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New Antihypertensive Agents. III.[1] Synthesis and Antihypertensive Activity of Some Arylalkyl Piperidines Carrying a Heterocycle at the 4-Position

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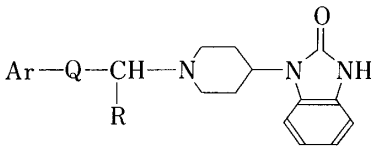
We synthesized a series of arylalkyl piperidines (II) carrying a heterocycle at the 4-position of piperidine and examined the hypotensive activities of the products. Compound **23** had the highest hypotensive activity in anesthetized normotensive rats (−78 mmHg, 30 mg/kg, *i.p.*) and compound **12** showed the strongest hypotensive activity (−95 mmHg, 30 mg/kg, *p.o.*) in unanesthetized spontaneously hypertensive rats. Only compound **16** produced a considerable decrease in blood pressure in both animal models.

Keywords——antihypertensive activity; indolinone; benzotriazole; octahydrobenzimidazolinone; structure–activity relationship

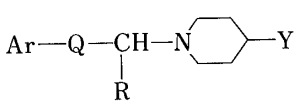
As a part of a research program aimed at the development of new antihypertensive agents, we have investigated various kind of compounds showing selective inhibitory activity against α_1-adrenoreceptor. We recently reported the synthesis and pharmacological activity of a series of 4-piperidinylbenzimidazolinones (I),[2-5] among which the *threo* form of compound I (Ar=3,4,5-trimethoxyphenyl and 3,4-dimethoxyphenyl, Q=CH(OH), R=CH_3) showed



Q : CO, CH(OH)
R : H, CH_3

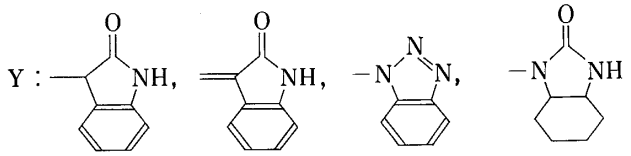
I

potent antihypertensive activity with long duration of action in various animal models.[2-5] These findings prompted us to carry out the structural modification of I by replacing the 1,3-dihydro-2-oxo-2*H*-benzimidazole group with other heterocycles. The present paper describes the synthesis and antihypertensive activities of compound II (Tables I and II).



Q : CO, CH(OH)
R : H, CH_3

II



Chemistry

The synthetic sequences leading to 3-(4-piperidinyl)-indolin-2-ones (**1**—**3**, **14**—**16**) are outlined in Chart 1. Oxindole was reacted with 1-benzyl-4-piperidone (**27**) in the presence of ammonia in ethanol to afford piperidinylideneindolinone (**29**) in 69.5% yield, which was reduced catalytically (Pd-C, 50 °C, 3.5 kg/cm^2 H_2 pressure) giving **31** in high yield. Condensation of **31** with arylbromoalkylketones yielded aminoketones (**1**—**3**), which were generally reduced with sodium borohydride to the corresponding arylethanolamines (**14**—**16**). Reduction of **3** with $NaBH_4$ in methanol afforded two products, which were separated by preparative thin layer chromatography (TLC). The more mobile product on TLC[6] (**16a**) and the less mobile one (**16b**) were obtained in approximately 4:6 ratio. Since **16** has three asymmetric carbons, one pair of *threo* diastereomers was anticipated from our earlier investigation.[2] However, **16a** was identified as a pair of *erythro* isomers and **16b** as a pair of *threo* ones on the basis of the proton nuclear magnetic resonance (^{1}H-NMR) and carbon nucelar magnetic resonance (^{13}C-NMR) spectra (Table III). Therefore, the selective reduction

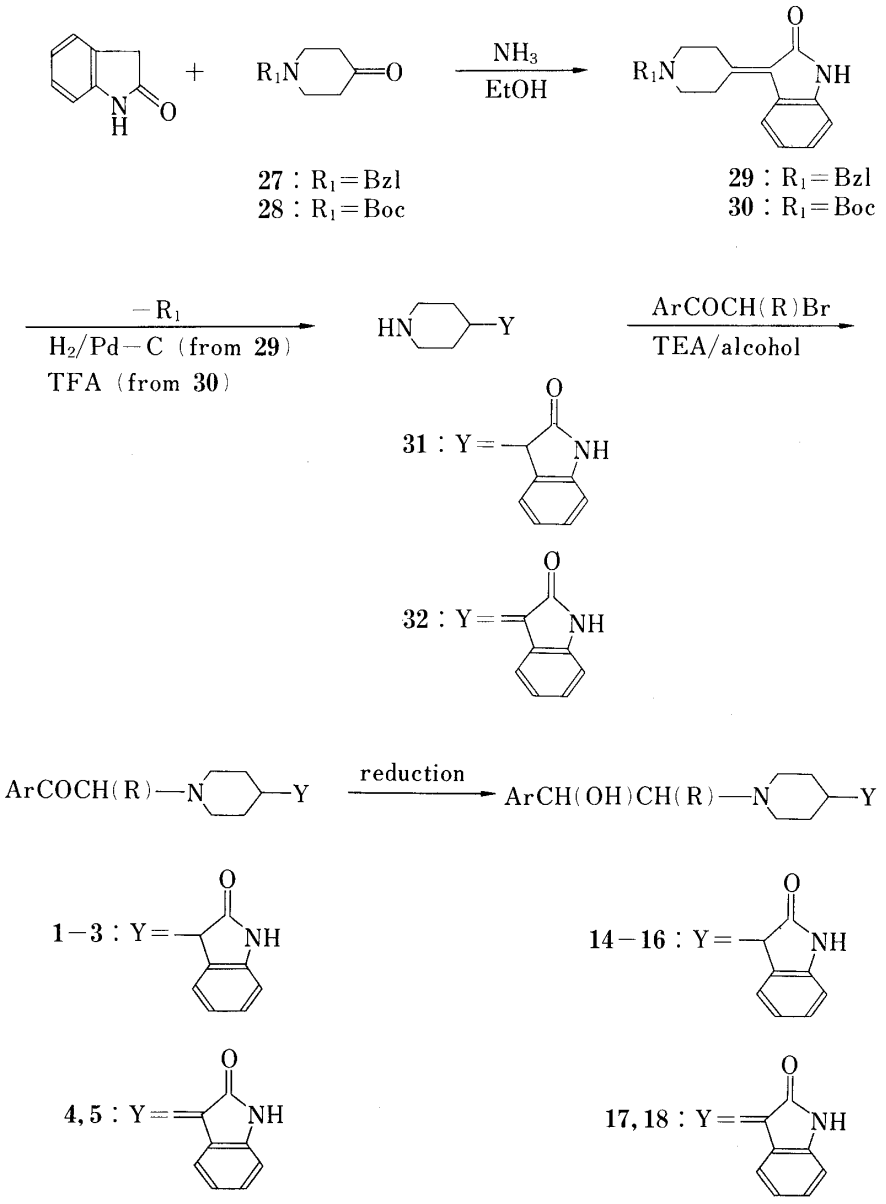
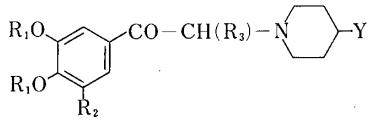
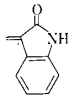


Chart 1

TABLE I.



