A CONFORMATIONAL STUDY OF THE SEMISYNTHETIC ERGOT ALKALOID – TERGURIDE

Michal HUŠÁK[a], Bohumil KRATOCHVÍL[a], Petr SEDMERA[b], Josef STUCHLÍK[c]
and Alexandr JEGOROV[d,]*

[a] Department of Solid State Chemistry,
Prague Institute of Chemical Technology, 166 28 Prague 6, The Czech Republic
[b] Institute of Microbiology,
Academy of Sciences of the Czech Republic, 142 20 Prague 4, The Czech Republic
[c] Galena Co., R. & D., 747 70 Opava-Komárov, The Czech Republic
[d] Galena Co., Research Unit, 370 05 České Budějovice, The Czech Republic

Received June 7, 1993
Accepted October 4, 1993

Conformational analyses studied by 2D NMR techniques and X-ray diffraction methods are reported for the semisynthetic ergot alkaloid – terguride, in the form of free base and as the protonated species. The structure of terguride hydrogen maleate monohydrate $(C_{20}H_{29}N_4O)^+(C_4H_3O_4)^- \cdot H_2O$ (*II*) was solved by direct methods and refined anisotropically to an *R* value of 0.068 for 1 991 unique observed reflections. The title compound crystallizes in the triclinic space group *P1* with lattice parameters $a = 7.061(2)$, $b = 9.205(1)$, $c = 12.223(4)$ Å, $\alpha = 96.36(2)$, $\beta = 107.15(2)$, $\gamma = 106.67(1)°$. Studies revealed that terguride monohydrate (*I*) and its protonized form (terguride hydrogen maleate monohydrate) possesses the identical conformations both in solution and in the solid state – an envelope for C and a chair for D ergoline rings.

Terguride (1,1-diethyl-3-[(5*R*,8*S*,10*R*)-6-methyl-8-ergolinyl]urea, *trans*-dihydrolisuride, Scheme 1) is a semisynthetic ergot derivative which was first synthesized by Semonský and coworkers[1]. It acts as a partial dopaminergic antagonist with antiparkinsonian efficacy, as prolactin inhibitor is effective in treatment of pathological and pospartum hyperprolactinaemia and exhibits stimulating effect on secretion of gonadotropins[2]. To increase its solubility, terguride can be alternatively applied in a form of its hydrogen phosphate[3] or hydrogen maleate (Mysalfon$^{(R)}$).

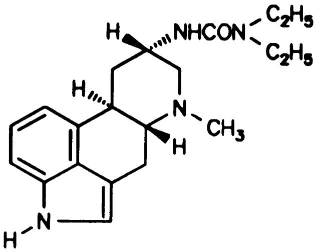
Obviously the D ring of 9,10-ergolene[4] as well as ergoline[5] derivatives may assume conformations which differ in the spacial orientation of the N6 atom depending on its, i.e. ionic or neutral, state. Among the criteria proposed for the biological activity of ergot derivatives the orientation of this atom was considered to play the crucial import-

---

* The author to whom correspondence should be addressed.

ance[6]. Hence, one may speculate, if the biological effectivness of some ergot alkaloids might be influenced by the pH at the particular biological milieu.

The aim of this paper is to compare the conformation of terguride in the form of free base[7] and its hydrogen maleate in solution and the solid state.



SCHEME 1

EXPERIMENTAL

Preparation of Crystals

Terguride monohydrate (*I*) and terguride hydrogen maleate monohydrate (*II*) were from Galena Co. (The Czech Republic). Single crystals of *II* were obtained by the slow cooling of its hot solution in 96% ethanol (800 mg per 10 ml). Crystals were washed with acetone and dried in air.

