Characterization of Two Polymorphic Forms of Tolfenamic Acid, *N*-(2-Methyl-3-chlorophenyl)anthranilic Acid: Their Crystal Structures and Relative Stabilities

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The crystal structures of two polymorphic forms of tolfenamic acid have been determined by *X*-ray diffraction methods. The two forms contain the molecule as different conformers. In the yellow form the planes of the two benzene rings form an angle of 46°, in the white one the corresponding angle is 73°. This difference is also reflected in the geometry of the amino group, where the yellow form exhibits a larger degree of conjugation. An analysis of the crystal structures and their physical properties suggests that the yellow form is the stable low temperature modification.

Tolfenamic acid, *N*-(3-chloro-2-methylphenyl)anthranilic acid, is a potent anti-inflammatory drug which inhibits the biosynthesis of prostaglandins as effectively as indomethacin and in markedly lower concentrations than acetylsalicylic acid.[1] Like other fenemates it also has an inhibitory action on prostaglandin receptors. Tolfenamic acid is normally precipitated as a white crystalline material, however, occasionally a yellow crystalline form is generated instead. The biological activity of tolfenamic acid and its actual use in medicine makes it important to establish the structures of the yellow and white forms and to relate the structures to their physical properties. Furthermore, such an analysis should facilitate the industrial manufacturing of tolfenamic acid in the medicinally preferred white modification.

Results and Discussion

The *X*-ray structure determinations revealed that the white and yellow form of tolfenamic acid contain different conformers, as shown in Figure 1. Thus tolfenamic acid exhibits a type of polymorphism earlier[2] classified as conformational. The phenyl rings of tolfenamic acid are planar in both structures with an interplanar angle of 73° in the white form and 46° in the yellow form. The colour difference between the two compounds could lead one to expect that the conjugated system has a larger extension in the yellow form than in the white. Table 1 contains a listing of the bond lengths and angles observed in the two structures. An inspection of this table shows that the only significant difference between the two structures is found in the geometry of the amino group [N(10)]. In the white form the two N–C(phenyl) bonds are markedly different N(10)–C(9) = 1.372(2) Å and N(10)–C(11) = 1.423(2) Å, compared with the more equivalent distances in the yellow form 1.377(1) Å and 1.406(1) Å. The C(9)–N(10)–C(11) angle is 124.3(1)° in the white form and 129.04(5)° in the yellow form. Since both phenyl groups have bulky substituents the more planar arrangement in the yellow form could result in short intramolecular contacts. The larger C(9)–N(10)–C(11) angle in the yellow form has the effect of reducing some of these contacts. From the drawing in Figure 1(*b*) of the yellow form it is apparent that there are short contacts between hydrogen atoms bonded to N(10), C(17), C(8), and C(12), H[N(10)]–H[C(17)] = 2.14(2) Å and H[(C(8)–H[C(12)] = 2.330(14) Å. Similar short intramolecular distances are not observed in the white form where the shortest H–H distance is 2.3(2) Å between H[C(8)] and H[C(17)] from a molecule related by translational symmetry along the *a*-axis.

Both modifications of tolfenamic acid form hydrogen bonded dimers in the crystal as frequently observed for carboxylic acids. The packing arrangements in the two crystal forms are shown in Figures 2 and 3. An inversion centre relates the hydrogen bonded dimers in both structures. The geometry and apparent strength of the hydrogen bonds are identical in the two modifications, O(2)–O(3) is 2.648(3) in the white and 2.6479(9) Å in the yellow form; the O(2)–H(21)–O(3) angles are 170(4) and 176(2)° respectively. In addition to this intermolecular hydrogen bond both conformers of tolfenamic acid seem to be stabilized by an intramolecular hydrogen bond between N(10) and O(3). The N(10)–O(3) distance is 2.676(3) in the white and 2.653(1) Å in the yellow form, the N(10)–H(101)–O(3) angles are 141(2) and 138(1)°.

Other compounds related to tolfenamic acid are known for their biological activity and are used as anti-inflammatory analgesics. Some of these have been characterized structurally.[3–7] In all these crystal structures the molecules form hydrogen bonded dimers and the carboxylic acid group is almost coplanar with the phenyl group to which it is bonded, as observed in the two modifications of tolfenamic acid. The interplanar angle between the two aromatic rings exhibits much larger variations. In niflumic acid,[5] 2-[(3- trifluoromethylphenyl)amino]pyridine-3-carboxylic acid, the two rings are almost coplanar making an angle of 9°, whereas in meclofenamic acid,[6] *N*-(2,6-dichloro-3-methylphenyl)anthranilic acid, the two planes are virtually perpendicular, the angle between the planes being 81°. It seems obvious that the conformation of the molecules is determined by steric interactions between the substituents on the phenyl groups. In meclofenamic acid, which has two equivalent chlorine atoms close to the amino group, the molecule is in a conformation in which the two phenyl rings are almost perpendicular, thus reducing the steric interactions.