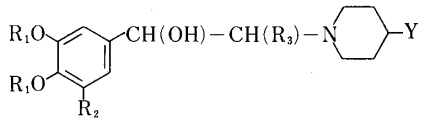
Compound	R_1	R_2	R_3	Y[a]	Form	Cryst. solv.	mp (°C)	Formula
1	CH_2	H	H		Base	EtOH	158—165	$C_{22}H_{22}N_2O_4$
2	CH_3	H	H		Base	—	Oil	$C_{23}H_{26}N_2O_4$
3	CH_3	H	CH_3		Base	Iso-PrOH	174—176	$C_{24}H_{28}N_2O_4$
4	CH_2	H	H		Base	EtOH	167.5—171	$C_{22}H_{20}N_2O_4$
5	CH_3	H	H		Base	EtOH	145—146	$C_{23}H_{24}N_2O_4$
6	CH_2	H	H		Base	Iso-PrOH	144.5—146	$C_{20}H_{20}N_4O_3$
7	CH_3	H	H		Fumarate	EtOH	184—186	$C_{21}H_{24}N_4O_3 \cdot C_4H_4O_4$
8	CH_3	H	CH_3		Base	Iso-PrOH	174.5—177	$C_{22}H_{26}N_4O_3$
9[b]	CH_3	H	H		Base	EtOH	179—181	$C_{22}H_{31}N_3O_4$
10[b]	CH_3	H	CH_3		Fumarate	Iso-PrOH	194—196.5	$C_{23}H_{33}N_3O_4 \cdot C_4H_4O_4$
11[b]	CH_3	OCH_3	CH_3		Fumarate	EtOH	197—199	$C_{24}H_{35}N_3O_5 \cdot C_4H_4O_4$
12[c]	CH_3	H	CH_3		Base	Iso-PrOH	130—132.5	$C_{23}H_{33}N_3O_4$
13[c]	CH_3	OCH_3	CH_3		Base	Iso-PrOH	130—133	$C_{24}H_{35}N_3O_5$

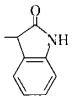
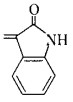
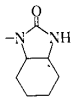
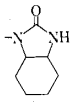
a) Where there is a blank space in this column, the Y group is the preceding structure.
b), *c*) Prepared from octahydrobenzimidazole **39** and **42**.

to **16a** and **16b** was briefly explored. When **3** was reduced by using lithium aluminium hydride[7] at 0 °C in tetrahydrofuran (THF), only **16b** was produced in 75% yield. No indole derivative was detected in this reduction. Catalytic reduction[2] of **3** (with PtO_2 as a catalyst in acidic media, under atmospheric pressure of hydrogen) gave **16a** exclusively.

We also investigated the synthesis of piperidinylideneindolinone **4**, **5** and **17**, **18**). The attempted synthesis of piperidinylideneindolinone (**32**) from **29** failed; the reduction of the exo double bond occurred exclusively and 3-(1-benzyl-4-piperidinyl)oxindolin-2-one (mp 220—223 °C, IR ν_{max}^{KBr} 1685, 1623 cm^{-1}) was obtained in 60% yield when **29** was subjected to Birch reduction (Na/NH_3). Alternatively 1-*tert*-butoxycarbonyl-4-piperidone (**28**), prepared by reaction of 4-piperidone with *tert*-butyl *S*-(4,6-dimethylpyrimidin-2-yl)-thiocarbonate (Boc-S), was condensed with oxindole as described for **29** to give piperidinylideneindolinone (**30**), which was treated with trifluoroacetic acid to afford **32** (Chart 1). Compound **32** was condensed with aryl bromoalkyl ketones to afford aminoketones (**4**, **5**). Sodium borohydride is known to reduce the 3-exo double bond in several isoindogenides.[8] Indeed, the 3-exo double bond as well as carbonyl group was reduced upon treatment of **4** with $NaBH_4$ and **14** was obtained exclusively. Therefore, alternative reducing agents were further investigated. A number of reducing reagents, including aluminium hydride, sodium cyanobrohydride and aluminium isopropoxide, were tried but the desired product **17** was not obtained efficiently.[9] Finally we were able to reduce **4** to **17** by using diisobutyl aluminium hydride (DIBAH). Thus,

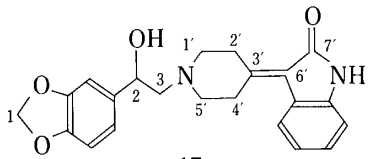
TABLE II.



Compound	R_1	R_2	R_3	Y[a]	Form	Cryst. solv.	mp (°C)	Formula
14	CH_2	H	H		Base	AcOEt	177—178	$C_{22}H_{24}N_2O_4$
15	CH_3	H	H		Succinate	EtOH	166—167	$C_{25}H_{31}N_2O_6 \cdot C_4H_6O_4$
16	CH_3	H	CH_3		Fumarate	Iso-PrOH	148—152	$C_{24}H_{30}N_2O_4 \cdot C_4H_4O_4$
17	CH_2	H	H		Base	MeOH–CH_2Cl_2	176—178	$C_{22}H_{22}N_2O_4$
18	CH_3	H	H		Base	AcOEt	98—99	$C_{23}H_{26}N_2O_4$
19	CH_2	H	H		Base	EtOH	148—149	$C_{20}H_{22}N_4O_3$
20	CH_3	H	H		Base	EtOH	173—174	$C_{21}H_{26}N_4O_3$
21	CH_3	H	CH_3		Base	EtOH	222—224	$C_{22}H_{28}N_4O_3$
22[b]	CH_3	H	H		Base	AcOEt	171—172	$C_{22}H_{33}N_3O_4$
23[c]	CH_3	H	CH_3		Fumarate	EtOH	208.5—209.5	$C_{23}H_{35}N_3O_4 \cdot C_4H_4O_4$
24[d]	CH_3	OCH_3	CH_3		Base	Iso-PrOH	123—126	$C_{24}H_{37}N_3O_5$
25[e]	CH_3	H	CH_3		Fumarate	Iso-PrOH	152—153.5	$C_{23}H_{35}N_3O_4 \cdot C_4H_4O_4$
26[f]	CH_3	OCH_3	CH_3		Base	Iso-PrOH	144—146.5	$C_{24}H_{37}N_3O_5$

a) Where there is a blank space in this column, the Y group is the preceding structure.
b), *c*), *d*), *e*), *f*) Prepared from **9**, **10**, **11**, **12** and **13**, respectively.

