

Chart 3

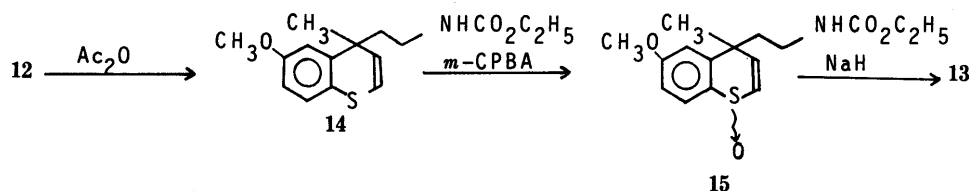


Chart 4

6 are shown in Chart 2. Preparation of 4-(2-aminoethyl)-6-methoxy-4-methyl-3,4-dihydro-2H-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-2H-1-benzothiopyran-4-one (7).

Wittig-Horner reaction of the ketone 1⁴⁾ 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 7⁵⁾ with ethyl cyanoacetate gave the α,β -unsaturated ester 8 in 35% yield. Conjugate addition⁶⁾ of methylmagnesium iodide to the olefinic ester 8 followed by hydrolysis and decarboxylation 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 chloroformate. Chlorination of the 2-position of 11 with *N*-chlorosuccinimide (NCS) or sulfonyl 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 sulfonyl chloride smoothly proceeded⁷⁾ 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}-CH₃ and C_{3a}-H in the

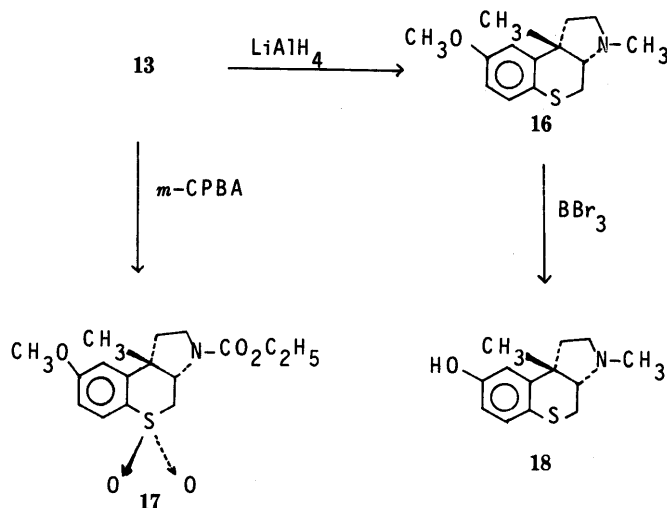


Chart 5

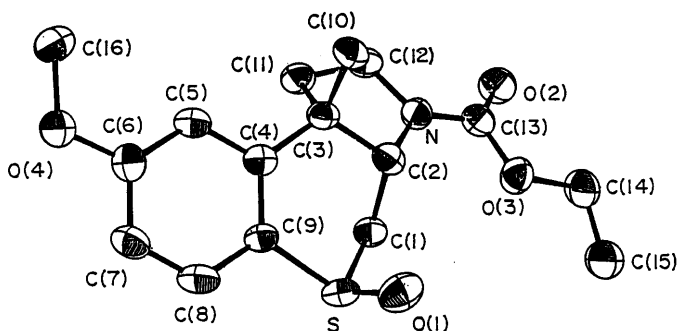


Fig. 1. X-Ray Structure of (13b)

