

The Molecular and Crystal Structure of the Alkaloid Haloxine

BY BO NILSSON

Crystallography Group, University of Göteborg, Göteborg, Sweden

(Received 31 January 1967 and in revised form 23 June 1967)

A new alkaloid, haloxine, has been isolated from *Haloxylon salicornicum* (Chenopodiaceae). Although it is a natural product with asymmetric carbon atoms, its hydrobromide $C_{16}H_{27}N_2O_2^+Br^-$ crystallizes in the centrosymmetric space group $P\bar{1}$ demanding a racemate. Its structure has been solved by single-crystal heavy-atom techniques. The oxygen and nitrogen atoms were differentiated from the carbon atoms by least-squares refinement of the isotropic temperature factors.

Introduction

The alkaloid content of *Haloxylon salicornicum* (Moq.-Tand.) Boiss. (Chenopodiaceae) has previously been studied by Sandberg, Svanquist, Ödberg & Sonmark (1960). A number of bases were detected and the main alkaloid, haloxine, was isolated as the hydrochloride ($C_{16}H_{27}O_2N_2^+Cl^-$, m.p. 193.5–196.0°C). Chemical work established the quantitative formula and the presence of amide and amine nitrogen and of a keto oxygen atom (Michel, Sandberg, Haglid & Norin, 1967). As further information about the structure could not easily be obtained by other methods a single-crystal X-ray analysis was performed on the hydrobromide.

Experimental

Good single crystals of the hydrobromide were kindly provided by Prof. Sandberg. They were colourless needles with the following cell dimensions (precession and Weissenberg photographs, Cu $K\alpha$ radiation, 1.5418 Å).

$$a = 8.73 \pm 0.02, \quad b = 9.12 \pm 0.02, \quad c = 11.76 \pm 0.04 \text{ \AA}$$

$$\alpha = 106.07 \pm 0.06^\circ, \quad \beta = 107.84 \pm 0.06^\circ, \quad \gamma = 81.33 \pm 0.08^\circ$$

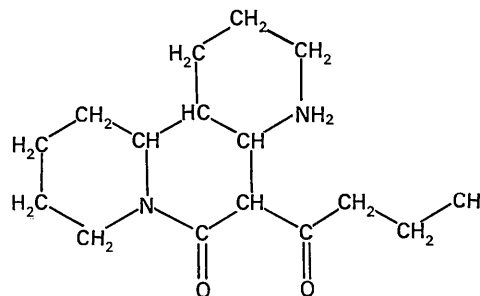
Weissenberg multiple-film photographs were taken for the 0–4 layers about the a axis (needle direction) and the 0 and 1 layers about the c axis. The intensities of 1368 independent reflexions were measured visually and corrected for the Lorentz and polarization factors but not for absorption. The integrated intensity distribution function $N(z)$ (Rogers & Wilson, 1953) favours space group $P\bar{1}$, which is in accordance with the fact that the alkaloid shows no optical activity in solution. An expected value of the calculated density of the crystals (1.3968 g.cm^{-3}) is obtained for two molecules per unit cell.

Structure determination

The bromine position was found from a three-dimensional sharpened ('point atoms at rest') Patterson series. A bromine phased electron density series gave 22 peaks

higher than $1.5 \text{ e.}\text{\AA}^{-3}$. A model was built and all 20 atoms of the molecule could be recognized. The remaining two peaks were too close to the bromine atom and could not correspond to atoms. In order to test the possibilities of automatic structure determinations these two 'ghost' peaks were included in the following rounds of structure factor and least-squares calculations. All light atoms were treated as carbon. The bromine parameters were refined with anisotropic vibration components whereas only isotropic temperature factors were varied (together with positional parameters) for the remaining atoms. After two cycles the R value was 0.25. The temperature factors for the two 'ghost' peaks had then, as expected, increased from the original value of 3.4 obtained from a Wilson plot to 11, and these sites were not included in the following calculations. Four atoms had B values (0.0, 0.3, 0.4 and 1.6 \AA^2) considerably smaller than the rest of the atoms ($2.9\text{--}4.5 \text{ \AA}^2$).