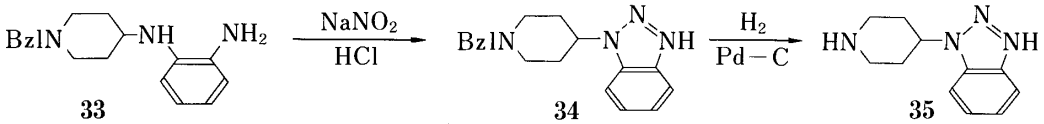
4 was treated with 1.4 mol eq of DIBAH in CH_2Cl_2 at $-10\,°C$ to give **17** as almost the sole product in 57% yield. The structure of **17** was determined by elemental and spectroscopic analyses. In the ^{1}H-NMR spectrum of **17** the benzylic proton signal was observed at δ 4.72 as



17

a triplet. The C-3′ and C-6′ signals appeared at δ 140.6 and 157.6 in the ^{13}C-NMR spectrum. In the infrared spectrum, **17** absorbed strongly at 1692 cm^{-1} due to the presence of the conjugated CONH group, while **14** absorbed at 1700 cm^{-1} (isolated CONH group).

With regard to the synthesis of benzotriazoles (**6**—**8** and **19**—**21**), 1-benzyl-4-(2-aminoanilino)piperidine [**33**; prepared from 1-benzyl-4-aminopiperidine essentially by the method reported previously[10]] was treated with sodium nitrite in hydrochloric acid to afford 1-benzyl-4-(1*H*-benzotriazol-1-yl)piperidine (**34**) in 47% yield after purification by chromatography. Debenzylation of **34** by catalytic hydrogenolysis gave 4-(1*H*-benzotriazol-1-yl)-

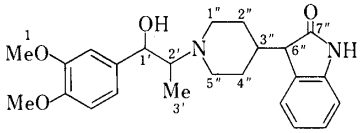


33 **34** **35**

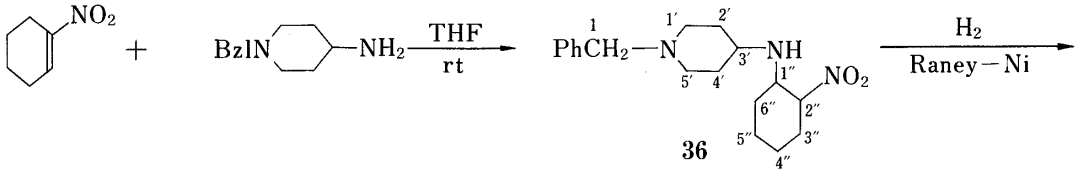
TABLE III. ^{1}H- and ^{13}C-NMR Spectral Data for **16a** and **16b**[a]

Position	16a		16b	
	^{13}C-NMR[b]	^{1}H-NMR[c]	^{13}C-NMR	^{1}H-NMR
1	55.85	3.83, 3.85, 3.87	55.85	3.86, 3,87
1′	72.08	4.81, $J_{1',2'}=3.06$[d]	74.03	4.17, $J_{1',2'}=9.76$
2′	64.72		66.57	
3′	9.94	0.85, $J_{2',3'}=6.59$	7.99	0.75, $J_{2',3'}=6.60$
1″	52.49, 52.88		52.93, 53.27	
2″	29.68, 30.02		29.88, 30.27	
3″	38.89	3.40, $J_{3'',6''}=2.93$	39.09	3.43, $J_{3'',6''}=2.69$
4″	27.63, 27.97		27.73, 28.07	
5″	49.13, 49.52		44.16, 44.50	
6″	50.88		50.98	
7″	179.79		179.79	

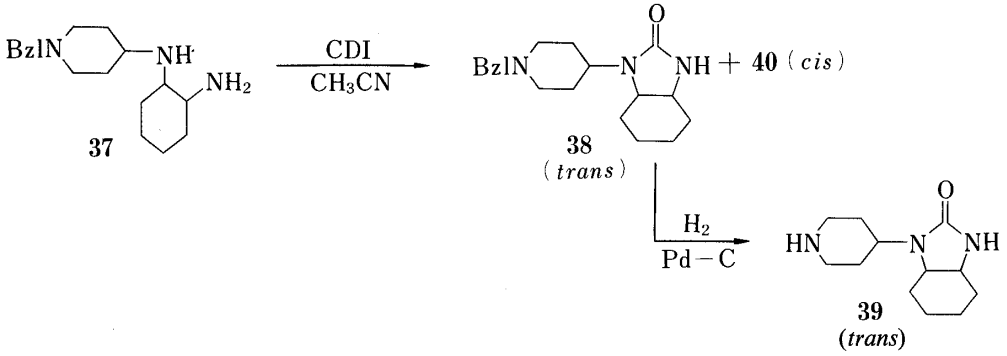
a) Numbering of **16**:



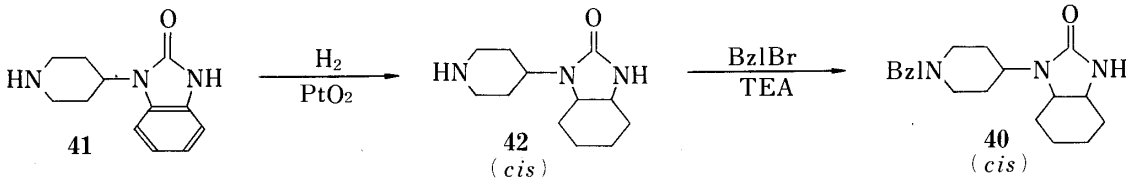
b) Measured in $CDCl_3$ at 25.1 MHz. Chemical shifts are reported in values relative to Me_4Si.
c) Measured in $CDCl_3$ at 100 MHz.
d) Expressed in Hż.



36



37 **38** (*trans*) **39** (*trans*)



41 **42** (*cis*) **40** (*cis*)

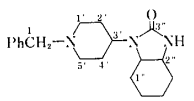
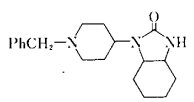
Bzl = benzyl

Chart 2

piperidine (**35**) in 91% yield. Following the same procedure as described above, **35** was converted to various ethanolamines (**19**—**21**) *via* the aminoketones (**6**—**8**).

