SYNTHESIS AND CRYSTAL STRUCTURE OF PERGOLIDE SULFOXIDE

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Pergolide sulfoxide (**1**), a metabolite of pergolide (**2**), has been prepared by oxidation of **2** with hydrogen peroxide. Its structure was determined by X-ray diffraction and compared with the structures of related ergot alkaloids. Two molecules of pergolide (*S*)- and (*R*)-sulfoxide crystallize with one molecule of water in the orthorhombic space group $P2_12_12_1$ with a = 12.216(3) Å, b = 13.733(2) Å, c = 22.186(6) Å, Z = 4, V = 3 722(2) $Å^3$.

Key words: Ergot alkaloids; Pergolide sulfoxide; X-Ray crystal structure; NMR spectroscopy.

Pergolide (6-demethyl-8-[(methylsulfanyl)methyl]-6-propylergoline (**2**) is a semisynthetic ergot derivative used mainly in the treatment of Parkinson's disease[1–3]. It is a potent agonist acting at D_1, D_2, and D_3 dopamine receptors (see ref.[4] for a review). Some animal studies indicate that pergolide is significantly more potent and selective in its central activity compared with some other dopamine agonists like bromokryptine[5] (**5**). Four pergolide metabolites have been characterized: pergolide sulfoxide (**1**), pergolide sulfone, *N*-depropylpergolide, and *N*-depropylpergolide sulfoxide[6–8]. Oxidation of xenobiotics often produces metabolites of different pharmacological activity. In contrast to any expectation, oxidation of the pergolide methylsulfanyl group either to sulfoxide or sulfone does not alter significantly pharmacological properties of these derivatives compared with the parent drug[8]. However, the *N*-depropyl analogues are devoid of any dopaminergic activity[8]. A simple semisynthetic route to **1** and its detailed structural comparison with related ergot alkaloid derivatives are described here. This

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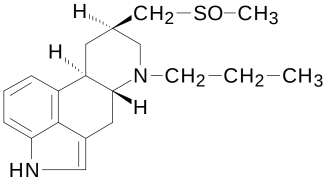
paper is our 19th communication on the structure and polymorphism of ergot alkaloids[9–26].

EXPERIMENTAL

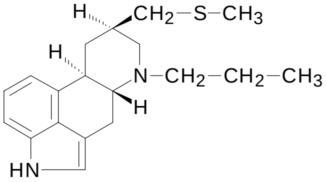
Synthesis

Pergolide (5.0 g, 16 mmol) was dissolved in mixture of dichloromethane (120 ml) and methanol (40 ml). Hydrogen peroxide (4.3%, 35 ml) was added dropwise under vigorous stirring and the mixture was stirred at ambient temperature for 10 h. Another portion of hydrogen peroxide (30%, 5 ml) was added and stirring continued for another 10 h. The organic layer was separated, washed three times with water (20 ml) and evaporated to dryness. The residue was purified by column chromatography on a silica gel (Merck 100, 63–200 μm, 52 g) using a stepwise gradient elution with dichloromethane–methanol (0.25–3.5% of methanol). Pooled fractions were evaporated, dissolved in methanol, decolourized with charcoal and methanol was partly evaporated. White crystals of pergolide sulfoxide hemihydrate (0.6 g, 11%, m.p. 175 °C) were separated and dried at 50 °C.



