

Synthesis of the Metabolites of Clentiazem

Hirozumi INOUE,^a Susumu NAKAMURA,^{*b} Hisao OTSUKA,^a Mitsunori GAINO,^a Tsunehiro HARADA,^a Kenji MATSUKI,^a and Mikio TAKEDA^a

Organic Chemistry Research Laboratory^a and Research Laboratory of Drug Metabolism,^b Tanabe Seiyaku Co., Ltd., 2–2–50, Kawagishi, Toda, Saitama 335, Japan. Received February 16, 1993

The metabolites of clentiazem in the urine or bile of rats and dogs were investigated. Fifteen basic, 6 acidic, 2 neutral and 4 conjugated metabolites were isolated. In the present paper, fourteen reference compounds as shown in Charts 1, 2 and 3 were synthesized to identify the structures of the metabolites in procedures fundamentally similar to those employed in the synthesis of the corresponding metabolites of diltiazem.

Keywords metabolite; basic metabolite; acidic metabolite; neutral metabolite; synthesis; clentiazem

Clentiazem, an 8-chlorinated isomer of diltiazem, is a potent calcium channel blocker and useful as a cerebral vasodilating and antihypertensive agent.¹⁾ The metabolites of clentiazem in urine and/or bile of rats and dogs were investigated.

In the metabolic study of diltiazem, the principal metabolic pathways were deacetylation, *N*-demethylation, deamination, and conjugation in animals and human.^{2–6)} The metabolites of clentiazem were substantially similar: 15 basic, 6 acidic, 2 neutral and 4 conjugated metabolites were reported previously.⁷⁾

In the present paper we describe the syntheses of fourteen reference compounds for the purpose of identifying 8 basic, 4 acidic and 2 neutral metabolites.

Basic Metabolites The synthetic pathways of basic metabolites are shown in Chart 1.

MB1 (**2**), deacetylated metabolite of clentiazem (**1**), is an intermediate for the synthesis of **1**. *N*-Demethylated metabolite MB2 (**4**) was synthesized in 77% overall yield from **1** by treatment with trichloromethyl chloroformate in the presence of NEt₃ at room temperature followed by heating the resultant *N*-chloroformyl compound in aq. MeCN under reflux. Hydrolysis of **4** with dil. HCl gave MB3 (**5**).

O-Demethylation of **2** and **5** with BBr₃ at 0–5 °C afforded MB4 (**6**) and MB6 (**7**) in 62.2 and 77.3% yields, respectively. *O*-Demethylation of **1** and **4** produce 3-acetoxy metabolites, MB7 (**13**) and MB5 (**11**), under the same reaction conditions, however, contamination with the corresponding 3-deacetylated by-products **6** and **7** was inevitable and removal of these contaminants from **11** and **13** was very hard.

O-Demethylation of (+)-lactam (**3**) with trimethylsilyl chloride (TMSCl) and NaI in MeCN followed by *O*-benzylation with benzyl bromide (BzI Br) in MeOH in the presence of K₂CO₃ at 70 °C afforded **8** in 54% yield. This *O*-benzylation in another solvent, such as aq. MeOH or dimethylformamide (DMF), gave a complex mixture consisting of *N*- and/or *O*-benzylated and C₂-epimerized products (2,3-*trans*-isomer).

Conversion of **8** into **12** was performed in 71.7% overall yield by the same procedure as employed for the synthesis of clentiazem (**1**).¹⁾ On the other hand, *N*-alkylation of **8** with 2-(*N*-benzyl-*N*-methylamino)ethyl chloride in acetone in the presence of K₂CO₃ under reflux gave **9**

in quantitative yield which was converted into **10** by heating with benzyloxycarbonyl chloride (ZCl) in toluene after acetylation of 3-hydroxyl group, or, inversely, by acetylation after the reaction with ZCl. Finally, **10** was successfully debenzylated by HBr–AcOH to afford MB5 (**11**) in 79.9% yield. However, debenzylation of **12** to afford MB7 (**13**) was accompanied by the formation of diacetyl compound **14** (10.9%) by phenol acetylation as by-product, which was easily separated by column chromatography.

MB8 (**15**) was synthesized from **3** by *N*-alkylation with 2-aminoethyl chloride·HCl in the presence of 2 eq of KOH in dimethylsulfoxide (DMSO) and subsequent selective acetylation of 3-hydroxyl group with acetyl chloride, according to the method used for the synthesis of the corresponding metabolite of diltiazem.²⁾

Acidic Metabolites Acidic metabolites were also synthesized in the manner employed for the synthesis of acidic metabolites of diltiazem as shown in Chart 2.²⁾

N-Alkylation of **3** with ethyl chloroacetate in the presence of K₂CO₃ in acetone afforded **17**, followed by alkaline hydrolysis to give MA2 (**18**) in 92.0% overall yield which was converted to MA1 (**19**) by acetylation with Ac₂O–pyridine at room temperature.

Removal of benzyl groups of **22** by treating with TMSCl–NaI in MeCN gave MA4 (**20**) in 98% yield, while acetylation of **22** followed by debenzylation yielded MA3 (**23**) in 54.4% overall yield.

The intermediate **22** was prepared by alkaline hydrolysis of **21**.

