Synthesis and Antihypertensive Activity of Stereoisomers of 4-Piperidyl-1,3-dihydro-2-oxo-2*H*-benzimidazoles. Enhanced Potencies of (+) Isomers

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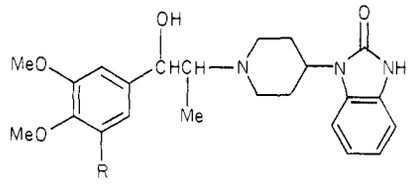
To elucidate the relationship between the pharmacological activity and stereochemical structure, we resolved 1-[2-(3,4,5-trimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (1 and 2) and 1-[2-(3,4-dimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (3), which produced hypotensive effects mainly through their α-blocking actions. Threo isomers 1 and 3 were resolved via diastereomeric carbamates. Erythro isomer 2 was obtained by an oxidation and reduction sequence from optically active 1. No significant difference was found between the pharmacological activities of the threo and erythro isomers of the corresponding compounds. However, a clear difference was found between the pharmacological activities of the optical isomers. Difference was most clearly shown in the hypotensive actions of normotensive rats and in α-adrenergic blocking activities of isolated rat vas deferens. In these actions, (+) isomers were always more potent than the corresponding (−) isomers.

We have previously reported the synthesis and biological properties of a series of 4-piperidinyl-1,3-dihydro-2-oxo-2*H*-benzimidazoles, from which series compounds **1–4** were identified as highly promising potent antihypertensive agents.[1] We have also reported the selective synthesis of 1–4 in racemic forms and the preliminary investigation of their biological activities.[1] Extensive pharmacological studies on (±)-1 and (±)-3 have been reported.[2,3] Compounds 1–4 showed strong α-adrenergic blocking activities



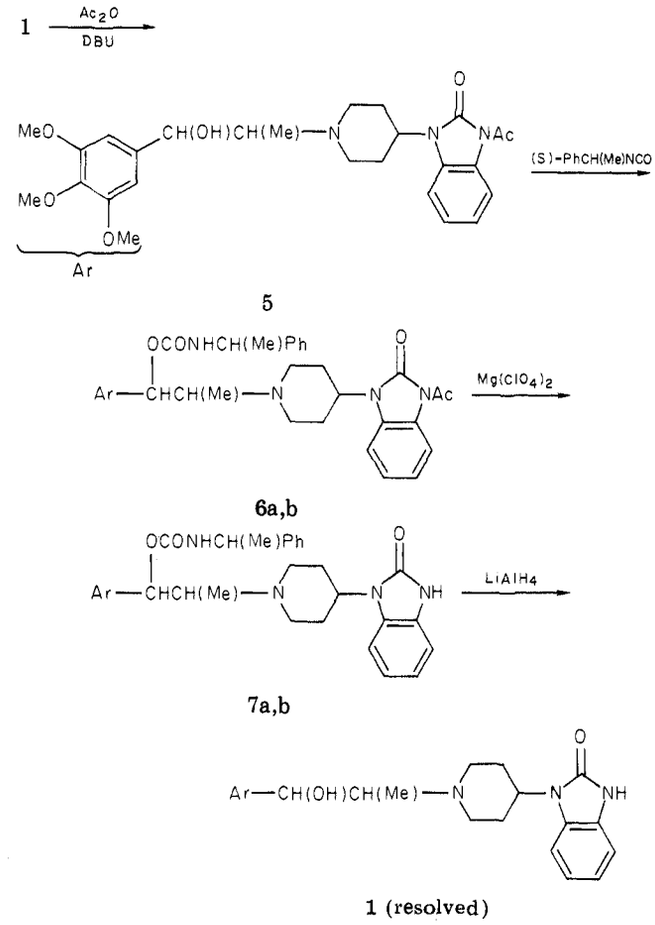
1 (threo), R = OCH_3
2 (erythro), R = OCH_3
3 (threo), R = H
4 (erythro), R = H

and were considered to produce their hypotensive effects mainly through their α-blocking action.[2,3]

Along with development of the studies on adrenergic mechanisms, it appeared essential to study the relationship between pharmacological activity and stereoisomerism of various adrenergic drugs. Many β-adrenergic agents have been synthesized, resolved, and tested for pharmacological activity.[4] However, very little work has been reported on the stereoisomeric effect of α-adrenergic antagonists or agonists.[4] We are therefore interested in resolving the present compounds and examining their pharmacological properties by measuring the hypotensive activities (in normotensive and spontaneously hypertensive rats) and α-adrenergic blocking activities.

Chemistry. Threo isomer 1 was resolved as outlined in Scheme I. Compound **5**, which was prepared by the selective acetylation of 1 with Ac_2O and 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), was reacted with (*S*)-1-phenylethyl isocyanate in dioxane, and the resulting diastereomeric mixture of carbamates **6a,b** were separated with preparative HPLC. The carbamates of higher (**6a**) and lower R_f (**6b**) were obtained in 33 and 31% yields, respectively. Diastereomer **6a** was deacetylated under mild

Scheme I



1 (resolved)

conditions [MeOH/$Mg(ClO_4)_2$][5] to afford **7a**, which was reduced with $LiAlH_4$[6,7] to give an alcohol [(+)-1]. Similar

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(1) H. Obase, N. Nakamizo, H. Takai, M. Teranishi, K. Kubo, K. Shuto, Y. Kasuya, H. Kato, K. Shigenobu, and J. Kurihara, *Chem. Pharm. Bull.*, **30**, 462 (1982).
(2) Y. Kasuya, J. Kurihara, and H. Kato, *Arzneim.-Forsch.*, submitted for publication.
(3) A. Karasawa, K. Shuto, K. Kubo, M. Hashikami, K. Shigenobu, and Y. Kasuya, *Arch. Int. Pharmacodyn. Ther.*, submitted for publication.
(4) P. N. Patil, D. D. Miller, and U. Trendelenburg, *Pharmacol. Rev.* **26**, 323 (1974).

