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Pergolide mesylate form II

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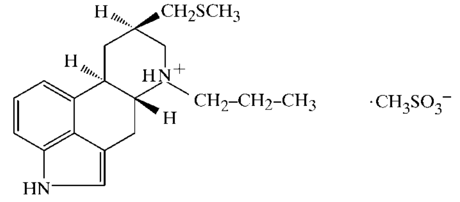
A new polymorph of pergolide mesylate or 8β-[(methylsulfanyl)methyl]-6-propylergoline methanesulfonate, $C_{19}H_{27}N_2S^+\cdot CH_3SO_3^-$, is reported. Pergolide mesylate form II crystallizes in the trigonal system, which is unique for ergot derivatives. Although the hydrogen-bond system in form II differs completely from that in form I, the conformation of the pergolide moiety in various related structures is very similar.

Comment

Pergolide mesylate, (I), is a semisynthetic ergot derivative used as an important drug mainly in the treatment of Parkinson's disease (Wachtel, 1991). The crystal structure of pergolide mesylate [triclinic $P1$; $a = 6.841$ (2), $b = 9.314$ (2), $c = 9.678$ (2) Å, $\alpha = 64.42$ (2), $\beta = 69.67$ (2) and $\gamma = 76.74$ (2)°] and the pergolide base have been described previously by Ma *et al.* (1987). The former structure refers to form I as described by Sprankle & Jensen (1992). Pergolide mesylate form II was described only in a mixture with form I, based on only one new diffraction line that appeared in the powder diffraction data and some differences in the fingerprint region of the IR spectrum (775, 607 and 544 cm^{-1}). However, no further evidence of form II was ever reported. As well as the structures of pergolide and pergolide mesylate, the structure of pergolide sulfoxide, a pergolide metabolite exhibiting pharmacological activity roughly equal to pergolide, has been reported (Čejka *et al.*, 1998).

Pergolide mesylate form II crystallizes in the trigonal space group $P3_221$. Conformational analysis has shown that there are only subtle differences between the independent molecules in individual structures. The ergoline skeleton is virtually identical in all pergolide derivatives. Only one of the two independent molecules of pergolide sulfoxide differs in the orientation of the sulfoxy group (see Fig. 1). Although there are a number of coincidences of diffraction lines in powder diffractograms, pergolide mesylate forms I and II can easily be distinguished by the presence of the sole diffraction lines (014) 6.329 Å and (003) 14.96 Å in form II, and (001) 8.372 Å in form I, which can potentially also serve for the quantitative analysis of the mixtures.



(I)

The differential thermal analysis thermogram for pergolide mesylate form II shows a sharp endotherm at 534.5 K (decomposition), which is identical, within experimental error, to pergolide mesylate form I. In addition to a number of subtle changes in the fingerprint region of the IR spectrum in the range 450–800 cm^{-1}, there are also noticeable changes in the range 1400–1500 cm^{-1} (aliphatic C—H deformation), which can serve to discriminate between the two forms. More interestingly, changes in N—H deformation (~780 cm^{-1} for indole N—H), N^+—H stretching (2556 cm^{-1} in form I and

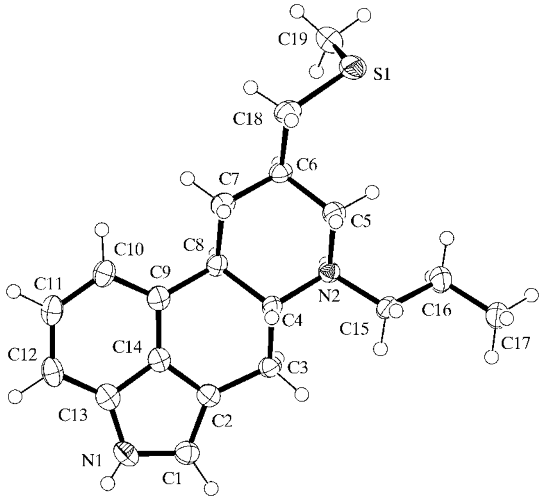


Figure 1
ORTEP-3 (Farrugia, 1997) drawing of pergolide form II, with the atom-numbering scheme for non-H atoms and 50% probability displacement ellipsoids. H atoms are shown as small circles of arbitrary radii.

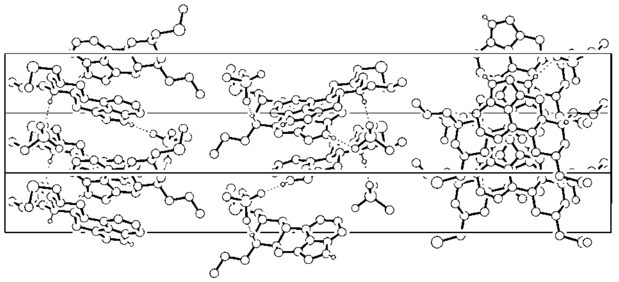


Figure 2
A packing diagram of pergolide form II (*ORTEP*-3; Farrugia, 1997), viewed normal to (010).