X-Ray Structure Determination of *II*

Space group $P1$ (No. 1) , a = 7.061(2), b = 9.205(1), c = 12.223(4) Å, α = 96.36(2), β = 107.15(2), γ = 106.67(1)°, V = 622.0(3) Å^3, Z = 1, D_{calc} = 1.267, D_{exp} = 1.26(1) g cm^{-3}, μ(MoKα) = 0.09 mm^{-1}, F(000) = 254. The density was determined by flotation in aqueous solution of NaCl and structure solved by direct methods. All non-H atoms were refined anisotropically by full-matrix least-squares (LS) based on F_o values. The sum of x, sum of y and sum of z of all atoms were held constant for fixation of the origin. The C-bonded hydrogens were included in calculated positions (C–H = 1.00 Å) with fixed U_{iso} values equal to U_{eq} values of the attached carbons. The N-bonded hydrogen positions were found from the difference electron density map and held fixed during refinement with U_{iso} = 0.05. The maleate OH-hydrogen was not successful to find. Because during refinement a geometry of ethyl group C24–C25 became unrealistic, their bond lenghts were restrained. The theoretical values 1.475(1) Å for N21–C24 and 1.422(1) Å for C24–C25 were taken for calculating weights in the restrain procedure (see program CRYSTALS, ref.[8]). The difference electron density synthesis revealed the presence of a water molecule, similarly as for *I*. The parameters for data collection and refinement are listed in Table I.

NMR Measurements

^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (observing frequency 399.95 and 100.577 MHz, respectively) in $CDCl_3$ (*I*) and $(CD_3)_2SO$ (*II*) at 25 °C. Residual solvent resonance served as an internal standard ($CDCl_3$ δ_H 7.265, δ_C 77.00; $(CH_3)_2SO$ δ_H 2.500, δ_C 39.60).

Digital resolution in 1D ^{1}H and ^{13}C NMR spectra was 0.0003 and 0.006 ppm, respectively. 2D NMR experiments – J-resolved (HOM2DJ), COSY, delay-COSY (ref.[14]), NOESY, ROESY (ref.[15]), and $^{1}H,^{13}C$-COSY (HETCOR) – were performed using the manufacturer's software. Data tables were 4 K × 0.5 K (HOM2DJ, HETCOR), 2 K × 2 K (COSY, delay-COSY), and 1 K × 1 K (phase-sensitive NOESY and ROESY), where K means 1 024 data points.

TABLE I
Data collection and structure refinement parameters *(II)*

Crystal dimensions	0.8 × 0.5 × 0.6 mm
Diffractometer and radiation used	Enraf–Nonius CAD4, graphite monochromator, Mo$K\alpha$, $\lambda = 0.71073$ Å
Scan technique	$\omega/2\theta$
Temperature	293 K
Number and θ range of reflections for lattice parameter refinement	20; 19 – 20°
Range of h, k and l	-8 → 8,-10 → 10, -14 → 14
Standard reflections monitored in interval; intensity fluctuation	120 min; -1.3%
Total number of reflections measured; 2θ range	4 275; 0 → 50°
Value of R_{int}	0.019
Number of unique observed reflections	1 991
Criterion for observed reflections	$I \geq 1.96\,\sigma(I)$
Function minimized	$\Sigma w(\lvert F_o\rvert - \lvert F_c\rvert)^2$
Weighting scheme	$w = [\sigma^2(F_o)]^{-1}$
Parameters refined	307
Value of R, wR and S	0.068; 0.068; 3.63
Ratio of max. LS shift to e.s.d. in the last cycle	0.04
Max. and min. heights in final $\Delta\rho$ map	0.53, -0.26 e Å^{-3}
Source of atomic scattering factors	Ref.[9]
Programs used	CRYSTALS (ref.[8]), SDP (ref.[10]), PARST (ref.[11]), SHELXS86 (ref.[12]), MOLDRAW (ref.[13])
Computer used	PDP 11/73, PC AT 386

RESULTS AND DISCUSSION

X-Ray Analysis and Conformation in the Solid State

The final positional and thermal parameters of the non-H atoms of *II* are summarized in Table II. Bond distances for *I* and *II* are compared in Table III. Figure 1 shows the molecule of *II* and its crystal packing is presented in Fig. 2.

