uv max 339 mμ (ε 3.8 × 10⁴), which showed a characteristic bathochromic shift to uv max 404 mμ on the addition of 1 drop of 50% NaOH; ir (KBr) 3410 (OH), 1670 (conjugated, C=O), 1610, 1600 (C=C), 1520 cm⁻¹ (aromatic); nmr (d_6-acetone) δ 3.52 (s, 3, OCH_3), 4.01 (s, 3, OCH_3), 6.69 (m, 1, J = 7.8 Hz, J = 15.4 Hz, CH=CHCHO), 7.56 (s, 1, CH=CCHO), 7.58 (d, 1, J = 15.4 Hz, CH=CHCHO), 9.57 (d, 1, J = 7.8 Hz, CHO), 9.65 (s, 1, CHO); mol wt 354 (mass spectrum).

Anal. Calcd for $C_{20}H_{18}O_6$: C, 67.79; H, 5.12. Found: C, 68.02; H, 5.08.

α-(2-Methoxyphenoxy)coniferaldehyde Methyl Ether (14).—**14** was synthesized by the condensation of veratraldehyde, which is commercially available, and 2-methoxyphenoxyacetaldehyde (**15**) using the method described[13] for the synthesis of **1**: uv max 339 mμ (ε 2.36 × 10⁴), unchanged by the addition of 1 drop of 50% sodium hydroxide; ir (KBr) 1685 (conjugated C=O), 1625, 1600 (C=C), 1515, 1505 cm⁻¹ (aromatic); nmr ($CDCl_3$), δ 3.75 (s, 1, OCH_3), 3.81 (s, 1, OCH_3), 3.91 (s, 1, OCH_3), 9.43 (s, 1, CHO), and a complex aromatic region which was not interpreted; mol wt 314 (mass spectrum).

Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.77; H, 5.77. Found: C, 68.75; H, 5.57.

2-Methoxyphenoxyacetaldehyde (15).—This compound was synthesized by the $Pb(OAc)_4$ oxidation of guaiacol glyceryl ether, which is available commercially, following a previously reported procedure,[15] and the compound was crystallized from benzene, mp 72–74°.

Anal. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.02. Found: C, 65.16; H, 6.18.

Registry No.—**1**, 20649-42-7; **3**, 24058-19-3; **4**, 24058-20-6; **5**, 24058-21-7; **14**, 24058-22-8.

(15) R. J. Speer and H. R. Mahler, *J. Amer. Chem. Soc.*, **71**, 1133 (1949).

Synthesis of *cis*- and *trans*-4-Mercapto-L-proline Derivatives

ANTHONY J. VERBISCAR AND BERNHARD WITKOP

Institute of Drug Design, Inc., Sierra Madre, California 91024, and the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, Bethesda, Maryland 20014

Received October 16, 1969

Both *cis*- and *trans*-N,O-ditosyl-4-hydroxy-L-proline methyl esters under special precautions underwent almost complete SN2 displacements by potassium thiobenzoate to 4-benzoylmercaptoprolines, which were cleaved by dilute methoxide to the autoxidizable (and in the *cis* series lactonizable) N-tosyl-4-mercaptoprolines, easily alkylatable to the N-tosyl-*p*-methoxybenzylmercaptoprolines. These were electrolytically detosylated and converted to N-*t*-butylcarbonyl-*cis*- and -*trans*-4-*p*-methoxybenzylmercapto-L-prolines suitable for incorporation into oligopeptides by the conventional or the solid-phase method.

Although many analogs and homologs of proline and hydroxyproline have been reported,[1,2] the sulfur-substituted prolines[3,4] have not received much attention. For the synthesis of inhibitors of proline hydroxylase,[5] we needed sulfur analogs of natural and *allo*-4-hydroxy-L-proline suitably protected for incorporation into synthetic polypeptides.

The synthesis of such mercaptoprolines becomes an exercise in the proper sequence of putting on and taking off protecting groups with sufficient lability and differential activity to permit these steps to be selective.

