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The Chemistry of Lactim Ethers. V.[1] Reaction of Lactim Thioethers with β-Aminoesters[2]

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Reaction of a cyclic β-aminoester such as 2-ethoxycarbonylmethylpiperidine (**5**) with the lactim thioethers **1b** and **1c** gave a 10-membered cyclic diamide (**7**) and an 11-membered ring compound (**9**), respectively. On the other hand, though acyclic β-aminoesters (**6**) reacted with **1** to afford methyl 3-methylthiopropionate (**11**), N-alkyl 3-methylthiopropionamide (**12**), lactams (**13**), and amidines (**14**), no cyclic diamide was obtained.

Keywords——lactim thioethers; cyclic β-aminoesters; acyclic β-aminoesters; cyclic diamide; medium-ring; methyl 3-methylthiopropionate; N-alkyl 3-methylthiopionamide; amidines; lactams; β-lactmams

In recent publications,[1,3,4] we reported the annulation reaction of lactim thioethers (**1**) and lactim ethers (**2**) with cyclic β-aminoesters. Interestingly, the annulation of **1** with β-aminoesters (**3**) and (**4**) gave exclusively the imine type products and provided two kinds of products, the cyclic diamide (**I**) and the enaminoamide (**II**). On the basis of these results, we examined the cyclization of lactim thioethers (**1**) with β-aminoesters lacking an aromatic moiety, such as 2-ethoxycarbonylmethylpiperidine (**5**), and acyclic β-aminoesters (**6**) in anticipation of the predominant formation of the type **I** product having a medium-sized ring.

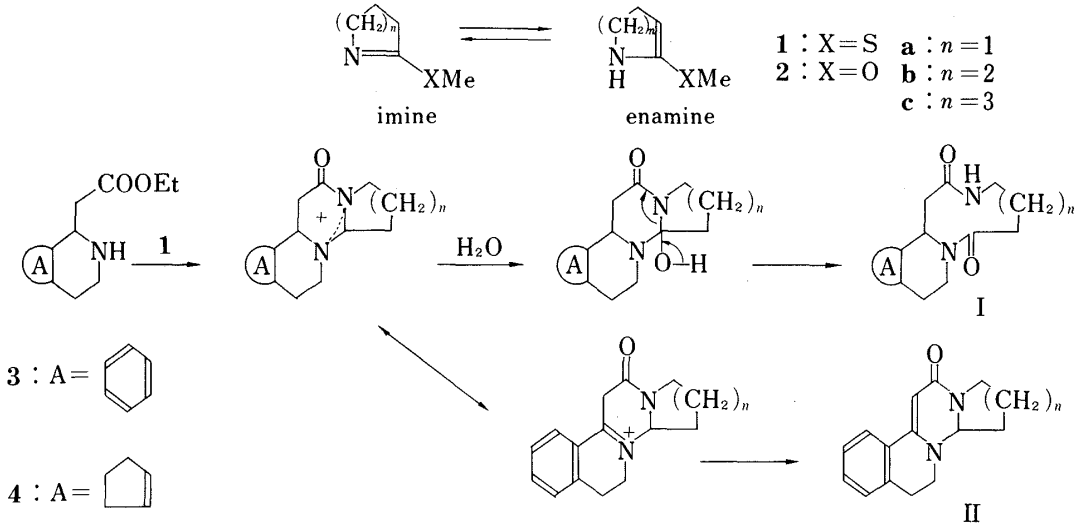

Chart 1

First, treatment of **1b** with **5** in a sealed tube at 100—110°C for 10 days afforded a 10-membered ring diamide (**7**) (mp 186—188°C) in 42% yield together with **8** (mp 297—298°C)[3] in 3% yield, attributable to the enamine form of **1b**; these products were isolated by alumina column chromatography. The spectral data of **7** [ν_{max}^{KBr} NH (3300 cm^{-1}) and C=O (1650 cm^{-1}); PMR δ (DMSO-d_6) 7.5—9 (NH, 1H, broad singlet)], MS *m/e* 224 (M^+), and elemental analysis (molecular formula $C_{12}H_{20}N_2O_2$) supported this structure. A similar annulation of **1c** with **5** gave only an 11-membered diamide (**9**) (mp 190—192°C)[3] in 53% yield. However, reaction of with **5** did not give a 9-membered ring product but furnished a non-cyclized product (**10**)

