Synthesis and Analgesic Activity of Novel Heterocycles, [1]Benzothiopyrano[3,4-*b*]pyrrole Derivatives

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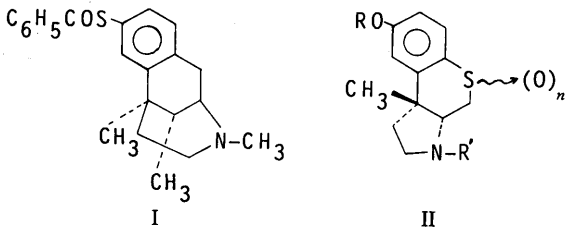
In order to develop analgesic compounds possessing a sulfur atom in the alicyclic ring, novel *cis*-fused heterocycles, [1]benzothiopyrano[3,4-*b*]pyrrole derivatives (II) were synthesized *via* a unique cyclization reaction starting from 4-(4-methoxyphenylthio)-2-butanone (1) or 6-methoxy-3,4-dihydro-2*H*-1-benzothiopyran-4-one (7).

The analgesic effects of benzothiopyranopyrroles (16, 18) were measured by means of the writhing test. The phenolic derivative 18 completely inhibited the appearance of writhing at the dose of 50 mg/kg, but the methoxy derivative 16 had no analgesic effect.

Keywords analgesic compound; heterocycle; [1]benzothiopyrano[3,4-*b*]pyrrole; stereoselective cyclization; analgesic activity; 3,4-dihydro-2*H*-1-benzothiopyran; vinyl sulfoxide; Michael-type addition; acetic acid-induced writhing test

In the previous paper,[1] we reported that 8-(benzoylthio)-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (I) (S-metazocine) had strong analgesic activity without appreciable side effects such as respiratory depression, gastrointestinal constipation, change of body temperature and change of blood glucose level in animal tests. Metazocine itself has such side effects. Therefore, we anticipated that the pharmacological difference of S-metazocine from metazocine might be based on the interaction between the opioid receptor and sulfur or oxygen atom. We have been interested in analgesic compounds containing a sulfur atom in the alicyclic ring.[2]

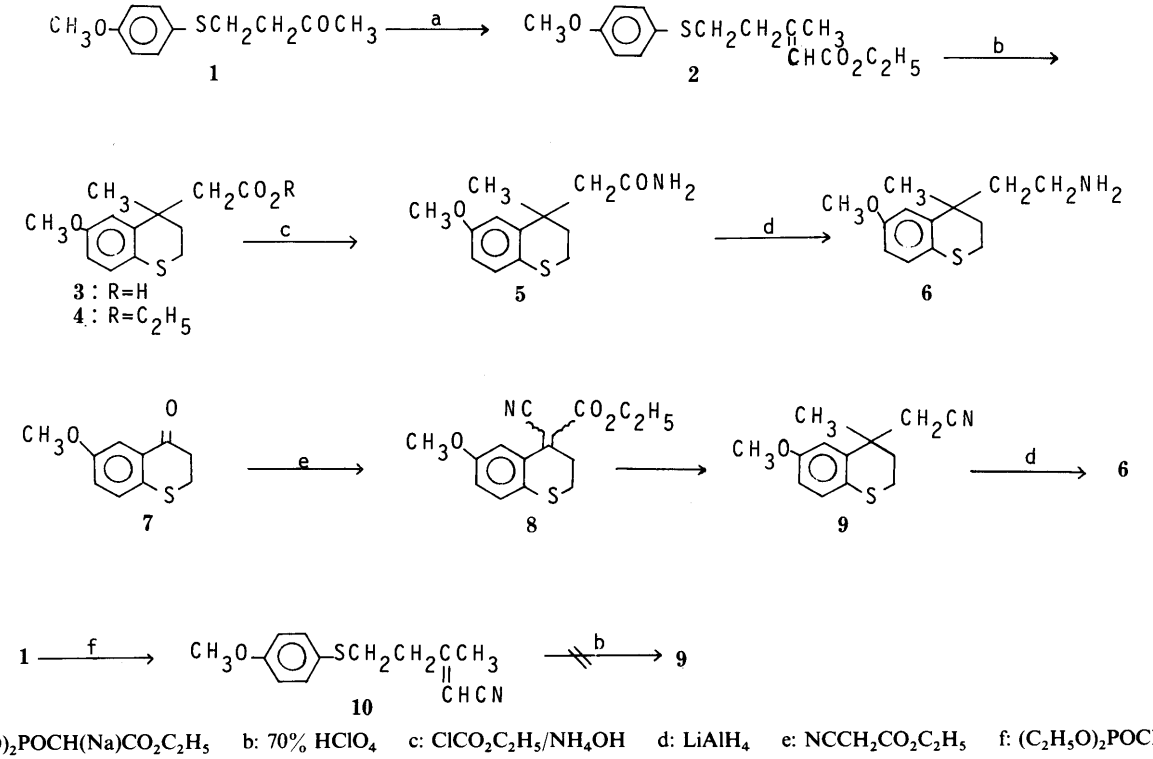


I II

Chart 1

In the course of our studies on sulfur-containing analgesics, we succeeded in synthesizing the title compounds (II) *via* a unique cyclization reaction[3] and found that some of them had a moderate analgesic activity. This paper presents full details of the synthesis, structure assignment and analgesic activity of [1]benzothiopyrano[3,4-*b*]pyrrole derivatives (II).

