Polycondensed Heterocycles. I. Synthesis of 11-Oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine, Derivative of a Novel Ring System [1]

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The synthesis of the title compound **4** by cyclization of 1-(2-ethoxycarbonylthiobenzyl)pyrrole **9**, prepared by treating with ethyl chloroformate the 1-(2-mercaptobenzyl)pyrrole **7** previously obtained by debenzylation of 1-(2-benzylthiobenzyl)pyrrrole **6**, failed. On the other hand **4** was successfully synthesized by intramolecular cyclization of 1-(2-mercaptobenzyl)pyrrole-2-carboxylic acid **15** by DMAP-catalyzed DCC method. The pyrrole **6** and 1-(2-benzylthiobenzyl)pyrrole-2-carboxaldehyde **11** were useful as starting materials to obtain 1-(2-benzylthiobenzyl)pyrrole-2-carbonitrile **13**, which was hydrolyzed to corresponding amide **16**. Debenzylation of **16** afforded 1-(2-mercaptobenzyl)pyrrole-2-carboxyamide **17**, whose hydrolysis led to required acid **15**.

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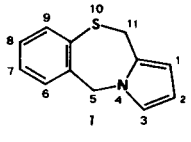
In an extension of our investigation on unknown nitrogen and sulphur polycyclic systems with potential pharmacological properties, which already produced the pyrrolo[2,1-*c*][1,4]benzothiazine [2], the pyrrolo[2,1-*d*][1,5]benzothiazepine [3] (of the latter nucleus were prepared 5-phenyl derivatives, some of which showed sedative activity [4]) and derivatives of pyrrolo[1,2-*b*][1,2,5]benzothiadiazepine [5], it was of interest to us to attempt the synthesis of the novel 5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine ring system 1.

Our interest in this tricyclic nucleus was both from the point of view of its structural features closely similar to the 5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepine **2**, which is the fundamental skeleton of sibiromycin **3** [6], along with anthramycin [7], tomaymycin [8], oxotomaymycin [8] and neothramycin A and B [9], a new class of antitumoral antibiotics, and the presence in its molecular framework of the 1,4-benzothiazepine moiety, some derivatives of which showed antidepressant [10] and antihypertensive [11] activities.

This work then broadened our knowledge in the field of pyrrolobenzothiazepines, which has recently attracted the attention of other researchers [12].



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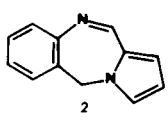

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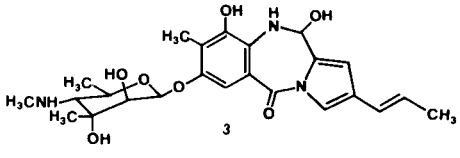

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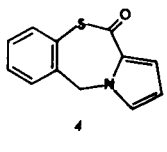

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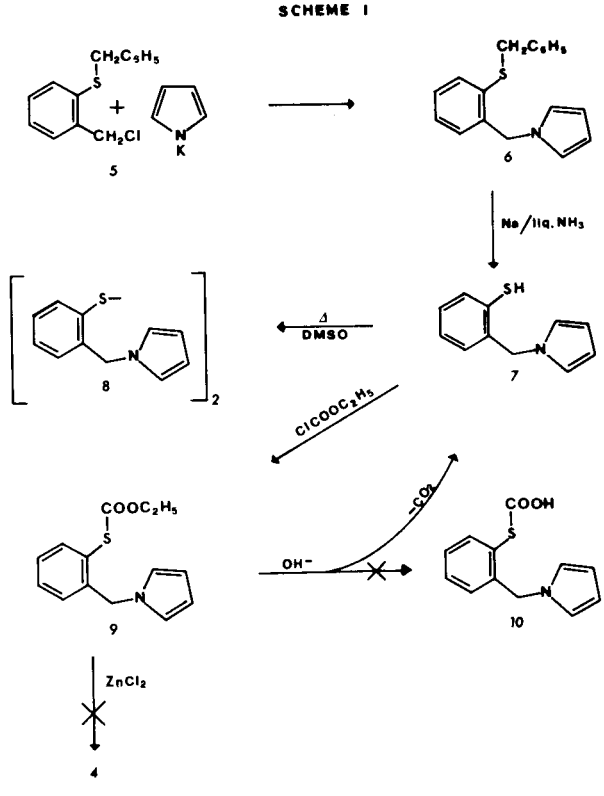
As a first approach to this purpose, we decided to synthesize 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **4** and selected as potential starting material two compounds, namely, bis[2-(bromomethyl)phenyl]disulphide [13] and *o*-benzylthiobenzyl chloride [14].

