[Chem. Pharm. Bull. 28(11)3315—3322(1980)]

Syntheses of N-(1-Methyl-2-piperazinoethyl)propionanilides and 2-Alkoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]benzothiazoles[1]

Jutaro Okada and Masaharu Shimabayashi

Faculty of Pharmaceutical Sciences, Kyoto University[2]

(Received June 6, 1980)

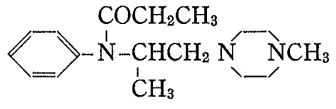
N-(1-Methyl-2-piperazinoethyl)anilines (**5a**—**e**) and 2-alkoxy-6-[1-methyl-2-(4-phenethylpiperazino)ethyl]-amino-benzothiazoles (**8a**—**d**) were prepared by the reduction of 1-(2-anilinopropionyl)piperazines (**4a**—**e**) and 1-[2-(2-alkoxy-benzothiazolyl-(6))-amino-propionyl]-4-phenethylpiperazines (**7a**—**d**). N-(1-Methyl-2-piperazinoethyl)propionanilides (**6a**—**e**) and 2-alkoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]propionamide]-benzothiazoles (**9a**—**d**) were prepared by N-propionylation of **5a**—**e** and **8a**—**d**.

Analgesic activity testing showed that (A) N-[1-methyl-2-(4-benzylpiperazino)ethyl]-propionanilide (**6d**) and N-[1-methyl-2-(4-phenethylpiperazino)ethyl]propionanilide (**6e**) possessed *ca.* 1/3 of the analgesic effect of pentazocine; (B) N-propionylation of N-[1-methyl-2-(4-benzylpiperazino)ethyl]aniline (**5d**) and N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-aniline (**5e**) increased the analgesic activity, but N-propionylation of **8a**—**d** decreased the analgesic activity; (C) an aniline derivative (**6e**) was more potent than the 2-alkoxy-6-aminobenzothiazole derivatives (**9a**—**d**).

Keywords——syntheses of analgesics; piperazines; lithium aluminium hydride; 2-alkoxy-6-aminobenzothiazoles; N-propionylation

In a previous paper[3] we reported the synthesis and analgesic activity of N-[1-methyl-2-(4-methylpiperazino)ethyl]propionanilide (**1**).

The piperazine derivative (**1**) was examined for analgesic activity by subcutaneous administration to mice according to Haffner's method.[4] The piperazine derivative (**1**) possessed *ca.* 1/9 of the analgesic effect of morphine and exhibited more rapid onset and shorter duration of action than morphine. Nalorphine antagonized the analgesic effect of the piperazine derivative (**1**).



1

In this paper, the syntheses and analgesic activities of N-(1-methyl-2-piperazinoethyl)propionanilides (**6a**—**e**) are reported. In addition, 2-alkoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]propionamide]-benzothiazoles (**9a**—**d**) were prepared and examined for analgesic activities.

The piperazine derivatives (**6a**—**e**) were prepared as shown in Chart 1. Namely, 1-ethyl-(**2a**),[5a] 1-isopropyl- (**2b**),[5b] 1-*n*-butyl- (**2c**),[5c] 1-benzyl -(**2d**)[5d] and 1-phenethyl-piperazine (**2e**)[5d] were used as starting materials for the following syntheses. Acylation could be conducted by stirring a mixture of mono-substituted piperazines (**2a**—**e**) and α-bromopropionyl bromide (mole ratio 2: 1) in absolute Et_2O to afford 1-(2-bromopropionyl)piperazine (**3a**—**e**). Crude **3a**—**e** and anilines were condensed by refluxing in ethanol in the presence of potassium carbonate to afford 1-(2-anilinopropionyl)piperazines (**4a**—**e**). The overall yields of **4a**—**e** based on **2a**—**e** were in the range of about 40% to 68%.

1) Reported at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1980.
2) Location: *Yoshida Shimoadachi-cho, Sakyo-ku, Kyoto, 606, Japan.*
3) J. Okada and M. Shimabayashi, *Yakugaku Zasshi*, **98**, 1619 (1978).
4) F. Haffner, *Dtsch. Med. Wschr.*, **55**, 731 (1929).
5) *a*) T.S. Moore, M. Boyle, and V.M. Thorn, *J. Chem. Soc.*, **1929**, 39; *b*) H.W. Stewart, R.J. Turner, and J.J. Denson, *J. Org. Chem.*, **13**, 134 (1948); *c*) Y. Ikeda, Y. Nitta, and K. Yamada, *Yakugaku Zasshi*, **89**, 669 (1969); *d*) R. Baltzly, J.S. Buck, E. Lorz, and W. Schon, *J. Am. Chem. Soc.*, **66**, 263 (1944).

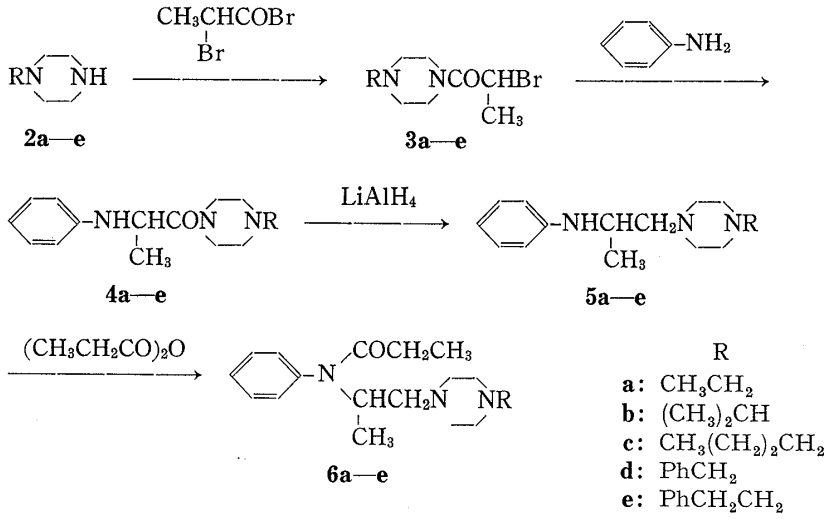


Chart 1

N-(1-Methyl-2-piperazinoethyl)anilines (**5a**—**e**) were prepared by lithium aluminium hydride reduction of **4a**—**e** in absolute Et_2O or absolute Et_2O–THF. These free bases (**5a**—**e**) were all viscous oils and were transformed into oxalates in the usual manner.

