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2-Substituted Thiazolines. III.[1a] Reaction with N-Benzoyl-α-amino Acids

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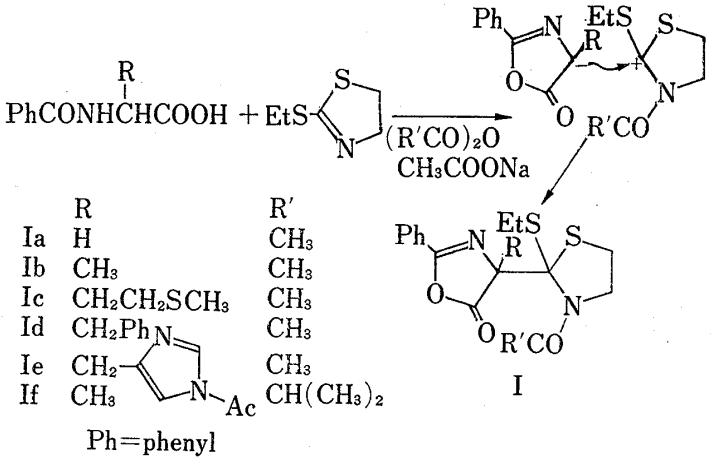
2-Ethylthiothiazoline was reacted with N-benzoyl-α-amino acids in acetic anhydride to give I. Ia was converted into II, III, IV, and V. The oxazolone ring of Ib and Ic was opened to give XI. XIb was converted into thiazoline (XII) and XIII. These thiazolines were reduced to thiazolidine (XIV) and XV, and then converted into the respective aldehydes, XVI and XVII.

In our preceding papers,[1a,b] we reported the reaction of 2-alkylthiothiazoline with some active methylene compounds, *e.g.*, ethyl cyanoacetate, cyanoacetic acid, and rhodanines. The present paper describes the reaction of 2-ethylthiothiazoline with N-benzoyl-α-amino acids and the new route to α-amino-aldehydes, such as N-benzoyl-2-aminopropanal (XVII).

2-Ethylthiothiazoline reacted with N-benzoyl-α-amino acids in acetic anhydride in the presence of sodium acetate at room temperature for several hours to give Ia—e. The use of benzoylglycine ethyl ester instead of benzoylglycine did not give the same product. N-Isobutyryl compound (If) was obtained by using isobutyric anhydride instead of acetic anhydride. Therefore, compounds I were probably formed by the cyclization of N-benzoyl-α-amino acids to 2-phenyloxazolones, followed by nucleophilic attack of 2-phenyloxazolones to the 2-position of 2-ethylthiothiazoline which was activated by the addition of an acyl group to the nitrogen (Chart 1). The infrared (IR) spectra of Ia—f showed absorption maxima in the region of 1804—1826 cm^{-1}, characteristic to saturated oxazolones. Ia showed one proton singlet at δ 6.33 in its nuclear magnetic resonance (NMR) spectrum. These data gave evidence that the oxazolone ring was linked at the 4-position to the thiazolidine ring by a single bond.



	R	R′
Ia	H	CH_3
Ib	CH_3	CH_3
Ic	$CH_2CH_2SCH_3$	CH_3
Id	CH_2Ph	CH_3
Ie	CH_2–(N-Ac)	CH_3
If	CH_3	$CH(CH_3)_2$

Chart 1

In the reaction using N-benzoylglycine, when the reaction time was prolonged to 48 hr at room temperature, the reaction was found to afford a mixture of II (21%), III (23%), IV

1) *a*) Part II: M. Kurumi, T. Okutome, Y. Sakurai, S. Sato, and K. Yamaguchi, *Chem. Pharm. Bull.* (Tokyo), **21**, 1431 (1973); *b*) Y. Sakurai, M. Kurumi, T. Okutome, S. Sato, and K. Yamaguchi, *ibid.*, **21**, 1426 (1973).

