ABSOLUTE CRYSTAL STRUCTURE DETERMINATION OF ERGOT ALKALOID – DIHYDROERGOCRISTINE METHANESULFONATE MONOHYDRATE

Jan CEJKA[a], Jan ONDRACEK[a], Michal HUSAK[a], Bohumil KRATOCHVIL[a], Alexandr JEGOROV[b,*] and Josef STUCHLIK[c]

[a] *Department of Solid State Chemistry, Prague Institute of Chemical Technology, 166 28 Prague 6, Czech Republic*

[b] *Galena Co., Research Unit, Branisovska 31, 370 05 Ceske Budejovice, Czech Republic*

[c] *Galena Co., R. & D., 747 70 Opava-Komarov, Czech Republic*

Received March 25, 1995
Accepted June 26, 1995

Dihydroergocristine methanesulfonate monohydrate crystallizes in orthorhorhombic space group $P2_12_12$ (No. 18) with $Z = 4$, $a = 12.736(2)$ Å, $b = 39.089(5)$ Å, $c = 7.130(1)$ Å, $V = 3\ 549.6(9)$ Å^3. The indole moiety is nearly planar, both the ergoline ring C and the tripeptide ring F addopt an envelope E_6 conformation. The ergoline ring D and the tripeptide ring E have a chair $^1C_4$ conformation. The conformation of the ring G is between E_1 and $^5T_1$. The benzene ring H is planar. The structure was solved by direct methods and refined anisotropically to the final R value of 0.078 for 4 219 statistically significant observed reflections [$I \geq 1.96\sigma(I)$]. The absolute chirality was determined based on anomalous dispersion as: C4 (*R*), C8 (*R*), C6 (*R*), C17 (*R*), C25 (*S*), C24 (*S*), C19 (*S*).

Dihydroergocristine belongs to the family of dihydroergopeptine alkaloids *I* which are produced by catalytic hydrogenation of natural ergot alkaloids. Although these compounds are very closely related, individual spectra of their pharmacological activity, and accordingly their therapeutic use are more or less different. Since ergot alkaloids act on many different receptor sites, including α-adreno, dopamine and serotonine receptor groups, their different pharmacological activity is explained as a combination of their agonist and/or antagonist action on various receptor sites[1]. For example ergotamine and dihydroergotamine are among the most potent 5-HT_{1C} agonists[2] and therefore, they are used particulary in the treatment of migraine[3]. Although dihydroergocristine is structurally almost identical with dihydroergotamine *I*, its binding affinity to various receptors is considerably different[4]. The important therapeutic use of dihydroergocristine consists in its complex action in the treatment of eldery

* The author to whom correspondence should be addressed.

patients suffering from organic brain psychosyndrome. Dihydroergocristine is used either alone[5] or as a mixture with other members of dihydroergotoxine group[6] (dihydroergocornine, α- and β-dihydroergokryptine). The present study was undertaken to obtain detailed structural parameters of dihydroergocristine methanesulfonate as a part of our structural study of ergot alkaloid pharmaceuticals[7–11].

EXPERIMENTAL

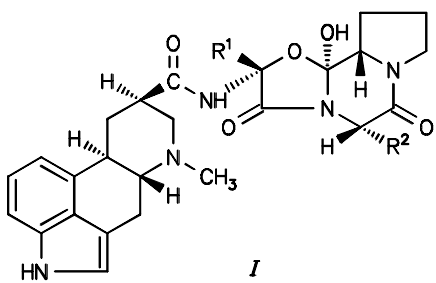
Preparation of Crystals

Dihydroergocristine methanesulfonate (250 mg, Galena Co., Czech Republic) was weighted into glass ampoule and dissolved in hot 96% ethanol (2 ml). Hot ethyl acetate (5 ml) was added, the ampoule was sealed and allowed to cool to ambient temperature. Crystals were washed with ethyl acetate and dried in air.

