POLYCONDENSED HETEROCYCLES. V. SYNTHESIS OF 5H,11H-PYRROLO[2,1-c][1,4]BENZOTHIAZEPINE

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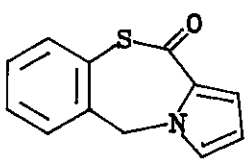
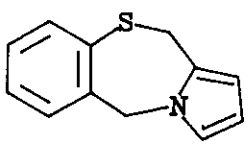
Abstract - The 5H,11H-pyrrolo[2,1-c][1,4]benzothiazepine ring system has been prepared by two synthetic pathways, involving the intramolecular nucleophilic displacement on 1-(2-fluorobenzyl)-2-mercaptomethylpyrrole or the Pummerer rearrangement of 1-(2-ethoxycarbonylmethylsulfinylbenzyl)pyrrole followed by in situ cyclization, respectively.

During our searches on nitrogen and sulfur containing polycyclic ring systems of biological interest, we reported the synthesis of 11-oxo-5H,11H-pyrrolo[2,1-c][1,4]benzothiazepine (1)[1] related to naturally occurring, antitumor pyrrolo[2,1-c][1,4]benzodiazepine derivatives.[2] The thiolactone (1) could be envisaged as a precursor of the unknown 5H,11H-pyrrolo[2,1-c][1,4]benzothiazepine (2), but our attempts to convert 1 to 2 were unsuccessful under various experimental conditions. Therefore, different routes to 2 were investigated.



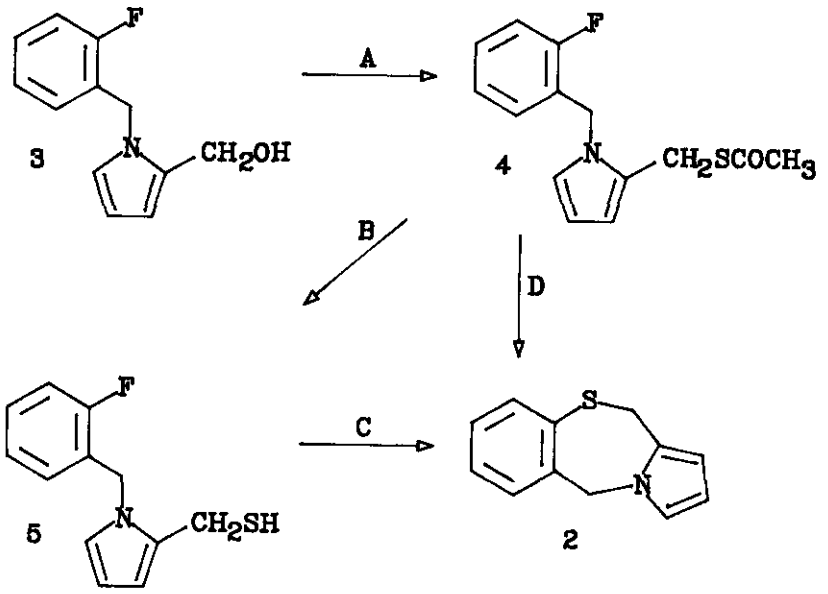
1



2

The synthetic approach, we examined first, involved intramolecular nucleophilic displacement of aromatic fluorine atom by a thiol group (Scheme 1). Thus, 1-(2-fluorobenzyl)-2-hydroxymethylpyrrole (3), obtained as reported[3] from the corresponding aldehyde,[4] was smoothly transformed into the thiolacetate 4 by a modified Mitsunobu procedure.[5] Treatment of 4 with sodium methoxide at -20°C afforded in almost quantitative yield the key intermediate 5, which was subjected to intramolecular cyclization in the presence of sodium hydride in N,N-dimethylformamide to give 2 in moderate yield. We developed a more convenient one-pot method to obtain 2 directly from the thiolacetate 4. The latter compound was deacetylated with sodium methoxide in N,N-dimethylformamide at -20°C and then the temperature was rised to 80°C in order to effect the cyclization to 2 (65% overall yield).

