

**X-RAY STRUCTURAL STUDY OF TERGURIDE SOLVATES –
TERGURIDE METHANOL SOLVATE**

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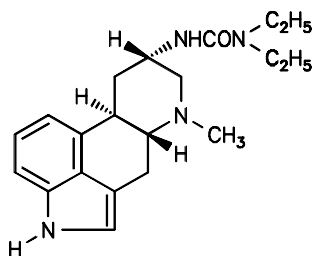
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The structure of the unstable solvate of the semisynthetic ergot derivative – terguride methanol solvate $C_{20}H_{28}N_4O \cdot CH_3OH$, was solved by direct methods and refined to an R value of 0.093 for 1 462 unique observed reflections. The title alkaloid crystallizes in the orthorhombic space group $P2_12_12_1$ with lattice parameters $a = 10.438(1)$, $b = 13.200(4)$, $c = 15.495(5)$ Å, $V = 2 134.8(9)$ Å³, $Z = 4$. An indole moiety of the terguride molecule is almost perfect planar, ring C has an E_6 envelope conformation and ring D adopts a 1C_4 chair shape. As found from X-ray powder diffraction study, terguride methanol solvate completely transforms to terguride monohydrate in air during several hours.

The semisynthetic ergot alkaloid – terguride (Scheme 1) is well-known for its anti-parkinsonian effect, stimulating effect on secretion of gonadotropins and inhibiting



SCHEME 1

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effect of prolactin secretion¹. Depending on water contents in solvent, terguride can crystallize as twothird hydrate² or monohydrate³. The protonized hydrated form – terguride hydrogen maleate monohydrate was also reported⁴. The presence of water in terguride structures has crucial importance for crystal stability. It links terguride molecules to the stable three-dimensional H-bond network.

This work deals with the other solvate – unstable terguride methanol solvate and its transformation to the stable monohydrate form in air.

EXPERIMENTAL

Preparation

Terguride (1 g, Galena Co., The Czech Republic) was dissolved in methanol (20 ml, p.a., Lachema Co., The Czech Republic) at 50 °C. Solution was filtered and allowed to crystallize overnight at 24 °C. Crystal used for X-ray structure analysis was transferred to the Lindemann capillary in mother liquor and there adjusted by a glass needle. Then the capillary was capped with a silicon grease and sealed to prevent attack of air moisture.

Crystal Structure Determination

Terguride (1,1-diethyl-3-[(5*R*,8*S*,10*R*)-6-methyl-8-ergolinyl]urea, *trans*-dihydrolisuride) (Scheme 1) methanol solvate, C₂₀H₂₈N₄O · CH₃OH, $M_r = 372.5$, orthorhombic system, space group $P2_12_12_1$ (No. 19), $a = 10.438(1)$, $b = 13.200(4)$, $c = 15.495(5)$ Å, $V = 2\,134.8(9)$ Å³, $Z = 4$, $D_{\text{calc}} = 1.159$ g cm⁻³, $\mu(\text{MoK}\alpha) \approx 0.7$ cm⁻¹, $F(000) = 808$.

Intensity data were corrected on crystal decay, not for absorption or extinction. The structure was solved by direct methods and subsequent Fourier techniques. The methanol molecule was found from the difference synthesis. A diffuse electron density peak in position of one ethyl group was interpreted so that methyl group C25–H₃ oscillates between two limiting positions (C251 and C252) with refined occupancy factor values (sum of both was held constant). The atoms C24, C251, C252 and C31 were refined isotropically due to their disordered character. The restrain procedure was applied to bonds C251–C24, C252–C24, N21–C24, C22–C23 and N21–C22 with the starting length value of 1.43(1) Å and weight corresponding to its e.s.d. The H-atom positions were calculated assuming ideal geometry. The methanol hydrogens were not found. The parameters for data collection and refinement are listed in Table I.

