Synthesis and Dopamine Antagonist Activity of 2-Thioether Derivatives of the Ergoline[1] Ring System

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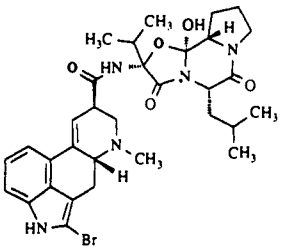
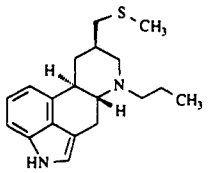
A series of 2-thioether derivatives of a number of clavine alkaloid (ergoline) ring systems have been synthesized and tested for dopamine antagonist activity. Of the compounds tested 2-(methylthio)-agroclavine (8,9-didehydro-6,8-dimethyl-2-(methylthio)ergoline) (**6**) was the most potent and had a profile of activity in animal models indicative of potential antipsychotic activity. The synthesis and biological activity of a number of metabolites of **6**, including the 13-hydroxy derivative, are also reported.

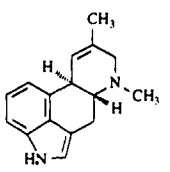
The ergot alkaloids, which were first isolated from the parasitic fungus Claviceps (clavicipitales), are now known to be metabolic products of several species of fungi and plants. They have been the subject of intensive chemical and biological research since the pioneering work of Dale,[2] and their spectrum of activity has been found to include central, neurohumoral, and peripheral effects. Although they often lack specificity, compounds have been identified which are selectively oxytocic[3] or are agonists or antagonists of 5-hydroxytryptaminergic[4] or α-noradrenergic[5] receptors, and some of these have been used to treat a number of clinical conditions. More recently, derivatives of the peptide ergots (e.g. bromocriptine, **1**)[6] or of the clavine alkaloids (e.g. pergolide, **2**)[7] have been shown to be partial agonists at the postsynaptic dopamine receptor and have been evaluated as replacements for, or adjuncts to, L-DOPA therapy in the treatment of Parkinson's disease.[8] They have also been used to treat prolactin-related disorders, such as galactorrhoea, puerperal mastitis, and prolactin-dependent mammary carcinoma, as the secretion of this pituitary hormone is under the inhibitory control of dopamine.[9]



BROMOCRYPTINE (1)



PERGOLIDE (2)



AGROCLAVINE (3)

Despite the well-documented affinity of certain ergot derivatives for the dopamine receptor, relatively few dopamine antagonists have been identified in this series.[10] With this in mind investigators in these laboratories have sought to elucidate the structural modifications required to transform the dopamine agonist properties of the ergot nucleus into dopamine antagonism. Such compounds would represent a novel structural class for the treatment of disease states, such as schizophrenia, in which an overactivity of central dopaminergic systems has been implicated.[11] It was hoped that a dopamine antagonist of this type, related to the agonist and not fulfilling the normal structural requirements for a dopamine antagonist,[12] may produce fewer of the side effects commonly seen with drugs of this therapeutic class.[13]

Most of our work in this area has focused on the clavine alkaloid, agroclavine (**3**),[14] obtained by fermentation using the organism claviceps purpurea AA-218.[15] Although the dopamine agonist activity of this alkaloid is only modest[16] by comparison with that of derivatives functionalized in the 8-position (e.g. pergolide, **2**) it offers the advantage of being relatively unexplored in terms of the detailed pharmacology of its derivatives. We were encouraged to concentrate on the 2-position of the nucleus by two literature reports of significant changes in the biological activity following modification in this position. Yui and Takeo[17] report that agroclavine has an "excitant" profile of activity based on the gross behavior of mice and rats, whereas 2-bromoagroclavine has a depressant profile. Semonsky et al.[18] report significant changes in activity on a number of pharmacological tests following 2-bromination, 2-chlorination, or 2-methylation of ergoline 8-acetamide and 8-hydrazide derivatives. In our hands agroclavine derivatives functionalized in the 2-position by bromo, chloro, or methyl substituents failed to demonstrate a potential antipsychotic profile in the range of animal models used, whereas the 2-methylthio derivative **6** was effective in these tests. We report in this paper the synthesis of a series of 2-thioether derivatives of the clavine alkaloid (ergoline) ring system and their pharmacological evaluation as dopamine antagonists.

Chemistry

Introduction of the appropriate thioether functionality was achieved in all cases by direct substitution with the appropriate sulfenyl chloride. In the case of the aliphatic thioethers (**6–18**) (Table I) the sulfenyl chlorides were prepared by the action of sulfuryl chloride on the appropriate disulfide at −20 °C in dichloromethane (method A).

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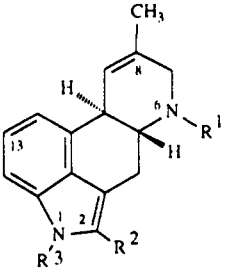
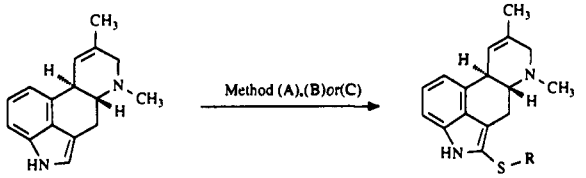
Table I. 2-Thioether Derivatives



