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The Crystal and Molecular Structure of Cyclosarcosyl-L-valyl

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The crystal structure of cyclosarcosyl-L-valyl ($C_8H_{14}N_2O_2$) has been determined with the program *MULTAN*. The space group is $P2_12_12_1$ with $a = 6{\cdot}5185$ (14), $b = 9{\cdot}9053$ (23), $c = 14{\cdot}5818$ (33) Å and $Z = 4$. Intensities were measured by a four-circle diffractometer and the structure was solved by direct methods and refined by least-squares calculations to $R = 0{\cdot}057$ for 766 observed reflexions. The diketopiperazine ring is in the form of a twist-boat with the valyl side chain, which is disordered, in the flagpole position.

Introduction

The crystal structure analyses of cyclic dipeptides (2,5-piperazinediones, DKP) show a variety of ring conformations from the boat with axial substituent as found in cyclo-Gly-L-Tyr (Webb & Lin, 1972) and predicted by n.m.r. (Kopple & Ohnishi, 1969) through planar for DKP (Degeilh & Marsh, 1959) and cyclo-L-Ala-D-Ala (Sletten, 1970) to the boat form with equatorial substituents in cyclo-L-Ala-L-Ala (Sletten, 1970). The buckling in cyclo-Gly-L-Tyr has been explained (Webb & Lin, 1972) in terms of the interaction between the DKP and benzene rings but no study of a monosubstituted DKP derivative with a large aliphatic group has been carried out. The crystal structure of cyclo-Sar-L-Val has been carried out to investigate such a structure and for comparison with the solution structure as determined by n.m.r. (Davies, Khaled & Timmins, 1975).

Experimental

Lath-shaped crystals of Sar-Val elongated along **c** were grown from chloroform. Weissenberg and precession photographs indicated space group $P2_12_12_1$ (No. 19). Unit-cell dimensions obtained from 20 high-angle reflexions measured on a four-circle diffractometer were: $a = 6{\cdot}5185$ (14), $b = 9{\cdot}9053$ (23) and $c = 14{\cdot}5818$ (33) Å. The unit-cell volume is 941·5 Å^3 giving a calculated density of 1·199 g cm^{-3} for $Z = 4$. The linear absorption coefficient for Cu $K\alpha$ radiation is 7·15 cm^{-1}.

A single crystal of dimensions approximately $0{\cdot}8 \times 0{\cdot}6 \times 0{\cdot}4$ mm was selected and intensity data were collected on a Hilger & Watts Y290 four-circle diffractometer in the ω–2θ mode. Data were collected to a maximum θ angle of 78° and totalled 1153 reflexions of which 766 were deemed significant ($I \geq 3\sigma$). The integrated intensities were measured as the summation of counts in steps of $\theta = 0{\cdot}02°$, the range of each scan being 0·9° and the total scan time per reflexion 45 s. The background was estimated in a single step count of 4·5 s.

Structure determination

The data were corrected for Lorentz and polarization effects in the usual manner but no absorption correction was applied. Phase determination was carried out with the program *MULTAN* (Germain, Main & Woolfson, 1971) using the 117 E values greater than 1·5. A number of phase sets were obtained and that with the highest figure of merit (1·15) was used to compute an E map. From this map were located ten atoms in stereochemically feasible positions which were then used in the computation of a Fourier map. Two further atomic positions were located and a structure-factor calculation gave a conventional R value of 0·35 and least-squares refinement commenced. The refinement was carried out by full-matrix least-squares calculations minimizing the function $M = \sum w\{(|F_o|) - G|F_c|\}^2$ where $|F_o|$, $|F_c|$ and G are the observed and calculated structure amplitudes and scale factor respectively.

The weight for each reflexion is given by: $w =$ if $|F_o| > F_{\min}$ then $\{1 - \exp[-a(\sin\theta/\lambda)^2]\}/(b + |F_o| + c|F_o|^2 + d|F_o|^3)$ else e where the final values of the constants were $a = 3{\cdot}0$, $b = 20{\cdot}0$, $c = 4{\cdot}0 \times 10^{-3}$, $d = 0{\cdot}00$, $e = 0{\cdot}00$, $F_{\min} = 0{\cdot}0$.

