Literatur

BORN, L. (1966). *N. Jb. Miner. Mh.* p. 24.
BUERGER, M. L. (1959). *Vector Space.* New York: John Wiley.
BULLEN, G. L. (1962). *J. Chem. Soc.* p. 3193.
CORBRIDGE, D. E. C. (1966). *The Structural Chemistry of Phosphorus Compounds,* in: *Topics in Phosphorus Chemistry,* Vol. 3. New York: Interscience Publishers.
DALY, J. J. & WHEATLEY, P. J. (1967). *J. Chem. Soc.* (A), p. 212.
FRITCHIE, C. J., JR (1966). *Acta Cryst.* **20**, 107.
HAMILTON, W. C. (1965). *Acta Cryst.* **18**, 502.
HOWELLS, E. R., PHILLIPS, D. C. & ROGERS, D. (1950). *Acta Cryst.* **3**, 210.
HUGHES, E. W. (1941). *J. Amer. Chem. Soc.* **63**, 1737.
JAIN, P. C. & LINGAFELTER, E. C. (1967). *Acta Cryst.* **23**, 127.
LIPSON, H. & COCHRAN, W. (1966). *The Determination of Crystal Structures,* p. 352. London: Bell.
NORDMAN, C. E. (1960). *Acta Cryst.* **13**, 535.
SRINIVASAN, R. (1961). *Acta Cryst.* **14**, 1163.
SUTTON, L. E. (1965). *Tables of Interatomic Distances.* Special Publication No. 18. London: The Chemical Society.
WAGNER, A. J. & VOS, A. (1964). *Rec. Trav. chim. Pays-Bas* **84**, 603.

Acta Cryst. (1969). B**25**, 1469

The Crystal Structures of DL-Cyclazocine and L-Cyclazocine.HBr.H_2O, and the Absolute Configuration of L-Cyclazocine.HBr.H_2O (2-Cyclopropylmethyl-2′-hydroxy--5,9-dimethyl-6,7-benzomorphan)

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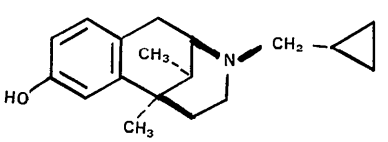
(*Received* 1 *August* 1968)

L-Cyclazocine, $C_{18}H_{25}NO$, is a non-addictive narcotic antagonist of morphine. The racemate crystallizes in space group $P2_1/n$ with $a=12{\cdot}367$, $b=12{\cdot}415$, $c=10{\cdot}229$ Å and $\beta=102{\cdot}9°$ while the HBr salt of the biologically active *levo*-form crystallizes in space group $P2_1$ with $a=10{\cdot}635$, $b=8{\cdot}128$, $c=11{\cdot}692$ Å and $\beta=116{\cdot}1°$. The cyclazocine molecule resembles a segment of the morphine molecule and has the same absolute configuration as morphine. The absolute configuration was determined from the anomalous dispersion of the Br atom. In the racemate, the molecules are linked in endless chains by N···HO hydrogen bonding. In the HBr salt, hydrogen bonding which involves the H_2O molecule, hydroxyl group, Br^- and NH^+ connects the molecules into endless double chains. Direct methods of phase determination were used to solve the structures.

Introduction

The relationship between chemical structure and the physiological activity of morphine has stimulated a search for a substituted fragment of the morphine molecule that would possess similar analgesic properties but would be free of addictive properties (*e.g.* Jacobson & May, 1965). One of the variations which has been prepared, cyclazocine (2-cyclopropylmethyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan),



(British Patent, 1965; Archer, Albertson, Harris, Pierson & Bird, 1964) was found to be a non-addictive narcotic antagonist of morphine and other analgesic agents (Martin, Gorodetzky & McClane, 1965; Martin, Fraser, Gorodetzky & Rosenberg, 1965). In view of its potentially important use, the crystal structures of the racemic free base and also of the biologically active optical isomer (*levo*-) have been determined. In addition, the absolute configuration of the biologically active optical isomer has been established by means of the anomalous scattering of the Br atom. (The initial ingredients in the synthesis of these materials were optically inactive.) The crystals were supplied by Dr R. K. Kullnig of the Sterling–Winthrop Research Laboratories.

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Cyclazocine

The racemate of the free base forms crystals in the shape of a rhombohedron with the *b* axis the diagonal of the base of the rhombohedron. The crystal used had the approximate dimensions of $0{\cdot}5\times0{\cdot}8\times0{\cdot}3$ mm but the diffraction patterns were obtained from the apex where the effective crystal size was considerably less. The apex of the crystal used scattered as a single

crystal although none of the crystals on hand were really single crystals but were composed of several individuals slightly displaced from one another. Accordingly, it was possible to collect data along the *b* axis only, 0–6 layers. Cell dimensions (Table 1) were determined from diffractometer data, although the intensity data were collected photographically by the equi-inclination, multiple-film Weissenberg technique and estimated visually by comparison with a calibrated film strip. The X-ray exposures and film development were controlled so as to have all data as nearly as possible on one scale. Corrections were made for Lorentz and polarization factors and spot size, and the normalized structure factor magnitudes $|E|$ as well as the structure factor magnitudes $|F|$ were derived.

Table 1. *Physical constants for cyclazocine and* L-*cyclazocine*.HBr.H_2O

Mol. formula	$C_{18}H_{25}NO$	$C_{18}H_{25}NO.HBr.H_2O$
Mol. wt.	271·39	370·33
Habit	Rhombohedron	Elongated prism
Space group	$P2_1/n$	$P2_1$
a	12·367 ± 0·006 Å	10·635 ± 0·010 Å
b	12·415 ± 0·006 Å	8·128 ± 0·008 Å
c	10·229 ± 0·006 Å	11·692 ± 0·010 Å
β	102° 54′ ± 5′	116° 05′ ± 5′
Z	4	2
Vol.	1530·9 Å^{-3}	905·6 Å^{-3}
ϱcalc	1·177 g.cm^{-3}	1·355 g.cm^{-3}
ϱmeas	1·197 g.cm^{-3}	
Radiation	Cu (1·5418 Å)	Cu (1·5418 Å) / Mo (0·71069 Å)
No. independent reflections	1563	1590

The structure was readily solved by obtaining phases from the normalized structure factor magnitudes by the symbolic addition procedure for centrosymmetric crystals (Karle & Karle, 1963; 1966). The origin was specified by assigning phases to the reflections 057, $\bar{5}64$ and $\bar{9}54$, all with $|E|>3$. Four other strong reflections, $\bar{5}11$, $\bar{1}52$, 404 and 066 were assigned symbols to represent the phases. These seven reflections were used to implement the Σ_2 relationship (Hauptman & Karle, 1953),

$$sE_{\mathbf{h}} \sim s \sum_{\mathbf{k}} E_{\mathbf{k}} E_{\mathbf{h}-\mathbf{k}} ,$$

a convenient form for expressing inequality (34) of Karle & Hauptman (1950) for centrosymmetric crystals. In the course of the phase determination, the sign of each symbol became apparent. The *E* map, computed from 365 terms with $|E|>1·0$ whose phases had been determined, revealed the positions of all 20 atoms unambigously. The configuration of the molecule is shown in Fig. 1.

The coordinates of the atoms as read from the *E* map were subjected to a least-squares refinement minimizing the function $\Sigma w(F_o-F_c)^2$ where $w=1$ for $|F_o|<15$ and $w=15/|F_o|$ for $|F_o|>15$. The scattering factors were taken from *International Tables for X-ray Crystallography* (1962). The scale factors for each layer were allowed to vary during the isotropic refinement but were kept constant (all near the value 1·1) during the anisotropic refinement. At $R=12·2\%$ a difference map was computed which revealed all but one of the hydrogen atoms. The missing hydrogen atom is on the 3-membered ring which has much more thermal motion than the remainder of the molecule. The approximate positions of the hydrogen atoms as read from the difference map are listed in Table 2. They were used as constant parameters in further least-squares refinement of the heavy atoms. The final *R* index was 8·4%. Observed and calculated structure factors are listed in Table 3. Table 4 lists the fractional coordinates and thermal parameters of the heavy atoms.

