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Reaction of 3-Phenylglycidic Esters. IV.[1] Reaction of Methyl 3-(4-Methoxyphenyl)glycidate with 2-Nitrophenol and Synthesis of 1,5-Benzoxazepine Derivatives

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The reaction of methyl *trans*-3-(4-methoxyphenyl)glycidate (**1**) with 2-nitrophenol was investigated under various conditions. Generally, the reaction proceeded predominantly by *cis*-opening of the oxirane ring of **1** to give the *threo*-nitro ester (**7**). Selective *trans*-opening of **1** was observed only in the reaction with sodium 2-nitrophenoxide to give the *erythro*-nitro ester (**8**).

Some 1,5-benzoxazepine derivatives (**16**—**19**), 1-oxa analogues of diltiazem, were synthesized from **7** and **8** for pharmacological evaluation. Compound **18a** showed the highest vasodilating activity in this series, but it was less active and more toxic than racemic diltiazem.

Keywords——methyl *trans*-3-(4-methoxyphenyl)glycidate; 2-nitrophenol; stereoselective oxirane-ring opening; 1,5-benzoxazepine derivative; cerebral vasodilating activity

Diltiazem hydrochloride, (+)-*cis*-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one hydrochloride (**3**),[2] has been used clinically as an effective antianginal agent having calcium channel blocking activity.[3] The mode of oxirane-ring opening of methyl *trans*-3-(4-methoxyphenyl)glycidate (**1**) by 2-nitrothiophenol was studied intensively by us in an attempt to achieve the stereospecific synthesis of **3**.[4] As a result, either the *threo*-nitro ester (**2**), the requisite intermediate for **3**, or its *erythro*-isomer could be stereospecifically produced by the choice of appropriate reaction conditions. Following these studies, we were interested both in the reaction of **1** with phenolic hydroxyl groups and in the synthesis of 1,5-benzoxazepine derivatives. We describe here the mode of oxirane-ring opening of **1** by 2-nitrophenol (**6**) as well as the synthesis and vasodilating activity of 1,5-benzoxazepine derivatives (**4**), which are 1-oxa analogues of diltiazem.

Chemistry

Alcoholysis of 3-arylglycidic esters was studied extensively by Fukawa and co-workers.[5] However, very few reports have appeared on the reaction with phenolic hydroxyl groups. Recently, in connection with studies on the synthesis of 1,4-benzoxazine derivatives, Banzatti and co-workers[6] reported that the reaction of ethyl *trans*-3-phenylglycidate with sodium 2-nitrophenoxide in ethanol gave a 52% yield of the *trans*-opening product (**5**).

When the glycidate (**1**) was heated with 2-nitrophenol (**6**) in acetonitrile, the *threo*-nitro ester (**7**), mp 83—85 °C, was obtained by *cis*-opening of the oxirane ring as a major product. The *erythro*-nitro ester (**8**) was isolated in low yield as an oil from the mother liquor by preparative thin-layer chromatography (TLC),[7] and the *threo*/*erythro* ratio of the total product was 9.4. In the nuclear magnetic resonance (NMR) spectra of **7** and **8**, the methine protons at C_2 and C_3, adjacent to hydroxyl and phenoxy groups, showed AB-type vicinal