Chemistry The synthetic routes to the key intermediate



a: $(C_2H_5O)_2POCH(Na)CO_2C_2H_5$ b: 70% $HClO_4$ c: $ClCO_2C_2H_5/NH_4OH$ d: $LiAlH_4$ e: $NCCH_2CO_2C_2H_5$ f: $(C_2H_5O)_2POCH(Na)CN$

Chart 2

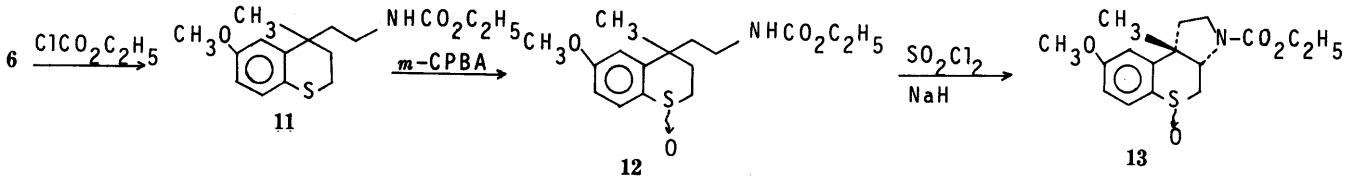


Chart 3

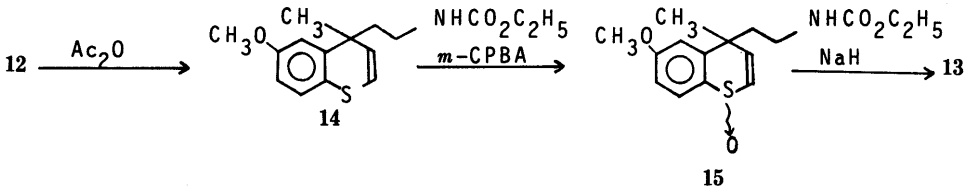


Chart 4

6 are shown in Chart 2. Preparation of 4-(2-aminoethyl)-6-methoxy-4-methyl-3,4-dihydro-2*H*-1-benzothiopyran (**6**) was accomplished by two methods: one started from 4-(4-methoxyphenylthio)-2-butanone (**1**) and the other from 6-methoxy-3,4-dihydro-2*H*-1-benzothiopyran-4-one (**7**).

Wittig–Horner reaction of the ketone **1**[4] with triethyl phosphonoacetate gave an olefinic ester **2** in 56% yield. Cyclization of the ester **2** with 70% perchloric acid gave a benzothiopyranylacetic acid **3** and its ester **4** in 20% and 6% yields, respectively. However, no cyclized products could be obtained by treatment with other strong acids such as concentrated sulfuric acid, trifluoromethanesulfonic acid and so on. Amidation of the carboxylic acid **3** by a mixed-anhydride method gave a benzothiopyranylacetamide **5** in 90% yield. Reduction of the amide **5** with lithium aluminum hydride gave an aminoethylbenzothiopyran **6** in 78% yield.

In the other route, condensation of the benzothiopyranone **7**[5] with ethyl cyanoacetate gave the α,β-unsaturated ester **8** in 35% yield. Conjugate addition[6] of methylmagnesium iodide to the olefinic ester **8** followed by hydrolysis and decarbonation gave 4-cyanomethyl-4-methyl-1-benzothiopyran (**9**) in 5% yield. Wittig–Horner reaction of the ketone **1** with diethyl cyanomethylphosphonate gave an olefinic nitrile **10** in 91% yield, but cyclization of the nitrile **10** with 70% perchloric acid did not proceed. Reduction of the cyanomethylbenzothiopyran **9** with lithium aluminum hydride gave the desired amine **6**. For the preparation of the amine **6**, the former route was superior to the latter one.

The synthesis of a novel [1]benzothiopyrano[3,4-*b*]pyrrole derivative from the aminoethylbenzothiopyran **6** is shown in Chart 3.

The aminoethylbenzothiopyran **6** was led to the urethane **11** in 94% yield by acylation with ethyl chlorocarbonate. Chlorination of the 2-position of **11** with *N*-chlorosuccinimide (NCS) or sulfuryl chloride did not proceed. Therefore, in order to activate the 2-position of **11** it was converted to the corresponding sulfoxide **12** by treatment with *m*-chloroperbenzoic acid (*m*-CPBA). Chlorination of the sulfoxide **12** with sulfuryl chloride smoothly proceeded[7] to give the chloride, which was treated immediately with an equimolar amount of sodium hydride to give the novel cyclized product **13** in 52% yield.

Generally, the reaction of an α-halosulfoxide with nucleophiles proceeds *via* an S_N2 mechanism.[8] However, the intramolecular nucleophilic reaction of the α-halosulfoxide **12** proceeded by successive elimination and addition to afford the cyclized product **13**. This mechanism is supported by the experimental fact that the yield of the benzothiopyranopyrrole **13** was increased from 52% to 83% by the use of 2 eq of sodium hydride and that compound **13** could also be obtained from a vinyl sulfoxide, **15**. The alternative synthetic route from the vinyl sulfoxide **15** is shown in Chart 4. Treatment of the sulfoxide **12** with acetic anhydride gave the vinyl sulfide **14** in 36% yield. Oxidation of the sulfide **14** with *m*-CPBA followed by treatment with sodium hydride gave the benzothiopyranopyrrole **13** in 80% yield *via* the intramolecular Michael-type addition of amide to the vinyl sulfoxide moiety of **15**.[9]

The benzothiopyranopyrrole **13** was a diastereomeric mixture and the diastereoisomers could be separated by preparative thin layer chromatography (TLC). Reduction of the diastereomeric mixture of the benzothiopyranopyrrole **13** with lithium aluminum hydride gave a single amine **16** in high yield. Furthermore, oxidation of the diastereomeric mixture of **13** with *m*-CPBA gave a sulfone **17** alone.

