4-Amido-3,4-dihydro-2*H*-1-benzothiopyran-3-ols and their Sulphoxide and Sulphone Derivatives—Cromakalim Analogues

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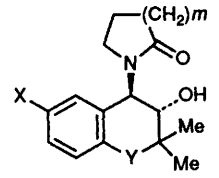
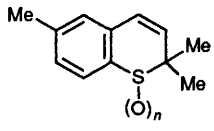
The racemic 6-methylbenzothiopyranols **26–28** and the dehydrated analogues **6**, **9** and **25** of the smooth muscle relaxant cromakalim (±)-**1** have been synthesised with the sulphur in different oxidation states. Problems of ring contraction to benzothiophene derivatives encountered during the attempted direct preparation of the sulphide **27** were overcome by protection as the sulphoxide **26** and subsequent deprotection.

Cromakalim (±)-(**1**) is the archetype of a series of 4-amido-3,4-dihydro-2,2-dimethylbenzopyran-3-ol derivatives which act as smooth muscle relaxants by the novel mechanism of potassium channel activation or opening, and as such have potential in those disease states where this relaxation plays an important role, *e.g.* hypertension, asthma, and urinary incontinence.[1] Closely related structures have been prepared by both ourselves[2,3,7] and other workers[4–6] which demonstrate that the cyano group is just one of a number of substituents which can be accommodated in the aromatic ring with retention of activity. Compounds have been prepared which have both electron-withdrawing and electron-donating substituents of varied steric bulk, and it has been shown that substitution at the 6-position tends to confer the greater potency.[2,3,6,7] Furthermore, the C-3 hydroxy group can be removed to give 2*H*-1-benzopyrans[2,3,6,7] or the dihydro analogues[3] which, in general, retain some or all of the activity associated with the parent system.

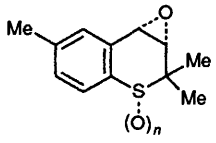
In an attempt to explore and define further the SAR associated with this type of compound we have now investigated the replacement of the benzopyran oxygen by sulphur, utilising the variable oxidation level of this atom to investigate the incorporation of polar entities at the 1-position. For synthetic expedience the derivatives with a 6-methyl substituent were chosen since SAR studies in the benzopyran series[2,7] have shown that this modification results in retention of smooth muscle relaxation.



	X	Y	*m*
(1)	CN	O	1
(26)	Me	S··· O	2
(27)	Me	S	2
(28)	Me	SO_2	2
(29)	Me	O	2



	n
(2)	0
(3)	1
(4)	2



	n
(5)	2
(8)	1
(10	0

Discussion

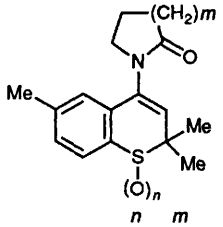
The most convenient entry to the benzothiopyran system is *via* the cyclodehydration of β-arylthiopropionic acids. Thus, following the procedure of Tercio *et al.*[8] 2,2,6-trimethyl-2*H*-1-benzothiopyran **2** is available in four steps from toluene-4-thiol and β,β-dimethylacrylic acid *via* reduction and dehydration of the intermediate thiopyran-4-one. Treatment of **2** with 2 equiv. of MCPBA† in dichloromethane for 5 min gave the sulphoxide **3** (39%) and sulphone **4** (22%), together with some recovered starting material (4%) but no epoxidised material. Only a trace of the epoxide **5** derived from the sulphone **4** was produced when the latter material was treated with a further equivalent of the same peracid in dichloromethane and the solution left at room temperature for 4 days. However, when the benzothiopyran **2** was treated with 4 equiv. of MCPBA in 1,2-dichloroethane containing a trace of 2,6-di-t-butyl-4-methylphenol[9] at 80 °C the epoxide **5** (64%) was obtained. Treatment of this material with pyrrolidin-2-one in DMSO† containing an excess of sodium hydride for 48 h furnished the benzothiopyran **6** directly without isolation of the intermediate benzothiopyranol.

Treatment of **2** with 1 equiv. of sodium metaperiodate in aqueous methanol gave the sulphoxide **3** in 94% yield with a small amount (4%) of the sulphone **4**. When this sulphoxide was treated with NBS† in wet DMSO, using conditions which result in good yields of *trans*-bromohydrins derived from benzopyrans[2,3] only a low yield (15%) of the corresponding bromohydrin **7a** resulted, starting material being recovered in 67% yield. Repetition of the experiment with a higher proportion of water present improved the yield of **7a** to 50% but use of *N*-bromoacetamide in aqueous acetone[10] resulted in a much improved yield (69%) of only one isomer of the required bromohydrin **7a**. This material was successfully ring closed to the epoxide **8** in quantitative yield using potassium hydroxide in tetrahydrofuran. Treatment of the epoxide **8** with the anion derived from pyrrolidin-2-one under the same conditions as those described for **5** above gave the sulphoxide **9** in 52% yield.

