Polycondensed Heterocycles. II. A New Preparative Route to 11-Oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine.

V. Nacci*, A. Garofalo and I. Fiorini

Dipartimento Farmaco Chimico Tecnologico, Università di Siena, I[a] Cattedra di Chimica Farmaceutica e Tossicologica, Via Banchi di Sotto, 57, 53100 Siena, Italy

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6-Methylthio-10-oxo-5*H*,10*H*-pyrrolo[1,2-*b*]isoquinoline **11** was isolated in an attempted synthesis of 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **1** from 1-(2-methylthiobenzyl)pyrrole-2-carboxylic acid chloride **9**, obtained using as starting material *o*-methylthiobenzyl bromide **3** and passing through 1-(2-methylthiobenzyl)pyrrole-2-carbonitrile **5**, by cyclization with aluminum chloride. However the successful demethylation with sodium in dimethylacetamide of 1-(2-methylthiobenzyl)pyrrole-2-carboxyamide **12**, formed by hydrolysis of nitrile **5**, allowed us to prepare by another way the corresponding thiol **13** and consequently the 1-(2-mercaptobenzyl)pyrrole-2-carboxylic acid **14**, which when subjected to intramolecular ring closure by CDI in place of DCC gave **1** in higher yield, 69% instead of 43%. Finally, the direct cyanation of 1-(2-ethoxycarbonylthiobenzyl)pyrrole **16**, prepared utilizing the 1-(2-mercaptobenzyl)pyrrole **15** obtained by demethylation of the corresponding thioanisol **4** which was carried out as above, afforded the unexpected 1-(2-ethylthiobenzyl)pyrrole-2-carbonitrile **17**.

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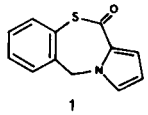
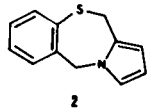
In the preceding paper we described the synthesis of 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **1** as a first approach to the preparation of the novel ring system **2** and reported the reasons of our interest in this tricyclic nucleus [1].



1



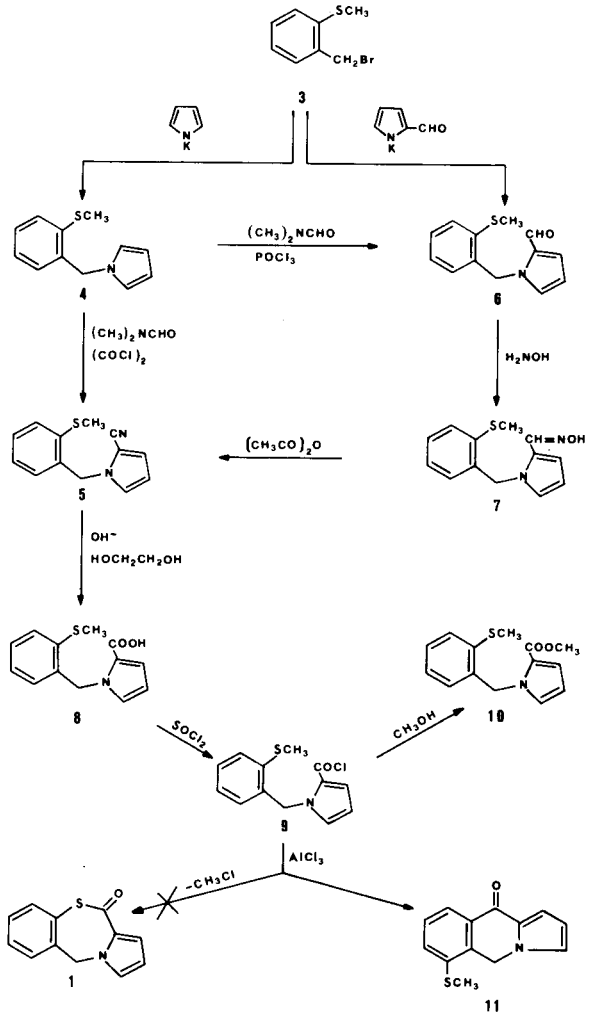
2

With the intention of setting up a new general synthetic route utilizing as starting materials thioanisoles, because of the particular stability of the methylthio ether function to a wide variety of reaction conditions and because of the relative ease of its introduction into aromatic systems [2,7], we decided to synthesize the pyrrolobenzothiazepinone **1** starting from *o*-methylthiobenzyl bromide [3].

