X-RAY ABSOLUTE STRUCTURE OF NICERGOLINE (FORM *I*). QUANTITATIVE ANALYSIS OF NICERGOLINE PHASE MIXTURE: FORM *I*/FORM *II*

Michal HUSAK[a], Jiri HAD[b], Bohumil KRATOCHVIL[a], Ladislav CVAK[c], Josef STUCHLIK[c] and Alexandr JEGOROV[d,*]

[a] *Department of Solid State Chemistry,*
Prague Institute of Chemical Technology, 166 28 Prague 6, The Czech Republic
[b] *Central Laboratories,*
Prague Institute of Chemical Technology, 166 28 Prague 6, The Czech Republic
[c] *Galena Co.,*
R. & D., 747 70 Opava-Komarov, The Czech Republic
[d] *Galena Co.,*
Research Unit, Branisovska 31, 370 05 Ceske Budejovice, The Czech Republic

Received December 7, 1993
Accepted March 4, 1994

The structure of semisynthetic ergot derivative nicergoline (form *I*) was determined from X-ray single crystal diffraction data. The title alkaloid (10α-methoxy-1,6-dimethylergoline-8β-methanol-5′-bromonicotinate, $C_{24}H_{26}BrN_3O_3$) crystallizes in the triclinic space group *P1*, with $a = 7.729(7)$, $b = 8.695(4)$, $c = 17.030(8)$ Å, $\alpha = 100.90(4)$, $\beta = 98.67(5)$, $\gamma = 93.04(5)°$, $Z = 2$. A structural comparison of nicergoline forms *I* and *II* was made. The quantitative analyses of some model phase mixtures form *I*/form *II* were carried out using both Rietveld full profile fitting method and linear regression of the peak intensity–concentration dependence. Results obtained are in good mutual agreement. The smallest limit of detection of form *II* in binary mixture with form *I* is about 3% as found from powder diffraction study.

Nicergoline (10α-methoxy-1,6-dimethylergoline-8β-methanol-5′-bromonicotinate, Scheme 1) is a semisynthetic ergot derivative, first described by Arcari et al.[1]. It has α-adrenolytic and vasodilating effects on the vascular system and stimulates cerebral and peripheral metabolism[2]. Two different crystal modifications of nicergoline, called forms *I* and *II* were obtained by Fabregas and Beneyto[3] by crystallization at different temperatures. Crystal structure determination of form *II* has been reported recently by us[4]. In the manner of manufacture of the drug, crystallization of form *I* can be accompanied by

---

[*] The author to whom correspondence should be addressed.

formation of small amount of form *II*, therefore the structure-study of form *I* and the quantitative analysis of the phase mixture form *I*/form *II* is reported here.

EXPERIMENTAL

Crystal Preparation

Nicergoline forms *I* and *II* were from Galena Co. (The Czech Republic). Single crystals of *I* were obtained by slow evaporation of saturated solution in ethanol (100 mg/1 ml) at ambient temperature. Crystals were washed with the 2-propanol–n-hexane mixture (12 : 88, v/v) and dried in air.

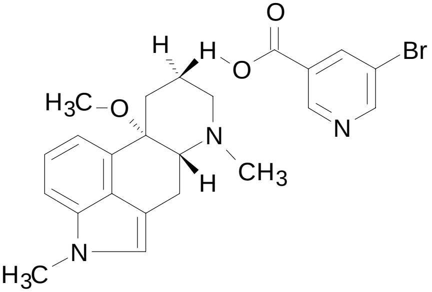
Crystal Structure Determination

$C_{24}H_{26}BrN_3O_3$ (M_r = 484.1), nicergoline form *I*, triclinic system, space group *P1*, a = 7.729(7), b = 8.695(4), c = 17.030(8) Å, α = 100.90(4), β = 98.67(5), γ = 93.04(5)°, V = 1 107(1) Å^3, Z = 2, D_{calc} = 1.453 g cm^{-3}, μ(MoKα) = 1.87 mm^{-1}, F(000) = 494.

