CRYSTAL STRUCTURES OF ERGOT ALKALOID DERIVATIVES. ERGOMETRINE MALEATE AND METHYLERGOMETRINE MALEATE

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Dedicated to Professor Jaroslav Podlaha on the occasion of his 60th birthday.

Two ergot alkaloid derivatives were examined by X-ray diffraction techniques. The crystal and molecular structure of ergometrine maleate (**1**) was evaluated from single-crystal data and the molecular structure of related methylergometrine maleate (**2**) was obtained by molecular modelling. The measured and calculated X-ray powder patterns of **1** and **2** were compared. Derivative **1** crystallizes in the orthorhombic space group $P2_12_12_1$ with a = 5.7112(7) Å, b = 12.337(2) Å, c = 33.276(6) Å, Z = 4, V = 2 344.5(6) Å^3. Derivative **2** is nearly isostructural with **1**, it has slightly expanded unit cell, a = 5.724(2) Å, b = 12.762(6) Å, c = 33.25(2) Å, Z = 4, V = 2 428(1) Å^3. No effect of an additional methyl group on the molecular packing of **2** was found.

Key words: Ergot alkaloids; Ergometrine; Methylergometrine; X-Ray crystal structure.

Ergometrine[1–4] **1a** (ergonovine, ergobasine) is a natural ergot alkaloid derived from (+)-lysergic acid and (*S*)-(+)-2-amino-1-propanol (L-alaninol). Methylergometrine **2a** is its synthetic analogue[5] containing (*S*)-(+)-2-amino-1-butanol. The stimulation of uterine motor activity is the oldest therapeutic use of both these compounds[6]. They enhance all three components of uterine contractibility: frequency and amplitude of contractions, and basal tone. Accordingly, the management and prevention of post-partum haemorrhage is still among the most important therapeutic uses of both metrins[7,8]. Functional studies suggested, that the stimulatory effect in rat uterus is mediated via 5-HT_{2A} receptors[9]. Both metrins exhibit also affinity at vascular 5-HT_1-like receptors and a weak activity at α-adrenoreceptors. A detailed mechanism of action in various tissues, how-

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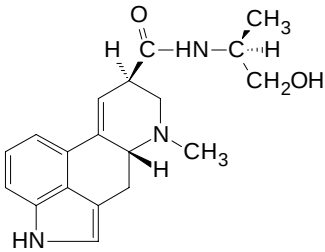
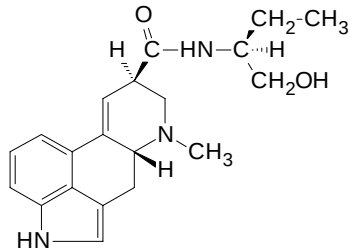
ever, is still waiting to be clarified. This paper is a continuation-in-part of our systematic study of the structure and polymorphism of ergot alkaloids[10–19].



1a



2a

EXPERIMENTAL

Preparation of Crystals

Ergometrine maleate (**1**) and methylergometrine maleate (**2**) were from Galena Co. (Czech Republic). Single crystals of **1** were obtained by slow evaporation of saturated solution of **1** in methanol at ambient temperature. Crystallization of **1** or **2** from various solvents (alcohols, acetic acid esters, acetone, dioxane, dimethyl sulfoxide) did not prove any polymorphism and hair-like long needle crystals were obtained in all cases.

Single Crystal Structure Determination of **1**

Ergometrine maleate, $C_{19}H_{23}N_3O_2 \cdot C_4H_4O_4$, m.w. 441.5, orthorhombic system, space group $P2_12_12_1$ (No. 19), a = 5.7112(7) Å, b = 12.337(2) Å, c = 33.276(6) Å, V = 2 344.5(6) Å^3, Z = 4, D_{calc} = 1.251 g cm^{-3}, μ(CuKα) = 0.07 mm^{-1}, F(000) = 936.

The structure of **1** was solved by direct methods and subsequent Fourier techniques. All non-H atoms were refined anisotropically by full-matrix least-squares based on F-values. The coordinates of all H-atoms (found from the difference map) and their thermal parameters were refined isotropically (except C18, C19, C52 and C53 hydrogens fixed in bond distances from carbon partners). One acid hydrogen of the maleic acid is attached to N2, the second one was not found. Data collection and refinement parameters are listed in Table I.

