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The Crystal Structure of 5-Bromo-12S-tetrahydroaustamide
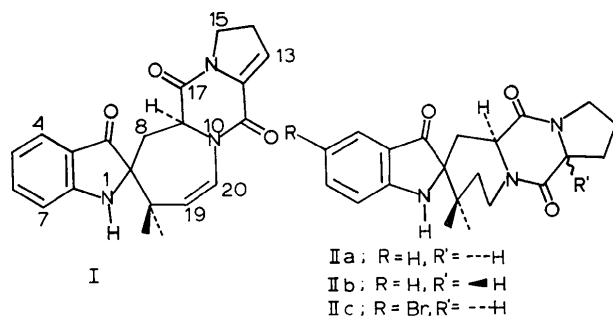
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The crystal structure of 5-bromo-12S-tetrahydroaustamide has been determined by three-dimensional X-ray analysis. The crystals are monoclinic with space group $P2_1$ and two molecules in the unit cell of dimensions $a = 7\cdot241$, $b = 13\cdot148$, $c = 11\cdot556$ Å and $\beta = 106\cdot68°$. The absolute configuration of the molecule was derived from the known stereochemistry at the 12-position established in earlier chemical and spectroscopic studies.

Introduction

In our continuing studies on biologically active fungal metabolites, austamide (I) was isolated as a toxic component from Aspergillus ustus (Steyn, 1971).

IIa ; R = H, R' = ---H
IIb ; R = H, R' = ◄H
IIc ; R = Br, R' = ---H

Prolonged hydrogenation of I gave two diastereoisomeric tetrahydroaustamides IIa and IIb. Acid hydrolysis of the major product, IIa, liberated S-proline, therefore establishing the 12S-configuration at this newly created chiral centre. The stereochemistry at position 9 was based on the 9S, 12S-configuration of prolyl-2-(1'1'-dimethylallyl)tryptophyldiketopiperazine, an apparent bioprecursor of I. The configuration at the spiro atom, position 2 relative to that of position 9, was based on n.m.r. shift data (Steyn, to be published).

5-Bromo-12S-tetrahydroaustamide (IIc) was prepared for an X-ray crystallographic study in an attempt to substantiate the above conclusions.

Experimental

12S-Tetrahydroaustamide (50 mg) in tetrahydrofuran (2 ml) was treated with pyridinium hydrobromide perbromide (44 mg) in tetrahydrofuran (2 ml). The colourless mixture was concentrated in a stream of nitrogen and the residue partitioned between chloroform and water. The organic phase was concentrated and crystallized from ethanol to yield IIc. [Analysis: Found: C, 54·31; H, 5·60; Br, 17·25; N, 9·05%. $C_{21}H_{24}BrN_3O_3 . H_2O$ requires C, 54·63; H, 5·44; Br, 17·06; N, 8·97%].

The bright yellow rhombic crystals are monoclinic with space group $P2_1$ ($0k0$ absent for k odd).

The other crystal data are:

Molecular formula $C_{21}H_{24}BrN_3O_3$
$\lambda(Mo\ K\alpha) = 0\cdot70926$ Å
$a = 7\cdot241\ (1)$ Å
$b = 13\cdot148\ (2)$
$c = 11\cdot556\ (1)$
$\beta = 106\cdot68\ (30)°$
$d_x = 1\cdot46$ g cm^{-3}
$d_m = 1\cdot46$ (measured by flotation in a mixture of bromoform and methanol)
M.W. 446·34
$Z = 2$.

Unit-cell dimensions were calculated from the accurate spot positions measured on a Hilger & Watts four-circle automatic diffractometer using a least-

Table 1. *Refined atomic parameters* ($\times 10^4$) (*fractional coordinates and anisotropic temperature factors*)

Thermal parameters are of the form $T = \exp\left[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl) \times 10^{-4}\right]$.

(Standard deviations are given in parentheses.)

