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The Crystal and Molecular Structure of Bundlin A *p*-Bromophenylsulphonylhydrazone

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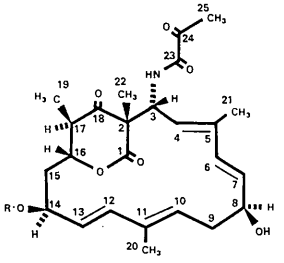
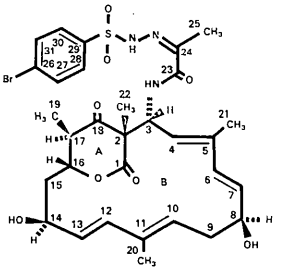
The crystal structure and absolute configuration of the *p*-bromophenylsulphonylhydrazone of bundlin A ($C_{31}H_{38}N_3O_8SBr$), an antibacterial antibiotic produced by *Streptomyces* sp., has been determined by three-dimensional X-ray analysis. The crystals are monoclinic, space group $P2_1$, with two molecules in the unit cell of dimensions $a=11{\cdot}24$, $b=26{\cdot}50$, $c=6{\cdot}17$ Å and $\beta=111{\cdot}3°$. The structure was solved by the heavy atom method. Refinement was carried out for the 2419 observed reflexions by the block-diagonal least-squares method to a final R value of 0·146. The absolute configuration was determined by the use of the anomalous dispersion effect of the bromine and the sulfur atoms for Cr $K\alpha$ radiation. The molecule of bundlin A consists of a seventeen-membered carbon skeleton, a six-membered β-keto-δ-lactone system and a pyruvamide group side chain.

Introduction

Bundlin A (I) is an antibacterial antibiotic isolated from the cultered broth of *Streptomyces griseofuscus* together with bundlin B (II) by Sakamoto, Kondo, Yumoto & Arishima (1962). Bundlin A is identical with lankacidin produced by *Streptomyces violaceoniger* (Gaumann, Hutter, Keller-Schierlein, Neipp, Prelog & Zahner, 1960). From the chemical investigation bundlin B, $C_{27}H_{35}NO_8$, was found to be the monoacetate of bundlin A, $C_{25}H_{33}N_7$. Further structural studies of these antibiotics were carried out by chemical methods. The complete structures, however, could not be deduced. The crystal structure analysis of bundlin A *p*-bromophenylsulphonylhydrazone (III) was undertaken in order to establish the entire molecular structure and the absolute configuration of the antibiotics. A preliminary short account has been published (Uramoto, Otake, Ogawa, Yonehara, Marumo & Saito, 1969).



(I) R=H: Bundlin A
(II) R=CO CH$_3$: Bundlin B



(III)

Experimental

Bundlin A *p*-bromophenylsulphonylhydrazone was prepared by treatment of bundlin A with *p*-bromophenylsulphonylhydrazine in methanol at room temperature. Slow evaporation of methanol gave crude crystals of the hydrazone. Recrystallization from methanol afforded colourless plates. The spectral data and elementary analysis showed that the molecule of the hydrazone was produced by reaction of bundlin A with equimolar *p*-bromophenylsulphonylhydrazine. The density was measured by the flotation method in aqueous potassium iodide solution. Weissenberg photographs were taken with Cu $K\alpha$ radiation ($\lambda=1{\cdot}5418$ Å). The crystal data are:

$C_{31}H_{38}N_3O_8SBr$, m.p. 194·5–197°C, M.W. 692.
Monoclinic,
$a=11{\cdot}24\pm0{\cdot}01$, $b=26{\cdot}50\pm0{\cdot}01$, $c=6{\cdot}17\pm0{\cdot}01$ Å,
$\beta=111{\cdot}3\pm0{\cdot}1°$.
$U=1712{\cdot}5$ Å^3.
$D_m=1{\cdot}37$ g.cm^{-3}.
$Z=2$.
$D_x=1{\cdot}34$ g.cm^{-3}
$F(000)=720$.
μ(Cu $K\alpha$) = 27·8 cm^{-1}

Absent spectra, $0k0$ when k is odd.
Space group $P2_1$ ($P2_1/m$ is excluded since the crystal is optically active.)

