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

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

Research Laboratories, Maruko Seiyaku Co., Ltd., 1212 Teramae, Gejo-cho, Kasugai, Aichi 486, Japan.
Received January 24, 1994; accepted March 10, 1994

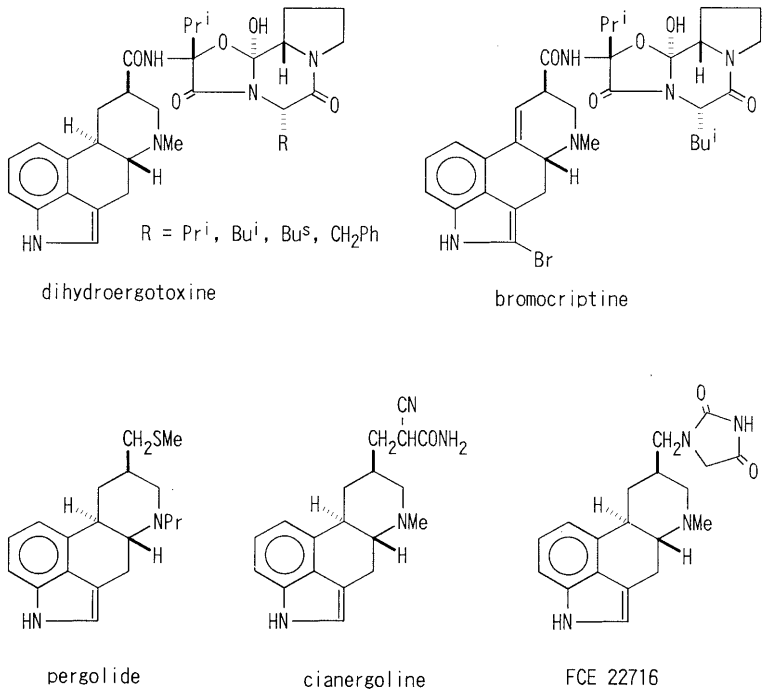
A series of new (5*R*,8*R*,10*R*)-ergoline derivatives was synthesized, and their antihypertensive and dopaminergic activities were tested in conscious spontaneously hypertensive rats and in rats with unilateral 6-hydroxydopamine-induced lesions of the substantia nigra. (5*R*,8*R*,10*R*)-6-Alkyl-8-ergolinemethanols, 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*R*,10*R*)-8-(1,2,4-Triazol-1-ylmethyl)-6-methylergoline (4s, maleate: BAM-1110) exhibited potent dopaminergic activity, about 18-fold greater than that of bromocriptine mesylate. (5*R*,8*R*,10*R*)-8-(1,2,4-Triazol-1-ylmethyl)-6-propylergoline (8b, fumarate: BAM-1602) showed extremely potent dopaminergic activity, being about 220 and 1.15 times more active than bromocriptine mesylate and pergolide mesylate, respectively. Several compounds exhibited potent antihypertensive activity. Structure–activity relationships for antihypertensive and dopaminergic activities are discussed.

Keywords antihypertensive; dopaminergic; structure–activity relationship; ergoline; BAM-1110; BAM-1602

Dihydroergotoxine has been clinically employed for patients with cerebral and peripheral circulatory disturbances. This compound possesses weak hypotensive activity[2)] and so has also been utilized as an antihypertensive. Bromocriptine[3)] and pergolide,[4)] dopamine D_2 receptor agonists, have been used in the therapy of Parkinson's disease, acromegaly, and hyperprolactinemia. Pergolide shows extremely potent D_2 receptor agonistic activity. These compounds have been reported to exhibit moderate antihypertensive activity in animals and humans.[5)] Cianergoline[6)] and FCE 22716,[7)] synthesized as antihypertensives, have relatively potent activities in animals.

Pergolide, dihydroergotoxine, cianergoline, and FCE 22716 contain the ergoline skeleton, while bromocriptine has the ergolene skeleton. It is known that these ergot-related compounds sometimes show undesirable side effects,[8)] such as nausea and vomiting, which could limit their clinical use.

We synthesized a series of new ergolines, hoping to find



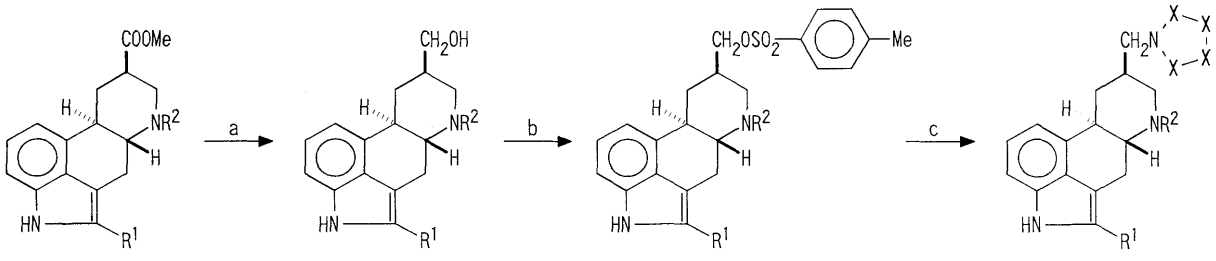
Pr^i=iso-Pr, Bu^i=iso-Bu, Bu^s=*sec*-Bu

Fig. 1

compounds with potent antihypertensive or dopaminergic activity and with weaker side effects. In this paper we describe the synthesis and structure–activity relationships of these new ergoline derivatives.

Chemistry

Methyl (5*R*,8*R*,10*R*)-8-ergolinecarboxylates (**1a—e**)[9] were reduced with $NaBH_4$ in a mixture of methanol and water or $LiAlH_4$ in tetrahydrofuran (THF) to afford the methanols (**2a—e**)[11] in good yields. The methanols **2a—e** were converted to (5*R*,8*R*,10*R*)-8-ergolinylmethyl tosylates (**3a—e**)[13] by treatment with *p*-toluenesulfonyl chloride (TsCl) in pyridine. The tosylates (**3a—e**) were treated with the sodium salts of various five-membered heterocycles containing nitrogen in *N*,*N*-dimethylformamide (DMF) to yield the desired new (5*R*,8*R*,10*R*)-ergoline derivatives (**4—8**).



1a—e **2a—e** **3a—e** **4—8**

	R^1	R^2
1—3a,4	H	Me
1—3b,5	Cl	Me
1—3c,6	Br	Me
1—3d,7	H	Et
1—3e,8	H	Pr

a) $NaBH_4$/MeOH-H_2O or $LiAlH_4$/THF; b) TsCl/pyridine; c) HNX_4, NaH/DMF

Chart 1

TABLE I. Physical Properties of (5*R*,8*R*,10*R*)-8-Methylergolines (**4—8**)

Compd. No.	R^1	R^2	NX_4	Yield (%)	mp (°C) Recryst. solv.	Formula	Analysis (%) Calcd (Found)		
							C	H	N
4a	H	Me		58	>260 (dec.) EtOH	$C_{19}H_{22}N_4$	74.48 (74.58	7.24 7.57	18.29 18.02)
4b	H	Me		51	>300 (dec.) EtOH	$C_{20}H_{24}N_4$	74.97 (74.71	7.55 7.83	17.48 17.16)
4c	H	Me		61	235—238 MeOH–iso-PrOH	$C_{21}H_{26}N_4$	75.41 (75.03	7.84 7.86	16.75 16.84)
4d	H	Me		41	223—237 (dec.) Me_2CO–hexane	$C_{22}H_{28}N_4$	75.82 (75.61	8.10 8.12	16.08 15.82)
4e	H	Me		49	282—288 (dec.) MeOH–iso-PrOH	$C_{22}H_{28}N_4$	75.82 (76.21	8.10 8.39	16.08 16.25)
4f	H	Me		66	193—195 CH_2Cl_2–AcO iso-Pr	$C_{25}H_{26}N_4 \cdot 1/2H_2O$	76.70 (76.79	6.95 6.77	14.31 14.34)
4f-m[a]					117—120 EtOH	$C_{25}H_{26}N_4 \cdot 5/2C_4H_4O_4$[b] $\cdot 1/2H_2O$	61.67 (61.87	5.47 5.74	8.22 8.38)
4g	H	Me		52	126—128 CH_2Cl_2	$C_{26}H_{28}N_4O \cdot 1/5CH_2Cl_2$	73.26 (73.12	6.66 6.83	13.04 12.95)
4h	H	Me		76	230—234 (dec.) Me_2CO	$C_{22}H_{26}N_4O_2$	69.82 (69.51	6.92 7.04	14.80 14.55)

TABLE I. (continued)

