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Structure and Absolute Configuration of Breynolide, $C_{15}H_{22}O_7S$

By Kyoyu Sasaki and Yoshimasa Hirata

Chemical Institute, Faculty of Science, Nagoya University, Chikusa, Nagoya, Japan

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Breynolide which is a sulphur-containing sesquiterpene component in a glycoside breynin A from *Breynia officinalis*, crystallizes in the monoclinic space group $P2_1$ with two molecules in a unit cell of dimensions $a=13{\cdot}434$ (1), $b=8{\cdot}628$ (1), $c=6{\cdot}652$ (1) Å, and $\beta=91{\cdot}08$ (2)°. The structure was determined by the symbolic addition method from data collected on a four-circle diffractometer using the θ–2θ scan technique. It was refined by the block-diagonal least-squares method to $R=0{\cdot}071$ for 1614 observed reflexions. The ring system of breynolide is novel and the most interesting feature is the five- and six-membered ketal rings.

Introduction

The hypocholesterolenic sulphur-containing glycoside, breynin A,* $C_{40}H_{56}O_{23}S$, was isolated from *Breynia officinalis* Hemsl. The glycoside was treated with hydrochloric acid ($3N$) to give an aglycone, breynogenin ($C_{32}H_{26}O_9S$, m.p. 260–262°), which was further hydrolysed to *p*-hydroxybenzoic acid and breynolide, $C_{15}H_{22}O_7S$ (I).

The difficulty in clarifying the structure of breynolide with chemical methods led us to undertake the present X-ray crystallographic study. We have determined the crystal structure of this compound by the direct phase determination method, and the preliminary results have been reported in an earlier communication (Sasaki & Hirata, 1973).

Crystal data

Breynolide, $C_{15}H_{22}O_7S$, M.W. 346·39, m.p. 241–243°. Monoclinic, $a=13{\cdot}434\,(1)$, $b=8{\cdot}628\,(1)$, $c=6{\cdot}652\,(1)$ Å; $\beta=91{\cdot}08$ (2)°. $U=770{\cdot}89$ Å^3. $D_m=1{\cdot}485$ g cm^{-3} (by flotation in a mixture of n-hexane and carbon tetrachloride). $D_x=1{\cdot}492$ g cm^{-3}, $Z=2$, $F(000)=368$, μ[Cu $K\alpha$ ($\lambda=1{\cdot}5418$ Å)]$=22{\cdot}9$ cm^{-1}. Space group $P2_1$.

Experimental

Breynolide was crystallized from ethyl acetate as colourless plates. The three-dimensional intensities were collected on a Hilger–Watts automatic four-circle diffractometer Y 290 controlled by a PDP-8 computer. Integrated intensities were measured for $\theta<78°$ by the θ–2θ step-scan technique using Cu $K\alpha$ radiation and a scintillation counter. Reflexions with $\theta\le 50°$ were integrated in 40 steps with intervals of 0·02° and reflexions with $\theta>50°$ were integrated in 50 steps with the same intervals. In this way 1614 non-zero independent reflexions having intensities greater than $3\sigma(I)$ were collected. They were corrected for Lorentz and polarization factors but no absorption or extinction corrections were applied since the specimen was considered to be small enough ($0{\cdot}15\times0{\cdot}20\times0{\cdot}20$ mm) for them to be negligible.

Structure determination and refinement

The structure was solved by direct methods (Karle & Karle, 1966). The scale factor and overall isotropic temperature factor ($B=3{\cdot}18$ Å^2) were derived from a Wilson plot and used to calculate the normalized structure factors, $|E|$. Phase determination was carried out by the method of Germain & Woolfson (1968) with the following reflexions as a starting set:

h	k	l	$\|E\|$	φ	
1	0	3	2·94	0	Origin
$\overline{12}$	0	1	2·20	0	
$\overline{4}$	1	5	2·34	0	
3	6	0	2·33		$\pm\pi/4$ or $\pm3\pi/4$
6	6	0	2·91		
11	3	0	2·44		