N-Propionylation could be conducted by warming **5a**—**e** with propionic anhydride without any solvent to afford N-(1-methyl-2-piperazinoethyl)propionanilides (**6a**—**e**). As it was difficult to purify **6a**—**e** by vacuum distillation because of thermal decomposition, the propionanilides (**6a**—**e**) were purified by extraction and alumina column chromatogrophy with $CHCl_3$. These free bases (**6a**—**e**) were all obtained as viscous oils in about 50%—98% yields and were transformed into oxalates in the usual manner.

From the pharmacological data for the oxalates described above, it became apparent that the N-benzylpiperazine derivative (**6d**) and the N-phenethylpiperazine derivative (**6e**) possessed

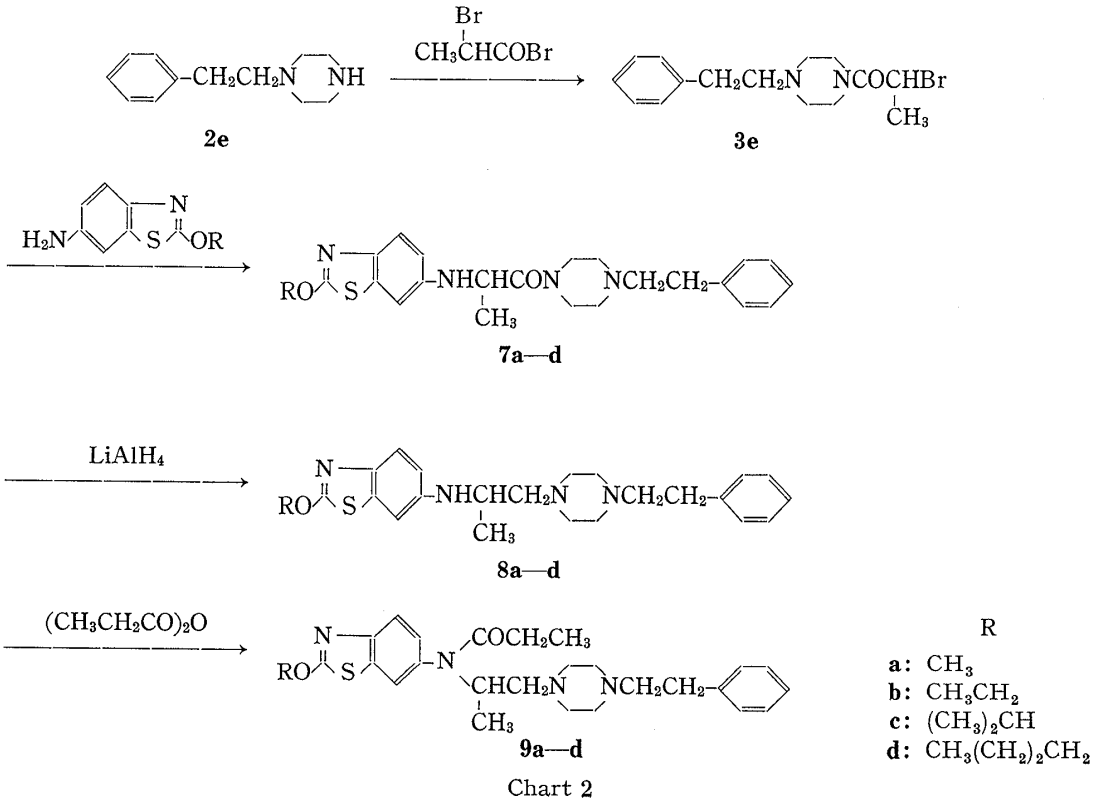


Chart 2

ca. 1/3 of the analgesic effect of pentazocine. It is also noteworthy that 2-amino-6-ethoxybenzothiazole[6] and 6-ethoxy-2-imino-3-methyl-2,3-dihydrobenzothiazole[7] have weak analgesic activity. Next, by using the similar compound, 2-alkoxy-6-aminobenzothiazole instead of aniline, 6-propionamide-benzothiazoles (**9a—d**) were prepared in a similar manner (Chart 2).

Namely, 1-(2-bromopropionyl)-4-phenethylpiperazine (**3e**) and 2-alkoxy-6-aminobenzothiazoles were condensed to afford **7a—d**. 2-Alkoxy-6-[1-methyl-2-(4-phenethylpiperazino)-ethyl]-amino-benzothiazoles (**8a—d**) were prepared by lithium aluminium hydride reduction of **7a—d**. These free bases (**8a—d**) were all obtained as viscous oils. They were purified by alumina column chromatogrophy with $CHCl_3$ and were transformed into oxalates in the usual manner. N-Propionylation could be conducted by warming **8a—d** with propionic anhydride without any solvent to afford **9a—d**. For the reason described above, **9a—d** were purified by extraction and column chromatography. These free bases **9a—d** were all pale yellow oils and were transformed into oxalates in the usual manner.

Pharmacological Results

The eighteen oxalates described above were examined, by subcutaneous administration to mice, for analgesic activity in terms of the inhibition of writhing induced by acetic acid[8] in comparison with pentazocine. These compounds were also tested for acute toxicity in mice. The pharmacological results are listed in Table I.

Table I. Analgesic Activity

Compd. No.	Route[a]	mg/kg	Inhibition (%) of writhing	Toxicity mg/kg (*s.c.*)
5a	*s.c.*	30	19	300 Sedation
5b	*s.c.*	30	45	300 Loss of weight
5c	*s.c.*	30	49	300 Sedation, mydriasis, catalepsy
5d	*s.c.*	30	29	300 Sedation
5e	*s.c.*	30	24	300 Sedation
6a	*s.c.*	30	15	300 Sedation
6b	*s.c.*	30	44	300 Sedation, mydriasis
6c	*s.c.*	30	47	100 Convulsion, mydriasis
6d	*s.c.*	10	51	100 Convulsion
	s.c.	30	68	
6e	*s.c.*	10	39	100 Sedation, mydriasis
	s.c.	30	78	30 Normality
8a	*s.c.*	30	62	1000 Myasthenia, sedation, death with in 24 hr
8b	*s.c.*	30	26	1000 Sedation, loss of weight
8c	*s.c.*	30	33	1000 Convulsion, death within 48 hr
8d	*s.c.*	30	29	1000 Convulsion, death within 48 hr
9a	*s.c.*	30	7	1000 Myasthenia, death within 24 hr
9b	*s.c.*	30	19	1000 Sedation
9c	*s.c.*	30	0	1000 Sedation
9d	*s.c.*	30	4	1000 Sedation
Pentazocine	*s.c.*	5	32	150 Convulsion, mydriasis
	s.c.	10	81	Trembling

a) subcutaneous administration

The conclusion can be summarized as follows.