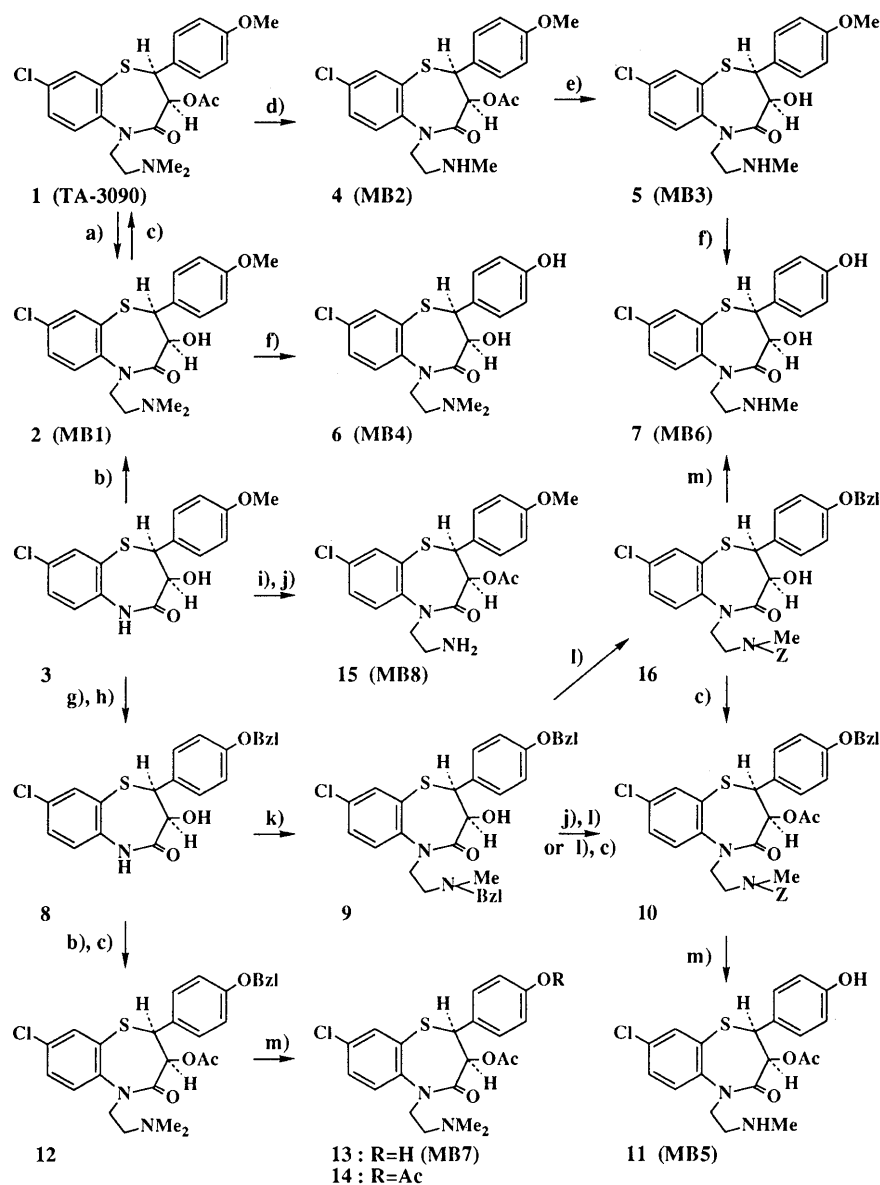
Neutral Metabolites As shown in Chart 3, MN2 (**24**) was synthesized by *N*-cyanomethylation of **3** and subjected to acetylation to afford MN1 (**26**).

Experimental

The analytical and spectral data are summarized in Tables I and II.

Synthesis of Basic Metabolites. (+)-(2*S*,3*S*)-8-Chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**2**, MB1) Method A: Clentiazem·maleate (**1**) (2.0 g, 3.54 mmol) was hydrolyzed by stirring in a mixture of 5% aq. NaOH (30 ml) and MeOH (30 ml) at room temperature for 20 h and worked up in the usual manner to give MB1·oxalate (1.69 g, 96.0%) after recrystallization from MeOH–CHCl₃–Et₂O, which was identical with an authentic sample.¹⁾

Method B: A mixture of (+)-(2*S*,3*S*)-8-chloro-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**3**) (10 g, 29.78 mmol), 2-(dimethylamino)ethyl chloride·HCl (4.4 g, 60.63 mmol),



- a) aq. NaOH/MeOH b) $\text{ClCH}_2\text{CH}_2\text{N}(\text{CH}_3)_2 \cdot \text{HCl}/\text{K}_2\text{CO}_3$ c) $\text{Ac}_2\text{O}/\text{pyridine}$
 d) $\text{ClCOOCCl}_3/\text{NEt}_3$ e) 10% HCl/MeOH f) BBr_3 g) TMSCl/NaI
 h) $\text{BzI}/\text{K}_2\text{CO}_3$ i) $\text{ClCH}_2\text{CH}_2\text{NH}_2 \cdot \text{HCl}/\text{KOH}$ j) AcCl
 k) $\text{ClCH}_2\text{CH}_2\text{N}(\text{Me})\text{Bzl}/\text{K}_2\text{CO}_3$ l) ZCl m) 25% HBr/AcOH

Chart 1

K_2CO_3 (12.36 g) and acetone (320 ml) were stirred under reflux for 20 h. Inorganic compounds were filtered off and washed with AcOEt. The filtrate and washings were combined and concentrated. The residual oil was dissolved in AcOEt. The solution was washed with H_2O , dried over MgSO_4 , concentrated, and then converted into oxalate and recrystallized from $\text{MeOH}-\text{CHCl}_3-\text{Et}_2\text{O}$ to give MB1·oxalate.

(+)-(2*S*,3*S*)-3-Acetoxy-8-chloro-2,3-dihydro-2-(4-methoxyphenyl)-5-[2-(methylamino)ethyl]-1,5-benzothiazepin-4(5*H*)-one (4, MB2) To a solution of 1 (free base, 11.03 g, 24.57 mmol) in toluene (72 ml) were added NEt_3 (2 ml) and trichloromethyl chloroformate (4.83 g, 24.51 mmol) successively under ice-cooling. The reaction mixture was stirred at room temperature for 20 h and concentrated. The residual oil was dissolved in $\text{CHCl}_3-\text{Et}_2\text{O}$ (1:1). The solution was washed with 10% HCl and H_2O , dried, and concentrated. The residual oil was heated in a mixture of MeCN (25 ml) and H_2O (30 ml) under reflux for 40 min and concentrated to remove MeCN. The residue was dissolved in H_2O , made basic with NH_4OH , and extracted with CHCl_3 . The extract was washed with H_2O , dried, and concentrated. The residual oil was converted into

oxalate and recrystallized from MeOH to give MB2·oxalate, 9.93 g (77.0%) after recrystallization from MeOH.

(+)-(2*S*,3*S*)-8-Chloro-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-5-[2-(methylamino)ethyl]-1,5-benzothiazepin-4(5*H*)-one (5, MB3) A mixture of MB2·oxalate (16.3 g, 31.05 mmol), 10% HCl (200 ml), and MeOH (50 ml) was heated under reflux for 2 h, made basic with conc. NH_4OH after cooling, and extracted with CHCl_3 . The extracts were washed with H_2O , dried, and converted into fumarate to give MB3·fumarate, 13.16 g (83.8%).

