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Cabergoline, form VII

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Key indicators

Single-crystal X-ray study
T = 150 K
Mean σ(C–C) = 0.003 Å
Disorder in main residue
R factor = 0.037
wR factor = 0.044
Data-to-parameter ratio = 8.5

For details of how these key indicators were automatically derived from the article, see http://journals.iucr.org/e.

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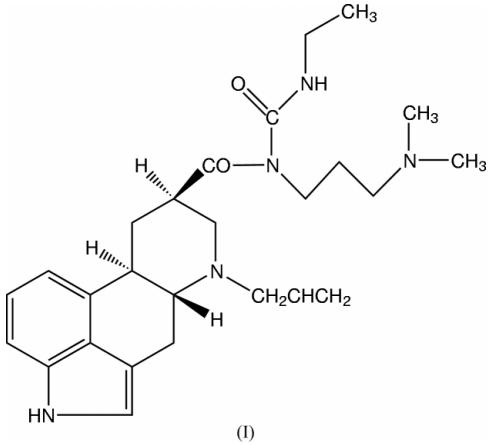
A new crystal structure of cabergoline ($C_{26}H_{37}N_5O_2$), polymorph form VII, is reported. It crystallizes in the same space group, $P2_1$, as the more stable form I, but there are two independent molecules in form VII. The molecular packing and the hydrogen-bond networks are, consequently, completely different.

Comment

The semisynthetic ergot derivative cabergoline {*N*-[3-(dimethylamino)propyl]-*N*-(ethylcarbamoyl)-6-allyl ergoline-8β-carboxamide} possesses very interesting long-term agonistic activity towards the D2 dopamine receptor. Owing to its potent and very long-acting inhibition of prolactin secretion, it is used for the treatment of hyperprolactinemia (Colao *et al.*, 2002). As with the structurally related terguride (Hušák *et al.*, 2002), the high degree of conformational freedom of cabergoline facilitates the existence of a number of crystalline forms. Powder diffraction data of these forms are described in various patents; however, only one crystal structure determination of cabergoline, form I ($P2_1$), has been described in the literature so far (Sabatino *et al.*, 1995). Here we report the crystal structure determination of cabergoline form VII, (I).



(I)

There are two independent molecules in the structure, labeled as C1–C33 (Fig. 1) and C41–C83 (Fig. 2), the latter having a side chain disordered over two positions (C70, N71, C72, C73, occupancy 0.6, and C80, N81, C82, C83, occupancy 0.4). The ergoline skeleton and adjacent allyl group are almost identical in the two molecules and also in form I. The orientation of the side chains on C8 clearly depends on rotation about the C8—C20 bond and here forms I and VII differ significantly. The torsion angle (C7—C8—C20—N22) of form I is 174°; for form VII it is 62.9 (2)° for molecule 1 and

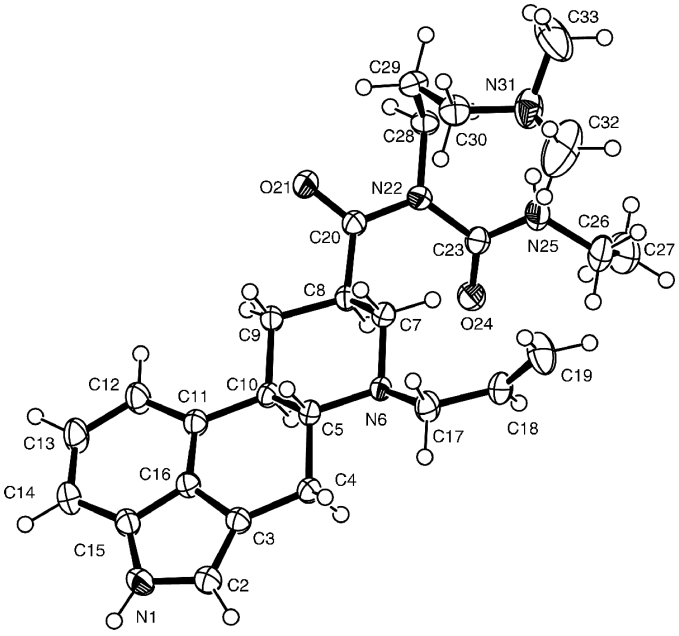


Figure 1
Molecule 1 of cabergoline, form VII, with the atom-numbering scheme for non-H atoms and 50% probability displacement ellipsoids. H atoms are shown as small circles of arbitrary radii.