The two atoms with the B values 0.3 and 1.6 \AA^2 could be identified from the model as the oxygen and nitrogen of the amide group. The value 0.0 corresponded to an atom which had to be the keto oxygen and 0.4 was the value of the amine nitrogen. The structural formula of the molecule is then determined as :



Further cycles of block-diagonal least-squares refinement with the correct form factors and anisotropic vibrational parameters on all atoms reduced the R value to 0.15. A difference synthesis was then prepared from which all hydrogen atoms of the molecule could be recognized as peaks ranging from 0.2 to $0.8 \text{ e.}\text{\AA}^{-3}$.

Table 1 (cont.)

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60	61	62	63	64	65	66	67	68	69	70	71	72	73	74	75	76	77	78	79	80	81	82	83	84	85	86	87	88	89	90	91	92	93	94	95	96	97	98	99	100

They were now included in the computations at positions calculated so that C-H as well as N-H bonds were 1.09 Å. After several more cycles the shifts were small and the refinement was discontinued. The ratios between shifts and standard deviations were less than 0.23 (mean value 0.05) for the coordinates of all atoms. For the vibrational parameters the average ratio was 0.06. However, for one parameter a value of 0.85 was found. A difference Fourier synthesis at this stage showed a peak of 0.8 e.Å⁻³ which disappeared when 34 strong reflexions most likely suffering from extinction were omitted. At the same time a negative region surrounding the bromine atom improved from -1.5 e.Å⁻³ to -1.0 e.Å⁻³ and the *R* value decreased from 0.126 to 0.114.

The form factor values used are those given in *International Tables for X-ray Crystallography* (1962). The refinement programs minimize the quantity $\sum w(F_o - F_c)^2$, where the weight *w* for a reflexion is

$$w = \frac{1}{1 + \left\{ \frac{|F_o| - a}{b} \right\}^2}$$

During the last cycles of refinement the constants *a* and *b* were 7|*F*_{min}| and 5|*F*_{min}| respectively.

The computations were performed on a Datasab D21 computer with programs developed at this Institute (Abrahamsson, Aleby, Larsson, Nilsson, Selin & Westerdahl, 1965).

Results and discussion

Observed and calculated structure factors are listed in Table 1. The coordinates for the heavier atoms are given with standard deviations in Table 2, the anisotropic vibrational parameters in Table 3. The standard deviations were obtained according to Ahmed &

Cruickshank (1953) and Darlow (1960). The hydrogen parameters were not refined and are given in Table 4, the bond distances and angles for the heavier atoms in Table 5. A composite drawing of the three-dimensional electron density series is shown in Fig. 1 and the stereochemistry in Fig. 2. There are four asymmetric carbons in the molecule. As the structure is centrosymmetric the crystals studied consist of one of the possible racemates. The natural alkaloid exhibits no optical rotation. However, on resolution by recrystallization with (-)-tartaric acid optically active samples of the free base could be obtained (Michel *et al.*, 1967). Thus, the naturally occurring haloxine is racemic. The molecule as a whole is rather flat and the heavier atoms deviate on an average 0.35 Å and not more than 1.42 Å from the best plane.

Table 2. Fractional atomic coordinates with standard deviations ($\times 10^4$) for the heavier atoms of the molecule

	<i>x</i>	<i>y</i>	<i>z</i>
Br(1)	0.3008 (2)	0.0718 (2)	0.3232 (1)
O(1)	0.2184 (14)	0.5327 (8)	0.5904 (8)
O(2)	0.1059 (10)	0.7864 (9)	0.3966 (7)
N(1)	0.1656 (12)	0.7333 (9)	0.7445 (7)
N(2)	0.3208 (12)	1.0350 (8)	0.5937 (7)
C(1)	0.2379 (17)	0.8991 (14)	0.9545 (9)
C(2)	0.1352 (19)	0.8127 (14)	0.9917 (9)
C(3)	0.1331 (18)	0.6473 (14)	0.9167 (11)
C(4)	0.0720 (15)	0.6413 (13)	0.7799 (10)
C(5)	0.2174 (14)	0.6703 (12)	0.6418 (8)
C(6)	0.2851 (14)	0.7722 (10)	0.5910 (8)
C(7)	0.2318 (14)	0.9414 (10)	0.6377 (8)
C(8)	0.2897 (17)	1.2109 (11)	0.6460 (11)
C(9)	0.3493 (18)	1.2417 (13)	0.7860 (11)
C(10)	0.2510 (17)	1.1560 (12)	0.8334 (10)
C(11)	0.2842 (13)	0.9837 (11)	0.7798 (8)
C(12)	0.1763 (14)	0.8941 (12)	0.8169 (8)
C(13)	0.2259 (14)	0.7201 (11)	0.4467 (8)
C(14)	0.3160 (12)	0.5951 (12)	0.3827 (9)
C(15)	0.2675 (14)	0.5770 (12)	0.2472 (9)
C(16)	0.3664 (22)	0.4350 (16)	0.1841 (11)

