Polycondensed Heterocycles. III. Synthesis of 5,11-Dioxo-1,2,3,11a-tetrahydro-5*H*,11*H*- and 5-Oxo-2,3,11,11a-tetrahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine [1]

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The syntheses of 5,11-dioxo-1,2,3,11a-tetrahydro-5*H*,11*H*- and 5-oxo-2,3,11,11a-tetrahydro-1*H*,5*H*-pyrrolo-[2,1-*c*][1,4]benzothiazepine **10** and **11** have been studied.

The former was obtained by intramolecular cyclization with CDI of *N*-(2-mercaptobenzoyl)-L-proline **19**, prepared on one hand by demethylation of *N*-(2-methylthiobenzoyl)-L-proline *t*-butyl ester **15**, obtained *via* the Pummerer rearrangement of the corresponding sulphoxide **17** and successive alkaline hydrolysis, and by deprotection of the mercapto ester **18** with TFA or trimethylsilyl iodide. The ester **15** was achieved by reaction of *o*-(methylthio)benzoic acid **12** with L-proline *t*-butyl ester or by treatment of the corresponding acid chloride **13** with L-proline and successive esterification of *N*-(2-methylthiobenzoyl)-L-proline **16**. On the other hand the proline **19** was also obtained by reduction with sodium dithionite of (*S*)-bis[2-[[2-(hydroxycarbonyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **20**, prepared by condensation of bis(2-chlorocarbonylphenyl) disulphide **14** with L-proline. The reduction of (*S*)-bis[2-[[2-(chloromethyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **28** with sodium borohydride in boiling ethanol afforded directly the benzothiazepinone **11** in 85% yield. The disulphide **28** was synthesized treating the corresponding alcohol **24** or *N*-(2-mercaptobenzoyl)-L-prolinol **25** with thionyl chloride. Compound **25** was obtained by demethylation of the corresponding methylthio ether **26** oxidized to sulphoxide **27** *via* the Pummerer rearrangement. The acid chloride **14** by condensation with (*S*)-2-(chloromethyl)pyrrolidine hydrochloride gave disulphide **28** as well. The acid chlorides **13** and **14** by reaction with L-prolinol provided respectively alcohols **26** and **24**.

Attempts to cyclodehydrate the mercapto alcohol **25**, obtained also by reduction of disulphide **24**, failed.

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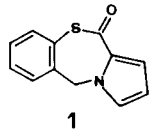
Recently we set up general synthetic pathways to obtain 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **1**, derivative of novel system ring, with the intention of preparing, amongst other things, compounds closely related to sibiromycin, a pyrrolo[2,1-*c*][1,4]benzodiazepine antitumor antibiotic [2,3].

While this program was in progress in our laboratory, a further aim was to synthesize new derivatives having structural affinities with the parent antibiotics, which contain the saturated pyrrole ring, namely the more recent DC-81 **2** [4] and chicamycin A **3** and B **4** [5], as well as SEN-215 **5** [6], tomaymycin **6** [7], oxotomaymycin **7** [7] and neothramycin A **8** and B **9** [8].



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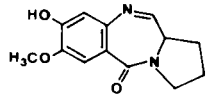

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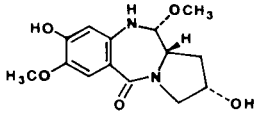

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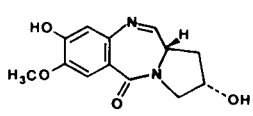

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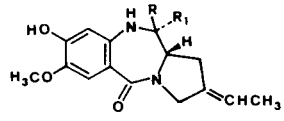
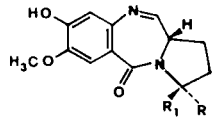
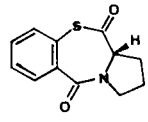


5 R = R_1 = H
6 R = H, R_1 = OCH_3
7 R R_1 = O



8 R = OH, R_1 = H
9 R = H, R_1 = OH

Therefore in order to find general synthetic methods we focused our attention on the synthesis of 5,11-dioxo-1,2,3,-11a-tetrahydro-5*H*,11*H*- and 5-oxo-2,3,11,11a-tetrahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **10** and **11**.



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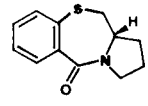
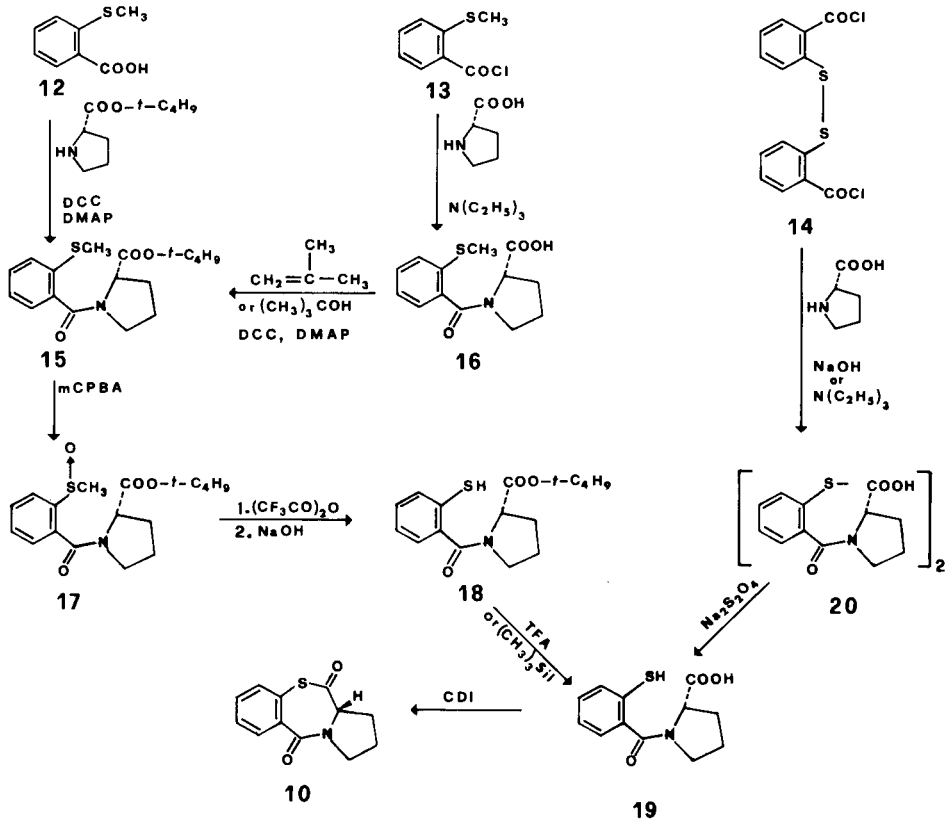