The synthesis of octahydrobenzimidazoles (**9**—**13** and **22**—**26**), saturated analogs of benzimidazoles, was next investigated. Judging from the observation reported by Chupp,[11] it appeared that a key intermediate 1-(1-benzylpiperidin-4-yl)-2-oxo-octahydrobenzimidazole (**38**) could not be prepared by pyrolysis of the corresponding enecarbamoyl azide. Consequently **38** was synthesized from 2-nitrocyclohexene as shown in Chart 2. Thus, 2-nitrocyclohexane prepared by Corey's procedure[12] reacted with 4-amino-1-benzylpiperidine in THF to afford nitroaminocyclohexane (**36**) in 78% yield; this product was purified by preparative high performance liquid chromatography (HPLC) (Waters prep-PAK 500, eluting with AcOEt) because of its instability on open column chromatography (SiO_2). Oily **36** slowly decomposes on prolonged storage at room temperature to give crystals of an unidentified compound.[13] Thus **36** was used for the next reaction immediately after purification by preparative HPLC. Compound **36** was hydrogenated over Raney nickel in methanol to afford the diamine derivative (**37**) in high yield. Subsequent cyclization of **37** with *N,N'*-carbonyldiimidazole (CDI) in acetonitrile gave **38** in 56% yield together with a small amount of by-product (**40**, 5%). From the physical properties of **38** and **40** (summarized in Table IV), **40** was assigned as the stereoisomer of **38**. The configurations of the 1''- and the 2''-position of **38** and **40** were obtained by correlation with those of the sample (**43**) prepared alternatively from 1-(4-piperidinyl)-1,3-dihydro-2-oxo-benzimidazole (**41**): catalytic reduction of **41** using PtO_2 in hydrochloric acid gave the octahydrobenzimidazole (**42**), and benzylation (benzyl bromide/triethylamine) afforded **43** in 66.6% yield. The sample (**43**) thus obtained was identical with the aforementioned **40**. From the reaction mechanism yielding **36** (*trans* addition)[12] and **42** (*cis* H_2 addition), the structures of **38** and **40** can be assigned as *trans*- and *cis*-fused octahydrobenzimidazole derivatives, respectively. Compound **38** was debenzylated by catalytic hydrogenation to afford **39** in high yield. Compounds **39** and **42** were converted to the corresponding phenylethanolamines (**22**—**24** and **25**—**26**) by usual procedures. The final compounds (**22**—**24** and **25**—**26**) are assumed to be mixtures of diastereomers. However, we

TABLE IV. Physical Properties of **38** and **40**

Physical properties		Compound **38**	Compound **40**
mp (°C)		192—193	141—142
IR (KBr, cm^{-1})[a]		1680 (νCO)	1674 (νCO)
Rf[b]		0.31	0.27
NMR	^{1}H-NMR[c]	1.0—2.5, 2.8—3.4 (4H, piperidine ring H, H-1'', H-2''), 3.50 ($PhCH_2N<$), 3.65—4.20 (1H, H-3'), 4.60 (NH), 7.2—7.6 (arom.)	1.0—2.5, 2.8—3.2 (2H, H-1', H-5'), 3.50 ($PhCH_2N<$), 3.60—4.0 (3H, H-3', H-1'', H-2''), 4.21 (NH), 7.2—7.6 (arom.)
	^{13}C-NMR[d]	58.73, 62.09 (C-1'', C-2''), 163.80 (C-3'')	53.32, 53.66. (C-1'', C-2''), 162.45 (C-3'')
Speculated structure			

a) The absorptions at the fingerprint regions of **38** and **40** are also different in their IR spectra.
b) Developing solvent, $CHCl_3$–MeOH–AcOH–H_2O (10 : 10 : 1 : 10), lower layer.
c) Measured in $CDCl_3$ at 100 MHz.
d) Measured in $CDCl_3$ at 25.1 MHz.

could not determine whether they actually are mixtures or not in terms of TLC, ^{1}H-NMR, and ^{13}C-NMR. Studies to determine the homogeneity of the products are in progress.

Biological Results

The hypothensive activities of these compounds were examined in anethetized normotensive rate and in unanethetized spontaneously hypotensive rats (SHR). In experiments with anethetized animals, male Wistar strain rats weighing 250—320 g were anesthetized with urethane 600 mg/kg, *i.p.* and alpha-chloralose, 600 mg/kg, *i.p.* Mean arterial blood pressure was measured from the left common carotid artery by means of a pressure transducer. Heart rate was also measured with a cardiotachometer triggered by blood pressure pulses. Both recordings were made on an ink-writing oscillograph for 4 h in most of the experiments. The compounds were administered intraperitoneally. The SHR were male Okamoto strain rats whose systolic pressure was higher than 180 mmHg at the 18th week. SHR were anesthetized with ether and a cannula was fixed in the carotid artery of each rat. After this surgical operation (3—4 d later), blood pressure was measured through the cannula by means of a pressure transducer and recorded on an ink-writing oscillograph. Animals were able to move freely during the course of blood pressure measurements. In these experiments, drug were administered orally. The results are summarized in Tables V and VI.

In anesthetized normotensive rats, most of the compounds tested showed hypotensive activity. Compounds **1**, **2**, **14**, **15**, **16**, **21**, **22**, and **23** produced relatively potent hypotension. The hypotensive effects produced by compounds **1**, **2**, and **14** were considerably prolonged. Hypotension produced by compound **15** developed slowly but that by compound **16** was of short duration. The duration of the hypotension produced by compound **22** and **23** is uncertain, because blood pressure was not measured for a long period of time in these experiments. Decreases in blood pressure produced by the remaining compounds were much

TABLE V. Changes in Blood Pressure of Anesthetized Normotensive Rats[a]

Compound No.	No. of animals	Initial level	Changes in blood pressure (mmHg)					
			10	30	60	120	180	240 (min)
1	3	137± 6	−33±10	−32± 5	−38± 6	−44± 8	−47± 5	−41± 6
2	3	138± 6	−25± 5	−32± 7	−37± 3	−42± 5	−44± 6	−39± 3
3	4	105± 6	−5± 6	−10± 4	−7±11	−4±14	−4±11	+4±14
8	3	103± 7	−9± 6	+15± 4	+5±17	0± 5	−10±14	+1± 8
9	2	145	−6	+1	−12			
10	2	158	−17	−17	−24			
11	2	150	−6	−6	−30			
12	4	109± 4	−6± 4	−17± 3	−17± 5	−9± 5	−13± 5	−5± 6
13	4	114± 9	−13± 2	−20± 4	−18± 9	−6± 5	−15±13	−9± 9
14	3	121± 6	−34± 6	−40± 3	−35± 4	−31± 3	−32± 5	−30± 5
15	3	121± 4	−9± 8	−17±13	−16± 7	−31± 4	−24± 3	−26± 2
16	3	100± 7	−24±14	−30±10	−23± 7	−9± 9	+2± 8	+7± 5
21	4	115±13	−30± 7	−23± 8	−20±11	−14±13	−16± 6	−21±11
22	2	146	−20	−50	−39			
23	2	143	−53	−66	−78			
24	2	157	−12	−21	−46			
25	4	109± 6	−8± 3	−17± 6	−13± 6	−11± 7	−18±11	−11± 8
26	4	109± 4	−9± 3	−13± 3	−16± 5	+2± 5	−4± 3	−11± 2

a) Compounds were administered intraperitoneally at the dose of 30 mg/kg. Each value represents the mean ± standard error. When only 2 experiments were done, simple arithmetic means are shown.

TABLE VI. Changes in Blood Pressure of Unanesthetized Spontaneously Hypertensive Rats[a]

Compound No.	Maximum changes in blood pressure in SHR[b),c)] Dose (mg/kg, *p.o.*)	Changes in BP (mmHg)
1	30	−6
2	30	−12
3	30	−12
4	50	0
	100	−18
5	30	−30
	30	−35
	50	−30
6	30	−15
	50	−35
7	25	−15
	30	−19
	50	−50
8	30	−22
9	30	−28
10	30	−7
11	30	−23
12	30	−95
13	30	−55
14	30	−8
15	30	−12
16	30	−29
17	50	0
18	50	0
19	30	−23
	50	−50
20	25	−30
	30	−28
	50	−50
21	30	−30
22	30	−10
23	30	0
24	30	0
25	30	−30
26	30	−24

a) Administered orally.
b) Each value is the mean of 3—4 experiments.
c) Maximum decrease in blood pressure was obtained 1.5—3 h after the administration.

less.