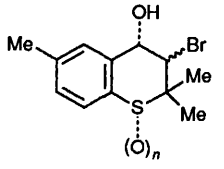
Attempts to form a cyclic amide analogue of an unoxidised

† MCPBA = *m*-Chloroperbenzoic acid; NBS = *N*-bromosuccinimide; DMSO = dimethyl sulphoxide.

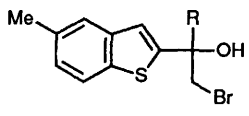
benzothiopyran system **24** or **27** were beset by problems of ring contraction of the required intermediates to benzothiophene derivatives. Thus, treatment of the benzothiopyran **2** with NBS/DMSO was not an efficient route to the *trans*-bromohydrin **7b** but gave a number of products from which the benzothiophenes **11** (18%) and **12** (10%) were isolated. Formation of these can be rationalised by invoking the participation of a thiiranium species of type **13**, formed by ring-opening of the intermediate cyclic bromonium ion by sulphur, which can collapse in the manner indicated to the dihydrobenzothiophene **14**. Aromatisation and bromohydrin formation would then account for **11** whilst an allylic bromination step prior to bromohydrin formation rationalises the presence of **12**. Attempted functionalisation of the double bond of **2** with bromine in dichloromethane gave products derived from a similar ring contraction, the bromohydrin **11** being formed in 35% yield presumably after aqueous work-up, and the vinyl bromides **15** (20%) and **16** (15%). The latter products probably arise from dehydration of the bromohydrins **11** and **12** and their geometry was established as *E* and *Z* respectively by the lack of an NOE enhancement of the vinylic



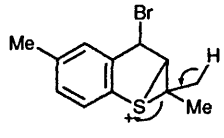
	n	*m*
(6)	2	1
(9)	1	1
(24)	0	1
(25)	1	2



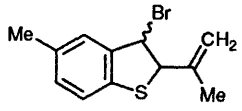
(7a) *n* = 1, *trans*
(7b) *n* = 0, *trans*
(7c) *n* = 0, *cis*



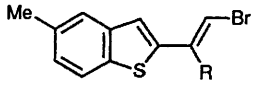
R	
(11)	Me
(12)	CH_2Br



(13)



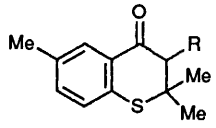
(14)



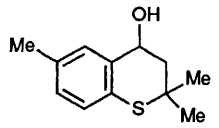
R	
(15)	Me
(16)	CH_2Br

methyl or bromomethyl group after irradiation of the vinylic protons. Similarly no NOE enhancement of the vinylic proton was seen when either the methyl group in **15** or the bromomethyl moiety in **16** was irradiated. In the latter cases, however, a small enhancement of the C-3 ring proton was observed. Ring contraction reactions have previously been documented[11] with the thiopyran system when a suitably disposed leaving group is present at C-3.

As an alternative route to the epoxide **10**, the bromoketone **17** was subjected to sodium borohydride reduction. At room temperature in methanol a mixture of the benzothiopyranol **18** and the dihydrobenzothiophene **19** (one isomer of unassigned stereochemistry) were isolated in a combined yield of 77%, together with traces of starting material and the benzothiopyran-4-one **20**. Presumably reaction occurs to give the *cis*-bromohydrin[12] **7c** which then undergoes ring contraction through an intermediate such as **21** and, after attack of methanol at C-2, generates the observed dihydrobenzothiophene. Elimination of HBr from the *cis*-bromohydrin **7c** would account for the formation of the benzothiopyran-4-one **20** which is known[8] to be reduced under these conditions to the dihydrobenzothiopyran-4-ol **18**. Change of solvent to isopropyl alcohol and reduction at 5 °C again gave the alcohol **18** together with both isomers of the ring contracted species **22**. Presumably, in this case, reductive cleavage of the thiiranium species is sterically favoured over attack by isopropyl alcohol at C-2. The similar 2-H, 3-H coupling constants (*J* 4.4 and 4.5 Hz) in the isomers of **22** mitigated against the ready assignment of *cis*/*trans*-configurations to these compounds. Both isomers were independently treated with HCl to give 2-isopropyl-5-methylbenzothiophene **23**.