2) Location: *3-14-3, Minami-Yawata, Ichikawa, Chiba, 272, Japan.*

(trace), and V (trace). III was not converted to II under the same conditions. From these facts Ia was considered to be an intermediate, which cleaved in either of two ways to give II (path a) or III (path b). This reaction mechanism is analogous to that of the reaction of 2-methylthiazoline with 2-phenyloxazolone. In the latter reaction, reported by Cook, *et al.*,[3] a mixture of VII and VIII was obtained. IV was also obtained exclusively from II by ethanethiol and sodium ethanethioxide at room temperature. Consequently, IV was considered to be the ring cleaved product of II by ethanethiol which was eliminated from Ia during the formation of the double bond in II (path a). II was easily deacetylated by boron trifluoride etherate in methanol to give VI, which was identical to that obtained by direct condensation of 2-alkylthiothiazoline with 2-phenyloxazolone, reported by Kishida, *et al.*[4] The structures of II, III, IV, and V were established from the physicochemical data. II, III, and V showed two ultraviolet (UV) absorption maxima between 230—260 and 370—390 nm, and the IR absorption band in the region of 1700—1750 cm^{-1}, characteristic to 4-unsaturated oxazolones. The characteristic mass fragment at *m/e* 86 due to $(CH_2CH_2NHAc)^+$ strongly supported the structure of III. IV showed IR absorption bands at 3320 (NH), 1689 (N-Ac), 1655 (NHCOPh), and 1628 (CO-S) cm^{-1}.

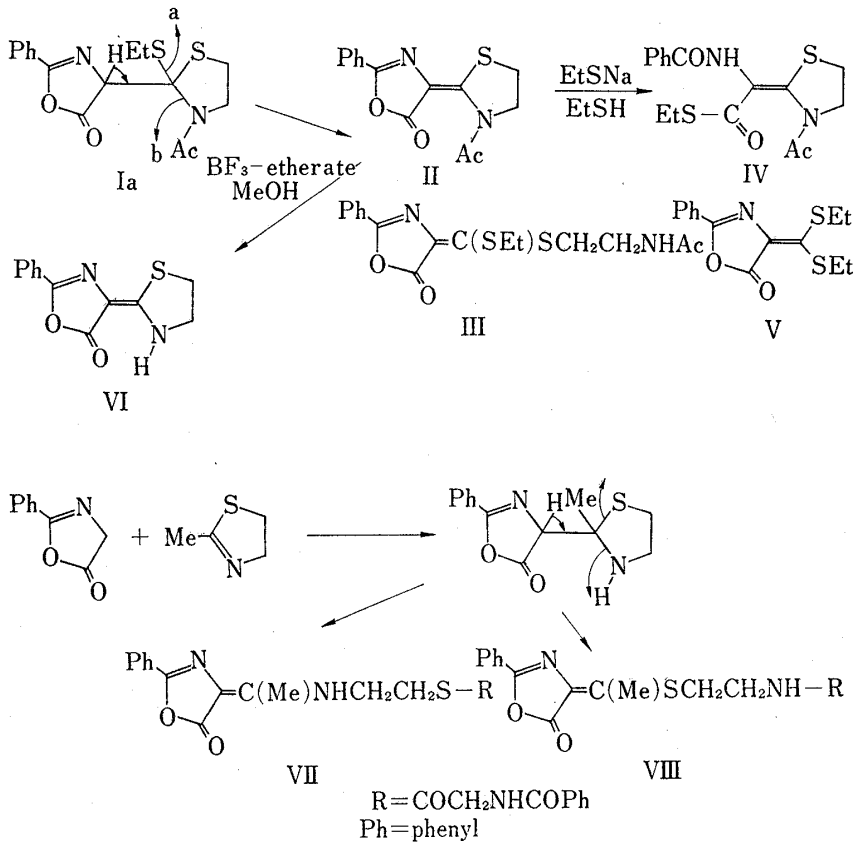


Chart 2

The oxazolone ring in II and VI was easily cleaved by an alkoxide giving an ester (IX). The oxazolone ring of III was also cleaved by an alkoxide giving an ester (X). However, selective cleavage of the oxazolone ring of Ia to XIa was unsuccessful, though Ib and Ic, having either a methyl group or a methylthioethyl group at 4-position of the oxazolone ring, gave the desired products XIb, c and XId, respectively, by alkali treatment.

3) D.C. Cook and A. Lawson, *J. Chem. Soc. Perkin 1*, **1973**, 465.
4) K. Hirai, H. Matsuda, and Y. Kishida, *Chem. Pharm. Bull.* (Tokyo), **20**, 97 (1972).