compd	R_1	R_2	R_3	$\Delta^{8,9}$	mol formula	mp, °C (solv)	% yield (method)	Anal.
3	Me	H	H	present	$C_{16}H_{18}N_2$			
4	Me	H	H	β	$C_{16}H_{20}N_2$			
5	Me	H	H	α	$C_{16}H_{20}N_2$			
6	Me	SMe	H	present	$C_{17}H_{20}N_2S{\cdot}CH_4SO_3$	222–228 (EtOH)	68 (A)	CHNS
7	Me	SMe	H	β	$C_{17}H_{22}N_2S$	201–202 (EtOH)	60 (A)	CHNS
8	Me	SMe	H	α	$C_{17}H_{22}N_2S{\cdot}C_4H_4O_4$	196–8 (EtOH/Et_2O)	40 (A)	CHNS
9	Me	SEt	H	present	$C_{18}H_{22}N_2S$	168–169 (IPA)	37 (A)	CHNS
10	Me	SPr	H	present	$C_{19}H_{24}N_2S{\cdot}CH_4SO_3$	181–2 (EtOH)	31 (A)	CHNS
11	Me	SPr	H	β	$C_{19}H_{26}N_2S{\cdot}C_4H_4O_4$	162–164 (EtOH)	54 (A)	CHNOS
12	Me	S-i-Pr	H	present	$C_{19}H_{24}N_2S{\cdot}CH_4SO_3$	197–202 dec (EtOH/Et_2O)	45 (A)	CHNOS
13	Me	SHex	H	present	$C_{22}H_{30}N_2S{\cdot}C_4H_4O_4$	199–201 (EtOH)	36 (A)	CHNOS
14	Me	SBz	H	present	$C_{23}H_{24}N_2S$	134–6 (C_6H_{12})	22 (A)	CHNS
15	H	SMe	H	present	$C_{16}H_{18}N_2S{\cdot}CH_4SO_3$	260–3 dec (EtOH)	85 (D)	CHNS
16	Et	SMe	H	present	$C_{18}H_{22}N_2S$	166–168 (C_6H_{12})	61 (E)	CHNS
17	Pr	SMe	H	present	$C_{19}H_{24}N_2S$	173–174 (IPA)	40 (E)	CHNS
18	Pr	SMe	H	β	$C_{19}H_{26}N_2S{\cdot}C_4H_4O_4$	217–219	75 (E)	CHN
19	Me	SPh	H	present	$C_{22}H_{22}N_2O{\cdot}CH_4SO_3$	>250 dec (EtOH/Et_2O)	70 (B)	CHNS
20	Me	SPh	H	β	$C_{22}H_{24}N_2S{\cdot}C_4H_4O_4$	156–8 (EtOH/Et_2O)	48 (B)	CHNS
21	Me	SPh	H	α	$C_{22}H_{24}N_2S{\cdot}C_4H_4O_4$	215–7 (EtOH/Et_2O)	55 (A)	CHNS
22	Me	SPh-*p*-OMe	H	present	$C_{23}H_{24}N_2OS$	202–4 (IPA)	29 (B)	CHNS
23	Me	SPh-*p*-Cl	H	present	$C_{22}H_{21}ClN_2S$	162–3 (C_6H_{12})	33 (C)	CHNClS
24	Me	SMe	Me	present	$C_{18}H_{22}NS$	115–116 (CH_3CN)	33	CHNS
25	Me	SMe	CH_2OH	present	$C_{18}H_{22}NOS$	133–5 (CH_3CN)	47	CHNS
26	Me	SOMe	H	present	$C_{17}H_{20}N_2OS$	233 dec (EtOH)	29	CHNS
27	Me	SO_2Me	H	present	$C_{17}H_{20}N_2O_2S$	217–8 (EtOH)	21	CHNS
28	Me	SMe	H(8CH_2OH)	present	$C_{17}H_{20}N_2OS$	194–7 dec (EtOH)	35	CHNS
29	Me	SMe	H(13OH)	present	$C_{17}H_{20}N_2OS$	>220 dec (EtOH)	47	CHNS

Scheme I

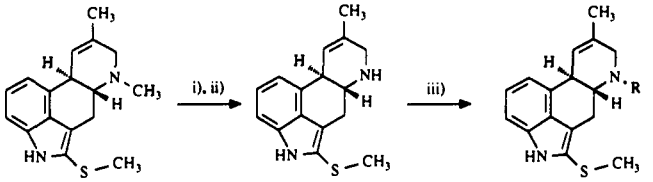


In the case of aromatic thioethers (**19–23**) it was also possible to prepare the required sulfenyl chlorides by the direct action of chlorine (method B) or *N*-chlorosuccinimide (method C) on the appropriate thiol (Scheme I).

If the ergoline nucleus required was other than agroclavine, this was usually prepared by modification after introduction of the thioether functionality. Hence, homologues in the 6-position (**15–18**) were prepared by N-demethylation using trichloromethyl chloroformate in dry toluene to give the carbamate followed by reductive cleavage using zinc in acetic acid.[19] Realkylation was achieved by modification of the method of Cassady[20] using the appropriate alkyl halide in dimethylformamide with triethylamine as base (Scheme II). Compounds having no $\Delta^{8,9}$ unsaturation were prepared by catalytic hydrogenation[21] (Scheme III). The major β-isomer (festuclavine) could be obtained in sufficiently pure form by crystallization. The minor α-isomer (pyroclavine) was obtained pure by high-pressure liquid chromatography using a Waters Prep HPLC system.

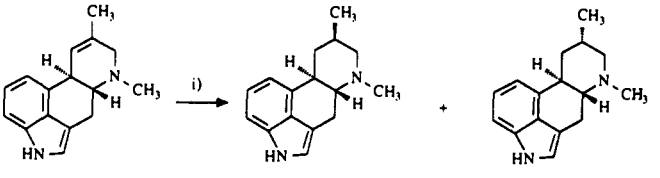
The 1-methyl derivative (**24**) was obtained by metalation of the indole nitrogen of agroclavine using sodium in liquid ammonia followed by methylation with methyl iodide. The 1-hydroxymethyl compound (**25**) was obtained by reaction of the thioether derivative **6** with 40% aqueous formaldehyde.

Scheme II[a]



[a] Reagents: (i) 2,2,2-triethyl chloroformate/toluene; (ii) Zn/EtOH/HOAc; (iii) RI/TEA/DMF.

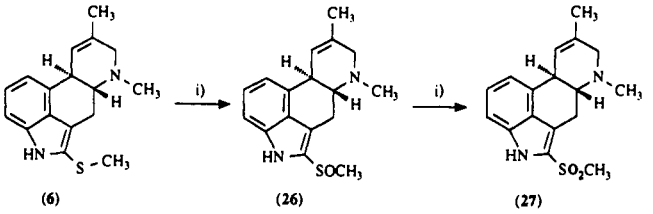
Scheme III[a]



[a] Reagents: (i) 10% Pd–C/EtOH/H_2.

