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New Antihypertensive Agents. I. Synthesis and Antihypertensive Activity of Some 4-Piperidylbenzimidazolinone Derivatives

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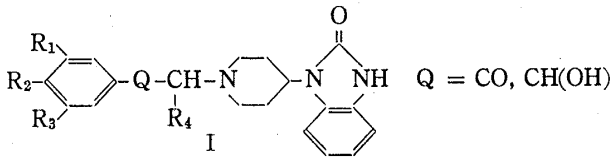
A series of 4-piperidylbenzimidazolinones, of formula I, has been synthesized. Selective syntheses of *erythro* and *threo* isomers of α-alkyl phenylethanolamines were investigated.

Most members of the series have been shown to have antihypertensive effects in various animal models. Compounds **27** and **31** (*threo* isomers) showed the strongest hypotensive activities in the present screening series.

Keywords——antihypertensive activity; 4-piperidylbenzimidazolinones; inversion; reduction; *threo*; *erythro*; structure–activity relationship

Compounds incorporating the piperidylbenzimidazolinone group show interesting biological activity. Pimozide (1{1-[4,4-bis(*p*-fluorophenyl)butyl]-4-piperidyl}-2-benzimidazolinone) and benperidol 1-{1-[3-(*p*-fluorobenzoyl)propyl]-4-piperidyl}-2-benzimidazolinone) are well-known neuroleptics, for example.

R-28935, the *erythro* form of 1-{1-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]-4-piperidyl}-2-benzimidazolinone has been reported to exhibit pronounced central hypotensive activity in various animal species.[2)] Its detailed mechanism of action remains unclear despite numerous attempts to elucidate it.[3)] However, the suggestion has been made that central α-blockade is responsible for the hypotensive action.[4)] The interesting pharmacological properties of R-28935 prompted us to investigate variants which might possess hypotensive activity. In this paper the synthesis and antihypertensive activity of piperidylbenzimidazolinone derivatives, of formula I, are described.



I

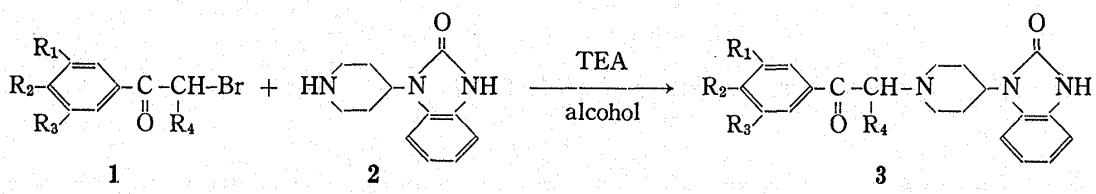
Little work has been reported on compound I having a two-carbon unit between the phenyl ring and the nitrogen atom of the piperidine ring.[5)]

Chemistry

Most compounds (**3**) listed in Table I were prepared by the reaction of a bromoketone derivative (**1**) with 1-(4-piperidyl)-1,3-dihydro-2*H*-benzimidazol-2-one (**2**) in the presence of triethylamine (TEA) in alcohol (Chart 1).

Most of the starting bromo ketones are known compounds, and new ones were generally prepared by bromination of the corresponding ketones with bromine or 2-pyrrolidone hydrotribromide.[6)]

Compounds **5** and **7** were synthesized by the dealkylation of **4** and **6** with BBr_3,[7)] respectively.



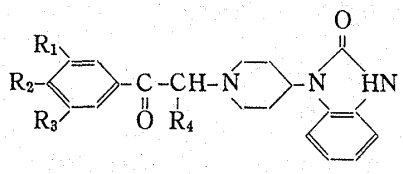
1 2 3

Chart 1

Compound **8** was obtained by selective hydrogenolysis of **16** using Pd on carbon as a catalyst.

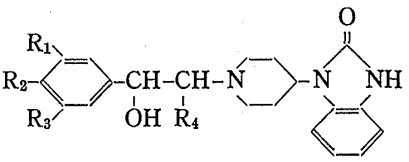
The compounds summarized in Table II were generally obtained by the reduction of **3** with complex metal hydride reducing agents. For phenylethanolamines carrying an alkyl group adjacent to the amino group, two conformations (*i.e.*, *threo* and *erythro*) exist. When **6**, **12**, **15**, **16** and **17** were reduced with a complex metal hydride such as sodium borohydride ($NaBH_4$) or lithium aluminium hydride ($LiAlH_4$), the products exhibited one spot on thin layer chromatography (TLC) with various kinds of developing solvents. In proton nuclear magnetic resonance (^{1}H-NMR) spectra, these samples showed a spin–spin coupling constant appropriate for the *threo* isomer (*e.g.*, J=9.8 Hz; δ=4.24 ppm for **31**). However, conflicting observations have been reported concerning the configuration of the products obtained by the complex metal hydride reduction of α-alkyl *tert*-amino ketones. Dijk *et al.*[8] and Mardle *et al.*[9] reported that a *threo* form predominated on $LiAlH_4$ reduction of phenethyl ketones with tertiary amino groups carrying bulky substituents. It has also been reported that the *erythro* form was obtained as a major product in the course of $NaBH_4$ reduction of piperidine alkanone hydrochloride.[10] On the other hand, an effect of dilution of the substrate on the stereoselectivity has been observed on the course of a study on the reduction of some α-amino ketones by $NaBH_4$ reduction.[11] For the determination of the configurations of the reduction products (**17**, **26**, **27**, **30**, and **31**) it is necessary to compare the NMR spectra with those of the compounds of opposite configuration. Thus, we investigated the inversion of the asym-

TABLE I.



Compd	R_1	R_2	R_3	R_4	Form	Crystn. solvent	mp [°C]	Formula
4			H	H	Base	MeOH	194—196	$C_{21}H_{21}N_3O_4$
5	OH	OH	H	H	HBr	EtOH	260—263	$C_{20}H_{21}N_3O_4\cdot HBr$
6			H	CH_3	Base	EtOH	150—160	$C_{22}H_{23}N_3O_4$
7	OH	OH	H	CH_3	HBr	H_2O	193—196	$C_{21}H_{23}N_3O_4\cdot HBr\cdot 0.5H_2O$
8	OH	H	H	CH_3	HCl	EtOH	163—166	$C_{21}H_{23}N_3O_3\cdot HCl$
9	CH_3O	CH_3O	H	H	HCl	EtOH	178—179	$C_{22}H_{25}N_3O_4\cdot HCl$
10			H	H	HCl	MeOH–AcOEt	177—179	$C_{24}H_{23}N_3O_2\cdot HCl\cdot H_2O$
11	H	H	H	H	Base	EtOH–AcOEt	175—177	$C_{20}H_{21}N_3O_2$
12	CH_3O	CH_3O	H	CH_3	Base	EtOH	178—180	$C_{23}H_{27}N_3O_4$
13	BzlO	BzlO	H	H	Base	EtOH–AcOEt	118—120.5	$C_{34}H_{33}N_3O_4$
14	CH_3O	CH_3O	CH_3O	H	Base	AcOEt	145—147	$C_{23}H_{27}N_3O_5$
15	BzlO	BzlO	H	CH_3	Base	*n*-Hexane	87—90	$C_{35}H_{35}N_3O_4\cdot 0.5H_2O$
16	BzlO	H	H	CH_3	Base	AcOEt	138—140	$C_{28}H_{29}N_3O_3$
17	CH_3O	CH_3O	CH_3O	CH_3	Base	EtOH	167—170	$C_{24}H_{29}N_3O_5$

TABLE II.



