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Ochrobirine, a Spirobenzylisoquinoline Alkaloid

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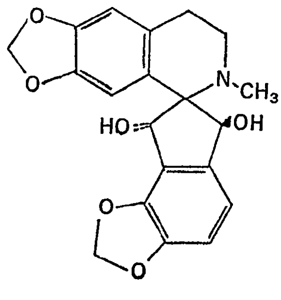
Abstract. Ochrobirine methanolate, $C_{21}H_{23}O_7N.CH_3OH$, M.W. 401·4, orthorhombic, $P2_12_12_1$, $a=13{\cdot}528$ (5), $b=17{\cdot}455$ (7), $c=7{\cdot}909$ (3) Å, $V=1867{\cdot}6$ Å^3; $d_m=1{\cdot}42$, $d_c=1{\cdot}427$ g cm^{-3} for $Z=4$. The final R is 0·069 for the 1944 reflections used in the analysis. Ochrobirine is a spirobenzylisoquinoline alkaloid and the two halves of the molecule are almost normal to each other. The molecular dimensions are normal. The ochrobirine and methanol molecules are hydrogen-bonded to each other in the solid state in a helical fashion around the twofold screw axis.

Introduction. Crystals of ochrobirine methanolate (I) were kindly supplied by Professor R. H. F. Manske. Preliminary precession photographs indicated orthorhombic symmetry. The systematic absences of $h00$ for $h=2n+1$, $0k0$ for $k=2n+1$ and $00l$ for $l=2n+1$ indicated that the space group was $P2_12_12_1$. A 0·24 × 0·12 × 0·13 mm crystal was used for the measurement of the cell constants and intensities. All measurements were made on a General Electric XRD-6 diffractometer automated by the Datex Corporation with Zr-filtered Mo $K\alpha$ radiation. The cell constants were deter-



(I)

Table 1. *Final parameters of the non-hydrogen atoms for ochrobirine*

All values are ×10⁴. The estimated standard deviations are given in parentheses. The temperature factor is of the form $\exp\left[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+\beta_{12}hk+\beta_{13}hl+\beta_{23}kl)\right]$.

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
O(1)	4146 (2)	6342 (2)	4864 (4)	94 (2)	35 (1)	201 (6)	30 (3)	32 (7)	−12 (5)
O(2)	3075 (2)	7041 (2)	3201 (5)	83 (2)	38 (1)	297 (8)	36 (3)	57 (8)	8 (6)
O(3)	3860 (2)	2651 (2)	4433 (4)	76 (2)	40 (1)	185 (6)	−12 (3)	35 (7)	46 (5)
O(4)	5040 (3)	2469 (2)	6520 (4)	111 (3)	47 (1)	145 (5)	−5 (3)	−2 (7)	44 (5)
O(5)	4342 (2)	3044 (1)	−11 (4)	95 (2)	30 (1)	171 (5)	−22 (3)	−21 (7)	−10 (4)
O(6)	6517 (2)	4950 (1)	1066 (4)	48 (2)	30 (1)	160 (5)	−10 (2)	14 (5)	−11 (4)
C(1)	4553 (3)	5378 (2)	2713 (5)	49 (2)	29 (1)	126 (7)	4 (3)	30 (8)	24 (6)
C(2)	4090 (3)	6008 (2)	3273 (5)	55 (3)	29 (1)	146 (7)	0 (4)	46 (8)	6 (6)
C(3)	3452 (3)	6426 (2)	2293 (6)	50 (3)	26 (1)	233 (10)	15 (3)	44 (9)	30 (7)
C(4)	3236 (3)	6213 (2)	664 (6)	46 (3)	43 (2)	225 (10)	8 (4)	−6 (9)	67 (8)
C(5)	3422 (3)	5289 (3)	−1715 (6)	62 (3)	50 (2)	184 (9)	4 (4)	−65 (9)	57 (7)
C(6)	3773 (4)	4494 (3)	−2100 (5)	76 (3)	49 (2)	139 (8)	−23 (5)	−80 (9)	20 (7)
N(7)	4784 (2)	4342 (2)	−1520 (4)	63 (2)	35 (1)	106 (5)	−15 (3)	−26 (7)	5 (5)
C(8)	4292 (3)	3678 (2)	1119 (5)	45 (2)	26 (1)	144 (7)	1 (3)	−2 (8)	21 (6)
C(9)	4712 (3)	3042 (2)	4029 (5)	58 (3)	27 (1)	154 (7)	5 (3)	30 (9)	8 (6)
C(10)	5422 (3)	2942 (2)	5284 (5)	80 (3)	31 (2)	121 (7)	8 (4)	4 (9)	15 (6)
C(11)	6338 (3)	3269 (2)	5208 (6)	68 (3)	40 (2)	145 (8)	20 (4)	−50 (9)	−13 (7)
C(12)	6546 (3)	3737 (2)	3797 (5)	55 (3)	30 (1)	144 (7)	15 (3)	−28 (8)	−18 (6)
C(13)	5915 (3)	4274 (2)	947 (5)	50 (2)	26 (1)	126 (6)	0 (3)	−12 (8)	−3 (5)
C(14)	4837 (3)	4405 (2)	357 (5)	45 (2)	29 (1)	113 (6)	−9 (3)	9 (7)	3 (6)
C(15)	4361 (3)	5130 (2)	1048 (5)	39 (2)	32 (1)	128 (7)	−5 (3)	2 (7)	35 (6)
C(16)	3686 (3)	5547 (2)	44 (6)	49 (3)	34 (2)	179 (8)	−3 (4)	17 (8)	48 (7)
C(17)	3536 (4)	7001 (2)	4806 (7)	92 (4)	26 (1)	271 (11)	4 (4)	77 (12)	5 (8)
C(18)	4891 (3)	3498 (2)	2643 (5)	56 (3)	23 (1)	132 (7)	2 (3)	15 (8)	0 (6)
C(19)	5825 (3)	3842 (2)	2581 (5)	44 (2)	22 (1)	117 (6)	13 (3)	9 (7)	−10 (5)
C(20)	4126 (5)	2191 (3)	5892 (6)	122 (5)	49 (2)	191 (10)	−7 (5)	41 (13)	64 (8)
C(21)	5499 (3)	4828 (3)	−2414 (6)	70 (3)	48 (2)	130 (7)	−18 (4)	4 (9)	23 (7)
O(7)	2999 (2)	632 (2)	856 (4)	83 (2)	47 (1)	252 (7)	−26 (3)	−140 (7)	67 (6)
C(22)	3331 (4)	1397 (3)	621 (7)	70 (3)	37 (2)	301 (13)	−2 (4)	−44 (11)	53 (8)

