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Polymorphism of N-(2,6-dioxo-3-piperidyl)pthalimide (thalidomide): Structural characterization of a second monoclinic racemic modification

M. R. Caira,*[1] S. A. Botha,[2] and D. R. Flanagan[3]

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The X-ray crystal structure of the drug N-(2,6-dioxo-3-piperidyl)pthalimide (thalidomide), $C_{13}H_{10}N_2O_4$, obtained from 1 : 1 dimethyformamide-ethanol solution, is reported. This species is monoclinic, space group $C2/c$, with a = 20.679(5), b = 8.042(2), c = 14.162(5)Å, β = 102.86(3)°, Z = 8, R = 0.051 for 1674 unique reflections. Crystal packing is determined by intermolecular N—H · · · O hydrogen bonding which is more extensive than that reported in the literature for a racemate of thalidomide crystallizing in space group $P2_1/n$. Comparison of the melting behavior and X-ray powder diffractograms of the two racemic polymorphs shows that they are distinctly different, allowing easy identification of these species. By comparing experimental X-ray powder patterns with those calculated from single crystal data, it was concluded that neither of these polymorphs undergoes a phase change on trituration.

Introduction

Thalidomide is an effective drug in the treatment of leprosy (Sheskin, 1965; Pearson and Vedagiri, 1969; Shannon *et al.*, 1992) and its immunosuppressive properties render it useful in the treatment of graft-versus-host and host-versus-graft reactions (McCarthy *et al.*, 1989; Vogelsang *et al.*, 1992).

During a detailed study of the polymorphism of both the chiral and racemic forms of thalidomide by thermal analysis, X-ray diffraction and spectroscopic methods (Botha *et al.*, 1993), a racemic polymorph melting in the range 276–279°C was isolated and designated as Form I. We report the characterization of this species by differential scanning calorimetry (DSC), single crystal X-ray analysis and powder X-ray diffractometry and compare the results with analogous data for the racemic polymorph crystallizing in space group $P2_1/n$ (Allen and Trotter, 1971). The latter polymorph, which we have designated Form III, was reported to melt in the range 269–271°C. Evidence for the existence of a third polymorph of thalidomide (tentatively designated Form II) will be reported elsewhere (Botha *et al.*, 1993).

[1] Department of Chemistry, University of Cape Town, Private Bag, Rondebosch, 7700, South Africa.
[2] Center for Advanced Drug Development, University of Iowa, College of Pharmacy, 100 Oakdale Campus, Iowa City, Iowa 52242.
[3] College of Pharmacy, University of Iowa, Iowa City, Iowa 52242.

Experimental

Thalidomide was obtained from Pharm Eco (Simi Valley, CA) and was used as received in the preparation of recrystallized samples.

Form I was obtained as colorless bipyramids by dissolving thalidomide in 1 : 1 dimethylformamide–ethanol at room temperature and allowing crystallization to occur at room temperature. For comparative purposes, Form III was prepared as colorless prismatic crystals from boiling 1,4-dioxane which was filtered and allowed to crystallize at room temperature. The identity of these crystals with those reported by Allen and Trotter (1971) was established by single crystal X-ray photography and melting point determination.

Differential scanning calorimetric traces were recorded on a Perkin Elmer DSC-7 system equipped with

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a Perkin Elmer TAC 7/7 Instrument Controller and a Perkin Elmer Professional Computer. The instrument was calibrated for temperature and energy with pure indium and lead standards. Samples were weighed into aluminum pans for volatile substances and sealed with a Perkin Elmer volatile pan crimper, a sealed empty pan being used as reference. A heating rate of 5°C min^{-1} with constant nitrogen purge was employed.

Powder diffractograms were recorded on an automated Philips PW1710 diffractometer using Philips Analytical PC-APD.

Diffraction Software

Samples were lightly ground in an agate mortar and spread on double-sided tape on a glass plate which was inserted in a standard aluminum holder. Recording conditions were: 40 kV, 30 mA, scan rate 3°2θ min^{-1}, angular range 2–62° 2θ, automatic divergence slit, receiving slit 0.2°.