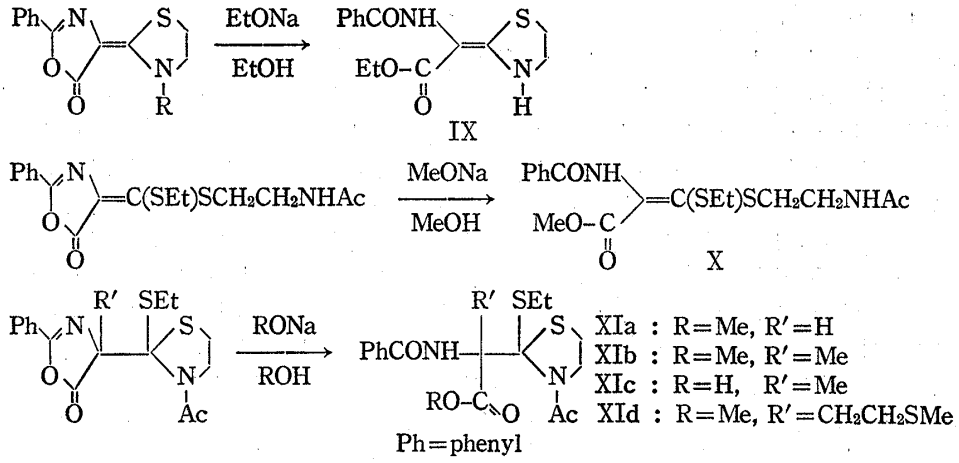


Chart 3

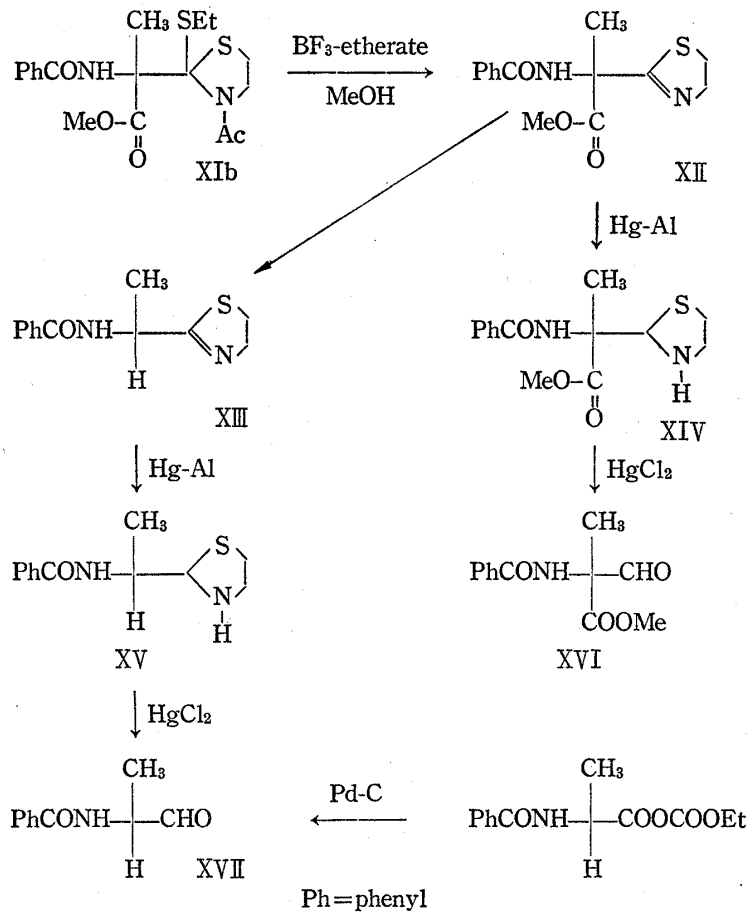


Chart 4

When XIb was treated with boron trifluoride etherate in methanol, the ethylthio and acetyl groups were eliminated simultaneously to give a thiazoline (XII), showing IR absorption bands at 1744 (COOMe), 1652 (NHCO), and 1612 (C=N) cm^{-1}. XII was easily decarboxylated by treatment with aqueous alkali and acid to give a thiazoline (XIII). The C=N double bond in XII and XIII was reduced by aluminum amalgam[5] in moist ether to give thiazolidines, XIV and XV, respectively. Four stereoisomers of XIV, one of these two thiazolidines, were separated after tosylation as two racemates by preparative thin-layer chromatography.

5) A.I. Meyers, R. Munavu, and J. Durandetta, *Tetrahedron Letters*, 1972, 3929.