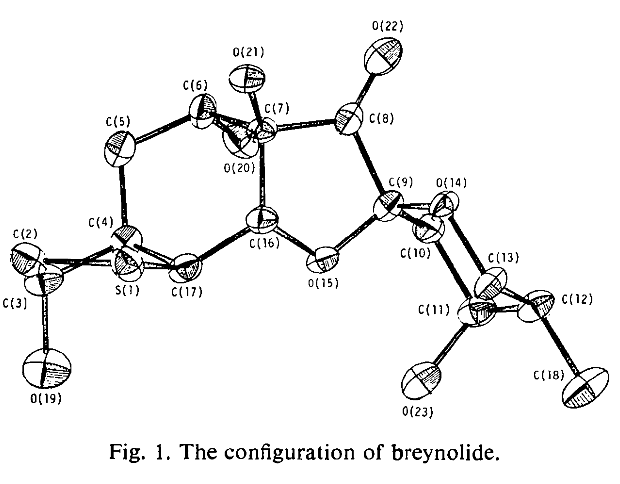

Fig. 1. The configuration of breynolide.

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* The full details of breynin, breynogenin, and breynolide will be reported elsewhere, from the Bristol-Banyu Research Institute.

For all possible combinations, the tangent formula was applied to 141 reflexions ($|E|>1{\cdot}6$). A figure of merit, M, where

$$M=\sum_H Z_H$$

can be defined, in which Z_H is equal to the sum of the squares of numerator and denominator of the tangent formula. Two sets (enantiomorphs) resulted in a larger value of M, $4{\cdot}39\times10^5$ as compared with $4{\cdot}31$–$1{\cdot}75\times10^5$ for the others. One of the most consistent sets was selected and extended to include 291 reflexions ($|E|>1{\cdot}3$) and these were used in the calculation of an E map. On this map all the non-hydrogen atoms were located from the 23 heighest peaks. A structure-factor calcula-

Table 1. *Fractional atomic coordinates and thermal parameters for breynolide*

Thermal parameters are of the form $T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+\beta_{12}hk+\beta_{23}kl+\beta_{31}lh)]$. The β_{ij}'s are multiplied by 10^4.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{23}	β_{31}
S(1)	1·0151	0·6914	0·0266	29	104	150	−17	7	−5
C(2)	1·0485	0·7399	−0·2299	35	106	154	−28	−17	1
C(3)	0·9781	0·6505	−0·3679	34	72	182	5	−20	37
C(4)	0·8766	0·6465	−0·2659	29	73	120	7	12	20
C(5)	0·8246	0·8035	−0·2747	36	85	148	16	48	0
C(6)	0·7285	0·8021	−0·1578	33	82	105	8	42	−13
C(7)	0·7471	0·7638	0·0618	35	43	100	−2	−27	−6
C(8)	0·6497	0·7056	0·1525	34	63	113	13	21	−2
C(9)	0·6615	0·5297	0·1914	30	55	126	12	23	10
C(10)	0·5806	0·4232	0·1101	28	61	167	4	−5	−15
C(11)	0·5946	0·2562	0·1903	28	64	186	−5	14	33
C(12)	0·6034	0·2595	0·4200	36	67	165	−4	37	45
C(13)	0·6875	0·3686	0·4898	47	61	148	13	59	2
O(14)	0·6719	0·5239	0·4054	46	54	78	2	25	−4
O(15)	0·7533	0·4923	0·1007	24	45	150	−1	17	28
C(16)	0·8190	0·6274	0·1018	32	49	121	0	−22	1
C(17)	0·8979	0·5957	−0·0512	28	59	148	−4	31	18
C(18)	0·6211	0·0996	0·5134	80	80	222	14	97	61
O(19)	1·0139	0·4950	−0·4003	53	96	234	28	−123	60
O(20)	0·6577	0·6889	−0·2321	36	121	121	−26	−24	−4
O(21)	0·7846	0·8954	0·1703	41	51	149	−4	−49	−7
O(22)	0·5780	0·7800	0·1946	43	78	176	33	13	42
O(23)	0·6820	0·1841	0·1014	43	68	179	21	−21	51
Standard deviations:									
S(1)	0·0001	0·0003	0·0004	1	3	5	3	7	3
O(14, 15, 19–23)	0·0004	0·0008	0·0009	3	8	14	10	21	12
C(2–13, 16–18)	0·0006	0·0010	0·0012	4	11	17	11	23	14