1) Amoung the eighteen oxalates, seven oxalates (**5b, c, 6b, c, d, e, 8a**) exhibited over 44% inhibition at 30 mg/kg *s.c.*

6) Kaufmann, *Arch. Pharm.*, **273**, 31 (1935).
7) T. Takahashi and J. Okada, *Yakugaku Zasshi*, **71**, 423 (1951).
8) R. Kostar, M. Anderson, and E.J. Debbeer, *Fed. Proc.*, **22**, 248 (1963).

2) The N-benzylpiperazine derivative (**6d**) and the N-phenethylpiperazine derivative (**6e**) possessed *ca.* 1/3 of the analgesic effect of pentazocine.

3) The N-ethylpiperazine derivatives (**5a**) and (**6a**) were practically inactive,

4) It is noteworthy that N-propionylation of **5d** and **5e** increased the analgesic activity, while N-propionylation of **8a**—**d** decreased the analgesic activity.

5) The aniline derivative (**6e**) showed more potent analgesic activity than 2-alkoxy-6-aminobenzothiazole derivatives (**9a**—**d**).

Experimental

All melting and boiling points are uncorrected. IR spectra were recorded on a Hitachi 215 spectrometer or a Hitachi 260-10 spectrometer and ^{1}H-NMR spectra on a Varian A-60 spectrometer or a JEOL JNM-PMX 60 spectrometer operating at 60 MHz in $CDCl_3$ solution with tetramethylsilane as an internal standard. Mass spectra were determined with a JEOL JMS-01SG-2 mass spectrometer.

1-(2-Anilinopropionyl)piperazines——1-(2-Anilinopropionyl)-4-ethylpiperazine (**4a**): A solution of α-bromopropionyl bromide (10.4 g) in absolute Et_2O (90 ml) was added dropwise to a solution of 1-ethylpiperazine (**2a**) (11 g) in absolute Et_2O (80 ml) at 5° over a period of 2 hr with stirring. The mixture was stirred at 5° for 1 hr. The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The pale yellow oily residue (**3a**) (12 g) was dissolved in EtOH (100 ml). K_2CO_3 (6.8 g) and aniline (4.6 g) were added to the solution. The mixture was refluxed for 8 hr. The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The residue was crystallized from petroleum ether and the crystals were collected by filtration and washed with petroleum ether. Recrystallization from isopropyl alcohol (iso-PrOH) gave **4a** (7.1 g, 56.4% yield) as colorless fine prisms, mp 127—127.5°. IR ν_{max}^{KBr} cm^{-1}: 1630 (C=O). NMR ($CDCl_3$) δ: 1.03 (3H, t, J=7 Hz, $NCH_2\underline{CH_3}$), 1.33 (3H, d, J=6 Hz, $CH\underline{CH_3}$), 4.57 (1H, broad s, NH). MS *m/e*: 261 (M^+). *Anal.* Calcd for $C_{15}H_{23}N_3O$: C, 68.97; H, 8.81; N, 16.09. Found: C, 69.22; H, 8.84; N, 16.10.

1-(2-Anilinopropionyl)-4-isopropylpiperazine (**4b**): A solution of α-bromopropionyl bromide (17 g) in absolute Et_2O (150 ml) was added dropwise to a solution of 1-isopropylpiperazine (**2b**) (20 g) in absolute Et_2O (100 ml) at 5° over a period of 3 hr with stirring. The mixture was stirred at 5° for 2 hr. The post-treatment described above (c.f. **4a**) was carried out to afford a pale yellow oily residue (**3b**) (15 g). A mixture of **3b** (15 g), K_2CO_3 (7.9 g), aniline (5.3 g) and EtOH (120 ml) was refluxed for 8 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crude **4b**. Recrystallization from iso-PrOH-H_2O gave **4b** (6.7 g, 42.8% yield) as colorless prisms, mp 110—111°. IR ν_{max}^{KBr} cm^{-1}: 1625 (C=O). NMR ($CDCl_3$) δ: 1.03 (6H, d, J=6 Hz, $NCH(\underline{CH_3})_2$), 1.38 (3H, d, J=6 Hz, $CH\underline{CH_3}$), 4.57 (1H, broad s, NH). MS *m/e*: 275 (M^+). *Anal.* Calcd for $C_{16}H_{25}N_3O$: C, 69.82; H, 9.09; N, 15.27. Found: C, 69.76; H, 8.93; N, 15.04.

1-(2-Anilinopropionyl)-4-*n*-butylpiperazine (**4c**): A solution of α-bromopropionyl bromide (11.4 g) in absolute Et_2O (100 ml) was added dropwise to a solution of 1-*n*-butylpiperazine (**2c**) (15 g) in absolute Et_2O (80 ml) at 5° over a period of 2 hr with stirring. The mixture was stirred at 5° for 2 hr. The post-treatment described above (c.f. **4a**) was carried out to afford the pale yellow oily residue (**3c**) (12.3 g). A mixture of **3c** (12.3 g), K_2CO_3 (6.2 g), aniline (4.2 g) and EtOH (100 ml) was refluxed for 8 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crude **4c**. Recrystallization from dioxane-H_2O gave **4c** (6.0 g, 39.3% yield) as colorless prisms, mp 95—96°. IR ν_{max}^{KBr} cm^{-1}: 1625 (C=O). NMR ($CDCl_3$) δ: Exact values could not be determined because of broadening or overlapping. MS *m/e*: 289 (M^+). *Anal.* Calcd for $C_{17}H_{27}N_3O$: C, 70.59; H, 9.34; N, 14.53. Found: C, 70.39; H, 9.40; N, 14.42.