XIV and XV were transformed into aldehydes, XVI and XVII, respectively, by mercuric chloride in aqueous methanol. XVII thus obtained was identical with that reported by Yamada, *et al.*,[6] who prepared it by direct reduction of mixed carbonic carboxylic acid anhydride obtained from N-benzoylalanine and ethyl chloroformate.

Experimental

All melting points are uncorrected. NMR spectra were taken with a Varian T-60 spectrometer, using tetramethylsilane as internal standard. Unless otherwise stated, NMR spectra were measured in $CDCl_3$ solution. Abbreviation used: s=singlet, d=doublet, q=quartet, m=multiplet, and b=broad. Coupling constants J are given in Hz. IR spectra were taken using a JASCO Model IR-G spectrophotometer.

General Procedure for the Preparation of Ia—f——2-Ethylthiothiazoline (0.01 mole), N-benzoyl-α-amino acid (0.01 mole), and AcONa (0.01 mole) were dissolved in Ac_2O (50 ml) and the mixture was stirred at room temperature for 4 hr. The reaction mixture was poured into ice water, the precipitate formed was collected, and washed with H_2O and EtOH. Recrystallization from $CHCl_3$–hexane gave I a—e as white needles. Compound If was prepared in the same manner using $[(CH_3)_2CHCO]_2O$ instead of Ac_2O. Data of Ia—f are summarized in Table I.

Table I

Compound No.	Yield (%)	mp (°C)	IR ν_{max}^{KBr} cm^{-1}	Formula	Analysis (%) Calcd. (Found) C	H	N
Ia	40	123—124	1826 1655	$C_{16}H_{18}O_3N_2S_2$	54.83 (54.50)	5.18 (5.34)	7.99 (8.17)
Ib	80	136	1818 1807 1663	$C_{17}H_{20}O_3N_2S_2$	56.02 (55.80)	5.53 (5.43)	7.69 (7.82)
Ic	90	122	1804 1655	$C_{19}H_{24}O_3N_2S_3$	53.74 (53.55)	5.70 (5.77)	6.60 (6.60)
Id	80	131	1811 1660	$C_{23}H_{24}O_3N_2S_2$	62.70 (62.51)	5.49 (5.65)	6.36 (6.50)
Ie	70	148—149	1812 1737 1655	$C_{22}H_{24}O_4N_4S_2$	55.91 (55.40)	5.12 (5.32)	11.86 (12.05)
If	70	130—131	1822 1660	$C_{19}H_{24}O_3N_2S_2$	58.16 (57.66)	6.12 (6.37)	7.14 (6.93)

Reaction of 2-Ethylthiothiazoline with N-Benzoylglycine——2-Ethylthiothiazoline (1.47 g), N-benzoylglycine (1.79 g), and AcONa (0.82 g) were dissolved in Ac_2O (50 ml) and the mixture was stirred at room temperature for 48 hr. The reaction mixture was poured into ice water and extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ solution and H_2O, dried over anhyd. Na_2SO_4, and evaporated. The residue was separated into four components by silica gel column chromatography ($CHCl_3$). II eluted first, followed successively by III, IV, and V.

Reaction of II with Ethanethiol——II (1 g) was suspended in EtSH (5 ml) containing Na (0.5 g) and the suspension was left for 1 hr. The reaction mixture was poured into ice water, the precipitate was collected, and its recrystallization from EtOAc–hexane gave IV as white needles (0.8 g). Data of II, III, IV, and V are summarized in Table II.

2-(5′-Oxo-2′-phenyl-4′-oxazolidinylidene)thiazolidine (VI)——II (5 g) was stirred in MeOH (50 ml) containing BF_3–etherate (5 ml) at room temperature for 2 hr. The reaction mixture was poured into ice water and the precipitate was collected. Recrystallization from dimethylformamide (DMF)–MeOH gave VI as yellow needles (4 g), mp 232.5°. IR ν_{max}^{KBr} cm^{-1}: 3290, 1701, 1620. NMR δ (DMSO-d_6): 3.50 (2H, t, J=6.8), 3.90 (2H, t, J=6.8), 7.3—8.0 (5H, m), 9.3 (1H, b). UV λ_{max}^{EtOH} nm (ε): 235 (10500), 240 (10700), 266 (7500), 296 (6700), 355 (33300), 371 (25700). *Anal.* Calcd. for $C_{12}H_{10}O_2N_2S$: C, 58.52; H, 4.09; N, 11.38. Found: C, 58.27; H, 4.32; N, 10.93.