The ring-junction of the newly-formed ring and the thiopyran ring of **13** was determined to be *cis* by the nuclear Overhauser effect (NOE) method and X-ray analysis. The NOE was observed between C_{9b}-CH_3 and C_{3a}-H in the

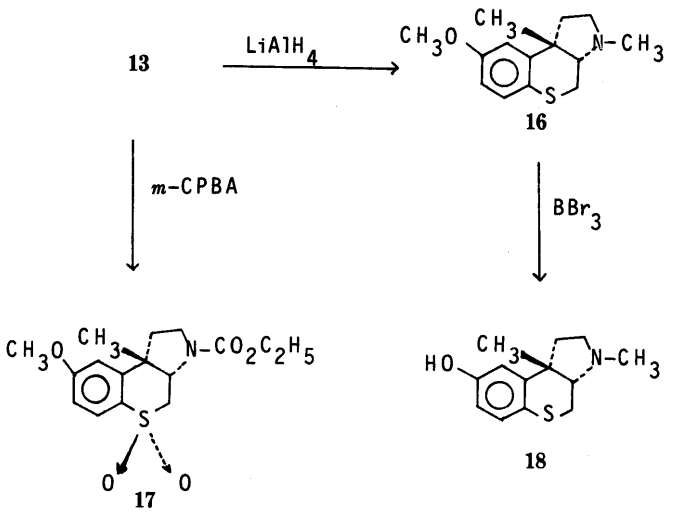


Chart 5

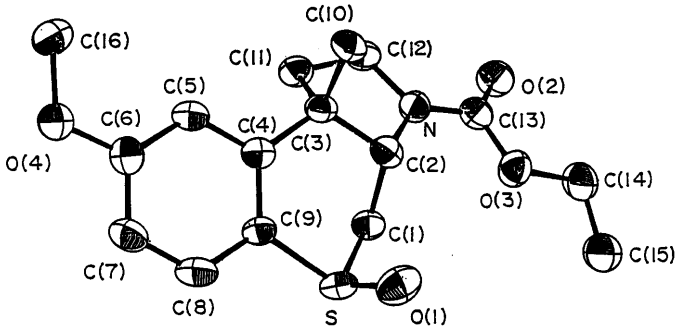


Fig. 1. X-Ray Structure of (**13b**)

TABLE I. Analgesic Activity of Benzothiopyranopyrroles **16** and **18**

Compounds	Dose (mg/kg, s.c.)	Number of mice	Number of writhings (mean ± S.E.)
Control	—	8	15±4
16	50	8	11±2
Codeine phosphate	10	8	5±2
Control	—	8	18±4
18	10	8	14±1
	50	8	0±0
Codeine phosphate	10	8	9±3

400 MHz proton nuclear magnetic resonance (^{1}H-NMR) spectra. The structure of the more polar diastereoisomer of the benzothiopyranopyrrole **13b** was confirmed by X-ray crystallography to be as shown in Fig. 1.

The methoxybenzothiopyranopyrrole **16** was demethylated with boron tribromide to give the phenol derivative **18** in 92% yield.

Pharmacology The analgesic effects of the benzothiopyranopyrroles **16** and **18** were investigated in comparison with that of codeine phosphate. Analgesic activity was assayed by the acetic acid-induced writhing method according to Zetler.[10] Writhing was elicited by intraperitoneal injection of 0.7% (v/v) acetic acid into ddY male mice weighing 26—31 g. An aqueous solution of a benzothiopyranopyrrole was administered subcutaneously 10 min after injection of acetic acid and the number of writhings was counted for 30 min starting at 5 min after acetic acid injection. Data were expressed as the ratio (%) with respect to the control value (Table I).

The benzothiopyranopyrrole **16** had no effect, but **18** completely inhibited the appearance of writhing at the dose of 50 mg/kg. Codeine phosphate showed 67% suppression of the appearance of writhing at the dose of 10 mg/kg. It was estimated that the benzothiopyranopyrrole **18** had analgesic activity, which was less potent than that of codeine phosphate. It is clear that the presence of the phenolic hydroxyl group in **18** enhances the analgesic activity, compared with **16**.[11]

Experimental

Melting points are uncorrected. Infrared (IR), ^{1}H-NMR and mass spectra (MS) were taken on a JASCO IRA-1 or IR-810 spectrometer, a Hitachi R-20B or JEOL PMX-60 nuclear magnetic resonance instrument and a JEOL JMS-DX300 or D300 spectrometer, respectively. X-Ray analysis was performed on a Syntex R3 instrument. Elemental analyses were performed on a Yanaco CHN Corder-MT3. TLC was performed on silica gel (Merck Art. 5715 or 5717). Column chromatography was performed on silica gel (Fuji-Davison silica gel BW-820MH or Wakogel C-200). All reactions were carried out under an argon atmosphere. Sodium sulfate was used as a drying agent unless otherwise mentioned.

4-(4-Methoxyphenylthio)-2-methyl-1-butenecarbonitrile (10) Diethyl cyanomethylphosphonate (3.55 g, 20 mmol) was added dropwise to a stirred suspension of 60% NaH (800 mg, 20 mmol) in tetrahydrofuran (THF) (40 ml) at 0—5 °C. When the evolution of hydrogen had ceased, 4-(4-methoxyphenylthio)-2-butanone (**1**) (4.20 g, 20 mmol) was added dropwise to the reaction mixture at 0—5 °C, and stirring was continued for 3 h. The reaction mixture was poured into ice-water and extracted with Et_2O. The Et_2O extract was washed with water, dried, and concentrated to give 4.25 g (91.2%) of **10** as a colorless oil. IR (film): 2210 (CN), 1630 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.88 (3H, d, J=1.5 Hz, C_2-CH_3), 2.45—3.15 (4H, m, C_3-H_2 and C_4-H_2), 3.75 (3H, s, OCH_3), 5.18 (1H, m, C_1-H), 7.13 (4H, m, ArH). MS m/z: 233 (M^+), 153 (base). High-resolution MS m/z: 233.0874. Found: 233.0874.

