, 6.56; N, 11.26.

4-Acetyl-1,2,3,4,6,7,11b,12-octahydro-13H-isoquino[2,1-a][1,8]naphthylidin-13-one (10)——A mixture of 7 (370 mg, 1.46 mmol) and Ac₂O (1.49 g, 14.6 mmol) in dry pyridine (20 ml) was heated in a boiling water bath for 4 hr. The reaction mixture was concentrated *in vacuo* to leave an oil. This was extracted with CHCl₃ and the extract was washed with 10% Na₂CO₃, dried over anhyd. MgSO₄, and concentrated *in vacuo*. The residue was purified by silica gel chromatography, eluting with CHCl₃, to give 10 (200 mg, 46%) as colorless plates on recrystallization from acetone-ether, mp 144—146°. IR r_{\max}^{RBF} cm⁻¹: 1660, 1640, 1590, 1570. NMR (CDCl₃) δ : 2.2 (3H, s, -N-COCH₃). UV $\lambda_{\max}^{\text{EtoH}}$ nm (ε): 337 (13000), 235 (7600). MS m/ε : 296 (M⁺), 253. Anal. Calcd for C₁₈H₂₀N₂O₂: C, 72.95; H, 6.80; N, 9.45. Found: C, 73.09; H, 6.93; N, 9.43.

1,2,3,4,6,7,8,9,9a,10-Decahydro-11H-pyrido[1,2-a][1,8]naphthylidin-11-one (11)—A mixture of 4 (2 g, 11 mmol) and 3 (2.5 g, 22 mmol) was kept in a sealed tube at 100° for 14 days. After cooling, the precipitate was filtered off, washed with benzene, and dried in vacuo, giving a crude crystalline mass, which was recrystallized from isopropyl alcohol to afford 11 (1.4 g, 54%) mp 290—292°. IR $v_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3240, 1580, 1560, 1500. NMR (CD₃OD) δ : 1.2—1.9 (12H, m), 2.1—2.5 (4H, m), 2.5—2.9 (1H, m). UV $\lambda_{\text{max}}^{\text{Btot}}$ nm

¹¹⁾ 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.

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¹³⁾ The integral values are the means of four measurements.

(\$\epsilon\$): 308 (17000), 239 (7200). MS m/e: 206 (M+), 205, 177. Anal. Calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.85. Found: C, 69.65; H, 8.59; N, 13.82.

1,2,3,4,6,7,8,9-Octahydro-11H-pyrido[1,2- α][1,8]naphthylidin-11-one (12)——A solution of 11 (370 mg, 1.78 mmol) and Hg (OAc)₂ (1.8 g, 7.7 mmol) in the 5% AcOH (20 ml) was treated with Hg(OAc)₂ (1.78 g, 7.4 mmol) in the manner described for 9 to give 12 (200 mg, 54%) as colorless plates on recrystallization from methanol-ether, mp 286—288°. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3200, 1630, 1560, 1500. NMR (CDCl₃) δ : 3.3 (2H, m), 3.8 (2H, t, J = 6 Hz), 5.8 (1H, s, -C=CH), 6.3 (1H, brs, NH). UV $\lambda_{\text{max}}^{\text{EiOH}}$ nm (ε): 233 (36000), 285 (11000). MS m/e: 204 (M⁺), 203, 189. Anal. Calcd for C₁₂H₁₆N₂O: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.39; H, 7.72; N, 13.42.

