Reagents——Uracil and 6-methyluracil were obtained from Wako Pure Chemical Industries, Tokyo. Glycylglycine was obtained from Tokyo Kasei Co. Other reagents were purchased from Wako Pure Chemical Industries, Tokyo

Preparation——Cu(II)(GG)(6-MeuraH)HBr·H_2O and Cu(II)(GG)(UraH)HBr·3/2H_2O: In 30 ml of 0.1 M KOH dissolving 5 mM of (Glycylglycinato)Cu(II)·3H_2O, 5 mM of 6-methyluracil in 5 ml of 1 M KOH added with stirring. Into this solution, 5 mM of NaBr in 2 ml of 0.1 M KOH was added with stirring and the color changed from dark-blue to violet. Evaporating this solution, a violet compound was obtained and recrystallized from water. This complex was washed with ethanol and dried under reduced pressure.

(Glycylglycinato)Cu(II)·3H_2O was prepared according to ref. 15.

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Synthesis of the Metabolites and Related Compounds of Diltiazem

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Major metabolites of the antianginal drug, Diltiazem, 3(*S*)-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2(*S*)-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one, have been synthesized. In connection with these metabolites, several S- and N-oxides were prepared.

Keywords——metabolites of Diltiazem; synthesis of benzothiazepines; preferential N-oxidation; preferential S-oxidation; stepwise oxidation; catalytic hydrogenation of N-oxides

Diltiazem (**1**),[2] 3(*S*)-(acetyloxy)-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2(*S*)-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one,[3] is an antianginal drug developed by Tanabe Seiyaku company in 1974. The metabolic fate of this drug has been investigated extensively by Sato and co-workers.[4] Thus, they obtained seven metabolites (M-1—M-7) and an unseparable mixture of N-oxide metabolites from the urine of the rats administered the drug and assigned their structures on the basis of the spectral data to 3-hydroxy-5-[2-(dimethylamino)-ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (M-1) and its congeners. This paper describes the synthesis of the major metabolites and related compounds achieved for confirmation of Sato's assignment.

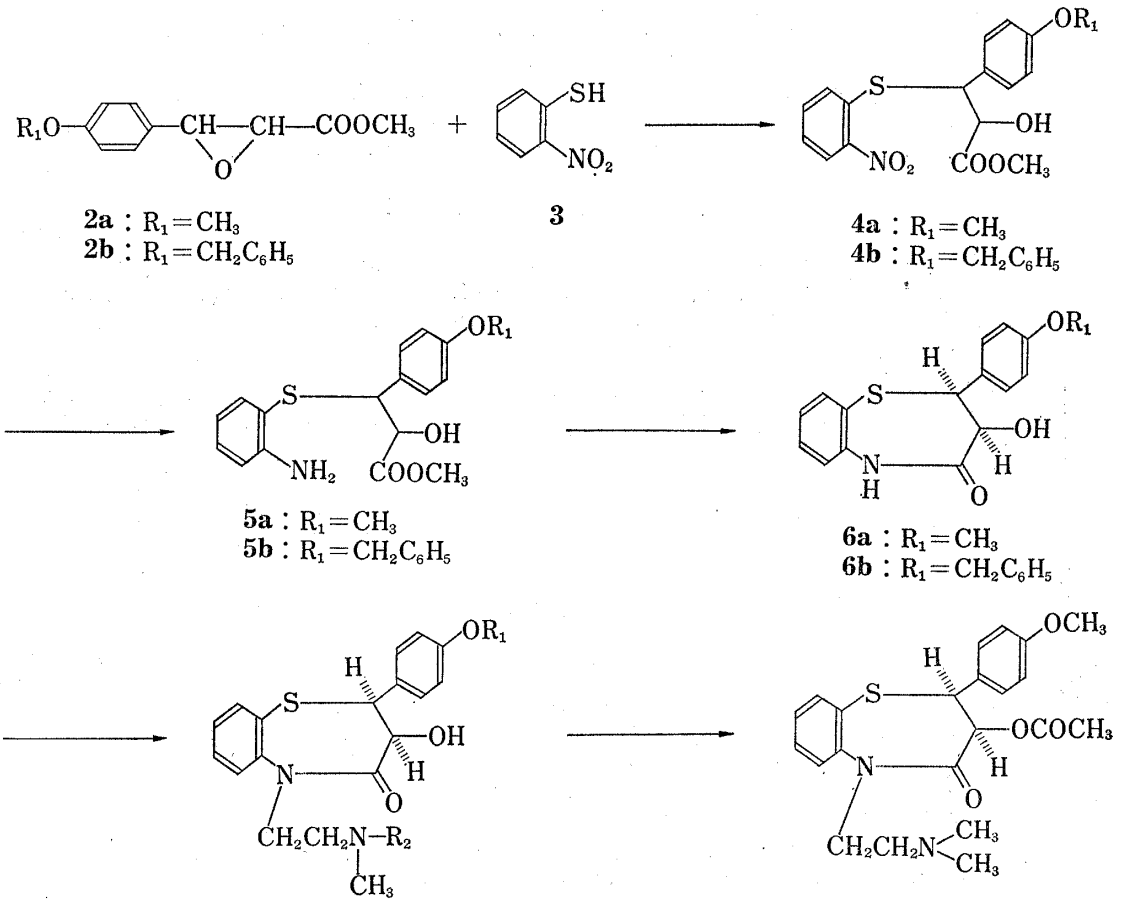
M-1: Kugita and co-workers have prepared Diltiazem (**1**) starting with the methoxyphenylglycidate (**2a**) *via* **4a**, **5a**, **6a**, and **7a** (Chart 1).[5] One of the intermediates, (**7a**), was identical with M-1 by mixed melting point and spectral comparisons.