(17) R = Br
(20) R = H



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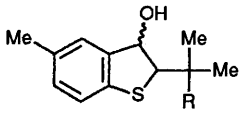
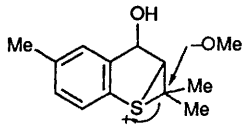


R	
(19)	OMe
(22)	H



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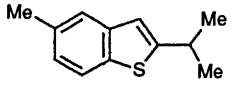

(23)

The problems encountered above suggested that an unoxidised benzothiopyran would be better prepared *via* deoxygenation of an intermediate *S*-oxide. Thus treatment of the epoxide **8** with 1 equiv. of the anion derived from δ-valerolactam for 4 h, using the amide as solvent, gave the 3,4-dihydrothiobenzopyran-3-ol **26** (46%) together with some benzothiopyran **25** and recovered starting material (11%). Presumably, the shorter reaction time in this instance (4 h compared with 2 and 3 days for reaction of **5** and **8** with pyrrolidinone anion) accounts for the presence of the thiopyranol **26**. Deoxygenation of the sulphoxide was accomplished using the triethyl phosphite/iodine/sodium iodide procedure developed by Singh.[13] However, the ^1H NMR spectrum of the crude reaction product revealed the presence of a small amount (*ca.* 5%) of another product, possibly a ring-contracted species formed in a similar manner to those described above. Modification of the reaction conditions to ensure that the sulphoxide was present in excess and dispensing with the sodium iodide resulted in the absence of this undesired product and gave the sulphide **27** (23%), after separation from starting material.

Treatment of the sulphoxide **26** with 1 equiv. of MCPBA gave the sulphone **28** (59%). Comparison of the ^1H NMR spectrum of **28** with that of the sulphoxide **26** revealed that the 3-H in **28** resonates at 0.53 ppm downfield from TMS compared with the same proton in the sulphoxide, providing good evidence for a *cis* orientation of the 3-OH and the sulphoxide oxygen in **26**. From this it follows that the intermediates **8** and **7a** have the orientations shown. This is in keeping with the expected attack

of the incoming bromine cation at the face *anti* to the sulphoxide oxygen in the sulphoxide **3**, since attack would then be at the least hindered face (*i.e.* 'equatorial' rather than 'axial' 2-methyl) with the sulphoxide oxygen in an 'equatorial' environment.

Biological evaluation of **27** revealed that it was approximately equipotent with its benzopyranol analogue **29** but, interestingly, oxidation of the sulphur atom, either to the sulphoxide or the sulphone level, produced a marked decline in biological activity, both in the benzothiopyranols **26** and **28** and in the benzothiopyrans **6** and **9**.

Experimental

M.p.s were determined using a Buchi apparatus and are recorded uncorrected. IR spectra were measured as liquid films for oils or as dispersions in KBr for solids, using a Perkin-Elmer 197 spectrometer. NMR spectra were obtained with a Varian EM 360 (60 MHz), EM390 (90 MHz), Jeol 270 GMX (270 MHz) or Bruker AM-400 (400 MHz) spectrometer with solutions in deuteriochloroform, unless otherwise noted, containing tetramethylsilane as internal standard. Mass spectral data were obtained from a VG-Micromass 70-70F instrument using electron impact ionisation techniques. All organic extracts were dried over $MgSO_4$ and samples were chromatographed on silica except where stated.

Oxidation of 2,2,6-*Trimethyl*-2H-1-*benzothiopyran* **2**.—(*a*) m-*Chloroperbenzoic acid.* MCPBA (80% pure; 0.565 g, 3.28 mmol) in dichloromethane (30 ml) was added dropwise to a stirred solution of the benzothiopyran **2**[8] (0.500 g, 2.63 mmol) in dichloromethane (10 ml) at room temperature. After 5 min the solution was evaporated and chromatographed on alumina. Elution with chloroform gave starting material (20 mg, 4%) followed by 2,2,6-trimethyl-2*H*-1-benzothiopyran 1,1-dioxide **4** (130 mg, 22%), m.p. 137–138 °C; ν_{max} 2 990, 1 595, 1 460, 1 280 and 1 120 cm^{-1}; δ 1.5 (6 H, s, 2-Me), 2.45 (3 H, s, 6-Me), 6.0 (1 H, d, *J* 11 Hz, 3-H), 6.55 (1 H, d, *J* 11 Hz, 4-H), 7.1 (1 H, d, *J* 2 Hz, 5-H), 7.3 (1 H, dd, *J* 8, 2 Hz, 7-H), 7.9 (1 H, d, *J* 8 Hz, 8-H) and finally 2,2,6-trimethyl-2*H*-1-benzothiopyran 1-oxide **3** (210 mg, 39%), as an oil, ν_{max} 2 980, 1 595, 1 460, 1 065 and 1 040 cm^{-1}; δ 1.3 (3 H, s, 2-Me), 1.55 (3 H, s, 2-Me), 2.4 (3 H, s, 6-Me), 5.85 (1 H, d, *J* 10 Hz, 3-H), 6.6 (1 H, d, *J* 10 Hz, 4-H), 7.1 (1 H, d, *J* 2 Hz, 5-H), 7.25 (1 H, dd, *J* 2, 8 Hz, 7-H) and 7.7 (1 H, d, *J* 8 Hz, 8-H).