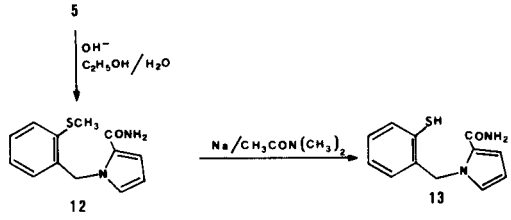
To this purpose a convenient synthesis was devised (Scheme I).

Treatment of *o*-methylthiobenzyl bromide **3** with the potassium salt of pyrrole in anhydrous tetrahydrofuran under a nitrogen atmosphere gave 1-(2-methylthiobenzyl)-pyrrole **4**, which when subjected to cyanation with *N,N*-dimethylformamide in the presence of oxalyl chloride, following the modified Vilsmeier-Haack reaction [4], afforded 1-(2-methylthiobenzyl)pyrrole-2-carbonitrile **5**. Moreover this compound was obtained by dehydration with acetic anhydride of 1-(2-methylthiobenzyl)pyrrole-2-carboxaldehyde oxime **7**, obtained from the corresponding aldehyde **6**. Reaction of *o*-methylthiobenzyl bromide **3** with the potassium salt of pyrrole-2-carboxaldehyde in anhydrous tetrahydrofuran under a nitrogen atmosphere or, alternatively, the Vilsmeier-Haack formylation of 1-(2-methylthiobenzyl)pyrrole **4** with *N,N*-dimethylformamide in the pre-

Scheme I

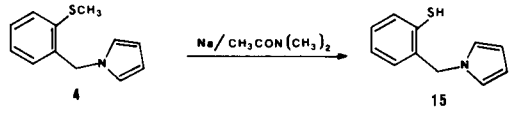


Scheme II



Scheme III

Scheme IV



sence of phosphorus oxychloride led to above-said 1-(2-methylthiobenzyl)pyrrole-2-carboxaldehyde **6**.

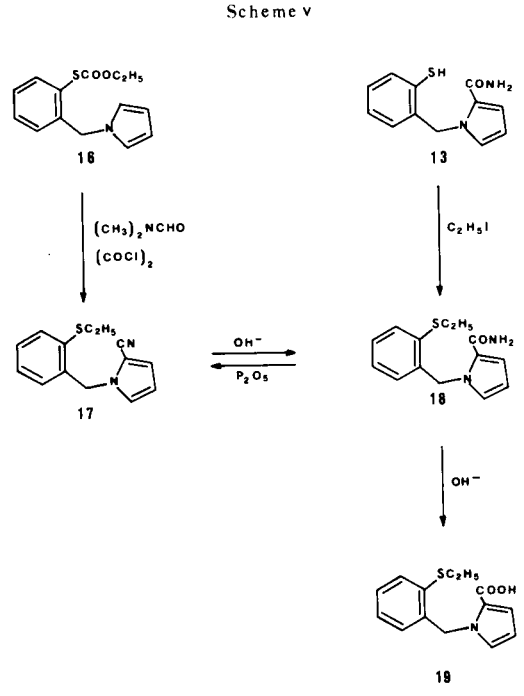
The alkaline hydrolysis of nitrile **5** with potassium hydroxide in ethylene glycol gave 1-(2-methylthiobenzyl)pyrrole-2-carboxylic acid **8**, which was transformed by treatment with thionyl chloride in anhydrous benzene into the corresponding chloride **9**, converted in turn into methyl 1-(2-methylthiobenzyl)pyrrole-2-carboxylate **10**, by reaction with methanol.

Then 1-(2-methylthiobenzyl)pyrrole-2-carboxylic acid chloride **9** was subjected to cyclization to obtain **1** by methyl chloride elimination in the presence of aluminum chloride, following a method described by Ruwet and Reson to prepare 1-thiocoumarins [5] and also used successfully for an analogous case [6]. Unfortunately, also in a variety of solvents such as benzene, carbon disulphide, petroleum ether (bp 40-60°), ligroin, and under a variety of temperatures, no reaction was observed or mixtures of products difficult to work up were formed.