1) Location: *Kawagishi, Toda-shi, Saitama.*
2) International non-proprietary name. Code designation of the hydrochloride of Diltiazem is CRD-401, of which the brand name is "Herbesser".
3) The absolute configuration of this compound has been determined by X-ray crystallography; K. Kotera and T. Date, unpublished data.
4) T. Meshi, J. Sugihara and Y. Sato, *Chem. Pharm. Bull.* (Tokyo), **19**, 1546 (1971).
5) *a*) H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), **19**, 593 (1971); *b*) H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), **18**, 2284 (1970); *c*) H. Kugita, H. Inoue, M. Ikezaki and S. Takeo, *Chem. Pharm. Bull.* (Tokyo), **18**, 2028 (1970).

Other major metabolites, M-2, M-4, and M-6 had their supposed structures, 2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-5-[2-(methylamino)ethyl]-(**7e**), 5-[2-(dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-hydroxyphenyl)-(**7c**), and 2,3-dihydro-3-hydroxy-2-(4-hydroxyphenyl)-5-[2-(methylamino)ethyl]-1,5-benzothiazepin-4(5*H*)-one (**7f**), respectively. Our synthetic routes toward them were as follows.

M-2 and M-6: By applying Kugita's procedure, 4-benzyloxyphenylglycidate (**2b**) was condensed with *o*-nitrothiophenol (**3**) in acetonitrile in the presence of sodium bicarbonate to give the nitro-ester (**4b**) which was reduced to the amino-ester (**5b**) with ferric sulfate in alkaline solution. Subsequent cyclization of **5b** in refluxing toluene afforded the 4-benzyloxyphenyl-lactam (**6b**).

This was treated with 1 eq. of dimethylsulfinyl carbanion prepared from dimethyl sulfoxide and sodium hydride and the resultant sodio salt of **6b** was allowed to react with benzyl (2-chloroethyl)methylcarbamate.[6] The 4-benzyloxyphenyl-[2-(N-benzyloxycarbonyl-N-methylamino)ethyl] compound (**7b**), thus obtained, gave **7f** by treating with hydrogen bromide-acetic acid followed by alkaline hydrolysis in 68.7% overall yield from **6b**.