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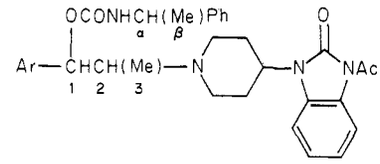
Table I. Physical Properties of Diastereomeric Carbamates (6 and 9)



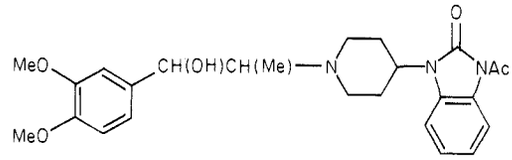
	Ar: 3,4,5-trimethoxyphenyl		Ar: 3,4-dimethoxyphenyl	
	6a	6b	9a	9b
mp, °C	104–105	162–164	148–149	194–196
$[\alpha]^{25}_D$, deg	+24.8° (c 0.2, $CHCl_3$)	−41.5° (c 0.2, $CHCl_3$)	−33.0° (c 0.2, $CHCl_3$)	+48.8° (c 0.2, $CHCl_3$)
^{1}H NMR				
1	5.58	5.56	5.61	5.59
2[b]				
3	0.76	0.80	0.74	0.78
β	1.59	1.51	1.58	1.49
^{13}C NMR				
1	77.4	77.6	77.2	77.3
2	63.8	63.4	63.7	63.3
3	10.4	10.8	10.4	10.9
α	50.9	50.8	51.3	50.6
β	22.8	22.5, 23.3 (br)	23.0	22.6

[a] ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$. All chemical shifts are given in parts per million relative to Me_4Si as an internal standard. [b] C^2 H proton signals were overlapped with piperidine ring protons.

treatments of **6b** gave (−)-**1**. Removal of the carbamoyl group could be also effected by trichlorosilane-induced cleavage.[8,9]

From the pharmacological results, (+)-**1**, which was derived from carbamate **6a**, proved to have more potent antihypertensive activity than its antipode. However, **6a** was a less crystallizable carbamate; therefore, we attempted optical resolution of **3** (threo form) using (*R*)-1-phenylethyl isocyanate with the hope of improving the crystallizability of the diastereomer in order to produce an enantiomer [(+)-**3**] with presumably more potent antihypertensive activity.

Actually, *N*-Ac-**3** (**8**) was treated with (*R*)-1-phenylethyl



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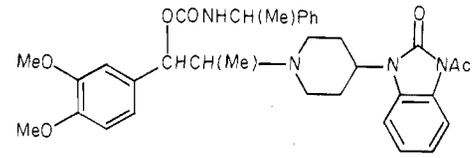
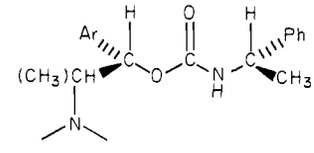


9a,b

isocyanate to afford a diastereomeric mixture of carbamates (**9a,b**). Isolation of each diastereomer by preparative HPLC gave a less polar carbamate (**9a**) and a more polar carbamate (**9b**) in 24 and 28% yields, respectively. Liberation of **3a** and **3b** was carried out by treatment with $LiAlH_4$. The enantiomer (−)-**3** was obtained from **9a** in 49% yield, and the enantiomer (+)-**3** was obtained in 59% yield from **9b**. As we presumed above, the more readily crystallized carbamate **9b** gave (+)-**3**, which exhibited stronger biological activity than the (−) enantiomer. The physical properties of intermediate carbamates **6** and **9** are summarized in Table I.

From the data in Table I, we can predict the absolute configuration of the resolved carbinol. Assignment of stereochemistry to a pair of diastereomeric carbamates is elucidated from two independent arguments. The first is based on the observation that **6a** elutes prior to **6b** on silica gel with AcOEt–*n*-hexane as eluent. On the basis of Pirkle's observation,[10] which correlates elution order and configuration of the diastereomers, faster eluting **6a** would have a threoid configuration concerning 1 and α carbons (see Table I).[11] A second argument comes from the NMR spectra.[12] Due to the shielding effect of the *cis*-aryl group (see ref 11), the doublet signal of the β-methyl of **6b** appears upfield compared with that of **6a** in the ^{1}H NMR spectra (cf. δ 1.51 for **6b**, δ 1.59 for **6a**). Also in ^{13}C NMR spectra, the C-2 carbon signal of **6b** (see Table I) exhibits an upfield shift compared with that of **6a**. From these observations, it is speculated that **6a** has the 1*S*,2*S* con-

(5) J. Sunamoto, H. Kondo, and D. Horiguchi, "Abstracts of Papers", *6th meeting of the Enzymic Organic Reaction*, Tokyo, March, 1978, p 9. M. Caplow, *J. Am. Chem. Soc.*, **87**, 5774 (1965).
(6) G. Schmid, T. Fukuyama, K. Akasaka, and Y. Kishi, *J. Am. Chem. Soc.*, **101**, 259 (1979).
(7) K. N. Slessor, A. C. Oehlschlager, B. D. Johnston, H. D. Pierce, Jr., S. K. Grewal, and L. K. G. Wickremesinghe, *J. Org. Chem.*, **45**, 2290 (1980).
(8) W. H. Pirkle and C. W. Boeder, *J. Org. Chem.*, **43**, 2091 (1978).
(9) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **42**, 2781 (1977).
(10) W. H. Pirkle and J. R. Hauske, *J. Org. Chem.*, **41**, 801 (1976); *ibid.*, **42**, 1839 (1977).
(11) The following figure illustrates the threoid conformation. Ph and $-CH(CH_3)N<$ groups were considered as warding off groups:



Ar = 3,4,5-trimethoxyphenyl

(12) W. H. Pirkle and P. L. Rinaldi, *J. Org. Chem.*, **43**, 3803 (1978); W. H. Pirkle, K. A. Simmons, and C. W. Boeder, *ibid.*, **44**, 4891 (1979).