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
Br	14017 (2)	0	11674 (1)	300 (3)	156 (2)	143 (2)	14 (3)	−46 (2)	10 (2)
O(1)	8713 (10)	2133 (6)	7644 (6)	292 (18)	53 (5)	81 (6)	− 8 (8)	61 (9)	− 2 (5)
O(2)	4511 (15)	2925 (8)	2998 (8)	503 (33)	96 (8)	132 (10)	96 (14)	102 (15)	44 (8)
O(3)	8452 (12)	− 329 (7)	4371 (8)	335 (24)	64 (6)	126 (9)	54 (10)	91 (11)	1 (6)
O(4)	8150 (15)	3764 (9)	5765 (8)	497 (33)	142 (11)	135 (10)	−89 (16)	106 (15)	−5 (9)
N(1)	6288 (10)	− 146 (8)	7973 (7)	220 (17)	57 (6)	83 (7)	−19 (10)	36 (9)	4 (6)
N(2)	5443 (12)	1744 (8)	4467 (7)	252 (22)	83 (7)	66 (7)	48 (10)	32 (10)	10 (6)
N(3)	8338 (13)	1202 (9)	3456 (7)	299 (24)	88 (8)	67 (7)	29 (12)	56 (11)	5 (7)
C(1)	11582 (13)	− 129 (12)	10485 (8)	193 (21)	107 (11)	75 (8)	38 (17)	26 (11)	11 (10)
C(2)	10453 (19)	− 965 (10)	10461 (10)	339 (34)	61 (8)	100 (12)	6 (15)	35 (16)	9 (8)
C(3)	8691 (16)	−1036 (9)	9649 (9)	277 (28)	65 (8)	75 (9)	7 (13)	37 (13)	3 (7)
C(4)	8075 (14)	− 236 (8)	8831 (8)	231 (22)	48 (7)	72 (8)	−16 (11)	39 (11)	− 12 (6)
C(5)	9207 (13)	618 (8)	8847 (8)	163 (19)	66 (7)	52 (7)	1 (10)	33 (10)	−9 (6)
C(6)	11046 (15)	728 (9)	9687 (9)	218 (23)	73 (8)	65 (8)	16 (11)	37 (11)	−5 (7)
C(7)	8192 (13)	1283 (8)	7894 (8)	207 (21)	41 (6)	63 (8)	0 (10)	49 (11)	−8 (6)
C(8)	6284 (13)	727 (8)	7207 (8)	186 (21)	60 (7)	66 (8)	−10 (10)	23 (11)	7 (7)
C(9)	4427 (14)	1375 (9)	7115 (9)	199 (23)	67 (8)	84 (9)	5 (11)	59 (12)	3 (7)
C(10)	2686 (14)	643 (11)	6833 (11)	152 (21)	108 (11)	118 (12)	−16 (13)	21 (13)	−3 (10)
C(11)	4631 (17)	1891 (10)	8345 (10)	287 (29)	82 (9)	117 (12)	1 (14)	111 (16)	− 13 (9)
C(12)	4121 (17)	2213 (10)	6148 (11)	281 (30)	68 (9)	97 (11)	62 (14)	64 (15)	7 (8)
C(13)	3721 (16)	1851 (12)	4839 (10)	221 (27)	129 (13)	86 (11)	72 (16)	29 (14)	24 (10)
C(14)	7088 (13)	1118 (8)	5183 (8)	202 (22)	64 (7)	62 (8)	28 (11)	44 (11)	−5 (7)
C(15)	6521 (13)	326 (7)	5972 (7)	238 (22)	50 (7)	51 (7)	10 (9)	41 (10)	−6 (6)
C(16)	5712 (21)	2341 (9)	3591 (10)	445 (41)	50 (7)	72 (10)	43 (15)	73 (17)	10 (7)
C(17)	7656 (20)	2270 (11)	3374 (11)	403 (38)	73 (9)	97 (12)	34 (16)	101 (18)	12 (8)
C(18)	7611 (25)	2586 (13)	2043 (13)	631 (58)	129 (16)	128 (15)	73 (25)	211 (26)	36 (12)
C(19)	9037 (25)	1906 (14)	1796 (12)	579 (57)	136 (16)	104 (13)	64 (26)	130 (23)	9 (13)
C(20)	9092 (17)	889 (11)	2466 (10)	323 (30)	107 (12)	73 (9)	26 (16)	90 (14)	−5 (9)
C(21)	8022 (17)	587 (10)	4272 (11)	188 (24)	84 (10)	86 (10)	8 (13)	33 (13)	−15 (9)