1-(2-Anilinopropionyl)-4-benzylpiperazine (**4d**): A solution of α-bromopropionyl bromide (19 g) in absolute Et_2O (200 ml) was added dropwise to a solution of 1-benzylpiperazine (**2d**) (30 g) in absolute Et_2O (150 ml) at 5° over a period of 3 hr with stirring. The mixture was stirred at 5° for 2 hr. The post-treatment described above (c.f. **4a**) was carried out to afford a pale yellow oily residue (**3d**) (27.5 g). A mixture of **3d** (27.5 g), K_2CO_3 (13 g), aniline (8.3 g) and EtOH (200 ml) was refluxed for 7.5 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crude **4d**. Recrystallization from iso-PrOH gave **4d** (13.7 g, 49.8% yield) as colorless prisms, mp 112—112.5°. IR ν_{max}^{KBr} cm^{-1}: 1635 (C=O). NMR ($CDCl_3$) δ: 1.33 (3H, d, J=6 Hz, $CH\underline{CH_3}$), 4.53 (1H, broad s, NH), 7.23 (5H, s, $NCH_2\underline{Ph}$). MS *m/e*: 323 (M^+). *Anal.* Calcd for $C_{20}H_{25}N_3O$: C, 74.30; H, 7.74; N, 13.00. Found: C, 74.40; H, 7.80; N, 12.97.

1-(2-Anilinopropionyl)-4-phenethylpiperazine (**4e**): A solution of α-bromopropionyl bromide (11.9 g) in absolute benzene (50 ml) was added dropwise to a solution of 1-phenethylpiperazine (**2e**) (21 g) in absolute benzene (100 ml) at 5° over a period of 25 min with stirring. The mixture was stirred at 5° for 2 hr. The post-treatment described above (c.f. **4a**) was carried out to afford a pale yellow oily residue (**3e**) (16 g). A mixture of **3e** (16 g), K_2CO_3 (6.8 g), aniline (4.6 g) and EtOH (50 ml) was refluxed for 10 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crude **4e**. Recrystallization from MeOH gave **4e** (12.7 g, 68.2% yield) as colorless prisms, mp 105—106°. IR ν_{max}^{KBr} cm^{-1}: 1630 (C=O). NMR ($CDCl_3$) δ:

1.34 (3H, d, J=6 Hz, CH$\underline{CH_3}$), 4.40 (1H, broad s, NH), 7.23 (5H, s, NCH$_2$CH$_2\underline{Ph}$). MS *m/e*: 337 (M^+). *Anal.* Calcd for $C_{21}H_{27}N_3O$: C, 74.78; H, 8.01; N, 12.46. Found: C, 74.62; H, 7.93; N, 12.56.

N-(1-Methyl-2-piperazinoethyl)anilines——N-[1-Methyl-2-(4-ethylpiperazino)ethyl]aniline (**5a**): A solution of **4a** (2.5 g) in absolute THF (40 ml) was added dropwise to a solution of $LiAlH_4$ (0.74 g) in absolute THF (50 ml) at 2° over a period of 1.5 hr with stirring. The mixture was refluxed for 7 hr, then cooled, and H_2O (0.9 ml), 15% aqueous NaOH solution (2.4 ml) and H_2O (2.4 ml) were successively added to the reaction mixture at below 5° with vigorous stirring. The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The oily residue was distilled under reduced pressure to give **5a** (1.0 g, 41.9% yield) as a pale yellow oil, bp 126° (1.0 mmHg). IR ν_{max}^{Film} cm^{-1}: 1600 (benzene nucleus). NMR ($CDCl_3$) δ: 1.05 (3H, t, J=7 Hz, NCH$_2\underline{CH_3}$), 1.18 (3H, d, J=6 Hz, CH$\underline{CH_3}$), 4.20 (1H, broad s, NH). MS *m/e*: 247 (M^+). Oxalate: mp 213—214° (dioxane-H_2O). *Anal.* Calcd for $C_{15}H_{25}N_3\cdot 2C_2H_2O_4$: C, 53.39; H, 6.79; N, 9.84. Found: C, 53.34; H, 6.93; N, 9.95.

N-[1-Methyl-2-(4-isopropylpiperazino)ethyl]aniline (**5b**): A solution of **4b** (3 g) in absolute Et_2O (20 ml) and THF (20 ml) was added dropwise to a solution of $LiAlH_4$ (0.83 g) in absolute THF (60 ml) at 2° over a period of 2 hr with stirring. The mixture was stirred at room temperature for 21 hr. The post-treatment described above (c.f. **5a**) was carried out to afford **5b** (1.64 g, 57.6% yield) as a pale yellow oil, bp 126° (0.4 mmHg). IR ν_{max}^{Film} cm^{-1}: 1597 (benzene nucleus). NMR ($CDCl_3$) δ: 1.01 (6H, d, J=6 Hz, NCH($\underline{CH_3}$)$_2$), 1.17 (3H, d, J=6 Hz, CH$\underline{CH_3}$), 4.33 (1H, broad s, NH). MS *m/e*: 261 (M^+). Oxalate: mp 203—204° (dioxane-H_2O). *Anal.* Calcd for $C_{16}H_{27}N_3\cdot 2C_2H_2O_4$: C, 54.42; H, 7.03; N, 9.52. Found: C, 54.58; H, 6.96; N, 9.32.

N-[1-Methyl-2-(4-*n*-butylpiperazino)ethyl]aniline (**5c**): A solution of **4c** (3 g) in absolute Et_2O (20 ml) and THF (20 ml) was added dropwise to a solution of $LiAlH_4$ (0.79 g) in absolute Et_2O (60 ml) at 2° over a period of 2 hr with stirring. The mixture was stirred at room temperature for 22 hr. The post-treatment described above (c.f. **5a**) was carried out to afford **5c** (1.26 g, 44.1% yield) as a pale yellow oil, bp 136° (0.5 mmHg). IR ν_{max}^{Film} cm^{-1}: 1600 (benzene nucleus). NMR ($CDCl_3$) δ: Exact values could not be determined because of broadening or overlapping. MS *m/e*: 275 (M^+). Oxalate: mp 202.5—203° (dioxane-H_2O). *Anal.* Calcd for $C_{17}H_{29}N_3\cdot 2C_2H_2O_4\cdot 1/2H_2O$: C, 54.31; H, 7.33; N, 9.05. Found: C, 54.45; H, 7.22; N, 9.05.