Powder Diffraction Measurement

X-Ray powder patterns were collected on a Seifert diffractometer XRD 3000 P with Bragg–Brentano focusing geometry. Radiation CoK α monochromatized with a graphite monochromator was used. Measurement was provided in range 7 – 35° 2 θ by step scan mode (step width 0.01° θ , preset time 2 s). The measured sample was not protected against air moisture. Quantitative analysis of the phase mixture was made by Rietveld method⁹. The weight fraction of component in the sample was estimated by

$$x_1 = \frac{S_1 V_1 Z_1 M_1}{\sum_i S_i V_i Z_i M_i}$$

where i is number of phase, S scale factor, V cell volume, Z number of formula unit per cell, M molecular weight. Profile shape parameters were refined only, no structure. The following Rietveld agreement factor values were obtained: $R_B(\text{monohydrate}) = 0.121$, $R_B(\text{methanol s.}) = 0.141$, $R = 0.173$, $R_w = 0.225$.

RESULTS AND DISCUSSION

The final positional and thermal parameters of the non-H atoms of terguride methanol solvate are summarized in Table II. Bond distances and angles are listed in Table III. Lower precision of resulted structural parameters is caused by unstability of crystals available (see intensity loss during measurement – Table I).

TABLE I
Data collection and refinement parameters

Crystal dimensions	≈ 1 mm
Diffractometer and radiation used	Enraf–Nonius CAD4, MoK α , $\lambda = 0.71073$ Å
Scan technique	$\omega/2\theta$
Number and θ range of reflections for lattice parameter refinement	23; 18.62 – 19.22°
Range of h , k and l	$-13 \rightarrow 13$, $-16 \rightarrow 16$, $0 \rightarrow 20$
Maximum value of $(\sin \theta)/\lambda$	0.703
Standard reflections	0 2 0, 0 3 1
Standard reflections monitored in interval; intensity fluctuation	120 min; -28.5%
Total number of reflections measured; 2θ range	7 816; $0 - 50^\circ$
Value of R_{int}	0.024
Number of unique observed reflections	1 462
Criterion for observed reflections	$I \geq 1.96 \sigma(I)$
Function minimized	$\Sigma w (F_o - F_c)^2$
Weighting scheme	$w = 1/\sigma^2(F_o)$
Parameters refined	233
Value of R , wR and S	0.093, 0.092, 3.38
Ratio of max. LS shift to e.s.d. in the last cycle	0.07
Max. and min. heights in final $\Delta\rho$ map	0.37, -0.33 e Å $^{-3}$
Source of atomic scattering factors	CRYSTALS (ref. ⁵)
Programs used	SDP (ref. ⁶), SHELXS86 (ref. ⁷), PARST (ref. ⁸), CRYSTALS (ref. ⁵)
Computer used	PDP 11/73, PC 486

TABLE II

Atomic coordinates for non-H atoms and their equivalent thermal parameters ($\cdot 10^3$) with e.s.d.'s in parentheses. $U_{\text{eq}} = (U_{11} + U_{22} + U_{33})/3$

Atom	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{eq}}, \text{\AA}^2$
O20	-0.1494(9)	0.1088(6)	-0.7136(5)	103(4)
O30	-0.1585(13)	0.0613(7)	-0.3756(7)	206(6)
N1	0.4413(10)	-0.1151(7)	-0.3294(7)	90(4)
N6	-0.1001(8)	-0.1232(6)	-0.4571(6)	71(3)
N18	-0.1502(7)	0.0502(6)	-0.5784(5)	63(3)
N21	-0.1899(11)	0.2162(7)	-0.6084(6)	105(5)
C2	0.3192(14)	-0.1402(8)	-0.2949(8)	91(5)
C3	0.2297(11)	-0.1170(8)	-0.3574(8)	76(5)
C4	0.0875(10)	-0.1277(8)	-0.3592(7)	80(5)
C5	0.0418(9)	-0.1309(7)	-0.4535(6)	64(4)
C7	-0.1464(10)	-0.1310(7)	-0.5461(7)	78(4)
C8	-0.0997(9)	-0.0477(7)	-0.6043(7)	64(4)
C9	0.0484(8)	-0.0496(8)	-0.6022(6)	68(4)
C10	0.0981(8)	-0.0436(7)	-0.5101(6)	55(4)
C11	0.2461(9)	-0.0439(7)	-0.5050(8)	63(4)
C12	0.3308(10)	-0.0083(6)	-0.5691(7)	68(4)
C13	0.4643(11)	-0.0083(8)	-0.5475(9)	87(5)
C14	0.5144(11)	-0.0394(8)	-0.4717(9)	93(6)
C15	0.4293(11)	-0.0767(8)	-0.4100(9)	74(5)
C16	0.2966(10)	-0.0766(7)	-0.4297(8)	64(4)
C17	-0.1616(10)	-0.2012(7)	-0.4041(7)	93(4)
C19	-0.1611(11)	0.1253(9)	-0.6371(9)	79(5)
C22	-0.2025(10)	0.2436(9)	-0.5194(8)	118(7)
C23	-0.3295(10)	0.2392(9)	-0.4817(8)	117(6)
C24	-0.2025(16)	0.3020(9)	-0.6688(9)	140(5) ^a
C31	-0.1735(18)	0.0901(13)	-0.2890(11)	172(7) ^a
C251 ^b	-0.3291(18)	0.3291(18)	-0.6930(15)	150 ^c
C252 ^b	-0.0853(20)	0.3497(21)	-0.6886(18)	150 ^c

