

## Synthesis and Structure–Activity Relationships of New (5*R*,8*R*,10*R*)-Ergoline Derivatives with Antihypertensive or Dopaminergic Activity<sup>1)</sup>

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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-methylethylergoline (4a, 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-propylethylergoline (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.

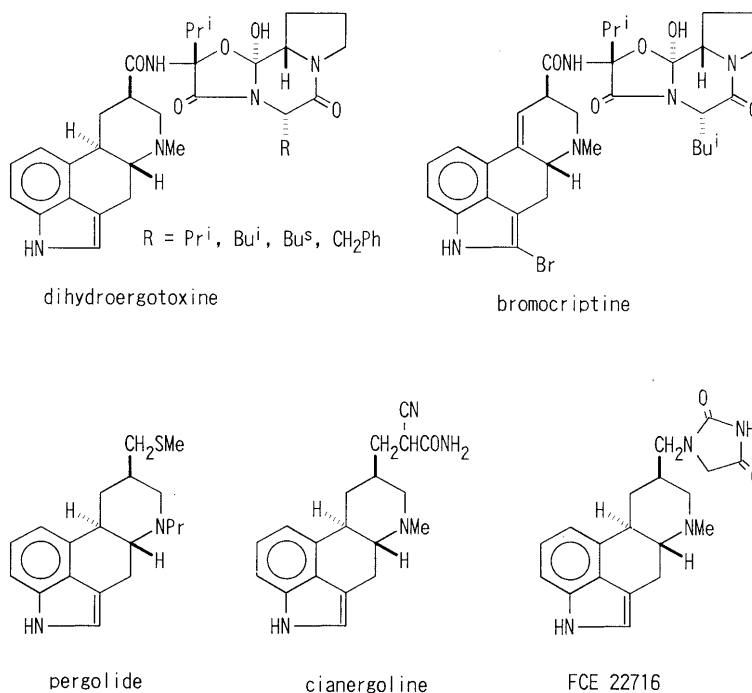
**Keywords** antihypertensive; dopaminergic; structure–activity relationship; ergoline; BAM-1110; BAM-1602

Dihydroergotamine has been clinically employed for patients with cerebral and peripheral circulatory disturbances. This compound possesses weak hypotensive activity<sup>2)</sup> and so has also been utilized as an anti-hypertensive. Bromocriptine<sup>3)</sup> and pergolide,<sup>4)</sup> dopamine D<sub>2</sub> receptor agonists, have been used in the therapy of Parkinson's disease, acromegaly, and hyperprolactinemia. Pergolide shows extremely potent D<sub>2</sub> receptor agonistic activity. These compounds have been reported to exhibit moderate antihypertensive activity in animals and

humans.<sup>5)</sup> Cianergoline<sup>6)</sup> and FCE 22716,<sup>7)</sup> synthesized as antihypertensives, have relatively potent activities in animals.

Pergolide, dihydroergotamine, 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,<sup>8)</sup> such as nausea and vomiting, which could limit their clinical use.

We synthesized a series of new ergolines, hoping to find



Pr<sup>i</sup> = iso-Pr, Bu<sup>i</sup> = iso-Bu, Bu<sup>s</sup> = *sec*-Bu

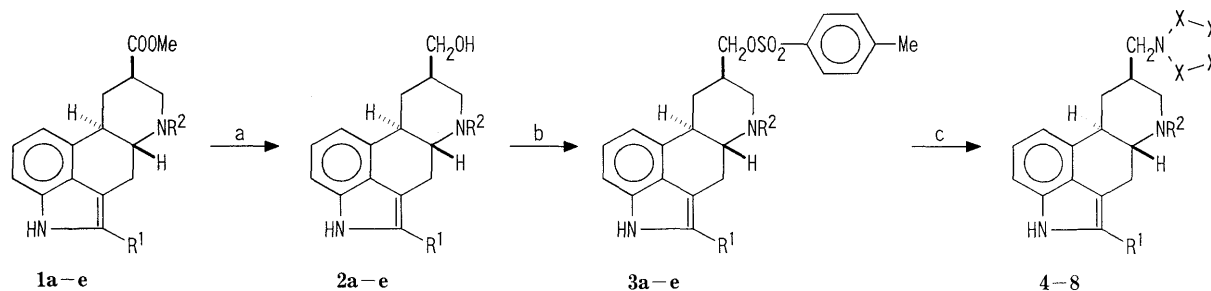
Fig. 1

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**)<sup>9</sup> were reduced with NaBH<sub>4</sub> in a mixture of methanol and water or LiAlH<sub>4</sub> in tetrahydrofuran (THF) to afford the

methanols (**2a–e**)<sup>11</sup> in good yields. The methanols **2a–e** were converted to (5*R*,8*R*,10*R*)-8-ergolinylmethyl tosylates (**3a–e**)<sup>13</sup> 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**).