The sulfoxide (**26**) and sulfone (**27**) derivatives of lead compound **6** were prepared by oxidation using either 1 or 2 equiv of *m*-chloroperbenzoic acid, respectively. The oxidation was run in the presence of 1 equiv of methanesulfonic acid to exclude possible interference by N-oxidation at position 6 (Scheme IV). 2-(Methylthio)-elymoclavine (**28**) was prepared in the normal manner using

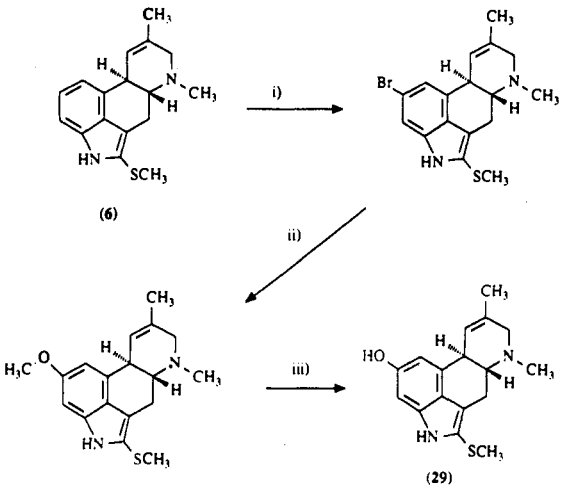
Scheme IV[a]



(6) (26) (27)

[a] Reagents: (i) *m*-chloroperbenzoic acid/methanesulfonic acid.

Scheme V[a]



(6) (29)

[a] Reagents: (i) pyridinium bromide perbromide/methanol; (ii) NaOMe/MeOH/DMF/CuI; (iii) $AlCl_3/C_2H_5SH$.

methyl sulfenyl chloride after protection of the 8-hydroxymethyl group as its *tert*-butyldimethylsilyl ether. Elymoclavine was obtained from the same fermentation as agroclavine using claviceps purpurea AA-218.[15] Introduction of a 13-substituent was achieved by bromination of **6** using pyridinium bromide perbromide followed by displacement of the bromine using sodium methoxide in methanol/dimethylformamide in the presence of cuprous iodide. Demethylation to the 13-hydroxy derivative was achieved using ethanethiol and aluminum chloride in dichloromethane (Scheme V). This procedure resulted in only low levels of the 13-hydroxyagroclavine byproduct seen extensively in other demethylation procedures. This procedure is significantly more convenient than the only reported literature method.[22] This patent preparation involved protection of the 1-position of a 13-bromoergoline system by lithiation with *n*-butyllithium followed by treatment with trimethylsilyl chloride. The protected system was then subjected to lithium/halogen exchange by *tert*-butyllithium and the whole subjected to alkaline hydrolysis to give the 13-hydroxy derivative in low yield.

Discussion

The antipsychotic activity of neuroleptics correlates with their ability to interact with dopamine (D_2) receptors,[23] and this can be assessed by evaluating their ability to compete in vitro with the D_2 receptor antagonist, [^{3}H]-spiperone, for binding sites on calf caudate membranes. The receptor binding assays are nonfunctional, and it is difficult to determine whether the activity observed is that of an agonist or antagonist. Compounds were, therefore, also evaluated for their ability to alter rat serum prolactin concentrations in vivo. The secretion of this pituitary hormone is under the inhibitory control of dopamine,[9] and antagonists at the D_2 receptor increase its concentration in serum while agonists produce a decrease.[13]

Dopamine antagonists block a conditioned avoidance response (CAR) and produce catalepsy (CAT) in rats. The former activity is thought to be indicative of antipsychotic activity while the latter correlates with the extrapyramidal side effects produced with this class of compounds. Dopamine agonists show little activity at blocking a CAR, and in many cases they produce a characteristic stereotyped behavior. The results obtained in these tests are shown in Table II.

In keeping with literature observations,[16] agroclavine (**3**) was found to be a dopamine agonist in that it competed with [^{3}H]spiperone for binding sites in calf caudate membranes ($IC_{50} = 0.89 \pm 0.39\ \mu M$), and in rats, it produced stereotyped behavior in the conditioned avoidance test. The other two naturally occurring clavine derivatives tested, festuclavine (**4**) and pyroclavine (**5**), had lower affinity for the dopamine receptor (IC_{50} on spiperone binding = 4.18 ± 2.19 and $7.94 \pm 6.49\ \mu M$, respectively), and neither compound produced stereotyped behavior in the rat. Introduction of the 2-*S*-methyl group into agroclavine to produce compound **6** did not markedly affect the affinity of the compound for the dopamine receptor (IC_{50} on spiperone binding = $0.43 \pm 0.29\ \mu M$), but it converted the agonist activity into that of an antagonist. Like other dopamine antagonists, **6** blocked a conditioned avoidance response and produced catalepsy in rats (ED_{min} = 2.5 and 10 mg/kg po, respectively) and also elevated serum prolactin levels by 532% at a dose of 2.0 mg/kg ip. In common with all of the compounds in this series, **6** was only modestly active at inhibiting the climbing induced in mice by the dopamine agonist apomorphine. Pharmacokinetic studies of **6** showed differences in metabolism between rats and mice which may explain this observation.[24]

Substitution of festuclavine (**4**) with a 2-methylthio group also produced a dopamine antagonist (compound **7**) which had a very similar profile but was slightly less potent than the agroclavine derivative **6**. The 2-methylthio derivative of pyroclavine (**8**) was only a weak dopamine antagonist producing a 63% elevation of prolactin at 2.0 mg/kg ip.