^a Refined isotropically; ^b occupation factor refined: 0.54(1) for C251 and 0.46(1) for C252; ^c fixed.

TABLE III
Bond distances (Å) and angles (°) with e.s.d.'s in parentheses

Atoms	Distances	Atoms	Distances
O20-C19	1.211(16)	C4-C5	1.537(14)
O30-C31	1.403(20)	C5-C10	1.564(13)
N1-C2	1.421(18)	C7-C8	1.504(14)
N1-C15	1.353(17)	C8-C9	1.547(12)
N6-C5	1.485(12)	C9-C10	1.521(13)
N6-C7	1.465(14)	C10-C11	1.546(13)
N6-C17	1.466(13)	C11-C12	1.410(15)
N18-C8	1.451(12)	C11-C16	1.351(16)
N18-C19	1.350(14)	C12-C13	1.434(15)
N21-C19	1.316(15)	C13-C14	1.350(19)
N21-C22	1.433(16)	C14-C15	1.395(18)
N21-C24	1.473(16)	C15-C16	1.419(15)
C2-C3	1.380(18)	C22-C23	1.449(15)
C3-C4	1.491(16)	C24-C251	1.420(25)
C3-C16	1.423(17)	C24-C252	1.410(28)
Atoms	Angles	Atoms	Angles
C2-N1-C15	110.6(1.0)	C9-C10-C11	112.9(8)
C7-N6-C17	109.5(8)	C5-C10-C11	110.2(7)
C5-N6-C17	111.5(7)	C10-C11-C16	115.8(9)
C5-N6-C7	111.1(8)	C10-C11-C12	126.1(9)
C8-N18-C19	119.8(9)	C12-C11-C16	118.0(9)
C22-N21-C24	114.2(9)	C11-C12-C13	116.4(1.0)
C19-N21-C24	120.5(1.0)	C12-C13-C14	125.5(1.1)
C19-N21-C22	125.2(1.0)	C13-C14-C15	117.2(1.1)
N1-C2-C3	106.9(1.1)	N1-C15-C14	134.9(1.1)
C2-C3-C16	107.7(1.0)	C14-C15-C16	118.3(1.1)
C2-C3-C4	131.7(1.1)	N1-C15-C16	106.8(1.0)
C4-C3-C16	120.6(1.0)	C11-C16-C15	124.6(1.1)
C3-C4-C5	109.2(9)	C3-C16-C15	108.0(1.0)
N6-C5-C4	110.1(8)	C3-C16-C11	127.4(1.0)
C4-C5-C10	113.4(8)	N18-C19-N21	117.5(1.1)
N6-C5-C10	107.7(7)	O20-C19-N21	121.1(1.2)
N6-C7-C8	113.9(8)	O20-C19-N18	121.3(1.1)
N18-C8-C7	111.6(8)	N21-C22-C23	117.5(1.0)
C7-C8-C9	107.4(8)	N21-C24-C252	113.8(1.3)
N18-C8-C9	111.8(7)	N21-C24-C251	116.4(1.3)
C8-C9-C10	111.1(7)	C251-C24-C252	129.6(1.7)
C5-C10-C9	111.1(7)		