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† Deceased.

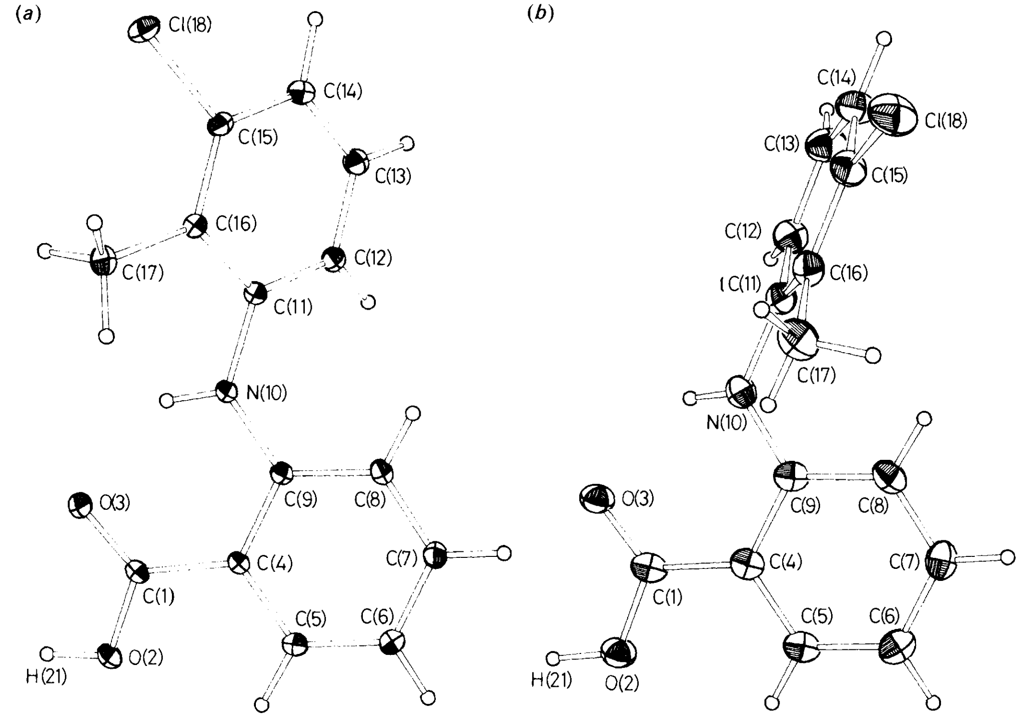

Figure 1. ORTEP drawings showing the yellow (*a*) and the white (*b*) forms of tolfenamic acid. The thermal ellipsoids are scaled to include 50% probabilities. The hydrogen atoms are drawn as spheres.

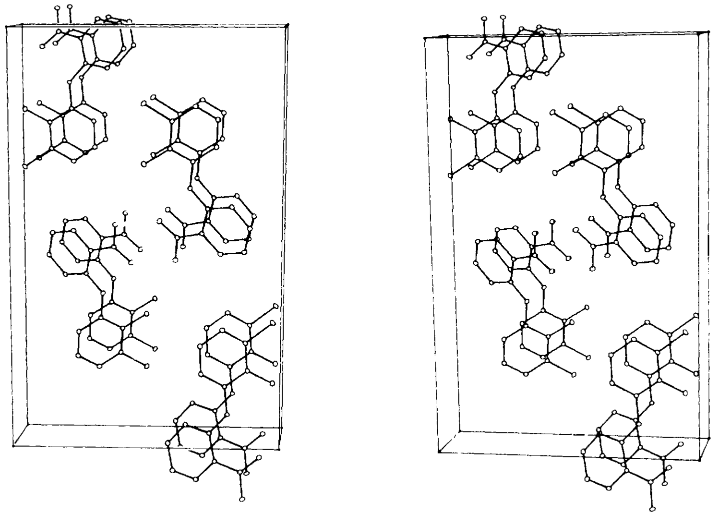

Figure 2. Stereo pair illustrating the packing in the yellow form of tolfenamic acid viewed perpendicular to the *b,c* plane.