Table 2. *Approximate fractional coordinates for the hydrogen atoms for cyclazocine*

	x	*y*	*z*
H(0)	1·022	0·308	−0·005
H(1)	0·642	0·012	0·477
H(3,1)	0·683	0·348	0·512
H(3,2)	0·790	0·287	0·445
H(4,1)	0·542	0·320	0·325
H(4,2)	0·673	0·375	0·257
H(8,1)	0·855	0·083	0·473
H(8,2)	0·817	−0·033	0·383
H(9)	0·522	0·133	0·300
H(10,1)	0·485	0·225	0·108
H(10,2)	0·567	0·333	0·050
H(10,3)	0·583	0·200	−0·005
H(11,1)	0·555	−0·092	0·225
H(11,2)	0·528	0·017	0·108
H(11,3)	0·662	0·000	0·175
H(12,1)	0·713	0·258	0·697
H(12,2)	0·803	0·170	0·642
H(13)	0·595	0·083	0·700
H(14,1)	0·712	0·008	0·904
H(14,2)	0·842	0·075	0·859
H(15,1)	0·808	−0·040	0·675
H(15,2)			
H(1′)	0·747	0·312	0·042
H(3′)	1·047	0·167	0·167
H(4′)	0·992	0·067	0·342

L-Cyclazocine.HBr.H_2O

The hydrobromide salt of cyclazocine forms colorless, prismatic crystals elongated along the *b* axis. The space

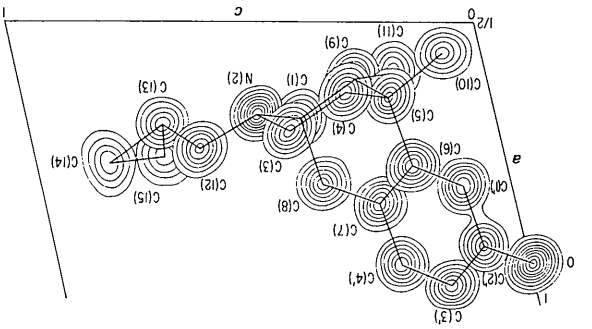
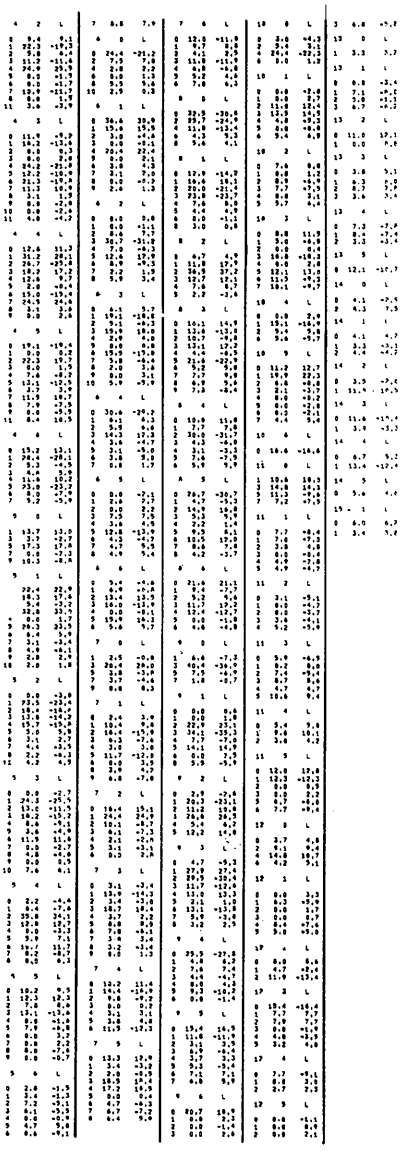


Fig. 1. A composite electron density map of cyclazocine projected along the *b* axis. The contours are evenly spaced at 1 e.Å^{-3} beginning with the 1 e.Å^{-3} contour.

Table 3. *Observed and calculated structure factors for cyclazocine*

The column headings are the index l, $|F_o|$ and F_c.

Tabie 3 (*cont.*)



group and cell dimensions are listed in Table 1. A crystal of size 0·1 × 0·7 × 0·2 mm was mounted on the *b* axis and intensity data were collected with a Picker automatic diffractometer with Cu radiation. The intensities were measured by the θ–2θ technique with a 1° scan over θ. The background was recorded on each side of each reflection and a reflection was considered unobserved if the total count was less than 1·2 times the background count. Reflections were measured to $2\theta \sim 133°$ ($\sin\theta/\lambda = 0{\cdot}595$ Å^{-1} for Cu $K\alpha$ radiation). A total of 1590 independent reflections were measured of which 1528 had intensities assigned greater than zero. The readings were corrected for Lorentz and polarization factors and structure factor magnitudes $|F|$ as well as normalized structure factor magnitudes $|E|$ were derived.

Since the bromine atoms alone are related by the effective space group $P2_1/m$, phases based only on this atomic arrangement must lead to an electron density distribution with false mirror planes of symmetry. Therefore in space group $P2_1$ it is desirable to know the coordinates of more than one atom. The *y* coordinate of the Br atom was arbitrarily set at zero and the *x* and *z* coordinates were determined from an $|E|^2$–1 Patterson function. Coordinates of two other atoms, later shown to be the O and N atoms, were also obtained from the Patterson function. These three atoms were used as a known partial structure for the application of the tangent formula (Karle & Hauptman, 1956),

$$\tan\varphi_{\mathbf{h}} = \frac{\sum_{\mathbf{k}} (E_{\mathbf{k}} E_{\mathbf{h}-\mathbf{k}}) \sin(\varphi_{\mathbf{k}} + \varphi_{\mathbf{h}-\mathbf{k}})}{\sum_{\mathbf{k}} (E_{\mathbf{k}} E_{\mathbf{h}-\mathbf{k}}) \cos(\varphi_{\mathbf{k}} + \varphi_{\mathbf{h}-\mathbf{k}})}, \qquad (2)$$

in a recycling procedure (Karle, 1968). Structure factors based on the three atoms were computed and phases were accepted for input into equation (2) if both $|E|_{\text{obs}} > 1{\cdot}5$ and $|F|_{\text{calc}} > 0{\cdot}4\,|F|_{\text{obs}}$ for a particular reflection. These initial phases were held as constant parameters, since any recycling with the tangent formula on these phases shifted the values toward 0 or π, or in other words, the influence of the Br atom at $y = 0$ was so great that it could eliminate the contributions to the phase from the lighter atoms. From these initial phases, additional phases for reflections with $|E| > 1{\cdot}0$ were determined with the use of equation (2). An *E* map based on these phases revealed the benzene ring and several atoms of the other two rings. The process was repeated with the initial phases for equation (2) now based on all the known atoms. Again the initial phases had to be held constant in the recycling with the tangent formula in order to minimize the influence of the Br atom. In the ensuing *E* map, all the atoms in the asymmetric unit were located except for two in the cyclopropane ring. These two atoms were found in a difference map. They were not well defined, and the very large thermal factors determined for them in the least-squares refinement suggest considerable disorder for the cyclopropane ring.

Coordinates and anisotropic thermal factors, for all atoms except the hydrogen atoms, were refined in a full-matrix least-squares procedure to $R = 7{\cdot}3\%$. Eighteen of the 28 hydrogen atoms were located approximately in a difference map and were included as constant parameters in subsequent cycles of refinement. The function $\Sigma\, w(F_o - F_c)^2$ was minimized and with $w = 1$ the refinement proceeded to $R = 6{\cdot}2\%$. The introduction of a weighting factor based on counting statistics, plus a 1% random error assumed in each intensity measurement, reduced the *R* value to 6·0%. Observed and calculated structure factors are listed in Table 5. The bond lengths and angles were affected

almost unnoticeably by the weighting. Coordinates and thermal factors for the heavier atoms are shown in Table 6 whereas the approximate coordinates for the hydrogen atoms are shown in Table 7.

Table 4. *The fractional coordinates and thermal factors † for cyclazocine*

$T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)\times 10^4]$

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}	B*
O	0·9376	0·3015	−0·0059	59	81	108	3	49	40	3·6
C(1)	0·6728	0·0907	0·4160	48	33	66	1	28	−9	2·4
N(2)	0·6644	0·1863	0·5018	47	30	72	−1	24	−7	2·5
C(3)	0·6971	0·2874	0·4476	65	23	102	−10	36	0	3·2
C(4)	0·6289	0·3065	0·3071	62	44	99	14	42	12	3·4
C(5)	0·6341	0·2100	0·2138	37	58	71	8	16	13	2·5
C(6)	0·7549	0·1963	0·1991	44	23	71	3	22	1	2·5
C(7)	0·8269	0·1289	0·2865	47	24	69	−4	27	3	2·5
C(8)	0·7917	0·0661	0·3988	47	39	79	5	29	8	2·7
C(9)	0·5962	0·1100	0·2782	45	28	84	−7	25	−1	2·5
C(10)	0·5545	0·2334	0·0758	42	108	94	7	13	29	3·6
C(11)	0·5895	0·0070	0·1940	75	41	96	−18	20	−26	3·9
C(12)	0·7261	0·1731	0·6446	64	52	74	−3	22	1	3·2
C(13)	0·6840	0·0804	0·7106	70	73	92	5	33	30	3·8
C(14)	0·7534	0·0438	0·8442	146	95	88	21	18	30	5·9
C(15)	0·7385	−0·0292	0·7219	105	74	84	25	8	17	4·8
C(1′)	0·7942	0·2518	0·1010	56	22	76	5	27	7	2·8
C(2′)	0·9045	0·2421	0·0902	53	45	79	−3	33	3	2·8
C(3′)	0·9748	0·1718	0·1741	43	61	100	0	37	3	3·0
C(4′)	0·9362	0·1179	0·2711	45	38	85	3	19	8	2·9
Standard deviation										
O	0·0003	0·0004	0·0003	3	6	4	3	3	4	
N	0·0003	0·0004	0·0004	3	7	4	3	3	4	
C	0·0004	0·0006	0·0004	3	9	6	4	4	5	
C(13–15)	0·0006	0·0008	0·0006	6	11	6	6	5	7	

* The last column lists the isotropic thermal parameters obtained prior to the anisotropic refinement.
† Since layer scale factors for DL-cyclazocine were refined with the assumption of isotropic temperature factors, the anisotropies indicated by this Table are to be regarded as relative.