(*b*) *Sodium metaperiodate.* Sodium metaperiodate (3.94 g, 0.018 mol) in water (30 ml) was added dropwise to a stirred solution of the benzothiopyran **2** (3.03 g, 0.016 mol) in methanol (120 ml) and, after complete addition of oxidant, the solution was heated under reflux for 1 h. The methanol was evaporated and the aqueous layer extracted with chloroform. The organic layers were combined, washed with brine, dried, filtered and evaporated to give an oil (3.64 g) which was chromatographed. Elution with light petroleum (b.p. 40–60 °C)–ether (1:3) gave benzothiopyran **4** (157 mg, 4%), followed by benzothiopyran **3** (3.085 g, 94%), as an oil. The spectroscopic properties of both compounds were identical with those reported under (*a*) above.

3,4-*Epoxy*-3,4-*dihydro*-2,2,6-*trimethyl*-2H-1-*benzothiopyran* 1,1-*Dioxide* **5**.—MCPBA (80% pure; 13.2 g, 0.061 mol) in 1,2-dichloroethane (120 ml) was added dropwise to a stirred solution of the benzothiopyran **2** (2.92 g, 0.015 mol) and 2,6-di-t-butyl-4-methylphenol (0.050 g) in 1,2-dichloroethane (25 ml) at room temperature. After 0.5 h the reaction mixture was heated under reflux for 4 h. The reaction mixture was cooled, filtered and the filtrate evaporated; the residue was then flash chromatographed on alumina (chloroform). Further chromatography on silica (chloroform) gave the title compound **5** (2.33 g, 64%), as a white solid, m.p. 148–151 °C; ν_{max} 2 995, 1 605, 1 460, 1 300 and 1 140 cm^{-1}; δ 1.41 (3 H, s, 2-Me), 1.7 (3 H, s, 2-Me), 2.45 (3 H, s, 6-Me), 3.7 (1 H, d, *J* 4 Hz, 3-H), 4.0 (1 H, d, *J* 4 Hz, 4-H), 7.42 (1 H, d, *J* 8 Hz, 7-H), 7.5 (1 H, s, 5-H) and 7.97 (1 H, d, *J* 8 Hz, 8-H).

2,2,6-*Trimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzothiopyran* 1,1-*Dioxide* **6**.—Sodium hydride (60% dispersion in oil; 0.129 g, 3.25 mmol) was added to a stirred solution of the benzothiopyran **5** (0.412 g, 1.73 mmol) and pyrrolidin-2-one (0.225 g, 2.65 mmol) in dry dimethyl sulphoxide at room temperature under nitrogen and the reaction mixture was stirred for 48 h. It was then poured into water and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried and evaporated to give an oil which was chromatographed. Elution with chloroform and trituration of the resulting oil with ether gave the *title compound* **6** (0.317 g, 60%), m.p. 135–138 °C; ν_{max} 2 995, 1 710, 1 625, 1 595, 1 410, 1 305, 1 155 and 1 120 cm^{-1}; δ 1.55 (6 H, s, 2-Me), 2.23 (2 H, m, $CH_2CH_2CH_2$), 2.44 (3 H, s, 6-H), 2.60 (2 H, t, *J* 7 Hz, CH_2CO), 3.59 (2 H, t, *J* 7 Hz, CH_2N), 6.03 (1 H, s, 3-H), 6.96 (1 H, s, 5-H), 7.34 (1 H, dd, *J* 8, 1 Hz, 7-H) and 7.94 (1 H, d, *J* 8 Hz, 8-H) (Found: C, 62.9; H, 6.3; N, 4.55. $C_{16}H_{19}NO_3S$ requires C, 62.9; H, 6.25; N, 4.6%).

3β-*Bromo*-3,4-*dihydro*-2,2,6-*trimethyl*-2H-1-*benzothiopyran*-4α-*ol* 1α-*Oxide* **7a**.—*N*-Bromoacetamide (3.18 g, 0.023 mol) was added portionwise to a stirred solution of the benzothiopyran **3** (2.198 g, 0.011 mol) in acetone (107 ml) containing water (20 ml) at room temperature. The solution was stirred for 4.5 h after which the acetone was evaporated and the residue partitioned between chloroform and water. The organic layer was washed with aqueous sodium thiosulphate, dried and evaporated to give a solid which was chromatographed. Elution with chloroform gave the *title compound* **7a** (2.02 g, 63%), as a white solid, m.p. 173–177 °C; ν_{max} 3 320, 1 600, 1 455, 1 040 and 1 015 cm^{-1}; δ 1.11 (3 H, s, 2-Me), 1.53 (3 H, s, 2-Me), 2.40 (3 H, s, 6-Me), 4.78 (1 H, dd, *J* 9.5, 8 Hz, 4-H), 4.85 (1 H, d, *J* 9.5 Hz, 3-H), 6.44 (1 H, d, *J* 8 Hz, OH), 7.33 (1 H, d, *J* 7.6 Hz, 7-H), 7.57 (1 H, s, 5-H) and 7.61 (1 H, d, *J* 7.6 Hz, 8-H) (Found: C, 47.5; H, 5.1. $C_{12}H_{15}BrO_2S$ requires C, 47.55; H, 5.0%).