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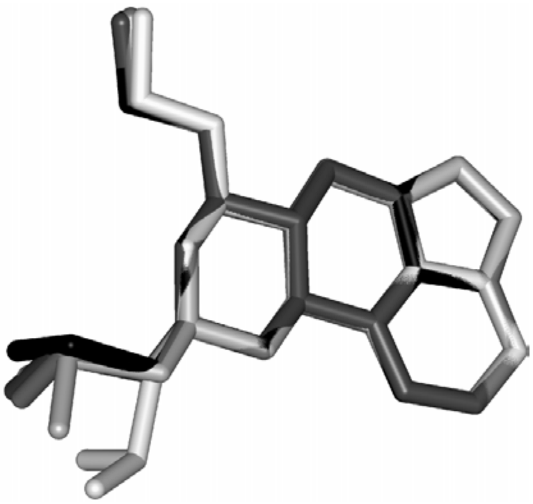

Figure 3
Fitted pergolide derivatives (fit based on fused rings to reveal differences in side chains). Key: form I black, form II dark grey, pergolide grey and the two independent molecules of pergolide sulfoxide light grey.

~2600–2700 cm^{-1} in form II) and N—H stretching (3180 cm^{-1} in form I and 3200 cm^{-1} in form II for indole N—H) bands indicate the substantially different hydrogen-bond network in the individual forms. Although the same atoms and similar hydrogen bonds are utilized in the hydrogen-bond networks (see Table 1), the final arrangement is very different. In form I, the molecules form bridges to each other through the mesylate anions, forming simple narrow chains. In contrast, pergolide molecules and mesylate anions create zigzag screwed chains in several directions in form II. It should be noted that the orientations of the mesylate methyl groups are also different in both structures.

Experimental

Pergolide mesylate (1.64 kg, obtained from IVAX Pharmaceuticals) was dissolved in a stainless steel drum in aqueous ethanol (22 l of ethanol, 4 l of water and 3.3 g of ascorbic acid) under nitrogen at 333 K. Crystals of pergolide mesylate form II (1.13 kg, 68.9%) were obtained upon cooling the solution to 295 K and these crystals were isolated by filtration and dried in air.

Crystal data

$C_{19}H_{27}N_2S^+\cdot CH_3O_3S^-$
$M_r = 410.60$
Trigonal, $P3_221$
$a = 8.8510\ (2)$ Å
$c = 44.8860\ (8)$ Å
$V = 3045.27\ (11)$ Å^3
$Z = 6$
$D_x = 1.343$ Mg m^{-3}

Mo $K\alpha$ radiation
Cell parameters from 4009 reflections
$\theta = 1.0$–$26.0°$
$\mu = 0.29$ mm^{-1}
$T = 293$ K
Block, white
0.35 × 0.26 × 0.23 mm

Data collection

Nonius KappaCCD area-detector diffractometer
φ and ω scans
7908 measured reflections
2389 independent reflections
1937 reflections with $I > 1.96\sigma(I)$

$R_{\text{int}} = 0.02$
$\theta_{\max} = 26.0°$
$h = -10 \rightarrow 10$
$k = -8 \rightarrow 8$
$l = -55 \rightarrow 55$

Refinement

Refinement on F
$R = 0.030$
$wR = 0.034$
$S = 1.15$
1937 reflections
244 parameters
H-atom parameters constrained

Prince-modified Chebychev polynomial (Watkin, 1994) with 3 parameters; $W = [\text{weight}][1 - (\delta F/6\sigma F)^2]^2$, with 0.551, 0.377 and 0.369
$(\Delta/\sigma)_{\max} < 0.001$
$\Delta\rho_{\max} = 0.22$ e Å^{-3}
$\Delta\rho_{\min} = -0.23$ e Å^{-3}

Table 1
Hydrogen bonds (Å, °) in pergolide mesylate polymorphs.

	Symmetry code	$D\cdots A$	D—H$\cdots A$
Pergolide form I†			
N1—H···O2	$x, y - 1, z + 1$	2.853	
N2—H521···O2	$x + 1, y, z$	2.723	
Pergolide form II			
N1—H511···O1	$x - y + 1, -y + 1, -z + \frac{1}{3}$	2.946 (3)	176
N2—H521···O2		2.726 (2)	166

† Ma *et al.* (1987).

H atoms were placed in calculated positions and allowed for as riding on their attached C atoms at distances of 1.0 Å. Atoms H511 and H521 were located in difference Fourier maps and refined fixed. The absolute configuration could not be determined reliably *via* anomalous dispersion and was chosen to be consistent with that of the natural product.

Data collection: *COLLECT* (Nonius, 1997); cell refinement: *DENZO*/*SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO*/*SCALEPACK*; program(s) used to solve structure: *SIR*92 (Altomare *et al.*, 1994); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*, 2001); molecular graphics: *ORTEP*-3 (Farrugia, 1997).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1650). Services for accessing these data are described at the back of the journal.

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