N-[1-Methyl-2-(4-benzylpiperazino)ethyl]aniline (**5d**): A solution of **4d** (3.2 g) in absolute Et_2O (20 ml) and THF (20 ml) was added dropwise to a solution of $LiAlH_4$ (0.75 g) in absolute Et_2O (60 ml) at 2° over a period of 2 hr with stirring. The mixture was stirred at room temperature for 4 hr. The post-treatment described above (c.f. **5a**) was carried out to afford **5d** (1.302 g, 42.5% yield) as a pale yellow oil, bp 165° (0.2 mmHg). IR ν_{max}^{Film} cm^{-1}: 1598 (benzene nucleus). NMR ($CDCl_3$) δ: 1.18 (3H, d, J=6 Hz, CH$\underline{CH_3}$), 3.47 (2H, s, N$\underline{CH_2}$Ph), 4.43 (1H, broad s, NH), 7.23 (5H, s, NCH$_2\underline{Ph}$). MS *m/e*: 309 (M^+). Oxalate: mp 204—205° (dioxane-H_2O). *Anal.* Calcd for $C_{20}H_{27}N_3\cdot 2C_2H_2O_4$: C, 58.89; H, 6.34; N, 8.59. Found: C, 58.62; H, 6.43; N, 8.50.

N-[1-Methyl-2-(4-phenethylpiperazino)ethyl]aniline (**5e**): A solution of **4e** (6.7 g) in absolute Et_2O (50 ml) and THF (50 ml) was added dropwise to a solution of $LiAlH_4$ (1.52 g) in absolute Et_2O (100 ml) at 2° over a period of 40 min with stirring. The mixture was refluxed for 2 hr. The post-treatment described above (c.f. **5a**) was carried out to afford **5e** (2.6 g, 40.5% yield) as a pale yellow oil, bp 179° (0.5 mmHg). IR ν_{max}^{Film} cm^{-1}: 1595 (benzene nucleus). NMR ($CDCl_3$) δ: 1.20 (3H, d, J=6 Hz, CH$\underline{CH_3}$), 4.06 (1H, broad s, NH), 7.18 (5H, s, NCH$_2$CH$_2\underline{Ph}$). MS *m/e*: 323 (M^+). Oxalate: mp 207—208° (dioxane-H_2O). *Anal.* Calcd for $C_{21}H_{29}N_3\cdot 2C_2H_2O_4\cdot 1/2H_2O$: C, 58.60; H, 6.64; N, 8.20. Found: C, 58.73; H, 6.52; N, 8.35.

N-(1-Methyl-2-piperazinoethyl)propionanilides——N-[1-Methyl-2-(4-ethylpiperazino)ethyl]propionanilide (**6a**): A mixture of **5a** (1.0 g) and propionic anhydride (4.3 ml) was heated at 100° for 3 hr. The mixture was poured over ice in a beaker and neutralized with $NaHCO_3$. The solution was made acidic with 20% aqueous HCl solution and washed with Et_2O. The acidic aqueous solution was made alkaline with 15% aqueous NaOH solution and extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and concentrated *in vacuo*. The oily residue was subjected to alumina column chromatography with $CHCl_3$ to afford a pale yellow viscous oil **6a** (1.2 g, 97.8% yield). IR ν_{max}^{Film} cm^{-1}: 1645 (C=O). NMR ($CDCl_3$) δ: 5.23 (1H, q, J= 7 Hz, $\underline{CH}CH_3$). Other values could not be determined exactly because of overlapping. MS *m/e*: 303 (M^+).

A solution saturated with oxalic acid (anhydrous) in absolute Et_2O was added dropwise to the mixture of **6a** (1.2 g) and absolute Et_2O (20 ml). The crystals were collected by filtration and recrystallized from dioxane-H_2O to give the oxalate of **6a** (1.8 g, 92.1% yield) as a colorless powder, mp 203—203.5°. *Anal.* Calcd for $C_{18}H_{29}N_3O\cdot 2C_2H_2O_4$: C, 54.66; H, 6.83; N, 8.70. Found: C, 54.40; H. 6.81; N, 8.67.

N-[1-Methyl-2-(4-isopropylpiperazino)ethyl]propionanilide (**6b**): A mixture of **5b** (1.0 g) and propionic anhydride (4.5 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **6b** (0.852 g, 70.1% yield). IR ν_{max}^{Film} cm^{-1}: 1638 (C=O). NMR ($CDCl_3$) δ: 5.20 (1H, q, J=7 Hz, $\underline{CH}CH_3$). Other values could not be determined exactly because of overlapping. MS *m/e*: 317 (M^+). Oxalate: 1.2 g, 61.9% yield. Colorless powder, mp 192—193° (dioxane-H_2O). *Anal.* Calcd for $C_{19}H_{31}N_3O\cdot 2C_2H_2O_4\cdot 1/2H_2O$: C, 54.54; H, 7.12; N, 8.30. Found: C, 54.87; H, 7.12; N, 8.45.

N-[1-Methyl-2-(4-*n*-butylpiperazino)ethyl]propionanilide (**6c**): A mixture of **5c** (0.8 g) and propionic anhydride (4 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **6c** (0.929 g, 96.5% yield). IR ν_{max}^{Film} cm^{-1}: 1640 (C=O). NMR ($CDCl_3$) δ: 5.17 (1H, q, J=7 Hz, $\underline{CH}CH_3$). Other values could not be determined exactly because of overlapping.

MS *m/e*: 331 (M^+). Oxalate: 1.356 g, 91.2% yield. Colorless powder, mp 211—211.5° (dioxane-H_2O). *Anal.* Calcd for $C_{20}H_{33}N_3O \cdot 2C_2H_2O_4$: C, 56.36; H, 7.24; N, 8.22. Found: C, 56.28; H, 7.36; N, 7.93.

