Chem. Pharm. Bull. 42(10) 2042—2048 (1994) Vol. 42, No. 10

Synthesis and Structure–Activity Relationships of New (5*R*,8*S*,10*R*)-Ergoline Derivatives with Antihypertensive or Dopaminergic Activity[1)]

Sachio OHNO,* Masayuki KOUMORI, Yuko ADACHI (née EBIHARA), Kiyoshi MIZUKOSHI, Mitsuaki NAGASAKA, and Kenji ICHIHARA

Research Laboratories, Maruko Seiyaku Co., Ltd., 1212 Teramae, Gejo-cho, Kasugai, Aichi 486, Japan.

Received February 16, 1994; accepted June 3, 1994

A series of new (5*R*,8*S*,10*R*)-ergoline derivatives was synthesized, and their antihypertensive and dopaminergic activities were evaluated in conscious spontaneously hypertensive rats and in rats with unilateral 6-hydroxydopamine-induced lesions of the substantia nigra, respectively. (5*R*,8*S*,10*R*)-6-Methyl-8-ergolinemethanols, prepared from the corresponding ergolinecarboxylates, were converted to the tosylates, which were treated with various five-membered heterocycles containing nitrogen atoms to afford the new ergolines. (5*R*,8*S*,10*R*)-8-(1-Imidazolylmethyl)-6-methylergoline (5a, BAM-2101) and (5*R*,8*S*,10*R*)-2-bromo-6-methyl-8-(1,2,4-triazol-1-ylmethyl)ergoline (7c, BAM-2202) exhibited potent antihypertensive activities. The maximum falls of systolic blood pressure after oral administration of 5a and 7c at 3 mg/kg were 95 and 132 mmHg, respectively, while those of cianergoline, bromocriptine mesylate, hydralazine, and nifedipine at the same dose were 40, 37, 47, and 49 mmHg, respectively. The durations of significant antihypertensive effects of these compounds except nifedipine were more than 7 h. None of the ergolines exhibited potent dopaminergic activity. Structure–activity relationships are discussed.

Keywords antihypertensive; dopaminergic; structure–activity relationship; ergoline; BAM-2101; BAM-2202

Dihydroergotoxine, bromocriptine,[2)] and pergolide[3)] are ergot-related compounds and have been reported to exhibit moderate antihypertensive activity in animals and humans.[4)] The first has been clinically employed to treat patients with cerebral and peripheral circulatory disturbances and with hypertension. The others are dopamine D_2-receptor agonists and have been used in the therapy of Parkinson's disease, acromegaly, and hyperprolactinemia. In particular, pergolide possessed extremely potent D_2-receptor agonistic activity. It is known that these ergot-related compounds sometimes show undesirable side effects,[5)] such as nausea and vomiting, which could limit their clinical use. Cianergoline[6)] and FCE 22716[7)] were synthesized as antihypertensives, but showed only moderate activities in animals.

We are searching for new ergolines with potent antihypertensive or dopaminergic activity and with weaker side effects. In a previous paper[8)] we reported synthesis of new (5*R*,8*R*,10*R*)-8-methylergolines with antihypertensive or dopaminergic activity. Among these compounds, (5*R*,8*R*,10*R*)-6-methyl-8-(1,2,4-triazol-1-ylmethyl)ergoline (maleate: BAM-1110) is an excellent and potent dopamine D_1- and D_2-receptor agonist. (5*R*,8*R*,10*R*)-6-Propyl-8-(1,2,4-triazol-1-ylmethyl)ergoline (fumarate: BAM-1602) is an extremely potent and selective D_2-receptor agonist. Further investigations on both of them are in progress. (5*R*,8*R*,10*R*)-2-Bromo-8-(1-imidazolylmethyl)-6-methylergoline also exhibited a potent antihypertensive activity, but the effect rapidly decreased.

In this paper we report the synthesis and structure–activity relationships of new (5*R*,8*S*,10*R*)-8-methylergoline derivatives with antihypertensive and dopaminergic activities.

Chemistry Epimerization of methyl (5*R*,8*R*,10*R*)-6-methyl-8-ergolinecarboxylate (**1a**)[9)] and the chloride (**1b**)[10)] with lithium diisopropylamide in tetrahydrofuran (THF) gave the (5*R*,8*S*,10*R*)-6-methyl-8-ergolinecarboxylates (**2a**,[9,11)] **2b**) in 66 and 62% yields, respectively. The chloride **1b** was prepared from **1a** by treatment with *N*-chlorosuccinimide in dioxane. The ester **2b** was also obtained by chlorination of **2a** in 69% yield. Treatment of **2a** with trimethylanilinium perbromide in THF afforded **2c**[11b)] in 74% yield. The esters **2a**—**c** were reduced with lithium aluminum hydride in THF to give the methanols (**3a**,[12)] **3b**, **3c**) in good yields. The methanols **3a**—**c** were converted to the tosylates (**4a**,[13)] **4b**, **4c**) by treatment with *p*-toluenesulfonyl chloride in pyridine.

The tosylates **4a**—**c** were treated with the sodium salts of various five-membered heterocycles containing nitrogen in *N*,*N*-dimethylformamide to yield the desired new (5*R*,8*S*,10*R*)-ergoline derivatives (**5**—**7**).

Alternatively **6b** and **6c** were prepared by chlorination of **5f** and **5j** with *N*-chlorosuccinimide in dioxane, respectively. Compounds **7b** and **7c** were prepared by bromination of **5f** and **5j** with trimethylanilinium perbromide in THF in the presence of triethylamine, respectively.

Structural assignments of some azole compounds were made on the basis of their NMR spectra in a similar manner to that described previously.[8)] Reaction of **4a** with tetrazole gave the isomers **5k** and **5l** in 27 and 21% yields, respectively. It is known that the signal of the 5-proton of 1-alkyltetrazole appears at a higher field than that of 2-alkyltetrazole.[14)] Those of **5k** and **5l** appear at δ 8.46 and 8.69, respectively. Therefore **5k** and **5l** are 1- and 2-substituted tetrazoles, respectively.