Direct methods (program SHELXS86, ref.[5]) evaluated only positions of Br atoms and nicotinate fragments of two symmetrically-independent molecules, denoted *A* and *B*. Because subsequent Fourier series were complicated with pseudosymmetry, direct methods were applied to the difference of observed and calculated (from known fragment) *F*-values (program DIRDIF, ref.[6]). The refinement confirmed the space group *P1*. The corresponding bond lengths for *A* and *B* molecules were refined with restraint of their values being equal (program CRYSTALS, ref.[7]). The restrained refinement was necessary because of the pseudosymmetry ($P\overline{1}$) involving undesirable correlation between parameters. All H-atom positions were calculated assuming ideal geometry (C–H = 1 Å, $U_{iso} = U_{eq}$ of the attached atom). The correction for absorption did not influence the refinement results. Absolute configuration was determined using refinement of Flack's enantiopole parameter[8] described by equation $|F(\boldsymbol{h},x)|^2 = (1 - x)\ |F(\boldsymbol{h})|^2 + x\ |F(-\boldsymbol{h})|^2$ to final value of x = 0.04(2). The parameters for data collection and refinement are listed in Table I.

Phase Analysis

X-Ray powder patterns were collected on a Seifert diffractometer XRD 3000 P with Bragg–Brentano focusing geometry. Radiation CoKα monochromatized with a graphite monochromator was used. Measurement was provided in range 5 – 36° 2θ by step scan mode (step width 0.01° θ, preset time 2 s). Four nicergoline model phase mixtures *I*/*II* were measured (see Table II) and two methods



SCHEME 1

were used for quantitative analysis: Rietveld refinement and linear regression of the peak intensity–concentration dependence. To estimate the limit of detection of form *II* in the nicergoline binary mixture, the diffractogram of *I*/*II* = 95/5 (wt.%) was subsequently measured.

Rietveld method. The shape function of the diffractogram profile was refined with the DBWS-PC program[12]. Single crystal structure parameters of forms *I* and *II* were introduced and fixed. The weight fraction of component in the sample was estimated by $x_1 = (S_1 V_1 Z_1 M_1)/\Sigma_i(S_i V_i Z_i M_i)$, where: *i* number of phase, *S* scale factor, *V* cell volume, *Z* number of formula unit per cell, *M* molecular weight. The Rietveld agreement factor values are given in Table II. The relatively high value of the *R* factor for pure form *I* is brought about the texture effects of material available (crystals of the thin slice shape).

Method of linear regression. Integral intensities of the reflections (001), (01–1), (021), (1–21), (113) for form *I* and (110), (202), (322) for form *II* were measured. These reflections were chosen since they were strong enough and did not coincide with any other reflection. Considering the same

TABLE I
Data collection and refinement parameters for nicergoline form *I*

Crystal dimensions	0.8 × 0.35 × 0.03 mm
Diffractometer and radiation used	Enraf–Nonius CAD4, MoKα, $\lambda = 0.71073$ 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*	$-8 \to 8$, $-9 \to 9$, $-19 \to 19$
Standard reflections monitored in interval; intensity fluctuation	120 min; –0.9%
Total number of reflections measured; 2θ range	6 497; 0 – 48°
Number of unique obsrved reflections	5 358
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	559
Value of *R*, *wR* and *S*	0.070, 0.070 and 2.56
Ratio of max. LS shift to e.s.d. in the last cycle	0.08
Max. and min. heights in final Δρ map	1.75, –1.23 e $Å^{-3}$ (diffuse peaks max. 1.2 Å away from Br atoms)
Source of atomic scattering factors	International Tables for X-Ray Crystallography (ref.[9])
Programs used	CRYSTALS (ref.[7]) SDP (ref.[10]), SHELXS86 (ref.[5]), PARST (ref.[11]), DIRDIF (ref.[6])
Computer used	PDP 11/73, PC AT 386

absorption coefficients for both nicergoline phases, the dependence of peak intensity vs concentration should be linear. Good linearity was found for form *II*, while intensities of form *I* were strongly influenced due to texture effects. Hence, the weight fraction of form *II* was determined only and the content of form *I* was calculated as a difference to 100% in the studied binary system. Correlation coefficients of the linear regression for form *II* are as follows: reflection (110) 0.987, reflection (202) 0.985 and reflection (322) 0.994. These three dependencies were used for the quantitative phase analysis.