Compd	R_1	R_2	R_3	R_4	Form	Crystn. solvent	mp [°C]	Formula
18			H	H	Base	MeOH	249—251	$C_{21}H_{23}N_3O_4$
19	OH	OH	H	H	HCl	EtOH	181—183	$C_{20}H_{23}N_3O_4 \cdot HCl$
20			H	CH_3	Base	EtOH	241—245	$C_{22}H_{25}N_3O_4$
21	OH	OH	H	CH_3	HCl	*n*-BuOH	187—189	$C_{21}H_{25}N_3O_4 \cdot HCl \cdot 0.5H_2O$
22	OH	H	H	CH_3	HCl	*n*-BuOH	182—185	$C_{21}H_{25}N_3O_3 \cdot HCl$
23	CH_3O	CH_3O	H	H	Base	MeOH	220—227.5	$C_{22}H_{27}N_3O_4$
24			H	H	Base	EtOH	222—223.5	$C_{24}H_{25}N_3O_2$
25	H	H	H	H	Base	EtOH	205—206	$C_{20}H_{23}N_3O_2$
26	BzlO	BzlO	H	CH_3	Base	EtOH	146—148.8	$C_{35}H_{37}N_3O_4$
27	CH_3O	CH_3O	H	CH_3	Base	EtOH	210—211	$C_{23}H_{29}N_3O_4$
28	BzlO	BzlO	H	H	HCl	EtOH	138—140	$C_{34}H_{35}N_3O_4 \cdot HCl$
29	CH_3O	CH_3O	CH_3O	H	Base	EtOH	207—208.5	$C_{23}H_{29}N_3O_5$
30	BzlO	H	H	CH_3	Base	EtOH	162—165	$C_{28}H_{31}N_3O_3$
31	CH_3O	CH_3O	CH_3O	CH_3	Base	EtOH	215—216	$C_{24}H_{31}N_3O_5$

metric center carrying the hydroxyl group. As a representative, **27** was chosen and the inversion of **27** was examined in detail.

An initial attempt to achieve the inversion of **27** in the manner reported by Usoković *et al.*[12] (tosylate/Et_3N^+ OAc^-) was unsuccessful because of low reactivity of the hydroxyl group or the presumed lability of the tosylate or mesylate. As an alternative method, the use of triphenylphosphine (Ph_3P) and diethyl azodicarboxylate (DAD)[13–18] was investigated, as shown in Chart 2.

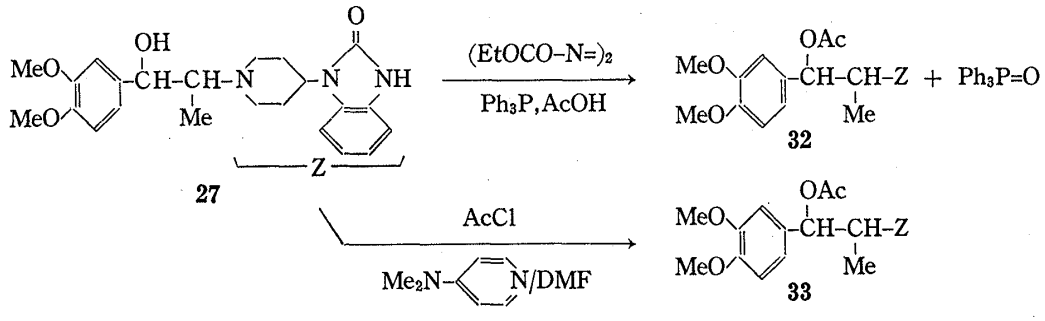


Chart 2

The reaction of **27** with Ph_3P, diethyl azodicarboxylate and acetic acid (AcOH) in terahydrofuran (THF) at room temperature afforded an acetate (**32**) in 63.3% yield after chromatographic separation of triphenylphosphine oxide. However, the resulting **32** was identical with the acetate **33** which was directly prepared by the acetylation of **27** with acetyl chloride and 4-dimethylaminopyridine in dimethylformamide (DMF). It may be concluded that the present reaction proceeded with complete retention of the configuration. To our knowlege, only one report[19] describing a similar result has appeared.

Next, the reaction of **27** with 3-ethyl-2-fluorobenzothiazolium fluoroborate and AcOH in CH_2Cl_2 was attempted according to the inversion sequence reported by Mukaiyama *et al.*[20]

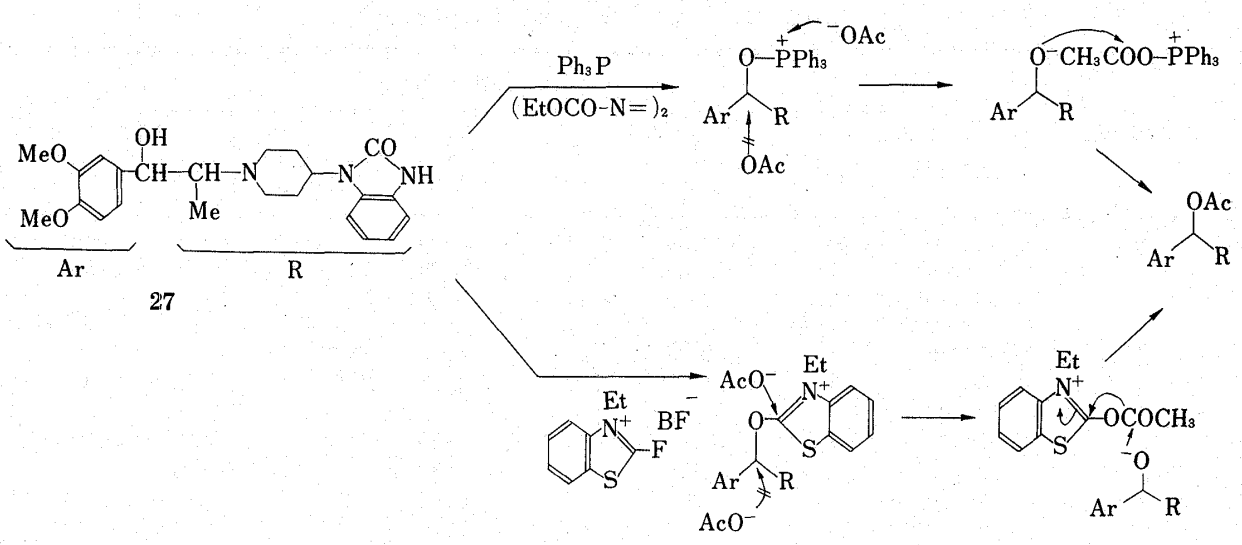


Chart 3

However, almost the same result as in the Ph_3P–DAD method was obtained by this procedure. These results may be rationalized as follows (Chart 3).

Because of its steric crowding, the intermediate alkoxyonium salts would be attacked by carboxylate (AcO^-) at the phosphonium or C-2 position of the benzothiazole nucleus rather than at the benzylic carbon of the onium salt of **27**.

