[Chem. Pharm. Bull. 20(3) 543—549 (1972)] UDC 547.461.4.02.04 : 547.451.1.04

Stereochemical Studies. XIII.[1] Determination of the Absolute Configuration of Mercaptosuccinic Acid by Chemical Correlation with Glyceraldehyde[2]

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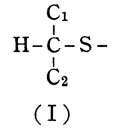
(Received September 21, 1971)

The absolute configuration of mercaptosuccinic acid was unequivocally determined by its chemical correlation with glyceraldehyde *via* (−)N-acetyl-4-allomercapto-L-proline thiol-lactone ((−)XI), as shown in Chart 2 and Chart 3. It becomes clear that mercaptosuccinic acid, with a positive rotation in water, belongs to the R-series. Our results show that Fredga's proposal, based on the method of quasi-racemate formation, is correct.

This method of configurational correlation is unique since chemical correlation was performed without replacing the C-S bond with the C-O bond.

Compounds of type I, which carry sulfur at the asymmetric carbon atom, have been synthesized and found in natural products. Absolute configurations of this type of compounds are either tentative or unknown except for biotin, whose absolute configuration was unequivocally determined by X-ray fluorescence method.[4] In mercaptosuccinic acidand its analogs, which are considered to be most suitable for the configurational standard of these compounds, the absolute configurations have been proposed by the method of quasi-racemates.[5] Mechanistic considera tions[6] and optical properties[7] are also used to estimate the absolute configuration. Chemical correlation of mercaptosuccinic acid withglyceraldehyde, a configurational standard for hydroxy acids and carbohydrates, or with serine, a configurational standard for amino acids, appears impossible, because replacement of the C-S bond to the C-O bond or the C-N bond seems inevitable in their correlation. Some devices are, therefore, required for this correlation without affecting the bonds at their asymmetric carbon atoms.



(I)

Consulting references, however, we found that the absolute configuration of serine had been chemically correlated with glyceraldehyde, as shown in Chart 1. It has been shown that the carboxyl group and the hydroxyl group are *trans* in L-hydroxyproline (L-III) by chemical[8] as well as X-ray[9] studies, while *cis* in L-al-lohydroxyproline by formation of a lactone (L-II).[10] Moreover, L-III was chemically correlated *via* (+)methoxysuccinic acid (IV) to D-glyceraldehyde by removing the asymmetry at 2-position.[8] On the other hand,

1) Part XII: K. Koga, Y. Yamamoto and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 616 (1972).
2) For a preliminary communication on this work, see S. Yamada, Y. Murakami and K. Koga, *Tetrahedron Letters*, **1968**, 1501.
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4) J. Trotter and J.A. Hamilton, *Biochemistry*, **5**, 713 (1966).
5) A. Fredga, *Tetrahedron*, **8**, 126 (1960).
6) *a*) W.A. Bonner, *J. Org. Chem.*, **32**, 2496 (1967); *b*) G. Claeson and J. Pedersen, *Tetrahedron Letters*, **1968**, 3975.
7) *a*) A. Fredga, J.P. Jennings, W. Klyne, P.M. Scopes, B. Sjöberg, and S. Sjöberg, *J. Chem. Soc.*, **1965**, 3928; *b*) W.A. Bonner and R.A. Grimm, *J. Org. Chem.*, **32**, 3022 (1967).
8) *a*) T. Kaneko, *Nippon Kagaku Zasshi*, **61**, 207 (1940); *b*) A. Neuberger, *J. Chem. Soc.*, **1945**, 429.
9) J. Zussman, *Acta Cryst.*, **4**, 72 (1951).
10) A.A. Patchett and B. Witkop, *J. Am. Chem. Soc.*, **79**, 185 (1957).

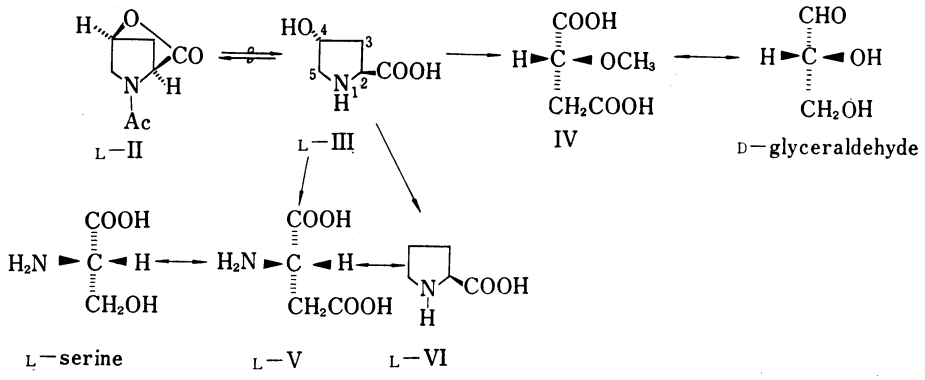

Chart 1

L-III was chemically correlated to L-aspartic acid (L-V), to L-proline (L-VI),[8] and further to L-serine[11] by removing the asymmetry at 4-position. Thus, glyceraldehyde and serine are chemically correlated *via* L-III.