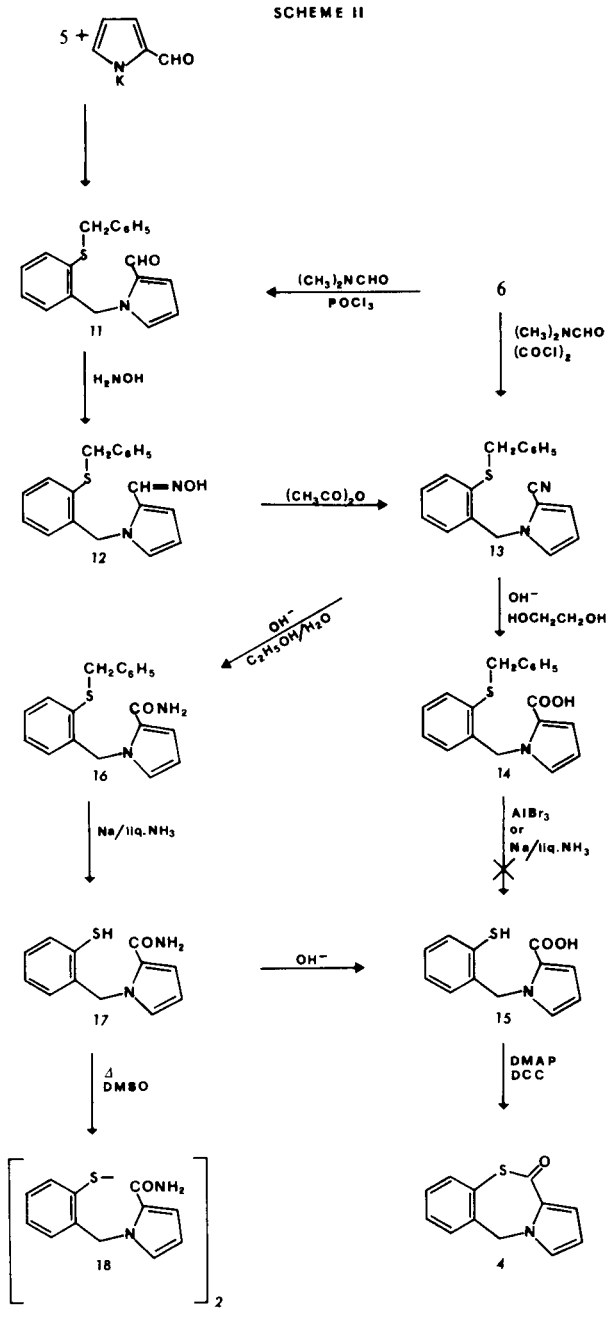
Attempted reactions of the former with the potassium salts of pyrrole and pyrrole-2-carboxaldehyde were unsuccessful.

Starting therefore from the latter compound the first synthetic route chosen for preparation of **4** was that outlined in Scheme I.

SCHEME I



SCHEME II



Reaction of *o*-benzylthiobenzyl chloride **5** with the potassium salt of pyrrole in anhydrous tetrahydrofuran under a nitrogen atmosphere led to 1-(2-benzylthiobenzyl)pyrrole **6**, which produced 1-(2-mercaptobenzyl)pyrrole **7** by debenzylation with sodium in liquid ammonia. Heating of the latter compound in dimethylsulphoxide at 80-90° afforded bis[2-(*N*-pyrrolylmethyl)phenyl] disulphide **8**.

Treatment of sodium salt of **7** with ethyl chloroformate in anhydrous tetrahydrofuran gave 1-(2-ethoxycarbonylthiobenzyl)pyrrole **9**. When this latter compound was subjected to cyclization by action of anhydrous zinc chloride in boiling *o*-dichlorobenzene, as reported by one of us for an analogous case [2], to obtain the desired 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **4**, no reaction was observed.

