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Different Crystal Modifications of 3a*β*,4*α*-Dihydro-4*β*,10-dimethyl-2-phenyl-1*H*,3*H*,5*H*-pyrrolo[3,4-*b*]carbazol-1,3-dione – Crystal Data and Theoretical Calculations

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Abstract

Two crystal modifications of $C_{22}H_{18}N_2O_2$ were investigated. Crystal data: $M_r = 342.34$, $\lambda(\mathrm{Cu}\,K\alpha) = 1.5418$ Å, $T = 298$ K; crystal (I): monoclinic, $C2/c$, $a = 14.9853\ (5)$, $b = 10.1607\ (5)$, $c = 23.729\ (2)$ Å, $\beta = 108.680\ (4)^\circ$, $V = 3422.7\ (3)$ Å^3, $Z = 8$, $D_x = 1.333\ \mathrm{g\,cm^{-3}}$, $\mu = 6.04\ \mathrm{cm^{-1}}$, $F(000) = 1440.0$, $R = 0.069$, $wR = 0.081$ for 2628 observed unique reflections; crystal (II): monoclinic, $C2/c$, $a = 14.977\ (9)$, $b = 10.177\ (1)$, $c = 23.663\ (2)$ Å, $\beta = 108.17\ (2)^\circ$, $V = 3426\ (2)$ Å^3, $Z = 8$, $D_x = 1.333\ \mathrm{g\,cm^{-3}}$, $\mu = 6.04\ \mathrm{cm^{-1}}$, $F(000) = 1440.0$, $R = 0.076$, $wR = 0.084$ for 1984 observed unique

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reflections. The hydrogen-bonded molecules of crystals (I) and (II) are differently placed in the (slightly but significantly different) unit cells. Calculations with the program packages *SYBYL* and *CERIUS* provide *e.g.* information about the strong hydrogen bonding and the differences between the unit cells.

Introduction

[*b*]-Annellated carbazoles are of general interest as cytostatically active compounds, while some derivatives of the 6*H*-pyrido[4,3-*b*]carbazole series, for example the ellipticines, are now undergoing clinical trials against several human tumors (Gribble, 1990). In the light of the medical necessity to develop more selective antineoplastic drugs, we have synthesized a variety of annellated carbazole derivatives from appropriately functionalized indoles by way of various pericyclic strategies (Pindur, 1994; Pindur & Haber, 1993; Pindur, Kim, Rogge & Massa, 1992; Dräger, Haber, Erfanian-Abdoust, Pindur & Sattler, 1993) and studied their intercalative interactions towards the B-DNA by means of computer molecular modeling and biophysical tests (Pindur, Haber & Sattler, 1993; Sattler, 1994). In several cases we have performed X-ray structural analyses of the [*b*]-annellated carbazoles and thus obtained reliable starting geometries (Dräger, Haber, Erfanian-Abdoust, Pindur & Sattler, 1993; Schollmeyer, Fischer & Pindur, 1993) for molecular mechanics and dynamics calculations on the drug–DNA intercalation complexes. In the present paper we report, in continuation of our studies, the X-ray structural analysis of the title carbazole derivative 3aβ,4α-dihydro-4β,10-dimethyl-2-phenyl-1*H*,3*H*,5*H*-pyrrolo[3,4-*b*]carbazol-1,3-dione (Fig. 1). The crystal structures (I) and (II) of the title compound were analysed and calculated by molecular mechanics methods in their different crystal packing arrangements. By means of the program package *SYBYL*, the unit cells were freely minimized without constraints, and with the help of the special options of the program package *CERIUS* only the positions of the molecules in the fixed cell were minimized. Thus, the modification of the molecules and the hydrogen bonds in the unit cells as well as the differences between the two crystal structures could be analysed.

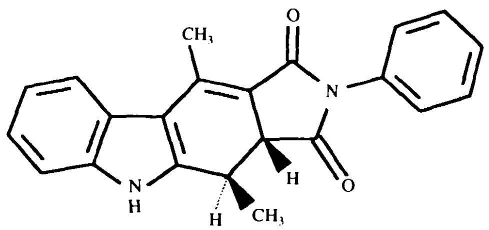

Fig. 1. Molecular diagram of the title compound.