Using this method of chemical correlation, it seems possible to determine the absolute configuration of mercaptosuccinic acid by synthesis of the thiol-lactone ((−)-XI) instead of the lactone (L-II) to determine the *cis*-relationship at C-2 and C-4 in (−)-XI, followed by removing the asymmetry at C-2. The present paper reports synthesis of the thiol-lactone ((−)-XI) from L-III followed by the chemical correlation of its configuration with mercaptosuccinic acid *via* 4-methylsulfonylpyrrolidone (XV), as shown in Chart 2 and Chart 3.

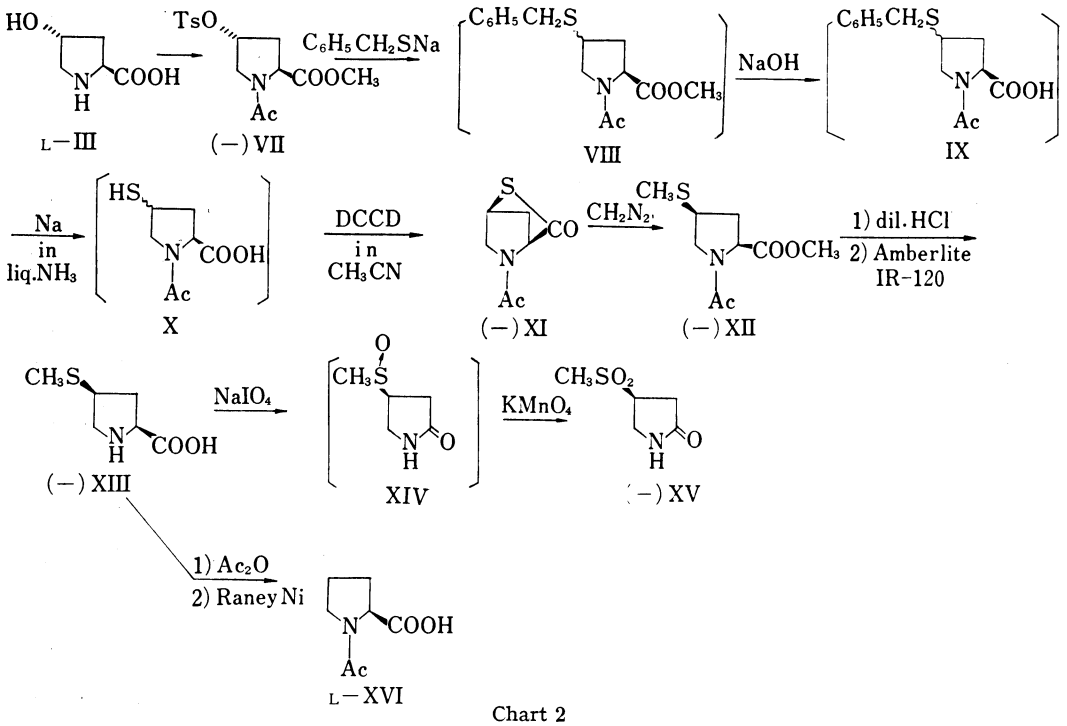

Chart 2

11) J.P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," Vol. 1, John Wiley and Sons, Inc. New York and London, 1961, Chapter II.

The reaction of (−)N-acetyl-O-*p*-tolylsulfonyl-L-hydroxyproline methyl ester ((−)VII) prepared from L-hydroxyproline (L-III), according to the reported method,[8b 10] with sodium benzylmercaptide in methanol gave the 4-benzylthio derivative (VIII) as an oily substance. Hydrolysis of VIII with an equimolar amount of sodium hydroxide in aqueous methanol afforded the corresponding carboxylic acid (IX). Debenzylation of IX with sodium in liquid ammonia afforded the 4-thiol derivative (X), which was converted to the thiol-lactone ((−)XI), bp 142° (0.08 mmHg), $[\alpha]_D^{24}$ −114° ($CHCl_3$), with N,N'-dicyclohexylcarbodiimide in acetonitrile. Mass spectral data, as well as molecular weight measurements, proved this to be a monomer. Therefore, we concluded that the relative configuration at C-2 and C-4 in (−)XI is *cis*. (−)XI was subjected to a mild ring opening reaction with diazomethane in a mixture of methanol and ether[12] to yield (−)XII as an oil. Hydrolysis of (−)XII with dilute hydrochloric acid and treatment of the product with Amberlite IR-120 gave the amino acid ((−)XIII).[10] To ascertain whether the configuration at C-2 was retained during the reactions from L-III to (−)XIII, the amino acid ((−)XIII) was subjected to acetylation with acetic anhydride in acetic acid followed by desulfurization with Raney nickel to (−)N-acetyl-L-proline (L-XVI). It was shown that the configuration at C-2 was retained during the above processes.