Table 3. Mean-square-amplitude tensors. Allowance was made for anisotropic vibrations with $\exp[-2\pi^2(h^2a^{*2}U_{11} + k^2b^{*2}U_{22} + l^2c^{*2}U_{33} + 2klb^*c^*U_{23} + 2lhc^*a^*U_{31} + 2hka^*b^*U_{12})]$

The *U*_{*ij*}'s (Å²) are given together with standard deviations ($\times 10^4$) within brackets.

	<i>U</i> ₁₁	<i>U</i> ₂₂	<i>U</i> ₃₃	<i>U</i> ₂₃	<i>U</i> ₃₁	<i>U</i> ₁₂
Br(1)	0.0663 (9)	0.0717 (8)	0.0560 (6)	0.0234 (6)	0.0051 (6)	-0.0032 (8)
O(1)	0.1695 (105)	0.0285 (41)	0.0759 (49)	0.0013 (36)	0.0412 (60)	-0.0226 (55)
O(2)	0.0641 (58)	0.0555 (46)	0.0560 (38)	0.0093 (35)	-0.0081 (39)	0.0051 (46)
N(1)	0.0749 (73)	0.0279 (42)	0.0542 (41)	0.0117 (35)	0.0175 (47)	-0.0058 (49)
N(2)	0.0652 (69)	0.0190 (38)	0.0493 (38)	0.0056 (32)	0.0075 (42)	0.0084 (46)
C(1)	0.0905 (103)	0.0706 (79)	0.0415 (48)	0.0074 (50)	0.0041 (58)	-0.0185 (81)
C(2)	0.1387 (129)	0.0683 (74)	0.0451 (48)	0.0214 (49)	0.0431 (66)	-0.0260 (82)
C(3)	0.0852 (103)	0.0707 (80)	0.0697 (65)	0.0262 (60)	0.0146 (69)	-0.0188 (81)
C(4)	0.0595 (80)	0.0568 (66)	0.0613 (53)	0.0210 (51)	0.0166 (57)	-0.0161 (68)
C(5)	0.0497 (72)	0.0491 (59)	0.0433 (43)	0.0142 (42)	0.0177 (49)	-0.0038 (61)
C(6)	0.0606 (81)	0.0174 (44)	0.0441 (42)	-0.0040 (36)	0.0135 (50)	0.0054 (57)
C(7)	0.0519 (74)	0.0421 (55)	0.0471 (43)	0.0046 (38)	0.0038 (48)	-0.0498 (60)
C(8)	0.0865 (105)	0.0239 (51)	0.0856 (71)	0.0055 (49)	0.0018 (72)	-0.0227 (67)
C(9)	0.0876 (106)	0.0467 (66)	0.0685 (64)	-0.0088 (53)	-0.0058 (68)	-0.0231 (78)
C(10)	0.0925 (107)	0.0324 (55)	0.0697 (60)	0.0085 (46)	0.0221 (67)	-0.0226 (66)
C(11)	0.0370 (65)	0.0382 (53)	0.0419 (42)	-0.0050 (40)	-0.0058 (45)	-0.0123 (59)
C(12)	0.0505 (73)	0.0502 (59)	0.0446 (44)	0.0103 (43)	0.0040 (49)	-0.0106 (63)
C(13)	0.0662 (84)	0.0302 (50)	0.0480 (45)	0.0141 (41)	0.0116 (52)	0.0066 (58)
C(14)	0.0221 (59)	0.0460 (61)	0.0612 (52)	0.0151 (48)	0.0238 (48)	0.0410 (58)
C(15)	0.0518 (77)	0.0501 (63)	0.0567 (52)	0.0148 (47)	0.0223 (54)	-0.0057 (64)
C(16)	0.1515 (157)	0.0826 (97)	0.0478 (57)	0.0053 (61)	0.0291 (77)	0.0081 (102)

Table 4. Fractional coordinates and isotropic temperature factors for the hydrogen atoms

The number of the parent atom is obtained by omitting the last digit.

