SYNTHESIS AND ANTI-ACETYLCHOLINESTERASE ACTIVITY OF THIAPHYSOSTIGMINE DERIVATIVES†

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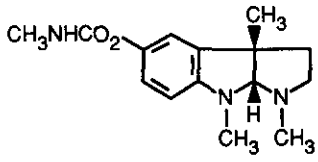
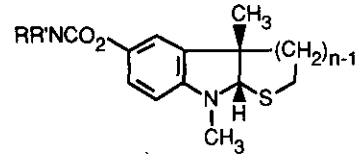
Abstract - A series of thiaphysostigmine derivatives (**2a**, **b** and **3a**, **b**), with a sulfur atom instead of *N*-methyl group in B ring or C ring of physostigmine (**1**), were synthesized, and their inhibitory effects on AChE and BuChE activity, and acute toxicity were evaluated.

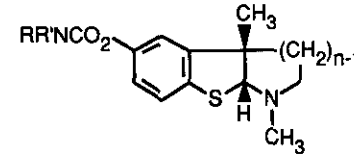
Physostigmine (**1**), also called eserine, is an alkaloid obtained from the carabar or ordeal bean, and is reported to be effective in the treatment of glaucoma and the symptomatic therapy of myasthenia gravis. The alkaloid has also been shown to improve memory and learning in patients with Alzheimer's disease by inhibiting the metabolic enzyme acetylcholinesterase (*AChE*) in brain.[1] However, its therapeutic usefulness is limited by



Physostigmine (1)



2a, b



3a, b

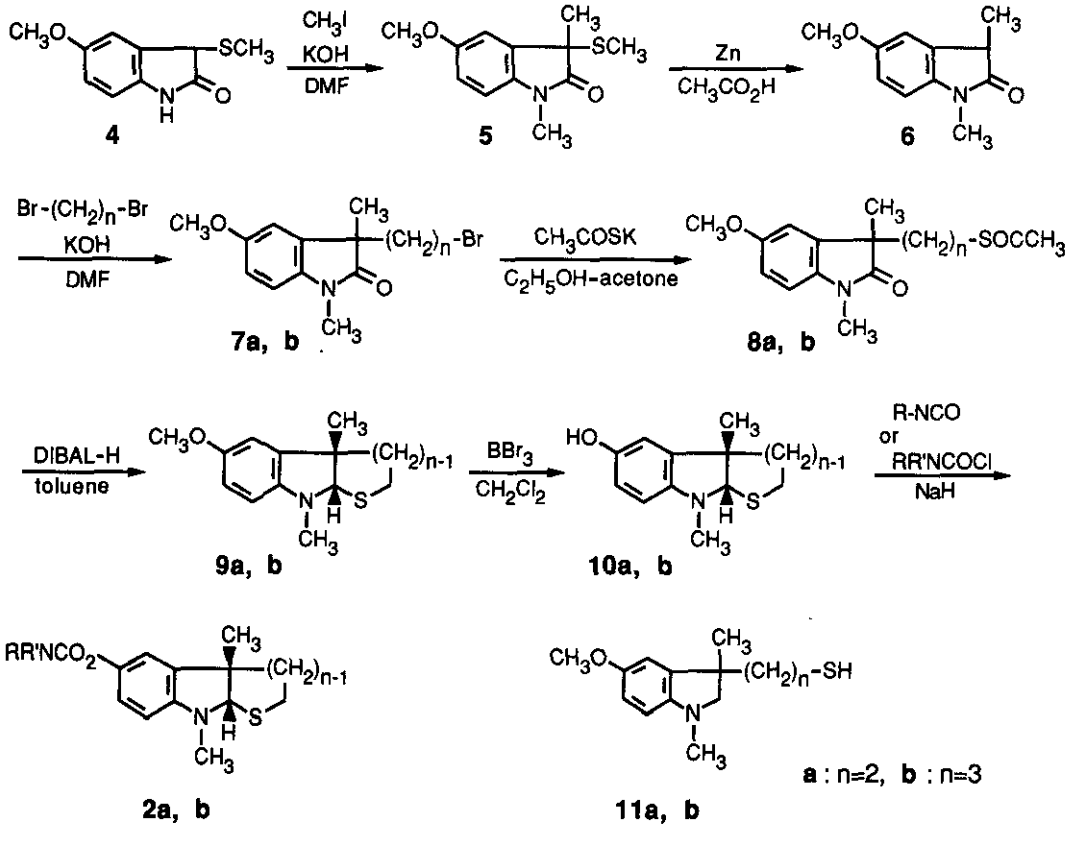
a : n=2, b : n=3

† This paper is dedicated to Professor Arnold Brossi on the occasion of his 70th birthday, and with gratitude for his many contributions in organic chemistry.

its high toxicity, narrow effective dose range, and short half-life.

In our search for new drugs similar in physiological effect to **1**, we have prepared a series of thiaphysostigmine derivatives (**2a**, **b** and **3a**, **b**), expecting that these compounds would have a higher lipophilicity, when compared with **1**, and consequently a different distribution in body and different pharmacokinetics. And the inhibitory potency of **2a**, **b** and **3a**, **b** have been evaluated in vitro against rat AChE and human serum butyrylcholinesterase (BuChE), and the acute toxicity of these compounds in mice has also been examined.

Chemistry 1-Thia analogues (**2a** and **2b**) were synthesized starting from Gassman's oxindole (**4**)[2] as shown in Scheme 1. Dimethylation of **4** with excess iodomethane and potassium hydroxide in *N*,*N*-dimethylformamide (DMF), followed by desulfurization with zinc dust in acetic acid, gave 5-methoxy-1,3-dimethyl-2-oxindole (**6**) in good yields (89%, 93%). Alkylation of **6** with 1,2-dibromoethane or 1,3-dibromopropane in the presence of potassium hydroxide in DMF gave the bromoethyl (**7a**, 95%), or the bromopropyl derivative



Scheme 1

(**7b**, 80%), respectively. Reaction of the bromides (**7a** and **7b**) with potassium thioacetate in a 1:1 mixture of ethanol and acetone at reflux temperature afforded the thioacetates (**8a**, 91% and **8b**, 96%).

By reductive cyclization of **8a** with sodium in ethanol[3] or lithium aluminum hydride (LAH) in ether,[4] the desired 1-thiaesermethole (**9a**) was obtained in poor yield (31% or 18%) and a major product separated was the indoline derivative (**11a**). Reduction of the thioacetates (**8a** and **8b**) with diisobutylaluminum hydride (DIBAL-H), as a reducing agent of choice, in toluene gave the corresponding tricyclic compounds in good yields (**9a**, 72% and **9b**, 81%). The stereochemistry of the ring junction of **9a** was confirmed to be *cis* by proton NOE between the methyl hydrogens and the angular hydrogen (Figure 1), and the *cis* configuration of **9b** was determined by X-ray crystallographic analysis (Figure 3) and proton NOE (Figure 1). Cleavage of the methyl ether of the tricyclic compounds (**9a** and **9b**) with boron tribromide in dichloromethane gave the phenols (**10a**, 88% and **10b**, 85%), which were treated with some isocyanates or dimethylcarbamoyl chloride in the presence of sodium hydride to afford 1-thiaphysostigmine derivatives (**2a**)[5] and 1-thia-homophysostigmine derivatives (**2b**), respectively (Table 2).