Table II. Effects of Optical Isomers of the Compounds 1-4 on the Mean Arterial Blood Pressure and Heart Rate of Anesthetized Normotensive Rats

compd	optical isomer	no. of animals	initial level, mmHg	changes in BP, mmHg, at the following times[a] 10 min	30 min	60 min	120 min	180 min	240 min
1	+	4	117 ± 1	−45 ± 3	−36 ± 1	−38 ± 5	−41 ± 5	−42 ± 5	−44 ± 5
(threo)	±	4	116 ± 3	−37 ± 3	−37 ± 4	−41 ± 7	−31 ± 3	−32 ± 5	−31 ± 10
	−	4	119 ± 8	−26 ± 6	−34 ± 1	−32 ± 2	−37 ± 5	−39 ± 4	−31 ± 4
2	+	3	138 ± 4	−59 ± 7	−47 ± 6	−49 ± 4	−40 ± 4	−40 ± 5	−35 ± 10
(erythro)	±	4	137 ± 8	−37 ± 7	−34 ± 3	−35 ± 4	−31 ± 5	−29 ± 9	−25 ± 14
	−	4	116 ± 8	−27 ± 4	−21 ± 2	−26 ± 4	−8 ± 6	−6 ± 8	−15 ± 9
3	+	3	138 ± 3	−39 ± 1	−41 ± 6	−45 ± 6	−45 ± 8	−40 ± 5	−30 ± 2
(threo)	±	4	117 ± 4	−43 ± 3	−35 ± 3	−36 ± 4	−49 ± 5	−42 ± 10	−42 ± 5
	−	3	111 ± 4	−19 ± 5	−15 ± 2	−8 ± 3	+2 ± 3	+1 ± 2	+3 ± 4
4	±	5	132 ± 4	−26 ± 9	−32 ± 8	−29 ± 8	−25 ± 5	−26 ± 7	−25 ± 3

compd	optical isomer	no. of animals	initial level, beats/min	changes in HR, beats/min, at the following times[a] 10 min	30 min	60 min	120 min	180 min	240 min
1	+	4	340 ± 27	−39 ± 14	−31 ± 4	−33 ± 12	−40 ± 24	−76 ± 16	−73 ± 17
(threo)	±	4	393 ± 12	−5 ± 3	−23 ± 11	−31 ± 14	−38 ± 16	−50 ± 12	−43 ± 7
	−	4	374 ± 4	−24 ± 14	−41 ± 19	−47 ± 22	−67 ± 19	−86 ± 12	−77 ± 7
2	+	3	344 ± 23	−38 ± 42	−39 ± 31	−38 ± 37	−65 ± 63	−40 ± 58	−40 ± 54
(erythro)	±	4	386 ± 32	−32 ± 18	−33 ± 22	−27 ± 27	−51 ± 31	−51 ± 35	−21 ± 56
	−	4	333 ± 30	−15 ± 42	−8 ± 43	−10 ± 39	−9 ± 43	0 ± 29	−15 ± 9
3	+	3	372 ± 8	−22 ± 26	−10 ± 10	−12 ± 10	−21 ± 18	−24 ± 21	−24 ± 21
(threo)	±	4	410 ± 9	−27 ± 16	−4 ± 2	−6 ± 5	−39 ± 11	−51 ± 10	−50 ± 21
		3	345 ± 23	−55 ± 36	−52 ± 8	−38 ± 16	−40 ± 25	−48 ± 25	−30 ± 30
4	±	5	411 ± 24	−41 ± 19	−63 ± 32	−70 ± 32	−95 ± 32	−87 ± 55	−67 ± 47

[a] Time after the intraperitoneal administration of the test compounds at a dose of 30 mg/kg. BP = blood pressure; HR = heart rate.

figuration and its counterpart **6b** has the 1*R*,2*R* configuration. So, (+)-**1** is assumed to have the 1*S*,2*S* configuration, and (−)-**1** is assumed to have the 1*R*,2*R* configuration. This speculative correlation is also applied to compound **9**; the less polar diastereomer **9a** would have the 1*R*,2*R* configuration, and the more polar isomer would have the 1*S*,2*R* configuration. Therefore, (−)-**3** is deduced to be the 1*R*,2*R* alcohol, and (+)-**3** is deduced to be the 1*S*,2*S* alcohol. These speculations could be confirmed directly by X-ray crystallographic analysis, and this approach is now in progress.

Next, the optical resolution of erythro isomer **2** was investigated. A similar procedure adapted to threo isomers was first attempted. A similar reaction of *N*-Ac-**2** with (*S*)-1-phenylethyl isocyanate gave a diastereomeric mixture of carbamates in good yield. However, neither carbamate was separated on TLC with various solvent systems. Attempted separation with (*R*)-isocyanate also gave a disappointing result. Alternatively, optical resolution involving the oxidation and reduction sequence shown in Scheme II was undertaken. At first, oxidation of optically active **1** was examined. A number of oxidants, including manganase dioxide (ordinary and activated by Attenburrow's procedure), dimethyl sulfoxide–dicyclohexylcarbodiimide, dimethyl sulfoxide–acetic anhydride, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, 2,3,4,5-tetrachloro-*p*-benzoquinone, pyridinium chlorochromate, dimethyl sulfide–*N*-chlorosuccinimide, were tried, but desired amino ketone **10** was not detected.[13] Finally, we could oxidize (+)-**1** to the corresponding (+)-**10** (**10b**) with pyridinium dichromate (PDC)[14] in DMF at −5 to −10 °C. The hydrogenation of (+)-**10** reported previously (PtO_2 as catalyst, at atmospheric pressure of H_2)[1] gave (−)-**2** in good yield. No threo isomer was detected in this hydrogenation. In the same way (−)-**1** gave (−)-**10** (**10a**) on oxidation, which afforded (+)-**2** on further hydrogenation.

