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The displacement reaction between sodium thiophene-3-thiolate and methyl 3-(bromomethyl)thiophene-2-carboxylate (**5**) gave the expected thioether **7a**. Basic hydrolysis afforded the carboxylic acid **7b**; conversion to the acid chloride, and treatment of the latter with stannic chloride then produced the bisthienothiepinone **1**. Using analogous reactions the isomers **2-4** were also synthesized.

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Doubly annulated cycloheptanes, and heterocyclic analogues thereof, comprise the lipophilic aromatic nucleus of a wide variety of pharmacologically active compounds. For example, variously substituted dibenzazepines have been shown to possess significant activity as antidepressants [2], antihistamines [3], and anti-inflammatory agents [4]. The medicinal chemistry of compounds incorporating dibenzothiepin ring systems has also been reported [5]. The replacement of one or both of the flanking benzene rings by a thiophene ring has led, in this field as in other areas of medicinal chemistry, to compounds with useful biological activities. Thus a number of benzothienothiepinacetic acids were found to have anti-inflammatory properties [5d] and compounds derived from bisthienocycloheptenones have been shown to be antidepressants [6]. Bisthienothiepins have not so far been described, and we report here the syntheses and properties of the isomers **1-4** of this system.

The syntheses are shown in Schemes Ia-Ic. Displacement of the benzylic bromine substituent of **5** and **9** with the sodium salt of thiophene-2-(or -3-)thiol proceeded in good yields to afford the expected esters **7a**, **11a**, **12a** and **13a**. Basic hydrolysis of **7a** afforded the corresponding free acid **7b** which was converted into the acid chloride by treatment with thionyl chloride in methylene chloride containing a trace of dimethylformamide. The acid chloride was unstable, however, and complex mixtures were obtained when it was reacted with either boron trifluoride etherate or with stannic chloride, in attempts to effect cyclization to **1**. The procedure of Gronowitz [7], in which the acid chloride, produced by reaction of the acid with phosphorus pentachloride in benzene, is, without isolation, treated with stannic chloride, was then applied, and a good yield of **1** was obtained. These conditions were then utilized successfully in the syntheses of the isomers **2-4**. Two possible directions of cyclization are available to the acid chlorides derived from **7b** and **12b**; the products obtained were, however, shown by their nmr spectra (Table I) to be the expected products of acylation α to the thiophene sulphur atom [8], rather than the isomers **14** and **15** which would result from cyclization at the β -carbon. Since the yields of **1** and **3** were 85% and 95% respectively, it is clear that the alternative products **14** and **15**, if formed at all, were present in very small amounts.