Scheme 1

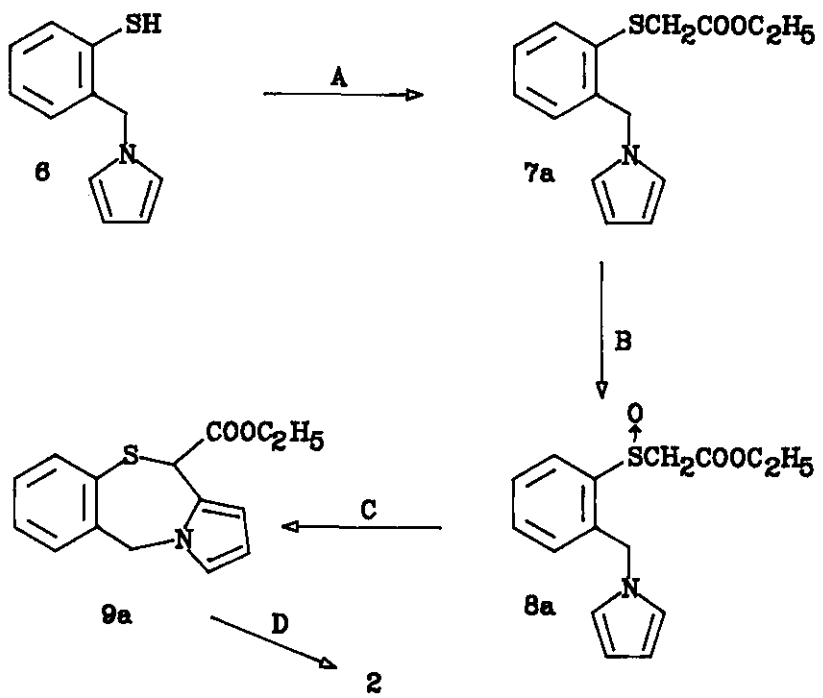


Reagents: A, $CH_3COSH/DIPAD/Ph_3P$; B, CH_3ONa/CH_3OH; C, NaH/DMF; D, CH_3ONa/DMF

Alternatively, 2 was prepared by a route involving the Pummerer rearrangement of 1-(2-alkylsulfinylbenzyl)pyrroles (8a-d) followed by *in situ* acid catalysed cyclization as a key step. This procedure has been developed by Bates *et al.*[6] for the synthesis of benzothiazines.

The presence of an electron withdrawing group on the α-carbon to the sulfoxide is a crucial structural requirement for the success of the reaction. In light of these findings 1-(2-ethoxycarbonylmethylsulfinylbenzyl)pyrrole (8a) was prepared by m-chloroperbenzoic acid oxidation of 7a, which was in turn obtained from 1-(2-mercaptobenzyl)pyrrole (6)[1] and ethyl bromoacetate (Scheme 2). Treatment of 8a with trifluoroacetic acid in refluxing toluene directly gave 11-ethoxycar-

Scheme 2

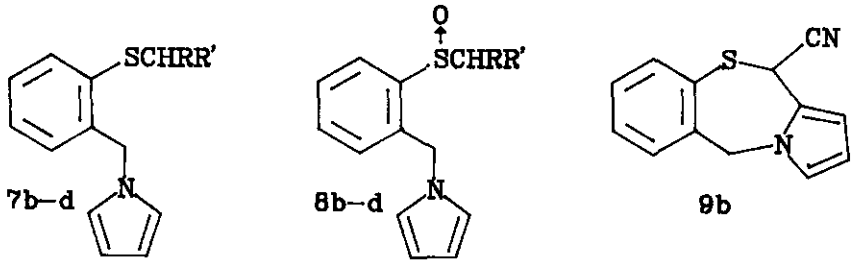


Reagents: A, $BrCH_2COOC_2H_5/C_2H_5ONa$; B, m-CPBA; C, CF_3COOH; D, 1.NaOH/2.HCl

bonyl-5H,11H-pyrrolo[2,1-c][1,4]benzothiazepine (9a), which easily lost the ethoxycarbonyl group under hydrolytic conditions to afford 2 in moderate yield.