Five cycles of refinement with isotropic temperature factors and three cycles with anisotropic temperature factors reduced R to 0·145 with atomic shifts less than 0·1 standard deviations. A difference map calculated with these refined coordinates revealed residual electron density up to about 2 e Å^{-3} within 1·6 Å of the valyl C^β. This was interpreted as being due to disorder in the valyl side chain by rotation about C^α–C^β. The two C^γ atoms were located in five partially occupied sites designated $C^{\gamma1} \cdots C^{\gamma5}$ and the positions, temperature factors and occupancies of these sites refined. This refinement converged at $R = 0{\cdot}108$ and all bond lengths and angles except those involving the C^γ atoms were sensible. The hydrogen atoms of the *N*-methyl group, the amide N and the two C^α atoms were

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located from a difference Fourier and their positions and isotropic thermal parameters refined, reducing R to 0·072. Owing to the disorder in the side chain no attempt was made to locate the hydrogen atoms on C^{β} and $C^{\gamma 1}, C^{\gamma 2}$. An inspection of the large F_{obs} at low angles indicated that secondary extinction might be present and an extinction coefficient (Zachariasen, 1963, 1967) applied to F_{calc} and refined reduced R to 0·057 at which the refinement was terminated. The final extinction coefficient was $7{\cdot}960 \times 10^{-5}$. Bond lengths and angles involving the C^{γ} atoms remained non-sensible and thus any discussion of this portion of the molecule must remain qualitative. A calculation of R for all except the C^{γ} atoms gave a value of 0·119.

Scattering factors for C, N, O were from Berghuis, Haanappel, Potters, Loopstra, MacGillavry & Veenendaal (1955) and for H from Stewart, Davidson & Simpson (1965).

Refinement calculations were carried out with the program of D. W. J. Cruickshank and J. F. Smith modified by Dr D. S. Moss. All other computations were carried out with the programs of the Birkbeck College Crystallography Department Program Library.

Description of structure

The most notable feature in the structure analysis was the difficulty of locating the C^{γ} atoms of the valyl side chain. The final results show five partially occupied sites within 1·9 Å of C^{β} and the structure may be described qualitatively in terms of the three conformations shown in Fig. 1, co-existing within the crystal. Conformations (*a*) and (*b*) are clearly very similar whilst (*c*) is that which might be predicted from simple stereochemical considerations. A simplified description of the crystal conformation is that two-thirds of the molecules have one C^{γ} over the ring and one pointing away and the other one-third have both C^{γ} atoms pointing away from the ring. The true situa-

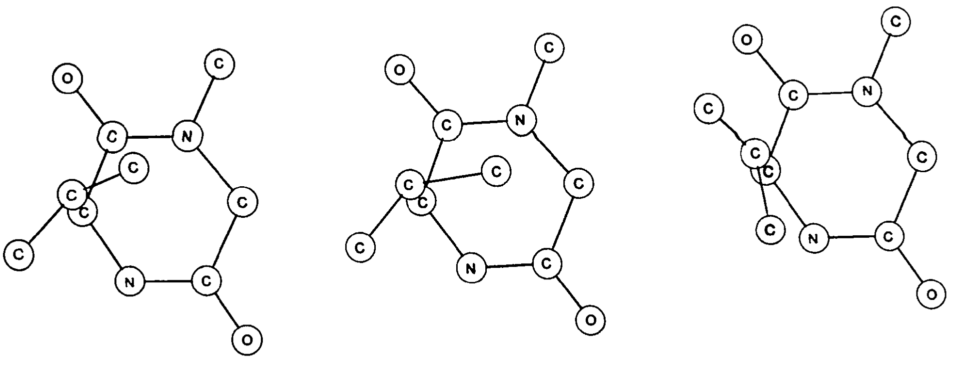
Table 1. *Apparent C^{β}–C^{γ} bond lengths calculated from final atomic parameters (e.s.d.'s in parentheses)*

C^{β}–$C^{\gamma 1}$	1·502 (12) Å
C^{β}–$C^{\gamma 2}$	1·326 (22)
C^{β}–$C^{\gamma 3}$	1·256 (17)
C^{β}–$C^{\gamma 4}$	1·619 (29)
C^{β}–$C^{\gamma 5}$	1·835 (59)