Ethyl 5-(4-Methoxyphenylthio)-3-methyl-2-pentenoate (2) In a similar manner to the synthesis of **10**, **1** (4.20 g, 20 mmol) afforded **2** (3.12 g, 55.7%) except that **2** was purified on a silica gel column (Et_2O:*n*-hexane=1:10 as an eluent) and diethylphosphonoacetate (4.48 g, 20 mmol) was used instead of diethylcyanomethylphosphonate. IR (film): 1720 (C=O), 1645 (C=C) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.24 and 1.25 (3H, t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 1.88 and 2.11 (3H, d, J=1.5 Hz, CH_3), 2.20—2.60 (2H, m, C_4-H_2), 2.70—3.10 (2H, m, C_5-H_2), 3.76 (3H, s, OCH_3), 4.11 and 4.14 (2H, q, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$), 5.60—5.80 (1H, m, C_2-H), 7.10 (4H, A_2B_2, ArH). MS m/z: 280 (M^+), 141 (base). High-resolution MS m/z: 280.1130. Found: 280.1113.

6-Methoxy-4-methyl-3,4-dihydro-2*H*-1-benzothiopyran-4-acetic Acid (3) and Its Ethyl Ester (4) A mixture of **2** (500 mg, 1.78 mmol) and 70% $HClO_4$ (10 ml) was stirred at room temperature for 2 h. The reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with water, dried, and concentrated. The residue was separated by TLC (Et_2O:*n*-hexane=1:2) to give 92 mg (20.4%) of **3** as colorless prisms and 32 mg (6.40%) of **4** as a colorless oil.

3: mp 77.5—78.5 °C. *Anal.* Calcd for $C_{13}H_{16}O_3S$: C, 61.88; H, 6.39. Found: C, 61.95; H, 6.45. IR (KBr): 1715 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, s, CH_3), 1.6—2.6 (2H, m, C_3-H_2), 2.70 (2H, ABq, J=14.3 Hz, $\Delta\nu$=16.4 Hz, $C\underline{H}_2CO_2H$), 2.90—3.25 (2H, m, C_2-H_2), 3.74 (3H, s, OCH_3), 6.64 (1H, dd, J=9.0, 3.0 Hz, C_7-H), 6.91 (1H, d, J=3.0 Hz, C_5-H), 7.03 (1H, d, J=9.0 Hz, C_8-H), 9.96 (1H, br, CO_2H). MS m/z: 252 (M^+), 193 (base).

4: IR (film): 1735 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 1.46 (3H, s, C_4-CH_3), 1.85—3.25 (6H, m, C_2-H_2, C_3-H_2 and $C\underline{H}_2CO_2CH_2CH_3$), 3.75 (3H, s, OCH_3), 4.08 (2H, q, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$), 6.67 (1H, dd, J=8.3, 3.0 Hz, C_7-H), 6.92 (1H, d, J=3.0 Hz, C_5-H), 7.04 (1H, d, J=8.3 Hz, C_8-H). MS m/z: 280 (M^+, base). High-resolution MS m/z: 280.1133. Found: 280.1138.

6-Methoxy-4-methyl-3,4-dihydro-2*H*-1-benzothiopyran-4-ylacetamide (5) Ethyl chlorocarbonate (80 mg, 0.84 mmol) was added dropwise to a stirred solution of Et_3N (120 mg, 0.86 mmol) and **3** (200 mg, 0.79 mmol) in CH_2Cl_2 (5 ml) at −20 °C and stirring was continued for 5 min. Ammonia water was added to the reaction mixture and stirring was continued for 5 min. The CH_2Cl_2 layer was separated, dried, and concentrated. The residue was chromatographed on a silica gel column (Et_2O:*n*-hexane=1:1 and AcOEt) to give 180 mg (90.4%) of **5** as a colorless oil. IR (film): 3325, 3200 (NH), 1660 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.46 (3H, s, C_4-CH_3), 1.6—2.55 (2H, m, C_3-H_2), 2.55 (2H, ABq, J=14.8 Hz, $\Delta\nu$=7.3 Hz, $C\underline{H}_2CONH_2$), 2.85—3.25 (2H, br, NH_2), 3.74 (3H, s, OCH_3), 6.65 (1H, dd, J=9.0, 3.0 Hz, C_7-H), 6.93 (1H, d, J=3.0 Hz, C_5-H), 7.09 (1H, d, J=9.0 Hz, C_8-H). MS m/z: 251 (M^+, base). High-resolution MS m/z: 251.0978. Found: 251.0958.

Ethyl (*E*)- and (*Z*)-α-Cyano-6-methoxy-3,4-dihydro-2*H*-1-benzothiopyran-4-ylidene-4-acetate (8) A mixture of **7** (1.00 g, 5.15 mmol), ethyl cyanoacetate (0.56 ml, 5.23 mmol), AcOH (0.26 ml, 4.54 mmol), benzylamine (60.0 μl, 0.55 mmol) and benzene (20 ml) was refluxed with a Dean-Stark apparatus for 24 h. The reaction mixture was washed with 10% HCl, 5% $NaHCO_3$, and water successively, dried, and concentrated. The residue was chromatographed on a silica gel column (AcOEt:*n*-hexane=1:10) to give 519 mg (34.8%) of **8** as a colorless oil. IR (film): 2220 (CN), 1730 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 and 1.38 (3H, t, J=7.0 Hz, $CO_2CH_2C\underline{H}_3$), 2.75—3.75 (4H, m, C_2-H_2 and C_3-H_2), 3.80 and 3.83 (3H, s, OCH_3), 4.26 and 4.36 (2H, q, J=7.0 Hz, $CO_2C\underline{H}_2CH_3$), 6.67—7.25 (2H, m, C_7-H and C_8-H), 7.46 and 7.68 (1H, d, J=3.0 Hz, C_6-H). MS m/z: 298 (M^+, base). High-resolution MS m/z: 289.0772. Found: 289.0760.