With the aim to obtain 11-substituted-5H,11H-pyrrolo[2,1-c][1,4]benzothiazepines via this latter synthetic approach, sulfoxides (8b-d)[7] were prepared from the corresponding sulfides (7b-d), but attempts to transform them into tricyclic compounds were disappointing. In fact, while 8b actually provided the tricyclic cyano derivative (9b), albeit in moderate yield, 8c gave a complex mixture of products and 8d failed to react at all.

Scheme 3



b: R=H,R'=CN
c: R=Ph,R'=$COOC_2H_5$
d: R=H,R'=p-$C_6H_4NO_2$

Physical and chemical data of new compounds are listed in the Table.

EXPERIMENTAL

Melting points were taken on an Electrothermal 8103 apparatus and are uncorrected. Ir spectra (neat or nujol mulls) were taken on a Perkin-Elmer 398 spectrophotometer. Mass spectra were recorded on a VG 70/250S spectrometer with an electron beam of 70 eV. ^{1}H-Nmr spectra were recorded on a Varian XL 200 spectrometer for $CDCl_3$ solution (TMS as internal standard): the values of chemical shifts are expressed in ppm and coupling constants (J) in Hz. Chromatographic purifications were performed on columns packed with Merck silica gel 60, 230-400 mesh,

by flash technique. Microanalyses were performed on a Perkin-Elmer 240 C Elemental Analyzer. Anhydrous sodium sulfate was utilized to dry organic extracts. All the reactions were carried out under an argon atmosphere.

2-(Acetylthiomethyl)-1-(2-fluorobenzyl)pyrrole (4).

To a well stirred and cooled (0°C) solution of triphenylphosphine (5.25 g, 20 mmol) in anhydrous tetrahydrofuran (50 ml), diisopropyl azodicarboxylate (DiPAD) (4.16 g, 20 mmol) was added dropwise. After 30 min a solution of 3 (2.05 g, 10 mmol) and thiolacetic acid (1.52 g, 20 mmol) in anhydrous tetrahydrofuran (25 ml) was added slowly. The mixture was stirred for 1 h at 0°C and then for 3 h at room temperature. Removal of the solvent left a residue, which was taken up in ether. The insoluble material was filtered off and the oily residue obtained after evaporation of the solvent was chromatographed with 0 → 2% ether in hexanes to afford 4 (2.16 g, 82%) as a pale yellow oil. Ir: 1695 (CO) cm^{-1}. ^1H-Nmr: 2.27 (s, 3H, CH_3), 4.14 (s, 2H, CH_2S), 5.13 (s, 2H, CH_2N), 6.14 (m, 2H, pyrrole β-H), 6.66 (m, 1H, pyrrole α-H), 6.72-7.32 (m, 4H, Ar-H).

1-(2-Fluorobenzyl)-2-mercaptomethylpyrrole (5).

Sodium methoxide (0.3 g, 5.5 mmol) was added portionwise to a cooled (-20°C) solution of 4 (1.31 g, 5 mmol) in anhydrous methanol (13 ml). The cooling bath was removed and after 1 h at room temperature, the mixture was concentrated in vacuo (bath temperature 30°C), diluted with water and acidified (pH 5) with 1N hydrochloric acid. Extraction with dichloromethane provided 5 (1.04 g, 95%). Ir: 2560 (SH) cm^{-1}. ^1H-Nmr: 1.71 (t, J=6.7, 1H, SH, exch.), 3.70 (d, J=6.7, 2H, CH_2S), 5.25 (s, 2H, CH_2N), 6.13 (m, 2H, pyrrole β-H), 6.67 (t, J=2.3, 1H, pyrrole α-H), 6.70-7.35 (m, 4H, Ar-H). Ms m/z: 221 (M^+).

General procedure for the preparation of 7a-d.

