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Reactions of 3-Phenylglycidic Esters. V.[1] Reaction of Methyl 3-(4-Methoxyphenyl)glycidate with 2-Nitroaniline and Synthesis of 1,5-Benzodiazepine Derivatives

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Stereochemical aspects of the oxirane-ring opening of methyl *trans*-3-(4-methoxyphenyl)-glycidate (**1**) with 2-nitroaniline (**5**) were investigated. ZnI_2 showed good catalytic activity in this reaction, giving the *cis*-opening product (**6a**) predominantly. On the other hand, the reaction on the surface of silica gel proceeded predominantly by *trans*-opening. Silica gel had rather little effect on the reaction of **1** with 2-nitrothiophenol or 2-nitrophenol. Some 1,5-benzodiazepine derivatives (**18**—**21**), 1-aza analogues of diltiazem, were synthesized from **6a, b** for pharmacological evaluation. Some oxidative epimerization of **9a, b** was observed during cyclization in boiling xylene in the presence of air. The cerebral vasodilating activity of **21a**, the most potent compound in this series, was about 0.5 that of racemic diltiazem. The structure–activity relationships are discussed.

Keywords——methyl *trans*-3-(4-methoxyphenyl)glycidate; 2-nitroaniline; silica gel-promoted reaction; 1,5-benzodiazepine derivative; cerebral vasodilating activity; structure–activity relationship

Previous papers of this series described the results of detailed studies on the reaction of methyl 3-(4-methoxyphenyl)glycidate (**1**) with 2-nitrothiophenol[2] or 2-nitrophenol.[1] Stereoselective opening of the oxirane ring of **1** by these nucleophiles could be achieved by the choice of appropriate reaction conditions, making it possible to produce either the *threo*- or *erythro*-isomer of the hydroxy esters (**2a, b**). The *threo*-isomer of **2a** has served as a key intermediate for diltiazem (**4a**), a potent antianginal agent,[3c,d] and *threo*-**2b** was also converted to the 1-oxa analogue (**4b**) of diltiazem.[1]

Our continued interest both in the stereochemical aspects of the ring opening of 3-arylglycidic esters by various nucleophiles and in the structure–activity relationships of diltiazem derivatives prompted us to examine the reaction of **1** with 2-nitroaniline (**5**). We describe here the mode of ring opening of **1** by **5** under various conditions as well as the synthesis and vasodilating activity of several 1,5-benzodiazepine derivatives (**3**), 1-aza analogs of diltiazem.

Reaction of Methyl *trans*-3-(4-Methoxyphenyl)glycidate (1) with 2-Nitroaniline (5)

Aminolysis of 3-phenylglycidic esters is known to give *trans*-opening products resulting from S_N2-type nucleophilic attack of amines in all cases.[4] Zymalkowski and coworkers reported that treatment of 3-phenylglycidic acid derivatives with various aromatic amines also gives *erythro*-3-amino-2-hydroxy-3-phenylpropionic acid derivatives (*trans*-opening products).[4a]

The results of the reaction of **1** with **5** under a variety of conditions are summarized in Table I. When **1** was allowed to react with **5** in the absence of catalyst, no reaction was