2a : $R_1=CH_3$
2b : $R_1=CH_2C_6H_5$

3

4a : $R_1=CH_3$
4b : $R_1=CH_2C_6H_5$

5a : $R_1=CH_3$
5b : $R_1=CH_2C_6H_5$

6a : $R_1=CH_3$
6b : $R_1=CH_2C_6H_5$

7a : $R_1=R_2=CH_3$ (M-1)
7b : $R_1=CH_2C_6H_5$ $R_2=CO_2CH_2C_6H_5$
7c : $R_1=H$ $R_2=CH_3$ (M-4)
7d : $R_1=CH_3$ $R_2=CO_2CH_2C_6H_5$
7e : $R_1=CH_3$ $R_2=H$ (M-2)
7f : $R_1=R_2=H$ (M-6)

1 Diltiazem

Chart 1

6) *a*) S. Pinchas and D. Ben-Ishai, *J. Am. Chem. Soc.*, **79**, 4099 (1957); *b*) H. Wenker, *J. Am. Chem. Soc.*, **58**, 2608 (1936).

By the same manner as with **6b**→**7b**, the 4-methoxyphenyl-lactam (**6a**) was converted to the 4-methoxyphenyl-[2-(N-benzyloxycarbonyl-N-methylamino)ethyl]compound (**7d**), which was hydrolyzed with hydrogen bromide-acetic acid to afford, after neutralization, **7e** in 54% overall yield from **6a**.

M-4: Demethylation of **7a** with a mixture of 57% hydroiodic acid, hydrophosphorous acid and acetic acid at reflux temperature gave **7c** in 48% yield.

The paper chromatograms and major peaks in the absorption spectra of M-2, M-4, and M-6 were well consistent with those of the synthetic products, (**7e**), (**7c**), and (**7f**), respectively.

Oxidation of the lactam (**7a**) with 1 eq. of sodium metaperiodate in aqueous acetic acid gave the sulfoxide (**9**), whereas use of 1 eq. of *m*-chloroperbenzoic acid in chloroform afforded the N-oxide (**8**) together with a trace of the 1, N-dioxide (**10**).

The structural assignment of **9** was based on the upfield shift of the proton at C-2 (δ 4.25—4.45) compared to those of **7a** (δ 4.94) and **8** (δ 4.90) due to the magnetic anisotropy of the newly formed S→O bond. The N-oxide (**8**) was characterized by its infrared (IR) (945 cm^{-1} for aliphatic N→O stretching) and mass spectra [*m/e* 327, M^+- $\begin{matrix}CH_3\\CH_3\end{matrix}$>N–OH].

Further oxidation of **9** with 1 eq. of the peracid yielded the 1, N-dioxide (**10**), with 2 eq. of the acid 1,1,N-trioxide (**11**), exclusively.