4-(2-Aminoethyl)-6-methoxy-4-methyl-3,4-dihydro-2*H*-1-benzothio-

pyran (6) Lithium aluminum hydride (200 mg, 5.27 mmol) was added portionwise to a stirred solution of **5** (485 mg, 1.93 mmol) in Et_2O (20 ml) and THF (2 ml) at 0—5 °C. After being refluxed for 4 h, the reaction mixture was treated with 5% NaOH and filtered. The filtrate was evaporated and oxalic acid (243 mg, 1.93 mmol) was added to the residue. The mixture was crystallized from acetone to give 490 mg (77.6%) of **6** oxalate as colorless prisms. Free base (**6**) IR (film): 3320 (NH_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (2H, s, NH_2), 1.41 (3H, s, C_4-CH_3), 1.55—2.40 (4H, m, C_3-H_2 and C_4-CH_2CH_2N), 2.50—3.15 (4H, m, C_2-H_2 and C_4-CH_2CH_2N), 3.76 (3H, s, OCH_3), 6.66 (1H, dd, J=9.0, 3.0 Hz, C_7-H), 6.89 (1H, d, J=3.0 Hz, C_5-H), 7.02 (1H, d, J=9.0 Hz, C_8-H). MS m/z: 237 (M^+).

Oxalate: mp 211—214 °C (dec.). *Anal.* Calcd for $C_{13}H_{19}NOS \cdot C_2H_2O_4$: C, 55.03; H, 6.47; N, 4.28. Found: C, 54,98; H, 6.53; N, 4.22. IR (KBr): 3440 (NH^+_3) cm^{-1}.

4-Cyanomethyl-6-methoxy-4-methyl-3,4-dihydro-2*H*-1-benzothiopyran (9) Cu_2I_2 (7 mg, 37 mmol) and **8** (350 mg, 1.21 mmol) were added to a stirred solution of MeMgI (2 mmol) in Et_2O (10 ml) at 0—5 °C. The reaction mixture was stirred for 2 h at room temperature and refluxed for 2 h. After being treated with dilute HCl, the Et_2O layer was separated and dried over $MgSO_4$. After filtration, the residue was chromatographed on a silica gel column (Et_2O : *n*-hexane = 1 : 8) to give the crude 1,4-adduct.

This 1,4-adduct was treated with KOH (24 mg) and $HOCH_2CH_2OH$ (4 ml). The mixture was stirred for 1 h at 190 °C. The reaction mixture was treated with H_2O and Et_2O and the Et_2O layer was separated and dried over $MgSO_4$. After filtration, the filtrate was evaporated and the residue was submitted to preparative TLC (Et_2O : *n*-hexane = 1 : 2) to give 14 mg (4.96%) of **9** as colorless prisms. mp 51.5—54.0 °C. *Anal.* Calcd for $C_{13}H_{15}NOS$: C, 66.92; H, 6.48; N, 6.00. Found: C, 66.62; H, 6.54; N, 5.94. IR (KBr): 2240 (CN) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.53 (3H, s, C_4-CH_3), 1.95—2.30 (2H, m, C_3-H_2), 2.67 (2H, s, C_4-CH_2CN), 2.85—3.20 (2H, m, C_2-H_2), 3.76 (3H, s, OCH_3), 6.69 (1H, dd, J=9.0, 3.0 Hz, C_7-H), 6.87 (1H, d, J=3.0 Hz, C_5-H), 7.02 (1H, d, J=9.0 Hz, C_8-H). MS m/z: 233 (M^+), 193 (base).

Ethyl 3,4-Dihydro-6-methoxy-4-methyl-2*H*-1-benzothiopyran-4-ethanecarbamate (11) A mixture of **6** (130 mg, 0.55 mmol), $NaHCO_3$ (51 mg, 0.6 mmol), ethyl chlorocarbonate (55 μl, 0.58 mmol) and benzene (5 ml) was refluxed for 10 h. The reaction mixture was washed with H_2O and the benzene layer was dried over $MgSO_4$. After filtration, the filtrate was concentrated to give 160 mg (94.4%) of **11** as colorless prisms. mp 117.0—119.5 °C. *Anal.* Calcd for $C_{16}H_{23}NO_3S$: C, 62.11; H, 7.49; N, 4.53. Found: C, 61.93; H, 7.42; N, 4.53. IR (KBr): 3310 (NH), 1675 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 1.33 (3H, s, C_4-CH_3), 1.60—2.20 (4H, m, C_3-H_2 and C_4-CH_2CH_2N), 2.80—3.35 (4H, m, C_2-H_2 and C_4-CH_2CH_2N), 3.77 (3H, s, OCH_3), 4.08 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 4.35—4.75 (1H, br, NH), 6.63 (1H, dd, J=9.0, 3.0 Hz, C_7-H), 6.88 (1H, d, J=3.0 Hz, C_5-H), 7.01 (1H, d, J=9.0 Hz, C_8-H). MS m/z: 309 (M^+), 193 (base).

