View Article Online / Journal Homepage / Table of Contents for this issue

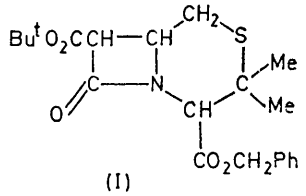
Published on 01 January 1973. Downloaded by Michigan State University on 19/01/2016 02:17:25.

Crystal and Molecular Structure of a Synthetic Compound Related to the Penicillins and Cephalosporins, 3-Benzyl 7-t-Butyl 2,2-Dimethyl-8-oxo-4-thia-1-aza-6α*H*-bicyclo[4.2.0]octane-3β,7α-dicarboxylate

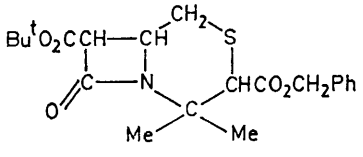
By **Kalyani Vijayan,*† B. F. Anderson,** and **D. C. Hodgkin,** Laboratory of Molecular Biophysics, Department of Zoology, South Parks Road, Oxford OX1 3PS

An intermediate obtained by Lowe and Ramsay in the synthesis of a homopenicillin has been shown by *X*-ray analysis to have a structure including a β-lactam ring fused to a thiomorpholine ring carrying 2,2-dimethyl and 3-benzyloxycarbonyl substituents. The compound crystallises in the space group $P2_1/c$, with $Z = 4$ in the unit cell of dimensions $a = 19{\cdot}160$, $b = 6{\cdot}369$, $c = 19{\cdot}052$ Å, $\beta = 111{\cdot}59°$. The crystal structure was solved from diffractometer data by the symbolic addition method and refined to an *R* value of 5·16% for 2697 independent reflections by iterative block-diagonal least-squares procedures. The central six-membered ring exists in a distorted chair form and is oriented at 140·8° to the fused β-lactam ring.

ALTHOUGH *X*-ray crystallographic measurements were used early to find the chemical structures of both penicillins and cephalosporins, rather few accurate *X*-ray analyses have been made since in either series.[1-3] The present study began as an aid to the synthetic experiments of Lowe and Ramsay [4] to define the structure and stereochemistry of the homopenicillins they had obtained. The particular stereoisomer investigated was found not to have the gross structure (I), as at first hoped for, but to correspond with structure (II), with



(I)



(II)

the benzyloxycarbonyl side-chain and dimethyl group transposed. As would be expected on a number of grounds, the compound is biologically inactive. It is all the same interesting to compare details of the molecular geometry it presents with that observed in both biologically active and inactive β-lactams.

EXPERIMENTAL

Thin transparent needle-like crystals were supplied by Lowe and Ramsay and were recrystallised as larger, acicular plates by solution in ether and precipitation with light petroleum. The unit-cell dimensions were determined from preliminary measurements on oscillation and Weissenberg photographs and refined on a Hilger Watts four circle diffractometer.

Crystal Data.—$C_{20}H_{27}NO_5S$, $M = 405{\cdot}5$. Monoclinic, $a = 19{\cdot}160 \pm 0{\cdot}003$, $b = 6{\cdot}369 \pm 0{\cdot}002$, $c = 19{\cdot}052 \pm 0{\cdot}003$ Å, $\beta = 111{\cdot}59 \pm 0{\cdot}10°$, $U = 2161{\cdot}9$ Å^3, $D_m = 1{\cdot}221$ (by flotation), $Z = 4$, $D_c = 1{\cdot}243$, $F(000) = 216$. Space group $P2_1/c$. Cu-K_α radiation, $\lambda = 1{\cdot}5418$ Å.

Intensity data were collected from a crystal 1 mm long and *ca.* 0·40 mm wide on a computer-controlled Hilger and Watts four-circle diffractometer fitted with a scintillation counter, by use of nickel-filtered copper K_α radiation. The crystal was mounted with the b^* axis parallel to the ϕ axis. The *X*-ray intensities were measured using the ω—2θ scan, in accordance with the ordinate analysis procedure described by Watson *et al.*[5] A total of 3353 independent reflections were measured within the range $2\theta \leqslant 130°$, of which 2697 reflections had integrated intensities $>\sigma(I)$. The data were corrected for Lorentz and polarisation factors and also for the crystal-shape factor.[6]

Structure Determination.—The structure was solved by the symbolic addition procedure.[7] Normalised structure factors, $E_{h,N}$, defined as

$$|E_h|^2 = |F_h|^2/\varepsilon \sum_{j=1} f_j^2$$

† *Present address:* Department of Physics, Indian Institute of Science, Bangalore 12, India.

