

Synthesis and Evaluation of Antidepressive Activity of  
[1]Benzothieno[2',3':4,5]furo[3,2-*d*]pyrimidines and Their Precursors

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Synthesis of [1]benzothieno[2',3':4,5]furo[3,2-*d*]pyrimidines is described. Antidepressive evaluation of these compounds and their precursors were screened by inhibitory action of reserpine-induced hypothermia.

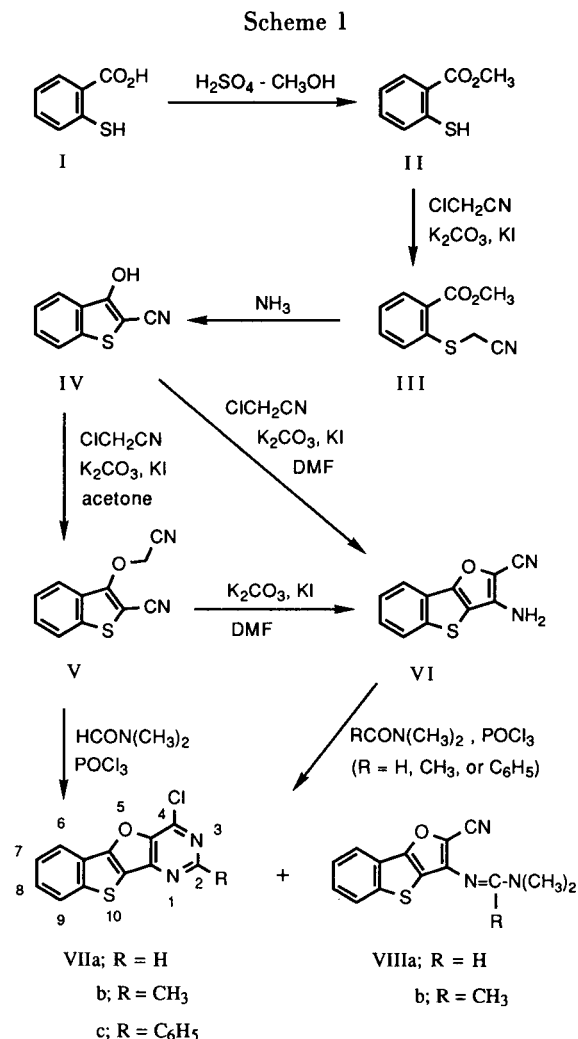
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We have previously reported the synthesis and antidepressive activity of benzofuro[2,3-*e*]imidazo[1,2-*c*]pyrimidines [1] corresponding to B-nor-6-oxa-11,13,15-triazasteroid and their precursors, and a few compounds exhibited more potent activity than imipramine which was one of the iminodibenzyl derivatives and a typical tricyclic antidepressant. In that paper, we have also reported one step synthesis of 4-chlorobenzofuro[3,2-*d*]pyrimidine from 2-cyanophenoxyacetonitrile. If this synthetic method was applied to *O*-(2-cyano-3-benzo[*b*]thienyl)glycolonitrile (V), it was thought that a new ring system compound, 4-chloro[1]benzothieno[2',3':4,5]furo[3,2-*d*]pyrimidine (VIIa), could be obtained.

In this report, we describe a convenient synthesis and evaluation of anti-reserpine activity as a first screening of the antidepressive activity for 4-chloro[1]benzothieno[2',3':4,5]furo[3,2-*d*]pyrimidines (VII) and their precursors.

As shown in Scheme 1, commercially available thiosalicylic acid (I) was used as a starting material. After esterification of this acid with sulfuric acid in methanol, *S*-alkylation of the ester II was carried out with chloroacetonitrile by a similar method for the preparation of 3,5-dimethoxyphenylthioacetone nitrile previously reported [2] to give methyl 2-cyanomethylthiobenzoate (III). The latter ester was easily cyclized to 3-hydroxybenzo[*b*]thiophene-2-carbonitrile (IV) with ammonia. Görlitzer [3], Philipp *et al.* [4] and Kojima *et al.* [5] have already reported the synthesis of IV from II on the same route. However, all of them obtained III from the reaction of II with chloroacetonitrile in the presence of sodium methoxide and also used sodium methoxide for cyclization of III.