2,3,4,5,7,8,12b,13-Octahydro-1H,14H-azepino[2,3-c]benzo[h]quinolizin-14-one (13), 1,2,3,4,5,5a,7,8-Octahydro-14H-isoquino[1,2-f]azepino[2,1-b]pyrimidin-14-one (14), and 1-(1,5-Diaza-2,6-dioxocyclounde-canyl)-1,2,3,4-tetrahydroisoquinoline (15)——A mixture of 3 (2.3 g, 18 mmol) and 4 (2 g, 9.1 mmol) was heated in a sealed tube at 100° for 14 days. The reaction mixture was separated by silica gel chromatography to give 14 (1.1 g, 44%) with CHCl₃, then 15 (340 mg, 13%), and 13 (30 mg, 1.2%) with CHCl₃-EtOH, 30: 1. 13 Recrystallized from isopropanol to give white plates, mp 298—300°. IR $v_{\max}^{\rm BBr}$ cm⁻¹: 3280, 1570, 1550, 1490. UV $\lambda_{\max}^{\rm EiOH}$ nm (ε): 316 (19000), 240 (10000). MS m/e: 268 (M+). Anal. Calcd for $C_{17}H_{20}N_{2}O$: C, 76.08; H, 7.51; N, 10.44. Found: C, 76.00; H, 7.24; N, 10.44. 14, Recrystallized from benzene to afford colorless needles, mp 160—162°. IR $v_{\max}^{\rm BBr}$ cm⁻¹: 1620, 1590, 1550, 1480. NMR (CDCl₃) δ : 1.0—3.5 (13H, m), 4.1—4.6 (2H, m), 5.4 (1H, s, -C=CH), 6.6—7.7 (4H, aromatic protons). UV $\lambda_{\max}^{\rm BIOH}$ nm (ε): 252 (22000), 356 (10000). MS m/e: 268 (M+), 225, 185. Anal. Calcd for $C_{17}H_{20}N_{2}O$: C, 76.12; H, 7.46; N, 10.45. Found: C, 76.02; H, 7.51; N, 10.66. 15, Recrystallized from acetone to furnish colorless meedles, mp 135—145°. IR $v_{\max}^{\rm RBr}$ cm⁻¹: 3320, 1620, 1540. NMR (DMSO- d_{6}) δ : 7.0—7.3 (4H, aromatic protons), 8.1 (1H, brs, NH). MS m/e: 286 (M+), 145, 132. Anal. Calcd, for $C_{17}H_{22}N_{2}O$: C, 67.08; H, 7.95; N, 9.20. Found: C, 66.88; H, 7.93; N, 9.40.

2,3,4,5,7,7a,8,9,10,11-Decahydro-1H,6H-azepino[2,3-c]quinolizin-6-one (16) and 1-(1,5-Diaza-2,6-dioxocycloundecanyl)piperidine (17)—A mixture of 5 (2 g, 11.7 mmol) and 3 (2.9 g, 23.4 mmol) was kept in a sealed tube at 100° for 14 days. The precipitate was filtered off, washed with benzene, and dried in vacuo to give 16 (670 mg, 26%) as a solid, which was recrystallized from isopropanol to afford an analytical sample as colorless needles. The filtrate was concentrated to leave an oil, which was purified by alumina column chromatography, eluting with CHCl₃-EtOH 30: 1, to afford a crystalline mass, which was recrystallized from ethyl acetate to give 17 (370 mg 13%) as colorless needles. 16, mp 245—247°. IR $\nu_{\rm max}^{\rm KBT}$ cm⁻¹: 3280, 1580, 1560, 1490. NMR (CD₃OD) δ : 1.1—2.0 (12H, m), 2.0—2.7 (5H, m), 3.6—4.1 (1H, brd). UV $\lambda_{\rm max}^{\rm EtOH}$ nm (ε): 318 (22000), 228 (8600). MS m/ε : 220 (M⁺), 205. Anal. Calcd for $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 71.14; H, 9.42; N, 12.90. 17, mp 170—172°. IR $\nu_{\rm max}^{\rm KBT}$ cm⁻¹: 3300, 1600, 1610, 1550. NMR (CDCl₃) δ : 1.0—3.9 (20H, m), 4.3—5.0 (1H, m), 5.8—6.4 (1H, brs, NH). MS m/ε : 238 (M⁺), 210. Anal. Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.32; H, 9.23; N, 12.00.