(mp 35—38°C) in a low yield. This compound (**10**) gave appropriate MS [*m/e* 286 (M^+)] and elemental analysis (molecular formula $C_{14}H_{26}N_2O_2S$). In the IR spectrum of **10**, a band due to NH (3330 cm^{-1}) and one attributable to C=O (1710 cm^{-1}) were observed. The PMR spectrum of **10** exhibited a triplet (3H, J=7 Hz) at δ 1.27 and a quartet (2H, J=7 Hz) at δ 4.17, a singlet (3H) at δ 2.03, and a broad singlet (1H) at δ 5.40 indicating ethylester, SMe, and NH, respectively.

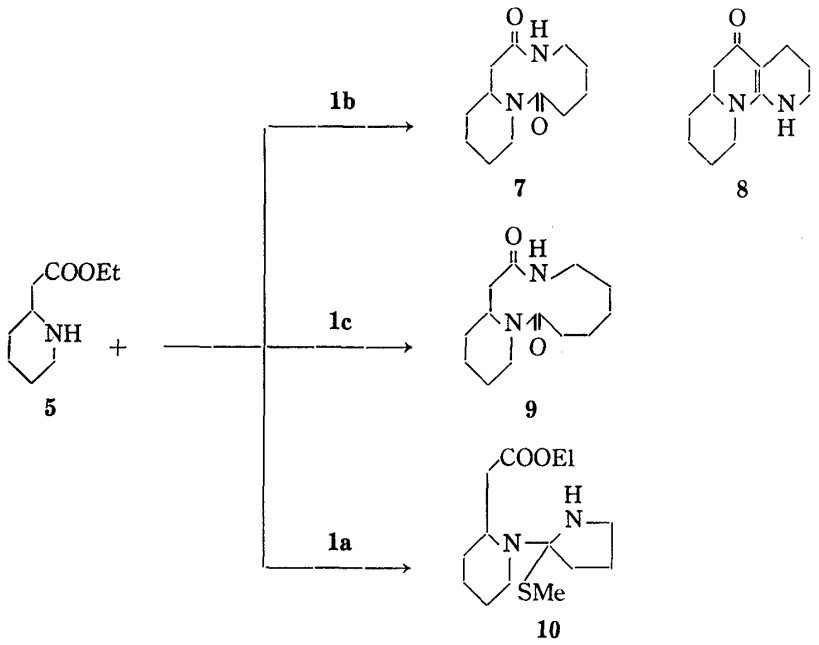

Chart 2

Next, the reaction of acyclic β-aminoester (**6**) with **1** was carried out in a similar manner. However, the desired products could not be obtained. In the reaction of **6a** with **1a**, a mixture of methyl 3-methylthiopropionate (**11**) (bp 65°C/6 mmHg), N-benzyl 3-methylthiopropionamide (**12a**) (mp 50—51°C), butyrolactam [**13**(n=1)], and N-benzyl 2-iminopyrrolidine [**14a**-(n=1)] was obtained. Both **11** and **12a** were characterized spectroscopically and gave satisfactory elemental analyses. All reactions of **1a, b, c** with acyclic β-aminoesters (**6a, b, c**) afforded similar products. The results are summarized in Table I.