Table 2. *Positional and anisotropic thermal parameters* ($\times 10^4$) *and occupancies with e.s.d.'s in parentheses for non-*H *atoms*

$$\overline{U^2} = U_{11}l_1^2 + U_{22}l_2^2 + U_{33}l_3^2 + 2U_{32}l_3l_2 + 2U_{31}l_3l_1 + 2U_{21}l_2l_1 \text{ (Cruickshank, 1964)}$$

	x	y	z	U_{11}	U_{22}	U_{33}	$2U_{32}$	$2U_{31}$	$2U_{21}$	Occupancy
C_1^{α}	560 (10)	1087 (4)	247 (3)	1045 (39)	578 (21)	625 (20)	−250 (32)	189 (53)	− 62 (50)	1·00
N_1	948 (7)	−309 (3)	498 (2)	858 (26)	560 (18)	587 (16)	31 (26)	36 (34)	−38 (34)	1·00
C_1'	238 (8)	2027 (4)	1036 (3)	833 (30)	510 (17)	714 (20)	−14 (32)	−159 (44)	6 (41)	1·00
O_1	392 (9)	3246 (3)	909 (3)	1597 (41)	501 (16)	984 (22)	−224 (27)	−214 (56)	96 (42)	1·00
C_{N_1}	1908 (16)	−1157 (7)	−192 (4)	1565 (75)	857 (36)	715 (31)	204 (53)	371 (80)	−309 (89)	1·00
C_2^{α}	−663 (7)	68 (4)	1981 (3)	592 (24)	623 (19)	586 (18)	−4 (30)	−32 (35)	18 (36)	1·00
N_2	−165 (6)	1479 (3)	1841 (2)	800 (26)	522 (15)	607 (18)	97 (25)	−56 (33)	79 (33)	1·00
C_2'	382 (8)	−832 (4)	1295 (2)	744 (25)	566 (18)	566 (17)	−63 (28)	−222 (37)	183 (38)	1·00
O_2	661 (7)	−2036 (3)	1478 (2)	1306 (30)	518 (14)	757 (16)	−177 (24)	−152 (39)	−27 (40)	1·00
C^{β}	−2927 (11)	−259 (10)	2000 (5)	797 (41)	1692 (73)	1145 (45)	677 (99)	414 (71)	911 (90)	1·00
$C^{\gamma 1}$	−3834 (17)	267 (15)	2877 (7)	900 (63)	1477 (97)	1074 (58)	−125 (130)	813 (105)	−133 (131)	0·66
$C^{\gamma 2}$	−3955 (34)	−209 (22)	1216 (2)	608 (82)	1083 (112)	767 (87)	−155 (176)	−51 (161)	250 (159)	0·39
$C^{\gamma 3}$	−3890 (30)	−1290 (20)	2257 (18)	996 (107)	1091 (96)	1995 (186)	−823 (238)	−530 (243)	994 (187)	0·44
$C^{\gamma 4}$	−3892 (60)	265 (50)	1041 (25)	1255 (204)	3163 (512)	1721 (222)	−2749 (563)	−1619 (358)	1269 (509)	0·45
$C^{\gamma 5}$	−4189 (33)	1322 (25)	2335 (27)	661 (104)	1068 (130)	2503 (324)	617 (384)	831 (310)	−257 (211)	0·34



(*a*) (*b*) (*c*)

Fig. 1. Three conformations of the valyl side chain which are consistent with the five partially occupied C^{γ} sites. Hydrogen atoms are omitted.

tion is clearly more complicated than this as indicated by the high anisotropic thermal components in the plane of the rotating group.

None of the C^β–C^γ bond lengths obtained from the final parameters is chemically feasible as Table 1 shows.

A discussion of these conformations and a comparison with the solution structure as determined by n.m.r. will be given later (Davies *et al.*, 1975).

The coordinates, anisotropic thermal parameters and occupancies of the non-hydrogen atoms are given in Table 2 and the coordinates and isotropic thermal parameters for the hydrogen atoms where detected are given in Table 3. Bond lengths and angles not involving the side chain are given in Fig. 2. These are in very good agreement with those found in diketopiperazine and derivatives as shown in Table 4. In particular the dimensions are in very good agreement with those of the only other sarcosyl compound (Groth, 1969). The slightly shorter C'–C_N distance in Sar-Val would probably be insignificant if correction for the considerable thermal motion of C_{N_1} were made.