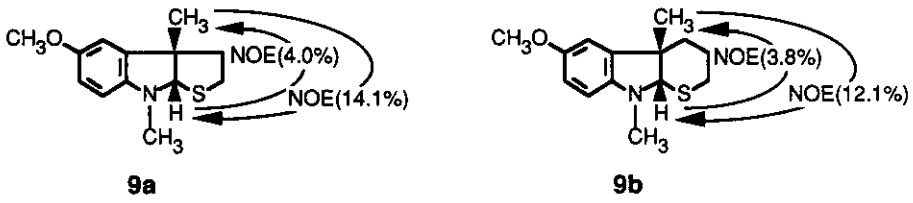
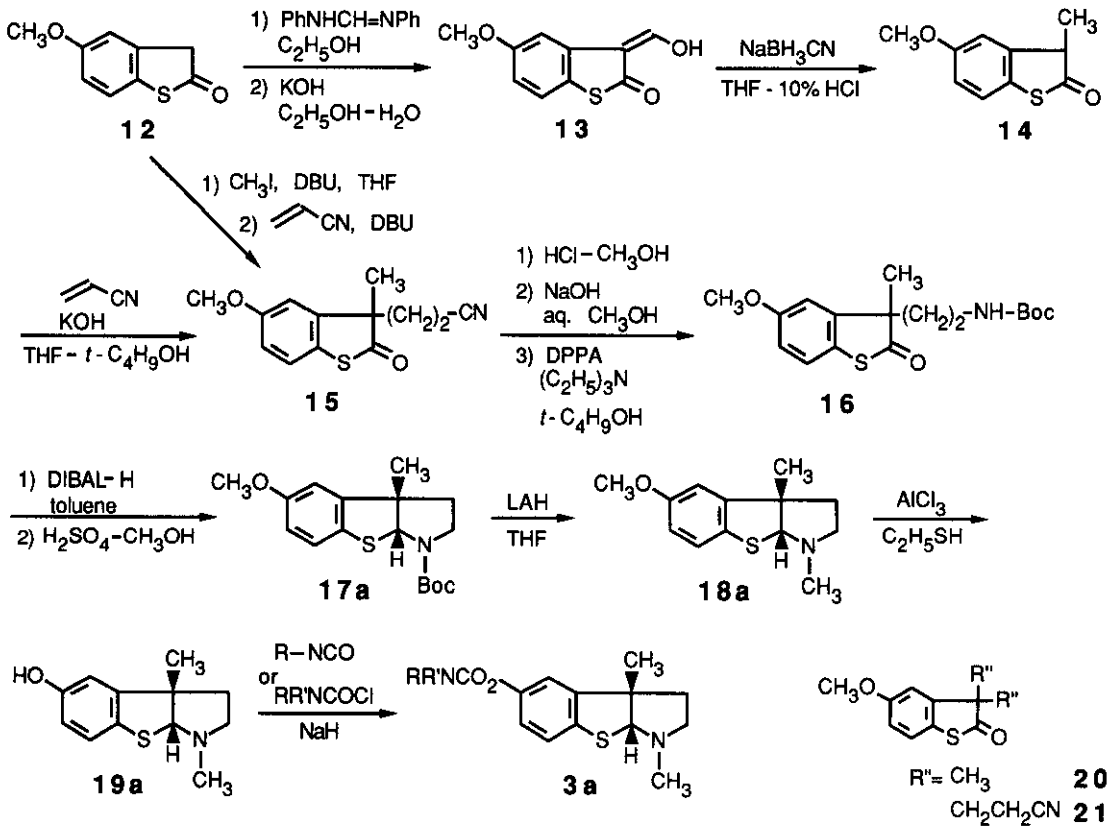


Figure 1. Proton NOE of **9a,b**

8-Thiaphysostigmine derivatives (**3a** and **3b**) were synthesized as shown in Scheme 2 and Scheme 3, and the starting benzothiophenone (**12**) was prepared by the improved method of the reported procedure.[6] Direct monomethylation of **12**, having two acidic hydrogens on the 3-position, with iodomethane to the 3-methyl-thiollactone (**14**) under various reaction conditions was unsuccessful. A major product was invariably 3,3-dimethyl compound (**20**), and separation of **14** and **20** by means of chromatography was not effective because their Rf values were almost identical. When **12** was stirred for 10 minutes at room temperature with iodomethane (1 eq.) and a hindered organic base, 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU, 0.75 eq.), and then treated with acrylonitrile (1.5 eq.) and DBU (1 eq.) in one-pot, the desired propanenitrile (**15**) was obtained in 42% yield together with the 3,3-dipropanenitrile (**21**, 16%). The key intermediate (**15**) was also prepared by an alternative route. The benzothiophenone (**12**) was readily condensed in boiling ethanol with

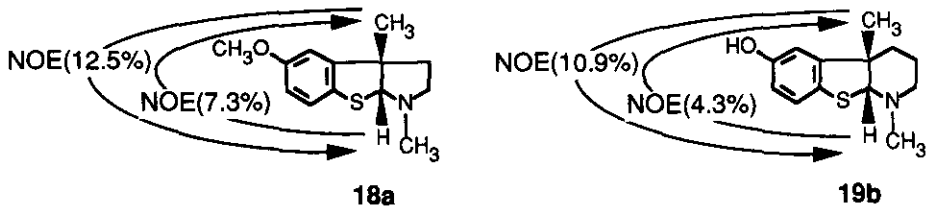


Scheme 2

N,N'-diphenylformamidine to give the anil (82%), which was hydrolyzed to give the 3-formylthiollactone (**13**, 84%) . Reduction of the formyl group of **13** with sodium cyanoborohydride in THF in the presence of 10% aqueous hydrochloric acid directly gave **14** in 56% yield.[7] Base catalyzed Michael addition of **14** to acrylonitrile gave the corresponding propanenitrile (**15**, 81%).

The compound (**15**) thus obtained was treated with saturated hydrochloric acid in methanol (97%), followed by alkaline hydrolysis to give the propionic acid (92%), which was allowed to react with diphenylphosphoryl azide (DPPA) in *tert*-butanol in the presence of triethylamine to give the Curtius rearrangment product (**16**) in 74% yield. Reduction of the thiollactone of **16** with DIBAL-H in toluene gave the benzothiophen-2-ol as a mixture of diastereomers (88%), which was stirred in methanol in the presence of sulfuric acid to give the tricyclic compound (**17a**) in quantitative yield. The *tert*-butyloxycarbonyl (Boc) group of **17a** was readily reduced to the methyl group with LAH in THF to give 8-thiaesermethole (**18a**, 77%). The *cis* configuration of **18a** was determined by X-ray crystallographic analysis as its tartaric acid salt[8] (Figure 3), and the NOE data of

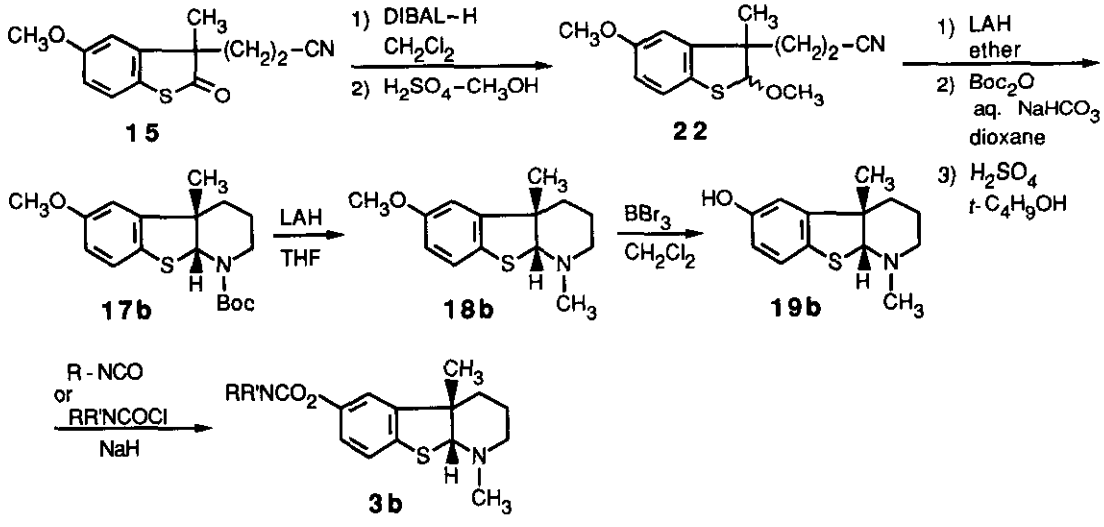
18a were shown in Figure 2. Cleavage of the methyl ether of **18a** with aluminum chloride in ethanethiol afforded 8-thiaeseroline (**19a**, 80%), while treatment of **18a** with boron tribromide gave a poor result. The phenol (**19a**) was converted into 8-thiaphysostigmine derivatives (**3a**, Table 3).