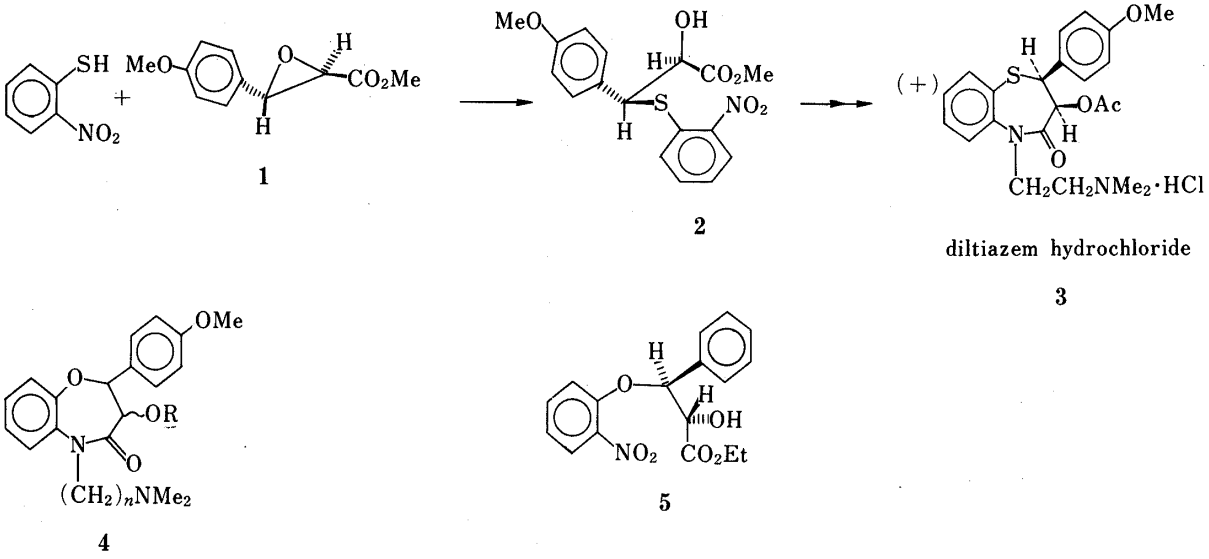


Chart 1

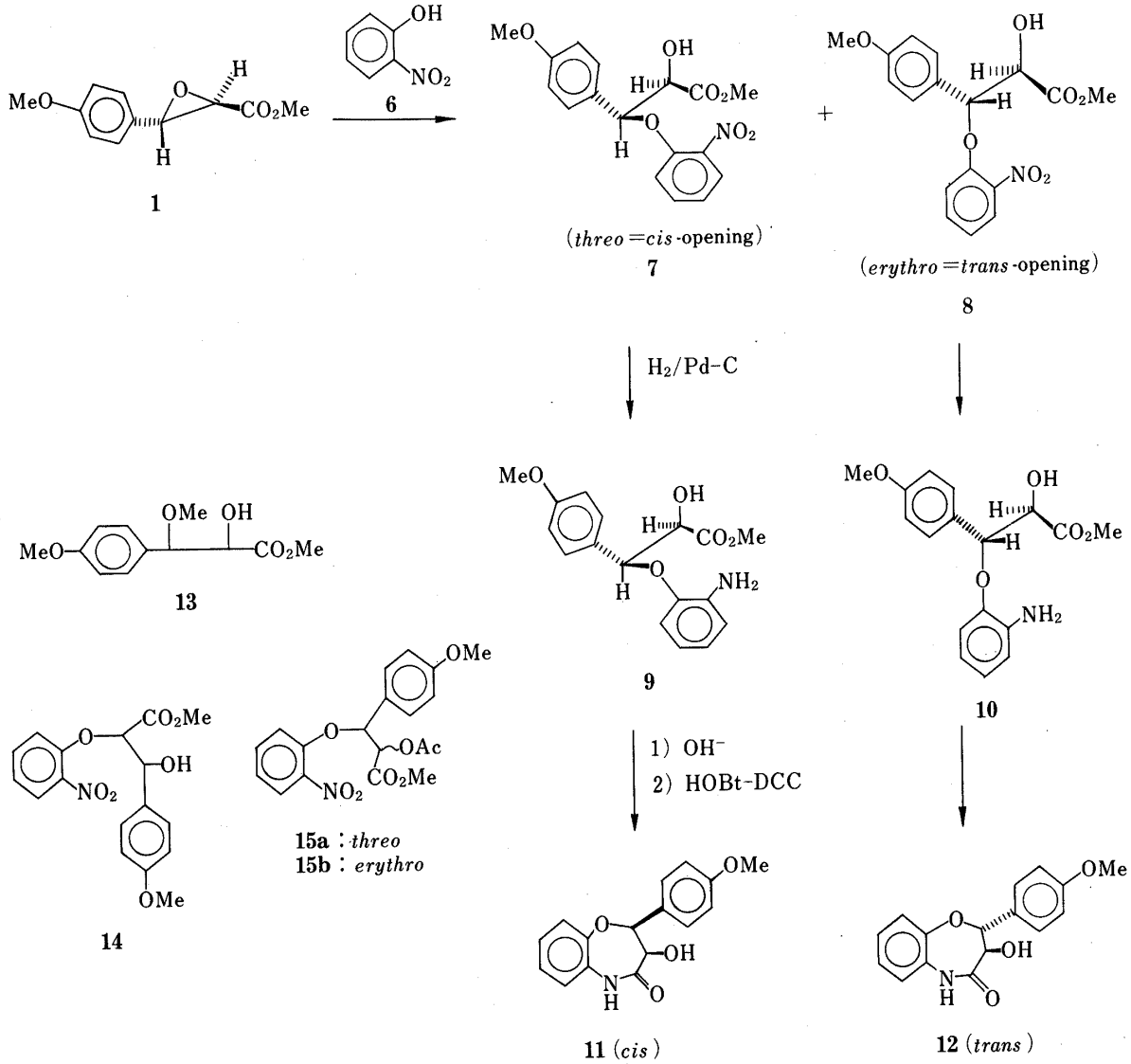


Chart 2

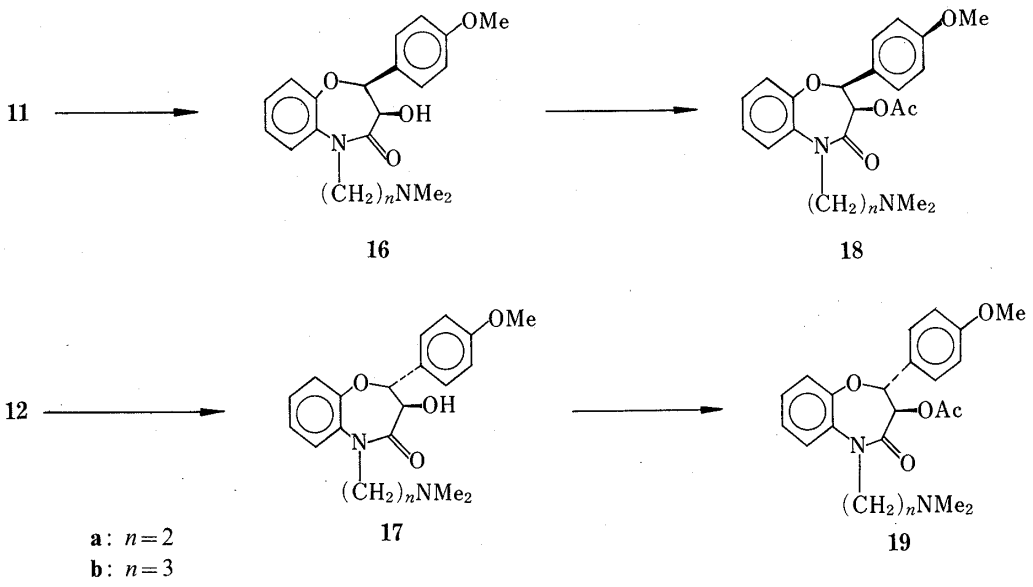


Chart 3

coupling ($J=3$ and 4). The mass spectra (MS) of **7** and **8** were superimposable on each other and showed the fragment ion peaks characteristic of a 2-hydroxy-3-phenoxypropionic acid structure; *m/e* 258 $(M-CH(OH)CO_2Me)^+$, *m/e* 209 $(MeOC_6H_4CHCH(OH)CO_2Me)^+$, and *m/e* 139 $(2\text{-}NO_2C_6H_4OH)^+$. These fragment peaks are quite similar to those observed in 2-hydroxy-3-arylthiopropionic esters.[4] Thus, the nitro esters (**7** and **8**) were proved to be the diastereoisomers of methyl 2-hydroxy-3-(4-methoxyphenyl)-3-(2-nitrophenoxy)propionate. The stereochemistry of **7** and **8** was determined by converting them to the corresponding *cis*- and *trans*-lactams (**11** and **12**). The nitro esters (**7** and **8**) were hydrogenated to the amino esters (**9** and **10**). Alkaline hydrolysis of **9** and **10** followed by cyclization with dicyclohexyl carbodiimide (DCC)–1-hydroxybenzotriazole (HOBt) gave the 7-membered lactams (**11** and **12**), respectively. The NMR spectral behavior of these isomeric lactams was quite similar to that of the 1,5-benzothiazepine derivatives.[4b] The vicinal coupling constants between the methine protons at C_2 and C_3 of **11** and **12** were 6 and 10 Hz, respectively. Therefore, we assigned the *cis*-lactam structure for **11** and the *trans* structure for **12**. Hence, the stereochemistry of the nitro esters (**7** and **8**) was proved to be *threo* (*cis*-opening product) and *erythro* (*trans*-opening product), respectively.