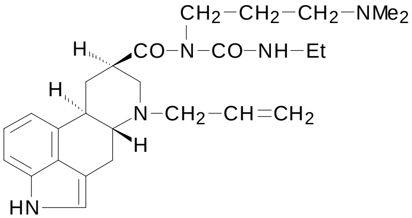
pergolide sulfoxide

1



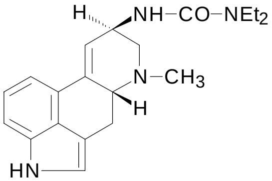
pergolide

2



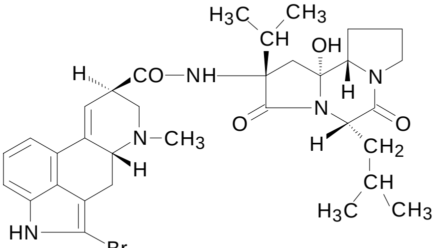
cabergoline

3



lisuride

4



bromokryptine

5

Characterization

Mass spectra were measured on a Finnigan MAT 90 spectrometer (double-focusing, BE geometry), with positive-ion electron impact ionization, ionizing energy 70 eV, source temperature 200 °C, emission current 0.5 mA, accelerating voltage 5 kV, direct inlet at 190 °C. EI-MS, *m/z* (rel. int. %): 331 (5), 330.1764 ($M^{+\bullet}$, 330.1766 calculated for $C_{19}H_{26}N_2OS$, 21), 315 (7), 314 (25), 313.1735 (313.1738 calculated for $C_{19}H_{25}N_2S$, 100), 301 (4), 268 (3), 267.1851 (267.1861 calculated for $C_{18}H_{23}N_2$, 17), 266 (16), 265 (18), 252 (5), 251.1544 (251.1548 calculated for $C_{17}H_{19}N_2$, 12), 238 (4), 237.1391 (237.1392 calculated for $C_{16}H_{17}N_2$, 15), 223 (4), 196 (5), 194 (5), 181 (5), 168 (8), 167 (13), 155 (12), 154 (33), 127 (7), 43 (4), 41 (4). Collisionally-induced dissociation (CID) mass spectrum of the molecular ion radical, *m/z* (rel. int. %): 313 (100), 267 (7), 266 (12), 265 (6), 251 (1), 237 (1), 194 (1), 168 (2), 167 (3).

A Varian VXR-400 spectrometer was used for ^1H and ^{13}C NMR measurements at 399.95 and 100.58 MHz for ^1H and ^{13}C, respectively, in $CDCl_3$ at 25 °C. Residual solvent signal (δ_H 7.265, δ_C 77.00) was used as an internal standard. Full assignment based on APT, HOM2DJ, COSY, delayed-COSY, and HETCOR experiments is given in Table I.

Single-Crystal Structure Determination

Pergolide sulfoxide (**1**, 80 mg) was dissolved in butan-2-one (8 ml) by short refluxing and the solution was allowed to cool overnight. The formed crystals were separated, washed with a little cold butan-2-one and dried on air. $(C_{19}H_{26}N_2OS)_2 \cdot H_2O$, M_r = 678.98, orthorhombic system, space group $P2_12_12_1$ (No. 19), a = 12.216(3) Å, b = 13.733(2) Å, c = 22.186(6) Å, V = 3 722(2) Å^3, Z = 4, D_{calc} = 1.21 g cm^{-3}, μ(CuKα) = 1.61 mm^{-1}, F(000) = 1 464.

The structure of **1** was solved by direct methods. All non-H atoms were refined anisotropically by the full-matrix least-squares method based on *F*-values. The hydrogen atoms were set geometrically, H811 and H812 were set to follow the O81–H811···O1 and O81–H812···O51 hydrogen bonds. Due to lower quality of the measured crystal (R_{int} = 0.197), the empirical absorption correction routine DIFABS (ref.[27]) was used and the Friedel pairs were merged yielding thus a 6% lowering of *R*. Data collection and refinement parameters are listed in Table II. Consecutive numbering of all individual C, N, O, and S atoms was used for the independent (*S*)-sulfoxide molecule (Fig. 1). The same numbers larger by 50 were used for the independent (*R*)-sulfoxide molecule (Fig. 2). Water molecule is denoted as H811–O81–H812.

RESULTS AND DISCUSSION

Pergolide sulfoxide (**1**) was recently reported as pergolide (**2**) metabolite[6–8] or a product of microbial oxidation[28] of **2**. It was also found as an impurity in **2**, probably as the result of degradation by oxygen[29]. We report here a simple route to **1** by oxidation of **2** with hydrogen peroxide. Even if the yield of pure **1** is poor (11% based on final crystalline **1**), this method is valuable. Because of many side and consecutive reactions were observed (oxidation to *N*6-oxide, oxidation in position 2 of ergoline skeleton, oxidation to sulfone), the conversion of peroxide was held low (50–60%) and the desired pergolide sulfoxide was isolated by chromatography.