Flufenamic acid, *N*-(3-trifluoromethylphenyl)anthranilic acid, has also been isolated in two different crystal forms,[3,7] which contain the molecule as different conformers. The angles between the two phenyl rings are 53° and 43° in the two conformers. In tolfenamic acid we found that the difference in conformation lead to significant variations in the geometry of the amino group. The structural data for the related compounds are not, in all cases, of an accuracy that allows for the observation of small variations in the N–C distances, but the C–N–C angles show a systematic variation with the conformation of the phenyl group. The C–N–C angle is 123° in meclofenamic acid with two perpendicular phenyl rings[6] and 131° in niflumic acid where the phenyl rings are almost coplanar. In the structure of 4-(4-nitroanilino)phenylisothiocyanate[8] the C–N–C angle is 128° and the angle between the two benzene rings is 47°, which compares well with the results for the yellow form of tolfenamic acid.

A major reason for determining the crystal structures was to obtain insight into the relative stability of the two forms. A comparison of their physical data shows that the yellow form is slightly more dense than the white form at room temperature and at 110 K. The melting point is also slightly higher (214.5 °C, 487.65 K) than that of the white form (210.9 °C, 484.05 K). This could indicate that the yellow is the stable low temperature form, which is supported by the observation that the crystal of the white form deteriorated at 110 K during the data collection. It is likely that the less dense packing of the white form could be related to larger thermal vibrations, as is apparent from Figure 1.

Solutions of the two modifications are colourless and have identical physical properties. As the conformation of tolfenamic acid seems strongly influenced by steric interactions, ^1H n.m.r. in perdeuteriated acetone was recorded in the temperature

Table 1. Bond lengths/Å and bond angles/°.

	Yellow form	White form
C(1)–O(2)	1.323(1)	1.334(2)
C(1)–O(3)	1.241(1)	1.234(2)
C(1)–C(4)	1.469(1)	1.458(2)
C(4)–C(5)	1.406(1)	1.406(2)
C(4)–C(9)	1.425(1)	1.422(2)
C(5)–C(6)	1.381(1)	1.377(2)
C(6)–C(7)	1.399(1)	1.392(2)
C(7)–C(8)	1.381(1)	1.373(2)
C(8)–C(9)	1.411(1)	1.410(2)
C(9)–N(10)	1.377(1)	1.372(2)
N(10)–C(11)	1.406(1)	1.423(2)
C(11)–C(12)	1.401(1)	1.377(2)
C(11)–C(16)	1.413(1)	1.410(2)
C(12)–C(13)	1.391(1)	1.382(2)
C(13)–C(14)	1.392(1)	1.388(2)
C(14)–C(15)	1.388(1)	1.374(2)
C(15)–C(16)	1.395(1)	1.402(2)
C(15)–Cl(18)	1.746(1)	1.752(1)
C(16)–C(17)	1.507(1)	1.481(2)
O(2)–C(1)–O(3)	121.18(5)	120.8(1)
O(2)–C(1)–C(4)	115.27(5)	115.0(1)
O(3)–C(1)–C(4)	123.56(5)	124.2(1)
C(1)–C(4)–C(5)	118.59(5)	119.8(1)
C(1)–C(4)–C(9)	121.82(5)	121.3(1)
C(5)–C(4)–C(9)	119.59(5)	118.9(1)
C(4)–C(5)–C(9)	121.52(5)	121.8(1)
C(5)–C(6)–C(7)	118.71(5)	118.9(1)
C(6)–C(7)–C(8)	121.28(5)	120.8(1)
C(7)–C(8)–C(9)	120.93(5)	121.5(1)
C(4)–C(9)–C(8)	117.88(5)	118.1(1)
C(4)–C(9)–N(10)	119.96(5)	121.7(1)
C(8)–C(9)–N(10)	122.13(5)	120.2(1)
C(9)–N(10)–C(11)	129.04(5)	124.3(1)
N(10)–C(11)–C(12)	122.02(5)	119.1(1)
N(10)–C(11)–C(16)	117.35(5)	119.4(1)
C(12)–C(11)–C(16)	120.45(5)	121.4(1)
C(11)–C(12)–C(13)	120.23(5)	121.1(2)
C(12)–C(13)–C(14)	120.48(5)	119.4(2)
C(13)–C(14)–C(15)	118.44(5)	118.9(2)
C(14)–C(15)–C(16)	123.31(5)	123.8(1)
C(14)–C(15)–Cl(18)	117.58(4)	117.4(1)
C(16)–C(15)–Cl(18)	119.11(4)	118.7(1)
C(11)–C(16)–C(15)	117.09(5)	115.4(1)
C(11)–C(16)–C(17)	121.62(5)	122.7(1)
C(15)–C(16)–C(17)	121.30(5)	121.9(1)