RESULTS AND DISCUSSION

Crystal Structure of Nicergoline Form I

The final positional and thermal parameters of the non-H atoms of nicergoline form *I* are summarized in Table III. Bond distances and angles are listed in Table IV. Lower precision of resulted structural parameters is probably caused by the poor quality of the single crystal available (see Table I). Figure 1 shows the two symmetrically-independent nicergoline molecules *A* and *B*, Fig. 2 their shape difference, which is evident in bromonicotinate fragments. Figure 3 shows a very good agreement between calculated and observed powder diffraction patterns of nicergoline phase mixture *I*/*II* = 50/50.

The basic structure of nicergoline is derived from the tetracyclic ring system designated as ergoline[13], therefore the corresponding atom numbering system was chosen. Pyrrole and benzene rings of ergoline moiety are planar. The χ^2 test value is 5.71 (molecule *A*) and 3.35 (molecule *B*) for pyrrole ring and 4.71 (molecule *A*) and 1.98 (molecule *B*) for phenyl ring, respectively. Dihedral angles of pyrrole and phenyl ring planes are the same for both molecules (2.75(5)°).

Both C ergoline rings (C5,C10,C11,C16,C3,C4) and (C105,C110,C111,C116,C103,C104) have an ^1E shape with C5 and C105 atoms displaced by 0.68(1) Å and 0.67(1) Å, respectively, from the mean plane of remaining five atoms. Puckering parameters

TABLE II
Results of Rietveld refinement (in %)

Mixture No.	Phase *I*	Phase *II*	*R*	*wR*	$R_B{}^{I}$	$R_B{}^{II}$
1	90	10	13.1	16.6	34.0	23.6
2	80	20	13.2	16.7	25.6	15.1
3	50	50	14.1	17.9	26.4	12.9
4	30	70	13.4	17.5	33.6	11.1
Pure *I*	100	–	16.9	22.3	38.0	–
Pure *II*	–	100	12.8	16.5	–	12.2

TABLE III

Final positional and thermal parameters of non-H atoms for nicergoline form *I*. The atoms of the *B* molecule have the same index + 100

Atom	*x*	*y*	*z*	U_{eq}, Å^2
Br29[a]	0.1469(3)	0.1840(2)	0.7216(1)	0.0545(7)
Br129	0.4844(3)	0.1072(3)	0.0838(1)	0.0699(8)
O20	0.047(1)	–0.1715(8)	1.0127(5)	0.047(4)
O22	0.107(1)	–0.280(1)	0.8899(6)	0.070(5)
O30	0.0120(8)	–0.3725(8)	1.2855(4)	0.035(3)
O120	0.662(1)	0.4443(9)	–0.2016(5)	0.048(4)
O122	0.555(1)	0.561(1)	–0.0917(6)	0.060(5)
O130	0.4745(8)	0.6602(8)	–0.4730(4)	0.031(3)
N1	–0.304(1)	–0.8893(9)	1.3212(6)	0.043(5)
N6	–0.275(1)	–0.3194(9)	1.1732(5)	0.037(4)
N25	0.028(2)	0.264(1)	0.9490(7)	0.063(7)
N101	0.217(1)	1.181(1)	–0.5115(6)	0.049(5)
N106	0.261(1)	0.6150(9)	–0.3590(5)	0.029(4)
N125	0.584(2)	0.007(1)	–0.1507(7)	0.061(6)
C2	–0.401(1)	–0.759(1)	1.3175(9)	0.037(6)
C3	–0.308(1)	–0.647(1)	1.2895(7)	0.036(5)
C4	–0.352(1)	–0.497(1)	1.2641(6)	0.035(5)
C5	–0.252(1)	–0.474(1)	1.1935(6)	0.039(5)
C7	–0.201(1)	–0.302(1)	1.1008(6)	0.035(5)
C8	–0.003(1)	–0.320(1)	1.1138(6)	0.041(5)
C9	0.028(2)	–0.472(1)	1.1422(7)	0.046(6)
C10	–0.051(1)	–0.4919(9)	1.2140(5)	0.029(4)
C11	–0.026(1)	–0.654(1)	1.2333(7)	0.039(5)
C12	0.113(1)	–0.748(1)	1.2199(7)	0.046(6)
C13	0.117(2)	–0.896(1)	1.2428(8)	0.051(7)
C14	–0.013(1)	–0.963(1)	1.2765(8)	0.050(6)
C15	–0.154(1)	–0.866(1)	1.2913(7)	0.041(5)
C16	–0.157(1)	–0.717(1)	1.2712(6)	0.036(4)
C17	–0.355(2)	–1.024(1)	1.3549(7)	0.052(6)
C18	–0.470(1)	–0.292(2)	1.159(1)	0.047(7)
C19	0.063(2)	–0.320(1)	1.0383(6)	0.047(6)
C21	0.077(2)	–0.169(1)	0.9389(6)	0.048(6)
C23	0.066(2)	–0.009(1)	0.9171(6)	0.035(6)
C24	0.033(2)	0.124(1)	0.9713(7)	0.054(7)
C26	0.068(2)	0.273(2)	0.8754(8)	0.065(9)
C27	0.112(2)	0.151(1)	0.8204(6)	0.051(7)
C28	0.106(2)	0.009(1)	0.8433(7)	0.036(6)