Electron impact mass spectrum of **1** afforded the molecular ion-radical of medium intensity at *m/z* 330. The most intense peak (*m/z* 313) both in conventional and CID mass spectra was assigned to the hydroxyl radical loss from the $M^{+\bullet}$ ion. Although this

TABLE I
^{1}H and ^{13}C NMR data for pergolide sulfoxide (**1**)

Atom	δ_C	Multiplicity	δ_H	n_H	Multiplicity	*J*, Hz
2	117.75	d	6.895	1	dd	1.6, 1.6
3	111.99	s	–	0		
4	26.73	t	3.361	1	dd	14.7, 4.0
			2.722	1	ddd	14.7,11.1, 1.6
	26.68	t	3.354	1	dd	14.6, 4.0
			2.718	1	ddd	14.6, 11.1, 1.6
5	63.48	d	2.536	1	m	
	63.44	d	2.536	1	m	
7	55.17	t	3.190	1	ddd	11.3, 3.8, 2.1
			2.283	1	dd	11.3, 11.1
	54.98	t	3.255	1	ddd	11.1, 3.6,2.2
			2.262	1	dd	11.1, 11.1
8	31.70	d	2.465	1	m	
	31.66	d	2.465	1	m	
9	34.78	t	1.236	1	ddd	12.4, 12.1, 12.1
			2.913	1	m	
	34.40	t	1.315	1	ddd	12.6, 12.2, 12.2
			2.782	1	m	
10	40.65	d	2.999	1	m	
	40.37	d	2.999	1	m	
11	133.07	s	–	0		
	133.03	s	–	0		
12	113.07	d	6.909	1	ddd	6.6, 1.2, 1.2
			6.895	1	ddd	6.6, 1.2, 1.2
13	123.04	d	7.160	2	dd	8.2, 6.6
14	108.61	d	7.192	1	ddd	8.2, 1.2, 0.7
	108.60	d	7.192	1	ddd	8.2, 1.2, 0.7
15	133.31	s	–	0		
	133.30	s	–	0		
16	126.12	s	–	0		
17	60.44	t	2.850	1	dd	12.9, 5.8
			2.604	1	dd	12.9, 5.1
	60.24	t	2.818	1	dd	12.9, 5.8
			2.584	1	dd	12.9, 4.8
SCH_3	39.35	q	2.651	3	s	
	39.31	q	2.641	3	s	
α	58.69	t	2.803	2	m	
	58.40	t	2.803	2	m	
β	17.29	t	1.542	2	m	
	17.19	t	1.524	2	m	
γ	11.94	q	0.916	3	t	7.4
	11.92	q	0.912	3	t	7.3
NH	–	–	8.052	1	d	unresolved

mechanism cannot be rationalized by a simple mechanistic interpretation, the nature of this ion was confirmed by exact mass measurement. Ion *m/z* 267 arises by elimination of the CH_3SO radical from the parent molecular ion. Other abundant ions (*m/z* 251, 237, 167, 154, 127) are common fragments present in EI mass spectra of ergolines[30].