[1] D. C. Hodgkin and E. N. Maslen, *Biochem. J.*, 1961, **79**, 393.
[2] R. D. Diamond, D. Phil. Thesis, University of Oxford, 1963.
[3] R. M. Sweet and L. F. Dahl, *J. Amer. Chem. Soc.*, 1970, **92**, 5489.
[4] G. Lowe and M. V. J. Ramsay, preceding paper.
[5] H. C. Watson, D. M. Shotton, J. M. Cox, and H. Muirhead, *Nature*, 1970, **225**, 806.
[6] A. C. T. North, D. C. Phillips, and F. S. Matthews, *Acta Cryst.*, 1968, *A*, **24**, 351.
[7] I. L. Karle and J. Karle, *Acta Cryst.*, 1966, **21**, 849.

View Article Online

Published on 01 January 1973. Downloaded by Michigan State University on 19/01/2016 02:17:25.

where $\varepsilon = 2$ for the $h0l$ and the $0k0$ data and $\varepsilon = 1$ otherwise, were calculated using the temperature factor and the absolute scale-factor derived from Wilson statistics.[8] The distribution of the E values and the other relevant statistics presented in Table 1 agree well with the corresponding theoretical values for centrosymmetric structures.

TABLE 1

E Statistics

	Calc.	Obs.
$\langle\|E\|\rangle$	0·798	0·826
$\langle\|E^2 - 1\|\rangle$	0·968	0·949
$\langle E^2\rangle$	1·0	1·010
% Data with		
$\|E\| > 1$	32·0	30·82
$\|E\| > 2$	5·0	5·06
$\|E\| > 3$	0·3	0·27

A $\sum_2$ listing of interactions was computed[9] using all reflections with $|E_h| \geqslant 1{\cdot}7$. The phases of three reflections with large $|E_h|$ values and large numbers of interactions were fixed to specify the origin. In addition, five more symbolic phases were assigned as follows:

h	l	k	$\|E_h\|$	Sign	
4	$\bar{1}\bar{7}$	2	4·195	+	Origin
7	11	3	3·802	+	Origin
7	8	4	3·315	+	Origin
8	$\bar{1}\bar{2}$	5	3·361	A	Symbols
5	$\bar{1}\bar{0}$	5	3·163	B	Symbols
7	$\bar{1}\bar{9}$	2	3·382	C	Symbols
4	11	1	2·950	D	Symbols
4	$\bar{8}$	5	2·599	E	Symbols

The criterion used for accepting any new sign from the relation: $SE_h \sim S\sum_k E_k E_{h-k}$ was that the probability: $P_+(E_h) = \frac{1}{2} + \frac{1}{2}\sum_3\sum_2^{-3/2}|E_h|\sum_k E_k E_{h-k}$ should be $\geqslant 99{\cdot}75\%$. Phases of 267 out of 291 reflections with $|E_h| \geqslant 1{\cdot}7$ could thus be determined from the starting set. In the course of the sign determination, relationships of the type $C = AB$, $E = -A$, $D = -A$, $A = +$ and $E = +$, were indicated very strongly. Hence, a three-dimensional Fourier map was computed for the sign combination, $A = +$, $B = +$, $C = +$, $D = -$, and $E = -$ using the 267 E values as coefficients. The position of the sulphur atom was clearly indicated in the E map. Identification of other atomic sites was, however, not unambiguous, as there were nearly 65 peaks which appeared as high as might be expected for the lighter atoms in the molecule.* It was then decided to repeat the symbolic addition procedure using reflections with $|E_h| \geqslant 1{\cdot}4$ and a lower acceptance limit of 99·55% for the probability of any interaction. With these modifications, the signs of 472 reflections were determined by use of a computer programme.[9] It was noticed that the signs of the 267 reflections used for the earlier E map remained exactly the same. In the E map computed with 472 reflections, the sulphur atom came up at essentially the same position as in the first map and the positions of all the non-hydrogen atoms other than those in the t-butyl group could clearly be identified. There were four spurious peaks in the map, the heights of which were of the order of that of the lowest peak for a real non-methyl atomic site.