On the other hand it was impossible to attempt the cyclodehydration by polyphosphoric acid, as reported in the literature for analogous cases [15], of 1-(2-hydroxycarbonylthiobenzyl)pyrrole **10** because of the instability of this compound. In fact alkaline hydrolysis of 1-(2-ethoxycarbonylthiobenzyl)pyrrole **9** by refluxing for 1 hour gave, after acidification of the solution, the starting 1-(2-mercaptobenzyl)pyrrole **7**.

Thus these failures prompted us to explore a novel synthetic route which was successful. Scheme II summarizes the reactions leading to 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]-benzothiazepine **4**. Starting materials were once more the *o*-benzylthiobenzyl chloride **5** or the above described 1-(2-benzylthiobenzyl)pyrrole **6**.

Treatment of **5** with the potassium salt of pyrrole-2-carboxaldehyde in anhydrous tetrahydrofuran under a nitrogen atmosphere afforded 1-(2-benzylthiobenzyl)pyrrole-2-carboxaldehyde **11**, which was prepared, alternatively, by Vilsmeier-Haack formilation of 1-(2-benzylthiobenzyl)pyrrole with *N,N*-dimethylformamide in the presence of phosphorus oxychloride. The aldehyde **11** was transformed into the corresponding oxime **12**, which was dehydrated by acetic anhydride to give 1-(2-benzylthiobenzyl)pyrrole-2-carbonitrile **13**. This compound was also prepared, with higher yield, by direct cyanation of the pyrrole **6** following the modified Vilsmeier-Haack reaction, which involves the use of oxalyl chloride instead of phosphorus oxychloride [16].

Hydrolysis of nitrile **13** with potassium hydroxide in ethylene glycol led to 1-(2-benzylthiobenzyl)pyrrole-2-carboxylic acid **14**. Several attempts of debenzylation of this compound with anhydrous aluminium bromide in benzene or with sodium in liquid ammonia to obtain 1-(2-mercaptobenzyl)pyrrole-2-carboxylic acid **15**, key intermediate for the synthesis, failed.

Then the nitrile **13** was hydrolyzed with potassium hydroxide in boiling hydroalcoholic mixture for 12 hours to undergo 1-(2-benzylthiobenzyl)pyrrole-2-carboxyamide **16**, which was converted into 1-(2-mercaptobenzyl)pyrrole-2-carboxyamide **17** by debenzylation with sodium in liquid ammonia in good yield. When this compound was heated in dimethylsulphoxide at 90-100° for 3 hours bis[2-(*N*-α-carboxyamidopyrrolylmethyl)phenyl] disulphide **18** formed.

Hydrolysis of amide **17** with sodium hydroxide in dioxane-water (1:3) mixture on heating at reflux led to required 1-(2-mercaptobenzyl)pyrrole-2-carboxylic acid **15**.

This acid was in turn subjected to intramolecular ring closure by 4-dimethylaminopyridine-catalyzed *N,N'*-di-

cyclohexylcarbodiimide method [17] in anhydrous methylene chloride at room temperature for 6 hours, under a nitrogen atmosphere, to afford the expected 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **4** in 43% yield.

Evidence for the assigned structure to this compound were analytical data, ir and nmr spectra and molecular weight determined by mass spectrometry. The ir spectrum showed a strong carbonyl band at 1613 cm^{-1}. The ^1H nmr spectrum in DMSO-d_6 showed a singlet at δ 5.46 ppm for the two methylenic hydrogens, a triplet at δ 6.20 ppm for H-2, a multiplet at δ 6.81 ppm for H-3 and a multiplet at δ 7.2-8.0 ppm for H-1 and four benzenoid hydrogens. The mass spectrum showed a peak at m/e 215 (M^+).

Further studies concerning this novel ring system are in progress, particularly to prepare on one hand thioanalogues of sibiromycin and parent antibiotics and on the other new compounds with potential psychotropic activity.