The basic structure of terguride is derived from the tetracyclic ring system designated as ergoline[16]. The atom numbering system corresponding to ergoline nomenclature was chosen, similarly to our previous terguride monohydrate (*I*) structure study[7]. The pyrrole moiety (N1,C2,C3,C16,C15) is nearly planar (χ^2 = 2.91), the displacements are from −0.007(7) Å for C16 and C2 to 0.008(8) Å for C3. The bond C2–C3 has expected multiple bond character as follows from its bond order value of 1.72. The largest deviations, out of the benzene plane (C11,C12,C13,C14, C15,C16) being −0.0099(72) Å at C11 and 0.008(7) Å at C16; χ^2 = 4.18. The dihedral angle of these two planes is 1.47(2)°. The C ring (C3,C4,C5,C10,C11,C16), according to ergoline nomenclature, possesses the ^3E conformation, puckering parameters are Q = 0.475(7) Å, ϕ = −50(1)° and θ = 127.7(8)°. The C5 atom is displaced from the plane of remaining five atoms by 0.650(7) Å. The D ring (C5,C10,C9,C8,C7,N6) adopts almost the perfect chair conformation $^1C_4$ with puckering parameters Q = 0.566(7) Å, ϕ= −124(6)° and θ = 1.61(7)°. The C8 atom is pointing down by −0.662(7) Å and the C5 atom is pointing up by 0.680(7) Å. Conformations of C and D rings found for the title compound (*II*) are practically the same as those found for molecule *A* of *I* (molecule *B* has for D ring also

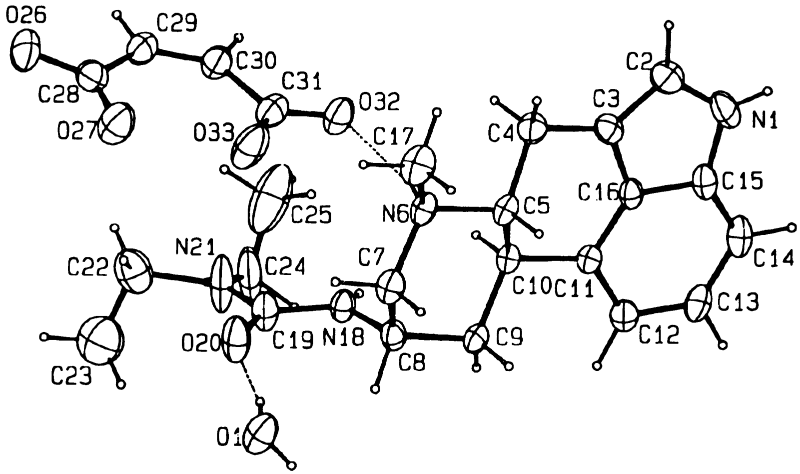


FIG. 1

An ORTEP drawing of terguride hydrogen maleate monohydrate (*II*). Thermal ellipsoids are drawn at the 50% probability

TABLE II
Atomic coordinates for non-H atoms and their equivalent isotropic thermal parameters (*II*) with e.s.d.'s in parentheses
$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i \cdot \mathbf{a}_j$

Atom	*x*	*y*	*z*	U_{eq}, Å^2
O1(water)	−0.357(1)	0.4128(8)	0.0749(5)	0.061(2)
O20	0.126(1)	0.4909(7)	0.2432(5)	0.061(2)
O26	0.599(1)	0.4706(8)	0.8364(6)	0.078(3)
O27	0.306(1)	0.3616(9)	0.6210(6)	0.078(3)
O32	0.465(1)	0.1554(7)	0.3599(5)	0.061(2)
O33	0.249(1)	0.2189(9)	0.4214(6)	0.075(3)
N1	0.330(1)	−0.3584(8)	−0.1418(7)	0.057(3)
N6	0.033(1)	0.0297(7)	0.1193(5)	0.040(2)
N18	0.2836(9)	0.3786(7)	0.1546(5)	0.040(2)
N21	0.533(1)	0.5859(9)	0.3551(7)	0.061(3)
C2	0.292(1)	−0.3576(9)	−0.0416(8)	0.056(2)
C3	0.240(1)	−0.2291(8)	−0.0214(7)	0.043(3)
C4	0.185(1)	−0.1637(8)	0.0725(7)	0.048(3)
C5	0.057(1)	−0.0542(8)	0.0151(6)	0.039(2)
C7	−0.085(1)	0.1432(9)	0.0752(7)	0.047(3)
C8	0.043(1)	0.2681(8)	0.0384(7)	0.042(2)
C9	0.068(1)	0.1883(8)	−0.0682(6)	0.040(2)
C10	0.190(1)	0.0745(7)	−0.0211(6)	0.036(2)
C11	0.224(1)	−0.0053(8)	−0.1228(6)	0.038(2)
C12	0.244(1)	0.0513(9)	−0.2189(7)	0.052(3)
C13	0.298(1)	−0.033(1)	−0.2960(8)	0.054(3)
C14	0.330(1)	−0.173(1)	−0.2812(8)	0.054(3)
C15	0.307(1)	−0.2302(8)	−0.1870(7)	0.047(3)
C16	0.252(1)	−0.1468(8)	−0.1105(6)	0.039(2)
C17	−0.105(1)	−0.089(1)	0.1544(8)	0.059(3)
C19	0.306(1)	0.486(1)	0.2511(8)	0.054(4)
C22	0.568(2)	0.683(1)	0.484(1)	0.083(4)
C23	0.551(2)	0.824(1)	0.459(1)	0.112(6)
C24	0.757(2)	0.629(1)	0.351(1)	0.088(5)
C25	0.846(2)	0.521(1)	0.406(1)	0.116(6)
C28	0.522(2)	0.403(1)	0.7187(9)	0.061(4)
C29	0.701(2)	0.374(1)	0.6988(8)	0.058(3)
C30	0.672(1)	0.297(1)	0.5867(7)	0.055(3)
C31	0.447(1)	0.217(1)	0.4474(7)	0.057(3)