Replacement of the 2-methylthio substituent in compound **6** with an ethylthio group (**9**) reduced both the affinity of the compound for the dopamine receptor (IC_{50} for [^{3}H]spiperone = $0.92 \pm 0.18\ \mu M$) and the dopamine antagonist activity in the rat. Increase in the 2-alkylthio group to 2-propylthio (**10**) did not reduce the affinity for the dopamine receptor any further (IC_{50} for [^{3}H]spiperone binding = $0.74 \pm 0.36\ \mu M$). The 2-isopropylthio derivative **12** was equipotent with **6** at blocking a conditioned avoidance response and producing catalepsy in rats, but it was less active at competing with [^{3}H]spiperone for binding sites in calf caudate membranes. This was reflected in a reduced ability to elevate serum prolactin levels. The 2-benzylthio (**14**) and 2-hexylthio (**13**) compounds had very little in vivo activity even though the [^{3}H]spiperone binding results indicate that they have affinity for the dopamine receptor in vitro.

The 2-phenylthio derivatives of agroclavine (**19**) and festuclavine (**20**) had the highest in vitro affinity for the dopamine receptor of all the compounds in this series (IC_{50} on [^{3}H]spiperone binding = 0.15 ± 0.09 and 0.18 ± 0.09 μM, respectively). An increase in affinity for spiperone binding sites in compounds with large lipophylic groups has been reported previously.[25] In vivo, however, **19** and **20** had similar potency to the 2-methylthio derivatives on

Table II. Pharmacological Results

no.	IC_{50} (μM) [^{3}H]spiperone binding	ED_{min} (mg/kg po) apomorphine climbing[a] (mice)	CAR[b]	catalepsy[c]	serum prolactin[d] % change (mg/kg ip)[e]
3	0.89 ± 0.39[f]		stereotype[g]		
4	4.18 ± 2.19		>40		
5	7.94 ± 6.49		>50		
6	0.43 ± 0.29	50	2.5	10	+532 (2.0) $p < 0.001$
7	0.75 ± 0.33	40	5.0	20	+570 (2.0) $p < 0.001$
8	3.0 ± 1.2	>25	40		+63 (2.0) $p < 0.05$
9	0.92 ± 0.18	>100	25	40	+67 (2.0) $p < 0.001$
10	0.74 ± 0.36	>50			
11	2.0 ± 1.4		>50		+76 (2.0) ns
12	1.36 ± 0.3		2.5	10	+132 (2.0) $p < 0.001$
13	0.45 ± 0.19	>100	50		−4 (2.0) ns
14	0.22 ± 0.15	100	25	80	−9 (2.0) ns
15	3.43 ± 1.34	50	>50		+24 (1.0) ns
16	2.1 ± 0.9	100	25		−65 (2.0) $p < 0.001$
17	1.7 ± 0.3	>50	stereotype[g]		−74 (2.0) $p < 0.001$
18	insoluble		>50		−71 (2.0) $p < 0.001$
19	0.15 ± 0.09	25	2.5	10	+141 (2.0) $p < 0.001$
20	0.18 ± 0.09		10	20	+106 (2.0) $p < 0.001$
21	0.55 ± 0.24	>50	>50		+15 (2.0) ns
22	insoluble	>100	>80		+31 (2.0) ns
23	insoluble	>100	100		
24	0.76 ± 0.56	100	100		−23 (2.0) ns
25	3.4 ± 2.7	>100	20	80	+91 (2.0) $p < 0.001$
26	>10	>100	>50		+98 (1.0) $p < 0.02$
27	>10	>100	>50		+30 (1.0) ns
28	0.32	>25	6.0[h]	12.5[h]	+481 (1.0) $p < 0.001$
29	0.32 ± 0.11	25	25[h]	25[h]	−50 (1.0) $p < 0.001$
CLOZ[i]	0.45 ± 0.10	20	30	80	+1.6 (20) ns
CPZ[j]	0.08 ± 0.01		10	10	
HALO[k]	0.03 ± 0.03	1.0	0.5	0.5	+1413 (1.0) $p < 0.001$

[a] Groups of eight animals per dose level. [b] Groups of five animals per dose level. [c] Groups of eight animals per dose level. [d] Groups of 10 animals per dose level. [e] Percentage change from control values generated in the same experiment. Numbers in brackets are the dose. ns = not significant. [f] Mean result ± SEM. [g] Observed during the conditioned avoidance test. [h] ip administration. [i] **CLOZ** = clozapine. [j] **CPZ** = chlorpromazine. [k] **HALO** = haloperidol.

the rat behavioral tests, and they were less potent at elevating serum prolactin levels. This increase in affinity for spiperone binding sites was also observed with 2-(phenylthio)pyroclavine (**21**). Substitution of the 2-phenylthio **19** with a *p*-methoxy (**22**) or *p*-chloro (**23**) group led to a marked reduction in activity. This may have been due to the very low solubility of these compounds in aqueous media.

The 1-methyl derivative (**24**) of 2-(methylthio)agroclavine (**6**) retained affinity for the dopamine receptor in vitro (IC_{50} for spiperone binding = 0.76 ± 0.56 μM) but was inactive in vivo. This was in contrast to the 1-hydroxymethyl compound (**25**) which had the profile of a weak dopamine antagonist.

It has been previously reported in the literature[26] that homologation of the alkyl group in the 6-position of ergot-based dopamine agonists has a marked effect on their potency. This effect has also been observed in the present series. Removal of the 6-*N*-methyl group from **6** to give the NH derivative **15** markedly reduced both the in vitro and in vivo activity of the compound. The 6-*N*-ethyl compound **16**, in contrast to the 6-*N*-methyl derivative **6** only produced a weak block (ED_{min} = 25 mg/kg po) of a conditioned avoidance response in the rat. It also produced a significant, 65%, decrease in rat serum prolactin levels at 2.0 mg/kg ip, indicating that, in this test, it behaved like a dopamine agonist. Further extension of the 6-*N*-alkyl chain to propyl (**17**) did not alter the affinity for the dopamine receptor but enhanced the dopamine agonist activity. In addition to lowering serum prolactin levels, this compound produced stereotyped behavior which is indicative of postsynaptic dopamine receptor stimulation. Similarly, alteration of the *N*-methyl group in **7** to an *N*-propyl group (**18**) led to an increase in agonist activity as shown by the ability of the latter compound to significantly decrease serum prolactin levels.