	x	y	z	B
H(11)	0.3616	0.8483	0.9746	5.1 Å ²
H(12)	0.2356	1.0180	1.0072	5.1
H(21)	0.1856	0.8154	1.0893	5.9
H(22)	0.0131	0.8659	0.9755	5.9
H(31)	0.2548	0.5922	0.9370	5.9
H(32)	0.0536	0.5872	0.9412	5.9
H(41)	0.0820	0.5228	0.7276	4.7
H(42)	-0.0541	0.6851	0.7583	4.7
H(61)	0.4161	0.7609	0.6253	2.9
H(71)	0.1021	0.9639	0.6033	3.7
H(27)*	0.4497	1.0039	0.6235	3.1
H(28)*	0.2801	1.0092	0.4934	3.1
H(81)	0.3560	1.2747	0.6130	4.4
H(82)	0.1613	1.2446	0.6173	4.4
H(91)	0.4764	1.2025	0.8133	5.2
H(92)	0.3348	1.3642	0.8261	5.2
H(101)	0.2899	1.1824	0.9338	4.7
H(102)	0.1228	1.1891	0.8022	4.7
H(111)	0.4135	0.9566	0.8140	3.1
H(121)	0.0529	0.9454	0.7954	3.8
H(141)	0.4437	0.6159	0.4186	3.1
H(142)	0.2970	0.4892	0.4008	3.1
H(151)	0.1390	0.5594	0.2104	4.2
H(152)	0.2910	0.6802	0.2277	4.2
H(161)	0.3429	0.3315	0.2035	6.7
H(162)	0.4949	0.4524	0.2207	6.7
H(163)	0.3298	0.4230	0.0849	6.7

* Refers to the amine nitrogen.

The bond distances and angles are shown in Fig. 3. The average value for C-C single bonds is 1.533 Å. Only one C-C distance deviates more than 3σ from

this value. C(13)-C(14) is 1.45 Å and this difference (6σ) is most likely real. β-Keto compounds are known to possess enolic forms, *i.e.* they have double bond character between the carbon atoms α and β [in this case referred to the amide carbon atom C(5)]. Such a conjugated system does not exist in this molecule in the solid state as seen by the C(6)-C(13) bond of 1.57 Å and the fact that the two carbonyl groups are not in the same plane. However, O(2) is in hydrogen bond contact with the positively charged nitrogen atom N(2) which might influence the electronic character of the keto group to cause a shortening of the C(13)-C(14) bond.

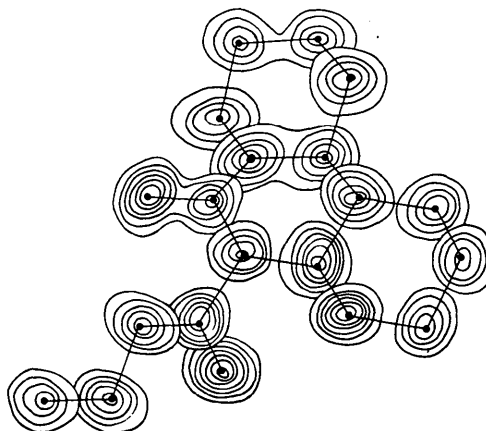


Fig. 1. Composite drawing of the three-dimensional electron density of haloxine seen along the *a* axis. Contours are given at intervals of 1 e.Å⁻³ starting at 1 e.Å⁻³.

Table 5. Bond distances with standard deviations and bond angles with standard deviations