The optical purity of resolved threo isomer (**1** and **3**) was determined as follows. It was found that racemic **1** or **3** did not exhibit any nonequivalence in the NMR spectrum upon addition of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) [Eu(hfc)$_3$, Aldrich Chemical Co.]. However, (±)-*O*,*N*-Ac_2-**1**[1] in $CDCl_3$ (0.19 M) showed two doublet methine peaks (ArC*H*OAc) at δ 6.01 and 6.06 by the addition of 0.18 equiv of Eu(hfc)$_3$. (+)-*O*,*N*-Ac_2- and (−)-*O*,*N*-Ac_2-**1**[15] each exhibited one doublet at the expected position. Similar results were obtained for (±)-, (+)-, and (−)-*O*,*N*-Ac_2-**3**. These facts confirmed that resolved **1** and **3** were essentially optically pure. However, the method could not be applied to the erythro isomer because nonequivalence was not observed in Eu(hfc)$_3$-induced NMR spectra for racemic **2** and racemic *O*,*N*-Ac_2-**2**. Another approach to determine the optical purity of the erythro isomers **2a**,**b** is now under investigation.[16]

Results and Discussion

Hypotensive Action in Anesthetized Normotensive Rats. Male Wister strain rats (body weight 250–300 g) were anesthetized with an ip injection of urethane–chloralose (urethane, 600 mg/kg; α-chloralose, 60 mg/kg), and blood pressure was measured with a pressure transducer (Nihon Kohden, Model MPU-0.5) connected to a canula inserted in the common carotid artery.[17] Test compounds

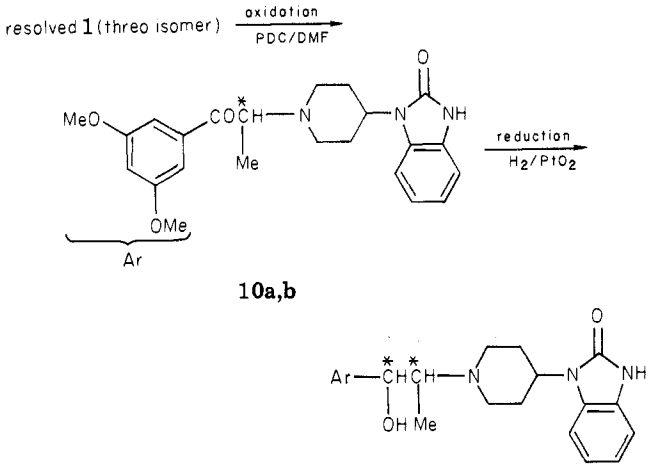
(13) The results of this oxidation will be reported elsewhere in more detail.

(14) E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, 399 (1979).

(15) *O*,*N*-Diacetyl derivatives were obtained easily by the reaction of optically active **1** and **3** with 2 equiv of Ac_2O and 4-(dimethylamino)pyridine in DMF.

(16) A series of reactions to yield optically active **2** would proceed without racemization, judging from the observed rotations (see Experimental Section) of intermediate amino ketones (**10a**,**b**) and final products (**2**).

Scheme II



were administered ip. Changes in blood pressure and heart rate produced by optical isomers of compounds 1–4 at a dose of 30 mg/kg are summarized in Table II. All of the compounds tested produced hypotensive activity, and the hypotension produced by most of the compounds was relatively long lasting. When (±)-1 and (±)-2 were compared, hypotensive activities were about the same, although the hypotensive produced by (±)-1 (threo) was slightly larger. When the optical isomers were compared, (+)-1 and (−)-1 or (+)-2 and (−)-2, the hypotension produced by the (+) isomer was much larger than that produced by the (−) isomer in both cases (compound 1 vs. 2). The hypotensive activity of (±)-3 was slightly higher than that of (±)-4, but the difference was small. Also in the case of compound 3, hypotension produced by the (+) isomer was much larger than that by the (−) isomer. With respect to heart rate, responses to the present compounds were very variable, and consistent results could not be obtained. Although reflux tachycardia was expected, heart rates tended to decrease in most cases. The reason for this is unclear at present. However, in our preliminary experiments, some of this series of compounds were shown to have direct cardiac depressant action. Therefore, the present compounds might have direct cardiac action apart from their α-blocking effects.

Hypotensive Action in Unanesthetized, Spontaneously Hypertensive Rats (SHR). Male SHR (Hoshino) whose systolic blood pressure was higher than 180 mmHg at 15th week after birth were selected for the study. Systolic blood pressure was measured with a plethysmograph after preheating the tail at 37 °C for 15 min.[18] Test compounds were given po. Maximum hypotension produced by optical isomers is summarized in Table III. The difference between the hypotensive activities of (±)-1 and (±)-2 was very small, although the hypotension produced by (±)-1 was slightly larger. When the optical isomers were compared, (+)-1 and (−)-1 or (+)-2 and (−)-2, hypotensive activities of the (+) isomers were much higher than those of the corresponding (−) isomers in both cases. However, in contrast to the case of anesthetized normotensive rats, the hypotension produced by (+)-3 was about the same as that by (−)-3. Hypotensive activities of (±)-3 and (±)-4 were difficult to compare because of the lack of the dose dependency. However, there seemed to be no large difference between their hypotensive activities. We made preliminary experiments on the hypotensive effect of a generally accepted α-blocker, prazosin, for a comparison. Prazosin at a dose of 1 mg/kg po produced a decrease in blood pressure of 85 mmHg in SHR (N = 4). Therefore, concerning hypotensive activity, a prazosin was much more potent.