To a stirred solution of sodium ethoxide (1.63 g, 24 mmol) (potassium hydroxide for 7b) in absolute ethanol (50 ml), 2-mercaptobenzylpyrrole (3.56 g, 20 mmol) in absolute ethanol (20 ml) was added dropwise. After stirring an additional 15 min, the proper alkyl halide (20 mmol) in absolute ethanol (40 ml) was added dropwise. The solution was stirred overnight (and gently warmed in the case of

Table. Physical and chemical data of new compounds

Compd.	mp (°C)	Cryst. solvent	Yield %	Formula	Elemental analysis Calculated / Found		
					C	H	N
2	86-88	petroleum ether	a	$C_{12}H_{11}NS$	71.60 71.56	5.51 5.68	6.96 6.75
4	oil		82	$C_{14}H_{14}FNOS$	63.86 63.66	5.36 5.23	5.32 5.16
5	oil		95	$C_{12}H_{11}FNS$		b	
7a	oil		90	$C_{15}H_{17}NO_2S$	65.42 65.19	6.22 6.37	5.09 4.85
7b	75-76	cyclohexane	75	$C_{13}H_{12}N_2S$	68.39 68.46	5.30 5.25	12.27 11.99
7c	oil		84	$C_{21}H_{21}NO_2S$	71.76 72.01	6.02 6.08	3.99 3.92
7d	94-95	ethanol	73	$C_{18}H_{16}N_2O_2S$	66.65 66.53	4.97 4.95	8.63 8.53
8a	87-88	ethanol	77	$C_{15}H_{17}NO_3S$	61.83 61.58	5.88 5.93	4.81 4.76
8b	122	ethanol	49	$C_{13}H_{12}N_2OS$	63.91 64.11	4.95 4.95	11.46 11.42
8c	124	ethanol	82	$C_{21}H_{21}NO_3S$	68.64 68.51	5.76 5.90	3.81 3.77
8d	138-139	ethanol	81	$C_{18}H_{16}N_2O_2S$	63.51 63.60	4.74 4.78	8.23 8.07
9a	84-85	petroleum ether	60	$C_{15}H_{15}NO_2S$	65.90 65.81	5.53 5.52	5.13 5.10
9b	124-125	cyclohexane	44	$C_{13}H_{10}N_2S$	69.00 68.83	4.45 4.56	12.38 12.39

[a] See experimental

[b] The instability of the compound did not allow to obtain satisfactory analytical data.

7d), then concentrated in vacuo. The semisolid residue was treated with water and dichloromethane. The organic layer was washed with water and dried. Evaporation of the solvent gave the crude product, which was purified by column chromatography (benzene-cyclohexane 2:1) or by crystallization.

1-(2-Ethoxycarbonylmethylthiobenzyl)pyrrole (7a).

Ir: 1740 (CO) cm^{-1}. ^1H-Nmr: 1.23 (t, J=7.1, 3H, CH_3), 3.55 (s, 2H, CH_2S), 4.16 (q, J=7.1, 2H, CH_2O), 5.27 (s, 2H, CH_2N), 6.21 (t, J=2.0, 2H, pyrrole β-H), 6.71 (t, J=2.0, 2H, pyrrole α-H), 6.87 (m, 1H, Ar-H), 7.24-7.55 (m, 3H, Ar-H).

1-(2-Cyanomethylthiobenzyl)pyrrole (7b).

Ir: 2250 (CN) cm^{-1}. ^1H-Nmr: 3.11 (s, 2H, CH_2S), 5.29 (s, 2H, CH_2N), 6.17 (t, J=2.0, 2H, pyrrole β-H), 6.66 (t, J=2.0, 2H, pyrrole α-H), 7.10-7.70 (m, 4H, Ar-H).

1-[2-(α-Ethoxycarbonyl)benzylthiobenzyl]pyrrole (7c).