Molecular Modelling of **2**

Methylergometrine maleate, $C_{20}H_{25}N_3O_2 \cdot C_4H_4O_4$, m.w. 455.5, orthorhombic system, space group $P2_12_12_1$ (No. 19), a = 5.724(2) Å, b = 12.762(6) Å, c = 33.25(2) Å, V = 2 428(1) Å^3.

Since the single crystals of **2** were not available, the position of an additional methyl group in the molecule of **2** was obtained by the molecular modelling. The global minimum at 84° for the torsion angle C19–C17–C18–C(additional methyl) was obtained using the expected geometry and the calculation of van der Waals interactions by the program MOLDRAW (ref.[20]). For the calculation of the energetic changes the Buckingham potential calculated according to the atoms surrounding C18 (r = 5 Å) was used.

Powder Diffraction Study of **1** and **2**

X-Ray powder patterns of **1** and **2** were collected on a Seifert diffractometer XRD 3000 P with a Bragg–Brentano focusing geometry. CoKα radiation monochromatized with a graphite monochromator was used. The crystal structure of **2** was evaluated from the powder diffraction patterns of **1**. The atomic coordinates of **1** supplemented with the methyl group were used for the calculation of the theoretical powder patterns of **2**. Indexing of diffractogram of **2** was taken from that calculated for **1**. The shape function and lattice parameters of **2** were refined with DBWS-PC program[21].

RESULTS AND DISCUSSION

For the therapeutic purposes ergometrine and methylergometrine are used in the form of their maleates. From all solvents we tested, these maleates crystallize in a form of extremly thin, hair-like needle crystals which are far from to be good candidates for the

TABLE I
Data collection and refinement parameters

Crystal dimensions	0.53 × 0.14 × 0.14 mm
Diffractometer and radiation used	Enraf-Nonius CAD4, λ(CuKα) = 1.54056 Å
Scan technique	ω/2θ
Temperature	293 K
No. and θ range of reflections for lattice parameter refinement	20; 35–40°
Range of *h*, *k* and *l*	0→5, 0→12, –32→32
Standard reflections monitored in interval; intensity fluctuation	60 min; –1.5%
Total number of reflections measured; 2θ range	2 746; 5–100°
No. of observed reflections	2 724
Criterion for observed reflections	$I \geq 1.96\sigma(I)$
Function minimized	$w(\|F_o\| - \|F_c\|)^2$
Weighting scheme	$w = w'(1 - (\Delta\frac{F}{6}\,\Delta F_{est})^2)^2 w' =$ $1/[A_0T_0'(X) + A_1T_1'(X) \ldots + A_{n-1}T_{n-1}'(X)]$, where $X = F_o/F_o(\max)$ $A_0 = 1.92(8)$, $A_1 = 2.1(1)$, $A_2 = 1.34(6)$ (ref.[23])
Parameters refined	365
Value of *R*, *wR*, and *S*	0.0583, 0.0529, 0.9572
Ratio of max. least-squares shift to e.s.d. in the last cycle	0.0377
Max. and min. heights in final Δρ map	0.290, –0.218 eÅ^{-3}
Source of atomic scattering factors	International Tables for X-Ray Crystallography[24]
Programs used	CRYSTALS (ref.[25]), PARST (ref.[26]), SIR 92 (ref.[27])

TABLE II
Final atomic parameters with e.s.d's in parentheses. $U_{eq} = \frac{1}{3}\sum_i \sum_j U_{ij}\, a_i^* a_j^*\, \boldsymbol{a}_i.\boldsymbol{a}_j$