	R <sup>1</sup>	R <sup>2</sup>
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<sub>4</sub>/MeOH-H<sub>2</sub>O or LiAlH<sub>4</sub>/THF; b) TsCl/pyridine; c) HNX<sub>4</sub>, NaH/DMF

Chart 1

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

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

TABLE I. (continued)


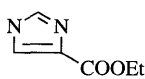
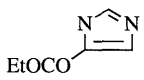
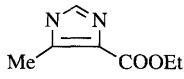
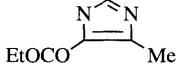
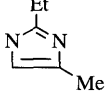

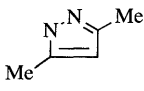
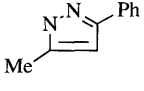
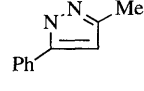




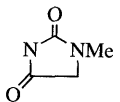

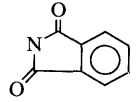











Compd. No.	R <sup>1</sup>	R <sup>2</sup>	NX <sub>4</sub>	Yield (%)	mp (°C) Recryst. solv.	Formula	Analysis (%)		
							Calcd	(Found)	
							C	H	N
4i	H	Me		64	233—237 (dec.) MeOH—Me <sub>2</sub> CO	C <sub>25</sub> H <sub>26</sub> N <sub>4</sub>	78.50 (78.16)	6.85 6.87	14.65 14.58
4j	H	Me		57	260—265 (dec.) CH <sub>2</sub> Cl <sub>2</sub> —Me <sub>2</sub> CO	C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub>	69.82 (69.44)	6.92 6.87	14.80 14.83
4k	H	Me		18	160—163 Me <sub>2</sub> CO	C <sub>22</sub> H <sub>26</sub> N <sub>4</sub> O <sub>2</sub> · 1/2H <sub>2</sub> O	68.19 (68.33)	7.02 6.78	14.46 14.50
4l	H	Me		21	248—251 (dec.) EtOH—CH <sub>2</sub> Cl <sub>2</sub>	C <sub>23</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub>	70.38 (70.45)	7.19 7.20	14.27 14.23
4m	H	Me		18	225—227 CH <sub>2</sub> Cl <sub>2</sub> —Et <sub>2</sub> O	C <sub>23</sub> H <sub>28</sub> N <sub>4</sub> O <sub>2</sub>	70.38 (70.44)	7.19 7.26	14.27 14.18
4n	H	Me		29	172—174 MeOH	C <sub>22</sub> H <sub>28</sub> N <sub>4</sub>	75.82 (75.79)	8.10 8.25	16.08 16.00
4o	H	Me		91	192—194 CH <sub>2</sub> Cl <sub>2</sub> —iso-Pr <sub>2</sub> O	C <sub>19</sub> H <sub>22</sub> N <sub>4</sub>	74.48 (74.56)	7.24 7.50	18.29 18.08
4p	H	Me		31	187—190 iso-PrOH	C <sub>21</sub> H <sub>26</sub> N <sub>4</sub> · 1/2H <sub>2</sub> O	73.44 (73.58)	7.92 7.89	16.31 16.02
4q	H	Me		60	225—230 (dec.) Me <sub>2</sub> CO	C <sub>26</sub> H <sub>28</sub> N <sub>4</sub> · 1/6H <sub>2</sub> O	78.16 (78.27)	7.15 7.12	14.02 14.16
4r	H	Me		7	169—171 Me <sub>2</sub> CO	C <sub>26</sub> H <sub>28</sub> N <sub>4</sub> · 1/2H <sub>2</sub> O	77.00 (76.72)	7.21 7.19	13.82 13.76
4s	H	Me		64	> 243 (dec.) MeOH	C <sub>18</sub> H <sub>21</sub> N <sub>5</sub>	70.33 (70.42)	6.89 7.07	22.78 22.73
4s-m <sup>a)</sup>					208—212 (dec.) MeOH	C <sub>18</sub> H <sub>21</sub> N <sub>5</sub> · C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> <sup>a)</sup>	62.40 (62.44)	5.95 5.97	16.54 16.49
4t	H	Me		7	> 270 (dec.) CH <sub>2</sub> Cl <sub>2</sub> —MeOH	C <sub>18</sub> H <sub>21</sub> N <sub>5</sub>	70.33 (70.53)	6.89 6.86	22.78 22.82
4u	H	Me		31	206—209 Me <sub>2</sub> CO	C <sub>17</sub> H <sub>20</sub> N <sub>6</sub>	66.21 (66.46)	6.54 6.53	27.25 27.50
4v	H	Me		49	> 235 (dec.) EtOH	C <sub>20</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub>	71.19 (71.30)	6.87 6.95	12.45 12.49
4w	H	Me		70	> 215 (dec.) CH <sub>2</sub> Cl <sub>2</sub> —hexane	C <sub>20</sub> H <sub>24</sub> N <sub>4</sub> O <sub>2</sub> · 1/12CH <sub>2</sub> Cl <sub>2</sub>	67.10 (67.21)	6.78 7.04	15.58 15.38
4x	H	Me		82	> 255 (dec.) iso-PrOH	C <sub>19</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub>	70.13 (70.01)	7.12 7.34	12.91 12.88
4x-s <sup>b)</sup>					> 265 (dec.) H <sub>2</sub> O—EtOH	C <sub>19</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub> · CH <sub>4</sub> O <sub>3</sub> S <sup>b)</sup>	56.99 (57.07)	6.46 6.55	9.97 9.99
4y	H	Me		69	> 270 (dec.) CH <sub>2</sub> Cl <sub>2</sub> —hexane	C <sub>24</sub> H <sub>23</sub> N <sub>3</sub> O <sub>2</sub>	74.78 (74.83)	6.01 6.07	10.90 10.68