11

The benzothiazepindione **10** was prepared by the procedures shown in Scheme I using as starting material *o*-(methylthio)benzoic acid **12** [9] or its acid chloride **13** [10] or bis(2-chlorocarbonylphenyl)disulphide **14** [11].

N-(2-Methylthiobenzoyl)-L-proline *t*-butyl ester **15** was conveniently prepared by treatment in anhydrous dimethylformamide at room temperature of *o*-(methylthio)benzoic

SCHEME I



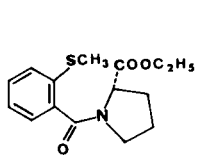
acid **12** with L-proline *t*-butyl ester [12,13] with use of *N,N'*-dicyclohexylcarbodiimide (DCC) in presence of 4-dimethylaminopyridine (DMAP) as the amide-generating reagent.

Alternatively, the ester **15** was synthesized by reaction at room temperature of *o*-(methylthio)benzoyl chloride **13** with L-proline and triethylamine in dichloromethane and esterifying *N*-(2-methylthiobenzoyl)-L-proline **16** so formed, by methods reported in literature [12,13], with isobutylene in dichloromethane in presence of concentrated sulphuric acid or with *t*-butyl alcohol in presence of *N,N'*-dicyclohexylcarbodiimide and 4-dimethylaminopyridine in anhydrous dichloromethane.

To provide the key intermediate of synthesis, the *N*-(2-mercaptobenzoyl)-L-proline **19** [14], the proline *t*-butyl ester **15** was transformed by oxidation with *m*-chloroperbenzoic acid (mCPBA) followed by treatment with calcium hydroxide in chloroform to *N*-(2-methylsulphinylbenzoyl)-L-proline *t*-butyl ester **17**, which crude was subjected to Pummerer rearrangement by action of trifluoroacetic anhydride at reflux and then of sodium hydroxide following the literature procedure [15]; finally the crude *N*-(2-mercaptobenzoyl)-L-proline *t*-butyl ester **18** thus obtained was deprotected with either trifluoroacetic acid in anisole or by means of trimethylsilyl iodide in dichloromethane, both at room temperature.

The acid **19** was also prepared with best results using bis(2-chlorocarbonylphenyl) disulphide **14**, which by condensation with L-proline under standard Schotten-Bauman acylating conditions or in presence of triethylamine in dichloromethane afforded (*S*)-bis[2-[[2-(hydroxycarbonyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **20**; this latter **20** without further purification was converted to **19** by reduction with sodium dithionite in presence of sodium carbonate under reflux.

Initially attempts by us to obtain directly *N*-(2-mercaptobenzoyl)-L-proline **19** from *N*-(2-methylsulphinylbenzoyl)-L-proline ethyl ester **22** under Pummerer rearrangement conditions followed by treatment with three equivalents of sodium hydroxide in aqueous methanol gave unsatisfactory results. The sulphoxide **22** was achieved by oxidation with *m*-chloroperbenzoic acid in chloroform of *N*-(2-methylthiobenzoyl)-L-proline ethyl ester **21**, prepared by reaction of *o*-(methylthio)benzoic acid **12** with L-proline ethyl ester [12,16] in presence of *N,N'*-dicyclohexylcarbodiimide and 4-dimethylaminopyridine in anhydrous tetrahydrofuran or with its hydrochloride **16** using *N,N'*-dicyclohexylcarbodiimide and triethylamine in dichloromethane, according to the literature procedure [17].



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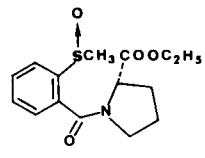
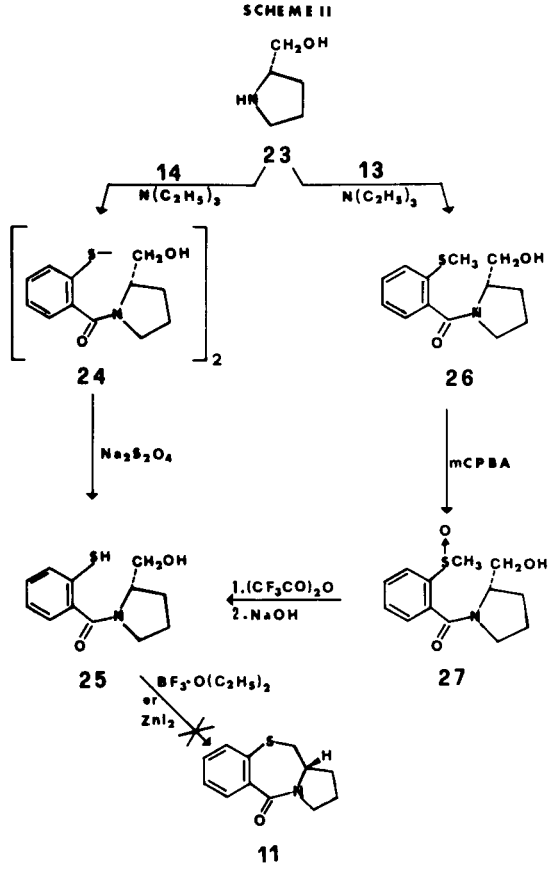


22

Finally *N*-(2-mercaptobenzoyl)-L-proline **19** was subjected to intramolecular cyclizing reaction by treatment with *N,N'*-carbonyldiimidazole (CDI) in anhydrous tetrahydrofuran at room temperature for 40 hours and then at reflux for 7 hours to give 5,11-dioxo-1,2,3,11a-tetrahydro-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **10** in 43% yield.

