Polycondensed Heterocycles. IV. Synthesis of 1,4-Dioxo-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzothiazine [1]

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Received August 3, 1989

A method for the synthesis of the title compound **3** consisted of an intramolecular cyclization in a stannic chloride catalyzed Friedel-Crafts reaction of *N*-(2-methylthiophenyl)-5-oxoproline chloride **10**, prepared by chlorination of the corresponding acid **9** obtained by hydrolysis of its ethyl ester **8**. Condensation of 2-methylthioaniline **4** with diethyl bromomalonate **5** afforded diethyl 2-methylthioanilinomalonate **6** which gave **8** either directly by reaction with ethyl acrylate or by alkylation with ethyl β-bromopropionate or ethyl acrylate and cyclization of resulting triethyl 2-(2-methylthio)anilino-2-carboxyglutarate **7**. This method was not convenient because of the poor yield of **3** (14%).

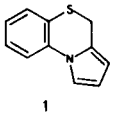
On the other hand, cyclization of *N*-(2-mercaptophenyl)-5-oxoproline **14** with DCC and DMAP provided **3** in 45% yield. Oxidation with *m*-CPBA of the esters **11** and **8**, demethylation *via* the Pummerer rearrangement of the respective sulphoxides **12** and **17** with TFAA and oxidation with iodine of resulting *N*-(2-mercaptophenyl)-5-oxoproline esters **13** and **18** gave the corresponding disulphides **16** and **19**. Hydrolysis of these latter compounds and reduction of the resulting bis[2-[2-(hydroxycarbonyl)-5-oxo-1-pyrrolidinyl]phenyl] disulphide **15** with sodium dithionite afforded the required **14**. Deprotection of *t*-butyl ester **13** with TFA at 55° to obtain **14** led to **3** in 42% yield. Finally the Pummerer rearrangement of *N*-(2-methylsulphinylphenyl)-5-oxoproline **20** yielded the mixture of **14** and **15**.

J. Heterocyclic Chem., **27**, 1329 (1990).

In 1973, in the course of our investigations concerning the synthesis of unknown *N,S*-containing polycyclic systems with potential pharmacological properties, we prepared a novel tricyclic nucleus, the 4*H*-pyrrolo[2,1-*c*][1,4]-benzothiazine **1** and its precursor, the thiolactone **2** [2]. This system is especially interesting owing to the presence in the molecule of 1,4-benzothiazine ring, which occurs in natural products as well as in pharmacologically active compounds [2-6]. Now we decided to resume the subject, also in the light that in the meantime no work has been done on the chemistry of pyrrolo[2,1-*c*][1,4]benzothiazines. In fact the two papers describing the syntheses of 4-substituted derivatives of **1** [7] and of some 1*H*-pyrrolo[2,1-*c*]-[1,4]benzothiazin-1-one [8] appeared just recently during the course of this work.

It was of particular interest for us to synthesize derivatives having the saturated pyrrole ring for biological evaluation.

Thus, as a first approach, we studied the synthesis of 1,4-dioxo-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzothiazine **3**.



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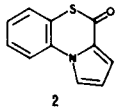

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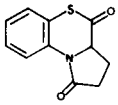


3

The first synthetic route chosen was that outlined in Scheme I, which involved the intramolecular cyclization of 1-(2-methylthiophenyl)proline chloride **10**.

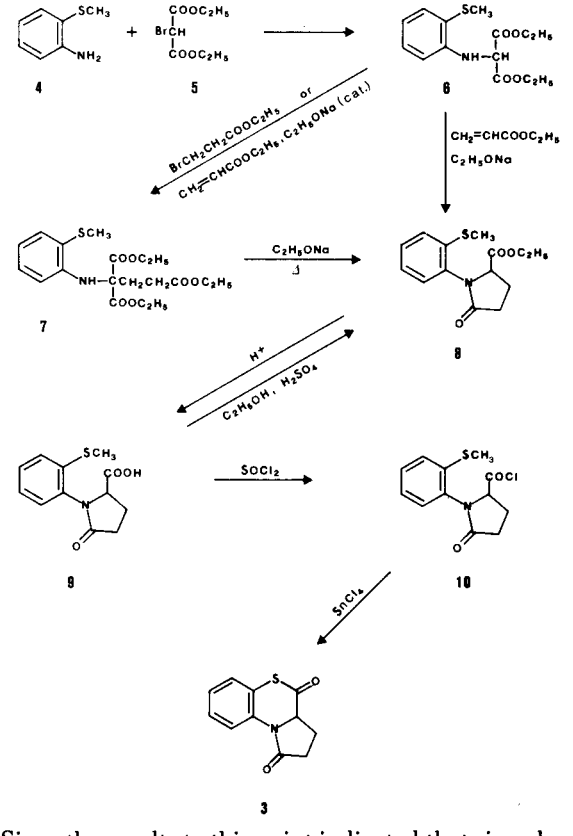
Reaction of 2-methylthioaniline **4** with diethyl bromomalonate **5** in anhydrous ethanol yielded diethyl 2-methylthioanilinomalonate **6**. Alkylation of **6** with ethyl β-bromopropionate or, in a sodium ethoxide catalyzed Michael reaction, with ethyl acrylate gave triethyl 2-(2-methylthio)-anilino-2-carboxyglutarate **7**. The triethyl ester **7**, by treatment with an equimolecular amount of sodium ethoxide in anhydrous ethanol under reflux, was most conveniently cyclized with subsequent elimination of diethyl carbonate, as occurred previously in analogous cases [9], to the required crude *N*-(2-methylthiophenyl)-5-oxoproline ethyl ester **8**; this compound was used in the next step without further purification because of difficulties obtaining it pure by distillation or chromatography. The same crude ester **8** was formed when a Michael reaction of anilinomalonate **6** with ethyl acrylate was carried out using an equimolecular amount of sodium ethoxide. Hydrolysis of ester **8** with hydrochloric acid in acetic acid afforded *N*-(2-methylthiophenyl)-5-oxoproline **9**.

