Ergot Alkaloids.[1] New Ergolines as Selective Dopaminergic Stimulants

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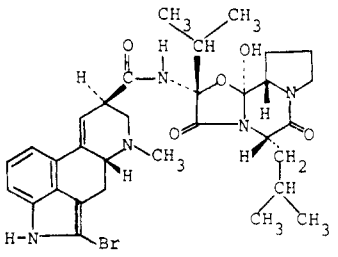
A new two-step sequence for the epimerization of methyl dihydrolysergate (**5**) at C-8 leading to methyl dihydroisolysergate (**7**) is presented. The latter compound was used as a starting material for the synthesis of various ergolines, of which (5*R*,8*R*,10*R*)-8-(cyanomethyl)-6-methylergoline (**4**) is a very strong and long-lasting central dopaminergic agent. Furthermore, it was found that some 8-(arylthiomethyl)-6-methylergolenes are not able to induce apomorphine-like stereotyped behavior in normal rats but exhibit a remarkable activity in rats unilaterally lesioned by 6-OH-DA in the nigrostriatal region. Compound **4** and (5*R*,8*R*)-8-[(2-pyridyl)thiomethyl]-6-methylergolene (**9**) were further tested for their ability to inhibit ovum implantation and to depress serum prolactin levels in rats. Their potency was evaluated in comparison with (5*R*,8*S*,10*R*)-8-(cyanomethyl)-6-methylergolines (**2a** and **2b**) and 2-bromo-α-ergocryptine (**1**) as standards.

In recent years an increasing number of papers have appeared reporting various ergolines as potent inhibitors of pituitary prolactin release.[2] The most important representatives of this class of compounds are 2-bromo-α-ergocryptine (**1**) (CB 154, bromocriptine, a derivative of the naturally occurring ergot alkaloid α-ergocryptine[3]), (5*R*,8*S*,10*R*)-8-(cyanomethyl)-6-methylergoline (**2a**) (VUFB 6605),[4] and its 2-chloro derivative **2b** (lergotrile).[5]



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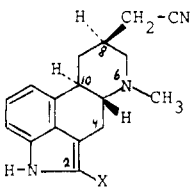


2a: X = H

2b: X = Cl

Concerning the mechanisms of their biological action, some evidence has been found that tuberoinfundibular dopamine neurons are involved in the regulation of prolactin release.[6] Furthermore, 2-bromo-α-ergocryptine has been determined to act as a dopamine receptor agonist in the basal ganglia.[7] Clinical studies using 2-bromo-α-ergocryptine in the treatment of Parkinson's disease,[8] of which striatal dopamine deficiency is a generally accepted cause, have confirmed these findings.

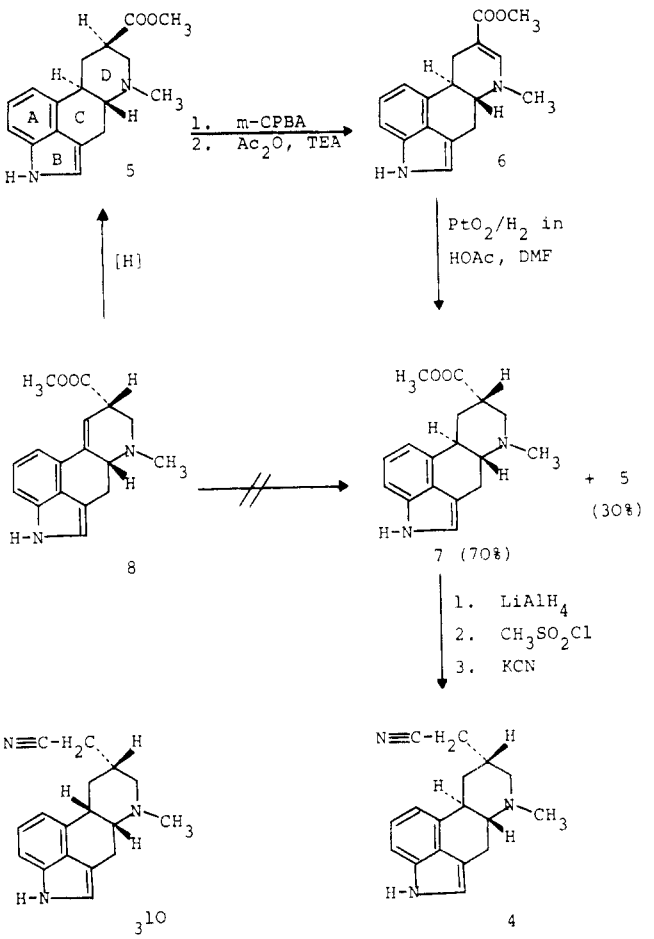
Consequently, a screening program was initiated in our laboratories to discover new and possibly more selective central dopaminergic agents useful in parkinsonism.