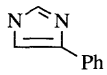
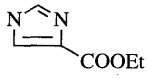
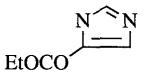
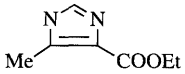
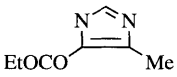
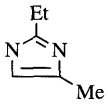
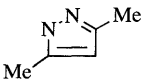
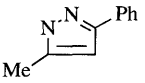
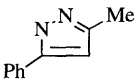
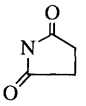
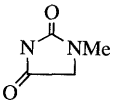
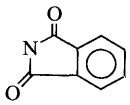
Compd. No.	R^1	R^2	NX_4	Yield (%)	mp (°C) Recryst. solv.	Formula	Analysis (%) Calcd (Found) C	H	N
4i	H	Me		64	233—237 (dec.) MeOH–Me_2CO	$C_{25}H_{26}N_4$	78.50 (78.16	6.85 6.87	14.65 14.58)
4j	H	Me		57	260—265 (dec.) CH_2Cl_2–Me_2CO	$C_{22}H_{26}N_4O_2$	69.82 (69.44	6.92 6.87	14.80 14.83)
4k	H	Me		18	160—163 Me_2CO	$C_{22}H_{26}N_4O_2 \cdot 1/2H_2O$	68.19 (68.33	7.02 6.78	14.46 14.50)
4l	H	Me		21	248—251 (dec.) EtOH–CH_2Cl_2	$C_{23}H_{28}N_4O_2$	70.38 (70.45	7.19 7.20	14.27 14.23)
4m	H	Me		18	225—227 CH_2Cl_2–Et_2O	$C_{23}H_{28}N_4O_2$	70.38 (70.44	7.19 7.26	14.27 14.18)
4n	H	Me		29	172—174 MeOH	$C_{22}H_{28}N_4$	75.82 (75.79	8.10 8.25	16.08 16.00)
4o	H	Me		91	192—194 CH_2Cl_2–iso-Pr_2O	$C_{19}H_{22}N_4$	74.48 (74.56	7.24 7.50	18.29 18.08)
4p	H	Me		31	187—190 iso-PrOH	$C_{21}H_{26}N_4 \cdot 1/2H_2O$	73.44 (73.58	7.92 7.89	16.31 16.02)
4q	H	Me		60	225—230 (dec.) Me_2CO	$C_{26}H_{28}N_4 \cdot 1/6H_2O$	78.16 (78.27	7.15 7.12	14.02 14.16)
4r	H	Me		7	169—171 Me_2CO	$C_{26}H_{28}N_4 \cdot 1/2H_2O$	77.00 (76.72	7.21 7.19	13.82 13.76)
4s	H	Me		64	>243 (dec.) MeOH	$C_{18}H_{21}N_5$	70.33 (70.42	6.89 7.07	22.78 22.73)
4s-m[a]					208—212 (dec.) MeOH	$C_{18}H_{21}N_5 \cdot C_4H_4O_4$[a]	62.40 (62.44	5.95 5.97	16.54 16.49)
4t	H	Me		7	>270 (dec.) CH_2Cl_2–MeOH	$C_{18}H_{21}N_5$	70.33 (70.53	6.89 6.86	22.78 22.82)
4u	H	Me		31	206—209 Me_2CO	$C_{17}H_{20}N_6$	66.21 (66.46	6.54 6.53	27.25 27.50)
4v	H	Me		49	>235 (dec.) EtOH	$C_{20}H_{23}N_3O_2$	71.19 (71.30	6.87 6.95	12.45 12.49)
4w	H	Me		70	>215 (dec.) CH_2Cl_2–hexane	$C_{20}H_{24}N_4O_2 \cdot 1/12CH_2Cl_2$	67.10 (67.21	6.78 7.04	15.58 15.38)
4x	H	Me		82	>255 (dec.) iso-PrOH	$C_{19}H_{23}N_3O_2$	70.13 (70.01	7.12 7.34	12.91 12.88)
4x-s[b]					>265 (dec.) H_2O–EtOH	$C_{19}H_{23}N_3O_2 \cdot CH_4O_3S$[b]	56.99 (57.07	6.46 6.55	9.97 9.99)
4y	H	Me		69	>270 (dec.) CH_2Cl_2–hexane	$C_{24}H_{23}N_3O_2$	74.78 (74.83	6.01 6.07	10.90 10.68)

TABLE I. (continued)

Compd. No.	R^1	R^2	NX_4	Yield (%)	mp (°C) Recryst. solv.	Formula	Analysis (%) Calcd (Found) C	H	N
5a	Cl	Me		41	>252 (dec.) EtOH–Et_2O	$C_{19}H_{21}ClN_4$	66.95 (66.91	6.21 6.28	16.44 16.26)
5b	Cl	Me		22	255—260 (dec.) EtOH–Et_2O	$C_{25}H_{25}ClN_4$	72.02 (71.75	6.04 6.05	13.44 13.33)
5c	Cl	Me		17	241—245 EtOH–Et_2O	$C_{18}H_{20}ClN_5$	63.24 (63.00	5.90 5.88	20.49 20.24)
6a	Br	Me		56	>260 (dec.) $CHCl_3$–Me_2CO	$C_{19}H_{21}BrN_4$	59.23 (58.96	5.49 5.47	14.54 14.38)
6b	Br	Me		48	>260 (dec.) $CHCl_3$–Et_2O	$C_{22}H_{27}BrN_4$	61.83 (61.55	6.37 6.39	13.11 13.00)
6c	Br	Me		19	>255 (dec.) EtOH–hexane	$C_{25}H_{25}BrN_4$	65.08 (64.77	5.46 5.56	12.14 11.94)
6d	Br	Me		36	225—230 CH_2Cl_2–AcOEt	$C_{18}H_{20}BrN_5 \cdot 1/12CH_2Cl_2$	55.21 (55.26	5.17 5.02	17.80 17.77)
7	H	Et		66 86[c]	>265 (dec.) MeOH	$C_{19}H_{23}N_5$	71.00 (70.84	7.21 7.19	21.79 21.92)
7-f[d]						$C_{19}H_{23}N_5 \cdot C_4H_4O_4$[d] $\cdot H_2O$	60.65 (60.81	6.42 6.33	15.37 15.22)
8a	H	Pr		60	212—214 (dec.) iso-PrOH–Et_2O	$C_{21}H_{26}N_4$	75.41 (75.41	7.84 7.98	16.75 16.49)
8b	H	Pr		84 88[c]	201—203 Me_2CO	$C_{20}H_{25}N_5$	71.61 (71.97	7.51 7.59	20.88 20.68)
8b-f[d]					>205 (dec.) MeOH	$C_{20}H_{25}N_5 \cdot C_4H_4O_4$[d]	63.84 (64.05	6.47 6.50	15.51 15.57)
8c	H	Pr		6	>235 (dec.) EtOH	$C_{20}H_{25}N_5$	71.61 (71.88	7.51 7.62	20.88 20.62)

a) Maleate. *b*) Methanesulfonate. *c*) Yield from **10**. *d*) Fumarate.

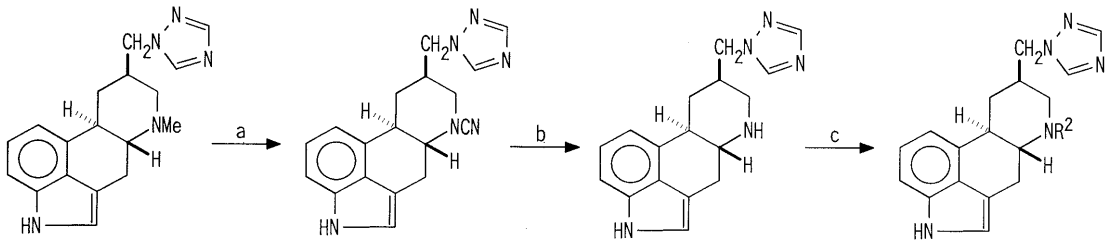
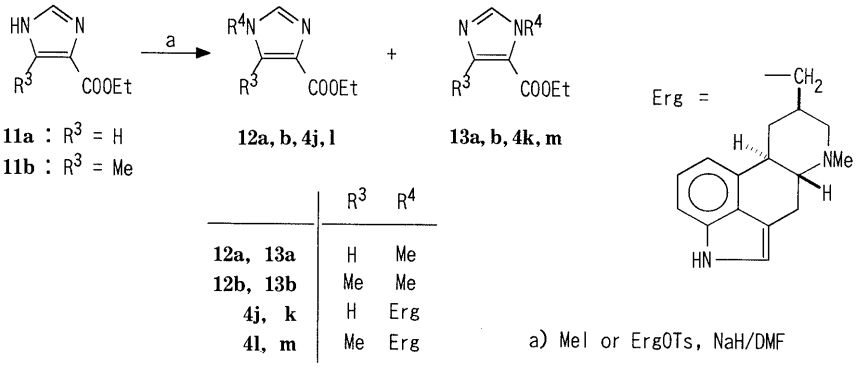


Chart 2

Alternatively **7** and **8b** were prepared from **4s**. Treatment of **4s** with cyanogen bromide in chloroform gave **9** in 93% yield, and **9** was reduced with $LiAlH_4$ in THF to afford **10** in 65% yield. Alkylation of **10** with alkyl iodide and K_2CO_3 in DMF yielded **7** and **8b** in good yields.