The crystals deteriorated in the X-ray beam. It was therefore necessary to use a number of crystals for the collection of data. Intensities of the 2419 independent reflexions were measured visually from equi-inclination Weissenberg photographs around the b and the c axes ($h0l$ to $h2l$ and $hk0$ to $hk6$) taken with Cu $K\alpha$ radiation using the multiple-film technique. These data were corrected for the Lorentz and polarization factors and then brought to the same arbitrary scale. The structure factors were then placed on an absolute scale by

Wilson's statistical method. No absorption correction was applied in view of the small size of the specimen used for the analysis.

Determination and refinement of the structure

A three-dimensional Patterson function was calculated. The bromine atom was easily located from the Harker section. The position of the sulphur atom was found by seeking peaks at a distance of 6·4 Å, the length from the bromine atom to the sulphur atom in the *p*-bromophenylsulphonyl group, in the Patterson maps. The first electron density maps, which were synthesized using phases based on the contribution of the bromine and sulphur atoms, revealed the positions of six lighter atoms. At this stage the *R* value was 0·34 for 1500 reflexions excluding very weak ones. From successive calculations of three-dimensional Fourier and difference synthesis all of the 44 atomic positions were fixed and the *R* value was reduced to 0·19. However, the lighter atoms could not be distinguished except for those in the *p*-bromophenylsulphonylhydrazone portion of the molecule. Refinement of the structural parameters was carried out by five-cycles of block-diagonal least-squares calculation with isotropic thermal parameters and the *R* value then became 0·15.

Table 1. *Fractional atomic coordinates* ($\times 10^4$) with *standard deviations in parentheses*

	x	*y*	*z*
Br	−2099 (3)	7498 (2)	−0622 (7)
S	2664 (7)	8043 (3)	−3390 (14)
O(1)	−0417 (14)	5331 (6)	1135 (25)
O(2)	1519 (16)	5350 (7)	3743 (30)
O(3)	5318 (15)	3716 (6)	−2000 (31)
O(4)	−3057 (15)	4293 (6)	−3410 (29)
O(5)	0425 (14)	6390 (6)	−2753 (26)
O(6)	4638 (18)	6504 (7)	4091 (32)
O(7)	2551 (19)	7745 (8)	−5378 (37)
O(8)	2916 (26)	8596 (8)	−3390 (46)
N(1)	2906 (17)	6497 (7)	0759 (34)
N(2)	3596 (18)	7375 (7)	−0169 (36)
N(3)	3810 (20)	7849 (8)	−0913 (37)
C(1)	0727 (23)	5527 (9)	2100 (40)
C(2)	1021 (20)	6015 (8)	0878 (39)
C(3)	2472 (20)	5986 (8)	1231 (41)
C(4)	2717 (22)	5605 (8)	−0351 (43)
C(5)	3642 (21)	5245 (8)	0525 (41)
C(6)	3714 (21)	4866 (10)	−1074 (43)
C(7)	4333 (21)	4419 (9)	−0647 (40)
C(8)	4150 (22)	4020 (8)	−2543 (47)
C(9)	3116 (22)	3634 (9)	−2372 (48)
C(10)	1814 (21)	3875 (9)	−3178 (43)
C(11)	1240 (20)	4050 (8)	−1689 (37)
C(12)	−0016 (21)	4292 (9)	−2794 (43)
C(13)	−0789 (21)	4425 (8)	−1649 (44)
C(14)	−2060 (21)	4678 (9)	−2999 (44)
C(15)	−2410 (21)	5104 (8)	−1791 (39)
C(16)	−1441 (22)	5518 (9)	−0926 (39)
C(17)	−0875 (21)	5699 (9)	−2714 (40)
C(18)	0171 (20)	6075 (8)	−1652 (39)
C(19)	−1925 (24)	5925 (10)	−4744 (42)
C(20)	1839 (22)	4049 (9)	1062 (38)
C(21)	4504 (24)	5175 (9)	2954 (43)
C(22)	0752 (24)	6465 (9)	2229 (39)
C(23)	3950 (23)	6706 (9)	2243 (49)
C(24)	4270 (22)	7243 (9)	1678 (46)
C(25)	5334 (28)	7495 (13)	3496 (47)
C(26)	−0770 (26)	7685 (10)	−1595 (53)
C(27)	−0791 (31)	7505 (12)	−3742 (49)
C(28)	0364 (25)	7619 (10)	−4235 (41)
C(29)	1351 (25)	7942 (10)	−2663 (41)
C(30)	1225 (27)	8151 (10)	−0733 (47)
C(31)	0222 (27)	8026 (11)	−0045 (57)