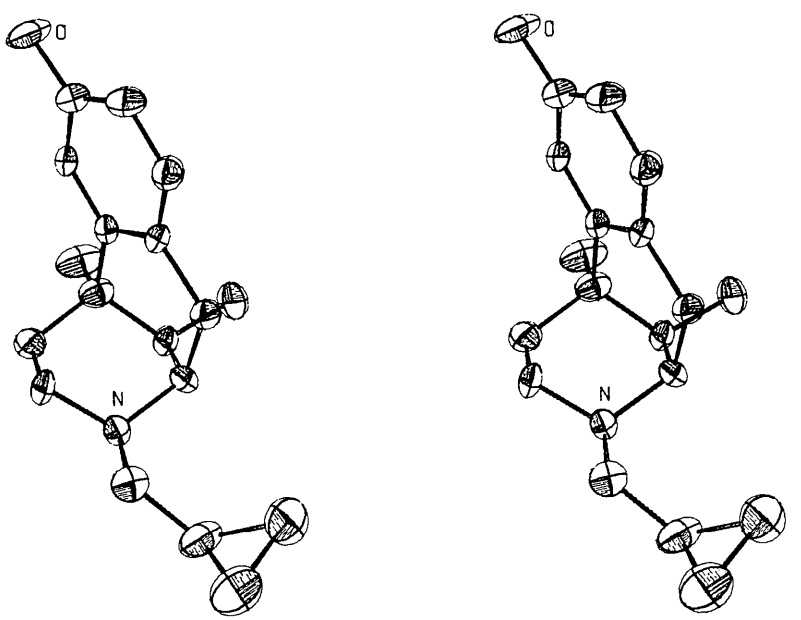


Fig. 2. Stereodiagrams of cyclazocine prepared from a computer program by Johnson (1965). The configuration shown is the absolute configuration as determined by anomalous dispersion experiments on the HBr salt (See † in Table 4).

Table 5. *Observed and calculated structure factors for* L-*cyclazocine*.HBr.H_2O

The column headings are the index l, $|F_o|$, $|F_c|$ and φ (in radians).

Table 5 (*cont.*)