N-[1-Methyl-2-(4-benzylpiperazino)ethyl]propionanilide (**6d**): A mixture of **5d** (0.8 g) and propionic anhydride (3 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **6d** (0.47 g, 49.8% yield). IR ν_{max}^{Film} cm^{-1}: 1640 (C=O). NMR ($CDCl_3$) δ: 1.00 (3H, t, $J=7$ Hz, $NCOCH_2\underline{CH_3}$), 1.02 (3H, d, $J=7$ Hz, $CH\underline{CH_3}$), 5.20 (1H, q, $J=7$ Hz, $\underline{CH}CH_3$), 7.23 (5H, s, $NCH_2\underline{Ph}$). MS *m/e*: 365 (M^+). Oxalate: 0.573 g, 40.6% yield. Colorless powder, mp 184—185° (dioxane-H_2O). *Anal.* Calcd for $C_{23}H_{31}N_3O \cdot 2C_2H_2O_4$: C, 59.45; H, 6.42; N, 7.71. Found: C, 59.22; H, 6.67; N, 7.62.

N-[1-Methyl-2-(4-phenethylpiperazino)ethyl]propionanilide (**6e**): A mixture of **5e** (1.0 g) and propionic anhydride (3 ml) was heated at 100° for 2.5 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **6e** (0.605 g, 51.6% yield). IR ν_{max}^{Film} cm^{-1}: 1643 (C=O). NMR ($CDCl_3$) δ: 1.00 (3H, t, $J=7$ Hz, $NCOCH_2\underline{CH_3}$), 1.03 (3H, d, $J=7$ Hz, $CH\underline{CH_3}$), 5.20 (1H, q, $J=7$ Hz, $\underline{CH}CH_3$), 7.20 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 379 (M^+). Oxalate: 0.716 g, 41.4% yield. Colorless powder, mp 196—197° (dioxane-H_2O). *Anal.* Calcd for $C_{24}H_{33}N_3O \cdot 2C_2H_2O_4$: C, 60.11; H, 6.62; N, 7.51. Found: C, 60.33; H, 6.77; N, 7.42.

2-Alkoxy-6-aminobenzothiazoles——6-Amino-2-methoxy-benzothiazole,[9c] 6-amino-2-ethoxy-benzothiazole[9c] and 6-amino-2-*n*-butoxy-benzothiazole[9c] were used as starting materials for the syntheses. The method of Takahashi *et al.*[9a-c] could be applied to prepare the novel compounds 2-isopropoxy-6-nitro-benzothiazole and 6-amino-2-isopropoxy-benzothiazole.

2-Isopropoxy-6-nitro-benzothiazole: 2-Chloro-6-nitro-benzothiazole[10] (22 g) was added to a solution of sodium (2.3 g) in absolute iso-PrOH (150 ml). The mixture was refluxed for 5 hr. The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The crystalline residue was recrystallized from 50% aqueous MeOH solution to give 2-isopropoxy-6-nitro-benzothiazole (12.5 g, 51.2% yield) as yellow needles, mp 96—97°. IR ν_{max}^{Nujol} cm^{-1}: 760 (benzene nucleus). NMR ($CDCl_3$) δ: 1.50 (6H, d, $J=6$ Hz, $CH(\underline{CH_3})_2$), 5.47 (1H, m, $J=6$ Hz, $\underline{CH}(CH_3)_2$), 7.66—8.70 (3H, m, aromatic protons). MS *m/e*: 238 (M^+). *Anal.* Calcd for $C_{10}H_{10}N_2O_3S$: N, 11.76; S, 13.45. Found: N, 12.02; S, 13.55.

6-Amino-2-isopropoxy-benzothiazole: Iron (15 g) was added to a solution of 2-isopropoxy-6-nitro-benzothiazole (12.5 g) in 50% aqueous acetic acid (120 ml) and EtOH (100 ml) at room temperature over a period of 30 min with stirring. The mixture was refluxed for 2 hr, then cooled, made alkaline with 25% aqueous NaOH solution and extracted with Et_2O. The Et_2O extract was dried over $MgSO_4$ and concentrated. The oily residue was distilled under reduced pressure to afford 6-amino-2-isopropoxy-benzothiazole (3.7 g, 33.9% yield) as a pale yellow oil, bp 166° (5 mmHg), mp *ca.* 78°. IR ν_{max}^{Film} cm^{-1}: 3300 (NH_2), 1600 (benzene nucleus). NMR ($CDCl_3$) δ: 1.40 (6H, d, $J=6$ Hz, $CH(\underline{CH_3})_2$), 3.62 (2H, s, NH_2), 5.28 (1H, m, $J=6$ Hz, $\underline{CH}(CH_3)_2$), 6.53—7.70 (3H, m, aromatic protons). MS *m/e*: 208 (M^+). *Anal.* Calcd for $C_{10}H_{12}N_2OS$: H, 5.77; N, 13.46; S, 15.39. Found: H, 5.39; N, 13.78; S, 15.40.

1-[2-(2-Alkoxy-benzothiazolyl-(6))-aminopropionyl]-4-phenethylpiperazines——1-[2-(2-Ethoxy-benzothiazolyl-(6))-aminopropionyl]-4-phenethylpiperazine (**7b**): A solution of α-bromopropionyl bromide (6.2 g) in absolute Et_2O (70 ml) was added dropwise to a solution of 1-phenethylpiperazine (**2e**) (10.8 g) in absolute Et_2O (70 ml) at 5° over a period of 1 hr with stirring. The mixture was stirred at 5° for 1.5 hr. The precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The pale yellow oily residue (**3e**) (9.1 g, 98.5% yield) was dissolved in EtOH (70 ml). K_2CO_3 (4.0 g) and 6-amino-2-ethoxy-benzothiazole (5.5 g) were added to the solution. The mixture was refluxed for 6 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crystals. Recrystallization from iso-PrOH gave **7b** (6.9 g, 55.4% yield) as colorless fine prisms, mp 127—128°. IR ν_{max}^{Nujol} cm^{-1}: 3270 (NH), 1623 (C=O). NMR ($CDCl_3$) δ: 1.42 (3H, t, $J=7$ Hz, $OCH_2\underline{CH_3}$), 4.50 (1H, broad s, NH), 7.20 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 438 (M^+). *Anal.* Calcd for $C_{24}H_{30}N_4O_2S$: C, 65.75; H, 6.85; N, 12.78; S, 7.31. Found: C, 65.69; H, 6.94; N, 12.64; S, 7.29.