Oxidative decarboxylation of the amino acid ((−)XIII) was performed with $NaIO_4$,[13] followed by further oxidation of the expected sulfoxide (XIV) with $KMnO_4$[14] to yield the sulfonyl lactam ((−)XV), mp 167—169° (decomp.), $[\alpha]_D^{23}$ −28.5° (methanol). Therefore, the absolute configuration of (−)XV is demonstrated to be S.

The configurational correlation of (−)XV with mercaptosuccinic acid was attempted, as shown in Chart 3. Using the reported method,[15] L-asparagine (L-XVII) was converted to (−)-2-bromosuccinamic acid ((−)XVIII), the absolute configuration of which had been previously determined as S.[16] The reaction of (−)XVIII with sodium methylmercaptide gave the methylthio derivative ((+)XIX), which was esterified with diazomethane to (+)XX. Treatment of (+)XX with an equimolar amount of normal sodium hydroxide in cold methanol, according to the method of Sondheimer,[17] afforded the imide. Although this reaction was

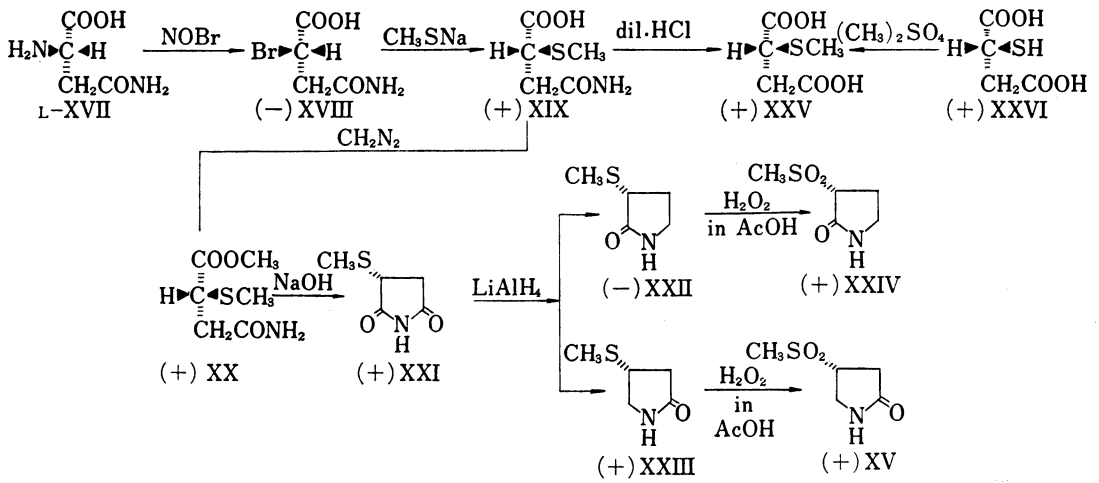

Chart 3

12) M. Akagi, S. Tejima and M. Haga, *Chem. Pharm. Bull.* (Tokyo), **8**, 1114 (1960).
13) P.D. Bragg and L. Hough, *J. Chem. Soc.*, **1958**, 4050 .
14) N.J. Leonard and C.R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).
15) *a*) P. Walden, *Ber.*, **28**, 2766 (1895); *b*) S. Kallenberg, *ibid.*, **50**, 90 (1917).
16) Y. Murakami and Y. Iidaka, *Chem. Pharm. Bull.* (Tokyo), **17**, 2397 (1969).
17) E. Sondheimer and R.W. Holley, *J. Am. Chem. Soc.*, **76**, 2467 (1954).