Experimental

The racemic title compound was synthesized, together with other isomeric compounds, in our laboratories starting from *N*-phenylmaleimide and 1,4-dimethylpyrano[3,4-*b*]indol-3-one (Erfanian-Abdoust & Pindur, 1989) *via* Diels–Alder reaction, CO_2 extrusion and stabilization by formal *antara*-[1,5]H shift.

Crystals of (I) and (II) were grown from their solution in acetone with a surrounding acetone/H_2O (I: 1:1, II: 2:1) atmosphere. Weissenberg photographs indicated the monoclinic space group $C2/c$, which was confirmed by the structure analysis. Because of the limited amount of substance available, no powder diffraction analyses to differentiate (I) and (II) were undertaken. The data collection and refinement parameters are summarized in Table 1. The data were corrected for Lorentz and polarization factors; no absorption correction was applied. The direct methods option from *SHELXS86* (Sheldrick, 1985) provided the locations for all non-H atoms. Nearly all H atoms were found by difference-Fourier syntheses, as also were the H_{N5} atoms, which are involved in the hydrogen bonding. Final refinements converged for (I) to $R = 0.069$ and for (II) to $R = 0.076$. Positions and equivalent displacement parameters for non-H atoms are presented in Table 2. Bond lengths and selected bond and torsion angles are listed in Table 3.* A molecular diagram is shown in Fig. 1, the numbering scheme is given in Fig. 2 (*PLUTO*; Motherwell & Clegg, 1978). Figs. 3(*a*) and (*b*) depict, viewed in the direction of the *b* axis, the linear arrangement of the hydrogen-bonded molecules and their different placements in each unit cell.

Molecular mechanics (MM) calculations were performed using the *SYBYL*5.5 (Tripos Associates Inc., 1992) molecular modeling software package installed on a microVAX 3000, employing *SYBYL* Tripos force-field *MAXIMIN*2. Cells (I_x, II_x) with the eight molecules of (I) and (II) in their symmetry-equivalent positions were built up, starting with the geometry from the X-ray analysis. Care was taken to ensure that as many atoms as possible were inside the cell. Using Gasteiger–Hückel charges (Gasteiger & Marsili, 1980) for the electrostatic term $E_{\rm elec}$, the MM energy $E_{\rm tot}$† was obtained by minimization with the termination option r.m.s. GRADIENT [Δ r.m.s. (kcal mol^{-1} Å^{-1}) between two iterations]. The molecular modeling software package *CERIUS* was installed on an IBM RS 6000. The cells I_x and II_x were minimized using the CRYSTAL PACKER and $Q_{\rm eq}$ charges (Rappé & Goddard III, 1991). The GRADIENT termination criterion (Δ0.042 kJ mol^{-1}) was used.

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* Lists of structure factors, isotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: PA0302). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

† $E_{\rm tot}(SYBYL) = E_{\rm bond\ stretching} + E_{\rm angle\ bending} + E_{\rm torsional} + E_{\rm out\text{-}of\text{-}plane\ bending} + E_{\rm elec} + E_{\rm vdW}$.