Structural assignments of some azole compounds were made on the basis of their NMR spectra as follows. Reaction of **3a** with ethyl 4-imidazolecarboxylate (**11a**) gave **4j** and **4k**, and reaction with ethyl 5-methyl-4-imidazolecarboxylate (**11b**) gave **4l** and **4m**. Methylation of **11** yielded the known imidazoles **12** and **13**.[15] Protons of the 1-methyl or the 1-methylene groups of **4k**, **4m**, and



	R^3	R^4
12a, 13a	H	Me
12b, 13b	Me	Me
4j, k	H	Erg
4l, m	Me	Erg

Chart 3

TABLE II. Selected ^{1}H- and ^{13}C-NMR Spectral Data for Ethyl 4- (**4j, l, 12**) and 5-Imidazolecarboxylates (**4k, m, 13**) in $CDCl_3$

Compd. No.	R^3	R^4	^{1}H-NMR (ppm)					^{13}C-NMR (ppm)				
			1-Me or CH_2	2-H	5-H	5-Me	$J_{2,5}$ (Hz)	1-Me or CH_2	2-C	4-C	5-C	5-Me
12a	H	Me	3.74	7.46	7.59	—	1.4	33.8	138.7	133.6	126.3	—
4j	H	Erg[a]	3.58—4.10	7.45	7.59	—	1.2	51.5	138.0	133.2	126.0	—
12b	Me	Me	3.57	7.38	—	2.52	—	31.4	137.0	135.8	128.9	9.5
4l	Me	Erg	3.79	7.36	—	2.57	—	48.8	136.8	135.3	129.5	9.8

Compd. No.	R^3	R^4	1-Me or CH_2	2-H	4-H	4-Me	$J_{2,4}$ (Hz)	1-Me or CH_2	2-C	4-C	5-C	4-Me
13a	H	Me	3.92	7.53	7.73	—	0.8	34.0	137.3	142.4	123.4	—
4k	H	Erg	3.97—[b]	7.52	7.71	—	*ca.* 0	50.7	137.9	142.1	122.9	—
13b	Me	Me	3.84	7.40	—	2.48	—	34.7	140.5	147.9	119.2	15.8
4m	Me	Erg	3.83—[b]	7.39	—	2.49	—	51.5	140.7	148.7	118.7	16.3

a) (5*R*,8*R*,10*R*)-6-Methyl-8-ergolinylmethyl. *b*) The downfield side of the peaks was overlapped with the peaks of the other protons.

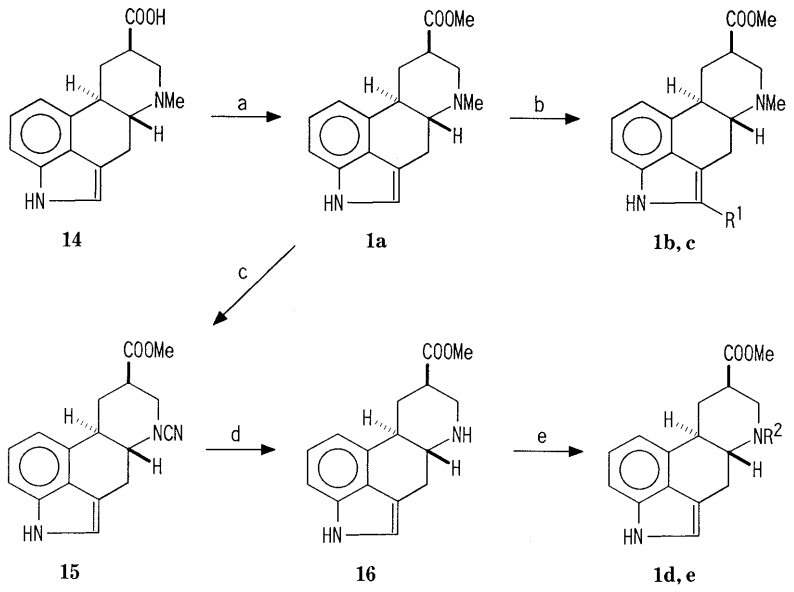
13 are deshielded by the adjacent carbonyl groups, and downfield shifts were observed in the ^{1}H-NMR spectra. In 4-imidazolecarboxamic acid derivatives the coupling constants between the 2- and the 5-protons have been reported to be 1.1—1.3 Hz. On the other hand, the coupling constants between the 2- and 4-protons in 5-imidazolecarboxamic acid derivatives are known to be *ca.* 0 Hz.[16] Coupling constants of the 4-carboxylates **4j** and **12a** were 1.2 and 1.4 Hz, while those of **4k** and **13a** were *ca.* 0 and 0.8 Hz, respectively. In the ^{1}H- and ^{13}C-NMR spectra, the chemical shifts of **4j**—**m** agreed very closely with those of the corresponding known compounds **12** or **13** (Table II). These results show that **4j** and **4l** are the 1-substituted 4-imidazolecarboxylates, whereas **4k** and **4m** are the 5-imidazolecarboxylates.

Treatment of **3a** with 5-methyl-3-phenylpyrazole gave **4q** and **4r** in 60 and 7% yields, respectively. The phenyl ring and the pyrazole ring of **4q** are nearly coplanar and conjugated. Consequently, the 2- and 6-protons of the phenyl group are deshielded because of the anisotropy of the pyrazole ring. In the ^{1}H-NMR spectrum of **4q**, downfield shifts of the 2- and 6-protons of the phenyl group were observed (δ 7.72, center of multiplet). The spectrum of **4r** exhibited no downfield shift of the protons of the phenyl group due to a loss of coplanarity between two rings as a result of the steric hindrance between the ergolinylmethyl and the phenyl groups. Therefore compound **4q** is the 1-substituted 5-methyl-3-phenylpyrazole and **4r** is the 3-methyl-5-phenylpyrazole. Compound **4i**, prepared from **3a** and 4-phenylimidazole, exhibited a similar downfield shift and therefore **4i** is the 1-substituted 4-phenylimidazole.

Reaction of **3a** and 1,2,4-triazole afforded **4s** and **4t** in 64 and 7% yields, respectively. The signals of two protons of the 1,2,4-triazolyl group of **4s** appear at δ 7.99 and 8.11, indicating that the two protons are non-equivalent. The two protons of **4t** are equivalent, and their signals appear as a singlet at δ 8.22. These results support the conclusion that **4s** and **4t** are the 1- and 4-substituted 1,2,4-triazoles, respectively. Similarly, triazoles **5c**, **6d**, **7**, and **8b** are 1-substituted compounds and **8c** is a 4-substituted compound.

The tetrazole **4u** is a 1-substituted compound. This was determined by comparison with the chemical shift of the 5-proton of the tetrazolyl group of (5*R*,8*S*,10*R*)-6-methyl-8-(1-tetrazolylmethyl)ergoline and that of the corresponding 8-(2-tetrazolylmethyl) compound.[17]

The starting compounds **1a**—**e**[9] were prepared from (5*R*,8*R*,10*R*)-6-methyl-8-ergolinecarboxylic acid (**14**), 9,10-dihydrolysergic acid, as shown in Chart 4.



a) H_2SO_4/MeOH; b) NCS/dioxane or $PhNMe_3^+Br_3^-$/THF; c) $BrCN/CH_2Cl_2$;
d) H_2, W-7 Raney Ni/DMF or Zn/AcOH; e) R^2I, K_2CO_3/DMF

Chart 4

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 III.

The ergolines **4a**, **4b**, **4e**, **4f**, **4o**, **4p**, **4s**, **4t**, **4v**, **4w**, **5b**, and **5c** showed antihypertensive activity comparable to that of cianergoline or hydralazine hydrochloride. The addition of a bromine atom at the 2-position of the ergolines remarkably enhanced the activity (**6a—d**) and the addition of a chlorine atom also increased the activity (**5a**). In this series, **6a** had the highest potency. It seems that 1-imidazolyl and 2-phenyl-1-imidazolyl groups as heterocyclic substituents are preferable for antihypertensive activity (**5a**, **6a**, **6c**). The 6-ethylergoline **7** exhibited relatively high potency, but the 6-propyl compounds **8a** and **8b** were inactive.

Detailed results for some compounds are given in Table IV. The maximum falls of systolic blood pressure after oral administration of **5a**, **6a**, **6b**, and **6c** at 3.0 mg/kg were 88, 110, 63, and 76 mmHg, respectively, while those of cianergoline, bromocriptine mesylate, hydralazine, and nifedipine were 40, 37, 47, and 49 mmHg, respectively. The effects of these new ergolines were observed for more than 7 h.

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 V.

Many ergolines showed activity comparable to that of bromocriptine mesylate, although only a few compounds exhibited more than 10 times the activity of bromocriptine. Among the 6-methylergolines, the 2-ethoxycarbonylimidazole (**4h**), the 5-methyl-3-phenylpyrazole (**4q**), and especially the 1,2,4-triazole (**4s**) exhibited the activity superior to that of bromocriptine mesylate. The activity was not increased by the introduction of a chlorine or bromine atom at the 2-position of the ergoline ring. The conversion of the methyl group at the 6-position to an ethyl group increased the activity (**7**). Furthermore, the replacement of the methyl group with a propyl group markedly enhanced the activity (**8a**,**b**). The 6-propyl ergoline (**8b**) showed extremely potent activity, superior to that of pergolide mesylate. It seems that a 1,2,4-triazol-1-yl group is preferable for dopaminergic activity.

As shown in Table VI, these new ergolines exhibited remarkable dopaminergic activity. Dopaminergic activity of **4s** was about 18-fold greater than that of bromocriptine mesylate, although emetic activity was 10-fold less. Compound **8b** was about 220 and 1.15 times more active than bromocriptine mesylate and pergolide mesylate, respectively.

The ergoline **4s** (maleate: BAM-1110) is a potent dopamine D_1- and D_2-agonist and clinical trials are in progress. Further investigation of the ergoline **8b** (fumarate: BAM-1602), an extremely potent and selective dopamine D_2-agonist, is in progress.