As regards the synthesis of 5-oxo-2,3,11,11a-tetrahydro-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **11**, the first attempt was carried out utilizing the above seen *o*-(methylthio)benzoyl chloride **13** or bis(2-chlorocarbonylphenyl) disulphide **14**, as illustrated in Scheme II.

SCHEME II

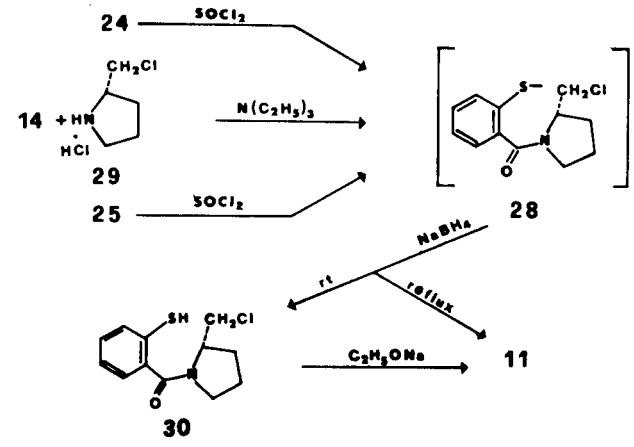


Treatment of the disulphide **14** with L-prolinol **23** at −10° in presence of triethylamine in dichloromethane gave (*S*)-bis[2-[[2-(hydroxymethyl)-1-pyrrolidinyl]carbonyl]-phenyl] disulphide **24**, the reduction of which with sodium dithionite afforded in good yield *N*-(2-mercaptobenzoyl)-L-prolinol **25**. By alternative route, *N*-(2-methylthiobenzoyl)-L-prolinol **26** could be obtained by reaction of the acid chloride **13** with L-prolinol **23**, carried out in an analogous manner to that described above for disulphide **24**. The prolinol **26** was converted, in a similar manner to that previously described for ethyl ester **22**, to *N*-(2-methylsulphinylbenzoyl)-L-prolinol **27**, which *via* the Pummerer rearrangement by reaction with trifluoroacetic anhydride followed by hydrolysis with sodium hydroxide provided the desired *N*-(2-mercaptobenzoyl)-L-prolinol **25**.

But when the prolinol **25** was subjected to cyclodehydration by the action of boron trifluoride ethyl etherate in acetic acid [19] or by zinc iodide in 1,2-dichloroethane [20] to prepare the benzothiazepinone **11**, no reaction was observed.

Thus these failures prompted us to realize the synthesis of **11** following the route depicted in Scheme III.

SCHEME III



(*S*)-bis[2-[[2-(Hydroxymethyl)-1-pyrrolidinyl]carbonyl]-phenyl] disulphide **24** in chloroform at low temperature and *N*-(2-mercaptobenzoyl)-L-prolinol **25** in anhydrous benzene at reflux were transformed into (*S*)-bis[2-[[2-(chloromethyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **28** both by means of thionyl chloride. The disulphide **28** could be also prepared directly by condensation of bis(2-chlorocarbonylphenyl) disulphide **14** with (*S*)-2-(chloromethyl)pyrrolidine hydrochloride **29** [18] in presence of triethylamine in anhydrous dichloromethane at −10° in quantitative yield.

Reduction of disulphide **28** with sodium borohydride in ethanol by heating to reflux for 2 hours afforded directly the desired 5-oxo-2,3,11,11a-tetrahydro-1*H*,5*H*-pyrrolo-[2,1-*c*][1,4]benzothiazepine **11** in 85% yield.

If reduction was carried out at room temperature for 30 minutes, (*S*)-*N*-(2-mercaptobenzoyl)-2-(chloromethyl)pyrrolidine **30** was formed. The crude thiol **30** by action of sodium ethylate in anhydrous ethanol at room tempera-

ture overnight and then heated to reflux for 2 hours cyclized to **11**.

EXPERIMENTAL

Melting points were determined with an Electrothermal 8103 digital melting point apparatus and are uncorrected. Optical rotations were measured on Optical Activity polarimeter. 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 ^1H nmr spectra were recorded on a Varian XL 200 spectrometer with TMS as internal standard. The mass spectra were recorded on a Finnigan 1020 spectrometer with an electron beam energy of 70 eV. Merck silica gel (70 - 230 mesh) was used for chromatographic purifications. Flash chromatography was performed according to the method of Still [21] using Kieselgel 60 230-400 mesh (E. Merck No. 9385). Microanalyses were performed by Professor A. Pietrogrande, Padova, Italy.

N-(2-Methylthiobenzoyl)-L-proline (**16**).

To a solution of 4 g (0.035 mole) of L-proline and 3.58 g (0.035 mole) of triethylamine in 250 ml of dichloromethane was added dropwise at $-10°$, in an atmosphere of nitrogen, a solution of 6.5 g (0.035 mole) of *o*-(methylthio)benzoyl chloride **13** [10] in 100 ml of dichloromethane. After stirring at room temperature for 18 hours the mixture was washed twice with water, dried over anhydrous sodium sulphate and evaporated to give a residue which was crystallized from benzene-petroleum ether (bp 40-60°) to afford 7.8 g (85%) of *N*-(2-methylthiobenzoyl)-L-proline **16**. An analytical sample of mp 153-156° was obtained as colourless prisms; ir: 1745 cm^{-1} (carboxylic C=O), 1615 (amide C=O); nmr (deuteriochloroform): δ 1.8-2.7 (m, 4H), 2.48 (s, 3H), 3.32 (t, 2H), 4.78 (dd, 1H), 7.0-7.5 (m, 4H), 9.7-10.3 (s, broad, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{13}H_{15}NO_3S$: C, 58.86; H, 5.70; N, 5.28. Found: C, 58.89; H, 5.74; N, 5.25.