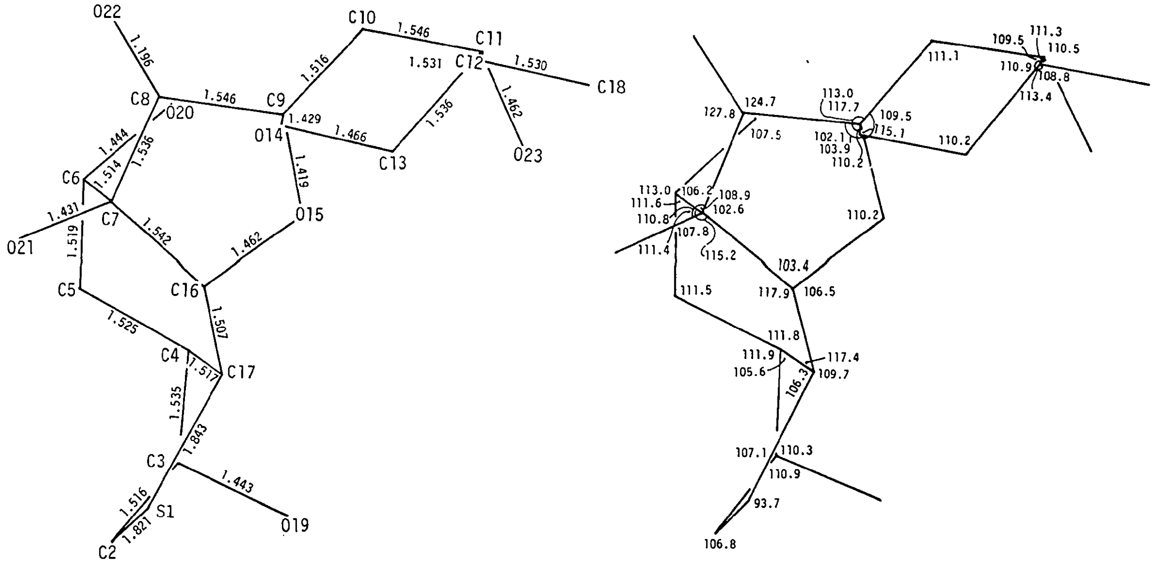

Fig. 2. Bond lengths (Å) and angles (°) of breynolide. The ranges of their e.s.d.'s are 0·009–0·014 Å and 0·5–0·8°.

tion based on these coordinates gave a value of $R=$ 0·30. All the atoms except sulphur were assigned carbon form factors. Refinement proceeded with individual isotropic thermal motion to give an R value of 13%. At this stage the final atomic species were identified on the basis of the bond lengths and angles, the electron population of the Fourier synthesis maxima, and the thermal parameter values. Further refinement led to an R value of 8% with anisotropic thermal motion, and then 22 hydrogen atoms were clearly visible in a difference map. The hydrogen atoms were given anisotropic thermal factors equal to those of the carbon and oxygen atoms to which they were attached, and no attempt was made to determine their individual motions. Their positions were refined, however, together with the thermal factors of the heavier atoms, leading to an R value of 7·1%. Possible positions for six hydrogen atoms were indicated weakly in a subsequent difference map. Attempts to refine these positions by least-squares calculations resulted in large oscillating shifts. Coordinates obtained from the difference map are included for those six atoms together with the least-squares results for all other atoms in Tables 1 and 2.