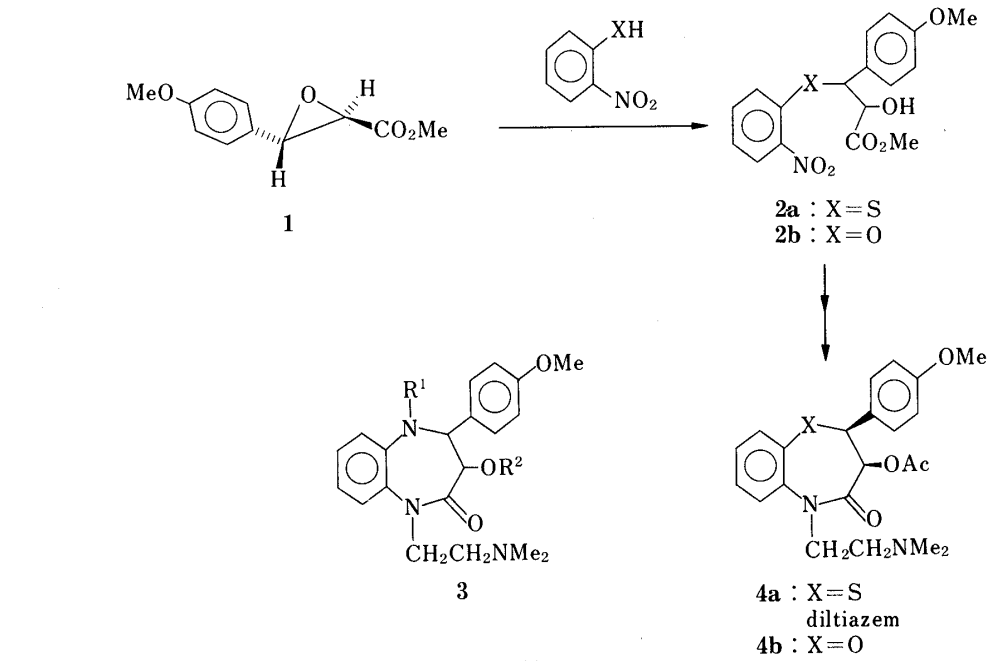


Chart 1

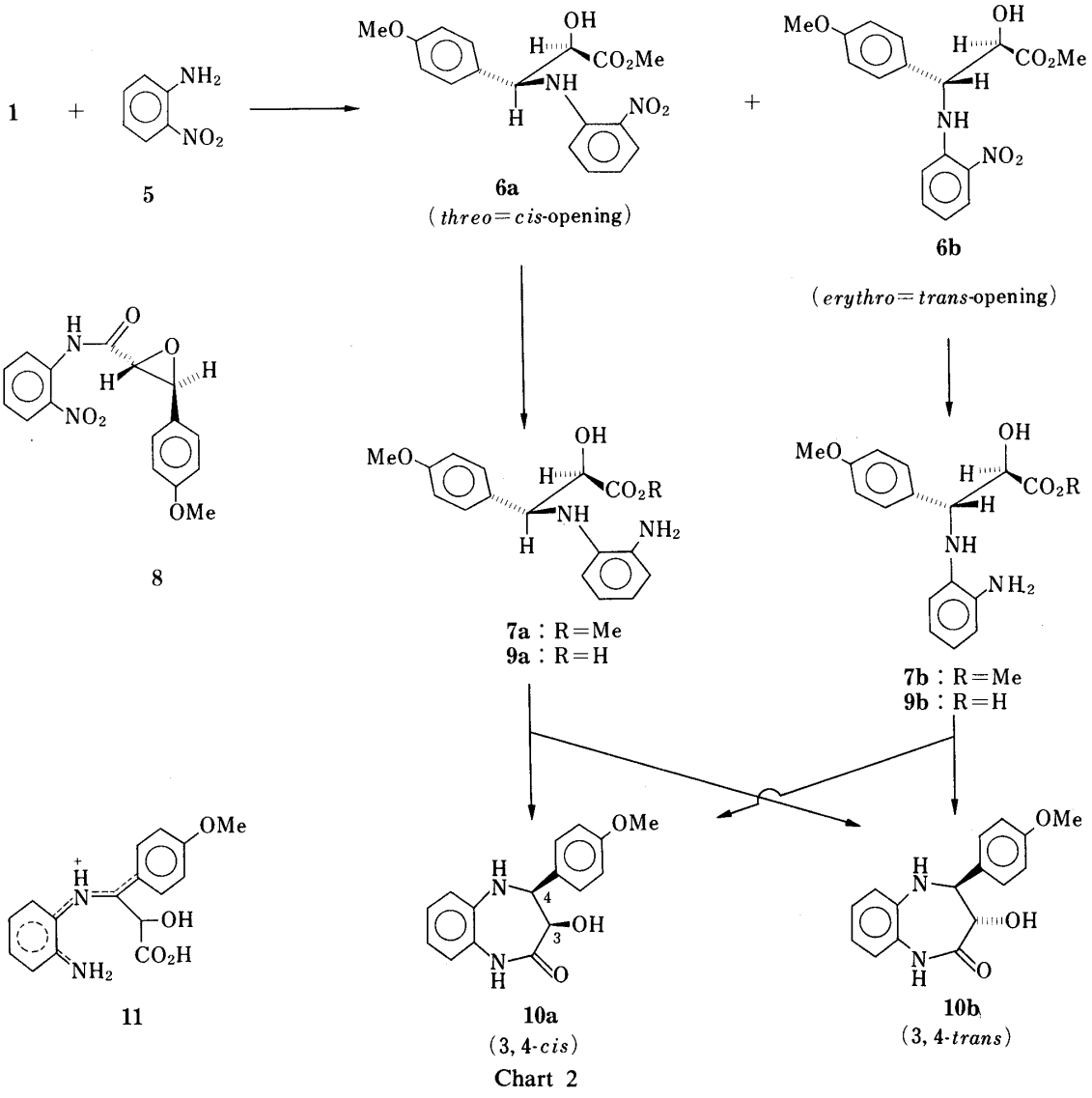


Chart 2

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

Entry	Solvent	Additive	Reaction conditions		Total yield of **6a** and **6b** (%)	*threo/erythro* ratio
			Temperature (°C)	Time (h)		
1	Toluene		60	48	*f*)	
2	CH_3CN		60	72	*f*)	
3	HMPA		22	72	*f*)	
4	Toluene	$MgCl_2$[a,b]	22	48	*f*)	
5	CH_3CN	KOH[a]	22	48	*f*)	
6	Toluene	$SnCl_2$[a]	22	48	16.8	2.0
7	Toluene	ZnI_2[a]	22	21	100	2.0
8	Benzene	SiO_2[c]	22	17	58.4	0.5
9	Benzene	Al_2O_3[d]	22	17	17.9	0.3
10	DMSO	NaH[e]	22	0.5	*g*)	

a) About 0.3 eq of catalyst was used. *b*) $Sn(OCOC_7H_{15})_2$ and $Zn(OAc)_2$ were also ineffective. *c*) The reaction was carried out in a silica gel chromatographic column. Stirring of the reaction mixture with a slurry of SiO_2 gave a similar result. See Experimental. *d*) The reaction was carried out in an aluminum oxide chromatographic column. *e*) 1 eq of NaH was used. *f*) No nitro ester (**6**) was obtained. *g*) 3-(4-Methoxyphenyl)-2′-nitroglycidanilide (**8**) was obtained in 62.8% yield.

observed at temperatures in the range of 22—60 °C (entries 1—3). The reaction also proved to be refractory in the presence of catalysts such as $MgCl_2$, stannous 2-ethylhexanoate, zinc acetate, and KOH, which were effective in the reaction of **1** with thiophenols.[2] The reaction in the presence of $SnCl_2$, however, gave a low yield (16.8%) of a diastereoisomeric mixture of the nitro ester (**6a**, **b**). This mixture was hydrogenated to give the amino esters (**7a**, **b**), since the separation of **6a**, **b** was unsuccessful. The mixture of **7a**, **b** could be readily separated by preparative thin layer chromatography (TLC) to give the *threo*-isomer (**7a**), mp 91—92 °C, and the *erythro*-isomer (**7b**), mp 120—122 °C, in yields of 40.7 and 21.7%, respectively. Thus, estimation of the *threo/erythro* ratio of **6a**, **b** was also carried out by this procedure in other cases.

The mass spectra (MS) of **7a**, **b** were superimposable on each other and showed a fragment ion characteristic of the α-hydroxy-ester structure at *m/e* 227 $(M-CH(OH)CO_2Me)^+$.[5] The stereochemistry of **7a**, **b** was determined by converting them into the 1,5-benzodiazepine derivatives (**10a**, **b**) as shown in Chart 2 (see below). The nuclear magnetic resonance (NMR) spectral characteristics of these isomeric lactams was quite similar to those of the corresponding 1-thia[2a,3] and 1-oxa analogues.[1] The vicinal coupling constant between the methine protons at C_3 and C_4 of **10a** derived from **7a** was 5 Hz, while that of **10b** obtained from **7b** was 9 Hz. Therefore, we assigned the *cis*-lactam structure for **10a** and the *trans* one for **10b**, and it follows that the amino esters (**7a** and **7b**) are the *threo* (*cis*-opening product) and *erythro*- (*trans*-opening product) isomers, respectively.

Accordingly, the reaction of **1** with **5** in the presence of $SnCl_2$ proceeded predominantly by *cis*-opening, the *threo/erythro* ratio of the product being about 2. This result is noteworthy, since no previous report has appeared on the predominant *cis*-opening of glycidic esters with amines.[4] When ZnI_2 was used as a catalyst, the reaction was accelerated dramatically to give a mixture of **6a**, **b** in quantitative yield. The *threo/erythro* ratio of this mixture, however, was not improved (Table I, entry 7).

During the course of this study, we noticed that **1** reacts slowly with **5** on the surface of silica gel. The preparative utility of the reaction assisted by silica gel was, therefore, examined. When a solution of an equimolar mixture of **1** and **5** in benzene was allowed to stand in a silica gel column (Kieselgel 60, 230—400 mesh, Merck) at 22 °C for 17 h, a mixture of **6a**, **b** was

Table II. Reaction of Methyl *trans*-3-(4-Methoxyphenyl)glycidate with Nucleophiles on the Surface of Silica Gel in a Chromatographic Column at 22 °C for 17 h

Nucleophile[a]	Product	Total yield of the *threo*- and *erythro*-nitro esters (%)	*threo/erythro* ratio
2-Nitroaniline (**5**)	**6**	58.4	0.5[d]
2-Nitrothiophenol	**2a**	15.0	*erythro*[b]
2-Nitrophenol	**2b**	17.2	5.75[c]

a) 1 eq of nucleophile was used. *b*) No *threo*-isomer was detected. *c*) The *threo/erythro* ratio was determined by separation by preparative TLC. See reference 1. *d*) See Table I.

obtained in 58.4% yield after elution with benzene–AcOEt.[6] From this mixture, the *erythro*-nitro ester (**6b**) could be isolated as yellow needles, mp 140—143 °C, by trituration with isopropanol.[7] The *threo/erythro* ratio of the whole mixture in this case was estimated to be about 0.5. Therefore, the reaction assisted by silica gel proceeded predominantly by *trans*-opening. Stirring of a mixture of **1** and **5** with silica gel in toluene at room temperature gave a similar result (see Experimental).

Posner and Rogers reported that neutral alumina catalyzes stereoselective *trans*-opening of epoxides by various nucleophiles under very mild conditions.[8] In the reaction of **1** with **5**, however, the catalytic effect of neutral alumina (Aluminiumoxide 90, activity II—III, Merck) was rather small (Table I, entry 9).