Fig. 3 is a stereo diagram of the Sar-Val conformation with sites $C^{\gamma 1}$ and $C^{\gamma 2}$ occupied. This is basically a boat conformation with the valyl side chain in the 'flagpole' position. The boat is twisted, having equivalent torsion angles unequal as shown in Table 5. The peptide bond to which the *N*-methyl group is attached is essentially planar ($\omega = -0{\cdot}5°$) whereas the other is significantly non-planar ($\omega = -12{\cdot}5°$) due perhaps to strain imposed by hydrogen bonding to the N–H group.

Table 3. *Positional* (× 10^4) *and isotropic thermal parameters* (× 10^3) *for hydrogen atoms where detected*

$U = \overline{u^2}$ = mean square amplitude of vibration (Cruickshank, 1964)

	x	y	z	U
H(1)	−654 (114)	1139 (66)	−154 (48)	65 (17)
H(2)	1746 (106)	1375 (68)	−199 (47)	65 (17)
H(3)	2365 (150)	−1922 (102)	240 (72)	107 (30)
H(4)	1068 (144)	−1373 (88)	−650 (61)	87 (25)
H(5)	3190 (177)	−632 (102)	−332 (69)	112 (31)
H(6)	−279 (73)	1918 (45)	2349 (32)	31 (10)
H(7)	−189 (88)	−135 (49)	2585 (36)	42 (12)

Table 5. *Torsion angles for Sar-Val*

The convention used is that of the IUPAC-IUB Commission on Biochemical Nomenclature (1970).

$(C'_2{-}N_1{-}C^\alpha_1{-}C'_1)\varphi_1$	20·9°
$(C'_1{-}N_2{-}C^\alpha_2{-}C'_2)\varphi_2$	31·9
$(N_1{-}C^\alpha_1{-}C'_1{-}N_2)\psi_1$	−14·3
$(N_2{-}C^\alpha_2{-}C'_2{-}N_1)\psi_2$	−24·4
$(C^\alpha_1{-}C'_1{-}N_2{-}C^\alpha_2)\omega_1$	−12·5
$(C^\alpha_2{-}C'_2{-}N_1{-}C^\alpha_1)\omega_2$	−0·5

Table 6. *Observed and calculated structure amplitudes*

Table 4. *Comparison of bond lengths and angles for DKP and some derivatives* (*e.s.d.'s in parentheses*)

Bond (angle)	DKP (Degeilh & Marsh, 1959)	L-Ala-L-Ala (Sletten, 1970)		L-Ala-D-Ala (Sletten, 1970)	Gly-L-Tyr (Webb & Lin, 1970)		Sar-Sar (Groth, 1969)	Sar-Val (This paper)	
C'–C^α	1·499	1·516 (3)	1·518 (2)	1·509 (1)	1·50	1·47	1·508 (4)	1·503 (6)	1·495 (6)
C'–O	1·239	1·235 (2)	1·239 (3)	1·236 (1)	1·23	1·23	1·234 (3)	1·235 (5)	1·225 (5)
C'–N	1·325	1·329 (3)	1·330 (2)	1·322 (1)	1·32	1·31	1·348 (3)	1·325 (5)	1·321 (6)
C^α–N	1·449	1·461 (3)	1·454 (3)	1·454 (1)	1·50	1·47	1·455 (3)	1·449 (5)	1·452 (5)
C^α–C^β	–	1·514 (3)	1·517 (3)	1·525 (2)	1·54		–	1·511 (8)	
N–C_N	–	–	–	–	–		1·475 (3)	1·452 (7)	
N–H_N	0·86	–	–	–	–		–	0·86 (5)	
(N–C'–O)	122·6	122·99 (18)	122·53 (17)	122·94 (10)	123	124	123·6 (2)	121·8 (4)	123·7 (4)
(C^α–C'–O)	118·5	120·17 (17)	120·56 (17)	118·43 (9)	117	118	118·3 (2)	119·1 (4)	119·7 (4)
(C^α–C'–N)	118·9	116·84 (19)	116·89 (19)	118·61 (8)	119	119	118·1 (2)	118·6 (3)	117·2 (3)
(C'–N–C^α)	126·0	125·87 (16)	126·16 (14)	127·89 (9)	126	126	124·6 (2)	124·5 (4)	123·0 (4)
(C'–C^α–N)	115·1	111·97 (16)	110·53 (14)	113·44 (8)	112	113	117·0 (2)	115·1 (4)	112·2 (3)
(C'–N–H_N)	123·0	–	–	–	–	–	–	125·1 (2·8)	
(C^α–N–H_N)	111·0	–	–	–	–	–	–	110·3 (2·8)	