Table 2. *Fractional atomic coordinates for the hydrogen atoms*

	x	y	z
H(2*a*)	1·122	0·700	−0·250
H(2*b*)	1·047	0·852	−0·233
H(3)	0·972	0·709	−0·499
H(4)	0·830	0·570	−0·353
H(5*a*)	0·858	0·885	−0·196
H(5*b*)	0·809	0·841	−0·425
H(6)	0·708	0·909	−0·147
H(10*a*)	0·575	0·420	−0·057
H(10*b*)	0·503	0·454	0·145
H(11)*	0·520	0·211	0·142
H(12)	0·531	0·303	0·460
H(13*a*)	0·764	0·347	0·459
H(13*b*)	0·694	0·381	0·636
H(16)	0·852	0·643	0·240
H(17)	0·866	0·491	−0·055
H(18*a*)*	0·554	0·041	0·470
H(18*b*)*	0·696	0·083	0·481
H(18*c*)*	0·611	0·107	0·655
H(19)*	1·095	0·500	−0·437
H(20)	0·662	0·696	−0·358
H(21*)	0·725	0·945	0·210
H(23)	0·745	0·215	0·024
Standard deviations:			
	0·008	0·014	0·016

* Atoms not refined by least-squares; their positions were estimated (±0·008) from a difference map.

The final R value omitting unobserved reflexions was 7·1%, with unit weights. After the last cycle of the refinement most parameter shifts were less than 0·1σ and the largest was 0·3σ.

Coordinates, thermal parameters, and the scale factor were refined by the block-diagonal approximation of the least-squares method.

The absolute configuration of breynolide was determined by Bijvoet's method (Bijvoet, Peerdeman & van Bommel, 1951), based on sulphur ($\Delta f'=0{\cdot}3$, $\Delta f''=0{\cdot}6$) and oxygen ($\Delta f'=0{\cdot}0$, $\Delta f''=0{\cdot}1$), using values from *International Tables for X-ray Crystallography* (1968). The differences between Friedel pairs were measured on a Hilger and Watts diffractometer with Cu $K\alpha$ radiation. In Table 3, the square root of the counter intensities, G, is reported for the Friedel pairs. The G values have not been placed on an absolute scale or corrected for Lp factors. These corrections will not affect the calculation of the percentage deviation from Friedel's law, as expressed by the parameter Δ:

$$\Delta = 100[|F(\bar{h}\bar{k}\bar{l})| - |F(hkl)|] \Bigg/ \frac{|F(\bar{h}\bar{k}\bar{l})| + |F(hkl)|}{2}\,.$$

The values of Δ_{obs} are listed in Table 3, together with values of Δ_{calc} for the correct absolute configuration of breynolide. The coordinates in Table 1 give the correct absolute configuration if a left-handed coordinate system is used, and the structure in Fig. 1 shows the correct absolute configuration.*

Table 3. *Observed and calculated Bijvoet differences (percentages) for breynolide*

h	k	l	$\lvert G(hkl)\rvert$	$\lvert G(\bar{h}\bar{k}\bar{l})$	Δ(obs)	Δ(calc)
1	2	1	187	172	−8·4	−6·1
1	3	2	157	152	−3·2	−4·6
2	1	2	140	135	−3·6	−6·5
2	1	3	168	178	5·8	4·2
2	3	2	95	100	5·1	4·0
2	4	3	103	97	−6·0	−7·0
3	1	2	143	135	−5·8	−4·2
3	4	1	196	206	5·0	5·3
4	3	2	96	90	−6·5	−8·0
4	4	1	141	147	4·2	7·1
6	3	2	101	93	−8·2	−6·8
7	2	1	96	92	−4·3	−5·8
−1	2	2	122	117	−4·2	−4·9
−1	4	1	198	186	−6·3	−7·0
−2	2	1	210	219	4·2	4·6
−2	2	2	165	160	−3·1	−5·1
−4	4	2	80	86	7·2	4·7
−6	2	4	89	95	6·5	7·5
−7	2	1	149	155	3·9	6·2
−7	2	2	81	77	−5·1	−6·5
−8	3	1	84	80	−4·9	−4·7
−10	2	1	105	101	−3·9	−4·6

Results and discussion

The structure of breynolide, shown in Fig. 1, is in agreement with the results of n.m.r. and mass spectra measurements. The ring system of breynolide is novel and is characterized by a tetrahydrothiophene and two spiro-ketal rings (tetrahydrofuran and tetrahydropyran).