(+)-(2*S*,3*S*)-8-Chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-hydroxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (6, MB4) A solution of BBr_3 (32 g, 127.3 mmol) in CH_2Cl_2 (50 ml) was added to a solution of MB1 (free base, 10 g, 24.57 mmol) in CH_2Cl_2 (350 ml) at 0–5°C during a period of 20 min. After stirring the mixture at 4–5°C for 3 h, MeOH (50 ml) and cracked ice were added to the reaction mixture. The mixture was neutralized with K_2CO_3 (pH 7) and extracted with CHCl_3 . The extracts were washed with H_2O , dried, and concentrated. The residual oil was purified by column chromatography (SiO_2 ,

eluted with MeOH-CHCl₃ (1:50—1:10)). The obtained foam was recrystallized from aq. EtOH to give MB4 EtOH adduct, 6.72 g (62.2%).

(+)-(2*S*,3*S*)-2-(4-benzyloxyphenyl)-8-chloro-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-one (**8**) (i): TMSCl (28.5 ml, 225.61 mmol) was added to a solution of the (+)-lactam (**3**) (30 g, 89.34 mmol) and NaI (34.1 g) in MeCN (700 ml) at room temperature. After stirring for 2 h, additional NaI (34.1 g) and TMSCl (28.5 ml) were added to the reaction mixture at 57–60 °C, and the mixture was stirred for 2 h. Subsequently, NaI (34.1 g) and TMSCl (28.5 ml) were added again and stirring at 60 °C was continued for 15 h. The reaction mixture was concentrated and the residue was poured into a solution of Na₂S₂O₃ (150 g) in H₂O (1.2 l). The precipitated crystals were collected on a filter, washed with H₂O, and recrystallized from AcOEt to give (+)-(2*S*,3*S*)-8-chloro-2,3-dihydro-3-hydroxy-2-(4-hydroxyphenyl)-1,5-benzothiazepin-4(5*H*)-one, mp 233–234 °C (dec.), 28.24 g (98.2%), [α]_D²⁰ +100.8° (*c*=1.00, DMF).

(ii): A solution of K₂CO₃ (6.57 g) in H₂O (67 ml) was added to a solution of the 2-(4-hydroxyphenyl) compound (13.3 g, 35.77 mmol)

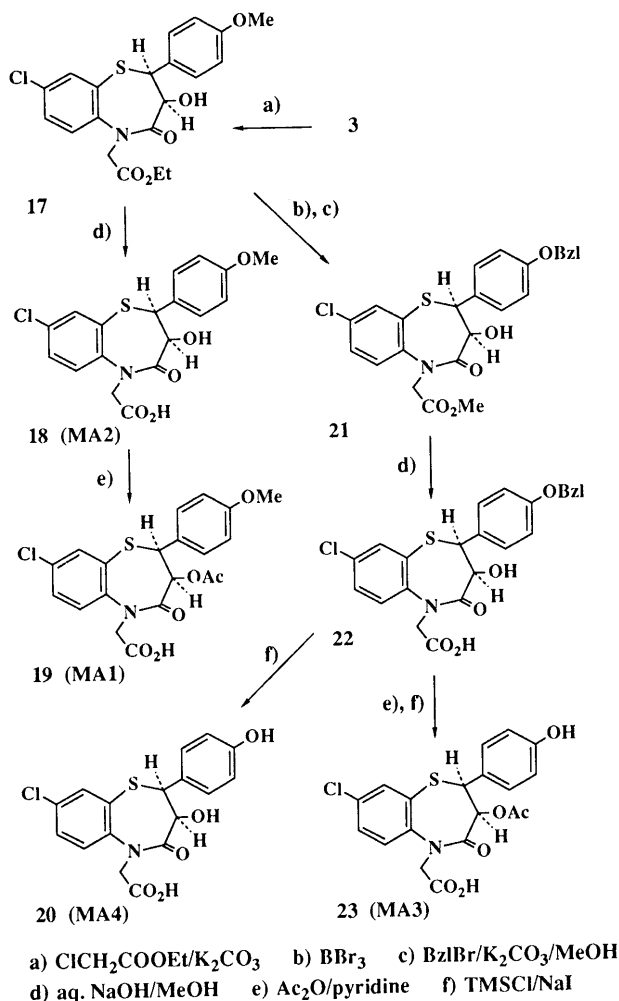


Chart 2

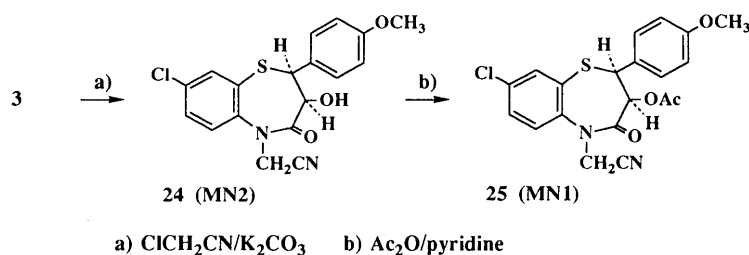


Chart 3

obtained above and BzlBr (8.13 g, 47.53 mmol) in MeOH-H₂O (2:1) (400 ml) at 70 °C during a period of 15 min, and then the mixture was stirred at 70 °C for 1 h and cooled. The precipitated crystals were filtered and recrystallized from AcOEt-acetone to give **8**, 9.2 g (54%).

(+)-(2*S*,3*S*)-5-[2-(*N*-benzyl-*N*-methylamino)ethyl]-2-(4-benzyloxyphenyl)-8-chloro-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-one (**9**) A mixture of **8** (13.03 g, 30.34 mmol), 2-(*N*-benzyl-*N*-methylamino)ethyl chloride·HCl (7.34 g, 33.34 mmol), K₂CO₃ (10.94 g), and acetone (790 ml) was heated under reflux and vigorous stirring for 20 h and worked up in the same manner as described in the preparation of **1** to give **9**, 17.7 g (quantitative yield) as an oil.

The oil was converted into oxalate and recrystallized from MeOH to give **9**·oxalate.

(+)-(2*S*,3*S*)-3-Acetoxy-5-[2-(*N*-benzyloxycarbonyl-*N*-methylamino)ethyl]-2-(4-benzyloxyphenyl)-8-chloro-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**10**) Method A: Acetyl chloride (360 mg, 4.59 mmol) was added to a mixture of **9** (2.13 g, 3.81 mmol) and pyridine (25 ml) at -5–0 °C and the mixture was stirred at room temperature for 5 h and then concentrated. The residual oil was dissolved in AcOEt. The AcOEt solution was washed with H₂O, 5% NaHCO₃, and H₂O successively, dried, and concentrated. The obtained oil was converted into oxalate to give (+)-(2*S*,3*S*)-3-acetoxy-5-[2-(*N*-benzyl-*N*-methylamino)ethyl]-8-chloro-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one·oxalate, mp 173–175 °C (from EtOH), 2.05 g, (84.7%), [α]_D²⁰ +78.4° (*c*=1.00, MeOH).