The requirement for the S-protecting group of the resulting *cis*- and *trans*-4-mercapto-L-proline peptides was easy removal to liberate sulfhydryl without cleavage of peptide bonds. We chose *p*-methoxybenzyl, which is easily removed from S-protected cysteine peptides by anhydrous hydrogen fluoride.[6,7]

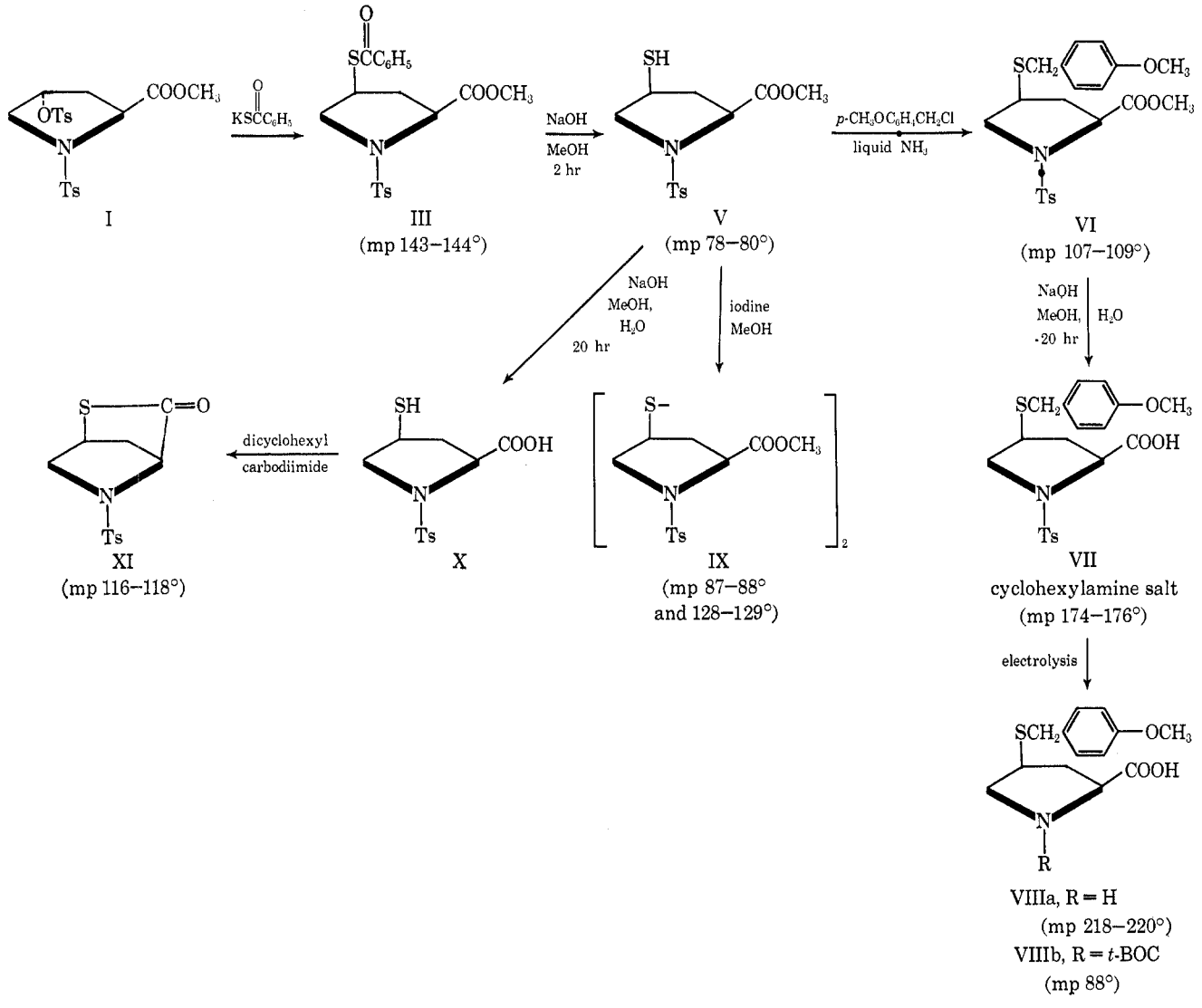
The starting material for the *cis*-mercapto series was N,O-ditosylhydroxy-L-proline methyl ester (I) (Scheme I).[8,9] Analogously the *trans*-mercapto series started with N,O-ditosyl-*allo*-hydroxy-L-proline methyl ester (II) (Scheme II).[2,8]