Finally, under the mildest conditions found to effect the cyclization, in nitrobenzene at 0° for 1.5 hours and at room temperature for 3 hours, a solid product was isolated which, on the basis of analytical data, molecular weight determined by mass spectrometry and ir and ^{1}H nmr spectra, consisted of 6-methylthio-10-oxo-5*H*,10*H*-pyrrolo-[1,2-*b*]isoquinoline **11**.

At any rate the successful demethylation of 1-(2-methylthiobenzyl)pyrrole-2-carboxyamide **12**, carried out as reported by Testaferri *et al* [7], allowed us to utilize the intermediate nitrile **5** and to obtain the 1-(2-mercaptobenzyl)-pyrrole-2-carboxyamide **13** (Scheme II), previously prepared by us as a precursor of the 1-(2-mercaptobenzyl)pyrrole-2-carboxylic acid **14** [1]. In fact hydrolysis of 1-(2-methylthiobenzyl)pyrrole-2-carbonitrile **5** with potassium hydroxide in hydroalcoholic mixture by refluxing for 12 hours furnished the amide **12**, which when treated with sodium in dimethylacetamide on heating at 95-100° for 15 hours under a nitrogen atmosphere was converted into the thiol **13** in 81% yield. Attempts to demethylate 1-(2-methylthiobenzyl)pyrrole-2-carboxylic acid **8** under the same reaction conditions were unsuccessful.

Scheme V



Moreover, when *N,N'*-carbonyldiimidazole (CDI) [8] was used in place of *N,N'*-dicyclohexylcarbodiimide to cyclize 1-(2-mercaptobenzyl)pyrrole-2-carboxylic acid **14** intramolecularly, pure 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*] [1,4]benzothiazepine **1** was obtained in 69% yield instead of 43% [1] (Scheme III). The cyclizing reaction was carried out in anhydrous tetrahydrofuran at room temperature for 24 hours and then at reflux for 8 hours.

In our attempts to synthesize by other means the acid **14**, 1-(2-ethoxycarbonylthiobenzyl)pyrrole **16** [1] was subjected to direct cyanation with *N,N*-dimethylformamide in the presence of oxalyl chloride [4]. Surprisingly (Scheme V) 1-(2-ethylthiobenzyl)pyrrole-2-carbonitrile **17** was isolated in 70% yield. This was demonstrated by its alkaline hydrolysis products, 1-(2-ethylthiobenzyl)pyrrole-2-carboxyamide **18** and 1-(2-ethylthiobenzyl)pyrrole-2-carboxylic acid **19** and confirmed by an unambiguous synthesis of the amide **18** and of the nitrile **17**. Compound **18** was obtained by ethylation with iodoethane of the sodium salt of

1-(2-mercaptobenzyl)pyrrole-2-carboxyamide **13** in anhydrous tetrahydrofuran. Compound **19** was obtained by dehydration with phosphorous pentoxide in anhydrous benzene of the amide **18**. Hydrolysis of nitrile **17** was carried out with sodium hydroxide in boiling aqueous alcohol for 24 hours. The hydrolysis of the amide **18** was accomplished with potassium hydroxide in ethylene glycol at 180° for 5 hours.

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 mulls and liquids as thin films between sodium chloride plates on a Perkin-Elmer 283 spectrophotometer. The ^{1}H nmr spectra were recorded on a Perkin-Elmer R20/B or a Varian XL 200 spectrometers with TMS as the internal standard. The mass spectra were recorded on a Finnigan 1020 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-Methylthiobenzyl)pyrrole (**4**).