18a **19b**

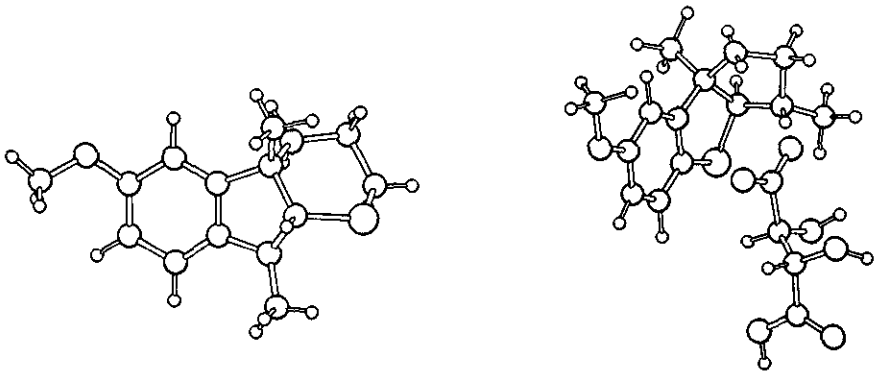
Figure 2. Proton NOE of **18a**, and **19b**

The propanenitrile (**15**), also a good intermediate for synthesis of 8-thia-homophysostigmine derivatives (**3b**) as shown in Scheme 3, was reduced with DIBAL-H in dichloromethane, followed by being stirred in acidic methanol to give the diastereomeric compound (**22**, 95%). The cyano group of **22** was then reduced with LAH in ether to the amino group, which was protected with Boc group, and the Boc compound was stirred with sulfuric acid in *tert*-butanol to give the tricyclic product (**17b**) in 88% yield (three steps). Successive reduction of **17b** with LAH in THF gave the *N*-methyl compound (**18b**) quantitatively. The methyl ether cleavage of **18b** with boron tribromide in dichloromethane (**19b**, 98%), followed by treatment with the isocyanates or



Scheme 3

dimethylcarbamoyl chloride gave corresponding 8-thia-homophysostigmine derivatives (**3b**) as shown in Table 3. The *cis* configuration of **19b** was also confirmed by the proton NOE (Figure 2).



9b (+) - **18a** • D-tartaric acid

Figure 3. Parallel view of **9b**, and (+) - **18a** • D-tartaric acid

Biological Results and Discussion The thiaphysostigmine derivatives (**2a,b** and **3a,b**) were tested for their inhibitory potencies (IC_{50}) in vitro using rat brain AChE and human serum BuChE. The results are shown in Table 1. Among compounds prepared in this study, **2a-1** was the most potent inhibitor of AChE, and more potent than **1**. But **2a-1** also inhibited the BuChE activity and its selectivity to AChE over BuChE was very poor. On the effects of the substituents on the carbamate, the compounds having longer side chain (**2a-2,3,4**, **3a-2,3**, and **3b-2,3**) showed lower AChE inhibitory activity than the corresponding methylcarbamates, while these compounds (**2a-2,3,4**, and **3a-3**) strongly inhibited the BuChE activity. The *N,N*-dimethyl–carbamates (**2b-5**, **3a-5**, and **3b-5**) showed a good selectivity to AChE over BuChE. Although C ring expansion of the thiaphysostigmine resulted in a slight decrease of inhibitory potency, the selectivity of these homo-compounds (**2b** and **3b**) for AChE was found to be higher than that of **2a** and **3a**.

In acute toxicity study using mice, the test compounds showed considerably higher maximal tolerance dose (MTD) than **1** as shown in Table 1. Further pharmacological evaluation in detail are now in progress.

EXPERIMENTAL

All the melting points were uncorrected. Infrared spectra were taken with a Hitachi IR-215 or an Analect FX-6200 FT-IR spectrophotometer. Nmr spectra were recorded with a Hitachi R-90H, a JEOL JNM-FX-200 or a JEOL JNM-GSX-400 spectrometer. Mass spectra (EI) were recorded with a Hitachi RMU-6 or a JEOL JMS-

Table 1. Inhibitory Effects on AChE and BuChE Activity, and Acute Toxicity of Thiaphysostigmine Derivatives

Compounds(RR'N)	IC_{50}(M)		B/A ratio	MTD in mice (mg/kg, p.o.)
	AChE(A)	BuChE(B)		
Physostigmine (1)	1.4×10^{-6}	4.5×10^{-7}	0.32	1.5-1
2a-1 (CH_3NH-)	5.2×10^{-7}	1.3×10^{-7}	0.25	50-5
2a-2 (C_2H_5NH-)	1.1×10^{-5}	2.4×10^{-8}	0.002	50 >
2a-3 (n-C_4H_9NH-)	4.4×10^{-6}	1.9×10^{-8}	0.004	100-50
2a-4 (n-$C_7H_{15}NH$-)	8.0×10^{-6}	9.0×10^{-9}	0.001	NT[a]
2a-5 ($(CH_3)_2N$-)	8.6×10^{-6}	2.4×10^{-6}	0.28	100-50
2b-1 (CH_3NH-)	3.0×10^{-6}	2.7×10^{-6}	0.90	> 50
2b-5 ($(CH_3)_2N$-)	7.0×10^{-5}	$> 10^{-4}$	> 1.43	> 300
3a-1 (CH_3NH-)	2.3×10^{-6}	3.8×10^{-6}	1.65	50-5
3a-2 (C_2H_5NH-)	$> 10^{-4}$	1.8×10^{-6}	0.02 >	300-50
3a-3 (n-C_4H_9NH-)	1.8×10^{-5}	7.4×10^{-7}	0.04	> 50
3a-5 ($(CH_3)_2N$-)	4.1×10^{-5}	$> 10^{-4}$	> 2.44	> 50
3b-1 (CH_3NH-)	4.6×10^{-6}	2.4×10^{-5}	5.2	50-25
3b-2 (C_2H_5NH-)	$> 10^{-4}$	5.9×10^{-6}	0.06 >	NT
3b-3 (n-C_4H_9NH-)	4.4×10^{-5}	4.3×10^{-6}	0.10	NT
3b-5 ($(CH_3)_2N$-)	4.8×10^{-5}	$>10^{-4}$	> 2.1	NT

[a] NT : not tested

HX 100 mass spectrometer. Microanalyses were performed on a Perkin-Elmer 240B C, H, N analyzer and a Yokokawa IC-100 ion chromatographic analyzer.

5-Methoxy-1,3-dimethyl-3-methylthio-1*H*-indol-2(3*H*)-one (5): A solution of 4[2] (52.4 g, 0.25 mol) in DMF (600 ml) was degassed and bubbled with argon under ice-cooling. Powdered KOH (42.1 g, 0.75 mol) was added to the solution by portions over a 10 min period. After being stirred for 15 min, the brown reaction mixture was poured onto ice-cold water and extracted twice with ethyl acetate. The combined organic layers were washed with water and brine, dried over Na_2SO_4, treated with charcoal, and evaporated. The oily residue was crystallized from ether-hexane to give **5** (52.9 g, 89%) as pale yellow prisms.

5-Methoxy-1,3-dimethyl-1*H*-indol-2(3*H*)-one (6): A mixture of **5** (18.6 g, 78.4 mmol) and zinc dust (51 g, 0.78 mol) in CH_3CO_2H (150 ml) was refluxed for 1 h, cooled and filtered. The filtrate and washings (toluene) were concentrated in vacuo, and the residue was dissolved in toluene, filtered and evaporated to give an oil, which was crystallized from isopropyl ether to give **6** (13.9 g, 93%) as colorless needles.

3-(2-Bromoethyl)-5-methoxy-1,3-dimethyl-1*H*-indol-2(3*H*)-one (7a): A solution of **6** (0.38 g, 2 mmol) and 1,2-dibromoethane (0.75 g, 4 mmol) in DMF (3 ml) was degassed and bubbled with argon under ice-cooling. Powdered KOH (0.23 g, 4 mmol) was added to the solution in one portion, and the reaction mixture was stirred for 1 h at room temperature, diluted with H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The residue was purified on a silica gel column (eluent : hexane-ethyl acetate (3 : 1)) to give **7a** (0.56 g, 95%) as a colorless oil.