A structure-factor calculation with the 25 atoms located from the E map gave R 30·34%. An overall temperature factor of 4 Å^2 was used. Two rounds of block-diagonal least-squares refinement with individual isotropic temperature factors reduced R to 23·96%. The carbon atoms in the t-butyl group could also be located from an electron-density map computed at this stage. The structure was further refined to R 16·31% in five more structure-factor least-squares cycles. Reflections measuring less than three times the respective estimated standard deviations were omitted from subsequent calculations and anisotropic temperature factors were introduced. Three further SFLS cycles brought R to 10·07%. A difference-Fourier map was then synthesised and all the hydrogen atoms except those belonging to the t-butyl group (18 out of 27) could be located. One more refinement cycle including these 18 hydrogen atoms reduced R to 5·67%. The remaining 9 hydrogen atoms could also be located from a new difference-Fourier map. Five more cycles of SFLS calculations were carried out and the final R was 5·16%. In the foregoing calculations, hydrogen atoms were refined isotropically, and atomic scattering factors were taken from ref. 10. In the final least-squares cycle, the indicated shifts for all but six parameters were less than the corresponding standard deviations. Six hydrogen atom parameters, however, had least-squares shifts lying between σ and 2σ.

A residual electron-density map was synthesised at the end of the refinement and the largest density in both the positive and the negative regions was $<0{\cdot}1$ e.†

RESULTS AND DISCUSSION

The final positional parameters of the atoms are given in Table 2. Stereoscopic views of the molecule are shown in Figure 1, and the bond lengths and bond angles of the non-hydrogen atoms in Figures 2(a) and 2(b). Those involving the hydrogen atoms are recorded in Table 3. The standard deviations of the bond lengths and angles were calculated ignoring the off-diagonal terms of the inverse matrix and should probably be increased by a factor of *ca.* 1·5. The stereochemical form of the molecule is such that the hydrogen atom at C(7) is *trans* to the hydrogen atom at C(6), as had been established by n.m.r. spectroscopy,[4] and also to that at C(3). The configuration of the carbon chains attached to the β-lactam ring in this particular isomer is therefore unlike that found in the biologically active natural compounds.

Dimensions throughout most of the molecule are much as would be expected.[11] There is a tendency for bond lengths in the t-butyl group and benzene rings to be smaller than normal, perhaps due to inaccuracies in atom placing associated with the high thermal parameters of end groups in the molecule. Table 4(*c*) shows the planarity of the benzene ring.

* It was realised later that, of these 65 peaks, 43 were spurious and had heights $\geqslant$ the lowest peak height for a non-methyl atomic site in the molecule.

† Final observed and calculated structure factors and thermal parameters are listed in Supplementary Publication No. SUP 20548 (19 pp., 1 microfiche). For details see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20.

[8] A. J. C. Wilson, *Nature*, 1942, **150**, 152.
[9] O. J. R. Hodder, C. K. Prout, and J. S. Rollett, 1968, unpublished results.
[10] 'International Tables for *X*-Ray Crystallography,' vol. III, Kynoch Press, Birmingham, 1962.
[11] *Chem. Soc. Special Publ.*, No. 11, 1958.

View Article Online

Published on 01 January 1973. Downloaded by Michigan State University on 19/01/2016 02:17:25.

The six-membered thiomorpholine ring has a non-planar conformation approximating to the chair form of cyclohexane [*cf.* Table 4(*a*)]. Its geometry is illustrated in Figure 3 which combines two two-dimensional projections of the ring and also records the dihedral angles. These may be compared with the angles found in cyclohexane derivatives which vary between 56 and 58°.[12,13] The bond lengths are normal except for C(5)–C(6), which is a little short (1·51 Å) compared with the value accepted for C(sp^3)–C(sp^3) bonds (1·54 Å).