In the ^{1}H-NMR spectra, the signals of the 9β-protons of the (5*R*,8*S*,10*R*)-ergolines **5**—**7** appear in the vicinity of δ 1.6—1.8 as a triplet of doublets with coupling constants of 12.6—13.8 and 4.2—5.0 Hz, while those of the corresponding (5*R*,8*R*,10*R*)-ergolines[8)] appear in the vicinity of 1.0—1.2 as a quartet with coupling constants

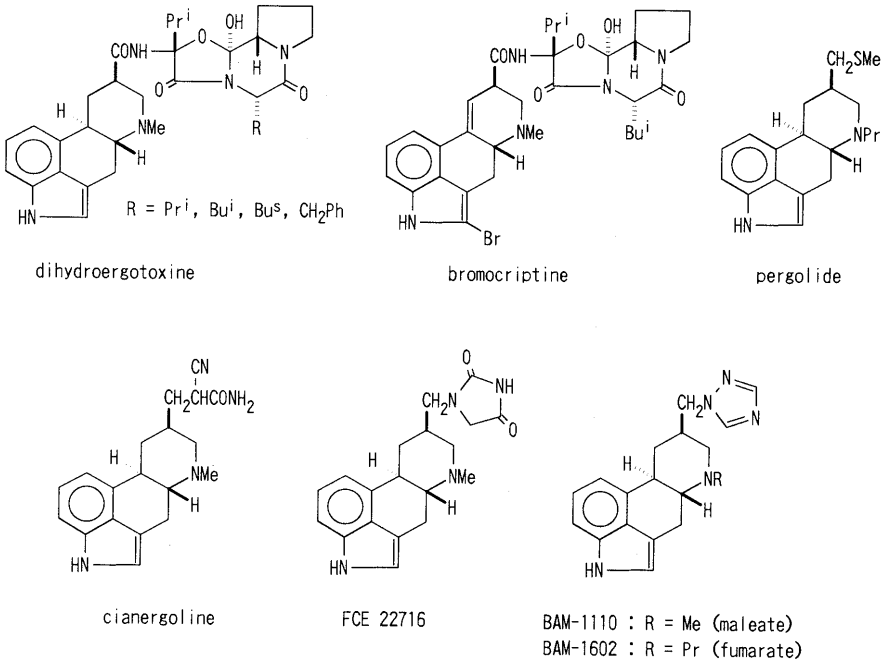


Fig. 1

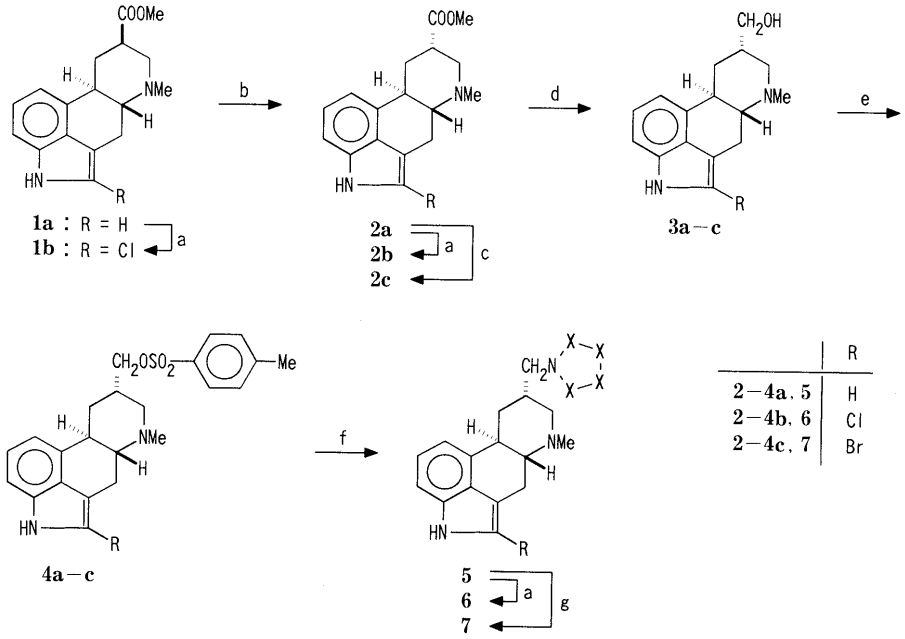


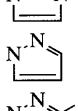
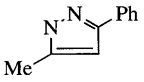
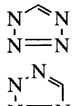
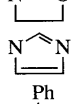
Chart 1

of 11.4—12.5 Hz. The signals of **5**—**7** appear at 0.5—0.6 ppm lower field than those of the corresponding (5*R*,8*R*,10*R*)-ergolines. In the (5*R*,8*S*,10*R*)-ergolines, the coupling constants between the 9β- and 9α-protons and between the 9β- and 10-protons were equal and were different from that between the 9β- and 8β-protons. In the (5*R*,8*R*,10*R*)-ergolines, the coupling constants between the 9β- and 9α-protons, between the 9β- and 10-protons, and between the 9β- and 8α-protons were equal.[15]

Structure–Activity Relationship Antihypertensive activity was evaluated by a tail-cuff method in conscious spontaneously hypertensive rats and heart rate was measured simultaneously. Test drugs were administered orally. The results are summarized in Table II.

The ergolines **5b**, **5e**, **5h**, **5i**, and **7b** showed antihypertensive activity comparable to that of hydralazine or

TABLE I. Physical Properties of (5*R*,8*S*,10*R*)-8-Methylergolines (**5**—**7**)

Compd. No.	R	NX_4	Yield (%)	mp (°C) Recryst. solv.	Formula	Analysis (%) Calcd (Found)		
						C	H	N
5a	H		58	242—246 (d)[a] $CHCl_3$–hexane	$C_{19}H_{22}N_4$	74.48 (74.54	7.24 7.26	18.29 18.06)
5b	H		60	>250 (d) iso-PrOH–hexane	$C_{20}H_{24}N_4$	74.97 (74.78	7.55 7.66	17.48 17.33)
5c	H		51	263—268 (d) iso-PrOH–hexane	$C_{21}H_{26}N_4$	75.41 (75.12	7.84 7.91	16.75 16.52)
5d	H		63	209—212 (d) $CHCl_3$–hexane	$C_{22}H_{28}N_4$	75.82 (75.43	8.10 8.18	16.08 16.01)
5e	H		60	234—236 (d) $CHCl_3$–hexane	$C_{22}H_{28}N_4$	75.82 (76.11	8.10 8.32	16.08 16.15)
5f	H		51	>250 (d) EtOH–hexane	$C_{25}H_{26}N_4$	78.50 (78.80	6.85 9.98	14.65 14.79)
5g	H		65	216—219 Me_2CO–hexane	$C_{22}H_{26}N_4O_2$	69.82 (69.95	6.92 7.00	14.80 14.77)
5h	H		50	147—149 iso-PrOH–hexane	$C_{19}H_{22}N_4$	74.48 (74.19	7.24 7.20	18.20 18.02)
5i	H		37	146—149 $CHCl_3$–hexane	$C_{26}H_{28}N_4$	78.75 (78.45	7.12 7.18	14.13 13.88)
5j	H		45	94—96 iso-PrOH–hexane	$C_{18}H_{21}N_5 \cdot H_2O$	66.44 (66.37	7.12 7.15	21.52 21.36)
5k	H		27	122—124 $CHCl_3$–hexane	$C_{17}H_{20}N_6$	66.21 (66.35	6.54 6.56	27.25 26.98)
5l	H		21	114—116 iso-PrOH–hexane	$C_{17}H_{20}N_6 \cdot 1/2H_2O$	64.33 (64.41	6.67 6.63	26.48 26.45)
5m	H		49	253—256 (d) C_6H_6–Et_2O	$C_{19}H_{23}N_3O_2 \cdot 1/3H_2O$	68.86 (68.80	7.20 7.20	12.68 12.55)
6a	Cl		46	252—258 (d) $CHCl_3$–hexane	$C_{19}H_{21}ClN_4$	66.95 (66.87	6.21 6.11	16.44 16.26)
6b	Cl		37 41[b]	>265 (d) $CHCl_3$–Et_2O	$C_{25}H_{25}ClN_4$	72.02 (72.12	6.04 6.21	13.44 13.22)
6c	Cl		52 45[b]	186—188 Me_2CO–hexane	$C_{18}H_{20}ClN_5$	63.24 (63.57	5.90 5.95	20.49 20.44)
7a	Br		50	250—255 (d) $CHCl_3$–Me_2CO	$C_{19}H_{21}BrN_4$	59.23 (58.98	5.49 5.43	14.54 14.25)
7b	Br		55 48[c]	>275 (d) EtOH–hexane	$C_{25}H_{25}BrN_4$	65.08 (65.29	5.46 5.54	12.14 12.05)
7c	Br		34 46[c]	191—194 Me_2CO–hexane	$C_{18}H_{20}BrN_5$	55.97 (56.35	5.22 5.24	18.13 18.18)

a) Decomposition. *b*) By chlorination. *c*) By bromination.