Program LAZY PULVERIX (Yvon *et al.*, 1977) was used to generate theoretical powder patterns. Input for the program included the refined unit cell parameters, atomic coordinates, thermal parameters and space group data for Form I, obtained from the single crystal X-ray analysis described below. The data of Allen and Trotter (1971) were used to generate the pattern for Form III.

Crystals of Form I were found to be optically biaxial. They are monoclinic, space group $C2/c$ or Cc, from systematic absences. Intensity statistics indicated $C2/c$ as the correct space group. Intensity data were collected at 294K in the ω–2θ mode on an Enraf–Nonius CAD4 diffractometer with graphite-monochromated Mo$K\alpha$-radiation (λ = 0.71069 Å). Crystal data, data-collection parameters and details of the structure refinement are listed in Table 1. Accurate cell parameters were determined by least-squares analysis of 24 accurately-centered reflections in the θ-range 16–17°. Reflections in the θ-range 1–25° were collected using a variable scan speed depending on I and σ(I) with a maximum recording time of 40 s per reflection. Intensity control was performed every hour and orientation control every 200 measured reflections. The data were corrected for Lorentz-polarization effects. The structure was solved by direct methods using program SHELX86 (Sheldrick, 1985) and refined by full-matrix least-squares using program SHELX76 (Sheldrick, 1976). Refinement involved minimization of $\Sigma w(|F_o|-|F_c|)^2$ with anisotropic thermal parameters assigned to all nonhydrogen atoms. All H atoms were located in difference Fourier syntheses. Atom H(2), which is involved in hydrogen bonding, was allowed to refine freely while all other H atoms were included in idealized positions with C—H = 1.00 Å and with separate common variable isotropic thermal parameters for the H atoms of the pthalimide and glutarimide rings. Thermal parameters for the H atoms refined in the range 0.06–0.08 $Å^2$.

Table 1. Crystal data, data-collection parameters, and details of the structural analysis

Formula	$C_{13}H_{10}N_2O_4$
M_r	258.23
Space group	$C2/c$
a/Å	20.679(5)
b/Å	8.042(2)
c/Å	14.162(5)
β/deg	102.86(3)
V/Å	2296(1)
Z	8
D_x/g cm^{-3}	1.494
μ(MoKα)/cm^{-1}	1.058
F(000)	1072
Crystal size/mm	.34 × .38 × .47
Index range	−24, 24; 0, 9; 0, 16
Standard reflections	−4 6 4; −16 2 1; −7 1 11
Intensity variation/%	−2.1
Scan width in ω/deg	.80 + .35 tan θ
Vertical aperture/mm	4
Aperture width/mm	1.12 + 1.05 tan θ
Reflections measured	2267
Unique reflections	1883
R_{int}	0.030
Observed reflections, $I > 2\sigma(I)$	1674
Parameters refined	178
R	.051
R_w	.052
S	3.88
w	$[\sigma^2(F_o)]^{-1}$
Max Δ/σ	0.02
$\Delta\rho$/e $Å^{-3}$ min, max	−.24, +.42

Complex neutral atomic scattering factors (International Tables for X-Ray Crystallography, 1974) were used. Other programs used were PARST (Nardelli, 1983) and PLUTO (Motherwell, 1979).

Fractional atomic coordinates and equivalent isotropic thermal parameters ($U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* a_i \cdot a_j$) for non-hydrogen atoms are listed in Table 2. H atom coordinates are listed in Table 3.

Results and discussion

Thermal analysis

The DSC traces for the two Forms are unremarkable. Each shows a single endotherm with the following

Table 2. Fractional atomic coordinates ($\times 10^4$) and equivalent isotropic thermal parameters ($Å^2 \times 10^3$) for Form I