O(1)-C(5)	1.233 (0.012) Å	C(4)-N(1)-C(5)	118.3 (0.8)°
O(2)-C(13)	1.200 (0.013)	C(4)-N(1)-C(12)	115.0 (0.9)
N(1)-C(4)	1.468 (0.018)	C(5)-N(1)-C(12)	126.3 (1.0)
N(1)-C(5)	1.366 (0.014)	C(7)-N(2)-C(8)	112.0 (0.9)
N(1)-C(12)	1.478 (0.012)	C(2)-C(1)-C(12)	111.5 (1.0)
N(2)-C(7)	1.513 (0.016)	C(1)-C(2)-C(3)	110.1 (1.2)
N(2)-C(8)	1.566 (0.012)	C(2)-C(3)-C(4)	110.1 (1.1)
C(1)-C(2)	1.499 (0.023)	N(1)-C(4)-C(3)	111.5 (1.0)
C(1)-C(12)	1.530 (0.014)	O(1)-C(5)-N(1)	123.9 (1.2)
C(2)-C(3)	1.522 (0.016)	O(1)-C(5)-C(6)	117.4 (1.0)
C(3)-C(4)	1.520 (0.016)	N(1)-C(5)-C(6)	118.6 (0.8)
C(5)-C(6)	1.502 (0.017)	C(5)-C(6)-C(7)	111.1 (0.9)
C(6)-C(7)	1.540 (0.012)	C(5)-C(6)-C(13)	107.8 (0.8)
C(6)-C(13)	1.570 (0.012)	C(7)-C(6)-C(13)	111.1 (0.7)
C(7)-C(11)	1.542 (0.012)	N(2)-C(7)-C(6)	107.0 (0.9)
C(8)-C(9)	1.524 (0.017)	N(2)-C(7)-C(11)	108.5 (0.8)
C(9)-C(10)	1.547 (0.022)	C(6)-C(7)-C(11)	108.9 (0.8)
C(10)-C(11)	1.542 (0.013)	N(2)-C(8)-C(9)	107.0 (0.9)
C(11)-C(12)	1.558 (0.018)	C(8)-C(9)-C(10)	110.1 (1.0)
C(13)-C(14)	1.450 (0.014)	C(9)-C(10)-C(11)	106.7 (1.1)
C(14)-C(15)	1.485 (0.014)	C(7)-C(11)-C(10)	111.9 (0.8)
C(15)-C(16)	1.581 (0.018)	C(7)-C(11)-C(12)	105.1 (0.8)
		C(10)-C(11)-C(12)	108.2 (1.0)
		N(1)-C(12)-C(11)	109.7 (0.9)
		N(1)-C(12)-C(13)	112.6 (0.9)
		C(1)-C(12)-C(11)	110.8 (0.9)
		O(2)-C(13)-C(6)	116.9 (0.9)
		O(2)-C(13)-C(14)	124.2 (0.9)
		C(6)-C(13)-C(14)	118.9 (0.8)
		C(13)-C(14)-C(15)	113.4 (0.9)
		C(14)-C(15)-C(16)	110.2 (0.9)

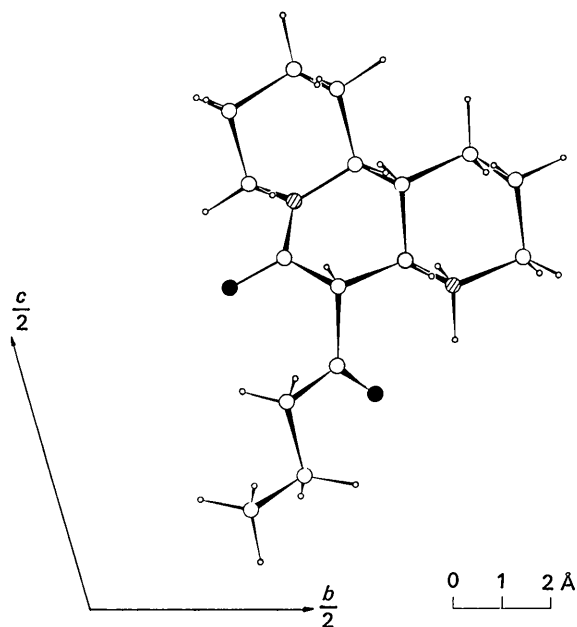


Fig. 2. Stereochemistry of the molecule. Large open circles, carbon; small open circles, hydrogen; hatched circles, nitrogen; filled circles, oxygen.