Beck has reported that *O*-alkylation of methyl 3-hydroxybenzo[*b*]thiophene-2-carboxylate with chloroacetonitrile in the presence of potassium *t*-butoxide in DMSO gave methyl 3-(cyanomethoxy)benzo[*b*]thiophene-2-carboxylate [6]. In this paper, we carried out *O*-alkylation of IV with chloroacetonitrile by a similar method for the preparation of phenoxyacetonitrile previously reported [7], and desired compound V could be obtained, which appeared to be an excellent precursor for



annulation of a furo[3,2-*d*]pyrimidine moiety to benzo[*b*]thiophene skeleton. Thus obtained V was converted to VIIa by heating with Vilsmeier reagent using *N,N*-dimethylformamide (DMF) and phosphoryl chloride. Furthermore, the similar reaction of V with *N,N*-dimethylacetamide (DMA) or *N,N*-dimethylbenzamide (DMB) in the presence of phosphoryl chloride was carried with the intention of introducing methyl or phenyl group at the 2-position of VIIa. But, the desired products could not be

Table I  
Effect of Compounds **VIIIa** and **VIIIb** on Reserpine-Induced Hypothermia in Mice

Compound	Before administration	Body temperature (°C), mean value ± SE			
		30 minutes	Time after administration		
			1 hour	2 hours	4 hours
saline	24.2 ± 0.3	25.6 ± 0.4	25.9 ± 0.6	26.7 ± 0.9	28.8 ± 0.7
imipramine	24.1 ± 0.3	28.4 ± 0.3 [a]	31.9 ± 0.6 [a]	32.5 ± 1.6 [b]	34.0 ± 1.4 [b]
<b>VIIIa</b>	24.4 ± 0.1	25.9 ± 0.3	26.1 ± 0.5	27.3 ± 0.9	32.3 ± 1.2 [b]
<b>VIIIb</b>	24.3 ± 0.3	26.1 ± 1.6	26.5 ± 1.5	28.4 ± 1.0	31.7 ± 1.0 [b]

Five male ICR-JCL mice weighing 20 to 34 g were used in all experiments and test compounds (10 mg/kg, *i.p.*) were injected at 18 hours after reserpine (2 mg/kg, *i.p.*) was administered to mice. [a] Significantly different from the control (saline) at  $p < 0.01$ . [b] Significantly different from the control (saline) at  $p < 0.05$ .

obtained, and only starting material, **V**, was recovered. These results were exactly similar to that of previous report [1]. Therefore, we planned to obtain these derivatives *via* 3-amino[1]benzothieno[3,2-*b*]furan-2-carbonitrile (**VI**). Some 2,3-disubstituted [1]benzothieno[3,2-*b*]furans have been already reported [6], but our desired compound **VI** has not been reported. So, this compound was prepared by heating **V** with potassium carbonate and potassium iodide in DMF at 50° for 3 hours. Compound **VI** also could be obtained in a one-step reaction of **IV** by heating with chloroacetonitrile in DMF in the presence of potassium carbonate and potassium iodide at 80° for 42 hours. The reaction of thus obtained **VI** with DMA and DMB under the Vilsmeier reaction condition gave desired 4-chloro-2-methyl- and 4-chloro-2-phenyl[1]benzothieno[2',3':4,5]furo[3,2-*d*]pyrimidines **VIIb,c**, respectively. Compound **VIIa** was also obtained by the similar treatment of **VI** with DMF. In the cases of the preparation of **VIIa,b** from **VI**, 3-(*N,N*-dimethylaminomethyleneamino)-[1]benzothieno[3,2-*b*]furan-2-carbonitrile (**VIIIa**) and 3-(*C*-methyl-*N,N*-dimethylaminomethyleneamino)[1]benzothieno[3,2-*b*]furan-2-carbonitrile (**VIIIb**) were respectively obtained as a by-product.

Evaluation of the antidepressive activity of thus obtained **IV-VIII** was screened by the method of Askew [8] which including inhibitory activity against reserpine-induced hypothermia in mice and those data were compared with those of control (saline) and imipramine. When the body temperature of mice administered with a test compound was significantly different from that of mice administered with saline at  $p < 0.05$  on the statistical analysis using Student's *t*-test, the test compound was estimated as a potent one. Compounds **VIIIa** and **VIIIb** exhibited potent anti-reserpine activity, and effects of those on reserpine-induced hypothermia were shown in Table I.