A mixture of the 3-acetoxy compound (free base, 1.76 g, 2.93 mmol) and ZCl (1.50 g, 8.79 mmol) in toluene (80 ml) was heated under reflux for 7 h. After removal of the solvent, benzyl chloride, and excess of ZCl by evaporation *in vacuo*, the residual oil was purified by column chromatography (SiO₂, eluted with CHCl₃-AcOEt (9:1)) to give **10**, 1.79 g (94.7%) as an oil.

Method B: A solution of ZCl (300 mg, 1.76 mmol) in toluene (6 ml) was added to a solution of **9** (350 mg, 0.63 mmol) in toluene (10 ml) at 80 °C during a period of 9 min; the mixture was heated at 82 °C for 5 h and concentrated. The residual oil was purified by column chromatography (SiO₂, eluted with CHCl₃-AcOEt (95:5)) and recrystallized from AcOEt-hexane to give (+)-(2*S*,3*S*)-5-[2-(*N*-benzyloxycarbonyl-*N*-methylamino)ethyl]-2-(4-benzyloxyphenyl)-8-chloro-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-one (**16**), 290 mg (82.8%).

The benzyloxycarbonyl compound (**16**) (110 mg, 1.82 mmol) was acetylated by heating at 100 °C for 7 h with Ac₂O (15 ml) and pyridine (5 drops) and worked up in the usual manner to give **10**, 110 mg (91.7%) as an oil.

(+)-(2*S*,3*S*)-3-Acetoxy-8-chloro-2,3-dihydro-2-(4-hydroxyphenyl)-5-[2-(methylamino)ethyl]-1,5-benzothiazepin-4(5*H*)-one (**11**, MB5) Twenty-five percent HBr-AcOH (30 ml) was added to a solution of **10** (16.9 g, 26.19 mmol) in AcOH (18 ml) under ice-cooling and the mixture was stirred at room temperature for 5 h and concentrated (at below 30 °C). After the solubilization of residual oil into H₂O, the solution was washed with Et₂O to remove BzlBr, made basic with conc. NH₄OH, and extracted with CHCl₃. The extracts were combined, washed with H₂O, dried, and concentrated. The obtained oil (12.86 g) was purified by column chromatography (SiO₂, eluted with CHCl₃-MeOH (9:1–85:5)). The obtained oil was converted into oxalate and recrystallized from MeOH to give MB5·oxalate-hemihydrate, 10.69 g (79.9%).

(+)-(2*S*,3*S*)-8-Chloro-2,3-dihydro-3-hydroxy-2-(4-hydroxyphenyl)-5-[2-(methylamino)ethyl]-1,5-benzothiazepin-4(5*H*)-one (**7**, MB6) A solution of BBr₃ (30.4 g, 121.35 mmol) in CH₂Cl₂ (120 ml) was added to a solution of MB3 (free base, 9.52 g, 24.23 mmol) in CH₂Cl₂ (800 ml) at 0–5 °C and the reaction mixture was stirred at 0–5 °C for 2.5 h and concentrated. CHCl₃ (1 l), MeOH (200 ml) and cracked ice were added