In seeking other applications for the nucleophilic opening of **1** assisted by silica gel, we examined the reaction of **1** with 2-nitrothiophenol and 2-nitrophenol. In both cases, however, neutral silica gel showed rather little catalytic effect (Table II). The relative reactivity of nucleophiles thus decreased in the following order, $2\text{-}NO_2C_6H_4NH_2 > 2\text{-}NO_2C_6H_4SH = 2\text{-}NO_2C_6H_4OH$. 2-Nitrophenol gave mainly the *threo*-isomer of **2b** under these conditions in accordance with its pronounced susceptibility to *cis*-opening.[1]

Finally, the reaction of **1** with sodium 2-nitroanilide in dimethyl sulfoxide (DMSO) gave the epoxy anilide (**8**) as a sole product in 62.8% yield. In this reaction, no nucleophilic opening of the oxirane ring by amide anion was observed.

Synthesis of Benzodiazepine Derivatives

Alkaline hydrolysis of the amino esters (**7a** and **7b**) gave the corresponding amino carboxylic acids (**9a** and **9b**). Thermal cyclization of **9a**, **b** to the lactams (**10a**, **b**) gave some anomalous results. Heating of the *threo*-acid (**9a**) in boiling xylene in the presence of air afforded, after chromatographic separation, the *cis*- (**10a**) and *trans*-lactam (**10b**) in yields of 61.8 and 14.7%. The *cis*-lactam (**10a**) was recovered completely unchanged after heating in xylene in the presence of air. When the cyclization of **9a** was carried out under an argon atmosphere, formation of the anomalous product (**10b**) was greatly diminished (2.3%), the *cis*-lactam (**10a**) being obtained in 76.4% yield. The *erythro*-amino carboxylic acid (**9b**) behaved similarly, and the formation of the *cis*-lactam (**10a**) was observed only in the presence of air. These results are summarized in Table III. As we reported previously,[2a] the thia analogues of **9a**, **b** cyclized to the corresponding lactams (1,5-benzothiazepin-4(5*H*)-one) without isomerization. On the basis of the above results, formation of the anomalous products (**10a** from **9b** and **10b** from **9a**) might be explained in terms of oxidative epimerization at the benzylic position of **9a**, **b** *via* a plausible intermediate, **11**. Cyclization of **9a** by the use of 1-hydroxybenzotriazole (HOBt) and dicyclohexylcarbodiimide (DCC) gave the *cis*-lactam (**10a**) as a sole product in 94.9% yield. Direct cyclization of the *erythro*- amino

TABLE III. Cyclization of the Amino Carboxylic Acid (**9**) in Boiling Xylene

Starting material	Atmosphere	Reaction time (h)	Products (**10**)	
			cis-Lactam : *trans*-Lactam	Total yield (%)
9a	Air	30	4 : 1	76.5
9a	Argon gas	17	33 : 1	78.7
9b	Air	11	1 : 9	79.7
9b	Argon gas	4	0 : 1	88.4

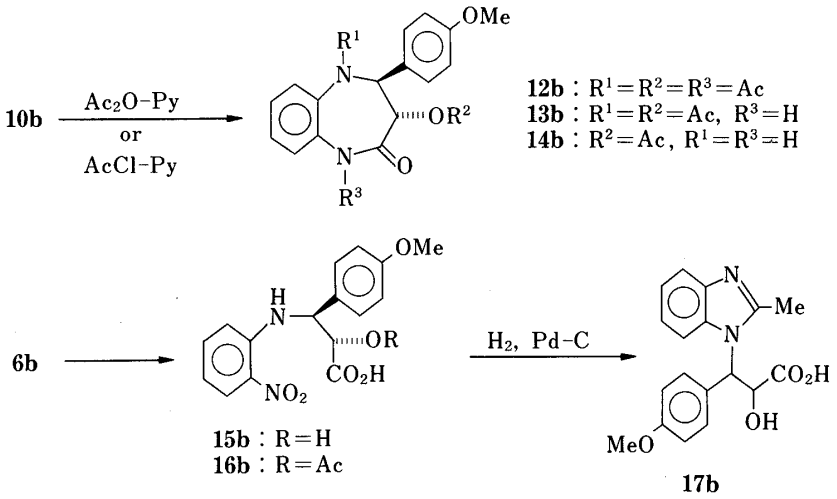


Chart 3

ester (**7b**) with dimethylsulfinyl carbanion in DMSO gave the *trans*-lactam (**10b**) in 48.7% yield.

Acetylation of the lactam (**10b**) with Ac_2O and pyridine at 100 °C for 2 h gave the triacetate (**12b**), while the reaction at room temperature for 3 h gave the N^5,*O*-diacetate (**13b**) and the *O*-acetate (**14b**) in 60.4 and 24.7% yields, respectively. Treatment of **10b** with 2.1 eq of AcCl in pyridine gave **13b** in 92% yield.

As an alternative route to the *O*-acetate (**14b**), introduction of the acetoxy group at an early stage of the synthesis was attempted. The nitro ester (**6b**) was hydrolyzed to the corresponding acid (**15b**). The hydroxyl group of **15b** could be acetylated selectively with Ac_2O and pyridine, giving **16b** in quantitative yield. Catalytic reduction of the nitro group of **16b**, however, gave the benzimidazole derivative (**17b**) in 55% yield *via* O→N migration of the acetyl group followed by cyclization. The spectral data of **17b** given in Experimental are compatible with the assigned structure.

The *cis*- and *trans*-lactams (**10a, b**) were alkylated with 2-(dimethylamino)ethyl chloride to give the corresponding amines (**18a, b**). Heating of **18a** with Ac_2O gave the diacetate (**19a**). The corresponding *trans*-isomer (**19b**) was prepared by N-alkylation of **13b**. Methylation of **18a, b** with HCHO and HCO_2H gave the *N*-methyl derivatives (**20a, b**), which were converted into the *O*-acetates (**21a, b**) by heating with Ac_2O. The yields, physical data, and elemental analysis data of these products are summarized in Table IV.

Pharmacology

The 1,5-benzodiazepine derivatives (**18**—**21**) were tested for cerebral vasodilating activity in anesthetized dogs after intraarterial administration by the method reported previously.[1)]