TABLE I. (continued)

Compd. No.	R <sup>1</sup>	R <sup>2</sup>	NX <sub>4</sub>	Yield (%)	mp (°C) Recryst. solv.	Formula	Analysis (%)		
							Calcd	(Found)	
							C	H	N
<b>5a</b>	Cl	Me		41	> 252 (dec.) EtOH-Et <sub>2</sub> O	C <sub>19</sub> H <sub>21</sub> ClN <sub>4</sub>	66.95 (66.91)	6.21 6.28	16.44 16.26
<b>5b</b>	Cl	Me		22	255—260 (dec.) EtOH-Et <sub>2</sub> O	C <sub>25</sub> H <sub>25</sub> ClN <sub>4</sub>	72.02 (71.75)	6.04 6.05	13.44 13.33
<b>5c</b>	Cl	Me		17	241—245 EtOH-Et <sub>2</sub> O	C <sub>18</sub> H <sub>20</sub> ClN <sub>5</sub>	63.24 (63.00)	5.90 5.88	20.49 20.24
<b>6a</b>	Br	Me		56	> 260 (dec.) CHCl <sub>3</sub> -Me <sub>2</sub> CO	C <sub>19</sub> H <sub>21</sub> BrN <sub>4</sub>	59.23 (58.96)	5.49 5.47	14.54 14.38
<b>6b</b>	Br	Me		48	> 260 (dec.) CHCl <sub>3</sub> -Et <sub>2</sub> O	C <sub>22</sub> H <sub>27</sub> BrN <sub>4</sub>	61.83 (61.55)	6.37 6.39	13.11 13.00
<b>6c</b>	Br	Me		19	> 255 (dec.) EtOH-hexane	C <sub>25</sub> H <sub>25</sub> BrN <sub>4</sub>	65.08 (64.77)	5.46 5.56	12.14 11.94
<b>6d</b>	Br	Me		36	225—230 CH <sub>2</sub> Cl <sub>2</sub> -AcOEt	C <sub>18</sub> H <sub>20</sub> BrN <sub>5</sub> · 1/12CH <sub>2</sub> Cl <sub>2</sub>	55.21 (55.26)	5.17 5.02	17.80 17.77
<b>7</b>	H	Et		66 86 <sup>c)</sup>	> 265 (dec.) MeOH	C <sub>19</sub> H <sub>23</sub> N <sub>5</sub>	71.00 (70.84)	7.21 7.19	21.79 21.92
<b>7-f<sup>d)</sup></b>						C <sub>19</sub> H <sub>23</sub> N <sub>5</sub> · C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> <sup>d)</sup> · H <sub>2</sub> O	60.65 (60.81)	6.42 6.33	15.37 15.22
<b>8a</b>	H	Pr		60	212—214 (dec.) iso-PrOH-Et <sub>2</sub> O	C <sub>21</sub> H <sub>26</sub> N <sub>4</sub>	75.41 (75.41)	7.84 7.98	16.75 16.49
<b>8b</b>	H	Pr		84 88 <sup>c)</sup>	201—203 Me <sub>2</sub> CO	C <sub>20</sub> H <sub>25</sub> N <sub>5</sub>	71.61 (71.97)	7.51 7.59	20.88 20.68
<b>8b-f<sup>d)</sup></b>						C <sub>20</sub> H <sub>25</sub> N <sub>5</sub> · C <sub>4</sub> H <sub>4</sub> O <sub>4</sub> <sup>d)</sup>	63.84 (64.05)	6.47 6.50	15.51 15.57
<b>8c</b>	H	Pr		6	> 235 (dec.) EtOH	C <sub>20</sub> H <sub>25</sub> N <sub>5</sub>	71.61 (71.88)	7.51 7.62	20.88 20.62