The effect of catalysts on the stereochemical mode of the reaction of **1** with **6** was examined next, and the results are summarized in Table I. Generally, the reaction proceeded predominantly by *cis*-opening, even in the presence of $NaHCO_3$ or $MgCl_2$, which are effective catalysts for the stereospecific *trans*-opening of **1** with thiophenols.[4c,d] In the $NaHCO_3$- or NEt_3-catalyzed reaction, however, the *trans*-opening ratio of the oxirane ring was apparently higher than that in the reaction without catalyst (entries 7 and 8). Predominant *trans*-opening of **1** was observed only in the reaction with sodium 2-nitrophenoxide (entry 9), though the reaction proceeded in rather low yield due to the concomitant formation of the solvolysis product (**13**).[8]

Previously, we reported that halides or carboxylates of tin (II) or tin (IV) were highly effective catalysts for stereospecific *cis*-opening of **1** with thiophenols.[4c,d] However, they showed little catalytic effect in the reaction with 2-nitrophenol (entries 3 and 4). This is probably because of the difference in affinity of the catalysts to sulfur and oxygen. The reaction in hexamethylphosphortriamide (HMPA) gave a low yield of the *cis*-opening product (**7**), and no formation of the regioisomer (**14**) was observed (entry 10). This also constitutes a major deviation from the reaction of **1** with thiophenol, where considerable formation of the

TABLE I. Reaction of Methyl *trans*-3-(4-Methoxyphenyl)glycidate (**1**) with 2-Nitrophenol (**6**)

Entry	6[a]	Catalyst[b]	Solvent	Conditions	Total yield of 7 and 8	*threo*/*erythro* ratio
1	Free	—	MeCN	80 °C, 52 h	86.6	9.4[c]
2	Free	—	Toluene	r.t., 22 h	—[d]	—
3	Free	$Sn(OCOC_7H_{15})_2$	Toluene	r.t., 22 h	—[d]	—
4	Free	$SnCl_2$	Toluene	r.t., 22 h	35.3	8.0
5	Free	$MgCl_2$	Toluene	r.t., 22 h	68.0 (*threo*-isomer)[e]	ND[f]
6	Free	—	MeOH	65 °C, 9 h	33.7	14
7	Free	NEt_3	MeOH	65 °C, 13 h	50.0	2.0
8	Free	$NaHCO_3$	MeOH	65 °C, 9 h	88.0	3.22
9	Na salt	—	MeOH	65 °C, 29 h	38.0[g]	0.1
10	Free	—	HMPA	50—60 °C, 19 h	17.0	*threo*

a) One eq of 2-nitrophenol (**6**) was used, except for entry 9.
b) 0.2 eq of catalyst was added.
c) When the reaction was carried out at room temperature for 8 d, the *threo*-isomer (**7**) was obtained in 6.7% yield.
d) No nitro ester (**7** or **8**) was obtained.
e) Isolated yield as crystalline form.
f) Not determined.
g) Compound **13** was obtained in 20.3% yield.

TABLE II. Physical Data for 1,5-Benzoxazepine Derivatives

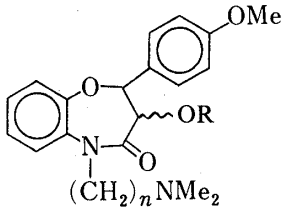
Compound		*n*	Salt	mp (°C)	Recryst.[a] solvent	Yield (%)	Formula	Analysis (%) Calcd (Found)		
								C	H	N
2,3-*cis*-Series	**16a**	2	HCl	206—210 (dec.)	A	86.0	$C_{20}H_{25}ClN_2O_4 \cdot H_2O$	58.46 (58.83	6.62 6.34	6.82 6.85)
	16b	3	HCl	194—197	B	87.0	$C_{21}H_{27}ClN_2O_4 \cdot 1/2H_2O$	60.64 (61.00	6.79 6.95	6.87 6.57)
	18a	2	Oxalate	185—187	C	65.6	$C_{24}H_{28}N_2O_9$	59.01 (58.97	5.78 5.70	5.73 5.77)
	18b	3	Oxalate	173—176	D	48.6	$C_{25}H_{30}N_2O_9 \cdot 1/2H_2O$	58.70 (58.89	6.11 5.92	5.48 5.42)
2,3-*trans*-Series	**17a**	2	HCl	244—247	C	70.7	$C_{20}H_{25}ClN_2O_4$	61.14 (61.06	6.41 6.44	7.13 7.11)
	17b	3	Oxalate	60—70	C	54.6	$C_{23}H_{28}N_2O_8 \cdot H_2O$	57.73 (57.71	6.32 6.04	5.85 5.71)
	19a	2	Oxalate	142—152	E	75.4	$C_{24}H_{28}N_2O_9$	59.01 (58.81	5.78 5.74	5.73 5.63)
	19b	3	Oxalate	68—95	E	61.3	$C_{25}H_{30}N_2O_9 \cdot 1/2H_2O$	58.70 (58.54	6.11 6.10	5.48 5.23)

a) A = MeOH–EtOH–Et_2O, B = EtOH–Et_2O, C = EtOH, D = acetone–Et_2O, E = acetone.

regioisomer corresponding to **14** (possibly by single electron transfer from the thiol group) was observed in this solvent.[4d] The difference might be due to the low electron-transfer ability of phenols compared with that of thiophenols.