Table 1. *Crystal data, data collection parameters. solution and refinement*

	(I)	(II)
Crystal data		
Chemical formula	$C_{22}H_{18}N_2O_2$	$C_{22}H_{18}N_2O_2$
Molecular weight	342.34	342.34
Crystal color	Pale yellow	Pale yellow
Crystal size (mm)	0.45 × 0.42 × 0.20	0.10 × 0.18 × 0.22
Absorption μ (cm^{-1})	6.04	6.04
Absorption correction	None	None
Crystal system	Monoclinic	Monoclinic
Space group	*C*2/*c*	*C*2/*c*
a (Å)	14.9853 (5)	14.977 (9)
b (Å)	10.1607 (5)	10.177 (1)
c (Å)	23.729 (2)	23.663 (2)
β (°)	108.680 (4)	108.17 (2)
V (Å^3)	3422.7 (3)	3426 (2)
Z	8	8
F(000)	1440.0	1440.0
No of reflections for cell parameters	75	66
Range for cell parameters (°)	$60 < \theta < 70$	$61 < \theta < 70$
Temperature (K)	298	298
D_x (g cm^{-3})	1.333	1.333
Data collection		
Diffractometer	Enraf–Nonius CAD-4	Enraf–Nonius CAD-4
Radiation	Cu $K\alpha$	Cu $K\alpha$
Wavelength (Å)	1.5418	1.5418
Scan type	$\omega/2\theta$	$\omega/2\theta$
$\theta_{\max}$ (°)	70.0	70.0
Rangle of h, k, l	$-19 \rightarrow 0$	$0 \rightarrow 18$
	$0 \rightarrow 13$	$0 \rightarrow 12$
	$-29 \rightarrow 29$	$-28 \rightarrow 28$
No. of measured reflections	3575	3583
No. of independent reflections	3025	2743
R_{int}	0.061	0.069
No. of observed reflections	2628 $[F/\sigma(F) > 4.0]$	1984 $[F/\sigma(F) > 4.0]$
No. of standard reflections	3 every 4000 s	3 every 4000 s
Intensity variation (%)	5	5
Data reduction		
Corrections	Lorentz and polarization correction Correction of the variation of the intensity of the standard reflections with cubic spline function	
Solution and refinement		
Solution	Direct methods (*SHELXS*86; Sheldrick, 1986)	
Refinement	Full-matrix refinement (*SHELX*76; Sheldrick, 1976)	
Atomic scattering factors	*SHELX*76 (Sheldrick, 1976)	
Extinction parameter	*SHELX*76 (Sheldrick, 1976)	
No. of parameters used	255	236
Treatment of H-atoms	Riding with grouped isotropic parameters	Riding with fixed isotropic parameters
Extinction parameter	0.0030 (6)	0.0018 (5)
R	0.069	0.076
wR	0.081	0.084
S	4.81	3.74
Weighting	$1/[\sigma^2(F_o) + 0.00087F_o^2]$	$1/[\sigma^2(F_o) + 0.00084F_o^2]$
$(\Delta/\sigma)_{\max}$	0.001	0.001
$\Delta\rho_{\max}$ (e Å^{-3})	0.523	0.498
$\Delta\rho_{\min}$ (e Å^{-3})	−0.351	−0.283

Table 2. *Fractional atomic coordinates and equivalent isotropic thermal parameters* (Å^2)

$$U_{\text{eq}} = (1/3)\textstyle\sum_i \sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i \mathbf{a}_j.$$