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

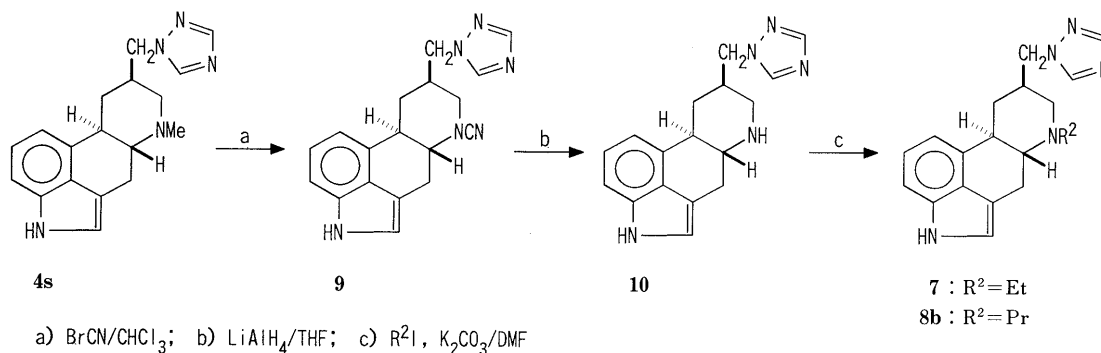


Chart 2

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<sub>4</sub> in THF to afford **10** in 65% yield. Alkylation of **10** with alkyl iodide and K<sub>2</sub>CO<sub>3</sub> 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**.<sup>15)</sup> Protons of the 1-methyl or the 1-methylene groups of **4k**, **4m**, and

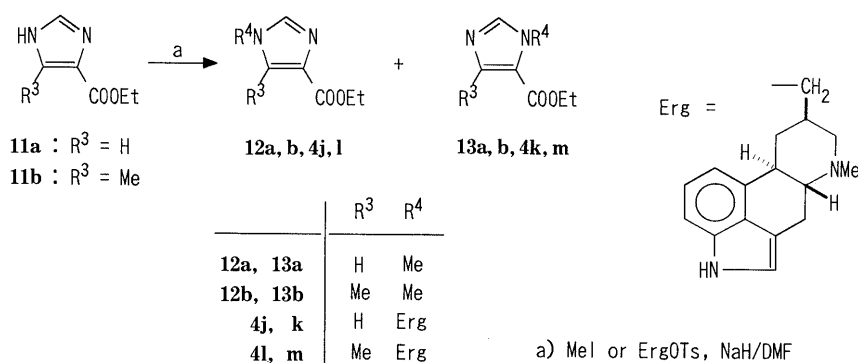


Chart 3

TABLE II. Selected <sup>1</sup>H- and <sup>13</sup>C-NMR Spectral Data for Ethyl 4- (**4j**, **l**, **12**) and 5-Imidazolecarboxylates (**4k**, **m**, **13**) in CDCl<sub>3</sub>