Crystal Structure Determination

Formula $C_{35}H_{42}N_5O_5^+ . CH_3O_3S^- . H_2O$ (M_r 725.855), orthorhombic system, space group $P2_12_12$ (No. 18), a = 12.736(2) Å, b = 39.089(5) Å, c = 7.130(1) Å, V = 3 549.6(9) Å^3, Z = 4, D_{calc} = 1.358 g cm^{-3}, μ(CuKα) = 1.29 mm^{-1}, F(000) = 1 544.

The structure was solved by direct methods and subsequent Fourier techniques. The Friedel's pairs were not merged. All non-H atoms were refined anisotropically by full-matrix least-squares based on F^2 values. The positions of all H-atoms found from the difference map and their isotropical thermal parameters were refined using the DFIX procedure to the final distance of d(X–H) = 1.03(2) Å. The



I

I	R^1	R^2	Name
a	Me	CH_2Ph	dihydroergotamine
b	iPr	CH_2Ph	dihydroergocristine
c	iPr	iBu	dihydro-α-ergokryptine
d	iPr	sBu	dihydro-β-ergokryptine
e	iPr	iPr	dihydroergocornine

angles including H-atoms are within 95 to 134° range. The water and methyl hydrogens of the methanesulfonate anion were not found. The absolute configuration was determined by refinement of the Flack's enantiopole parameter[12] to the final value of $x = 0.04(6)$. This chirality is in agreement with that found for related (–)-dihydroergotamine methanesulfonate monohydrate[13]. For description of the methanesulfonate disorder a two half occupied molecules model was proposed. Both the atom positions and their anisotropical temperature factors were refined using the DFIX procedure with the values of d(C–S) = 1.737(26) Å; d(O–S) = 1.473(14) Å; d(O–O) = 2.429 Å and d(C–O) = 2.589 Å. The distance between S8 and S9 is 0.29(2) Å. The water molecule is also disordered between two positions in distance 0.48 Å. Due to strong disorder the water oxygen was assumed in two fixed positions with half occupation factor. Data collection and refinement parameters are listed in Table I. Drawing of dihydroergocristine is shown in Fig. 1.

TABLE I
Data collection and refinement parameters

Crystal dimensions	$0.53 \times 0.14 \times 0.14$ mm
Diffractometer and radiation used	Enraf–Nonius CAD4, $\lambda(\mathrm{CuK}\alpha_1) = 1.54056$ Å
Scan technique	$\omega/2\theta$
Temperature	293 K
No. and θ range of reflections for lattice parameter refinement	20; 35–40°
Range of h, k and l	$0\rightarrow14$, $-42\rightarrow42$, $0\rightarrow10$
Standard reflections monitored in interval; intensity fluctuation	60 min; –3%
Total number of reflections measured; 2θ range	4 288; 7–110°
No. of observed reflections	4 219
Criterion for observed reflections	$I \geq 1.9\sigma(I)$
Function minimized	$\Sigma w(\lvert F_o\rvert - \lvert F_c\rvert)^2$
Weighting scheme	$w = [\sigma^2(F_o^2) + (0.1196P)^2 + 8.8207P]^{-1}$; $P = (F_o^2 + 2F_c^2)/3$
Parameters refined	682
Value of R, wR and S	0.0784, 0.2072, 1.068
Ratio of max. least-squares shift to e.s.d. in the last cycle	–0.526
Max. and min. heghts in final Δρ map	0.32, –0.26 e Å^{-3}
Source of atomic scattering factors	International Tables for X-Ray Crystallography[15]
Programs used	SHELXL93 (ref.[16]), PARST91 (ref.[17]), SIR92 (ref.[18])
Computer used	PDP 11/73, PC 486

TABLE II

Final atomic parameters (. 10^4) with e.s.d's in parentheses. $U_{eq} = 1/3 \sum_i \sum_j U_{ij} a_i^* a_j^* \boldsymbol{a}_i \boldsymbol{a}_j$