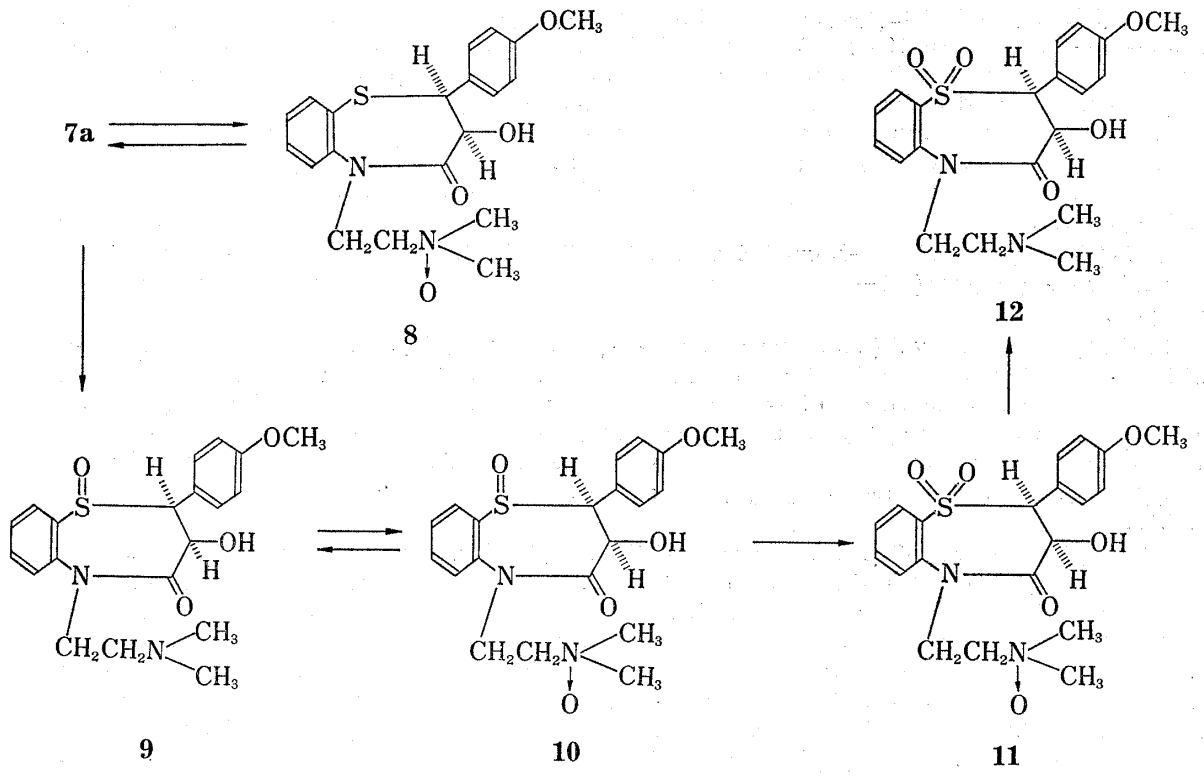


Chart 2

These N-oxides, (**8**), (**10**), and (**11**) gave the amines, (**7a**), (**9**), and (**12**) respectively, by catalytic hydrogenation over palladium-charcoal almost quantitatively.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IR-E spectrometer, Ultraviolet (UV) spectra with a Hitachi EPS-2U spectrometer, Nuclear magnetic resonance (NMR) spectra with a JEOL JNM-ME-60 spectrometer (tetramethylsilane as internal standard), and mass spectra with a Hitachi RMS-4 spectrometer. All the experiments have been carried out by using racemic compounds.

2-(4-Benzyloxyphenyl)-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4(5*H*)-one (6b)——This compound was prepared from methyl *p*-benzyloxyphenylglycidate (**2b**) and *o*-nitrothiophenol (3) *via* **4b** and **5b**, by Kugita's method.[5] Physical constants and spectral data of the intermediates are shown below.

2b: mp 104—106° (60% MeOH); 47.5% yield from *p*-benzyloxybenzaldehyde; IR ν_{max}^{Nujol} cm^{-1}: 1730, 1250, and 910; *Anal.* Calcd. for $C_{17}H_{16}O_4$: C, 71.81; H, 5.67 Found: C, 71.70; H, 5.81.

Methyl 3-(4-Benzyloxyphenyl)-2-hydroxy-3-(2-nitrophenylthio)-propionate (4b): mp 138—140° (AcOEt); 52.9% yield from **2b**; IR ν_{max}^{Nujol} cm^{-1}: 3495, 1730, and 1610; *Anal.* Calcd. for $C_{23}H_{21}NO_6S$: C, 62.85; H, 4.81; N, 3.19; S, 7.29. Found: C, 63.01; H, 4.77; N, 3.32; S, 7.40.