The boat conformation may also be described in terms of the fold between the two peptide planes. In the case of Sar-Val the angle between these planes is 157·5° compared with 143° in cyclo-L-prolyl-L-leucyl (Karle, 1972). The two C′ and two N atoms also lie very close to a plane with the C_1^α and C_2^α atoms deviating by 0·225 Å and 0·336 Å respectively from this plane.

In Sar-Val there are three potential hydrogen-bonding sites, two of which, N–H and C_2'=O are used in the crystal structure forming chains of molecules along the screw axis parallel to **b**. The hydrogen bond length is 2·878 Å. The molecular packing is shown in Fig. 4.

The crystal structure of Sar-Val essentially confirms the structure found in solution by n.m.r. methods indicating that in this particular case crystal packing forces do not play an important part in defining the molecular conformation.

Table 6 is a list of the observed and calculated structure factors.

I should like to thank Dr D. B. Davies and M. A. Khaled for supplying crystals and for many helpful discussions.

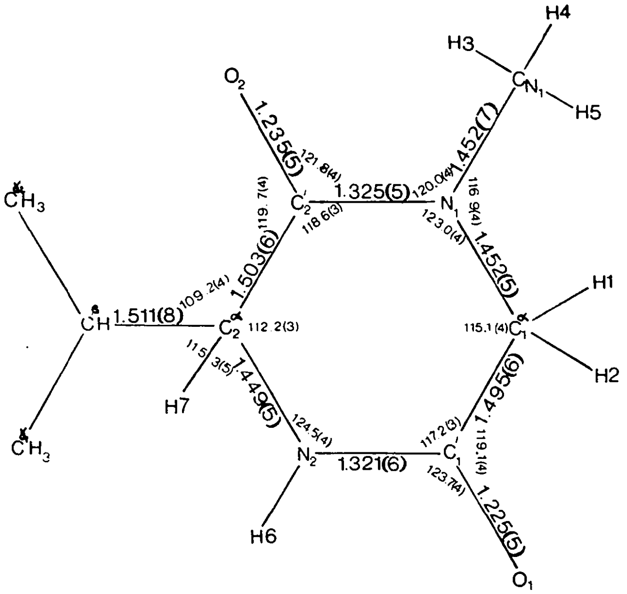


Fig. 2. Bond lengths and angles between non-hydrogen atoms but excluding those involving C^γ atoms.

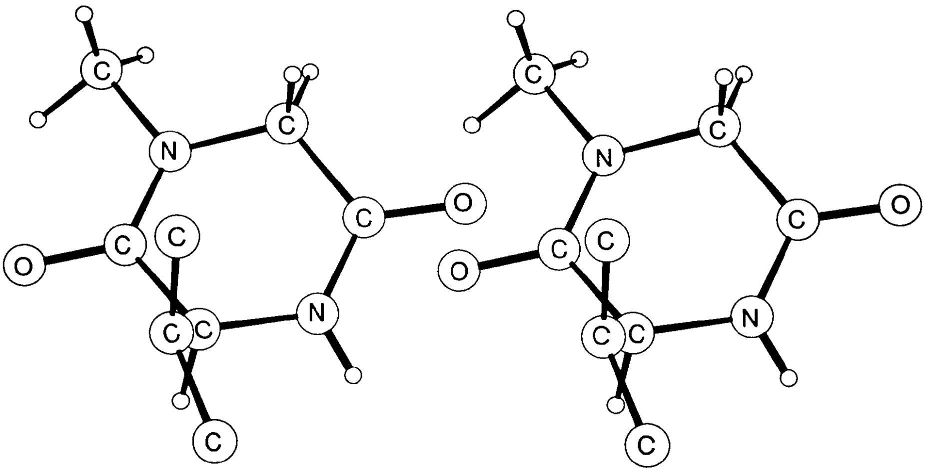


Fig. 3. Stereo diagram of Sar-Val molecule with side-chain conformation $C^{\gamma 1}$,$C^{\gamma 2}$. Hydrogen atoms shown where detected. Viewing direction parallel to **a**.