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. All acid salts were prepared in the usual way.

(5*R*,8*R*,10*R*)-8-Ergolinemethanols (2) a) (5*R*,8*R*,10*R*)-6-Methyl-8-ergolinemethanol (**2a**)[12]: $NaBH_4$ (20 g, 529 mmol) was added in portions to a mixture of **1a**[10a] (20 g, 70.3 mmol), MeOH (160 ml), and H_2O (80 ml) and the whole was refluxed for 2 h with stirring. After being cooled, the reaction mixture was diluted with ice water. The resulting crystals were

TABLE III. Antihypertensive Activities of the Ergolines (**4**—**8**) Administered Orally in Spontaneously Hypertensive Rats

Compd. No.	Dose (mg/kg)	Systolic blood pressure: Initial value (mmHg)	Systolic blood pressure: Maximum change (mmHg)	Systolic blood pressure: Duration[a] (h)	Heart rate: Initial value (beats/min)	Heart rate: Maximum change (beats/min)
4a	3	191	−43	>7	397	−24
4b	3	225	−45	>7	375	−42
4c	3	212	−35	>7	395	−10
4d	3	203	−39	>7	393	−39
4e	3	214	−48	>24	376	−35
4f	3	202	−49	>7	406	−56
4g	3	202	−10	—	407	−45
4h	3	207	—[b]	—	368	—[b]
4i	3	207	−26	>7	380	−33
4j	3	222	−6	—	408	−13
4k	3	206	−24	3—5	353	−25
4l	3	198	−34	>7	428	−15
4m	3	204	−35	5—7	383	9, −10
4n	3	197	−35	>7	384	−18
4o	10	228	−62	>7	377	−46
4p	3	202	−53	>7	411	−17
4q	3	219	−33	>7	387	−42
4r	3	233	−3	—	403	7, −32
4s	3	204	−43	>7	388	−22
4t	3	201	−48	>7	377	−26
4u	10	218	−31	5—7	400	−42
4v	3	224	−47	>7	359	−17
4w	10	230	−60	>7	388	16, −16
4x	3	215	−39	>7	418	−28
4y	10	234	−12	—	371	−18
5a	3	229	−88	>7	406	34
5b	3	220	−54	>7	371	22
5c	3	222	−41	>7	420	−37
6a	3	238	−110	>7	418	22, −11
6b	3	215	−63	>7	387	45
6c	3	235	−81	>7	382	−6, 8
6d	3	240	−57	>24	428	−47
7	1	199	−44	5—7	385	−29
8a	3	206	−3[c]	—	411	−11[c]
8b	3	209	−6	—	388	−11
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) The time at which blood pressure recovered to within 10% of the initial value. *b*) The pressure was not detectable after oral administration by the tail-cuff method. *c*) The pressure was not detectable after 3 h. *d*) Cianergoline. *e*) Bromocriptine mesylate. *f*) Dihydroergotoxine mesylate. *g*) Hydralazine. *h*) Nifedipine.

collected, washed with hot water, and dried to give **2a** (14.8 g, 82%). An analytical sample was obtained by recrystallization from EtOH, mp >255 °C (dec.) [lit.[12] mp 280 °C (dec.)]. ^{1}H-NMR (CD_3OD) δ: 0.93 (1H, q, J=11.1 Hz), 1.56—2.10 (3H, m), 2.20—3.60 [10H, m, 2.33 (3H, s)], 6.63—7.17 (4H, m), 10.53 (1H, br). *Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.69; H, 7.96; N, 10.71.

The methanol (**2c**) was prepared in the same manner as above.

2c: 61% yield, mp >252 °C (dec., MeOH–iso-PrOH). ^{1}H-NMR (DMSO-d_6) δ: 0.94 (1H, q, J=11.7 Hz), 1.62—2.08 (3H, m), 2.16—3.43 [10H, m, 2.34 (3H, s)], 4.46 (1H, t, J=5.2 Hz), 6.62—7.04 (3H, m), 10.23 (1H, br). *Anal.* Calcd for $C_{16}H_{19}BrN_2O$: C, 57.32; H, 5.71; N, 8.36. Found: C, 57.22; H, 5.83; N, 8.31.

b) (5*R*,8*R*,10*R*)-2-Bromo-6-methyl-8-ergolinemethanol (**2c**): A suspension of $LiAlH_4$ (0.31 g, 8.17 mmol) in THF (40 ml) was added dropwise to a solution of **1c** (2.0 g, 5.51 mmol) in THF with stirring in an ice bath. The mixture was stirred for 0.5 h, and AcOEt and then H_2O were added to it to decompose excess $LiAlH_4$. The precipitate was filtered off using Celite. The filtrate was concentrated *in vacuo*. The resulting crystals were washed with H_2O and dried to yield **2c** (1.7 g, 92%). An analytical sample was obtained by recrystallization from MeOH–iso-PrOH, mp >252 °C (dec.).

The methanols (**2b**, **2d**, **2e**) were prepared in the same manner as above.

2b: 87% yield, mp >244 °C (dec., EtOH). ^{1}H-NMR (DMSO-d_6) δ: 0.93 (1H, q, J=11.4 Hz), 1.57—2.13 (3H, m), 2.16—3.55 [10H, m, 2.34 (3H, s)], 4.47 (1H, t, J=5.2 Hz), 6.65—7.12 (3H, m), 10.73 (1H, br). *Anal.* Calcd for $C_{16}H_{19}ClN_2O$: C, 66.09; H, 6.59; N, 9.63. Found: C, 65.98; H, 6.67; N, 9.62.

2d[10f]: 94% yield, mp >235 °C (dec., iso-PrOH) (lit.[10f] mp 252—254 °C). ^{1}H-NMR (DMSO-d_6) δ: 0.81—1.02 [4H, m, 0.96 (3H, t, J=6.8 Hz)], 1.79—2.03 (2H, m), 2.20—3.57 (10H, m), 4.53 (1H, t, J=5.1 Hz), 6.76 (1H, d, J=6.8 Hz), 6.97 (1H, s), 7.00 (1H, t, J=6.8 Hz), 7.10 (1H, d, J=6.8 Hz). *Anal.* Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.61; H, 8.33; N, 10.38.

2e[10f]: 96% yield, mp 181—183 °C (AcOEt) (lit.[10f] mp 181—182 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.79—1.80 [6H, m, 0.90 (3H, t, J=7.5 Hz)], 1.90—3.80 (12H, m), 6.73—7.36 (4H, m), 7.95 (1H, br). *Anal.* Calcd for $C_{18}H_{24}N_2O \cdot 1/2H_2O$: C, 73.68; H, 8.59; N, 9.55. Found: C, 73.38; H, 8.57; N, 9.42.

(5*R*,8*R*,10*R*)-8-Ergolinylmethyl *p*-Toluenesulfonates (3) a) (5*R*,8*R*,10*R*)-6-Methyl-8-ergolinylmethyl *p*-Toluenesulfonate (**3a**)[14a]: TsCl (11.2 g, 58.7 mmol) was added in portions to a mixture of **2a** (5.0 g, 19.5 mmol) and pyridine (100 ml) with stirring at room temperature. 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 and diluted with ice-water. The resulting crystals were collected, washed with H_2O, and dried. Recrystallization from CH_2Cl_2–AcOiso-Pr afforded **3a** (6.4 g, 80%), mp 193—196 °C (dec.) (lit.[14a] mp 191—193 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.07 (1H, q, J=11.8 Hz), 1.70—3.16 [13H, m, 2.41 (3H, s), 2.44 (3H, s)], 3.33 (1H, dd, J=14.4, 4.1 Hz), 3.69—4.13 (2H, m), 6.63—6.88 (2H, m), 6.96—7.40 [4H, m, 7.33 (2H, A_2B_2 type d, J=8.2 Hz)], 7.78 (2H, A_2B_2 type d, J=8.2 Hz), 8.04 (1H, br).

b) (5*R*,8*R*,10*R*)-2-Chloro-6-methyl-8-ergolinylmethyl *p*-Toluenesulfonate (**3b**): TsCl (9.3 g, 48.8 mmol) was added in portions to a mixture of **2b** (7.0 g, 24.1 mmol) and pyridine (100 ml) with stirring at room

TABLE IV. Effects of New Ergolines Administered Orally on Systolic Blood Pressure and Heart Rate in Spontaneously Hypertensive Rats

Compd. No.	Dose (mg/kg)	*n*	Initial value[a] (mmHg)	Changes in blood pressure (mmHg)[a]: 1	3	5	7	24 (h)	Initial value[a] (beats/min)	Changes in heart rate (beats/min)[a]: 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	229±21	−64± 3	−78±12	−85±19	−88±16	−4±2	406± 9	16±15	22± 9	23± 7	34± 6	13±10
6a	3	3	238± 4	−110± 9	−68± 8	−58± 4	−49± 7	−6±3	418±12	22±21	−6±18	3±35	−11±31	−17±15
6b	3	3	215±10	−55± 9	−60±11	−63±10	−55± 8	−1±2	387±30	39±15	36±15	45±14	30±10	19±13
6c	3	3	235±12	−66±12	−63± 6	−76± 8	−66± 9	−6±5	382± 1	−7± 8	3±20	8±13	−2± 1	11±11
Cianergoline	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
Bromocriptine	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
mesylate	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
Hydralazine	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
Nifedipine	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.