squares procedure (Busing & Levy, 1967). A crystal with dimensions 0·12×0·14×0·20 mm was chosen to collect intensities for 2112 independent reflexions with $\theta < 25°$ using the diffractometer with graphite mono-chromated Mo $K\alpha$ radiation and applying the ω–2θ scanning technique. Of these intensities 1656 were greater than $3\sigma(I)$, where $\sigma(I)$ is given by $[I_0 + I_b]^{1/2}$. I_0 is the total number of counts during the peak scan and I_b the number of counts for the background intensity. Background corrections were made from scans of intensity against θ, parallel to central lattice rows. The reflexions were corrected for Lorentz and polarization factors but no absorption corrections were applied.

Structure analysis

The structure was solved by the heavy-atom meth-od. Refinement of the atomic parameters assign-ing unit weights to the 1656 observed reflexions in a full-matrix least-squares program (Busing, Martin & Levy, 1962) which minimizes the function $\sum \omega(|F_o| - |kF_c|)^2$ gave an R index $[R = (\sum ||F_o| - |F_c||)/\sum |F_o|]$ of 0·14 with individual isotropic thermal parameters for all the atoms. Refinement with anisotropic thermal parameters reduced the R index to 0·065. The form factors used were those of Hansen, Herman, Lea & Skillman (1964). A list of the final atomic parameters is given in Table 1. Bond lengths and angles were cal-culated using the function and error program *ORFFE*

(Busing, Martin & Levy, 1964). These values are given in Tables 2 and 3. Table 4 lists the observed and cal-culated structure factors.

Table 2. *Interatomic distances* (Å) (*standard deviations in parentheses*)

C=O		C=C (arom)	
C(7)—O(1)	1·24 (2) Å	C(1)–C(2)	1·37 (2) Å
C(16)–O(2)	1·21 (2)	C(2)–C(3)	1·35 (2)
C(21)–O(3)	1·24 (3)	C(3)–C(4)	1·40 (2)
		C(4)–C(5)	1·39 (2)
		C(5)–C(6)	1·41 (2)
sp^2C–N		C(6)–C(1)	1·44 (3)
C(4)—N(1)	1·39 (2)		
C(16)–N(2)	1·34 (2)		
C(21)–N(3)	1·31 (3)	sp^2C–sp^2C	
		C(5)–C(7)	1·43 (2)
sp^3C–N			
C(8)—N(1)	1·45 (3)	sp^2C–sp^3C	
C(13)–N(2)	1·44 (3)	C(7)—C(8)	1·56 (2)
C(21)–N(2)	1·49 (2)	C(16)–C(17)	1·50 (3)
C(17)–N(3)	1·48 (3)	C(14)–C(21)	1·57 (3)
C(20)–N(3)	1·46 (2)		
		C–C	
C(1)—Br	1·91 (3)	C(8)—C(9)	1·57 (3)
		C(9)–C(10)	1·54 (3)
O(1)···O(4)	2·99 (4)	C(9)—C(11)	1·54 (2)
O(2)···O(4)	2·77 (4)	C(9)—C(12)	1·54 (2)
		C(12)–C(13)	1·53 (2)
		C(8)—C(15)	1·58 (3)
		C(14)–C(15)	1·52 (2)
		C(17)–C(18)	1·58 (3)
		C(18)–C(19)	1·46 (2)
		C(19)–C(20)	1·54 (3)

Discussion

The stereo pair in Fig. 1 illustrates the molecular geometry and the atomic numbering used in the X-ray analysis while the structure formula (I) shows the chemical numbering (Steyn, 1971). The assignment of the absolute configuration of the molecule is based on the known stereochemistry at the 12-position [C(17)