Table I

Both effects of **VIIIa** and **VIIIb** showed significant difference from that of saline at  $p < 0.05$  at 4 hours later after administration of test compound. However, neither **VIIIa** nor **VIIIb** showed higher potent activity than imipramine

at any time after administration of test compound.

## EXPERIMENTAL

All melting points were determined on a Yanagimoto micro-melting point apparatus, and are uncorrected. Elemental analyses were performed on a Yanagimoto MT-2 CHN Corder elemental analyzer. The EI-*ms* spectra were taken on a Shimadzu LKB-9000 Instrument. The ir spectra were recorded on a Japan Spectroscopic IRA-102 diffraction grating infrared spectrophotometer. The pmr spectra were recorded on a Hitachi R-22 FTS FT-NMR spectrometer (90-MHz) or Varian VXR-200 Instrument (200-MHz). The chemical shifts ( $\delta$ ) in ppm are measured relative to tetramethylsilane as an internal standard, and the signals are designated as follows; s, singlet; m, multiplet; br, broad.

### Methyl Thiosalicylate (**II**).

A solution of thiosalicylic acid (31.4 g, 0.19 mole) in 5% sulfuric acid-methanol (500 ml) was refluxed under nitrogen atmosphere for 18 hours. After concentration of the reaction mixture, 10-fold of water was added to the mixture, and the resulting mixture was made alkaline with sodium hydrogen carbonate and extracted with benzene. The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and evaporated to dryness to give the titled compound (33.2 g) as yellow oil. This product was supplied for the next reaction without further purification.

### Methyl 2-Cyanomethylthiobenzoate (**III**) [3-5].

After stirring of a mixture of **II** (33.2 g), potassium carbonate (55.2 g, 0.4 mole) and potassium iodide (1.3 g) in dry acetone (400 ml) for 15 minutes, chloroacetonitrile (22.7 g, 0.3 mole) was added dropwise to the mixture during 30 minutes. After removal of potassium carbonate by filtration, the filtrate was evaporated to dryness. The resulting residue was extracted with hot cyclohexane to give the titled compound (38.7 g), quantitatively. This product was supplied for the next reaction without further purification.

### 3-Hydroxybenzo[*b*]thiophene-2-carbonitrile (**IV**) [3-5].

A solution of **III** (38.7 g) in methanol (1.8 l) was stirred at room temperature under bubbling of ammonia gas for 3 hours. After evaporation of the solvent of the reaction mixture, the resulting residue was recrystallized from methanol-water to give the title compound (30.3 g) mp 154-156° dec (lit mp *ca.* 163° dec [3a], mp *ca.* 175° dec [4], mp 176.5° sublimes [5]).

*Anal.* Calcd. for  $C_9H_8NOS$ : C, 61.70; H, 2.88; N, 7.99. Found: C, 61.97; H, 2.76; N, 7.85.

*O*-(2-Cyano-3-benzothienyl)glycolonitrile (**V**).

After stirring of a mixture of **IV** (17.5 g, 0.1 mole), dry potassium carbonate (27.6 g, 0.2 mole), and potassium iodide (0.65 g) in dry acetone (400 ml) at room temperature for 15 minutes, chloroacetonitrile (15.1 g, 0.2 mole) was added dropwise to the mixture. The resulting mixture was refluxed for 10 hours. After removal of potassium carbonate by filtration, the filtrate was evaporated and the residue was chromatographed on silica gel. The dichloromethane eluate was recrystallized from benzene-*n*-hexane to give the title compound (14.9 g, 70%) as colorless needles, mp 113-114°; ms: *m/z* 214 ( $M^+$ ); ir (potassium bromide): 2200 ( $C\equiv N$ )  $cm^{-1}$ ; pmr (deuteriochloroform): 5.34 (s, 2H,  $OCH_2$ ), 7.40-8.00 (m, 4H, aromatic H).

*Anal.* Calcd. for  $C_{11}H_8N_2OS$ : C, 61.67; H, 2.82; N, 13.08. Found: C, 61.62; H, 2.61; N, 12.94.

3-Amino[1]benzothieno[3,2-*b*]furan-2-carbonitrile (**VI**).

a) From Compound **IV**.