N-(2-Methylthiobenzoyl)-L-proline *t*-Butyl Ester (**15**).

I.

To a stirred and cooled in an ice bath solution of 4.22 g (0.025 mole) of *o*-(methylthio)benzoic acid **12** [9], 0.28 g of 4-dimethylaminopyridine and 4.3 g (0.025 mole) of L-proline *t*-butyl ester [12,13] in 27 ml of anhydrous dimethylformamide, kept under nitrogen, were added 5.2 g (0.025 mole) of *N,N'*-dicycloexylcarbodiimide in small portions. The reaction mixture was then allowed to stir for 5 minutes at 0° and for 5 hours at room temperature. The precipitated *N,N'*-dicyclohexylurea was filtered off and the filtrate was evaporated down *in vacuo* at 35-40°. The residue was taken up in dichloromethane and, if necessary, filtered free of any further precipitated urea. The solution was washed twice with 0.5 *N* hydrochloric acid and with saturated sodium bicarbonate solution, and then dried over anhydrous sodium sulphate. The solvent was removed by evaporation and the oily residue was distilled to give 6.5 g (81%) of *N*-(2-methylthiobenzoyl)-L-proline *t*-butyl ester **15** as a colourless oil (bp 185°/0.1 mm); ir: 1743 cm^{-1} (ester C=O), 1645 (amide C=O).

Anal. Calcd. for $C_{17}H_{23}NO_3S$: C, 63.54; H, 7.21; N, 4.36; S, 9.96. Found: C, 63.67; H, 7.42; N, 4.56; S, 9.72.

II.

To a solution of 7.7 g (0.029 mole) of *N*-(2-methylthiobenzoyl)-L-proline **16** in 55 ml of dichloromethane was added concentrated sulphuric acid (0.35 ml). The solution was cooled in an ice bath and was saturated with isobutylene with stirring, causing a volume increase of 28 ml. After 24 hours at room temperature, concentrated sulphuric acid (a few drops) was added and isobutylene was bubbled over a period of 30 minutes. When the addition was stopped the solution was stirred at room temperature for 40 hours and then poured into 40 ml of water containing sodium carbonate sufficient to neutralize all acids. The organic layer was separated, washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oily residue, which after distillation afforded 6.8 g (73%) of **15**.

III.

To a stirred solution of 5.3 g (0.02 mole) of *N*-(2-methylthiobenzoyl)-L-proline **16** in 20 ml of anhydrous dichloromethane, in an atmosphere of nitrogen, were added 0.2 g of 4-dimethylaminopyridine and 4.44 g (0.06 mole) of *t*-butyl alcohol. A solution of 4.55 g (0.022 mole) of *N,N'*-dicyclohexylcarbodiimide in 5 ml of dichloromethane was added at 0° in small portions to the reaction mixture, which was then stirred for 5 minutes at 0° and 3 hours at room temperature. The *N,N'*-dicyclohexylurea was filtered off and the filtrate was washed twice with 0.5 *N* hydrochloric acid and with saturated sodium bicarbonate solution. After drying over anhydrous sodium sulphate and removing of the solvent, the residue was dissolved in anhydrous diethyl ether, filtered to remove remaining urea and evaporated to give, after distillation, 4.35 g (68%) of **15**.

N-(2-Methylsulphinylbenzoyl)-L-proline *t*-Butyl Ester (**17**).

To a well stirred solution of 9 g (0.028 mole) of *N*-(2-methylthiobenzoyl)-L-proline *t*-butyl ester **15** in 150 ml of chloroform, kept under nitrogen, was added *m*-chloroperbenzoic acid (70% grade, 6.88 g, 0.028 mole) with ice-cooling. The resultant suspension was stirred for a further 2 hours at 0°, treated with 1.55 g (0.021 mole) of calcium hydroxide and then stirred for 15 minutes at room temperature. The precipitate was filtered off and washed with chloroform. The combined filtrates were evaporated to afford 9.5 g (quantitative yield) of the crude *N*-(2-methylsulphinylbenzoyl)-L-proline *t*-butyl ester **17** as a semi-solid material, which was used without further purification in the next step; ir: 1740 cm^{-1} (ester C=O), 1638 (amide C=O).

N-(2-Mercaptobenzoyl)-L-proline *t*-Butyl Ester (**18**).

The crude *N*-(2-methylsulphinylbenzoyl)-L-proline *t*-butyl ester **17** (9.5 g) was dissolved in 60 ml of trifluoroacetic anhydride and heated to reflux for 45 minutes under a nitrogen atmosphere with stirring. The solution was evaporated under reduced pressure to give a oily residue, which was treated with 56 ml (0.056 mole) of 1*N* sodium hydroxide solution and allowed to stir for 1 hour at room temperature. After filtration the solution was made acidic with 6*N* hydrochloric acid and extracted with ethyl acetate. After washing with saturated ammonium chloride solution and drying over anhydrous sodium sulphate the solvent was removed *in vacuo* to provide 5.94 g (69% overall yield) of crude *N*-(2-mercaptobenzoyl)-L-proline *t*-butyl ester **18** as an oily material, which was used without further purification in the next step; ir: 2525 cm^{-1} (SH), 1745 (ester C=O), 1642 (amide C=O).

(*S*)-bis[2-[[2-(Hydroxycarbonyl)-1-pyrrolidinyl]carbonyl]phenyl] Disulphide (**20**).

I.