3-(3-Bromopropyl)-5-methoxy-1,3-dimethyl-1*H*-indol-2(3*H*)-one (7b): A mixture of **6** (1.99 g, 10.4 mmol), 1,3-dibromopropane (2.55 g, 12.6 mmol) and KOH (1.17 g, 20.8 mmol) in DMF (20 ml) was reacted and worked up as above to give a brown oil. The oil was purified on a silica gel column (eluent : hexane-ethyl acetate (3 : 1)) to give **7b** (2.61 g, 80%) as a colorless oil.

***S*-2-(2,3-Dihydro-5-methoxy-1,3-dimethyl-2-oxo-1*H*-indol-3-yl)ethyl Thioacetate (8a)**: A mixture of **7a** (1.36 g, 4.2 mmol) and potassium thioacetate (0.96 g, 8.4 mmol) in C_2H_5OH-acetone (1:1, 20 ml) was refluxed for 2.3 h and concentrated. The residue was partitioned between ethyl acetate and H_2O, and the ethyl acetate layer was washed with H_2O and brine, dried over Na_2SO_4 and evaporated. Purification of the oily residue on a silica gel column (eluent : hexane-ethyl acetate (4 : 1)) gave **8a** (1.13 g, 91%) as a pale yellow oil.

***S*-3-(2,3-Dihydro-5-methoxy-1,3-dimethyl-2-oxo-1*H*-indol-3-yl)propyl Thioacetate (8b)**: Compound **(7b)** (2.58 g, 8.26 mmol) and potassium thioacetate (1.88 g, 16.5 mmol) were treated in the same procedure described above to give **8b** (2.45 g, 96%) as a pale yellow oil.

***cis*-3,3a,8,8a-Tetrahydro-5-methoxy-3a,8-dimethyl-2*H*-thieno[2,3-*b*]indole (9a)**: A solution of DIBAL-H (1M in hexane, 20.4 ml, 20.4 mmol) was added dropwise at -60°C during a period of 30 min under argon to a solution of **8a** (2.72 g, 9.27 mmol) in toluene (90 ml), and the reaction mixture was stirred for 30 min at the same temperature. The excess hydride was carefully destroyed with ethyl acetate (10 ml) and the complex was decomposed with saturated $NaHCO_3$ solution (100 ml). The mixture was filtered, and the two-phase filtrate was separated. The aqueous layer was extracted with ethyl acetate. The organic layeres were combined, washed with H_2O, dried over Na_2SO_4 and evaporated to give a yellow oil, which was purified on a

silica gel column (eluent: hexane-ethyl acetate (15 : 1)) to give **9a** (1.57 g, 72%) as colorless crystals and **11a** (0.17 g, 8%) as a pale yellow oil.

***cis*-2,3,4,4a,9,9a-Hexahydro-6-methoxy-4a,9-dimethylthiopyrano[2,3-*b*]indole (9b)**: Compound **8b** (404 mg, 1.31 mmol) was reduced with DIBAL-H similarly to the case of **8a** to give **9b** (265 mg, 81%) and **11b** (28 mg, 9%).

***cis*-3,3a,8,8a-Tetrahydro-3a,8-dimethyl-2*H*-thieno[2,3-*b*]indol-5-ol (10a)**: A solution of **9a** (22.3 g, 94.8 mmol) in CH_2Cl_2 (500 ml) was cooled to -60°C under argon. Boron tribromide (95.0 g, 0.38 mol) was added dropwise to the solution during a period of 12 min, and the mixture was stirred for 2.3 h at -60°C-room temperature. Water was added to the mixture at -45°C, and the whole mixture was stirred for 1 h at room temperature and adjusted to pH 4 with saturated $NaHCO_3$ solution. The two phase mixture was separated, and the aqueous phase was extracted with CH_2Cl_2. The organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give a solid. Recrystallization from ethyl acetate-hexane afforded **10a** (18.6 g, 88%) as needles.

***cis*-2,3,4,4a,9,9a-Hexahydro-4a,9-dimethylthiopyrano[2,3-*b*]indol-6-ol (10b)**: Compound **9b** (96 mg, 0.385 mmol) was treated in the same procedure described above to give **10b** (77 mg, 85%) as colorless needles.

5-Methoxybenzo[*b*]thiophen-2(3*H*)-one (12)[6]: A solution of ethyl 3-methoxyphenylacetate (58.3 g, 0.30 mol) and thionyl chloride (22 ml, 0.30 mol) in CH_2Cl_2 (120 ml) was cooled to -30°C. Chlorosulfonic acid (90 ml, 1.35 mol) was added dropwise to the solution during a period of 50 min, and the mixture was stirred for 2 h at 30°C, and then poured onto ice water-$CHCl_3$. The two-phase mixture was separated, and the aqueous phase was extracted with $CHCl_3$. The organic layers combined were washed with brine, dried over Na_2SO_4 and evaporated to give a colorless solid. A solution of 6N-HCl (300 ml, 1.80 mmol) was added dropwise to the mixture of the solid and zinc dust (60.4 g, 0.92 mol) in ether (600 ml) under vigorous stirring during a period of 2.5 h at room temperature. The reaction mixture was stirred for 1 h at room temperature, and concentrated to remove ether. The aqueous suspension was refluxed for 2 h, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give a solid. Recrystallization from CH_3OH afforded **12** (40.0 g, 74%) as colorless prisms.

3-Hydroxymethylene-5-methoxybenzo[*b*]thiophen-2(3*H*)-one (13): A mixture of **12** (3.81 g, 21.1 mmol) and diphenylformamidine (4.14 g, 21.1 mmol) in C_2H_5OH (30 ml) was refluxed for 30 min and cooled. The yellow needles separated was obtained by filtration (4.88 g, 82%).

A mixture of the needles (3.82 g, 17.0 mmol) and KOH (20 g, 356 mmol) in C_2H_5OH (50 ml) and H_2O (100 ml) was refluxed for 50 min. The reaction mixture was cooled and acidified with conc.HCl to give a crystalline solid, which was collected by filtration, washed with H_2O, and recrystallized from $CHCl_3$ to give **13** (2.99 g, 84%) as yellow needles.

5-Methoxy-3-methylbenzo[*b*]thiophen-2(3*H*)-one (14): Sodium cyanoborohydride (130 mg, 2 mmol) and 10% HCl (1 drop) was added to a solution of **13** (420 mg, 2 mmol) in THF (10 ml) under ice-cooling. The mixture was stirred for 24 h at room temperature. 10% aqueous CH_3CO_2H was added to the mixture, and the mixture was concentrated and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, evaporated, and the residue was purified on a silica gel column (eluent: hexane-CH_2Cl_2-acetone (10 : 9 : 1)) to give **14** (220 mg, 56%) as colorless needles.

3-(2,3-Dihydro-5-methoxy-3-methyl-2-oxobenzo[*b*]thiophen-3-yl)propanenitrile (15): From **14** —— Powdered KOH (210 mg, 3.7 mmol) was added to a mixture of **14** (9.70 g, 50.0 mmol) and acrylonitrile (10.0 g, 189 mmol) in *tert*-butanol (140 ml) and THF (140 ml). The mixture was stirred for 20 min at 30°C. A saturated NH_4Cl solution was added to the mixture, and the whole mixture was concentrated and extracted with $CHCl_3$. The organic layer was dried over Na_2SO_4, evaporated and purified on a silica gel column (eluent: hexane-ethyl acetate (3 : 1)) to give **15** (9.98 g, 81%) as colorless needles.

From **12** —— Iodomethane (12.4 ml, 0.2 mol) and DBU (22 ml, 0.15 mol) was added dropwise to a solution of **12** (36 g, 0.2 mol) in THF (1.5 l) at room temperature. The mixture was stirred for 10 min at room temperature. Acrylonitrile (20 ml, 0.3 mol) and DBU (30 ml, 0.2 mol) was added to the mixture, and the mixture was stirred for 45 min and then filtered. The filtrate was evaporated and the residue was purified on a silica gel column (eluent: hexane-ether (3 : 1)) to give **15** (20.7 g, 42%) as colorless crystals and **21** (9.3 g, 16%) .