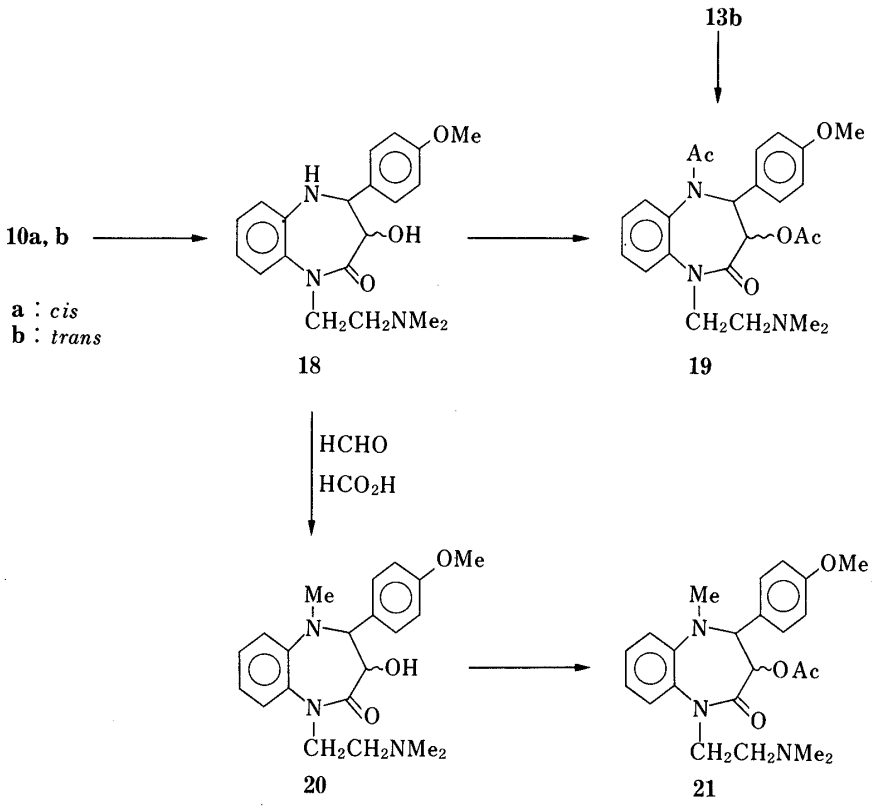


Chart 4

TABLE IV. Physical Data for 1,5-Benzodiazepine Derivatives

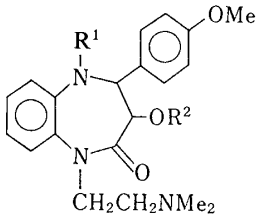
Compound	Salt	mp (°C)	Recryst. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd (Found)			
						C	H	N	Cl
18a	$HClO_4$	208—209	A	59.4	$C_{20}H_{26}ClN_3O_7$	52.69	5.75	9.22	7.78
						(52.67	5.72	9.21	7.75)
19a	Oxalate	147—149	B	61.7	$C_{26}H_{31}N_3O_9 \cdot H_2O$	57.03	6.07	7.67	—
						(56.87	5.53	7.57	—)
20a	$HClO_4$	229—230 (dec.)	C	69.2	$C_{21}H_{28}ClN_3O_7$	53.68	6.01	8.94	7.54
						(53.57	6.13	8.89	7.70)
21a	$HClO_4$	162—164	D	73.4	$C_{23}H_{30}ClN_3O_8 \cdot 1/3H_2O$	53.33	5.90	8.11	6.84
						(53.34	5.83	8.13	7.02)
18b	$HClO_4$	202—205	E	73.4	$C_{20}H_{26}ClN_3O_7$	52.69	5.75	9.22	7.78
						(52.80	5.77	9.22	7.80)
19b	HCl	261—262 (dec.)	D	64.9	$C_{24}H_{30}ClN_3O_5$	60.57	6.35	8.83	7.45
						(60.24	6.31	8.82	7.30)
20b	$HClO_4$	215—219	E	88.7	$C_{21}H_{28}ClN_3O_7$	53.68	6.01	8.94	7.59
						(53.53	6.01	8.78	7.43)
21b	Oxalate	152—155	F	93.0	$C_{25}H_{31}N_3O_8$	59.87	6.23	8.38	—
						(59.84	6.13	8.33	—)

a) A = H_2O, B = EtOH–Et_2O, C = DMF–EtOH, D = EtOH, E = acetone–EtOH, F = iso-PrOH–Et_2O.

The results are summarized in Table V together with comparative data for racemic diltiazem ((±)-**4a**).

Activity was found to reside only in the *cis*-isomers, and this stereoselectivity parallels the

TABLE V. Cerebral Vasodilating Activity of 1,5-Benzodiazepine Derivatives



Compound	Isomer	R^1	R^2	Cerebral vasodilating activity[a]	
				vs. papaverine[b]	*vs.* (±)-**4a**[c]
18a[d]	*cis*	H	H	0.20	0.05
19a[e]	*cis*	Ac	Ac	0.07	—
20a[d]	*cis*	Me	H	2.28	0.40
21a[d]	*cis*	Me	Ac	2.92	0.50
18b[d]	*trans*	H	H	0.04	—
19b[f]	*trans*	Ac	Ac	0.1	—
20b[d]	*trans*	Me	H	0.06	—
21b[e]	*trans*	Me	Ac	0.16	0.04
(±)-**4a**	(racemic diltiazem)			4.30	1.0

a) Determined by measuring the increase in blood flow in the vertebral artery in anesthetized dogs after *i.a.* administration. See reference 1. *b*) Potency ratio to papaverine. *c*) Potency ratio to (±)-**4a**. *d*) Perchlorate. *e*) Oxalate. *f*) Hydrochloride.

reported observations in the 1,5-benzothiazepine (**4a**)[3d] and 1,5-benzoxazepine (**4b**)[1] series. As for the effect of the R^1 group, methyl substitution was the most favorable, while introduction of an acetyl group at this position caused a marked fall in activity. On the other hand, as in the previous cases,[1,3d] acetylation of the 3-OH group conferred increased activity. The highest activity in this series was thus observed with the *cis*-3-acetoxy-5-methyl derivative (**21a**). However, it was about one-half as active as racemic diltiazem ((±)-**4a**). Thus, the sulfur atom of diltiazem (**4a**) could not be replaced by nitrogen or oxygen[1] without a decrease in potency.

Experimental

Infrared (IR) spectra were taken on a Hitachi IR-215 (Hitachi) or an Analect Instruments FX-6200 FTIR spectrophotometer. NMR spectra were recorded on a JEOL PMX-60 instrument. 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, brs=broad singlet, t=triplet, q=quartet, and m=multiplet. MS were recorded on a Hitachi RMU-6D spectrometer. Preparative TLC was carried out on Kieselgel GF_{254} (Merck). Kieselgel 60 (230—400 mesh) (Merck) was used for flash column chromatography. Aluminiumoxide 90 (activity II—III) (Merck) was used for column chromatography.

Reaction of Methyl *trans*-3-(4-Methoxyphenyl)glycidate (1) with 2-Nitroaniline (5)——a) The Reaction in the Presence of $SnCl_2$ (Table I, Entry 6): $SnCl_2$ (120 mg) was added to a solution of the glycidate (**1**) (4.98 g, 23.9 mmol) and 2-nitroaniline (**5**) (3.00 g, 21.7 mmol) in toluene (60 ml) at room temperature. After being stirred at 22 °C for 48 h, the reaction mixture was separated by column chromatography on Al_2O_3. After elution of the starting materials (**1** and **5**) with $CHCl_3$–hexane (1 : 1), the eluate with $CHCl_3$–EtOH (10 : 1) gave a mixture of the *threo*- and *erythro*-nitro esters (**6a** and **6b**) as an oil (1.26 g, 16.8%).

This mixture (1.22 g, 3.52 mmol) was hydrogenated in the presence of 10% Pd–C (200 mg) in EtOH (30 ml) under ordinary pressure and temperature for 2.5 h. After removal of Pd–C and solvent, the resulting oil (1.008 g) was separated by preparative TLC (developed twice with $CHCl_3$–EtOH (40 : 1)). From the fast-moving band, the *threo*-amino ester (**7a**) (496 mg, 40.7%), mp 91—92 °C (from iso-PrOH), was obtained. IR ν_{max}^{Nujol} cm^{-1}: 3500, 3390, 1740, 1730, 1610. MS *m/e*: 316 (M^+), 227 ($M-CH(OH)CO_2Me)^+$. NMR ($CDCl_3$) δ: 1.19 (3H, d, J=7 Hz, iso-PrOH),

3.6—4.2 (1/2H, m, iso-PrOH), 3.75 (6H, s, OCH_3 and CO_2CH_3), 4.48 (1H, d, $J=3$ Hz, C_2-H), 4.83 (1H, d, $J=3$ Hz, C_3-H), 6.3—7.4 (8H, m, aromatic H). *Anal.* Calcd for $C_{17}H_{20}N_2O_4 \cdot 1/2$ iso-PrOH: C, 64.05; H 7.12; N, 8.07. Found: C, 64.13; H, 6.93; N, 7.95.