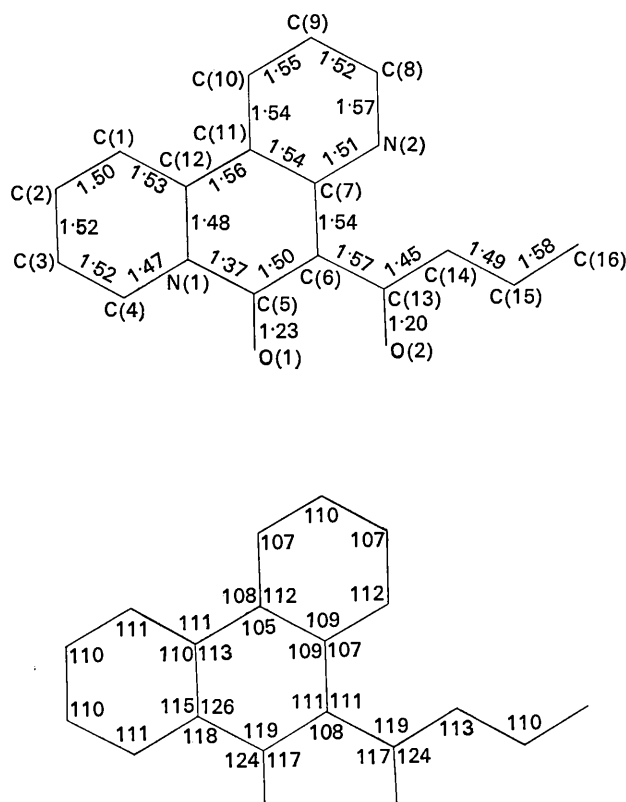


Fig. 3. Atomic numbering and bond distances (Å) and angles (°).

The side chain, including the keto oxygen, is planar with a maximum deviation from the best plane of 0.11 Å for C(15).

The N(2)⁺-C bonds of 1.51 Å and 1.57 Å are longer than ordinary N-C distances (1.47 Å). Such elongated ring N⁺-C_{sp³} bonds are reported in a number of cases, e.g. in *N(a)*-acetyl-7-ethyl-5-desethyl-aspidospermidine *N(b)*-methiodide (Camerman, Camerman & Trotter, 1965) and in heteratisine hydrobromide monohydrate (Przybylska, 1965) where values of about 1.55 Å were found.

The molecular packing is illustrated in Fig. 4, where some short C-O and H-H intermolecular distances are also shown together with the shortest distances to the bromine ion. The molecules are held together by hydrogen bonds in which the bromine ions and the amine nitrogens are involved. They form rings [Fig. 5(a)], each ring tying together two enantiomorphs and two bromine atoms. As the two nitrogen atoms and two bromine atoms are related by a centre of symmetry, these four atoms form a plane. Of the two hydrogen atoms, H(27) is 0.045 Å from this plane and the N(2)-H(27)-Br(1') angle is 176.4°. Within experimental error H(27)

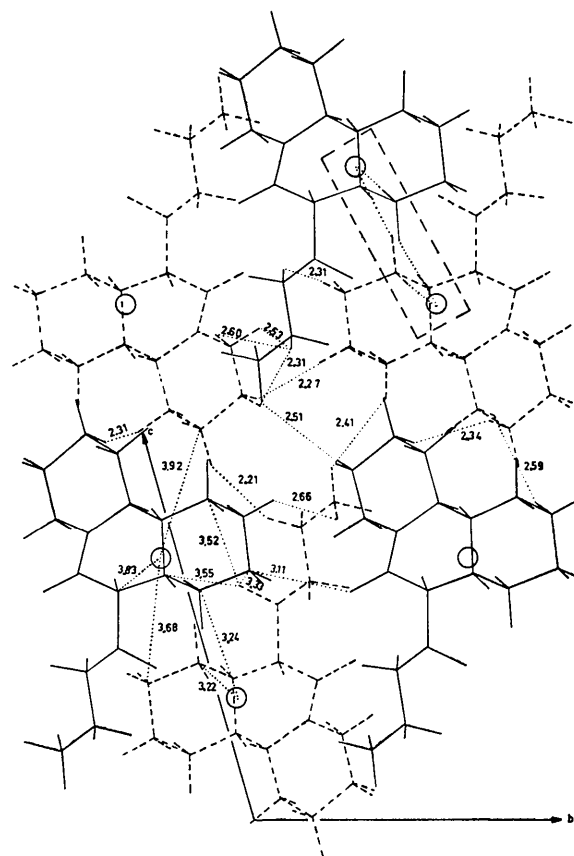


Fig. 4. The molecular packing seen along the *a* axis. The shortest intermolecular distances are indicated (Å). The bromine ions are shown as circles. The dashed rectangle encloses the ring shown in detail in Fig. 5(a).