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* The structure-factor table has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 30351 (11pp.). Copies may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Bond distances and angles are shown in Fig. 2. The average values of the bond distances are 1·525 for C–C, 1·445 for C–O, 1·832 for S–C, and 1·196 Å for C=O, in agreement with the expected values. The structure is tetracyclic and the central cyclohexane ring is in the distorted chair form and is *cis*-fused to two five-membered rings. Breynolide has four hydroxyl groups, three of which adopt an axial form in two six-membered rings. The oxygen atom of the ketone group on the tetrahydrofuran ring, O(22), and the atoms C(7), C(8) and C(9) lie within 0·014 Å of the least-squares mean plane defined by:

$$0{\cdot}3630X + 0{\cdot}1807Y + 0{\cdot}9074Z - 5{\cdot}2031 = 0.$$

O(15) and C(16) are −0·154 and 0·384 Å out of the plane, respectively.

The arrangement of molecules in the unit cell is shown in Fig. 3 and selected intermolecular contacts less than 3·8 Å are listed in Table 4. The shortest intermolecular distances are 3·16 Å for C···O and 3·65 Å for C···C.

Table 4. *Selected intermolecular contacts less than* 3·8 Å

		Symmetry operation on primed atoms
C(18)···O(21′)	3·65 Å	$x,\quad y-1{\cdot}0,\quad z$
C(18)···O(22′)	3·52	
O(23)···C(6′)	3·78	
C(18)···C(6′)	3·65	$x,\quad y-1{\cdot}0,\quad z+1{\cdot}0$
C(13)···O(20′)	3·35	$x,\quad y,\quad z+1{\cdot}0$
O(14)···C(4′)	3·64	
C(10)···O(22′)	3·16	$-x+1{\cdot}0,\ y-0{\cdot}5,\ -z$
C(11)···O(20′)	3·45	
O(22)···C(18′)	3·68	$-x+1{\cdot}0,\ y+0{\cdot}5,\ -z+1{\cdot}0$
O(22)···C(12′)	3·57	
O(19)···C(2′)	3·40	$-x+2{\cdot}0,\ y-0{\cdot}5,\ -z-1{\cdot}0$
O(19)···C(3′)	3·35	
O(19)···C(5′)	3·50	
C(2)····C(17′)	3·66	$-x+2{\cdot}0,\ y+0{\cdot}5,\ -z$
S(1)····C(17′)	3·68	
S(1)····O(19′)	3·64	
C(2)····O(23′)	3·74	
C(2)····O(15′)	3·53	
O(21)···C(2′)	3·74	
O(21)···O(19′)	3·20	

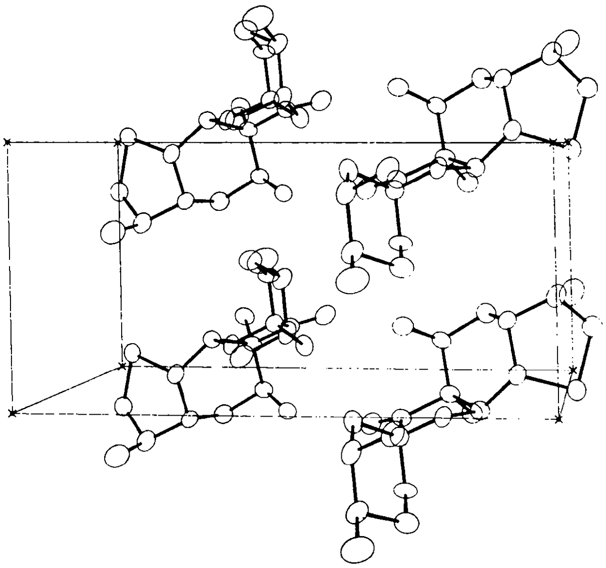

Fig. 3. A view of the unit cell of breynolide. **c** is downwards, **a** left to right and **b** away from the observer.

The authors are indebted to Bristol-Banyu Research Institute Ltd., for the crystal sample. Figs. 1 and 3 were drawn with the help of the *ORTEP* program of Johnson (1965). All computations were performed on a FACOM 230-60 at the Nagoya University Computation Centre.

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