EXPERIMENTAL

Melting points were determined with a Buchi SPM/20K melting point apparatus and are uncorrected. The ir spectra of solids were recorded in nujol mull and liquids as thin films between sodium chloride plates on a Perkin-Elmer 283 spectrophotometer. The ^1H nmr spectra were recorded on a Perkin-Elmer R20/B or a Varian XL 200 spectrometer with TMS as internal standard. The mass spectrum was recorded on a VG 70-70 spectrometer with an electron beam energy of 70 eV. Merck silica gel (0.063-0.200 mm) was used for chromatographic purifications. Microanalyses were performed by A. Pietrogrande, Padova, Italy.

1-(2-Benzylthiobenzyl)pyrrole (**6**).

To a well stirred suspension of potassium pyrrole [prepared from pyrrole (12.17 g, 0.1818 mole) and potassium metal (6.9 g, 0.1777 g-atom)] in anhydrous tetrahydrofuran (300 ml), kept under nitrogen, a solution of *o*-benzylthiobenzyl chloride **5** [14] (45.06 g, 0.1818 mole) in the same solvent (300 ml) was added dropwise and the mixture was heated under reflux for 24 hours. After cooling to room temperature, the reaction mixture was poured onto crushed ice and extracted several times with diethyl ether. The combined organic layers were washed with water, dried over anhydrous sodium sulphate and the solvent removed. The oily residue was purified by distillation under reduced pressure to give 39 g (77%) of 1-(2-benzylthiobenzyl)pyrrole **6** (bp 140°/0.05 mm) which on standing solidified. An analytical sample of mp 61-62° was obtained as colourless prisms by crystallization from petroleum ether (bp 40-60°); nmr (carbon tetrachloride): δ 3.92 (s, 2H, SCH_2), 4.95 (s, 2H, CH_2N), 6.07 (t, 2H, β-pyrrolic H), 6.45 (t, 2H, α-pyrrolic H), 6.8-7.6 (m, 9H, benzenoid H).

Anal. Calcd. for $C_{18}H_{17}NS$: C, 77.40; H, 6.13; N, 5.01; S, 11.46. Found: C, 77.32; H, 6.14; N, 4.64; S, 11.60.

1-(2-Mercaptobenzyl)pyrrole (**7**).

To a stirred solution of 10 g (0.053 mole) of 1-(2-benzylthiobenzyl)pyrrole **6** in 350 ml of liquid ammonia small pieces of sodium were added until the blue colour was permanent for at least 15 minutes. Solid ammonium chloride was added to decompose the excess of sodium and the ammonia was permitted to evaporate in a stream of nitrogen. The residue was dissolved in ice-water. The solution obtained was washed with diethyl ether, made acidic with concentrated hydrochloric acid and then extracted with diethyl ether. The combined organic layers were washed with water, dried over anhydrous sodium sulphate and the solvent removed. The crude oily product (6.4 g, 96%) was distilled to give 1-(2-mercaptobenzyl)pyrrole **7** as a colourless liquid (bp 100-101°/0.15 mm); ir: 2545 cm^{-1} (SH); nmr (carbon tetrachloride): δ 3.22 (s, 1H, SH, deuterium oxide exchangeable), 4.92 (s, 2H, CH_2), 5.97 (t, 2H, β-pyrrolic H), 6.41 (t, 2H, α-pyrrolic H), 6.5-7.6 (m, 4H, benzenoid H).

Anal. Calcd. for $C_{11}H_{11}NS$: C, 69.83; H, 5.86; N, 7.40; S, 16.91. Found: C, 69.53; H, 5.77; N, 7.19; S, 16.89.

bis[2-(*N*-Pyrrolylmethyl)phenyl] Disulphide (**8**).

A mixture of 1.75 g (0.0092 mole) of 1-(2-mercaptobenzyl)pyrrole **7** and 0.75 ml of dimethylsulphoxide was heated at 90-100° for 3 hours. After cooling the reaction mixture was poured onto crushed ice. The oily material that had separated was extracted with chloroform. The chloroform extracts were combined, washed with 2*N* sodium hydroxide solution and with water to neutrality and dried on anhydrous sodium sulphate. Removal of the solvent *in vacuo* afforded an oily product (1.47 g, 84%), which solidified upon trituration with petroleum ether (40-60°). The bis[2-(*N*-pyrrolylmethyl)phenyl] disulphide **8** was obtained as a white solid, mp 72-73°, after crystallization from ethanol.