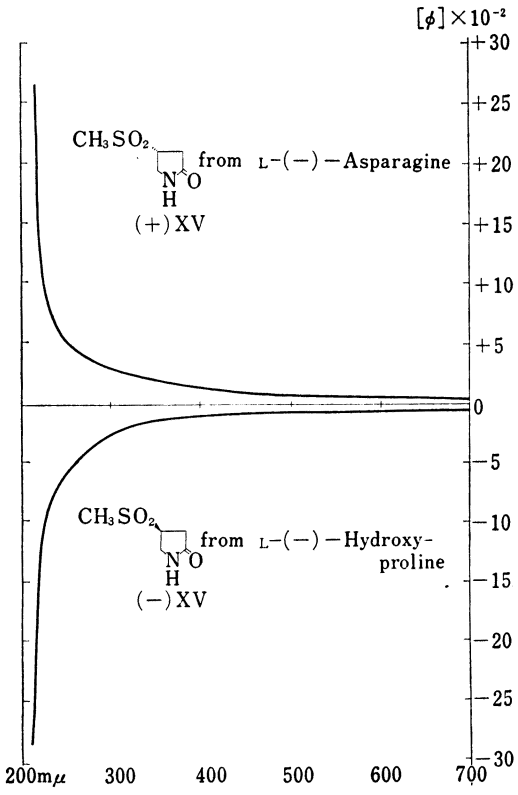

Fig. 1. ORD curves of (+)- and (−)-XV

accompanied with considerable racemization, an optically active imide ((+)XXI) was easily separated by treatment of the reaction product with benzene. Partial reduction of (+)XXI with a restricted amount of lithium aluminum hydride (about 0.75 molar equivalent) in dehydrated tetrahydrofuran afforded a reaction mixture containing two kinds of lactams ((−) XXII and (+)XXIII). Separation of (−)XXII and (+)XXIII was successful using column chromatography on alumina with chloroform followed by column chromatography on silica gel with 5% ethanol in benzene. Oxidation of (−)XXII and (+)XXIII with hydrogen peroxide in acetic acid gave (+)XXIVand (+)XV, respectively. (+)XV, in this way, obtained mp 166—168° (decomp.), $[\alpha]_D^{27}$ +26.8° (methanol) was found to be an antipode of (−)XV obtained from L-III, because their IR spectra (KBr) were superimposable, but their ORD curves were antipodal, as shown in Fig. 1.

Hydrolysis of (+)XIX with 10% hydrochloric acid afforded (+)XXV.[18] The reaction of (+)mercaptosuccinic acid ((+) XXVI)[19] with dimethyl sulfate afforded the same (+)-methylsulfide ((+)XXV). Accordingly, the absolute configuration of (+)mercaptosuccinic acid ((+)XXVI) was determined to be R, as shown in Chart 3. Fortunately, Fredga's proposal, based on the quasi-racemates method, agreed with our demonstration.

Studies on optical rotatory dispersion of the optically active sulfides obtained will be published in the near future.

Experimental[20]

N-Acetyl-4-benzylthio-L-proline Methyl Ester (VIII)——A solution of (−) VII (mp 71—73°, $[\alpha]_D^{28}$ −40.7° (c=0.486, MeOH). Reported mp[8b] 60°, mp[10] 71—73°) (70 g, 0.205 mole) in ab. MeOH (750 ml) containing Na (6.15 g, 0.267 atom) and benzylmercaptan (33.1 g, 0.267 mole) was refluxed for 3 hr under N_2. After the solvent was removed *in vacuo*, H_2O was added to the residue, and the whole was extracted with ether. The ether solution was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to give an oil. Column chromatography on silica gel (400 g) with benzene followed by $CHCl_3$ afforded VIII (44 g, 73.2%) as an oil, $[\alpha]_D^{33}$ −24.7° (c=1.258, MeOH). IR ν_{max}^{liq} cm^{-1}: 1750 (ester), 1667 (amide). This sample was used in

18) M. Matell, *Arkiv. Kemi.*, **5**, 17 (1952).
19) P.A. Levene and L.A. Mikeska, *J. Biol. Chem.*, **60**, 685 (1924).
20) All melting and boiling points are uncorrected. IR spectra were measured with a spectrometer, Model DS-402G, Japan Spectroscopic Co., Ltd. NMR spectra were measured with a spectrometer, Model 3H-60, Japan Electron Optics Lab. using DSS as the internal standard. Optical rotations were measured with a Yanagimoto photomagnetic direct reading polarimeter, Model OR-20. Optical rotatory dispersion measurements were carried out with a spectrometer, Model ORD/UV-5, Japan Spectroscopic Co., Ltd. Microanalyses and spectral measurements were performed by the members of the Central Analysis Room of this Faculty.

the next step without further purification.

N-Acetyl-4-benzylthio-L-proline (IX)——To a solution of VIII (44 g, 0.150 mole) in MeOH (200 ml) was added 1N NaOH (155 ml, 0.155 mole) under ice-cooling and the whole was kept overnight in a refrigerator. The reaction mixture was diluted with H_2O, acidified with 1N HCl (170 ml, 0.17 mole) and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried over anhyd. Na_2SO_4 and evaporated to dryness to give IX (40.8 g, 97.3%), as a hard oily substance, $[\alpha]_D^{33}-31.3°$ ($c=1.046$, MeOH).

Cyclohexylammonium Salt: The salt was prepared by mixing IX and cyclohexylamine in ether and was recrystallized from EtOH–isopropyl ether to a colorless amorphous powder of mp 155—158°, $[\alpha]_D^{18}-71.7°$ ($c=0.920$, MeOH). IR ν_{max}^{KBr} cm^{-1}: 1628 (amide and carboxylate). *Anal.* Calcd. for $C_{20}H_{30}O_3N_2S$: C, 63.46; H, 7.98; N, 7.40. Found: C, 63.75; H, 7.88; N, 7.19.