Finally, for pharmacological evaluation, *cis*- and *trans*-lactams (**11** and **12**) were alkylated with (dimethylamino)alkylchlorides and K_2CO_3 in boiling acetone to give the amines (**16** and **17**). Heating of **16** and **17** with Ac_2O gave the 3-acetoxy derivatives (**18** and **19**), which are 1-oxa analogues of diltiazem. The yields, physical data, and elemental analyses

TABLE III. Cerebral Vasodilating Activity of 1,5-Benzoxazepine Derivatives



Compounds	Isomer	n	R	Cerebral vasodilating activity[a] *vs.* papaverine[b]	*vs.* (±)-3[c]
16a[d]	*cis*	2	H	1.4	0.33
16b[d]	*cis*	3	H	0.5	0.12
18a[e]	*cis*	2	Ac	2.8	0.66
18b[e]	*cis*	3	Ac	0.8	0.19
17a[d]	*trans*	2	H	0.08	0.02
17b[e]	*trans*	3	H	0.11	0.03
19a[e]	*trans*	2	Ac	0.16	0.04
19b[e]	*trans*	3	Ac	0.29	0.07
(±)-**3** (Racemic diltiazem)				4.24	1.0

a) Determined by measuring the increase in blood flow in the vertebral artery in anesthetized dogs after *i.a.* administration.
b) Potency ratio with respect to papaverine.
c) Potency ratio with respect to (±)-**3**.
d) Hydrochloride.
e) Oxalate.

of these derivatives are summarized in Table II.

Pharmacology

The compounds prepared in the present study were tested for cerebral vasodilating activity by measuring the increase in blood flow in the vertebral artery of anesthetized dogs after intraarterial administration. The results are summarized in Table III together with comparative data for racemic diltiazem ((±)-**3**).

In parallel with the previous observation[3a] in the 1,5-benzothiazepine series, activity was quite dependent on the stereochemistry of the 2- and 3-substituents. The *cis*-isomers were invariably much more active than the *trans*-counterparts. Among the *cis*-isomers, the activity of the aminoethyl derivatives surpassed that of the aminopropyl ones, and O-acetylation conferred increased activity. These structure–activity relationships are quite similar to those of the 1,5-benzothiazepine derivatives.[3a]

Thus, the highest activity in this series was observed with **18a**, the closest analogue of diltiazem. The activity of **18a**, however, was only about two-thirds of that of racemic diltiazem ((±)-**3**). Moreover, **18a** was much more toxic (maximum tolerated dose (MTD) = 10 mg/kg, mouse, *i.p.*) than (±)-**3** (MTD = 100 mg/kg). Thus, the replacement of the sulfur atom of diltiazem by oxygen caused a decrease of the vasodilating activity with increased toxicity.

Experimental

Infrared (IR) spectra were taken on a Hitachi IR-215 (Hitachi) or FX-6200 FTIR (Analect Instruments) spectrophotometer. NMR spectra were recorded on a JEOL PMX-60 or FX-100S machine. Chemical shifts are given as δ values from tetramethylsilane as an internal standard. The following abbreviations are used; s = singlet, d = doublet, dd = double doublet, t = triplet, m = multiplet, br s = broad singlet, and br d = broad doublet. MS spectra

were recorded on a Hitachi RMU-60 spectrometer. Preparative TLC was carried out on Kieselgel PF_{254} (Merck). Kieselgel 60 (230—400 mesh) (Merck) was used for flash column chromatography.