Table III. Hypotensive Activities of the Optical Isomers of Compounds 1–4 in Unanesthetized Spontaneously Hypertensive Rats

compd	optical isomer	dose, mg/kg po	max decrease in BP, mmHg
1 (threo)	+	10	61
	±	10	67
		30	72
	−	10	28
2 (erythro)	+	30	85
	±	10	34
		30	60
	−	30	55
3 (threo)	+	30	74
	±	10	15
		30	69
	−	30	75
4 (erythro)	±	10	30
		30	55

[a] Decrease in systolic blood pressure recorded from tail. Maximum decrease was obtained at 1.5–2 h after administration. Values are average of experiments with three to five animals.

Table IV. α-Adrenergic Blocking Activity Determined with Isolated Rat Vas Deferens

compd	optical isomer	pA_2 [a] (n)
1 (threo)	+	7.62 (4)
	±	7.26 (4)
	−	6.88 (4)
2 (erythro)	+	7.78 (5)
	±	7.50 (4)
	−	7.26 (3)
3 (threo)	+	7.23 (7)
	±	7.15 (4)
	−	6.52 (4)
4 (erythro)	±	7.12 (4)

[a] pA_2 values were determined on the basis of the shift of the dose–response curves for NE after the application of the test compounds.

α-Adrenergic Blocking Activity Examined with Isolated Rat Vas Deferens. Most of the present series of compounds had strong α-adrenergic blocking activities. In fact, in the case (±)-1, its hypotensive action was largely due to the α-adrenergic blocking action.[3] Therefore, we compared the α-adrenergic blocking activities of the optical isomers in the present study. Isolated rat vas deferens is one of the most suitable preparations to test for α-adrenergic blocking activity;[19] thus, we decided to use this preparation. Results are summarized in Table IV. The pA_2 values for the known α blocker prazosin was 8.2 ± 0.10 (N = 5) in our preliminary experiments. As shown in Table IV, all of the compounds tested showed potent α-adrenergic blocking activity. Again, the pA_2 values of the (+) isomers of compounds 1–3 were larger than those of the corresponding (−) isomers, indicating the stronger

(17) P. B. M. W. M. Timmermans and P. A. van Zwieten, *Life Sci.*, **28**, 653 (1981).
(18) T. Sakamoto, K. Shiono, T. Watanabe, and H. Sokabe, *J. Pharmacobiodyn.*, **3**, 1 (1980).
(19) Y. Kasuya and N. Suzuki, *Arch. Int. Pharmacodyn. Ther.*, **241**, 24 (1979).

α-adrenergic blocking activities of (+) isomers. The difference between the pA_2 values of (±)-1 and (±)-2 or between (±)-3 and (±)-4 was very small, suggesting about the same degree of α-adrenergic blocking activity of the threo and erythro isomers of the corresponding compounds. It has already been reported that this series of compounds does not have substantial α_2 blocking activity.[2,3]

All of the compounds tested in the present study showed hypotensive action both in anesthetized normotensive rats after the ip administration and in unanesthetized SHR after po administration. In addition, all of the compounds showed strong α-adrenergic blocking activity in the isolated rat vas deferens. As is shown in the cases of (+)-1 and (+)-3, the hypotension produced by the present agents are likely to be largely due to α-adrenergic blockade.

Clear difference could not be found between the pharmacological activities of the threo and erythro isomers of the corresponding compounds. However, a clear difference was found between the pharmacological activities of the optical isomers. Differences were most clearly shown in the hypotensive actions of the normotensive rats and in the α-adrenergic blocking activities. In these actions, (+) isomers were always more potent than (-) isomers of the corresponding compounds. In the case of hypotensive action in SHR after oral administration, the difference was sometimes unclear. However, in this case, many factors may be involved, e.g., absorption of the compounds in the alimentary tracts, etc.; therefore, the results may not reflect the direct pharmacological activities of the compounds per se. Direct pharmacological activity is probably most clearly shown in the results of the in vitro testing, i.e., greater potency of the (+) isomers.

For α-adrenoreceptor blocking agents, only a few compounds (e.g., benzodioxanes[20] and naphazolines[21]) have been resolved, and their pharmacological activities were examined. From these reports, it can be seen that enantiomers of α-adrenoreceptor blocking agents exhibited little differences from one another in their anti adrenergic potency. This is in marked contrast to β-adrenergic agents.[22,23] Our results are interestingly dissimilar with those reported previously for α-adrenergic agents.

The pharmacological results strongly suggest that (+)-1 and (+)-3 have the same absolute configuration as do (-)-1 and (-)-3. Compounds (+)-1 and (+)-3 was speculated to have a 1*S* configuration as discussed in the chemistry section; also, (+)-2 may have a 1*S* configuration because (+)-2 was derived from (-)-1. Thus, the compounds [(+)-1, -2, -3] that were speculated to have 1*S* configuration had higher pharmacological activities than their counterpart compounds. In the case of β-adrenoreceptor blocking agents (e.g., pronethalol and nifenalol), it has been reported that the active isomers possess the same (*R*) absolute configuration as that of naturally occurring sympathomimetic catecholamines (NE, epi).[24,25] However, in the resolved α,β-adrenoreceptor blocking agents (labetalol), the active isomers for the α adrenoreceptor have a 1*S* configuration.[26] These findings are in good agreement with our results. An *S* configuration at the benzylic alcohol function may be a stereochemical requirement for arylethanolamines acting on α-adrenergic receptors.