The *erythro*-amino ester (**7b**) (242 mg, 21.7%), mp 120—122 °C (from iso-PrOH–iso-Pr_2O), was obtained from the slower-moving band. IR ν_{max}^{Nujol} cm^{-1}: 3420, 3380, 1740, 1620. MS *m/e*: 316 (M^+), 227 ($M-CH(OH)CO_2Me)^+$. NMR ($CDCl_3$) δ: 3.72 (3H, s, OCH_3), 3.76 (3H, s, CO_2CH_3), 4.1—4.4 (2H, m, C_2-H and C_3-H). This signal changed to a double doublet on addition of D_2O as follows: 4.62 (1H, d, $J=4$ Hz, C_2-H) and 4.76 (1H, d, $J=4$ Hz, C_3-H), 6.5—7.4 (8H, m, aromatic H). *Anal.* Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.34; N, 8.86. Found: C, 64.43; H, 6.34; N, 8.82.

Therefore, the *threo/erythro* ratio of the nitro esters was estimated to be $40.7/21.7 = ca.$ 2.0.

The ZnI_2-catalyzed reaction (Table I, Entry 7) was carried out essentially in the same manner.

b) The Reaction in a Silica Gel Chromatographic Column (Table I, Entry 8): A solution of **1** (15.0 g, 72.0 mmol) and **5** (10.0 g, 72.4 mmol) in benzene (100 ml) was poured into a column of silica gel (Kieselgel 60, 230—400 mesh for flash column chromatography, Merck, 400 g). After standing at 22 °C for 17 h, the starting materials were eluted with benzene, and then a mixture of the *threo*- and *erythro*-nitro esters (**6a** and **6b**) (14.53 g, 58.4%) was obtained as an oil by elution with benzene–AcOEt (6 : 1). This mixture was triturated with iso-PrOH to give the crystalline *erythro*-nitro ester (**6b**). Recrystallization from iso-PrOH gave pure **6b** (8.93 g, 35.9%), mp 140—143 °C as yellow needles. IR ν_{max}^{Nujol} cm^{-1}: 3450, 3380, 1755, 1740, 1615, 1510, 1360. MS *m/e*: (M^+ was not seen), 257 ($M-CH(OH)CO_2Me)^+$, 224, 210. NMR ($CDCl_3$) δ: 2.85 (1H, d, $J=7.5$ Hz, OH), 3.75 (6H, s, OCH_3 and CO_2CH_3), 4.67 (1H, dd, $J=4$, 7.5 Hz, C_2-H), 4.95 (1H, dd, $J=4$, 7.5 Hz, C_3-H), 6.4—7.5 (7H, m, aromatic H), 8.15 (1H, dd, $J=2$, 8 Hz, aromatic H), 9.00 (1H, d, $J=7.5$ Hz, NH). *Anal.* Calcd for $C_{17}H_{18}N_2O_6$: C, 58.96; H, 5.24; N, 8.09. Found: C, 59.02; H, 5.20; N, 8.11.

Hydrogenation of **6b** (1.45 g, 4.19 mmol) over 10% Pd–C in EtOH (30 ml) gave the *erythro*-amino ester (**7b**) in 73.5% yield; this product was identical with the sample previously isolated.

A small portion of the whole mixture of the *threo*- and *erythro*-nitro esters (**6a** and **6b**) obtained above was hydrogenated similarly. The *threo/erythro* ratio of the resulting mixture (**7a**/**7b**) was determined to be 0.5.

c) The Reaction in the Presence of a Slurry of Silica Gel: A mixture of **1** (830 mg, 3.99 mmol), **5** (500 mg, 3.62 mmol), silica gel (Kieselgel 60 for flash chromatography, 5.5 g), and toluene (20 ml) was stirred at room temperature for 17 h. The silica gel was removed by filtration and washed with AcOEt. The filtrates and washing were concentrated, and the residual oil was separated by flash column chromatography on silica gel. After elution of the starting material with benzene, a mixture of the *threo*- and *erythro*-nitro esters (**6a** and **6b**) (605 mg, 48.2%) was obtained by elution with benzene–AcOEt (7 : 1); the *threo/erythro* ratio was estimated to be 0.5.

d) The Reaction on Alumina (Table I, Entry 9): A solution of **1** (1.5 g, 7.20 mmol) and **5** (1.0 g, 7.24 mmol) in benzene (10 ml) was poured onto a column of Aluminiumoxide 90 (activity II—III, Merck, 60 g). After standing at room temperature for 17 h, the starting materials were washed out with benzene, and then a mixture of **6a** and **6b** (446 mg, 17.9% as an oil) was eluted with benzene–EtOAc (1 : 1); the *threo/erythro* ratio was estimated to be 0.3.

e) The Reaction in the Presence of NaH in DMSO (Table I, Entry 10): A solution of **1** (1.58 g, 7.59 mmol) was added to a solution of **5** (1.0 g, 7.24 mmol) and NaH (63% dispersion in mineral oil, 276 mg, 7.24 mmol) in DMSO (5 ml) under an argon atmosphere during a period of 30 min. The reaction mixture was poured into ice-water, and the precipitated crystals were collected on a filter, washed with water, dried, and recrystallized from $CHCl_3$ to give *trans*-3-(4-methoxyphenyl)-2′-nitroglycidanilide (**8**) (1.43 g, 62.8%), mp 165—167 °C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1700, 1510, 1340. MS *m/e*: 314 (M^+), 176, 148, 121. NMR (DMSO-d_6) δ: 3.80 (3H, s, OCH_3), 3.97 and 4.26 (2H, AB system dd, $J=2$ Hz, C_2-H and C_3-H), 6.9—8.3 (8H, m, aromatic H), 10.6 (1H, br s, NH). *Anal.* Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.04; H, 4.37; N, 8.92.

Reaction of 1 with 2-Nitrothiophenol on Silica Gel (Table II)——A solution of **1** (1.3 g, 6.24 mmol) and 2-nitrothiophenol (1.0 g, 6.44 mmol) in benzene (10 ml) was poured onto the column of silica gel (for flash column chromatography, 60 g). After standing at room temperature for 17 h, the reaction mixture was worked up in the same manner as described for the reaction of **1** with **5**.

The *erythro*-nitro ester (*erythro*-isomer of **2a**) (340 mg, 15.0%), mp 135—136.5 °C, was obtained by elution with benzene–AcOEt (5 : 1), and was identical with an authentic sample.[3a]

Reaction of 1 with 2-Nitrophenol on Silica Gel (Table II)——A solution of **1** (1.5 g, 7.20 mmol) and 2-nitrophenol (1.0 g, 7.19 mmol) in benzene (10 ml) was allowed to react in a column of silica gel (Kieselgel 60 for flash column chromatography, 60 g). After standing at room temperature for 17 h, the starting materials were washed out with benzene, and then a mixture of the *threo*- and *erythro*-nitro esters (**2b**) (430 mg, 17.2%, as an oil) was eluted with benzene–AcOEt (5 : 1). The *threo/erythro* ratio of the mixture was 5.75, which was determined by separation by preparative TLC as reported in our previous paper.[1]

***threo*-3-(2-Aminoanilino)-2-hydroxy-3-(4-methoxyphenyl)propionic Acid (9a)**——A solution of the *threo*-amino ester (**7a**) (2.83 g, 8.17 mmol) in a mixture of 5% aqueous NaOH (10 ml) and EtOH (10 ml) was stirred at room temperature for 2 h, then neutralized with 10% HCl. The precipitated crystals were filtered off, washed with water, dried, and recrystallized from *N*,*N*-dimethyl formamide (DMF)–EtOH to give **9a** (1.995 g, 74.1%), mp 150—155 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3350, 1650, 1610. MS *m/e*: 302 (M^+), 227 ($M-CH(OH)CO_2H)^+$. NMR (DMSO-d_6) δ: 3.72 (3H, s, OCH_3), 4.15 (1H, d, $J=3$ Hz, C_2-H), 4.75 (1H, d, $J=3$ Hz, C_3-H), 6.1—7.4 (8H, m, aromatic H). *Anal.* Calcd

for $C_{16}H_{18}N_2O_4 \cdot 1/2H_2O \cdot 1/4DMF$: C, 61.04; H, 6.34; N, 9.56. Found: C, 61.31; H, 6.01; N, 9.33.