Reaction of Methyl *trans*-3-(4-Methoxyphenyl)glycidate (1) with 2-Nitrophenol (6)——A solution of the glycidate (**1**) (20.8 g, 0.10 mol) and 2-nitrophenol (**6**) (13.9 g, 0.10 mol) in acetonitrile (400 ml) was heated at 80 °C for 52 h and concentrated under reduced pressure. The residual oil was dissolved in AcOEt. The AcOEt solution was washed with 10% aq. Na_2CO_3 (three times) and sat. NaCl, dried, and concentrated to give an oil (34 g). The oil was dissolved in Et_2O (70 ml) and then allowed to stand at room temperature to give the *threo*-nitro ester (**7**), 22.16 g, mp 82.5—83.5 °C. Recrystallization from Et_2O gave pure **7**, 21.4 g (61.6%), mp 83—85 °C as prisms. NMR (60 MHz, $CDCl_3$) δ: 3.30 (d, $J=8$ Hz, 1H, OH, disappeared on addition of D_2O), 3.76 (s, 6H, OCH_3), 4.45 (dd, $J=3$ and 8 Hz, 1H, C_2-H, changed to doublet ($J=3$ Hz) on addition of D_2O), 5.60 (d, $J=3$ Hz, 1H, C_3-H), 6.7—7.85 (m, 8H, aromatic H). IR ν_{max}^{Nujol} cm^{-1}: 1735, 3500. MS *m/e*: (M^+ was not seen), 258 ($M-CH(OH)CO_2Me)^+$, 209 ($MeOC_6H_4CHCH(OH)CO_2Me)^+$, 151, 149, 148, 139 ($2\text{-}NO_2C_6H_4OH)^+$, 135, 122, 121. *Anal.* Calcd for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.93; N, 4.03. Found: C, 58.67; H, 4.90; N, 4.00.

The mother liquors were combined and concentrated under reduced pressure. The residual oil was separated by flash column chromatography (eluted with benzene–AcOEt (5 : 1)) to give 8.7 g (25%) of a mixture of the *threo*- and *erythro*-nitro esters (**7** and **8**). The *threo*/*erythro* ratio of this mixture was 2 as determined by the separation of a small portion of the mixture (by preparative TLC, developed three times with benzene–AcOEt (9 : 1); the *threo*- and *erythro*-isomers were obtained from the faster and slower moving bands, respectively). Accordingly, the *threo*/*erythro* ratio of the total product was 9.4. The physical data for **8** are given below.

Other experiments listed in Table I were carried out in essentially the same manner.

Methyl *threo*-2-Acetoxy-3-(4-methoxyphenyl)-3-(2-nitrophenoxy)propionate (15a) and Methyl *erythro*-2-Acetoxy-3-(4-methoxyphenyl)-3-(2-nitrophenoxy)propionate (15b)——The *threo*-nitro ester (**7**) was acetylated by heating with an excess of Ac_2O on a boiling water bath in the usual manner and the mixture was concentrated under reduced pressure to give **15a** as a yellow oil. NMR (100 MHz, $CDCl_3$) δ: 2.10 (s, 3H, $COCH_3$), 3.66 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.40 (d, $J=5$ Hz, 1H, C_3-H), 5.72 (d, $J=5$ Hz, 1H, C_2-H), 6.8—7.8 (m, 8H, aromatic H).

Acetylation of **8** as described above gave **15b** as a yellow oil. NMR (100 MHz, $CDCl_3$) δ: 2.12 (s, 3H, $COCH_3$), 3.74 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 5.57 (d, $J=5$ Hz, 1H, C_3-H), 5.70 (d, $J=5$ Hz, 1H, C_2-H), 6.8—7.8 (m, 8H, aromatic H).

Reaction of 1 with Sodium 2-Nitrophenoxide——A solution of the glycidate (**1**) (25 g, 0.12 mol) and sodium 2-nitrophenoxide (19.3 g, 0.12 mol) in MeOH (600 ml) was heated under reflux for 20 h. After addition of further **1** (20 g, 0.096 mol), the reaction mixture was heated for 9 h, then concentrated. The residual oil was dissolved in AcOEt, washed with 10% aq. Na_2CO_3 and sat. NaCl, dried, and concentrated under reduced pressure to give an oil (42 g). This oil was separated by flash column chromatography. The first eluate with benzene–AcOEt (9 : 1) gave a mixture of **8** and **7** (15.8 g, 37.9%, based on 2-nitrophenol) as an oil. The mixture was separated by preparative TLC to give pure **8** (oil) and **7** as described above. The ratio of **7**/**8** was 0.1. Spectral data for **8** were as follows: NMR (60 MHz, $CDCl_3$) δ: 3.78 (s, 6H, OCH_3), 4.65 (br d, 1H, C_2-H; changed to a doublet ($J=4$ Hz) on D_2O-exchange), 5.60 (d, $J=4$ Hz, 1H, C_3-H), 6.7—8.0 (m, 8H, aromatic H). MS *m/e*: superimposable on that of **7**.

The second eluate from flash column chromatography gave methyl 2-hydroxy-3-methoxy-3-(4-methoxyphenyl)propionate (**13**) (10.5 g, 20.3%, based on **1**) as an oil. NMR (60 MHz, $CDCl_3$) δ: 3.29 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.46 (br s, 2H, C_2-H and C_3-H), 6.7—7.3 (m, 4H, aromatic H). MS *m/e*: 240 (M^+), 151 ($M-CH(OH)CO_2Me)^+$, 137, 121.