***tert*-Butyl *N*-2-(2,3-Dihydro-5-methoxy-3-methyl-2-oxobenzo[*b*]thiophen-3-yl)ethyl-carbamate (16)**: A solution of **15** (9.98 g, 40.4 mmol) in a saturated HCl-CH_3OH solution (200 ml) was stirred for 2.5 days at room temperature. Water (0.75 ml, 46.8 mmol) was added to the mixture and the mixture was refluxed for 30 min and evaporated. The residue was partitioned between $CHCl_3$ and H_2O. The organic layer separated was dried over Na_2SO_4, evaporated and purified on a silica gel column (eluent: hexane-ethyl acetate (4 : 1)) to give the ester (11.0 g, 97%) as a pale yellow oil.

A 3N-NaOH solution (50 ml) in CH_3OH (60 ml) and the mixture was stirred for 50 min at room temperature. The reaction mixture was acidified with 10% HCl, concentrated and extracted with $CHCl_3$. The organic layer

was dried over Na_2SO_4, evaporated and purified on a silica gel column (eluent: $CHCl_3$-C_2H_5OH (19 : 1)) to give the corresponding acid (9.60 g, 92%) as a colorless solid.

A mixture of the acid (9.30 g, 34.9 mmol), DPPA (10.57 g, 38.4 mmol), and triethylamine (3.84 g, 38.4 mmol) in *tert*-butanol (150 ml) was refluxed for 23 h and evaporated. The residue was taken up with ethyl acetate, and the organic layer was washed with 5% citric acid, H_2O, saturated $NaHCO_3$, and brine, dried over Na_2SO_4 and evaporated. The residue was purified on a silica gel column (eluent: hexane-CH_2Cl_2-acetone (20 : 20 : 1)) to give **16** (8.70 g, 74%) as colorless crystals.

***tert*-Butyl *cis*-2,3,3a,8a-Tetrahydro-5-methoxy-3a-methyl-1*H*-benzo[*b*]thieno[2,3-*b*]-pyrrole-1-carboxylate (17a):** A solution of DIBAL-H (1M in toluene, 38.7 ml, 38.7 mmol) was added dropwise at -62°C to a solution of **16** (8.70 g, 25.8 mmol) in toluene (160 ml), and the mixture was stirred for 1 h at the same temperature. The excess hydride was carefully destroyed with isopropyl alcohol (40 ml). The mixture was concentrated and the residue was dissolved in H_2O and $CHCl_3$, and then filtered on celite. The two-phase filterate was separated, and the organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give an oily residue, which was purified on a silica gel column (eluent: hexane-CH_2Cl_2-acetone (5 : 4 : 1)) to give a colorless foam (7.71 g, 88%) as a mixture of diastereomers.

A solution of the foam (7.71 g, 22.7 mmol) and 98% H_2SO_4 (1.5 ml) in CH_3OH (140 ml) was stirred for 100 min at room temperature, diluted with H_2O (100 ml), concentrated, and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give **17a** (7.28 g, 100%) as a colorless oil.

***cis*-2,3,3a,8a-Tetrahydro-5-methoxy-1,3a-dimethyl-1*H*-benzo[*b*]thieno[2,3-*b*]pyrrole (18a):** A mixture of **17a** (15.1 g, 47 mmol) and LAH (5.21 g, 137 mmol) in THF (400 ml) was refluxed for 1 h. The excess hydride was destroyed with H_2O (5 ml), 10% NaOH (5 ml), and H_2O (15 ml) under ice-cooling. The mixture was filtered and the filtrate was evaporated to give the residue, which was purified on a silica gel column (eluent: hexane-ethyl acetate (2 : 1)) to give **18a** (8.56 g, 77%) as colorless crystals.

***cis*-2,3,3a,8a-Tetrahydro-1,3a-dimethyl-1*H*-benzo[*b*]thieno[2,3-*b*]pyrrol-5-ol (19a):** Compounds **(18a)** (7.45 g, 31.7 mmol) was added to a solution of $AlCl_3$ (8.44 g, 63.3 mmol) in C_2H_5SH (20 ml) under ice-cooling, and the mixture was stirred for 25 min at room temperature. The complex was decomposed with 10% HCl, and the mixture was basified with a saturated $NaHCO_3$ solution. The whole mixture was extracted with $CHCl_3$, and the organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated. Recrystallization of the residual crystals from hexane afforded **19a** (5.60 g, 80%) as colorless crystals.

3-(2,3-Dihydro-2,5-dimethoxy-3-methylbenzo[*b*]thiophen-3-yl)propanenitrile (22): A solution of DIBAL-H (1.5M in toluene, 48.7 ml, 73 mmol) was added dropwise to a solution of **15** (18.1 g, 73 mmol) in CH_2Cl_2 (700 ml) at -60°C under argon. The reaction mixture was stirred for 1 h at the same temperature, and worked up as usual to give the thiolactol as a colorless oil (18.4 g).

A solution of 98% H_2SO_4 (3 ml) in CH_3OH (50 ml) was added dropwise to the solution of the thiolactol (18.4 g, 73 mmol) in CH_3OH (300 ml). The reaction solution was stirred for 18 h at room temperature, concentrated, and diluted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give a yellow oil, which was passed through a short silica gel column to afford **22** (18.2 g, 95%) as a mixture of diastereomers.

***tert*-Butyl *cis*-1,2,3,4,4a,9a-Hexahydro-6-methoxy-4a-methylbenzo[*b*]thieno[2,3-*b*]pyridine-1-carboxylate (17b)**: A solution of **24** (11.0 g, 42 mmol) in ether-THF (80 ml-20 ml) was added dropwise to a suspension of LAH (6.36 g, 167 mmol) in ether (500 ml) ar room temperature, and the mixture was stirred for 2 h at room temperature. The excess hydride was destroyed with H_2O (6.5 ml), 15% NaOH (6.5 ml), and H_2O (20 ml). The mixture was filtered, and the filtrate was evaporated to give a pale yellow oil (13 g).

A solution of Boc_2O (13.7 g, 63 mmol) in dioxane (100 ml) was added to a stirred mixture of the oil (13 g) and $NaHCO_3$ (7.1 g, 84 mmol) in H_2O-dioxane (300 ml-200 ml) under ice-cooling. The reaction mixture was stirred for 18 h at room temperature, and then extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to give the Boc compound as a yellow oil (13.5 g).

The Boc compound (13.5 g) was dissolved in *tert*-butanol (250 ml), and 98% H_2SO_4 (3 ml) was added dropwise to the solution. The reaction solution was stirred for 18 h at room temperature, and treated similary to the case of **17a** to give **17b** (12.3 g, 88%) as colorless crystals.

***cis*-1,2,3,4,4a,9a-Hexahydro-6-methoxy-1,4a-dimethylbenzo[*b*]thieno[2,3-*b*]pyridine (18b)**: Compound **(17b)** (6.35 g, 19 mmol) was reduced with LAH (2.88 g, 76 mmol) in THF (350 ml) in the same procedure described in synthesis of **18a** to give **18b** (4.73 g, 100%) as a colorless oil.

***cis*-1,2,3,4,4a,9a-Hexahydro-1,4a-dimethylbenzo[*b*]thieno[2,3-*b*]pyridin-6-ol (19b)**: Compound **(18b)** (1.00 g, 4.0 mmol) was treated with BBr_3 (3.8 ml, 40 mmol) in CH_2Cl_2 (10 ml) in a same procedure described in synthesis of **10a** to give **19b** (920 mg, 98%) as colorless needles.

***cis*-3,3a,8,8a-Tetrahydro-3a,8-dimethyl-2*H*-thieno[2,3-*b*]indol-5-yl *N*-methylcarbamate**

(2a-1, R=CH_3, R'=H): Sodium hydride (63% dispersion, 0.11 g, 4.6 mmol) was added to a mixture of **10a** (5.22 g, 23.6 mmol) and methyl isocyanate (4.04 g, 70.8 mmol) in THF (100 ml) under ice cooling. The mixture was stirred for 1.5 h at room temperature. Brine was added to the mixture, and the whole mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give a solid. The solid was purified on a silica gel column (eluent: hexane-ethyl acetate (4 : 1)) to give **2a-1** as colorless needles (5.43 g, 83%).