TABLE I. Analgesic Activity of Benzothiopyranopyrroles 16 and 18

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

400 MHz proton nuclear magnetic resonance ($^1\text{H-NMR}$) 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), $^1\text{H-NMR}$ 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.88 (3H, d, $J=1.5$ Hz, $\text{C}_2\text{-CH}_3$), 2.45–3.15 (4H, m, $\text{C}_3\text{-H}_2$ and $\text{C}_4\text{-H}_2$), 3.75 (3H, s, OCH_3), 5.18 (1H, m, $\text{C}_1\text{-H}$), 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.24 and 1.25 (3H, t, $J=7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.88 and 2.11 (3H, d, $J=1.5$ Hz, CH_3), 2.20–2.60 (2H, m, $\text{C}_4\text{-H}_2$), 2.70–3.10 (2H, m, $\text{C}_3\text{-H}_2$), 3.76 (3H, s, OCH_3), 4.11 and 4.14 (2H, q, $J=7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 5.60–5.80 (1H, m, $\text{C}_2\text{-H}$), 7.10 (4H, ArH, s, 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-2H-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 $\text{C}_{13}\text{H}_{16}\text{O}_5$: C, 61.88; H, 6.39. Found: C, 61.95; H, 6.45. IR (KBr): 1715 (C=O) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.48 (3H, s, CH_3), 1.6–2.6 (2H, m, $\text{C}_3\text{-H}_2$), 2.70 (2H, ABq, $J=14.3$ Hz, $\Delta\nu=16.4$ Hz, $\text{CH}_2\text{CO}_2\text{H}$), 2.90–3.25 (2H, m, $\text{C}_2\text{-H}_2$), 3.74 (3H, s, OCH_3), 6.64 (1H, dd, $J=9.0, 3.0$ Hz, $\text{C}_7\text{-H}$), 6.91 (1H, d, $J=3.0$ Hz, $\text{C}_5\text{-H}$), 7.03 (1H, d, $J=9.0$ Hz, $\text{C}_8\text{-H}$), 9.96 (1H, br, CO_2H). MS m/z : 252 (M^+), 193 (base).

4: IR (film): 1735 (C=O) cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.20 (3H, t, $J=7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.46 (3H, s, $\text{C}_4\text{-CH}_3$), 1.85–3.25 (6H, m, $\text{C}_2\text{-H}_2$, $\text{C}_3\text{-H}_2$ and $\text{CH}_2\text{CO}_2\text{CH}_3$), 3.75 (3H, s, OCH_3), 4.08 (2H, q, $J=7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.67 (1H, dd, $J=8.3, 3.0$ Hz, $\text{C}_7\text{-H}$), 6.92 (1H, d, $J=3.0$ Hz, $\text{C}_5\text{-H}$), 7.04 (1H, d, $J=8.3$ Hz, $\text{C}_8\text{-H}$). MS m/z : 280 (M^+ , base). High-resolution MS m/z : 280.1133. Found: 280.1138.

6-Methoxy-4-methyl-3,4-dihydro-2H-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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (3H, s, $\text{C}_4\text{-CH}_3$), 1.6–2.55 (2H, m, $\text{C}_3\text{-H}_2$), 2.55 (2H, ABq, $J=14.8$ Hz, $\Delta\nu=7.3$ Hz, CH_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, $\text{C}_7\text{-H}$), 6.93 (1H, d, $J=3.0$ Hz, $\text{C}_5\text{-H}$), 7.09 (1H, d, $J=9.0$ Hz, $\text{C}_8\text{-H}$). 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-2H-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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.30 and 1.38 (3H, t, $J=7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 2.75–3.75 (4H, m, $\text{C}_2\text{-H}_2$ and $\text{C}_3\text{-H}_2$), 3.80 and 3.83 (3H, s, OCH_3), 4.26 and 4.36 (2H, q, $J=7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.67–7.25 (2H, m, $\text{C}_7\text{-H}$ and $\text{C}_8\text{-H}$), 7.46 and 7.68 (1H, d, $J=3.0$ Hz, $\text{C}_6\text{-H}$). 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-2H-1-benzothiopyran-4-ylidene-4-acetate (8)

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 Et₂O (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 (NH₂) cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.38 (2H, s, NH₂), 1.41 (3H, s, C₄-CH₃), 1.55–2.40 (4H, m, C₃-H₂ and C₄-CH₂CH₂N), 2.50–3.15 (4H, m, C₂-H₂ and C₄-CH₂CH₂N), 3.76 (3H, s, OCH₃), 6.66 (1H, dd, *J* = 9.0, 3.0 Hz, C₇-H), 6.89 (1H, d, *J* = 3.0 Hz, C₅-H), 7.02 (1H, d, *J* = 9.0 Hz, C₈-H). MS *m/z*: 237 (M⁺).