TABLE III

A comparison of bond distances (Å) for terguride monohydrate (*I*) and terguride hydrogen maleate monohydrate (*II*); bond angles for terguride hydrogen maleate monohydrate (°) and hydrogen bonds for terguride hydrogen maleate monohydrate with e.s.d.'s in parentheses

Atoms	Distances		
	II	*I*[a]	
		A molecule	*B* molecule
C2–C3	1.368(9)	1.361(7)	1.365(6)
N1–C2	1.38(1)	1.377(6)	1.376(8)
N1–C15	1.37(1)	1.366(8)	1.375(8)
C15–C16	1.410(9)	1.391(5)	1.387(6)
C3–C16	1.418(9)	1.390(7)	1.441(8)
C3–C4	1.505(9)	1.519(6)	1.476(6)
C4–C5	1.537(9)	1.532(7)	1.539(7)
C5–C10	1.546(8)	1.563(6)	1.547(7)
C10–C11	1.531(8)	1.531(5)	1.518(6)
C11–C16	1.386(9)	1.410(7)	1.387(6)
C14–C15	1.38(1)	1.416(8)	1.383(9)
C13–C14	1.38(1)	1.342(9)	1.385(9)
C12–C13	1.416(9)	1.384(5)	1.426(8)
C11–C12	1.391(9)	1.365(7)	1.376(8)
C9–C10	1.525(8)	1.537(6)	1.526(6)
C8–C9	1.537(8)	1.530(5)	1.534(6)
C7–C8	1.51(1)	1.494(8)	1.515(9)
N6–C7	1.497(9)	1.481(7)	1.460(7)
N6–C5	1.524(8)	1.474(5)	1.478(5)
N6–C17	1.501(9)	1.472(8)	1.482(8)
N18–C8	1.472(8)	1.443(7)	1.463(7)
N18–C19	1.363(8)	1.352(7)	1.342(7)
O20–C19	1.237(9)	1.257(7)	1.239(6)
N21–C19	1.360(9)	1.321(7)	1.334(6)
N21–C22	1.59(1)	1.47(1)	1.477(9)
N21–C24	1.540(9)	1.47(1)	1.463(9)
C24–C25	1.379(9)	1.40(2)	1.47(1)
C22–C23	1.39(1)	1.44(1)	1.44(1)
O26–C28	1.251(9)		
O27–C28	1.27(1)		
O32–C31	1.238(9)		
O33–C31	1.269(9)		
C28–C29	1.49(1)		
C29–C30	1.35(1)		
C30–C31	1.50(1)		

TABLE III
(*Continued*)