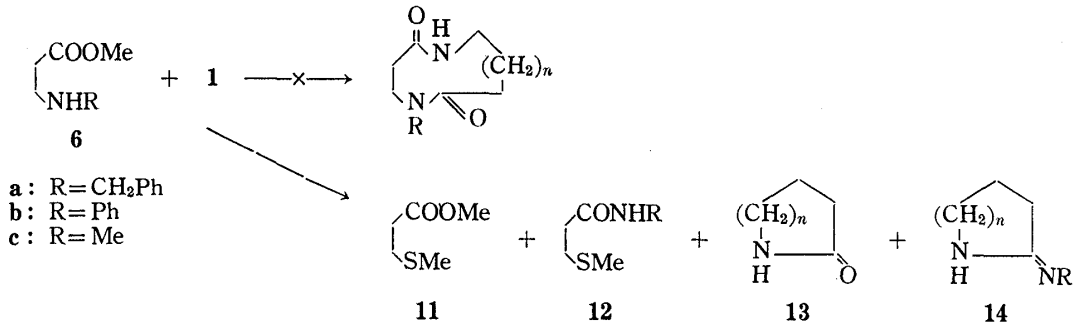

Chart 3

In order to investigate the mechanism of these reactions, we carried out the following experiment. The reaction of amidine [**14a**(n=1)] with methyl 3-ethylthiopropionate (**15**) afforded an amide (**16**) (mp 49—50°C) and **13** (n=1) in 56% and 62% yields, respectively. A possible mechanism for the formation of the products obtained by the reaction of acyclic β-aminoesters with **1** is shown in Chart 4; *i.e.*, the first stage might involve the formation of a

Table I. Reaction of **1** with **6** Yields (%)[a] and Melting Points (mp) or Boiling Points (bp) for Products

6	**1**	**11** (bp 65°C/6mmHg)	**12**	(mp)	**13**	**14**	(mp)
a, R=CH_2Ph	$n=1$	36	26	(51°C)	66	31	(79°C)[b]
	$n=2$	21	48	(51°C)	67	28	(95°C)
	$n=3$	45	39	(51°C)	55	41	(71°C)[c]
b, R=Ph	$n=1$	22	—		43	40	(113°C)[d]
	$n=3$	56	—		28	50	(107°C)[e]
c, R=Me	$n=1$	14	32	(35°C)	34	36	(95°C)[f]

a) The yields of (**11** and **12**) and (**13** and **14**) are based on **6** and **1**, respectively.
b) Lit.[5] mp 82°C. *c*) Lit.[5] mp 76°C. *d*) Lit.[6] mp 115° *e*) Lit.[6] mp 107°C. *f*) Lit.[7] mp 95°C.

1:1 adduct (**17**) as an intermediate. This view is supported by the formation of compound (**10**) in Chart 2. Subsequently, the intermediate (**17**) would be concertedly cleaved to produce the amidine (**14**) and **11**. The next stage would involve the condensation of **14** with **11** to afford **12a, c** and **13** (preliminary results). However, because the nucleophilicity of nitrogen of **14b** would be weakened by a phenyl group, N-phenyl 3-methylthiopropionamide (**12b**) could not be obtained. Next, the β-aminoester (**6a**) was treated with ethanethiol in both the presence and absence of triethylamine, but no replacement of the benzylamino group by an ethylthio group took place. This suggested that the β-aminoester did not undergo self retro-Michael reaction to the acrylate.