TABLE I. Analytical and Spectral Data for Synthetic Reference Compounds

| Compound | mp (°C) | [α] _D ²⁰ | Formula | Analysis (%) | | | | | | IR $\nu_{\text{max}}^{\text{Nujol}}$ cm ⁻¹ |
|---|-------------------|---|---|------------------|----------------|----------------|----------------|----------------|----------------|---|
| | | | | Calcd (Found) | | | | | | |
| | | | | C | H | Cl | N | S | Na | |
| 2 (MB1)·oxalate | 206—208 | +82.5° ^{a)} (<i>c</i> = 0.314, DMF) | C ₂₀ H ₂₃ ClN ₂ O ₃ S ·C ₂ H ₂ O ₄ | 53.17 (53.10) | 5.07 (5.02) | 7.13 (7.25) | 5.64 (5.61) | 6.45 (6.56) | | N.D. |
| 4 (MB2)·oxalate | 172—173 | +63.3° (<i>c</i> = 0.422, MeOH) | C ₂₁ H ₂₃ ClN ₂ O ₄ S ·C ₂ H ₂ O ₄ | 52.63 (52.38) | 4.84 (4.84) | 6.75 (6.72) | 5.15 (5.15) | 6.11 (6.22) | | 1740, 1680, 1640 |
| 5 (MB3)·fumarate | 168—170 | +75.5° (<i>c</i> = 0.339, MeOH) | C ₁₉ H ₂₁ ClN ₂ O ₃ S ·C ₄ H ₄ O ₄ | 54.24 (54.19) | 4.95 (4.97) | 6.94 (7.00) | 5.50 (5.47) | 6.30 (6.42) | | 3400—2300, 1670, 1600, 1510 |
| 6 (MB4)·EtOH | 149.5—151 | +129.1° (<i>c</i> = 0.50, CHCl ₃) | C ₁₉ H ₂₁ ClN ₂ O ₃ S ·C ₂ H ₅ OH | 57.46 (57.18) | 6.20 (6.17) | 8.08 (8.26) | 6.38 (6.35) | 7.30 (7.30) | | 3410, 3090, 1670, 1610 |
| 7 (MB6)·fumarate | 157—160 (dec.) | +87.2° (<i>c</i> = 0.59, MeOH) | C ₁₈ H ₁₉ ClN ₂ O ₃ S ·C ₄ H ₄ O ₄ | 53.38 (53.13) | 4.68 (4.97) | 7.16 (7.39) | 5.66 (5.67) | 6.48 (6.63) | | 3350, 3070, 2490, 1665, 1610 |
| 8·1/5AcOEt | 236—238 | +75.4° (<i>c</i> = 1.00, DMF) | C ₂₂ H ₁₈ ClNO ₃ S ·1/5AcOEt | 63.76 (63.68) | 4.60 (4.35) | 8.25 (7.97) | 3.26 (3.26) | 7.46 (7.31) | | 3320, 3170, 3090, 1680, 1630, 1600 |
| 9·oxalate | 108—115 (dec.) | +85.8° (<i>c</i> = 1.00, MeOH) | N.D. | | | | | | | 3505, 3100—2200, 1670, 1610, 1585 |
| 10 (Oil) | N.D. | +79.0° (<i>c</i> = 1.00, CHCl ₃) | N.D. | | | | | | | N.D. |
| 11 (MB5)·oxalate ·hemihydrate | 194—195 (dec.) | +77.0° (<i>c</i> = 1.00, MeOH) | C ₂₀ H ₂₁ ClN ₂ O ₄ S ·C ₂ H ₂ O ₄ ·1/2H ₂ O | 50.82 (50.97) | 4.65 (4.46) | 6.82 (6.83) | 5.39 (5.40) | 6.17 (6.37) | | 3280, 3050, 1740, 1655, 1610, 1590 |
| 12·1/2·oxalate | 168—172 (dec.) | +78.4° (<i>c</i> = 1.00, MeOH) | C ₂₃ H ₂₉ ClN ₂ O ₄ S ·1/2C ₂ H ₂ O ₄ | 61.10 (60.80) | 5.30 (5.50) | 6.22 (5.91) | 4.91 (4.61) | 5.62 (5.44) | | 3100—2500, 1760, 1695, 1605 |
| 13 (MB7) ·1/2fumarate | 212—213 (dec.) | +112.0° (<i>c</i> = 0.50, DMF) | C ₂₁ H ₂₃ ClN ₂ O ₄ S ·1/2C ₄ H ₄ O ₄ | 56.04 (55.82) | 5.11 (5.07) | 7.19 (7.35) | 5.68 (5.65) | 6.50 (6.55) | | 1740, 1670 |
| 14·oxalate·1/2EtOH | 120—124 (dec.) | +76.0° (<i>c</i> = 0.50, H ₂ O) | C ₂₃ H ₂₅ ClN ₂ O ₅ S ·C ₂ H ₂ O ₄ ·1/2C ₂ H ₅ OH | 52.93 (52.93) | 5.13 (5.06) | 6.01 (6.11) | 4.74 (4.67) | 5.43 (5.51) | | 1750, (broad), 1690 |
| 15 (MB8)·fumarate ·3/4H ₂ O | 158—161 (dec.) | +68.3° (<i>c</i> = 0.25, MeOH) | C ₂₀ H ₂₁ ClN ₂ O ₄ S ·C ₄ H ₄ O ₄ ·3/4H ₂ O | 52.36 (52.26) | 4.85 (4.65) | 5.09 (5.13) | 5.82 (5.93) | 6.44 (6.76) | | N.D. |
| 16 | 94—96 | +126.0° (<i>c</i> = 1.00, CHCl ₃) | C ₃₃ H ₃₁ ClN ₂ O ₅ S | 65.61 (65.86) | 5.18 (5.21) | 5.88 (5.61) | 4.64 (4.66) | 5.32 (5.32) | | 3420, 1685, 1670, 1605, 1585 |
| 17 | 117—119 | +109.6° (<i>c</i> = 1.00, MeOH) | C ₂₀ H ₂₀ ClNO ₅ S | 56.93 (57.04) | 4.78 (4.75) | 8.40 (8.36) | 3.32 (3.25) | 7.60 (7.51) | | 3470, 1735, 1650, 1600 |
| 18 (MA2) Na salt 2 hydrate | 200 (dec.) | +129.4° (<i>c</i> = 1.181, MeOH) | C ₁₈ H ₁₅ ClNO ₅ SNa ·2H ₂ O | 47.85 (47.96) | 4.24 (4.06) | 7.85 (8.18) | 3.10 (3.05) | 7.10 (7.25) | 5.09 (5.59) | 3400, 1670 |
| 19 (MA1) Na salt | N.D. | +119.5° (<i>c</i> = 1.316, MeOH) | C ₂₀ H ₁₇ ClNO ₆ SNa ·1/2H ₂ O | 51.45 (51.67) | 3.89 (4.10) | 7.59 (7.53) | 3.00 (3.06) | 6.87 (6.83) | 4.92 (4.91) | 3450, 1740, 1670, 1605 |
| 20 (MA4) Na salt | N.D. | +140.0° (<i>c</i> = 1.060, MeOH) | C ₁₉ H ₁₃ ClNO ₅ SNa ·2H ₂ O | 46.64 (46.44) | 3.91 (3.99) | 8.10 (8.00) | 3.20 (3.16) | 7.32 (7.51) | 5.25 (5.19) | 3380, 1670, 1580 |
| 21 (Oil) | N.D. | N.D. | N.D. | | | | | | | 3500, 1750, 1670 |
| 22·EtOH·1/3H ₂ O | 90—92 | N.D. | C ₂₄ H ₂₀ ClNO ₅ S·EtOH ·1/3H ₂ O | 59.82 (59.77) | 5.15 (4.87) | 6.14 (6.90) | 2.68 (2.67) | 6.14 (6.34) | | 3300, 1730, 1660 |
| 23 (MA3) Na salt 4.5H ₂ O | N.D. | +122.8° (<i>c</i> = 1.026, MeOH) | C ₁₉ H ₁₅ ClNO ₆ SNa ·4.5H ₂ O | 43.48 (43.69) | 4.61 (4.51) | 6.75 (7.01) | 2.67 (2.71) | 6.11 (6.31) | 4.38 (4.39) | 3450, 1740, 1670, 1610 |

Melting points were determined on a Yamato melting point apparatus Model MP-12 and are uncorrected. a) [α]_D²⁴. N.D.: not determined.

to the residual oil. The mixture was neutralized with K₂CO₃ (pH 7) and extracted with CHCl₃. The extracts were combined, dried, and concentrated. The residual oil was purified by flash column chromatography (SiO₂, eluted with MeOH-CHCl₃ (1:4)) to give MB6 as a foam, 7.10 g (77.3%), which was converted into fumarate to give white powder.

MB6 was also prepared by removal of the protective groups of **16** in 29% yield according to the method described in reference 8.

(+)-(2*S*,3*S*)-3-Acetoxy-2-(4-benzyloxyphenyl)-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one (**12**) A mixture of **8** (33 g, 76.83 mmol), 2-(dimethylamino)ethyl chloride·HCl (12.72 g, 118.29 mmol), K₂CO₃ (27.7 g), and acetone (1 l) was heated under reflux and vigorous stirring overnight and the reaction mixture was worked up in the same manner as described in the preparation of **1**.