To a well stirred solution of 1.4 g (0.0122 mole) of L-proline and 0.6 g (0.015 mole) of sodium hydroxide in 20 ml of water was added dropwise a solution of 2.1 g (0.0061 mole) of bis(2-chlorocarbonylphenyl)disulphide **14** [11] in 40 ml of chloroform at room temperature with stirring under nitrogen stream. Then a solution of 0.5 g of sodium hydroxide in 60 ml of water was added dropwise so as to maintain the *p*H on low alkaline values. After about 3 hours the solution was washed twice with ethyl acetate, acidified with 4*N* hydrochloric acid and left to stand in a cool place. The precipitate that had separated, after decantation, was dissolved in chloroform and the resulting solution was dried over anhydrous sodium sulphate. Removal of the solvent afforded 2.9 g (95%) of crude (*S*)-bis[2-[[2-(hydroxycarbonyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **20** as a colourless amorphous solid, which was used for next step without further purification. An analytical sample was prepared by recrystallization from hot ethyl acetate. The precipitated semi-solid material was isolated by decantation and dried *in vacuo*; ir: 1740 cm^{-1} (carboxylic C=O), 1610 (amide C=O).

Anal. Calcd. for $C_{24}H_{24}N_2O_6S_2$: C, 57.60; H, 4.83; N, 5.60. Found: C, 57.44; H, 4.73; N, 5.26.

II.

The condensation reaction of L-proline (2.3 g, 0.02 mole, 100 ml of

anhydrous dichloromethane) with bis(2-chlorocarbonylphenyl) disulphide **14** [11] (3.42 g, 0.01 mole, 100 ml of anhydrous dichloromethane) in presence of triethylamine (2 g, 0.02 mole) was carried out as described above in the preparation of *N*-(2-methylthiobenzoyl)-L-proline **16** stirring for 12 hours. Evaporation of solvent gave 3.6 g (72%) of crude **20**.

N-(2-Mercaptobenzoyl)-L-proline (**19**).

I.

A mixture of 8 g (0.016 mole) of crude (*S*)-bis[2-[[2-(hydroxycarbonyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **20**, 4 g (0.025 mole) of sodium dithionite, 4.8 g (0.045 mole) of sodium carbonate and 45 ml of water was heated to reflux for 45 minutes, then cooled and filtered. Acidification of the filtrate at −5 to 0° with 4*N* hydrochloric acid, followed by ethyl acetate extraction, gave a solution which was washed with brine and dried over anhydrous sodium sulphate. Concentration afforded 6.4 g (79%) of *N*-(2-mercaptobenzoyl)-L-proline **19** as a thick oil, which on standing solidified and after crystallization from ethyl acetate melted at 158-161°. An analytical sample of mp 161-163° (lit [14], 169.5-171°) was obtained by crystallization from chloroform as colourless prisms; $[\alpha]_D^{23}$ −138.4° (cl, chloroform); ir: 2525 cm^{-1} (SH), 1740 (carboxylic C=O), 1610 (amide C=O); nmr (deuteriochloroform): δ 1.6-2.6 (m, 4H), 3.1-3.7 (m, 2H), 4.12 (s, 1H, deuterium oxide exchangeable), 4.75 (dd, 1H), 6.5-7.8 (m, 4H), 6.99 (s, broad, 1H, deuterium oxide exchangeable); ms: m/e (%) 251 (M^+, 6), 205 (15), 136 (100), 108 (32), 70 (43), 55 (19), 44 (30).

Anal. Calcd. for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57; S, 12.76. Found: C, 57.03; H, 5.21; N, 5.36; S, 12.85.

II.

Trifluoroacetic acid (1.4 ml) was added dropwise to a stirred mixture of 2 g (0.0065 mole) of crude *N*-(2-mercaptobenzoyl)-L-proline *t*-butyl ester **18** and 0.5 ml of anisole chilled in an ice-water bath to about 10° under a nitrogen atmosphere. The resulting solution was stirred for 30 minutes with external cooling and then for 24 hours at room temperature. At the end the reaction mixture was concentrated *in vacuo* while the temperature was maintained below 60°. The residue was dissolved in 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 organic phase was washed twice with water, dried on anhydrous sodium sulphate and evaporated *in vacuo*. The residue was applied to a column of 17 g of Dowex 50 x 2-200 ion-exchange resin (Aldrich) and eluted with methanol. The methanol was evaporated *in vacuo* and the residue was dissolved in chloroform. The chloroform solution was washed twice with water, dried over anhydrous sodium sulphate and evaporated to give 1.15 g (70%) of **19** as a thick oil, which solidified upon trituration with petroleum ether (bp 40-60°).

III.

To a solution of 3.5 g (0.0114 mole) of crude *N*-(2-mercaptobenzoyl)-L-proline *t*-butyl ester **18** in 15 ml of dichloromethane under nitrogen was added trimethylsilyl iodide (2.26 g, 0.0113 mole) dropwise. The reaction mixture was stirred at room temperature for 90 minutes and then another portion of trimethylsilyl iodide (1.61 g, 0.008 mole) was added. After the mixture was stirred for an additional hour, water (3 ml) was added and stirring was continued for 5 minutes. The product was extracted several times with saturated aqueous sodium bicarbonate. The combined sodium bicarbonate layer was washed twice with ethyl acetate and then acidified cautiously to *p*H 2 by the dropwise addition of concentrated hydrochloric acid. The separated product was extracted several times with ethyl acetate, washed twice with water and dried over anhydrous sodium sulphate. Removal of solvent *in vacuo* afforded an oily product (2 g), which was applied to a column of 17 g of Dowex 50 x 2-200 ion-exchange resin (Aldrich) and eluted with methanol. Evaporation *in vacuo* of the solvent gave an oily residue, which was dissolved in chloroform, washed twice with water and dried over anhydrous sodium sulphate. Evaporation *in vacuo* of the solvent afforded 1.6 g (56%) of **19** as a thick oil, which solidified upon trituration with petroleum ether (bp 40-60°).

5,11-Dioxo-1,2,3,11a-tetrahydro-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine (**10**).