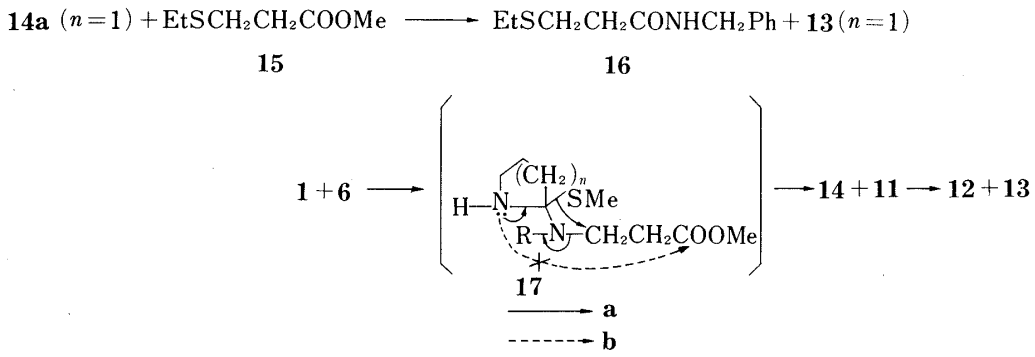

Chart 4

Reaction of ethyl 3-benzylamino-3-phenylpropionate (**18**) with **1a** gave a similar product; *i.e.*, a mixture of ethyl 3-methylthio-3-phenylpropionate (**19**), N-benzyl 3-methylthio-3-phenylpropionamide (**20**), **13a** (n=1), and **14a** (n=1). In the case of acyclic β-aminoesters

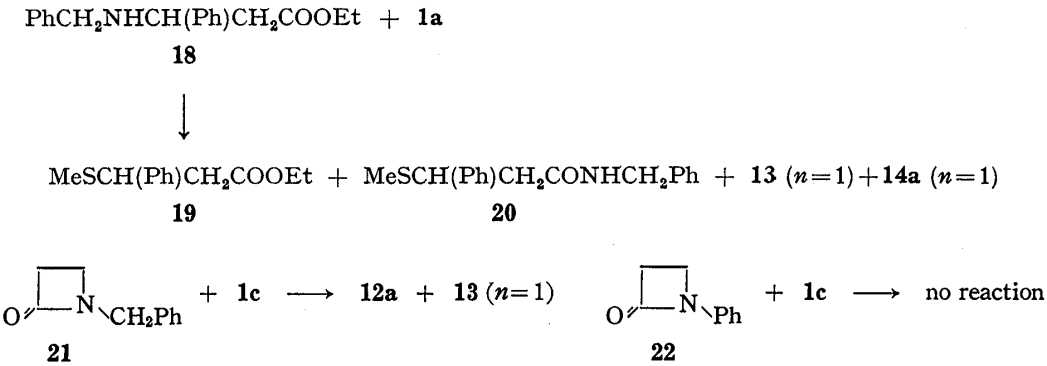

Chart 5

it was found that annulation as shown by the arrow (-----→b) never occurred, in contrast to the results for the cyclic β-aminoesters.

Next, β-lactam rings are well known to react with an amino group to cleave the N_1–C_2 bond.[8] 1-Benzyl-2-azetidinone (**21**) was thus allowed to react with **1c**, but the unexpected amide (**12a**)[9] (60%) and **13** ($n=1$) were obtained. On the other hand, reaction of 1-phenyl-2-azetidinone (**22**) with **1c** resulted in recovery of the β-lactam in spite of the use of a higher temperature.

Experimental

Infrared spectra were determined on a Jasco IRA 1 spectrophotometer and are given in units of cm^{-1}. Proton NMR spectra were determined in the indicated solvent on a JEOL C-60H machine and chemical shifts are given in δ units downfield from internal Me_4Si. Spilitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, brosd singlet. Mass spectra were obtained on a JEOL OlSG spectrometer. Melting points were determined on a Yanaco MP apparatus and are uncorrected.