***erythro*-3-(2-Aminoanilino)-2-hydroxy-3-(4-methoxyphenyl)propionic Acid (9b)**——The *erythro*-amino ester (**7b**) was hydrolyzed in the same manner as described for **9a**. The acid (**9b**), mp 150—153 °C (dec.), was obtained in 67.1% yield after recrystallization from DMF–iso-PrOH–H_2O. IR ν_{max}^{Nujol} cm^{-1}: 3340, 3300, 1640, 1610. MS *m/e*: 302 (M^+), 227 ($M-CH(OH)CO_2H)^+$. NMR (DMSO-d_6) δ: 3.72 (3H, s, OCH_3), 4.27 (1H, d, $J=6$ Hz, C_2-H), 4.64 (1H, d, $J=6$ Hz, C_3-H), 6.3—7.5 (8H, m, aromatic H). *Anal.* Calcd for $C_{16}H_{18}N_2O_4 \cdot 1/2H_2O$: C, 61.72; H, 6.15; N, 9.00. Found: C, 61.60; H, 6.26; N, 8.94.

Cyclization of the Amino Carboxylic Acid (9)——a) The Reaction in Boiling Xylene in the Presence of Air: The *threo*-amino carboxylic acid (**9a**) (1.5 g, 4.55 mmol) was heated in boiling xylene (20 ml) for 30 h. After removal of the solvent, the residue was separated by flash column chromatography. *cis*-3-Hydroxy-4-(4-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (**10a**) (800 mg, 61.8%), mp 145—148 °C (from EtOH–iso-Pr_2O), was obtained from the first eluate with benzene–AcOEt (7:1). IR ν_{max}^{Nujol} cm^{-1}: 3370, 3330, 3240, 1700, 1680. MS *m/e*; 284 (M^+), 237. NMR ($CDCl_3$) δ: 3.42 (1H, d, $J=6$ Hz, OH), 3.74 (3H, s, OCH_3), 4.16 (1H, d, $J=5$ Hz, NH), 4.63 (1H, dd, $J=5$, and 6 Hz, C_3-H), 5.07 (1H, t, $J=5$ Hz, C_4-H), 6.7—7.5 (8H, m, aromatic H). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.60; H, 5.62; N, 9.80.

From the second eluate with the same solvent, the *trans*-lactam (**10b**) (190 mg, 14.7%), mp 188—191.5 °C (EtOH), was obtained. IR ν_{max}^{Nujol} cm^{-1}: 3490, 3420, 3360, 3340, 1670. MS *m/e*: 284 (M^+), 237. NMR (DMSO-d_6) δ: 3.74 (3H, s, OCH_3), 4.06 (1H, dd, $J=6$, 9 Hz, C_3-H), 4.43 (1H, d, $J=9$ Hz, C_4-H), 4.77 (1H, d, $J=6$ Hz, OH), 5.38 (1H, s, NH), 6.7—7.4 (8H, m, aromatic H). *Anal.* Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.68; H, 5.61; N, 9.84.

The *cis*-lactam (**10a**) was completely unchanged after heating in boiling xylene for 30 h in the presence of air.

Similarly, the *erythro*-amino carboxylic acid (**9b**) (500 mg, 1.61 mmol) in xylene (10 ml) was heated and worked up to give the *trans*-lactam (**10b**) (329 mg, 71.8%) and the *cis*-lactam (**10a**) (36 mg, 7.9%).

b) The Reaction in Boiling Xylene under an Argon Atmosphere: The *threo*-amino carboxylic acid (**9a**) (500 mg, 1.52 mmol) was heated in boiling xylene (10 ml) under an argon atmosphere for 17 h. The reaction mixture was worked up in the same manner as described above to give the *cis*-lactam (**10a**) (330 mg, 76.4%) and the *trans*-lactam (10 mg, 2.3%), and some starting material (**9a**, 93 mg, 18.6%) was recovered.

Similarly, the *erythro*-amino carboxylic acid (**9b**) was heated under an argon atmosphere in the same manner as described above to give the *trans*-lactam (**10b**) in 88.4% yield as a sole product.

c) The Cyclization with HOBt–DCC: DCC (464 mg, 2.25 mmol) was added to a mixture of the *threo*-amino carboxylic acid (**9a**) (500 mg, 1.52 mmol) and HOBt hydrate (50 mg, 0.32 mmol) in DMF (10 ml) at room temperature. The reaction mixture was stirred at the same temperature for 17 h and concentrated under reduced pressure. Water and AcOEt 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 dicyclohexyl urea were filtered off. The AcOEt solution was separated and the water layer was extracted with AcOEt. The combined AcOEt solutions were washed with sat. $NaHCO_3$ to remove HOBt and water, then dried, and concentrated. The residual solid was recrystallized from EtOH–iso-Pr_2O to give the *cis*-lactam (**10a**) (410 mg, 94.9%), mp 145—148 °C as a sole product.

Cyclization of the *erythro*-Amino Ester (7b) with NaH–DMSO——A solution of **7b** (3.0 g, 8.66 mmol) in DMSO (9 ml) was added to a solution of dimethylsulfinyl carbanion in DMSO, prepared from 63% NaH (760 mg, 19.9 mmol, dispersion in mineral oil) and DMSO (15 ml), under ice-cooling. The reaction mixture was warmed to 30 °C, stirred at 30 °C for 20 min, and poured into ice-water. The mixture was acidified with HOAc and extracted with $CHCl_3$. The extracts were washed with water, dried, and evaporated. The residual solid was recrystallized from EtOH to give the *trans*-lactam (**10b**) (1.2 g, 48.7%), mp 188—191.5 °C.