TABLE III
(*Continued*)

Atom	x	y	z	U_{eq}, Å^2
C31	0.192(1)	–0.361(1)	1.3227(7)	0.058(6)
C102	0.102(1)	1.051(1)	–0.5105(8)	0.047(6)
C103	0.197(1)	0.944(1)	–0.4751(7)	0.041(5)
C104	0.149(1)	0.793(1)	–0.4503(6)	0.038(5)
C105	0.293(1)	0.768(1)	–0.3809(6)	0.031(4)
C107	0.378(1)	0.603(1)	–0.2845(6)	0.024(5)
C108	0.569(1)	0.603(1)	–0.3012(6)	0.042(5)
C109	0.605(1)	0.754(1)	–0.3306(5)	0.019(5)
C110	0.484(1)	0.7806(9)	–0.4010(5)	0.028(4)
C111	0.518(1)	0.944(1)	–0.4179(6)	0.039(4)
C112	0.680(1)	1.034(1)	–0.4028(7)	0.046(6)
C113	0.694(1)	1.181(1)	–0.4269(8)	0.048(6)
C114	0.550(1)	1.242(1)	–0.4636(7)	0.044(6)
C115	0.378(1)	1.153(1)	–0.4811(8)	0.052(6)
C116	0.371(1)	1.006(1)	–0.4577(6)	0.035(5)
C117	0.167(2)	1.317(1)	–0.5443(8)	0.058(6)
C118	0.068(1)	0.590(1)	–0.3490(9)	0.047(7)
C119	0.690(1)	0.590(1)	–0.2283(7)	0.049(6)
C121	0.593(2)	0.446(1)	–0.1350(6)	0.047(5)
C123	0.577(2)	0.287(1)	–0.1115(7)	0.050(6)
C124	0.597(2)	0.152(1)	–0.1676(9)	0.059(8)
C126	0.557(2)	0.001(1)	–0.0753(6)	0.044(7)
C127	0.535(2)	0.129(1)	–0.0174(5)	0.026(5)
C128	0.539(2)	0.275(1)	–0.0363(7)	0.046(7)
C131	0.623(2)	0.655(2)	–0.5170(8)	0.058(7)

[a] At position 29.

defined by Cremer and Pople[14] are $Q = 0.49(1)$ Å, $\phi = -169(2)°$, $\theta = 126(1)°$ for molecule *A* and $Q = 0.49(1)$ Å, $\phi = -166(2)°$, $\theta = 129(2)°$ for molecule *B*. Both D ergoline rings (N6,C7,C8,C9,C10,C5) and (N106,C107,C108,C109,C110,C105) have $^1C_4$ conformations with $Q = 0.58(1)$ Å, $\phi = -46(1)°$, $\theta = 6(1)°$ for molecule *A* (N6 displaced by 0.68(1) Å and C9 by –0.62(1) Å) and $Q = 0.60(1)$ Å, $\phi = 13(1)°$, $\theta = 7(1)°$ for molecule *B* (N106 displaced by 0.72(1) Å and C109 by –0.61(1) Å). The chair conformation of molecule *B* has a small distorsion towards an ^1E form.