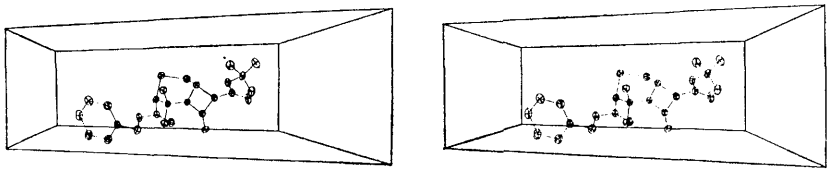


FIGURE 1 Stereoscopic view of the molecule as seen along the [100] direction

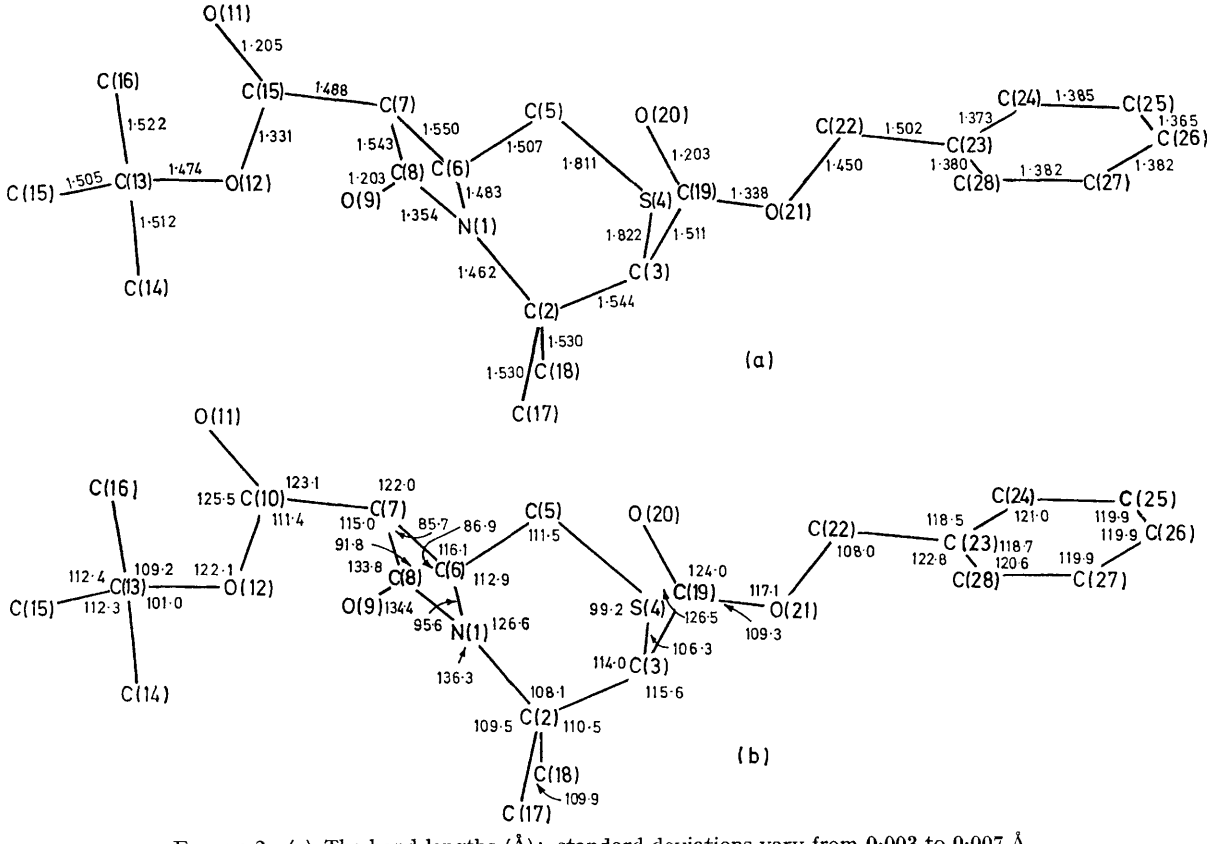


FIGURE 2 (a) The bond lengths (Å); standard deviations vary from 0·003 to 0·007 Å
(b) The valency angles (deg.); standard deviations vary from 0·14 to 0·38°

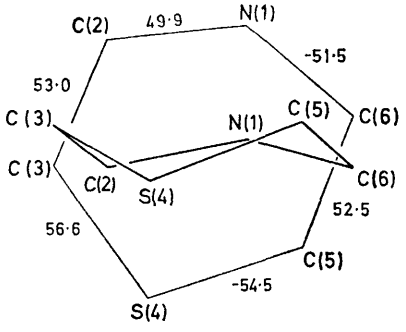


FIGURE 3 A combined view of two projections of the six-membered ring containing atoms N(1), C(2), C(3), S(4), C(5), and C(6)