Table 3. *Bond angles (standard deviations in parentheses)*

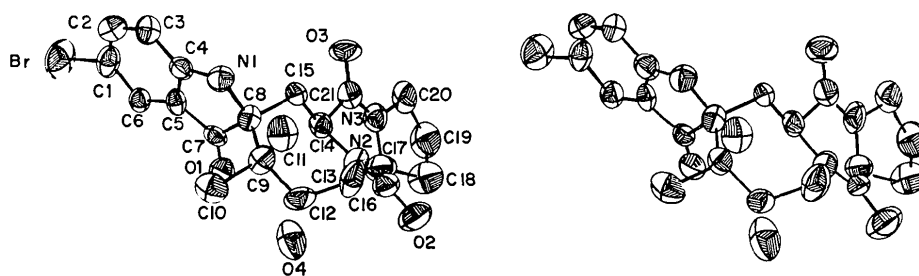|				
C(4)—N(1)–C(8)	109·9 (1)°		C(8)—C(9)—C(10)	107·9 (3)°
C(13)–N(2)–C(14)	120·9 (2)		C(8)—C(9)—C(11)	108·8 (2)
C(13)–N(2)–C(16)	119·7 (1)		C(8)—C(9)—C(12)	112·4 (2)
C(14)–N(2)–C(16)	118·5 (2)		C(10)–C(9)—C(11)	108·9 (2)
C(17)–N(3)–C(20)	114·2 (1)		C(10)–C(9)—C(12)	110·7 (2)
C(17)–N(3)–C(21)	120·4 (2)		C(11)–C(9)—C(12)	108·0 (3)
C(20)–N(3)–C(21)	124·8 (2)		C(9)—C(12)–C(13)	116·2 (2)
Br——C(1)–C(2)	120·7 (2)		N(2)—C(13)–C(12)	113·1 (2)
Br——C(1)–C(6)	114·6 (2)		N(2)—C(14)–C(21)	107·7 (2)
C(2)—C(1)–C(6)	124·6 (2)		N(2)—C(14)–C(15)	113·7 (2)
C(1)—C(2)–C(3)	120·7 (2)		C(15)–C(14)–C(21)	109·9 (3)
C(2)—C(3)–C(4)	118·1 (2)		C(8)—C(15)–C(14)	115·7 (2)
N(1)—C(4)–C(3)	126·6 (1)		O(2)—C(16)–N(2)	124·1 (2)
N(1)—C(4)–C(5)	111·5 (2)		O(2)—C(16)–C(17)	120·0 (2)
C(3)—C(4)–C(5)	121·8 (2)		N(2)—C(16)–C(17)	115·9 (1)
C(4)—C(5)–C(6)	121·9 (2)		N(3)—C(17)–C(16)	111·1 (1)
C(6)—C(5)–C(7)	129·8 (2)		N(3)—C(17)–C(18)	103·0 (1)
C(1)—C(6)–C(5)	112·8 (1)		C(16)–C(17)–C(18)	112·8 (2)
O(1)—C(7)–C(5)	127·2 (2)		C(17)–C(18)–C(19)	102·2 (2)
O(1)—C(7)–C(8)	125·9 (1)		C(18)–C(19)–C(20)	110·6 (2)
C(5)—C(7)–C(8)	106·8 (3)		N(3)—C(20)–C(19)	100·8 (2)
N(1)—C(8)–C(7)	102·4 (2)		O(3)—C(21)–N(3)	125·0 (2)
N(1)—C(8)–C(9)	108·9 (2)		O(3)—C(21)–C(14)	121·0 (1)
N(1)—C(8)–C(15)	107·9 (2)		N(3)—C(21)–C(14)	114·0 (3)
C(7)—C(8)–C(9)	113·3 (3)			
C(7)—C(8)–C(15)	107·9 (2)			
C(9)—C(8)–C(15)	115·7 (2)			