-8	5.0	5.1	-2.58
-7	7.7	8.4	-0.07
-6	5.7	5.7	0.05
-5	1.7	2.1	-1.71
-4	8.3	8.7	2.37
-3	7.1	6.7	-1.55
-2	10.9	11.8	0.24
-1	6.2	5.6	1.66
0	10.7	11.2	-2.84
1	8.9	8.9	-3.09
2	7.6	7.6	0.17
3	10.8	11.2	-0.40
4	1.6	1.4	2.33
5	7.8	8.2	3.11
5 7 L			
-9	5.8	5.0	2.37
-8	3.4	3.2	-1.93
-7	2.8	2.3	-1.00
-6	1.6	1.4	0.59
-5	6.6	5.7	1.22
-4	7.7	7.5	2.87
-3	10.2	9.5	-0.91
-2	7.6	6.8	-1.69
-1	6.8	5.9	1.46
0	5.3	5.0	1.25
1	6.9	7.0	-2.79
2	4.0	3.9	-0.40
3	2.9	2.8	-0.25
4	5.1	5.3	1.82
6 0 L			
-13	7.3	7.3	3.14
-12	4.0	4.8	0.00
-11	3.7	3.6	0.00
-10	2.2	0.4	0.00
-9	17.4	17.4	3.14
-8	2.7	0.9	3.14
-7	27.6	27.8	0.00
-6	19.1	18.7	0.00
-5	22.9	23.4	3.14
-4	26.1	26.2	3.14
-3	6.6	6.8	0.00
-2	26.2	25.6	0.00
-1	6.3	5.5	3.14
0	29.8	29.2	3.14
1	6.5	6.5	0.00
2	17.6	18.3	0.00
3	14.6	15.0	0.00
4	11.3	11.3	3.14
5	9.5	9.7	3.14
6	0.4	0.9	3.14
7	6.3	6.7	0.00
8	1.3	2.1	0.00
6 1 L			
-13	3.5	3.9	-1.13
-12	4.0	4.1	-1.45
-11	5.1	4.9	0.87
-10	16.0	15.9	2.44
-9	4.7	4.8	1.86
-8	21.1	20.4	-0.99
-7	9.1	8.2	-1.93
-6	24.6	23.7	1.13
-5	24.5	22.7	-2.68
-4	25.6	23.0	-1.27
-3	22.1	20.8	-1.33
-2	4.7	5.0	1.68
-1	38.5	37.0	1.60
0	8.9	7.6	-2.58
1	23.3	21.7	-1.63
2	4.8	4.8	-1.04
3	10.2	9.4	1.44
4	14.3	13.6	1.39
5	11.2	10.0	-1.85
6	12.6	12.1	-1.72
7	5.8	6.0	1.03
6 2 L			
-13	5.3	5.5	-2.19
-12	3.7	4.7	-0.22
-11	8.8	9.3	-0.46
-10	10.2	11.2	1.99
-9	11.0	11.8	2.74
-8	8.7	8.5	-2.15
-7	22.8	22.4	-0.27
-6	8.2	6.8	0.22
-5	20.6	20.7	2.99
-4	13.2	13.8	-2.78
-3	10.2	10.3	-0.13
-2	25.9	26.0	0.09
-1	5.7	5.2	-0.03
0	34.1	34.2	2.71
1	14.3	13.6	-3.05
2	29.3	30.1	-0.53
3	4.3	4.2	0.73
4	5.8	5.4	-2.68
5	10.1	10.3	2.56
6	1.8	1.9	2.18
7	8.7	9.9	-0.24
6 3 L			
-13	4.8	4.8	-2.67
-12	4.0	4.0	-1.01
-11	5.5	5.8	1.78
-10	5.5	5.3	2.49
-9	10.8	11.0	-0.52
-8	7.5	7.5	-1.81
-7	7.7	7.9	-0.63
-6	19.5	20.1	1.65
-5	13.7	13.4	2.39
-4	13.5	12.7	-1.55
-3	25.9	26.5	-1.78
-2	14.2	12.9	1.76
-1	18.0	18.3	1.43
0	4.2	3.4	-0.02
1	24.7	23.9	-0.81
2	9.4	9.7	-1.88
3	17.0	16.9	1.97
4	15.0	15.0	1.81
5	11.7	10.9	-2.14
6	14.0	14.0	-1.28
7	4.8	4.6	1.30
6 4 L			
-12	2.8	3.6	-0.43
-11	6.2	6.8	0.33
-10	3.2	4.0	2.27
-9	11.5	11.7	2.89
-8	6.0	6.4	-1.74
-7	13.3	13.5	-0.02
-6	2.6	2.9	-0.75
-5	8.2	7.9	-3.03
-4	7.1	6.1	-2.55
-3	2.2	2.5	0.44
-2	18.0	17.0	0.47
-1	8.2	7.8	1.68
0	25.2	26.3	3.02
1	15.8	15.8	-1.64
2	16.3	16.9	-0.08
3	8.8	9.4	0.22
4	7.5	8.1	3.10
5	6.4	6.6	-3.05
6	3.1	3.7	0.26
6 5 L			
-11	1.4	1.5	1.03
-10	6.3	6.0	1.78
-9	1.2	0.1	-2.41
-8	9.1	9.2	-1.61
-7	5.1	4.0	-1.80
-6	13.9	14.2	0.41
-5	20.8	20.9	1.84
-4	18.0	18.3	-2.51
-3	15.8	16.8	-1.02
-2	1.3	1.4	2.83
-1	11.2	11.0	0.98
0	5.4	5.6	1.60
1	8.3	8.1	-2.67
2	7.9	7.5	-0.93
3	4.6	4.6	1.62
4	4.2	4.3	1.71
5	4.0	3.4	-0.98
6 6 L			
-10	3.6	4.2	1.65
-9	7.0	7.4	-2.71
-8	2.1	2.1	-2.69
-7	5.3	5.8	-0.29
-6	6.2	5.9	0.75
-5	9.3	10.1	-3.08
-4	7.1	6.7	-2.77
-3	9.4	10.2	-0.03
-2	10.1	10.8	-0.25
-1	8.7	8.3	1.88
0	12.0	12.0	-2.89
1	5.0	5.1	-2.12
2	8.4	8.3	0.28
3	4.9	5.3	0.68
4	5.3	4.8	-2.97
6 7 L			
-9	2.4	2.7	-2.12
-8	3.3	3.0	-1.91
-7	3.9	3.8	-0.29
-6	7.3	6.9	1.30
-5	6.1	5.4	2.37
-4	7.4	6.5	-2.19
-3	5.8	4.5	-1.28
-2	7.8	7.1	0.61
-1	6.2	5.8	2.14
0	0.9	2.4	-1.12
1	9.2	8.2	-1.94
2	0.0	0.5	2.99
3	5.5	5.8	1.01
7 0 L			
-13	0.0	0.4	0.00
-12	2.8	3.0	0.00
-11	3.2	3.0	0.00
-10	7.6	6.2	3.14
-9	9.7	10.2	3.14
-8	3.5	3.0	0.00
-7	18.4	17.1	0.00
-6	12.5	13.0	3.14
-5	2.9	3.7	3.14
-4	3.9	4.0	3.14
-3	14.8	15.0	0.00
-2	20.1	20.4	0.00
-1	14.2	14.5	3.14
0	21.9	22.9	3.14
1	3.9	2.9	3.14
2	23.0	22.8	0.00
3	2.0	2.0	0.00
4	12.9	13.6	3.14
5	2.3	2.2	3.14
6	6.3	7.1	0.00
7 1 L			
-13	5.2	4.9	-1.43
-12	4.4	4.2	-1.30
-11	8.7	8.6	1.52
-10	7.4	7.1	1.01
-9	13.3	13.5	-2.08
-8	6.5	6.9	-1.32
-7	6.6	6.0	0.55
-6	18.6	18.0	1.80
-5	14.8	13.8	1.13
-4	31.2	30.3	-1.97
-3	17.6	17.0	-1.54
-2	27.4	26.1	1.33
-1	16.8	15.1	1.38
0	16.0	13.2	-1.89
1	20.4	19.1	-1.31
2	5.6	4.8	1.90
3	15.1	14.5	1.65
4	6.9	7.1	1.66
5	12.4	11.4	-1.54
6	9.0	8.5	-1.72
7 2 L			
-13	1.2	1.6	-1.39
-12	2.8	3.3	-0.08
-11	3.7	3.6	-0.49
-10	2.8	1.9	-2.26
-9	18.4	19.2	2.56
-8	11.4	12.0	-0.45
-7	14.5	15.4	-0.11
-6	4.7	5.2	-2.71
-5	15.0	15.7	2.94
-4	6.2	6.4	-3.03
-3	15.3	15.3	-0.39
-2	14.0	13.4	0.34
-1	11.9	11.9	-3.05
0	10.9	11.5	-2.86
1	6.8	7.5	1.49
2	16.1	16.6	0.08
3	5.9	5.9	-0.72
4	15.5	16.5	-3.10
5	4.3	4.8	-1.21
6	3.4	3.8	0.24
7 3 L			
-12	2.5	2.1	-1.88
-11	5.8	6.1	1.61
-10	11.7	11.4	2.34
-9	6.7	7.7	-1.44
-8	17.0	16.5	-1.09
-7	2.4	4.0	0.70
-6	13.7	13.3	1.43
-5	15.9	14.5	2.09
-4	16.9	16.6	-1.30
-3	17.6	16.9	-1.51
-2	15.5	15.7	1.43
-1	18.2	17.7	2.07
0	18.7	18.6	-2.28
1	8.0	7.5	-0.51
2	11.2	11.7	-0.32
3	6.9	6.3	1.48
4	6.3	6.8	1.62
5	4.4	4.0	-1.77
6	6.1	5.9	-2.03
7 4 L			
-12	2.8	3.7	0.16
-11	5.0	5.4	0.28
-10	6.4	7.2	2.20
-9	6.5	6.6	-3.01
-8	5.4	6.2	-1.15
-7	11.0	11.5	0.01
-6	11.2	11.7	1.93
-5	24.6	26.1	-2.88
-4	9.4	9.3	-0.44
-3	20.3	21.0	-0.32
-2	5.7	6.6	0.14
-1	9.2	9.3	2.06
0	22.5	22.8	3.08
1	3.3	3.6	0.64
2	16.0	16.3	-0.21
3	3.6	3.0	-2.96
4	6.3	6.8	2.77
5	4.4	5.6	-2.86
7 5 L			
-11	3.0	3.1	1.77
-10	1.0	0.5	-0.19
-9	2.1	2.8	-2.22
-8	8.4	7.9	-1.20
-7	3.1	3.1	0.56
-6	9.7	9.1	2.15
-5	3.8	3.5	0.28
-4	3.9	3.9	3.08
-3	11.0	10.0	-1.62
-2	11.1	10.5	1.16
-1	4.8	4.5	2.73
0	7.3	8.5	-1.23
1	4.7	4.2	-1.77
2	1.8	2.5	1.46
3	6.7	6.5	1.36
4	2.2	2.1	2.54
7 6 L			
-10	3.0	3.8	2.37
-9	2.2	2.3	-2.83
-8	5.4	6.1	-1.35
-7	7.2	6.9	0.36
-6	3.7	4.4	2.38
-5	6.6	6.6	-2.79
-4	4.2	3.9	-2.93
-3	6.2	6.9	0.37
-2	7.3	7.4	0.07
-1	5.4	4.9	2.79
0	8.6	8.5	-2.79
1	5.3	3.7	-1.06
2	7.3	8.2	0.26
3	0.6	1.4	0.61
7 7 L			
-7	2.9	2.5	0.58
-6	6.0	5.7	1.31
-5	4.3	4.2	2.70
-4	8.3	7.8	-1.74
-3	3.9	2.9	-0.52
-2	4.1	3.7	0.80
-1	8.4	7.8	1.41
0	5.3	5.1	3.07
1	8.6	7.9	-1.49
8 0 L			
-13	1.6	2.3	0.00
-12	5.4	5.9	0.00
-11	0.0	0.6	0.00
-10	2.7	2.4	3.14
-9	7.8	7.7	3.14
-8	3.6	2.1	0.00
-7	6.7	7.1	0.00
-6	7.4	7.1	3.14
-5	17.6	16.6	3.14
-4	17.7	17.4	0.00
-3	19.7	11.5	0.00
-2	0.6	1.4	3.14
-1	13.9	13.6	3.14
0	6.5	5.9	3.14
1	8.4	9.0	0.00
2	10.8	10.6	0.00
3	4.8	5.0	3.14
4	8.0	8.8	3.14
5	2.2	2.1	0.00
8 1 L			
-13	5.8	5.4	-1.66
-12	1.9	0.9	-2.00
-11	9.0	9.1	1.71
-10	3.5	2.3	2.23
-9	21.8	22.0	-1.33
-8	8.7	8.1	-2.39
-7	14.8	14.7	1.40
-6	22.7	21.6	1.65
-5	3.7	2.9	0.94