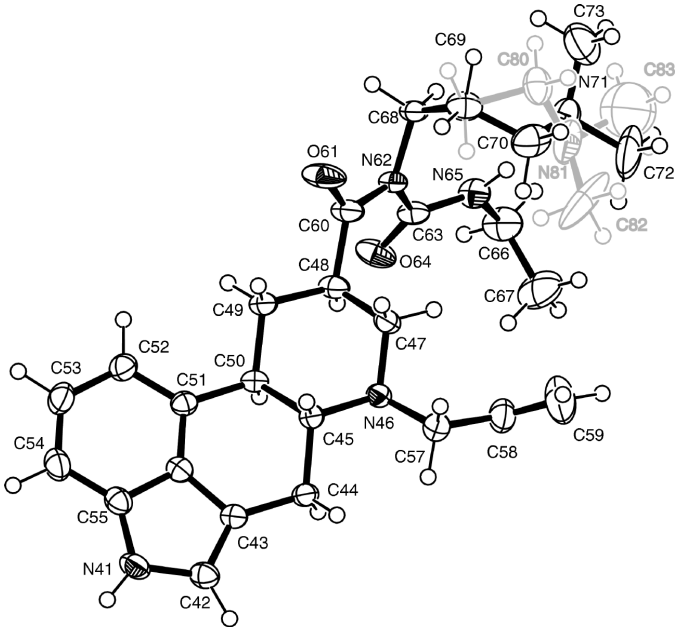


Figure 2
Disordered molecule 2 of cabergoline, form VII, with the atom-numbering scheme for non-H atoms and 50% probability displacement ellipsoids. H atoms are shown as small circles of arbitrary radii.

87.5 (2)° for molecule 2 (Fig. 3). It is noteworthy that the amide linkage is roughly coplanar with one of the adjacent bonds (C7—C8 or C8—C9) in ring *D* (N6, C7, C8, C9, C10, C5) of the ergoline skeleton in form I. The torsion angle C9—C8—C20—N22 is −175.5 (2)° in molecule 1 and the corresponding angle is −152.8 (2)° in molecule 2 of form VII. There are intramolecular hydrogen bonds N25—H···N31 and N65—H···N71/N81, characteristic of cabergolines (Table 1). Both

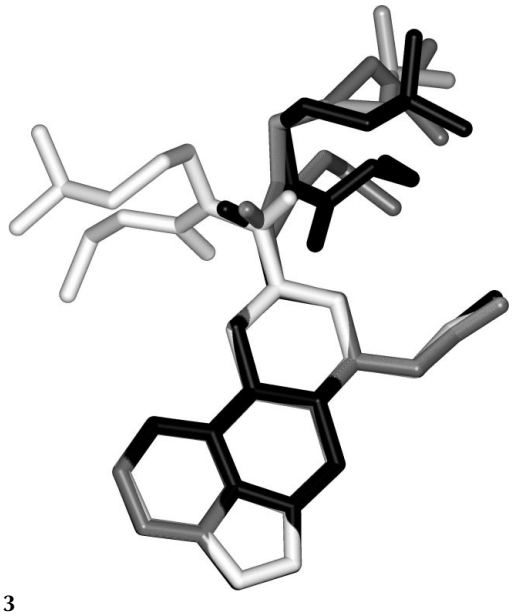


Figure 3
A least-squares fit of the fused rings of form I (white), the ordered molecule of form VII (black), and the disordered molecule of form VII (light and dark grey), showing the differences in the side chains.

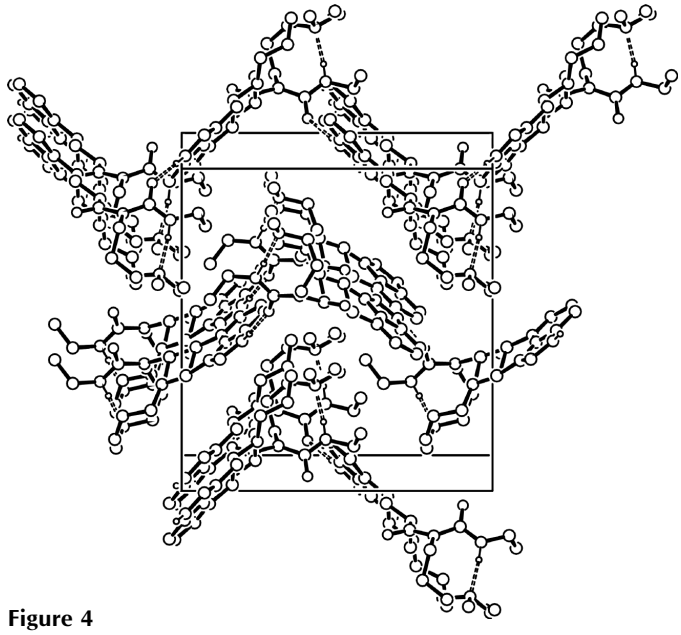


Figure 4
A packing diagram of cabergoline, form VII, normal to (100).

molecules form infinite chains (Fig. 4) with symmetry-equivalent molecules along the *b* axis. There are also two weak hydrogen bonds between the indole skeleton and the amide O atom. Surprisingly, no intermolecular contact is found between the independent molecules. The molecular packing of form VII differs substantially from that found in form I (Table 1).