Piperidino[1,2-*a*][1,5]diazecane-2,8-dione (7) and 1,2,3,4,6,6a,7,8,9,10-Decahydro-5H-pyrido[1,2-*a*][1,8]-naphthyldin-5-one (8)——A mixture of **1b** (2.58 g) and **5**[10] (1.71 g) was heated in a sealed tube at 100—110°C for 10 d. The resulting precipitate was collected by filtration and washed with CH_2Cl_2 to give **8** (65 mg, 3.2%). The filtrate was concentrated *in vacuo* to leave an oil, which was purified by column chromatography on alumina with $CHCl_3$: EtOH (30: 1) as an eluant to afford **7** (937 mg, 41.8%). **7**: mp 186—188°C (recrystallized from ethyl acetate–isopropylether). IR ν_{max}^{Nujol}: 3300, 1650. NMR (DMSO-d_6): 7.5—7.9 (1H, brs, NH). MS *m/e*: 224 (M^+). *Anal.* Calcd for $C_{12}H_{20}N_2O_2$: C, 64.25; H, 8.99; N, 12.49. Found: C, 64.47; H, 9.23; N, 12.23. **8**: mp 292—294°C (recrystallized from ethyl acetate-MeOH) (lit.,[3] mp 290—292°C). The product was identical with an authentic sample prepared from methyl valerolactim (**2b**),[3] with respect to spectroscopic data.

Piperidino[1,2-*a*][1,5]diazacycloundecane-2,9-dione——A mixture of **5** (1 g) and **1c** (1.68 g) was heated in a sealed tube at 100—110°C for 10 d. The reaction mixture was separated by column chromatography on alumina to give **9** (730 mg, 52.9%) using $CHCl_3$: EtOH (30: 1) as an eluant. mp 170—172°C (recrystallized from ethyl acetate) (lit.[3] 170—172°C). The product was identical with an authentic sample, with respect to spectral data.

2-Ethoxycarbonylmethyl-1-(2′-methylthiopyrrolidinyl)piperidine (10)——A mixture of **1a** (1.30 g) and **5** (1.55 g) was heated in a sealed tube at 100°C for 7 d. The reaction mixture was purified by column chromatography on alumina to afford **10** (190 mg, 6.6%) using $CHCl_3$: EtOH (10: 1) as an eluant. mp 35—38°C (recrystallized from petro. ether-isopropylether). IR ν_{max}^{Neat}: 3330 (NH), 1710 (C=O). NMR ($CDCl_3$): 1.27 (3H, t, $J=7$ Hz), 2.03 (3H, s), 4.17 (2H, q, $J=7$ Hz), 5.4 (1H, brs). MS *m/e*: 286 (M^+). *Anal.* Calcd for $C_{14}H_{26}N_2O_2S$: C, 58.71; H, 9.15; N, 9.78. Found: C, 58.99; H, 8.89; N, 9.45.

General Procedure for the Reaction of 1a, b, c with Acyclic β-Aminoesters (6a, b, c)——A mixture of **1** (0.01 mol) and **6** (0.01 mol) was heated in a sealed tube at 100—110°C for 7 d. The reaction mixture was separated by column chromatography on alumina with benzene (A), $CHCl_3$ (B), and then $CHCl_3$: MeOH (30: 1) (C) as eluents to give methyl 3-methylthiopropionate (**11**) (A) and N-alkyl 3-methylthiopropionamide (**12**) (B) in the early fraction, lactams (**13**) (B) in the later fraction, and the amidine (**14**) (C). **11**: (bp 65°C/6 mmHg) (lit[11]. bp 170—180°C). IR ν_{max}^{Nujol}: 1740. NMR ($CDCl_3$): 2.13 (3H, s, SMe), 2.67 (4H, m), 3.73 (3H, s, OMe). N-Benzyl 3-methylthiopropionamide (**12a**): mp 50—51°C (recrystallized from isopropylether). IR ν_{max}^{Nujol}: 3280, 1630 NMR ($CDCl_3$): 2.13 (3H, s, SMe), 2.60 (4H, m), 4.43 (2H, d, $J=6$ Hz), 6.50 (1H, brs), 7.33 (5H, s). *Anal.* Calcd for $C_{11}H_{15}NOS$: C, 63.12; H, 7.22; N, 6.69. Found: C, 63.20; H, 7.08; N, 6.63.