Fig. 1. Stereoscopic drawing of 5-bromo-12*S*-tetrahydroaustamide showing the atomic numbering used in the X-ray analysis.
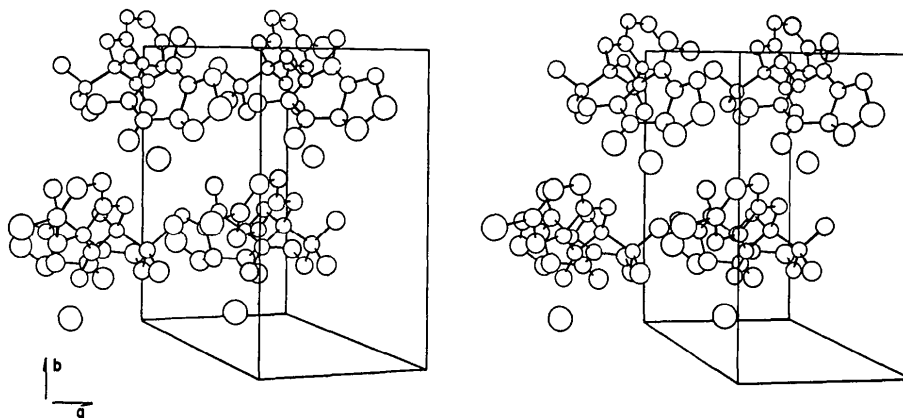

Fig. 2. Stereoscopic diagram of the molecular packing in the unit cell.

Table 4. *Observed and calculated structure factors*

The columns are k, l, $F_{obs} \times 10$ and $F_{calc} \times 10$.

Table 5. *Equations of least-squares planes*

Atoms	Equation	Maximum deviation from plane (Å)
C(1), C(2), C(3), C(4), C(5), C(6)	$-0.6236x + 0.4431y + 0.6441z = 4.3421$*	0.005 (1)
O(3), C(21), C(14), N(3)	$0.7659x + 0.2199y + 0.6042z = 6.4011$	0.01 (2)
O(2), C(16), C(17), N(2)	$0.1592x + 0.7232y + 0.6721z = 5.3713$	0.005 (3)
O(1), C(7), C(5), C(8)	$0.6684x - 0.4228y - 0.6120z = -3.8434$	0.003 (4)

* x, y and z (in Å) refer to the crystallographic axes a, b and c, respectively.

in the X-ray numbering] from chemical data. The predicted stereochemistry of the *spiro* atom and carbon 9 [C(14)] is shown to be in agreement with the X-ray structure.

As expected the six benzene carbon atoms are all coplanar. This is shown by the maximum atomic deviation of 0.005 Å from the least-squares plane (Equation 1, Table 5) passing through the benzene ring. The three aromatic substituent atoms, Br, N(1) and C(7), show insignificant deviations of 0.07, 0.07 and 0.03 Å, respectively, from this plane.

The mean C=C aromatic bond length is 1.39 Å while the distances of 1.43 and 1.39 Å for the pairs C(5)–C(7) and C(4)–N(1) are typical of C(aromatic)–C and C(aromatic)–N bond types (Sutton, 1965).

Equations 2, 3 and 4 in Table 5 give the respective least-squares planes through the trigonal arrangements associated with the carbonyl carbon atoms C(7), C(16) and C(21). The respective maximum atomic deviations are 0.003, 0.005 and 0.01 Å, making all three sets of atoms planar.

Despite the planarity of the latter two groups of atoms the diketopiperazine ring is folded and assumes the boat conformation as shown in Fig. 1.

The carbonyl bond lengths are 1.24 [C(7)–O(1)], 1.24 [C(21)–O(3)] and 1.21 Å [C(16)–O(2)], respectively, and show good agreement with the values quoted by Sutton (1965) for these distances, *viz.* 1.235 (O=C–N) and 1.25 Å (in 3,3′-dibromobenzophenone).

The mean sp^3C–sp^3C bond length of 1.54 Å compares favourably with the value of 1.545 Å in diamond. The crystals of 5-bromo-12S-tetrahydroaustamide contain one molecule of crystal water per formula unit. The oxygen atom of the water molecule, O(4), is removed from the two carbonyl oxygen atoms O(1) and O(3) by distances of 2.99 and 2.77 Å, respectively, indicating hydrogen bonding to both carbonyl oxygens.

The molecular packing in the unit cell is shown in Fig. 2. The shortest contact distance of 3.53 Å occurs between the atoms C(6) and C(19) in molecules which are separated by a unit-cell translation in the **c** direction.

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