TABLE IV
Bond distances (Å) and angles (°) for nicergoline form *I*

A molecule		*B* molecule	
Atoms	Distances	Atoms	Distances
Br29–C27	1.815(11)	Br129–C127	1.865(10)
O29–C19	1.441(13)	O120–C119	1.443(14)
O20–C21	1.316(14)	O120–C121	1.323(15)
O22–C21	1.209(14)	O122–C121	1.209(14)
O30–C10	1.445(9)	O130–C110	1.444(9)
O30–C31	1.431(11)	O130–C131	1.461(15)
N1–C2	1.402(14)	N101–C102	1.403(14)
N1–C15	1.354(14)	N101–C115	1.333(13)
N1–C17	1.457(15)	N101–C117	1.446(15)
N6–C5	1.465(13)	N106–C105	1.467(13)
N6–C7	1.466(14)	N106–C107	1.468(12)
N6–C18	1.529(12)	N106–C118	1.535(13)
N25–C24	1.345(16)	N125–C124	1.343(16)
N25–C26	1.350(19)	N125–C126	1.343(17)
C2–C3	1.372(17)	C102–C103	1.380(15)
C3–C4	1.493(15)	C103–C104	1.501(14)
C3–C16	1.391(14)	C103–C116	1.392(12)
C4–C5	1.557(16)	C104–C105	1.552(13)
C5–C10	1.561(12)	C105–C110	1.562(12)
C7–C8	1.532(13)	C107–C108	1.544(12)
C8–C9	1.509(16)	C108–C109	1.514(15)
C8–C19	1.457(16)	C108–C119	1.464(14)
C9–C10	1.483(16)	C109–C110	1.471(11)
C10–C11	1.526(13)	C110–C111	1.520(12)
C11–C12	1.402(14)	C111–C112	1.407(13)
C11–C16	1.420(15)	C111–C116	1.417(13)
C12–C13	1.410(16)	C112–C113	1.413(16)
C13–C14	1.382(18)	C113–C114	1.377(15)
C14–C15	1.440(14)	C114–C115	1.462(13)
C15–C16	1.399(14)	C115–C116	1.404(15)
C21–C23	1.508(14)	C121–C123	1.510(15)
C23–C24	1.399(15)	C123–C124	1.403(16)
C23–C28	1.372(17)	C123–C128	1.376(19)
C26–C27	1.372(17)	C126–C127	1.379(14)
C27–C28	1.368(16)	C127–C128	1.363(15)

TABLE IV
(*Continued*)

A molecule		*B* molecule	
Atoms	Angles	Atoms	Angles
C21–O20–C19	116.0(11)	C121–O120–C119	118.9(12)
C31–O30–C10	119.8(11)	C131–O130–C110	118.2(11)
C15–N1–C2	108.5(12)	C115–N101–C102	108.0(12)
C17–N1–C2	124.8(14)	C117–N101–C102	125.2(14)
C17–N1–C15	126.7(13)	C117–N101–C115	126.7(14)
C7–N6–C5	112.4(11)	C107–N106–C105	111.0(11)
C18–N6–C5	110.2(11)	C118–N106–C105	109.9(11)
C18–N6–C7	108.3(11)	C118–N106–C107	110.7(11)
C26–N25–C24	117.6(14)	C126–N125–C124	115.8(14)
C3–C2–N1	109.7(14)	C103–C102–N101	108.8(13)
C4–C3–C2	133.7(14)	C104–C103–C102	134.4(14)
C16–C3–C2	104.9(12)	C116–C103–C102	106.4(12)
C16–C3–C4	120.4(12)	C116–C103–C104	119.1(12)
C5–C4–C3	109.5(12)	C105–C104–C103	108.8(11)
C4–C5–N6	111.2(11)	C104–C105–N106	111.0(11)
C10–C5–N6	108.3(11)	C110–C105–N106	108.6(11)
C10–C5–C4	112.4(10)	C110–C105–C104	113.8(10)
C8–C7–N6	110.5(10)	C108–C107–N106	108.9(10)
C9–C8–C7	109.0(12)	C109–C108–C107	106.3(12)
C19–C8–C7	109.4(11)	C119–C108–C107	110.5(11)
C19–C8–C9	110.7(12)	C119–C108–C109	113.1(12)
C10–C9–C8	115.1(12)	C110–C109–C108	116.7(11)
C5–C10–O30	105.5(10)	C105–C110–O130	103.0(10)
C9–C10–O30	113.9(11)	C109–C110–O130	114.2(10)
C9–C10–C5	107.6(10)	C109–C110–C105	107.8(10)
C11–C10–O30	109.7(9)	C111–C110–O130	111.8(9)
C11–C10–C5	108.9(11)	C111–C110–C105	107.3(11)
C11–C10–C9	111.0(11)	C111–C110–C109	112.1(10)
C12–C11–C10	128.2(12)	C112–C111–C110	126.9(12)
C16–C11–C10	115.9(12)	C116–C111–C110	115.6(12)
C16–C11–C12	115.9(12)	C116–C111–C112	117.4(12)
C13–C12–C11	120.6(14)	C113–C111–C111	120.6(14)
C14–C13–C12	124.8(14)	C114–C113–C112	121.8(14)
C15–C14–C13	114.5(13)	C115–C114–C113	119.7(13)
C14–C15–N1	132.4(13)	C114–C115–N101	134.3(13)
C16–C15–N1	106.3(13)	C116–C115–N101	108.8(13)