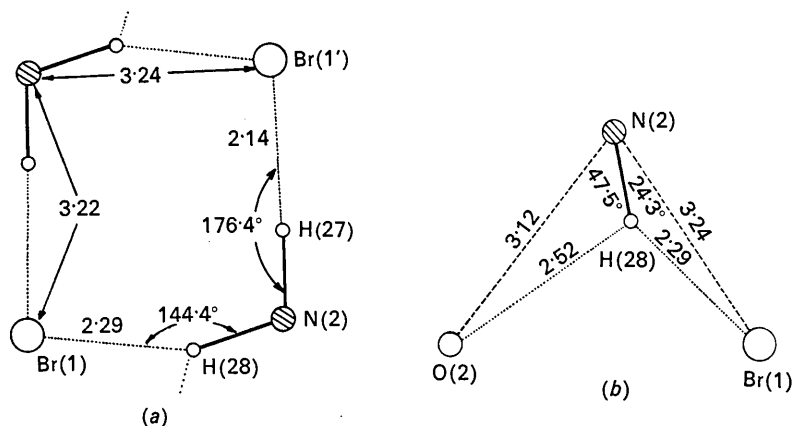


Fig. 5. The geometry of the hydrogen bonds to the amine nitrogen (distances in Å). (a) The ring constituted by symmetry related amine groups and bromine atoms. Projection along the b axis. (b) The bifurcated hydrogen bond, shown in the plane of the four atoms.

is in the plane and on the line Br(1')–N(2). H(28), on the other hand, is 0.40 Å from the plane and the angle N(2)–H(28)–Br(1) is 144.4°. This makes possible weak intramolecular hydrogen bonding between N(2) and O(2) (3.12 Å) involving H(28). Conditions are favourable for a bifurcation of the H(28) bond to both O(2) and Br(1) as all involved atoms N(2), H(28), O(2) and Br(1) are in one plane. The maximum deviation is 0.02 Å for H(28). The geometry within this plane is shown in Fig. 5(b). It seems likely that also two weaker hydrogen bonds exist in the structure, one from O(1) to C(8) (3.11 Å) via H(81) and one from O(2) to C(8) (3.33 Å) via H(82).

I am greatly indebted to Prof. Sixten Abrahamsson for continuous advice and support, and to Mrs Anita Johansson for technical assistance. I also want to thank Prof. Finn Sandberg and his co-workers for crystal samples. Financial support has been obtained from the

Swedish Natural Science and Swedish Medical Research Councils and the U.S. Public Health Service (GM 11653).

References

- ABRAHAMSSON, S., ALEBY, S., LARSSON, K., NILSSON, B., SELIN, K. & WESTERDAHL, A. (1965). *Acta Chem. Scand.* **19**, 758.
 AHMED, F. R. & CRUICKSHANK, D. W. J. (1953). *Acta Cryst.* **6**, 385.
 CAMERMAN, A., CAMERMAN, N. & TROTTER, J. (1965). *Acta Cryst.* **19**, 314.
 DARLOW, S. F. (1960). *Acta Cryst.* **13**, 683.
International Tables for X-ray Crystallography (1962). Vol. III, p. 202. Birmingham: Kynoch Press.
 MICHEL, K.H., SANDBERG, F., HAGLID, F. & NORIN, T. (1967). *Acta Pharm. Suec.* **4**, 97.
 PRZYBYLSKA, M. (1965). *Acta Cryst.* **18**, 536.
 ROGERS, D. & WILSON, A. J. C. (1953). *Acta Cryst.* **6**, 439.
 SANDBERG, F., SVANQUIST, L., ÖDBERG, M. & SONMARK, L. (1960). *Svensk Farm. Tidskr.* **64**, 541.

Acta Cryst. (1968). B24, 258

Nine New Zinc Sulphide Polytypes of the Family 24L-72R

BY S. MARDIX AND O. BRAFMAN

Department of Physics, The Hebrew University, Jerusalem, Israel

(Received 16 May 1967)

Nine hitherto unknown ZnS polytypes of the family 24L-72R were found in one crystal. Their unit-cell and Zhdanov symbols are: 24L(15 9); 24L(9 5 6 4); 24L(16 4 2 2); 24L(7 10 5 2); 24L(8 9 4 3); 24L(3 3 2 4 2 2 5 3); 24L(3 3 4 2 2 4 3 3); and 72R(6 11 5 2)₃; 72R(9 5 4 6)₃.

Polytypes of the 24L-72R family are already known (Farkas-Jahnke, 1965; Mardix, Brafman & Steinberger, 1967) but only one detailed structure was published, namely 24L (7 5 5 7) (Mardix, Brafman & Stein-

berger, 1967). The vapour-phase grown zinc-sulphide crystal 220/58 contained polytypic regions, nine of which were identified as new polytypes of the family 24L-72R. A microphotograph of the specimen 220/58,