Experimental Section

The melting points for the samples were determined with a Mitamura hot-stage apparatus and are uncorrected. IR spectra were recorded on a Shimadzu, IR-27G grating IR spectrometer. ^{1}H NMR spectra were determined on a JNM-PFT-100 or JNM-FX-100 spectrometer. Chemical shifts are reported in δ values relative to Me_4Si as a standard. ^{13}C NMR spectra were obtained at 25.1 MHz on a JNM-FX-100 spectrometer, operating in the Fourier transform mode with Me_4Si as in internal standard. TLC was carried out on silica gel plates (silica gel 60, F254, Merck). High-pressure liquid chromatographic separations of diastereomeric mixtures were made with a Waters Associates prep LC/system 500 equipped with a RI detector with a prep PAK-500/silica column (×2).

***threo*-1-[2-(3,4,5-Trimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(3-acetyl-1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (5).** A solution of 1[1] (32.6 g, 73.8 mmol), DBU, 1,5-diazabicyclo[5.4.0]undec-5-ene (11.3 g, 74.3 mmol), and Ac_2O (7.6 g, 74.3 mmol) in 200 mL of DMF was stirred at 10 °C for 5 h. The mixture was concentrated in vacuo, and the residue was diluted with water and extracted with AcOEt. The extract was washed with water and dried (Na_2SO_4), and the AcOEt was removed at reduced pressure. The residue was crystallized from Et_2O to give 27.0 g (76%) of **5**. An analytical sample was recrystallized from dioxane: mp 171–174 °C; IR (KBr) ν_{max} 1720, 1698 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 [CH(CH_3)N], 2.73 ($NCOCH_3$), 4.2 (ArCHOH). Anal. ($C_{26}H_{33}N_3O_6$) C, H, N.

***threo*-1-(3,4,5-Trimethoxyphenyl)-2-methyl-2-[4-(3-acetyl-1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidin-1-yl]ethyl *N*-(1-Phenylethyl)carbamate (6a,b).** A solution of **5** (25 g, 51.7 mmol), DBU (8.0 g, 52.6 mmol), and (*S*)-1-phenylethyl isocyanate (17.5 g, 119 mmol) in 400 mL of dioxane was stirred at room temperature for 3 h. The solution was concentrated under reduced pressure. The residue was passed through an SiO_2 column with AcOEt. The eluate gave 30.5 g (94%) of an oily mixture of **6a** and **6b**, which was subjected to preparative HPLC (AcOEt–*n*-hexane, 5:3). The fraction eluted first gave an oil, which was crystallized from *n*-hexane–2-propanol to give **6a** (10.8 g, 33%). The second fraction eluted gave a white solid, which was crystallized from AcOEt to give **6b** (10.2 g, 31%). Properties of **6a** and **6b** are presented in Table I.

***threo*-1-(3,4,5-Trimethoxyphenyl)-2-methyl-2-[4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidin-1-yl]ethyl *N*-(1-Phenylethyl)carbamate (7a,b).** A solution of **6a** (1.81 g, 2.87 mmol) and $Mg(ClO_4)_2$ (642 mg, 2.88 mmol) in 15 mL of MeOH was stirred at room temperature for 1 h. The solution was concentrated under reduced pressure and residual oil was dissolved in AcOEt, washed with water, dried (Na_2SO_4), and concentrated. Oily **7a** (1.6 g, 95%) was obtained: IR ($CHCl_3$) ν_{max} 1687 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.78 [CH(CH_3)N], 1.56 (β-CH_3), 5.59 (ArC*H*OCONH), 9.90 (NH). Anal. ($C_{33}H_{40}N_4O_6$) C, H, N. **7b** was prepared in a similar manner in 98% yield: IR ($CHCl_3$) ν_{max} 1685 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 [CH(CH_3)N], 1.54 (β-CH_3), 5.56 (ArC*H*OCONH), 9.97 (NH). Anal. ($C_{33}H_{40}N_4O_6$) C, H, N.

(+)-*threo*-1-[2-(3,4,5-Trimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)-piperidine [(+)-1]. A solution of **7a** (1.5 g, 2.55 mmol) in 20 mL of dry THF was added dropwise to a cooled suspension of $LiAlH_4$ (0.2 g, 5.27 mmol) in dry THF (20 mL). When the addition was completed, the mixture was allowed to warm to room temperature and stirred for an addition 2 h. Then it was poured onto crushed ice, and the whole was extracted four times with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated. The residue was recrystallized from AcOEt to afford 0.72 g (64%) of (+)-1: melting at 116.5 °C, resolidifying and remelting at 184–185.5 °C; $[\alpha]^{25}_D$ 54.9° (*c* 0.2, EtOH). Anal. ($C_{24}H_{31}N_3O_5$) C, H, N.

(-)-*threo*-1-[2-(3,4,5-Trimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)-piperidine [(-)-1]. A solution of **7b** (1.5 g, 2.55 mmol), triethylamine (0.3 g, 2.96 mmol), and trichlorosilyl hydride (0.38 g, 2.81 mmol) in 20 mL of CH_2Cl_2 was stirred at room temperature for 12 h. The mixture was poured into an aqueous NH_4Cl solution, and the whole was extracted with $CHCl_3$. The usual workup of

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the $CHCl_3$ extract gave crude crystals, which were recrystallized from AcOEt to afford 462 mg (41%) of (−)-1: mp, moistening around 120 °C, resolidifying around 150 °C, and remelting at 185–186.5 °C; $[\alpha]^{25}_D$ −55.0° (c 0.2, EtOH). Anal. ($C_{24}H_{31}N_3O_5$) C, H, N.