	x	y	z	U_{eq}
(I)				
O1	0.0617 (1)	0.4432 (3)	0.66908 (9)	0.0825 (9)
O2	0.1174 (1)	0.1556 (2)	0.53697 (9)	0.0659 (8)
C1	0.0756 (2)	0.2396 (3)	0.5549 (1)	0.0502 (9)
N2	0.1105 (1)	0.2954 (2)	0.61168 (9)	0.0516 (7)
C3	0.0504 (2)	0.3911 (3)	0.6221 (1)	0.0564 (10)
C3*A*	−0.0246 (2)	0.4142 (4)	0.5639 (1)	0.069 (1)
C4	−0.1186 (2)	0.4591 (3)	0.5611 (1)	0.0570 (10)
C4*A*	−0.1853 (2)	0.4307 (2)	0.5011 (1)	0.0458 (8)
N5	−0.2757 (1)	0.4779 (2)	0.47960 (9)	0.0561 (8)
C5*A*	−0.3195 (2)	0.4235 (3)	0.4245 (1)	0.0513 (9)
C6	−0.4112 (2)	0.4115 (3)	0.3861 (1)	0.066 (1)
C7	−0.4370 (2)	0.3752 (4)	0.3328 (1)	0.070 (1)
C8	−0.3748 (2)	0.2951 (3)	0.3170 (1)	0.068 (1)
C9	−0.2828 (2)	0.2771 (3)	0.3546 (1)	0.0574 (10)
C9*A*	−0.2547 (2)	0.3409 (2)	0.4098 (1)	0.0474 (8)
C9*B*	−0.1694 (2)	0.3462 (2)	0.4602 (1)	0.0434 (8)
C10	−0.0820 (2)	0.2727 (2)	0.4741 (1)	0.0463 (8)
C10*A*	−0.0151 (2)	0.3031 (3)	0.5260 (1)	0.0508 (9)
C11	0.1963 (2)	0.2558 (3)	0.6562 (1)	0.0498 (8)
C12	0.2076 (2)	0.1290 (3)	0.6772 (1)	0.0578 (10)
C13	0.2902 (2)	0.0928 (3)	0.7206 (1)	0.068 (1)
C14	0.3615 (2)	0.1835 (4)	0.7422 (1)	0.071 (1)
C15	0.3495 (2)	0.3092 (4)	0.7219 (2)	0.081 (1)
C16	0.2672 (2)	0.3483 (3)	0.6782 (1)	0.068 (1)
C17	−0.0720 (2)	0.1666 (3)	0.4329 (2)	0.075 (1)
C18	−0.1293 (2)	0.5884 (4)	0.5880 (2)	0.079 (1)
(II)				
C1	0.2702 (3)	0.5109 (4)	0.4453 (2)	0.057 (2)
N2	0.3472 (3)	0.4567 (4)	0.3881 (2)	0.061 (1)
C3	0.1772 (3)	0.3608 (5)	0.3775 (2)	0.069 (2)
C3*A*	0.1584 (4)	0.3408 (6)	0.4351 (2)	0.092 (2)
C4	0.0695 (3)	0.2897 (5)	0.4389 (2)	0.065 (2)
C4*A*	0.0623 (3)	0.3176 (4)	0.4981 (2)	0.053 (2)
N5	−0.0049 (3)	0.2696 (4)	0.5199 (2)	0.066 (2)
C5*A*	0.0058 (3)	0.3230 (5)	0.5754 (2)	0.061 (2)
C6	−0.0486 (4)	0.3039 (5)	0.6135 (2)	0.079 (2)
C7	−0.0214 (4)	0.3698 (6)	0.6668 (2)	0.084 (2)
C8	0.0571 (4)	0.4507 (6)	0.6826 (2)	0.078 (2)
C9	0.1095 (3)	0.4705 (5)	0.6444 (2)	0.067 (2)
C9*A*	0.0844 (3)	0.4070 (4)	0.5900 (2)	0.055 (2)
C9*B*	0.1192 (3)	0.4036 (4)	0.5394 (2)	0.053 (2)
C10	0.1917 (3)	0.4767 (4)	0.5258 (2)	0.053 (2)
C10*A*	0.2071 (3)	0.4487 (4)	0.4737 (2)	0.059 (2)
C11	0.2892 (3)	0.4957 (5)	0.3434 (2)	0.062 (2)
C12	0.2802 (3)	0.6234 (5)	0.3231 (2)	0.067 (2)
C13	0.3212 (4)	0.6582 (5)	0.2800 (2)	0.080 (2)
C14	0.3687 (4)	0.5680 (6)	0.2580 (2)	0.084 (2)
C15	0.3767 (4)	0.4413 (6)	0.2785 (3)	0.096 (3)
C16	0.3383 (4)	0.4024 (5)	0.3219 (2)	0.078 (2)
O1	0.1418 (3)	0.3084 (4)	0.3306 (2)	0.097 (2)
O2	0.3295 (2)	0.5934 (3)	0.4633 (1)	0.073 (1)
C17	0.2439 (4)	0.5814 (5)	0.5669 (2)	0.083 (2)
C18	0.0338 (4)	0.1621 (5)	0.4120 (2)	0.089 (2)

Table 3. *Bond distances* (Å), *selected bond and torsion angles* (°)

(I)		(II)	
O1—C3	1.195 (4)	C3—O1	1.196 (6)
O2—C1	1.213 (3)	C1—O2	1.200 (6)
C1—N2	1.401 (3)	C1—N2	1.400 (6)
C1—C10*A*	1.461 (4)	C1—C10*A*	1.464 (6)
N2—C3	1.400 (4)	N2—C3	1.398 (6)
N2—C11	1.435 (3)	N2—C11	1.445 (6)
C3—C3*A*	1.494 (4)	C3—C3*A*	1.489 (7)
C3*A*—C4	1.462 (4)	C3*A*—C4	1.457 (7)
C3*A*—C10*A*	1.479 (4)	C3*A*—C10*A*	1.469 (7)
C4—C4*A*	1.482 (4)	C4—C4*A*	1.466 (7)
C4—C18	1.492 (5)	C4—C18	1.471 (7)
C4*A*—N5	1.372 (3)	C4*A*—N5	1.358 (6)
C4*A*—C9*B*	1.372 (4)	C4*A*—C9*B*	1.388 (6)
N5—C5*A*	1.378 (3)	N5—C5*A*	1.384 (6)
C5*A*—C6	1.396 (4)	C5*A*—C6	1.404 (7)
C5*A*—C9*A*	1.409 (4)	C5*A*—C9*A*	1.408 (6)
C6—C7	1.374 (4)	C6—C7	1.373 (7)