Nearly all carbon signals in the ^{13}C NMR spectrum of **1** were doubled (in the ratio approximately 1 : 1). The same feature was apparent in the ^1H NMR spectrum and more clearly in the *J*-resolved (HOM2DJ) experiment. Protons forming such doublets had similar or identical coupling patterns. Two three-proton singlets at 2.651 and 2.641 ppm (coupled to carbons resonating at 39.35 and 39.31 ppm) and changes in the environment of the original methysulfanyl group indicated the presence of the CH_3SO– moiety (CH_3SO: δ_H 2.50, δ_C 39.6; for comparison CH_3S in pergolide[31]: δ_H 2.11, δ_C 16.29 and CH_3S in pergolide mesylate: δ_H 2.132, δ_C 15.48, in $(CD_3)_2SO$). Taking into account the X-ray diffraction study, the two observed molecules were assigned to two diastereomers which differ in the chirality of the sulfoxide group. The comparison of these two compounds based on proton and carbon chemical shifts of the corresponding atoms (Fig. 3) shows an interesting pattern. Large effects observed on D-ring and *N*-propyl atoms indicate probable preferred orientation of the CH_3SOCH_2– group (folded over the ring so that the sulfoxide oxygen may interact with the nitrogen lone pair). Further assignment was attempted using the molecular mechanics calculation based on structural parameters obtained from the X-ray diffraction study.

The X-ray crystal structure determination confirmed the presence of two independent molecules of pergolide (*S*)- and (*R*)-sulfoxide in the crystal structure and one molecule

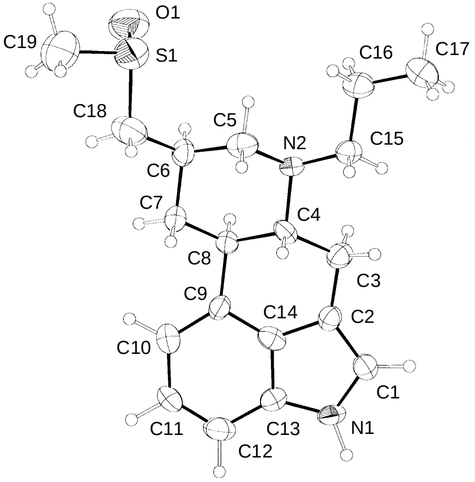


FIG. 1
The ORTEP drawing of pergolide (*S*)-sulfoxide with atom numbering

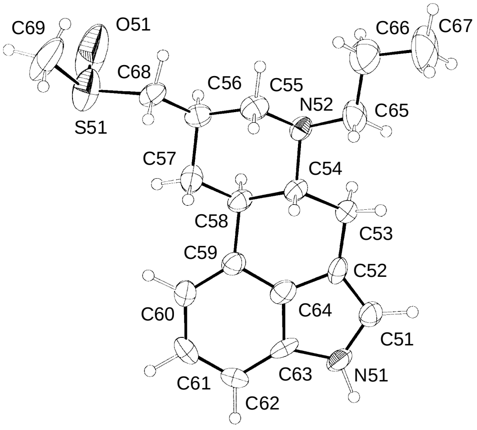


FIG. 2
The ORTEP drawing of pergolide (*R*)-sulfoxide with the atom numbering

TABLE II
Data collection and refinement parameters

Crystal dimension	0.25 × 0.42 × 0.56 mm
Diffractometer and radiation used	Enraf–Nonius CAD4, CuKα, $\lambda = 1.54056$ Å
Scan technique	$\omega/2\theta$
Temperature	293 K
No. and θ range of reflections for lattice parameter refinement	20; 38 –40°
Range of *h, k, l*	$0\to12$, $0\to14$, $-23\to23$
Standard reflections monitored in the interval; intensity fluctuation	60 min; 3.21%
Total number of reflections measured; 2θ range	4 850; 4–110°
No. observed reflections	2 095
Criterion for observed reflections	$I \geq 1.96\sigma(I)$
Function minimized	$w(\lvert F_o\rvert - \lvert F_c\rvert)^2$
Weighting scheme	Chebychev polynomial[33]
Parameter refined	425
Value of *R*, *wR*, *S*	0.0752, 0.0856, 1.1109
Ratio of the maximum least-squares shift to e.s.d. in the last cycle	0.001
Maximum and minimum heights in final $\Delta\rho$ map	0.74; –0.34 e Å^{-3}
Source of atomic scattering factors	ref.[34]
Programs used	CRYSTALS (ref.[34]), PARST (ref.[35]), SIR92 (ref.[36])