Acetylation of the *trans*-Lactam (10b)——a) With Ac_2O–Pyridine at 100 °C: A mixture of **10b** (1.0 g, 3.52 mmol), pyridine (1 ml), and Ac_2O (10 ml) was heated at 100 °C for 2 h, then concentrated under reduced pressure. The residual solid was recrystallized from EtOH to give the triacetate (**12b**), mp 153—155 °C (1.086 g, 73.6%). IR ν_{max}^{Nujol} cm^{-1}: 1780, 1745, 1730, 1670, 1645, 1610. MS *m/e*: 410 (M^+), 350, 308. NMR ($CDCl_3$) δ: 1.80 (3H, s, $NCOCH_3$), 2.00 (3H, s, $OCOCH_3$), 2.74 (3H, s, $NCOCH_3$), 5.20 (1H, d, $J=11$ Hz, C_3-H), 6.15 (1H, d, $J=11$ Hz, C_4-H), 6.7—7.6 (8H, m, aromatic H). *Anal.* Calcd for $C_{22}H_{22}N_2O_6 \cdot 1/2H_2O$: C, 63.00; H, 5.53; N, 6.68. Found: C, 63.69; H, 5.86; N, 6.57.

b) With Ac_2O–Pyridine at Room Temperature: A mixture of **10b** (500 mg, 1.76 mmol), Ac_2O (5 ml), and pyridine (0.5 ml) was stirred at room temperature for 3 h, then poured into ice-water, neutralized with $NaHCO_3$, and extracted with EtOAc. The extracts were washed with water, dried, and concentrated. The residual oil was separated by preparative TLC (developed with $CHCl_3$–EtOAc (3:1)). The monoacetate (**14b**) (162 mg, 24.7%), mp 188—191 °C (from EtOH), was obtained from the faster-moving band. IR ν_{max}^{Nujol} cm^{-1}: 3340, 1760, 1675, 1610. MS *m/e*: 326 (M^+), 283, 266. NMR (DMSO-d_6) δ: 1.91 (3H, s, $OCOCH_3$), 3.78 (3H, s, OCH_3), 4.83 (1H, d, $J=10.5$ Hz, C_4-H), 5.38 (1H, d, $J=10.5$ Hz, C_3-H), 6.3—7.4 (8H, m, aromatic H), 8.36 (1H, s, NH). *Anal.* Calcd for $C_{18}H_{18}N_2O_4 \cdot EtOH$: C, 64.50; H, 6.50; N, 7.52. Found: C, 64.56; H, 6.42; N, 7.57.

The diacetate (**13b**) (440 mg, 60.4%), mp 229—240 °C (from EtOH), was obtained from the slower-moving band. IR ν_{max}^{Nujol} cm^{-1}: 3340, 1750, 1700, 1635, 1610. MS *m/e*: 368 (M^+), 308, 283, 265. NMR ($CDCl_3$) δ: 1.71 (3H, s,

$NCOCH_3$), 1.97 (3H, s, $OCOCH_3$), 3.76 (3H, s, OCH_3), 5.44 (1H, d, J=11 Hz, C_3-H), 6.25 (1H, d, J=11 Hz, C_4-H), 6.7—7.5 (8H, m, aromatic H), 8.66 (1H, s, NH). *Anal.* Calcd for $C_{20}H_{20}N_2O_5 \cdot EtOH$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.78; H, 6.07; N, 6.76.

c) With AcCl–Pyridine: A solution of AcCl (290 mg, 3.69 mmol) in DMF (2 ml) was added to a solution of **10b** (500 mg, 1.76 mmol) in DMF (8 ml) and pyridine (417 mg, 5.27 mmol) at room temperature. The reaction mixture was stirred at room temperature for 1 h, poured into ice-water, and extracted with EtOAc. The extracts were washed with sat. aqueous NaCl, dried, and evaporated to give the diacetate (**13b**), mp 229—240 °C, 670 mg (91.9%).

***erythro*-2-Hydroxy-3-(4-methoxyphenyl)-3-(2-nitroanilino)propionic Acid (15b)**——A solution of the *erythro*-nitro ester (**6b**) (10.0 g, 28.9 mmol) in 5% aqueous NaOH (30 ml) and EtOH (10 ml) was stirred at room temperature for 3 h, then neutralized with dil. HCl and extracted with EtOAc. The extracts were washed with water, dried, and evaporated. The residue was recrystallized from iso-PrOH to give **15b** (7.64 g, 67.4%), mp 100—134 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3370, 1730, 1710, 1610, 1510, 1350. MS *m/e*: (M^+ was not seen), 257 ($M-CH(OH)CO_2H)^+$. NMR ($CDCl_3$–DMSO-d_6) δ: 3.73 (3H, s, OCH_3), 4.63 (1H, d, J=3 Hz, C_2-H), 5.00 (1H, dd, J=3, 8 Hz, C_3-H), 6.4—7.5 (7H, m, aromatic H), 8.12 (1H, dd, J=2, 8 Hz, aromatic H), 9.00 (1H, d, J=8 Hz, NH). *Anal.* Calcd for $C_{16}H_{16}N_2O_6 \cdot$ iso-PrOH: C, 58.15; H, 6.16; N, 7.14. Found: C, 58.06; H, 6.11; N, 7.13.

***erythro*-2-Acetoxy-3-(4-methoxyphenyl)-3-(2-nitroanilino)propionic Acid (16b)**——The nitro carboxylic acid (**15b**) (5.0 g, 12.7 mmol) was heated in Ac_2O (10 ml) and pyridine (0.1 mol) on a boiling water bath for 2 h, then poured into a mixture of ice and sat. $NaHCO_3$, and the whole was extracted with $CHCl_3$. The extracts were washed with water, dried, and evaporated to give crude **16b** (5.2 g, quantitative yield) as an oil. IR ν_{max}^{Nujol} cm^{-1}: 3020, 1755, 1620. MS *m/e*: (M^+ was not seen), 257 ($M-CH(OAc)CO_2Me)^+$. NMR (DMSO-d_6) δ: 2.16 (3H, s, $OCOCH_3$), 3.76 (3H, s, OCH_3), 5.33 and 5.41 (2H, AB system dd, J=4 Hz, C_2-H and C_3-H), 6.6—7.6 (7H, m, aromatic H), 8.12 (1H, dd, J=2, 8 Hz aromatic H).

Hydrogenation of 16b——The crude acetoxy compound (**16b**) obtained above was hydrogenated in EtOH (30 ml) in the presence of 10% Pd–C (500 mg) under ordinary pressure and temperature for 18 h. After removal of the Pd–C and solvent, the residue was triturated with EtOAc to give *erythro*-2-hydroxy-3-(2-methyl-1*H*-benzimidazol-1-yl)-3-(4-methoxyphenyl)propionic acid (**17b**) (2.35 g, 55.0%) as colorless prisms of mp 211—212 °C (from DMF–EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3340, 1660, 1610. MS *m/e*: 326 (M^+), 251 ($M-CH(OH)CO_2H)^+$, 131, 121. NMR (DMSO-d_6) δ: 2.56 (3H, s, CH_3), 3.73 (3H, s, OCH_3), 5.04 (1H, d, J=7.5 Hz, C_2-H), 5.85 (1H,d, J=7.5 Hz, C_3-H), 6.8—7.7 (8H, m, aromatic H). *Anal.* Calcd for $C_{18}H_{18}N_2O_4 \cdot 1/2H_2O$: C, 64.47; H, 5.71; N, 8.35. Found: C, 64.49; H, 5.56; N, 8.42.

***cis*-1-[2-(Dimethylamino)ethyl]-3-hydroxy-4-(4-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (18a)**——A mixture of the *cis*-lactam (**10a**) (510 mg, 1.79 mmol), 2-(dimethylamino)ethyl chloride hydrochloride (285 mg, 1.98 mmol), and K_2CO_3 (powdered, 571 mg, 4.13 mmol) in acetone (30 ml) was heated under reflux for 17 h, then allowed to cool. Inorganic compounds were removed by filtration. The filtrates were evaporated under reduced pressure, and the residue was converted into the perchlorate, which was recrystallized from water to give **18a**·perchlorate (485 mg, 59.4%), mp 208—209 °C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1650. MS *m/e*: 355 (M^+), 284, 266. NMR (DMSO-d_6) δ: 2.80 (6H, s, NCH_3), 3.0—4.2 (4H, m, NCH_2), 3.70 (3H, s, OCH_3), 4.35 (1H, d, J=6 Hz, C_3-H), 4.80 (1H, d, J=5, 6 Hz, C_4-H), 5.64 (1H, d, J=5 Hz, NH), 6.75 and 7.35 (4H, AB system dd, J=8 Hz, *p*-substituted aromatic H), 7.15 (4H, br s, aromatic H).