range 290–210 K in order to investigate whether a preferred conformation exists. The spectra showed no significant temperature variation in the interval studied, indicating that tolfenamic acid does not exist in any favoured conformation between 210 K and 290 K. The heats of fusion for the two polymorphic forms were obtained from differential thermal analysis, ΔH_{fus}(white) = 42.50 kJ mol^{-1} and ΔH_{fus}(yellow) = 48.40 kJ mol^{-1}. As the liquid phases resulting from melting of the two forms are identical, these results indicate that the yellow form is stabilized by *ca.* 6 kJ mol^{-1} relative to the white. We have attempted to determine the transition temperature by measuring the solubility in propan-2-ol as a function of temperature for the two modifications. In the investigated temperature range the two forms have comparable solubilities, but as kinetic factors seem to influence the precipitation strongly, it was virtually impossible to obtain thermodynamic equilibrium. However, the experiments indicate that the transition temperature is in the range 273.15–283.15 K.

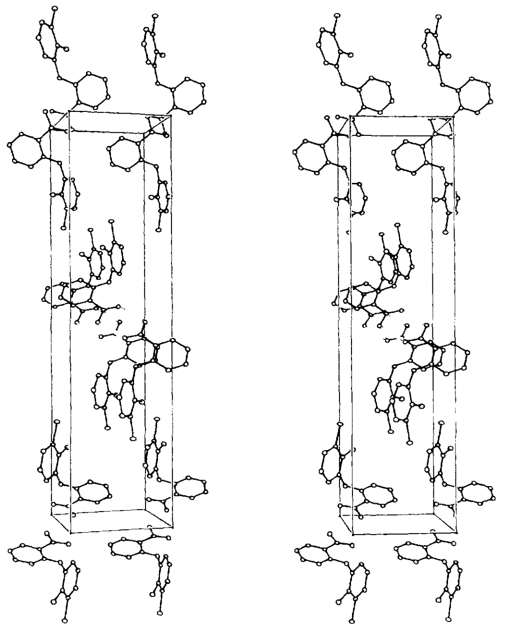

Figure 3. Stereo pair illustrating the packing in the white form of tolfenamic acid viewed perpendicular to the *b,c* plane.

Experimental

Tolfenamic acid was supplied from GEA Ltd. A Mettler TA 3000 differential scanning calorimeter was used for the determination of the heat of fusion and melting point. ^{1}H N.m.r. spectra were recorded as a function of temperature in the range 290–210 K (250 MHz; solvent [^{2}H$_6$]acetone; internal standard tetramethylsilane) δ_{H} 2.31 (3 H, s, CH$_3$), 6.75–7.42 (7 H, m, aromatic), 8.01–8.05 (1 H, q, amine), and 9.59 (1 H, s, carboxylic acid).

X-*Ray Crystallography*.*—Crystals suitable for the *X*-ray diffraction experiment were obtained by recrystallization from absolute ethanol for the white form; crystals of the yellow form can be obtained by rapid cooling of a boiling 96% ethanol solution using an ice bath. The crystal data and a summary of the data collection and structure refinement results for the two crystalline forms are given in Table 4. An account of the two structure determinations is presented below.

White form of tolfenamic acid. Weissenberg photographs of the white plate crystals showed that they belonged to the monoclinic system. The systematically absent reflections $h0l$ for $l = 2n + 1$ and $0k0$ for $k = 2n + 1$ are only consistent with the space group $P2_1/c$. The plates were elongated in the direction of the a-axis, and the plate face was [010]. A single crystal 0.35 × 0.15 × 0.14 mm was selected for the data collection on a Picker FACS 1 diffractometer. Due to the long translational period along the *b*-axis, Cu-K_{α} radiation obtained from a graphite monochromator was used for the data collection. The crystal was cooled to *ca.* 110 K during the data collection by a modified Enraf–Nonius gas flow low temperature device. The temperature was monitored by a thermocouple placed a few centimetres above the crystal in the exhaust pipe; the variations were within 1 K. Fourteen reflections and their Friedel mates with $18.1 < \theta < 25.5°$ were used in the refinement of the unit cell parameters. The diffractometer was operated in the $\omega/2\theta$ scan mode, with a rate of 1° min^{-1} in 2θ. The scan range was

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* *Supplementary data* [see section 5.6.3 of Instructions for Authors (1989), in the January issue]. Full lists of bond lengths and angles and of thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

Table 2. Fractional co-ordinates for the yellow modification.