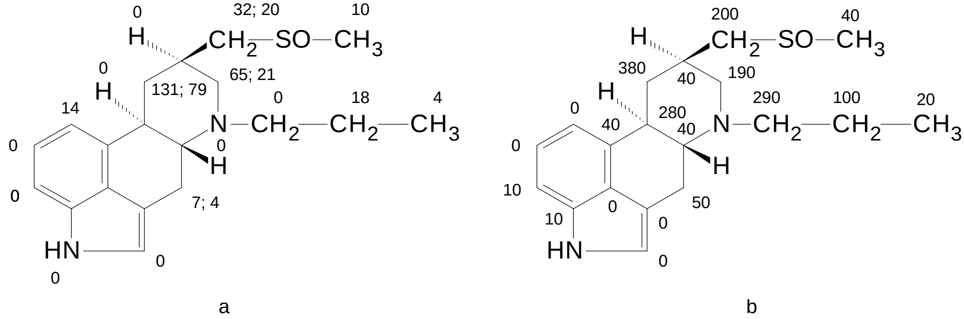


FIG. 3
^{1}H NMR (a) and ^{13}C NMR (b) chemical shift (ppb) differences between the two diastereomers of pergolide sulfoxide

of water (the displacements of S1 and S51 are –0.707(4) and 0.620(4) Å from the planes C18–C19–O1 and C68–C69–O51, respectively). The final positional and thermal parameters of the non-H atoms of pergolide sulfoxide are deposited in the Cambridge Crystallographic Data Base. The ergoline A and B rings, forming the indole moiety, are nearly planar, ring C (C8, C9, C14, C2, C3, C4) possesses the E_6 envelope conformation, and ring D (C4, N2, C5, C6, C7, C8) has the $^4C_1$ chair conformation. It is generally assumed, that the ergoline skeleton is a rigid moiety the structural parameters of which are nearly the same for all ergot derivatives. Whereas all structural parametres of **2**, pergolide mesylate and **1** are virtually nearly identical, a comparison of some ergot alkaloid derivatives (Table III) indicates, that there are marked differences in various puckering parameters even for related alkaloids, which seems likely to explain their different spectra of pharmacological activity.

Apart from the ergoline skeleton which is almost rigid for all ergot alkaloids, the sulfoxide side chain has fairly large conformation freedom. Single-point calculations were carried out for torsion angles ω_S = C5–C6–C18–S1, ψ_S = C6–C18–S1–O1, ω_R = C55–C56–C68–S51, and ψ_R = C56–C68–S51–O51 with 10° steps and the limit of convergence set to 0.0001. The values of heat of formation were obtained using the semi-empirical PM3 method[32] (Figs 4 and 5). Three regions of low energy were found. The flat global minima are located at $\omega_S = 130°$, $\psi_S = 130°$, and $\omega_R = 130°$, $\psi_R = –130°$ for (*S*)- and (*R*)-sulfoxides, respectively. These global minima are separated by a 8 kJ/mol barrier from another two broad local minima at $\omega_S = 130°$, $\psi_S = –50°$ and $\omega_R = 130°$, $\psi_R = 50°$, and with a 24 kJ/mol barrier from sharp local minima at $\omega_S = \omega_R = –60°$, $\psi_S = 130°$,

TABLE III
Comparison of structrural parameters of ergot alkaloid derivatives exhibiting similar pharmacological effects

Puckering parameter[40]	Pergolide (*S*)-sulfoxide	Pergolide[38]	Pergolide mesylate[38]	Cabergoline[39]	Lisuride maleate[13]	Bromokryptine mesylate[23]
A/B[a], °	1.3(5)	1.23(19)	1.16(16)	0.85(19)	3.11(17)	1.32(62)
Ring C, *Q*, Å	0.47(1)	0.424(6)	0.452(4)	0.465(6)	0.357(6)	0.42(2)
Ring C, φ_2, °	–54(2)	–46(1)	–50.3(7)	–50.4(9)	–65(1)	–66(3)
Ring C, θ, °	50(1)	48.7(7)	53.4(5)	51.2(7)	53.5(9)	51(2)
Ring D, *Q*, Å	0.60(1)	0.586(6)	0.593(4)	0.595(5)	0.484(6)	0.495(15)
Ring D, φ_2, °	–150(13)	–91(15)	–146(10)	–107(6)	–91(1)	–83(2)
Ring D, θ, °	175(1)	178.0(6)	177.4(4)	174.4(6)	130.2(7)	125(2)

[a] The angle between the mean planes of the A and B ergolene rings.