Atom	*x*	*y*	*z*	U_{eq}, Å^2
N1	0.2803(8)	0.2793(3)	0.8028(1)	0.067(1)
N2	–0.2490(6)	0.2342(3)	0.6478(1)	0.050(1)
N3	–0.0392(8)	–0.1103(3)	0.5866(1)	0.061(1)
O1	–0.3516(5)	–0.0918(2)	0.62726(7)	0.0544(9)
O2	0.318(1)	–0.2595(5)	0.6173(2)	0.125(2)
O101	–0.3110(6)	0.4175(5)	0.4937(1)	0.124(2)
O102	–0.1242(6)	0.5027(4)	0.4471(1)	0.099(2)
O103	0.0719(6)	0.3228(3)	0.5993(1)	0.081(1)
O104	–0.2284(6)	0.3355(5)	0.5581(1)	0.121(2)
C1	0.115(1)	0.3377(4)	0.7812(1)	0.067(2)
C2	0.0678(7)	0.2861(3)	0.7461(1)	0.051(1)
C3	–0.0734(9)	0.3127(3)	0.7098(1)	0.055(2)
C4	–0.1440(7)	0.2081(3)	0.6882(1)	0.045(1)
C5	–0.3189(8)	0.1339(4)	0.6264(1)	0.054(2)
C6	–0.1100(7)	0.0651(3)	0.6157(1)	0.048(1)
C7	0.0671(7)	0.0659(3)	0.6492(1)	0.043(1)
C8	0.0536(6)	0.1255(3)	0.6823(1)	0.039(1)
C9	0.2162(6)	0.1117(3)	0.7164(1)	0.039(1)
C10	0.3719(8)	0.0279(3)	0.7234(1)	0.049(1)
C11	0.5111(9)	0.0274(5)	0.7585(1)	0.062(2)
C12	0.4958(9)	0.1059(4)	0.7870(2)	0.060(2)
C13	0.3403(8)	0.1886(3)	0.7815(1)	0.054(2)
C14	0.2074(7)	0.1922(3)	0.7457(1)	0.045(1)
C15	–0.450(1)	0.3085(5)	0.6505(2)	0.063(2)
C16	–0.1818(8)	–0.0523(3)	0.6096(1)	0.048(1)
C17	–0.0505(9)	–0.2265(4)	0.5813(2)	0.068(2)
C18	–0.162(2)	–0.2561(7)	0.5413(2)	0.136(3)
C19	0.192(2)	–0.2759(5)	0.5833(3)	0.119(3)
C101	–0.1217(8)	0.4536(4)	0.4791(1)	0.063(2)
C102	0.0985(8)	0.4325(5)	0.4996(1)	0.078(2)
C103	0.1431(9)	0.3884(5)	0.5347(1)	0.081(2)
C104	–0.0146(8)	0.3494(4)	0.5661(2)	0.068(2)

TABLE III
Bond distances (Å) and angles (°) with e.s.d.'s in parentheses and the list of the hydrogen bonds

Atoms	Distances	Atoms	Distances
N1–C1	1.387(7)	C4–C8	1.533(5)
N1–C13	1.369(6)	C5–C6	1.506(6)
N2–C4	1.507(5)	C6–C7	1.505(6)
N2–C5	1.484(6)	C6–C16	1.519(6)
N2–C15	1.472(6)	C7–C8	1.326(5)
N3–C16	1.329(6)	C8–C9	1.476(5)
N3–C17	1.445(7)	C9–C10	1.384(6)
O1–C16	1.233(5)	C9–C14	1.391(5)
O2–C19	1.362(9)	C10–C11	1.412(6)
O101–C101	1.267(6)	C11–C12	1.358(7)
O102–C101	1.224(5)	C12–C13	1.366(6)
O103–C104	1.255(6)	C13–C14	1.413(6)
O104–C104	1.261(6)	C17–C18	1.519(8)
C1–C2	1.358(6)	C17–C19	1.50(1)
C2–C3	1.488(6)	C101–C102	1.454(7)
C2–C14	1.406(5)	C102–C103	1.314(7)
C3–C4	1.531(6)	C103–C104	1.461(7)
Atoms	**Angles**	**Atoms**	**Angles**
C1–N1–C13	109.9(4)	C9–C10–C11	120.3(4)
C4–N2–C5	111.0(3)	C10–C11–C12	122.6(5)
C4–N2–C15	112.9(4)	C11–C12–C13	118.7(5)
C5–N2–C15	109.8(4)	N1–C13–C12	134.7(4)
C116–N3–C17	125.2(5)	N1–C13–C14	106(4)
N1–C1–C2	109.8(4)	C12–C13–C14	119.2(4)
C1–C2–C3	134.6(4)	C2–C14–C9	127.9(3)
C1–C2–C14	106.3(4)	C2–C14–C13	108.8(3)
C3–C2–C14	118.8(3)	C9–C14–C13	123.2(4)
C2–C3–C4	109.7(3)	N3–C16–O1	122.9(4)
N2–C4–C3	110.0(3)	N3–C16–C6	115.2(4)
N2–C4–C8	108.7(3)	O1–C16–C6	121.7(4)
C3–C4–C8	115.3(3)	N3–C17–C18	111.3(5)
N2–C5–C6	111.7(3)	N3–C17–C19	110.9(5)
C5–C6–C7	110.8(3)	C18–C17–C19	108.8(5)
C5–C6–C16	110.8(4)	O2–C19–C17	117.9(7)
C7–C6–C16	106.6(3)	O101–C101–O102	119.9(4)
C6–C7–C8	125.4(4)	O101–C101–C102	119.7(3)