Ir: 1740 (CO) cm^{-1}. ^1H-Nmr: 1.16 (t, J=7.1, 3H, CH_3), 4.12 (m, 2H, CH_2O), 4.66 (s, 1H, CH), 5.03 (half of AB q, J=15.9, 1H, CH_2N), 5.19 (half of AB q, J=15.9, 1H, CH_2N), 6.17 (t, J=2.0, 2H, pyrrole β-H), 6.59 (t, J=2.0, 2H, pyrrole α-H), 6.74 (m, 1H, Ar-H), 7.18-7.47 (m, 8H, Ar-H).

1-[2-(4-Nitrobenzyl)thiobenzyl]pyrrole (7d).

^1H-Nmr: 3.91 (s, 2H, CH_2S), 5.08 (s, 2H, CH_2N), 6.17 (t, J=2.1, 2H, pyrrole β-H), 6.59 (t, J=2.1, 2H, pyrrole α-H), 6.91 (m, 1H, Ar-H), 7.18-7.30 (m, 5H, Ar-H), 8.10 (d, J=8.8, 2H, Ar-H).

General procedure for the preparation of 8a-d.

A cold solution of 80% m-chloroperbenzoic acid (4.52 g, 21 mmol) in dichloromethane (100 ml) was added dropwise at 0°C to the appropriate sulfide (20 mmol) dissolved in dichloromethane (60 ml). The reaction mixture was stirred at 0°C for 1 h, then filtered. The filtrate was washed with 5% aqueous potassium carbonate, dried and evaporated to give the crude sulfoxide. Recrystallization from ethanol afforded

pure 8a-d.

1-(2-Ethoxycarbonylmethylsulfinylbenzyl)pyrrole (8a).

Ir: 1740 (CO), 1070 (SO) cm^{-1}. ^1H-Nmr: 1.24 (t, J=7.1, 3H, CH_3), 2.47 (half of AB q, J=14.5, 1H, CH_2S), 3.21 (half of AB q, J=14.5, 1H, CH_2S), 5.08 (half of AB q, J=15.0, 1H, CH_2N), 5.31 (half of AB q, J=15.0, 1H, CH_2N), 6.11 (t, J=2.1, 2H, pyrrole β-H), 6.60 (t, J=2.1, 2H, pyrrole α-H), 7.25-8.11 (m, 4H, Ar-H).

1-(2-Cyanomethylsulfinylbenzyl)pyrrole (8b).

Ir: 2250 (CN), 1040 (SO) cm^{-1}. ^1H-Nmr: 1.94 (half of AB q, J=16.2, 1H, CH_2S), 2.96 (half of AB q, J=16.2, 1H, CH_2S), 5.03 (half of AB q, J=14.7, 1H, CH_2N), 5.32 (half of AB q, J=14.7, 1H, CH_2N), 6.16 (t, J=2.1, 2H, pyrrole β-H), 6.56 (t, J=2.1, 2H, pyrrole α-H), 7.40-8.25 (m, 4H, Ar-H).

1-[2-(α-Ethoxycarbonyl)benzylsulfinylbenzyl]pyrrole (8c).

Ir: 1725 (CO), 1040 (SO) cm^{-1}. ^1H-Nmr: 1.31 (t, J=7.1, 3H, CH_3), 3.56 (half of AB q, J=16.5, 1H, CH_2N), 4.33 (m, 2H, CH_2O), 4.54 (s, 1H, CH), 4.86 (half of AB q, J=16.5, 1H, CH_2N), 6.12 (t, J=2.1, 2H, pyrrole β-H), 6.31 (t, J=2.0, 2H, pyrrole α-H), 6.40 (d, J=7.5, 1H, Ar-H), 7.09-7.48 (m, 7H, Ar-H), 8.05 (d, J=7.5, 1H, Ar-H).

1-[2-(4-Nitrobenzyl)sulfinylbenzyl]pyrrole (8d).