Experimental

Single crystals of cabergoline form VII were obtained from a saturated solution of cabergoline (IVAX Pharmaceuticals, Czech Republic) in dry diethyl ether at ambient temperature (298 K).

Crystal data

$C_{26}H_{37}N_5O_2$	D_x = 1.168 Mg m^{-3}
M_r = 451.61	Mo Kα radiation
Monoclinic, $P2_1$	Cell parameters from 6047 reflections
a = 10.9448 (2) Å	θ = 1–27°
b = 15.1406 (2) Å	μ = 0.08 mm^{-1}
c = 15.6896 (3) Å	T = 150 K
β = 99.1231 (9)°	Prism, white
V = 2567.23 (8) Å^3	0.37 × 0.23 × 0.21 mm
Z = 4	

Data collection

Nonius Kappa CCD diffractometer	R_{int} = 0.01
φ and ω scans	θ_{max} = 27.5°
Absorption correction: none	$h = -14 \rightarrow 14$
46767 measured reflections	$k = -19 \rightarrow 19$
6104 independent reflections	$l = -20 \rightarrow 20$
5301 reflections with $I > 1.96\sigma(I)$	

Refinement

Refinement on F	Weighting scheme: modified Chebychev polynomial (Watkin, 1994), with coefficients 0.912 0.735 0.593
R = 0.037	$(\Delta/\sigma)_{max}$ = 0.001
wR = 0.044	$\Delta\rho_{max}$ = 0.26 e Å^{-3}
S = 1.13	$\Delta\rho_{min}$ = −0.22 e Å^{-3}
5301 reflections	
626 parameters	
H-atom parameters constrained	

Table 1
Hydrogen-bond networks in Cabergoline forms I and VII (Å,°).

	$D\cdots A$	H$\cdots A$
Cabergoline form I[a]		
N4—H20$\cdots$N5	2.887	161
N1—H1$\cdots$N2^{i}	2.956	167
Cabergoline form VII[b]		
N25—H251$\cdots$N31	2.893 (3)	173
N65—H651$\cdots$N71	2.934 (9)	174
N65—H651$\cdots$N81	2.768 (12)	165
N1—H11$\cdots$O24^{ii}	2.973 (2)	167
N41—H411$\cdots$O64^{iii}	2.861 (2)	171
C14—H141$\cdots$N6^{ii}	3.458 (3)	166
C2—H21$\cdots$O21^{iv}	3.296 (3)	171
C42—H421$\cdots$O61^{iv}	3.286 (3)	156

Notes: (*a*) Sabatino *et al.* (1995); (*b*) this work. Symmetry codes: (i) $-x, \frac{1}{2}+y, 2-z$; (ii) $-x, \frac{1}{2}+y, 1-z$; (iii) $x-1, y-\frac{1}{2}, -z$; (iv) $1+x, y, z$.

After free refinement of the occupancy factors for the disorder components of the second molecule to values close to 0.6 and 0.4, these values were constrained; no restraints were applied to the disorder components, but atom C83 was refined as isotropic because of unsatisfactory anisotropic behaviour.

All H atoms bonded to N were located in a difference map and fixed in those positions, with U_{iso} = 0.05 Å^2. Other H atoms were positioned geometrically and refined riding on their parent C atoms, with C—H = 1.0 Å and U(H) = 1.2U_{eq}(C). In the absence of significant anomalous dispersion, Friedel pairs were merged; the absolute structure was assigned according to stereochemistry of already solved structure of cabergoline.

Data collection: *COLLECT* (Nonius, 1997); cell refinement: *DENZO/SCALEPACK* (Otwinowski & Minor, 1997); data reduction: *DENZO/SCALEPACK*; program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1986); program(s) used to refine structure: *CRYSTALS* (Watkin *et al.*, 2001); molecular graphics: *ORTEP*3 (Farrugia, 1997); software used to prepare material for publication: *CRYSTALS*.

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