4-Benzylthio-L-proline Hydrochloride Monohydrate: A mixture of IX (130 mg) and 2N HCl (15 ml) was refluxed for 2 hr, then evaporated to dryness *in vacuo* to give a solid residue. An analytical sample was obtained by recrystallization of the solid from EtOH–$(C_2H_5)_2O$ to colorless needles of mp 90.5—92°, $[\alpha]_{350}^{23.5}+26°$ ($c=0.940$, MeOH) from ORD curve. IR ν_{max}^{KBr} cm^{-1}: 3356 (H_2O), 1735 (carboxyl). *Anal.* Calcd. for $C_{12}H_{16}O_2NSCl\cdot H_2O$: C, 49.38; H, 6.21; N, 4.80. Found: C, 49.58; H, 6.41; N, 4.65.

N-Acetyl-4-mercapto-L-proline (X)——Na (9.5 g, 0.41 atom) was added to a solution of IX (40.8 g, 0.146 mole) in liquid ammonia (*ca.* 700 ml) until the blue color persisted for more than 15 sec. After evaporation of the ammonia, H_2O was added to the residue and the whole was washed with ether to remove toluene. The aqueous solution was acidified with 1N HCl to pH 2, then evaporated to dryness *in vacuo* under N_2. The residue was extracted with a mixture of $CHCl_3$–MeOH, and the organic solution was evaporated *in vacuo* to give X (23.5 g, 85%) as a pale yellow oil, $[\alpha]_D^{14}-42.5°$ ($c=0.922$, MeOH). IR $\nu_{max}^{liq.}$ cm^{-1}: 2560 (SH). This sample became solid on standing, but was used in the next step without further purification.

(−)N-Acetyl-4-allomercapto-L-proline Thiol-lactone ((−)XI)——A solution of N,N′-dicyclohexylcarbodiimide (25.0 g, 0.121 mole) in dehyd. CH_3CN (80 ml) was slowly added to a solution of X (23.0 g, 0.123 mole) in dehyd. CH_3CN (420 ml). After stirring for 2.5 hr, the reaction mixture was left at room temperature for 2 days. Precipitated N,N′-dicyclohexylurea was filtered off, and the filtrate was evaporated to dryness *in vacuo* to give a colorless oil. This oil was purified by column chromatography on silica gel (150 g) with $CHCl_3$ to give (−)XI (13.3 g, 64%) as a colorless oil of bp 142° (0.08 mmHg), $[\alpha]_D^{24}-114°$ ($c=1.006$, $CHCl_3$). IR ν_{max}^{liq} cm^{-1}: 1735, 1715 (thiol-lactone), 1650 (amide). Molecular weight[21] Calcd. for $C_7H_9O_2NS$: 171. Found: 173. Mass Spectrum[22] *m/e*: 171 (M^+, 1% of the base peak). *Anal.* Calcd. for $C_7H_9O_2NS$: C, 49.10; H, 5.30; N, 8.18; S, 18.73. Found: C, 49.03; H, 5.56; H, 8.10; S, 18.96.

(−)N-Acetyl-4-allomethylthio-L-proline Methyl Ester ((−)XII)——A solution of CH_2N_2 (prepared from nitrosomethylurea (35 g, 0.34 mole)) in ether (400 ml) was added to a solution of (−)XI (10.8 g, 0.063 mole) in MeOH (150 ml) and the whole was left for a week in a refrigerator. After decomposing the excess CH_2N_2 with AcOH, the solvent was evaporated to dryness *in vacuo* to give an oil (12.2 g), which was purified by column chromatography on silica gel with $CHCl_3$ to give XII (11.2 g, 82%) as a colorless oil of bp 156—157° (0.06 mmHg), $[\alpha]_D^{25}-47.3°$ ($c=1.174$, MeOH). IR ν_{max}^{liq} cm^{-1}: 1748 (ester), 1650 (amide). *Anal.* Calcd. for $C_9H_{15}O_3NS$: C, 49.75; H, 6.96; N, 6.45. Found: C, 49.77; H, 7.09; N, 6.58.

(−)4-Allomethylthio-L-proline ((−)XIII)——To a solution of (−)XII (10.0 g) in MeOH (25 ml) was added 2N HCl (250 ml) and the whole was refluxed for 2 hr. The reaction mixture was evaporated to dryness *in vacuo* to give an oily residue, which was passed through a column of Amberlite IR-120 (H^+-form, 150 ml of wet volume) with 7% aqueous ammonia as the eluting solvent. The solvent was evaporated *in vacuo* to dryness to give the amino acid ((−)XIII) (6.20 g, 83.5%), mp 227—228° (decomp.). An analytical sample was obtained by recrystallization from H_2O–EtOH–$(C_2H_5)_2O$ as colorless needles of mp 242° (decomp.), $[\alpha]_D^{28}-60.8°$ ($c=0.914$, H_2O) (reported[12] mp 243—244°). This sample showed one spot on paper partition chromatography: $Rf=0.32$ (BuOH–EtOH–2N aqueous NH_3 (5: 1: 2)), $Rf=0.49$ (BuOH–AcOH–H_2O (4: 1: 2)). IR ν_{max}^{KBr} cm^{-1}: 1619 (COO^-, NH_3^+). NMR (in D_2O) τ: 7.87 (3H, singlet, -SCH_3). *Anal.* Calcd. for $C_6H_{11}O_2NS$: C, 44.70; H, 6.88; N, 8.69. Found: C, 44.99; H, 6.71; N, 8.97.