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

Compd. No.	R <sup>3</sup>	R <sup>4</sup>	<sup>1</sup> H-NMR (ppm)				<sup>13</sup> C-NMR (ppm)					
			1-Me or CH <sub>2</sub>	2-H	4-H	4-Me	J <sub>2,4</sub> (Hz)	1-Me or CH <sub>2</sub>	2-C	4-C	5-C	4-Me
<b>13a</b>	H	Me	3.92	7.53	7.73	—	0.8	34.0	137.3	142.4	123.4	—
<b>4k</b>	H	Erg	3.97 <sup>b)</sup>	7.52	7.71	—	ca. 0	50.7	137.9	142.1	122.9	—
<b>13b</b>	Me	Me	3.84	7.40	—	2.48	—	34.7	140.5	147.9	119.2	15.8
<b>4m</b>	Me	Erg	3.83 <sup>b)</sup>	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 <sup>1</sup>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.<sup>16)</sup> 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 <sup>1</sup>H- and <sup>13</sup>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 <sup>1</sup>H-NMR spectrum of **4q**, downfield shifts of the 2- and 6-protons of the phenyl group were observed ( $\delta$  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  $\delta$  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  $\delta$  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.<sup>17)</sup>

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

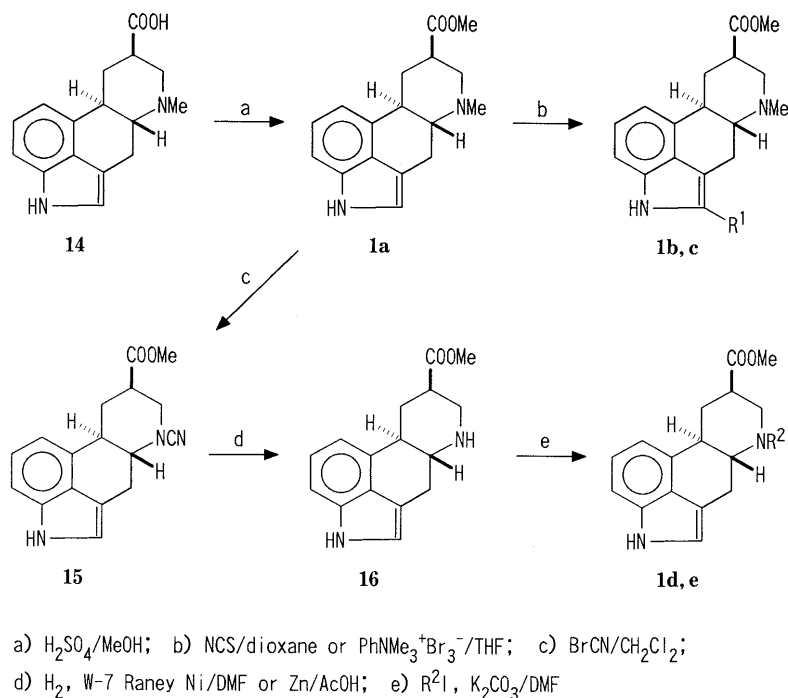


Chart 4

**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 cyanergoline 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 cyanergoline, 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-ethoxycarbonyl-imidazole (**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  $\text{D}_1$ - and  $\text{D}_2$ -agonist and clinical trials are in progress. Further investigation of the ergoline **8b** (fumarate: BAM-1602), an extremely potent and selective dopamine  $\text{D}_2$ -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.

**(5R,8R,10R)-8-Ergolinemethanols (2)** a) (5R,8R,10R)-6-Methyl-8-ergolinemethanol (**2a**)<sup>12)</sup>:  $\text{NaBH}_4$  (20 g, 529 mmol) was added in portions to a mixture of **1a**<sup>10a)</sup> (20 g, 70.3 mmol), MeOH (160 ml), and  $\text{H}_2\text{O}$  (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			Heart rate	
		Initial value (mmHg)	Maximum change (mmHg)	Duration <sup>a)</sup> (h)	Initial value (beats/min)	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	— <sup>b)</sup>	—	368	— <sup>b)</sup>
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 <sup>c)</sup>	—	411	-11 <sup>c)</sup>
8b	3	209	-6	—	388	-11
Cia <sup>d)</sup>	3	201	-40	>7	398	-28
	10	199	-56	>7	390	-32
Bro <sup>e)</sup>	3	216	-37	>7	375	-8
	10	222	-54	>7	364	-13
Dih <sup>f)</sup>	10	224	-20	—	394	-41
Hyd <sup>g)</sup>	3	230	-47	>7	394	38
Nif <sup>h)</sup>	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) Dihydroergotamine 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.<sup>12)</sup> mp 280 °C (dec.)]. <sup>1</sup>H-NMR (CD<sub>3</sub>OD) 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<sub>16</sub>H<sub>20</sub>N<sub>2</sub>O: 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). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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<sub>16</sub>H<sub>19</sub>BrN<sub>2</sub>O: 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<sub>4</sub> (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<sub>2</sub>O were added to it to decompose excess LiAlH<sub>4</sub>. The precipitate was filtered off using Celite. The filtrate was concentrated *in vacuo*. The resulting crystals were washed with H<sub>2</sub>O 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). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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<sub>16</sub>H<sub>19</sub>ClN<sub>2</sub>O: C, 66.09; H, 6.59; N, 9.63. Found: C, 65.98; H, 6.67; N, 9.62.