N-Tosyl-*cis*-4-benzoylmercapto-L-proline methyl ester (III) was prepared from I and potassium thiobenzoate following procedures similar to those developed for conversion of serines to cysteines.[10] The proline reactions are slower and proceed with inversion of configuration requiring additional precautions. When the *trans* → *cis* inversion reaction is run for 6–10 days at a temperature not exceeding 35–40°, the conversion is essentially stereoselective, in contrast to the reaction in refluxing methanol for 20 hr which gave a poor yield of III along with a substantial quantity of N-tosyl-*trans*-4-benzoylmercapto-L-proline methyl ester (IV). The presence of *trans* products in similar displacements on *trans*-4-tosylhydroxy-L-proline methyl ester has been explained by intramolecular participation of the ester carbonyl to form a cyclic carbonium intermediate which favors SN1 substitutions.[11] However, the corresponding *cis* → *trans* inversion to N-tosyl-*trans*-4-benzoylmercapto-L-proline methyl ester (IV) at 35–40° for 6 days also gave a small quantity of the *cis* epimer. The *cis* product probably arose by solvolysis of the *trans*-tosylate with subsequent attack by S-benzoyl anion in a normal SN1 reaction. Thin layer chromatography showed the product resulting from inversion to be major and retention to be the minor pathway.

In analogy to S-benzoyl derivatives of cysteine, sodium alkoxides[12,13] easily cleaved the benzoylthioprolines. With 0.5 *M* methanolic sodium hy-

(1) A. B. Mauger and B. Witkop, *Chem. Rev.*, **66**, 47 (1966).
(2) R. H. Andreatta, V. Nair, A. V. Robertson, and W. R. J. Simpson, *Aust. J. Chem.*, **20**, 1493 (1967).
(3) A. A. Patchett and B. Witkop, *J. Amer. Chem. Soc.*, **79**, 185 (1957).
(4) S.-I. Yamada, Y. Murakami, and K. Koga, *Tetrahedron Lett.*, 1501 (1968).
(5) J. J. Hutton, Jr., A. Marglin, B. Witkop, J. Kurtz, A. Berger, and S. Udenfriend, *Arch. Biochem. Biophys.*, **125**, 779 (1968).
(6) S. Akabori, S. Salikibara, Y. Shimonishi, and Y. Nabuhara, *Bull. Chem. Soc. Jap.*, **37**, 433 (1964).
(7) S. Sakikibara, Y. Shimonishi, M. Okada, and Y. Kishida, "Peptides," North Holland Publishing Co., Amsterdam, 1967, pp 44–49.
(8) Y. Fujita, A. Gottlieb, B. Peterkofsky, S. Udenfriend, and B. Witkop, *J. Amer. Chem. Soc.*, **86**, 4709 (1964).
(9) P. S. Portoghese and A. A. Mikhail, *J. Org. Chem.*, **31**, 1059 (1966).
(10) I. Photaki and V. Bardakos, *J. Amer. Chem. Soc.*, **87**, 3489 (1965).
(11) A. A. Gottlieb, Y. Fujita, S. Udenfriend, and B. Witkop, *Biochemistry*, **4**, 2509 (1965).
(12) L. Zervas, I. Photaki, and N. Ghelis, *J. Amer. Chem. Soc.*, **85**, 1337 (1963).
(13) R. G. Hiskey, T. Mizoguchi, and H. Igeta, *J. Org. Chem.*, **31**, 1188 (1966).

SCHEME I



droxide at room temperature, benzoylthioprolines were selectively split in preference to the methyl esters. The resulting N-tosyl-*cis*-4-mercapto-L-proline methyl ester (V) and the *trans* epimer XII are highly sensitive to air oxidation to form the stable crystalline disulfides IX and XVI, which are also easily prepared by oxidation of the mercaptans with iodine in methanol.

In analogy to procedures developed for the cysteines[6] the free thiol groups were protected by *p*-(chloromethyl)anisole in liquid ammonia[14] in good yield. Hydrolysis of the methyl esters gave the corresponding N-tosyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline (VII) and the *trans* epimer XIV which were easily crystallized and purified as the cyclohexylamine salts.