The pure ethyl ester **8** was obtained by esterification of the acid **9** with anhydrous ethanol in the presence of sulphuric acid.

The oxoproline **9** was treated with thionyl chloride in benzene and the resulting chloride **10** was subjected to cyclization in an aluminum chloride catalyzed Friedel-Crafts reaction to obtain **3** by methyl chloride elimination, according to a literature method used for the 1-thiocoumar-

ins preparation [10]. The reaction carried out in boiling benzene gave **3** in very poor yield (5%). No reaction was observed in benzene or dichloromethane at room temperature. When a milder catalyst, stannic chloride, was used in benzene under reflux, the dioxopyrrolobenzothiazine **3** was obtained in 14% yield. An attempt to obtain **3** by using as an alternate solvent nitrobenzene was unsuccessful as was the use of benzene with boron trifluoride.

Scheme I

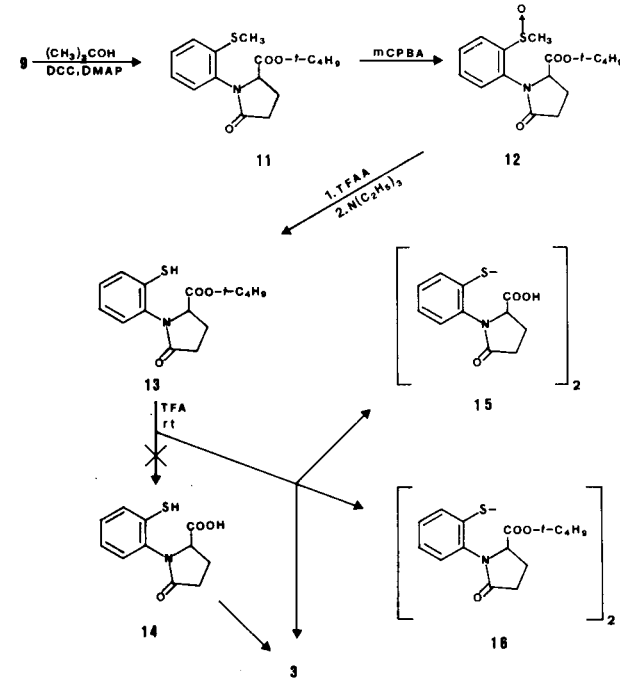


Since the results to this point indicated that ring closure did not occur satisfactorily, an alternative route was investigated.

This synthesis was based on the intramolecular cyclization of *N*-(2-mercaptophenyl)-5-oxoproline **14**, as illustrated in Scheme II.

Treatment of the above-mentioned acid **9** with *t*-butyl alcohol in the presence of *N,N'*-dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in anhydrous dichloromethane gave the corresponding *t*-butyl ester **11**. This latter material was converted to its sulphoxide **12** by oxidation with *m*-chloroperbenzoic acid (*m*-CPBA). Demethylation of the crude sulphoxide **12** *via* the Pummerer rearrangement using trifluoroacetic anhydride, followed by triethylamine, provided *N*-(2-mercaptophenyl)-5-oxoproline *t*-butyl ester **13**. Deprotection of the ester **13**, carried out in anisole with trifluoroacetic acid at room temperature, afforded, instead of the expected acid precursor **14**, the thiolactone **3**, bis[2-[2-(hydroxycarbonyl)-5-oxo-1-pyrrolidinyl]phenyl] disulphide **15** and its *t*-butyl ester **16** in 8, 20 and 62% yields, respectively.

Scheme II

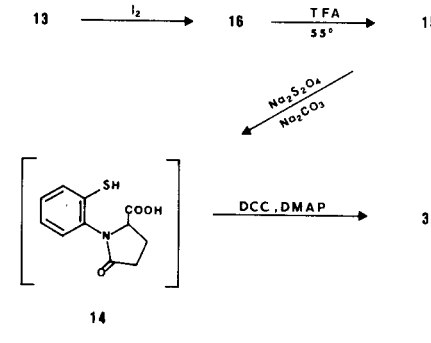


The same reaction, carried out at 55°, deprotected completely **13** giving the thiolactone **3** and the acid disulphide **15** in 42 and 49% yields, respectively. Also in this case no formation of the oxoproline **14** was observed.