Recently a naturally occurring clavine alkaloid, agroclavine, was reported to possess apomorphine-like dopaminergic activity.[9] Unfortunately, however, this compound is unacceptably toxic.

This paper deals with the syntheses and pharmacological properties of new ergoline and ergolene derivatives, some of which exhibit an unconventional profile of CNS activity, such as more selective dopaminergic stimulation and longer duration of action in comparison with apomorphine.

Chemistry. In an attempt to better understand the stereochemical requirements for biological activity of the ergoline compound **2a**, the 8*R* epimers **3** and **4** (Scheme I) with C/D-cis and C/D-trans ring junction, respectively, were initially synthetized. These were obtained by conventional nucleophilic displacement of the corresponding dihydroisolysergol methanesulfonate esters with potassium cyanide.

Scheme I



5 **6** **8** **3** **4**

Zikan et al. reported preparation of **3** and **4** via the corresponding 8-(chloromethyl)-6-methylergolines.[10] But since the syntheses of the intermediate dihydroisolysergols are time-consuming and as compound **4** was rather unexpectedly found to be a highly active dopaminergic stimulant in the Ungerstedt test, a more efficient method for the preparation of this particular type of isomer was sought.

This led to the development of a new two-step process for the epimerization of methyl dihydrolysergate (**5**) at C-8 (Scheme I). Methyl dihydroisolysergate (**7**) was obtained in 70% yield by hydrogenation of the enamino methyl ester **6**, the synthesis of which was recently described by Bach and Kornfeld[11] and by Stütz and Stadler.[12]

The considerable stereoselectivity of the hydrogenation

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step is very useful since the hydrogenation of methyl isolysergate (8) leads exclusively to the 8-epimer, methyl dihydrolysergate (5).

This, at first sight, rather surprising observation can be explained as follows. Derivatives of lysergic acid and isolysergic acid epimerize easily at C-8 and there are marked differences in the rate of hydrogenation of these C-8 epimers. Therefore, amides of lysergic acid can generally be hydrogenated stereospecifically to the corresponding amides of dihydrolysergic acid I with ring C/D trans junction. Amides of isolysergic acid which are not so prone to 8-epimerization in protic solvents are hydrogenated to a mixture of diastereomers of which that with the undesired ring C/D cis junction usually predominates.

Therefore, concerning the hydrogenation reaction of 8, we assume that epimerization and subsequently fast and stereospecific hydrogenation of the thermodynamically more stable epimer with an equatorial carboxylate group at C-8 explains the exclusive formation of 5.

The preparation of the pharmacologically interesting (5*R*,8*R*,10*R*)-8-(cyanomethyl)-6-methylergoline (4) offered no further problems once this new epimerization process was developed, and the synthesis was completed as indicated in Scheme I.

A series of new 8-(arylthiomethyl)-6-methylergolene and -ergoline compounds was prepared by means of a nucleophilic displacement of the corresponding methanesulfonate esters with various thiophenolate anions; the introduction of bulky but movable substituents in that region of the molecule was a further attempt to explore the stereochemical requirements for selective dopaminergic activity.