II

Atoms	Angles	Atoms	Angles
C3–C2–N1	108.7(7)	C16–C11–C10	114.8(6)
C15–N1–C2	110.5(6)	C16–C11–C12	117.0(6)
C7–N6–C5	112.9(5)	C13–C12–C11	119.8(7)
C17–N6–C5	110.8(5)	C14–C13–C12	122.8(7)
C17–N6–C7	109.2(6)	C15–C14–C13	117.5(7)
C19–N18–C8	119.8(5)	C14–C15–N1	134.7(7)
C22–N21–C19	117.8(7)	C16–C15–N1	105.4(6)
C24–N21–C19	125.1(7)	C16–C15–C14	119.9(7)
C24–N21–C22	116.7(7)	C11–C16–C3	128.0(6)
C4–C3–C2	134.0(7)	C15–C16–C3	108.9(6)
C16–C3–C2	106.5(6)	C15–C16–C11	123.0(7)
C16–C3–C4	119.4(6)	N18–C19–O20	120.8(7)
C5–C4–C3	108.5(6)	N21–C19–O20	122.3(7)
C4–C5–N6	108.3(5)	N21–C19–N18	116.9(7)
C10–C5–N6	108.3(5)	C23–C22–N21	103.5(10)
C10–C5–C4	113.8(5)	C25–C24–N21	100.7(11)
C8–C7–N6	112.7(6)	O27–C28–O26	122.8(8)
C7–C8–N18	112.5(6)	C29–C28–O26	115.9(9)
C9–C8–N18	108.8(5)	C29–C28–O27	121.3(7)
C9–C8–C7	110.3(6)	C30–C29–C28	130.2(8)
C10–C9–C8	110.6(5)	C31–C30–C29	129.0(7)
C9–C10–C5	112.4(5)	O33–C31–O32	122.1(7)
C11–C10–C5	109.8(5)	C30–C31–O32	117.4(8)
C11–C10–C9	112.6(5)	C30–C31–O33	120.5(7)
C12–C11–C10	128.1(6)		

Hydrogen bond contacts of *II* (*i*: $x - 1, y, z - 1$; *ii*: $x - 1, y, z$; *iii*: $x, y + 1, z + 1$):

	D–A	D–H–A
N6–H...O32	2.715(10)	147
O20...H–O1	2.738(8)	167
O1–H...O26^{i}	2.898(11)	171
O1...H–N18^{ii}	3.101(11)	155
O26...H–N1^{iii}	2.881(12)	147

---

[a] Ref.[7].

${}^1C_4$ shape, but with a small distorsion towards ${}^3E$). Torsion angles about the C/D ring junction C4–C5–C10–C11 and N6–C5–C10–C9 are 58.0(8)° and –55.4(8)°. The sp^3 hybridized N6 atom is deviated by –0.463(6) Å from the plane of atoms C7,C5,C17. The atoms of the urea side chain N18,C19,O20,N21 lie in one plane ($\chi^2 = 0.03$) and two ethyl groups are oriented above and below of this plane. The corresponding torsion angles of C8–N18–C19–N21, N18–C19–N21–C22 and N18–C19–N21–C24 equal –179.3(7), –165.7(8) and 22(1)°. The absolute configuration of three chiral centres at C5(*R*), C8(*S*) and C10(*R*) was respected as reported in ref.[17]. A comparison of two symetrically-independent terguride molecules (denoted as *A* and *B*) found in the structure of *I* with its protonized form, *II*, shows very closed angle values around N6 atom (C7–N6–C5 112.9(5)°, C17–N6–C5 110.8(5)° and C17–N6–C7 109.2(6)° for *II*; C7–N6–C5 111.6(4)°, 109.7(4)°, C17–N6–C5 112.3(4)°, 111.9(5)°, C17–N6–C7 108.4(4)°, 108.1(5)° for *A* and *B* molecule of *I*). The maleate moiety contains the expected double bond C29=C30. The three-dimensional H-bridge network was found in the structure. Besides electrostatic forces the terguride–maleate interaction is also formed by the N6–H...O32 contact. The water molecule connects the terguride moiety with neighbouring maleate anion through O20...H–O1 and O1–H...O26^i bonds (i: $x - 1$, y, $z - 1$). Water oxygen O1 acts also as the H acceptor (O1...H–N18^{ii}, where ii: $x - 1$, y, z) and oxygen O26 as the double H acceptor (see mentioned O1–H...O26^i and O26...H–N1^{iii}, where iii: x, $y + 1$, $z + 1$). The similar three-dimensional H-bridge arrangement, mediated through water molecules only was observed for the structure of *I*.