Hoping to improve the yield of tricyclic compound **3**, we decided to prepare the key intermediate **14** passing through the acid disulphide **15**, as depicted in Scheme III.

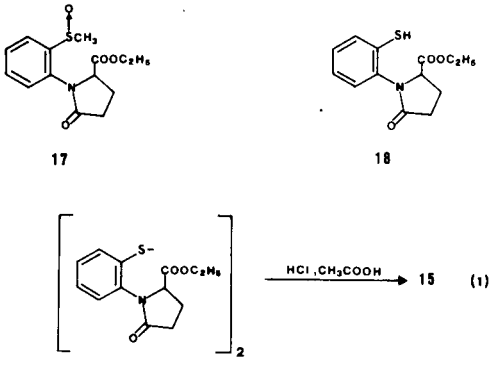
Oxidation of the *t*-butyl ester **13** by an ethanolic iodine solution afforded the previously observed disulphide **16**, which was deprotected with trifluoroacetic acid at 55° to give **15** in quantitative yield. Reduction of disulphide **15** with sodium dithionite in the presence of sodium carbonate under reflux gave the required acid **14**, which was not isolated because of its instability (it easily oxidized to the disulphide **15**). It was immediately used in the next step

Scheme III



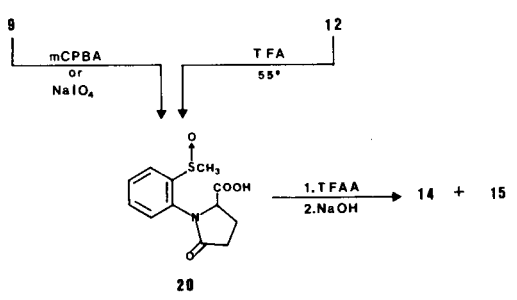
without further purification. On that account the oxoproline **14** was subjected to cyclizing reaction by treatment with DCC and DMAP in chloroform to give the expected thiolactone **3** in 45% yield.

In order to optimize the yield of acid disulphide **15**, we prepared, starting from the previously observed ester **8**, *N*-(2-methylsulphinylphenyl)-5-oxoproline ethyl ester **17**, *N*-(2-mercaptophenyl)-5-oxoproline ethyl ester **18** and the corresponding disulphide **19** using the same conditions described for the *t*-butyl esters **12, 13** and **16**, respectively. Hydrolysis of **19** with hydrochloric acid in glacial acetic acid (Equation 1) gave the required acid disulphide **15** in good yield (overall 73%).



Finally attempts to demethylate *N*-(2-methylsulphinylphenyl)-5-oxoproline **20**, always by the Pummerer rearrangement, were successful. The sulphoxide **20** was easily accessible from the acid **9** by oxidation with *m*-CPBA in anhydrous chloroform or, most conveniently, with sodium periodate in aqueous methanol or from sulphoxide *t*-butyl ester **12** by action of trifluoroacetic acid in anisole. Treatment of **20** with trifluoroacetic anhydride in anhydrous dichloromethane, followed by sodium hydroxide, gave **14** and **15** in 23 and 42% yields, respectively (Scheme IV).

Scheme IV



EXPERIMENTAL

Melting points were determined with an Electrothermal 8103 digital melting point apparatus and are uncorrected. The ir spectra of solids were recorded in nujol mulls and liquids as thin films between sodium chloride plates on a Perkin-Elmer 398 spectrophotometer. The ^{1}H nmr spectra were recorded on a Varian XL 200 spectrometer with TMS as internal standard. The mass spectrum was recorded on a VG 70-250S spectrometer with an electron beam energy of 70 eV. Merck silica gel (70-230 mesh) was used for chromatographic purifications. Microanalyses were performed by Professor A. Pietrogrande, Padova, Italy, and in the Microanalysis Laboratory of our Department on a Perkin-Elmer 240C Elemental Analyzer.

Diethyl 2-Methylthioanilinomalonate (**6**).

To a well stirred solution of 13.92 g (0.1 mole) of 2-methylthioaniline **4** in 50 ml of anhydrous ethanol, kept under nitrogen, was added dropwise 11.95 g (0.05 mole) of diethyl bromomalonate **5**. The solution was allowed to stir for 10 hours at room temperature and then heated under reflux for 30 hours. After cooling to room temperature and evaporation of the solvent *in vacuo*, the residue was poured onto crushed ice and extracted with diethyl ether. The combined organic layers were washed with water and dried over anhydrous sodium sulphate. Removal of the solvent afforded an oily residue which was first purified by passing through a silica gel column (chloroform as eluent) and second distilled *in vacuo* to give 14.12 g (95%) of **6** as a colourless oil (bp 150°/0.1 mm); ir: 3360 cm^{-1} (NH), 1735 (2 ester C=O); ^{1}H nmr (deuteriochloroform): δ 1.27 (t, 6H), 2.35 (s, 3H), 4.27 (q, 4H), 4.79 (s, 1H), 6.10 (s, broad, 1H, deuterium oxide exchangeable), 6.4-7.5 (m, 4H).