***threo*-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(3-acetyl-1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine** (8) was prepared in a similar manner as **5** from **3**[1] (10 g, 24.3 mmol). Crude 8 (9.6 g, 87%) was obtained as colorless crystals. An analytical sample was recrystallized from AcOEt: mp 193–194.5 °C; NMR ($CDCl_3$) δ 2.77 ($NCOCH_3$). Anal. ($C_{25}H_{31}N_3O_5$) C, H, N.

***threo*-1-(3,4-Dimethoxyphenyl)-2-methyl-2-[4-(3-acetyl-1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidin-1-yl]ethyl *N*-(1-Phenylethyl)carbamate (9a,b).** The method described for **6a,b** was followed, 8 (8.0 g, 17.64 mmol), (*R*)-1-phenylethyl isocyanate (6.6 g, 35.33 mmol), and DBU (2.72 g, 17.89 mmol). A mixture of **9a** and **9b** was obtained as crystals. The crystals were recrystallized from AcOEt to yield almost pure **9b** (2.0 g). The mother liquor was concentrated, and the residue was applied on preparative HPLC (AcOEt–*n*-hexane, 5:3, as eluent). The first fraction gave 3.4 g of **9a**, which was recrystallized from AcOEt to give pure **9a** (2.55 g, 24%). The second fraction gave 2.1 g of **9b**, which was combined with the sample obtained above. The combined **9b** was recrystallized from AcOEt to afford pure **9b** (3.0 g, 28%). Properties of **9a** and **9b** are presented in Table I.

(−)-*threo*-1-[2-(3,4-Dimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine [(−)-3]. A solution of **9a** (1.5 g, 2.5 mmol) in 20 mL of THF was added to a suspension of $LiAlH_4$ (300 mg, 7.9 mmol) in 20 mL of dry THF at 0 °C for 2 h. After workup, as described for the preparation of (+)-1, the residue was recrystallized from EtOH to yield 0.5 g (49%) of (−)-**3**: mp 204–205 °C; $[\alpha]^{25}_D$ −69.0° (c 0.2, EtOH). Anal. ($C_{23}H_{29}N_3O_4$) C, H, N. Similar treatment of **9b** (1.9 g, 3.2 mmol) with $LiAlH_4$ (0.36 g, 9.42 mmol) in dry THF gave 0.77 g (59%) of (+)-**3**: mp 204.5–205.5 °C (EtOH); $[\alpha]^{25}_D$ 69.5° (c 0.2, EtOH). Anal. ($C_{23}H_{29}N_3O_4$) C, H, N.

(−)-1-[2-(3,4,5-Trimethoxyphenyl)-2-oxo-1-methylethyl]-4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (10a). A mixture of (−)-1 (1.0 g, 2.26 mmol) and pyridinium dichromate (1.83 g, 4.86 mmol) in 10 mL of DMF was stirred at −10 °C for 24 h, poured onto crushed ice, and extracted with $CHCl_3$. The extract was washed with water, dried over Na_2SO_4, and concentrated. The residue was chromatographed on silica gel and the product eluted with AcOEt–$CHCl_3$. After evaporation of the solvent, the product was recrystallized from EtOH to yield **10a** (560 mg, 56%): mp 160.5–162 °C; IR (KBr) ν_{max} 1702 cm^{-1}; $[\alpha]^{25}_D$ −16.8° (c 0.25, EtOH). Anal. ($C_{24}H_{29}N_3O_5$) C, H, N.

From (+)-1, **10b** was obtained in 61.9% yield: mp 168.5–169.5 °C (EtOH); $[\alpha]^{25}_D$ 16.2° (c 0.25, EtOH). Anal. ($C_{24}H_{29}N_3O_5$) C, H, N.

(+)-*erythro*-1-[2-(3,4,5-Trimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine [(+)-2]. A suspension of **10a** (482 mg, 1.1 mmol) and 25 mg of PtO_2 in MeOH and aqueous AcOH was stirred under a stream of H_2 at room temperature for 3 h. The catalyst was filtered, and the filtrate was concentrated under reduced pressure. The residue was diluted with water, made alkaline, and extracted with $CHCl_3$. The extract was washed with water, dried (Na_2SO_4), and concentrated. The residue was recrystallized from EtOH to yield 332 mg (68%) of (+)-**2**: mp 171–174 °C; $[\alpha]^{25}_D$ 17.8° (c 0.5, $CHCl_3$). Anal. ($C_{24}H_{31}N_3O_5$) C, H, N. In a similar manner, (−)-**2** was obtained in 50% yield from **10b**: mp 170–173 °C (EtOH); $[\alpha]^{25}_D$ −18.0° (c 0.5, $CHCl_3$). Anal. ($C_{24}H_{31}N_3O_5$) C, H, N.

Attempted Resolution of 2 Involving the Carbamate Intermediate. The similar procedures as described for **5** using **2**[1] (3.26 g, 7.38 mmol), Ac_2O (763 mg, 7.43 mmol), and DBU (1.13 g, 7.43 mmol) in DMF gave 2.8 g (79%) of *erythro*-1-[2-(3,4,5-trimethoxyphenyl)-2-hydroxy-1-methylethyl]-4-(3-acetyl-2-oxo-1,3-dihydro-2*H*-benzimidazol-1-yl)piperidine (*N*-Ac-**2**). The product was recrystallized from AcOEt–*n*-hexane: mp 148–150 °C; IR (KBr) ν_{max} 1730, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76 ($NCOCH_3$), 4.83 (ArC*H*OH). Anal. ($C_{26}H_{33}N_3O_6$) C, H, N.