Ir: 1030 (SO) cm^{-1}. ^1H-Nmr: 2.79 (half of AB q, J=12.9, 1H, CH_2S), 3.36 (half of AB q, J=12.9, 1H, CH_2S), 5.03 (half of AB q, J=14.5, 1H, CH_2N), 5.30 (half of AB q, J=14.5, 1H, CH_2N), 6.22 (t, J=2.1, 2H, pyrrole β-H), 6.66 (t, J=2.1, 2H, pyrrole α-H), 7.03-8.11 (m, 8H, Ar-H).

11-Ethoxycarbonyl-5H,11H-pyrrolo[2,1-c][1,4]benzothiazepine (9a).

To a solution of 8a (2.33 g, 8 mmol) in dry toluene (100 ml), trifluoroacetic acid (1.19 ml, 16 mmol) was added dropwise. The mixture was refluxed for 4 h, then evaporated *in vacuo* to leave a residue, which was chromatographed (chloroform). Pure 9a was isolated and recrystallized from petroleum ether to give

white needles. Ir: 1730 (CO) cm^{-1}. ^{1}H-Nmr: 1.20 (t, J=7.1, 3H, CH_3), 4.13 (q, J=7.1, 2H, CH_2O), 5.15 (s, 1H, H-11), 5.20 (half of AB q, J=14.3, 1H, H-5), 5.37 (half of AB q, J=14.3, 1H, H-5), 6.05 (m, 2H, H-1, H-2), 6.70 (t, J=2.2, 1H, H-3), 7.20-7.50 (m, 4H, Ar-H). Ms m/z : 273 (M^+).

11-Cyano-5H,11H-pyrrolo[2,1-c][1,4]benzothiazepine (9b).

The same synthetic procedure described for 9a was used to obtain 9b as colourless needles. Ir: 2250 (CN) cm^{-1}. ^{1}H-Nmr: 5.17 (half of AB q, J=14.3, 1H, H-5), 5.25 (s, 1H, H-11), 5.36 (half of AB q, J=14.3, 1H, H-5), 6.08 (t, J=3.3, 1H, H-1), 6.18 (m, 1H, H-2), 6.71 (t, J=2.3, 1H, H-3), 7.25-7.65 (m, 4H, Ar-H). Ms m/z : 226 (M^+).

5H,11H-Pyrrolo[2,1-c][1,4]benzothiazepine (2).

Starting from 9a.

9a (1.36 g, 5 mmol) was dissolved in ethanol (100 ml) and 10% aqueous sodium hydroxide (11 ml). The solution was stirred for 15 min at room temperature. The solvent was evaporated *in vacuo* (bath temp 30°C) and the resulting residue was poured into crushed ice and acidified with concentrated hydrochloric acid. Extraction with chloroform and subsequent chromatography (benzene-cyclohexane 1:1) afforded 2 (0.72 g, 72%). ^{1}H-Nmr: 4.26 (s, 2H, H-11), 5.16 (s, 2H, H-5), 6.03 (m, 2H, H-1,H-2), 6.66 (m, 1H, H-3), 7.03-7.28 (m, 4H, Ar-H). Ms m/z: 201 (M^+).

Starting from 4.

4 (1.31 g, 5 mmol) was dissolved in freshly distilled N,N-dimethylformamide (30 ml) and cooled to -20°C. Sodium methoxide (0.69 g, 12.5 mmol) was added portionwise. The mixture was stirred at -20°C for 1 h, then gradually heated to 80°C and kept at this temperature for 3 h. Neutralization (1N hydrochloric acid) and evaporation *in vacuo* of the volatiles gave a residue, which was purified as above to give 2 (0.65 g, 65%).

Starting from 5.

A mixture of 5 (0.88 g, 4 mmol) and sodium hydride (288 mg, 12 mmol) in freshly

distilled N,N-dimethylformamide (50 ml) was stirred at 80°C for 1 h. Neutralization (1N hydrochloric acid) and evaporation in vacuo of the volatiles afforded a residue which was purified to furnish 2 (0.54 g, 67%).

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7. On the basis of its spectral and chromatographic properties, 8c appeared as a single diastereomer. No attempts were made to establish its stereochemistry.

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