Atom	*x*	*y*	*z*	U_{eq}, Å^2
S8[a]	2950(10)	4950(3)	1330(20)	0.085(5)
O81[a]	1870(20)	4942(5)	1880(30)	0.069(9)
O82[a]	3160(20)	4761(4)	–450(20)	0.088(6)
C83[a]	3390(20)	5363(5)	870(30)	0.098(10)
O84[a]	3690(10)	4807(5)	2720(30)	0.164(11)
S9[a]	2888(7)	4972(2)	960(20)	0.058(3)
O91[a]	2050(20)	4900(5)	2340(30)	0.059(6)
O92[a]	3530(10)	4696(4)	470(30)	0.083(5)
C93[a]	3580(20)	5315(6)	1870(30)	0.089(9)
O94[a]	2330(10)	5125(4)	–800(20)	0.099(5)
C1	–1853(6)	4190(2)	6460(10)	0.053(2)
N1	–1864(5)	3920(2)	7700(9)	0.051(2)
O1	3411(4)	3528(1)	388(7)	0.0523(13)
C2	–934(5)	4188(2)	5460(10)	0.048(2)
N2	727(4)	4370(1)	1170(8)	0.0342(12)
O2	3706(3)	3580(1)	–3792(7)	0.0418(11)
C3	–466(6)	4397(2)	3930(10)	0.039(2)
N3	3533(4)	4002(1)	–1428(8)	0.0427(14)
O3	5910(4)	3864(1)	–1287(8)	0.0498(13)
C4	262(5)	4167(2)	2837(9)	0.0341(15)
N4	5252(4)	3385(1)	–2687(7)	0.0358(13)
O4	6596(5)	2589(1)	–3201(9)	0.068(2)
C5	1461(6)	4145(2)	50(10)	0.042(2)
N5	5292(4)	2824(1)	–4897(8)	0.0430(14)
O5	3720(4)	3059(1)	–2262(7)	0.0441(12)
C6	2345(5)	4007(2)	1240(10)	0.0348(15)
C7	1880(6)	3784(2)	2790(10)	0.043(2)
C8	1127(5)	3991(2)	3980(10)	0.042(2)
C9	618(5)	3782(2)	5540(10)	0.044(2)
C10	1018(6)	3494(2)	6350(10)	0.048(2)
C11	431(7)	3332(2)	7840(10)	0.054(2)
C12	–527(6)	3449(2)	8410(10)	0.055(2)
C13	–945(6)	3738(2)	7580(10)	0.046(2)
C14	–358(5)	3903(2)	6114(8)	0.0326(14)
C15	–58(6)	4525(2)	–80(10)	0.045(2)
C16	3140(5)	3821(2)	0(9)	0.036(2)
C17	4217(5)	3868(2)	–2913(9)	0.0348(15)
C18	5225(5)	3718(2)	–2120(10)	0.044(2)
C19	6057(5)	3142(2)	–2240(10)	0.040(2)

TABLE II
(*Continued*)

Atom	*x*	*y*	*z*	U_{eq}, Å^2
C20	5998(5)	2830(2)	–3510(10)	0.048(2)
C21	5155(7)	2520(2)	–6070(10)	0.053(2)
C22	4129(7)	2574(2)	–7100(10)	0.064(2)
C23	3579(6)	2869(2)	–6100(10)	0.059(2)
C24	4472(6)	3080(2)	–5290(10)	0.043(2)
C25	4258(5)	3274(2)	–3500(10)	0.037(2)
C26	4382(6)	4149(2)	–4370(10)	0.041(2)
C27	5001(8)	4021(2)	–6020(10)	0.063(2)
C28	4921(8)	4467(2)	–3530(10)	0.057(2)
C29	5961(6)	3020(2)	–130(10)	0.045(2)
C30	6938(5)	3069(2)	1052(9)	0.042(2)
C31	7085(6)	3372(2)	2040(10)	0.051(2)
C32	7965(7)	3413(2)	3140(10)	0.059(2)
C33	8687(7)	3160(2)	3340(10)	0.066(2)
C34	8575(7)	2857(2)	2290(10)	0.063(2)
C35	7671(6)	2813(2)	1180(10)	0.051(2)
O101[a]	2063	4716	6204	0.135(9)
O102[a]	1778	4790	6373	0.164(11)

[a] One half occupation factor value.