Anal. Calcd. for $C_{22}H_{20}N_2S_2$: C, 70.20; H, 5.36; N, 7.44; S, 17.00. Found: C, 70.05; H, 5.36; N, 7.40; S, 16.55.

1-(2-Ethoxycarbonylthiobenzyl)pyrrole (**9**).

To a solution of 0.897 g (0.039 g-atom) of sodium metal in 30 ml of anhydrous ethanol was added a solution of 7.37 g (0.039 mole) of 1-(2-mercaptobenzyl)pyrrole **7** in 10 ml of anhydrous ethanol and the solvent removed *in vacuo*. To the residue dissolved in 35 ml of anhydrous tetrahydrofuran was added dropwise, at room temperature with stirring under nitrogen atmosphere, a solution of 7.38 g (0.068 mole) of ethyl chloroformate in 40 ml of anhydrous tetrahydrofuran. When adding stopped the mixture was allowed to stir at room temperature overnight and then poured onto crushed ice. The oil which formed was extracted with diethyl ether and the organic solution was dried on anhydrous sodium sulphate. After removal of the solvent the residue was distilled to afford 2.2 g (91%) of 1-(2-ethoxycarbonylthiobenzyl)pyrrole **9** as colourless oil (bp 136°/0.11 mm), which solidified on standing in a cool place. An analytical sample of mp 37-38° was obtained as a white solid after crystallization from aqueous ethanol; ir: 1720 cm^{-1} (ester C=O); nmr (carbon tetrachloride): δ 1.31 (t, 3H, CH_3), 4.21 (q, 2H, CH_2CH_3), 5.11 (s, 2H, CH_2N), 5.97 (t, 2H, β-pyrrolic H), 6.48 (t, 2H, α-pyrrolic H), 7.0-7.6 (m, 4H, benzenoid H).

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 64.36; H, 5.79; N, 5.36; S, 12.24. Found: C, 63.97; H, 5.40; N, 5.37; S, 11.92.

Saponification of 1-(2-Ethoxycarbonylbenzyl)pyrrole **9**.

A solution of 4.9 g (0.0187 mole) of 1-(2-ethoxycarbonylbenzyl)pyrrole **9** and 2.25 g (0.562 mole) of sodium hydroxide pellets in a mixture of 27 ml of ethanol and 13 ml of water was heated to reflux for 1 hour. After cooling the solution was poured onto crushed ice, acidified with concentrated hydrochloric acid and extracted with diethyl ether. The ethereal extracts were washed with water, dried over anhydrous sodium sulphate and the solvent removed to give 2.62 g (74%) of crude 1-(2-mercaptobenzyl)pyrrole **7**.

1-(2-Benzylthiobenzyl)pyrrole-2-carboxaldehyde (**11**). I.

To a well stirred suspension of potassium pyrrole-2-carboxaldehyde [prepared from pyrrole-2-carboxaldehyde (10.69 g, 0.1125 mole) and potassium metal (4.38 g, 0.1125 g-atom)] in anhydrous tetrahydrofuran (280 ml), in an atmosphere of nitrogen, a solution of *o*-benzylthiobenzyl chloride **5** (27.9 g, 0.1125 mole) in the same solvent (280 ml) was added by dropping. The reaction mixture was heated under reflux for 21 hours, after which it was cooled, poured onto crushed ice and extracted several times with diethyl ether. The combined ethereal fractions were washed with water and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded 34 g (99%) of crude 1-(2-benzylthiobenzyl)pyrrole-2-carboxaldehyde **11** as an oily material, which on standing solidified. An analytical sample of mp 48.5-50° was obtained by crystallization from petroleum ether (bp 40-60°); ir: 1670 cm^{-1} (CHO); nmr (carbon tetrachloride): δ 4.01 (s, 2H, SCH_2), 5.56 (s, 2H, CH_2N), 6.14 (dd, 1H, H-4), 6.4-7.6 (m, 11H, H-3, H-5 and benzenoid H), 9.46 (s, 1H, CHO).

Anal. Calcd. for $C_{19}H_{17}NOS$: C, 74.25; H, 5.58; N, 4.56; S, 10.41. Found: C, 74.41; H, 5.64; N, 4.73; S, 10.25.