Compounds 9 and 14–18 with a double bond at C-9 and C-10 have been prepared from lysergol which bears an equatorial 8-hydroxymethyl group; i.e., it has the same stereochemistry as lysergic acid. Compound 10 is derived from isolysergol, 11 from 1-methyllysergol, 12 from dihydrolysergol, and 13 from dihydroisolysergol, respectively (Table I).

Pharmacology. Pharmacological evaluation of the above compounds was based mainly on two tests.

(1) Induction of turning by drugs administered systemically in rats with unilateral functional degeneration of the nigrostriatal pathways resulting from injection of 6-OH-DA into the substantia nigra. Contralateral turning caused by apomorphine has been explained as a stimulation of the DA receptors which become hypersensitive because of degeneration of the nigrostriatal pathways.[13]

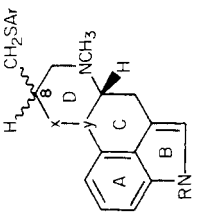
(2) Observation and quantification of stereotyped behavior. Licking, sniffing, and biting[14,15] was assessed using a score system based on that described by Costall et al.[16] This stereotypy is probably due to the stimulation of dopaminergic mechanisms in the striatum.[17,18]

As reported in Table II, compound 4 induces very strong turning behavior in lesioned rats but does not produce comparably strong apomorphine-like stereotypy in normal rats. On the other hand, compounds **2a** and **2b** are more active in intact rats, inducing only slight turning behavior in lesioned rats. Compound 3 was weakly active in both tests.

Most compounds of the second group (9–18) induce contralateral turning in lesioned rats and, unlike 1 and **2b**, do not cause stereotypy in normal rats at the dose indicated.

Pharmacological results of compounds 4 and 9 (Table II) prompted further investigation. In addition to turning behavior and stereotypy, these two substances were tested

Table I



no.	salt form[a]	Ar	X—Y	R	config at C-8	mp, °C dec	$[\alpha]^{20}_D$, deg	formula	analyses
9	1	2-pyridyl	double bond	H	β	200–201	+13 (DMF)	$C_{21}H_{21}N_3S$	C, H, N, S
10	2	2-pyridyl	double bond	H	α	220–224	+158 (DMF)	$C_{21}H_{21}N_3S$	C, H, N, S (free base)
11	3	2-pyridyl	double bond	CH_3	β	200–202	−13.5 (DMF)	$C_{22}H_{23}N_3S \cdot C_4H_4O_4$	C, H, N, S
12	1	2-pyridyl	single bond, C/D trans	H	β	191–193	−113 (pyridine)	$C_{21}H_{23}N_3S$	C, H, N, S
13	1	2-pyridyl	single bond, C/D trans	H	α	195–197	−58 (DMF)	$C_{21}H_{23}N_3S$	C, H, N
14	1	3-pyridyl	double bond	H	β	192–196	+38 (DMF)	$C_{21}H_{21}N_3S$	C, H, N
15	1	4-pyridyl	double bond	H	β	191–194	+52 (Me_2SO)	$C_{21}H_{21}N_3S$	C, H, N
16	4	*p*-chlorophenyl	double bond	H	β	194–197	+50 (CH_3OH)	$C_{22}H_{21}ClN_2S \cdot CH_4SO_3$	C, H, N, S
17	1	2-thiazolyl	double bond	H	β	192–196	+58 (Me_2SO)	$C_{19}H_{19}N_3S_2$	C, H, N
18	5	2-benzothiazolyl	double bond	H	β	180–182	+14 (DMF)	$C_{23}H_{21}N_3S_2$	C, H, N, S (free base)

[a] Forms: 1, free base; 2, bishydrochloride; 3, fumarate; 4, methanesulfonate; 5, tartrate.