Anal. Calcd. for $C_{14}H_{19}NO_4S$: C, 56.50; H, 6.44; N, 4.71; S, 10.78. Found: C, 56.32; H, 6.42; N, 4.55; S, 10.78.

Triethyl 2-(2-Methylthio)anilino-2-carboxyglutarate (**7**).

Method A.

A solution of 1.5 g (5 mmoles) of diethyl 2-methylthioanilinomalonate **6** in 5 ml of anhydrous ethanol was added to a solution of 0.115 g (5 mg-atom) of sodium metal in 10 ml of the same solvent. To this well stirred solution, under a nitrogen atmosphere, was added 1.14 g (6.3 mmoles) of ethyl β-bromopropionate over a period of 30 minutes. After 12 hours at room temperature and removal of the solvent *in vacuo*, the residue was poured onto crushed ice and extracted with diethyl ether. The ethereal fractions were washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded an oily residue which was distilled to give 1.58 g (79%) of **7** as a pale yellow liquid (bp 170°/0.1 mm); ir: 3320 cm^{-1} (NH), 1730 (3 ester C=O); ^{1}H nmr (deuteriochloroform): δ 1.17 (t, 9H), 2.20 (t, 2H), 2.34 (s, 3H), 2.71 (t, 2H), 4.00 (q, 2H), 4.21 (q, 4H), 6.4-6.8 [m, 3H (1H, deuterium oxide exchangeable)], 7.0-7.5 (m, 2H).

Anal. Calcd. for $C_{19}H_{27}NO_6S$: C, 57.40; H, 6.85; N, 3.52; S, 8.06. Found: C, 57.41; H, 6.87; N, 3.57; S, 7.90.

Method B.

To a solution of 8 mg (0.34 mg-atom) of sodium metal in 10 ml of anhydrous ethanol were added dropwise 1 g (3.3 mmoles) of diethyl 2-methylthioanilinomalonate **6** and after a few minutes 0.31 g (4.6 mmoles) of ethyl acrylate with stirring under a nitrogen atmosphere. The mixture was heated under reflux for 20 hours. Removal of the solvent under reduced pressure afforded an oily residue, which was poured onto crushed ice (50 g) containing 3 ml of 6*N* hydrochloric acid and extracted with diethyl ether. The organic layer was washed with water and dried over anhydrous sodium sulphate. The solvent was removed by evaporation and the oily residue was purified by passing through a silica gel column [chloroform-petroleum ether (bp 60-80°) (20:1) as eluent] to give 1.14 g (87%) of **7**.

N-(2-Methylthiophenyl)-5-oxoproline Ethyl Ester (**8**).

Method A.

A mixture of 3 g (0.012 mole) of *N*-(2-methylthiophenyl)-5-oxoproline **9**, 50 ml of anhydrous ethanol and 1 ml of sulphuric acid was heated under reflux for 4 hours. After cooling to room temperature the solution was poured onto crushed ice and extracted with diethyl ether. The organic layer was washed with a saturated sodium bicarbonate solution and then with water, and then dried over anhydrous sodium sulphate. The solvent was removed by evaporation and the oily residue was purified by passing through a silica gel column [dichloromethane-methanol (20:0.3) as a eluent] to give 2.81 g (84%) of **8** as an oily product, which on standing solidified (mp 108-110°). An analytical sample was prepared as a pale yellow oil (bp 174-175°/0.1 mm); ir: 1740 cm^{-1} (ester C=O), 1720 (lactam C=O); ^1H nmr (deuteriochloroform): δ 1.17 (t, 3H), 2.1-2.8 [m, 7H (2.38, s, 3H)], 4.13 (q, 2H), 4.68 (d, 1H), 7.0-7.4 (m, 4H).

Anal. Calcd. for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.17; H, 6.13; N, 4.94.

Method B.

To a stirred solution of 0.094 g (4 mg-atom) of sodium metal in 10 ml of anhydrous ethanol was added dropwise under nitrogen a solution of 1.64 g (4 mmoles) of triethyl 2-(2-methylthio)anilino-2-carboxyglutarate **7** in 5 ml of anhydrous ethanol. The reaction mixture was refluxed for 20 hours, then cooled to room temperature. Evaporation of the solvent gave a residue which was poured onto crushed ice. The resulting oil was extracted with diethyl ether and the organic solution was washed with water and dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by passing through a silica gel column using chloroform as eluent to give 0.76 g (66%) of **8**, which was used in the next step without further purification.

Method C.