TABLE III
(*Continued*)

Atoms	Angles	Atoms	Angles
C4–C8–C7	121.2(3)	O102–C101–C102	120.4(4)
C4–C8–C9	116.1(3)	C101–C102–C103	131.4(4)
C7–C8–C9	122.6(3)	C102–C103–C104	130.7(5)
C8–C9–C10	128.3(3)	O103–C104–O104	122.1(4)
C8–C9–C14	115.7(3)	O103–C104–C103	118.2(4)
C10–C9–C14	116.0(3)	O104–C104–C103	119.4(5)

Hydrogen bonds

D	H	A	D...A, Å	D–H...A, Å	Symmetry code		
N2	HN2	O103	2.67(2)	159(9)	*x*	*y*	*z*
N1	HN1	O1	2.84(3)	151(6)	–*x*	*y* + 1/2	–*z* + 3/2
N3	HN3	O102	2.94(1)	163(14)	*x* + 1	*y*	*z*

single X-ray crystal study. Thus, despite the molecule is small and simple, the proper choice of a suitable crystal has made a considerable inroad upon our time.

The final positional and thermal parameters of the non-H atoms of ergometrine maleate are listed in Table II, bond distances and angles in Table III. The ergoline A and

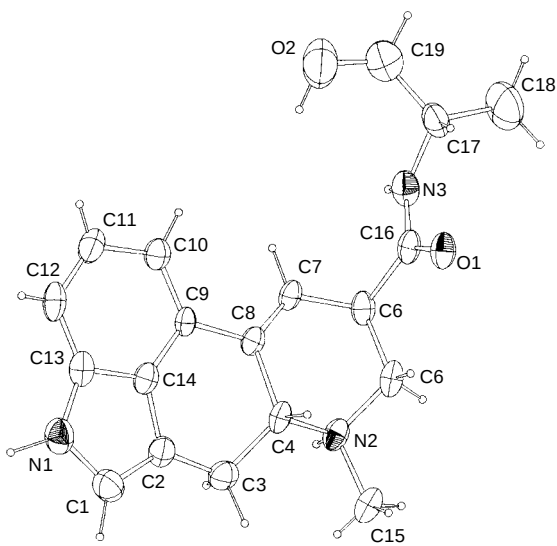


FIG. 1
The ORTEP drawing of protonated ergometrine (maleate anion was deled) with the atom numbering

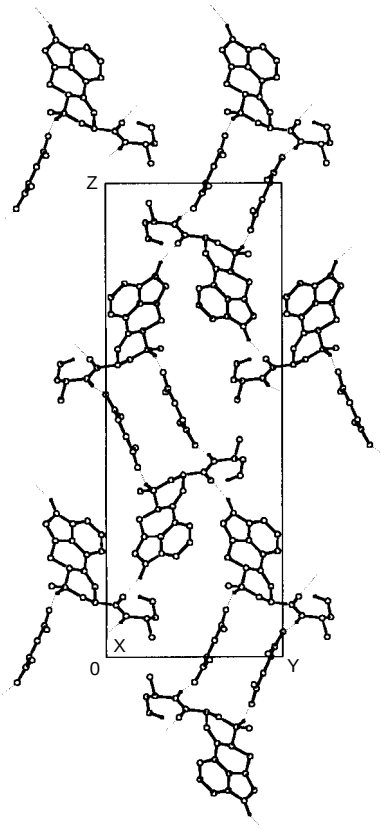


FIG. 2
Packing scheme of ergometrine maleate. Dotted lines represent hydrogen bonds