The five compounds with the greatest antidopaminergic activity in the behavioral tests (**6**, **7**, **12**, **19**, and **20**) were tested for their ability to inhibit the stereotyped behavior produced in the rat by the indirect dopamine agonist amphetamine.[27] In this test for dopamine antagonist activity, the two 2-methylthio compounds (**6** and **7**) as well as the 2-isopropylthio derivative (**12**) had very similar activities with ED_{min} in the range 5–10 mg/kg po. The two 2-phenylthio derivatives (**19** and **20**) were less active with ED_{min} of 20 mg/kg po. The results on this test confirmed previous findings that these five compounds were dopamine antagonists in vivo.

Compound **6**, 2-(methylthio)agroclavine, was selected as a potential clinical candidate for the treatment of schizophrenia and other psychotic illnesses. Its ability to inhibit the binding of [^{3}H]spiperone to calf caudate membranes, in vitro, is similar to that of the clinically effective antipsychotic, clozapine, although it is more active in vivo (Tables II and III). It has been suggested that the ability of clozapine to block a conditioned avoidance response at a dose lower than that required to produce catalepsy relates to the absence of extrapyramidal side effects observed with this compound.[28] Compound **6**, like clozapine, blocks a CAR at noncataleptogenic doses. Also, like clozapine, **6** is an antagonist at the dopamine D_1 and 5-HT_2 receptors.[29] Studies on the metabolism of this compound in the rat led to the identification of a number of metabolic products, some of which were synthesized and biologically evaluated. Several of the routes of metabolism involved the oxidation of the parent com-

Table III. Amphetamine Stereotyped Behavior

compd no.[b]	amphetamine stereotype[a] ED_{min} (mg/kg po)	compd no.[b]	amphetamine stereotype[a] ED_{min} (mg/kg po)
6	5	20	20
7	5	CLOZ	40
12	10	HALO	0.5
19	20		

[a] Groups of eight animals per dose level. [b] CLOZ = clozapine, HALO = haloperidol.

pound. Oxidation of the 2-methylthio group to give either the sulfoxide 26 or the sulfone 27 resulted in a marked reduction in activity. Although the sulfoxide retained some antidopaminergic activity (98% increase in rat serum prolactin levels at 1.0 mg/kg ip) the sulfone was inactive in all in vivo and in vitro studies. A further point of oxidation was found to be the 8-methyl group leading to the 2-methylthio derivative of elymoclavine (28). This compound had an activity profile similar to that of the parent compound 6, adding further support to the idea that it is the 2-position which is of paramount importance in the determination of agonist or antagonist activity in this series. The 13-hydroxy derivative of 6, compound 29 was also identified as a major metabolite in the rat. This is in common with the known metabolic fate of a number of ergot derivatives, for example LSD[30] and lergotrile.[31] Despite the frequent occurrence of 13-hydroxy metabolites of ergolines, no convenient synthesis was available, most examples having been proved by isolation.[31] Although this compound had a very similar affinity for the dopamine receptor to that of 6 (IC_{50} on [^{3}H]spiperone binding = 0.32 ± 0.11 μM), it was much less active at blocking a conditioned avoidance response or producing catalepsy in the rat. One possible explanation is that this compound is a partial agonist, as indicated by its ability to decrease serum prolactin levels (50% decrease at 1.0 mg/kg ip).

The only other metabolite of 6 which was synthesized and biologically evaluated was the *N*-desmethyl derivative 15. As stated earlier, this compound was inactive at dopamine receptors in all tests performed.

The progression of 6 as a potential antipsychotic was terminated when it produced marked hepatotoxicity in a subacute toxicological study in dogs.

Experimental Section

Chemistry. Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. All compounds were characterized by physical methods using IR, UV, NMR, and MS. NMR spectra were run on a Bruker AM300 spectrometer in either $CDCl_3$ or CD_3OD using TMS as reference. Mass spectra were recorded on a VG 7070E double-focusing spectrometer using chemical ionization with NH_3 at 200 eV. Column chromatography was carried out using Florisil, Woelm alumina, or Sorbsil U30 grade silica gel. $MgSO_4$ was used as drying agent. Microanalysis are within ±0.4% of calculated values.

Method A. 8,9-Didehydro-6,8-dimethyl-2-(methylthio)-ergoline (6). Sulfuryl chloride (0.8 mL, 9.8 mmol) in dichloromethane (5 mL) was added to a stirred solution of dimethyl disulfide (0.85 mL, 9.4 mmol) in dichloromethane (10 mL) at 0 °C. After 30 min this solution was added to agroclavine (3) (3.6 g, 15 mmol) in dichloromethane (30 mL) at 0 °C under a nitrogen atmosphere. The reaction was allowed to attain room temperature, and after 2 h water was added, followed by 0.88 M ammonia until basic. Extraction with chloroform, washing with brine, drying, and evaporation under reduced pressure gave a brown oil (4.1 g). Crystallization from cyclohexane with carbon treatment gave a pale yellow solid (3.4 g, 79%): mp 137–139 °C. A sample was crystallized as its methanesulfonic acid salt: mp 222–228 °C (ethanol). Anal. ($C_{18}H_{24}N_2O_3S_2$) C, H, N, S.

Method B. 8,9-Didehydro-6,8-dimethyl-2-(4-methoxyphenyl)thioergoline (22). An ice-cold solution of carbon tetrachloride (50 mL) was saturated with chlorine gas. *p*-Methoxybenzenethiol (1.35 mL, 11 mmol) in carbon tetrachloride (10 mL) was added dropwise with stirring. After 10 min the solvent was removed under reduced pressure at room temperature. The deep red oil was dissolved in dichloromethane (10 mL) and added dropwise to a stirred solution of agroclavine (2.36 g, 10 mmol) in dichloromethane (200 mL) at 0 °C. The reaction was allowed to attain room temperature overnight, ice–water was added, followed by 0.88 M ammonia until basic. The product was extracted with chloroform, washed with water, dried, and evaporated to dryness under reduced pressure to give an oil, which after chromatography gave a solid which was recrystallized from 2-propanol (1.1 g, 29%): mp 202–204 °C. Anal. ($C_{23}H_{24}N_2OS$) C, H, N, S.