We also attempted a stepwise method involving the 2-piperidone intermediate (**34**), as shown in Chart 4. Oxidation of **27** with $Hg(OAc)_2$-EDTA[21–23] in aq. AcOH afforded 2-piperidones (**34a** and **34b** in Fig. 1), which were separated by preparative high-pressure LC (prep-HPLC). From carbon nuclear magnetic resonance (^{13}C-NMR) spectral observations, the low *Rf* piperidone (**34b**) was considered to be a mixture. Successive treatment of **34b** with Ac_2O/4-dimethylaminopyridine provided three diacetyl derivatives (**35a**, **35b**, **35d**), which showed three very close spots on TLC (Fig. 1). On the other hand, the

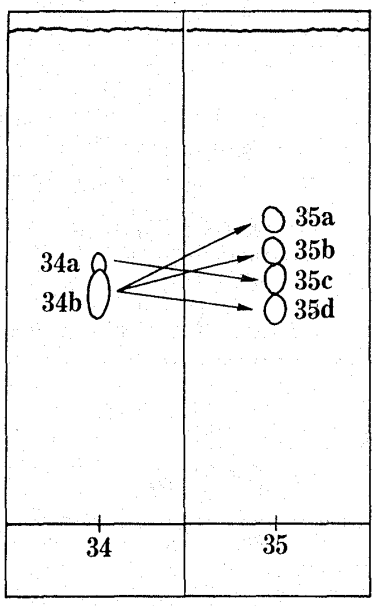


Fig. 1. TLC Patterns of **34** and **35**

Plate, Merck SiO_2 F^{254}; developing solvent, $CHCl_3$–MeOH 10:1 for **34**, AcOEt for **35**.

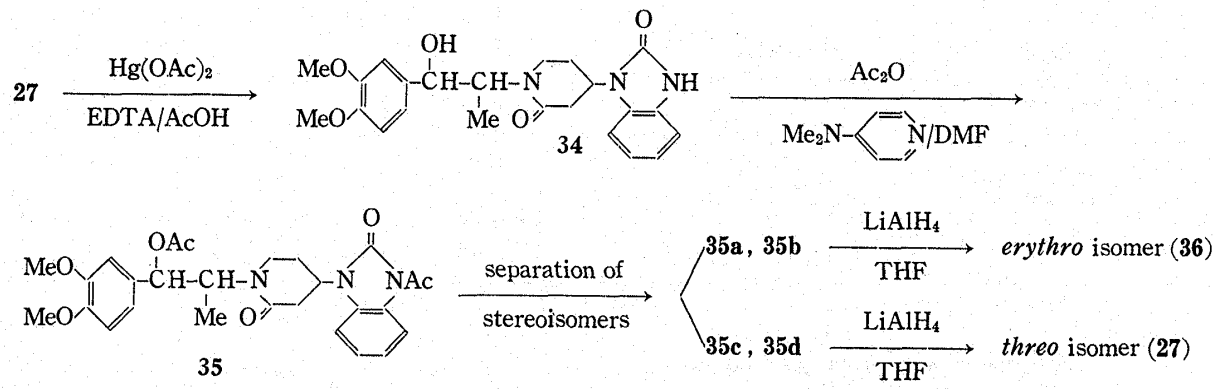


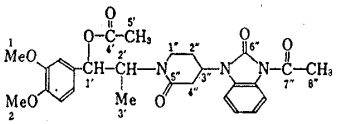
Chart 4

Table III. NMR[a] Spectral Data for **35**[b]

Position	Compounds. Nuclear							
	35a		**35b**		**35c**		**35d**	
	CMR[c]	PMR[d]	CMR	PMR	CMR	PMR	CMR	PMR
1, 2	55.90	3.90	56.04	3.88	56.09	3.89	56.09	3.89
	56.04	3.91	55.85	3.92	55.89	3.93	55.90	3.92
1′	77.19	5.89[e] (J=8.54)	77.29	5.89 (J=8.55)	75.29	5.84 (J=9.77)	75.77	5.78 (J=9.77)
2′	51.80	5.11	51.75	5.14	51.70	5.38	51.56	5.42
3′	13.69	1.33	14.03	1.36	14.18	1.01	14.33	0.99
4′	170.02	—	170.02	—	170.17	—	170.21	—
5′	21.25	2.09	21.20	2.09	21.20	2.13	21.30	2.10
1″	34.79		34.55		34.89		35.04	
2″	26.80		26.66		26.66		26.90	
3″	47.22	4.09—4.4	47.73	4.42—4.77	47.41	4.44—4.9	47.51	4.46 5.0
4″	40.74		41.27		40.40		39.42	
5″	167.49	—	167.38	—	167.92	—	167.92	—
6″	151.60	—	151.55	—	151.55	—	151.74	—
7″	170.36	—	170.31	—	170.36	—	170.36	—
8″	25.68	2.71	25.68	2.71	25.68	2.75	25.73	2.74

a) Measured in $CDCl_3$. Chemical shifts are reported in values relative to Me_4Si.

b) Numbering of **35**:

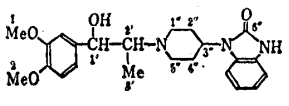


c) Measured at 25.1 MHz.
d) Measured at 100 MHz.
e) Expressed in Hz.

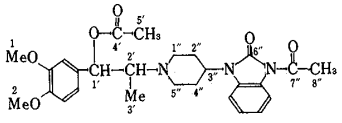
Table IV. NMR Spectral Data for **27**, **36**[a] and Their *O*,*N*-Diacetyl Derivatives[b]

Position	Compounds							
	27		**36**		*O*,*N*-Diacetyl **27**		*O*,*N*-Diacetyl **36**	
	CMR	PMR	CMR	PMR	CMR	PMR	CMR	PMR
1	55.89	3.90 3.87	55.89	3.90 3.88	56.00	3.81 3.88	55.89 55.99	3.91
1′	74.21		72.75	4.903 (J=4.15 Hz)	76.61	5.73 (J=9.52 Hz)	76.36	5.79 (J=6.83 Hz)
2′	66.57		64.66		63.50		63.69	
3′	8.09	0.812 (J=6..35 Hz)	10.14	0.963 (J=6.84 Hz)	10.58	0.785 (J=6.84 Hz)	10.72	1.13 (J=6.60 Hz)
4′	—		—		169.94		169.97	
5′	—		—		21.49	2.18	21.34	2.11
1″	52.63		52.00		51.17		50.29	
2″	29.63		29.48		29.10		28.99	
3″	50.87		50.78		51.76		51.36	
4″	30.67		29.48		29.68		29.34	
5″	43.66		48.58		46.54		47.41	
6″	155.30		155.30		151.81		151.74	
7″	—		—		170.58		170.50	
8″	—		—		25.73	2.76	25.73	2.74

a) Numbering of **27** and **36**:



b) Numbering of *O*,*N*-acetyl derivatives:



same successive treatment of the high *Rf* piperidone (**34a**) gave a diacetyl derivative (**35C**) as a sole product. **35a**, **35b** and **35d** were separated by preparative TLC. The ratio of (**35a**+**35b**) to (**35c**+**35d**) was approximately 1: 1.17.