4-[2-(Ethoxycarbonylamino)ethyl]-6-methoxy-4-methyl-3,4-dihydro-2*H*-1-benzothiopyran 1-Oxide (12) *m*-CPBA (800 mg, 3.25 mmol) was added portionwise to a stirred solution of **11** (1.00 g, 3.23 mmol) in CH_2Cl_2 (20 ml) at 0—5 °C. After being stirred for 30 min, the reaction mixture was washed with 5% $NaHCO_3$, dried, and concentrated. The residue was chromatographed on a silica gel column (AcOEt : acetone = 2 : 1) to give 1.00 g (95.1%) of **12** as colorless crystals, mp 110 °C. *Anal.* Calcd for $C_{16}H_{23}NO_4S$: C, 59.06; H. 7.12; N, 4.30. Found: C, 59.04; H, 7.22; N, 4.27. IR (KBr): 3310 (NH), 1675 (C=O), 1055 (SO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15 and 1.21 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 1.33 and 1.44 (3H, s, C_4-CH_3), 1.55—2.55 (4H, m, C_3-H_2 and C_4-CH_2CH_2N), 2.75—3.80 (4H, m, C_2-H_2 and C_4-CH_2CH_2N), 3.86 (3H, s, OCH_3), 4.01 and 4.08 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 4.70—5.50 (1H, br, NH), 6.70—7.10 (2H, m, C_5-H and C_7-H), 7.60 and 7.68 (1H, d, J=7.5 Hz, C_8-H). MS m/z: 309 (M^+), 193 (base).

4-[2-(Ethoxycarbonylamino)ethyl]-6-methoxy-4-methyl-4*H*-1-benzothiopyran (14) A mixture of **12** (408 mg, 1.25 mmol) and Ac_2O (30 ml) was refluxed for 12 h. The reaction mixture was concentrated and the residue was chromatographed on a silica gel column (Et_2O : *n*-hexane = 1 : 2) to give 138 mg (35.8%) of **14** as a colorless oil. IR (film): 3315 (NH), 1710 (C=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 1.44 (3H, s, C_4-CH_3), 1.50—2.25 (2H, m, C_4-CH_2CH_2N), 2.85—3.50 (2H, m, C_4-CH_2CH_2N), 3.78 (3H, s, OCH_3), 4.06 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 5.57 (1H, d, J=9.8 Hz, C_3-H), 6.08 (1H, d, J=9.8 Hz, C_2-H), 6.74 (1H, dd, J=9.0, 3.0 Hz, C_7-H), 6.93 (1H, d, J=3.0 Hz, C_5-H), 7.10 (1H, d, J=9.0 Hz, C_8-H). MS m/z: 307 (M^+), 191 (base). High-resolution MS m/z: 307.1241. Found: 307.1217.

4-[2-(Ethoxycarbonylamino)ethyl]-6-methoxy-4-methyl-4*H*-1-benzothiopyran 1-Oxide (15) *m*-CPBA (100 mg, 0.41 mmol) was added portionwise to a stirred solution of **14** (130 mg, 0.42 mmol) in CH_2Cl_2 (10 ml) at 0—5 °C. After being stirred for 5 min, the reaction mixture was washed with 5% $NaHCO_3$, dried, and concentrated to give 130 mg (95.1%) of **15** as a colorless oil. IR (film): 3280 (NH), 1710 (C=O), 1030 (SO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.14 and 1.18 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 1.37 and 1.60 (3H, s, C_4-CH_3), 1.50—3.25 (4H, m, C_4-CH_2CH_2N), 3.87 (3H, s, OCH_3), 4.05 and 4.14 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 4.95—5.40 and 5.40—6.10 (1H, br, NH), 6.34 and 6.44 (1H, d, J=10.5 Hz, C_3-H), 6.75—7.30 (3H, m, C_2-H, C_5-H and C_7-H), 7.65—8.00 (1H, m, C_8-H). MS m/z: 323 (M^+), 191 (base). High-resolution MS m/z: 323.1190. Found: 323.1183.

8-Methoxy-3,9b-dimethyl-1,2,3,3a,4,9b-hexahydro[1]benzothiopyrano[3,4-*b*]pyrrole (16) Lithium aluminum hydride (220 mg, 5.80 mmol) was added portionwise to a stirred solution of **13** (420 mg, 1.30 mmol) in Et_2O (40 ml) at 0—5 °C. After being refluxed for 3 h, the reaction mixture was treated with 5% NaOH, filtered, and concentrated. The residue was chromatographed on a silica gel column (Et_2O : *n*-hexane = 1 : 2) to give 306 mg (92.6%) of **16** as a colorless oil. IR (film): 2775 (N-CH_3) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s, C_{9b}-CH_3), 1.95—3.25 (7H, m, C_1-H_2, C_2-H_2, C_{3a}-H and C_4-H_2), 2.45 (3H, s, NCH_3), 3.76 (3H, s, OCH_3), 6.65 (1H, dd, J=9.0, 3.0 Hz, C_7-H), 6.86 (1H, d, J=3.0 Hz, C_9-H), 7.18 (1H, d, J=9.0 Hz, C_6-H). MS m/z: 249 (M^+, base). High-resolution MS m/z: 249.1188. Found: 249.1191.

3,9b-Dimethyl-1,2,3,3a,4,9b-hexahydro[1]benzothiopyrano[3,4-*b*]pyrrole-8-ol (18) BBr_3 (70.0 μl, 0.57 mmol) was added dropwise to a stirred solution of **16** (88 mg, 0.35 mmol) in CH_2Cl_2 (5 ml) at −30—−20 °C. After being stirred for 1.5 h, the mixture was removed from the cooling bath and stirring was continued till the temperature reached 25 °C. The reaction mixture was washed with 5% $NaHCO_3$, dried, and concentrated to give 76 mg (91.5%) of **18** as colorless prisms. mp 192—194.5 °C. *Anal.* Calcd for $C_{13}H_{17}NOS$: C, 66.35; H, 7.28; N, 5.95. Found: C, 66.07; H, 7.39; N, 5.88. ^{1}H-NMR ($CDCl_3$ + CD_3OD) δ: 1.32 (3H, s, C_{9b}-CH_3), 1.90—3.30 (7H, m, C_1-H_2, C_2-H_2, C_{3a}-H and C_4-H_2), 2.49 (3H, s, NCH_3), 6.59 (1H, dd, J=9.0, 3.0 Hz, C_7-H), 6.82 (1H, d, J=3.0 Hz, C_9-H), 7.09 (1H, d, J=9.0 Hz, C_6-H). MS m/z: 235 (M^+, base).