Table II

compd	induction of turning toward the intact side in the rat with unilateral degeneration of the nigrostriatal tract induced by 6-OH-DA (Ungerstedt model): dose, mg/kg	route	total no. of rotations	production of stereotypy in the rat; signs observed—sniffing, licking, biting (0–7 h): dose, mg/kg ip	total act. per rat (0–7 h)
1	1	sc	1721	30	13.0
2a	1	ip	1299	30	17.3
2b	1	ip	1350	30	27
3	1	ip	576	30	0.3
4	1	ip	2607	30	14.3
9	1	ip	796	30	1.0
10	1	ip	544	30	0
11	1	ip	0	30	0
12	1	ip	10	30	3
13	1	ip	979	30	0
14	1	ip	694	30	0
15	1	ip	848	30	0.5
16	1	ip	1385	30	4.3
17	1	ip	1040	30	1.0
18	1	ip	0	30	0
apomorphine	0.25	sc	560	10 sc	12.7

Table III. Comparison of the Pharmacological Profiles of Prominent Dopaminergic Ergot Derivatives

compd	mg/kg	Ungerstedt model, total no. of turnings ± SEM	stereotypy of apomorphine type: mg/kg	stereotypy of apomorphine type: score (0–7 h)	inhibn of Prl (4 h), ED_{50},[a] mg/kg sc	inhibn of implantation, ED_{50},[b] mg/kg sc
1	1.0 sc	1721 ± 511	30.0 sc	13.0	0.007	0.75
2a	1.0 ip	1299 ± 233	30 ip	17.3	0.06	1.0
2b	1.0 ip	1350 ± 135	30 ip	27	0.08	2.0
4	0.1 ip	2477 ± 409	1.0 ip	5.8	0.06	3.0
	1.0 ip	2607 ± 155	10.0 ip	12.3		
	0.5 po	1385 ± 152	30.0 ip	14.3		
	1.0 po	1933 ± 315				
9	0.3 sc	68 ± 31	3.0 sc	0.5	1.47	11.5
	1.0 sc	1132 ± 121	10.0 sc	0.7		
	3.0 sc	2551 ± 228	30.0 sc	1.5		
	10.0 po	2731 ± 672				

[a] Prolactin was measured by RIA and expressed as NIH-RP. Dose-response relationships were used to calculate ED_{50}.[19] [b] Ovum implantation inhibition potencies were measured in inseminated rats.[20]

for serum prolactin inhibition 4 h after application[19] and for implantation inhibition in rats. The results and the corresponding values for compounds **1**, **2a**, and **2b** are given in Table III.

Compound **4**, when compared with its C-8 epimer **2a**, was significantly more active in the turning model while inducing less apomorphine-like stereotypy. Its ability to inhibit implantation in rats[20] was also less pronounced; **9**, on the other hand, was strongly active only in the turning test.

The results presented in Tables II and III indicate that selective dopaminergic activity can be successfully achieved by chemical variation of ergot structures. As secretion of prolactin can be inhibited after infusion of DA into the pituitary portal vein system,[21] inhibition of implantation in rats mediated by an effect on prolactin can also been understood as a dopaminergic stimulation of hypophyseal or tuberoinfundibular neurons.

We assume that **2a** acts as a dopaminergic stimulant in the nigrostriatal system, the pituitary and hypothalamic system, while its 8-epimer **4** rather selectively acts in the striatum only.

Compound **9** acts primarily on the DA system responsible for the induction of contralateral turnings of lesioned rats.

Indeed, further biochemical data have confirmed the differences between these two compounds. Compound **9** induces a reduction of DA turnover only in the subcortical limbic system and the islandic DA system of the neostriatum unlike **4**, which reduces DA turnover in the whole striatum.[21] Again the compounds may have different affinities for the DA tubero-infundibular system, which could explain their different potencies in the inhibition of implantation and prolactin secretion.

The relevance of these findings is under investigation and clinical studies with both compounds in Parkinson's disease are in progress.

Experimental Section

Chemistry. The melting points were determined on a Tottoli apparatus and are not corrected. Microanalyses and ^1H NMR spectra (δ values, ppm) of all compounds are in accordance with the expected structures.