Methyl *threo*-3-(2-Aminophenoxy)-2-hydroxy-3-(4-methoxyphenyl)propionate (9)——The *threo*-nitro ester (**7**) (20 g, 57.6 mmol) was hydrogenated in the presence of 10% Pd–C (3 g) in EtOH (600 ml) under normal pressure at room temperature for 7 h. After completion of H_2 gas absorption, catalyst and solvent were removed to give an oil. The residual oil was triturated with Et_2O–*n*-hexane (2 : 1) (150 ml), filtered, and recrystallized from Et_2O to give **9** (16.34 g, 86.9%), mp 109—111 °C. NMR (60 MHz, $CDCl_3$) δ: 3.5 (br, 3H, NH_2 and OH), 3.70 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.44 (d, $J=3$ Hz, 1H, C_2-H), 5.37 (d, $J=3$ Hz, 1H, C_3-H), 6.4—7.4 (m, 8H, aromatic H). IR ν_{max}^{Nujol} cm^{-1}: 3550, 3400, 3330, 1740. MS *m/e*: 317 (M^+), 228 ($M-CH(OH)CO_2Me)^+$, 209 ($M-NH_2C_6H_4O)^+$, 149, 121, 109 ($2\text{-}NH_2C_6H_4OH)^+$. *Anal.* Calcd for $C_{17}H_{19}NO_5 \cdot 1/2H_2O$: C, 62.56; H, 6.18; N, 4.29. Found: C, 62.73; H, 6.19; N, 4.34.

***cis*-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzoxazepin-4(5*H*)-one (11)**——A solution of the *threo*-amino ester (**9**) (21.76 g, 66.7 mmol), 10% aqueous NaOH (70 ml), and MeOH (400 ml) was stirred at room temperature for 30 min. The reaction mixture was adjusted to pH 5 with 10% HCl[9] and concentrated to dryness under reduced pressure. The residual solid was powdered and dried under reduced pressure at 45 °C. The residual crude amino carboxylic acid contaminated with NaCl was suspended in dimethylformamide (DMF) (300 ml), and HOBt hydrate (10.5 g, 68.6 mmol) and DCC (21.2 g, 103 mmol) were added successively to the suspension under ice-cooling (5 °C). The reaction mixture was stirred at room temperature for 3 h and then concentrated under reduced pressure. Water (500 ml) and AcOEt (300 ml) were added to the residue, and the mixture was stirred at room temperature for 1 h to decompose excess DCC. The precipitated white crystals of dicyclohexylurea were filtered off. The AcOEt layer was separated, washed with sat. $NaHCO_3$ to remove HOBt, dried, and concentrated. The residual crystals were recrystallized from AcOEt to give the *cis*-lactam (**11**) (13.9 g), mp 170—171.5 °C.[10] Additional **11**

(1.33 g, total 15.23 g, 80.0%) was obtained from the mother liquor by flash column chromatography (eluted with benzene–AcOEt (7:3)). NMR (60 MHz, $CDCl_3$) δ: 3.20 (br s, 1H, OH), 3.80 (s, 3H, OCH_3), 4.79 (br d, 1H, C_3-H; changed to a doublet (J=6 Hz) on D_2O-exchange), 5.65 (d, J=6 Hz, 1H, C_2-H), 6.7—7.5 (m, 8H, aromatic H), 8.70 (br s, 1H, –NHCO; disappeared on treatment with D_2O). IR ν_{max}^{Nujol} cm^{-1}: 3300, 3200, 3080, 1680. MS *m/e*: 285 (M^+), 267, 228, 226, 150, 121. *Anal.* Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.19; H, 5.24; N, 4.84.

Methyl *erythro*-3-(2-Aminophenoxy)-2-hydroxy-3-(4-methoxyphenyl)propionate (10)——The *erythro*-nitro ester (**8**) (15 g, 43.2 mmol) in EtOH (550 ml) was hydrogenated in the presence of 10% Pd–C (3 g) under normal pressure and temperature for 4 h. After removal of Pd–C and the solvent, the residual oil was dissolved in AcOEt and extracted with conc. HCl–H_2O (2:1). The HCl layer was made basic with Na_2CO_3 and extracted with AcOEt. The extracts were washed with water, dried, and evaporated. The oil obtained was purified by column chromatography (SiO_2). From the eluate with benzene–AcOEt (7:3), **10** (8.4 g, 61.3%) was obtained as an oil. NMR (60 MHz, $CDCl_3$) δ: 3.65 (br, 3H, OH and NH_2) 3.69 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 4.61 (d, J=3.6 Hz, 1H, C_2-H), 5.38 (d, J=3.6 Hz, 1H, C_3-H), 6.5—7.3 (m, 8H, aromatic H). MS *m/e*: 317 (M^+), 228, 209, 208, 149, 136, 121, 109.