**2d**<sup>10f)</sup>: 94% yield, mp >235 °C (dec., iso-PrOH) (lit.<sup>10f)</sup> mp 252–254 °C). <sup>1</sup>H-NMR (DMSO-*d*<sub>6</sub>) 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<sub>17</sub>H<sub>22</sub>N<sub>2</sub>O: C, 75.52; H, 8.20; N, 10.36. Found: C, 75.61; H, 8.33; N, 10.38.

**2e**<sup>10f)</sup>: 96% yield, mp 181–183 °C (AcOEt) (lit.<sup>10f)</sup> mp 181–182 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sub>18</sub>H<sub>24</sub>N<sub>2</sub>O · 1/2H<sub>2</sub>O: 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**)<sup>14a)</sup>: 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<sub>2</sub>O (4 ml) and stirring for 0.5 h, the reaction mixture was made alkaline with aqueous K<sub>2</sub>CO<sub>3</sub> and diluted with ice-water. The resulting crystals were collected, washed with H<sub>2</sub>O, and dried. Recrystallization from CH<sub>2</sub>Cl<sub>2</sub>-AcOiso-Pr afforded **3a** (6.4 g, 80%), mp 193–196 °C (dec.) (lit.<sup>14a)</sup> mp 191–193 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sub>2</sub>B<sub>2</sub> type d, *J* = 8.2 Hz)], 7.78 (2H, A<sub>2</sub>B<sub>2</sub> 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)	<i>n</i>	Initial value <sup>a)</sup> (mmHg)	Changes in blood pressure (mmHg) <sup>a)</sup>					Initial value <sup>a)</sup> (beats/min)	Changes in heart rate (beats/min) <sup>a)</sup>				
				1	3	5	7	24 (h)		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 mesylate	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
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 <sup>a)</sup> 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 <sup>b)</sup>									0/2	0/2
Bro <sup>c)</sup>						0/5	3/5			
Dih <sup>d)</sup>							0/2		1/2	1/2
Per <sup>e)</sup>		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 <sup>a)</sup>	Onset (h) <sup>a)</sup>	End (h) <sup>a)</sup>
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 <sup>a)</sup> vomited/treated animals (μg/kg, i.v.) or/and ED <sub>50</sub> (mg/kg, p.o.)	LD <sub>50</sub> 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 <sup>b)</sup>	30(0/2), 100(2/2)	> 1500
Bro <sup>c)</sup>	3(0/4), 10(3/4), 30(4/4), 0.028	2800
Dih <sup>d)</sup>	3(0/4), 10(4/4)	> 1500
Per <sup>e)</sup>	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<sub>2</sub>O (4 ml) and stirring for 0.5 h, the reaction mixture was made alkaline with aqueous K<sub>2</sub>CO<sub>3</sub>, diluted with H<sub>2</sub>O and extracted with AcOEt. The extract was washed with H<sub>2</sub>O, dried over MgSO<sub>4</sub>, and concentrated *in vacuo*. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub>, treated with activated carbon, and recrystallized from CH<sub>2</sub>Cl<sub>2</sub>-hexane to yield **3b** (9.0 g, 84%), mp 145—148 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sub>2</sub>B<sub>2</sub> type d, J=8.1 Hz), 7.76 (2H, A<sub>2</sub>B<sub>2</sub> type d, J=8.1 Hz), 7.95 (1H, br). *Anal.* Calcd for C<sub>23</sub>H<sub>25</sub>ClN<sub>2</sub>O<sub>3</sub>S: 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). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sub>2</sub>B<sub>2</sub> type d, J=8.1 Hz), 7.83 (2H, A<sub>2</sub>B<sub>2</sub> type d, J=8.1 Hz), 7.99 (1H, br). *Anal.* Calcd for C<sub>23</sub>H<sub>25</sub>BrN<sub>2</sub>O<sub>3</sub>S: 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<sub>2</sub>Cl<sub>2</sub>-AcOiso-Pr). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sub>2</sub>B<sub>2</sub> type d, J=8.1 Hz), 7.83 (2H, A<sub>2</sub>B<sub>2</sub> type d, J=8.1 Hz), 7.91 (1H, br). *Anal.* Calcd for C<sub>24</sub>H<sub>28</sub>N<sub>2</sub>O<sub>3</sub>S: C, 67.90; H, 6.65; N, 6.60. Found: C, 67.80; H, 6.71; N, 6.48.