Methyl 3-(2-Aminophenylthio)-3-(4-benzyloxyphenyl)-2-hydroxy-propionate (5b): mp 119—120° (AcOEt); 43% yield; IR ν_{max}^{Nujol} cm^{-1}: 3450, 3360, 1719, and 1610; *Anal.* Calcd. for $C_{23}H_{23}NO_4S$: C, 67.48; H, 5.66; N, 3.42; S, 7.83. Found: C, 67.31; H, 5.48; N, 3.28; S, 7.63.

6b: mp 230—232° (dec.)(PhMe); 83% yield; IR ν_{max}^{Nujol} cm: 3320, 1685, 1637, and 1608; *Anal.* Calcd. for $C_{22}H_{19}NO_3S$: C, 70.00, H, 5.07; N, 3.71; S, 8.50. Found: C, 69.62; H, 5.20; N, 4.06; S, 8.58.

5-[2-(N-Benzyloxycarbonyl-N-methyl) aminoethyl]-2-(4-benzyloxyphenyl)-2,3-dihydro-3-hydroxy-1,5-benzothiazepin-4 (5*H*)-one (7b)——Dimethylsulfinyl carbanion was prepared from 80 ml of DMSO and 1.37 g (0.029 mol) of NaH (50% oil dispersion) by the usual manner. To this solution was added 9.0 g (0.024 mol) of **6b** at room temperature under N_2. After 1 hr's stirring, a solution of 7.1 g (0.033 mol) of benzyl (2-chloroethyl)methyl carbamate in 5 ml of DMSO was added in one portion and the mixture was kept at 50—55° for 5 hr. Then 0.6 g of the carbamate was added again and stirring was continued at the same temperature for another 2 hr. The reaction mixture was poured onto *ca.* 500 ml of ice-water and extracted three times with 100 ml of benzene. The whole benzene extracts were combined, treated with Norite, dried over Na_2SO_4. Removal of the solvent and recrystallization of the residue gave 9.2 g (68%) of **7b** in colorless prisms, mp 122—123° (AcOEt); *Anal.* Calcd. for $C_{33}H_{32}N_2O_5S$: C, 69.70; H, 5.67; N, 4.93. Found: C, 71.01; H, 5.81: N, 4.69.

5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-hydroxyphenyl)-1,5-benzothiazepin-4(5*H*)-one-(7c)(M-4)——A mixture of 19.8 g of **7a**, 120 ml of 57% HI, 80 ml of H_3PO_2 and 120 ml of AcOH was refluxed for 10 hr. The reaction mixture was concentrated *in vacuo*, poured onto ice-water, made alkaline with NH_4OH and extracted with $CHCl_3$. After usual work-up, 9.2 g (48% yield) of crude **7c** was obtained as a solid, which was recrystallized from EtOH to give colorless needles, mp 135—138° (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3400, 2200 (bro.), and 1665; NMR ($CDCl_3$-d_6-DMSO) δ: 2.26 (S, 6H), 4.28 (d, 1H, J=7 Hz), and 4.88 (d, 1H, J=7 Hz); *Anal.* Calcd. for $C_{19}H_{22}N_2O_3S$: C, 63.66; H, 6.19; N, 7.82; S, 8.95. Found: C, 63.48; H, 6.11; N, 7.79; S, 8.77.

5-[2-(N-Benzyloxycarbonyl-N-methyl) aminoethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one(7d)——By the same procedure as with **6b**→**7b**, **6a** was converted to **7d** in 90% yield; oil.

2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-5-[2-(methylamino)ethyl]-1,5-benzothiazepin-4(5*H*)-one(7e)-(M-2)——A solution of 12.8 g (0.026 mol) of **7d** in 30 ml of 25% HBr-AcOH was stirred at 30° for 3 hr. The reaction mixture was poured onto ice-water and shaked with ether. The water layer was separated and made alkaline with solid Na_2CO_3 and the gum separated was taken up in AcOEt. After removal of the solvent, the residue was treated with EtOH–HCl to give the hydrochloride of **7e** in 47% yield; mp 203—207° (dec.)(EtOH); *Anal.* Calcd. for $C_{19}H_{22}N_2O_3SHCl$: C, 57.78; H, 5.87; N, 7.99. Found: C, 57.86; H, 5.66; N, 8.12.