RESULTS AND DISCUSSION

The final positional and thermal parameters of the non-H atoms of dihydroergocristine methanesulfonate monohydrate are listed in Table II, bond distances and angles in Table III. The ergoline A and B rings, forming the indole moiety, are nearly planar. The plane displacements vary from –0.010(7) Å [C9] to 0.014(8) [C10] for ring A (χ^2 test value is 7.81) and –0.014(8) [C13] to 0.10(7) [C14] for ring B (χ^2 test value is 5.99). The dihedral angle between these two planes is 1.7(2)°. Ring C (C8,C9,C14,C2,C3,C4) possesses an envelope E_6 conformation [puckering parameters according to Cremer and Pople[14] are: Q = 0.472(7) Å, ϕ = –59(1)°, θ = 53.1(8)°] with the C4 atom 0.641(7) Å below the C2,C3,C8,C9,C14 mean plane. Ring D (C4,N2,C5,C6,C7,C8) with the protonized N2 (found from the Fourier map) has regular chair conformation $^1C_4$ [Q = 0.574(7) Å, ϕ = –20(5)°, θ = 173.0(7)°]. The ring E is planar (χ^2 test value is 5.99), ring F (C24,N5,C20,C19,N4,C25) forms an envelope E_6 conformation [Q = 0.460(7), ϕ = 0.240(7)°, θ = 58.7(8)°], with displacement of –0.636(7) Å for C25. The conformation

of L-proline residue creating ring G [Q = 0.305(8), ϕ = 170(1)°] lies between E_1 and $^5T_1$. The displacements of the C23 and C24 atoms from the C22, C21, N5 plane are 0.351(9) and –0.150(7) Å respectively. L-Phenylalanine residue adopts an eclipsed conformation (χ_3^1 (N4–C19–C29–C30) = –124.2(6)°, $\chi_3^{2,1}$ (C19–C29–C30–C31) = 90.0(8)°, ψ_3^1 (N4–C19–C20–N5) = –174.8(6)°), similarly as in dihydroergotamine methanesulfonate monohydrate[13]. The 2-hydroxyvaline forms a gauche *I* conformation ($\chi_2^{1,1}$ = 61.2(8)°, $\chi_2^{1,2}$ = –175.1(6)°). The following absolute chirality at carbon centres was determined as: C4 (*R*), C8 (*R*), C6 (*R*), C17 (*R*), C25 (*S*), C24 (*S*), C19 (*S*) (Fig. 1).

There is an intramolecular hydrogen bond between the hydroxyl group at O5 and the amide carbonyl oxygen; the O5…O1 distance is 2.95(1) Å and the angle O5–HO5…O1 = 177.4(3)°. Both positions of the methanesulfonate anion are fixed by two hydrogen bonds. Another intermolecular hydrogen bond was found between the indole moiety at N1 and the tripeptide moiety at O3 (x – 1, y, z + 1); the N1…O3 separation is 2.934(8) Å and the angle N1–H1N1…O3 = 130(7)°. Due to this bond the molecules are connected into infinite chains (Fig 2). The summary of all hydrogen bonds is listed in Table IV.