Table 3 (*cont.*)

(I)		(II)	
C7—C8	1.378 (5)	C7—C8	1.387 (8)
C8—C9	1.393 (4)	C8—C9	1.383 (7)
C9—C9*A*	1.399 (4)	C9—C9*A*	1.385 (6)
C9*A*—C9*B*	1.446 (3)	C9*A*—C9*B*	1.448 (6)
C9*B*—C10	1.451 (3)	C9*B*—C10	1.433 (6)
C10—C10*A*	1.351 (4)	C10—C10*A*	1.352 (6)
C10—C17	1.494 (4)	C10—C17	1.490 (7)
C11—C12	1.372 (4)	C11—C12	1.377 (7)
C11—C16	1.389 (4)	C11—C16	1.390 (7)
C12—C13	1.382 (4)	C12—C13	1.391 (7)
C13—C14	1.379 (5)	C13—C14	1.360 (8)
C14—C15	1.356 (5)	C14—C15	1.370 (9)
C15—C16	1.391 (5)	C15—C16	1.382 (8)
N2—C1—O2	123.1 (2)	O2—C1—N2	123.4 (3)
C10*A*—C1—N2	106.1 (2)	C10*A*—C1—N2	106.0 (3)
C3—N2—C1	112.8 (2)	C3—N2—C1	113.1 (3)
C11—N2—C1	124.4 (2)	C11—N2—C1	124.6 (3)
N2—C3—O1	124.5 (2)	O1—C3—N2	124.6 (4)
C3*A*—C3—N2	106.4 (2)	C3*A*—C3—N2	106.1 (4)
C4*A*—C4—C3*A*	109.1 (2)	C4*A*—C4—C3*A*	109.3 (4)
C9*B*—C4*A*—C4	125.7 (2)	C9*B*—C4*A*—C4	125.6 (3)
C10—C9*B*—C4*A*	120.7 (2)	C10—C9*B*—C4*A*	120.7 (3)
C5*A*—N5—C4*A*	109.1 (2)	C5*A*—N5—C4*A*	109.8 (3)
O2—C1—N2—C3	179.5 (3)	O2—C1—N2—C3	178.9 (5)
O2—C1—C10*A*—C10	9.3 (4)	O2—C1—C10*A*—C10	7.8 (6)
C1—N2—C11—C12	−60.2 (3)	C1—N2—C11—C12	−60.8 (5)
N2—C3—C3*A*—C4	152.5 (3)	N2—C3—C3*A*—C4	155.9 (5)
C3—C3*A*—C10*A*—C1	−14.4 (3)	C3—C3*A*—C10*A*—C1	−12.8 (4)
C10*A*—C3*A*—C4—C4*A*	−28.2 (3)	C10*A*—C3*A*—C4—C4*A*	−24.1 (5)
C4—C3*A*—C10*A*—C1	−154.1 (3)	C4—C3*A*—C10*A*—C1	−158.2 (5)
C3*A*—C4—C4*A*—N5	−169.0 (3)	C3*A*—C4—C4*A*—N5	−170.9 (5)
C4*A*—C9*B*—C10—C17	170.7 (3)	C4*A*—C9*B*—C10—C17	171.9 (5)
C18—C4—C4*A*—C9*B*	155.1 (3)	C18—C4—C4*A*—C9*B*	154.9 (5)
C4*A*—N5—C5*A*—C6	179.4 (3)	C4*A*—N5—C5*A*—C6	178.4 (5)
C9—C9*A*—C9*B*—C10	−7.5 (4)	C9—C9*A*—C9*B*—C10	−5.6 (7)
C4*A*—C9*B*—C10—C10*A*	−6.8 (3)	C4*A*—C9*B*—C10—C10*A*	−5.9 (5)
O1—C3—C10*A*—C13	−29.3 (4)	O1—C3—C3*A*—C4	−24.2 (7)
C4—C3*A*—C10*A*—C10	26.2 (3)	C4—C3*A*—C10*A*—C10	22.2 (6)
C16—C11—C12—C13	−0.1 (4)	C16—C11—C12—C13	0.2 (6)