2,3-Dihydro-3-hydroxy-2-(4-hydroxyphenyl)-5-[2-(methylamino)ethyl]-1,5-benzothiazepin-4(5*H*)-one(7f)-(M-6)——A solution of 1.0 g of **7b** in 8 ml of 25% HBr-AcOH was allowed to stand at 15—20° for 15 hr. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in a mixture of 300 ml of EtOH and 20 ml of 5% aqueous NaOH. The solution was, after stirring for 4 hr at room temperature, made acidic with 10% HCl and the solvent was evaporated *in vacuo*. The residue was treated with aqueous $NaHCO_3$, taken up in AcOEt and dried. The solvent was removed and the residue was dissolved in ethanolic HCl, treated with Norite, and the solution was concentrated to give the crude hydrochloride. Recrystallization from EtOH afforded 1.0 g (83.5% yield) of **7f** in tan yellow prisms, mp>235° (dec.); IR ν_{max}^{Nujol} cm^{-1}: 3100—3400, 1655, and 1610; NMR ($CDCl_3$-d_6-DMSO) δ: 2.35 (S, 3H), 2.40—3.00 (m, 2H), 3.40—4.00 (m, 2H), 4.22 (d, 1H, J=7.5 Hz, 3-H), and 4.84 (d, 1H, J=7.5 Hz, 2-H); *Anal.* Calcd. for $C_{18}H_{20}N_2O_3S\cdot HCl$: C, 56.76; H, 5.56; N, 7.35; C, 9.31; S, 8.42. Found: C, 56.62; H, 5.73; N, 7.20; Cl, 9.17; S, 8.38.

5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-brnzothiazepin-4(5*H*)-one-N-oxide (8)——A solution of 1.86 g (0.005 mol) of **7a** and 1.12 g (0.005 mol as 85% purity) of *m*-chloroperbenzoic acid in 30 ml of $CHCl_3$ was allowed to stand at 15—20° for 2 days. Then, the solvent was removed *in vacuo* and the residue was passed through an alumina column using $CHCl_3$–MeOH (9: 1). The eluent was evaporated *in vacuo* and the residue (2 spots on TLC using silica gel-MeOH) was dissolved in 100 ml of $CHCl_3$. The $CHCl_3$ solution was shaked with 15 ml of H_2O until the thin layer chromatogram of the organic layer had shown a single spot. Usual work-up gave a solid residue which was recrystalized from MeOH–ether to give 2.79 g (69.0% yield) of **8** in colorless needles; mp 160—161° (dec.); IR ν_{max}^{Nujol} cm^{-1}: 1679 and 945; NMR (d_6-DMSO) δ: 3.45 (3H, S), 3.48 (3H, S), 3.76 (3H, S), 4.25 (1H, d, J=8 Hz, 3-H), and 4.90 (1H, d,

J=8 Hz, 2-H); MS m/e: 327 (M^+-$\begin{matrix}Me\\ \diagdown\\ \diagup\\ Me\end{matrix}$N-OH). This compound forms *m*-chlorobenzoate, mp 137—138° (EtOH-MeOH); *Anal.* Calcd. for $C_{20}H_{24}N_2O_4S$, C_7H_5ClO; C, 59.49; H, 5.36; N, 5.14; S, 5.88. Found: C, 59.21; H, 5.43; N, 5.05; S, 6.08.