To a well stirred suspension of potassium pyrrole [prepared from pyrrole (3.35 g, 0.05 mole) and potassium metal (1.95 g, 0.05 g-atom)] in anhydrous tetrahydrofuran (80 ml), kept under nitrogen, a solution of *o*-methylthiobenzyl bromide **3** [3] (11.5 g, 0.05 mole) in the same solvent (100 ml) was added slowly dropwise and the mixture was heated under reflux of 8 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 and dried over anhydrous sodium sulphate. Evaporation of the solvent afforded 10 g (93%) of crude 1-(2-methylthiobenzyl)pyrrole **4** as an oily material, which solidified on standing in a cool place. An analytical sample of mp 54-55° was obtained as colourless prisms by crystallization from aqueous methanol; nmr (carbon tetrachloride): δ 2.35 (s, 3H, CH_3), 5.00 (s, 2H, CH_2), 5.99 (t, 2H, β-pyrrolic H), 6.48 (t, 2H, α-pyrrolic H), 6.5-7.5 (m, 4H, benzenoid H).

Anal. Calcd. for $C_{12}H_{13}NS$: C, 70.92; H, 6.45; N, 6.89; S, 15.74. Found: C, 70.98; H, 6.55; N, 6.59; S, 15.45.

1-(2-Methylthiobenzyl)pyrrole-2-carboxaldehyde (**6**). I.

To a well stirred suspension of potassium pyrrole-2-carboxaldehyde [prepared from pyrrole-2-carboxaldehyde (3.3 g, 0.0347 mole) and potassium metal (1.35 g, 0.0347 g-atom)] in anhydrous tetrahydrofuran (80 ml), in an atmosphere of nitrogen, a solution of *o*-methylthiobenzyl bromide **3** [3] (7.73 g, 0.0347 mole) in the same solvent (90 ml) was added by dropping. The reaction mixture was refluxed for 8 hours, then 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 gave an oily residue, which was purified by passing through a silica gel column (benzene as eluent). The collected eluates were evaporated *in vacuo* to afford 3.15 g (93%) of 1-(2-methylthiobenzyl)pyrrole-2-carboxyaldehyde **6** as a pale yellow oil, which on standing solidified. An analytical sample of mp 53-54° as colourless needles was obtained by crystallization from petroleum ether (bp 40-60°); ir: 1665 cm^{-1} (CHO); nmr (deuteriochloroform): δ 2.49 (s, 3H, CH_3), 5.65 (s, 2H, CH_2), 6.27 (t, 1H,H-4), 6.6-7.5 (m, 6H, H-3, H-5 and benzenoid H), 9.60 (s, 1H, CHO).

Anal. Calcd. for $C_{13}H_{13}NOS$: C, 67.52; H, 5.67; N, 6.06; S, 13.84. Found: C, 67.28; H, 5.62; N, 5.80; S, 13.70.

II.

To 15.6 ml of *N,N*-dimethylformamide, cooled at 0-5° in an ice-bath, 6.9 g (0.045 mole) of phosphorus oxychloride was added by dropping while stirring. When the addition stopped the mixture was kept at room temperature for 15 minutes. Then a solution of 9.1 g (0.045 mole) of 1-(2-methylthiobenzyl)pyrrole **4** in 20 ml of *N,N*-dimethylformamide was added dropwise and the mixture was heated at 105° for 3 hours, cooled to room temperature, poured onto crushed ice and finally basified with ammonium hydroxide. The oil which formed was extracted with diethyl ether. The ethereal extracts were combined, washed with water to neutrality and dried over anhydrous sodium sulphate. Evaporation of the solvent gave an oily residue, which after chromatographic purification as above afforded 8.9 g (86%) of **6**.

1-(2-Methylthiobenzyl)pyrrole-2-carboxaldehyde Oxime (**7**).

To a stirred solution of 6.7 g (0.029 mole) of 1-(2-methylthiobenzyl)pyrrole-2-carboxaldehyde **6** in 80 ml of boiling methanol a warm solution of 4.2 g(0.06 mole) of hydroxylamine hydrochloride and 7.58 g (0.03 mole) of sodium carbonate decahydrate in 30 ml of water was added dropwise over a period of 30 minutes. The reaction mixture was then allowed to reflux for 2 hours, after which it was cooled and poured onto crushed ice. The oxime **7** that had precipitated was filtered and crystallized from aqueous ethanol (5.9 g, 83%). An analytical sample of mp 107-108° was obtained as tan prisms.

Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.40; H, 5.73; N, 11.38; S, 12.98. Found: C, 63.77; H, 6.03; N, 11.57; S, 12.86.