The β-lactam ring is the one part of the molecule common to all the cephalosporins and penicillins. Here it is closely planar as shown in Table 4(*b*) and inclined to the mean plane of the thiomorpholine ring at an angle of 140·8°. The bond C(7)–C(8) appears a little lengthened to 1·54 Å, a distance similar to those observed in cyclobutane and its derivatives[14,16] and in several other β-lactams.[2,3,15] The relatively short N(1)–C(8) bond (1·35 Å) is consistent with normal amide reson-

[12] W. Klyne and V. Prelog, *Experientia*, 1960, **16**, 521.
[13] H. J. Geise, C. Altona, and C. Romers, *Tetrahedron*, 1967, **23**, 439.
[14] J. D. Dunitz, *Acta Cryst.*, 1949, **2**, 1.
[15] R. Parthasarathy, *Acta Cryst.*, 1970, *B*, **26**, 1283.
[16] J. D. Dunitz and V. J. Schomaker, *J. Chem. Phys.*, 1952, **20**, 1703.

View Article Online

Published on 01 January 1973. Downloaded by Michigan State University on 19/01/2016 02:17:25.

TABLE 2

Final positional co-ordinates of atoms in fractional units, with estimated standard deviations in parentheses

Atom	*x*	*y*	*z*
N(1)	0·2263(1)	0·3468(3)	0·3931(1)
C(2)	0·2332(1)	0·3213(4)	0·4716(1)
C(3)	0·3145(1)	0·3767(4)	0·5228(1)
S(4)	0·3458(0)	0·6327(1)	0·5033(0)
C(5)	0·3296(2)	0·5977(5)	0·4042(2)
C(6)	0·2499(2)	0·5319(5)	0·3601(2)
C(7)	0·2377(2)	0·3939(5)	0·2895(2)
C(8)	0·2158(2)	0·2185(5)	0·3334(2)
O(9)	0·1962(2)	0·0390(4)	0·3192(1)
C(10)	0·1797(2)	0·4447(5)	0·2145(2)
O(11)	0·1824(1)	0·3815(4)	0·1559(1)
O(12)	0·1242(1)	0·5580(4)	0·2214(1)
C(13)	0·0612(2)	0·6361(6)	0·1553(2)
C(14)	0·0183(3)	0·7629(9)	0·1932(3)
C(15)	0·0162(2)	0·4539(9)	0·1111(2)
C(16)	0·0912(3)	0·7743(9)	0·1080(3)
C(17)	0·1793(2)	0·4722(6)	0·4887(2)
C(18)	0·2148(2)	0·0948(5)	0·4853(2)
C(19)	0·3737(1)	0·2210(4)	0·5222(1)
O(20)	0·3784(1)	0·1371(3)	0·4675(1)
O(21)	0·4235(1)	0·1953(3)	0·5925(1)
C(22)	0·4910(2)	0·0778(6)	0·6012(2)
C(23)	0·5500(1)	0·1361(5)	0·6759(1)
C(24)	0·6088(2)	0·0003(6)	0·7082(2)
C(25)	0·6677(2)	0·0526(6)	0·7742(2)
C(26)	0·6674(2)	0·2410(6)	0·8083(2)
C(27)	0·6084(2)	0·3786(6)	0·7770(2)
C(28)	0·5500(2)	0·3256(5)	0·7110(2)
H(3)	0·3170(15)	0·3907(42)	0·5761(15)
H(51)	0·3631(19)	0·4905(57)	0·3954(19)
H(52)	0·3388(17)	0·7351(55)	0·3879(18)
H(6)	0·2145(15)	0·6503(45)	0·3515(15)
H(7)	0·2853(18)	0·3638(49)	0·2827(17)
H(141)	0·0486(28)	0·8628(78)	0·2318(29)
H(142)	−0·0092(31)	0·6486(88)	0·2166(30)
H(143)	−0·0313(29)	0·8224(78)	0·1537(28)
H(151)	0·0009(28)	0·3651(79)	0·1422(27)
H(152)	−0·0296(26)	0·5058(72)	0·0663(26)
H(153)	0·0475(22)	0·3616(62)	0·0903(22)
H(161)	0·0502(26)	0·8435(76)	0·0707(27)
H(162)	0·1186(29)	0·6784(82)	0·0788(28)
H(163)	0·1232(29)	0·8740(81)	0·1468(28)
H(171)	0·1850(19)	0·4557(57)	0·5436(21)
H(172)	0·1301(21)	0·4334(57)	0·4574(20)
H(173)	0·1861(18)	0·6257(57)	0·4793(18)
H(181)	0·2479(20)	−0·0069(59)	0·4749(19)
H(182)	0·2217(18)	0·0794(53)	0·5393(20)
H(183)	0·1617(20)	0·0506(58)	0·4489(20)
H(221)	0·5074(25)	0·1116(69)	0·5541(26)
H(222)	0·4796(20)	−0·0695(63)	0·5946(20)
H(24)	0·6043(20)	−0·1344(61)	0·6808(20)
H(25)	0·7112(19)	−0·0507(56)	0·7959(19)
H(26)	0·7075(19)	0·2738(56)	0·8563(20)
H(27)	0·6058(19)	0·5206(60)	0·7983(19)
H(28)	0·5102(21)	0·4226(60)	0·6840(21)