Method C. 2-[(4-Chlorophenyl)thio]-8,9-didehydro-6,8-dimethylergoline (23). A solution of 4-chlorothiophenol (3.18 g, 22 mmol) in benzene (20 mL) was added slowly with ice cooling to a stirred solution of *N*-chlorosuccinimide (2.94 g, 22 mmol). The solution was allowed to attain room temperature overnight and filtered and the solvent removed under reduced pressure at room temperature. The resultant red oil was dissolved in dichloromethane (15 mL) and added to a stirred solution of agroclavine (4.74 g, 20 mmol) in dichloromethane (300 mL) at 0 °C. The solution was allowed to attain room temperature over 1 h, at which time no starting material remained. Ice–water was added, followed by 0.88 M ammonia until basic. The product was extracted with dichloromethane, washed with water, dried, and evaporated under reduced pressure to a solid which was recrystallized from cyclohexane (1.2 g, 33%): mp 162–163 °C. Anal. ($C_{22}H_{21}ClN_2S$) C, H, N, S, Cl.

Method D. 8,9-Didehydro-8-methyl-2-(methylthio)ergoline (15). A solution of 8,9-didehydro-6,8-dimethyl-2-(methylthio)ergoline (6) (11.36 g, 40 mmol) in toluene (250 mL) was heated at reflux under a Dean and Stark trap for 1 h. After cooling, 2,2,2-trichloroethyl chloroformate (6 mL, 44 mmol) was added and the solution heated at reflux overnight under a nitrogen atmosphere. After cooling, the solution was filtered through Celite and washed with 5 N hydrochloric acid and then with water. The solution was dried and evaporated under reduced pressure to give an oil (20.7 g).

The oil was dissolved in ethanol (60 mL) and acetic acid (60 mL), and zinc powder (40 g) was added in portions over 6 h at room temperature. The solution was filtered through Celite, diluted with water (150 mL), and washed with ether. After being made basic with 0.88 M ammonia the solution was extracted with ethyl acetate, washed with water, dried, and evaporated under reduced pressure to give a pale yellow solid which was crystallized from ethanol (9.18 g, 85%): mp 177–178 °C. A sample was crystallized as its methanesulfonic acid salt: mp 260–263 °C (ethanol). Anal. ($C_{17}H_{22}N_2O_3S_2$) C, H, N, S.

Method E. 8,9-Didehydro-6-ethyl-8-methyl-2-(methylthio)ergoline (16). A solution of 8,9-didehydro-8-methyl-2-(methylthio)ergoline (15) (2.7 g, 10 mmol), triethylamine (1.8 mL), and ethyl iodide (1 mL) in dimethylformamide (40 mL) was stirred at room temperature for 18 h. The reaction mixture was diluted with water, extracted with ether, washed with water, dried, and evaporated under reduced pressure to give a buff-colored solid which was crystallized from 2-propanol (2.2 g, 75%): mp 166–168 °C. Anal. ($C_{18}H_{22}N_2S$) C, H, N, S.

8,9-Didehydro-2-(methylthio)-1,6,8-trimethylergoline (24). A solution of absolute ethanol (8 mL) in dry ether (10 mL) was added to a solution of sodium (1.68 g, 73 mmol) in liquid ammonia (150 mL). After 15 min 8,9-didehydro-6,8-dimethyl-2-(methylthio)ergoline (6) (2.3 g, 8.1 mmol) was added. After a further 15 min methyl iodide (2.52 mL, 40 mmol) in ether (10 mL) was added dropwise over 10 min. The blue color disappeared to leave a clear solution which was allowed to attain room temperature overnight. The residue was dissolved in dichloromethane and washed, first with saturated sodium bicarbonate solution and then with water. The solution was dried and evaporated to dryness under reduced pressure to give an oil which after chromatography followed by crystallization from acetonitrile gave the product (0.8 g, 33%): mp 115–116 °C. Anal. ($C_{18}H_{22}NS$) C, H, N, S.

8,9-Didehydro-6,8-dimethyl-1-(hydroxymethyl)-2-(methylthio)ergoline (25). A solution of 8,9-didehydro-6,8-dimethyl-2-(methylthio)ergoline (**6**) (2.84 g, 10 mmol) in 40% aqueous formaldehyde (35 mL) was heated at reflux for 2 h. After cooling, water (100 mL) was added and the solution extracted with ethyl acetate. The extracts were washed with water, dried, and evaporated under reduced pressure to give a yellow oil which was purified by chromatography and crystallized from acetonitrile (1.15 g, 47%): mp 133–135 °C. Anal. ($C_{18}H_{22}NOS$) C, H, N, S.

8,9-Didehydro-6,8-dimethyl-2-(methylsulfinyl)ergoline (26). A solution of *m*-chloroperbenzoic acid (1.9 g, 11 mmol) in chloroform (50 mL) was added dropwise, at room temperature, to a solution of 8,9-didehydro-6,8-dimethyl-2-(methylthio)ergoline (**6**) and methanesulfonic acid (0.8 mL, 11 mmol) in chloroform (100 mL). The reaction was stirred for 2 h, poured into ice–water, and made basic with 0.88 M ammonia solution. The product was extracted into chloroform, washed with water, dried, evaporated under reduced pressure, and crystallized from ethanol (0.87 g, 29%): mp 233 °C dec. Anal. ($C_{17}H_{20}N_2OS$) C, H, N, S.