To a stirred solution of 2.013 g (0.087 g-atom) of sodium metal in 130 ml of anhydrous ethanol under nitrogen were slowly added 26.04 g (0.087 mole) of diethyl 2-methylthioanilinomalonate **6** and after a few minutes, dropwise, 8.76 g (0.087 mole) of ethyl acrylate. The mixture was heated under reflux for 20 hours, cooled and evaporated under reduced pressure. The resulting oily residue was poured onto crushed ice containing 8 ml of concentrated hydrochloric acid, extracted several times with diethyl ether, washed with water and dried over anhydrous sodium sulphate. Removal of the solvent afforded an oily residue which was purified by passing through a silica gel column (chloroform as eluent) to give 24.01 g (87%) of **8**, which was used in the next step without further purification.

N-(2-Methylthiophenyl)-5-oxoproline (**9**).

A suspension of 13.91 g (0.049 mole) of *N*-(2-methylthiophenyl)-5-oxoproline ethyl ester **8** in 300 ml of 6*N* hydrochloric acid and 150 ml of glacial acetic acid was heated under reflux for 15 hours, under a nitrogen atmosphere with stirring. The still hot solution was treated with charcoal, filtered and concentrated *in vacuo*. The resulting white solid was collected, washed with water and crystallized from acetone to give 10.64 g (85%) of **9**. An analytical sample of mp 174-176° was obtained as colourless prisms; ir: 1720 cm^{-1} (carboxylic C=O), 1635 (lactam C=O); ^1H nmr (DMSO-d_6): δ 2.0-2.8 (m, 7H), 4.51 (d, 1H), 7.0-7.6 (m, 4H), 13.04 (s, broad, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57; S, 12.76. Found: C, 57.54; H, 5.40; N, 5.36; S, 12.68.

N-(2-Methylthiophenyl)-5-oxoproline Chloride (**10**).

To a stirred solution of 0.7 g (2.78 mmoles) of *N*-(2-methylthiophenyl)-5-oxoproline **9** in 20 ml of anhydrous benzene, cooled to 0°, was added slowly 1.75 ml (24 mmoles) of thionyl chloride and a drop of *N,N*-dimethylformamide. The reaction mixture was refluxed for 2 hours and, after evaporation of the solvent *in vacuo*, the excess of thionyl chloride was removed off under reduced pressure. The resulting residue was washed twice with anhydrous benzene to afford 0.74 g (98%) of crude **10** as a solid material, which was used in the next step without further purification; ir: 1820 cm^{-1} (acid chloride C=O), 1735 (lactam C=O); ^1H nmr (deuteriochloroform): δ 2.1-3.0 [m, 7H (2.45, s, 3H)], 5.07 (m, 1H), 7.0-7.6 (m, 4H).

N-(2-Methylthiophenyl)-5-oxoproline *t*-Butyl Ester (**11**).

To a well stirred suspension of 4.06 g (0.016 mole) of *N*-(2-methylthiophenyl)-5-oxoproline **9** in 50 ml of anhydrous dichloromethane, kept under nitrogen, were added 4.55 ml of *t*-butyl alcohol, 0.55 g of 4-dimethylaminopyridine and at 0° a solution of 3.31 g (0.016 mole) of *N,N'*-dicyclohexylcarbodiimide. The reaction mixture was then stirred for 15 hours at room temperature. The precipitate was filtered off and the filtrate was washed twice with 0.5*N* hydrochloric acid and with saturated sodium bicarbonate solution and dried over anhydrous sodium sulphate. After removal of the solvent, the residue was crystallized from aqueous ethanol to give 4.52 g (91%) of **11**. An analytical sample of mp 80° was obtained as colourless prisms; ir: 1700 cm^{-1} (ester and lactam C=O); ^1H nmr (deuteriochloroform): δ 1.39 (s, 9H), 2.1-2.8 [m, 7H (2.42, s, 3H)], 4.58 (d, 1H), 7.1-7.4 (m, 4H).

Anal. Calcd. for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.88; N, 4.55; S, 10.43. Found: C, 62.71; H, 6.97; N, 4.68; S, 10.26.

N-(2-Methylsulphinylphenyl)-5-oxoproline *t*-Butyl Ester (**12**).

To a stirred solution of 0.79 g (2.57 mmoles) of *N*-(2-methylthiophenyl)-5-oxoproline *t*-butyl ester **11** in 15 ml of anhydrous chloroform, kept under nitrogen and cooled to 0°, was added a solution of *m*-chloroperbenzoic acid (70% grade, 0.63 g, 2.57 mmoles) in 10 ml of anhydrous chloroform dropwise, maintaining the same temperature. After 12 hours at 5°, the suspension was filtered, then washed with a saturated sodium bicarbonate solution and dried over anhydrous sodium sulphate. Evaporation under reduced pressure of the solvent gave an oily residue which was purified by passing through a silica gel column (ethyl acetate as eluent) to provide 0.47 g (57%) of **12** as an oil. This product was used in the next step without further purification; ir: 1725 cm^{-1} (ester C=O), 1685 (lactam C=O).