A mixture of 1 g (0.004 mole) of *N*-(2-mercaptobenzoyl)-L-proline **19**, 0.645 g of *N,N'*-carbonyldiimidazole (CDI) and 16 ml of anhydrous tetrahydrofuran was allowed to stir at room temperature for 40 hours and then heated under reflux for 7 hours in an atmosphere of nitrogen. Evaporation *in vacuo* of the solvent afforded a residue which was dissolved in chloroform, washed with brine and dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* gave a product which was purified by passing through a silica gel column (ethyl acetate as eluent) to afford 0.4 g (43%) of 5,11-dioxo-1,2,3,11a-tetrahydro-5*H*,11*H*-pyrrolo-[2,1-*c*][1,4]benzothiazepine **10** as an oily material, which on standing solidified. An analytical sample of mp 91-93° was obtained as colourless translucent flakes by crystallization from petroleum ether (bp 60-80°); ir: 1703 cm^{-1} (thiolactone C=O), 1640 (lactam C=O); nmr (deuteriochloroform): δ 1.8-2.8 (m, 4H), 3.5-4.0 (m, 2H), 4.1-4.4 (m, 1H), 7.3-8.2 (m, 4H); ms: m/e (%) 233 (M^+, no peak), 205 (30), 136 (100), 108 (23), 69 (20).

Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.80; H, 4.75; N, 6.01; S, 13.72. Found: C, 61.88; H, 4.75; N, 5.94; S, 13.92.

N-(2-Methylthiobenzoyl)-L-proline Ethyl Ester (**21**).

I.

A solution of 1.44 g (0.007 mole) of *N,N'*-dicyclohexylcarbodiimide in 5 ml of anhydrous tetrahydrofuran was added to a stirred solution of 1.18 g (0.007 mole) of *o*-(methylthio)benzoic acid **12** [9], 81 mg of 4-dimethylaminopyridine and 1 g (0.007 mole) of L-proline ethyl ester [12,16] in 10 ml of anhydrous tetrahydrofuran at 0° in an atmosphere of nitrogen. The reaction mixture was then stirred for 5 minutes at 0° and 4 hours at room temperature. Precipitate *N,N'*-dicyclohexylurea was filtered off and the filtrate evaporated down *in vacuo*. The oily residue was purified by passing through a silica gel column [ethyl acetate-petroleum ether (bp 40-60°) (1:1) as eluent] and then distilled to give 1.6 g (78%) of *N*-(2-methylthiobenzoyl)-L-proline ethyl ester **21** as a colourless liquid (bp 176°/0.03 mm); ir: 1760 cm^{-1} (ester C=O), 1650 (amide C=O).

Anal. Calcd. for $C_{15}H_{19}NO_3$: C, 61.42; H, 6.53; N, 4.78; S, 10.91. Found: C, 61.57; H, 6.63; N, 4.77; S, 10.67.

II.

To a stirred mixture of 17.1 g (0.102 mole) of *o*-(methylthio)benzoic acid **12** [9] and 17.9 g (0.1 mole) of L-proline ethyl ester hydrochloride [16] in 60 ml of dichloromethane was added a solution of 9.88 g (0.098 mole) of triethylamine in 20 ml of dichloromethane during 30 minutes at −5° under nitrogen. Then a solution of 20 g (0.097 mole) of *N,N'*-dicyclohexylcarbodiimide in 35 ml of dichloromethane was added during 80 minutes. After the mixture had been stirred at −5° for 4 hours, the cooling bath was removed, the temperature was allowed to reach room temperature and stirring was continued overnight. The white precipitate was filtered off and the filtrate was washed successively with 3*N* hydrochloric acid (10 ml x 2), saturated sodium bicarbonate solution (10 ml x 2) and water (10 ml x 3) and then dried over anhydrous sodium sulphate. The solvent was evaporated under reduced pressure and the residue was dissolved in anhydrous diethyl ether and filtered to remove remaining *N,N'*-dicyclohexylurea. Removal of the solvent afforded an oily product, which after distillation (bp 178°/0.02 mm) gave 18.8 g (64%) of **21**.

N-(2-Methylsulphinybenzoyl)-L-proline Ethyl Ester (**22**).

To a stirred, cooled (0°) solution of 6.45 g (0.022 mole) of *N*-(2-methylthiobenzoyl)-L-proline ethyl ester **21** in 110 ml of chloroform was added *m*-chloroperbenzoic acid (70% grade, 5,4 g, 0.022 mole) under a nitrogen atmosphere and the resulting suspension was stirred for a further 1 hour at 0°, treated with calcium hydroxide (1.22 g, 0.0165 mole) and then stirred for 15 minutes at room temperature. Filtration and evaporation afforded a residue which was purified by passing through a silica gel col-

umn (ethyl acetate as eluent) to give 5.45 g (96%) of *N*-(2-methylsulphinylbenzoyl)-L-proline ethyl ester **22** as a pale yellow oil. An analytical sample distilled at 199-200°/0.03 mm; ir: 1740 cm^{-1} (ester C=O), 1640 (amide C=O).

Anal. Calcd. for $C_{15}H_{19}NO_4S$: C, 58.25; H, 6.19; N, 4.53; S, 10.34. Found: C, 58.14; H, 6.25; N, 4.27; S, 10.38.

(*S*)-bis[2-[[2-(Hydroxymethyl)-1-pyrrolidinyl]carbonyl]phenyl] Disulphide (**24**).

A solution of 1.69 g (0.0049 mole) of bis(2-chlorocarbonylphenyl) disulphide **14** [11] in 35 ml of anhydrous dichloromethane was added dropwise, very slowly, to a vigorously stirred solution of 1 g (0.01 mole) of L-prolinol **23** and 1 g (0.01 mole) of triethylamine in 35 ml of dichloromethane under an atmosphere of nitrogen, at −10°. The reaction mixture was stirred for a further 30 minutes at room temperature, then washed with brine and dried over anhydrous sodium sulphate. Evaporation of the solvent *in vacuo* afforded 2.2 g (94%) of (*S*)-bis[2-[[2-(hydroxymethyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **24** as a thick oil which solidified upon trituration with petroleum ether (bp 40-60°). An analytical sample was prepared as a white amorphous solid by flash chromatography over silica gel [dichloromethane-methanol (23:2) as eluent]; ir: 3380 cm^{-1} (OH, broad), 1625 (amide C=O).

Anal. Calcd. for $C_{24}H_{28}N_2O_4S_2$: N, 5.93; S, 13.54. Found: N, 5.96; S, 13.66.