mined from a least-squares fit of 2θ values. The stationary-crystal stationary-counter technique was used to measure the intensities. A 20 s count was taken for each reflection in one octant (h,k, and $l \geq 0$) and then for each reflection in one quadrant of the hemisphere, giving up to three measurements for each reflection. Equivalent reflections were averaged and the 1944 reflections (out of 2446 with $h,k,l \geq 0$) with intensities greater than 1·2 times the appropriate background count were used in the analysis. These data were reduced to a set of structure amplitudes on an arbitrary scale by the application of Lorentz–polarization corrections.

The structure was solved by direct methods with *MULTAN* (Germain, Main & Woolfson, 1971). R was reduced to 0·13 by full-matrix least-squares refinement with isotropic thermal parameters and then to 0·098 with anisotropic thermal parameters. A difference Fourier synthesis was calculated and indicated the positions of all the H atoms. Subsequent refinement by the block-diagonal approximation of all parameters reduced R to 0·069. The final parameters are given in Tables 1 and 2.*

The quantity minimized in the calculations was $\sum w(|F_o|-|F_c|)^2$, where $w=F_o^2/a^2$ if $|F_o|<a$, $w=1$ if $a \leq |F_o| \leq b$ and $w=b^2/F_o^2$ if $|F_o|>b$, where $a=12{\cdot}4$ and $b=24{\cdot}8$. The scattering factors for O, N, and C were taken from Hanson, Herman, Lea & Skillman (1964) and for H from Stewart, Davidson & Simpson (1965).

Discussion. This structural study was undertaken (in 1968) to confirm the structure of ochrobirine deduced from chemical studies. Subsequently, the structure of ochrobirine was deduced from n.m.r. measurements by Manske, Rodrigo, MacLean, Gracey & Saunders (1969). The absolute configuration was determined from c.d. measurements by Shamma, Moniot, Manske, Chan & Nakanishi (1972). An *ORTEP* drawing of ochrobrine in the correct absolute configuration is given in Fig. 1 together with the atomic numbering.