Results after the oral administration of the drugs in SHR were quite different from those described above. Relatively strong hypotension was produced by compounds **5**, **9**, **12**, **13**, **16**, **20**, **21**, **25** and **26**. In particular, compounds **12** and **13** produced potent hypotension. These compounds produced only small decreases in blood pressure after intraperitoneal administration in normotensive rats. Similarly, the decreases in blood pressure produced by compounds **9**, **21**, **25** and **26** were also relatively small in normotensive rats. Only compound **16** produced considerable decrease in blood pressure in normotensive rats. The reason for this discrepancy is unclear at present, but it may be due to the difference in the route of administration or to differences between the hypotensive and normotensive rats. Further studies, including investigations on drug metabolism of these compounds, are needed to clari-

fy the reason for the different results obtained in SHR and normotensive rats.

Experimental

Melting points 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-PFT-100, or JNM-FX-100 spectrometer. Chemical shifts are given in δ values relative to Me_4Si as an internal 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 in ternal standard. For the numbering of carbons in **36**, refer to Chart 2.

3-(1-Benzyl-4-piperidinylidene)indolin-2-one (29)——Compound **27** (9.88 g, 0.052 mol) and indolin-2-one (6.86 g, 0.052 mol) were added to a solution of NH_3 (14.1 g, 0.83 mol) in 140 ml of EtOH at 0—5 °C. After the addition had been completed, the solution was gently heated to reflux for 2 h. The solution was concentrated under reduced pressure and the residue was recrystallized from MeOH–$CHCl_3$ to yield 11.0 g (0.036 mol, 69.5%) of **29**, mp 220—223 °C. IR ν_{max}^{KBr} cm^{-1}: 1685. *Anal.* Calcd for $C_{20}H_{20}N_2O$: 78.92; H, 6.62; N, 9.20. Found: C, 78.89; H, 6.63; N, 9.17.

4-(2-Oxoindolin-3-yl)piperidine Hydrochloride (31·HCl)——A mixture of **29** (9.5 g, 31.2 mol), AcOH (2.04 g), and 1.0 g of Pd-C in 200 ml of MeOH was shaken under 3.5 kg/cm^2 H_2 pressure at 40 °C for 5 h. The catalyst was filtered off, the filtrate was concentrated and the residue was dissolved in 50 ml of EtOH. HCl (1.15 g) in AcOEt was added to the solution. The crystals that separated were filtered and recrystallized from EtOH to obtain 6.7 g (27 mmol, 86.5%) of **31**·HCl, mp 284—286 °C. IR ν_{max}^{KBr} cm^{-1}: 1718. *Anal.* Calcd for $C_{13}H_{16}N_2O$·HCl: C, 61.78; H, 6.78; N, 11.08. Found: C, 61.65; H, 6.86; N, 11.04.

1-(3,4-Methylenedioxybenzoylmethyl)-4-(2-oxoindolin-3-yl)piperidine (1)——A solution of the hydrochloride of **31** (4.62 g, 18.3 mmol), ω-bromo-3,4-methylenedioxyacetophenone (4.45 g, 18.3 mmol) and triethylamine (3.8 g, 37.5 mmol) in 100 ml of MeOH was stirred at room temperature for 12 h. The solution was concentrated and the residue was diluted with water. The resulting precipitates were collected by filtration, washed with EtOH and dried. The crude product was recrystallized from EtOH to give 5.0 g (13.2 mmol, 72.2%) of **1**. IR ν_{max}^{KBr} cm^{-1}: 1695—1692, 1673. ^{1}H-NMR (DMSO-d_6) δ: 3.6 ($COCH_2N$), 6.1 (OCH_2O), 6.7—7.8 (arom), 10.3 (NH). *Anal.* Calcd for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5,86; N, 7.40. Found: C, 69.77; H, 5.85; N, 7.38.

1-[2-Hydroxy-2-(3,4-methylenedioxyphenyl)ethyl]-4-(2-oxoindolin-3-yl)piperidine (14)——$NaBH_4$ (0.3 g) was added portionwise to a suspension of **1** (2.9 g, 7.66 mmol) in 50 ml of EtOH. The suspension was stirred for 2 h then concentrated, and the residue was extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated. The residue was recrystallized from AcOEt to yield 2.0 g (5.26 mmol, 68.7%) of **14**. IR ν_{max}^{KBr} cm^{-1}: 1700. ^{1}H-NMR (DMSO-d_6) δ: 4.4—4.8 (CHOH), 5.9 (OCH_2O), 6.6—7.4 (arom.), 10.2 (NH). *Anal.* Calcd for $C_{22}H_{24}N_2O_4$: C, 69.45; H, 6.36; N, 7.36. Found: C, 69.30; H, 6.37; N, 7.07.

1-[3(3,4-Dimethoxyphenyl)-3-oxo-2-propyl]-4-(2-oxoindolin-3-yl)piperidine (3)——A reaction similar to that described for **1** was carried out with the hydrochloride of **31** (2.34 g, 9.26 mmol), triethylamine (1.88 g, 18.6 mmol), and 2-bromo-1-(3,4-dimethoxyphenyl)propan-1-one (2.53 g, 9.26 mmol). The crude crystals (3.55 g) were recrystallized from 2-propanol to give 3.0 g (7.34 mmol, 79.3%) of **3**, IR ν_{max}^{KBr} cm^{-1}: 1690, 1660—1650, 1264. ^{1}H-NMR ($CDCl_3$) δ: 1.2 [$COCH(CH_3)N$], 3.8—4.2 ($2\times CH_3O$), 9.1 (NH). *Anal.* Calcd for $C_{24}H_{28}N_2O_4$: C, 70.56; H, 6.91; N, 6.86. Found: C, 70.42; H, 6.90; N, 6.77.

1-[3-(3,4-Dimethoxyphenyl)-3-hydroxy-2-propyl]-4-(2-oxoindolin-3-yl)piperidine (16a, b)——$NaBH_4$ (1.0 g) was added portionwise to a solution of **3** (1.6 g, 3.9 mmol) in 70 ml of MeOH at room temperature. The solution was stirred for 2 h, then concentrated. The residue was mixed with water and the precipitates were collected, washed with water, and dried. The crude product (1.49 g, 92.6%) was converted to its fumarate in 2-propanol. A mixture of **16 a, b** (1.23 g, as the fumarate) was obtained, mp 148—152 °C. *Anal.* Calcd for $C_{28}H_{34}N_2O_8$: C, 63.86; H, 6.51; N, 5.32. Found: C, 63.76; H, 6.32; N, 5.51. A mixture of **16 a, b** (200 mg) was subjected to preparative TLC developed with $CHCl_3$–MeOH–AcOH–H_2O (10:10:1:10), lower layer, to afford two bands. The first band was extracted with MeOH and the extract was concentrated. The residue was basified with 1 N NaOH and extracted with $CHCl_3$. Usual work-up of the extract gave 42 mg of **16a**. Similar treatment of the second band afforded 51 mg of **16b**. **16a**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1465, 1258. **16b**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1465, 1255. ^{1}H-NMR and ^{13}C-NMR spectra are included in Table III.