A variety of methods are available for the cleavage of sulfonamides, many of which are rather drastic.[15] Although prolines have been detosylated by 45% hydrogen bromide in acetic acid, opening of the proline ring has been reported, and several attempts with this reagent were unsuccessful. Electrolytic reductive detosylation[16] proved to be the method of choice. Advantages of the method are low temperature, pure products, ease of separation from the split group, and resistance of the formyl, carbobenzyloxy, and benzylmercapto groups to normal reductive electrolysis. With all of these advantages 80–90% yields of the *cis*- and *trans*-*p*-methoxybenzylmercapto-L-prolines were obtained. The two mercaptoprolines VIIIa and XVa were converted to the *t*-butyloxycarbonyl(*t*-BOC) derivatives VIIIb and XVb which are readily usable for incorporation into peptides by conventional or Merrifield methods.

Lactonization of N-tosyl-*cis*-4-mercaptoproline X to the well-crystallized XI was easily brought about by dicyclohexylcarbodiimide reagent. Thiolactone XI is analogous to N-acetyl lactone[4] in which the absolute configuration at C-4 is *S*.[17]

Experimental Section

All melting points are corrected. Thin layer chromatograms were done on Merck silica gel G with detection by iodine vapor. Solvent systems were (1) methanol; (2) benzene–methanol, 40:1; (3) 1-butanol–pyridine–acetic acid–water, 4:1:1:2; (4) 2-propanol. Elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Ind.

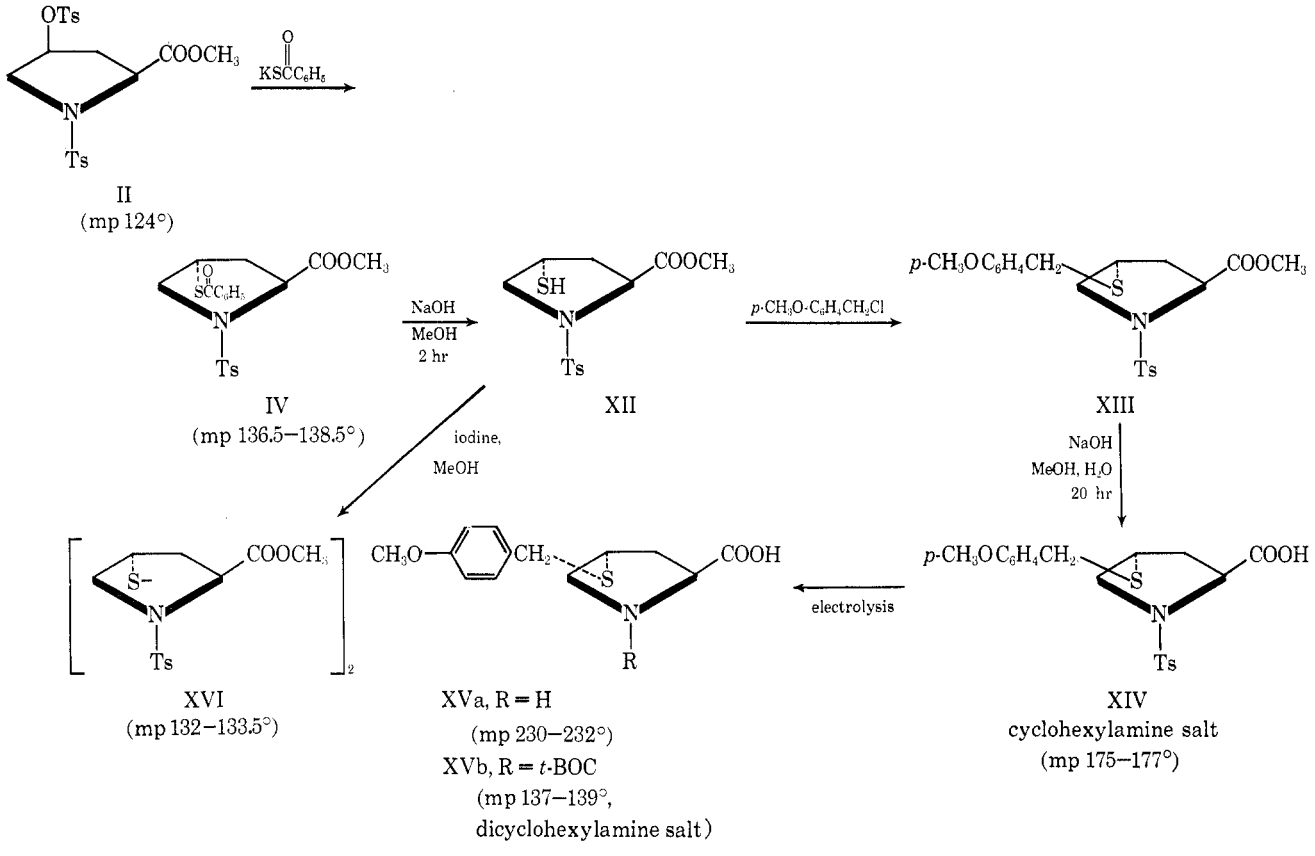
(14) Eastman Kodak No. 3406. This commercial product is stabilized with sodium carbonate but is still dangerous. A 25-g bottle about two-thirds full exploded on the shelf after standing closed for several months.