nifedipine. The ergolines with 1-imidazolyl (**5a**), 1,2,4-triazol-1-yl (**5j**), 1-tetrazolyl (**5k**), and 2-tetrazolyl (**5l**) groups exhibited potent activities, **5j** being extremely active. The ergoline **5l** with a 2-tetrazolyl group was more potent than **5k**. Introduction of chlorine and bromine atoms at the 2-position of the ergoline skeleton retained the activity. The imidazoles **6a** and **7a** exhibited relatively potent activities. The triazoles **6c** and **7c** showed extremely high potency. It seems that 1-imidazolyl, 1,2,4-triazol-1-yl, and 2-tetrazolyl groups as the heterocyclic substituent are preferable for antihypertensive activity. The ergoline **5m** scarcely affected the blood pressure, but strongly lowered

the heart rate.

Detailed results for some compounds are given in Table III. The maximum falls of systolic blood pressure after oral administration of **5a**, **5j**, **5k**, **6c**, and **7c** at 3.0 mg/kg were 95, 119, 88, 110, and 132 mmHg, respectively, while those of cianergoline, bromocriptine mesylate, hydralazine, and nifedipine at the same dose were 40, 37, 47, and 49 mmHg, respectively. The durations of significant antihypertensive effects of these new ergolines were more than 7 h. The change of the blood pressure by **5m** was small, but heart rate fell by 146 beats/min. The fall lasted for more than 7 h. This response to **5m** is not due to β-adrenoceptor blockade and the mechanism is still unknown.

Table II. Antihypertensive Activities of (5*R*,8*S*,10*R*)-8-Methylergolines (**5**—**7**) Administered Orally in Spontaneously Hypertensive Rats

Compd. No.	Dose (mg/kg)	Systolic blood pressure[a] Initial value (mmHg)	Maximum change (mmHg)	Duration[b] (h)	Heart rate[a] Initial value (beats/min)	Maximum change (beats/min)
5a	3	226	−95	>7	415	−29
5b	3	218	−47	>7	422	−22
5c	3	223	−40	5—7	411	−9, 16
5d	3	232	−33	>7	397	27
5e	3	228	−52	>24	430	−36
5f	3	210	−34	3—5	449	−31
5g	3	238	−14	—	356	−9, 7
5h	3	233	−53	>7	418	−46
5i	3	236	−44	>7	401	−5, 3
5j	3	212	−119	>7	421	57
5k	3	234	−66	>7	385	26
5l	3	235	−88	>7	382	−6, 9
5m	3	229	24	3—5	430	−146[c]
6a	3	224	−77	—	403	−10, 13
6b	3	211	−13	—	389	29
6c	3	230	−110	>7	406	46
7a	3	227	−72	>7	402	−21, 7
7b	3	223	−52	5—7	414	35, −7
7c	3	220	−132	>7	386	−8
Cia[d]	3	201	−40	>7	398	−28
	10	199	−56	>7	390	−32
Bro[e]	3	216	−37	>7	375	−8
	10	222	−54	>7	364	−13
Dih[f]	10	224	−20	—	394	−41
Hyd[g]	3	230	−47	>7	394	38
Nif[h]	3	194	−49	2—4	381	30
	10	197	−72	>7	382	42

a) Each value is the mean from three or more animals. *b*) The time at which blood pressure recovered to within 10% of the initial value. *c*) Decrease of heart rate lasted more than 7 h. *d*) Cianergoline. *e*) Bromocriptine mesylate. *f*) Dihydroergotoxine mesylate. *g*) Hydralazine. *h*) Nifedipine.

Dopaminergic activity was evaluated by observation of contralateral rotational behavior after oral administration in rats with unilateral 6-hydroxydopamine-induced lesions of the substantia nigra. The results are summarized in Table IV.

Ergolines **5e**, **5g**—**k**, and **5l** showed activity equal or superior to that of bromocriptine mesylate. But these compounds were far less active than BAM-1110, BAM-1602, or pergolide mesylate. The activity was not enhanced by introduction of a chlorine or bromine atom at the 2-position of the ergoline ring. It seems that (5*R*,8*S*,10*R*)-ergolines are inferior to (5*R*,8*R*,10*R*)-ergolines[8] in dopaminergic activity. For example, the activity of **5j**, the epimer of BAM-1110, was remarkably weaker than that of BAM-1110.

In the new (5*R*,8*R*,10*R*)-[8] and (5*R*,8*S*,10*R*)-ergolines, antihypertensive and dopaminergic activities appear to be separated.[15] For example, **5a** and **7c** with potent antihypertensive activity showed weak dopaminergic activity, and BAM-1602, an extremely potent dopaminergic compound, exhibited no significant antihypertensive activity.[8]

Emetic activity in dogs and acute toxicity in mice are summarized in Table V. None of the ergolines was highly toxic.

We have selected **5a** (BAM-2101) and **7c** (BAM-2202), with extremely potent antihypertensive activity, for further pharmacological investigations. Antihypertensive effects of **5a** and **7c** are considered to be mainly attributable to blockade of α_1-adrenoceptors. Details will be reported in the near future.

Experimental

All melting points were measured on a Yanagimoto MP-S3 apparatus and are uncorrected. NMR spectra were measured on a Hitachi R-90H or a JEOL JNM-EX270 spectrometer with tetramethylsilane as an internal standard. IR spectra were measured on a Shimadzu FTIR-4200 spectrometer. Column chromatography was carried out on Fuji Davison BW-80 silica gel or Wako activated alumina.