TABLE IV
(*Continued*)

A molecule		*B* molecule	
Atoms	Angles	Atoms	Angles
C16–C15–C14	121.3(14)	C116–C115–C114	116.7(13)
C11–C16–C3	126.6(12)	C111–C116–C103	128.1(12)
C15–C16–C3	110.6(13)	C115–C116–C103	108.0(13)
C15–C16–C11	122.7(13)	C115–C116–C111	123.8(13)
C8–C19–O20	112.1(11)	C108–C119–O120	113.8(12)
O22–C21–O20	126.2(13)	O122–C121–O120	125.4(13)
C23–C21–O20	113.5(11)	C123–C121–O120	114.1(12)
C23–C21–O22	120.3(12)	C123–C121–O122	120.3(12)
C24–C23–C21	123.0(11)	C124–C123–C121	119.2(12)
C28–C23–C21	118.2(12)	C128–C123–C121	120.7(12)
C28–C23–C24	118.5(13)	C128–C123–C124	120.1(13)
C23–C24–N25	120.5(13)	C123–C124–N125	122.3(14)
C27–C26–N25	125.8(14)	C127–C126–N125	124.7(13)
C26–C27–Br29	119.1(11)	C126–C127–Br129	121.6(10)
C28–C27–Br29	125.7(10)	C128–C127–Br129	119.1(10)
C28–C27–C26	114.7(12)	C128–C127–C126	119.2(11)
C27–C28–C23	122.7(12)	C127–C128–C123	117.7(13)

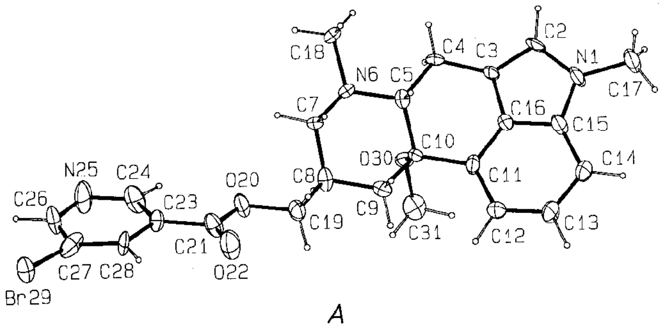


FIG. 1
Two symmetrically-independent nicergoline *I* molecules *A* and *B* (on the opposite page)

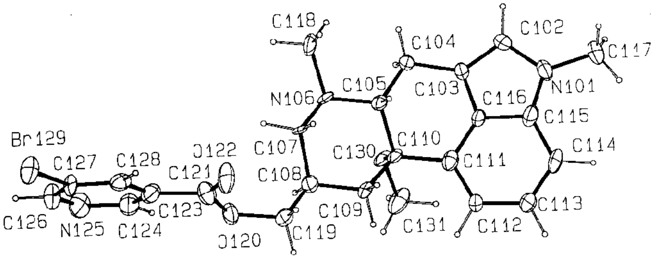
The intermolecular contacts are caused by van der Waals forces only. The closest distance of 3.45(1) Å was found between C109 and N125 of the neighbouring molecule at *x*, *y* + 1, *z*. The following absolute configurations of chiral centres are C5(*R*), C105(*R*), C8(*R*), C108(*R*), C10(*S*) and C110(*S*). They are the same as those found for form *II*. This paper corrects the work reported by Foresti et al.[15], where the absolute configurations of nicergoline and related ergoline compounds are incorrect.