Atom	*x/a*	*y/b*	*z/c*	U_{eq}
C(1)	78(1)	862(3)	3748(2)	32(1)
C(2)	495(1)	−458(3)	3695(2)	33(1)
C(3)	289(1)	−2080(3)	3741(2)	44(1)
C(4)	−358(1)	−2330(4)	3823(2)	51(1)
C(5)	−775(1)	−1010(4)	3861(2)	47(1)
C(6)	−562(1)	619(3)	3831(2)	40(1)
C(7)	461(1)	2420(3)	3714(2)	39(1)
C(8)	1151(1)	192(3)	3621(2)	38(1)
C(9)	1644(1)	3012(3)	3586(2)	41(1)
C(10)	1863(1)	3890(3)	4558(2)	39(1)
C(11)	2427(1)	5989(3)	3755(2)	37(1)
C(12)	2131(1)	5274(4)	2787(2)	48(1)
C(13)	1518(1)	4219(3)	2753(2)	45(1)
N(1)	1091(1)	1910(3)	3616(2)	39(1)
N(2)	2229(1)	5305(3)	4537(2)	45(1)
O(1)	291(1)	3836(2)	3767(2)	56(1)
O(2)	1650(1)	−560(2)	3571(1)	53(1)
O(3)	1773(1)	3331(3)	5305(1)	59(1)
O(4)	2834(1)	7095(2)	3883(1)	53(1)

characteristics: Form I, onset of melting 278.6°C, enthalpy of fusion 40.9 kJ mol^{-1}; Form III, onset of melting 272.9°C, enthalpy of fusion 39.4 kJ mol^{-1}. Although onset temperatures are reproducible, the enthalpies of fusion vary somewhat due to sublimation which sets in from about 150°C.

X-ray powder diffractometry

Figure 1 shows the experimental X-ray powder patterns for Forms I and III together with superimposed lines calculated from the single crystal data. The angular positions of the major experimental peaks are accounted for by the predicted patterns although the intensity matches are generally poor. The latter may be attributed to the paucity of sample material available and preferred

Table 3. Hydrogen atom coordinates ($\times 10^4$) for Form I

Atom	*x/a*	*y/b*	*z/c*
H(3)	596	−3031	3716
H(4)	−528	−3489	3851
H(5)	−1241	−1237	3913
H(6)	−862	1580	3868
H(9)	2015	2303	3468
H(121)	2016	6211	2315
H(122)	2471	4547	2593
H(131)	1399	3602	2125
H(132)	1143	4963	2816
H(2)	2407(16)	5756(38)	5149(24)

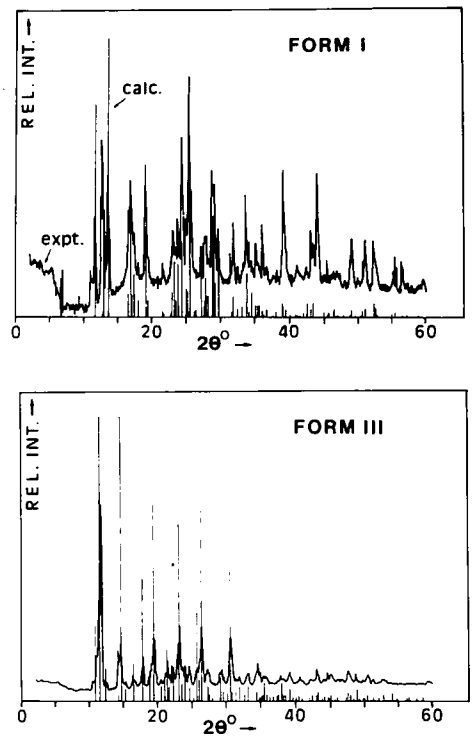

Fig. 1 Experimental and calculated X-ray powder patterns for thalidomide Form I (this study) and Form III (Allen and Trotter, 1971).

orientation effects. Comparison of the patterns does however confirm that Forms I and III are distinctly different phases and that neither form undergoes a polymorphic transition on grinding.

Crystal structure analysis

Figure 2 is a perspective view of the thalidomide molecule in Form I. The atomic nomenclature is that used by Allen and Trotter (1971) to describe Form III.

Bond lengths and bond angles are listed in Table 4. Detailed comparison of the bond lengths in Forms I and III shows that they are identical within experimental error, the largest difference being 2.6σ (σ = combined standard deviation). The maximum difference in corre-

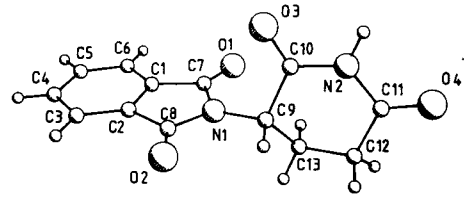

Fig. 2. Perspective view of the molecular conformation of thalidomide in Form I.