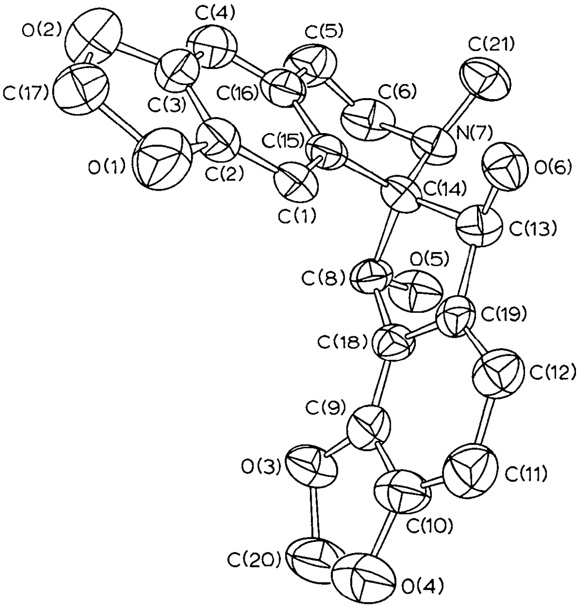


Fig. 1. An *ORTEP* drawing of the alkaloid ochrobirine showing the atomic numbering and thermal ellipsoids.

Table 2. *Final parameters of the hydrogen atoms for ochrobirine*

The atom is given followed by the positional parameters ($\times 10^3$) the isotropic temperature factor and the distance to the atom to which it is bonded. The estimated standard deviations are given in parentheses.

	x	y	z	B (Å^2)	Distance	to atom
H(1)	465 (3)	333 (3)	−97 (6)	7·7 (1·3)	1·00 (5)	O(5)
H(2)	706 (3)	477 (2)	43 (6)	6·9 (1·2)	0·94 (4)	O(6)
H(3)	502 (3)	509 (2)	335 (5)	5·2 (1·0)	0·95 (4)	C(1)
H(4)	278 (3)	649 (2)	−1 (5)	4·2 (0·9)	0·95 (4)	C(4)
H(5)	369 (3)	568 (2)	−262 (5)	4·2 (0·9)	1·05 (4)	C(5)
H(6)	269 (4)	537 (3)	−154 (7)	8·7 (1·4)	1·01 (5)	C(5)
H(7)	376 (4)	439 (3)	−343 (8)	10·4 (1·6)	1·07 (6)	C(6)
H(8)	332 (3)	410 (2)	−167 (5)	4·8 (0·9)	0·98 (4)	C(6)
H(9)	351 (2)	379 (2)	126 (5)	3·3 (0·8)	1·09 (4)	C(8)
H(10)	690 (2)	318 (2)	604 (4)	2·6 (0·7)	1·02 (3)	C(11)
H(11)	724 (2)	400 (2)	378 (4)	3·3 (0·8)	1·05 (3)	C(12)
H(12)	625 (2)	389 (2)	13 (4)	2·4 (0·7)	1·03 (3)	C(13)
H(13)	388 (3)	751 (3)	514 (6)	6·1 (1·0)	1·04 (4)	C(17)
H(14)	290 (5)	692 (3)	565 (8)	12·2 (1·9)	1·10 (6)	C(17)
H(15)	359 (4)	227 (2)	692 (6)	7·4 (1·2)	1·10 (5)	C(20)
H(16)	422 (3)	158 (2)	528 (5)	5·9 (1·0)	1·18 (4)	C(20)
H(17)	619 (3)	466 (2)	−224 (5)	5·0 (0·9)	0·99 (4)	C(21)
H(18)	528 (3)	484 (2)	−359 (5)	4·2 (0·9)	0·98 (4)	C(21)
H(19)	546 (4)	545 (3)	−217 (6)	8·3 (1·4)	1·11 (4)	C(21)
H(20)	330 (3)	42 (2)	193 (5)	5·7 (1·1)	1·01 (4)	O(7)
H(21)	288 (4)	164 (3)	−12 (8)	12·0 (1·8)	0·95 (6)	C(22)
H(22)	411 (5)	138 (3)	18 (10)	14·3 (2·1)	1·11 (7)	C(22)
H(23)	343 (5)	164 (4)	162 (10)	15·6 (2·4)	0·91 (8)	C(22)

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* Tables of structure factors and bond distances and angles have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31276 (14 pp., 1 microfiche). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars. Chester CH1 1NZ, England.