2-(Benzamidoethoxycarbonylmethylene)thiazolidine (IX)——II (2 g) was suspended in EtOH (20 ml) containing Na (0.5 g) and the suspension was stirred at room temperature for 1 hr. The reaction mixture was acidified with AcOH and poured into ice water. The precipitate was collected and recrystallized from

6) H. Seki, K. Koga, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 361 (1972).

Table II

Compound No.	Yield mg (%)	mp (°C)	IR ν_{max}^{KBr} cm^{-1}	NMR δ	UV λ_{max}^{EtOH} nm (ε)	Formula	Analysis (%) Calcd. (Found) C	H	N
II	600 (21)	148	1765 1737 1693 1628	2.45(s) 3.19(t) 4.38(t) 7.4—8.2(m)	257.5 (11900) 282 (10000) 371 (22100)	$C_{14}H_{12}O_3N_2S$	58.32 (58.10)	4.20 (4.38)	9.72 (9.86)
III	800 (23)	101	3300 1749 1645 1617	1.38(t) 1.99(s) 3.22(q) 3.5—3.7(m) 6.4(b) 7.4—8.2(m)	239 (8300) 247 (8800) 264 (10900) 294 (6700) 391 (26600)	$C_{16}H_{18}O_3N_2S_2$	54.83 (54.35)	5.18 (5.30)	7.99 (8.13)
IV	20 (0.6)	164—165	3320 1689 1655 1628	1.26(t) 2.22(s) 2.93(q) 3.03(t) 4.05(t) 7.4—8.8(m)	230 (12500) 263 (9100) 322 (15300)	$C_{16}H_{18}O_3N_2S_2$	54.83 (54.52)	5.18 (5.37)	7.99 (8.26)
V	50 (1.7)	113—114	1745 1726 1612 1504	1.40(t) 3.24(q) 3.56(q) 7.4—8.3(m)	239 (8300) 247 (8900) 264 (10700) 294 (6900) 391 (27700)	$C_{14}H_{15}O_2NS_2$	57.31 (57.04)	5.13 (5.30)	4.77 (4.93)

acetone to IX as white needles (1.5 g), mp 182.5—183°. IR ν_{max}^{KBr} cm^{-1}: 3330, 3280, 1648. NMR δ (DMSO-d_6): 1.14 (3H, t, J=7.5), 3.17 (2H, t, J=7.0), 3.89 (2H, t, J=7.0). 4.07 (2H, q, J=7.5), 7.4—8.1 (5H, m), 8.19 (1H, b), 9.17 (1H, b). UV λ_{max}^{EtOH} nm (ε): 226.5 (14300), 287.5 (20100). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2S$: C, 57.53; H, 5.52; N, 9.59. Found: C, 57.30; H, 5.50; N, 9.54.

α-(Acetamidoethylthioethylthiomethylene)-N-benzoylglycine Methyl Ester (X)——III (1 g) was dissolved in MeONa solution (10 ml MeOH and 0.5 g Na) and the solution was stirred at room temperature for 1 hr. The reaction mixture was acidified with AcOH, poured into water, and the precipitate was collected and recrystallized from EtOAc–hexane to X as white needles (0.7 g), mp 130°. IR ν_{max}^{KBr} cm^{-1}: 3252, 1712, 1670, 1622. NMR δ: 1.29 (3H, t, J=7.3), 1.98 (3H, s), 2.78 (2H, q, J=7.3), 3.00 (2H, t, J=6.2), 3.49 (2H, t, J=6.2), 3.91 (3H, s), 6.1 (1H, b), 7.4—8.1 (5H, m), 8.9 (1H, b). UV λ_{max}^{EtOH} nm (ε): 231.5 (15100), 310 (13700). *Anal.* Calcd. for $C_{17}H_{22}O_4N_2S_2$: C, 53.38; H, 5.75; N, 7.32. Found: C, 53.01; H, 6.06; N, 7.39.