1-(2-Methylthiobenzyl)pyrrole-2-carbonitrile (**5**). I.

A solution of 5 g (0.02 mole) of 1-(2-methylthiobenzyl)pyrrole-2-carboxaldehyde oxime **7** in 50 ml of acetic anhydride was heated at 140° for 2 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 resulting oil was extracted with chloroform and the organic solution was washed with water and dried over anhydrous sodium sulphate. Removal of the solvent *in vacuo* afforded an oily product, which was purified by passing through a silica gel column (chloroform as eluent) to give 3.9 g (87%) of 1-(2-methylthiobenzyl)pyrrole-2-carbonitrile **5** as a yellow solid. An analytical sample of mp 51-52° was obtained after crystallization from petroleum ether (bp 40-60°); ir: 2218 cm^{-1} (C≡N); nmr (DMSO-d_6): δ 2.45 (s, 3H, CH_3), 5.25 (s, 2H, CH_2), 6.20 (dd, 1H, H-4), 6.4-7.7 (m, 6H, H-3, H-5 and benzenoid H).

Anal. Calcd. for $C_{13}H_{12}N_2S$: C, 68.41; H, 5.30; N, 12.27; S, 14.02. Found: C, 68.28; H, 5.51; N, 12.00; S, 13.73.

II.

A solution of 8.1 ml (0.105 mole) of *N,N*-dimethylformamide in 23 ml of 1,2-dichloroethane was cooled in an ice-salt bath. To the well stirred and cooled solution, in an atmosphere of nitrogen, a solution of 13.34 g (0.105 mole) of oxalyl chloride in 15 ml of 1,2-dichloroethane was added over a period of 10 minutes. When the addition was stopped the suspension was allowed to stir at room temperature for 15 minutes. The suspension was then cooled in an ice-bath and a solution of 19.4 g (0.0955 mole) of 1-(2-methylthiobenzyl)pyrrole **4** in 20 ml of 1,2-dichloroethane was added dropwise over 20 minutes. The light orange solution obtained was allowed to stir at room temperature for 15 minutes. A solution of 7.29 g (0.105 mole) of hydroxylamine hydrochloride in 20 ml of warm *N,N*-dimethylformamide to which were added 8.28 ml (0.105 mole) of pyridine was prepared. This solution was then added rapidly to the complex prepared above and the reaction mixture was refluxed for 10 hours. After cooling, a saturated sodium bicarbonate solution (about 200 ml) was added and the dark brown mixture obtained 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 over anhydrous sodium sulphate the solvents were removed *in vacuo* on a steam bath. The oily residue was purified by distillation (bp 166-168/0.06 mm) to give 17.6 g (80%) of **5**.

1-(2-Methylthiobenzyl)pyrrole-2-carboxylic Acid (**8**).

A mixture of 4 g (0.0175 mole) of 1-(2-methylthiobenzyl)pyrrole-2-carbonitrile **5**, 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, washed with water and air dried. The 1-(2-methylthiobenzyl)pyrrole-2-carboxylic acid 8 (3.9 g, 90%) after crystallization from ethanol melted at 139° (brown prisms); ir: 1683 cm^{-1}(carboxylic C=O); nmr (deuteriochloroform): δ 2.43 (s, 3H, CH_3), 5.59 (s, 2H, CH_2), 6.17 (dd, 1H, H-4), 6.5-7.6 (m, 6H, H-3, H-5 and benzenoid H), 10.9-11.9 (s, broad, 1H, COOH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{13}H_{13}NO_2S$: C, 63.15; H, 5.30; N, 5.66; S, 12.94. Found: C, 63.32; H, 5.45; N, 5.69; S, 12.58.

1-(2-Methylthiobenzyl)pyrrole-2-carboxylic Acid Chloride (**9**).