Oxalate: mp 211–214°C (dec.). Anal. Calcd for C₁₃H₁₉NOS·C₂H₂O₄: C, 55.03; H, 6.47; N, 4.28. Found: C, 54.98; H, 6.53; N, 4.22. IR (KBr): 3440 (NH₃) cm⁻¹.

4-Cyanomethyl-6-methoxy-4-methyl-3,4-dihydro-2H-1-benzothiopyran (9) Cu₂I₂ (7 mg, 37 mmol) and **8** (350 mg, 1.21 mmol) were added to a stirred solution of MeMgI (2 mmol) in Et₂O (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 Et₂O layer was separated and dried over MgSO₄. After filtration, the residue was chromatographed on a silica gel column (Et₂O: *n*-hexane = 1:8) to give the crude 1,4-adduct.

This 1,4-adduct was treated with KOH (24 mg) and HOCH₂CH₂OH (4 ml). The mixture was stirred for 1 h at 190°C. The reaction mixture was treated with H₂O and Et₂O and the Et₂O layer was separated and dried over MgSO₄. After filtration, the filtrate was evaporated and the residue was submitted to preparative TLC (Et₂O: *n*-hexane = 1:2) to give 14 mg (4.96%) of **9** as colorless prisms. mp 51.5–54.0°C. Anal. Calcd for C₁₃H₁₅NOS: 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. ¹H-NMR (CDCl₃) δ: 1.53 (3H, s, C₄-CH₃), 1.95–2.30 (2H, m, C₃-H₂), 2.67 (2H, s, C₄-CH₂CN), 2.85–3.20 (2H, m, C₂-H₂), 3.76 (3H, s, OCH₃), 6.69 (1H, dd, *J* = 9.0, 3.0 Hz, C₇-H), 6.87 (1H, d, *J* = 3.0 Hz, C₅-H), 7.02 (1H, d, *J* = 9.0 Hz, C₈-H). MS *m/z*: 233 (M⁺), 193 (base).

Ethyl 3,4-Dihydro-6-methoxy-4-methyl-2H-1-benzothiopyran-4-ethanecarboxylate (11) A mixture of **6** (130 mg, 0.55 mmol), NaHCO₃ (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 H₂O and the benzene layer was dried over MgSO₄. 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 C₁₆H₂₃NO₃S: 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. ¹H-NMR (CDCl₃) δ: 1.21 (3H, t, *J* = 7.0 Hz, CO₂CH₂CH₃), 1.33 (3H, s, C₄-CH₃), 1.60–2.20 (4H, m, C₃-H₂ and C₄-CH₂CH₂N), 2.80–3.35 (4H, m, C₂-H₂ and C₄-CH₂CH₂N), 3.77 (3H, s, OCH₃), 4.08 (2H, q, *J* = 7.0 Hz, CO₂CH₂CH₃), 4.35–4.75 (1H, br, NH), 6.63 (1H, dd, *J* = 9.0, 3.0 Hz, C₇-H), 6.88 (1H, d, *J* = 3.0 Hz, C₅-H), 7.01 (1H, d, *J* = 9.0 Hz, C₈-H). MS *m/z*: 309 (M⁺), 193 (base).

4-[2-(Ethoxycarbonylamino)ethyl]-6-methoxy-4-methyl-3,4-dihydro-2H-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 CH₂Cl₂ (20 ml) at 0–5°C. After being stirred for 30 min, the reaction mixture was washed with 5% NaHCO₃, 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 C₁₆H₂₃NO₄S: 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. ¹H-NMR (CDCl₃) δ: 1.15 and 1.21 (3H, t, *J* = 7.0 Hz, CO₂CH₂CH₃), 1.33 and 1.44 (3H, s, C₄-CH₃), 1.55–2.55 (4H, m, C₃-H₂ and C₄-CH₂CH₂N), 2.75–3.80 (4H, m, C₂-H₂ and C₄-CH₂CH₂N), 3.86 (3H, s, OCH₃), 4.01 and 4.08 (2H, q, *J* = 7.0 Hz, CO₂CH₂CH₃), 4.70–5.50 (1H, br, NH), 6.70–7.10 (2H, m, C₅-H and C₇-H), 7.60 and 7.68 (1H, d, *J* = 7.5 Hz, C₈-H). MS *m/z*: 309 (M⁺), 193 (base).