cis-3,4-*Epoxy*-3,4-*dihydro*-2,2,6-*trimethyl*-2H-1-*benzothiopyran* 1-*Oxide* **8**.—Powdered potassium hydroxide (3.9 g, 70 mmol) was added in one portion to a stirred solution of the benzothiopyran **7a** (1.974 g, 6.5 mmol) in dry tetrahydrofuran (100 ml) at room temperature. The reaction mixture was stirred for 1 h, filtered, and evaporated to give the title compound **8** as a white solid which was used without further purification; ν_{max} 2 990, 1 605, 1 460 and 1 040 cm^{-1}; δ 1.17 (3 H, s, 2-Me), 1.67 (3 H, s, 2-Me), 2.44 (3 H, s, 6-Me), 3.63 (1 H, d, *J* 3.8 Hz, 3-H), 3.97 (1 H, d, *J* 3.8 Hz, 4-H), 7.35 (1 H, d, *J* 7.7 Hz, 7-H), 7.44 (1 H, s, 5-H) and 7.66 (1 H, d, *J* 7.7 Hz, 8-H).

2,2,6-*Trimethyl*-4-(2-*oxopyrrolidin*-1-*yl*)-2H-1-*benzothiopyran* 1-*Oxide* **9**.—Sodium hydride (60% dispersion in oil; 0.112 g, 2.82 mmol) was added to a stirred solution of the benzothiopyran **8** (0.308 g, 1.39 mmol) and pyrrolidin-2-one (0.185 g, 2.18 mmol) in dry dimethyl sulphoxide (3 ml) at room temperature under nitrogen and the solution stirred for 3 days. The reaction mixture was poured into water, extracted with chloroform and ethyl acetate and the combined organic layers were washed with water, dried and evaporated to give an oil which was chromatographed. Elution with chloroform and trituration of the resultant oil with ether gave the *title compound* **9** (210 mg, 52%), as a white solid, m.p. 139–141 °C; ν_{max} 1 695, 1 615, 1 055 and 1 040 cm^{-1}; δ 1.38 (3 H, s, 2-Me), 1.46 (3 H, s, 2-Me), 2.20 (2 H, m, $CH_2CH_2CH_2$), 2.39 (3 H, s, 6-Me), 2.60 (2 H, t, CH_2CO), 3.53–3.67 (2 H, m, CH_2N), 5.79 (1 H, s, 3-H), 6.92

(1 H, s, 5-H), 7.28 (1 H, d, *J* 7.6 Hz, 7-H) and 7.65 (1 H, d, *J* 7.6 Hz, 8-H) (Found: M^+, 289.1127; C, 66.45; H, 6.35; N, 4.9. $C_{16}H_{19}NO_2S$ requires *M*, 289.1137; C, 66.4; H, 6.6; N, 4.85%).

Reaction between 2,2,6-*Trimethyl*-2H-1-*benzothiopyran* **2** *and NBS.*—*N*-Bromosuccinimide (1.0 g, 5.6 mmol) was added portionwise to a stirred solution of the benzothiopyran **2** (0.51 g, 2.68 mmol) in dimethyl sulphoxide (5 ml) containing water (0.2 ml, 11.1 mmol). The solution was stirred for 1.5 h and then poured into water and the mixture extracted with ether; the ether layers were washed with water, dried, and evaporated to give a yellow oil (0.63 g) which was chromatographed. Elution with chloroform gave 1,1-*bis*(*bromomethyl*)-1-(5-*methyl*-2-*benzothienyl*)*methanol* **12** (100 mg, 10%), m.p. 127–130 °C (ether–petroleum); ν_{max} 3 540, 1 320, 1 235 and 1 115 cm^{-1}; δ 2.45 (3 H, s, 5-Me), 3.16 (1 H, s, OH), 3.87 (2 H, d, *J* 10.8 Hz, CH_2Br), 3.96 (2 H, d, *J* 10.8 Hz, CH_2Br), 7.16 (1 H, dd, *J* 1, 8.2 Hz, 6-H), 7.24 (1 H, s, 3-H), 7.54 (1 H, d, *J* 1 Hz, 4-H) and 7.68 (1 H, d, *J* 8.2 Hz, 7-H) (Found: M^+, 361.8978. $C_{12}H_{12}Br_2OS$ requires *M*, 361.8976), followed by 1-bromomethyl-1-(5-methyl-2-benzothienyl)ethanol **11** (140 mg, 18%), as an oil; ν_{max} 3 540, 3 480, 2 990 and 1 605 cm^{-1}; δ 1.68 [3 H, s, MeC(OH)], 2.40 (3 H, s, 5-Me), 3.75 (1 H, d, *J* 10.2 Hz, CHBr), 3.80 (1 H, d, *J* 10.2 Hz, CHBr), 6.12 (1 H, s, OH), 7.13 (2 H, dd, *J* 1.6, 8.4 Hz, 6-H), 7.24 (1 H, s, 3-H), 7.55 (1 H, br s, 4-H) and 7.77 (1 H, d, *J* 8.4 Hz, 7-H). The sample was too unstable to allow measurement of the molecular ion.