1-[2-(2-Methoxy-benzothiazolyl-(6))-aminopropionyl]-4-phenethylpiperazine (**7a**): A solution of **3e** (9.8 g) [prepared from **2e** (11 g) and α-bromopropionyl bromide (6.3 g) by the method described above (c.f. **7b**)], K_2CO_3 (4.0 g) and 6-amino-2-methoxy-benzothiazole (5.2 g) in EtOH (70 ml) was refluxed for 6 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crystals. Recrystallization from iso-PrOH gave **7a** (5.0 g, 40.7% yield) as colorless fine prisms, mp 159—160°. IR ν_{max}^{Nujol} cm^{-1}: 3320 (NH), 1643 (C=O). NMR ($CDCl_3$) δ: 1.40 (3H, d, $J=6$ Hz, $CH\underline{CH_3}$), 4.11 (3H, s, OCH_3), 4.53 (1H, broad s, NH), 7.21 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 424 (M^+). *Anal.* Calcd for $C_{23}H_{28}N_4O_2S$: C, 65.09; H, 6.60; N, 13.21; S, 7.55. Found: C, 65.37; H, 6.69; N, 13.06; S, 7.68.

1-[2-(2-Isopropoxy-benzothiazolyl-(6))-aminopropionyl]-4-phenethylpiperazine (**7c**): A solution of **3e** (6.5 g) [prepared from **2e** (6.4 g) and α-bromopropionyl bromide (3.6 g) by the method described above

9) *a*) T. Takahashi and H. Taniyama, *Yakugaku Zasshi*, **66**, 37 (1946); *b*) *Idem, ibid.*, **67**, 42 (1947); *c*) *Idem, ibid.*, **67**, 123 (1948).
10) T. Takahashi and H. Taniyama, *Yakugaku Zasshi*, **66**, 25 (1946).

(c.f. **7b**)], K_2CO_3 (2.3 g) and 6-amino-2-isopropoxy-benzothiazole (3.5 g) in EtOH (40 ml) was refluxed for 5 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crystals. Recrystallization from iso-PrOH gave **7c** (4.0 g, 52.5% yield) as colorless fine prisms, mp 138—139°. IR ν_{max}^{Nujol} cm^{-1}: 3340 (NH), 1630 (C=O). NMR ($CDCl_3$) δ: 1.55 (6H, d, J=6 Hz, $OCH(\underline{CH_3})_2$), 4.56 (1H, broad s, NH), 7.32 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 452 (M^+). *Anal.* Calcd for $C_{25}H_{32}N_4O_2S$: C, 66.37; H, 7.08; N, 12.39; S, 7.08. Found: C, 66.61; H, 7.36; N, 12.14; S, 7.03.

1-[2-(2-*n*-Butoxy-benzothiazolyl-(6))-aminopropionyl]-4-phenethylpiperazine (**7d**): A solution of **3e** (7.3 g) [prepared from **2e** (8.6 g) and α-bromopropionyl bromide (4.9 g) by the method described above (c.f. **7b**)], K_2CO_3 (3.2 g) and 6-amino-2-*n*-butoxy-benzothiazole (5.0 g) in EtOH (60 ml) was refluxed for 5.5 hr. The post-treatment described above (c.f. **4a**) was carried out to afford crystals. Recrystallization from iso-PrOH gave **7d** (5.9 g, 55.9% yield) as colorless fine prisms, mp 89—90°. IR ν_{max}^{Nujol} cm^{-1}: 3350 (NH), 1630 (C=O). NMR ($CDCl_3$) δ: 4.27 (1H, broad s, NH), 7.20 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 466 (M^+). *Anal.* Calcd for $C_{26}H_{34}N_4O_2S$: C, 66.95; H, 7.30; N, 12.01; S, 6.87. Found: C, 66.89; H, 7.31; N, 11.85; S, 7.05.

2-Alkoxy-6-[1-methyl-2-(4-phenethylpiperazino)ethyl]-amino-benzothiazoles——6-[1-Methyl-2-(4-phenethylpiperazino)ethyl]-amino-2-ethoxy-benzothiazole (**8b**): A solution of **7b** (4.5 g) in absolute Et_2O (70 ml) and THF (80 ml) was added dropwise to a solution of $LiAlH_4$ (0.8 g) in absolute Et_2O (100 ml) at 0° over a period of 2 hr with stirring. The mixture was refluxed for 5 hr, then cooled and the post-treatment described above (c.f. **5a**) was carried out to afford a dark reddish-purple oily residue. The oily residue was subjected to alumina column chromatography with $CHCl_3$ to afford a dark purple viscous oil **8b** (4.1 g, 94.1% yield): IR ν_{max}^{Film} cm^{-1}: 3325 (NH), 1600 (benzene nucleus). NMR ($CDCl_3$) δ: 1.18 (3H, d, J=6 Hz, $CH\underline{CH_3}$), 1.25 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 4.23 (1H, broad s, NH), 7.17 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 424 (M^+). Oxalate: mp 197—198° (MeOH). *Anal.* Calcd for $C_{24}H_{32}N_4OS\cdot 2C_2H_2O_4\cdot 1/2H_2O$: C, 54.81; H, 6.04; N, 9.13; S, 5.22. Found: C, 54.91; H, 5.91; N, 9.18; S, 5.03.

6-[1-Methyl-2-(4-phenethylpiperazino)ethyl]-amino-2-methoxy-benzothiazole (**8a**): A solution of **7a** (4.0 g) in absolute Et_2O (25 ml) and THF (240 ml) was added dropwise to a solution of $LiAlH_4$ (0.8 g) in absolute Et_2O (90 ml) at 0° over a period of 2 hr with stirring. The mixture was refluxed for 5 hr. The post-treatment described above (c.f. **8b**) was carried out to afford a dark purple viscous oil **8a** (3.7 g, 95.7% yield): IR ν_{max}^{Film} cm^{-1}: 3320 (NH), 1600 (benzene nucleus). NMR ($CDCl_3$) δ: 4.23 (3H, s, OCH_3), 7.33 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 410 (M^+). Oxalate: mp 201—202° (MeOH). *Anal.* Calcd for $C_{23}H_{30}N_4OS\cdot 2C_2H_2O_4$: C, 54.92; H, 5.76; N, 9.49; S, 5.42. Found: C, 54.78; H, 5.83; N, 9.04; S, 4.81.