(15) S. Searles and S. Nukina, *Chem. Rev.*, **59**, 1077 (1959).

(16) L. Horner and H. Neumann, *Chem. Ber.*, **98**, 1715, 3462 (1965).

(17) *Cf.* B. Witkop, *Chem. Soc., Spec. Publ.*, No. 3, 60 (1955).

SCHEME II



N-Tosyl-*cis*-4-benzoylmercapto-L-proline Methyl Ester (III).—A solution of 4.53 g (0.01 *m*) of N,O-ditosyl-4-hydroxy-L-proline methyl ester (I) and 8.9 g (0.05 *m*) of potassium thiobenzoate in 60 ml of anhydrous methanol was stirred magnetically, and the temperature was kept at 35–40°. A precipitate gradually formed and progress of the reaction was followed by tlc in solvent system 2. After 10 days there was little starting material left. The mixture was cooled; the solid was collected and washed with water, then methanol, to give 2.70 g (68%) of a crude *cis* product, mp 136.5–141°. Tlc indicated contamination by a trace of the *trans*-4-benzoylmercapto isomer. Recrystallization from a mixture of ethyl acetate and ether gave 2.26 g (54%) of orange needles, mp 142.5–144.5°. The compound crystallized well from methanol as orange plates.

Anal. Calcd for $C_{20}H_{21}NO_5S_2$: C, 57.26; H, 5.04; N, 3.34. Found: C, 57.20; H, 5.60; N, 3.41.

N-Tosyl-*trans*-4-benzoylmercapto-L-proline Methyl Ester (IV).—The analogous displacement on II for 6 days at 35–40° eventually yielded 55% crystals, mp 132–135°. Tlc in solvent system 2 showed this product to contain a small amount of the *cis* epimer. Several recrystallizations from ethanol or ethyl acetate–ether gave pink rhomboids, mp 136.5–138.5°.

Anal. Calcd for $C_{20}H_{21}NO_5S_2$: C, 57.26; H, 5.04; S, 15.26. Found: C, 57.17; H, 5.13; S, 15.72.

When this reaction was run on a 10-g scale for 10 days the yield was lower. Also, when the temperature was raised to 50° for 6 days tlc indicated that a variety of other products formed. The main product then became difficult to separate and purify. In one 6-day run at 35° with no warming, 78% of unreacted II was recovered.