Reaction between 2,2,6-*Trimethyl*-2H-1-*benzothiopyran* **2** *and Bromine.*—Bromine (0.42 g, 2.63 mmol) in dichloromethane (10 ml) was added dropwise at room temperature to a stirred solution of the benzothiopyran **2** (0.5 g, 2.63 mmol) in dichloromethane (10 ml) and the solution was stirred for 15 min. The reaction mixture was washed with aqueous sodium thiosulphate and then extracted with dichloromethane. The combined organic layers were washed with water, dried, and evaporated to give an oil (0.93 g) which was chromatographed. Gradient elution with 5–20% ether–hexane gave (E)-1-*bromo*-2-(5-*methyl*-2-*benzothienyl*)*prop*-1-*ene* **15** (140 mg, 20%); ν_{max} 1 585, 1 440 and 1 305 cm^{-1}; δ 2.29 (3 H, d, *J* 1.1 Hz, olefinic Me), 2.44 (3 H, s, 5-Me), 6.73 (1 H, q, *J* 1.1 Hz, olefinic H), 7.15 (1 H, dd, *J* 1.1, 8 Hz, 6-H), 7.18 (1 H, s, 3-H), 7.50 (1 H, br s, 5-H) and 7.62 (1 H, d, *J* 8 Hz, 7-H) (Found: M^+, 265.9755. $C_{12}H_{11}BrS$ requires *M*, 265.9765), followed by (Z)-1,3-*dibromo*-2-(5-*methyl*-2-*benzothienyl*)*prop*-1-*ene* **16** (140 mg, 15%); ν_{max} 1 605 and 1 440 cm^{-1}; δ 2.45 (3 H, s, 5-H), 4.52 (2 H, s, CH_2Br), 6.91 (1 H, s, olefinic H), 7.18 (1 H, dd, *J* 1.3, 8.3 Hz, 6-H), 7.35 (1 H, s, 3-H), 7.56 (1 H, br s, 4-H) and 7.65 (1 H, d, *J* 8.3 Hz, 7-H) (Found: M^+, 343.8865. $C_{12}H_{10}Br_2S$ requires *M*, 343.8870), followed by the ethanol **11** (0.26 g, 35%) whose spectroscopic properties were identical with those reported above.

3-*Bromo*-2,2,6-*trimethyl*-2H-1-*benzothiopyran*-4-*one* **17**.—Bromine (0.8 g, 5.01 mmol) in dichloromethane (10 ml) was added dropwise to a stirred solution of 2,2,6-trimethyl-2*H*-1-benzothiopyran-4-one **20** (1.03 g, 5 mmol) in dichloromethane (10 ml) at room temperature and the solution was stirred for 1 h. The solvent was evaporated and the residue triturated with ether–petroleum (1:4) to give 3-bromo-2,2,6-trimethyl-2*H*-1-benzothiopyran-4-one **17** (1.19 g, 84%), of sufficient purity as to be used in subsequent reactions; δ 1.48 (3 H, s, 2-Me), 1.53 (3 H, s, 2-Me), 2.32 (3 H, s, 6-Me), 4.65 (1 H, s, 3-H), 7.1–7.3 (2 H, m, 7-H, 8-H) and 7.95 (1 H, m, 5-H).

Reduction of 3-*Bromo*-2,2,6-*trimethyl*-2H-1-*benzothiopyran*-4-*one* **17** *with Sodium Borohydride.*—(*a*) *In methanol.* Sodium borohydride (0.25 g, 6.6 mmol) was added portionwise to the benzothiopyran **17** (0.78 g, 2.73 mmol) suspended in methanol (7 ml) and the reaction mixture stirred for 1 h at ambient temperature. The mixture was then poured into water, extracted with ethyl acetate, and the combined extracts were dried and evaporated to give an oil (0.72 g) which was chromatographed. Elution with ether–petroleum (1:3) gave traces of starting material **17** and the benzothiopyran **20** followed by 2,3-dihydro-2-[(1-methoxy-1-methyl)ethyl]-5-methylbenzothiophen-3-ol **19** (238 mg, 37%); δ 1.34 (3 H, s, *Me*COMe), 1.50 (3 H, s, *Me*COMe), 2.30 (3 H, s, 5-H), 3.33 (3 H, s, OMe), 3.88 (1 H, d, *J* 5 Hz, 2-H), 4.75–4.9 (1 H, br, OH), 5.25 (1 H, d, *J* 5 Hz, 3-H), 7.01 (1 H, br d, *J* 8 Hz, 6-H), 7.10 (1 H, d, *J* 8 Hz, 7-H), 7.17 (1 H, br s, 4-H), followed by mixed fractions (173 mg) before 3,4-dihydro-2,2,6-trimethyl-2*H*-1-benzothiopyran-4-ol[8] **18** (74 mg, 13%) was eluted pure.