Table V. Contralateral Rotational Activities of the Ergolines (**4**—**8**) Administered Orally in Rats with Unilateral 6-Hydroxydopamine-Induced Lesion of Substantia Nigra

Compd. No.	Rotational behavior[a] rotated/treated animals									
	Dose (mg/kg)									
	0.03	0.1	0.3	1.5	3.12	6.25	25	50	100	200
4a						0/2	2/2		2/2	
4b									1/2	
4c							0/2		2/2	
4d							1/2		2/2	
4e							1/2	2/2		
4f							0/2		2/2	
4g									0/2	
4h				1/5	4/5	5/5	2/2		2/2	
4i							0/2			
4j									0/2	
4k							1/2	1/2		
4l							0/2		2/2	
4m							1/2		2/2	
4n							0/2			
4o						0/2	2/2		2/2	
4p						0/2	2/2			
4q				0/5	4/5	5/5			2/2	
4r							0/2			
4s			0/5	3/5	5/5	5/5			2/2	
4u						0/2	2/2		2/2	
4v						0/2	2/2	2/2		
4w									0/2	
4x							1/2		2/2	
4y							0/2		1/2	
5a					0/2	2/2	2/2			
5b							1/2			
5c					0/2	2/2	2/2			
6a							1/2			
6c							0/2	0/2		
6d						1/2	2/2			
7-m			0/4	4/4	4/4					
8a		0/4	3/4	4/4			2/2			
8b							2/2			
8b-m	0/6	4/6	6/6							
Cia[b]									0/2	0/2
Bro[c]						0/5	3/5			
Dih[d]							0/2		1/2	1/2
Per[e]		1/2	2/2							

a) Observed for 8 h. *b*) Cianergoline. *c*) Bromocriptine mesylate. *d*) Dihydroergotoxine mesylate. *e*) Pergolide mesylate.

Table VI. Contralateral Rotational Behavior after Oral Administration of the Ergolines in Rats with Unilateral 6-Hydroxydopamine-Induced Lesion of Substantia Nigra

Compd. No.	Dose (mg/kg)	Turned/ treated	Maximum turns/5 min[a]	Onset (h)[a]	End (h)[a]
4s	1	6/6	29.8± 7.7	0.46±0.08	2.00±0.22
	3	6/6	76.0± 6.7	0.33±0.05	3.33±0.31
7-m	1	4/4	31.8± 9.4	1.13±0.38	4.00±0.58
	3	4/4	66.8± 3.5	0.38±0.07	6.25±0.63
8a	1	4/4	32.0± 4.8	1.13±0.31	>8
	3	4/4	70.0± 3.2	0.69±0.12	>24
8b-m	0.1	4/6	25.0±11.0	0.25±0.00	3.38±0.43
	0.3	6/6	50.5± 3.5	0.29±0.04	4.16±0.33
	1	6/6	60.7± 4.4	0.25±0.00	>8
Bromocriptine mesylate	10	4/6	16.5± 6.7	3.63±0.24	7—8
	30	6/6	60.0± 4.3	0.92±0.14	>8
Pergolide mesylate	0.1	3/6	1.8± 0.8	3.83±0.17	4.33±0.17
	0.3	6/6	50.0± 7.4	0.71±0.16	>8
	1	6/6	65.5± 6.2	0.33±0.05	>24

a) Each value is the mean±standard error for turned animals.

Table VII. Emetic Activity in Dogs and Acute Toxicity in Mice

Compd. No.	Emetic activity[a] vomited/treated animals (μg/kg, i.v.) or/and ED_{50} (mg/kg, *p.o.*)	LD_{50} or mortality (mg/kg, *p.o.*)
4a	100(0/2), 300(1/2)	330
4b	300(0/2), 1000(2/2)	500(0/2), 1000(2/2)
4c	100(0/2), 300(1/2)	215
4d		200(0/2), 500(2/2)
4e	100(0/2), 300(1/2)	640
4f	100(0/2), 300(2/2)	1200
4g		>1000
4h	30(1/4), 100(2/4)	900
4i		100(1/2), 200(2/2)
4j		>1000
4k		200(0/2), 500(2/2)
4l		1000(1/2)
4m		200(0/2), 500(2/2)
4n		200(1/2), 500(2/2)
4o		200(0/2), 500(2/2)
4p		200(0/2), 500(2/2)
4q	100(0/4), 300(3/4)	>1500
4s	100(2/4), 300(4/4)	525
4s-m	0.31	
4u		200(0/2), 500(2/2)
4v		200(0/2), 500(2/2)
4w		200(0/2), 500(1/2), 1000(2/2)
4x	100(0/4), 300(4/4)	>2000
4y		500(0/2), 1000(1/2)
5a		200(0/2), 500(2/2)
5b		200(0/2), 500(1/2), 1000(2/2)
5c		200(0/2), 500(2/2)
6a		100(0/2), 200(2/2)
6c	100(0/2), 300(0/2)	950
6d		100(0/2), 200(1/2), 500(2/2)
7		100(0/5), 200(2/5), 250(2/5)
7-m	20(4/4), 0.01	
8a	2(4/4)	100(0/2),200(2/2)
8b-m	0.5(4/4), 0.0041	108
Cia[b]	30(0/2), 100(2/2)	>1500
Bro[c]	3(0/4), 10(3/4), 30(4/4), 0.028	2800
Dih[d]	3(0/4), 10(4/4)	>1500
Per[e]	1(0/2), 3(2/2), 10(2/2), 0.0050	190

a) Observed for 7 h. *b*) Cianergoline. *c*) Bromocriptine mesylate. *d*) Dihydroergotoxine mesylate. *e*) Pergolide mesylate.

temperature. 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 dissolved in CH_2Cl_2, treated with activated carbon, and recrystallized from CH_2Cl_2–hexane to yield **3b** (9.0 g, 84%), mp 145—148 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (1H, q, J=11.4 Hz), 1.73—3.38 [14H, m, 2.43 (6H, s), 3.24 (1H, dd, J=14.7, 4.2 Hz)], 3.96 (2H, d, J=5.4 Hz), 6.62—7.13 (3H, m), 7.30 (2H, A_2B_2 type d, J=8.1 Hz), 7.76 (2H, A_2B_2 type d, J=8.1 Hz), 7.95 (1H, br). *Anal.* Calcd for $C_{23}H_{25}ClN_2O_3S$: C, 62.08; H, 5.66; N, 6.30. Found: C, 61.93; H, 5.56; N, 6.31.

Compounds **3c**—**e** were prepared in the same manner as described for **3a** or **3b**.

3c: 86% yield, mp 138—141 °C (EtOH). ^{1}H-NMR ($CDCl_3$) δ: 1.08 (1H, q, J=11.4 Hz), 1.78—3.35 [14H, m, 2.47 (6H, s)], 3.80—4.19 (2H, m), 6.69—6.93 (1H, m), 6.98—7.18 (2H, m), 7.37 (2H, A_2B_2 type d, J=8.1 Hz), 7.83 (2H, A_2B_2 type d, J=8.1 Hz), 7.99 (1H, br). *Anal.* Calcd for $C_{23}H_{25}BrN_2O_3S$: C, 56.44; H, 5.15; N, 5.72. Found: C, 56.44; H, 5.15; N, 5.71.

3d: 81% yield, mp 184—186 °C (CH_2Cl_2–AcOiso-Pr). ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, t, J=7.0 Hz), 1.09 (1H, q, J=12.1 Hz), 2.11—3.12 [12H, m, 2.47 (3H, s)], 3.37 (1H, dd, J=14.9, 4.3 Hz), 3.93—4.08 (2H, m), 6.81 (1H, d, J=5.9 Hz), 6.89 (1H, s), 7.11—7.21 (2H, m), 7.38 (2H, A_2B_2 type d, J=8.1 Hz), 7.83 (2H, A_2B_2 type d, J=8.1 Hz), 7.91 (1H, br). *Anal.* Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.90; H, 6.65; N, 6.60. Found: C, 67.80; H, 6.71; N, 6.48.