N-Tosyl-*cis*-4-mercapto-L-proline Methyl Ester (V).—To a suspension of 5.23 g (0.0125 *m*) of N-tosyl-*cis*-4-benzoylmercapto-L-proline methyl ester (III) in 220 ml of anhydrous methanol under hydrogen was added 30 ml of 0.5 *M* methanolic sodium hydroxide. The reactant dissolved completely after a short time of stirring. After 2 hr, 2 ml of water was added and stirring was continued for 0.5 hr. Neutralization with methanolic hydrochloric acid and evaporation of the solvent left a solid which was extracted into 20 ml of water and 120 ml of ethyl acetate. The organic phase was washed with 10-ml portions of water, 5% sodium bicarbonate, and water again, and then dried over sodium sulfate. Evaporation gave a product which crystallized from carbon tetrachloride–petroleum ether to yield 3.36 g (85%) of colorless crystals, mp 75–80°. Tlc of this crude product in solvent system 2 indicated the presence of a small quantity of the disulfide, which is more slowly detected by iodine than the –SH compound. Recrystallization gave a pure product, mp 78–80°, as a colorless microcrystalline powder.

Anal. Calcd for $C_{13}H_{17}NO_4S_2$: C, 49.52; H, 5.43; S, 20.30. Found: C, 49.65; H, 5.55; S, 20.54.

N-Tosyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline Methyl Ester (VI).—A mixture of 3.50 g (0.011 *m*) of N-tosyl-*cis*-4-mercapto-L-proline methyl ester (V) and 2.85 g (0.0182 *m*) of *p*-(chloromethyl)anisole in an ice–alcohol cooled flask was treated with 80 ml of liquid ammonia. A colorless precipitate formed immediately and stirring was continued for 0.5 hr with cooling and then at room temperature as excess ammonia evaporated. The crystalline product was washed with water until neutral. One recrystallization of the crude product from carbon tetrachloride yielded 4.28 g (89%) of a powder, mp 99–106°. An analytical sample was recrystallized to colorless fluffy crystals of VI, mp 108–110°.

Anal. Calcd for $C_{21}H_{25}NO_5S_2$: C, 57.92; H, 5.79; S, 14.70. Found: C, 57.47; H, 5.95; S, 15.06.

N-Tosyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline (VII).—A suspension of 800 mg (1.9 mmol) of N-tosyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline methyl ester (VI) in 8 ml of 0.5 *M* methanolic sodium hydroxide, 10 ml of methanol, and 10 drops of water was stirred for 20 hr at room temperature. The resulting clear solution was evaporated to dryness, and the solid was taken up in water. Acidification with citric acid gave a precipitate which was extracted into ether and dried over sodium sulfate. Addition of a solution of 220 mg (2.2 mmol) of cyclohexylamine in acetonitrile to the filtered ether solution caused 880 mg of a colorless powder, mp 158–179°, to precipitate. Recrystallization from acetonitrile gave 660 mg (67%) of colorless needles, the cyclohexylammonium salt of VII, mp 175–177°, homogeneous on tlc in solvent system 1.

Anal. Calcd for $C_{20}H_{23}NS_2O_5 \cdot C_6H_{11}NH_2$: C, 59.97; H, 6.97; S, 12.31. Found: C, 59.55; H, 7.25; S, 11.72.

N-Tosyl-*cis*-4-mercapto-L-proline Lactone (XI).—A suspension of 150 mg of N-tosyl-*cis*-4-mercapto-L-proline methyl ester (VI) in 2 ml of 0.5 *M* methanolic sodium hydroxide containing 3 drops of water was allowed to stand at room temperatures for 20

hr under hydrogen. The resulting solution was evaporated to dryness and the residue was taken up in 3 ml of water. Acidification with citric acid released the sulfhydryl compound X which was salted out, extracted into methylene chloride, and dried over magnesium sulfate. A solution of 120 mg of dicyclohexylcarbodiimide in methylene chloride was added, and the reaction mixture was allowed to stand overnight. Evaporation of the solvent left a colorless solid. The lactone was extracted into ethyl acetate leaving behind pure dicyclohexylurea, more of which precipitated upon adding petroleum ether. The mother liquor was treated with Nuchar C190 N and evaporated to a colorless solid, 70 mg, mp 98–112°. Recrystallization from carbon tetrachloride gave fine crystals of lactone XI, mp 116–118°.

Anal. Calcd for $C_{12}H_{13}S_2NO_3$: C, 50.85; H, 4.62; S, 22.63. Found: C, 51.22; H, 4.87; S, 22.34.