ψ_R = –130°. Values ω_S = 64(1), ψ_S = 62(1)°, and ω_R = 169.3(7), ψ_R = –60(1)° were found in the crystal structure. As follows from Figs 4 and 5, these values are very near to the global minima for both diastereomers and a possible distortion caused by a H-bond with the water molecule in the crystal structure is very low, if any. Although calculated minima of energy are relatively broad, even a first inspection of Figs 4 and 5 clearly indicates that the zig-zag conformation with opposite orientation of $CH_3CH_2CH_2N6$– and CH_3SOCH_2C8– groups is preferred for (*R*)-sulfoxide, whereas that one which brings these moieties to proximity is preferred for (*S*)-sulfoxide (see also Figs 1 and 2). These differences make it possible to tentatively assign the molecule with up-field resonating protons of the *N*-propyl group and of C7 atom to (*S*)-sulfoxide, and with up-field resonating protons of the C9 atom to (*R*)-sulfoxide.

Two neighbouring molecules of pergolide (*S*)- and (*R*)-sulfoxides are linked with hydrogen bonds between the NH group of the indole moiety and free electron pair of the *N*-propyl group forming infinite chains (N1–H1N···N52^i, D···A = 2.95(1) Å, (i): $-x + 1/2$, $-y + 1$, $z + 1/2$ and N51–H51N···N2^{ii}, D···A = 2.93(1) Å, (ii): $-x - 1/2$, $-y + 1$, $z - 1/2$). Water molecule crosslinks individual chains thus creating a three-dimensional hydrogen bond network, O81–H811···O1, D···A = 2.85(2) Å and O81–H112···O51, D···A = 2.95(2) Å.

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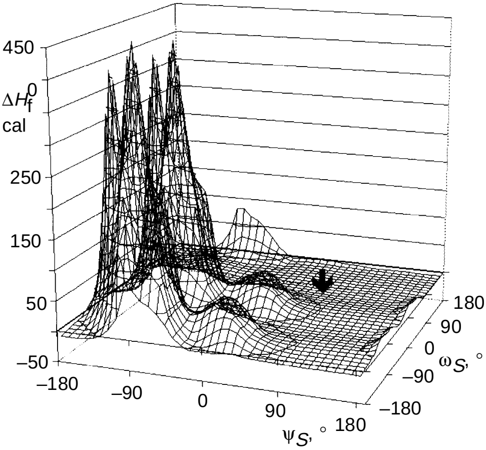

FIG. 4
The three-dimensional map of heat of formation *vs* torsion angles ω_S and ψ_S for pergolide (*S*)-sulfoxide (the arrow indicates the angle combination found in the crystal structure)

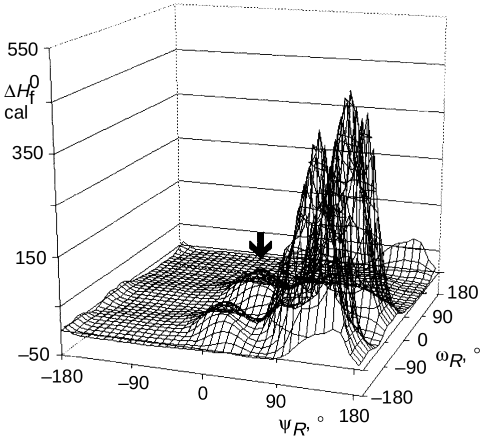

FIG. 5
The three-dimensional map of heat of formation *vs* torsion angles ω_R and ψ_R for pergolide (*R*)-sulfoxide (the arrow indicates the angle combination found in the crystal structure)

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