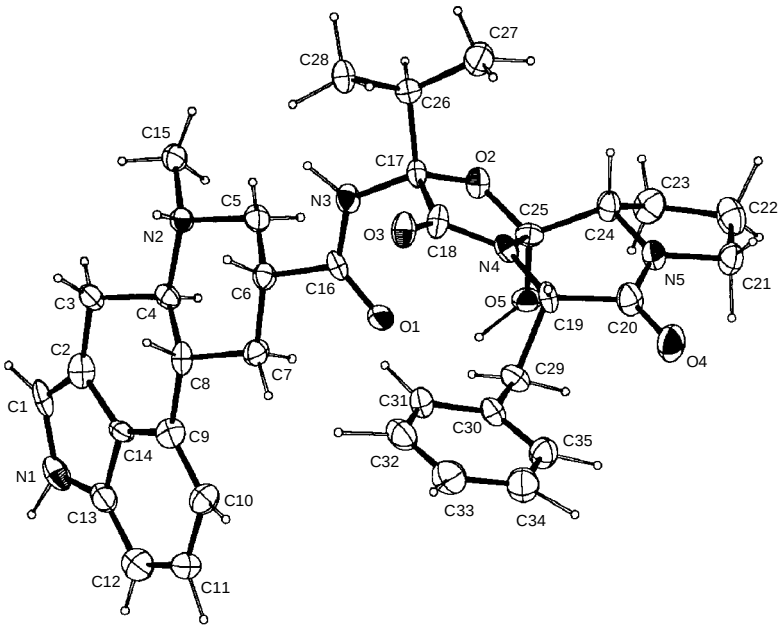


FIG. 1
The ORTEP drawing of dihydroergocristine with the atom numbering

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

Atoms	Distances	Atoms	Distances
S8–O81	1.43(2)	N5–C21	1.464(9)
S8–O82	1.49(2)	N5–C24	1.473(9)
S8–C83	1.74(2)	O5–C25	1.397(9)
S8–O84	1.48(2)	C6–C7	1.53(1)
S9–O91	1.48(2)	C6–C16	1.53(1)
S9–O92	1.40(2)	C7–C8	1.51(1)
S9–C93	1.73(2)	C8–C9	1.53(1)
S9–O94	1.556(16)	C9–C10	1.36(1)
C1–N1	1.38(1)	C9–C14	1.391(9)
C1–C2	1.37(1)	C10–C11	1.44(1)
N1–C13	1.37(1)	C11–C12	1.37(1)
O1–C16	1.228(9)	C12–C13	1.38(1)
C2–C3	1.49(1)	C13–C14	1.44(1)
C2–C14	1.41(1)	C17–C18	1.52(1)
N2–C4	1.547(9)	C17–C26	1.53(1)
N2–C5	1.511(9)	C19–C20	1.52(1)
N2–C15	1.470(9)	C19–C29	1.59(1)
O2–C17	1.444(8)	C21–C22	1.51(1)
O2–C25	1.403(8)	C22–C23	1.53(1)
C3–C4	1.51(1)	C23–C24	1.52(1)
N3–C16	1.337(9)	C24–C25	1.51(1)
N3–C17	1.468(9)	C26–C27	1.50(1)
O3–C18	1.201(9)	C26–C28	1.54(1)
C4–C8	1.53(1)	C29–C30	1.52(1)
N4–C18	1.363(9)	C30–C31	1.39(1)
N4–C19	1.433(8)	C30–C35	1.37(1)
N4–C25	1.458(8)	C31–C32	1.38(1)
O4–C20	1.232(9)	C32–C33	1.36(1)
C5–C6	1.51(1)	C33–C34	1.41(1)
N5–C20	1.335(9)	C34–C35	1.41(1)
Atoms	**Angles**	**Atoms**	**Angles**
N1–C1–C2	109.7(7)	O2–C17–C18	104.0(6)
C1–N1–C13	110.3(7)	C18–C17–C26	114.5(6)
C1–C2–C14	106.2(6)	N4–C18–C17	106.3(6)
C1–C2–C3	136.0(7)	O3–C18–C17	127.9(7)
C3–C2–C14	117.8(6)	O3–C18–N4	125.6(6)
C5–N2–C15	109.9(5)	N4–C19–C29	110.7(5)
C4–N2–C15	114.6(5)	N4–C19–C20	111.4(5)
C4–N2–C5	110.1(5)	C20–C19–C29	108.7(6)