Results and discussion

Bond distances and angles, and torsion angles of the crystal structures (I) and (II) show standard values. A comparison of (I) with (II) reveals some statistical deviations (standard deviation 3δ on mean value) for the unit-cell parameters *b*, *c* and β and for the torsion angles in the region C10*A*/C1/N2/C3/O1/C3*A*/C4/C18/C4*A*. The molecule in the crystal structure (I) is somewhat more twisted in the five-membered amide ring/six-membered ring system than in (II), *e.g.* O1—C3—C3*A*—C4 for (I) −29.3 (4)° against (II) −24.2 (7)° as the highest deviation found, or C4—C3*A*—C10*A*—C1 for (I) −154.1 (3)° against (II) 158.2 (5)°.

The single bonds C9*B*—C10 of the diene partial structure C4*A*—C9*B*—C10—C10*A* in (I) with 1.451 (3) Å and in (II) with 1.433 (6) Å are typical for a single bond in a conjugated system of the butadiene type, as found for some 3-vinyl-1*H*-indoles [1.41–1.47 Å (Fischer & Pindur, 1995)].

The H atoms bonded on the sp^3 hybridized atoms C3*A* and C4 are in the *s-trans* conformation; H_{C4} could be localized in both cases, the position of H_{C3A} is sterically unequivocally determined. The hydrogen bond lengths, bond angles and the partial contributions $E_{\rm tot(H\,bond)}$ of one $O_2\cdots H_{5N}$ bond to the calculated $E_{\rm tot}$ are summarized in Table 4; they differ for the cells minimized by *SYBYL* because the program takes no account of the symmetry relations.

Although the separation of N5···O2 with 3.01 Å in the crystal structures is a little too long for a strong hydrogen bond (Testa, 1983), the respective angles are found to be 172.35 (I) and 177.34° (II); angles close to 180° are characteristic for strong hydrogen bonds (Brown, 1976). In crystal structures, stabilizing electrostatic and van der Waals (vdW) effects, charge distribution, crystal packing forces and the type of hydrogen bonds (*e.g.* N—H···O or O—H···O) influence the strength and the geometric parameters of hydrogen bonds. MM minimizations with *SYBYL* and *CERIUS* both keep the strong hydrogen bondings [see $E_{\rm tot(H\,bond)}$], but modify their geometry (Table 4).

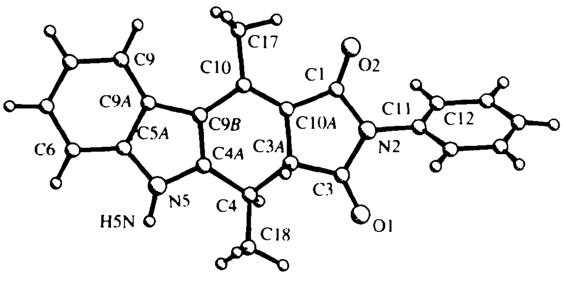

Fig. 2. *PLUTO* (Motherwell, 1978) plot of (I). The IUPAC numbering scheme is used for (I) and (II).

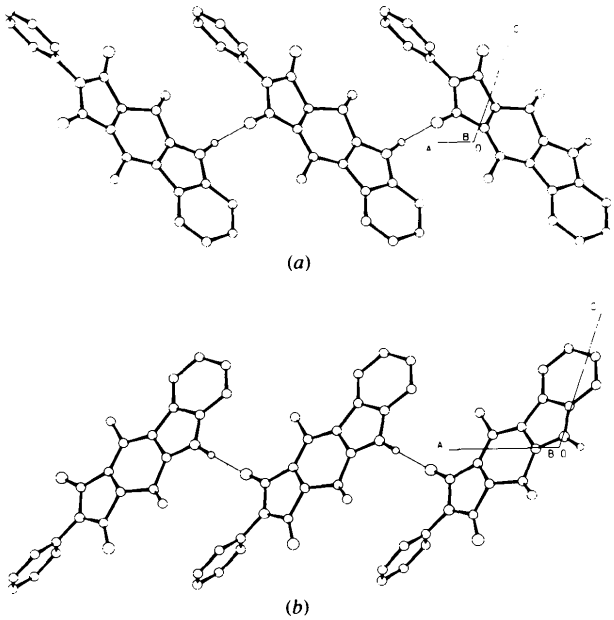

Fig. 3. View of the crystal structure of (*a*) (I) and (*b*) (II). The linear alignment of neighbouring molecules by hydrogen bonds is indicated by thin lines.