Methyl (5*R*,8*R*,10*R*)-2-Chloro-6-methyl-8-ergolinecarboxylate (1b)[10] *N*-Chlorosuccinimide (6.0 g, 44.9 mmol) was added in portions to a

Table III. Effects of New Ergolines Administered Orally on Systolic Blood Pressure and Heart Rate in Spontaneously Hypertensive Rats[a]

Compd.	Dose (mg/kg)	*n*	Initial value (mmHg)	Changes in blood pressure (mmHg) 1	3	5	7	24 (h)	Initial value (beats/min)	Changes in heart rate (beats/min) 1	3	5	7	24 (h)
Control		4	213± 9	−1± 4	−2± 5	−4± 5	−7± 6	−1± 5	399±13	−3±10	−7±10	−7±10	−4±11	−4±12
5a	3	3	226±10	−95±11	−90± 6	−86± 3	−84±10	−9±12	415±10	−19±18	−20± 6	−18±15	−29± 9	−29±14
5j	3	3	212± 8	−119±11	−109± 7	−101± 9	−99± 8	−20±15	421±27	31±28	48±23	46±30	57±20	−10±20
5l	3	3	235±11	−88±10	−78±12	−66±17	−66±20	−7± 4	382±14	−1±21	−6± 9	−1±14	9± 7	8± 2
5m	3	3	229± 6	22± 9	24± 7	16±12	−12± 8	−8±10	430± 9	−125±13	−146±12	−119±26	−105±15	−18± 5
6c	3	3	230±10	−110±23	−99±18	−76±14	−96±18	4±16	406±16	46±42	35±44	4±29	6±25	2± 1
7c	3	3	220±16	−132± 9	−100±12	−89±22	−78±21	5± 4	386±10	−8±13	−8±21	−6±11	−5±11	12±10
Cia[b]	3	5	201± 7	−27± 3	−33± 3	−40± 3	−30± 7	−1± 6	398± 5	−17± 9	−28±11	−25±11	−25±11	−6±14
	10	5	199± 2	−39± 9	−55± 6	−56± 5	−48± 4	−20± 7	390±10	−27± 6	−32±11	−24±10	−16±11	−11± 7
Bro[c]	3	4	216± 6	−31± 8	−37±10	−25±14	−27± 8	−6± 4	375±16	5±14	−8±16	−4±13	−4±13	−2±14
	10	4	222± 5	−46± 7	−54± 4	−49± 5	−45± 7	−4± 2	364± 8	−14± 9	−5±20	−4±19	−3±14	23±11
Hyd[d]	3	4	230±13	−44± 3	−47± 4	−43± 6	−39± 2	−20± 5	394± 6	38± 8	28± 3	22± 7	19± 8	9±14
Nif[e]	3	4	194± 3	−49± 5	−40± 3	−17± 5	−12± 1	1± 2	381± 2	30± 4	25± 6	7± 3	0± 3	1± 2
	10	4	197± 1	−70±11	−72±10	−46± 6	−37± 6	−5± 4	382± 4	42± 5	34± 7	12± 5	7± 8	−1± 2

a) Each value is the mean ± standard error. *b*) Cianergoline. *c*) Bromocriptine mesylate. *d*) Hydralazine. *e*) Nifedipine.

TABLE IV. Contralateral Rotational Behavior After Oral Administration of New Ergolines in Rats with Unilateral 6-Hydroxydopamine-Induced Lesion of Substantia Nigra

Compd. No.	Rotational behavior Rotated/treated animals									
	Dose (mg/kg)									
	0.03	0.1	0.3	1.5	3.12	6.25	25	50	100	200
5a							0/2	1/2	2/2	
5b								0/2		
5c							0/2			
5d							0/2	1/2		
5e						1/2	2/2		2/2	
5f								0/2		
5g						0/2	2/2			
5h					1/2	2/2	2/2			
5i					0/2	2/2	2/2			
5j						1/2	2/2	2/2		
5k					1/2	2/2	2/2			
5l						0/2	2/2			
5m							0/2	1/2		
6a							0/2			
6b							0/2			
6c							0/2			
7a							0/2			
7b							0/2			
7c							0/2			
BAM-1110			0/5	3/5	5/5	5/5				
BAM-1602	0/6	4/6	6/6							
Cia[a]									0/2	0/2
Bro[b]						0/5	3/5			
Dih[c]							0/2		1/2	1/2
Per[d]		1/2	2/2							

a) Cianergoline. *b*) Bromocriptine mesylate. *c*) Dihydroergotoxine mesylate. *d*) Pergolide mesylate.

TABLE V. Emetic Activity in Conscious Dogs and Acute Toxicity in Mice

Compd. No.	Emetic activity Vomited/treated animals (μg/kg, i.v.)	LD_{50} or mortality (mg/kg, *p.o.*)
5a	30(0/4), 100 (1/4), 300 (2/4)	270
5b		500 (1/2), 1000 (2/2)
5c		200 (0/2), 500 (2/2)
5d		200 (0/2), 500 (2/2)
5e		200 (0/2), 500 (2/2)
5f		500 (1/2), 1000 (2/2)
5g		200 (0.2), 500 (2/2)
5h		200 (1/2), 500 (2/2)
5i		100 (0/2), 200 (2/2)
5j	30 (0/4), 100 (3/4)	290
5k		200 (0/2), 500 (2/2)
5l	30 (0/2), 100 (2/2)	950
5m		200 (0/2), 500 (2/2)
6a		100 (0/2), 200 (1/2), 500 (2/2)
6b		500 (0/2)
6c		100 (0/2), 200 (1/2), 500 (2/2)
7a		200 (0/2), 500 (2/2)
7b		>1000
7c		100 (0/2), 200 (2/2)
Cia[a]	30 (0/2), 100 (2/2)	>1500
Bro[b]	3 (0/4), 10 (3/4), 30 (4/4)	2800
Dih[c]	3 (0/4), 10 (4/4)	>1500
Per[d]	1 (0/2), 3 (2/2), 10 (2/2)	190

a) Cianergoline. *b*) Bromocriptine mesylate. *c*) Dihydroergotoxine mesylate. *d*) Pergolide mesylate.

solution of methyl (5*R*,8*R*,10*R*)-6-methyl-8-ergolinecarboxylate (**1a**,[9] 10 g, 35.2 mmol) in dioxane (100 ml) heated at 60 °C with stirring. The mixture was heated and stirred for 1 h, then the solvent was evaporated off *in vacuo*. The residue was chromatographed on a silica gel column with iso-Pr_2O. The product was crystallized with hexane to give **1b** (9.1 g, 81%). An analytical sample was recrystallized from Et_2O–hexane to afford colorless needles, mp 203—207 °C (dec.) (Lit.[10] mp 209—211 °C). IR (KBr): 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.58 (1H, q, J=13.8 Hz), 2.16 (1H, td, J=10.2, 4.5 Hz), 2.36 (1H, t, J=11.4 Hz), 2.52 (3H, s), 2.59 (1H, dd, J=15.2, 4.2 Hz), 2.86—3.03 (3H, m), 3.22—3.35 [2H, m, 3.30 (1H, dd, J=15.2, 4.5 Hz)], 3.75 (3H, s), 6.97 (1H, d, J=6.9 Hz), 7.11 (1H, d, J=7.9 Hz), 7.16 (1H, dd, J=7.9, 6.9 Hz), 7.90 (1H, br s).