To a solution of 1,2 g (0.0048 mole) of 1-(2-methylthiobenzyl)pyrrole-2-carboxylic acid **8** in 15 ml of anhydrous benzene was added slowly a solution of 1.5 ml of thionyl chloride in 10 ml of the same solvent. The reacting mixture was then allowed to stir at room temperature for 1 hour and after evaporation of the solvent *in vacuo* the excess of thionyl chloride was stripped off under reduced pressure. The resulting residue on standing solidified and after crystallization from ligroin gave 0.75 g (60%) of 1-(2-methylthiobenzyl)pyrrole-2-carboxylic acid chloride **9**. An analytical sample of mp 77-78° was obtained as pale yellow crystals; ir: 1735 cm^{-1} (C=O); nmr (carbon tetrachloride): δ 2.49 (s, 3H, CH_3), 5.49 (s, 2H, CH_2), 6.22 (dd, 1H, H-4), 6.5-7.7 (m, 6H, H-3, H-5 and benzenoid H).

Anal. Calcd. for $C_{13}H_{12}ClNOS$: C, 58.77; H, 4.52; N, 5.27; S, 12.07. Found: C, 58.66; H, 4.65; N, 5.37; S, 12.15.

Methyl 1-(2-Methylthiobenzyl)pyrrole-2-carboxylate (**10**).

A solution of 0.6 g (0.0022 mole) of 1-(2-methylthiobenzyl)pyrrole-2-carboxylic acid chloride **9** in 10 ml of methanol was heated under reflux for 1 hour. After cooling, the solvent was removed under reduced pressure and the solid residue was washed with water and air dried. The ester 10 (0.48 g, 81%) after crystallization from aqueous ethanol melted at 77-78° (light brown needles); ir: 1722 cm^{-1}(ester C=O); nmr (deuteriochloroform): δ 2.50 (s, 3H, SCH_3), 3.73 (s, 3H, OCH_3), 5.60 (s, 2H, CH_2), 6.23 (dd, 1H, H-4), 6.4-7.6 (m, 6H, H-3, H-5 and 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, 64.27; H, 5.82; N, 5.34; S, 12.07.

6-Methylthio-10-oxo-5*H*,10*H*-pyrrolo[1,2-*b*]isoquinoline (**11**).

To a well stirred suspension of 6.2 g (0.047 mole) of aluminum chloride in 100 ml of nitrobenzene, cooled in an ice-salt bath, a solution of 4.1 g (0.015 mole) of 1-(2-methylthiobenzyl)pyrrole-2-carboxylic acid chloride **9** in 50 ml of nitrobenzene was added by dropping under nitrogen atmosphere. When the addition was complete, the reaction mixture was left to stir at 0° for 1.5 hours and at room temperature for 3 hours and then poured into about 200 ml of ice-water containing 6 ml of concentrated hydrochloric acid. The solution obtained after extraction with chloroform was washed several times with water and dried over anhydrous sodium sulphate. Evaporation of chloroform *in vacuo* followed by distillation of nitrobenzene at 50° under reduced pressure afforded a residual solid, which was dissolved in boiling benzene, treated with charcoal, filtered, concentrated and left to crystallize. The solid was collected, washed with petroleum ether (bp 40-60°) and air dried to yield 1.58 g (45%) of crude product. Recrystallization from benzene gave 6-methylthio-10-oxo-5*H*,10*H*-pyrrolo[1,2-*b*]isoquinoline **11** as light brown crystals, mp 190-193°; ir: 1643 cm^{-1} (C=O); nmr (deuteriochloroform): δ 2.57 (s, 3H, CH_3), 5.32 (s, 2H, CH_2), 6.46 (dd, 1H, H-2), 6.9-8.3 (m, 5H, H-1, H-3, H-7, H-8 and H-9); ms: m/e (%) 229 (M^+, 82), 214 (100), 182 (23), 153 (28), 127 (15), 115 (25), 77 (19), 63 (22), 51 (18), 44 (52).

Anal. Calcd. for $C_{13}H_{11}NOS$: C, 68.11; H, 4.84; N, 6.11; S, 13.96. Found: C, 68.41; H, 4.74; N, 6.02; S, 13.53.

1-(2-Methylthiobenzyl)pyrrole-2-carboxyamide (**12**).