TABLE III
(*Continued*)

Atoms	Angles	Atoms	Angles
C17–O2–C25	112.0(5)	N5–C20–C19	119.2(6)
C2–C3–C4	107.3(6)	O4–C20–C19	118.4(6)
C16–N3–C17	125.6(5)	O4–C20–N5	122.5(7)
N2–C4–C3	109.0(6)	N5–C21–C22	105.4(6)
C3–C4–C8	116.0(6)	C21–C22–C23	106.1(7)
N2–C4–C8	111.2(5)	C22–C23–C24	104.1(7)
C19–N4–C25	120.8(5)	N5–C24–C23	103.5(6)
C18–N4–C19	112.3(5)	C23–C24–C25	117.3(7)
C18–N4–C19	125.9(5)	N5–C24–C25	108.0(6)
N2–C5–C6	112.0(6)	O5–C25–C24	108.6(6)
C21–N5–C24	111.0(5)	N4–C25–C24	109.2(5)
C20–N5–C24	127.3(6)	N4–C25–O5	110.8(5)
C20–N5–C21	121.2(6)	O2–C25–C24	113.1(6)
C5–C6–C16	110.1(6)	O2–C25–O5	111.2(5)
C5–C6–C7	108.7(6)	O2–C25–N4	103.9(5)
C7–C6–C16	113.8(6)	C17–C26–C28	112.1(6)
C6–C7–C8	110.2(6)	C17–C26–C27	111.5(6)
C4–C8–C7	113.7(6)	C27–C26–C28	109.9(7)
C7–C8–C9	113.0(6)	C19–C29–C30	115.3(6)
C4–C8–C9	108.8(5)	C29–C30–C35	120.3(7)
C8–C9–C14	114.3(6)	C29–C30–C31	120.0(6)
C8–C9–C10	126.2(6)	C31–C30–C35	119.7(7)
C10–C9–C14	119.4(7)	C30–C31–C32	119.8(7)
C9–C10–C11	118.6(7)	C31–C32–C33	121.7(8)
C10–C11–C12	122.5(7)	C32–C33–C34	119.2(8)
C11–C12–C13	119.1(7)	C33–C34–C35	119.0(7)
N1–C13–C12	136.3(7)	C30–C35–C34	120.4(7)
C12–C13–C14	118.7(7)	C83–S8–O84	106(1)
N1–C13–C14	105.0(6)	O82–S8–O84	105(1)
C9–C14–C13	121.7(7)	O82–S8–C83	104(1)
C2–C14–C13	108.8(6)	O81–S8–O84	115(2)
C2–C14–C9	129.5(6)	O81–S8–C83	112(1)
N3–C16–C6	115.8(6)	O81–S8–O82	114(1)
O1–C16–C6	120.1(6)	C93–S9–O94	104(1)
O1–C16–N3	124.1(7)	O92–S9–O94	111(1)
O2–C17–N3	108.9(5)	O92–S9–C93	113(1)
N3–C17–C26	108.4(5)	O91–S9–O94	106(1)
N3–C17–C18	111.8(5)	O91–S9–C93	105(1)
O2–C17–C26	109.1(5)	O91–S9–O92	116(1)

TABLE IV
The list of hydrogen bonds

D	H	A	D…A, Å	D–H…A, Å	Symmetry code		
N2	H1N2	O81	2.72(2)	149(6)	*x*	*y*	*z*
N2	H1N2	O91	2.80(2)	160(6)	*x*	*y*	*z*
N3	H1N3	O82	3.085(9)	159(6)	*x*	*y*	*z*
N3	H1N3	O92	3.032(9)	139(5)	*x*	*y*	*z*
O5	H1O5	O1	2.662(6)	131(9)	*x*	*y*	*z*
N1	H1N1	O3′	2.934(7)	130(7)	*x* – 1	*y*	*z* + 1