II.

To 7.5 ml of *N,N*-dimethylformamide, cooled at 0-5° in an ice-bath, 3.3 g (0.0215 mole) of phosphorus oxychloride were added by dropping while stirring. When adding stopped the mixture was kept at room temperature for 15 minutes. Then a solution of 6 g (0.0215 mole) of 1-(2-benzylthiobenzyl)pyrrole **6** in 10 ml of *N,N*-dimethylformamide was added dropwise during 15 minutes. The mixture was heated at 60° for 90 minutes, cooled at room temperature, poured onto crushed ice, left to stir for 2 hours and then basified with saturated potassium carbonate solution. The dark oil which formed was extracted with diethyl ether. The ethereal extracts were combined, washed with water to neutrality and dried on anhydrous sodium sulphate. Evaporation of the solvent gave 5.52 g (84%) of **11**.

1-(2-Benzylthiobenzyl)pyrrole-2-carboxaldehyde Oxime (**12**).

To a stirred solution of 19.8 g (0.0645 mole) of 1-(2-benzylthiobenzyl)-pyrrole-2-carboxaldehyde **11** in 150 ml of boiling methanol a warm solution of 8.97 g (0.129 mole) of hydroxylamine hydrochloride and 6.8 g of decahydrate sodium carbonate in 100 ml of water was added dropwise. The reaction mixture was then allowed to reflux gently for 8 hours, after which it was cooled, poured onto crushed ice and extracted with diethyl ether. The combined organic layers were washed with water, dried over anhydrous sodium sulphate and the solvent removed. The residue (19.04 g, 92%) after crystallization from aqueous ethanol gave 1-(2-benzylthiobenzyl)pyrrole-2-carboxaldehyde oxime **12** as a solid which melted at 70-77°.

Anal. Calcd. for $C_{19}H_{18}N_2OS$: C, 70.79; H, 5.63; N, 8.69; S, 9.93. Found: C, 70.85; H, 5.59; N, 8.10; S, 9.89.

1-(2-Benzylthiobenzyl)pyrrole-2-carbonitrile (**13**). I.

A solution of 14.5 g (0.045 mole) of 1-(2-benzylthiobenzyl)pyrrole-2-carboxaldehyde oxime **12** in 140 ml of acetic anhydride was heated at 140° for 4 hours. After cooling to room temperature the reaction mixture was poured onto crushed ice and sodium bicarbonate was added in small portions to neutralize the acetic acid which formed. The solution obtained after extractions with diethyl ether was washed with water, dried over anhydrous sodium sulphate and evaporated to give a brownish oil, which was purified by passing through a silica gel column (chloroform as eluent). The collected eluates were evaporated *in vacuo* to afford 10.8 g (81%) of thick oil, which was distilled to give 1-(2-benzylthiobenzyl)pyrrole-2-carbonitrile **13** as a pale yellow oil (bp 173-175°/0.11 mm); ir: 2205 cm^{-1} (C≡N); nmr (carbon tetrachloride): δ 3.92 (s, 2H, SCH_2), 5.03 (s, 2H, CH_2N), 6.01 (dd, 1H, H-4), 6.4-8.0 (m, 11H, H-3, H-5 and benzenoid H).

Anal. Calcd. for $C_{19}H_{16}N_2S$: C, 74.98; H, 5.30; N, 9.20; S, 10.51. Found: C, 74.65; H, 5.48; N, 9.32; S, 10.35.

II.