N-(2-Mercaptophenyl)-5-oxoproline *t*-Butyl Ester (**13**).

The crude *N*-(2-methylsulphinylphenyl)-5-oxoproline *t*-butyl ester **12** (0.47 g, 1.4 mmoles) was dissolved in 3.03 ml (0.021 mole) of trifluoroacetic anhydride with ice-cooling. The resulting solution was allowed to stir for 2 hours at 0° and for 30 minutes at room temperature under a nitrogen atmosphere. Evaporation of the volatile components under reduced pressure afforded a residue which was treated with 30 ml of triethylamine previously dissolved in 30 ml of methanol. After stirring for 30 minutes at room temperature the solution was evaporated *in vacuo* to give a

residue which was dissolved in chloroform. The organic solution was washed with 0.5*N* hydrochloric acid and dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* afforded a residue which after chromatographic purification by passing through a silica gel column (ethyl acetate as eluent) gave 0.43 g (88%) of **13** as colourless oil; ir: 2517 cm^{-1} (SH), 1730 (ester C=O), 1705 (lactam C=O); ^1H nmr (deuteriochloroform): δ 1.38 (s, 9H), 1.95-3.0 (m, 4H), 3.48 (s, 1H, deuterium oxide exchangeable), 4.2-4.7 (m, 1H), 6.9-7.8 (m, 4H).

Anal. Calcd. for $C_{15}H_{19}NO_3S$: C, 61.40; H, 6.52; N, 4.77. Found: C, 61.31; H, 6.53; N, 5.07.

Bis[2-[2-(*t*-butoxycarbonyl)-5-oxo-1-pyrrolidinyl]phenyl] Disulphide (**16**).

A 10% ethanolic iodine solution (2.5 ml) was added dropwise to a solution of 3 g (0.01 mole) of *N*-(2-mercaptophenyl)-5-oxoproline *t*-butyl ester **13** in 30 ml of ethanol until reaching a brownish colour. After evaporation of the solvent *in vacuo* and dissolving of the residue in chloroform, the resulting organic solution was washed with water and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave 2.95 g (99%) of crude **16** as an oily colourless liquid, which was used in the next step without further purification. An analytical sample was obtained by chromatography over silica gel [dichloromethane-ethanol (20:0.3) as eluent]; ir: 1715 cm^{-1} (ester C=O), 1710 (lactam C=O); ^1H nmr (deuteriochloroform): δ 1.40 (s, 18H), 2.1-2.9 (m, 8H), 4.55 (m, 2H), 7.1-7.7 (m, 8H).

Anal. Calcd. for $C_{30}H_{36}N_2O_6S_2$: C, 61.61; H, 6.20; N, 4.80. Found: C, 61.26; H, 6.10; N, 4.73.

N-(2-Methylsulphinylphenyl)-5-oxoproline Ethyl Ester (**17**).

This compound was obtained in an analogous manner to that described above for sulphoxide **12** starting from 2.81 g (0.01 mole) of *N*-(2-methylthiophenyl)-5-oxoproline ethyl ester **8** and 2.45 g (0.01 mole) of *m*-chloroperbenzoic acid (70% grade). The oily residue after chromatography gave 2.37 g (80%) of **17** as a colourless oil which was used without further purification in the next step; ir: 1720 cm^{-1} (ester and lactam C=O).

N-(2-Mercaptophenyl)-5-oxoproline Ethyl Ester (**18**).

The crude *N*-(2-methylsulphinylphenyl)-5-oxoproline ethyl ester **17** (1.71 g, 5.7 mmoles) was dissolved in trifluoroacetic anhydride (12 ml, 0.083 mole) under a nitrogen atmosphere with stirring. After the reaction mixture had been stirred for 1 hour at 5° and for 1 additional hour at room temperature, the solution was evaporated under reduced pressure to give an oily residue to which a solution of 35 ml of triethylamine in 35 ml of methanol was added. After stirring for 30 minutes at room temperature, the solution was evaporated *in vacuo* and the residue was taken up in chloroform. The chloroformic solution was washed with 0.5*N* hydrochloric acid and with water and then dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* afforded an oily residue which was purified by passing through a silica gel column (chloroform as eluent) to give 1.47 g (96%) of **18** as a colourless oily liquid. This product was used in the next step without further purification; ir: 2515 cm^{-1} (SH), 1716 (ester C=O), 1695 (lactam C=O).

Bis[2-[2-(ethoxycarbonyl)-5-oxo-1-pyrrolidinyl]phenyl] Disulphide (**19**).

The oxidation reaction of *N*-(2-mercaptophenyl)-5-oxoproline **18** (3 g, 0.011 mole) was carried out as described above in the preparation of disulphide **16**. The oily residue after chromatographic purification over silica gel (ethyl acetate as eluent) gave 2.9 g (98%) of **19**. An analytical sample was prepared as a colourless oil; ir: 1720 cm^{-1} (ester C=O), 1710 (lactam C=O); ^1H nmr (deuteriochloroform): δ 1.22 (t, 6H), 2.1-2.9 (m, 8H), 4.15 (m, 4H), 4.66 (m, 2H), 7.2-7.8 (m, 8H).