-4	33.5	31.8	-1.18
-3	9.1	9.0	-2.58
-2	19.2	18.1	1.87
-1	8.8	8.8	1.97
0	10.0	8.3	-1.50
1	14.5	13.8	-1.57
2	9.7	8.3	0.80
3	12.7	11.8	1.52
4	1.5	1.4	-2.40
5	7.6	6.9	-1.28
8 2 L			
-13	2.1	3.1	-0.26
-12	4.8	5.8	-0.21
-11	2.8	3.3	1.79
-10	3.1	4.1	3.14
-9	9.1	10.2	-1.73
-8	8.5	8.5	2.37
-7	11.3	11.9	0.44
-6	7.7	8.3	2.91
-5	9.7	10.3	2.82
-4	16.5	17.1	-0.31
-3	15.0	16.5	-0.51
-2	5.4	5.2	2.22
-1	16.0	16.6	-3.13
0	12.5	13.2	2.92
1	14.0	14.3	-0.10
2	8.9	9.4	0.23
3	6.1	6.3	2.74
4	6.8	7.5	3.13
5	1.2	0.6	-1.36
8 3 L			
-12	3.3	3.0	-1.02
-11	7.5	7.2	1.47
-10	3.3	3.3	-2.02
-9	9.1	8.8	-2.28
-8	4.8	4.2	-1.14
-7	8.9	9.1	1.59
-6	8.9	8.4	1.89
-5	3.2	3.3	-1.57
-4	7.7	7.8	-0.90
-3	11.6	11.7	-0.65
-2	11.3	10.6	1.97
-1	6.9	6.6	2.04
0	12.0	11.3	-1.88
1	9.1	8.2	-1.98
2	10.3	10.6	1.21
3	7.3	6.9	1.18
4	4.6	5.6	-2.52
8 4 L			
-12	4.4	5.0	-0.77
-11	1.8	1.9	0.79
-10	3.7	4.7	2.86
-9	6.0	5.9	-2.77
-8	8.2	9.5	-0.18
-7	5.1	4.9	0.30
-6	1.5	2.2	1.20
-5	18.2	20.5	2.55
-4	9.5	9.5	-2.30
-3	21.9	23.1	-0.21
-2	1.9	2.0	-1.65
-1	6.0	6.8	-2.99
0	5.3	6.1	3.06
1	1.9	3.0	1.31
2	12.2	13.6	0.20
3	3.4	4.0	-2.43
4	6.6	7.9	-3.06
8 5 L			
-10	2.9	2.6	3.12
-9	7.2	7.4	-1.81
-8	3.0	2.8	-0.69
-7	5.5	5.6	1.02
-6	5.8	5.2	1.79
-5	6.9	6.8	-2.29
-4	7.6	7.3	-1.00
-3	7.3	6.8	0.16
-2	10.6	9.6	1.92
-1	10.2	9.0	2.38
0	13.0	11.7	-1.72
1	4.4	4.1	-0.93
2	5.3	5.6	0.53
3	5.9	5.4	1.76
8 6 L			
-9	4.1	4.2	-2.64
-8	4.6	5.1	0.18
-7	5.1	5.7	0.18
-6	5.6	6.1	2.47
-5	8.0	8.1	-2.75
-4	6.2	6.5	-0.75
-3	5.7	5.5	-0.19
-2	6.0	6.2	1.18
-1	8.1	8.3	2.87
0	5.3	5.6	-2.28
1	4.7	4.9	-0.15
8 7 L			
-7	2.5	2.6	1.19
-6	4.9	4.5	1.86
-5	3.6	3.1	-2.90
-4	6.5	6.0	-1.71
-3	4.0	3.8	-0.38
-2	5.6	5.1	1.57
-1	1.4	0.9	-1.47
9 0 L			
-13	4.0	5.6	0.00
-12	4.3	4.9	0.00
-11	1.1	3.0	3.14
-9	6.3	7.1	3.14
-8	1.8	1.2	3.14
-7	10.1	10.2	0.00
-6	9.3	9.1	3.14
-5	6.9	6.9	0.00
-4	5.8	5.4	0.00
-3	2.4	1.9	0.00
-2	6.5	6.8	3.14
-1	16.9	17.2	3.14
0	1.9	3.2	0.00
1	16.5	17.4	0.00
2	0.0	0.5	3.14
3	6.4	7.1	3.14
4	3.1	2.5	3.14
9 1 L			
-12	3.1	2.4	1.08
-11	4.7	3.6	2.11
-10	4.3	4.2	-1.58
-9	11.1	10.1	-1.35
-8	2.1	2.2	-2.55
-7	19.1	18.6	1.74
-6	6.5	5.6	1.85
-5	12.1	11.5	-2.14
-4	21.3	20.1	-0.86
-3	5.7	5.5	-0.35
-2	20.0	18.9	1.82
-1	3.9	4.3	2.28
0	12.5	11.3	-1.64
1	2.2	2.8	-0.92
2	9.0	7.6	2.36
3	5.2	5.0	1.48
4	4.6	3.4	-1.97
9 2 L			
-12	3.0	3.2	0.09
-11	0.5	0.7	2.55
-10	8.2	9.2	2.56
-9	4.9	6.0	-1.64
-8	12.8	13.4	-0.81
-7	6.4	7.6	1.55
-6	5.7	6.5	2.62
-5	13.3	13.0	2.52
-4	10.2	10.7	-0.12
-3	13.1	13.5	-0.77
-2	5.0	5.3	-3.13
-1	10.8	11.0	2.85
0	2.5	2.0	-2.25
1	11.7	12.7	-0.15
2	5.4	5.8	-0.02
3	8.0	8.7	2.94
9 3 L			
-12	2.7	3.1	1.00
-11	3.6	4.4	2.49
-10	1.9	2.7	-0.92
-9	9.7	9.7	-1.06
-8	5.7	6.0	2.74
-7	11.7	12.0	1.28
-6	9.8	9.8	2.36
-5	18.6	17.8	-1.89
-4	15.9	16.0	-0.52
-3	9.4	8.5	1.57
-2	11.6	11.2	1.98
-1	1.8	2.0	3.02
0	10.0	9.4	-1.54
1	3.7	4.7	-0.56
2	4.9	4.4	2.12
3	5.9	6.2	1.86
9 4 L			
-11	2.4	3.6	2.84
-10	4.9	5.4	-2.78
-9	4.4	4.2	-2.32
-8	6.4	6.9	0.21
-7	7.1	6.8	0.29
-6	6.6	7.2	-3.13
-5	2.5	2.8	-1.19
-4	5.1	5.3	1.21
-3	3.9	3.4	-0.35
-2	2.0	2.3	2.37
-1	10.1	11.1	-3.10
0	5.0	5.2	-1.08
1	6.9	7.8	-0.27
2	4.9	5.4	1.56
9 5 L			
-10	2.2	2.4	-2.97
-9	1.6	1.5	-1.64
-8	0.9	0.9	0.11
-7	5.3	5.6	1.35
-6	5.4	4.8	2.63
-5	7.1	6.9	-1.81
-4	8.2	8.0	-1.23
-3	6.4	6.1	0.77
-2	5.8	5.4	1.48
-1	1.3	1.3	-3.06
0	4.4	3.5	-2.07
1	2.5	2.8	-2.15
9 6 L			
-8	4.3	4.2	0.20
-7	3.6	3.4	0.73
-6	3.8	3.8	2.53
-5	6.5	6.4	-3.03
-4	4.2	4.4	-0.64
-3	6.6	6.5	0.17
-2	2.0	3.0	-2.80
-1	4.6	4.8	2.35
10 0 L			
-12	3.1	2.5	0.00
-11	1.6	2.4	3.14
-10	5.9	5.4	3.14
-9	4.8	6.6	0.00
-8	4.7	4.1	0.00
-7	1.0	1.7	3.14
-6	8.6	9.5	3.14
-5	0.0	0.3	3.14
-4	14.1	14.2	0.00
-3	3.6	2.9	3.14
-2	5.5	5.7	3.14
-1	4.2	3.9	3.14
0	1.8	2.9	0.00
1	5.4	6.6	0.00
2	2.7	1.6	0.00
10 1 L			
-12	3.1	2.7	1.91
-11	3.6	3.4	1.49
-10	6.1	6.1	-1.83
-9	10.6	9.8	-0.73
-8	10.5	10.0	1.50
-7	7.7	6.6	2.16
-6	2.9	2.9	-2.97
-5	12.7	11.5	-1.82
-4	11.0	10.0	-1.60
-3	15.3	14.4	1.28
-2	11.2	10.4	1.54
-1	9.3	8.2	-1.63
0	7.8	7.3	-1.57
1	6.6	5.2	0.29
2	7.7	6.9	1.73
10 2 L			
-11	2.0	2.6	-3.11
-10	5.8	5.8	2.71
-9	3.2	3.4	2.60
-8	14.6	15.4	-0.58
-7	1.9	0.9	-0.47
-6	6.6	6.4	-2.83
-5	3.4	4.2	0.86
-4	8.9	9.2	1.76
-3	5.8	5.0	-0.86
-2	5.3	5.9	-3.11
-1	5.0	5.6	-2.73
0	1.9	2.9	0.03
1	6.3	5.9	-0.11
2	3.1	2.8	-0.77
10 3 L			
-11	2.2	2.2	2.04
-10	3.7	4.0	-1.89
-9	6.5	6.4	0.14
-8	2.4	3.2	0.45
-7	10.3	10.2	2.63
-6	1.8	1.1	2.25
-5	7.3	7.6	-1.98
-4	10.6	10.6	-1.31
-3	12.2	12.2	0.81
-2	10.0	10.3	1.86
-1	7.0	6.7	-1.96
0	5.0	4.9	-1.30
1	4.7	4.4	1.59
10 4 L			
-10	5.2	5.3	3.03
-9	7.8	8.6	-1.07
-8	6.2	6.0	-0.37
-7	6.5	7.0	1.94
-6	6.3	6.2	2.97
-5	3.8	3.6	-2.29
-4	9.0	10.0	-0.21
-3	3.6	3.5	1.14
-2	4.8	5.1	2.51
-1	5.8	5.6	-2.98
0	4.8	4.7	-1.74
10 5 L			
-8	1.5	2.3	1.01
-7	3.9	4.3	1.83
-6	3.8	3.7	3.03
-5	5.9	5.8	-1.58
-4	2.1	2.1	-0.71
-3	3.7	3.8	1.51
-2	4.9	5.1	1.66
-1	5.3	5.4	-1.77
11 0 L			
-11	5.2	5.2	3.14
-10	0.0	1.2	0.00
-9	2.0	3.2	0.00
-8	5.3	5.3	0.00
-7	0.0	1.4	3.14
-6	8.6	9.0	3.14
-5	1.8	1.9	0.00
-4	9.0	9.2	0.00
-3	1.4	1.6	3.14
-2	5.4	6.0	3.14
-1	4.4	4.0	3.14
0	4.2	4.4	0.00
11 1 L			
-11	0.8	1.3	2.06
-10	4.3	4.4	-2.29
-9	3.9	4.0	-1.24
-8	7.3	6.6	0.79
-7	6.0	6.0	1.91
-6	3.1	2.6	-1.15
-5	6.1	5.6	-2.06
-4	4.8	4.2	-1.12
-3	8.2	8.0	1.57
-2	3.0	3.5	1.99
-1	7.5	7.0	-1.56
0	4.7	4.3	-2.01
11 2 L			
-10	1.1	1.6	-0.89
-9	1.7	1.8	0.95
-8	1.8	2.0	2.08
-7	1.5	1.8	-1.44
-6	9.0	9.3	-3.09
-5	9.4	9.5	-0.68
-4	10.5	11.1	0.16
-3	8.9	9.6	2.29
-2	3.2	3.2	-2.75
-1	3.7	3.6	-2.37
0	2.2	2.4	0.31
11 3 L			
-9	3.3	3.6	0.46
-8	8.1	8.8	1.38
-7	0.9	1.0	3.03
-6	4.4	5.4	-2.63
-5	5.4	5.4	-1.40
-4	2.3	3.3	1.54
-3	3.7	4.0	2.01
-2	0.9	1.3	0.51
-1	6.2	6.3	-1.53
11 4 L			
-8	8.8	8.5	-0.17
-7	3.8	3.6	-2.91
-6	4.3	4.2	2.72
-5	0.7	0.5	2.11
-4	4.0	4.3	-0.38
-3	2.8	3.3	0.53
12 0 L			
-9	4.5	3.9	0.00
-8	2.2	2.4	3.14
-7	4.2	4.1	3.14
-6	1.5	0.6	3.14
-5	7.8	8.5	0.00
-4	3.5	3.4	0.00
-3	3.9	4.1	3.14
-2	4.1	4.5	3.14
12 1 L			
-9	2.9	2.6	-2.84
-8	4.6	4.2	1.33
-7	4.4	3.3	1.06
-6	5.5	5.2	-1.96
-5	2.5	2.3	-0.13
-4	2.1	2.2	2.67
-3	1.8	1.0	2.21
12 2 L			
-8	2.4	1.6	0.46
-7	5.1	5.6	2.91
-6	2.9	2.8	-2.22
-5	2.2	2.5	0.79
-4	7.3	7.5	-0.61
-3	1.8	2.0	-2.57