A solution of 8.6 ml (0.11 mole) of *N,N*-dimethylformamide in 25 ml of 1,2-dichloroethane was cooled in an ice-salt bath. To the stirred and cooled solution, kept under nitrogen, was added a solution of 14 g (0.11 mole) of oxalyl chloride in 20 ml of 1,2-dichloroethane over a period of 10 minutes. When adding stopped the suspension was allowed to stir at room temperature for 15 minutes. The suspension was cooled in ice and a solution of 28.27 g (0.101 mole) of 1-(2-benzylthiobenzyl)pyrrole **6** in 20 ml of 1,2-dichloroethane was added dropwise during 10 minutes. The light orange solution obtained was allowed to stir for 15 minutes at room temperature. A solution of 7.72 g (0.11 mole) of hydroxylamine hydrochloride in 20 ml of warm *N,N*-dimethylformamide to which were added 8.77 g (0.11 mole) of pyridine was prepared. This solution was then added rapidly to the complex prepared above. The reaction mixture was refluxed for 10 hours and, after cooling, about 200 ml saturated sodium bicarbonate solution was added. The dark brown solution was extracted with diethyl ether. The combined ethereal extracts were washed with saturated sodium chloride solution, then with 1*M* hydrochloric acid and saturated sodium bicarbonate solution, finally with water to neutrality. After drying on anhydrous sodium sulphate the solvents were removed *in vacuo* on a steam bath. The oily residue was distilled to yield 22.5 g (73%) of **13**.

1-(2-Benzylthiobenzyl)pyrrole-2-carboxylic Acid (**14**).

A mixture of 4 g (0.013 mole) of 1-(2-benzylthiobenzyl)pyrrole-2-carbonitrile **13**, 7.5 g (0.134 mole) of potassium hydroxide pellets and 70 ml of ethylene glycol was heated at 180° for 5 hours under stirring. After cooling the solution was treated with cold water, filtered and acidified with concentrated hydrochloric acid. The precipitate was collected and washed with water. The 1-(2-benzylthiobenzyl)pyrrole-2-carboxylic acid **14** (3.5 g, 82%) after crystallization from ethanol was obtained as tan needles and melted at 159-160°; ir: 1660 cm^{-1} (carboxylic C=O); nmr (deuteriochloroform): δ 3.94 (s, 2H, SCH_2), 5.43 (s, 2H, CH_2N), 6.05 (dd, 1H, H-4), 6.3-6.6 (m, 2H, H-3 and H-5), 6.9-7.5 (m, 9H, benzenoid H), 10-10.5 (s, broad, 1H, COOH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{19}H_{17}NO_2S$: C, 70.58; H, 5.30; N, 4.33; S, 9.89. Found: C, 70.55; H, 5.23; N, 4.07; S, 9.87.

1-(2-Benzylthiobenzyl)pyrrole-2-carboxyamide (**16**).

A solution of 15.68 g (0.0515 mole) of 1-(2-benzylthiobenzyl)pyrrole-2-carbonitrile **13** and 14.5 g (0.26 mole) of potassium hydroxide pellets in a mixture of 150 ml of ethanol and 150 ml of water was refluxed for 12 hours. After concentration to half its volume *in vacuo* and successive cooling were obtained 15.22 g (93%) of 1-(2-benzylthiobenzyl)pyrrole-2-carboxyamide **16**, which crystallized from benzene-petroleum ether (bp 40-60°) as colourless needles and melted at 102-103°; ir: 3365, 3180 cm^{-1} (NH_2), 1640 (amide C=O); nmr (deuteriochloroform): δ 3.99 (s, 2H, SCH_2), 5.2-5.8 [m, 4H, NH_2, deuterium oxide exchangeable, and CH_2N (s at 5.57)], 6.03 (m, 1H, H-4), 6.4-7.6 (m, 11H, H-3, H-5 and benzenoid H).

Anal. Calcd. for $C_{19}H_{18}N_2OS$: C, 70.79; H, 5.63; N, 8.69; S, 9.92. Found: C, 70.89; H, 5.58; N, 8.55; S, 10.19.

1-(2-Mercaptobenzyl)pyrrole-2-carboxyamide (**17**).

The reaction of debenzylation of 1-(2-benzylthiobenzyl)pyrrole-2-carboxyamide **16** (10 g, 0.031 mole) was carried out as described above in the preparation of compound **7**. The solid product obtained (6 g, 83%) after crystallization from ethanol gave an analytical sample of 1-(2-mercaptobenzyl)pyrrole-2-carboxyamide **17**, which melted at 125-129° (yellow-brown prisms); ir: 3442, 3340 cm^{-1} (NH_2), 2575 (SH), 1640 (amide C=O); nmr (deuteriochloroform): δ 3.40 (s, 1H, SH, deuterium oxide exchangeable), 5.4-5.9 [m, 4H, NH_2, deuterium oxide exchangeable, and CH_2 (s at 5.58)], 6.05 (dd, 1H, H-4), 6.5-6.8 (m, 2H, H-3 and H-5), 6.85-7.5 (m, 4H, benzenoid H).