N-Methyl 3-Methylthiopropionamide (**12c**): mp 33—35°C (recrystallized from isopropylether). IR ν_{max}^{Nujol}: 3280, 1630, 1570. NMR ($CDCl_3$): 2.10 (3H, s, SMe), 2.8 (3H, d, $J=5$ Hz), 6.80 (1h, brs). *Anal.* Calcd for $C_5H_{11}NOS$: C, 45.10; H, 8.33; N, 10.52. Found: C, 45.42; H, 8.49; N, 10.14. Spectral data for butyrolactam [**13** ($n=1$)], valerolactam [**13** ($n=2$)], and caprolactam [**13** ($n=3$)] were identical with those of authentic samples. Melting points of 2-benzyliminopyrrolidine [**14a** ($n=1$)], 2-benzyliminoazacycloheptane [**14a** ($n=3$)], 2-phenyliminopyrrolidine [**14b** ($n=1$)], 2-phenyliminoazacycloheptane [**14b** ($n=3$)], and 2-methyliminopyrrolidine [**14c** ($n=1$)] are shown in Table I.

2-Benzyliminopiperidine [**14a** ($n=2$)]: mp 92—95°C (recrystallized from CH_2Cl_2-isopropylether). IR ν_{max}^{KBr}: 3400, 1620. NMR ($CDCl_3$): 4.33 (2H, s), 5.3 (1H, s), 7.33 (5H, s). *Anal.* Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.86; H, 8.42; N, 14.68.

Reaction of 1a with 18——A mixture of **1a** (0.6 g) and **18** (1.20 g) was heated in a sealed tube at 100—110°C for 7 d. The reaction mixture was separated by column chromatography on alumina to give ethyl 3-methylthio-3-phenylpropionate (**19**) (470 mg, 56%) using benzene as an eluant. **19**: bp 81°C/6 mmHg. IR ν_{max}^{Neat}: 1740. NMR ($CDCl_3$): 1.17 (3H, t, 6 Hz), 1.91 (3H, s), 2.90 (2H, d, $J=8$ Hz), 4.10 (1H, t, $J=8$ Hz), 4.20 (2H, q, $J=6$ Hz), 7.40 (5H, s). *Anal.* Calcd for $C_{12}H_{16}O_2S$: C, 64.26; H, 7.19. Found: C, 63.89; H, 7.17. **20**: mp 98—100°C (recrystallized from isopropylether). IR ν_{max}^{Nujol} 3280, 1640, 1560. NMR

($CDCl_3$): 1.90 (3H, s), 2.73 (2H, d, $J=8$ Hz), 4.23 (3H, m), 7.33 (11H, m). *Anal.* Calcd for $C_{17}H_{19}NOS$: C, 71.54; H, 6.71; N, 4.51. Found: C, 71.70; H, 6.87; N, 4.73.

Reaction of 14a ($n=1$) with 15——A mixture of **14a** ($n=1$) (1.74 g) and **15** (1.48 g) was heated in a sealed tube at 100—110°C for 7 d. The reaction mixture was separated by column chromatography on alumina to afford N-benzyl 3-ethylthiopropionamide (**16**) (1.25 g, 56%) and **13** ($n=1$) (530 mg, 62%) using $CHCl_3$ as an eluant. **16**: mp 49—50°C (recrystallized from isopropylether). IR ν_{max}^{Nujol}: 3240, 1630, 1560. NMR ($CDCl_3$): 1.20 (3H, t, $J=6$ Hz), 4.33 (2H, d, $J=6$ Hz), 7.3 (5H, s). *Anal.* Calcd for $C_{12}H_{17}NOS$: C, 64.53; H, 7.67; N, 6.27. Found: C, 64.46; H, 7.53; N, 6.11.

Reaction of 21 with 1c——A mixture of **21** (1.61 g)[12] and **1c** (1.43 g) was heated in a sealed tube at 140°C for 3 d. The reaction mixture was separated by column chromatography on alumina to afford **12a** (1.25 g, 59.8%) and **13** ($n=3$) (1.01 g, 88.5%) using $CHCl_3$ as an eluant.

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References and Notes

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