Selective Reduction of 3 to 16b——A solution of **3** (530 mg, 1.3 mmol) in 20 ml of absolute THF was added to a cooled suspension of $LiAlH_4$ (100 mg, 2.6 mmol) in 10 ml of absolute THF at 0—5 °C under a nitrogen atmosphere. The suspension was allowed to warm to room temperature, then poured onto crushed ice. The whole was extracted with $CHCl_3$. The extract was worked up as usual to obtain 400 mg (75%) of **16b**, which was identical with the sample mentioned above.

1-*tert*-Butoxycarbonyl-4-piperidone (28)——A solution of 4-piperidone hydrate hydrochloride (9.3 g, 0.061 mol), triethylamine (12.5 g, 0.124 mol), and Boc-S (14.8 g, 0.062 mol) in 100 ml of dioxane and 30 ml of water was stirred for 6 h at room temperature then concentrated under reduced pressure. The residue was extracted with AcOEt. The

extract was washed successively with saturated aqueous $NaHCO_3$ and water, then dried over $MgSO_4$. Removal of the solvent gave crystals which were recrystallized from petroleum ether to give 9.8 g (0.049 mol, 81.3%) of **28**, mp: 70—72 °C. IR ν_{max}^{KBr} cm^{-1}: 1730 (sh), 1720, 1695. *Anal.* Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 60.38; H, 8.78; N, 6.92.

3-[1-(*tert*-Butoxycarbonyl)-4-piperidylidene]-indolin-2-one (30)——A reaction similar to that described for **29** was carried out: **30** was obtained in 67.9% yield from **28** (1.51 g, 7.58 mmol), oxindole (1.01 g, 7.59 mmol), and NH_3 (2.4 g). mp: 204—205 °C. IR ν_{max}^{KBr} cm^{-1}: 1700, 1690 (sh), 1670. *Anal.* Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.66; H, 7.05; N, 8.82.

3-(4-Piperidylidene)-indolin-2-one (32)——Compound **30** (7.5 g, 23.9 mmol) was treated with 25 ml of trifluoroacetic acid (TFA) at 0 °C. The mixture was stirred for 1.5 h at the same temperature, then TFA was removed by distillation and the residue was dissolved in water. The solution was basified and the crystals that separated were collected, washed and dried. Crude **32** was recrystallized from AcOEt to yield 4.4 g (20.5 mmol, 85.9%) of pure **32**, mp 234—238 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1697, 1680 (sh). *Anal.* Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.08. Found: C, 72.59; H, 6.60; N, 12.81.

3-[1-(3,4-Methylenedioxy)benzoylmethyl-4-piperidylidene]-indolin-2-one (4)——A reaction similar to that described for **1** was carried out with **32** (2.5 g, 11.7 mmol), ω-bromo-3,4-methylenedioxyacetophenone (2.8 g, 11.7 mmol), and triethylamine (1.2 g, 11.8 mmol) in MeOH. Compound **4** was obtained in 82.2% yield. IR ν_{max}^{KBr} cm^{-1}: 1698, 1680 (sh), 1260. ^{1}H-NMR (DMSO-d_6) δ: 3.8 ($COCH_2N$), 6.1 (OCH_2O), 10.3 (NH). *Anal.* Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44. Found: C, 69.96; H, 5.29; N, 7.33.

3[-1-(2-Hydroxy-2-(3,4-methylenedioxyphenyl)ethyl]-4-piperidylidene]-indolin-2-one (17)——A solution of DIBAH (8 g, 56.3 mmol) in 100 ml of CH_2Cl_2 was added to a cooled solution of **4** (4 g, 10.6 mmol) in 100 ml of CH_2Cl_2 at −15 °C over 2 h. The solution was stirred for a further 5 h at the same temperature, then MeOH (100 ml) and water (300 ml) were successively added. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The residue was recrystallized from MeOH–CH_2Cl_2 to give 2.3 g (57.4%) of **17**. IR ν_{max}^{KBr} cm^{-1}: 1692, 1245. ^{1}H-NMR (DMSO-d_6) δ: 4.72 (ArC<u>H</u>OH, triplet), 5.95 (OCH_2O), 10.35 (NH). *Anal.* Calcd for $C_{22}H_{22}N_2O_4$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.67; H, 5.84; N, 7.33.

1-Benzyl-4-(1*H*-benzotriazol-1-yl)piperidine (34)——A solution of $NaNO_2$ (0.36 g, 5.22 mmol) in 5 ml of water was added to a cooled solution of **33**·3HCl[10] (2.0 g, 5.1 mmol) in 30 ml of water at 0—5 °C under an atmosphere of N_2. After the addition, the solution was stirred for 1 h at 0—5 °C. The solution was basified with 1 N NaOH and extracted with $CHCl_3$. The extract was worked up as usual to obtain 1.38 g of crude **34**, which was purified by chromatography on SiO_2 with $CHCl_3$–MeOH (100 : 1) to give 0.71 g (47.1%) of **34**. The sample was used in the next reaction without further purification. An analytical sample was recrystallized from hexane. mp 110—111 °C. IR ν_{max}^{KBr} cm^{-1}: 1461, 1140, 1083. *Anal.* Calcd for $C_{18}H_{20}N_4$: C, 73.94; H, 6.90; N, 19.16. Found: C, 74.12; H, 6.88; N, 19.27.

4-(1*H*-Benzotriazol-1-yl)piperidinium Acetate (35·AcOH)——A mixture of **34** (8.76 g, 0.03 mmol), AcOH (9.0 g, 0.15 mmol), and Pd carbon (2.0 g) in 200 ml of MeOH was shaken in a Parr apparatus under 3.5 kg/cm^2 H_2 pressure at 50 °C. 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 AcOEt–EtOH to yield 8.82 g (91.3%) of **35**·AcOH, mp 132.5—135.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1583, 1175. *Anal.* Calcd for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.31; H, 6.97; N, 21.62.

1-(3,4-Methylenedioxybenzoylmethyl)-4-(1*H*-benzotriazol-1-yl)piperidine (6)——A solution of **35**·AcOH (40 g, 15.3 mmol), ω-bromo-3,4-methylenedioxyacetophenone (3.7 g, 15.2 mmol), and triethylamine (3.1 g, 30.6 mmol) was stirred at room temperature for 12 h. The solution was concentrated and the residue was mixed with AcOEt and water. The organic layer was separated, washed with water, dried over $MgSO_4$, and concentrated. The residue was recrystallized from 2-propanol to yield 3.2 g (57.8%) of **6**. IR ν_{max}^{KBr} cm^{-1}: 1675, 1455, 1440, 1261, 1040. ^{1}H-NMR (DMSO-d_6) δ: 3.8 ($COCH_2N$), 6.1 (OCH_2O). *Anal.* Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38. Found: C, 65.86; H, 5.52; N, 15.68.