Compounds **(2a-2)** (R=C_2H_5, R'=H), **2a-3** (R=n-C_4H_9, R'=H), **2a-4** (R=n-C_7H_5, R'=H), **2b-1** (R=CH_3, R'=H), **3a-1** (R=CH_3, R'=H), **3a-2** (R=C_2H_5, R'=H), **3a-3** (R=n-C_4H_9, R'=H), **3b-1** (R=CH_3, R'=H), **3b-2** (R=C_2H_5, R'=H), and **3b-3** (R=n-C_4H_9, R'=H) were obtained in the same procedure described above in 89, 84, 83, 54, 93, 84, 97, 76, 77, and 69% yields respectively.

***cis*-3,3a,8,8a-Tetrahydro-3a,8-dimethyl-2*H*-thieno[2,3-*b*]indol-5-yl *N*,*N*-dimethylcarbamate (2a-5, R=R'=CH3)**: Sodium hydride (63% dispersion, 0.26 g, 6.8 mmol) was added to a solution of **10a** (1.37 g, 6.19 mmol) in DMF (15 ml) under ice cooling. The mixture was stirred for 15 min at room temperature. *N*,*N*-Dimethylcarbamoyl chloride (0.87 g, 8.1 mmol) was added to the mixture under ice cooling, and the mixture was stirred for 50 min at the same temperature. The whole mixture was poured onto ice-H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, and evaporated. The residue was purified on a silica gel column (eluent: hexane-ethyl acetate (6 : 1)) to give **2a-5** (1.54 g, 85%) as colorless prisms.

Compounds **2b-5** (R=R'=CH_3), **3a-5** (R=R'=CH_3), and **3b-5** (R=R'=CH_3) were obtained in the same procedure described above in 83, 97, and 68% yields respectively.

X-Ray crystallographic analysis of 9b: Crystal data $C_{14}H_{19}NOS$, M=249.376, orthorhombic, a=20.755(2), b=9.085(1), c=7.179(1) Å, V=1353.6(3) $Å^3$, Z=4, Space group $Pca2_1$, Dcalc.=1.224 kg/m^3, μ=19.27 cm^{-1}, CuKα radiation λ=1.5418 Å. Diffraction experiments were performed on a diffractometer (AFC5R/RIGAKU). Cell parameters were refined using setting angles of 25 reflections in the range of $40° < 2\theta < 60°$. Intensity data were collected in the range of $2\theta < 120°$ using $\omega/2\theta$ scan technique. The structure was solved by the direct method using MULTAN, and refined by the full matrix least square's method using anisotropic temperature factors for all non-hydrogen atoms and isotropic ones for all hydrogen atoms, which were located on a difference Fourier map. The final R and W_R values are 0.033 and 0.034 ($\sqrt{w} = 1/\sigma$ (Fobs)).

X-Ray crystallographic analysis of (+)-18a·D-tartaric acid: Crystal data $C_{17}H_{23}NO_7S$, M= 385.435, monoclinic, a=15.979(2), b=7.125(1), c=8.229(1) Å, β-103.22(3)°, V=912.1(2) $Å^3$, Z=2, Space

Table 2. Spectroscopic Data and Elemental Analysis Data for the Compounds in the Series of 2a, b.

Compounds (Formula)	mp °C	Ir ν_{max}^{nujol} cm^{-1}	^{1}H-Nmr ($CDCl_3$)δ	Analysis % or ms m/z calcd (found) C	H	N	S
5 ($C_{12}H_{15}NO_2S$)	68.5-69.5	1690, 1625	1.64(3H, s), 1.90(3H, s), 3.21(3H, s), 3.81(3H, s), 6.7-7.0(3H, m)	60.73 (60.70	6.37 6.32	5.90 6.04	13.51 13.29)
6 ($C_{11}H_{13}NO_2$)	84.5-85.5	1705, 1620	1.47(3H, d, *J*=7.9 Hz), 3.17(3H, s), 3.40(1H, q, *J*=8.1 Hz), 3.78(3H, s), 6.5-7.0(3H, m)	69.09 (69.03	6.85 6.75	7.32 7.40)	
7a ($C_{13}H_{16}BrNO_2$)	oil	1700[a]	1.38(3H, s), 2.0-2.7(2H, m), 2.8-3.2 (2H, m), 3.19(3H, s), 3.81(3H, s), 6.6-6.9(3H, m)	299, 297(M^+), 191, 190			
7b ($C_{14}H_{18}BrNO_2$)	oil	1705[a]	1.36(3H, s), 1.2-2.1(4H, m), 3.19(3H, s), 3.24(2H, t, *J*=6.5 Hz), 3.81(3H, s), 6.6-6.9(3H, m)	313, 311(M^+), 298, 296, 190			
8a ($C_{15}H_{19}NO_3S$)	oil	1700[a]	1.37(3H, s), 1.8-2.3(2H, m), 2.24(3H, s), 2.3-2.7(2H, m), 3.20(3H, s), 3.82(3H, s), 6.6-6.9(3H, m)	293(M^+), 250, 191			
8b ($C_{16}H_{21}NO_3S$)	oil	1705[a]	1.0-1.4(2H, m), 1.34(3H, s), 1.5-2.1 (2H, m), 2.27(3H, s), 2.74(2H, t, *J*=7.0 Hz), 3.17(3H, s), 3.80(3H, s), 6.6-6.9(3H, m)	307(M^+), 264			
9a ($C_{13}H_{17}NOS$)	46-47	1595, 1490	1.41(3H, s), 2.0-2.9(4H, m), 2.75(3H, s), 3.75(3H, s), 5.07(1H, s), 6.3-6.8(3H, m)	66.35 (66.58	7.28 7.34	5.95 5.86	13.62 13.88)
9b ($C_{14}H_{19}NOS$)	86.5-87.5	1590, 1485	1.44(3H, s), 1.4-2.0(4H, m), 2.1-2.4(1H, m), 2.5-3.0(1H, m), 2.78(3H, s), 3.58(1H, s), 3.75(3H, s), 6.3-6.8(3H, m)	67.43 (67.48	7.68 7.70	5.62 5.71	12.86 13.11)
10a ($C_{12}H_{15}NOS$)	120.5-121.5	3370	1.39(3H, s), 5.13(1H, s), 1.8-7.0(8H, broad)	65.12 (65.36	6.83 6.89	6.33 6.56	14.49 14.62)

(Table 2. continued)