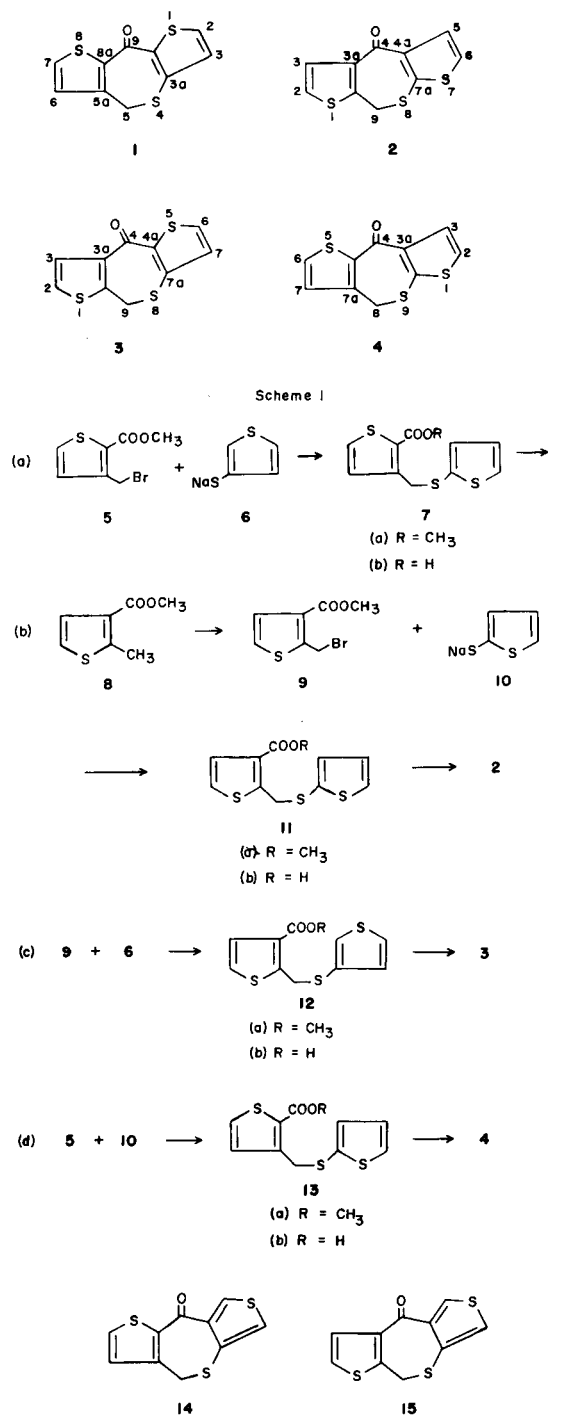


Table I
NMR Spectra of 1-4

Compound	C or H Position	δH	J_{H-H}	δC	$^1J_{C-H}$	$^2J_{C-H}$	$^3J_{C-H}$
1	2	7.56	5.0	133.4	186.0	5.9	
	7	7.56		133.8	186.0	5.9	
			and				
	3	6.93	5.0	129.0	172.8	3.7	
	6	6.98		130.4	169.5	3.7	3.7 (a)
	5	4.06		31.2	141.6		2.2 (b)
	9			177.0			
	3a			139.4			
	5a			139.8			
	8a			141.2			
	9a			141.7			
2	2	7.53	5.0	123.3	189.7	6.6	
	6	7.65		121.9	190.0	7.4	
			and				
	3	6.93	5.5	131.7	172.8	3.7	
	5	6.98		132.1	173.5	3.7	
	4			176.9			
	8	4.18		32.7	143.7		
	3a			139.3			
	4a			141.0			
	7a			143.5			
	9a			144.9			
3	2	7.60	5.0	122.3	188.7	6.8	
	6	7.54		133.5	185.9	6.8	
			and				
	3	7.02	5.5	130.3	172.9	4.5	
	7	7.08		130.5	172.9	4.5	
	9	4.22		30.4	143.5		
	4			178.6			
	3a			138.7			
	4a			139.1			
	7a			139.9			
	9a			143.5			
4	2	7.68	5.0	123.6	185.6	6.3	
	6	7.57		133.7	189.7	6.6	
			and				
	3	7.07	5.5	131.7	165.1	3.7	
	7	6.96		129.5	173.5	3.7	3.7 (c)
	8	4.08		33.4	142.0		2.2 (d)
	4			178.0			
	3a			139.8			
	4a			140.7			
	7a			142.5			
	9a			142.8			
(a)	Coupling	Constant	Between	C-6	and	H-5	
(b)	Coupling	Constant	Between	C-5	and	H-6	
(c)	Coupling	Constant	Between	C-7	and	H-8	
(c)	Coupling	Constant	Between	C-8	and	H-7	

The products **1-4** are stable yellow or yellow-brown solids. Their structures were confirmed by their nmr spectra (Table I). Because of the closeness or coincidence of some of the proton resonances, it was not possible to make complete assignments. However, the protons on carbons α to the thiophene sulphur atom are expected to resonate at lower field than the β -protons, and have been designated accordingly. Somewhat more complete assignments of the carbon resonances were possible by measurement of C-H coupling constants. Thus, the α -carbons could be distinguished from the β -carbons by the higher $^1J_{CH}$ values (*ca.* 185-190 Hz compared to *ca.* 165-173 Hz) which they exhibit [9]. The values of the two-bond C-H coupling constants ($^2J_{CH}$) for the α -carbons were also consistently higher than for the β -carbons (6-7 Hz, compared to 4-5 Hz). In addition, carbon 6 of **1**, and carbon 7 of **4** showed three-bond coupling constants ($^3J_{CH}$) of 3.7 Hz to the protons at carbons 5 and 8 respectively. The presence of this additional coupling constant allowed the resonances to be distinguished from those due to carbon 3, which showed no such coupling constant.

The syntheses described above are sufficiently short and high-yielding to allow preparation of considerable amounts of the tricyclic products **1-4**. In addition, some substituted analogs could be prepared utilizing suitably substituted precursors.

EXPERIMENTAL

Melting points were taken on a "Mel-temp" apparatus and are uncorrected. Ultraviolet spectra were taken in methanol on a Cary 14 spectrometer. Infrared spectra were taken on a Perkin-Elmer 710 B spectrometer and frequencies are quoted to the nearest 5 cm^{-1} . Mass spectra were obtained on Finnegan-Mat. CH-7 and 112-S instruments at 70 eV ionization voltage with a direct insertion probe. Proton nmr spectra were obtained on Varian A 60 and HA 100 instruments. Coupling constants are reported to the nearest 0.5 Hz. Carbon-13 nmr spectra were obtained on a Bruker WH 90 instrument at 22.62 MHz. Spectra were run using both broad-band and gated decoupling techniques. The digital resolution was 0.7 Hz. Chemical shifts are reported in parts per million relative to internal tetramethylsilane. Samples were dissolved in deuteriochloroform unless otherwise stated. All reactions were conducted under nitrogen.