3e[14b]: 85% yield, mp 175—177 °C (AcOEt) (lit.[14b] mp 147—150 °C). ^{1}H-NMR ($CDCl_3$) δ: 0.89 (3H, t, J=7.4 Hz), 1.07 (1H, q, J=12.2 Hz),

TABLE VIII. ^{1}H-NMR Spectral Data for (5*R*,8*R*,10*R*)-8-Methylergolines (**4**—**8**) in $CDCl_3$

Compd. No.	Chemical shifts (ppm)
4a	1.19 (1H, q, J=12.3 Hz), 1.97 (1H, t, J=11.3 Hz), 2.16 (1H, td, J=10.4, 4.2 Hz), 2.36—2.52 [4H, m, 2.44 (3H, s)], 2.59—2.74 (2H, m), 2.82—3.05 (2H, m), 3.41 (1H, dd, J=14.9, 4.2 Hz), 3.89 (1H, dd, J=13.8, 7.8 Hz), 3.96 (1H, dd, J=13.8, 6.5 Hz), 6.84—7.00 [3H, m, 6.97 (1H, s)], 7.10—7.25 (3H, m), 7.50 (1H, s), 7.95 (1H, br)
4b	1.18 (1H, q, J=12.0 Hz), 1.79—3.10 [13H, m, 2.41 (3H, s), 2.43 (3H, s)], 3.37 (1H, dd, J=14.2, 4.2 Hz), 3.77 (2H, d, J=6.9 Hz), 6.74—6.93 (4H, m), 6.97—7.21 (2H, m), 7.89 (1H, br)
4c	1.18 (1H, q, J=12.0 Hz), 1.38 (3H, t, J=7.4 Hz), 1.70—3.10 [12H, m, 2.43 (3H, s), 2.71 (2H, q, J=7.4 Hz)], 3.37 (1H, dd, J=14.4, 3.9 Hz), 3.78 (2H, d, J=6.9 Hz), 6.70—7.23 (6H, m), 8.03 (1H, br)
4d	1.01 (3H, t, J=6.9 Hz), 1.17 (1H, q, J=12.0 Hz), 1.60—3.12 [14H, m, 2.43 (3H, s)], 3.37 (1H, dd, J=14.4, 3.9 Hz), 3.78 (2H, d, J=6.8 Hz), 6.71—7.25 (6H, m), 7.94 (1H, br)
4e	1.18 (1H, q, J=11.7 Hz), 1.34 (3H, d, J=6.7 Hz), 1.35 (3H, d, J=6.7 Hz), 1.80—3.19 [11H, m, 2.43 (3H, s)], 3.37 (1H, dd, J=14.3, 4.4 Hz), 3.80 (2H, d, J=6.8 Hz), 6.65—7.25 (6H, m), 8.14 (1H, br)
4f	1.03 (1H, q, J=12.0 Hz), 1.58—3.04 [10H, m, 2.39 (3H, s)], 3.34 (1H, dd, J=14.7, 3.9 Hz), 3.97 (2H, d, J=6.6 Hz), 6.62—6.88 (2H, m), 6.94—7.24 (4H, m), 7.28—7.67 (5H, m), 8.04 (1H, br)
4g	1.03 (1H, q, J=12.0 Hz), 1.63—3.07 [10H, m, 2.40 (3H, s)], 3.36 (1H, dd, J=14.6, 4.2 Hz), 3.84 (3H, s), 3.96 (2H, d, J=6.8 Hz), 6.68—7.24 (8H, m), 7.41—7.64 (2H, m), 8.14 (1H, br)
4h	1.19 (1H, q, J=11.8 Hz), 1.42 (3H, t, J=7.1 Hz), 1.80—3.10 [10H, m, 2.41 (3H, s)], 3.34 (1H, dd, J=14.1, 4.2 Hz), 4.38 (2H, d, J=6.9 Hz), 4.38 (2H, q, J=7.1 Hz), 6.66—7.26 (6H, m), 7.97 (1H, br)
4i	1.18 (1H, q, J=11.7 Hz), 1.60—3.15 [10H, m, 2.42 (3H, s)], 3.38 (1H, dd, J=14.3, 4.2 Hz), 3.57—4.11 (2H, m), 6.68—7.55 (9H, m), 7.62—7.85 (2H, m), 7.98 (1H, br)
4j	1.15 (1H, q, J=12.0 Hz), 1.39 (3H, t, J=6.9 Hz), 1.60—3.10 [10H, m, 2.42 (3H, s)], 3.37 (1H, dd, J=14.3, 3.9 Hz), 3.58—4.10 (2H, m), 4.35 (2H, q, J=6.9 Hz), 6.63—7.25 (4H, m), 7.45 (1H, d, J=1.2 Hz), 7.59 (1H, d, J=1.2 Hz), 8.06 (1H, br)
4k	1.17 (1H, q, J=12.0 Hz), 1.37 (3H, t, J=7.2 Hz), 1.80—3.10 [10H, m, 2.41 (3H, s)], 3.36 (1H, dd, J=14.1, 4.0 Hz), 3.97—4.50 [4H, m, 4.28 (2H, q, J=7.2 Hz)], 6.66—7.23 (4H, m), 7.52 (1H, s), 7.71 (1H, s), 7.81 (1H, br)
4l	1.15 (1H, q, J=11.5 Hz), 1.40 (3H, t, J=7.0 Hz), 1.76—3.09 [13H, m, 2.41 (3H, s), 2.57 (3H, s)], 3.37 (1H, dd, J=14.7, 4.1 Hz), 3.79 (2H, d, J=6.5 Hz), 4.34 (2H, q, J=7.0 Hz), 6.63—6.88 (2H, m), 6.94—7.22 (2H, m), 7.36 (1H, s), 8.11 (1H, br)
4m	1.13 (1H, q, J=11.7 Hz), 1.38 (3H, t, J=7.1 Hz), 1.76—3.08 [13H, m, 2.41 (3H, s), 2.49 (3H, s)], 3.37 (1H, dd, J=14.4, 4.2 Hz), 3.83—4.44 [4H, m, 4.30 (2H, q, J=7.1 Hz)], 6.67—7.23 (4H, m), 7.39 (1H, s), 8.02 (1H, br)
4n	1.14 (1H, q, J=11.7 Hz), 1.33 (3H, t, J=7.3 Hz), 1.76—3.10 [15H, m, 2.20 (3H, d, J=0.8 Hz), 2.43 (3H, s)], 3.37 (1H, dd, J=14.8, 4.1 Hz), 3.69 (2H, d, J=6.8 Hz), 6.51 (1H, q, J=0.8 Hz), 6.63—7.23 (4H, m), 8.14 (1H, br)
4o	1.15 (1H, q, J=12.5 Hz), 1.81—3.10 (7H, m), 2.41 (3H, s), 3.35 (1H, dd, J=14.7, 4.4 Hz), 3.85—4.27 (2H, m), 6.24 (1H, dd, J=2.4, 2.2 Hz), 6.69—7.17 (4H, m), 7.35 (1H, d, J=2.4 Hz), 7.48 (1H, d, J=2.2 Hz), 8.13 (1H, br)
4p	1.19 (1H, q, J=12.5 Hz), 1.83—3.11 [15H, m, 2.21 (3H, s), 2.25 (3H, s), 2.43 (3H, s)], 3.37 (1H, dd, J=14.3, 4.1 Hz), 3.73—4.11 (2H, m), 5.76 (1H, s), 6.74—7.26 (4H, m), 7.84 (1H, br)
4q	1.25 (1H, q, J=12.3 Hz), 1.83—3.15 [13H, m, 2.33 (3H, s), 2.42 (3H, s)], 3.35 (1H, dd, J=14.2, 4.1 Hz), 3.81—4.20 (2H, m), 6.28 (1H, s), 6.67—7.44 (7H, m), 7.56—7.97 [3H, m, 7.85 (1H, br)]
4r	0.98 (1H, q, J=12.5 Hz), 1.66—3.02 [13H, m, 2.31 (3H, s), 2.36 (3H, s)], 3.30 (1H, dd, J=14.3, 4.0 Hz), 4.02 (2H, d, J=6.6 Hz), 6.03 (1H, s), 6.60—6.84 (2H, m), 6.90—7.20 (2H, m), 7.35 (5H, s), 7.95 (1H, br)
4s	1.21 (1H, q, J=12.2 Hz), 2.03 (1H, t, J=11.2 Hz), 2.17 (1H, td, J=10.4, 4.3 Hz), 2.38—2.78 [6H, m, 2.45 (3H, s)], 2.86—3.05 (2H, m), 3.40 (1H, dd, J=14.5, 4.3 Hz), 4.11 (1H, dd, J=13.9, 7.5 Hz), 4.20 (1H, dd, J=13.9, 6.3 Hz), 6.81—6.95 (2H, m), 7.10—7.30 (2H, m), 7.99 (1H, s), 7.99 (1H, br), 8.11 (1H, s)
4t	1.21 (1H, q, J=12.5 Hz), 2.10 (1H, t, J=11.1 Hz), 2.18 (1H, td, J=10.4, 4.3 Hz), 2.32—2.54 [4H, m, 2.45 (3H, s)], 2.62—2.75 (2H, m), 2.85—3.05 (2H, m), 3.41 (1H, dd, J=14.9, 4.3 Hz), 3.99 (1H, dd, J=14.0, 7.8 Hz), 4.05 (1H, dd, J=14.0, 7.0 Hz), 6.82—6.93 [2H, m, 6.91 (1H, s)], 7.12—7.38 (2H, m), 7.94 (1H, br), 8.22 (2H, s)
4u	1.26 (1H, q, J=12.5 Hz), 1.88—3.13 [10H, m, 2.42 (3H, s)], 3.37 (1H, dd, J=14.3, 3.9 Hz), 4.60 (2H, d, J=6.3 Hz), 6.68—6.92 (2H, m), 6.97—7.20 (2H, m), 7.89 (1H, br), 8.46 (1H, s)
4v	1.19 (1H, q, J=11.2 Hz), 1.82—3.10 [14H, m, 2.43 (3H, s), 2.72 (4H, s)], 3.21—3.60 [3H, m, 3.49 (2H, d, J=6.4 Hz)], 6.70—7.20 (4H, m), 7.89 (1H, br)
4w	1.18 (1H, q, J=11.8 Hz), 1.86—3.10 [13H, m, 2.45 (3H, s), 3.01 (3H, s)], 3.23—3.58 [3H, m, 3.49 (2H, d, J=6.2 Hz)], 3.87 (2H, s), 6.77—7.26 (4H, m), 7.88 (1H, br)
4x	1.15 (1H, q, J=11.8 Hz), 1.82—3.83 [15H, m, 2.47 (3H, s)], 4.20—4.47 (2H, m), 6.75—7.23 (4H, m), 7.98 (1H, br)
4y	1.22 (1H, q, J=11.7 Hz), 1.88—3.10 [10H, m, 2.43 (3H, s)], 3.36 (1H, dd, J=14.7, 3.8 Hz), 3.67 (2H, d, J=6.3 Hz), 6.72—7.28 (4H, m), 7.57—8.20 [5H, m, 7.97 (1H, br)]
5a	1.14 (1H, q, J=11.4 Hz), 1.75—3.10 [10H, m, 2.43 (3H, s)], 3.26 (1H, dd, J=14.6, 4.2 Hz), 3.70—4.10 (2H, m), 6.70—7.13 (5H, m), 7.43 (1H, br s), 8.10 (1H, br)
5b	1.03 (1H, q, J=12.4 Hz), 1.60—3.50 [11H, m, 2.44 (3H, s), 3.27 (1H, dd, J=14.8, 4.4 Hz)], 4.02 (2H, q, J=7.2 Hz), 6.67—7.70 (10H, m), 8.28 (1H, br)
5c	1.17 (1H, q, J=12.1 Hz), 1.83—3.04 [10H, m, 2.43 (3H, s)], 3.26 (1H, dd, J=14.4, 3.9 Hz), 4.13 (2H, d, J=6.3 Hz), 6.70—7.15 (3H, m), 7.91 (1H, br), 7.92 (1H, s), 8.03 (1H, s)
6a	1.13 (1H, q, J=11.7 Hz), 1.78—3.05 [10H, m, 2.43 (3H, s)], 3.18 (1H, dd, J=14.4, 3.9 Hz), 3.87 (2H, d, J=6.6 Hz), 6.65—7.12 (5H, m), 7.43 (1H, br s), 7.95 (1H, br)
6b	1.17 (1H, q, J=12.0 Hz), 1.37 (3H, d, J=6.8 Hz), 1.38 (3H, d, J=6.8 Hz), 1.80—3.43 [12H, m, 2.48 (3H, s)], 3.84 (2H, d, J=7.2 Hz), 6.77—7.23 (5H, m), 8.04 (1H, br)
6c	0.98 (1H, q, J=12.0 Hz), 1.56—2.97 [10H, m, 2.40 (3H, s)], 3.15 (1H, dd, J=14.3, 3.8 Hz), 3.96 (2H, d, J=6.8 Hz), 6.58—6.83 (1H, m), 6.90—7.68 (9H, m), 8.21 (1H, br)
6d	1.17 (1H, q, J=11.7 Hz), 1.85—3.05 [10H, m, 2.43 (3H, s)], 3.19 (1H, dd, J=14.7, 4.5 Hz), 4.12 (2H, d, J=6.3 Hz), 6.71—7.10 (3H, m), 7.91 (1H, s), 7.95 (1H, br), 8.02 (1H, s)
7	1.04 (3H, t, J=7.2 Hz), 1.21 (1H, q, J=11.9 Hz), 2.28 (1H, t, J=11.1 Hz), 2.45—2.80 (4H, m), 2.83—3.09 (4H, m), 3.38 (1H, dd, J=14.3, 3.8 Hz), 4.16 (1H, dd, J=14.0, 7.3 Hz), 4.21 (1H, dd, J=14.0, 5.9 Hz), 6.82—6.95 (2H, m), 7.12—7.23 (2H, m), 7.96 (1H, br), 7.99 (1H, s), 8.12 (1H, s)