Methyl (5*R*,8*S*,10*R*)-6-Methyl-8-ergolinecarboxylate (2a)[9,11] The ester **2a** was prepared according to method A for **2b**. 66% yield, mp 167—169 °C (C_6H_6–hexane) (Lit.[9] mp 187 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.57 (1H, td, J=13.5, 5.1 Hz), 1.96—3.57 [11H, m, 2.41 (3H, s)], 3.70 (3H, s), 6.70—7.17 (4H, m), 7.94 (1H, br). *Anal.* Calcd for $C_{17}H_{20}N_2O_2$: C, 71.81; H, 7.09; N, 9.85. Found: C, 71.72; H, 7.14; N, 9.72.

Methyl (5*R*,8*S*,10*R*)-2-Chloro-6-methyl-8-ergolinecarboxylate (2b) A) A solution of **1b** (10.0 g, 31.4 mmol) in THF (50 ml) was added dropwise to a solution of lithium diisopropylamide, prepared from butyllithium (1.6 M solution in hexane, 78.3 ml, 125 mmol), diisopropylamine (12.6 g, 125 mmol), and THF (150 ml), at −20 °C with stirring, and stirring was continued for 30 min at −20 °C. After being cooled to −50 °C, the reaction mixture was made acidic with 10% AcOH. The solvent was evaporated off *in vacuo* and a solution of $NaHCO_3$ was added to the residue. The whole was extracted with CH_2Cl_2. The extract was washed with H_2O and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on a silica gel column with isopropyl acetate–hexane (3:1). The product was recrystallized from C_6H_6–hexane to give colorless needles (6.2 g, 62%), mp 184—186 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (1H, td, J=13.5, 5.1 Hz), 1.92—3.56 [11H, m, 2.42 (3H, s)], 3.73 (3H, s), 6.80—7.18 (3H, m), 7.75 (1H, br). *Anal.* Calcd for $C_{17}H_{19}ClN_2O_2$: C, 64.05; H, 6.01; N, 8.79. Found: C, 64.03; H, 5.99; N, 8.70.

B) The ester **2b** was prepared in the same manner as described for **1b**. 69% yield, mp 184—186 °C (C_6H_6–hexane).

Methyl (5*R*,8*S*,10*R*)-Bromo-6-methyl-8-ergolinecarboxylate (2c)[11b] Trimethylanilinium perbromide (6.9 g, 18.4 mmol) was added in portions to a solution of **1a** (5.0 g, 17.6 mmol) in THF (100 ml) with stirring and cooling in a water bath. Stirring was continued for 1 h at room temperature. The reaction mixture was made alkaline with aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$, treated with activated charcoal and concentrated *in vacuo*. The residue was recrystallized from C_6H_6–hexane to give colorless needles (4.7 g, 74%), mp 193—196 °C (Lit.[11b] mp 185—186 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.56 (1H, td, J=13.6, 5.0 Hz), 1.92—3.56 [11H, m, 2.42 (3H, s)], 3.72 (3H, s), 6.81—7.13 (3H, m), 7.81 (1H, br).

(5*R*,8*S*,10*R*)-6-Methyl-8-ergolinemethanols (3) (5*R*,8*S*,10*R*)-2-Bromo-6-methyl-8-ergolinemethanol (**3c**): A suspension of $LiAlH_4$ (0.68 g, 17.9 mmol) in THF (50 ml) was added dropwise to a solution of **2c** (5.0 g, 13.8 mmol) in THF (50 ml) with stirring in an ice bath. Stirring was continued for 0.5 h, then AcOEt and H_2O were added to the reaction mixture to decompose excess $LiAlH_4$. The precipitate was filtered off using Celite. The filtrate was concentrated *in vacuo*, and the residue was recrystallized from AcOEt–hexane to give colorless needles (4.3 g, 93%), mp 137—139 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.53—2.80 [9H, m, 1.73 (1H, td, J=12.7, 5.1 Hz), 2.42 (3H, s)], 2.98—3.40 (3H, m), 3.89 (1H, dd, J=10.5, 3.6 Hz), 4.06 (1H, dd, J=10.5, 4.8 Hz), 6.76—7.14 (3H, m), 7.83 (1H, br). *Anal.* Calcd for $C_{16}H_{19}BrN_2O$: C, 57.32; H, 5.71; N, 8.36. Found: C, 57.42; H, 5.68; N, 8.06.

The methanols **3a** and **3b** were prepared in the same manner as described above.

3a[12]: 95% yield, mp >250 °C (dec.) (iso-PrOH–Et_2O) (Lit.[12] mp 293 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.79 (1H, td, J=13.0, 5.5 Hz), 1.95—2.06 (1H, m), 2.22 (1H, td, J=10.6, 4.3 Hz), 2.42 (3H, s), 2.56 (1H, dd, J=11.9, 2.4 Hz), 2.61—2.75 (2H, m), 3.08—3.17 (1H, m), 3.34—3.48 (2H, m), 3.99 (1H, dd, J=10.2, 2.4 Hz), 4.09 (1H, dd, J=10.2, 4.6 Hz), 6.84—6.96 (2H, m), 7.12—7.21 (2H, m), 7.88 (1H, br). *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.92; H, 7.99; N, 10.85.

3b: 82% yield, mp 173—175 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.51—2.76 [9H, m, 1.71 (1H, td, J=12.9, 5.2 Hz), 2.40 (3H, s)], 2.97—3.47 (3H, m), 3.89 (1H, dd, J=10.5, 3.6 Hz), 4.06 (1H, dd, J=10.5, 4.8 Hz), 6.73—7.12 (3H, m), 7.85 (1H, br). *Anal.* Calcd for $C_{16}H_{19}ClN_2O \cdot 1/3H_2O$: C, 64.75; H, 6.68; N, 9.44. Found: C, 64.95; H, 6.59; N, 9.18.

TABLE VI. ^{1}H-NMR Spectral Data for (5*R*,8*S*,10*R*)-8-Methylergolines (**5**—**7**) in $CDCl_3$