Disulfide of N-Tosyl-*cis*-4-mercapto-L-proline Methyl Ester (IX).—A solution of 90 mg (0.3 mmol) of N-tosyl-*cis*-4-mercapto-L-proline methyl ester (V) in 10 ml of methanol was treated dropwise with a 0.1 *N* solution of iodine in methanol until the color persisted. A few drops of concentrated sodium bisulfite solution were added to reduce excess iodine. The solvent was evaporated, and the resulting solid was washed with water, a small amount of methanol, and then ether to give 80 mg of product. Recrystallization from benzene gave colorless fluffy crystals, mp 95–125°, which after cooling and resolidifying had mp 128–129°. Slow recrystallization from dilute solutions in 2-propanol gave the low-melting modification as long needles, mp 87–88°. The product was homogeneous in solvent systems 1, 2, and 4. In system 4 it shows R_f 0.70.

Anal. Calcd for $(C_{13}H_{16}NO_4S_2)_2$: C, 49.66; H, 5.13; S, 20.40. Found: C, 49.41; H, 5.32; S, 20.55.

N-Tosyl-*trans*-4-*p*-methoxybenzylmercapto-L-proline (XIV).—In analogy to the sequence III → V → VI → VII, N-tosyl-*trans*-4-benzoylmercapto-L-proline methyl ester (IV) was converted into the highly sensitive XII which was alkylated with *p*-(chloromethyl)anisole[14] in liquid ammonia. The resulting oily N-tosyl-*trans*-4-*p*-methoxybenzylmercapto-L-proline methyl ester (XIII) was saponified to the acid XIV, a yellow oil which was dissolved in ethyl ether and dried over sodium sulfate. The filtered ether solution was treated with a solution of cyclohexylamine in 15 ml of acetonitrile. The cyclohexylamine salt, mp 171–173°, was recrystallized from an 80-ml portion of acetonitrile containing a few drops of cyclohexylamine to give matted colorless needles, mp 173–176°, homogeneous on tlc in solvent system 1.

Anal. Calcd for $C_{20}H_{23}NS_2O_5 \cdot C_6H_{11}NH_2$: C, 59.97; H, 6.97; S, 12.31. Found: C, 60.01; H, 6.89; S, 12.56.

Disulfide (XVI) of N-Tosyl-*trans*-4-mercapto-L-proline Methyl Ester.—Alkaline hydrolysis in methanolic sodium hydroxide and oxidation of the thiol XII by dropwise addition of 0.1 *M* methanolic iodine gave the disulfide XVI which was recrystallized from carbon tetrachloride–petroleum ether to give an 80% yield of fine colorless needles, mp 132–135°.

Anal. Calcd for $(C_{13}H_{16}NS_2O_4)_2$: C, 49.66; H, 5.13; S, 20.40. Found: C, 49.38; H, 5.15; S, 20.66.

***cis*-4-*p*-Methoxybenzylmercapto-L-proline (VIIIa).**—A solution of 1.1 g (2.1 mmol) of N-tosyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline (VII) cyclohexylamine salt in 30 ml of 0.85 *M* methanolic tetramethylammonium chloride was poured into a beaker containing a Teflon-coated magnetic stirring bar, a platinum electrode probe immersed in mercury as the cathode, and an RA-84 grade Alundum thimble containing a carbon anode and 3 ml of water as the anolyte. A current of 1 A at 20 V was applied while stirring. The current was maintained at 1 A for 20 min for a total of 1200 C (theoretical requirement 404 C). During this time the applied potential dropped to 10 V, and hydrogen evolution became vigorous. The reaction was monitored by tlc on microscope slides in solvent system 3. The methanolic supernate was brought to pH 6 with acetic acid and evaporated to a small volume. Following the addition of 6 ml of water and refrigeration, there was collected 450 mg (80%) of needles, mp 210–212° dec, homogeneous on tlc in solvent system 3. Recrystallization from water gave small colorless needles, mp 218–220° dec.

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.41; H, 6.41; S, 12.00. Found: C, 58.69; H, 6.68; S, 12.34.

N-*t*-Butyloxycarbonyl-*cis*-4-*p*-methoxybenzylmercapto-L-proline.—The proline VIIIa was converted in 90% yield to the N-*t*-BOC derivative VIIIb according to published procedure:[18] colorless small needles from ether–petroleum ether; mp 88°; $[\alpha]^{20}D$ −56.3° (*c* 1.0, MeOH); tlc in 1-butanol–acetic acid–water (4:1:2), R_f 0.85.

Anal. Calcd for $C_{18}H_{25}NO_5S$: C, 58.8; H, 6.81; N, 3.82. Found: C, 59.03; H, 6.76; N, 3.90.

***trans*-4-*p*-Methoxybenzylmercapto-L-proline (XVa).**—A solution of 1.5 g (2.85 mmol) of N-tosyl-*trans*-4-*p*-methoxybenzylmercapto-L-proline (XIV) cyclohexylamine salt in 40 ml of 0.85 *M* methanolic tetramethylammonium chloride was electrolyzed at 10–20 V and 1 A as described. The current was maintained at 1 A for 27 min for a total of 1620 C (theoretical: 550 C). Identical monitoring and work-up yielded 680 mg (89%) of crystals, mp 218–228° dec, homogeneous on tlc in solvent system 3. Recrystallization from water gave shiny colorless plates, mp 230–232° dec.

Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.41; H, 6.41; S, 12.00. Found: C, 58.47; H, 6.69; S, 12.23.

N-*t*-Butyloxycarbonyl-*trans*-4-*p*-methoxybenzylmercapto-L-proline.—Analogously, the proline XVa was converted to the oily *t*-BOC derivative, which was converted to the dicyclohexylammonium salt which formed microcrystalline powder from ether (87% yield): mp 137–139°; $[\alpha]^{20}D$ −11.5° (*c* 1.09, MeOH); tlc in 1-butanol–acetic acid–water (4:1:2), R_f, 0.9.

Anal. Calcd for $C_{30}H_{48}N_2O_5S$: C, 65.7; H, 8.82; N, 5.11. Found: C, 65.66; H, 8.78; N, 5.11.

Dicyclohexylamine Salt of N-Tosyl-*trans*-4-hydroxy-L-proline.—The dicyclohexylamine salt of N-tosyl-*trans*-4-hydroxy-L-proline (mp 152–154°) was prepared in acetonitrile and recrystallized from the same solvent to form colorless prisms, mp 150–152°, homogeneous on tlc in solvent systems 1, nicely separating the proline and dicyclohexylamine components.

Anal. Calcd for $C_{12}H_{15}NO_5S \cdot (C_6H_{11})_2NH$: N, 6.13. Found: N, 6.05.

The dicyclohexylamine salts of the epimeric N-tosyl-*cis*-4-hydroxy-L-proline did not form a crystalline derivative, nor did the *cis*- or *trans*-N-tosyl-4-*p*-methoxybenzylmercapto-L-proline.

N,O-Ditosyl-*cis*-4-hydroxy-L-proline.—This product appeared in 13% yield in the large-scale monotosylation reaction of *allo*-hydroxy-L-proline as a water-soluble by-product. It was recrystallized from ethanol–water to form colorless plates, mp 188–190°.

Anal. Calcd for $C_{19}H_{21}NO_7S_2$: C, 51.92; H, 4.82; S, 14.59. Found: C, 52.20; H, 4.86; S, 14.71.

Registry No.—III, 23912-23-4; IV, 23912-24-5; V, 23967-33-1; VI, 23912-25-6; VII, 23912-26-7; cyclohexylammonium salt of VII, 23912-27-8; VIII, 23912-28-9; VIIIb, 23912-29-0; IX, 23912-30-3; XI, 23912-31-4; cyclohexylamine salt of XIV, 23912-32-5; XVa, 23912-33-6; XVI, 23967-34-2; N-*t*-butyloxycarbonyl-*trans*-4-*p*-methoxybenzylmercapto-L-proline, 23912-34-7; dicyclohexylamine salt of N-tosyl-*trans*-4-hydroxy-L-proline, 23912-35-8; N,O-ditosyl-*cis*-4-hydroxy-L-proline, 20275-08-5.

Acknowledgment.—We are indebted to Dr. H. Aoyagi for the preparation of the *t*-BOC derivatives.

(18) Z. Schnabel, *Justus Liebigs Ann. Chem.*, **702**, 188 (1967).