Smaller coupling constants of the benzylic proton signals of **35a**, **b** (*cf.* J=8.5 Hz for **35a** and J=8.6 Hz for **35b**) in comparison with those of **35c**, **d** (*cf.* J=9.8 Hz for **35c** and **35d**) were observed in the ^{1}H-NMR spectra (Table III). The α-methyl signals of **35a**, **b** appeared at lower field than those of **35c**, **d**. In the ^{13}C-NMR spectra, the signals of **35a**, **b** due to C-1′ (shown in Table III) were found at lower field than those of **35c**, **d**. The NMR analyses mentioned above indicated that the configuration of **35a**, **b** might be *erythro*, while that of **35c**, **d** might be *threo*. These assignments were further confirmed by the conversion of **35** to the starting amino alcohol. Treatment of **35c** or **35d** with $LiAlH_4$ in THF gave a product which was identical with the starting **27**. On the other hand, similar treatment of **35a** or **35b** gave a product (**36**) which was not identical with **27** in terms or *Rf* on TLC [*cf.* *Rf* ($CHCl_3$–MeOH–AcOH, 9: 2: 0.1): 0.33 for **36** and 0.44 for **27**] and NMR spectra. The structure of **36** was also determined by comparison of the ^{1}H-NMR and ^{13}C-NMR spectra of **27** and its acetate with those of **36** and its acetate.[24]

As shown in Table IV, the benzylic proton and α-methyl proton signals of **36** appeared at lower field than those of **27**. The *N*,*O*-diacetyl derivative of **27** had a larger coupling constant for the benzylic proton than the *N*,*O*-diacetyl derivative of **36**. Thus, we assigned the structure of **36** as *erythro* and that of **27** as *threo*. The ^{1}H-NMR observations mentioned here were in good agreement with the data reported previously.[10,25]

The inversion mechanism of the reaction mentioned above presumably involves oxazolinium salt formation, followed by an attack of the oxazolinium salt on the C-2 position of piperidine (retention) or on the benzylic carbon from the back side (inversion), as shown in Fig. 2.

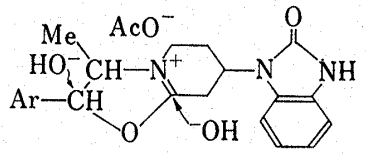
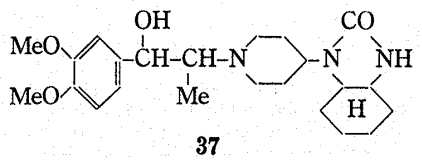


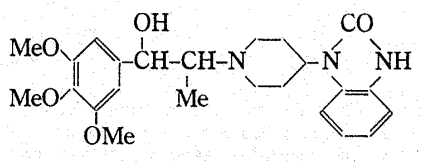
Fig. 2

Although the *erythro* isomer was obtained by this procedure, this process was not practical because the yield is less than 50% and the isolation of the products was troublesome. Thus, another method, catalytic hydrogenation of **12**, was studied for the unambiguous and practical synthesis of the *erythro* isomer. When Pd on carbon or Raney nickel was used as the catalyst, hydrogenation did not proceed under ordinary conditions. Smooth reduction was observed by the use of PtO_2 as the catalyst. It was found that the hydrogenation products depended on the H_2 pressure and on the pH of the reaction mixture.

Hydrogenation in a neutral medium (Parr apparatus, under 50—60 p.s.i. pressure, in MeOH) resulted in a formation of a 4: 6 mixture of *erythro* and *threo* isomers. In the presence of aq. HCl, the *erythro* form was obtained exclusively, but simultaneous reduction of the aromatic nucleus of benzimidazole occurred even at atmospheric pressure to give the octahydrogenzimidazole derivative (**37**). The reduction was considered to proceed through activation of the benzimidazole nucleus by protonation at N or O of benzimidazolinone. Hydrogenation of **12** in the presence of a weak acid such as AcOH under atmospheric pressure afforded the desired **36** (*erythro* isomer) in 80% yield together with a small amount of **27** (*threo* isomer) which was easily removed by simple recrystallization. Hydrogenation under pressure (40 p.s.i) in the presence of AcOH gave a substantial amount of **37**.



37



38 (*erythro* isomer)

Similar hydrogenation (at atmospheric pressure of hydrogen, in the presence of AcOH) afforded **38** from **17** in 77.1% yield.

In this manner we succeeded in the practical synthesis of *erythro* isomers in high yields.

Biological Results

The compounds herein were examined for hypotensive activities. In the first step of the screening, the hypotensive activities were measured after oral administration of the compounds to unanesthetized animals. For this purpose, spontaneously hypertensive rats (SHR, male Okamoto strain rats whose systolic presures was higher than 180 mmHg at the 18 th week), DOCA salt hypertensive rats (DHR; the left kidney was removed from 10-week-old male Wistar strain rats under ether anesthesia, and thereafter they were subcutaneously injected with 15 mg/kg of deoxycorticosterone acetate once a week; rats whose systolic pressures were higher than 180 mmHg were selected for study 5 weeks after the surgical operation), and normotensive rats (NTR, male Wistar strain rats with body weight of 280—370 g) were utilized. Rats (male) were anesthetized and a cannula was fixed in the carotid artery of each

Table V. Hypotensive Activities of Benzimidazolinone Compounds in Unanesthetized Rats

Compound No.	Animals		
	SHR	DHR	NTR
4	−47(50)	−34(50)	−12(50)
5	−10(50)		
6	−23(50)	−60(50)	−19(50)
7	−18(30)	−10(50)	
8		0(50)	0(50)
9	−71(30)	−75(13)	
	−50(30)		
10			
11			−6(50)
12	−41(50)		
13	−28(50)		0(50)
14	−38(30)		
15			
16			
17	−20(30)		
	−33(30)		
18	−85(50)	−65(50)	−13(50)
	−52(30)		
19	−35(30)	−41(30)	
20		−60(50)	
21	−60(50)	−42(50)	
	−26(30)		
22		0(50)	−13(50)
23	−37(30)	−32(50)	−26(50)
	−30(30)		
24	−24		−11(50)
25	−40(30)		−14(50)
26	−17(30)	−33(50)	0(50)
27	−69(30)		
28	−19(50)		0(50)
29	−53(30)		
30			
31	−50(30)		
	−79(30)		
	−73(30)		

SHR, DHR, and NTR indicate spontaneously hypertensive rats, DOCA salt hypertensive rats, and normotensive rats, respectively. Each number and number in parentheses represent the maximum decrease in blood pressure (mmHg) and the dose (mg/kg) given orally, respectively.

rat. After the surgical operation (3—4 d), blood was led to the pressure transducer through the cannula and recorded on an ink-writing oscillograph. Animals were freely mobile during the blood pressure measurements. The results from these experiments are summarized in Table V. As shown in Table V, compounds **9**, **18**, **27**, and **31** showed strong hypotensive activities.