10b ($C_{13}H_{17}NOS$)	132.5-133.5	3500-2400	1.43(3H, s), 1.3-1.6(2H, m), 1.6-1.9(2H, m), 2.1-2.4(1H, m), 2.6-2.9(1H, m), 2.86(3H, s), 3.55(1H, s), 4.69(1H, s), 6.3-6.7(3H, m)	66.35 (66.59	7.28 7.29	5.95 6.02	13.62 13.51)
11a ($C_{13}H_{19}NOS$)	oil	2560[a]	1.29(3H, s), 1.32(1H, t, *J*=7.5 Hz), 1.75-2.1 (2H, m), 2.1-2.7(2H, m), 2.68(3H, s), 2.91 (1H, d, *J*=8.8 Hz), 3.20(1H, d, *J*=8.8 Hz), 3.74(3H, s), 6.3-6.75(3H, m)	237(M^+), 176			
11b ($C_{14}H_{21}NOS$)	oil	2560[a]	1.28(3H, s), 1.32(1H, t, *J*=7.8 Hz), 1.4-1.9 (4H, m), 2.2-2.7(2H, m), 2.68(3H, s), 2.91 (1H, d, *J*=8.8 Hz), 3.16(1H, d, *J*=8.8 Hz), 3.74(3H, s), 6.2-6.7(3H, m)	251(M^+), 176			
2a-1 ($C_{14}H_{18}N_2O_2S$)	148.5-149	3360, 1700, 1670	1.43(3H, s), 1.9-2.9(4H, m), 2.78(3H,s), 2.86(3H, d, *J*=5.1 Hz), 4.86(1H, broad), 5.07 (1H, s), 6.2-6.9(3H, m)	60.41 (60.38	6.52 6.56	10.06 10.05	11.52 11.46)
2a-2 ($C_{15}H_{20}N_2O_2S$)	85.5-86.5	3350, 1705, 1670	1.19(3H, t, *J*=7.2 Hz), 1.42(3H, s), 2.0-2.9 (4H, m), 2.78(3H, s), 3.29(2H, dq, *J*=5.9 Hz, 7.3 Hz), 4.95(1H, broad), 5.07(1H, s), 6.2-6.9 (3H, m)	61.62 (61.67	6.89 6.98	9.58 9.59	10.97 11.04)
2a-3 ($C_{17}H_{24}N_2O_2S$)	86-87	3290, 1730, 1695	0.8-1.05(3H, m), 1.1-1.7(4H,m), 1.42(3H, s), 2.0-2.9(4H, m), 2.78(3H, s), 3.24(2H, q, *J*=6.1 Hz), 4.6-5.2(1H, broad), 5.07(1H, s), 6.2-6.9(3H, m)	63.72 (63.95	7.55 7.73	8.74 8.70	10.01 10.08)
2a-4 ($C_{20}H_{30}N_2O_2S$)	51-53	3320, 1735, 1700	0.89(3H, t, *J*=6.9 Hz), 1.31(10H, m), 1.43 (3H, s), 2.20(2H, m), 2.60(2H, m), 2.79 (3H, s),3.24(2H, dd, *J*=6.8 Hz, 12.7 Hz), 4.92 (1H, broad), 5.07(1H, s), 6.36(1H, d, *J*=8.3 Hz), 6.78(1H, d, *J*=2.5 Hz), 6.83(1H, dd, *J*=2.5 Hz, 8.3 Hz)	66.26 (66.34	8.34 8.36	7.73 7.56	8.84 8.65)
2a-5 ($C_{15}H_{20}N_2O_2S$)	86-87	1705, 1665, 1650	1.43(3H, s), 1.9-2.9(4H, m), 2.78(3H, s), 3.02(6H, broad s), 5.06(1H, s), 6.2-6.9(3H, m)	61.62 (61.81	6.89 6.99	9.58 9.55	10.97 10.97)

(Table 2. continued)

2b-1 ($C_{15}H_{20}N_2O_2S$)	109.5-111.5	3380, 1710, 1680	1.44(3H, s), 1.3-2.0(4H, m), 2.1-2.4(1H, m), 2.5-2.9(1H, m), 2.8(3H, s), 2.87(3H, d, *J*=4.8 Hz), 3.69(1H, s), 4.86(1H, broad), 6.4-6.9 (3H, m)	61.62 (61.55	6.89 6.89	9.58 9.62	10.97 10.89)
2b-5 ($C_{16}H_{22}N_2O_2S$)	135-136.5	1705, 1670, 1650	1.44(3H, s), 1.4-1.9(4H, m), 2.1-2.4(1H, m), 2.5-2.9(1H, m), 2.8(3H, s), 3.02(6H, broad s), 3.68(1H, s), 6.4-6.9(3H, m)	62.71 (62.95	7.24 7.29	9.14 9.24	10.44 10.58)

[a] The infrared spectrum was measured in a liquid film.

Table 3. Spectroscopic Data and Elemental Analysis Data for the Compounds in the Series of 3a, b.

Compounds (Formula)	mp °C	Ir ν $^{nujol}_{max}$ cm^{-1}	^{1}H-Nmr ($CDCl_3$)δ	Analysis % or ms m/z calcd (found) C	H	Cl	N	S
12 ($C_9H_8O_2S$)	120-122	1695	3.79(3H, s), 3.92(2H, s), 6.7-7.3(3H, m)	180(M^+), 152, 137				
13 ($C_{10}H_8O_3S$)	143-145	2800-2200 1660	3.77(3H, s), 6.86(1H, dd, *J*=2.6 Hz, 8.6 Hz), 7.35(1H, d, *J*=8.6 Hz), 7.50(1H, d, *J*=2.6 Hz), 8.04(1H, s), 10.25(1H, broad)[b]	57.68 (57.50	3.87 3.65			15.40 15.49)
14 ($C_{10}H_{10}O_2S$)	49-50	1690	1.53(3H, d, *J*=7.5 Hz), 3.77(1H, q, *J*=7.5 Hz), 3.81(3H, s), 6.7-7.3(3H, m)	61.83 (61.89	5.19 5.13			16.51 16.52)
15 ($C_{13}H_{13}NO_2S$)	56-57	2250, 1700	1.45(3H, s), 1.9-2.5(4H, m), 3.83(3H, s), 6.76(1H, d, *J*=2.6 Hz), 6.90(1H, dd, *J*=2.6 Hz, 8.5 Hz), 7.29(1H, d, *J*=8.5 Hz)	63.13 (63.29	5.30 5.20		5.66 5.62	12.97 13.03)
16 ($C_{17}H_{23}NO_4S$)	113-115	3340, 1700, 1680	1.39(9H, s), 1.41(3H, s), 1.9-2.4(2H, m), 2.7-3.1(2H, m), 3.82(3H, s), 4.30(1H, broad), 6.7-6.9(2H, m), 7.2-7.3(1H, m)	60.51 (60.79	6.87 6.75		4.15 4.21	9.50 9.77)
17a ($C_{17}H_{23}NO_3S$)	oil	1695[a]	1.45(3H, s), 1.50(9H, s), 1.8-2.5(2H, m), 3.0-3.3(1H, m), 3.4-3.8(1H, m), 3.78(3H, s), 5.34(1H, broad s), 6.6-7.1(3H, m)	321(M^+), 265, 178				

(Table 3. continued)

17b ($C_{18}H_{25}NO_3S$)	103-105	1690	1.40(3H, s), 1.48(9H, s), 1.5-2.0(4H, m), 3.02(1H, m), 3.78(3H, s), 4.03(1H, m), 6.05(1H, s), 6.63(1H, d, *J*=2.4 Hz), 6.71(1H, dd, *J*=2.4 Hz, 8.3 Hz), 7.07(1H, d, *J*=8.3 Hz)	335(M^+), 279, 262, 235			
18a ($C_{13}H_{17}NOS$)	39-41	1590, 1565	1.48(3H, s), 1.8-2.2(2H, m), 2.43(3H, s), 2.6-3.0(2H, m), 3.76(3H, s), 4.93(1H, s), 6.5-6.8(2H, m), 6.8-7.1(1H, m)	66.34 (66.07	7.28 7.26	5.95 6.05	13.63 13.76)
18b ($C_{14}H_{19}NOS$)	oil	1595, 1570[a]	1.48(3H, s), 1.2-1.9(4H, m), 2.42(3H, s), 2.55-2.73(2H, m), 3.76(3H, s), 5.15, 5.17 (total 1H, s), 6.62(1H, d, *J*=2.8 Hz), 6.65(1H, dd, *J*=2.8 Hz, 9.0 Hz), 7.11(1H, d, *J*=9.0 Hz)	249(M^+), 234			
19a ($C_{12}H_{15}NOS$)	134-136	3300-2400	1.46(3H, s), 2.0-2.2(2H, m), 2.44(3H, s), 2.6-2.9(2H, m), 4.84(1H, s), 5.08(1H, broad s), 6.5-6.6(2H, m), 6.92(1H, dd, *J*=2.0 Hz, 6.8 Hz)	65.12 (64.53	6.83 6.82	6.33 6.28	14.49 14.42)
19b ($C_{13}H_{17}NOS$)	147-149	2960	1.45(3H, s), 1.2-1.9(4H, m), 2.42(3H, s), 2.62(2H, m), 5.10(1H, broad s), 5.14, 5.15 (total 1H, s), 6.55(1H, dd, *J*=2.6 Hz, 9.0 Hz), 6.57(1H, d, *J*=2.6 Hz), 7.05(1H, d, *J*=9.0 Hz)	66.35 (66.21	7.28 7.35	5.95 5.65	13.62 13.83)
20 ($C_{11}H_{12}O_2S$)	oil	1705[a]	1.43(6H, s), 3.81(3H, s), 6.83(1H, dd, *J*=2.4 Hz, 7.0 Hz), 6.87(1H, d, *J*=2.4 Hz), 7.23(1H, d, *J*=7.0 Hz)	208(M^+), 179			
21 ($C_{15}H_{14}N_2O_2S$)	116-118	2250, 1705	1.9-2.5(8H, m), 3.86(3H, s), 6.76(1H, d, *J*=2.4 Hz), 6.96(1H, dd, *J*=2.4 Hz, 8.3 Hz), 7.35(1H, d, *J*=8.3 Hz)	286(M^+), 232			
22 ($C_{14}H_{17}NO_2S$)	oil	2250[a]	1.30(0.8H, s), 1.45(2.2H, s), 1.8-2.6(4H, m), 3.38(2.1H, s), 3.39(0.9H, s), 3.78(2H, s), 3.84(1H, s), 4.92(0.7H, s), 4.98(0.3H, s), 6.6-7.3(3H, m)	263(M^+), 232, 209, 178			
3a-1 ($C_{14}H_{18}N_2O_2S$)	120-123	3200, 1725	1.50(3H, s), 1.9-2.2(2H, m), 2.44(3H, s), 2.7-2.9(2H, m), 2.88(3H, d, *J*=4.9 Hz), 4.90(1H, broad s), 5.03(1H, s), 6.8-6.9(2H, m), 7.0-7.1(1H, m)	60.40 (60.23	6.52 6.47	10.06 10.04	11.52 11.30)