Figure 1 shows the terguride methanol solvate molecule and the crystal packing is presented in Fig. 2. The basic structure of terguride is derived from the tetracyclic ring system designated as ergoline¹⁰. The atom numbering system corresponding to ergoline nomenclature was chosen, similarly to our published terguride-structure studies. The absolute configurations of the three chiral centres at C5(*R*), C8(*S*), C10(*R*) were fixed as described by Sauer et al.¹¹. The indole moiety of A and B rings of ergoline fragment is perfect planar. The χ^2 test value is 0.34 for pyrrole ring and 2.71 for benzene, respectively. The ring planes are almost parallel [dihedral angle equals $0.5(3)^\circ$]. The bond C2–C3 has the expected multiple bond character as follows from its bond order value

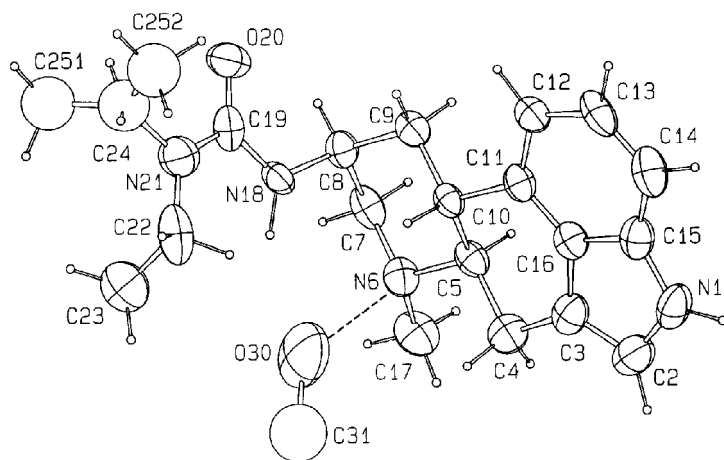


FIG. 1

An Ortepe view of terguride methanol solvate

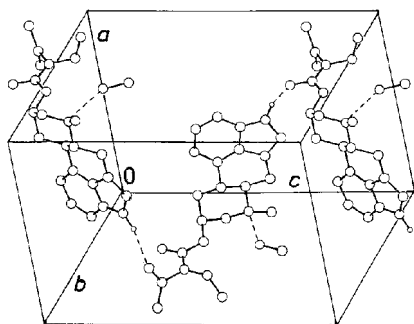


FIG. 2

Packing scheme. Dotted lines indicate H-bonds

of 1.66. Ring C (C4,C3,C16,C11,C10,C5) possesses an E_6 shape with C5 atom displaced by $-0.635(9)$ Å below the mean plane of remaining five atoms. Puckering parameters defined by Cremer and Pople¹² are $Q = 0.46(1)$ Å, $\phi = 110(2)^\circ$ and $\theta = 129(1)^\circ$. Ring D (C10,C5,N6,C7,C8,C9) has a 1C_4 conformation with $Q = 0.588(9)$ Å, $\phi = 81(3)^\circ$ and $\theta = 1.9(8)^\circ$, where C10 is pointing up by $0.690(9)$ Å and C7 pointing down by $-0.662(10)$ Å. Conformations of C and D rings of terguride methanol solvate are the same as those found in structures of terguride monohydrate and terguride hydrogen maleate monohydrate. Methanol is bonded through OH to N6 [O30...N6 = $2.810(13)$ Å] and the crystal is held together only by intermolecular linking N1-H...O20^{*i*} = $2.820(14)$ Å, where *i*: $-x + 1/2, -y, z + 1/2$.

Terguride methanol solvate immediately reacts with moisture in air to form terguride monohydrate, as found from powder diffraction study. This transformation probably proceeds through the transitional phase terguride methanol-hydrate. From the structural point of view it means that molecule CH_3OH is substituted by H_2O in the H-bond with N6 and water further interacts with the atoms O20 and N1 to form other H-bridges. After one hour contact of terguride methanol solvate with air moisture it was found 42% of terguride monohydrate to be formed. Transformation is complete during several hours. Figure 3 and Table IV show very good agreement between calculated and observed powder diffraction patterns of terguride methanol solvate and terguride monohydrate mixture, if we take into consideration re-ordering atom movement in the material studied.