A solution of 8.5 g (0.037 mole) of 1-(2-methylthiobenzyl)pyrrole-2-carbonitrile **5** and 10.35 g (0.184 mole) of potassium hydroxide pellets in a mixture of 90 ml of ethanol and 90 ml of water was refluxed for 12 hours. After concentration to half its volume *in vacuo* and successive cooling there was obtained a solid product which was filtered, washed with water and air dried to give 8.1 g (88%) of 1-(2-methylthiobenzyl)pyrrole-2-carboxyamide **12**. An analytical sample, after crystallization from benzene, melted at 164-165° (very light brown crystals); ir: 3395, 3198 cm^{-1} (NH_2), 1650 (amide C=O); nmr (deuteriochloroform): δ 2.48 (s, 3H, CH_3), 5.2-5.6 (s, broad, 2H, NH_2, deuterium oxide exchangeable), 5.69 (s, 2H, CH_2), 6.15 (dd, 1H, H-4), 6.5-7.5 (m, 6H, H-3, H-5 and benzenoid H).

Anal. Calcd. for $C_{13}H_{14}N_2OS$: C, 63.40; H, 5.73; N, 11.38; S, 12.98. Found: C, 63.03; H, 5.82; N, 11.23; S, 12.83.

1-(2-Mercaptobenzyl)pyrrole-2-carboxyamide (**13**).

To a solution of 1.97 g (0.008 mole) of 1-(2-methylthiobenzyl)pyrrole-2-carboxyamide **12** in 20 ml of dimethylacetamide small pieces of sodium (0.92 g, 0.04 g-atom) were added and the mixture was stirred under nitrogen at 95-100° for 15 hours. After cooling to room temperature the reaction mixture was poured onto crushed ice, filtered and made acidic with concentrated hydrochloric acid. The solid that had separated was filtered, washed with water and dried to give 1.5 g (81%) of 1-(2-mercaptobenzyl)pyrrole-2-carboxyamide **13**, mp 125-129° [1].

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

A mixture of 2.6 g (0.011 mole) of 1-(2-mercaptobenzyl)pyrrole-2-carboxylic acid 14 [1], 1.96 g (0.012 mole) of *N*,*N*'-carbonyldiimidazole and 20 ml of anhydrous tetrahydrofuran was allowed to stand with stirring at room temperature for 24 hours and then heated under reflux for 8 hours. After cooling the crystals which had separated were collected, washed with petroleum ether (bp 40-60°) twice and recrystallized from ethanol to give 1.62 g (69%) of 11-oxo-5*H*,11*H*-pyrrolo[2,1-*c*][1,4]benzothiazepine **1**, mp 214-216° [1].

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

The demethylation reaction of 1-(2-methylthiobenzyl)pyrrole **4** (1 g, 0.0049 mole) was carried out as described above in the preparation of amide **12**. The aqueous solution was washed with diethyl ether once, acidified with hydrochloric acid 4*N* to *p*H 3 and then extracted with diethyl ether. The organic solution was washed with water and dried over anhydrous sodium sulphate. After removal of the solvent the oily residue was distilled to give 0.65 g (70%) of 1-(2-mercaptobenzyl)pyrrole **15**, bp 95°/0.02 mm [1].

1-(2-Ethylthiobenzyl)pyrrole-2-carbonitrile (**17**). I.

To a stirred solution of 1.3 g (0.005 mole) of 1-(2-ethylthiobenzyl)pyrrole-2-carboxyamide **18** in 65 ml of anhydrous benzene, kept under nitrogen, 1.4 g (0.01 mole) of phosphorus pentoxide was added. The mixture was refluxed for 2.5 hours. After decantation the solvent was removed *in vacuo* on a steam bath. The resulting oil (1 g, 82%) was distilled to give 0.85 g (70%) of 1-(2-ethylthiobenzyl)pyrrole-2-carbonitrile **17** as a pale yellow liquid (bp 137°/0.04 mm); ir: 2215 cm^{-1} (C≡N); nmr (deuteriochloroform): δ 1.31 (t, 3H, CH_3), 2.93 (q, 2H, CH_2CH_3), 5.33 (s, 2H, CH_2N), 6.18 (t, 1H, H-4), 6.7-7.6 (m, 6H, H-3, H-5 and benzenoid H); ms: m/e (%) 242 (M^+, 44), 213 (9), 151 (100), 136 (13), 123 (26), 91 (15), 77 (13), 59 (14), 45 (34).