TABLE VIII. (continued)

Compd. No.	Chemical shifts (ppm)
8a	0.70—1.73 [6H, m, 0.87 (3H, t, J=7.3 Hz), 1.17 (1H, q, J=11.7 Hz)], 1.90—3.53 (10H, m), 3.88 (2H, d, J=6.4 Hz), 6.65—7.30 (6H, m), 7.47 (1H, s), 7.90 (1H, br)
8b	0.89 (3H, t, J=7.3 Hz), 1.19 (1H, q, J=12.2 Hz), 1.40—1.59 (2H, m), 2.23 (1H, t, J=11.1 Hz), 2.42—3.06 (8H, m), 3.36 (1H, dd, J=14.5, 4.0 Hz), 4.17 (1H, dd, J=14.2, 7.3 Hz), 4.19 (1H, dd, J=14.2, 6.3 Hz), 6.86 (1H, d, J=5.9 Hz), 6.89 (1H, s), 7.10—7.25 (2H, m), 7.99 (1H, s), 7.99 (1H, br), 8.11 (1H, s)
8c	0.89 (3H, t, J=7.2 Hz), 1.18 (1H, q, J=12.2 Hz), 1.48 (2H, m), 2.12—3.03 [9H, m, 2.19 (1H, t, J=10.9 Hz)], 3.36 (1H, dd, J=14.5, 4.0 Hz), 3.98 (1H, dd, J=14.1, 7.9 Hz), 4.03 (1H, dd, J=14.1, 6.6 Hz), 6.84 (1H, d, J=6.6 Hz), 6.90 (1H, s), 7.11—7.24 (2H, m), 7.98 (1H, br), 8.22 (2H, s)

1.41—1.58 (2H, m), 2.04—3.12 [12H, m, 2.11 (1H, t, J=11.0 Hz), 2.46 (3H, s)], 3.33 (1H, dd, J=14.8, 4.0 Hz), 3.96 (1H, dd, J=9.7, 6.9 Hz), 4.00 (1H, dd, J=9.7, 5.3 Hz), 6.80 (1H, d, J=6.3 Hz), 6.88 (1H, s), 7.10—7.22 (2H, m), 7.37 (2H, d, J=8.3 Hz), 7.82 (2H, d, J=8.3 Hz), 7.94 (1H, br). *Anal.* Calcd for $C_{25}H_{30}N_2O_3S$: C, 68.46; H, 6.89; N, 6.39. Found: C, 68.44; H, 6.95; N, 6.23.

(5*R*,8*R*,10*R*)-Ergolines (4—8) a) (5*R*,8*R*,10*R*)-6-Methyl-8-(4-phenyl-1-imidazolylmethyl)ergoline (**4i**): NaH (60% in oil, 0.40 g, 10.0 mmol) was added in portions to a solution of 4-phenylimidazole (1.9 g, 13.2 mmol) in DMF (50 ml) with stirring and then **3a** (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 MeOH–Me_2CO gave colorless needles (1.2 g, 64%), mp 233—237 °C (dec.).

b) (5*R*,8*R*,10*R*)-6-Methyl-8-(1-pyrazolylmethyl)ergoline (**4o**): NaH (60% in oil, 0.70 g, 17.5 mmol) was added in portions to a solution of pyrazole (1.5 g, 22.0 mmol) in DMF (20 ml) with stirring and then **3a** (2.5 g, 6.09 mmol) was added. The mixture was heated for 1 h at *ca.* 90 °C with stirring. After being cooled, the reaction mixture was diluted with H_2O. The resulting crystals were collected and washed with H_2O. Recrystallization from CH_2Cl_2–iso-Pr_2O yielded colorless scales (1.7 g, 91%), mp 192—194 °C.

c) (5*R*,8*R*,10*R*)-6-Methyl-8-(1,2,4-triazol-1-ylmethyl)ergoline (**4s**) and (5*R*,8*R*,10*R*)-6-Methyl-8-(1,2,4-triazol-4-ylmethyl)ergoline (**4t**): NaH (60% in oil, 0.96 g, 24.0 mmol) was added in portions to a solution of 1,2,4-triazole (2.5 g, 36.2 mmol) in DMF (30 ml) with stirring and then **3a** (5.0 g, 12.2 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. The resulting crystals were collected and washed with H_2O. The crude product was chromatographed on a silica gel column with AcOEt–EtOH–DMF (25 : 25 : 1). The first fraction afforded **4s**, which was recrystallized from MeOH to give colorless prisms (2.4 g, 64%), mp >243 °C (dec.). The second fraction afforded **4t**, which was recrystallized from CH_2Cl_2–MeOH to afford colorless needles (0.26 g, 7%), mp >270 °C (dec.).

d) (5*R*,8*R*,10*R*)-6-Propyl-8-(1,2,4-triazol-1-ylmethyl)ergoline (**8b**) and (5*R*,8*R*,10*R*)-6-Propyl-8-(1,2,4-triazol-4-ylmethyl)ergoline (**8c**): 1,2,4-Triazole (3.0 g, 43.4 mmol) was added in portions to a mixture of NaH (60% in oil, 1.5 g, 37.5 mmol) and DMF (50 ml) with stirring. After addition of **3e** (5.0 g, 11.4 mmol) the mixture was heated for 2 h at *ca.* 80 °C with stirring. The reaction mixture was cooled, diluted with H_2O, and extracted with AcOEt. The extract was washed with H_2O and dried over Mg_2SO_4. After removal of the solvent, the residue was chromatographed on a silica gel column with AcOEt–EtOH (5 : 1). The first fraction gave **8b**, which was recrystallized from Me_2CO to afford colorless leaflets (3.2 g, 84%), mp 201—203 °C. The second fraction afforded **8c**, which was recrystallized from EtOH to yield colorless needles (0.23 g, 6%), mp >235 °C (dec.).