Table 2. *Thermal parameters in the form exp* $[-(B_{11}h^2+B_{22}k^2+B_{33}l^2+B_{12}hk+B_{13}hl+B_{23}kl)]$

Standard deviations in parentheses. All $\times 10^4$.

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
Br	115 (3)	33 (1)	571 (15)	7 (4)	105 (11)	19 (8)
S	139 (10)	15 (1)	404 (33)	10 (6)	103 (27)	62 (11)
O(1)	79 (18)	11 (3)	198 (60)	−21 (12)	43 (51)	13 (21)
O(2)	108 (22)	17 (4)	314 (73)	−12 (15)	−109 (63)	79 (27)
O(3)	83 (19)	10 (3)	556 (87)	25 (13)	206 (68)	13 (27)
O(4)	91 (20)	12 (3)	433 (79)	25 (13)	231 (66)	−34 (26)
O(5)	90 (19)	11 (3)	221 (63)	−18 (12)	12 (54)	34 (22)
O(6)	136 (25)	15 (3)	452 (87)	−40 (15)	−79 (73)	59 (29)
O(7)	168 (28)	30 (5)	546 (98)	−50 (19)	316 (87)	−110 (36)
O(8)	341 (48)	17 (4)	927 (144)	18 (24)	459 (136)	207 (42)
N(1)	70 (21)	7 (3)	326 (83)	−24 (14)	−58 (67)	−7 (26)
N(2)	101 (23)	3 (3)	530 (101)	2 (14)	166 (80)	2 (27)
N(3)	118 (27)	13 (4)	313 (91)	−18 (17)	−52 (79)	48 (30)
C(1)	98 (30)	9 (4)	223 (98)	2 (19)	−31 (85)	26 (33)
C(2)	47 (23)	7 (4)	245 (92)	−7 (16)	3 (72)	14 (31)
C(3)	56 (25)	5 (3)	358 (107)	−4 (15)	106 (80)	11 (31)
C(4)	79 (28)	3 (3)	405 (112)	−5 (16)	128 (88)	12 (32)
C(5)	57 (24)	7 (4)	285 (101)	11 (16)	−63 (77)	10 (31)
C(6)	52 (25)	15 (5)	293 (105)	6 (18)	82 (83)	−32 (37)
C(7)	66 (26)	11 (4)	245 (95)	6 (17)	75 (82)	24 (32)
C(8)	75 (28)	6 (4)	515 (128)	5 (17)	183 (97)	−31 (36)
C(9)	72 (27)	11 (4)	532 (133)	−3 (19)	270 (99)	−28 (39)
C(10)	58 (25)	12 (4)	316 (104)	−17 (17)	30 (81)	−18 (35)
C(11)	60 (24)	9 (4)	161 (84)	2 (16)	81 (70)	2 (29)

Table 2 (*cont.*)