1-[2-Hydroxy-2-(3,4-methylenedioxyphenyl)ethyl]-4-(1*H*-benzotriazol-1-yl)piperidine (19)——$NaBH_4$ (0.19 g) was added portionwise to a solution of **6** (1.75 g, 4.8 mmol) in 30 ml of MeOH. After the addition, the solution was warmed to 40 °C and stirred for 1 h at the same temperature, then concentrated. The residue was mixed with water. The crystals separated were collected by filtration and washed with water. Crude **19** was recrystallized from EtOH to yield 1.4 g (79.6%) of **19**. IR ν_{max}^{KBr} cm^{-1}: 1493, 1255, 1245, 1040. ^{1}H-NMR ($CDCl_3$) δ: 4.7 (ArC<u>H</u>OH, triplet), 5.92 (OCH_2O), 6.6—8.3 (arom.). *Anal.* Calcd for $C_{20}H_{22}N_4O_3$: C, 65.55; H, 6.05; N, 15.29. Found: C, 65.32; H, 6.04; N, 15.44.

1-Benzyl-4-(2-nitrocyclohexylamino)piperidine (36)——A solution of 1-nitrocyclohexane (16.6 g, 0.13 mol) and 1-benzyl-4-aminopiperidine (23 g, 0.12 mol) in 150 ml of THF was stirred at room temperature for 12 h. The solution was concentrated under reduced pressure and the residue was dissolved in 250 ml of 0.6 N HCl. The aqueous solution was extracted twice with ether and basified with 1 N NaOH. The separated oil was extracted with ether (100 ml × 3). The extract was worked up as usual to give 30 g (78.1%) of crude **36**, which was subjected to preparative HPLC (AcOEt) to afford 22.2 g (53.4%) of **36** as an oil. IR ν_{max}^{neat} cm^{-1}: 1545. ^{1}H-NMR ($CDCl_3$) δ: 3.47 ($PhCH_2N$), 4.0—4.35

($CHNO_2$), 7.3 (arom.). ^{13}C-NMR ($CDCl_3$) δ: 23.9, 24.4 (C-2′, C-4′), 31.2, 32.6 (C-4″, C-5″), 32.7, 33.9 (C-3″, C-6″), 52.0, 52.1 (C-1′, C-3′, C-5′), 56.3 (C-1″), 63.0 (C-1), 92.1 (C-2″), 126.8—138.6 (four peaks for C-arom.). *Anal.* Calcd for $C_{18}H_{27}N_3O_2$: C, 68.11; H, 8.57; N, 13.24. Found: C, 68.10; H, 8.78; N, 13.21.

1-Benzyl-4-(2-aminocyclohexylamino)piperidine (37)——A mixture of **36** (1.0 g, 3.15 mmol) and Raney-Ni (1.0 g) in 25 ml of EtOH was shaken under atmospheric pressure of hydrogen at room temperature. After the theoretical amount of hydrogen had been absorbed, the catalyst was filtered off and the filtrate was concentrated to dryness *in vacuo* to afford oily **37**. The product was used in the next reaction without further purification. IR ν_{max}^{neat} cm^{-1}: 1580, 1450—1422. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (NH, NH_2), 3.5 ($PhCH_2N\langle$), 7.3 (arom.). For analysis, free **37** was converted to its hydrochloride. An analytical sample was recrystallized from MeOH. mp 245—247 °C (darkened). *Anal.* Calcd for $C_{18}H_{32}Cl_3N_3$: C, 54.48; H, 8.13; N, 10.59. Found: C, 54.25; H, 8.38; N, 10.43.

1-Benzyl-4-(octahydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (38)——A solution of **37** (631 mg, 2.2 mmol) and *N,N′*-carbonyldiimidazole (550 mg, 3.39 mmol) in 10 ml of CH_3CN was stirred for 12 h at room temperature. The resulting crystals were collected by filtration, washed with CH_3CN, and recrystallized from 2-propanol to afford 300 mg (43.5%) of **38**. The mother liquor was concentrated under reduced pressure and the residue was chromatographed on silica gel with $CHCl_3$–MeOH (50 : 1). The fraction eluted first gave 80 mg of **38** and the subsequent fraction gave **40** (34.5 mg, 5%). The physical properties of **38** and **40** are summarized in Table IV. **38**; *Anal.* Calcd for $C_{19}H_{27}N_3O$: C, 72.80; H, 8.68; N, 13.41. Found: C, 72.71; H, 8.97; N, 13.39. **40**; *Anal.* Calcd for $C_{19}H_{27}N_3O$: C, 72.80; H, 8.68; N, 13.41. Found: C, 72.77; H, 8.89; N, 13.46.

4-(Octahydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine Hydrochloride (39·HCl)——A mixture of **38** (6.1 g, 19.5 mmol) and Pd-C (5%, 1.0 g) in 100 ml of MeOH and 100 ml of 0.24 N HCl was shaken in a Parr apparatus at 3.5 kg/cm^2 H_2 pressure until the absorption of hydrogen had ceased. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was recrystallized from EtOH to give 3.9 g (77.1%) of **39**·HCl, mp > 300 °C. IR ν_{max}^{KBr} cm^{-1}: 1658, 1637 (sh.). *Anal.* Calcd for $C_{12}H_{22}ClN_3O$: C, 55.48; H, 8.54; N, 16.18. Found: C, 55.49; H, 8.80; N, 16.01.

1-[3-(3,4,5-Trimethoxyphenyl)-3-oxo-2-propyl]-4-(octahydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine Fumarate (11)——A solution of **39**·HCl (1.1 g, 3.96 mmol), triethylamine (0.18 g, 8.0 mmol), and 2-bromo-1-(3,4,5-trimethoxyphenyl)propan-1-one (1.2 g, 3.96 mmol) in 20 ml of MeOH was stirred at room temperature for 24 h and concentrated. The residue was extracted with AcOEt. Usual work-up of the extract gave crude **11** (1.31 g, 74.2%) as pale yellow crystals, which could be used directly in the next reaction. For analysis, free **11** was converted to its fumarate. An analytical sample was recrystallized from EtOH. IR ν_{max}^{KBr} cm^{-1}: 1680. *Anal.* Calcd for $C_{28}H_{39}N_3O_9$: C, 59.88; H, 7.00; N, 7.48. Found: C, 59.76; H, 7.23; N, 7.46.