***trans*-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzoxazepin-4(5*H*)-one (12)**——The *erythro*-amino ester (**10**) (8.4 g, 26.5 mmol) was hydrolyzed with 10% aqueous NaOH (27 ml) and MeOH (27 ml) at 40 °C for 30 min. The reaction mixture was neutralized with dil. HCl (pH 5) and concentrated to dryness under reduced pressure. The residual gum of the amino carboxylic acid was dissolved in tetrahydrofuran (THF) (30 ml) and then solutions of HOBt hydrate (4.1 g, 26.8 mmol) in THF (30 ml) and of DCC (8.2 g, 39.8 mmol) in THF (25 ml) were added successively. After stirring at room temperature for 20 h, the reaction mixture was worked up in the same manner as described for the *cis*-isomer (**11**) to give **12** (3 g, 40%), mp 174—176 °C (from AcOEt). NMR (60 MHz, $CDCl_3$) δ: 3.83 (s, 3H, OCH_3), 4.60 (d, J=10 Hz, 1H, C_3-H), 5.28 (d, J=10 Hz, 1H, C_2-H), 6.8—7.4 (m, 8H, aromatic H). MS *m/e*: 285 (M^+), 267, 150, 121. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3450, 3200, 3050, 1665. *Anal.* Calcd for $C_{16}H_{15}NO_4$: C, 67.36; H, 5.30; N, 4.91. Found: C, 67.29; H, 5.26; N, 4.89.

***cis*-2,3-Dihydro-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzoxazepin-4(5*H*)-one (16a)**——A mixture of the *cis*-lactam (**11**) (7.13 g, 25.0 mmol), 2-(dimethylamino)ethylchloride hydrochloride (4.68 g, 32.5 mmol), powdered K_2CO_3 (8.9 g, 64.4 mmol), acetone (150 ml), and H_2O (1.5 ml) was heated under reflux for 16 h, then cooled. Inorganic compounds were filtered off and the solvent was evaporated. The residual oil was dissolved in AcOEt, the solution was washed with water, dried, and concentrated. The residue was dissolved in Et_2O and converted to the HCl salt, which was recrystallized from MeOH–EtOH–Et_2O to give **16a**·hydrochloride hydrate (8.83 g, 86.0%), mp 206—210 °C (dec.).

Compounds **16b** and **17a**, **b** were prepared similarly (Table II).

***cis*-3-Acetoxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzoxazepin-4(5*H*)-one (18a)**——A solution of **16a**·hydrochloride hydrate (800 mg, 1.95 mmol) in Ac_2O (5 ml) and AcOH (5 ml) was heated at 110 °C for 3 h. After removal of Ac_2O and AcOH, the residual oil was dissolved in H_2O, made basic with K_2CO_3, and extracted with AcOEt. The AcOEt layer was washed with water, dried, and evaporated. The residue was dissolved in acetone, and converted to the oxalate. The oxalate was recrystallized from EtOH to give pure **18a**·oxalate, 625 mg (65.6%), mp 185—187 °C.

Compounds **18b** and **19a**, **b** were prepared similarly (Table II).

Cerebral Vasodilating Activity——Male dogs weighing 10.5 to 15.5 kg were anesthetized with sodium pentobarbital (30 mg/kg, intravenous injection). The blood flow in the vertebral artery was measured continuously by means of an electromagnetic flowmeter under artificial respiration. A test compound dissolved in aqueous 5% glucose solution was injected into the vertebral artery. The cerebral vasodilating activity of the test compound was estimated in terms of the potency ratio of the compound with respect to papaverine, calculated from the dose-response curves.

The results are shown in Table III.

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References and Notes

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7) The *threo*- and *erythro*-isomers (**7** and **8**) could be separated by preparative TLC. See the experimental section.
8) The yield in the reaction in EtOH under the same conditions was not improved, although formation of the solvolysis product was apparently decreased. In *tert*-BuOH, the reaction hardly proceeded, probably due to the insolubility of sodium 2-nitrophenoxide in this solvent.
9) The amino carboxylic acid was soluble in water.
10) In another run, **11** having mp 141—142 °C was obtained by recrystallization from Et_2O. Recrystallization from AcOEt gave crystals melting at 170—171.5 °C.