Compd. No.	Chemical shifts (ppm)
5a	1.73 (1H, td, *J*=13.1, 4.5 Hz), 1.96—3.56 [11H, m, 2.40 (3H, s), 3.38 (1H, dd, *J*=14.6, 4.5 Hz)], 4.27 (1H, dd, *J*=14.1, 7.2 Hz), 4.42 (1H, dd, *J*=14.1, 8.4 Hz), 6.70—7.34 (6H, m), 7.60 (1H, s), 8.10 (1H, br)
5b	1.72 (1H, td, *J*=12.9, 4.2 Hz), 2.00—3.52 [14H, 2.36 (3H, s), 2.43 (3H, s), 3.36 (1H, dd, *J*=14.1, 4.5 Hz)], 4.06 (1H, dd, *J*=13.8, 6.6 Hz), 4.30 (1H, dd, *J*=13.8, 8.6 Hz), 6.70—7.17 (6H, m), 7.88 (1H, br)
5c	1.36 (3H, t, *J*=7.1 Hz), 1.72 (1H, td, *J*=13.1, 4.8 Hz), 2.00—3.53 [13H, m, 2.36 (3H, s), 2.73 (2H, q, *J*=7.1 Hz), 3.36 (1H, dd, *J*=14.3, 4.4 Hz)], 4.06 (1H, dd, *J*=13.8, 6.8 Hz), 4.32 (1H, dd, *J*=13.8, 8.4 Hz), 6.67—7.19 (6H, m), 7.93 (1H, br)
5d	0.99 (3H, t, *J*=7.0 Hz), 1.47—3.51 [16H, m, 2.35 (3H, s), 2.69 (2H, t, *J*=7.5 Hz), 3.35 (1H, dd, *J*=14.1, 4.5 Hz)], 4.04 (1H, dd, *J*=13.8, 6.5 Hz), 4.33 (1H, dd, *J*=13.8, 8.3 Hz), 6.70—7.20 (6H, m), 7.99 (1H, br)
5e	1.30 (3H, d, *J*=6.8 Hz), 1.36 (3H, d, *J*=6.8 Hz), 1.72 (1H, td, *J*=13.0, 4.8 Hz), 1.99—3.51 [12H, m, 2.36 (3H, s), 3.36 (1H, dd, *J*=14.6, 4.4 Hz)], 4.08 (1H, dd, *J*=14.0, 6.8 Hz), 4.33 (1H, dd, *J*=14.0, 8.1 Hz), 6.69—7.20 (6H, m), 7.98 (1H, br)
5f	1.61 (1H, td, *J*=12.9, 4.4 Hz), 1.91—3.06 [10H, m, 2.27 (3H, s)], 3.29 (1H, dd, *J*=14.3, 4.0 Hz), 4.25 (1H, dd, *J*=14.1, 6.9 Hz), 4.53 (1H, dd, *J*=14.1, 8.2 Hz), 6.57—6.87 (2H, m), 6.93—7.47 (7H, m), 7.50—7.76 (2H, m), 8.01 (1H, br)
5g	1.45 (3H, t, *J*=7.2 Hz), 1.72 (1H, td, *J*=13.4, 4.8 Hz), 2.00—3.57 [11H, 2.42 (3H, s), 3.41 (1H, dd, *J*=14.6, 3.9 Hz)], 4.45 (2H, q, *J*=7.2 Hz), 4.78 (2H, d, *J*=7.8 Hz), 6.77—7.02 (2H, m), 7.07—7.33 (4H, m), 8.07 (1H, br)
5h	1.66 (1H, td, *J*=13.1, 4.8 Hz), 1.96—2.86 [9H, m, 2.36 (3H, s)], 2.92—3.50 [2H, m, 3.35 (1H, dd, *J*=14.1, 4.5 Hz)], 4.41 (1H, dd, *J*=13.4, 7.2 Hz), 4.51 (1H, dd, *J*=13.4, 7.4 Hz), 6.19 (1H, dd, *J*=2.1, 1.8 Hz), 6.60—6.87 (2H, m), 6.95—7.20 (2H, m), 7.37 (1H, d, *J*=2.1 Hz), 7.50 (1H, d, *J*=1.8 Hz), 7.83 (1H, br)
5i	1.72 (1H, td, *J*=13.0, 5.0 Hz), 2.02—2.94 [12H, m, 2.38 (3H, s), 2.42 (3H, s)], 3.00—3.59 [2H, m, 3.41 (1H, dd, *J*=14.7, 4.5 Hz)], 4.32 (1H, dd, *J*=13.8, 6.9 Hz), 4.49 (1H, dd, *J*=13.8, 8.1 Hz), 6.36 (1H, s), 6.78—7.58 (7H, m), 7.71—8.10 (3H, m)
5j	1.73 (1H, td, *J*=13.2, 4.7 Hz), 2.00—3.51 [11H, m, 2.36 (3H, s), 3.35 (1H, dd, *J*=14.4, 4.4 Hz)], 4.42 (1H, dd, *J*=13.5, 6.7 Hz), 4.60 (1H, dd, *J*=13.5, 8.1 Hz), 6.68—6.91 (2H, m), 6.97—7.20 (2H, m), 7.89 (1H, br), 7.93 (1H, s), 8.06 (1H, s)
5k	1.47—2.91 [10H, m, 1.69 (1H, td, *J*=13.4, 4.5 Hz), 2.39 (3H, s)], 2.98—3.51 [2H, m, 3.34 (1H, dd, *J*=14.7, 4.5 Hz)], 4.95 (1H, dd, *J*=13.5, 6.7 Hz), 5.05 (1H, dd, *J*=13.5, 7.7 Hz), 6.58—6.88 (2H, m), 6.91—7.20 (2H, m), 7.90 (1H, br), 8.46 (1H, s)
5l	1.83 (1H, td, *J*=13.5, 4.8 Hz), 2.06—3.59 [11H, m, 2.40 (3H, s), 3.42 (1H, dd, *J*=14.4, 3.9 Hz)], 4.75 (1H, dd, *J*=13.6, 6.4 Hz), 4.94 (1H, dd, *J*=13.6, 8.8 Hz), 6.70—7.03 (2H, m), 7.08—7.37 (2H, m), 7.68 (1H, br), 8.69 (1H, s)
5m	1.65 (1H, td, *J*=12.6, 5.0 Hz), 1.96—3.48 [11H, m, 2.38 (3H, s), 3.32 (1H, dd, *J*=14.3, 3.9 Hz)], 3.50—3.77 (4H, m), 4.17—4.47 (2H, m), 6.70—6.92 (2H, m), 6.95—7.20 (2H, m), 7.78 (1H, br)
6a	1.66 (1H, td, *J*=13.2, 5.0 Hz), 1.92—2.79 [9H, m, 2.37 (3H, s)], 2.81—3.41 [2H, m, 3.24 (1H, dd, *J*=14.7, 4.3 Hz)], 4.19 (1H, dd, *J*=14.4, 6.9 Hz), 4.36 (1H, dd, *J*=14.4, 8.3 Hz), 6.67—7.20 (5H, m), 7.46 (1H, br s), 7.94 (1H, br)
6b	1.59 (1H, td, *J*=13.5, 4.9 Hz), 2.00—2.85 [10H, m, 2.29 (3H, s)], 3.21 (1H, dd, *J*=14.6, 4.3 Hz), 4.29 (1H, dd, *J*=13.5, 6.8 Hz), 4.56 (1H, dd, *J*=13.5, 8.1 Hz), 6.78 (1H, d, *J*=7.1 Hz), 7.02—7.46 (7H, m), 7.64—7.73 (2H, m), 7.92 (1H, br)
6c	1.69 (1H, td, *J*=13.2, 4.8 Hz), 1.92—2.75 [9H, m, 2.37 (3H, s)], 2.78—3.39 [2H, m, 3.25 (1H, dd, *J*=14.6, 4.5 Hz)], 4.40 (1H, dd, *J*=13.2, 6.6 Hz), 4.59 (1H, dd, *J*=13.2, 8.0 Hz), 6.66—6.88 (1H, m), 6.92—7.21 (2H, m), 7.93 (1H, s), 8.02 (1H, br), 8.04 (1H, s)
7a	1.70 (1H, td, *J*=12.9, 4.5 Hz), 1.93—3.36 [11H, m, 2.38 (3H, s), 3.18 (dd, *J*=14.3, 4.0 Hz)], 4.19 (1H, dd, *J*=13.8, 7.2 Hz), 4.37 (1H, dd, *J*=13.8, 8.3 Hz), 6.58—7.23 (5H, m), 7.48 (1H, s), 8.17 (1H, br)
7b	1.58 (1H, td, *J*=13.8, 4.9 Hz), 2.06 (1H, td, *J*=10.1, 4.3 Hz), 2.15—2.50 [7H, m, 2.31 (3H, s), 2.43 (1H, dd, *J*=14.9, 11.3 Hz)], 2.62—2.82 (2H, m), 3.16 (1H, dd, *J*=14.9, 4.3 Hz), 4.29 (1H, dd, *J*=13.9, 6.9 Hz), 4.54 (1H, dd, *J*=13.9, 8.5 Hz), 6.73—6.82 (1H, m), 7.04—7.45 (7H, m), 7.68 (1H, d, *J*=1.6 Hz), 7.71 (1H, d, *J*=1.6 Hz), 7.98 (1H, br)
7c	1.72 (1H, td, *J*=13.1, 4.3 Hz), 1.94—2.76 [9H, m, 2.37 (3H, s)], 2.79—3.33 [2H, m, 3.19 (1H, dd, *J*=14.4, 4.5 Hz)], 4.40 (1H, dd, *J*=13.2, 6.3 Hz), 4.58 (1H, dd, *J*=13.2, 8.1 Hz), 6.60—6.86 (1H, m), 6.94—7.20 (2H, m), 7.93 (1H, s), 8.04 (1H, s), 8.09 (1H, br)