	B_{11}	B_{22}	B_{33}	B_{12}	B_{13}	B_{23}
C(12)	51 (24)	9 (4)	382 (110)	7 (17)	55 (84)	1 (36)
C(13)	39 (23)	7 (4)	489 (123)	−8 (16)	95 (86)	−40 (35)
C(14)	53 (25)	11 (4)	365 (114)	6 (18)	20 (84)	−39 (36)
C(15)	81 (27)	9 (4)	220 (91)	−2 (17)	191 (81)	−38 (31)
C(16)	96 (29)	9 (4)	194 (91)	−19 (18)	57 (82)	−1 (31)
C(17)	61 (25)	13 (5)	243 (99)	−15 (18)	−24 (78)	19 (34)
C(18)	58 (24)	8 (4)	217 (90)	8 (16)	10 (73)	−10 (30)
C(19)	92 (31)	17 (5)	229 (103)	−18 (21)	−3 (89)	45 (37)
C(20)	90 (30)	16 (5)	152 (86)	−7 (20)	185 (81)	−3 (34)
C(21)	104 (32)	12 (5)	219 (98)	20 (20)	−85 (87)	27 (34)
C(22)	142 (35)	8 (4)	174 (90)	1 (20)	143 (90)	−38 (33)
C(23)	72 (29)	7 (4)	537 (135)	6 (18)	−153 (96)	−3 (38)
C(24)	58 (26)	8 (4)	440 (120)	−9 (16)	−130 (88)	45 (35)
C(25)	215 (46)	15 (5)	450 (129)	−68 (33)	−223 (120)	53 (53)
C(26)	143 (37)	12 (5)	564 (142)	45 (23)	187 (118)	53 (43)
C(27)	285 (51)	10 (5)	533 (138)	−23 (33)	462 (142)	−41 (52)
C(28)	160 (36)	13 (5)	266 (103)	−15 (24)	33 (97)	−73 (39)
C(29)	145 (35)	15 (5)	159 (92)	40 (23)	84 (91)	55 (35)
C(30)	166 (41)	11 (5)	342 (119)	9 (24)	24 (111)	−41 (39)
C(31)	111 (35)	15 (5)	567 (144)	14 (24)	−26 (111)	−9 (49)