6-[1-Methyl-2-(4-phenethylpiperazino)ethyl]-amino-2-isopropoxy-benzothiazole (**8c**): A solution of **7c** (3.5 g) in absolute Et_2O (50 ml) and THF (60 ml) was added dropwise to a solution of $LiAlH_4$ (0.6 g) in absolute Et_2O (86 ml) at 0° over a period of 1 hr with stirring. The mixture was refluxed for 5 hr. The post-treatment described above (c.f. **8b**) was carried out to afford a dark reddish-purple viscous oil **8c** (3.2 g, 94.4% yield): IR ν_{max}^{Film} cm^{-1}: 3310 (NH), 1600 (benzene nucleus). NMR ($CDCl_3$) δ: 4.33 (1H, broad s, NH), 7.30 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 438 (M^+). Oxalate: mp 194° (MeOH). *Anal.* Calcd for $C_{25}H_{34}N_4OS\cdot 2C_2H_2O_4\cdot 1/2H_2O$: C, 55.50; H, 6.22; N, 8.93; S, 5.11. Found: C, 55.19; H, 6.20; N, 8.79; S, 5.22.

6-[1-Methyl-2-(4-phenethylpiperazino)ethyl]-amino-2-*n*-butoxy-benzothiazole (**8d**): A solution of **7d** (4.0 g) in absolute Et_2O (50 ml) and THF (70 ml) was added dropwise to a solution of $LiAlH_4$ (0.7 g) in absolute Et_2O (100 ml) at 0° over a period of 1.5 hr with stirring. The mixture was refluxed for 5 hr. The post-treatment described above (c.f. **8b**) was carried out to afford a dark reddish-purple viscous oil **8d** (3.7 g, 95.4% yield): IR ν_{max}^{Film} cm^{-1}: 3325 (NH), 1600 (benzene nucleus). NMR ($CDCl_3$) δ: 4.30 (1H, broad s, NH), 7.20 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 452 (M^+). Oxalate: mp 199—200° (MeOH). *Anal.* Calcd for $C_{26}H_{36}N_4OS\cdot 2C_2H_2O_4\cdot H_2O$: C, 55.38; H, 6.46; N, 8.62; S, 4.92. Found: C, 55.68; H, 6.29; N, 8.46; S, 4.53.

2-Alkoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]-benzothiazoles——2-Methoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]-benzothiazole (**9a**): A mixture of **8a** (2 g) and propionic anhydride (9 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **9a** (1.0 g, 44.0% yield): IR ν_{max}^{Film} cm^{-1}: 1640 (C=O). NMR ($CDCl_3$) δ: 1.13 (3H, t, J=7 Hz, $COCH_2\underline{CH_3}$), 1.25 (3H, d, J=7 Hz, $CH\underline{CH_3}$), 3.52 (3H, s, OCH_3), 7.18 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 466 (M^+). Oxalate: mp 186° (MeOH). *Anal.* Calcd for $C_{26}H_{34}N_4O_2S\cdot 2C_2H_2O_4$: C, 55.73; H, 5.88; N, 8.67; S, 4.95. Found: C, 55.45; H, 6.10; N, 8.61; S, 4.74.

2-Ethoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]-benzothiazole (**9b**): A mixture of **8b** (2 g) and propionic anhydride (9 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford an orange-colored viscous oil **9b** (1.5 g, 66.3% yield): IR ν_{max}^{Film} cm^{-1}: 1645 (C=O). NMR ($CDCl_3$) δ: 1.08 (3H, d, J=7 Hz, $CH\underline{CH_3}$), 1.50 (3H, t, J=7 Hz, $OCH_2\underline{CH_3}$), 4.62 (2H, q, J=7 Hz, $O\underline{CH_2}CH_3$), 7.20 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 480 (M^+). Oxalate: mp 199° (MeOH). *Anal.* Calcd for $C_{27}H_{36}N_4O_2S\cdot 2C_2H_2O_4$: C, 56.36; H, 6.06; N, 8.49; S, 4.85. Found: C, 56.33; H, 5.99; N, 8.54; S, 4.84.

2-Isopropoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]-benzothiazole (**9c**): A mixture of **8c** (2 g) and propionic anhydride (9 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **9c** (1.0 g, 44.3% yield): IR ν_{max}^{Film} cm^{-1}: 1640 (C=O). NMR ($CDCl_3$) δ: 3.43 (2H, q, J=7 Hz, $CO\underline{CH_2}CH_3$), 7.17 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 494 (M^+). Oxalate: mp 183° (MeOH). *Anal.* Calcd for $C_{28}H_{38}N_4O_2S\cdot 2C_2H_2O_4$: C, 56.97; H, 6.23; N, 8.31; S,

4.75. Found: C, 56.64; H, 6.30; N, 8.13; S, 4.62.

2-*n*-Butoxy-6-[N-[1-methyl-2-(4-phenethylpiperazino)ethyl]-propionamide]-benzothiazole (**9d**): A mixture of **8d** (2 g) and propionic anhydride (9 ml) was heated at 100° for 3 hr. The post-treatment described above (c.f. **6a**) was carried out to afford a pale yellow viscous oil **9d** (1.3 g, 57.8% yield): IR ν_{max}^{Film} cm^{-1}: 1645 (C=O). NMR ($CDCl_3$) δ: 1.25 (3H, d, J=7 Hz, $CH\underline{CH_3}$), 3.57 (2H, q, J=7 Hz, $CO\underline{CH_2}CH_3$), 7.30 (5H, s, $NCH_2CH_2\underline{Ph}$). MS *m/e*: 508 (M^+). Oxalate: mp 189—189.5° (MeOH). *Anal.* Calcd for $C_{29}H_{40}N_4O_2S \cdot 2C_2H_2O_4$: C, 57.56; H, 6.40; N, 8.14; S, 4.65. Found: C, 57.81; H, 6.48; N, 8.20; S, 4.44.

Acknowledgement The authors wish to express their gratitude to the staff of the Analysis Center of this faculty for elemental analyses, to Dr. Y. Kuroda for measurements of the NMR spectra, to Dr. N. Akimoto for measurements of the mass spectra and to Dr. H. Onishi, Central Research Laboratories of Mochida Co., Ltd., for obtaining the biological data.