(*b*) *In isopropyl alcohol.* Sodium borohydride (0.158 g, 4.14 mmol) was added portionwise over 5.5 h to a stirred suspension of the benzothiopyran **17** (0.378 mg, 1.32 mmol) in isopropyl alcohol (5 ml) and ether (10 ml) at 5 °C and the mixture was stirred at room temperature for 16 h. The solvent was evaporated, the residue taken up in water, and the solution extracted with ethyl acetate. The organic layers were washed with brine, dried and evaporated to give an oil (312 mg) which was chromatographed. Elution with ether–petroleum (1:3) gave one isomer of 2,3-dihydro-2-isopropyl-5-methylbenzothiophen-3-ol **22a** (133 mg, 49%); δ 1.09 (3 H, d, *J* 6.7 Hz, *Me*CH), 1.19 (3 H, d, *J* 6.7 Hz, *Me*CH), 1.75 (1 H, d, *J* 9 Hz, OH), 2.31 (3 H, s, +1 H, m, 5-Me + Me_2CH), 3.57 (1 H, dd, *J* 4.5, 10.6 Hz, 2-H), 4.94 (1 H, dd, *J* 4.5, 9 Hz, 3-H), 7.03 (1 H, br d, *J* 8 Hz, 6-H), 7.07 (1 H, d, *J* 8 Hz, 7-H) and 7.20 (1 H, d, *J* 0.6 Hz, 4-H), followed by the other isomer **22b** (38 mg, 14%); δ 0.94 (3 H, d, *J* 6.6 Hz, *Me*CH), 1.04 (3 H, d, *J* 6.6 Hz, *Me*CH), 2.04 (1 H, m, Me_2CH), 2.0–2.2 (1 H, br, OH), 2.30 (3 H, s, 5-Me), 3.58 (1 H, dd, *J* 4.4, 6.1 Hz, 2-H), 5.08 (1 H, d, *J* 4.4 Hz, 3-H), 7.03 (1 H, d, *J* 7.9 Hz, 6-H or 7-H), 7.07 (1 H, d, *J* 7.9 Hz, 6-H or 7-H) and 7.14 (1 H, s, 4-H), followed by 3,4-dihydro-2,2,6-trimethyl-2*H*-1-benzothiopyran-4-ol[8] **18** (99 mg, 36%).

Dehydration of 2,3-*Dihydro*-2-*isopropyl*-5-*methylbenzothiophen*-3-*ol* **22**.—Gaseous HCl was added to **22a** (20 mg, 0.074 mmol) dissolved in ether and the solution stirred for 2 h. Evaporation of the solvent gave 2-isopropyl-5-methylthiophene **23** (14 mg, 75%) as an oil, δ 1.38 (6 H, d, *J* 6.8 Hz, Me_2CH), 2.43 (3 H, s, 5-Me), 3.21 (1 H, heptet, *J* 6.8 Hz, Me_2CH), 6.93 (1 H, s, 3-H), 7.07 (1 H, dd, *J* 8.3, 0.8 Hz, 6-H), 7.45 (1 H, d, *J* 0.8 Hz, 4-H) and 7.63 (1 H, d, *J* 8.3 Hz, 7-H). Reaction of **22b** with HCl in chloroform gave an oil with the same ^1H NMR spectrum as the above.

3,4-*Dihydro*-2,2,6-*trimethyl*-4β-(2-*oxopiperidin*-1-*yl*)-2H-1-*benzothiopyran*-3α-*ol* 1α-*Oxide* **26**.—Sodium hydride (60% dispersion in oil; 0.147 g, 3.7 mmol) was added in one portion to a stirred solution of the benzothiopyran **8** (0.665 g, 3.0 mmol) in δ-valerolactam (6 ml) at 40 °C under nitrogen. The reaction mixture was stirred for 2.25 h after which a further portion of sodium hydride (0.028 g) was added and stirring continued for 1.75 h. The reaction mixture was poured into water, extracted with chloroform, and the combined organic layers were washed with water, dried and evaporated to give an oil which was chromatographed. Elution with chloroform gave starting material **8** (0.073 g, 11%), followed by 2,2,6-trimethyl-4-(2-oxopiperidin-1-yl)-2*H*-1-benzothiopyran 1-oxide **25** (168 mg, 19%), as an oil, δ 1.48 (6 H, s, 2-Me), 1.75–2.0 (4 H, m, $CH_2CH_2CH_2CH_2$), 2.37 (3 H, s, 6-Me), 2.63 (2 H, t, *J* 7 Hz, CH_2CO), 3.31 (2 H, t, *J* 5.6 Hz, CH_2N), 6.10 (1 H, s, 3-H), 7.07 (1 H, dd, *J* 1.1, 7.7 Hz, 7-H), 7.12 (1 H, br s, 5-H) and 7.45 (1 H, d, *J* 5.7 Hz, 8-H). Elution with methanol–chloroform (5–7.5:95–92.5) gave an oil which was triturated with ether to give the *title compound* **26** (0.437 g, 46%) as a white solid, m.p. 196–199 °C;