(−)4-Methylsulfonylpyrrolidone ((−)XV)——A solution of $NaIO_4$ (5.30 g, 24.8 mmoles) in H_2O (100 ml) was added to a solution of (−)XIII (1.0 g, 6.2 mmoles) in H_2O (30 ml) and the whole was left overnight in a dark place. The reaction mixture was evaporated to dryness *in vacuo* and the residue was extracted with EtOH. The EtOH solution was evaporated to dryness *in vacuo* to give a dark brown oil (0.8 g) (IR ν_{max}^{liq} cm^{-1}: 1042 (-SO-)). $KMnO_4$ (1.7 g, 11 mmoles) was added to a solution of this oil in H_2O (10 ml) and acetone (10 ml) under ice-cooling until the color of $KMnO_4$ persisted. After stirring the mixture for another 2 hr at room temperature, the excess $KMnO_4$ was decomposed with H_2O_2, then the precipitate was filtered off. The filtrate was neutralized with dil. HCl and evaporated to dryness *in vacuo*. The residue was treated with charcoal, followed by column chromatography on alumina (15 g) with 10% EtOH in $CHCl_3$ to give crystals of (−)XV (0.11 g, 11%) of mp 165—168° (decomp.). Two recrystallizations of this sample from EtOH–ether-hexane afforded colorless leaflets mp 167—169° (decomp.), $[\alpha]_D^{23}-28.5°$ ($c=0.604$, MeOH).

21) Performed with a Hitachi 115 type apparatus (vapor pressure method).
22) Performed with a Hitachi RMU-6D instrument, using an indirect inlet system.

IR ν_{max}^{KBr} cm^{-1}: 3212 (NH), 1690—1668 (five-membered lactam), 1289, 1270, 1128 (-SO_2-). *Anal.* Calcd. for $C_5H_9O_3NS$: C, 36.81; H, 5.56; N, 8.59. Found: C, 36.70; H, 5.73; N, 8.57.

(−)N-Acetyl-L-proline ((−)XVI)——To a suspension of (−)XIII (0.5 g) in AcOH (10 ml) was added Ac_2O (0.41 g). The whole was heated at 100° for 5 min and then kept at room temperature for further 2 hr. The reaction mixture was evaporated to dryness *in vacuo* to give an oil. A mixture of this oil and Raney Ni (prepared from 15 g of the alloy) in 75% aqueous EtOH (50 ml) was refluxed for 5 hr. The reaction mixture was filtered, and the filtrate was evaporated *in vacuo*. The residue and the Raney Ni was treated with a solution of NaOH (2.4 g) in H_2O (50 ml), filtered, and the filtrate was passed through a column of Amberlite IR-120 (H^+-form, 100 ml of wet volume) which was eluted with H_2O. The eluted solution was evaporated to dryness *in vacuo* to give crystalline (−)XVI (230 mg, 46%), which was recrystallized from acetone-hexane to give colorless needles of mp 115—116°, $[\alpha]_D^{28}$ −117.4° (c=0.834, H_2O). This sample was shown to be identical with an authentic sample of (−)N-acetyl-L-proline[10] by IR and mixed mp test. *Anal.* Calcd. for $C_7H_{11}O_3N$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.42; H, 7.08; N, 9.18.

(+)2-Methylthiosuccinamic Acid (((+)XIX)——A solution of MeSH (prepared from S-methylisothiourea sulfate (40 g, 0.286 mole) according to the known method[23] in 1N NaOH (158 ml) was added to a solution of (−)2-bromosuccinamic acid[15] (29.4 g, 0.15 mole) and Na_2CO_3 (7.95 g, 0.075 mole) in H_2O (150 ml). The reaction mixture was placed in a refrigerator for 3 days, then it was acidified with conc. HCl (16 ml) and condensed *in vacuo* to *ca.* 50 ml. After cooling in a refrigerator, the crystalline mass which deposited was collected and recrystallized from H_2O to give (+)XIX (17.3 g, 70.7%) as colorless pillars. Recrystallization from H_2O gave an analytical sample of mp 138—140°, $[\alpha]_D^8$ +113° (c=0.654, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3340, 3310, 3230, 3198 (NH_2), 1707, 1692 (carboxyl), 1642, 1603 (amide). NMR (in D_2O) τ: 7.74 (3H, singlet, -SCH_3). *Anal.* Calcd. for $C_5H_9O_3NS$: C, 36.81; H, 5.56; N, 8.59. Found: C, 36.77; H, 5.68; N, 8.81.

(+)2-Methylthiosuccinamic Acid Methyl Ester ((+)XX)——Esterification of (+)XIX was performed with CH_2N_2 as usual. Recrystallization of the product from MeOH–isopropyl ether afforded colorless pillars of mp 66—68°, $[\alpha]_D^{28}$ +99.5° (c=0.744, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3476, 3338, 3324 (NH_2), 1729 (ester), 1671, 1612 (amide). *Anal.* Calcd. for $C_6H_{11}O_3NS$: C, 40.68; H, 6.26; N, 7.91. Found: C, 40.60; H, 6.19; N, 8.01.

(+)3-Methylthiosuccinimide ((+)XXI) and Its Racemate——To a solution of (+)XX (21.0 g, 0.118 mole) in MeOH (30 ml) was added 1N NaOH (118 ml, 0.118 mole) under ice-cooling and the whole was kept under ice-cooling for 7 min. The reaction mixture was acidified with conc. HCl (11 ml), diluted with H_2O and extracted with AcOEt. The organic extract was dried over anhyd. Na_2SO_4 and evaporated to dryness *in vacuo* to give a slightly yellow oil (15.4 g), which became semi-solid on standing. This semi-solid was crushed well in benzene and warmed on a water bath. After cool, the benzene insoluble solid of mp 94—98° was collected (5.43 g). Recrystallization of this solid from MeOH–ether–hexane afforded colorless needles of mp 94—96°. Optical activity was not observed for this sample from its ORD curve in MeOH. IR ν_{max}^{KBr} cm^{-1}: 3173, 3061 (NH), 1783, 1694 (imide). *Anal.* Calcd. for $C_5H_7O_2NS$ (racemic 3-methylthiosuccinimide): C, 41.38; H, 4.86; N, 9.65. Found: C, 41.48; H, 4.91; N, 9.67.

The above benzene filtrate was evaporated to dryness *in vacuo* to give a yellow oil (10.18 g), which was purified by column chromatography on silica gel with 20% AcOEt in benzene to give a colorless oil. Recrystallizations from benzene–hexane gave colorless needles of mp 52.5—54.5°, $[\alpha]_D^{27}$ +63.7° (c=0.730, MeOH). IR ν_{max}^{KBr} cm^{-1}: 3154, 3069 (NH), 1780, 1702 (imide). *Anal.* Calcd. for $C_5H_7O_2NS$ ((+)XXI): C, 41.38; H, 4.86; N, 9.65. Found: C, 41.57; H, 5.08; N, 9.46.

(−)3-Methylthiopyrrolidone ((−)XXII) and (+)4-Methylthiopyrrolidone ((+)XXIII)——A solution of (+)XXI ($[\alpha]_D^{33}$ +55.2° (MeOH)) (8.0 g, 55 mmoles) in dehyd. THF (40 ml) was added to a suspension of $LiAlH_4$ (1.88 g, 49.5 mmoles) in dehyd. THF (200 ml) and the whole was refluxed for 4 hr. At the end of the reaction, 3% NaOH (0.4 ml) was slowly added under ice-cooling, then the precipitates were filtered off. The filtrate and THF-washings were combined, dried over anhyd. K_2CO_3, and evaporated to dryness *in vacuo* to give a brown oil (3.72 g). Using column chromatography on alumina (120 g) with 3% EtOH in $CHCl_3$, 1.91 g of the lactam-containing part was isolated from the reaction product. Further chromatography on silica gel (230 g) with 5% EtOH in benzene afforded two kinds of lactams; (−)XXII (350 mg, 4.8%) eluted initially, while (+)XXIII (190 mg, 2.6%) eluted secondary. On standing, (−)XXII slowly crystallized to give large plates, which were washed on a glass filter with ether–isopropyl ether to give an analytical sample of mp 63—64°, $[\alpha]_{300}^{31.5}$ −10° (c=0.280, MeOH) from ORD curve. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3439 (NH), 1696 (five-membered lactam). *Anal.* Calcd. for C_5H_9ONS: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.94; H, 7.05; N, 10.65.

Recrystallization of the above (+)XXIII (135 mg) from ether–hexane gave pale yellow needles (60 mg) of mp 89—91°, $[\alpha]_{300}^{34}$ +56° (c=0.308, MeOH) from the ORD curve. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3444 (NH), 1700 (five-membered lactam). *Anal.* Calcd. for C_5H_9ONS: C, 45.79; H, 6.92; N, 10.68. Found: C, 46.06; H, 6.98; N, 10.88.