8,9-Didehydro-6,8-dimethyl-2-(methylsulfonyl)ergoline (27). The reaction was done as above except that 2 equiv of *m*-chloroperbenzoic acid (3.8 g, 22 mmol) was used. Crystallization from ethanol gave the product (0.65 g, 21%): mp 217–218 °C. Anal. ($C_{17}H_{20}N_2O_2S$) C, H, N, S.

8,9-Didehydro-8-(hydroxymethyl)-6-methyl-2-(methylthio)ergoline (28). Imidazole (1.5 g, 22 mmol) and *tert*-butyldimethylsilyl chloride (3.31 g, 22 mmol) were added to a solution of 8,9-didehydro-8-(hydroxymethyl)-6-methylergoline (elymoclavine) (5 g, 20 mmol) in anhydrous dimethylformamide (30 mL) under nitrogen. The reaction was stirred at room temperature for 1 h, poured into water, extracted with chloroform, and washed, first with water and then with saturated sodium bicarbonate solution. The organic fraction was dried and evaporated under reduced pressure to an oil which was dissolved in dichloromethane (50 mL).

A solution of sulfuryl chloride (0.92 mL, 11.4 mmol) in dichloromethane (5 mL) was added to a solution of dimethyl disulfide (1 mL, 11 mmol) in dichloromethane (10 mL) at 5–10 °C. After being stirred for 30 min this solution was added to the protected silyl alcohol above and the resultant mixture allowed to attain room temperature over 1 h. The reaction was poured onto ice, made basic with 0.88 M ammonia solution, and extracted with chloroform. The organic phase was washed with water and the solvent removed under reduced pressure. The crude product was dissolved in a mixture of acetic acid, water, and tetrahydrofuran (25 mL, 3:1:1) and heated on a steam bath for 2 h. The resultant reaction mixture was made basic with 0.88 M ammonia, extracted with chloroform, washed with water, dried, and evaporated under reduced pressure to give the product which was crystallized from ethanol (2.1 g, 35%): mp 194–197 °C. Anal. ($C_{17}H_{20}N_2OS$) C, H, N, S.

8,9-Didehydro-6,8-dimethyl-13-hydroxy-2-(methylthio)ergoline (29). Pyridinium bromide perbromide (35 g, 110 mmol) was added portionwise over 1 h to a solution of 8,9-didehydro-6,8-dimethyl-2-(methylthio)ergoline (**6**) (28.4 g, 100 mmol) in methanol (2 L). The solution was stirred overnight, filtered through Celite, made basic with dilute aqueous ammonia, and extracted into chloroform. The chloroform extracts were washed with water, dried, and evaporated under reduced pressure to give a solid which was crystallized from cyclohexane to give 13-bromo-8,9-didehydro-6,8-dimethyl-2-(methylthio)ergoline (18.9 g, 66.5%). A sample was crystallized as its methanesulfonic acid salt: mp 245 °C dec (ethanol); ^{1}H NMR ($CDCl_3$ + DMSO-d^6) δ 1.91 (s, 8-CH_3), 2.47 (s, SCH_3), 2.70 (s, CH_3SO_3H), 3.0 (m, 5-H), 3.13 (s, 6-CH_3), 3.55 (m, 2 H, 4-H), 3.92 (m, 2 H, 7-H), 4.05 (m, 10-H), 6.38 (s, 9-H), 7.19 and 7.35 (s, 12,14-H). Anal. ($C_{17}H_{19}BrN_2S$) C, H, N, Br.

The above bromo compound (7.2 g, 20 mmol) was added in one portion to a solution of sodium methoxide (from 9.2 g, 400 mmol of sodium) in methanol (250 mL) containing dry dimethylformamide (50 mL) and cuprous iodide (11.43 g, 60 mmol). The reaction mixture was heated at 140 °C under nitrogen for 18 h. After cooling, the solution was added to dilute ammonia solution to dissolve all copper salts, diluted with brine, and extracted into ethyl acetate. The organic phase was washed with water, dried, and evaporated under reduced pressure to give a solid which was crystallized from cyclohexane to give 8,9-didehydro-6,8-dimethyl-13-methoxy-2-(methylthio)ergoline (4.4 g, 73%): mp 162–165 °C; ^{1}H NMR (MeOH-d_4) δ 1.76 (s, 8-CH_3), 2.36 (s, SCH_3), 2.44 (s, 6-CH_3), 2.40 and 3.19 (m, 2 H, 4-H), 2.58 (m, 5-H), 2.85 and 3.27 (m, 2 H, 7-H), 3.55 (m, 10 H), 3.78 (s, OCH_3), 6.06 (s, 9-H), 6.55 (s, 12-H), 6.60 (s, 14-H). Anal. ($C_{18}H_{22}N_2OS$) C, H, N, S.

The above methoxy derivative (6 g, 19 mmol) was added to a solution of aluminum chloride (10.2 g, 76 mmol) in dichloromethane (50 mL) containing ethanethiol (5 mL). The reaction was stirred at room temperature for 3 h, poured into aqueous ammonia solution, and filtered through Celite, and the product was extracted with dichloromethane. The extracts were washed with water, dried, and evaporated to dryness under reduced pressure. The product was purified by chromatography on neutral aluminum using 5% methanol in dichloromethane. Two products were isolated. (a) 8,9-Didehydro-6,8-dimethyl-13-hydroxy-2-(methylthio)ergoline (**29**) (2.7 g, 47%): mp 220 °C dec. Anal. ($C_{17}H_{20}N_2OS$) C, H, N, S. (b) 8,9-Didehydro-6,8-dimethyl-13-hydroxyergoline (0.85 g 15%): mp 226–228 °C; ^{1}H NMR (MeOH-d_4) δ 1.72 (s, 8-CH_3), 2.44–3.59 (m, 6 H, aliphatics), 2.44 (s, 6-CH_3), 6.03 (s, 9-H), 6.61 (s, 2-H), 6.55 and 6.7 (2 s, 12,14H), 8.4 (s, 13-OH).