Table 6. *The fractional coordinates and thermal factors for cyclazocine*.HBr.H_2O

$T=\exp[-(\beta_{11}h^2+\beta_{22}k^2+\beta_{33}l^2+2\beta_{12}hk+2\beta_{13}hl+2\beta_{23}kl)\times 10^4]$

	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}	B*
O	0·4021	0·8094	0·5380	152	163	100	−39	75	9	4·1
C(1′)	0·2912	0·6048	0·6032	80	160	66	−2	36	11	2·9
C(2′)	0·3527	0·7536	0·6234	66	127	71	−2	31	12	2·6
C(3′)	0·3686	0·8507	0·7258	97	102	105	−9	41	9	3·4
C(4′)	0·3181	0·7926	0·8089	90	162	84	−15	40	−21	3·7
C(1)	0·1483	0·4043	0·8676	95	258	59	−52	22	16	3·6
N(2)	−0·0079	0·4012	0·7918	65	294	62	−19	26	12	3·6
C(3)	−0·0532	0·4708	0·6602	80	260	56	−1	26	−3	3·3
C(4)	0·0188	0·3720	0·5945	85	204	62	−20	28	−10	3·4
C(5)	0·1815	0·3696	0·6702	85	137	65	−10	28	12	3·2
C(6)	0·2417	0·5405	0·6879	63	118	60	−7	23	6	2·8
C(7)	0·2574	0·6383	0·7934	78	179	65	−18	33	5	3·1
C(8)	0·2079	0·5793	0·8902	118	225	63	−66	39	−18	4·0
C(9)	0·2144	0·2935	0·8038	71	188	86	−18	11	37	3·2
C(10)	0·2355	0·2544	0·5973	124	136	120	−21	64	−27	4·1
C(11)	0·3721	0·2729	0·8896	81	254	101	−11	18	33	4·2
C(12)	−0·0839	0·4852	0·8610	131	435	103	−61	82	−32	4·9
C(13)	−0·2347	0·4517	0·8025	102	532	130	−26	60	−89	5·7
C(14)	−0·3153	0·5390	0·8574	133	536	191	−36	98	−184	6·6
C(15)	−0·3275	0·5485	0·7222	230	849	367	92	169	−181	11·8
Br	−0·0818	0·0000	0·7807	135	251	113	−42	33	20	5·4
W	0·4238	0·5617	0·3721	116	235	142	49	67	−7	5·0
Standard deviations										
O	0·0006	0·0008	0·0006	8	14	7	8	6	8	
N	0·0006	0·0011	0·0006	6	18	5	9	5	8	
C	0·0008	0·0012	0·0008	9	19	8	10	7	10	
C(12–14)	0·0010	0·0022	0·0011	12	50	15	21	10	22	
C(15)	0·0017	0·0036	0·0021	25	100	36	41	26	48	
Br	0·0001		0·0001	1	2	1	2	1	2	

* The last column lists the isotropic thermal parameters obtained prior to the anisotropic refinement.

Table 7. *Approximate fractional coordinates for eighteen of the hydrogen atoms for cyclazocine*.HBr.H_2O

	x	y	z
H(0)	0·470	0·912	0·564
H(1′)	0·284	0·500	0·520
H(3′)	0·420	0·968	0·734
H(4′)	0·675	0·852	0·116
H(N)	−0·061	0·254	0·767
H(1)	0·149	0·339	0·933
H(3,1)	−0·166	0·515	0·615
H(3,2)	−0·021	0·585	0·652
H(4,1)	−0·002	0·232	0·589
H(4,2)	0·015	0·364	0·534
H(8,1)	0·297	0·599	0·983
H(8,2)	0·142	0·642	0·908
H(10,1)	0·217	0·120	0·585
H(11,1)	0·440	0·400	0·915
H(11,2)	0·409	0·242	0·850
H(11,3)	0·359	0·322	0·958
H(12,1)	−0·051	0·584	0·854
H(W)	0·333	0·566	0·333

Absolute configuration

The same crystal of cyclazocine.HBr.H_2O described in the previous section was exposed to Mo radiation on the automatic diffractometer to measure the effects of anomalous dispersion on equivalent reflections (Bijvoet, 1954). A large number of weak reflections observed with Cu radiation were not discernible above background with Mo radiation and only a total of 1275 reflections for hkl, $h\bar{k}\bar{l}$, $\bar{h}kl$ and $\bar{h}k\bar{l}$ were recorded. A least-squares refinement using all the 1275 data recorded with the Mo radiation gave an R value of

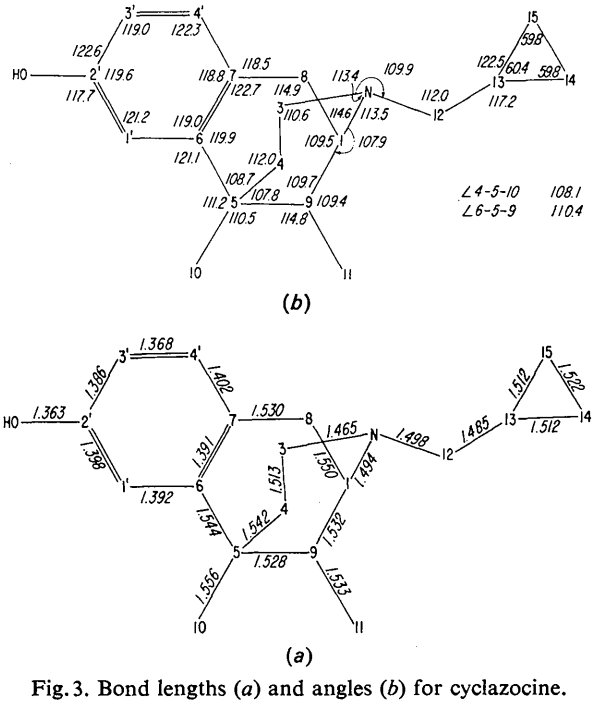


Fig. 3. Bond lengths (*a*) and angles (*b*) for cyclazocine.