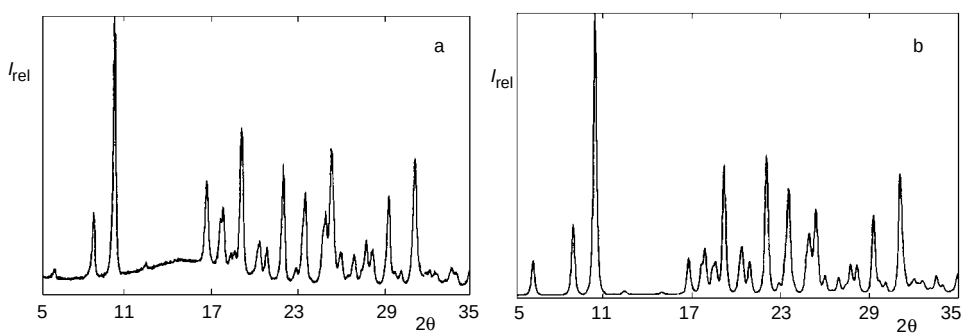


FIG. 3
Comparison of experimentally obtained powder patterns of ergometrine maleate (a) with the theoretical powder patterns (b) calculated from the single-crystal data

B rings, forming the indole moiety, are nearly planar (χ test values are 5.99 and 7.81, respectively). The dihedral angle between these two planes is 1.5(4)°. Ring C (C8,C9,C14,C2,C3,C4) possesses E_6 conformation (puckering parameters according to Cremer and Pople[22] are Q = 0.38(1) Å, ϕ = –79(3)°, θ = 52(2)°). Ring D (C4,N2,C5, C6,C7,C8) with the protonized N2 (found from the Fourier map) has usual $^2H_3$ (*E*, flap-up) conformation (Q = 0.51(1) Å, ϕ = 16(2)°, θ = 53(1)°). The torsion angles about the C/D ring junction C3–C4–C8–C7 and N2–C4–C8–C9 are –143(1)° and 165(1)°, respectively.

Apart from the 9-ergolene skeleton which is almost rigid for all ergot alkaloids, the amide side chain has a fairly large number of conformation freedom. Rotations around formal single bonds are described by torsion angles values (see Fig. 1 for the consecutive numbering system used here and Tables III and IV for the correlation with the chemical numbering): C7–C6–C16–N3 = –83(2)°, C7–C6–C16–O1 = 92(2)°, C6–C16–N3–C17 (ω) = 170(2)°, C16–N3–C17–C18 = 103(2)°, C16–N3–C17–C19 = –136(2)°, N3–C17–C19–O2 = 58(3)°. The values obtained indicate, that similarly as in ergopeptine alkaloids, the amide possesses a nearly planar *trans* configuration. The packing of ergometrine maleate molecules in the structure is shown in Fig. 2. The complex system of hydrogen bonds forms two-dimensional network, viewed along the X direction. The summary of hydrogen bonds is listed in Table III.

The theoretical and experimental powder patterns fit well for both ergometrine maleate, Fig. 3 and methylergtometrine maleate, Fig. 4 (proposed model derived from the former structure using molecular modelling).

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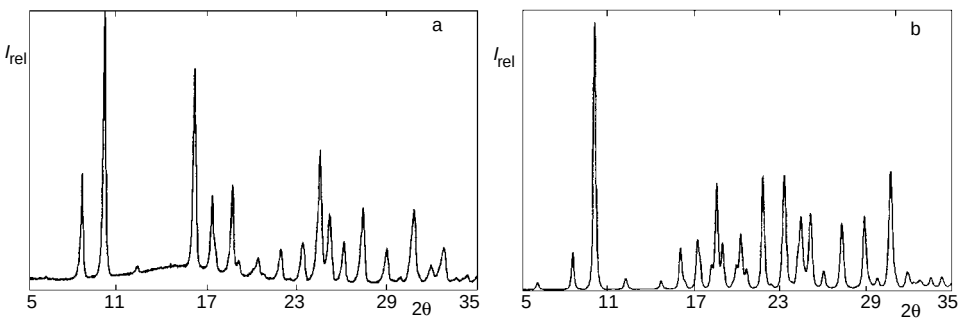

FIG. 4

Comparison of experimentally obtained powder patterns of methylergometrine maleate (a) with the theoretical powder patterns (b) calculated from the single-crystal data of ergometrine maleate supplemented with the positional parameters of the methyl group obtained by the molecular modelling

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