Pharmacological Methods. Conditioned Avoidance Response (CAR) in Rats. The method used was essentially that described by Jacobsen and Sonne.[32] Wistar rats (120–130 g) were trained to pass from one side of a shuttle box to the other on hearing a 5-s buzzer. Failure to respond within 1 s from the end of the buzzer resulted in the animals receiving a mild electric shock. Only those animals which showed a high level of conditioned response were subsequently administered the test compound. Groups of five animals were dosed orally 1 h 50 min prior to placing them individually in the shuttle boxes. After a 10-min habituation period, they were tested for 20 min for their degree of conditioned avoidance behavior. During this period the number of times the buzzer sounded, as well as the number of shocks received by the animal, were recorded. The degree of conditioned avoidance blockade was calculated by expressing the number of shocks received as a percentage of the number of stimuli presented.

Rat Catalepsy. The method used was essentially that described by Costall and Olley.[33] Groups of eight Wistar rats (180–190 g) were assessed for the presence of catalepsy at 0.5, 1, 1.5, 2, 3, 4, and 5 h after the oral administration of the compound dissolved in distilled water or suspended in 0.5% carboxymethyl cellulose. The front paws of each animal were placed on a wooden rod 1.5 cm in diameter suspended 7 cm above a table. The length of time the animal maintained this position was recorded up to a maximum of 20 min. Animals were considered to be noncataleptic if they removed their front paws from the bar within 10 s. Each cataleptic animal was assigned a score of from 0 to 5 depending on how long they maintained the imposed posture (0 = <10 s; 1 = 10 s to 2.5 min; 2 = 2.5–5 min; 3 = 5–10 min; 4 = 10–20 min; 5 = >20 min). The maximum scores obtained for each animal, regardless of time after dosing, were summed, thus giving a maximum score of 40 for each group. The ED_{min} is the lowest dose of compound which produced a score greater than 7.

Climbing Behavior in Mice. The method used was essentially that described by Moore and Axton.[34]

Groups of eight female TO mice (20–25 g) received test compounds or vehicle, by oral dosing, prior to being placed, individually, in cylindrical wire-mesh cages (height 13 cm, diameter 14 cm, mesh size 3 mm^2) for an habituation period of 60 min. Following habituation, each animal received apomorphine (2.5 mg/kg sc) and, after 10 min, climbing was assessed at 5-min intervals for 20 min using the following scoring system: 0 = no paws on cage, 1 = one paw on cage, 2 = two paws on cage, 3 = three paws on cage, and 4 = four paws on cage. The score recorded for each animal was based on the position of the animal at the moment it was first observed. The climbing score for each animal was taken as the sum of the individual scores at each time interval (maximum possible score 20). The ED_{min} is the lowest concentration of test compound used that produces a significant ($p < 0.05$) reduction in the climbing score.

Dopaminergic Receptor Binding ([^{3}H]Spiperone). (a) Tissue Preparation. Calf corpora striata (Froxfield Research

Supplies) were homogenized in 40 volumes (w/v) ice-cold 0.05 M Tris-HCl buffer (pH 7.7) in a glass–Teflon homogenizer (radial clearance 0.13–0.18 mm). After centrifugation at 30000*g* for 10 min at 4 °C, the resulting pellet was washed in a further 40 volumes of tris buffer and resuspended in 20 volumes of 0.05 M Tris-HCl (pH 7.7) containing 0.1% (w/v) ascorbic acid. The protein concentration of the suspension was determined and it was then stored in 2 mL aliquots at −20 °C for up to 3 months.

(b) Binding Assay. A tissue sample was thawed and diluted with TNA buffer (0.05 M Tris-HCl containing 100 mM NaCl and 0.1% (w/v) ascorbic acid, pH 7.7) to a protein concentration of 0.67 mg/mL. Incubations were carried out in triplicate at 37 °C for 15 min in 1.0 mL of TNA buffer containing 0.4 nM [^{3}H]-spiperone ([*phenyl*-4-^{3}H]spiperone, 15–30 Ci/mmol, Amersham International), 0.4 mg of purified calf striatal protein, and varying concentrations of test compound, either in the presence (non-specific binding) or absence (total binding) of 10^{-6} M unlabeled spiperone.

The [^{3}H]spiperone bound to the striatal membranes was separated from the free in the supernatant by rapid filtration through Whatman GF/B filters and washing twice with TNA buffer at 4 °C. The [^{3}H]spiperone on the filters was estimated by liquid scintillation counting.

For each concentration of test compound the specific binding was defined as the amount of [^{3}H]spiperone bound in the absence of 10^{-6} M unlabeled spiperone minus the amount bound in its presence. The IC_{50} value is the concentration of test compound which inhibits the specific binding of [^{3}H]spiperone by 50%.

Rat Serum Prolactin. The test compound dissolved in 0.5% lactic acid or vehicle were administered intraperitoneally to groups of 10 adult male Sprague–Dawley rats 2 h prior to decapitation. Trunk blood was collected and allowed to clot at 4 °C prior to centrifugation to spin down the clot. The serum was removed and assayed for prolactin according to the instructions provided with the radioimmunoassay kit distributed by the National Institutes of Arthritis, Metabolic and Digestive Diseases (NIAMDD). Serum prolactin levels were expressed in terms of the reference preparation NIAMDD-RP-1 rat prolactin. Differences between means were analyzed for significance using Student's *t*-test.

Amphetamine-Induced Stereotyped Behavior in Rats. Groups of eight Wistar rats received *d*-amphetamine sulfate (10 mg/kg ip) 1 h after the intraperitoneal administration of test compound. The resultant stereotyped behavior shown by the animals was assessed according to the following system at eight time periods up to 4 h after administration of the amphetamine: activity decrease = 1; normal = 2; increased alertness = 3; increased activity with exploratory sniffing = 4; stereotyped sniffing = 5; stereotyped licking = 6; stereotyped biting = 7; stereotyped gnawing = 8.

The mean of the scores for the eight animals in each dose group at each of the eight time periods was calculated. The ED_{min} is the lowest concentration of test compound used that produces a reduction in stereotyped behavior from that of amphetamine-treated controls by more than 25%.

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