After stirring of a mixture of **IV** (475 mg, 3 mmoles), dry potassium carbonate (828 mg, 6 mmoles), and potassium iodide (20 mg) in dry DMF (10 ml) at room temperature for 15 minutes, chloroacetonitrile (340 mg, 4.5 mmoles) was added dropwise. The mixture was stirred at 80° for 10 hours. After further addition of chloroacetonitrile (76 mg, 1 mmole), the mixture was stirred at 80° for additional 32 hours. Potassium carbonate was removed by filtration and the filtrate was evaporated. The chloroform soluble fraction of the residue at room temperature was recrystallized from benzene to give the title compound (424 mg 66%) as colorless needles, mp 178-180° sublimed; ms: *m/z* 214 ( $M^+$ ); ir (potassium bromide): 3450, 3360 (N-H), 2200 ( $C\equiv N$ )  $cm^{-1}$ ; pmr (acetone- $d_6$ ): 5.98 (br, 2H,  $NH_2$ , exchangeable with deuterium oxide), 7.30-7.60 (m, 2H, 6- and 7-H), 7.80-8.10 (m, 2H, 5- and 8-H).

*Anal.* Calcd. for  $C_{11}H_8N_2OS$ : C, 61.70; H, 2.82; N, 13.08. Found: C, 61.80; H, 2.60; N, 13.10.

b) From Compound **V**.

A mixture of **V** (7.6 g, 36 mmoles), dry potassium carbonate (9.8 g, 71 mmoles), and potassium iodide (0.24 g) in dry DMF (150 ml) was stirred at 50° for 3 hours. After removal of potassium carbonate by filtration, 1.5 l of water was added to the filtrate and the mixture was extracted with ethyl acetate. The organic layer was worked up usually and resulting residue was recrystallized from benzene to give the titled compound (6.5 g, 86%).

4-Chloro[1]benzothieno[2',3':4,5]furo[3,2-*d*]pyrimidine (**VIIa**) and 3-(*N,N*-Dimethylaminomethyleneamino)[1]benzothieno[3,2-*b*]furan-2-carbonitrile (**VIIIa**).

a) From Compound **V**.

The Vilsmeier reagent was prepared by stirring of DMF (0.5 ml, 6 mmoles) and phosphoryl chloride (1.7 ml, 18 mmoles) at 0° for 30 minutes. To this reagent, was added **V** (1.1 g, 5 mmoles) and dry ethanol-free chloroform (2 ml), and the mixture was refluxed for 10 hours. The reaction mixture was poured into ice water. The resulting mixture was made alkaline with sodium hydrogen carbonate and extracted with chloroform. The organic layer was worked up usually and the resulting residue was chromatographed on silica gel. Chloroform eluate was

recrystallized from cyclohexane to give **VIIa** (85 mg, 7%) as colorless cubes, mp 190-192°; ms: *m/z* 260 ( $M^+$ ), intensity ratio of the peak at *m/z* 260 to that at *m/z* 262 showed 3 to 1; pmr (deuteriochloroform): 7.40-7.70 (m, 2H, 7- and 8-H), 7.80-8.20 (m, 2H, 6- and 9-H), 8.93 (s, 1H, 2-H).

*Anal.* Calcd. for  $C_{12}H_8ClN_2OS$ : C, 55.29; H, 1.93; N, 10.75. Found: C, 55.36; H, 1.84; N, 10.63.

b) From Compound **VI**.

The Vilsmeier reagent was prepared in a similar manner described in method a) of synthesis of **VIIa**. To the Vilsmeier reagent, were added **VI** (1.1 g, 5 mmoles) and dry DMF (5 ml), and the mixture was stirred at 70° for 6 hours. The reaction mixture was poured into ice water, and the mixture was extracted with chloroform. The aqueous layer was made alkaline with sodium hydrogen carbonate and precipitated crystalline solid was collected on a filter. Thus obtained solid was recrystallized from cyclohexane to give **VIIa** (0.78 g, 60%).

The organic layer described above was worked up usually and the resulting residue was chromatographed on silica gel. Benzene eluate was recrystallized from tetrachloromethane to give **VIIIa** (0.51 g, 38%) as pale red prisms, mp 189-190°; ms: *m/z* 269 ( $M^+$ ); ir (potassium bromide): 2220 ( $C\equiv N$ )  $cm^{-1}$ ; pmr (deuteriochloroform): 3.14 (s, 6H,  $2 \times CH_3$ ), 7.30-7.50 (m, 2H, 6- and 7-H), 7.60-8.00 (m, 3H, 5- and 8-H and  $N=CH$ ).