3-Ethoxycarbonyl-8-methoxy-9b-methyl-1,2,3,3a,4,9b-hexahydro[1]benzothiopyrano[3,4-*b*]pyrrole 5,5-Dioxide (17) *m*-CPBA (150 mg, 0.62 mmol) was added portionwise to a stirred solution of **13** (200 mg, 0.62 mmol) in CH_2Cl_2 (10 ml) at 0—5 °C. The cooling bath was removed, and stirring was continued till the temperature reached 25 °C. The reaction mixture was washed with 5% $NaHCO_3$, dried, and concentrated. The residue was crystallized from Et_2O to give 170 mg (81.0%) of **17** as colorless prisms, mp 200.5—202.5 °C. *Anal.* Calcd for $C_{16}H_{21}NO_5S$: C, 56.62; H, 6.24; N, 4.13. Found: C, 56.49; H, 6.32; N, 4.14. IR (KBr): 1700 (C=O), 1295 and 1120 (SO_2) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 1.54 (3H, s, C_{9b}-CH_3), 1.90—2.30 (2H, m, C_1-H_2), 3.00 (1H, dd, J=13, 12 Hz, C_{3a}-H), 3.40—4.75 (4H, m, C_2-H_2 and C_4-H_2), 3.88 (3H, s, OCH_3), 4.25 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 6.80—7.10 (2H, m, C_7- and C_9-H), 7.93 (1H, dd, J=13.0, 1.0 Hz, C_6-H). MS m/z: 339 (M^+), 275 (base).

3-Ethoxycarbonyl-8-methoxy-9b-methyl-1,2,3,3a,4,9b-hexahydro[1]benzothiopyrano[3,4-*b*]pyrrole 5-Oxide (13) From **12**: SO_2Cl_2 (0.12 ml, 1.48 mmol) was added dropwise to a stirred solution of **12** (435 mg, 1.31 mmol) in CH_2Cl_2 (20 ml) at −15—−10 °C. After being stirred for 15 min, the reaction mixture was concentrated. To a stirred solution of the residue in THF (20 ml), 60% NaH (56 mg, 1.40 mmol) was added portionwise at 0—−5 °C. After being refluxed for 40 h, the reaction mixture was concentrated and the residue was treated with water, then extracted with CH_2Cl_2. The extract was dried and concentrated. The residue was chromatograhed on a silica gel column (AcOEt : Et_2O = 1 : 10—1 : 4) to give 151 mg (34.9%) of the less polar isomer of **13** as a colorless oil and 73 mg (16.9%) of the more polar isomer of **13** as colorless prisms.

When this reaction was carried out with a 2-fold molar excess of 60% NaH (112 mg, 2.80 mmol), 190 mg (43.8%) of the former and 169 mg (39.1%) of the latter were obtained.

From **15**: A mixture of **15** (110 mg, 0.34 mmol), 60% NaH (20 mg, 0.5 mmol) and THF (5 ml) was refluxed for 1.5 h. After the reaction mixture was concentrated, the residue was treated with water and extracted with CH_2Cl_2, dried and concentrated. The residue was chromatographed on a silica gel column (AcOEt : Et_2O = 1 : 10—1 : 4) to give 58.7 mg (53.4%) of the less polar isomer of **13** and 29.3 mg (26.6%) of the more polar isomer of **13**.

Less Polar Isomer **13a** (3a*RS*, 5*RS*, 9b*RS*): IR (film): 1695 (C=O), 1030

TABLE II. Atomic Coordinates ($\times 10^4$) and Thermal Parameter for Non-hydrogen Atoms of **13b** with Their e.s.d.'s in Parentheses

Atom	x	y	z	B_{eq} [a]
S	545 (2)	950 (3)	2010 (1)	3.0
N	3608 (5)	4218 (7)	4124 (3)	3.0
O(1)	−810 (4)	2228 (7)	1976 (3)	4.4
O(2)	4409 (4)	4778 (7)	5878 (3)	4.4
O(3)	1929 (4)	3759 (7)	5088 (3)	3.8
O(4)	3482 (5)	3040 (6)	−1333 (4)	4.1
C(1)	2096 (6)	1560 (8)	3158 (4)	2.8
C(2)	2427 (6)	3625 (9)	3159 (4)	2.9
C(3)	3111 (6)	4291 (8)	2275 (4)	2.6
C(4)	2603 (6)	3198 (8)	1257 (4)	2.6
C(5)	3243 (6)	3656 (8)	424 (4)	2.9
C(6)	2868 (6)	2665 (9)	−508 (4)	3.1
C(7)	1850 (6)	1143 (10)	−656 (4)	3.4
C(8)	1202 (6)	695 (9)	148 (4)	3.3
C(9)	1553 (6)	1694 (8)	1082 (4)	2.6
C(10)	2725 (7)	6379 (8)	2054 (5)	3.3
C(11)	4919 (6)	4074 (9)	2807 (5)	3.2
C(12)	5134 (6)	4593 (9)	3938 (5)	3.5
C(13)	3432 (6)	4305 (9)	5094 (5)	3.3
C(14)	1585 (8)	3756 (11)	6103 (5)	4.7
C(15)	199 (11)	2610 (14)	6017 (6)	7.5
C(16)	4354 (7)	4725 (10)	−1292 (5)	4.1

a) Equivalent isotropic thermal parameters were calculated from the refined anisotropic thermal parameters.