(+)4-Methylsulfonylpyrrolidone ((+)XV)——To a solution of 30% H_2O_2 (1.0 ml) in AcOH (10 ml) was

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added (+)XXIII (200 mg) and the whole was kept at room temperature for 2 days. After dilution with H_2O, the reaction mixture was evaporated to dryness *in vacuo* to a semi-solid (270 mg), from which (+)XV (130 mg, 52.2%) of mp 166—168° (decomp.) was isolated as crystals insoluble in a small amount of cold EtOH. Recrystallization from EtOH–ether–hexane afforded colorless leaflets of mp 167—168° (decomp.), $[\alpha]_D^{27}$ +26.8° (c=0.606, MeOH). The IR spectrum of this sample was superimposable with that of (−)XV prepared from L-III in a solid state. *Anal.* Calcd. for $C_5H_9O_3NS$: C, 36.81; H, 5.56; N, 8.59. Found: C, 36.99; H, 5.50; N, 8.53.

(+)3-Methylsulfonylpyrrolidone ((+)XXIV)——Conversion of (−)XXII to (+)XXIV was done in a manner similar to that for (+)XV, in 57% yield. Recrystallization from MeOH–ether–hexane gave pure (+)XXIV as colorless needles of mp 142—144.5° (decomp. darkened at 133°), $[\alpha]_D^{29.5}$ +12° (c=0.400, MeOH) from ORD curve. IR $\nu_{max}^{CH_3CN}$ cm^{-1}: 3344 (NH), 1716 (five-membered lactam), 1306, 1141 (-SO_2-). *Anal.* Calcd. for $C_5H_9O_3NS$: C, 36.81; H, 5.56; N, 8.59. Found: C, 37.06; H, 5.58; N, 8.44.

(+)Methylthiosuccinic Acid ((+)XXV)——a) Preparation of an Authentic Sample: A solution of MeSH (prepared from S-methylisothiourea sulfate (9.0 g, 0.0645 mole)) in 1N NaOH (28 ml) was added to a solution of (−)bromosuccinic acid[24] (mp 176—178°, $[\alpha]_D^{30}$ −39.9° (c=1.140, H_2O)) (5.0 g, 0.0255 mole) and Na_2CO_3 (2.70 g, 0.0255 mole) in H_2O (25 ml). The reaction mixture was placed in a refrigerator for 3 days, after which it was acidified with conc. HCl and extracted with ether. After washing with satd. aqueous NaCl the ether solution was dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to give crystals of (+)XXV (3.20 g, 77%) of mp 139—142°. Several recrystallizations from ether–hexane afforded leaflets of mp 141—143°, $[\alpha]_D^{24}$ +82.2° (c=0.730, H_2O). IR ν_{max}^{KBr} cm^{-1}: 1677 (broad, COOH). NMR (in D_2O) τ: 7.82 (3H, singlet, -SCH_3). *Anal.* Calcd. for $C_5H_8O_4S$: C, 36.59; H, 4.91. Found: C, 36.86; H, 4.89.

b) From (+)XIX: A solution of (+)XIX (2.0 g, $[\alpha]_D^{14}$ +109° (c=1.013, MeOH)) in 10% HCl (50 ml) was refluxed for 2 hr, then extracted with ether. The ether solution was washed with satd. aqueous NaCl, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to give (+)XXV (1.64 g, 84%) of mp 136—139° as colorless leaflets of mp 140—142°, $[\alpha]_D^{13}$ +84.7° (c=1.046, H_2O). This sample was shown to be identical with the authentic sample prepared in a) by IR (KBr) as well as mixed mp test. *Anal.* Calcd. for $C_5H_8O_4S$: C, 36.59; H, 4.91. Found: C, 36.91; H, 4.89.

c) From (+)XXVI: Dimethyl sulfate (770 mg, 6 mmoles) was added to a solution of (+)XXVI ($[\alpha]_D^{27}$ +28.5° (c=1.046, H_2O)) (900 mg, 6 mmoles) and NaOH (760 mg, 19 mmoles) in H_2O (1.5 ml) during 20 min under ice-cooling. The reaction generated heat and gave a clear solution. After stirring the mixture for an additional one and a half hr at room temperature, H_2O (10 ml) added and the whole was washed with ether. The aqueous solution was acidified with conc. HCl, and extracted with ether. The ether solution was washed with satd. aqueous NaCl, dried over anhyd. Na_2SO_4, and evaporated to dryness *in vacuo* to give crystalline (+)XXV (750 mg, 76%) of mp 127—132°. Recrystallizations from ether–hexane afforded crystals of mp 128—130°, $[\alpha]_D^{29}$ +44.6° (c=1.012, H_2O). The mixed mp test with the authentic sample prepared in a) was 127—130°. IR as well as NMR spectra of this sample were superimposable with those of the authentic sample. *Anal.* Calcd. for $C_5H_8O_4S$: C, 36.59; H, 4.91. Found: C, 36.69; H, 4.81.

24) L.J. Andrews and J.E. Hardwicke, *J. Am. Chem. Soc.*, **74**, 3582 (1952).