The other compounds were prepared in the same manner as described for a—d). The ergoline **8b** was also prepared in the following manner.

e) (5*R*,8*R*,10*R*)-6-Propyl-8-(1,2,4-triazol-1-ylmethyl)ergoline (**8b**): A mixture of **10** (2.0 g, 6.82 mmol), PrI (1.25 g, 7.35 mmol), K_2CO_3 (5.0 g, 36.2 mmol), and DMF (30 ml) was heated for 1.5 h at *ca.* 90 °C. After being cooled, the reaction mixture was diluted with H_2O. The resulting precipitate was collected, washed with H_2O, dried, and recrystallized from Me_2CO to give colorless leaflets (2.0 g, 87%), mp 201—203 °C.

The ergoline **7** was also prepared in the same manner as described above.

(5*R*,8*R*,10*R*)-6-Cyano-8-(1,2,4-triazol-1-ylmethyl)ergoline (9) Cyanogen bromide (5.2 g, 49.1 mmol) was added in portions to a mixture of **4s** (5.0 g, 16.3 mmol) and $CHCl_3$ (150 ml) with stirring. The mixture was stirred for 0.5 h and then refluxed for 5 h. After being cooled, the mixture was diluted with aqueous K_2CO_3. The resulting crystals were collected, washed with H_2O, and dried to give **9** (4.8 g, 92%). An analytical sample was obtained by recrystallization from MeOH, mp 274—279 °C (dec.). IR (KBr): 2205 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (1H, q, J=12.0 Hz), 2.58—2.78 (2H, m), 2.93—3.18 [4H, m, 2.99 (1H, t, J=12.0 Hz), 3.09 (1H, s)], 3.34—3.70 [2H, m, 3.60 (1H, dq, J=12.7, 2.0 Hz)], 4.18 (1H, dd, J=14.0, 7.1 Hz), 4.23 (1H, dd, J=14.0, 5.8 Hz), 6.86 (1H, d, J=6.9 Hz), 6.96 (1H, s), 7.18 (1H, t, J=7.6 Hz), 7.23 (1H, d, J=7.6 Hz), 8.01 [2H, s, 8.01 (1H, br s)], 8.12 (1H, s). *Anal.* Calcd for $C_{18}H_{18}N_6$: C, 67.90; H, 5.70; N, 26.40. Found: C, 67.68; H, 5.64; N, 26.36.

(5*R*,8*R*,10*R*)-8-(1,2,4-Triazol-1-ylmethyl)ergoline (10) The cyanide **9** (3.0 g, 9.42 mmol) was added in portions to a suspension of $LiAlH_4$ (3.0 g, 79.0 mmol) in THF with stirring at room temperature. Stirring was continued for 1 h. The reaction mixture was poured into aqueous KOH. The resulting precipitate was collected, washed with H_2O, dried, and chromatographed on a silica gel column with AcOEt–MeOH (3 : 1) to give colorless needles (1.8 g, 65%), mp 225—227 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (1H, q, J=11.9 Hz), 2.34—2.88 [6H, m, 2.54 (1H, t, J=11.2 Hz)], 2.94—3.20 (2H, m), 4.14 (1H, dd, J=13.9, 6.9 Hz), 4.16 (1H, dd, J=13.9, 6.5 Hz), 6.81—6.94 (2H, m), 7.15 (1H, t, J=8.3 Hz), 7.18 (1H, d, J=8.3 Hz), 7.99 (1H, s), 7.99 (1H, br s), 8.10 (1H, s). *Anal.* Calcd for $C_{17}H_{19}N_5$: C, 69.60; H, 6.53; N, 23.87. Found: C, 69.36; H, 6.47; N, 23.66.

Ethyl 1-Methyl-4-imidazolecarboxylates (12) and Ethyl 1-Methyl-5-imidazolecarboxylates (13) Ethyl 1-methyl-4-imidazolecarboxylate (**12a**) and Ethyl 1-methyl-5-imidazolecarboxylate (**13a**)[15a]: Ethyl imidazolecarboxylate (**11a**, 3.0 g, 21.4 mmol) was added in portions to a mixture of NaH (60% in oil, 1.0 g, 25.0 mmol) and DMF (30 ml) with stirring at room temperature. After addition of MeI (3.6 g, 25.4 mmol) the mixture was stirred for 0.5 h, then diluted with H_2O, and extracted with AcOEt. The extract was dried over $MgSO_4$. After removal of the solvent, the residual oil was chromatographed on a silica gel column with AcOEt–EtOH (100 : 1). The first fraction gave **13a**,[15a] colorless oil (1.2 g, 36%). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.1 Hz), 3.92 (3H, s), 4.33 (2H, q, J=7.1 Hz), 7.53 (1H, br s), 7.73 (1H, d, J=0.8 Hz).

The second fraction afforded **12a**,[15a] colorless oil (0.8 g, 24%). ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, t, J=7.2 Hz), 3.74 (3H, s), 4.35 (2H, q, J=7.2 Hz), 7.46 (1H, br s), 7.59 (1H, d, J=1.4 Hz).

The imidazoles **12b** and **13b** were prepared from **11b** in the same manner as described above.

12b[15b]: Colorless oil, 26% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.37 (3H, t, J=7.1 Hz), 2.52 (3H, s), 3.57 (3H, s), 4.36 (2H, q, J=7.1 Hz), 7.38 (1H, s).

13b[15b–d]: Colorless oil, 26% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (3H, t, J=7.2 Hz), 2.48 (3H, s), 3.84 (3H, s), 4.34 (2H, q, J=7.2 Hz), 7.40 (1H, s).

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, Dec. 1993, p. 17.
2) For example, R. Wilbrandt, *Angiology*, **4**, 183 (1953); A. Pöldre, *Acta Med. Scand.*, **155**, 437 (1956).
3) E. Flueckiger, F. Troxler, A. Hofmann, Ger. Offen., 1926045 (1969) [*Chem. Abstr.*, **72**, 43969*b* (1970)].

4) E. C. Kornfeld, N. J. Bach, Eur. Patent Appl., 3667 (1979) [*Chem. Abstr.*, **92**, 181450*q* (1979)].
5) For example, K. O. Stumpe, R. Kolloch, M. Higuchi, F. Krück, 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).
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) 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. Tomota, 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).
9) The carboxylates **1a**,[10a] **1b**,[10b] **1c**,[10c] **1d**,[10c–e] and **1e**[10d–f] were prepared from **14** by the known methods or our modifications thereof.
10) *a*) A. Stoll, A. Hofmann, *Helv. Chim. Acta*, **29**, 635 (1946); *b*) F. Troxler, A. Hofmann, *ibid.*, **40**, 2160 (1957); *c*) T. Fehr, P. A. Stadler, A. H. Hofmann, *ibid.*, **53**, 2197 (1970); *d*) A. M. Crider, R. Grubb, K. A. Bachmann, A. K. Rawat, *J. Pharm. Sci.*, **70**, 1319 (1981); *e*) J. Beneš, A. Černý, V. Miller, S. Kudrnáč, *Collect. Czech. Chem. Commun.*, **48**, 1333 (1983); *f*) J. Křepelka, A. Černý, R. Kotva, M. Semonský, *ibid.*, **42**, 1209 (1977).
11) The methanols **2a**,[12] **2d**,[10f] and **2e**[10f] are known compounds.
12) A. Stoll, A. Hofmann, W. Schlientz, *Helv. Chim. Acta*, **32**, 1947 (1949).
13) The tosylates **3a**[14a] and **3e**[14b] are known compounds.
14) *a*) E. Schreier, *Helv. Chim. Acta*, **41**, 1984 (1958); *b*) S. Mantegani, G. Arcari, A. M. Caravaggi, G. Bosisio, U. S. Patent 4321381 (1982) [*Chem. Abstr.*, **97**, 110254*w* (1982)].
15) *a*) Y. Takeuchi, K. L. Kilk, L. A. Cohen, *J. Org. Chem.*, **43**, 3570 (1978); *b*) H. A. Staab, G. A. Schwalbach, *Justus Liebigs Ann. Chem.*, **715**, 128 (1968); *c*) P. Haake, L. P. Bausher, J. P. McNeal, *J. Am. Chem. Soc.*, **93**, 7045 (1971); *d*) B. L. Ram, G. R. Wellman, C. S. Labaw, *J. Org. Chem.*, **47**, 144 (1982).
16) E. Belgodere, R. Bossio, V. Parrini, R. Pepino, *Arzneim.-Forsch.*, **30**, 1051 (1980).
17) The signal of the 5-proton of 1-alkyltetrazole appears at a higher field than that of 2-alkyltetrazole.[18,19] The 5-proton signals of (5*R*,8*S*,10*R*)-6-methyl-8-(1-tetrazolylmethyl)ergoline[19] and (5*R*, 8*S*,10*R*)-6-methyl-8-(2-tetrazolylmethyl)ergoline[19] appear at δ 8.46 and 8.69, respectively. That of **4u** appears at δ 8.46.
18) R. Raap, J. Howard, *Can. J. Chem.*, **47**, 813 (1969).
19) Details will be reported soon.