Further comparison of both nicergoline forms shows that bromonicotinic acid substituent possesses three different conformation due to rotation around the C19–O20 bond (Table V). The corresponding torsion angles in molecules *A* and *B* of form *I* differ by 59 and 120° from that found in form *II*. It seems likely that solvatation of nicergoline

TABLE V
Comparison of selected torsion angles (°) for nicergoline forms *I* and *II*

Fragment	Form *II*	Form *I* (*A*)	Form *I* (*B*)[a]
C5–N6–C7–C8	–64.0(5)	–61(1)	–66(1)
N6–C7–C8–C19	–176.8(4)	174(1)	180(1)
C7–C8–C19–O20	62.7(5)	64(1)	64(2)
C8–C19–O20–C21	132.0(5)	–169(1)	–108(1)
C19–O20–C21–C23	–170.8(4)	–177(1)	–178(1)
O20–C21–C23–C24	–9.9(7)	2(2)	–13(2)
C19–O20–C21–O22	6.6(8)	5(2)	–3(2)

[a] The atoms of the *B* molecule have the same index + 100.



B

molecule at N6 and O22 is in favour of opposite arrangement of these atoms in polar protic solvents thus contributing to the preference of the crystallization of form *I*. Changes in the total molecule energy (in vacuo) versus value of torsion angle C8–C19–O20–C21 were studied with the molecular mechanic calculation (MM+ method) and with the semi-empirical quantum mechanic method INDO (as implemented in program HYPERCHEM, ref.[16]). However, these calculations were not able to predict the optimal value of the torsion angle C8–C19–O20–C21. During rotation around the C19–

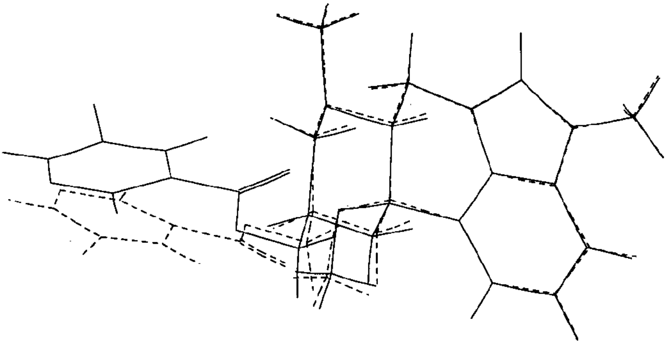


FIG. 2
The shape difference of *A* (dotted) and *B* nicergoline *I* molecules

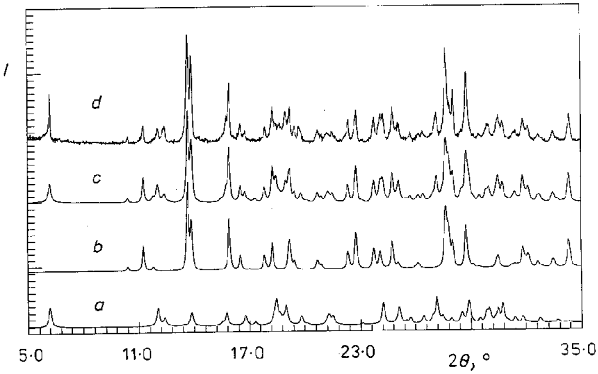


FIG. 3
X-Ray powder diagrams: *a* calculated patterns for nicergoline phase *I*; *b* calculated patterns for nicergoline phase *II*; *c* observed patterns for nicergoline phase mixture *I*/*II* = 50/50; *d* calculated patterns for nicergoline phase mixture *I*/*II*=50/50

O20 bond, the energetic barrier arose at torsion angle C8–C19–O20–C21 = –40° as corresponds to the contact of O22 with hydrogen H-C7.