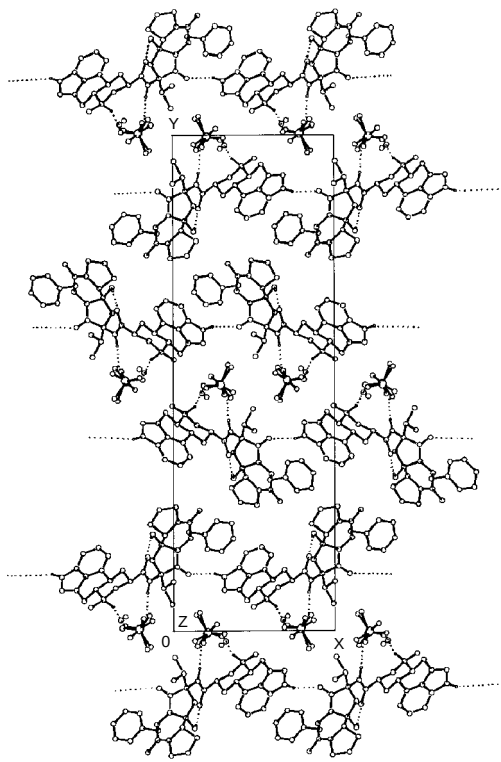


FIG. 2
Packing scheme. Dotted lines represent hydrogen bonds

This work was supported by the Grant Agency of the Czech Republic (Grant No. 203/94/0135).

REFERENCES

1. Berde B.: J. Roy. Soc. Med. *77*, 5 (1984).
2. Brown A. M., Patch T. L., Kaumann A. J.: Br. J. Pharmacol. *104*, 45 (1991).
3. Saxena P. R., DenBoer M. O.: J. Neurol. *238*, S28 (1991).
4. U'Prichard D. C.: *Advances in Biochemical Psychopharmacology*, Vol. 23, p. 103. Raven Press, New York 1980.
5. Franciosi A., Zavattini G.: Curr. Ther. Res. *55*, 1391 (1994).
6. Venn R. D.: *Advances in Biochemical Psychopharmacology*, Vol. 23, p. 363. Raven Press, New York 1980.
7. Husak M., Had J., Kratochvil B., Cvak L., Stuchlik J., Jegorov A.: Collect. Czech. Chem. Commun. *59*, 1624 (1994).
8. Husak M., Kratochvil B., Sedmera P., Stuchlik J., Jegorov A.: Collect. Czech. Chem. Commun. *58*, 2944 (1993).
9. Husak M., Kratochvil B., Jegorov A., Stuchlik J.: Z. Kristallogr. *209*, 363 (1994).
10. Cvak L., Jegorov A., Sedmera P., Havlicek V., Ondracek J., Husak M., Pakhomova S., Kratochvil B., Granzin J.: J. Chem. Soc., Perkin Trans. 2 *1994*, 1861.
11. Pakhomova S., Ondracek J., Husak M., Kratochvil B., Jegorov A., Stuchlik J.: Acta Crystallogr., in press.
12. Flack H. D.: Acta Crystallogr. A *39*, 876 (1983).
13. Hebert H.: Acta Crystallogr. B *35*, 2978 (1979).
14. Cremer D., Pople J. A.: J. Am. Chem. Soc. *97*, 1354 (1975).
15. *International Tables for X-Ray Crystallography*, Vol. IV. Kynoch Press, Birmingham 1974.
16. Sheldrick G. M.: *SHELXL93. Program for the Refinement of Crystal Structures*. University of Gottingen, Gottingen 1993.
17. Nardelli M.: *PARST. System of Computer Routines for Calculating Molecular Parameters from the Results of Crystal Structure*. University of Parma, Parma 1991.
18. Altomare A., Burla M. C., Camalli M., Cascarano G., Giaccovazzo C., Guagliardi A., Polidori G.: *SIR 92 – a Program for Automatic Solution of Crystal Structures by Direct Methods*. J. Appl. Cryst. *27*, 435 (1994).