(5*R*,8*S*,10*R*)-6-Methyl-8-ergolinylmethyl *p*-Toluenesulfonates (4) A) (5*R*,8*S*,10*R*)-2-Bromo-6-methyl-8-ergolinylmethyl *p*-Toluenesulfonate (**4c**): *p*-Toluenesulfonyl chloride (7.1 g, 37.2 mmol) was added in portions to a mixture of **3c** (5.0 g, 14.9 mmol) and pyridine (50 ml) with stirring at room temperature. Then stirring was continued for 3 h. After addition of H_2O (4 ml) and stirring for 0.5 h, the reaction mixture was made alkaline with aqueous K_2CO_3, diluted with H_2O, and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatograghed on a silica gel column with AcOEt–hexane (1 : 1). The product was recrystallized from AcOEt–hexane to give colorless needles (6.5 g, 89%), mp 101—103 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (1H, td, *J*=13.2, 4.5 Hz), 1.79—3.23 [14H, m, 2.27 (6H, s), 3.06 (1H, dd, *J*=14.4, 4.3 Hz)], 4.32 (1H, d, *J*=7.7 Hz), 4.34 (1H, d, *J*=6.6 Hz), 6.57—6.81 (1H, m), 6.88—7.30 (4H, m), 7.60—8.00 [3H, m, 7.85 (1H, br)]. *Anal.* Calcd for $C_{23}H_{25}BrN_2O_3S$: C, 56.44; H, 5.15; N, 5.72. Found: C, 56.75; H, 5.05; N, 5.92.

Compounds **4a** and **4b** were prepared in the same manner as described above.

4a[13]: 87% yield, mp 199—201 °C (dec.) ($CHCl_3$–AcOEt) (Lit.[13] mp 255—258 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.57 (1H, td, *J*=13.8, 4.8 Hz), 1.88—2.95 [13H, m, 2.27 (6H, s)], 3.26 (1H, dd, *J*=14.4, 4.2 Hz), 4.34 (1H, d, *J*=7.7 Hz), 4.36 (1H, d, *J*=5.9 Hz), 6.66—6.84 (2H, m), 6.95—7.27 [4H, m, 7.18 (2H, A_2B_2 type d, *J*=8.3 Hz)], 7.65—7.85 [3H, m, 7.74 (2H, A_2B_2 type d, *J*=8.3 Hz)]. *Anal.* Calcd for $C_{23}H_{26}N_2O_3S$: C, 67.29; H, 6.38; N, 6.82. Found: C, 67.00; H, 6.21; 6.79.

4b: 76% yield, mp 144—146 °C (AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 1.53 (1H, td, *J*=13.6, 4.7 Hz), 1.80—2.92 [13H, m, 2.26 (6H, s)], 3.15 (1H, dd, *J*=14.3, 3.9 Hz), 4.32 (1H, d, *J*=7.2 Hz), 4.33 (1H, d, *J*=6.8 Hz), 6.63—6.75 (1H, m), 6.91—7.26 [4H, m, 7.18 (2H, A_2B_2 type d, *J*=8.4 Hz)], 7.62—7.86 [3H, m, 7.73 (2H, A_2B_2 type d, *J*=8.4 Hz)]. *Anal.* Calcd for $C_{23}H_{25}ClN_2O_3S$: C, 62.08; H, 5.66; N, 6.30. Found: C, 62.25; H, 5.66; N, 6.01.

(5*R*,8*S*,10*R*)-6-Methylergolines (5—7) A) (5*R*,8*S*,10*R*)-6-Methyl-8-(1-imidazolylmethyl)ergoline (**5a**): Sodium hydride (60% in oil) (0.40 g, 10.0 mmol) was added in portions to a solution of imidazole (0.75 g, 11.0 mmol) in *N*,*N*-dimethylformamide (50 ml) with stirring in a water bath, and then **4a** (2.0 g, 4.87 mmol) was added. The mixture was heated for 2 h at *ca.* 90 °C with stirring. After removal of the solvent the residue was chromatographed on an alumina column with Me_2CO. Recrystallization from $CHCl_3$–hexane gave colorless needles (0.87 g, 58%), mp 242—246 °C (dec.).

B) (5*R*,8*S*,10*R*)-6-Methyl-8-(1-tetrazolylmethyl)ergoline (**5k**) and (5*R*,8*S*,10*R*)-6-Methyl-8-(2-tetrazolylmethyl)ergoline (**5l**): Sodium hydride (60% in oil) (0.88 g, 22.0 mmol) was added in portions to a solution of tetrazole (1.7 g, 24.3 mmol) in *N*,*N*-dimethylformamide (40 ml) with stirring in a water bath, and then **4a** (4.0 g, 9.74 mmol) was added. The mixture was heated for 2 h at *ca.* 90 °C with stirring. After being cooled, the reaction mixture was diluted with H_2O and extracted with AcOEt.

The extract was washed with H_2O, dried over Mg_2SO_4, and concentrated *in vacuo*. The residue was chromatographed on a silica gel column with AcOEt–EtOH (40 : 1). The first fraction afforded **5k**, which was recrystallized from $CHCl_3$–hexane to give colorless prisms (0.81 g, 27%), mp 122—124 °C. The second fraction afforded **5l**, which was recrystallized from iso-PrOH–hexane to afford colorless prisms (0.66 g, 21%), mp 114—116 °C.

The other compounds were prepared in the same manner as described under A and B. The ergolines **6b**, **6c**, **7b**, and **7c** were also prepared in the following manner.