(SO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.32 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 1.40 (3H, s, C_{9b}-CH_3), 2.10-2.40 (2H, m, C_1-H_2), 2.70 (1H, dd, J=10.8, 9.8 Hz, C_{3a}-H), 3.40—4.40 (4H, m, C_2-H_2 and C_4-H_2), 3.85 (3H, s, OCH_3), 4.21 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 6.80 (1H, d, J=3.0 Hz, C_9-H), 6.90 (1H, dd, J=8.7, 3.0 Hz, C_7-H), 7.71 (1H, d, J=8.7 Hz, C_6-H). MS m/z: 323 (M^+), 191 (base). High-resolution MS m/z: 323.1191. Found: 323.1164.

More Polar Isomer **13b** (3a*RS*, 5*SR*, 9b*RS*): mp 167.5 °C. *Anal.* Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33. Found: C, 59.22; H, 6.57; N, 4.26. IR (KBr): 1695 (C=O), 1025 (SO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.31 (3H, t, J=7.0 Hz, $CO_2CH_2CH_3$), 1.55 (3H, s, C_{9b}-CH_3), 1.75-2.25 (2H, m, C_1-H_2), 2.40—2.95 (1H, m, C_{3a}-H), 3.35—3.75 (3H, m, C_2-H_2 and C_4-H), 3.85 (3H, s, OCH_3), 4.21 (2H, q, J=7.0 Hz, $CO_2CH_2CH_3$), 4.45—4.85 (1H, m, C_4-H), 6.75—7.00 (2H, m, C_7-H and C_9-H), 7.55—7.75 (1H, m, C_6-H). MS m/z: 323 (M^+), 191 (base).

Determination of the Crystal Structure of 13b Crystal data: $C_{16}H_{21}NO_4S$, monoclinic, space group $P2_1$; a=8.831 (4), b=7.210 (3), c=13.207 (6) Å; β=105.77 (4)°, D_x=1.33 g/cm^3, z=2 and μ (MoK_α)=2.2 cm^{-1}. The cell dimensions and intensities were measured on a Syntex R3 four-circle diffractometer with graphite-monochromated Mo K_α radiation in the ω-scan mode within 2θ less than 45°. A total of 1167 independent reflections were collected, among which 1112 reflections ($I \geq 1.96\sigma(I)$) were stored as observed. The structure was solved by the heavy-atom method. The molecular structure is illustrated in Fig. 1.

A block-diagonal least-squares method was applied for the refinement. Thermal parameters were refined anisotropically for all non-hydrogen atoms and isotropically for hydrogen atoms. The final R-value was 0.040. The final atomic coordinates for non-hydrogen atoms and the bond distances and the bond angles are given in Tables II and III, respectively.

TABLE III. Bond Distances (Å) and Angles (°) of **13b** with Their e.s.d.'s in Parentheses

S–O(1)	1.501 (5)	S–C(1)	1.800 (6)
S–C(9)	1.781 (5)	N–C(2)	1.473 (7)
O(2)–C(13)	1.203 (7)	O(3)–C(13)	1.382 (7)
O(3)–C(14)	1.453 (7)	O(4)–C(6)	1.368 (7)
O(4)–C(16)	1.432 (8)	C(1)–C(2)	1.517 (8)
C(2)–C(3)	1.530 (8)	C(3)–C(4)	1.518 (8)
C(3)–C(10)	1.554 (8)	C(3)–C(11)	1.567 (7)
C(4)–C(5)	1.406 (8)	C(4)–C(9)	1.404 (8)
C(5)–C(6)	1.383 (8)	C(6)–C(7)	1.399 (9)
C(7)–C(8)	1.374 (8)	C(8)–C(9)	1.389 (8)
C(11)–C(12)	1.501 (8)	C(14)–C(15)	1.456 (12)
N–C(12)	1.459 (7)	N–C(13)	1.334 (7)
O(1)–S–C(1)	107.1 (3)	O(1)–S–C(9)	109.8 (3)
C(1)–S–C(9)	95.6 (3)	C(2)–N–C(12)	112.2 (4)
C(2)–N–C(13)	127.2 (5)	C(12)–N–C(13)	120.4 (5)
C(13)–O(3)–C(14)	115.8 (5)	C(6)–O(4)–C(16)	117.6 (5)
S–C(1)–C(2)	110.0 (4)	N–C(2)–C(1)	112.1 (5)
N–C(2)–C(3)	103.6 (4)	C(1)–C(2)–C(3)	115.0 (5)
C(2)–C(3)–C(4)	115.5 (5)	C(2)–C(3)–C(10)	109.6 (5)
C(2)–C(3)–C(11)	101.1 (4)	C(4)–C(3)–C(10)	109.9 (5)
C(4)–C(3)–C(11)	111.4 (5)	C(10)–C(3)–C(11)	109.0 (5)
C(3)–C(4)–C(5)	119.1 (5)	C(3)–C(4)–C(9)	124.7 (5)
C(5)–C(4)–C(9)	116.2 (5)	C(4)–C(5)–C(6)	121.7 (5)
O(4)–C(6)–C(5)	123.7 (5)	O(4)–C(6)–C(7)	115.0 (5)
C(5)–C(6)–C(7)	121.2 (5)	C(6)–C(7)–C(8)	117.6 (5)
C(7)–C(8)–C(9)	121.7 (5)	S–C(9)–C(4)	123.4 (4)
S–C(9)–C(8)	115.0 (4)	C(4)–C(9)–C(8)	121.6 (5)
C(3)–C(11)–C(12)	105.0 (5)	N–C(12)–C(11)	104.4 (5)
N–C(13)–O(2)	126.6 (6)	N–C(13)–O(3)	110.1 (5)
O(2)–C(13)–O(3)	123.3 (5)	O(3)–C(14)–C(15)	108.1 (6)

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