Table 3. *Observed and calculated structure amplitudes*

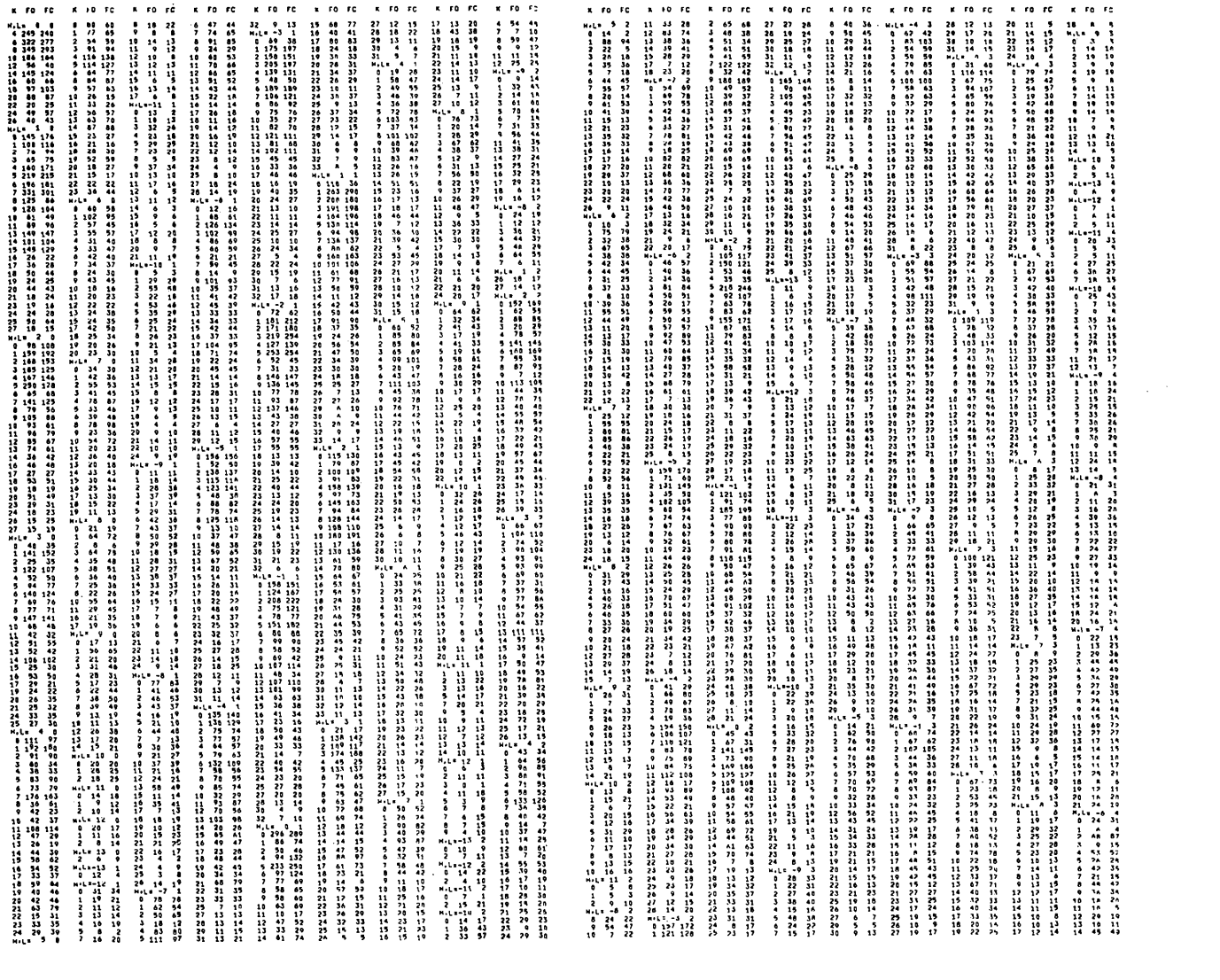
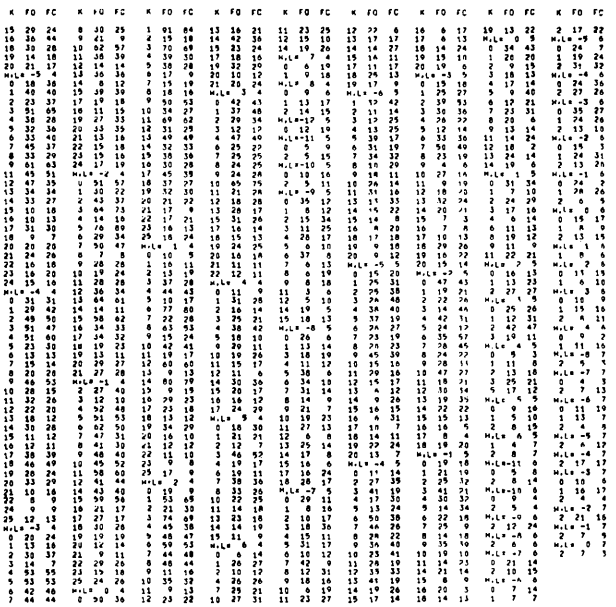


Table 3 (*cont.*)



Only 1500 reflexions were included in this refinement. Four further cycles of block-diagonal least-squares refinement with anisotropic thermal parameters for all the atoms including all 2419 reflexions were carried out and the R value dropped to 0·146, which is satisfactory in view of the poor data from the deteriorating crystals. At the final stage of the refinement all the atoms could be distinguished. The weighting functions were: $\omega=1$ when $F_o \geq 6{\cdot}0$, $\omega=0{\cdot}7$ when $F_o<6{\cdot}0$. The scattering factors used were taken from *International Tables for X-ray Crystallography* (1962). The final positional parameters are shown in Table 1. The thermal parameters are listed in Table 2. The values of the observed and calculated structure factors are compared in Table 3.