Anal. Calcd. for $C_{14}H_{14}N_2S$: C, 69.41; H, 5.82; N, 11.56; S, 13.21. Found: C, 69.58; H, 6.01; N, 11.45; S, 13.06.

II.

The modified Vilsmeier-Haack reaction with 1-(2-ethoxycarbonylthiobenzyl)pyrrole **16** [1] (10.44 g, 0.04 mole) was carried out as described above in the preparation of nitrile **5**. Vacuum distillation of crude oily product gave 6.75 g (70%) of **17** (bp 146°/0.05 mm).

1-(2-Ethylthiobenzyl)pyrrole-2-carboxyamide (**18**). I.

A solution of 5 g (0.02 mole) of the previous cyanation product **17** and 0.8 g (0.1 mole) of sodium hydroxide pellets in a mixture of 25 ml of ethanol and 20 ml of water was refluxed for 24 hours. After cooling, the reaction mixture was poured onto crushed ice. The 1-(2-ethylthiobenzyl)pyrrole-2-carboxyamide **18** that had precipitated was filtered, washed with water and then air dried (4.2 g, 78%). An analytical sample of mp 127°

was obtained as colourless needles by crystallization from ethanol; ir: 3420, 3210 cm^{-1} (NH_2), 1655 (amide C=O); nmr (deuteriochloroform): δ 1.32 (t, 3H, CH_3), 2.93 (q, 2H, CH_2CH_3), 5.61 (s, broad, 2H, NH_2, deuterium oxide exchangeable), 5.73 (s, 2H, CH_2N), 6.14 (dd, 1H, H-4), 6.5-7.5 (m, 6H, H-3, H-5 and benzenoid H).

Anal. Calcd. for $C_{14}H_{16}N_2OS$: C, 64.60; H, 6.20; N, 10.76; S, 12.29. Found: C, 64.43; H, 6.22; N, 10.66; S, 12.73.

II.

To a solution of 0.1 g (0.0043 g-atom) of sodium metal in 3.5 ml of anhydrous ethanol was added a solution of 1 g (0.0043 mole) of 1-(2-mercaptobenzyl)pyrrole-2-carboxyamide **13** in 20 ml of anhydrous ethanol and the solvent removed *in vacuo*. To the residue dissolved in 5 ml of anhydrous tetrahydrofuran was added dropwise, at room temperature with stirring under nitrogen atmosphere, a solution of 0.67 g (0.0043 mole) of iodoethane in 5 ml of anhydrous tetrahydrofuran. When the addition was stopped the mixture was allowed to stir at room temperature for 5 hours and then poured onto crushed ice. The solid was collected, washed with water and air dried to give 1.1 g (98%) of **18**, which after crystallization from ethanol melted at 127°.

1-(2-Ethylthiobenzyl)pyrrole-2-carboxylic Acid (**19**).

A mixture of 1.9 g (0.0073 mole) of 1-(2-ethylthiobenzyl)pyrrole-2-carboxyamide **18**, 2.3 g (0.041 mole) of potassium hydroxide pellets and 20 ml of ethylene glycol was heated at 180° for 5 hours under stirring. After cooling the solution was poured onto crushed ice, washed with diethyl ether and acidified with concentrated hydrochloric acid. The precipitate was filtered, washed with water and air dried. The 1-(2-ethylthiobenzyl)-pyrrole-2-carboxylic acid **19** (1.32 g, 69%) after crystallization from ethanol was obtained as colourless needles, mp 102-103°; ir: 1672 cm^{-1} (carboxylic C=O); nmr (DMSO-d_6): δ 1.24 (t, 3H, CH_3), 2.98 (q, 2H, CH_2CH_3), 5.57 (s, 2H, CH_2N), 6.1-6.3 (m, 2H, H-3 and H-4), 6.8-7.5 (m, 5H, H-5 and benzenoid H), 12.10 (s, broad, 1H, COOH, deuterium oxide exchangeable).

Anal. Calcd. for $C_{14}H_{15}NO_2S$: C, 64.36; H, 5.79; N, 5.36; S, 12.24. Found: C, 64.31; H, 5.74; N, 5.54; S, 11.79.

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