Table 4. Bond lengths (Å) and bond angles (degrees) for Form I

C(1)—C(2)	1.380(3)
C(1)—C(6)	1.369(3)
C(1)—C(7)	1.489(3)
C(2)—(C(3)	1.378(3)
C(2)—C(8)	1.479(3)
C(3)—C(4)	1.383(3)
C(4)—C(5)	1.376(4)
C(5)—C(6)	1.386(4)
C(7)—N(1)	1.402(3)
C(7)—O(1)	1.199(3)
C(8)—N(1)	1.387(3)
C(8)—O(2)	1.212(3)
C(9)—C(10)	1.524(4)
C(9)—C(13)	1.505(4)
C(9)—N(1)	1.455(3)
C(10)—N(2)	1.371(3)
C(10)—O(3)	1.202(3)
C(11)—C(12)	1.487(4)
C(11)—N(2)	1.378(4)
C(11)—O(4)	1.212(3)
C(12)—C(13)	1.517(3)
N(2)—H(2)	0.94(3)
C(6)—C(1)—C(7)	130.9(2)
C(2)—C(1)—C(7)	107.6(2)
C(2)—C(1)—C(6)	121.5(2)
C(1)—C(2)—C(8)	109.0(2)
C(1)—C(2)—C(3)	121.5(2)
C(3)—C(2)—C(8)	129.5(2)
C(2)—C(3)—C(4)	117.2(2)
C(3)—C(4)—C(5)	121.2(3)
C(4)—C(5)—C(6)	121.5(2)
C(1)—C(6)—C(5)	117.2(2)
C(1)—C(7)—O(1)	129.2(2)
C(1)—C(7)—N(1)	105.6(2)
N(1)—C(7)—O(1)	125.1(2)
C(2)—C(8)—O(2)	129.4(2)
C(2)—C(8)—N(1)	105.7(2)
N(1)—C(8)—O(2)	125.0(2)
C(13)—C(9)—N(1)	114.6(2)
C(10)—C(9)—N(1)	109.5(2)
C(10)—C(9)—C(13)	112.0(2)
C(9)—C(10)—O(3)	123.3(2)
C(9)—C(10)—N(2)	114.8(2)
N(2)—C(10)—O(3)	121.6(2)
N(2)—C(11)—O(4)	119.6(3)
C(12)—C(11)—O(4)	123.5(2)
C(12)—C(11)—N(2)	116.9(2)
C(11)—C(12)—C(13)	114.5(2)
C(9)—C(13)—C(12)	109.8(2)
C(8)—N(1)—C(9)	122.5(2)
C(7)—N(1)—C(9)	125.4(2)
C(7)—N(1)—C(8)	112.0(2)
C(10)—N(2)—C(11)	127.8(3)

sponding bond angles is 1.2° in the two polymorphs, amounting to 3.5σ. Allen and Trotter (1971) have given a detailed comparison between the molecular parameters of thalidomide observed in Form III and those found in related molecules and such a comparison would be redundant here. Although differences in the crystal packing modes of Forms I and III have no effect on the above parameters, they do affect the conformational parameters, as indicated by the torsion angles listed in Table 5. The orientation of the phthalimide residue with respect to the glutarimide residue is reflected in the torsion angles about the bond N(1)—C(9), for which there are differences up to 8° for the two polymorphs. The glutarimido-ring adopts slightly different conformations in the two polymorphs. These differences involve chiefly the torsion angles about C(10)—N(2) and N(2)—C(11). Since the OC—NH units engage in intermolecular hydrogen bonding in both polymorphs, the torsional differences noted above evidently result from the need to accommodate the different hydrogen bonding arrangements observed. That in Form I is shown in Fig. 3 and, for comparison, the in Form III in Fig. 4. The arrangement in Form III is simpler, thalidomide molecules forming discrete dimers by a pair of inversion-related N(2)—H(2)···O(4′) hydrogen bonds for which N(2)···O(4′) is 2.928(3) Å and the angle subtended at H(2) is 171(3)° (Allen and Trotter, 1971). The least-squares planes through atoms N(2), H(2), C(11), O(4), and the inversion-related set are separated by 0.26 Å only. In the present study, we find the same pair of inversion-related hydrogen bonds in Form I but the corresponding least-squares separation is 1.66 Å, resulting in a longer N(2)···O(4^{i}) distance of 3.087(3) Å (i = 0.5 − x, 1.5 − y, 1 − z) and a N(2)—H(2)···O(4^{i}) angle of 138(3)°. In addition, atom H(2) hydrogen bonds with atom O(2^{ii}) of a molecule related by a different inversion center (ii = 0.5 − x, 0.5 − y, 1 − z) from the former. This bond has N(2)···O(2^{ii}) 3.135(3) Å and N(2)—H(2)···O(2^{ii}) 141(3)°. Each of the bifurcated N—H···O hydrogen bonds in Form I is thus weaker