Anal. Calcd. for $C_{12}H_{12}N_2OS$: C, 62.06; H, 5.21; N, 12.06; S, 13.78. Found: C, 62.41; H, 5.27; N, 11.96; S, 13.89.

bis[2-(*N*-α-Carboxyamidopyrrolylmethyl)phenyl] Disulphide (**18**).

A mixture of 6.32 g (0.0272 mole) of 1-(2-mercaptobenzyl)pyrrole-2-carboxyamide **17** and 5.32 g (0.068 mole) of dimethylsulphoxide was heated at 90-100° for 3 hours. After cooling the reaction mixture was poured onto crushed ice. The bis[2-(*N*-α-carboxyamidopyrrolylmethyl)-phenyl] disulphide **18** that had precipitated was filtered and air dried (quantitative yield). An analytical sample of mp 215-216° was obtained as a light grey solid by crystallization from aqueous ethanol; ir: 3465, 3355, 3190 cm^{-1} (2 NH_2), 1660, 1635 (2 amides C=O).

Anal. Calcd. for $C_{24}H_{22}N_4O_2S_2$: C, 62.33; H, 4.80; N, 12.11; S, 13.84. Found: C, 62.25; H, 4.84; N, 12.02; S, 14.01.

1-(2-Mercaptobenzyl)pyrrole-2-carboxylic Acid (**15**).

A mixture of 5.75 g (0.0247 mole) of 1-(2-mercaptobenzyl)pyrrole-2-carboxyamide **17**, 6 g (0.15 mole) of sodium hydroxide pellets, 10 ml of dioxane and 30 ml of water was heated at reflux with stirring under a nitrogen atmosphere for 18 hours. The alkaline solution was concentrated *in vacuo* to about half its volume and, after cooling at room temperature, made acidic with concentrated hydrochloric acid. Extraction with diethyl ether gave a solution which was dried on anhydrous sodium sulphate and then evaporated. The residual solid (5.1 g, 88%) after crystallization from ethyl acetate gave an analytical sample of 1-(2-mercapto-

benzyl)pyrrole-2-carboxylic acid **15** as tan prisms, mp 140-141°; ir: 2560 cm^{-1} (SH), 1655 (carboxylic C=O); nmr (deuteriochloroform): δ 3.35 (s, 1H, SH, deuterium oxide exchangeable), 5.59 (s, 2H, CH_2), 6.22 (dd, 1H, H-4), 6.66 (d, 1H, H-3), 6.82 (t, 1H, H-5), 7-7.5 (m, 4H, benzenoid H), 10-11 (s, broad, 1H, COOH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.80; H, 4.75; N, 6.01; S, 13.72. Found: C, 61.74; H, 4.73; N, 5.85; S, 13.64.

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

To a stirred solution of 1.68 g (0.0072 mole) of 1-(2-mercaptobenzyl)-pyrrole-2-carboxylic acid **15** and 83 mg of 4-dimethylaminopyridine in 55 ml of anhydrous methylene chloride, kept under nitrogen, was added a solution of 1.46 g (0.0072 mole) of *N,N'*-dicyclohexylcarbodiimide in 5 ml of anhydrous methylene chloride with ice-cooling. The reaction mixture was then allowed to stir for 5 minutes at 0° and for 6 hours at room temperature. The *N,N'*-dicyclohexylurea was filtered off and washed with methylene chloride (2 × 5 ml). The combined filtrates were 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 residue was purified by crystallization from ethanol to give 0.66 g (43%) of 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]-benzothiazepine **4**. An analytical sample of mp 216° was obtained as colourless needles; ms: m/e (%) 215 (M^+, 100), 182 (100), 154 (28), 134 (11), 121 (69), 78 (28), 77 (20), 63 (10), 51 (12).

Anal. Calcd. for $C_{12}H_9NOS$: C, 66.97; H, 4.22; N, 6.51; S, 14.86. Found: C, 66.86; H, 4.02; N, 6.61; S, 14.21.

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