5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one-1-oxide (9)——To a solution of 1.49 g (0.004 mol) of **7a** in 20 ml of AcOH and 5 ml of H_2O was added a solution of 1.07 g (0.005 mol) of $NaIO_4$ in 15 ml of H_2O at 5—10° and the mixture was stirred 20—25° for 22 hr. The solvent was distilled *in vacuo* and the residue was extracted with AcOEt, washed with aqueous 10% Na_2CO_3 and dried. Column chroma ography on silica gel using $CHCl_3$–MeOH (9: 1) gave 1.18 g (76.1%) of **9** in colorless needles, mp 140—142.5° (*n*-hexane); IR ν_{max}^{Nujol} cm^{-1}: 1675, 1612, and 1582; NMR ($CDCl_3$) δ: 2.15 (6H, S), 2.45 (2H, t, J=6 Hz), 3.75 (3H, S), 4.25—4.45 (2H, m, 2-H and 3-H) *Anal.* Calcd. for $C_{20}H_{24}N_2O_4S$; C, 61.84; H, 6.23; N, 7.21. Found: C, 61.98; H, 6.29; N, 7.03.

5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one-1, N-dioxide (10)——A mixture of 0.23 g of **7a** and 0.02 g (0.006 mol as 85% purity) of *m*-chloroperbenzoic acid in 10 ml of $CHCl_3$ was allowed to stand at 20° for 45 min. The same work up as described in **7a**→**8** gave 0.21 g (86.7% yield) of **10** in colorless prisms, mp 157—159° (dec.)(MeOH–ether); IR ν_{max}^{Nujol} cm: 1678; NMR (D_2O) δ: 3.20 (3H, S), 3.30 (3H, S), and 3.85 (3H, S); *Anal.* Calcd. for $C_{20}H_{24}N_2O_5S\cdot H_2O$; C, 56.86; H, 6.20; N, 6.63. Found: C, 56.90; H, 6.09; N, 6.56.

5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one-1,1,N-trioxide (11)——A mixture of 1.12 g (0.003 mol) of **7a** and 2.40 g (0.0118 mol as 85% purity) of *m*-chloroperbenzoic acid in 30 ml of $CHCl_3$ was refluxed for 3 hr. Then, the solution was concentrated to 1/3 volume and chromatographed on alumina. Elution with $CHCl_3$–MeOH (5: 1) gave, after removal of the solvent, a colorless oil which was triturated with ether to give 1.2 g (95% yield) of crude **11**, mp 178—178.5° (dec.)(MeOH–ether); IR ν_{max}^{Nujol} cm^{-1}: 1682; NMR (D_2O) δ: 3.10 (3H, S), 3.21 (3H, S), 3.77 (3H, S), and 5.20 (1H, d, J=8 Hz, 2-H); MS m/e: 404 (M^+-16) and 359 (M^+-$\begin{matrix}Me\\ \diagdown\\ \diagup\\ Me\end{matrix}$N-OH).

5-[2-(Dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one-1,1-dioxide (12)——A solution of 1.05 g of the trioxide (**11**) in 80 ml of MeOH was shaken with hydrogen in the presence of 0.3 g of 10% Pd-C at room temperature (uptake 61 ml). Filtration and evaporation left a residue, which was recrystallized from AcOEt–*n*–hezane to give 0.84 g (83.1%) of **12** in colorless prisms, mp 185—186° (dec.); IR ν_{max}^{Nujol} cm^{-1}: 1680, NMR ($CDCl_3$-d_6-DMSO) δ: 2.23 (6H, S), 3.80 (3H, S), 4.58 (1H, d, J=8.5 Hz, 3-H) and 5.02 (1H, d, J=8.5 Hz, 2-H); *Anal.* Calcd. for $C_{20}H_{24}N_2O_5S$: C, 59.38; H, 5.98; N, 6.92: Found: C, 59.30: H, 5.85; N, 6.88.

Catalytic Hydrogenation of the Dioxide (10)——A solution of 1.2 g of **10** in 80 ml of MeOH was hydrogenated in the same manner as with **11**→**12**. The hydrogenation was stopped after 75 ml of H_2 had been absorbed. The product (**9**) was crystallized from benzene-isopropyl ether in colorless needles, mp 140°. The IR spectrum of this compound was agreed with that of an authentic specimen.

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