α-[2-(2-Ethylthio-3-acetylthiazolidinyl)]-N-benzoylalnine (XIc)——Ib (3.6 g) was suspended in 2% NaOH and the suspension was stirred at room temperature for 24 hr. The reaction mixture was filtered and the filtrate was acidified with 10% HCl. The precipitate was collected and recrystallized from DMF–MeOH to XIc as white needles (1.5 g), mp 171—172°. IR ν_{max}^{KBr} cm^{-1}: 1717, 1655. NMR δ (DMSO-d_6); 1.17 (3H, t, J=7.5), 1.49 (3H, s), 2.30 (3H, s), 7.4—8.1 (5H, m), 10.44 (1H, s), 12.5 (1H, b). *Anal.* Calcd. for $C_{17}H_{22}O_4N_2S_2$: C, 53.38; H, 5.75; N, 7.32. Found: C, 53.01; H, 5.80; N, 7.37.

α-[2-(2-Ethylthio-3-acetylthiazolidinyl)]-N-benzoylalanine Methyl Ester (XIb)——Ib (3.6 g) was dissolved in MeONa solution (20 ml MeOH and 0.3 g Na) and the solution was stirred at room temperature for 1 hr. The precipitate was collected and recrystallized from EtOAc to XIb as white prisms (3.8 g), mp 211°. IR ν_{max}^{KBr} cm^{-1}: 3230, 1731, 1655. NMR δ: 1.24 (3H, t, J=7.0), 1.54 (3H, s), 2.24 (3H, s), 2.2—3.3 (4H, m), 3.81

(3H, s), 4.01 (2H, m), 7.3—8.2 (5H, m), 10.15 (1H, s). *Anal.* Calcd. for $C_{18}H_{24}O_4N_2S_2$: C, 54.52; H,6. 10; N, 7.07. Found: C, 54.42; H, 6.14; N, 7.12.

α-[2-(2-Ethylthio-3-acetylthiazolidinyl)]-N-benzoylmethionine Methyl Ester (XId)——XId was prepared in the same manner as for XIb. mp 152—153°. IR ν_{max}^{KBr} cm^{-1}: 3240, 1732, 1650. NMR δ: 1.25 (3H, t, J= 7.5), 2.09 (3H, s), 2.28 (3H, s), 3.80 (3H, s), 7.3—8.2 (5H, m), 10.13 (1H, s). *Anal.* Calcd. for $C_{20}H_{28}O_4N_2S_3$: C, 52.60; H, 6.18; N, 6.13. Found: C, 52.42; H, 6.41; N, 6.15.

α-(2-Thiazolinyl)-N-benzoylalanine Methyl Ester (XII)——XIb (2 g) was refluxed in MeOH (50 ml) containing BF_3-etherate (4 ml) for 30 min. When cooled, the reaction mixture was evaporated and the residue was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$ solution and H_2O, dried over anhyd. Na_2SO_4, and evaporated. The oily residue was purified by silica gel column chromatography ($CHCl_3$). Recrystallization of the eluate from EtOAc–hexane gave XII as white prisms (0.7 g), mp 88°. IR ν_{max}^{KBr} cm^{-1}: 3390, 1744, 1652, 1612. NMR δ: 1.95 (3H, s), 3.41 (2H, t, J=8.5), 3.79 (3H, s), 4.35 (2H, t, J=8.5), 7.4—8.0 (m). *Anal.* Calcd. for $C_{14}H_{16}O_3N_2S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.84; H, 5.81; N, 9.56.

2-(1′-Benzoylaminoethyl)thiazoline (XIII)——XII (1 g) was stirred in 10% NaOH (30 ml) at room temperature for 18 hr. The reaction mixture was acidified with 10% HCl and extracted with EtOAc. The extract was washed with H_2O, dried over anhyd. Na_2SO_4, and evaporated. The residual oil was purified by silica gel column chromatography ($CHCl_3$) and recrystallization of the eluate from EtOAc–hexane gave XIII as white prisms (0.5 g), mp 96—97°. IR ν_{max}^{KBr} cm^{-1}: 3310, 1640, 1530. NMR δ: 1.52 (3H, d, J=7.0), 3.32 (2H, t, J=8.0), 4.25 (2H, t, J=8.0), 5.02 (1H, m), 7.3—8.0 (m). *Anal.* Calcd. for $C_{12}H_{14}ON_2S$: C, 61.51; H, 6.02; N, 11.97. Found: C, 61.45; H, 6.31; N, 11.97.