NMR Assignment

The identification of aromatic ABC spin system, ethyl side chain, and N-methyl is straightforward. Proton H-12 was differentiated from H-14 on the basis of its larger coupling to H-10 and using the NOE between H-9e and H-12. Both indole and side

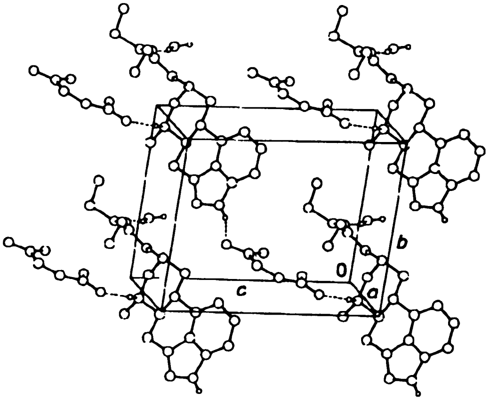


FIG. 2
The simplyfied crystal packing scheme of *II*. The H-bonds N18–H...O1^{ii} and O1–H...O26^{i} connecting neighbouring layers into a three-dimensional network are omitted for clarify

chain N–H's were used as the entry points for signal assignment. The dihydroergine moiety (C-2 to C-10), $-NH-CH=C-CH_2CHCHCH_2CH(NH-)CH_2-$, was revealed by COSY and delay-COSY experiments. Vicinal and long-range couplings (e.g., H-2 to H-4a, H-7e to H-9e) served to distinguish the axial and equatorial protons. Proton-bearing carbons were then assigned by HETCOR. The analogy with related compounds and the inspection of fine structure of multiplets in proton-coupled ^{13}C NMR spectra helped to assign the signals of quaternary carbons (Table IV).

TABLE IV
NMR data of terguride (*I*) and terguride hydrogen maleate (*II*)

Carbon	*I* [a]	*II* [b,c]	Proton	*I* [a]	*II* [b,d]
2	117.86	119.51	2	6.895	7.127
3	111.27	107.07	–		
4	26.95	24.00	4a	2.698	2.946
			4e	3.414	3.585
5	67.57	66.10	5	2.211	3.312
7	61.80	58.76	7a	2.484	3.354
			7e	2.890	3.733
8	45.03	44.28	8	4.315	4.321
9	32.52	30.52	9a	1.634	1.779
			9e	2.813	2.722
10	36.53	33.99	10	3.088	3.475
11	133.04	133.14	–		
12	112.90	112.81	12	6.857	6.839
13	122.85	122.32	13	7.135	7.085
14	108.59	109.56	14	7.182	7.127
15	133.30	129.56	–		
16	126.21	125.38	–		
$N-CH_3$	43.30	41.05	$N-CH_3$	2.417	2.996
N–C=O	156.67	156.47	–		
CH_3	13.80	13.78	CH_3	1.164	1.056
CH_2	41.09	40.11	CH_2	3.266	3.208
				3.362	3.309
			N1–H	8.726	8.885
			C8–NH	5.645	6.162

[a] In $CDCl_3$; [b] in $(CD_3)_2SO$; [c] maleate signals 135.75 d (–CH=), 167.50 s (C=O); [d] maleate signal 6.099 s.

Conformation in Solution

Proton-proton coupling constants (Table V) indicate that the ring C in *I* and *II* exists in the usual puckered form. Large $J(5,10)$ = 9.7 Hz in *I* confirms a *trans*-C/D ring junction. This coupling was not extractable from the ^{1}H NMR spectrum of *II* but the very similar multiplet pattern of H-10 pointed to the same type of arrangement. The magnitudes of $J(5,10)$ and $J(9a,10)$ correspond to axial-axial couplings in the six-membered ring existing in a chair form. Smaller couplings of H-8 to its neighbours (axial-equatorial and equatorial-equatorial) indicate that this atom is equatorial (so that the urea moiety is axial). This conclusion is further supported by NOE between H-10 and NHCO and H-5 and H-7a. NOE crosspeaks between N-methyl and H-4e and H-7e are consistent with an equatorial orientation of this group. Very interesting crosspeaks between H-12 or H-13 and diethyl urea methylene protons are evidence for a folded chain conformation coming close to the aromatic ring or for some intermolecular stacking.