Quantitative Analysis of Nicergoline Phase Mixture: Form I/Form II

The results of quantitative phase analysis obtained by both Rietveld and linear regression methods are compared in Table VI. No significant difference has been found, results obtained are in good agreement. Thus the linear regression method seems to be quite sufficient for the routine phase analysis of mixtures of nicergoline polymorphic forms. Further, the smallest detectable amount about 3% of form *II* in binary mixture form *I*/form *II* was estimated as follows from Fig. 4.

TABLE VI
Comparison of quantitative phase analysis results (in wt.%)

Mixture No.	Known content of form *II*	Found from Rietveld	Difference	Found from regression	Difference
1	10	13	3	10	0
2	20	24	4	17	3
3	50	53	3	53	3
4	70	72	2	69	1

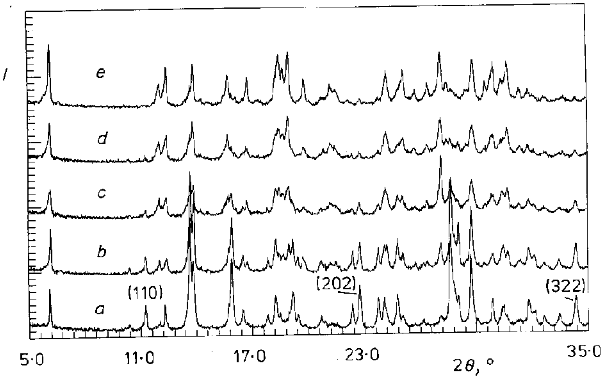


FIG. 4
Diffractograms of the nicergoline model phase mixtures *I/II* with Miller indices of selected reflections of phase *II* used for quantitative analysis: a *I/II* = 30/70; b *I/II* = 50/50; c *I/II* = 80/20; d *I/II* = 90/10; e *I/II* = 95/5

This work was supported by the Grant Agency of the Czech Republic, within the project No. 203/94/0135.

REFERENCES

1. Arcari G., Bernardi L., Bosisio G., Coda S., Fregnan G. B., Gläser A. H.: Experientia *28*, 819 (1972).
2. Brossi A. (Ed.): *The Alkaloids, Chemistry and Pharmacology*, Vol. 38, p. 142. Academic Press, San Diego 1990.
3. Fabregas L. L., Beneyto L. E.: Il Farmaco-Ed. Pr. *36*, 256 (1981).
4. Husak M., Kratochvil B., Ondracek J., Maixner J., Jegorov A., Stuchlik J.: Z. Kristallogr. *209*, 260 (1994).
5. Sheldrick G. M.: *SHELXS86. Program for Crystal Structure Solution*. University of Gottingen, Gottingen 1986.
6. Beurskens P. T., Admiral G., Beurskens G., Bosman W. P., García-Granda S., Gould R. O., Smits J. M. M., Smykalla C.: *The DIRDIF Program System*. Technical Report of the Crystallography Laboratory, University of Nijmegen, Nijmegen 1992.
7. Watkin D. J.: *CRYSTALS. Crystallographic Package*. University of Oxford, Oxford 1993.
8. Flack H. D.: Acta Crystallogr., A *39*, 876 (1983).
9. *International Tables for X-Ray Crystallography*, Vol. IV. Kynoch Press, Birmingham 1974.
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. Sakthivel A., Young R.: *DBWS-9006 PC. Program for Rietveld Analysis of X-Ray and Neutron Powder Diffraction Patterns*. Georgia Institute of Technology, Atlanta 1991.
13. Jacobs W. A., Gould R. G.: J. Biol. Chem. *120*, 141 (1937).
14. Cremer D., Pople J. A.: J. Am. Chem. Soc. *97*, 1354 (1975).
15. Foresti E., Sabatino P., Riva di Sanseverino L., Fusco R., Tosi C., Tonani R.: Acta Crystallogr., B *44*, 307 (1988).
16. *HYPERCHEM 2 for Windows. Package for Chemistry Calculation*. Autodesk, Inc., Sausalito 1992.

Translated by the author (B. K.).