In the next step, these four compounds were tested for hypotensive activities in anesthetized normotensive rats. Male Wistar strain rats weighing 250 to 320 g were anesthetized urethane 600 mg/kg *i.p.* and alpha-chloralose, 60 mg/kg *i.p.* Arterial blood pressure was measured from the left common carotid artery by means of a pressure transducer. Heart rates were also measured with a cardiotachometer triggered by blood pressure pulses. Both recordings were made on an ink-writing oscillograph for 4 h. The compounds were administered intraperitoneally. The results are summarized in Table VI. All of the compounds tested which showed strong hypotensive activities in unanesthetized animals exhibited marked hypotensive activities also in the anesthetized normotensive animals. Among these four compounds, the duration of the hypotensive action of compound **18** was relatively short. However, the effects of the remaining three compounds were comsiderably prolonged. Blood pressure remained at quite low levels even 4 h after the administration of these three compounds.

TABLE VI. Effects of Benzimidazolinone Derivatives on the mean Arterial Blood pressure and Heart Rate of Anesthetized Rats

Compd. No.	No. of animals	Initial level (mmHg)	Changes in blood pressure (mmHg)					
			10[a]	30[a]	60[a]	120[a]	180[a]	240[a]
9	5	118±6	−23±5	−44±7	−50±5	−50±3	−54±4	−51±6
18	4	113±6	−58±6	−40±6	−42±6	−36±7	−26±6	−18±6
27	4	117±4	−43±3	−35±3	−36±5	−49±5	−42±10	−42±5
31	4	116±3	−37±3	−37±4	−41±7	−31±3	−32±5	−31±10

Compd. No.	No. of animals	Initial level (beats/min)	Changes in heart rate (beats/min)					
			10[a]	30[a]	60[a]	120[a]	180[a]	240[a]
9	5	392±4	+3±3	−9±3	−17±5	−53±4	−50±7	−46±8
18	4	433±9	−78±17	−71±16	−74±13	−46±18	−28±19	−15±16
27	4	410±9	−27±16	−4±2	−6±5	−39±11	−51±10	−50±21
31	4	393±12	−5±3	−23±11	−31±14	−38±16	−50±12	−43±7

a) Time (min) after drug administration.
Each compound was administered intraperitoneally at the dose of 30 mg/kg.

In general, heart rate was decreased by these compounds. As in the case of blood pressure, the decrease in heart rate, though marked in the initial stages, lasted only for a relatively short period of time, and it was as small as 15 beats/min at the 3rd h. In contrast, the other three compounds produced long-lasting decreases in heart rate.

Compounds **27** and **31** which showed the strongest hypotensive activities in the present screening series were *threo*-isomers. Therefore, the *erythro*-isomers (**36** and **38**) were synthesized for comparison, and their hypotensive activities were examined preliminarily using SHR. The *erythro*-isomers (**36** and **38**) showed weaker hypotensive activities than the corresponding *threo*-isomers. Most compounds tested in the present study were found to have relatively strong alpha-adrenergic blocking activities, and the *threo*-isomers had higher pA values than the corresponding *erythro*-isomers. These studies on the stereoisomers and their alpha-adrenergic blocking activities will be reported elsewhere in more detail.

In conclusion, benzimidazolinone derivatives tested in the present study were found to decrease the blood pressure. Among the compounds, **9**, **18**, **27**, and **31** had the highest hypotensive activities. These four compounds were examined in anesthetized normotensive rats, and it was found that these agents also produced a large decrease in blood pressure after intraperitoneal injection, and that compounds **9**, **27** and **31** produced considerably long-lasting hypotensive effects. The decrease in blood pressure was generally accompanied by a decrease in heart rate. It is dificult to discuss the structure–activity relationship on the basis of the present results from only a limited number of experiments. However, it appears that two or three methoxy groups or a methylenedioxy group on the phenyl ring may be important for strong hypotensive activity. More detailed studies on compounds **27** and **31** will be reported elsewhere.

Experimental

The melting points for the samples were determined with a Mitamura hot-stage apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 215 grating infrared spectrometer or a Shimadzu IR-27G grating infrared spectrometer. ^{1}H-NMR spectra were determined on a Varian T-60, JNM-PET-100, or JNM-FX-100 spectrometer. Chemical shifts were 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 an internal standard. The numbering of carbons for samples in the experimental section is the same as in Table IV. Thin layer chromatography was carried out on silica gel plates (Silica gel 60, F_{254}, Merck).

Preparation of 1-[2-Oxo-2-(3,4-methylenedioxyphenyl)ethyl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)-piperidine (4)——A solution of 3,4-methylenedioxy-α-bromoacetophenone[26] (3.75 g, 15.43 mmol), **2** (3.35 g, 15.42 mmol) and triethylamine (1.6 g, 15.8 mmol) in 50 ml of MeOH was stirred at room temperature for 6 h and concentrated. The residue was mixed with H_2O and stirred. The resulting precipitate was collected by filtration, washed with EtOH and dried. Recrystallization of the crude crystals from MeOH yielded 3.7 g (63.2%) of **4**. IR ν_{max}^{KBr} cm^{-1}: 1700—1680. ^{1}H-NMR (DMSO-d_6) δ: 1.4—4.6 (piperidine ring H), 3.82 (COC$\underline{H}_2$N), 6.19 (O–C$\underline{H}_2$–O), 6.8—7.8 (arom.), 10.86 (N$\underline{H}$). *Anal.* Calcd for $C_{21}H_{21}N_3O_4$: C, 66.48; H, 5.58; N, 11.08. Found: C, 66.60; H, 5.52; N, 11.01.

Preparation of 1-[2-Hydroxy-2-(3,4-methylenedioxyphenylethyl)]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine (18)——$NaBH_4$ (0.6 g, 15.9 mmol) was added portionwise over 30 min to a suspension of **4** (2.0 g, 5.27 mmol) in 240 ml of MeOH at room temperature. The solution was concentrated to dryness and the residue was treated with H_2O. The precipitate was collected by filtration and dried. Recrystallization of the crude crystals from MeOH gave 1.8 g (89.6%) of pure **18**. IR ν_{max}^{KBr} cm^{-1}: 1700. ^{1}H-NMR (DMSO-d_6) δ: 6.0 (O–C$\underline{H}_2$–O). 10.8 (N$\underline{H}$). *Anal.* Calcd for $C_{21}H_{23}N_3O_4$: C, 66.12; H, 6.08; N, 11.02. Found: C, 66.06; H, 6.04; N, 10.98.

Preparation of 1-[2-Oxo-2-(3,4-dimethoxyphenyl)-1-methylethyl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine (12)——A solution of Br_2 (2.6 g, 16.3 mmol) in 20 ml of $CHCl_3$ was added to a solution of 3,4-methylenedioxypropiophenone (2.9 g, 16.3 mmol) in 50 ml of $CHCl_3$ at 10°C. After additional stirring for 1 h at room temperature, the solution was concentrated. The residue was recrystallized from petroleum ether to obtain 2.3 g (54.9%) of α-bromo-3,4-dimethoxypropiophenone. mp 52—53°C. IR ν_{max}^{KBr} cm^{-1}: 1675. *Anal.* Calcd for $C_{10}H_9BrO_3$: C, 46.72; H, 3.53. Found: C, 46.77; H, 3.51. A solution of α-bromo-3,4-methylenedioxypropiophenone (2.53 g, 9.26 mmol), **2** (2 g, 9.2 mmol) and triethylamine (0.95 g, 9.39 mmol) in 30 ml of MeOH was stirred for 24 h at room temperature. Work-up as described for **4** gave 2.7 g (71.7%) of **12**. IR ν_{max}^{KBr} cm^{-1}: 1702, 1678. ^{1}H-NMR ($CDCl_3$) δ: 1.33 (C$\underline{H}_3$–CH–N<), 3.97 (C$\underline{H}_3$O), 10.27 (N$\underline{H}$). *Anal.* Calcd for $C_{23}H_{27}N_3O_4$: C, 67.46; H, 6.65; N, 10.26. Found: C, 67.22; H, 6.71; N, 10.23.