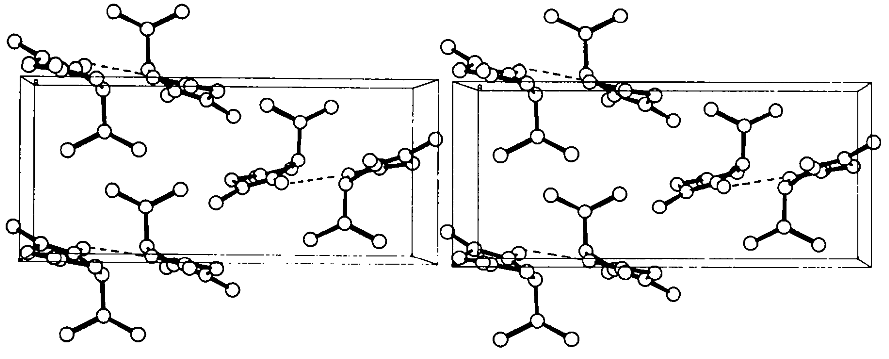


Fig. 4. Packing of Sar-Val molecules in unit cell – stereo view parallel to **b**.

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The Crystal and Molecular Structure of a Heterocyclic Dithiepane Derivative of an Octopyranose: $C_{17}H_{27}N_3O_5S_2$

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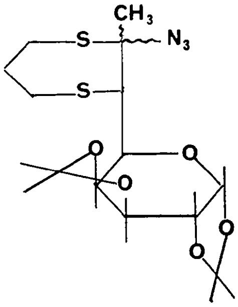
The crystal structure of 7-azido-8-deoxy-1,2,3,4-di-*O*-isopropylidene-6,7-*S*,*S*-trimethylene-6,7-dithio-α-D-erythro-D-*galacto*-octopyranose, $C_{17}H_{27}N_3O_5S_2$, has been determined. The crystals are orthorhombic, $P2_12_12_1$, with $a=9{\cdot}599$, $b=10{\cdot}835$, $c=19{\cdot}559$ Å, $Z=4$. The structure was solved by direct methods and refined by the full-matrix least-squares technique to an R value of 0·046 for 1929 independent reflexions collected with an automatic four-circle diffractometer. The configuration of carbon C(7) is *S*. The pyranose ring is boat shaped, the dithiepane ring is in a twist-chair conformation, and the conformations of the two dioxolane rings are envelope and twist-chair.

Introduction

Several new powerful antibiotics (lincomycin, aldgamicyn E, *etc.*) contain branched and extended-chain carbohydrate derivatives.

To synthesize the octose derivatives from the more abundant hexoses, M. Gero and his co-workers were led to prepare dithiane derivatives of octopyranoses (Sepulchre, Gateau-Olesker, Lukacs, Vass & Gero, 1972). One of these compounds was transformed into a new class of carbohydrate dithiepane derivative:



The configuration at C(7) could not be deduced from chemical considerations and so the crystal structure determination was undertaken. It was thought that the X-ray study could also produce some interesting results concerning the conformation of the still unknown dithiepane cycle, and that of the pyranose ring, substituted by the two isopropylidene groups. The preliminary results have been reported in a short note (Gateau-Olesker, Gero, Pascard-Billy, Riche, Sepulchre, Vass & Hughes, 1974).

Experimental

Crystal data

$C_{17}H_{27}N_3O_5S_2$, F.W. 417. Orthorhombic. Space group: $P2_12_12_1$; $a=9{\cdot}599(5)$, $b=10{\cdot}835(5)$, $c=19{\cdot}559(9)$ Å, $V=2034{\cdot}2$ Å^3, $D_x=1{\cdot}362$ g cm^{-3}, $Z=4$. Crystal dimensions: $0{\cdot}3\times0{\cdot}35\times0{\cdot}4$ mm.

Intensity recording

Automatic four-circle Philips PW1100 diffractometer, graphite monochromator, copper radiation ($\lambda=1{\cdot}5418$ Å), ω scan to $2\theta=60°$, ω–2θ scan for $60° <$