Absolute configuration

The absolute configuration was determined by use of the anomalous dispersion effect of the bromine and the sulphur atoms for Cr $K\alpha$ radiation ($\lambda=2{\cdot}2909$ Å: $\Delta f'_{Br}=-0{\cdot}6, \Delta f''_{Br}=2{\cdot}7, \Delta f'_{S}=0{\cdot}3, \Delta f''_{S}=1{\cdot}2$). The structure factors for the Friedel pairs of reflexions were evaluated by assuming that the coordinates of the atoms were derived from a right-handed set of axes. Some of the calculated intensities and observed relations are listed in Table 4. From the agreement in the Table, it may be concluded that the set of atomic coordinates given in Table 1 correctly represents the

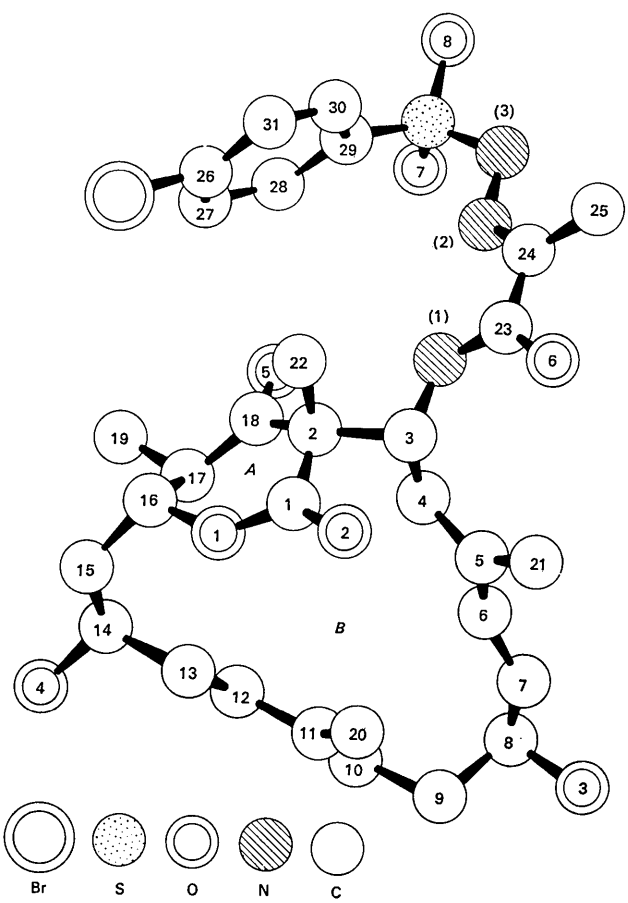


Fig. 1. The molecular structure of bundlin A *p*-bromophenylsulphonylhydrazone viewed along the *c* axis.

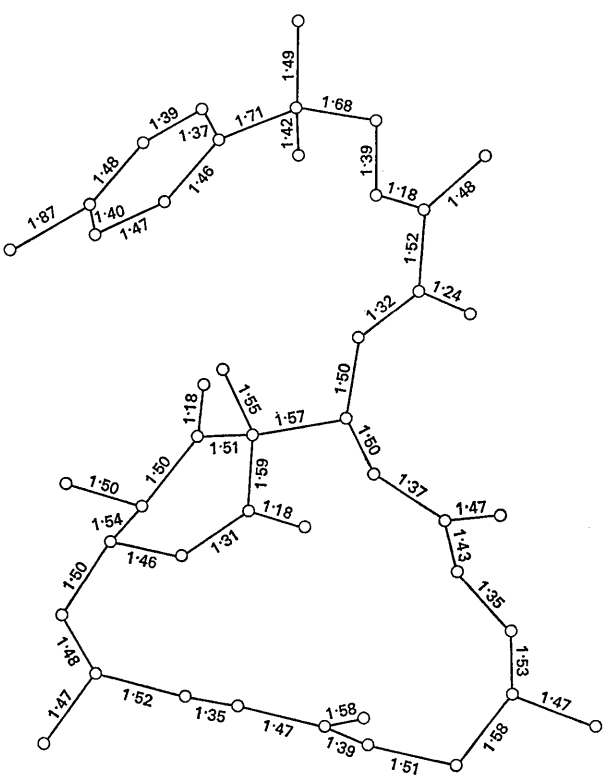


Fig. 2. Bond lengths (Å) in bundlin A *p*-bromophenylsulphonylhydrazone.

absolute configuration of the molecule. A perspective drawing of the molecular structure viewed along the *c* axis is illustrated in Fig. 1.

Table 4. *Determination of the absolute configuration*

Indices	F_c^2 (*hkl*)	Obs	F_c^2 ($\bar{h}\bar{k}\bar{l}$)
0 2 1	1835	<	2246
0 14 1	2880	<	3133
0 15 1	3234	>	2988
2 11 1	445	<	710
4 5 1	3355	>	3109
4 6 1	3432	<	3815
4 7 1	1567	>	1214

Description of the structure and discussion

The molecular structure

The molecular structure of bundlin A *p*-bromophenylsulphonylhydrazone revealed by the present investigation is shown in Fig. 1. It is essentially bicyclic and consists of six- and seventeen-membered rings forming a new type of ring system that has hitherto been unknown in naturally occurring compounds. The six-membered lactone ring *A* takes a boat form and its α and δ positions are linked to the seventeen-membered ring *B*. The methyl group attached to C(2) and the hydrogen atom attached to C(16) are in the *cis* position. A side chain pyruvamide group forming *p*-bromophenylsulphonylhydrazone, is linked to ring *B* at the 3-position.

Bond lengths and angles observed in the molecule are shown in Figs. 2 and 3. The mean standard deviations in bond lengths and angles are 0·04 Å and 2° respectively. The mean value of the seventeen C–C single-bond distances is 1·53 Å. That of the four C–C double-bonds is 1·36 Å.

The groups of the carbon atoms C(3)–C(8), C(21) and C(9)–C(14), C(20) are each roughly planar. This fact and the interatomic distances and bond angles within these groups indicate that they are conjugated diene systems. The deviations of the atoms from the least-squares planes are listed in Table 5. The planes of the two conjugated diene systems are nearly perpendicular to the mean plane of the seventeen-membered ring *B*. All the C–C double bonds are in the *trans* form in ring *B*. In view of the rather large standard deviations it may not be practicable to discuss the interatomic distances and bond angles further. There are six asymmetric carbon atoms in the molecule. The absolute configurations of these atoms are: C(2) *S*, C(3) *R*, C(8) *S*, C(14) *S*, C(16) *R* and C(17) *R* respectively.

The crystal structure of *p*-bromophenylhydrazone of bundlin B (T-2636 A) was determined quite independently (Kamiya, Harada, Wada, Nishikawa & Kishi, 1969). The structure has been refined by the least-squares method with isotropic temperature factors to an *R* value of 0·166 for the 2060 observed reflexions.*Their results are fully consistent with ours, including the absolute configuration. It is noteworthy that the conformations of the lactone ring *A* and the seventeen-membered ring *B* of bundlin A observed in

* In a private communication we were informed that no attempts would be made further to refine the structure.

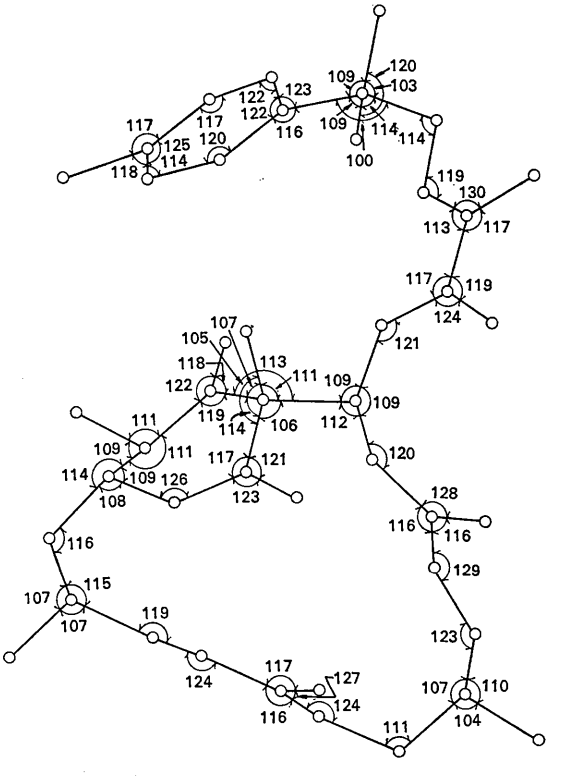


Fig. 3. Bond angles (degrees) in bundlin A *p*-bromophenylsulphonylhydrazone.

Table 5. *Least-squares planes and distances* (Å) *of atoms from the planes*

Equations of planes: $lX+mY+nZ=p$ with $X=ax+cz\cos\beta$, $Y=by$, $Z=cz\sin\beta$

Plane	*l*	*m*	*n*	*p*
1	+0·431	+0·902	+0·007	+10·445
2	+0·808	+0·529	−0·259	+10·381

Plane 1	C(9)	C(10)	C(11)	C(12)	C(13)	C(14)	C(20)
	0·02	0·00	0·00	−0·07	0·09	−0·02	−0·03
Plane 2	C(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(21)
	0·15	−0·06	−0·10	−0·17	0·04	0·14	0·01

the present investigation are remarkably similar to those of bundlin B observed by Kamiya *et al.* (1969), even though they exist in the crystals of a quite different derivative. In fact, the interatomic distances and bond angles in the main part of the molecules in the two derivatives agree well within the experimental error.

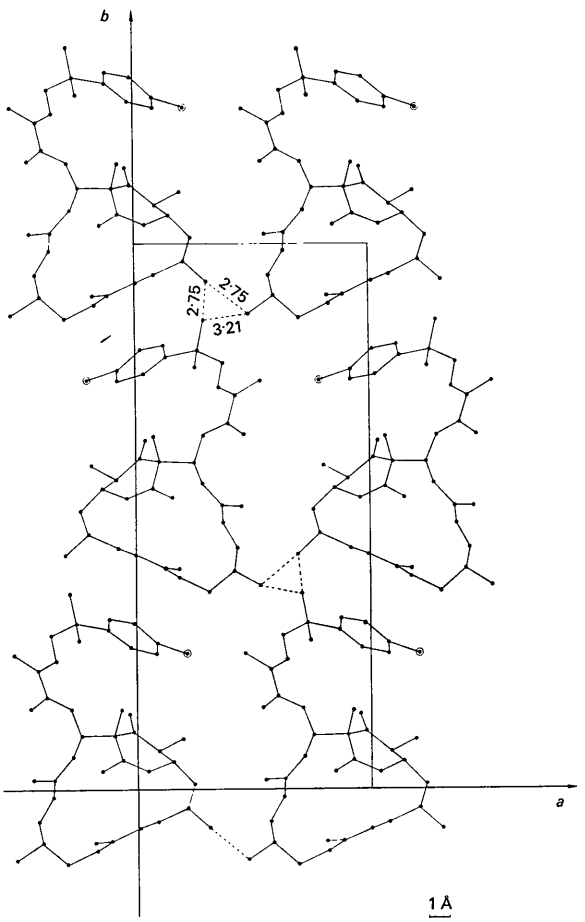


Fig. 4. Projection of the crystal structure of bundlin A *p*-bromophenylsulphonylhydrazone along the *c* axis. Some of the short contacts between molecules are shown by broken lines (Å).

The crystal structure

A projection of the crystal structure of bundlin A *p*-bromophenylsulphonylhydrazone viewed along the *c* axis is illustrated in Fig. 4. Some of the short contacts between the molecules are shown in the Figure. The hydroxyl oxygen atom O(3) is hydrogen bonded to the sulphonyl oxygen atom O(8) of another molecule related to the former by a twofold screw axis. O(3) is also bonded to the hydroxyl oxygen atom O(4) of a third molecule related to the first by the translation **a**. Thus the molecules are linked by hydrogen bonds to form a layer parallel to the plane (001). These layers are held together by van der Waals force to make up a whole crystal.

The calculations were carried out on the HITAC 5020E computer at the Computer Centre of this University.

The authors are grateful to Meiji Seika Kaisha Ltd. for providing crystals of bundlin A and B.

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