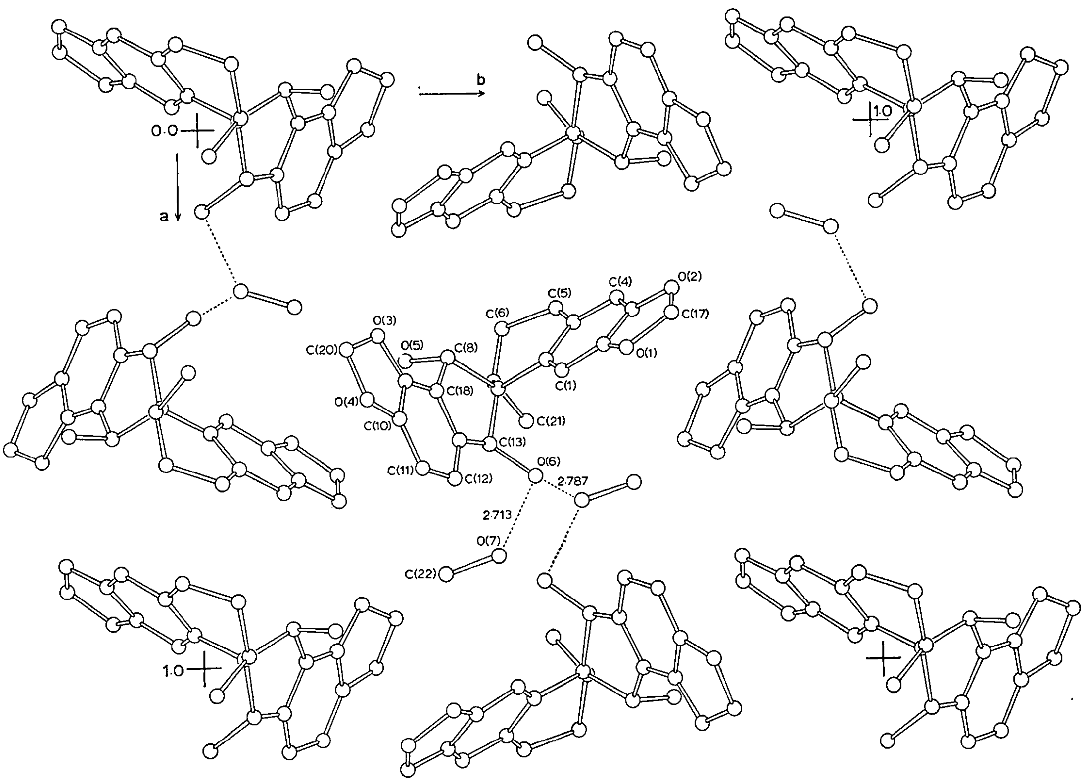

Fig. 2. A view of the structure of ochrobirine down **c** .The methanol molecule is C(22)–O(7). Note the helical arrangement of hydrogen bonds around the screw axis at $\frac{3}{4},\frac{1}{2}$.

Our study confirms the results of the n.m.r. investigation and is in agreement with the c.d. results.

The two aromatic rings are planar within experimental error (maximum deviation is 0·013 Å), the various substituents being only slightly displaced (maximum of 0·077 Å) from the plane of the appropriate ring. The dihedral angle between the two aromatic rings is 89·5° which is a good approximation to the relationship of the two halves of the molecule. A similar result was found for ochotensine, a related spirobenzylisoquinoline alkaloid, by Macdonald & Trotter (1966). The various intramolecular bond distances and angles are not unusual.

The molecular packing and hydrogen-bonding scheme are illustrated in Fig. 2. There are two strong O–H···O hydrogen bonds which join the molecules in a helical manner around the twofold screw axis parallel to **c**. The dimensions of O(6)···O(7) of 2·713 (4) Å, H(2)···O(7) of 1·77 (4) Å, O(6)–H(2)–O(7) angle of 174° and O(7)···O(6) of 2·787 (4) Å, H(20)···O(6) of 1·81 (4) Å and O(7)–H(20)–O(6) angle of 163° are indicative of the strengths of the two hydrogen bonds. There is a short intramolecular contact between O(5) and N(7) of 2·630 (4) Å. The H atom on O(5) is H(1) and H(1)···N(7) is 1·82 (5) Å which is less than the van der Waals contact. Although the angle O(5)–H(1)–N(7) is only 136°, which is rather small for a normal hydrogen bond, the intramolecular distances are certainly suggestive of a strong attraction.

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