**3e**<sup>14b)</sup>: 85% yield, mp 175—177 °C (AcOEt) (lit.<sup>14b)</sup> mp 147—150 °C). <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 0.89 (3H, t, J=7.4 Hz), 1.07 (1H, q, J=12.2 Hz),



TABLE VIII. <sup>1</sup>H-NMR Spectral Data for (5R,8R,10R)-8-Methylergolines (4–8) in CDCl<sub>3</sub>

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, $J=12.5$ 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)
<b>8a</b>	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)
<b>8b</b>	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)
<b>8c</b>	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.

**(5R,8R,10R)-Ergolines (4—8)** a) (5R,8R,10R)-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) (5R,8R,10R)-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) (5R,8R,10R)-6-Methyl-8-(1,2,4-triazol-1-ylmethyl)ergoline (**4s**) and (5R,8R,10R)-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) (5R,8R,10R)-6-Propyl-8-(1,2,4-triazol-1-ylmethyl)ergoline (**8b**) and (5R,8R,10R)-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) (5R,8R,10R)-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.

**(5R,8R,10R)-6-Cyano-8-(1,2,4-triazol-1-ylmethyl)ergoline (9)** Cyano-

gen 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  $cm^{-1}$ .  $^1H-NMR$  ( $CDCl_3$ )  $\delta$ : 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.

**(5R,8R,10R)-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.).  $^1H-NMR$  ( $CDCl_3$ )  $\delta$ : 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**)<sup>15a</sup>: 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**,<sup>15a</sup> colorless oil (1.2 g, 36%).  $^1H-NMR$  ( $CDCl_3$ )  $\delta$ : 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**,<sup>15a</sup> colorless oil (0.8 g, 24%).  $^1H-NMR$  ( $CDCl_3$ )  $\delta$ : 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**<sup>15b</sup>: Colorless oil, 26% yield.  $^1H-NMR$  ( $CDCl_3$ )  $\delta$ : 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**<sup>15b-d</sup>: Colorless oil, 26% yield.  $^1H-NMR$  ( $CDCl_3$ )  $\delta$ : 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**, 43969b (1970)].

- 4) E. C. Kornfeld, N. J. Bach, Eur. Patent Appl., 3667 (1979) [*Chem. Abstr.*, **92**, 181450q (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**, 149582y (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. Endocrinol. Metab.*, **53**, 772 (1981); A. Grossman, P.-M. G. Bouloux, T. Lonergan, L. H. Rees, J. A. H. Wass, G. M. Besser, *Clin. Endocrinol.*, **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**,<sup>10a)</sup> **1b**,<sup>10b)</sup> **1c**,<sup>10c)</sup> **1d**,<sup>10c-e)</sup> and **1e**<sup>10d-f)</sup> 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**,<sup>12)</sup> **2d**,<sup>10f)</sup> and **2e**<sup>10f)</sup> are known compounds.
- 12) A. Stoll, A. Hofmann, W. Schlientz, *Helv. Chim. Acta*, **32**, 1947 (1949).
- 13) The tosylates **3a**<sup>14a)</sup> and **3e**<sup>14b)</sup> 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**, 110254w (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.<sup>18,19)</sup> The 5-proton signals of (5*R*,8*S*,10*R*)-6-methyl-8-(1-tetrazolylmethyl)ergoline<sup>19)</sup> and (5*R*,8*S*,10*R*)-6-methyl-8-(2-tetrazolylmethyl)ergoline<sup>19)</sup> appear at  $\delta$  8.46 and 8.69, respectively. That of **4u** appears at  $\delta$  8.46.
- 18) R. Raap, J. Howard, *Can. J. Chem.*, **47**, 813 (1969).
- 19) Details will be reported soon.