4-[2-(Ethoxycarbonylamino)ethyl]-6-methoxy-4-methyl-4H-1-benzothiopyran (14) A mixture of **12** (408 mg, 1.25 mmol) and Ac₂O (30 ml) was refluxed for 12 h. The reaction mixture was concentrated and the residue was chromatographed on a silica gel column (Et₂O: *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. ¹H-NMR (CDCl₃) δ: 1.20 (3H, t, *J* = 7.0 Hz, CO₂CH₂CH₃), 1.44 (3H, s, C₄-CH₃), 1.50–2.25 (2H, m, C₄-CH₂CH₂N), 2.85–3.50 (2H, m, C₂-H₂ and C₄-CH₂CH₂N), 3.78 (3H, s, OCH₃), 4.06 (2H, q, *J* = 7.0 Hz, CO₂CH₂CH₃), 5.57 (1H, d, *J* = 9.8 Hz, C₃-H), 6.08 (1H, d, *J* = 9.8 Hz, C₂-H), 6.74 (1H, dd, *J* = 9.0, 3.0 Hz, C₇-H), 6.93 (1H, d, *J* = 3.0 Hz, C₅-H), 7.10 (1H, d, *J* = 9.0 Hz, C₈-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-4H-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 CH₂Cl₂ (10 ml) at 0–5°C. After being stirred for 5 min, the reaction mixture was washed with 5% NaHCO₃, 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. ¹H-NMR (CDCl₃) δ: 1.14 and 1.18 (3H, t, *J* = 7.0 Hz, CO₂CH₂CH₃), 1.37 and 1.60 (3H, s, C₄-CH₃), 1.50–3.25 (4H, m, C₄-CH₂CH₂N), 3.87 (3H, s, OCH₃), 4.05 and 4.14 (2H, q, *J* = 7.0 Hz, CO₂CH₂CH₃), 4.95–5.40 and 5.40–6.10 (1H, br, NH), 6.34 and 6.44 (1H, d, *J* = 10.5 Hz, C₃-H), 6.75–7.30 (3H, m, C₂-H, C₅-H and C₇-H), 7.65–8.00 (1H, m, C₈-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 Et₂O (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 (Et₂O: *n*-hexane = 1:2) to give 306 mg (92.6%) of **16** as a colorless oil. IR (film): 2775 (N-CH₃) cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.30 (3H, s, C_{9b}-CH₃), 1.95–3.25 (7H, m, C₁-H₂, C₂-H₂, C_{3a}-H and C₄-H₂), 2.45 (3H, s, NCH₃), 3.76 (3H, s, OCH₃), 6.65 (1H, dd, *J* = 9.0, 3.0 Hz, C₇-H), 6.86 (1H, d, *J* = 3.0 Hz, C₉-H), 7.18 (1H, d, *J* = 9.0 Hz, C₆-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) BBr₃ (70.0 μl, 0.57 mmol) was added dropwise to a stirred solution of **16** (88 mg, 0.35 mmol) in CH₂Cl₂ (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% NaHCO₃, dried, and concentrated to give 76 mg (91.5%) of **18** as colorless prisms. mp 192–194.5°C. Anal. Calcd for C₁₃H₁₇NOS: C, 66.35; H, 7.28; N, 5.95. Found: C, 66.07; H, 7.39; N, 5.88. ¹H-NMR (CDCl₃ + CD₃OD) δ: 1.32 (3H, s, C_{9b}-CH₃), 1.90–3.30 (7H, m, C₁-H₂, C₂-H₂, C_{3a}-H and C₄-H₂), 2.49 (3H, s, NCH₃), 6.59 (1H, dd, *J* = 9.0, 3.0 Hz, C₇-H), 6.82 (1H, d, *J* = 3.0 Hz, C₉-H), 7.09 (1H, d, *J* = 9.0 Hz, C₆-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 CH₂Cl₂ (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% NaHCO₃, dried, and concentrated. The residue was crystallized from Et₂O to give 170 mg (81.0%) of **17** as colorless prisms, mp 200.5–202.5°C. Anal. Calcd for C₁₆H₂₁NO₅S: 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 (SO₂) cm⁻¹. ¹H-NMR (CDCl₃) δ: 1.32 (3H, t, *J* = 7.0 Hz, CO₂CH₂CH₃), 1.54 (3H, s, C_{9b}-CH₃), 1.90–2.30 (2H, m, C₁-H₂), 3.00 (1H, dd, *J* = 13, 12 Hz, C_{3a}-H), 3.40–4.75 (4H, m, C₂-H₂ and C₄-H₂), 3.88 (3H, s, OCH₃), 4.25 (2H, q, *J* = 7.0 Hz, CO₂CH₂CH₃), 6.80–7.10 (2H, m, C₇-H and C₉-H), 7.93 (1H, dd, *J* = 13.0, 1.0 Hz, C₆-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**: SO₂Cl₂ (0.12 ml, 1.48 mmol) was added dropwise to a stirred solution of **12** (435 mg, 1.31 mmol) in CH₂Cl₂ (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 CH₂Cl₂. The extract was dried and concentrated. The residue was chromatographed on a silica gel column (AcOEt: Et₂O = 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 CH₂Cl₂, dried and concentrated. The residue was chromatographed on a silica gel column (AcOEt: Et₂O = 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** (3aRS, 5RS, 9bRS): 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.32 (3H, t, $J=7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.40 (3H, s, $\text{C}_{9b}\text{-CH}_3$), 2.10-2.40 (2H, m, $\text{C}_1\text{-H}_2$), 2.70 (1H, dd, $J=10.8$, 9.8 Hz, $\text{C}_{3a}\text{-H}$), 3.40-4.40 (4H, m, $\text{C}_2\text{-H}_2$ and $\text{C}_4\text{-H}_2$), 3.85 (3H, s, OCH_3), 4.21 (2H, q, $J=7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 6.80 (1H, d, $J=3.0$ Hz, $\text{C}_9\text{-H}$), 6.90 (1H, dd, $J=8.7$, 3.0 Hz, $\text{C}_7\text{-H}$), 7.71 (1H, d, $J=8.7$ Hz, $\text{C}_6\text{-H}$). MS m/z : 323 (M^+), 191 (base). High-resolution MS m/z : 323.1191. Found: 323.1164.