The *trans*-isomer (**18b**)·perchlorate, mp 202—205 °C, was obtained by alkylation of **10b** in the same manner as described above in 73.4% yield. IR ν_{max}^{Nujol} cm^{-1}: 3430, 3270, 1670. MS *m/e*: 355 (M^+), 284, 266. NMR (DMSO-d_6) δ: 2.85 (6H, s, NCH_3), 3.0—4.2 (4H, m, NCH_2–), 3.70 (3H, s, OCH_3), 4.14 (1H, d, J=10 Hz, C_3-H), 4.38 (1H, d, J=10 Hz, C_4-H), 5.32 (1H, s, NH), 6.7—7.4 (8H, m, aromatic H).

***cis*-3-Acetoxy-5-acetyl-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (19a)**——A mixture of **18a** (free base, 525 mg, 1.48 mmol), Ac_2O (5 ml), and pyridine (0.1 ml) was heated at 100 °C for 2 h. After removal of the Ac_2O, HOAc, and pyridine, the residue was converted into the oxalate, which was recrystallized from EtOH–Et_2O to give **19a**·oxalate (500 mg, 61.7%), mp 147—149 °C. IR ν_{max}^{Nujol} cm^{-1}: 1750, 1660. MS *m/e*: 439 (M^+), 379. NMR (DMSO-d_6) δ: 1.42 (3H, s, $NCOCH_3$), 1.83 (3H, s, $OCOCH_3$), 2.66 (6H, s, NCH_3), 2.8—4.3 (4H, m, NCH_2), 5.28 (1H, d, J=4 Hz, C_3-H), 6.28 (1H, d, J=4 Hz, C_4-H), 6.7—7.7 (8H, m, aromatic H).

***trans*-3-Acetoxy-5-acetyl-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (19b)**——A mixture of the *trans*-diacetyl lactam (**13b**) (670 mg, 1.62 mmol), 2-(dimethylamino)ethyl chloride hydrochloride (314 mg, 2.18 mmol), and K_2CO_3 (powdered, 628 mg, 4.55 mmol) in acetone (40 ml) was heated under reflux for 17 h, then allowed to cool. Inorganic compounds were filtered off, the filtrates were concentrated and the residue was converted into the hydrochloride. After recrystallization from EtOH, **19b**·hydrochloride (500 mg, 64.9%), mp 261—262 °C (dec.), was obtained. IR ν_{max}^{Nujol} cm^{-1}: 1760, 1690, 1670. MS *m/e*: 439 (M^+), 379. NMR ($CDCl_3$) δ: 1.72 (3H, s, $NCOCH_3$), 1.92 (3H, s, $OCOCH_3$), 2.80 (6H, s, NCH_3), 3.1—4.5 (4H, m, $-CH_2N$), 3.73 (3H, s, OCH_3), 5.12 (1H, d, J=11 Hz, C_3-H), 5.95 (1H, d, J=11 Hz, C_4-H), 6.7—8.0 (8H, m, aromatic H).

***cis*-1-[2-(Dimethylamino)ethyl]-3-hydroxy-4-(4-methoxyphenyl)-5-methyl-1,3,4,5-tetrahydro-2*H*-1,5-**

benzodiazepin-2-one (20a)——A mixture of **18a** (free base, 2.455 g, 6.91 mmol), 37% HCHO (4 ml), and HCOOH (20 ml) was heated at 50 °C for 3 h and concentrated under reduced pressure. Sat. aqueous $NaHCO_3$ was added to the residue, and the mixture was extracted with EtOAc. The extracts were washed with sat. NaCl, dried, and concentrated. The residue was dissolved in 5% aqueous NaOH (10 ml) and EtOH (10 ml) and the solution was stirred at room temperature for 1 h to hydrolyze the 3-formyloxy group, then neutralized with 10% HCl, and extracted with EtOAc. The extracts were washed with water, dried, and evaporated to give an oil which was converted to the perchlorate. Recrystallization from DMF–EtOH gave **20a**·perchlorate (2.247 g, 69.2%), mp 229—230 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3400, 1650, 1610. MS *m/e*: 369 (M^+), 340, 280. NMR (DMSO-d_6) δ: 2.55 (3H, s, NCH_3) (free base in $CDCl_3$, 2.62 (3H, s)), 2.88 (6H, s, NCH_3), 3.0—4.4 (4H, m, NCH_2), 3.78 (3H, s, OCH_3), 4.27 (2H, s, C_3- and C_4-H), 6.8—7.5 (8H, m, aromatic H).

The *trans*-isomer (**20b**), mp 215—219 °C (perchlorate), was prepared similarly (Table IV). IR ν_{max}^{Nujol} cm^{-1}: 3470, 1680, 1610. MS *m/e*: 369 (M^+), 340, 280. NMR (DMSO-d_6) δ: 2.55 (3H, s, NCH_3) (free base in $CDCl_3$, 2.29 (3H, s)), 2.85 (6H, s, NCH_3), 3.0—4.3 (6H, m, NCH_2, C_3- and C_4-H), 3.74 (3H, s, OCH_3), 6.85—7.5 (8H, m, aromatic H).

***cis*-3-Acetoxy-1-[2-(dimethylamino)ethyl]-4-(4-methoxyphenyl)-5-methyl-1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepin-2-one (21a)**——A mixture of **20a** (free base, 710 mg, 1.92 mmol), Ac_2O (5 ml), and pyridine (0.2 ml) was heated at 100 °C for 2 h, and then Ac_2O, AcOH, and pyridine were removed. The residue was dissolved in EtOH and converted into the perchlorate, which was recrystallized from EtOH to give **21a**·perchlorate (730 mg, 73.4%), mp 162—164 °C. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1680, 1610. MS *m/e*: 411 (M^+), 340, 280. NMR (DMSO-d_6) δ: 1.81 (3H, s, $OCOCH_3$), 2.48 (3H, s, NCH_3), 2.81 (6H, s, N–CH_3), 3.2—4.3 (4H, m, NCH_2), 3.76 (3H, s, OCH_3), 4.44 (1H, d, J= 6 Hz, C_4-H), 5.20 (1H, d, J=6 Hz, C_3-H), 6.8—7.5 (8H, m, aromatic H).

The *trans*-isomer (**21b**), mp 152—155 °C (oxalate), was prepared similarly (Table IV). IR ν_{max}^{Nujol} cm^{-1}: 1750, 1690, 1610. MS *m/e*: 411 (M^+), 340, 280. NMR (D_2O) δ: 1.94 (3H, s, $OCOCH_3$), 2.53 (3H, s, NCH_3), 2.96 (6H, s, NCH_3), 3.2—4.2 (4H, m, NCH_2), 3.73 (3H, s, OCH_3), 4.70 (1H, d, J=10 Hz, C_4-H), 5.32 (1H, d, J=10 Hz, C_3-H), 6.8—7.7 (8H, m, aromatic H).

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5) This fragment pattern is quite similar to those observed with the thia and oxa analogues (**2a, b**) and rules out reversed positions for the amino and hydroxyl groups. See references 1 and 2*b*.
6) During such a short period as that required for separation by column chromatography on silica gel or alumina, no appreciable reaction of **1** with **5** was observed. This rules out significant changes of the yields and isomer ratios of the product during work-up in entries 6 and 7.
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