The (*S*)-bis[2-[[2-(*p*-nitrobenzoyloxymethyl)-1-pyrrolidinyl]carbonyl]-phenyl] disulphide after crystallization from ethyl acetate melted at 177.5-179° (pale yellow prisms).

Anal. Calcd. for $C_{38}H_{34}N_4O_{10}S_2$: C, 59.21; H, 4.45; N, 7.27; S, 8.32. Found: C, 58.89; H, 4.47; N, 7.32; S, 7.93.

N-(2-Methylthiobenzoyl)-L-prolinol (**26**).

This compound was obtained in an analogous manner to that described above for disulphide **24** starting from 3.4 g (0.018 mole) of **o**-(methylthio)benzoyl chloride **13** [10], 1.85 g (0.018 mole) of L-prolinol **23** and 1.8 g (0.018 mole) of triethylamine. The oily residue, after purification by flash chromatography [dichloromethane-methanol (24:1) as eluent], afforded 4.5 g (98%) of *N*-(2-methylthiobenzoyl)-L-prolinol **26** as a thick oil, which on standing solidified and crystallized from benzene as colourless prisms, mp 121.5-122.5°; ir: 3310 cm^{-1} (OH, broad), 1600 (amide C=O); nmr (deuteriochloroform): δ 1.5-2.3 (m, 4H), 2.48 (s, 3H), 3.1-3.4 (m, 2H), 3.6-4.0 (m, 2H), 4.2-4.5 (m, 1H), 4.74 (m, 1H, deuterium oxide exchangeable).

Anal. Calcd. for $C_{13}H_{17}NO_2S$: C, 62.14; H, 6.82; N, 5.57; S, 12.73. Found: C, 62.09; H, 6.95; N, 5.52; S, 12.69.

N-(2-Methylsulphinylbenzoyl)-L-prolinol (**27**).

The oxidation reaction of *N*-(2-methylthiobenzoyl)-L-prolinol **26** (3 g, 0.012 mole) was carried out as described above in the preparation of ethyl ester **22**. The oily residue after chromatography, using dichloromethane-methanol (9:1) as eluent, gave 2,9 g (91%) of *N*-(2-methylsulphinylbenzoyl)-L-prolinol **27** as a semi-solid product; ir: 3390 cm^{-1} (OH, broad), 1610 (amide C=O); nmr (deuteriochloroform): δ 1.4-2.2 (m, 4H), 2.78 and 2.86 (2s, 3H), 3.0-3.4 (m, 2H), 3.5-4.4 [m, 4H, CH_2O, OH (deuterium oxide exchangeable) and CHN], 7.1-8.2 (m, 4H).

N-(2-Mercaptobenzoyl)-L-prolinol (**25**).

I.

The reduction reaction of (*S*)-bis[2-[[2-(hydroxymethyl)-1-pyrrolidinyl]-carbonyl]phenyl] disulphide **24** (2.5 g, 0.0053 mole) with sodium dithionite (1.47 g, 0.0084 mole) in presence of sodium carbonate (0.98 g, 0.0093 mole) was carried out as described above in the preparation of proline **19**. Evaporation of solvent afforded 2.4 g (95%) of crude *N*-(2-mercaptobenzoyl)-L-prolinol **25** as an oily product. An analytical sample was prepared as a colourless oil by chromatography over silica gel [dichloromethane-methanol (4:1) as eluent]; $[\alpha]_D^{23}$ −135.5 (cl, chloroform); ir: 3375 cm^{-1} (OH, broad), 2500 (SH), 1608 (amide C=O); nmr deuteriochloroform): δ 1.5-2.3 (m, 4H), 3.1-3.4 (m, 2H), 3.6-4.1 (m, 2H), 3.82 (s, 1H, deuterium oxide exchangeable), 4.2-4.5 (m, 1H), 4.73 (s, broad, 1H, deuterium oxide exchangeable), 7.1-7.5 (m, 4H).

Anal. Calcd. for $C_{12}H_{15}NO_2S$: C, 60.75; H, 6.37; N, 5.90; S, 13.48. Found: C, 60.30; H, 6.29; N, 5.78; S, 13.80.

II.

The *N*-(2-methylsulphinylbenzoyl)-L-prolinol **27** (2.9 g, 0.0108 mole) was dissolved in trifluoroacetic anhydride (25 ml) and heated to reflux for 45 minutes under nitrogen with stirring. To the residue obtained by evaporation of the volatile components under reduced pressure were added 32 ml (0.0324 mole) of 1*N* sodium hydroxide solution and mixture was allowed to stir for 30 minutes at room temperature. The solution was acidified with concentrated hydrochloric acid and extracted with chloroform. The organic phase was washed with brine and evaporated to dryness. The residue was taken up in 1*N* sodium hydroxide solution, treated with charcoal, filtered, acidified with concentrated hydrochloric acid and extracted with chloroform. After drying on anhydrous sodium sulphate the solvent was removed *in vacuo* to provide 1.5 g (59%) of **25**.

(*S*)-bis[2-[[2-(Chloromethyl)-1-pyrrolidinyl]carbonyl]phenyl] Disulphide (**28**).

I.

To a stirred solution of 5.66 g (0.012 mole) of (*S*)-bis[2-[[2-(hydroxymethyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **24** in 60 ml of chloroform, chilled at 0° and kept under nitrogen atmosphere, 3.5 ml of thionyl chloride were added by dropping over a period of 30 minutes. After all the thionyl chloride was added, the reaction mixture was stirred for 1 hour at room temperature and then heated for 2 hours to reflux. After evaporation of the solvent *in vacuo* the excess of thionyl chloride was stripped off under reduced pressure. The (*S*)-bis[2-[[2-(chloromethyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **28** was achieved as white flakes (6 g, 98%). An analytical sample was prepared by flash chromatography over silica gel (ethyl acetate as eluent), mp 58-67°; $[\alpha]_D^{27}$ −203 (cl, chloroform); ir: 1637 cm^{-1} (amide C=O).