*Anal.* Calcd. for  $C_{14}H_{11}N_3OS$ : C, 62.44; H, 4.12; N, 15.60. Found: C, 62.65; H, 4.34; N, 15.68.

4-Chloro-2-methyl[1]benzothieno[2',3':4,5]furo[3,2-*d*]pyrimidine (**VIIb**) and 3-(*C*-Methyl-*N,N*-dimethylaminomethyleneamino)[1]benzothieno[3,2-*b*]furan-2-carbonitrile (**VIIIb**).

The Vilsmeier reagent was prepared by stirring of DMA (0.52 g, 6 mmoles) and phosphoryl chloride (2.3 ml, 15 mmoles) at 0° for 30 minutes. To this reagent, was added **VI** (1.1 g, 5 mmoles) and dry ethanol-free chloroform (5 ml), and the mixture was stirred at 40° for 2.5 hours. The reaction mixture was poured into ice water. The resulting mixture was extracted with dichloromethane. The aqueous layer was made alkaline with sodium hydrogen carbonate and extracted with chloroform. The chloroform layer was worked up usually, and the resulting residue was chromatographed on silica gel. Chloroform eluate was recrystallized from ethyl acetate to give **VIIb** (0.85 g, 62%) as colorless prisms, mp 225-226°; ms: *m/z* 274 ( $M^+$ ), intensity ratio of the peak at *m/z* 274 to that at *m/z* 276 showed 3 to 1; pmr (deuteriochloroform): 2.85 (s, 3H,  $CH_3$ ), 7.40-7.60 (m, 2H, 7- and 8-H), 7.80-8.20 (m, 2H, 6- and 9-H).

*Anal.* Calcd. for  $C_{13}H_7ClN_2OS$ : C, 56.84; H, 2.57; N, 10.20. Found: C, 56.94; H, 2.75; N, 10.02.

The dichloromethane layer which was obtained from the first extraction described above was worked up usually, and the resulting residue was chromatographed on silica gel. Benzene-dichloromethane (3:1, v/v) eluate was recrystallized from *n*-hexane-cyclohexane to give **VIIIb** (0.45 g, 32%) as colorless needles, mp 139-140°; ms: *m/z* 283 ( $M^+$ ); ir (potassium bromide): 2200 ( $C\equiv N$ )  $cm^{-1}$ ; pmr (deuteriochloroform): 2.02 (s, 3H,  $N=CCH_3$ ), 3.14 (s, 6H,  $N(CH_3)_2$ ), 7.30-7.50 (m, 2H, 6- and 7-H), 7.60-8.00 (m, 2H, 5- and 8-H).

*Anal.* Calcd. for  $C_{15}H_{13}N_3OS$ : C, 63.59; H, 4.62; N, 14.83. Found: C, 63.71; H, 4.55; N, 14.91.

4-Chloro-2-phenyl[1]benzothieno[2',3':4,5]furo[3,2-*d*]pyrimidine (**VIIc**).

The Vilsmeier reagent was prepared by stirring of DMB (0.89 g, 6 mmoles) and phosphoryl chloride (2.3 ml, 15 mmoles) at 0° for 30 minutes. To this reagent, were added VI (1.1 g, 5 mmoles) and dry ethanol-free chloroform (5 ml), and the mixture was stirred at 40° for 15 hours. The reaction mixture was poured into ice water. The resulting mixture was made alkaline with sodium hydrogen carbonate and extracted with chloroform. The organic layer was worked up usually, and the resulting residue was chromatographed on silica gel. Benzene eluate was recrystallized from benzene-chloroform to give the titled compound (1.2 g, 70%) as colorless needles, mp 261-262°; ms: m/z 336 (M<sup>+</sup>), intensity ratio of the peak at m/z 336 to that at m/z 338 showed 3 to 1; pmr (deuteriochloroform): 7.40-7.60 (m, 5H, 7- and 8-H and phenyl-3', 4', and 5'-H), 7.80-8.20 (m, 2H, 6- and 9-H), 8.40-8.60 (m, 2H, phenyl-2'- and 6'-H).

*Anal.* Calcd. for C<sub>18</sub>H<sub>9</sub>ClN<sub>2</sub>OS: C, 64.19; H, 2.69; N, 8.32. Found: C, 64.32; H, 2.72; N, 8.60.

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