5·9% for the correct configuration 7·5% for the mirror image. Table 8 lists some representative reflections which were affected by the anomalous dispersion of the Br atom. The observed structure factors $|F_o|$ for a particular pair of reflections (hkl and $\bar{h}\bar{k}\bar{l}$) are compared with the computed structure factors $|F_c|$ from the refined coordinates for the configuration as given in this paper and also its enantiomorph. For each pair of reflections listed, the indication is consistent with the absolute configuration of the molecule as shown in Fig. 2 and the coordinates as listed in Table 6. (The Figure was drawn from parameters for the free base in the proper absolute configuration.) The absolute configuration of the biologically active L-cyclazocine is consistent with the absolute configuration of codeine and morphine (Kalvoda, Buchschacher & Jeger, 1955; Kartha, Ahmed & Barnes, 1962).

Table 8. *Effects of anomalous dispersion of* Br *atom*

h	k	l	$\|F_o\|$	$\|F_c\|$ (correct configuration)	$\|F_c\|$ (enantiomorph)
1	1	1	25·3	23·4	14·1
$\bar{1}$	$\bar{1}$	$\bar{1}$	15·3	14·9	22·8
4	1	0	18·2	16·3	9·2
$\bar{4}$	$\bar{1}$	0	11·4	9·7	16·0
3	2	$\bar{4}$	21·6	23·7	16·1
$\bar{3}$	$\bar{2}$	4	16·3	19·0	20·8
5	3	0	20·1	20·6	18·9
$\bar{5}$	$\bar{3}$	0	16·1	17·8	21·8
1	1	$\bar{1}$	48·5	50·6	42·4
$\bar{1}$	$\bar{1}$	1	39·7	43·1	49·8
1	1	$\bar{4}$	42·5	40·3	31·6
$\bar{1}$	$\bar{1}$	4	36·2	33·7	38·5
6	2	0	33·2	32·1	29·7
$\bar{6}$	$\bar{2}$	0	31·0	30·2	32·0
7	3	$\bar{1}$	14·9	14·3	15·7
$\bar{7}$	$\bar{3}$	1	15·8	15·0	14·7
2	2	0	43·9	43·4	47·9
$\bar{2}$	$\bar{2}$	0	47·7	45·8	45·5
0	6	3	11·7	11·6	14·5
0	$\bar{6}$	$\bar{3}$	13·4	13·0	13·1
3	4	$\bar{5}$	13·0	11·7	16·2
$\bar{3}$	$\bar{4}$	5	15·6	14·5	13·5

Bond distances based on the Mo data had larger standard deviations and a larger scatter from expected values than those derived from the Cu scattering data.

Discussion

The conformation of the cyclazocine molecule in the free base is very similar to that in the optically active ion. The stereodiagrams in Fig. 2 show the configuration of the free base with the absolute configuration as determined for the biologically active material. The cyclazocine molecule can be considered essentially as a segment of the codeine or morphine molecule with the corresponding parts having the same conformation. Cyclazocine closely resembles 2-allyl-2′-hydroxy-5,9-dimethyl-6,7-benzomorphan, which also shows antagonistic properties towards narcotics. The crystal structure of the HBr derivative of the allyl compound has been reported (Fedeli, Giacomello, Cerrini & Vaciago, 1966) but the absolute configuration could not be obtained since the racemate was used in the structure analysis.

Bond lengths and angles for the free base in racemic form (photographic data) and for the optically active

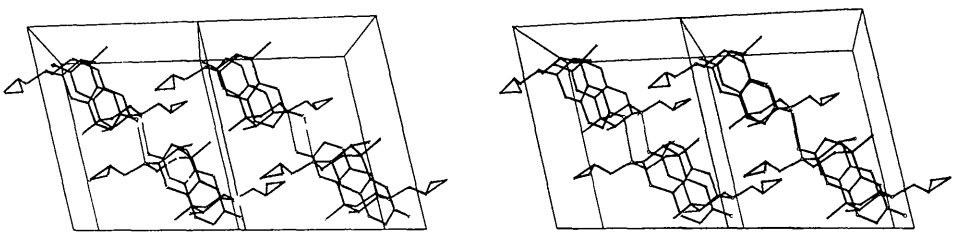


Fig. 4. Stereodiagram illustrating the packing in two unit cells of cyclazocine (free base). The c axis is →, the a axis is ↑ and the b axis is directed upward.

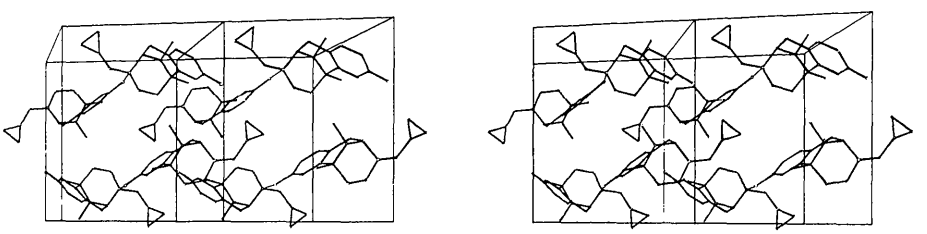


Fig. 5. Stereodiagram illustrating the packing in two unit cells of cyclazocine (free base). The c axis is →, the b axis is ↑ and the a axis is directed downward.

HBr salt (diffractometer data with Cu radiation) are listed in Table 9. The standard deviations for the bond lengths in the free base, based solely on the least-squares fit*, are 0·009 Å, except for the cyclopropane ring where they are 0·012 Å. In the HBr salt the standard deviations for comparable bonds are 0·018 and 0·040 Å. Although the data for the HBr salt were collected by a diffractometer and refined to an R value of 6·0% as compared to 8·4% for the visually estimated data, the standard deviations for the C–C bonds, as well as the range of values for similar bonds, are larger for the salt. The large scattering power of the Br atom apparently has a disturbing influence on the accuracy with which the coordinates of the lighter atoms can be determined.

The cyclopropylmethyl group in the salt crystal has very high thermal parameters, especially in the b direction and particularly for atom C(15). This implies the possibility that from cell to cell there is a disorder of this group and therefore the bond distances computed for an average position are considerably in error.

The bond lengths in the free base have nearly ideal values. They are shown in Fig. 3. The average of the six aromatic C–C bond lengths is 1·390 Å, while the average length of the nine saturated C–C bonds in two rings and their adjacent methyl groups is 1·536 Å. The three C–N bonds lengths average to 1·486 Å. The cyclopropane ring is an equilateral triangle with C-C bond lengths of 1·51–1·52 Å. It appears that this somewhat smaller value for the C–C bonds in the cyclopropane ring is significant. The only bond which is different from the expected single bond value is C(12)–C(13) at 1·485 Å. This bond connects the cyclopropyl group to the remainder of the molecule.

The phenyl group, along with atoms O, C(5) and C(8), lies in a plane with a maximum deviation of ±0·03 Å. The ring attached to the phenyl group has a slightly distorted half-chair conformation with C(1) 0·17 Å above and C(9) 0·61 Å below the plane which includes the other four atoms of the ring and the phenyl group. The piperidine ring is in the chair conformation. The atoms, N(2), C(3), C(4), C(12), C(13) and C(14) form a zigzag chain through the piperidine ring and the methyl cyclopropyl group. These atoms also lie nearly in a plane with the largest deviation from their least-squares plane being 0·10 Å.

The packing in the crystal of the free base is illustrated in the stereodiagrams in Figs. 4 and 5. Endless chains of molecules are formed along the [101] direc-

* If all the sources of error are considered, the standard deviations will be higher, perhaps by a factor of two.