ν_{max} 3 400, 1 630, 1 605 and 1 045 cm^{-1}; δ($CDCl_3/D_2O$) 1.14 (3 H, s, 2-Me), 1.64 (3 H, s, 2-Me), 1.69–1.91 (4 H, m, $CH_2CH_2CH_2CH_2$), 2.39 (3 H, s, 6-H), 2.56–2.62 (2 H, m, CH_2CO), 2.88–3.04 (2 H, m, CH_2N), 3.94 (1 H, d, *J* 9 Hz, 3-H), 5.97 (1 H, br d, *J* 9 Hz, 4-H), 6.97 (1 H, s, 5-H), 7.32 (1 H, d, *J* 8 Hz, 7-H) and 7.69 (1 H, d, *J* 8 Hz, 8-H) (Found: C, 63.55; H, 7.4; N, 4.4. $C_{17}H_{23}NO_3S$ requires C, 63.5; H, 7.2; N, 4.35%).

trans-3,4-*Dihydro*-2,2,6-*trimethyl*-4-(2-*oxopiperidin*-1-*yl*)-2H-1-*benzothiopyran*-3-*ol* **27**.—Iodine (0.126 g, 0.496 mmol) in dry acetonitrile (5 ml) was added dropwise to a stirred solution of triethyl phosphite (0.079 g, 0.476 mmol) and the benzothiopyran **26** (0.157 g, 0.489 mmol) in dry acetonitrile (10 ml) at room temperature until a faint brown colour persisted. The solution was stirred for 3.5 h after which the solvent was evaporated and the residue partitioned between dichloromethane and aqueous sodium thiosulphate. The aqueous phase was further extracted and the combined organic layers were dried and evaporated to give an oil which was chromatographed on alumina. Elution with chloroform and trituration of the resultant oil with ether gave the *title compound* **27** (0.035 g, 23%), as a white solid, m.p. 151–155 °C; ν_{max} 3 350 and 1 605 cm^{-1}; δ 1.37 (3 H, s, 2-Me), 1.41 (3 H, s, 2-Me), 1.68–1.90 (4 H, m, $CH_2CH_2CH_2CH_2$), 1.5–2.25 (1 H, br, OH), 2.27 (3 H, s, 6-Me), 2.56–2.62 (2 H, m, CH_2CO), 2.85–2.92 (1 H, m, CHN), 3.02–3.11 (1 H, m, CHN), 4.10 (1 H, d, *J* 9 Hz, 3-H), 5.92 (1 H, d, *J* 9 Hz, 4-H), 6.86 (1 H, s, 5-H), 6.95 (1 H, d, *J* 8 Hz, 7-H) and 7.02 (1 H, d, *J* 8 Hz, 8-H) (Found: M^+, 305.1451. $C_{17}H_{23}NO_2S$ requires *M*, 305.1450).

trans-3,4-*Dihydro*-2,2,6-*trimethyl*-4-(2-*oxopiperidin*-1-*yl*)-2H-1-*benzothiopyran*-3-*ol* 1,1-*Dioxide* **28**.—MCPBA (80% pure; 0.11 g, 0.508 mmol) in dichloromethane (10 ml) was added to a stirred solution of the benzothiopyran **26** (0.153 g, 0.477 mmol) in dichloromethane (10 ml) at room temperature and the solution stirred for 2.75 h. The reaction mixture was poured into 2M aqueous sodium hydroxide, the phases were separated and the aqueous phase was further extracted. The organic layers were combined, dried, filtered and evaporated to give a foam which was chromatographed. Elution with chloroform and trituration of the resultant oil with ether gave the *title compound* **28** (0.095 g, 59%), as a white solid, m.p. 225–228 °C; ν_{max} 3 220, 1 605, 1 295 and 1 075 cm^{-1}; δ 1.33 (3 H, s, 2-Me), 1.60 (3 H, s, 2-Me), 1.72–1.90 (4 H, m, $CH_2CH_2CH_2CH_2$), 2.41 (3 H, s, 6-Me), 2.59–2.64 (2 H, m, CH_2CO), 2.87–2.94 (1 H, m, CHN), 3.14–3.21 (1 H, m, CHN), 3.25–3.75 (1 H, br, OH), 4.47 (1 H, d, *J* 9 Hz, 3-H), 6.00 (1 H, d, *J* 9 Hz, 4-H), 7.01 (1 H, s, 5-H), 7.31 (1 H, dd, *J* 0.6, 8 Hz, 7-H) and 7.87 (1 H, d, *J* 8 Hz, 8-H) (Found: C, 60.55; H, 7.15; N, 4.0. $C_{17}H_{23}NO_4S$ requires C, 60.5; H, 6.85; N, 4.15%).

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