C) (5*R*,8*S*,10*R*)-2-Chloro-6-methyl-8-(1,2,4-triazol-1-ylmethyl)ergoline (**6c**): *N*-Chlorosuccinimide (1.1 g, 8.24 mmol) was added in portions to a solution of **5j** (2.0 g, 6.15 mmol) in dioxane (20 ml) at 60 °C with stirring. The mixture was heated and stirred for 1 h, then the solvent was evaporated off *in vacuo*. The residue was chromatographed on a silica gel column with AcOEt–EtOH (40 : 1). The product was recrystallized from Me_2CO–hexane to give colorless leaflets (1.27 g, 45%), mp 186—188 °C.

Compound **6b** was prepared in the same manner as described above.

D) (5*R*,8*S*,10*R*)-2-Bromo-6-methyl-8-(1,2,4-triazol-1-ylmethyl)ergoline (**7c**): Trimethylanilinium perbromide (2.9 g, 7.71 mmol) was added in portions to a solution of **5j** (2.0 g, 6.15 mmol) and triethylamine (0.70 g, 9.6 mmol) in THF (50 ml) with stirring and cooling in a water bath. Stirring was continued for 1 h at room temperature. The reaction mixture was made alkaline with aqueous K_2CO_3 and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed on an activated alumina column with Me_2CO. The product was recrystallized from Me_2CO–hexane to give colorless prisms (1.1 g, 46%), mp 191—194 °C.

Compound **7b** was also prepared in the same manner as described above.

Pharmacological Methods Antihypertensive activity[16] and acute toxicity[17] in mice were evaluated by the previously described method. Emetic activity in dogs was evaluated in the usual manner.

Dopaminergic activity was evaluated as follows. Male Wistar rats, weighing 180—230 g, were anesthetized with sodium pentobarbital (50 mg/kg, i.p.) and 6-hydroxydopamine (10 μg/5 μl) was injected into the right median forebrain bundle. Two weeks later, contralateral circling responses were confirmed by subcutaneous administration of apomorphine at dose of 0.25 mg/kg. After 7 d, the test compounds were administered orally and, thereafter, circling responses of the rats was observed for 5 min at an interval of 15 min during a period of 8 h.

References and Notes

1) A part of this work was presented previously; S. Ohno, Y. Adachi, M. Koumori, K. Mizukoshi, M. Nagasaka, K. Ichihara, E. Kato, Abstracts of Papers, 14th Symposium on Medicinal Chemistry, Shizuoka, Japan, December 1993, p. 17.
2) E. Flueckiger, F. Troxler, A. Hofmann, Ger. Offen. 1926045 (1969) [*Chem. Abstr.*, **72**, 43969*b* (1970)].
3) E. C. Kornfeld, N. J. Bach, Eur. Patent Appl. 3667 (1979) [*Chem. Abstr.*, **92**, 181450*q* (1979)].
4) For example, R. Wilbrandt, *Angiology*, **4**, 183 (1953); A. Pöldle, *Acta Med. Scand.*, **155**, 437 (1956); K. O. Stumpe, R. Kolloch, M. Higuchi, F. Kruck, H. Vetter, *Lancet*, **1977**, 211; T. T. Yen, N. B. Stamm, J. A. Clemens, *Life Sci.*, **25**, 209 (1979); K. J. De Meirleir, F. Gerlo, W. Hollmann, L. Vanhaelst, *Br. J. Clin. Pharmacol.*, **23**, 633P (1987).
5) For example, K. Kurachi, T. Aono, K. Koike, M. Suzuki, K. Momono, T. Tamada, T. Tamura, M. Igarashi, R. Ibuki, S. Sakamoto, H. Mizuguchi, R. Iizuka, Y. Nakamura, K. Katoh, K. Seki, Y. Tomoto, O. Narita, T. Nishimura, T. Asoh. S. Tojoh, K. Katayama, M. Kusuda, Y. Nagata, *Sanka To Rinsho*, **48**, 117 (1981); R. L. Perryman, A. D. Rogol, D. L. Kaiser, R. M. MacLeod, M. O. Thorner, *J. Clin. Endoclinol. Metab.*, **53**, 772 (1981); A. Grossman, P.-M. G. Bouloux, T. Lonergan, L. H. Rees, J. A. H. Wass, G. M. Besser, *Clin. Endoclinol.*, **22**, 611 (1985); G. Bise, C. Foletti, C. Beretta-Piccoli, P. Weidmann, W. H. Ziegler, R. Mordasini, C. Bachmann, *Eur. J. Clin. Pharmacol.*, **29**, 25 (1985).
6) L. Bernardi, G. Bosisio, S. Mantegani, O. Sapini, A. Temperilli, P. Salvati, E. di Salle, G. Arcari, G. Bianchi, *Arzneim.-Forsch.*, **33**, 1094 (1983); P. Salvati, A. M. Caravaggi, E. Lamberti, M. Monteggia, G. Bianchi, *ibid.*, **33**, 1098 (1983).
7) L. Bernardi, L. Chiodini, S. Mantegani, D. Ruggieri, A. Temperilli, P. Salvati, Eur. Patent Appl. 126968 (1984) [*Chem. Abstr.*, **102**, 149582*y* (1984)]; P. Salvati, G. P. Bondiolotti, C. Caccia, F. Vaghi, G. Bianchi, *Pharmacology*, **38**, 78 (1989).
8) S. Ohno, Y. Adachi, M. Koumori, K. Mizukoshi, M. Nagasaka, K. Ichihara, E. Kato, *Chem. Pharm. Bull.*, **42**, 1463 (1994).
9) A. Stoll, A. Hofmann, T. Petrzilka, *Helv. Chim. Acta*, **29**, 635 (1946).
10) F. Troxler, A. Hofmann, *Helv. Chem. Acta*, **40**, 2160 (1957).
11) *a*) P. L. Stutz, P. A. Stadler, J.-M. Vigouret, A. Jaton, *J. Med. Chem.*, **21**, 754 (1978); *b*) J. Beneš; A. Černý, V. Miller, S. Kudrnáč, *Collect. Czech. Chem. Commun.*, **48**, 1333 (1983).
12) A. Stoll, A. Hofmann, W. Schlientz, *Helv. Chem. Acta*, **32**, 1947 (1949).
13) E. Schreier, *Helv. Chem. Acta*, **41**, 1984 (1958).
14) G. B. Barlin, T. J. Batterham, *J. Chem. Soc.* (*B*), **1967**, 516; R. Raap, J. Howard, *Can. J. Chem.*, **47**, 813 (1969); R. N. Butler, *ibid.*, **51**, 2315 (1973).
15) The results of conformational analysis will be reported in the near future.
16) S. Ohno, O. Komatsu, K. Mizukoshi, K. Ichihara, Y. Nakamura, T. Morishima, K. Sumita, *Chem. Pharm. Bull.*, **34**, 1589 (1986).
17) S. Ohno, K. Mizukoshi, O. Komatsu, Y. Kunoh, Y. Nakamura, E. Katoh, M. Nagasaka, *Chem. Pharm. Bull.*, **34**, 4150 (1986).