Table 4. *Distances* (Å) *angles* (°) *and contributions to* E_{tot} (kJ mol^{-1}) *of the hydrogen bonds in the X-ray and in the calculated structures*

	Crystal structure unminimized cell		*SYBYL* minimized cell		*CERIUS* minimized cell	
	I_x	II_x	I_{SYBYL}	II_{SYBYL}	I_{CERIUS}	II_{CERIUS}
$H5—H_{5N}$	0.995 (3)	0.984 (5)	1.04/1.04	1.04/1.04	0.995	0.984
$O2\cdots H_{5N}$	2.025 (3)	2.031 (5)	1.77/1.69	1.68/1.72	2.269	2.315
$N5\cdots O2$	3.014 (3)	3.014 (5)	2.80/2.66	2.66/2.61	3.249	3.255
$N55—H_{5N}—O2$	172.4 (2)	177.3 (3)	168.06/153.24	156.30/141.60	168.24	159.57
SYBYL						
$E_{tot(H\ bond)}$	−30.98	−30.77	−39.44/−41.95	−42.20/−41.28		
CERIUS:						
$E_{tot(H\ bond)}$	−23.78	−24.49			−21.85	−22.57

Besides changes in the intramolecular geometry a full minimization with *SYBYL* also leads to changes in the cell arrangements. The E_{tot} values of the created cells differ before minimization by *ca* 27.0% (II_{SYBYL} 3736.3 kJ mol^{-1} > I_{SYBYL} 2728.5 kJ mol^{-1}) and after minimization by about 13.6% (I_{SYBYL} 453.8 kJ mol^{-1} > II_{SYBYL} 391.9 kJ mol^{-1}), mainly because of the different energy decrease by van der Waals contacts in the minimized cells [$E_{vdW}(I_{SYBYL}) > E_{vdW}(II_{SYBYL})$: *ca* 66.99 kJ mol^{-1}], because E_{tot} is strongly dependent on the created cell arrangement. The tendency is apparent that both created cells I_{SYBYL} and II_{SYBYL} converge to the same energy but they, as well as the nonminimized cells I_x and II_x, seem to be energetically different.

Energy differences in crystal packing should, therefore, be calculated using periodic boundary conditions. Lattice parameters and the molecular geometry of the molecule were held fixed and only their orientations in the unit cell were refined with respect to the space-group symmetry. Calculations with the *CERIUS* crystal packer indicate that the crystal packings of I_x and II_x are energetically equivalent: I_x is with an E_{tot}* of −1375.87 kJ per cell energetically favored over II_x with −1320.52 kJ per cell by only 4%, the minimized cell I_{CERIUS} with −1398.43 kJ per cell is energetically favored over II_{CERIUS} with −1367.66 kJ per cell by *ca* 2.2%.

The results of the present calculations reveal the similar highly stablizing contributions of the hydrogen bonds in both crystal structures, although the great variability of hydrogen bonds (Brown, 1976) cannot be described with only one MM parameter set – we agree to the referee's comment. *CERIUS* indicates further that both cells are approximately energetically equivalent. Since the crystals were grown under nearly identical conditions and in view of these calculations, the probability for obtaining crystals (I) or (II) seems to be practically the same.

Furthermore, two continuing statements should be pointed out due to these results: First, that powder pattern should be made from the *hole* batch of a compound and be compared with the calculated powder pattern, and second, that minimizing the energy of built-up cells (*CERIUS*!) combined with the measurement of the density of crystals is not sufficient to make an *absolute* prediction of crystal structures.

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* E_{tot} (special *CERIUS* crystal packer option) = $E_{elec} + E_{vdW} + E_{H\ bond}$.