α-(2-Thiazolidinyl)-N-benzoylalanine Methyl Ester (XIV)——Aluminum (5 g) was etched with 5% KOH (50 ml) until vigorous evolution of H_2 occurred. The aqueous solution was decanted and the residue was washed with H_2O. A solution of 0.5% $HgCl_2$ (30 ml) was added to aluminum, and the mixture was shaken for 2—3 min and decanted again. Water was added to wash the amalgam and the entire process of adding $HgCl_2$ solution was repeated. The amalgam was then washed first with EtOH and with ether. A moist ether solution of XII (1 g) containing the amalgam was refluxed for 1 hr, then the salts were filtered off, and the ether solution was dried and concentrated. The oily residue was purified by silica gel column chromatography ($CHCl_3$: MeOH=100: 1) to give XIV as colorless oil (0.9 g); hydrochloride, mp 115—118°. IR ν_{max}^{film} cm^{-1}: 3300, 1733, 1650, 1513. NMR δ: 1.82 (s), 1.87 (s), 2.61 (1H, s, NH), 3.84 (3H, s), 4.95 (s), 5.19 (s), 7.2—8.0 (m). *Anal.* Calcd. for (hydrochloride) $C_{14}H_{19}O_3N_2SCl$: C, 50.83; H, 5.79; N, 8.47. Found: C, 50.64; H, 6.16; N, 8.40.

Two racemates of N-tosylated XIV were separated by preparative thin-layer chromatography into compound A (*Rf* 0.85) and B (*Rf* 0.80) (solvent EtOAc: benzene=1: 1). A; mp 150—151°. *Anal.* Calcd. for $C_{21}H_{24}O_5N_2S_2$: C, 56.25; H, 5.36; N, 6.25. Found: C, 56.51; H, 5.61; N, 6.33. B; mp 195—196°. *Anal.* Calcd. for $C_{21}H_{24}O_5N_2S_2$: C, 56.25; H, 5.36; N, 6.25. Found: C, 56.21; H, 5.30; N, 6.70.

2-(1′-Benzoylaminoethyl)thiazolidine (XV)——XV was prepared in the same manner as for XIV. Recrystallization of the eluate from EtOAc–hexane gave XV as white needles, mp 111—112°. IR ν_{max}^{KBr} cm^{-1}: 3310, 3200, 1638, 1531. NMR δ: 1.29 (d, J=6.0), 1.34 (d, J=6.0), 2.11 (1H, s, –NH–), 7.3—8.0 (m). *Anal.* Calcd. for $C_{12}H_{16}ON_2S$: C, 60.98; H, 6.82; N, 11.85. Found: C, 61.10; H, 7.32; N, 11.73.

α-Formyl-N-benzoylalanine Methyl Ester (XVI)——MeOH solution (1 ml) of XIV (0.5 g) was added dropwise into 5% $HgCl_2$ solution (20 ml) and the mixture was stirred at room temperature for 1 hr. The reaction mixture was extracted with EtOAc, the extract was washed with H_2O, dried over anhyd. Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography ($CHCl_3$). Recrystallization of the eluate from EtOAc–hexane gave XVI as white prisms (0.2 g), mp 102—103°. IR ν_{max}^{KBr} cm^{-1}: 3350, 1760, 1729, 1633. NMR δ: 1.79 (3H, s), 3.84 (3H, s), 7.4—8.0 (m), 9.73 (1H, s, CHO). *Anal.* Calcd. for $C_{12}H_{13}O_4N$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.01; H, 5.83; N, 6.11. 2,4-Dinitrophenylhydrazone of XVI; mp 194°. *Anal.* Calcd. for $C_{18}H_{17}O_7N_5$: C, 52.05; H, 4.13; N, 16.86. Found: C, 52.18; H, 4.36; N, 16.87.

N-Benzoyl-2-aminopropanal (XVII)——XVII was prepared in the same manner as for XVI as colorless oil. IR ν_{max}^{film} cm^{-1}: 3330, 1725, 1635, 1525. NMR δ: 1.49 (3H, d, J=7.0), 4.8 (m), 7.3—8.0 (m), 9.68 (1H, s, CHO). 2,4-Dinitrophenylhydrazone of XVII; mp 183—184°. IR ν_{max}^{KBr} cm^{-1}: 3300, 1618. *Anal.* Calcd. for $C_{16}H_{15}O_5N_5$: C, 53.78; H, 4.23; N, 19.60. Found: C, 53.89; H, 4.22; N, 19.11.

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