Preparation of threo-1-[2-Hydroxy-2-(3,4-dimethoxyphenyl)-1-methylethyl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine (27)——A suspension of **12** (1.4 g, 3.42 mmol) in 50 ml of MeOH was treated with 0.23 g (6.08 mmol) of $NaBH_4$. Work-up as described for the preparation of **18** gave 1.3 g of crude crystals, which were recrystallized from MeOH to obtain 1.2 g (85.3%) of **27**. IR ν_{max}^{KBr} cm^{-1}: 1700. *Anal.* Calcd for $C_{23}H_{29}N_3O_4$: C, 67.13; H, 7.10; N, 10.21. Found: C, 67.00; H, 7.15; N, 10.22.

Preparation of 1-[2-Oxo-2-(3,4,5-trimethoxyphenyl)-1-methylethyl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine (17)——Similar reaction of α-bromo-3,4,5-trimethoxypropiophenone[27] (6.06 g, 20 mmol) with **2** (4.34 g, 20 mmol) in the presence of triethylamine (2.1 g, 20 mmol) in 50 ml of MeOH gave 7.6 g of crude crystals. Recrystallization from EtOH yielded 6.1 g (69.4%) of **17**. IR ν_{max}^{KBr} cm^{-1}: 1700, 1690. ^{1}H-NMR (DMSO-d_6) δ: 1.1 (COCH–C$\underline{H}_3$–N), 3.8, 3.9 (C$\underline{H}_3$O), 6.6—7.4 (arom.), 10.75 (N$\underline{H}$). *Anal.* Calcd for $C_{24}H_{29}N_3O_5$: C, 65.58; H, 6.65; N, 9.56. Found: C, 65.67; N, 6.74; N, 9.56.

Preparation of threo-1-[2-Hydroxy-2-(3,4,5-trimethoxyphenyl)-1-methylethyl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine (31)——A solution of **17** (4 g, 9.1 mmol) in 50 ml of absolute THF was

added to a cooled suspension of $LiAlH_4$ (720 mg, 19 mmol) in 10 ml of absolute THF at 0—5°C under a nitrogen atmosphere. The suspension was allowed to warm to room temperature and was then poured onto crushed ice. The whole was extracted with $CHCl_3$. The extract was worked up as usual to obtain 3.4 g (7.7 mmol, 84.6%) of crude **31**. Recrystallization from EtOH gave 3.1 g (7.02 mmol, 77.1%) of pure **31**. IR ν_{max}^{KBr} cm^{-1}: 1700. ^{1}H-NMR ($CDCl_3$) δ: 0.86 ($C\underline{H}_3$–CH–N—), 3.85, 3.89 ($C\underline{H}_3O$), 4.24 (ArC$\underline{H}$(OH)), 9.90 (NH). ^{13}C-NMR ($CDCl_3$) δ: 8.22 (C3′), 29.60, 30.03 (C2″, C4″), 43.67 (C5″), 50.86 (C3″), 52.57 (C1″), 56.10, 60.73 (C1, C2), 66.52 (C2′), 74.62 (C1′), 155.27 (C6″). *Anal.* Calcd for $C_{24}H_{31}N_3O_5$: C, 65.28; H, 7.08; N, 9.52. Found: C, 65.01; H, 7.08; N, 9.41. Treatment of **31** with **2** eq. of Ac_2O and 4-dimethylaminopyridine in DMF gave *N,O*-diacetyl-**31** (recrystallized from AcOEt). mp 202—204°C. IR ν_{max}^{KBr} cm^{-1}: 1735 (Sh.), 1729, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.82 ($C\underline{H}_3$–CH–N<), 2.22 ($C\underline{H}_3COO$), 2 75 ($NCOC\underline{H}_3$), 5 73 (ArC$\underline{H}$(OAc), J=9.53 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.57 (C3′), 21.49 (C5′), 25.68 (C8″), 29.04, 29.63 (C2″, C4″), 46.49 (C5″), 51.22 (C1″), 51.75 (C3″), 56.14 (C1), 60.77 (C2), 63.50 (C2′), 76.85 (C1′), 151.74 (C6″), 169.87 C4′), 170.50 (C7″).

Treatment of **17** (3.9 g, 8.87 mmol) with $NaBH_4$ (400 mg, 10.57 mmol) in 70 ml of MeOH and work-up as described for the synthesis of **27** gave 2.83 g (72.3%) of **31**, which was identical with the sample mentiond above.

Preparation of 1-[2-Oxo-2-(3,4-dihydroxyphenyl)ethyl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)-piperidine Hydrobromide (5)——A cooled suspension of **4**·HCl (2.3 g, 5.53 mmol) in 20 ml of CH_2Cl_2 was treated with 4.2 g (16.8 mmol) of BBr_3. The suspension was allowed to warm to room temperature with stirring. After 12 h, the mixture was filtered and the precipitate was washed successively with $CHCl_3$, EtOH and H_2O, then dried. Recrystallization of crude crystals (2.2 g) from EtOH gave 2.0 g (80.7%) of **5**. IR ν_{max}^{KBr} cm^{-1}: 1695, 1685. ^{1}H-NMR (DMSO-d_6) δ: 5.08 ($COC\underline{H}_2N$). 10.96 (N$\underline{H}$). *Anal.* Calcd for $C_{20}H_{21}N_3O_4$·HBr: C, 53.58; H, 4.95; N, 9.37. Found: C, 53.30; H, 5.00; N, 9.11.

Preparation of 1-[2-Hydroxy-2-(3,4-dihydroxyphenyl)ethyl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)-piperidine Hydrochloride (19)——A solution of 3,4-dibenzyloxy-α-bromoacetophenone[28] (5.0 g, 12.16 mmol), **2** (2.4 g, 11.05 mmol) and triethylamine (1.2 g, 11.9 mmol) in 20 ml of MeOH was stirred for 6 h at room temperature. Work-up as described above gave 5.7 g of crude crystals, which were recrystallized from EtOH–AcOEt to obtain 5.6 g (92.5%) of **13**. IR ν_{max}^{KBr} cm^{-1}: 1695, 1080. ^{1}H-NMR (DMSO-d_6) δ: 3.76(CO-C$\underline{H}_2$N), 5.2, 5.24 (PhC$\underline{H}_2$O), 10.4 (N$\underline{H}$). *Anal.* Calcd for $C_{34}H_{33}N_3O_4$: C, 74.56; H, 6.07; N, 7.67. Found: C, 74.44; H, 6.21; N, 7.59. $NaBH_4$ (1 g, 26.4 mmol) was added portionwise over 30 min to a suspension of **13** (4.7 g, 8.58 mmol) in 200 ml of MeOH. After the addition, the mixture was stirred for an additional 1 h at room temperature and concentrated. H_2O was added to the residue and the mixture was extracted with AcOEt. The extract was washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave an oily residue, which was treated with HCl in AcOEt to obtain crude **28**·HCl. Recrystallization from EtOH yielded 2.91 g (57.9%) of **28**·HCl. IR ν_{max}^{KBr} cm^{-1}: 1695. ^{1}H-NMR (DMSO-d_6) δ: 5.15 (PhC$\underline{H}_2$O), 10.61 (N$\underline{H}$). *Anal.* Calcd for $C_{34}H_{35}N_3O_4$·HCl: C, 69.67; H, 6.19; N, 7.17. Found: C, 69.50; H, 6.41; N, 7.01.