Anal. Calcd. for $C_{26}H_{28}N_2O_6S_2$: C, 59.07; H, 5.34; N, 5.30. Found: C, 59.37; H, 5.40; N, 5.04.

Bis[2-[2-(hydroxycarbonyl)-5-oxo-1-pyrrolidinyl]phenyl] Disulphide (**15**).

Method A.

Trifluoroacetic acid (2.8 ml) was added dropwise to a stirred mixture of 2 g (3.4 mmoles) of crude bis[2-[2-(*t*-butoxycarbonyl)-5-oxo-1-pyrrolidinyl]phenyl] disulphide **16** and 5.2 ml of anisole chilled in an ice-water bath to about 5° under a nitrogen atmosphere. The resulting solution was heated at 55° for 5 hours and concentrated *in vacuo* while the temperature was maintained below 60°. The residue was dissolved in 50 ml of ethyl acetate and extracted several times with saturated aqueous sodium bicarbonate. The aqueous phase was washed twice with ethyl acetate, acidified cautiously to *p*H 2 by the dropwise addition of concentrated hydrochloric acid, saturated with sodium chloride and extracted with ethyl acetate. The combined organic layer was washed with water, dried over anhydrous sodium sulphate and evaporated *in vacuo*. The crystallization from water of the residue afforded 1.57 g (97%) of **15** as an amorphous colourless solid. An analytical sample melted at 169° dec; ir: 1735 cm^{-1} (carboxylic C=O), 1670 (lactam C=O); ^1H nmr (DMSO-d_6): δ 1.9-2.8 (m, 8H), 4.58 (m, 2H), 7.0-7.8 (m, 8H), 13.07 (s, broad, 2H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{22}H_{20}N_2O_6S_2$: C, 55.91; H, 4.26; N, 5.92. Found: C, 55.66; H, 4.31; N, 5.80.

Method B.

A mixture of 0.44 g (8 mmoles) of bis[2-[2-(ethoxycarbonyl)-5-oxo-1-pyrrolidinyl]phenyl] disulphide **19**, 24 ml of 6*N* hydrochloric acid and 12 ml of glacial acetic acid was heated under reflux for 15 hours. The still hot solution was treated with charcoal, filtered and concentrated *in vacuo* to provide 0.36 g (92%) of crude **15**.

N-(2-Mercaptophenyl)-5-oxoproline (**14**).

Method A.

A mixture of 0.424 g (2.65 mmoles) of sodium dithionite, 0.5 g (4.78 mmoles) of sodium carbonate, 0.8 g (1.69 mmoles) of bis[2-[2-(hydroxycarbonyl)-5-oxo-1-pyrrolidinyl]phenyl] disulphide **15** and 20 ml of water was heated under reflux for 1 hour. The solution was cooled to 5°, acidified with 4*N* hydrochloric acid and extracted with chloroform under a nitrogen atmosphere. The combined organic layer containing **14** was dried over anhydrous sodium sulphate and immediately used in the next step.

Method B.

Trifluoroacetic anhydride [1.25 ml (8.9 mmoles)] was added to a well stirred solution of 2.37 g (8.9 mmoles) of *N*-(2-methylsulphenyl)-5-oxoproline **20** in 75 ml of anhydrous dichloromethane cooled to −10° and kept under nitrogen. After 24 hours at −10° and 48 hours at room temperature, removal of the volatile com-

ponents under reduced pressure gave a residue which was dissolved in 26.7 ml of 1*N* sodium hydroxide solution. The obtained aqueous solution was acidified to *p*H 3 by the dropwise addition of 4*N* hydrochloric acid and extracted with chloroform under nitrogen. The resulting suspension was filtered and the filtrate was dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* under nitrogen afforded 0.47 g (23%) of **14** which was taken up in 30 ml of chloroform and immediately used in the next step. The collected solid was crystallized from water to give 0.88 g (42%) of **15**.

N-(2-Methylsulphinylphenyl)-5-oxoproline (**20**).

Method A.

To a solution of 2 g (8 mmoles) of *N*-(2-methylthiophenyl)-5-oxoproline **9** in 30 ml of anhydrous chloroform was added a solution of 2.4 g (8 mmoles) of *m*-chloroperbenzoic acid (70% grade) in 30 ml of anhydrous chloroform with ice-cooling. The reaction mixture was then allowed to stir for 1 hour at 0° and for 30 minutes at room temperature. The solvent was removed under reduced pressure and the residue was taken up in 10 ml of cold ethyl ether. The insoluble product that had separated was collected and purified by passing through a silica gel column [ethyl acetate-acetic acid (1:1) as eluent] to give 1.1 g (52%) of **20**. An analytical sample was prepared by crystallization from methanol as colourless prisms, mp 250-251°; ir: 1708 cm^{-1} (ester and lactam C=O); ^1H nmr (DMSO-d_6): δ 2.0-2.8 [m, 7H (2.63, s, 3H)], 4.73 (m, 1H), 7.1-8.0 (m, 4H), 13.23 (s, broad, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 54.06; H, 4.97; N, 5.63.