Table 9. *Bond distances and angles for cyclazocine and cyclazocine*.HBr.H_2O

Bond	Free base	Salt
C(1)—N(2)	1·494 Å	1·500 Å
C(1)—C(8)	1·550	1·532
C(1)—C(9)	1·532	1·523
N(2) –C(3)	1·465	1·506
N(2) –C(12)	1·498	1·532
C(3)—C(4)	1·513	1·530
C(4)—C(5)	1·542	1·559
C(5)—C(6)	1·544	1·506
C(5)—C(9)	1·528	1·570
C(5)—C(10)	1·556	1·537
C(6)—C(7)	1·391	1·414
C(6)—C(1′)	1·392	1·410
C(7)—C(8)	1·530	1·521
C(7)—C(4′)	1·402	1·385
C(9)—C(11)	1·533	1·539
C(12)–C(13)	1·485	1·466
C(13)–C(14)	1·512	1·461
C(13)–C(15)	1·512	1·288
C(14)–C(15)	1·522	1·530
C(1′) –C(2′)	1·398	1·346
C(2′) –O	1·363	1·392
C(2′) –C(3′)	1·386	1·381
C(3′) –C(4′)	1·368	1·384

Angle	Free base	Salt
C(8)—C(1) –N(2)	114·6°	112·6°
C(9)—C(1) –N(2)	107·9	109·3
C(8)—C(1) –C(9)	109·5	112·9
C(1)—N(2)–C(3)	113·4	111·8
C(1)—N(2)–C(12)	113·5	112·6
C(3)—N(2)–C(12)	109·9	111·4
N(2)—C(3) –C(4)	110·6	108·0
C(3)—C(4) –C(5)	112·0	113·4
C(4)—C(5) –C(6)	108·7	111·4
C(4)—C(5) –C(9)	107·8	106·0
C(4)—C(5) –C(10)	108·1	106·5
C(6)—C(5) –C(9)	110·4	109·4
C(6)—C(5) –C(10)	111·2	113·5
C(9)—C(5) –C(10)	110·5	109·8
C(5)—C(6) –C(7)	119·9	121·2
C(5)—C(6) –C(1′)	121·1	120·8
C(1′) —C(6) –C(7)	119·0	117·8
C(6)—C(7) –C(8)	122·7	121·7
C(6)—C(7) –C(4′)	118·8	119·5
C(4′) —C(7) –C(8)	118·5	118·8
C(7)—C(8) –C(1)	114·9	114·6
C(1)—C(9) –C(5)	109·7	107·8
C(1)—C(9) –C(11)	109·4	110·5
C(5)—C(9) –C(11)	114·8	113·2
N(2)—C(12)–C(13)	112·0	113·2
C(12)—C(13)–C(14)	117·2	116·0
C(12)—C(13)–C(15)	122·5	123·8
C(14)—C(13)–C(15)	60·4	67·3
C(13)—C(14)–C(15)	59·8	51·0
C(14)—C(15)–C(13)	59·8	61·8
C(6)—C(1′) –C(2′)	121·2	120·9
C(1′) –C(2′) —O	117·7	118·4
C(1′) —C(2′) –C(3′)	119·6	121·9
O–C(2′)–C(3′)	122·6	119·7
C(2′) —C(3′) –C(4′)	119·0	118·5
C(3′) –C(4′) –C(7)	122·3	121·3

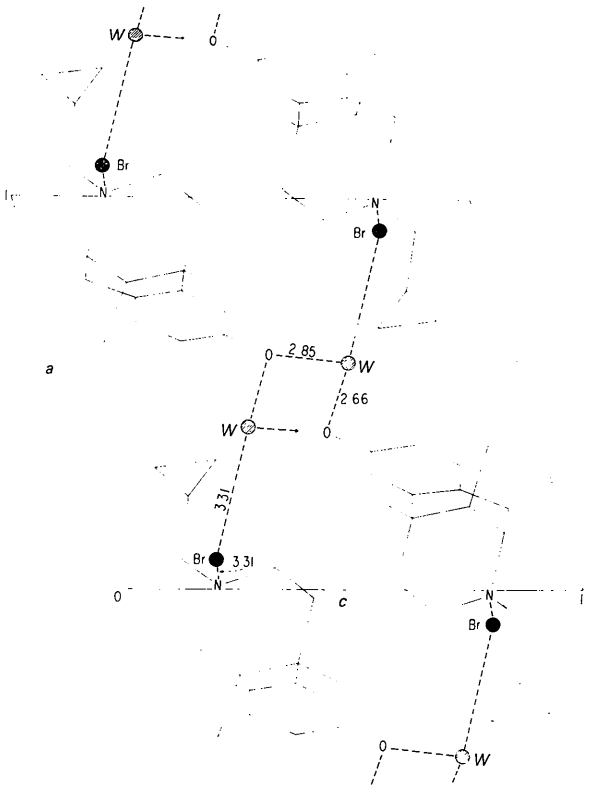


Fig. 6. The hydrogen bonding scheme in cyclazocine. HBr. H_2O

tion by hydrogen bonding between the N atom in the piperidine and the –OH group. The hydrogen atom is attached to the O atom and is directed toward N(2) to form a tetrahedral array of bonds about the N(2) atom. The OH...N(2) bond length is 2·79 Å. The closest approaches between molecules occur in the vicinity of the hydrogen bond. They are the intermolecular distances between the O atom and C(1), C(3), C(4), C(9), C(12), C(13) and C(15) with values ranging from 3·44 to 3·65 Å.

There is no obvious relationship between the packing in the free base, space group $P2_1/n$, and the optically active salt, space group $P2_1$. In the salt a proton is added to the N atom of the piperidine ring to form an ion. A hydrogen bond exists between the N^+ and Br^- ions with the H atom on the N^+ directed toward the Br^-. The four bonds to the N^+ ion are in a tetrahedral array. The Br^- ion also forms a hydrogen bond with the H_2O molecule. In addition, the H_2O molecules and the –OH groups form a continuous spiral of hydrogen bonds along the screw axis at $x=\frac{1}{2}, z=\frac{1}{2}$ (Fig. 6). In this way, the molecules are tightly bound into infinite double chains parallel to the *a* axis. The NH...Br and Br...HO distances are both 3·31 Å while the OH...O distances are 2·66 and 2·85 Å, all of which values have been previously observed in other systems. The nearest intermolecular approaches, other than hydrogen bonding, are listed in Table 10.

Table 10. *Short intermolecular approaches*

	Length	Symmetry relation
Cyclazocine. HBr. H_2O		
C(15)···O	3·42	$1+x, y, z$
C(15)···C(1′)	3·67	$1+x, y, z$
C(15)···C(2′)	3·46	$1+x, y, z$
C(3′)···H_2O	3·36	$\bar{x}, \frac{1}{2}+y, \bar{z}$
C(2′)···H_2O	3·45	$\bar{x}, \frac{1}{2}+y, \bar{z}$
C(3′)···C(10)	3·61	$x, 1+y, z$
C(4′)···C(11)	3·61	$\bar{x}, \frac{1}{2}+y, \bar{z}$
Cyclazocine		
C(1)····O	3·45	$\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z$
C(3)····O	3·52	
C(4)····O	3·61	
C(9)····O	3·44	
C(12)···O	3·57	
C(13)···O	3·65	
C(15)···O	3·45	$1\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$

We wish to express our appreciation to Dr R. K. Kullnig of the Sterling–Winthrop Research Laboratories for his cooperation in supplying us with the various crystals used in this investigation.

References

ARCHER, S., ALBERTSON, N. F., HARRIS, L. S., PIERSON, A. K. & BIRD, J. G. (1964). *J. Med. Chem.* **7**, 123.
BIJVOET, J. M. (1954). *Nature, Lond.* **173**, 888.
British Patent 1,000,506. Sterling Drug Inc. Aug. 4, 1965. See: *Chem. Abstr.* (1965) **63**, 16317.
FEDELI, W., GIACOMELLO, G., CERRINI, S. & VACIAGO, A. (1966). *Chem. Comm.* (17) p. 608.
HAUPTMAN, H. & KARLE, J. (1953). *Solution to the Phase Problem. I. The Centrosymmetric Crystal.* A.C.A. Monograph No. 3. Pittsburgh: Polycrystal Book Service.
International Tables for X-ray Crystallography (1962). Vol. III. Birmingham: Kynoch Press.
JACOBSON, A. E. & MAY, E. L. (1965). *J. Med. Chem.* **8**, 563.
JOHNSON, C. K. (1965). *ORTEP.* Report No. ORNL-3794. Oak Ridge National Laboratory, Oak Ridge, Tennessee, U.S.A.
KALVODA, J., BUCHSCHACHER, P. & JEGER, O. (1955). *Helv. Chim. Acta,* **38**, 1847.
KARLE, I. L. & KARLE, J. (1963). *Acta Cryst.* **16**, 969.
KARLE, J. (1968). *Acta Cryst.* B**24**, 182.
KARLE, J. & HAUPTMAN, H. (1950). *Acta Cryst.* **3**, 181.
KARLE, J. & HAUPTMAN, H. (1956). *Acta Cryst.* **9**, 635.
KARLE, J. & KARLE, I. L. (1966). *Acta Cryst.* **21**, 849.
KARTHA, G., AHMED, F. R. & BARNES, W. H. (1962). *Acta Cryst.* **15**, 326.
MARTIN, W. R., FRASER, H. F., GORODETZKY, C. W. & ROSENBERG, D. E. (1965). *J. Pharm. Exp. Therapeutics,* **150**, 426.
MARTIN, W. R., GORODETZKY, C. W. & MCCLANE, T. K. (1965). *The Pharmacologist,* **7**, 163.