The obtained oil of 5-[2-(dimethylamino)ethyl] compound (**28.08** g) was acetylated by stirring with Ac₂O (280 ml) and pyridine (280 ml) at room temperature for 2 h. After evaporation of Ac₂O, pyridine and AcOH, **12** (30 g, 71.7%) was obtained as an oil. The oil was converted into oxalate and recrystallized from MeOH-Et₂O to give **12**·1/2oxalate.

(+)-(2*S*,3*S*)-3-Acetoxy-8-chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-hydroxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**13**, MB7) Twenty-five percent HBr-AcOH (154 ml) was added to a solution of **12** (30.0 g, 57.14 mmol) in AcOH (180 ml) under ice-cooling. After stirring

at room temperature for 3.5 h, the reaction mixture was poured into Et₂O and the precipitated solid was collected on a filter, washed with Et₂O to remove BzI₂Br, and dissolved in ice-water. The aqueous solution was neutralized with NaHCO₃ (pH 8—9) and extracted with CHCl₃. The extracts were combined, washed with H₂O, dried, and concentrated. The residual oil was purified by column chromatography (SiO₂, eluted with CHCl₃-MeOH (10:1)). The oil obtained from the first eluate was converted into oxalate to give **14**·oxalate, 3.66 g (10.9%). From the second eluate, MB7 (**13**) was obtained as an oil which was converted into fumarate and recrystallized from EtOH to give MB7·1/2fumarate, 13.72 g (48.8%).

(+)-(2*S*,3*S*)-3-Acetoxy-5-(2-aminoethyl)-8-chloro-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**15**, MB8) MB8·fumarate was prepared from (+)-lactam (**3**) by the same procedure as described in reference 2 in 52.3% overall yield.

Synthesis of Acidic Metabolite Acidic metabolites MA1 (**19**), MA2 (**18**), MA3 (**23**), MA4 (**20**), **17**, **21** and **22** were synthesized by the same procedure as described in reference 2.

Ethyl (+)-(2*S*,3*S*)-8-Chloro-2,3,4,5-tetrahydro-3-hydroxy-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-5-acetate (**17**) **17** was obtained by alkylation of **3** with ethyl bromoacetate, K₂CO₃, acetone in 93.5% yield.