Table 5. Selected torsion angles (degrees)

	Form I[a]	Form III[b]
C(13)—C(9)—C(10)—N(2)	−32.6(3)	−37.7(3)
C(9)—C(10)—N(2)—C(11)	−1.3(4)	5.9(3)
C(10)—N(2)—C(11)—C(12)	10.1(4)	5.0(3)
N(2)—C(11)—C(12)—C(13)	15.9(3)	16.8(3)
C(11)—C(12)—C(13)—C(9)	−47.6(3)	−47.4(3)
C(12)—C(13)—C(9)—C(10)	55.6(3)	57.4(3)
C(7)—N(1)—C(9)—C(10)	65.2(3)	57.3(3)
C(8)—N(1)—C(9)—C(10)	−109.8(3)	−103.6(3)
C(7)—N(1)—C(9)—C(13)	−61.6(3)	−67.8(3)
C(8)—N(1)—C(9)—C(13)	123.5(3)	131.4(3)

[a] Present study.
[b] Allen and Trotter (1971).

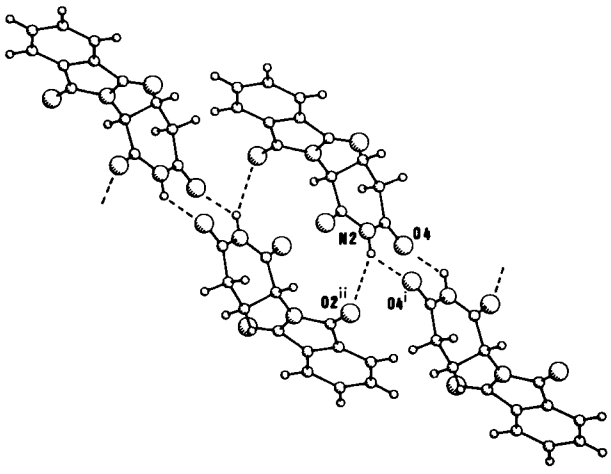

Fig 3. Hydrogen bonding arrangement in Form I.

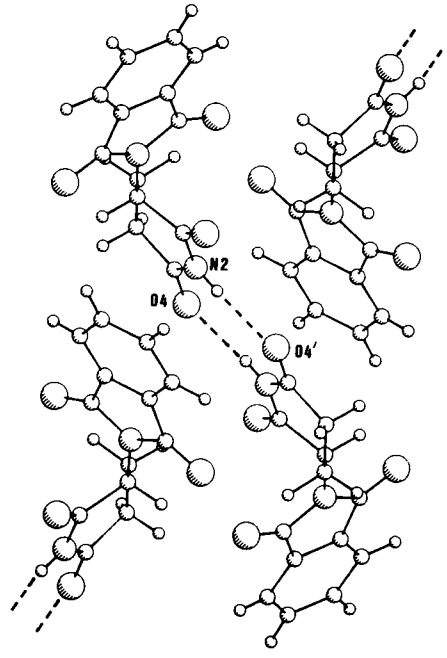

Fig. 4. Hydrogen bonding arrangement in Form III (prepared from the data of Allen and Trotter, 1971).

than the crystallographically unique N—H · · · O bond in Form III, but the extent of hydrogen bonding in Form I is much greater, involving polymeric chains formed by alternating eight- and fourteen-membered hydrogen bonded rings. The somewhat higher onset melting point of Form I (278.6°C) compared with that of Form III (272.9°C) is consistent with these results. The crystal structures will be used to attempt to rationalize the dissolution-rate data for these polymorphs (Botha *et al.*, 1993).

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