A suspension of **28**·HCl (2.31 g, 3.94 mmol) and 10% Pd on carbon (0.3 g) in 250 ml of MeOH was shaken under atmospheric pressure of H_2 at room temperature. After the absorption of hydrogen had ceased, the catalyst was filtered off and the filtrate was concentrated to dryness under reduced pressure. The residue was recrystallized from EtOH to obtain 1.52g (94.9%) of **19**·HCl, *Rf* ($CHCl_3$–MeOH–AcOH–H_2O, 10: 10: 1: 10, lower layer) 0.15. IR ν_{max}^{KBr} cm^{-1}: 1680. *Anal.* Calcd for $C_{20}H_{23}N_3O_4$·HCl: C, 59.19; H, 5.96; N, 10.35. Found: C, 60.11; H, 5.79; N, 10.36.

Attempted Inversion of 1-[2-Hydroxy-2-(3,4-dimethoxyphenyl)-1-methylethyl]-4-(1,3-dihydro-2*H*-benzimidazol-2-one-1-yl)piperidine (27)——i) Triphenylphosphine-diethyl Azodicarboxlate Method: A solution of diethyl azodicarboxylate (106 mg, 0.61 mmol) in THF (3 ml) was added to a solution of **27** (200 mg, 0.49 mmol), triphenyl phosphine (158 mg, 0.6 mmol), and AcOH (72 mg, 1.2 mmol) in THF (10 ml) at room temperature. The solution was stirred for 12 h and concentrated to dryness. The residue was diluted with H_2O, basified to pH 10.0 and extracted with AcOEt. The extract was worked up in the usual manner to give a crude oil which was subjected to prep-HPLC (AcOEt). The fraction eluted first gave 140 mg (=63.3%) of the acetate (**32**), mp 208—209°C (darkened at 206°C). IR ν_{max}^{KBr} cm^{-1}: 1720, 1688. ^{1}H-NMR ($CDCl_3$) δ: 0.80 (CH($C\underline{H}_3$)N), 2.20 ($OCOC\underline{H}_3$), 3.88, 3.91 ($C\underline{H}_3O$), 5.76 (C$\underline{H}$(OAc), J=9.5 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.53 (C3′, q), 21.54 (C4′, q), 29.68, 30.26 (C2″, C4″, t), 46.54 (C5″, t), 51.12 (C3″, d), 51.26 (C5″, t), 55.89, 55.99 (Cl, q), 63.50 (C2′, d), 76.70 (C1′, d), 155.40 (C6″, s), 169.97 (C4′, s). *Anal.* Calcd for $C_{25}H_{31}N_3O_5$: C, 66.20; H, 6.89; N, 9.27. Found: C, 66.08; H, 6.99; N, 9.27. **32** was identical with a sample of **33** in terms of mp, TLC, IR and NMR spectral data; **33** was prepared according to the following procedure. A mixture of **27** (2.0 g, 4.9 mmol), 4-dimethylaminopyridine (0.6 g, 4.91 mmol), and acetyl chloride (0.39 g, 4.97 mmol) in 10 ml of DMF was stirred for 12 h. The mixture was concentrated *in vacuo*. The residue was mixed with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried over Na_2SO_4 and concentrated under reduced pressure. The residual crystals were recrystallized from dioxane to yield 1.9 g (85.5%) of **33**.

ii) 2-Fluorobenzothiazolium Salt-AcOH Method: A solution of **27** (411.5 mg, 1 mmol) and triethylamine (101.2 mg, 1 mmol) in 2 ml of CH_2Cl_2 was added to a cooled solution of *N*-ethyl-2-fluorobenzothiazolium tetrafluoroborate (270 mg, 1 mmol) in 10 ml of CH_2Cl_2 at −60°C. The whole was stirred for 1 h at the same

temperature, then AcOH (61 mg, 1 mmol) and triethylamine (101.2 mg, 1 mmol) were added. The solution was warmed gradually to room temperature then washed with H_2O, dried over Na_2SO_4 and concentrated. The residue was subjected to preparative TLC (AcOEt) to obtain an acetate (72 mg, 15.9%), which was identical with the sample **33** prepared above.

iii) An Inversion involving the 2-Piperidone Intermediate: A mixture of **27** (1.5 g, 3.65 mmol), $Hg(OAc)_2$ (2.25 g, 7.06 mmol), EDTA-2Na·$2H_2O$ (2.64 g, 7.09 mmol) in aq. 4.8% AcOH (42 ml) was refluxed for 2.5 h. After cooling, the mixture was extracted with warm AcOEt. The extract was washed with 4.8% AcOH, sat. $NaHCO_3$, and H_2O, dried over Na_2SO_4 and concentrated to leave 1.0 g (64.7%) of an oily mixture of **34a** and **34b**. The mixture was subjected to prep-HPLC ($CHCl_3$–MeOH, 10: 1). The fraction eluted first gave 190 mg of **34a** and the fraction eluted second gave 765 mg of **34b** as a white powder.

A mixture of **34a** (100 mg, 0.24 mmol), 4-dimethylaminopyridine (60 mg, 0.49 mmol) and Ac_2O (50 mg, 0.49 mmol) in 5 ml of DMF was stirred for 12 h at room temperature. The solvent was removed *in vacuo* and the residue was diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O and dried over Na_2SO_4. Removal of the solvent gave a residue, which was recrystallized from AcOEt to obtain 80 mg (65.4%) of **35c**, mp 196—198°C. IR ν_{max}^{KBr} cm^{-1}: 1726, 1713, 1625. *Anal.* Calcd for $C_{27}H_{31}N_3O_7$: C, 63.64; H, 6.13; N, 8.25. Found: C, 63.44; H, 6.15; N, 8.00. ^1H and ^{13}C-NMR spectral data are summarized in Table III.

Similar treatment of **34b** (200 mg, 0.47 mmol) with Ac_2O (100 mg, 0.97 mmol) and 4-dimethylaminopyridine (120 mg, 0.98 mmol) gave 175 mg (73.1%) of crude crystals which were separated by preparative TLC developed with AcOEt to afford three bands. The first band afforded **35a** (12 mg), while the second and third bands afforded **35b** (77 mg) and **35d** (37 mg), respectively.

35a: mp 176—178°C. IR ν_{max}^{KBr} cm^{-1}: 1735, 1720 (sh), 1630. *Anal.* Calcd for $C_{27}H_{31}N_3O_7$: C, 63.64; H, 6.13; N, 8.25. Found: C, 63.56; H, 6.23; N, 8.24.