More Polar Isomer **13b** (3aRS, 5SR, 9bRS): mp 167.5 °C. Anal. Calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_4\text{S}$: 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} . $^1\text{H-NMR}$ (CDCl_3) δ : 1.31 (3H, t, $J=7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 1.55 (3H, s, $\text{C}_{9b}\text{-CH}_3$), 1.75-2.25 (2H, m, $\text{C}_1\text{-H}_2$), 2.40-2.95 (1H, m, $\text{C}_{3a}\text{-H}$), 3.35-3.75 (3H, m, $\text{C}_2\text{-H}_2$ and $\text{C}_4\text{-H}$), 3.85 (3H, s, OCH_3), 4.21 (2H, q, $J=7.0$ Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$), 4.45-4.85 (1H, m, $\text{C}_4\text{-H}$), 6.75-7.00 (2H, m, $\text{C}_7\text{-H}$ and $\text{C}_9\text{-H}$), 7.55-7.75 (1H, m, $\text{C}_6\text{-H}$). MS m/z : 323 (M^+), 191 (base).

Determination of the Crystal Structure of 13b Crystal data: $\text{C}_{16}\text{H}_{21}\text{NO}_4\text{S}$, monoclinic, space group $P2_1$; $a=8.831$ (4), $b=7.210$ (3), $c=13.207$ (6) Å; $\beta=105.77$ (4)°, $D_x=1.33$ g/cm³, $z=2$ 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 MoK_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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