TABLE II. ¹H-NMR Spectral Data for Synthetic Reference Compounds

| Compound | ¹ H-NMR |
|---------------------------------------|--|
| 2 (MB1)·oxalate | (DMSO- <i>d</i> ₆) 2.70 (s, 6H), 2.8—3.5 (m, 2H), 3.75 (s, 3H), 3.8—4.6 (m, 2H), 4.29 (d, <i>J</i> =7.0, 1H), 4.94 (d, <i>J</i> =7.0, 1H), 6.89 (d, <i>J</i> =8.8, 2H), 7.33 (d, <i>J</i> =8.8, 2H), 7.5—7.8 (m, 3H) |
| 4 MB2)·oxalate | (DMSO- <i>d</i> ₆) 1.84 (s, 3H), 2.59 (s, 3H), 3.78 (s, 3H), 5.04 (d, <i>J</i> =7.0, 1H), 2.6—3.3 (m, 2H), 3.6—4.3 (m, 2H), 5.19 (d, <i>J</i> =7.0, 1H), 6.92 (d, <i>J</i> =8.7, 2H), 7.37 (d, <i>J</i> =8.7, 2H), 7.2—7.8 (m, 3H) |
| 5 (MB3)·fumarate | (DMSO- <i>d</i> ₆) 2.49 (s, 3H), 2.6—3.3 (m, 2H), 3.76 (s, 3H), 3.6—4.2 (m, 2H), 4.28 (d, <i>J</i> =7.0, 1H), 4.95 (d, <i>J</i> =7.0, 1H), 6.49 (s, 2H, fumaric acid), 6.89 (d, <i>J</i> =8.5, 2H), 7.33 (d, <i>J</i> =8.5, 2H), 7.5—7.8 (m, 3H) |
| 6 (MB4)·EtOH | (CDCl ₃) 2.30 (s, 6H), 2.5—3.0 (m, 2H), 3.5—4.6 (m, 2H), 4.30 (d, <i>J</i> =7.1, 1H), 4.89 (d, <i>J</i> =7.1, 1H), 6.75 (d, <i>J</i> =8.5, 2H), 7.31 (d, <i>J</i> =8.5, 2H), 7.36—7.73 (m, 3H), signals for EtOH were also observed |
| 7 (MB6)·fumarate | (DMSO- <i>d</i> ₆) 2.50 (s, 3H), 2.6—3.2 (m, 2H), 3.6—4.6 (m, 2H), 4.24 (d, <i>J</i> =7.2, 1H), 4.89 (d, <i>J</i> =7.2, 1H), 6.46 (s, 2H, fumaric acid), 6.71 (d, <i>J</i> =8.5, 2H), 7.21 (d, <i>J</i> =8.5, 2H), 7.5—7.8 (m, 3H) |
| 8·1/5 AcOEt | (DMSO- <i>d</i> ₆) 3.30 (s, 2H), 4.34 (br d, <i>J</i> =7.0, 1H), 5.08 (d, <i>J</i> =7.0, 1H), 5.09 (s, 2H), 6.9—7.7 (m, 12H) |
| 9·oxalate | (DMSO- <i>d</i> ₆) 2.50 (s, 3H), 2.7—3.3 (m, 2H), 3.95 (s, 2H), 4.29 (d, <i>J</i> =7, 1H), 4.96 (d, <i>J</i> =7, 1H), 5.13 (s, 2H), 6.95 (d, <i>J</i> =9, 2H), 7.1—7.8 (m, 15H) |
| 10 (Oil) | (CDCl ₃) 1.88 (s, 3H), 3.00 (s, 3H), 3.1—4.6 (m, 4H), 5.04 (s, 6H), 6.92 (d, <i>J</i> =9, 2H), 6.8—7.9 (m, 15H) |
| 11 (MB5)·oxalate·hemihydrate | (DMSO- <i>d</i> ₆) 1.84 (s, 3H), 2.59 (s, 3H), 2.7—3.5 (m, 2H), 3.7—4.5 (m, 2H), 5.02 (d, <i>J</i> =8.0, 1H), 5.09 (d, <i>J</i> =8.0, 1H), 6.73 (d, <i>J</i> =8.4, 2H), 7.24 (d, <i>J</i> =8.4, 2H), 7.6—7.8 (m, 3H) |
| 12·1/2·oxalate | (DMSO- <i>d</i> ₆) 1.84 (s, 3H), 2.66 (s, 6H), 2.8—3.4 (m, 2H), 3.8—4.6 (m, 2H), 5.02 (d, <i>J</i> =8, 1H), 5.19 (d, <i>J</i> =8, 1H), 5.11 (s, 2H), 6.99 (d, <i>J</i> =9, 2H), 7.2—7.8 (m, 10H) |
| 13 (MB7)·1/2fumarate | (DMSO- <i>d</i> ₆) 1.83 (s, 3H), 2.21 (s, 6H), 2.0—2.9 (m, 2H), 3.4—4.5 (m, 2H), 4.99 (d, <i>J</i> =7.5, 1H), 5.12 (d, <i>J</i> =7.5, 1H), 6.78 (d, <i>J</i> =8.5, 2H), 7.28 (d, <i>J</i> =8.5, 2H), 7.4—7.9 (m, 3H), 6.77 (s, 1H, 1/2fumaric acid) |
| 14·oxalate·1/2EtOH | (DMSO- <i>d</i> ₆) 1.85 (s, 3H), 2.28 (s, 3H), 2.75 (s, 6H), 2.8—3.4 (m, 2H), 3.7—4.6 (m, 2H), 5.06 (d, <i>J</i> =7.7, 1H), 5.28 (d, <i>J</i> =7.7, 1H), 7.14 (d, <i>J</i> =8.5, 2H), 7.51 (d, <i>J</i> =8.5, 2H), 7.6—8.0 (m, 3H) |
| 15 (MB8)·fumarate·3/4H ₂ O | (DMSO- <i>d</i> ₆) 1.84 (s, 3H), 2.6—3.3 (m, 2H), 3.77 (s, 3H), 3.6—4.0 (m, 1H), 4.0—4.5 (m, 1H), 5.03 (d, <i>J</i> =7.5, 1H), 5.19 (d, <i>J</i> =7.5H, 1H), 6.47 (s, 2H), 6.92 (d, <i>J</i> =8.8, 2H), 7.37 (d, <i>J</i> =8.8, 2H), 7.5—7.8 (m, 3H) |
| 16 | (CDCl ₃) 2.80 (d, <i>J</i> =10, 1H), 3.00 (s, 3H), 3.3—3.4 (m, 4H), 4.27 (dd, <i>J</i> =7 and 10, 1H), 4.89 (d, <i>J</i> =7, 1H), 5.06 (s, 4H), 6.96 (d, <i>J</i> =9, 2H), 6.9—7.8 (m, 15H) |
| 17 | (CDCl ₃) 1.31 (t, <i>J</i> =7.6, 3H), 2.77 (d, <i>J</i> =9.9, 1H), 3.81 (s, 3H), 4.27 (q, <i>J</i> =7.6, 2H), 4.28 (dd, <i>J</i> =9.9 and 7.3, 1H), 4.33 (d, <i>J</i> =17.6, 1H), 4.82 (d, <i>J</i> =17.6, 1H), 4.96 (d, <i>J</i> =7.3, 1H), 6.83—7.73 (m, 7H) |
| 18 (MA2) Na salt 2 hydrate | (D ₂ O) 3.73 (d, <i>J</i> =17.7, 1H), 3.76 (s, 3H), 4.44 (d, <i>J</i> =7.3, 1H), 4.71 (d, <i>J</i> =17.7, 1H), 4.83 (d, <i>J</i> =7.3, 1H), 6.85 (d, <i>J</i> =8.8, 2H), 7.30 (d, <i>J</i> =8.8, 3H), 7.40 (dd, <i>J</i> =8.8 and 2.5, 1H), 7.49 (d, <i>J</i> =2.5, 1H) |
| 19 (MA1) Na salt | (D ₂ O) 1.86 (s, 3H), 3.73 (s, 3H), 3.75 (d, <i>J</i> =17.7, 1H), 4.68 (d, <i>J</i> =17.7, 1H), 4.93 (d, <i>J</i> =6.8H, 1H), 5.23 (d, <i>J</i> =6.8, 1H), 6.82 (d, <i>J</i> =8.8, 2H), 7.2—7.5 (m, 5H) |
| 20 (MA4) Na salt | (D ₂ O) 3.75 (d, <i>J</i> =17, 1H), 4.41 (d, <i>J</i> =7.0, 1H), 4.70 (d, <i>J</i> =17, 1H), 4.82 (d, <i>J</i> =7.0, 1H), 6.80 (d, <i>J</i> =8.8, 2H), 7.23 (d, <i>J</i> =8.8, 2H), 7.2—7.6 (m, 3H) |
| 21 (Oil) | (CDCl ₃) 2.76 (d, <i>J</i> =9.7, 0H), 3.82 (s, 3H), 4.33 (d, <i>J</i> =17.1, 1H), 4.44 (dd, <i>J</i> =9.7 and 6.8, 1H), 4.83 (d, <i>J</i> =17.1, 1H), 4.96 (d, <i>J</i> =6.8, 1H), 5.07 (s, 2H), 6.96 (d, <i>J</i> =8.8, 2H), 7.1—7.4 (m, 4H), 7.72 (d, <i>J</i> =2.4, 1H) |
| 22·EtOH·1/3H ₂ O | (CDCl ₃) 4.26 (d, <i>J</i> =17.1, 1H), 4.44 (d, <i>J</i> =6.8, 1H), 4.86 (d, <i>J</i> =17.1, 1H), 4.95 (d, <i>J</i> =6.8, 1H), 5.05 (s, 2H), 6.9—7.8 (m, 12H) |
| 23 (MA3) Na salt 4.5H ₂ O | (D ₂ O) 1.86 (s, 3H), 3.75 (d, <i>J</i> =16.9, 1H), 4.70 (d, <i>J</i> =16.9, 1H), 4.87 (d, <i>J</i> =7.0, 1H), 5.21 (d, <i>J</i> =7.0, 1H), 6.97 (d, <i>J</i> =8.8, 2H), 7.15 (d, <i>J</i> =8.8, 2H), 7.2—7.8 (m, 3H) |

¹H-NMR spectra were obtained on JEOL PMX-60, Hitachi RH-90, or JEOL FX-200 spectrometer. Coupling constants (*J*) are reported in hertz (Hz), and s, d, t, q, m, br d and dd refer to singlet, doublet, triplet, quartet, multiplet, broad doublet and double doublet. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (Me₄Si; 0.0) as an internal standard.