General Procedure for the Synthesis of 6-Methyl-8-(arylthiomethyl)ergolines 9–18. Methanesulfonyl chloride (25 mmol, 2.86 g) in 10 mL of CH_3CN was dropped into a stirred suspension of 10 mmol of the appropriate 6-methyl-8-(hydroxymethyl)ergoline[24] in 30 mL of CH_3CN with cooling. After 2 h the reaction mixture was poured into excess cold aqueous NH_3 and extracted three times with CH_2Cl_2. After evaporation of the organic solvent the crude methanesulfonate esters were dissolved without further purification in 15 mL of HMPA containing 1.5 mL of water and heated with 75 mmol of the corresponding arylthiol at 70–100 °C for 72 h in a closed vessel. The reaction product was poured into 200 mL of 2 N K_2CO_3 solution and filtered. The residues could in some cases be directly crystallized

or were chromatographed on silica gel with CH_2Cl_2 containing an increasing percentage of CH_3OH as eluent.

Methyl 7-Ergolene-8-carboxylate (6). Into a stirred solution of 8.53 g (30 mmol) of methyl 9,10-dihydrolysergate (**5**) in 140 mL of absolute CH_2Cl_2 was added at −40 °C a solution of 33 equiv of MCPBA in 60 mL of CH_2Cl_2. After stirring at this temperature for 30 min, 4.3 mL (90 mmol) of triethylamine was added to the clear solution which then was stirred for additional 60 min at 0 °C. The reaction mixture was poured into 200 mL of ice-cold 2 N Na_2CO_3 solution and, after separation of the organic layer, extracted three times with 300 mL of CH_2Cl_2. The combined organic layers were washed with water, dried over Na_2SO_4, filtered, and evaporated to dryness. The residual dark brown oil was chromatographed on silica gel with CH_2Cl_2 containing an increasing percentage of MeOH as eluent. The fractions eluted with CH_2Cl_2–MeOH (2%) yielded, after crystallization from EtOAc, 3.82 g (45%) of the title compound **6**: mp 232–234 °C dec; $[\alpha]^{20}_D$ − 257° (*c* 0.3, pyridine); UV (CH_2Cl_2) λ_{max} 223 nm (ϵ 32 000), 292 (24 500); IR (CH_2Cl_2) 1610, 1625, 1680 cm^{-1}, NMR ($CDCl_3$) 3.05 (s, 3 H), 3.75 (s, 3 H), 6.8–7.3 (m, 4 H), 7.45 (s, 1 H).

Methyl 9,10-Dihydroisolysergate (7) from Methyl 7-Ergolene-8-carboxylate (6). 6[12] (2.82 g, 10 mmol) was dissolved in a mixture of 40 mL of DMF and 80 mL of AcOH and hydrogenated at 40 °C at atmospheric pressure after the addition of 0.2 g of PtO_2. When H_2 consumption was complete, the reaction mixture was filtered and evaporated to dryness. The crystalline residue was dissolved in CH_2Cl_2 containing 5% MeOH and shaken repeatedly with cold K_2CO_3 solution. The organic layer was washed with H_2O, dried over Na_2SO_4, treated with charcoal, filtered, and evaporated to dryness. The semisolid residue yielded after two crystallizations from EtOAc and Et_2O a total of 1.76 g (62%) of **7**, mp 187–190 °C, $[\alpha]^{20}_D$ −80° (*c*, 0.5, pyridine), which was identical with an authentic sample:[22] NMR ($CDCl_3$) 1.30–1.90 (m, 1 H), 2.45 (s, 3 H), 3.75 (s, 3 H), 6.8–7.3 (m, 4 H). The mother liquor consisted of a mixture of **5** and **7**. Reduction of **7** with $LiAlH_4$ to 9,10-dihydroisolysergol I was carried out as described in the literature.[24]

Synthesis of (5*R*,8*R*,10*S*)-6-Methyl-8-(cyanomethyl)-ergoline (3). 9,10-Dihydroisolysergol II[24] was converted into its methanesulfonate ester as described above: yield 75%; mp 105–107 °C (from EtOAc); $[\alpha]^{20}_D$ +10° (*c* 0.2, DMF). The crude methanesulfonate ester (1 g) was dissolved in 10 mL of HMPA, diluted with 1 mL of H_2O, and stirred at 120 °C for 30 h after the addition of 4 g of KCN. **3** was isolated from the reaction mixture as its crystalline hydrochloride salt: mp 230 °C dec (from Me_2CO); $[\alpha]^{20}_D$ +15° (*c* 0.4, DMF); NMR (Me_2SO) 1.20–1.70 (m, 1 H), 1.80–2.15 (m, 1 H), 2.65 (s, 3 H), 6.70–7.35 (m, 4 H) [lit.[10] reports (for the base) mp 180–181 °C; $[\alpha]^{20}_D$ −19.5° (*c* 0.4, pyridine)].