Atom	*x*	*y*	*z*
Cl(18)	0.158 19(5)	0.162 87(1)	0.476 90(1)
O(2)	0.890 4(2)	0.538 20(3)	0.385 92(4)
O(3)	0.813 5(2)	0.444 61(3)	0.441 99(4)
N(10)	0.541 5(2)	0.360 54(3)	0.324 61(5)
C(1)	0.777 8(2)	0.481 55(3)	0.375 95(5)
C(4)	0.608 7(2)	0.466 60(3)	0.282 74(5)
C(5)	0.559 7(2)	0.513 25(3)	0.215 42(5)
C(6)	0.392 6(2)	0.502 73(4)	0.127 55(6)
C(7)	0.263 5(2)	0.444 44(4)	0.106 57(5)
C(8)	0.309 4(2)	0.397 42(3)	0.170 70(5)
C(9)	0.488 7(2)	0.406 72(3)	0.259 78(5)
C(11)	0.4736(2)	0.298 04(3)	0.313 60(5)
C(12)	0.552 3(2)	0.266 28(3)	0.232 28(5)
C(13)	0.502 1(2)	0.203 72(4)	0.226 63(5)
C(14)	0.379 0(2)	0.171 86(3)	0.302 17(6)
C(15)	0.306 5(2)	0.204 00(3)	0.382 58(5)
C(16)	0.346 9(2)	0.266 83(3)	0.391 17(5)
C(17)	0.259 7(2)	0.299 79(4)	0.479 48(5)

Table 3. Fractional co-ordinates for the white modification.

Atom	*x*	*y*	*z*
Cl(18)	0.243 0(1)	0.240 17(2)	0.413 99(8)
O(2)	0.930 3(3)	0.500 20(5)	0.713 6(2)
O(3)	0.766 8(3)	0.462 51(5)	0.475 1(2)
N(10)	0.415 7(4)	0.398 60(6)	0.484 8(2)
C(1)	0.769 8(5)	0.496 60(7)	0.626 4(3)
C(4)	0.605 9(5)	0.446 09(7)	0.723 7(3)
C(5)	0.617 3(5)	0.457 52(7)	0.894 1(3)
C(6)	0.458 0(5)	0.437 19(7)	0.988 6(3)
C(7)	0.283 9(5)	0.404 12(8)	0.913 5(3)
C(8)	0.271 5(5)	0.391 70(7)	0.748 3(3)
C(9)	0.430 3(5)	0.411 95(7)	0.648 9(3)
C(11)	0.244 4(5)	0.364 69(7)	0.403 1(3)
C(12)	0.002 0(5)	0.372 71(7)	0.273 3(3)
C(13)	−0.165 3(6)	0.340 67(8)	0.186 5(3)
C(14)	−0.087 6(6)	0.299 75(8)	0.230 7(3)
C(15)	0.153 8(5)	0.292 22(7)	0.361 1(3)
C(16)	0.332 5(5)	0.323 61(7)	0.451 4(3)
C(17)	0.593 6(5)	0.313 94(8)	0.589 1(3)

$\Delta 2\theta = 2.4 + 0.264 \tan\theta$. The background was measured for 40 s at each end of the scan range. The intensity of four standard reflections was measured after every 80 reflections. These measurements showed a systematic decrease of 9.6%. The data was corrected for Lorentz, polarization and absorption effects; the transmission factors were in the range 0.5958–0.7096. The data were corrected for decay by a rescale function, linear in exposure time. Averaging of symmetry related reflections yielded 1 599 independent reflections; 1 506 of these had $|F|^2 \geqslant 3\sigma(|F|^2)$, and were used in the structure determination and refinement. $\sigma^2(|F^2|)$ was estimated as $\sigma_{cs}^2(|F^2|) + (0.04|F^2|)^2$ where $\sigma_{cs}(|F^2|)$ is the variance calculated from counting statistics.