Diastereomers were obtained essentially by the same procedure as described for **6a,b**. Treatment of the foregoing *N*-Ac-**2** (100 mg, 0.21 mmol) with (*R*)-1-phenylethyl isocyanate (70 mg, 0.48 mmol) and DBU (40 mg, 0.26 mmol) in dioxane gave 81 mg (62%) of *erythro*-1-(3,4,5-trimethoxyphenyl)-2-methyl-2-[4-(3-acetyl-1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidin-1-yl]ethyl *N*-(1-phenylethyl)carbamate: mp 112–113 °C; IR (KBr) ν_{max} 1725, 1710, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.09 [$CH(CH_3)N$], 1.39 (β-CH_3), 2.74 ($NCOCH_3$), 5.6–5.9 (ArC*H*OCONH). Anal. ($C_{35}H_{42}N_4O_7$) C, H, N.

The reaction with (*S*)-1-phenylethyl isocyanate instead of (*R*)-isocyanate gave an oily diastereomer in 86% yield after chromatographic purification on silica gel: IR ($CHCl_3$) ν_{max} 1725, 1700, 1690 cm^{-1}; NMR ($CDCl_3$) δ 1.1 [$CH(CH_3)N$], 1.4 (β-CH_3), 2.8 ($NCOCH_3$), 4.8 (ArC*H*OCONH). Neither diastereomer could be separated by preparative HPLC with various solvent systems.

(+)-*threo*-1-[2-Acetoxy-2-(3,4,5-trimethoxyphenyl)-1-methylethyl]-4-(3-acetyl-1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine [(+)-*N*,*O*-Ac$_2$-1]. Treatment of (+)-1 (140 mg, 0.32 mmol) with 4-(dimethylamino)pyridine (78 mg, 0.64 mmol) and Ac_2O (71 mg, 0.69 mmol) in DMF gave (+)-*O*,*N*-Ac$_2$-1 in 79% yield: mp 204–206 °C; $[\alpha]^{25}_D$ 57.5° (c 0.2, $CHCl_3$). (−)-*O*,*N*-Ac$_2$-1, (+)-*O*,*N*-Ac$_2$-**3**, and (−)-*O*,*N*-Ac$_2$-**3** were prepared in a similar manner starting from (−)-1, (+)-**3**, and (−)-**3**, respectively. (−)-*O*,*N*-Ac$_2$-1: mp 199–202 °C; $[\alpha]^{25}_D$ −58.5° (c 0.2, $CHCl_3$). (+)-Ac$_2$-**3**: mp 150.5–151 °C; $[\alpha]^{25}_D$ 73.0° (c 0.2, $CHCl_3$). (−)-**3**: mp 152–152.5 °C, $[\alpha]^{25}_D$ −73.0° (c 0.2, $CHCl_3$). NMR spectra of these *O*,*N*-diacetyl derivatives, as well as the racemic *O*,*N*-diacetyl ones,[1] were obtained in the presence of 0.18 equiv of $Eu(hfc)_3$ in $CDCl_3$.

Pharmacology. Determination of α-Adrenergic Blocking Activity with Isolated Vas Deferens. Vasa deferentia were quickly excised from male Wister strain rats after killing by a blow on the head, and they were suspended in an organ bath containing a modified Krebs–Henseleit solution of the following composition (mM): NaCl, 119.0; KCl, 6.0; $CaCl_2$, 2.5; $MgSO_4$, 1.2; $NaHCO_3$, 25; glucose, 5.6.

Two vasa deferentia were obtained from each animal; one was used for examining the contraction by norepinephrine (NE) and the other for examining the effects of the test compounds on the NE-induced contraction. After confirming that both vasa deferentia contracted equally when exposed to a single concentration of NE (10^{-5} M), we washed the preparations repeatedly. NE was added cumulatively to the control vas deferens, and the control dose–response curve was obtained. With the other vas deferens, the dose–response curve for NE was obtained in the presence of the test compounds (given 5 min prior to the start of the application of the first dose of NE). Several dose–response curves were averaged and pA_2 values were calculated on the basis of the shift of the dose–response curves produced by the test compounds.

Registry No. (±)-1, 83259-49-8; (+)-1, 83259-47-6; (−)-1, 83259-48-7; (+)-*O*,*N*-Ac$_2$-1, 83708-96-7; (−)-*O*,*N*-Ac$_2$-1, 83708-97-8; (±)-**2**, 83665-44-5; (+)-**2**, 83708-93-4; (−)-**2**, 83708-94-5; (±)-*N*-Ac-**2**, 83665-45-6; (±)-**3**, 83665-42-3; (+)-**3**, 83273-01-2; (−)-**3**, 83708-92-3; (+)-*O*,*N*-Ac$_2$-**3**, 83708-98-9; (−)-*O*,*N*-Ac$_2$-**3**, 83708-99-0; (±)-**4**, 83665-46-7; (±)-**5**, 83259-44-3; **6a**, 83708-87-6; **6b**, 83708-88-7; **7a**, 83708-89-8; **7b**, 83708-90-1; (±)-**8**, 83665-41-2; **9a**, 83665-43-4; **9b**, 83708-91-2; **10a**, 83681-23-6; **10b**, 83681-24-7; (*S*)-1-phenylethyl isocyanate, 14649-03-7; (*R*)-1-phenylethyl isocyanate, 33375-06-3; 1-(3,4,5-trimethoxyphenyl)-2-methyl-2-[4-(3-acetyl-1,3-dihydro-2-oxo-2*H*-benzimidazol-1-yl)piperidin-1-yl]ethyl *N*-(1-phenylethyl)carbamate, 83708-95-6.