Reaction of 2 with 4 in the Presence of Triethylamine—A mixture of 2 (1 g, 9 mmol), 4 (1 g, 4.5 mmol), and triethylamine (0.2 g, 2 mmol) was heated in a sealed tube at 100° for 3 days to yield 7 as precipitate (240 mg, 21%). The residue was separated by silica gel chromatography, eluting with CHCl₃–EtOH (30:1), to afford 8 (160 mg, 14%) and subsequently a solid, which was recrystallized from ethyl acetat- to give 1-(1,5-diaza-2,6-dioxocyclodecanyl)-1,2,3,4-tetrahydroisoquinoline (26) (230 mg, 19%) as colorless plates, mp 170—172°. IR $r_{\rm max}^{\rm KBr}$ cm⁻¹: 3340, 1600, 1530, 1420. NMR (DMSO- d_6) δ : 4.4—4.9 (1H, m), 5.2—5.9 (1H, m), 6.8—7.4 (4H, aromatic protons), 7.7—8.3 (1H, brs, NH). MS m/e: 272 (M⁺), 132. Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.37; H, 7.67; N, 10.11.

Reaction of 3 with 4 in the Presence of Triethylamine—A mixture of 3 (1.3 g, 9 mmol), 4 (1 g 4.5 mmol), and triethylamine (0.2 g 2 mmol) was heated in a sealed tube at 100° for 7 days. The reaction mixture gave 14 (640 mg 52%) and 15 (80 mg, 6%) in the manner described above.

13-Oxo-2,3,6,7,11b,12-hexahydro-1H,13H-isoquino[1,2-f]pyrido[2,1-b]pyrimidine-4-carbonitrile (29)—A mixture of $27^{14,15}$) (1.1 g, 7.2 mmol) and 4 (1 g, 4.6 mmol) was heated in a sealed tube at 100° for 12 days. The reaction mixture was separated by silica gel chromatography, eluting with CHCl₃, to give a solid, which was recrystallized from isopropanol-acetone to afford 29 (460 mg, 36%) as white plates. Subsequent elution with CHCl₃-EtOH (50: 1) provided 27 (250 mg,) mp 170—172°. IR $\nu_{\text{max}}^{\text{KBF}}$ cm⁻¹: 2180, 1680, 1600. NMR (CDCl₃) δ : 1.4—3.5 (9H, m), 3.5—4.2 (2H, t, J=5 Hz), 4.2—5.0 (2H, D), 6.7—7.5 (4H, aromatic protons). UV $\lambda_{\text{max}}^{\text{EiOH}}$ nm (ε): 295 (17000), 236 (10000). MS m/ε : 279 (M⁺), 239. Anal. Calcd for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 73.32; H, 6.15; N, 15.22.

14-0xo-1,2,3,4,7,8,12b,13-octahydro-14H-isoquino[1,2-f]azepino[2,1-b]pyrimidine-5-carbonitrile (30)—A mixture of $28^{14,15}$) (1.3 g, 9 mmol) and 4 (1 g, 4.5 mmol) was heated in a sealed tube at 100° for 7 days. The reaction mixture was separated by silica gel chromatography, eluting with CHCl₃, to give a solid ,which was recrystallized from CHCl₃-acetone to afford 30 (350 mg, 26%) as white plates. Subsequent elution

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with CHCl₃–EtOH (50: 1) provided 28 (400 mg). 30, mp 178—180°. IR ν $_{\rm max}^{\rm KBr}$ cm⁻¹: 2180, 1680, 1570. NMR (CDCl₃) δ : 1.4—3.3 (10H, m), 4.0—4.3 (3H, m), 4.3—4.8 (2H, m), 6.8—7.3 (4H, aromatic protons). UV $\lambda_{\rm max}^{\rm EtOH}$ nm (ε): 304 (13000), 234 (8400). MS m/ε : 293 (M+), 253. Anal. Calcd for C₁₈H₁₉N₃O: C, 74.20; H, 5.88; N, 14.42. Found: C, 74.47; H, 5.83; N, 14.18.

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