1. Preparation of 4,9-Dihydrodithieno[3,2-*b*:2',3'-*e*]thiepin-9-one (**1**).

Sodium hydride (50% oil dispersion) (1.84 g, 38.3 mmoles) was added to a solution of 4.45 g (38.3 mmoles) of thiophene-3-thiol [10] in 75 ml of dimethylformamide, with ice cooling and stirring. When hydrogen evolution had stopped, 9.0 g (38.3 mmoles) of methyl 3-(bromomethyl)thiophene-2-carboxylate (**5**) [11] in 10 ml of dimethylformamide was added. After 1 hour, water and ether were added. The organic solution was washed with water, then dried and evaporated. The residue was chromatographed on silica gel, eluting with hexane:ether (30:1 to 15:1) so as to obtain 9.5 g (90%) of methyl 3-[(3-mercaptothienyl)methyl]thiophene-2-carboxylate (**7a**) as a yellow oil; uv: λ_{max} (e) 253 (12900); ir (film): 1700 cm^{-1} (C=O); ms: 270 (m^+ , 48), 155 (100); nmr: 3.77 (s, OCH_3), 4.37 (s, CH_2), 6.8-7.4 (m, 5H, arom).

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_2\text{S}_3$: C, 48.86; H, 3.73. Found: C, 48.78; H, 3.64.

This material was dissolved in 120 ml of methanol, and a solution of 7.3 g (174 mmoles) of lithium hydroxide monohydrate in 60 ml of water

was added. The mixture was heated to 65° for 45 minutes, then cooled and acidified with dilute hydrochloric acid. The solution was extracted with ethyl acetate, and the extract was dried and evaporated. The residue was recrystallized from acetone:hexane to afford 7.0 g (78%) of 3-[(3-mercaptothienyl)methyl]thiophene-2-carboxylic acid (**7b**), mp 150.5-152°; uv: λ max, nm (ϵ) 258 (12300); ir (nujol mull): 1670, 1650 cm^{-1} (C=O); nmr: 4.47 (s, CH_2), 6.9-7.5 (m, 5H, arom).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{O}_2\text{S}_3$: C, 46.85; H, 3.15. Found: C, 46.96; H, 3.10.

To a solution of 256 mg (1 mmole) of **7b** in 8 ml of benzene was added 244 mg (1.2 mmoles) of phosphorus pentachloride. The solution was refluxed for 10 minutes, then cooled. A slow stream of nitrogen was bubbled through for 10 minutes to remove hydrogen chloride. To the resultant solution at 5° was then added 2.6 ml (1 mmole) of a 22:1 mixture of benzene and stannic chloride. The mixture was refluxed for 10 minutes, then cooled and diluted with 25 ml of ether. The solution was then washed with dilute hydrochloric acid and with water, then dried and evaporated. The residue was dissolved in 5:1 hexane:ethyl acetate and filtered through ca. 10 gm of silica gel to afford 195 mg, (84%), of pure **1** which was recrystallized from acetone:hexane to give a yellow solid, mp 113-114.5°; uv: λ max nm (ϵ) 251 (4400), 325 (12900); ir (nujol mull): 1560, 1585 cm^{-1} (C=O); ms 238 (m^+ , 100), 209 (62), 205 (22).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{OS}_3$: C, 50.39; H, 2.54. Found: C, 50.31; H, 2.59.

2. Preparation of 4,8-Dihydrodithieno[2,3-b:3',2'-e]thiepin-4-one (**2**).

2-Methylthiophene-3-carboxylic acid [**12**] was converted into the methyl ester **8** (bp 124-127°/25 mm Hg) in 85% distilled yield by reaction with a two-fold molar excess of methyl iodide in dimethylformamide/potassium carbonate. A solution of 10.0 g (64 mmoles) of **8** was refluxed for 2 hours in 250 ml of carbon tetrachloride containing 11.4 g (64 mmoles) of *N*-bromosuccinimide and 0.1 g (0.4 mmoles) of benzoyl peroxide. The solution was cooled, filtered, washed with dilute sodium sulphite, dilute sodium bicarbonate, and water, then dried and evaporated to yield 13.5 g of an oil. The proton nmr spectrum showed this to be a 9:1 mixture of methyl 2-(bromomethyl)thiophene-3-carboxylate, nmr 3.94 (s, OCH_3), 5.17 (s, CH_2Br), 7.1-7.6 (m, arom) and unchanged **8**. This mixture was reacted, without purification, with sodium thiophene-2-thiolate [**13**] as described above for the preparation of **7a**, to afford a 68% yield of methyl 2-[(2-mercaptothienyl)methyl]thiophene-3-carboxylate (**11a**) as an oil; uv: λ max nm (ϵ) 245 (14200); ir (film): 1700 cm^{-1} (C=O); nmr 3.77 (s, OCH_3), 4.5 (s, CH_2S), 6.8-7.4 (m, arom).