The structure was solved by direct methods using the MULTAN[9] program system. MULTAN gave the starting position for all non-hydrogen atoms. The structure was refined by full matrix least-squares minimization of $\Sigma\sigma^{-2}(F)(|F_o| - |F_c|)^2$. After a refinement which included anisotropic thermal parameters for all the non-hydrogen atoms, all the hydrogen atoms were clearly located in a difference Fourier map, and their positional parameters and isotropic thermal parameters were also included in the refinements. The final residuals were $R = 0.052$ and $R_W = 0.071$ and the maximum shift was 0.01σ. The maximum and minimum peaks in the final difference Fourier was ±0.5 eÅ^{-3}.

Table 4. Crystal data, data collection, and structure refinement results.

	Yellow form	White form
Formula	$C_{14}H_{12}NO_2Cl$	$C_{14}H_{12}NO_2Cl$
M_w	261.71	261.71
Crystal system	Monoclinic	Monoclinic
Melting point	214.5 °C (487.65 K)	210.9 °C (484.05 K)
Unit-cell dimensions at 110 K		
a/Å	3.836(2)	4.826(2)
b/Å	21.997(5)	32.128(11)
c/Å	14.205(7)	8.041(4)
β/°	94.11(4)	104.88(3)
V/Å^3	1 196(2)	1 205(2)
Radiation, λ	Graphite-monochromated Mo-K_α, 0.710 73 Å	Graphite-monochromated Cu-K_α, 1.541 78 Å
Space group	$P2_1/n$	$P2_1/c$
D_m (293 K)	1.400 g cm^{-3}	1.397 g cm^{-3}
Z	4	4
D_x (110 K)	1.450 g cm^{-3}	1.443 g cm^{-3}
Absorption coefficient, μ	3.09 cm^{-1} (λ = 0.710 73 Å)	27.76 cm^{-1} (λ = 1.541 78 Å)
2θ range	2.00–69.93°	2.40–112.74°
Range of indices	$0 \leqslant h \leqslant 6$ $0 \leqslant k \leqslant 30$ $-17 \leqslant l \leqslant 17$	$0 \leqslant h \leqslant 5$ $0 \leqslant k \leqslant 34$ $-8 \leqslant l \leqslant 8$
Number of reflections measured	8 471	2 990

Yellow form of tolfenamic acid. This form crystallizes as yellow needles which have the *a*-axis parallel to the needle axis. Weissenberg photographs showed that they belong to the monoclinic system. The systematic absent reflections $h0l$ for $h + l = 2n + 1$ and $0k0$ for $k = 2n + 1$ are consistent with the space group $P2_1/n$, a non-standard setting of $P2_1/c$. A piece of a needle 0.30 × 0.30 × 0.30 mm was selected for the data collection on a CAD4 diffractometer, and Mo-K_α radiation obtained from a graphite monochromator was used for the collection of intensity data. An Enraf–Nonius gas flow temperature device similar to the one described above was used to keep the crystal cooled to *ca.* 110 K during the data collection. Eighteen reflections with θ values in the range 16.3–20.8° were used to determine the unit cell dimensions. Based on an analysis of reflection profiles the ω scan mode was selected for the data collection, $\Delta\omega = 1.00 + 0.34 \tan\theta$. The scan range was extended with 25% at each end to define the background, and the maximum scan time was 120 s. The intensities of three standard reflections were recorded after every 10 000 s; these measurements did not show any systematic variations. The data was corrected for Lorentz and polarization effects, and the symmetry related reflections were averaged resulting in 5 243 independent reflections, 4 346 of which had $|F|^2 \geqslant 2\sigma(|F|^2)$, where σ was defined as described above $[\sigma^2(|F^2|) = \sigma_{cs}^2(|F^2|) + (0.04|F^2|)^2]$, and these were used in the structure solution and refinement. The structure was solved and refined as described above for the white form. The hydrogen atoms were located in a difference Fourier map and included in the structure refinement with isotropic temperature factors. The final residuals were $R = 0.029$ and $R_W = 0.041$, the maximum shift was less than 0.01σ, and the maximum and minimum peaks in the final difference Fourier were ±0.5 e Å^{-3}. The crystallographic computations were performed using the Enraf–Nonius SDP-package[10] on a Digital PDP 11/23 computer. The atomic scattering factors used in the calculations were those listed by Cromer and Mann[11] for the non-hydrogen atoms (f' and f'' from Cromer and Liberman[12]) and those listed by Stewart *et al.*[13] for the hydrogen atoms.

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