Allowing for solvent effect, the comparison of ^{1}H and ^{13}C NMR chemical shifts (Table IV), especially the downfield shifts of N-methyl, H-5, and H-7, indicate that protonation takes place at N6. The couplings involving H-8 (Table V) and NOE in pairs H-10,NHCO; NMe,H-4e; NMe,H-7e lead to the same chair conformation of the ring D

TABLE V
Proton-proton coupling constants of *I* and *II*

Protons	J, Hz		Protons	J, Hz	
	I	*II*		*I*	*II*
2,NH	1.8	2.0	8,NH	8.2	5.5
2,4a	1.8	1.5	9a,9e	−13.4	−13.8
4a,4e	−14.6	−14.4	9a,10	12.8	12.8
4a,5	11.1	11.3	9e,10	4.2	2.9
4e,5	4.3	4.3	10,12	1.3	1.0
5,10	9.7	n.d.[a]	10,14	0.7	0.7
7a,7e	−11.7	−13.1	12,13	6.9	7.1
7a,8	2.6	3.4	12,14	1.1	0.7
7e,8	2.5	2.0	13,14	8.2	8.2
7e,9e	2.5	2.0	^2J(Et)	−14.8	−14.3
8,9a	3.3	4.1	^3J(Et)	7.1	7.1
8,9e	2.6	2.8			

[a] Not determined.

as for *I*. However, different J(8,NH) (5.5 Hz instead of 8.2 Hz) suggests a different conformation of the side chain. No NOE between the side chain methylene and the aromatic part of the molecule was observed in this case but that might be partly attributed to the different solvation. Therefore, it can be concluded that the conformation of both terguride and terguride maleate is the same in solution as in the solid state.

REFERENCES

1. Zikán V., Semonský M., Řežábek M., Ausková M., Šeda M.: Collect. Czech. Chem. Commun. *37*, 2600 (1972).
2. Řeháček Z., Sajdl P.: *Ergot Alkaloids, Chemistry, Biological Effects, Biotechnology.* Academia, Prague 1990.
3. Wachtel H., Dorow R.: Life Sci. *32*, 421 (1983).
4. Ma L. Y. Y., Camerman N., Swartzendruber J. K., Jones N. D., Camerman A.: Can. J. Chem. *65*, 256 (1987).
5. Nordmann R., Loosli H.-P.: Helv. Chim. Acta *68*, 1025 (1985).
6. Kidrič J., Kocjan D., Hadži D.: Experientia *42*, 327 (1986).
7. Kratochvíl B., Ondráček J., Novotný J., Hušák M., Jegorov A., Stuchlík J.: Z. Kristallogr. *206*, 77 (1993).
8. Watkin D. J.: *CRYSTALS. Crystallographic Package.* University of Oxford, Oxford 1989.
9. *International Tables for X-Ray Crystallography.* Vol. IV. Kynoch Press, Birmingham 1974. (Present distributor: Kluwer Academic Publishers, Dordrecht.)
10. Frenz B. A. & Associated, Inc.: *SDP. Structure Determination Package.* Enraf–Nonius, Delft 1985.
11. Nardelli M.: *PARST. System of Computer Routines for Calculating Molecular Parameters from the Results of Crystal Structure.* University of Parma, Parma 1991.
12. Sheldrick G. M.: *SHELXS86. Program for Crystal Structure Solution.* University of Göttingen, Göttingen 1986.
13. Ugliengo P., Borzani G., Viterbo D.: J. Appl. Crystallogr. *21*, 75 (1988).
14. Bax A., Freeman R.: J. Magn. Reson. *44*, 542 (1981).
15. Kessler H., Griesinger C., Kerssebaum R., Wagner K., Ernst R. R.: J. Am. Chem. Soc. *109*, 607 (1987).
16. Jacobs W. A., Gould R. G.: J. Biol. Chem. *120*, 141 (1937).
17. Sauer G., Haffer G., Wachtel H.: Synthesis *1986*, 1007.

Translated by the author (B. K.).