Method B.

A solution of 7 g (0.0278 mole) of *N*-(2-methylthiophenyl)-5-oxoproline **9** in 20 ml of methanol was added to a well stirred suspension of 5.95 g (0.0278 mole) of sodium periodate in 80 ml of methanol and 15 ml of water. The mixture was maintained for 20 hours at room temperature. The solid phase was removed by filtration and the filtrate was evaporated *in vacuo*. The resulting residue, after chromatography over silica gel column [ethyl acetate-acetic acid (1:1) as eluent], afforded 7.06 g (95%) of **20**.

Method C.

To a well stirred solution of 0.5 g (1.54 mmoles) of *N*-(2-methylsulphinylphenyl)-5-oxoproline *t*-butyl ester **12** in 1.25 ml of anisole were added dropwise 0.63 ml of trifluoroacetic acid. The solution was maintained for 1 hour at 5° and then heated at 55° for 5 hours. Removal of the volatile components under reduced pressure afforded a residue which, after chromatography over silica gel column [ethyl acetate-acetic acid (1:1) as eluent], gave 0.36 g (88%) of **20**.

1,4-Dioxo-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzothiazine (**3**).

Method A.

To a stirred solution of 0.8 g (3.3 mmoles) of crude *N*-(2-mercaptophenyl)-5-oxoproline **14** in 20 ml of anhydrous chloroform, obtained as described above, kept under nitrogen, were added 0.039 g of 4-dimethylaminopyridine followed by a solution of 0.68 g (3.3 mmoles) of *N,N'*-dicyclohexylcarbodiimide in 5 ml of anhydrous chloroform with ice-cooling. After 15 hours at room temperature and 1 hour at 30°, the *N,N'*-dicyclohexylurea was filtered off and the organic solution was washed twice with 0.5*N* hydrochloric acid and with saturated sodium bicarbonate solution and then dried over anhydrous sodium sulphate. Evaporation of the solvent afforded a residue which was purified by passing through a silica gel column (chloroform as eluent) to give 0.33 g (45%) of **3**. An analytical sample of mp 120-121° was obtained as colourless prisms by crystallization from cyclohexane; ir: 1720 cm^{-1} (thiolactone C=O), 1695 (lactam C=O); ^1H nmr (deuteriochloroform): δ 2.2-3.0 (m, 4H), 4.14 (dd, 1H), 7.2-7.4 (m, 3H), 7.93 (d, 1H); ms: m/e (%) 219 (M^+, 28), 191 (53), 162 (4), 136 (100), 109 (8).

Anal. Calcd. for $C_{11}H_9NO_2S$: C, 60.25; H, 4.13; N, 6.39; S, 14.62. Found: C, 60.32; H, 4.05; N, 6.37; S, 14.90.

Method B.

To a well stirred solution of 0.62 g (2.3 mmoles) of *N*-(2-methylthiophenyl)-5-oxoproline chloride **10** in 20 ml of anhydrous benzene, cooled in ice-bath, were added under a nitrogen atmosphere 1.16 g of anhydrous stannic chloride. When the addition was complete the reaction mixture was heated to reflux for 3 hours. After cooling to room temperature and addition of 30 ml of 6*N* hydrochloric acid, the organic layer was washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded a residue which, purified by passing through a silica gel column [chloroform-methanol (20:0.3) as eluent], gave 0.07 g (14%) of **3**.

Reaction of **13** with Trifluoroacetic Acid at 55°.

To a cooled (10°) and stirred solution of 2.06 g (7 mmoles) of *N*-(2-mercaptophenyl)-5-oxoproline *t*-butyl ester **13** in 5.7 ml of anisole, kept under nitrogen, were slowly added 28.32 ml (0.2 mole) of trifluoroacetic acid. The resulting solution was heated to 55° for 5 hours. The residue obtained by evaporation of the volatile components *in vacuo*, at below 60° temperature, was purified by passing through a silica gel column (50 x 2.5 cm), using ethyl acetate as eluent (50 ml fractions). Fractions 6-7 provided 0.64 g (42%) of 1,4-dioxo-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*]-[1,4]benzothiazine **3** and fractions 8-14 yielded 1 g (49%) of bis-[2-[2-(hydroxycarbonyl)-5-oxo-1-pyrrolidinyl]phenyl] disulphide **15**.

Acknowledgement.

This work was supported by grants from the Ministero della Pubblica Istruzione and the Consiglio Nazionale delle Ricerche. We thank Dr. Valoti Massimo, Centro Interdipartimentale di Analisi e Determinazioni Strutturali, Università di Siena, Siena, Italy, for obtaining the mass spectrum.

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