Anal. Calcd. for $C_{24}H_{26}Cl_2N_2O_2S_2$: C, 56.57; H, 5.14; Cl, 13.92; N, 5.50; S, 12.59. Found: C, 56.09; H, 5.42; Cl, 13.95; N, 5.80; S, 12.34.

II.

To a solution of 1.56 g (0.01 mole) of (*S*)-2-(chloromethyl)pyrrolidine hydrochloride **29** [18] in 40 ml of anhydrous dichloromethane, chilled at −10°, were added in one portion 2 g (0.02 mole) of triethylamine and then dropwise a solution of 1.77 g (0.005 mole) of bis(2-chlorocarbonylphenyl) disulphide **14** [11] in 40 ml of anhydrous dichloromethane with stirring under nitrogen stream. When the addition was stopped the reaction mixture was allowed to stir at room temperature for 30 minutes, washed with brine and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded 2.5 g (99%) of 28 as an oily product, which on standing solidified.

III.

To a well stirred solution of 3 g (0.0127 mole) of *N*-(2-mercaptobenzoyl)-L-prolinol **25** in 40 ml of anhydrous benzene a solution of 3.6 ml of thionyl chloride in 20 ml of anhydrous benzene was added dropwise. The reaction mixture was heated to reflux for 90 minutes and after evaporation of the solvent *in vacuo* the excess of thionyl chloride was stripped off under reduced pressure. The resulting residue was dissolved in 100 ml of chloroform. The organic phase was washed with 50 ml of 1*N* sodium hydroxide solution and with water and then dried over anhydrous sodium sulphate. After removal of the solvent 3.2 g (quantitative yield) of crude **28** was achieved.

(*S*)-*N*-(2-Mercaptobenzoyl)-2-(chloromethyl)pyrrolidine (**30**).

To a solution of 2 g (0.0039 mole) of (*S*)-bis[2-[[2-(chloromethyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **28** in 90 ml of ethanol were added in small portions 0.73 g (0.0192 mole) of sodium borohydride under nitrogen with vigorous stirring at room temperature. After the reduction

was complete (30 minutes, tlc), the reaction mixture was reduced to 30% volume by evaporation under reduced pressure at 35°, diluted with 80 ml of water, acidified to *p*H 6 with acetic acid (10%) and then extracted with chloroform. The combined extracts were washed with brine, dried over anhydrous sodium sulphate and evaporated *in vacuo* to afford 2 g (99%) of crude (*S*)-*N*-(2-mercaptobenzoyl)-2-(chloromethyl)pyrrolidine **30** as a viscous oil; ir: 2515 cm^{-1} (SH), 1620 (amide C=O); nmr (deuteriochloroform): δ 1.6-2.3 (m, 4H), 3.1-3.5 (m, 2H), 3.6-4.2 (m, 2H), 3.94 (s, 1H, deuterium oxide exchangeable), 4.4-4.7 (m, 1H), 7.1-7.8 (m, 4H).

5-Oxo-2,3,11,11a-tetrahydro-1*H*,5*H*-pyrrolo[2,1-c][1,4]benzothiazepine (**11**).

I.

To a well stirred solution of 2.5 g (0.0049) of (*S*)-bis[2-[[2-(chloromethyl)-1-pyrrolidinyl]carbonyl]phenyl] disulphide **28** in 110 ml of ethanol, kept under nitrogen, were added in small portions 0.9 g (0.0237 mole) of sodium borohydride. The reaction mixture was heated to reflux for 2 hours and, after concentration to small volume *in vacuo*, diluted with 100 ml of water and treated with acetic acid (10%) dropwise until to *p*H 6. After extraction with chloroform the combined extracts were washed with brine and dried over anhydrous sodium sulphate. Evaporation of the solvent *in vacuo* gave an oily residue, which was subjected to flash chromatography on silica gel [ethyl acetate-petroleum ether (bp 40-60°) (4:1) as eluent] to afford 1.85 g (85%) of 5-oxo-2,3,11,11a-tetrahydro-1*H*,5*H*-pyrrolo[2,1-c][1,4]benzothiazepine **11**. An analytical sample distilled as a thick pale yellow oil (bp 183°/0.1 mm); $[\alpha]_D^{23}$ + 502° (cl, chloroform); ir: 1630 cm^{-1} (C=O); nmr (deuteriochloroform): δ 1.5-2.2 (m, 4H), 2.78 (t, 1H, $J_{11,11a} = J_{gem}$ = 11.9 Hz), 3.21 (dd, 1H, $J_{11,11a}$ = 4.7 Hz, J_{gem} = 11.7 Hz), 3.3-3.8 (m, 3H), 7.1-7.7 (m, 4H); ms: m/e (%) 219 (M^+, 100), 202 (10), 190 (27), 176 (22), 164 (19), 150 (31), 136 (56), 108 (43), 83 (55), 69 (50), 55 (29), 43 (32).

Anal. Calcd. for $C_{12}H_{13}NOS$: C, 65.74; H, 5.98; N, 6.39; S, 14.59. Found: C, 65.28; H, 6.09; N, 6.21; S, 14.66.

II.

To a solution of 0.18 g (0.0078 g-atom) of sodium metal in 5 ml of anhydrous ethanol was added dropwise a solution of 2 g (0.0078 mole) of crude (*S*)-*N*-(2-mercaptobenzoyl)-2-(chloromethyl)pyrrolidine **30** in 7 ml of anhydrous ethanol at room temperature with stirring under nitrogen atmosphere. When the addition was stopped the mixture was allowed to stir overnight at room temperature and then heated to reflux for 2 hours. After filtration of sodium chloride the ethanolic solution was evaporated *in vacuo* and the residue was dissolved in chloroform. The solution was washed with 1*N* hydrochloric acid, twice with water and brine and then dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* afforded an oily product, which was subjected to flash chromatography on silica gel [ethyl acetate-petroleum ether (bp 40-60°) (4:1) as eluent] to give 0.85 g (50%) of **11**.

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