(+)-(2*S*,3*S*)-8-Chloro-2,3,4,5-tetrahydro-3-hydroxy-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-5-acetic Acid (18, MA2) MA2·hydrate was prepared by hydrolysis of 17 in a mixture of NaOH, H₂O, MeOH and tetrahydrofuran (THF) in 98.4% yield.

The MA2·hydrate was converted into Na salt by treatment with 1 eq of NaHCO₃ in H₂O to give MA2 Na salt 2 hydrate.

(+)-(2*S*,3*S*)-3-Acetoxy-8-chloro-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-5-acetic Acid (19, MA1) MA1 was obtained by acetylation of 18·hydrate with Ac₂O and pyridine in 77% yield as an oil. MA1 dissolved in MeOH and a solution of 0.9 eq of NaHCO₃ in H₂O was added at 0°C and concentrated under reduced pressure. The residual gum was dissolved in a small amount of MeOH and diluted with iso-Pr₂O to give MA1·Na salt as colorless powder.

Methyl (+)-(2*S*,3*S*)-2-(4-Benzoyloxyphenyl)-8-chloro-2,3,4,5-tetrahydro-3-hydroxy-4-oxo-1,5-benzothiazepin-5-acetate (21) 21 was prepared by *O*-demethylation of 17 with BBr₃ in CH₂Cl₂, followed by benzylation with BzI₂Br, and K₂CO₃ in MeOH in 64.4% overall yield, as an oil.

(+)-(2*S*,3*S*)-2-(4-Benzoyloxyphenyl)-8-chloro-2,3,4,5-tetrahydro-3-hydroxy-4-oxo-1,5-benzothiazepin-5-acetic Acid (22) 22 was prepared by hydrolysis of 21 in 84.9% yield.

(+)-(2*S*,3*S*)-3-Acetoxy-8-chloro-2,3,4,5-tetrahydro-2-(4-hydroxyphenyl)-4-oxo-1,5-benzothiazepin-5-acetic Acid (23, MA3) MA3 was synthesized by acetylation of 22, followed by debenylation with TMSCl, NaI in MeCN in 54.4% yield, as colorless foam. MA3·Na salt was

prepared in the same manner as described in the preparation of MA1·Na salt.

(+)-(2*S*,3*S*)-8-Chloro-2,3,4,5-tetrahydro-3-hydroxy-2-(4-hydroxyphenyl)-4-oxo-1,5-benzothiazepin-5-acetic Acid (20, MA4) MA4 was prepared by debenylation of 22 with TMSCl, NaI and MeCN in 98% yield, as colorless foam. MA4·Na salt, colorless powder (AcOEt-iso-Pr₂O).

Synthesis of Neutral Metabolite. (+)-(2*S*,3*S*)-8-Chloro-2,3,4,5-tetrahydro-3-hydroxy-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-5-acetonitrile (24, MN2) A mixture of 3 (15 g, 44.67 mmol), chloroacetonitrile (498 mg), and K₂CO₃ (2.76 g) in acetone (60 ml) was stirred at room temperature for 4 h. The reaction mixture was evaporated. The residue was purified by column chromatography (SiO₂, eluted with CHCl₃-MeOH (20:1, v/v)) and recrystallized from AcOEt-hexane to give MN2 (24) (1.35 g, 60%), mp 158—160°C, [α]_D²⁰ +91.3° (*c*=0.392, MeOH).

(+)-(2*S*,3*S*)-3-Acetoxy-8-chloro-2,3,4,5-tetrahydro-2-(4-methoxyphenyl)-4-oxo-1,5-benzothiazepin-5-acetonitrile (25, MN1) A mixture of MN2 (24) (413 mg, 1.10 mmol), Ac₂O (1 ml), and pyridine (2 ml) was stirred at 100°C for 4 h. The reaction mixture was evaporated. The residual solid was recrystallized from AcOEt to give MN1 (25) (439 mg, 95.6%), mp 196—197°C, [α]_D²⁰ +89.1° (*c*=0.384, MeOH).

Acknowledgements The authors are grateful to Dr. S. Saito, senior executive director, Dr. T. Oh-ishi, general manager of the Pharma-

cological Research Laboratory, and Dr. O. Takaiti, general manager of the Research Laboratory of Drug Metabolism, for discussions and suggestions. Thanks are also due to the staff of the analytical section of the Organic Chemistry Research Laboratory, presided over by Dr. A. Kinumaki, for spectral and elemental analyses.

References

- 1) H. Inoue, M. Konda, T. Hashiyama, H. Ohtsuka, K. Takahashi, M. Gaino, T. Date, K. Abe, M. Takeda, S. Murata, H. Narita, T. Nagao, *J. Med. Chem.*, **34**, 675 (1991).
- 2) Y. Sugawara, M. Ohashi, S. Nakamura, S. Usuki, T. Suzuki, Y. Ito, T. Kume, S. Harigayama, A. Nakao, M. Gaino, H. Inoue, *J. Pharmacobio-Dyn.*, **11**, 211 (1988).
- 3) Y. Sugawara, S. Nakamura, S. Usuki, Y. Ito, T. Suzuki, M. Ohashi, S. Harigaya, *J. Pharmacobio-Dyn.*, **11**, 224 (1988).
- 4) T. Meshi, J. Sugihara, Y. Sato, *Chem. Pharm. Bull.*, **19**, 1546 (1971).
- 5) J. Sugihara, Y. Sugawara, H. Ando, S. Harigaya, A. Etoh, K. Kohno, *J. Pharmacobio-Dyn.*, **7**, 24 (1984).
- 6) V. Rovei, R. Gomeni, M. Mitchard, J. Larribaud, Ch. Blatix, J. J. Thebault, P. L. Morselli, *Acta Cardiologica*, **35**, 35 (1980).
- 7) S. Nakamura, Y. Sugawara, T. Fukushima, Y. Ito, M. Ohashi, O. Takaiti, *Biol. Pharm. Bull.*, **16**, 635 (1993).
- 8) M. Miyazaki, T. Iwakuma, T. Tanaka, *Chem. Pharm. Bull.*, **26**, 2889 (1978).