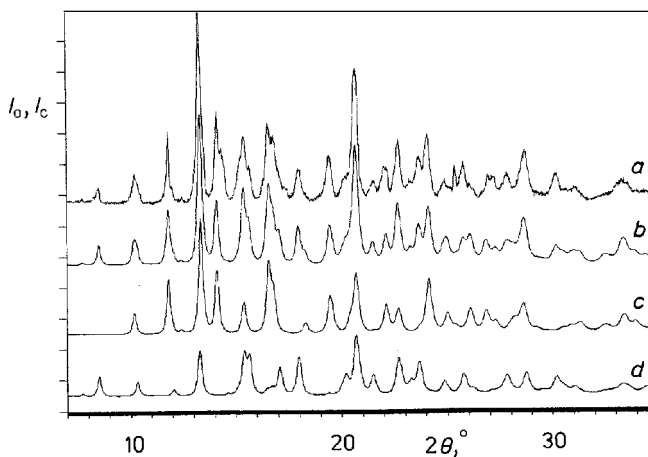


FIG. 3

X-Ray powder diagrams: *a* observed patterns for terguride methanol solvate–terguride monohydrate mixture, *b* calculated patterns for terguride methanol solvate–terguride monohydrate mixture, *c* calculated patterns for pure terguride methanol solvate, *d* calculated patterns for pure terguride monohydrate

TABLE IV

Powder patterns of mixture terguride methanol solvate with terguride monohydrate including the transition phase terguride methanol-hydrate. Values d_c are related to lattice parameters refined from powder data. Values I_c for terguride monohydrate in mixture are related to those pure terguride methanol solvate

No.	h	k	l	$d_o, \text{Å}$	$d_c, \text{Å}$	I_o	I_c	Phase
1	2	0	-1	12.08	12.07	7	15	B
2	0	1	1	10.06	10.09	14	16	G
3	1	0	1	8.68	8.69	35	45	G
4	0	0	2	7.72	7.69	100	100	G
	1	1	0		7.74		40	B
5	1	1	1	7.27	7.28	46	56	G
6				7.16		27		GB
7	0	2	0	6.66	6.68	33	24	G
	0	1	2		6.67		6	G
	3	1	0		6.68		29	B
8	1	1	1	6.56	6.57	17	32	B
9	1	0	2	6.21	6.21	40	63	G
10	0	2	1	6.13	6.13	34	34	G
11				5.95		7		GB
12	3	1	1	5.73	5.73	16	38	B
13	1	2	1	5.29	5.30	23	34	G
14	6	0	-2	5.10	5.10	11	18	B
15	2	0	1	4.98	4.98	67	63	G
16	5	1	1	4.79	4.80	9	22	B
	0	1	3		4.79		2	G
17	2	1	1	4.68	4.67	17	31	G
18	1	2	2	4.54	4.55	30	27	G
	5	1	-2		4.55		37	B
19	7	1	0	4.45	4.44	9	6	B
20	4	0	-3	4.36	4.36	21	38	B
	1	1	3		4.36		3	G
21	0	3	1	4.28	4.29	34	65	G
22	2	2	0	4.15	4.13	9	15	G
	6	0	2		4.16		15	B
23	0	2	3	4.07	4.07	17	6	G
24	7	1	-2	4.01	4.01	17	14	B
25	1	3	1	3.97	3.96	7	28	G
26	0	3	2	3.84	3.85	12	26	G

TABLE IV
(Continued)

No.	h	k	l	$d_o, \text{\AA}$	$d_c, \text{\AA}$	I_o	I_c	Phase
27	1	2	3	3.80	3.79	11	13	G
28	5	1	-3	3.71	3.71	13	12	B
	4	0	3		3.73		11	B
	0	1	4		3.69		9	G
29	1	3	2	3.61	3.62	24	30	G
	1	0	4		3.61		5	G
	8	0	-3		3.61		27	B
30	8	0	2	3.51	3.52	3	2	B
	9	1	-2		3.50		2	B
31	7	1	-3	3.43	3.44	13	18	B
32	6	2	0	3.34	3.34	6	7	B
	3	1	1		3.31		12	G
33	9	1	-3	3.12	3.12	10	6	B
	1	4	1		3.12		16	G

I_o observed intensity of component in mixture; I_c calculated intensity of component in mixture; B terguride monohydrate; G terguride methanol solvate; GB terguride methanol-hydrate.

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