(Table 3. continued)

3a-2 ($C_{15}H_{20}N_2O_2S$)	44-46	3335, 1705	1.21(3H, t, *J*=7.3 Hz), 1.50(3H, s), 1.9-2.2 (2H, m), 2.44(3H, s), 2.7-2.9(2H, m), 3.30(2H, quintet, *J*=7.3 Hz), 4.9(1H, broad s), 5.04(1H, s), 6.7-6.9(2H, m), 7.0-7.1 (1H, m)	61.61 (61.80	6.89 7.00		9.58 9.62	10.97 11.07)
3a-3 ($C_{17}H_{24}N_2O_2S$)	oil	3330, 1720[a]	0.8-1.1(3H, m), 1.2-2.8(4H, m), 1.49(3H, s), 1.9-2.1(2H, m), 2.43(3H, s), 2.7-2.9(2H, m), 3.25(2H, q, *J*=6.2 Hz), 5.00(1H, broad s), 5.04 (1H, s), 6.7-6.9(2H, m), 7.0-7.1(1H, m)	320(M^+), 221, 164				
3a-5 ($C_{15}H_{20}N_2O_2S$)	oil	1725[a]	1.50(3H, s), 1.9-2.1(2H, m), 2.44(3H, s) 2.7-2.9(2H, m), 3.00(3H, s), 3.09(3H, s), 5.06(1H, s), 6.8-6.9(2H, m), 7.0-7.1(1H, m)	292(M^+), 277, 96, 72				
3b-1 ($C_{15}H_{20}N_2O_2S$)	141.5-144	3320, 1705	1.48(3H, s), 1.2-1.9(4H, m), 2.42(3H, s), 2.64(2H, m), 2.87(3H, d, *J*=4.8 Hz), 5.03 (1H, broad s), 5.21(1H, s), 6.82(1H, d, *J*=2.4 Hz), 6.85(1H, dd, *J*=2.4 Hz, 9.0 Hz), 7.16(1H, d, *J*=9.0 Hz)	61.62 (60.99	6.89 6.95		9.58 9.91	10.96 11.01)
3b-2 · HCl ($C_{16}H_{22}N_2O_2S$ · HCl)	219-220 (dec.)	3240, 1745	1.19(3H, t, *J*=7.2 Hz), 1.53(3H, s), 1.7-2.3 (4H, m), 2.87(3H, s), 3.20(2H, m), 3.22 (2H, quintet, *J*=7.2 Hz), 5.05(1H, s), 5.90 (1H, broad s), 6.90(1H, d, *J*=2.5 Hz), 6.96(1H, dd, *J*=2.5 Hz, 9.0 Hz), 7.19(1H, d, *J*=9.0 Hz)[b]	56.05 (55.83	6.76 6.70	10.34 10.04	8.17 8.03	9.35 9.33)
3b-3 · HCl ($C_{18}H_{26}N_2O_2S$ · HCl)	191-193 (dec.)	3240, 1745	0.95(3H, t, *J*=5.7 Hz), 1.1-1.7(4H, m), 1.56 (3H, s), 1.8-2.3(4H, m), 2.82(3H, s), 3.17 (2H, m), 3.20(2H, q, *J*=5.7 Hz), 4.94(1H, s), 5.25(1H, broad s), 6.88(1H, d, *J*=2.4 Hz), 6.95 (1H, dd, *J*=2.4 Hz, 8.8 Hz), 7.20(1H, d, *J*=8.8 Hz)	58.28 (58.04	7.34 7.37	9.56 9.28	7.55 7.37	8.64 8.53)
3b-5 · HCl ($C_{16}H_{22}N_2O_2S$ · HCl)	225-229 (dec.)	1725	1.60(3H, s), 1.7-2.3(4H, m), 2.81(3H, s), 3.03(6H, s), 3.10(2H, m), 4.99(1H, s), 6.88 (1H, d, *J*=2.4 Hz), 6.96(1H, dd, *J*=2.4 Hz, 8.5 Hz), 7.17(1H, d, *J*=8.5 Hz)	56.05 (56.09	6.76 6.71	10.34 10.24	8.17 8.12	9.35 9.52)

[a] The infrared spectrum was measured in a liquid film.

[b] ^{1}H-Nmr spectrum was measured in DMSO-d6.

group $P2_1$, Dcalc.=1.403 kg/m^3, μ=18.93 cm^{-1}, CuKα radiation λ=1.5418 Å. Diffraction experiments were performed on a diffractometer (AFC5/RIGAKU). Cell parameters were refined using setting angles of 20 reflections in the range of $0° < 2\theta < 60°$. Intensity data were collected in the range of $2\theta < 130°$ using $\omega/2\theta$ scan technique. The structure was solved by the direct method using SIR, and refined by the block-diagonal matrix least square's method using anisotropic temperature factors for all non-hydrogen atoms. Of 23 hydrogen atoms, 15 atoms were located on a difference Fourier map and refined with isotropic temperature factors. The positions of other hydrogen atoms were assumed geometrically and fixed troughout the refinement. The final R and W_R values are 0.066 and 0.077 ($\sqrt{w} = 1/\sigma$ (Fobs)).

Determination of inhibitory activities of AChE and BuChE in vitro: The crude synaptosomal fraction (2.5 mg protein / ml), obtained from the brain of male rats (Slc : Wistar, 10weeks old), was used as a source of AChE. Human serum BuChE was purchased from Sigma Chemicals. Cholinesterase activity was measured by spectrophotometric method of Ellman *et al.*[9] Acetylthiocholine (AthCh) and butyrylthiocholine (ButhCh) were used as the substrates for measurement of AChE activity and BuChE activity, respectively. The enzyme reaction was initiated by an addition of an AChE solution (0.05 ml) or 0.02 unit of BuChE to the reaction medium containing 0.33 mM 5,5'-dithiobis(2-nitrobenzoic acid), and 0.5 mM AthCh or 0.5 mM ButhCh in 0.1 M potassium phosphate buffer (pH 7.6), and a DMSO solution of the test compound (0.05 ml) in a total volume of 3 ml. The production of the yellow 5-thio-2-nitrobenzoate anion was followed at a wave length of 412 nm. AChE and BuChE activities were measured in the presence of varying concentrations of each compound (10^{-9} - 10^{-4}M), and IC_{50} values were determined graphically from *log* concentration-inhibition curves (Table 3).

Acute toxicity study in mice: Groups of 3 to 5 male mice (Slc : ddY, about 25 g) were used. Mice were orally administered with one of the test compounds, suspended or dissolved in a 0.5% carboxymethyl-cellulose solution, at 5 to 300 mg/kg. Physostigmine was also administered orally at doses of 1 and 1.5 mg/kg. The number of deaths was counted for 2 weeks after administration, and MTD for each compound was determined.

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