35b: mp 182—183.5°C. IR ν_{max}^{KBr} cm^{-1}: 1730, 1720, 1705, 1631. *Anal.* Calcd for $C_{27}H_{31}N_3O_7$: C, 63.64; H, 6.13; N, 8.25. Found: C, 63.44; H, 6.32; N, 8.18.

35d: mp 184—185°C. IR ν_{max}^{KBr} cm^{-1}: 1732, 1719, 1701, 1631. *Anal.* Calcd for $C_{27}H_{31}N_3O_7$: C, 63.64; H, 6.13; N, 8.25. Found: C, 63.59; H, 6.33; N, 8.23.

A solution of **35b** (30 mg, 0.059 mmol) in 1 ml of dry THF was added dropwise to a cooled suspension of $LiAlH_4$ (5 mg, 0.13 mmol) in 1 ml of dry THF under a nitrogen atmosphere. When the addition was complete, the mixture was allowed to warm to room temperature, then it was poured onto crushed ice and the whole was extracted with $CHCl_3$. The usual work-up of the $CHCl_3$ extract gave crude crystals which were recrystallized from EtOH to afford the *threo* isomer **27** (20 mg, 82.4%). Its IR and ^1H-NMR spectra were identical with those of the sample obtained above.

Similar treatment of **35d** (30 mg, 0.059 mmol) with $LiAlH_4$ (5 mg, 0.13 mmol) gave the *erythro* isomer **36** (19 mg, 78.3%). mp 201—202°C. IR ν_{max}^{KBr} cm^{-1}: 1678. *Anal.* Calcd for $C_{23}H_{29}N_3O_4$: C, 67.13; H, 7.10; N, 10.21. Found: C, 67.01; H, 7.21; N, 10.22. The NMR data are summarized in Table IV. Treatment of **27** with 2 eq. of Ac_2O and 4-dimethylaminopyridine in DMF gave *O,N*-diacetyl-**27**. On treatment as described for **27**, **36** gave *O,N*-diacetyl-**36**. *O,N*-diacetyl-**27**, mp 165—166°C. IR ν_{max}^{KBr} cm^{-1}: 1733 (sh), 1720, 1709 (sh). *O,N*-diacetyl-**36**, mp 151—152°C. IR ν_{max}^{KBr} cm^{-1}: 1733 (sh), 1725, 1715 (sh). NMR spectral data for these samples are summarized in Table IV.

Preparation of the erythro Isomer (36, 38) by Catalytic Hydrogenation——i) Catalytic Reduction under Atmospheric Pressure in aq. AcOH–MeOH Solution: A mixture of **17** (4 g, 9.1 mmol) and 0.4 g of PtO_2 in 0.083 N AcOH (109 ml) and MeOH (200 ml) was stirred under a stream of hydrogen for 3 h at room temperature. The catalyst was filtered off and the filtrate was concentrated to 100 ml then basified to pH 10.6. $CHCl_3$ was added to the basified solution and the organic layer was separated, then washed with H_2O and dried over Na_2SO_4. Removal of the solvent left crystals which were recrystallized from EtOH to afford 3.1 g (77.1%) of **38**, mp 216—216.5°C. IR ν_{max}^{KBr} cm^{-1}: 1689. ^1H-NMR ($CDCl_3$) δ: 0.98 ($C\underline{H}_3$–CH–N$<$) 3 84, 3 87 ($C\underline{H}_3O$), 4.96 (C$\underline{H}$(OH)), 9.78 (N$\underline{H}$). ^{13}C-NMR ($CDCl_3$) δ: 9.89 (C3′), 29.24, 29.48 (C2″, C4″), 48.63 (C5″), 50.53 (C3″), 52.09 (C1″), 56.14, 60.86 (C1, C2), 64.81 (C2′), 72.61 (C1′), 154.86 (C6″). *Anal.* Calcd for $C_{24}H_{31}N_3O_5$: C, 65.28; H, 7.08; N, 9.52. Found: C, 65.15; H, 7.22; N, 9.39.

Treatment of **38** with 2 eq. of Ac_2O and 4-dimethylaminopyridine in DMF gave *N,O*-diacetyl-**38**. mp 160—160.5°C. IR ν_{max}^{KBr} cm^{-1}: 1733 (sh), 1729, 1710. ^1H-NMR ($CDCl_3$) δ: 2.14 ($C\underline{H}_3COO$), 2.73 ($NCOC\underline{H}_3$), 5.82 (ArC$\underline{H}$OCOCH$_3$, J=6.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 10.43 (C3′), 21.30 (C5′), 25.68 (C8″), 28.85, 29.34 (C2″, C4″), 47.41 (C5″). 50.44 (C1″), 51.22 (C3″), 56.19, 60.82 (C1, C2), 63.93 (C2′), 76.21 (C1′), 151.74 (C6″), 169.92 (C4′), 170.50 (C7″). Hydrogenation of **12** (4.52 g, 11.04 mmol) in the presence of PtO_2 (0.3 g) in 133 ml of 0.083 N AcOH and 500 ml of MeOH yielded 3.14 g (69.1%) of **36**. The sample was identical with the sample obtained by the procedure involving the 2-piperidone intermediate.

ii) Catalytic Reduction in aq. HCl–MeOH Solution: A mixture of **17** (0.5 g, 1.14 mmol) and PtO_2 (0.1 g) in 0.05 N HCl (25 ml) and MeOH (25 ml) was stirred under a stream of hydrogen for 3 h at room temperature. Work-up as described above afforded 482 mg of crude crystals. Recrystallization from EtOH gave 400 mg (78.4%) of 1-[2-hydroxy-2-(3,4,5-trimethoxyphenyl)-1-methylethyl]-4-(octahydro-2*H*-benzimidazol-2-one-1-yl)piperidine, mp 206—208°C. IR ν_{max}^{KBr} cm^{-1}: 1688, 1683 (sh). ^1H-NMR ($CDCl_3$) δ: 0.88 (CH($C\underline{H}_3$)N), 1.0—4.0 (ring H and C$\underline{H}$(OH)C$\underline{H}$CH$_3$), 3.88, 3.91 ($C\underline{H}_3O$), 4.42 (N$\underline{H}$), 4.8 (C_4–H in piperidine

ring), 6.56 (arom.). *Anal.* Calcd for $C_{24}H_{37}N_3O_5$: C, 64.40; H, 8.33; N, 9.39. Found: C, 64.22; H, 8.55; N, 9.29. The same product was obtained when the hydrogenation of **17** was carried out in a Parr apparatus under pressure (50 p.s.i.) at room temperature.

iii) Catalytic Reduction in a Neutral Medium: A mixture of **17** (0.5 g, 1.14 mmol) and PtO_2 (0.1 g) in 100 ml of MeOH in a Parr apparatus was shaken at 50°C under 50 p.s.i. H_2 pressure for 12 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was crystallized from Et_2O; 490 mg (=97.4%) of crude crystals was obtained. The sample was proved to be a mixture of *erythro* and *threo* isomers in a ratio of 6:4, as judged from TLC and ^{13}C-NMR analyses.

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