***thereo*-1-[3-Hydroxy-3-(3,4,5-trimethoxyphenyl)-2-propyl]-4-(octahydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (24)**——In a manner similar to that described for **14**, the reaction of **11** (as the free base, 0.69 g, 1.55 mmol) with 0.2 g of $NaBH_4$ in 20 ml of MeOH gave **24** in 69.2% yield. IR ν_{max}^{KBr} cm^{-1}: 1701, 1680. ^{1}H-NMR ($CDCl_3$) δ: 0.8 (CH–C$\underline{H}_3$), 3.83, 3.86 (CH_3O), 4.15 (C$\underline{H}$OH), J=9.77 Hz), 4.6 (NH), 6.58 (arom.). ^{13}C-NMR ($CDCl_3$) δ: 8.2 (C-3′), 20.1, 21.2 (C-10″), 28.3, 28.9 (C-9″), 30.5, 31.9 (C-2″, C-4″), 43.7 (C-5″), 50.5 (C-3″), 51.1, 53.8 (C-7″, C-8″), 52.5 (C-1″), 56.1 (C-1), 60.8 (C-2), 66.4 (C-2′), 74.6 (C-1′), 162. 3 (C-6″). For the numbering of carbons of **24** and **26**, see reference 14). *Anal.* Calcd for $C_{24}H_{37}N_3O_5$: C, 64.40; H, 8.33; N, 9.39. Found: C, 64.43; H, 8.51; N, 9.38.

4-(Octahydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine Hydrochloride (42·HCl) from 41 by Catalytic Hydrogenation——A mixture of **41** (10.0 g, 46 mmol) and PtO_2 (1.0 g) in 110 ml of 0.5 N HCl and 50 ml of MeOH was shaken in a Parr apparatus at 50 °C under 3.5 kg/cm^2 H_2 pressure for 5 d. Work-up as usual gave crystals, which were recrystallized from MeOH to yield **42**·HCl (6.9 g, 57.8%), mp > 300 °C. IR ν_{max}^{KBr} cm^{-1}: 1680. *Anal.* Calcd for $C_{12}H_{22}ClN_3O$: C, 55.48: H, 8.54; N, 16.18. Found: C, 55.23; H, 8.78; N, 16.10.

1-[3-Oxo-3-(3,4,5-trimethoxyphenyl)-2-propyl]-4-(octahydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (13)——The procedure described for **11** was carried out with **42** (as the hydrochloride, 1.5 g, 5.82 mmol), triethylamine (1.2 g, 11.9 mmol) and 2-bromo-2-(3,4,5-trimethoxyphenyl)propanone (1.77 g, 5.84 mmol) in 30 ml of MeOH. Crude **13** (1.86 g, 71.6%) obtained was recrystallized from 2-propanol to give 1.6 g (61.7%) of pure **13**. IR ν_{max}^{KBr} cm^{-1}: 1683 (sh), 1680. *Anal.* Calcd for $C_{24}H_{35}N_3O_5$: C, 64.69; H, 7.92; N, 9.43. Found: C, 64.53; H, 7.88; N, 9.36.

***threo*-1-[3-Hydroxy-3-(3,4,5-trimethoxyphenyl)-2-propyl]-4-octahydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (26)**——The procedure described for **24** was followed, using 1.18 g of **13** and 0.3 g of $NaBH_4$. Crude **26** (949 mg, 80.0%) thus obtained was chromatographed on SiO_2 with MeOH–AcOEt (1 : 1). Pure **26** was obtained in 65.5% yield, mp 144—146.5 °C. IR ν_{max}^{KBr} cm^{-1}: 1680 (sh), 1675 cm^{-1}. NMR ($CDCl_3$) δ: 0.80 (CH–C$\underline{H}_3$), 4.15 (C$\underline{H}$OH, J= 9.77 Hz), 4.33 (NH), 6.58 (arom.). ^{13}C-NMR ($CDCl_3$) δ: 8.2 (C-3′), 23.8, 24.3 (C-10″), 29.5, 30.5 (C-9″), 32.0, 32.5 (C-2″, C-4″), 43.9 (C-5″), 50.7 (C-3″), 52.6, 52.9 (C-7″, C-8″), 52.6 (C-1″), 56.1 (C-1), 60.8 (C-2), 66.5 (C-2′), 74.7 (C-1′), 163.7 (C-6″). *Anal.* Calcd for $C_{24}H_{37}N_3O_5$: C, 64.40; H, 8.33; N, 9.39. Found: C, 64.32; H, 8.29; N, 9.31.

1-Benzyl-4-(octahydro-2-oxo-2*H*-benzimidazol-1-yl)piperidine (40)——**42**·HCl (300 mg, 1.15 mmol) was treated with benzyl bromide (203 mg, 1.19 mmol) in 30 ml of MeOH in the presence of triethylamine (240 mg, 2.37 mmol). The reaction mixture was worked up as usual to give 240 mg (66.6%) of **40**. Physical data for **40** are listed in Table IV.

References and Notes

1) Part II: H. Obase, N. Nakamizo, H. Takai, M. Teranishi, K. Kubo, K. Shuto, Y. Kasuya, and K. Shigenobu, *Chem. Pharm. Bull.*, **30**, 474 (1982).
2) 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).
3) Y. Kasuya, K. Shigenobu, M. Hashikami, N. Karashima, H. Obase, H. Takai, M. Teranishi, A. Karasawa, and K. Kubo, *J. Med. Chem.*, **26**, 208 (1983).
4) Y. Kasuya, J. Kurihara, and H. Kato, *Arzneim.-Forsch.*, **33**, (1)4, 557 (1983).
5) A. Karasawa, K. Shuto, K. Kubo, M. Hashikami, K. Shigenobu, and Y. Kasuya, *Arch. Int. Pharmacodyn. Ther.*, **261**, 278 (1983).
6) Developing solvent: $CHCl_3$–MeOH–AcOH–H_2O (10 : 10 : 1 : 10), lower layer.
7) J. Van Dijk and H. D. Moed, *Rec. Trav. Chim. Pays-Bas*, **78**, 22 (1959); *idem, ibid.*, **80**, 573 (1961); M. J. Mardle, H. Smith, and B. A. Spicer, *J. Med. Chem.*, **17**, 513 (1974).
8) I. W. Elliott and P. Rivers, *J. Org. Chem.*, **29**, 2438 (1964); M. Mori and Y. Ban, *Tetrahedron Lett.*, **1979**, 1133.
9) The results of examination of the selective reduction of **4** will be reported elsewhere in detail.
10) P. A. J. Janssen, Japan Kokai, 51-13780 (1976).
11) J. P. Chupp, *J. Heterocycl. Chem.*, **8**, 557 (1971).
12) E. J. Corey and H. Esteicher, *J. Am. Chem. Soc.*, **100**, 6294 (1978).
13) The physical properties of the decomposition product of **36** are as follows: mp 173—176 °C. IR ν_{max}^{KBr} cm^{-1}: 1539. Elemental analysis: C, 68.36; H, 8.87; N, 13.15. Empirical formula: $C_{18}H_{27}N_3O_2$ (identical with that of **36**). ^{13}C-NMR ($CDCl_3$) δ: 21.8, 25.0, 25.4, 31,0, 47,0, 51,7, 62.4, 121.8, 122.1, 126.8—138.5 (four carbons attributable to arom. carbon). ^1H-NMR ($CDCl_3$) δ: Two signals (other than arom. signals) appeared at lower field (5.6—6.2, 1 H and 6.5—6.8, 1 H). For the physical properties of **36**, see the experimental section.
14) The numbering of carbons of **24** and **26** is as follows: