Crystal Structure of 6β-Trimethylammoniopenicillanate Hemihydriodide †

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Crystals of the title compound are monoclinic, space group $C2$, with a = 19·44(3), b = 6·28(1), c = 11·33(2) Å, β = 95·0(1)°, Z = 4. The atomic co-ordinates were obtained from X-ray measurements by Fourier and least-squares calculations, the final value of R being 9·0% for 1380 visually estimated reflections. The carboxylate groups of two penicillanate groups are related by a short O(13) $\cdots$ O(13^{I}) separation of 2·46(2) Å across a two-fold axis; this distance is typical of the short hydrogen-bonded separations in the acid salts of some carboxylic acids and the hemihydriodide is therefore formulated as $[RCO_2 \cdots H \cdots O_2CR]^+I^-$. The β-lactam ring is puckered, with C(7) displaced by 0·31 Å from the plane defined by atoms C(5), N(4), and C(6). The thiazolidine ring approximates closely to an envelope form, with C(3) displaced by 0·47 Å from the mean plane through atoms C(2), S, C(5), and N(4).

THE betaine 6β-trimethylammoniopenicillanate (1) forms a highly crystalline hemihydriodide ($C_{11}H_{18}N_2O_3S$)-$\frac{1}{2}$HI.[1] This material may be formulated as (R^+CO_2H, $^-O_2CR^+$)I^- with a combination of carboxy-group and carboxylate anion which is well known in the acid salts of monobasic and dibasic carboxylic acids, where it can give rise to a short symmetrical O $\cdots$ H $\cdots$ O hydrogen

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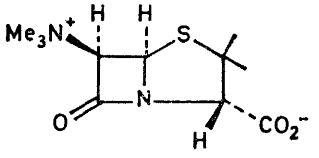
† No reprints available.

[1] T. Leigh, *J. Chem. Soc.*, 1965, 3616; J. P. Clayton, J. H. C. Naylor, R. Southgate, and E. R. Stone, *Chem. Comm.*, 1969, 129.

bond.[2] We undertook an X-ray analysis of the crystal structure of the hemihydriodide to determine whether this provides another example of such a short hydrogen bond and, in addition, to obtain structural parameters pertinent to the correlation of molecular geometry and biological activity in penicillin and cephalosporin antibiotics.[3]



(1)

The crystal structure of the hemihydriodide was elucidated from a three-dimensional Fourier synthesis based on the phases of the iodine atom. The atomic co-ordinates were adjusted by least-squares calculations and at the end of the analysis R was 9·0% over 1380 independent structure amplitudes. The molecular structure of the penicillin derivative is shown in Figure 1 and the crystal structure is illustrated in Figure 2. The atomic co-ordinates and thermal parameters are given in Table 1, while Tables 2—6 list the bond lengths, valency angles, torsion angles, displacements from mean planes, and intermolecular separations.

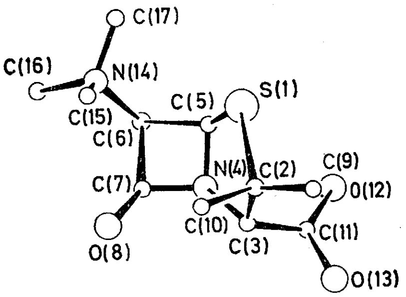


FIGURE 1 A general view of the molecular structure

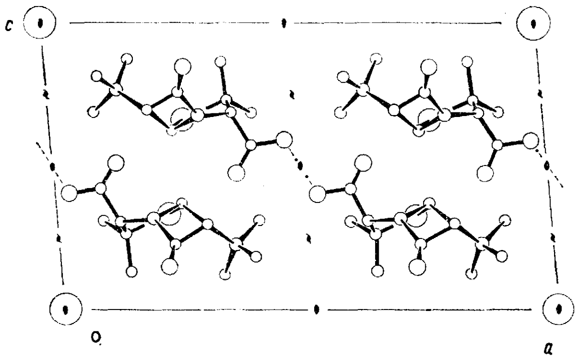


FIGURE 2 The crystal structure viewed in projection along the b axis; the positive direction of the b axis projects into the page

TABLE 1

Fractional atomic co-ordinates and temperature factors, with standard deviations in parentheses

	x	y	z	B
I	0·0000	0·0000	0·0000	*
S(1)	0·2281(2)	0·5161(11)	0·3330(3)	*
C(2)	0·1401(7)	0·4404(25)	0·2650(12)	2·1(3)
C(3)	0·1288(6)	0·2116(27)	0·3062(11)	1·8(2)
N(4)	0·1971(6)	0·1151(23)	0·3210(10)	2·1(2)
C(5)	0·2534(7)	0·2413(27)	0·3725(12)	1·9(2)
C(6)	0·3012(7)	0·1038(30)	0·3019(13)	2·2(2)
C(7)	0·2353(6)	0·0201(43)	0·2350(11)	2·3(2)
O(8)	0·2208(6)	−0·0717(24)	0·1485(11)	3·9(3)
C(9)	0·0904(10)	0·6050(39)	0·3070(17)	3·8(4)
C(10)	0·1409(8)	0·4441(30)	0·1283(14)	2·9(3)
C(11)	0·0953(7)	0·1952(30)	0·4218(12)	2·1(2)
O(12)	0·1283(6)	0·2162(25)	0·5183(11)	3·6(2)
O(13)	0·0286(6)	0·1697(25)	0·4074(10)	3·3(2)
N(14)	0·3568(6)	0·1914(24)	0·2304(10)	2·0(2)
C(15)	0·3301(9)	0·3190(36)	0·1248(15)	3·1(3)
C(16)	0·3950(7)	0·0069(63)	0·1843(13)	3·5(3)
C(17)	0·4071(9)	0·3266(37)	0·3090(15)	3·2(3)

* For the iodine and sulphur atoms anisotropic temperature factors were employed in the form: $T = \exp[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^2 + b_{12}hk + b_{13}hl + b_{23}kl)]$ $(b_{ij} \times 10^4)$

	b_{11}	b_{22}	b_{33}	b_{12}	b_{13}	b_{23}
I	13(0)	262(6)	95(2)	0	22(1)	0
S(1)	15(1)	42(10)	55(3)	3(7)	−4(2)	−2(14)

TABLE 2

Interatomic distances (Å)

S(1)–C(2)	1·88(2)	C(5)–C(6)	1·54(2)
S(1)–C(5)	1·84(2)	C(6)–C(7)	1·53(2)
C(2)–C(3)	1·53(2)	C(6)–N(14)	1·51(2)
C(2)–C(9)	1·52(3)	C(7)–O(8)	1·15(2)
C(2)–C(10)	1·55(2)	C(11)–O(12)	1·23(2)
C(3)–N(4)	1·46(2)	C(11)–O(13)	1·30(2)
C(3)–C(11)	1·52(2)	N(14)–C(15)	1·50(2)
N(4)–C(5)	1·43(2)	N(14)–C(16)	1·50(3)
N(4)–C(7)	1·41(2)	N(14)–C(17)	1·52(2)

The carboxy-groups of two penicillanate groups are in close proximity across the two-fold axis; the O(13) $\cdots$ O(13$^{\mathrm{I}}$) separation of 2·46(2) Å is substantially shorter than a normal van der Waals separation and accordingly characterizes a strong hydrogen-bonded association. If, in accord with formal space-group requirements, the hydrogen atom is situated on the two-fold

TABLE 3

Valency angles (deg.)

C(5)–S(1)–C(2)	94·4(8)	C(3)–C(2)–S(1)	105·2(8)
C(9)–C(2)–S(1)	106·3(9)	C(10)–C(2)–S(1)	108·5(7)
N(4)–C(5)–S(1)	104·0(6)	C(6)–C(5)–S(1)	124·0(6)
C(9)–C(2)–C(3)	115·5(11)	C(10)–C(2)–C(3)	109·4(10)
N(4)–C(3)–C(2)	105·8(10)	C(11)–C(3)–C(2)	114·2(9)
C(10)–C(2)–C(9)	111·5(12)	C(11)–C(3)–N(4)	109·2(10)
C(5)–N(4)–C(3)	118·2(11)	C(7)–N(4)–C(3)	128·8(9)
O(12)–C(11)–C(3)	122·1(9)	O(13)–C(11)–C(3)	113·5(8)
C(7)–N(4)–C(5)	95·0(10)	C(6)–C(5)–N(4)	87·3(10)
C(6)–C(7)–N(4)	88·9(10)	O(8)–C(7)–N(4)	134·3(9)
C(7)–C(6)–C(5)	86·1(10)	N(14)–C(6)–C(5)	124·5(10)
N(14)–C(6)–C(7)	118·0(9)	O(8)–C(7)–C(6)	136·7(9)
C(15)–N(14)–C(6)	114·2(10)	C(16)–N(14)–C(6)	107·8(15)
C(17)–N(14)–C(6)	110·1(10)	O(13)–C(11)–O(12)	124·3(10)
C(16)–N(14)–C(15)	106·5(14)	C(17)–N(14)–C(15)	109·2(13)
C(17)–N(14)–C(16)	108·8(11)		

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[2] J. C. Speakman, *Structure and Bonding*, 1972, **12**, 141.

[3] R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.*, 1970, **92**, 5489; E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *ibid.*, 1971, **93**, 4324; R. D. G. Cooper, P. V. Demarco, J. C. Cheng, and N. D. Jones, *ibid.*, 1969, **91**, 1408.

TABLE 4

Torsion angles (deg.), standard deviations are *ca.* 2°

C(5)–S(1)–C(2)–C(3)	14
C(5)–S(1)–C(2)–C(9)	137
C(5)–S(1)–C(2)–C(10)	−103
C(2)–S(1)–C(5)–N(4)	6
C(2)–S(1)–C(5)–C(6)	102
S(1)–C(2)–C(3)–N(4)	−30
S(1)–C(2)–C(3)–C(11)	90
C(9)–C(2)–C(3)–N(4)	−147
C(9)–C(2)–C(3)–C(11)	−27
C(10)–C(2)–C(3)–N(4)	86
C(10)–C(2)–C(3)–C(11)	−154
C(2)–C(3)–N(4)–C(5)	40
C(2)–C(3)–N(4)–C(7)	−84
C(11)–C(3)–N(4)–C(5)	−83
C(11)–C(3)–N(4)–C(7)	153
C(2)–C(3)–C(11)–O(12)	−81
C(2)–C(3)–C(11)–O(13)	96
N(4)–C(3)–C(11)–O(12)	38
N(4)–C(3)–C(11)–O(13)	−146
C(3)–N(4)–C(5)–S(1)	−28
C(3)–N(4)–C(5)–C(6)	−152
C(7)–N(4)–C(5)–S(1)	111
C(7)–N(4)–C(5)–C(6)	−13
C(3)–N(4)–C(7)–C(6)	146
C(3)–N(4)–C(7)–O(8)	−31
C(5)–N(4)–C(7)–C(6)	13
C(5)–N(4)–C(7)–O(8)	−164
S(1)–C(5)–C(6)–C(7)	−93
S(1)–C(5)–C(6)–N(14)	28
N(4)–C(5)–C(6)–C(7)	12
N(4)–C(5)–C(6)–N(14)	133
C(5)–C(6)–C(7)–N(4)	−12
C(5)–C(6)–C(7)–O(8)	164
N(14)–C(6)–C(7)–N(4)	−139
N(14)–C(6)–C(7)–O(8)	37
C(5)–C(6)–N(14)–C(15)	−66
C(5)–C(6)–N(14)–C(16)	175
C(5)–C(6)–N(14)–C(17)	57
C(7)–C(6)–N(14)–C(15)	39
C(7)–C(6)–N(14)–C(16)	−79
C(7)–C(6)–N(14)–C(17)	163

TABLE 5

Displacements (Å) of atoms from planes

Plane (1): N(4), C(5), C(6)

N(4) 0, C(5) 0, C(6) 0, S(1) 1·47, C(3) 0·59, C(7) 0·31, N(14) 0·90

Plane (2): S(1), C(2), N(4), C(5)

S(1) 0·03, C(2) −0·03, N(4) 0·03, C(5) −0·04, C(3) −0·47, C(6) 1·18, C(7) 1·31, C(9) −0·98, C(10) 1·41

axis then we have an example of a symmetrical O · · · H · · · O hydrogen bond. On the other hand, if the proton is randomly disordered over two alternative sites on either side of the two-fold axis then the hydrogen bond would be of the normal unsymmetrical O–H · · · O type. The O · · · O interaction at 2·46 Å may be compared with a number of 'very short' hydrogen bonds [2] found in acid salts of carboxylic acids: for example, intermolecular hydrogen bonds involving crystallographic two-fold symmetry occur in sodium hydrogen diacetate [2·44(1) Å],[4] potassium hydrogen succinate [2·446(4) Å],[5] ammonium hydrogen glutarate [2·406(7) Å],[6] and potassium hydrogen acetylenedicarboxylate [2·445(3) Å].[7] In the case of the acid salts there is strong evidence that 'very short' hydrogen bonds which lie across crystallographic elements of symmetry are genuinely symmetrical,[2] and this may also be true for the hydrogen bond in the hemihydriodide.

The bond lengths in the carboxy-group show that C(11)–O(12) (1·23 Å) has more double-bond character than C(11)–O(13) (1·30 Å), whereas in an unperturbed carboxylate anion both bonds are normally of the same length, *cf.* distances of 1·240 and 1·245 Å in the zwitterionic form of ampicillin trihydrate.[8]

TABLE 6

Intermolecular separations (<3·8 Å)

O(13) · · · O(13^{I})	2·46	C(10) · · · C(15^{V})	3·79
C(11) · · · O(13^{I})	3·22	C(10) · · · C(16^{V})	3·57
O(12) · · · O(13^{I})	3·25	S(1) · · · C(5^{VI})	3·61
S(1) · · · C(7^{II})	3·36	S(1) · · · O(12^{VI})	3·38
S(1) · · · O(8^{II})	3·32	O(8) · · · C(15^{VII})	3·24
C(2) · · · O(8^{II})	3·74	C(6) · · · O(12^{VIII})	3·39
O(8) · · · O(10^{III})	3·41	O(12) · · · C(17^{VIII})	3·24
O(13) · · · C(17^{IV})	3·32		

Roman numerals as superscripts refer to the following transformations of the atomic co-ordinates:

I $-x, y, 1-z$
II $x, 1+y, z$
III $x, -1+y, z$
IV $-\frac{1}{2}+x, -\frac{1}{2}+y, z$
V $\frac{1}{2}-x, \frac{1}{2}+y, -z$
VI $\frac{1}{2}-x, \frac{1}{2}+y, 1-z$
VII $\frac{1}{2}-x, -\frac{1}{2}+y, -z$
VIII $\frac{1}{2}-x, -\frac{1}{2}+y, 1-z$

The β-lactam ring in the hemihydriodide displays a buckled conformation, with atom C(7) displaced 0·31 Å above the plane defined by atoms C(5), N(4), and C(6). In phenoxymethylpenicillin [9] and potassium benzylpenicillin [10] atom C(7) of the β-lactam is displaced by 0·15 Å. The thiazolidine ring has an envelope conformation in which C(3) is 0·47 Å out of the plane containing atoms S(1), C(2), N(4), and C(5). In phenoxymethylpenicillin the corresponding displacement is 0·51 Å.[9]

The lactam nitrogen atom is displaced by 0·29 Å from the plane of its three substituents C(3), C(5), and C(7). In benzylpenicillin the displacement is 0·40 Å. Dahl has observed that the β-lactam nitrogen atom has a greater pyramidal character in active Δ^3-cephalosporin antibiotics than in the inactive Δ^2-cephalosporin, being displaced by *ca.* 0·2—0·3 Å from the plane of its three substituent atoms in the former case and by only 0·06 Å in the latter, and that the departure from coplanarity can be correlated with the ease of base hydrolysis of the β-lactam amide bond.[3]

EXPERIMENTAL

Crystal Data.—$C_{11}H_{18}N_2O_3S,\frac{1}{2}HI$, $M = 322·3$. Monoclinic, $a = 19·44(3)$, $b = 6·28(1)$, $c = 11·33(2)$ Å, $\beta =$

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[4] J. C. Speakman and H. H. Mills, *J. Chem. Soc.*, 1961, 1164.

[5] A. McAdam, M. Currie, and J. C. Speakman, *J. Chem. Soc.* (*A*), 1971, 1994.

[6] A. L. MacDonald and J. C. Speakman, *J. Cryst. Mol. Structure*, 1971, **1**, 189.

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[8] M. N. G. Jones, D. Hall, and D. C. Hodgkin, *Nature*, 1968, **220**, 168.

[9] S. Abrahamsson, D. C. Hodgkin, and E. N. Maslen, *Biochem J.*, 1963, **86**, 514.

[10] G. J. Pitt, *Acta Cryst.*, 1952, **5**, 770.

95·0(1)°, $U = 1377$ Å^3, $D_m = 1{\cdot}55$, $Z = 4$, $D_c = 1{\cdot}56$, $F(000) = 660$. Space group $C2$ (C_2^3). Mo-K_α radiation, $\lambda = 0{\cdot}7107$ Å; μ(Mo-K_α) = 13·7 cm^{-1}.

Crystallographic Measurements.—Rotation, Weissenberg, and precession photographs were taken. The systematically absent reflections for the optically active compound indicated the space group $C2$. Intensity data were obtained from layers $h0$—$6l$ of equi-inclination Weissenberg photographs taken with Zr-filtered Mo-K_α radiation. A Joyce–Loebl integrating microdensitometer was used to measure the intensities, which after correction for Lorentz and polarization effects gave 1380 independent structure amplitudes. The various layers were placed on a common scale by correlation with a limited set of intensities obtained from precession photographs.

Structure Analysis.—The iodine atom, which lies on a two-fold symmetry axis, was used to define the origin of the cell, and the co-ordinates of the sulphur atom were found from a Fourier synthesis. A subsequent Fourier synthesis based on the phases of the iodine and sulphur atoms showed little pseudo-symmetry and fourteen further atoms were unambiguously located. After two cycles of least-squares calculations with isotropic thermal parameters R was 24·1% and a Fourier difference synthesis gave the co-ordinates of the two remaining carbon atoms. A further two cycles of isotropic refinement lowered R to 15·1%.

The iodine and sulphur atoms were next assigned anisotropic temperature factors and one cycle of least-squares calculations gave R 9·5%. Corrections for anomalous dispersion were applied to the iodine scattering factor[11] and two further rounds of calculations reached convergence at R 9·0%. A final difference electron-density distribution gave no clear indication of hydrogen atom positions. A unitary weighting scheme ($w = 1$) was retained throughout the least-squares calculations as $\langle w\Delta^2\rangle$ was approximately constant over various ranges of $|F_o|$ and sin θ. Observed and calculated structure amplitudes are listed in Supplementary Publication No. SUP 20911 (9 pp., 1 microfiche).*

The various calculations were performed on an Atlas computer at the S.R.C. Chilton Laboratory, an ICL 1905 computer at the University of Sussex, and a KDF 9 computer at the University of Glasgow. We thank the S.R.C. for the purchase of the microdensitometer, the U.S. National Institutes of Health for a fellowship (to R. J. McC.), and Dr. J. H. C. Naylor (Beecham Research Laboratories) for a supply of the hemihydriodide.

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* See Notice to Authors No. 7 in *J.C.S. Dalton*, 1972, Index issue.

[11] ' International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1952.