(5*R*,8*R*,10*R*)-6-Methyl-8-(cyanomethyl)ergoline (4). 9,10-Dihydroisolysergol I[24] was converted into its methanesulfonic acid ester in 90% yield as described above: mp 139–141 °C; $[\alpha]^{20}_D$ −69° (*c* 0.5, pyridine). This compound (3.34 g, 10 mmol) was mixed with 6.6 g (100 mmol) of KCN and dissolved with a mixture of 30 mL of DMF and 6.6 mL of H_2O at 70 °C. After a reaction period of 60 h and workup by partition between 2 N Na_2CO_3 solution and CH_2Cl_2, the reaction product was chromatographed on 150 g of silica gel. Pure **4** (1.86 g, 70%) was eluted with a mixture of 4% MeOH in CH_2Cl_2 and crystallized from MeOH: mp 160–162 °C; $[\alpha]^{20}_D$ −96° (*c* 0.3, DMF) [lit.[10] mp 163–164 °C; $[\alpha]^{20}_D$ −73.4° (*c* 0.23, pyridine)]; NMR (Me_2SO) 1.45–1.80 (m, 1 H), 2.35 (s, 3 H), 6.60–7.20 (m, 4 H). The methanesulfonic acid salt had mp 260–265 °C dec; $[\alpha]^{20}_D$ −75° (*c* 0.3, pyridine). The more polar by-product (0.35 g, 13.5%) was identical in all respects with the 5*R*,8*S*,10*R* isomer.[4]

Hydrogenation of Methyl Isolysergate (8). Pure 8[23] when dissolved in AcOH or DMF was hydrogenated over Pd on alumina catalyst or PtO_2 at room temperature and 1 atm; H_2 consumption was not complete before 24 h. The only reaction product, after chromatographic separation and crystallization from EtOH, was methyl dihydrolysergate (**5**): mp 186–188 °C; $[\alpha]^{20}_D$ −96° (*c* 1, pyridine).

Pharmacological Methods. Ungerstedt Technique.[13] The animals, male OFA rats (140–160 g), were anesthetized with pentobarbitone (Nembutal) and mounted in a David-Kopf stereotaxis apparatus. A cannula with an external diameter of 0.3 mm was then introduced to a depth of 7.5 mm below the dura, ±4.2 mm anterior and 1 mm lateral to the bregma. A solution (4 μL) of 6-OH-DA (2 mg/mL of 6-OH-DA in 0.9% NaCl containing 0.2 mg/mL of ascorbic acid) was then injected. The injection was made over 2 min with the aid of a Hamilton syringe controlled by an Agla micrometer. One week later the rats were examined for nigrostriatal degeneration by administration of 0.25 mg/kg of apomorphine. To facilitate comparison between compounds and between different groups of animals, the total number of turning movements was corrected by a factor which was a function of the mean value of 560 turning movements per animal measured in 40 rats after administration of apomorphine. The animals were employed 2 weeks after the lesions were induced.

Evaluation of Stereotyped Behavior in Rats. Male OFA rats (180–250 g) were placed in separate plexiglass cylinders 30 cm in diameter with a wire-netting floor. After a 30-min period of acclimatization, the animals were treated with the investigational compounds. The rats were observed every 30 min for 2 h and then every 60 min for a total period of 7 h. Six rats were employed for each dose. The intensity of stereotypy was evaluated with the following scoring system described by Costall et al.:[16] 1, intermittent sniffing of moderate intensity; 2, continuous sniffing, occasional licking; 3, marked licking, occasional biting; 4, intense and persistent biting.

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