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}_2\text{S}_3$: C, 48.86; H, 3.73. Found: C, 49.09; H, 3.43.

Basic hydrolysis of **11a**, as described above for **7a**, yielded, after recrystallization from acetone:hexane, 68% of 2-[(2-mercaptothienyl)methyl]thiophene-3-carboxylic acid **11b**, mp 119-122° dec; uv: λ max, nm (ϵ) 246 (13300); ir (nujol mull): 1660 cm^{-1} (C=O); nmr (hexadeuterioacetone): 4.63 (s, CH_2S), 6.9-7.6 (m, arom).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{O}_2\text{S}_3$: C, 46.85; H, 3.15. Found: C, 46.90; H, 3.06.

The acid **11b** was then converted into the acid chloride which upon treatment with stannic chloride, as described above, yielded 55% of **2** as a yellow solid, mp 83.5-87° (acetone:hexane); uv: λ max nm (ϵ) 259 (17800), 345(3300); ir (nujol mull): 1600 cm^{-1} (C=O); ms 238 (m^+ , 100), 209 (78), 205 (30).

Anal. Calcd. for $\text{C}_{10}\text{H}_6\text{OS}_3$: C, 50.39; H, 2.54. Found: C, 50.73; H, 2.27.

3. Preparation of 4,9-Dihydrodithieno[3,2-b:3',2'-e]thiepin-4-one (**3**).

Condensation of the bromomethyl compound **9**, and sodium thiophene-3-thiolate, as described above, gave in 50% yield methyl 2-[(3-mercaptothienyl)methyl]thiophene-3-carboxylate (**12a**) as a colourless oil; uv: λ max nm (ϵ) 246 (10900); ir (film): 1700 cm^{-1} (C=O); nmr 3.75 (s, OCH_3), 4.52 (s, CH_2S), 6.8-7.4 (m, 5H, arom).

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_2\text{S}_3$: C, 48.86; H, 3.73. Found: C, 49.02; H, 3.88.

The ester was hydrolysed as described above to afford in 82% yield 2-[(3-mercaptothienyl)methyl]thiophene-3-carboxylic acid (**12b**), mp 97-99° (acetone:hexane); uv: λ max nm (ϵ) 247 (11900); ir (nujol mull): 1685 cm^{-1} (C=O); nmr 4.50 (s, CH_2S), 6.8-7.4 (m, 5H, arom).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{O}_2\text{S}_3$: C, 46.85; H, 3.15. Found: C, 47.11; H, 2.87.

The acid **12b** was then converted, as described above, in 95% yield to the tricycle **3** as a yellow-brown solid, mp 86-87° (ethyl acetate:hexane); uv: λ max nm (ϵ) 229 (11900), 307 (9500), 340 (plateau, 6000); ir (nujol mull): 1590 (C=O); ms: 238 (m^+ , 100), 209 (75).

Anal. Calcd. for $\text{C}_{10}\text{H}_6\text{OS}_3$: C, 50.39; H, 2.54. Found: C, 50.43; H, 2.37.

4. Preparation of 4,8-Dihydrodithieno[2,3-b:2',3'-e]thiepin-4-one (**4**).

Condensation of the bromo ester **5**, and sodium thiophene-2-thiolate, as described above, gave in 78% yield methyl-3-[(2-mercaptothienyl)methyl]thiophene-2-carboxylate as an oil; uv: λ max nm (ϵ) 250 (4700), 268 (4000); ir (film): 1700 cm^{-1} (C=O); nmr 3.77 (s, OCH_3), 4.37 (s, CH_2S), 6.8-7.5 (m, arom).

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{O}_2\text{S}_3$: C, 48.80; H, 3.73. Found: C, 48.71; H, 3.88.

Basic hydrolysis then afforded 3-[(mercaptothienyl)methyl]thiophene-2-carboxylic acid in 76% yield, mp 150-156.5° (ether:hexane); uv: λ max nm (ϵ) 248 (5000); ir (nujol mull): 1670 cm^{-1} (C=O); nmr 4.36 (s, CH_2S), 6.8-7.5 (m, arom).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{O}_2\text{S}_3$: C, 46.85; H, 3.15. Found: C, 47.02; H, 3.18.

Conversion to the acid chloride, followed by cyclization, gave in 74% yield the tricyclic product **4** as a pale yellow solid, mp 122-123° (ether:hexane); uv: λ max, nm (ϵ) 263 (11600), 281 (8900), 313 (9500); ir (nujol mull): 1590 cm^{-1} (C=O); ms 238 (m^+ , 100), 209 (33).

Anal. Calcd. for $\text{C}_{10}\text{H}_8\text{OS}_3$: C, 50.39; H, 2.54. Found: C, 50.09; H, 2.30.

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