TABLE 3

Bond lengths (Å) and bond angles (deg.) involving hydrogen atoms, with estimated standard deviations in parentheses

(*a*) Distances

C(3)–H(3)	1·00(0·03)	C(17)–H(171)	1·02(0·04)
C(5)–H(51)	0·99(0·04)	C(17)–H(172)	0·95(0·04)
C(5)–H(52)	0·97(0·04)	C(17)–H(172)	1·01(0·04)
C(6)–H(6)	0·99(0·03)	C(18)–H(181)	0·98(0·04)
C(7)–H(7)	0·99(0·03)	C(18)–H(182)	0·99(0·04)
C(14)–H(141)	0·98(0·06)	C(18)–H(183)	1·04(0·04)
C(14)–H(142)	1·09(0·06)	C(22)–H(221)	1·08(0·05)
C(14)–H(143)	1·04(0·06)	C(22)–H(222)	0·96(0·04)
C(15)–H(151)	0·94(0·05)	C(24)–H(24)	0·99(0·04)
C(15)–H(152)	1·03(0·05)	C(25)–H(25)	1·02(0·04)
C(15)–H(153)	1·02(0·04)	C(26)–H(26)	0·99(0·04)
C(26)–H(161)	0·96(0·05)	C(27)–H(27)	1·00(0·04)
C(16)–H(162)	1·08(0·06)	C(28)–H(28)	0·97(0·04)
C(16)–H(163)	0·99(0·06)		

TABLE 3 (*Continued*)

(*b*) Angles

S(4)–C(3)–H(3)	103·3(2)	H(162)–C(16)–H(163)	118·3(4)
C(19)–C(3)–H(3)	108·1(2)	C(3)–C(17)–H(171)	109·2(2)
S(4)–C(5)–H(51)	112·6(2)	C(3)–C(17)–H(172)	107·2(3)
S(4)–C(5)–H(52)	104·0(2)	C(3)–C(17)–H(173)	115·4(2)
C(6)–C(5)–H(52)	109·9(2)	H(171)–C(17)–H(172)	109·1(3)
C(6)–C(5)–H(51)	107·6(2)	H(171)–C(17)–H(173)	108·0(3)
H(51)–C(5)–H(52)	111·2(3)	H(172)–C(17)–H(173)	107·7(3)
C(5)–C(6)–H(6)	111·8(2)	C(3)–C(18)–H(181)	112·6(2)
C(7)–C(6)–H(6)	114·5(2)	C(3)–C(18)–H(182)	108·6(2)
C(6)–C(7)–H(7)	111·9(2)	C(3)–C(18)–H(183)	111·9(2)
C(10)–C(7)–H(7)	108·4(2)	H(181)–C(18)–H(182)	107·2(3)
C(13)–C(14)–H(141)	115·3(3)	H(181)–C(18)–H(183)	103·5(3)
C(13)–C(14)–H(142)	105·6(2)	H(182)–C(18)–H(183)	112·9(3)
C(13)–C(14)–H(143)	111·2(2)	O(21)–C(22)–H(221)	108·9(3)
H(141)–C(14)–H(142)	111·6(4)	O(21)–C(22)–H(222)	109·8(2)
H(141)–C(14)–H(143)	115·7(3)	C(23)–C(22)–H(221)	113·1(3)
H(142)–C(14)–H(143)	95·1(3)	C(23)–C(22)–H(222)	114·9(2)
C(13)–C(15)–H(151)	111·0(3)	C(23)–C(24)–H(24)	114·2(3)
C(13)–C(15)–H(152)	110·8(3)	C(25)–C(24)–H(24)	124·7(3)
C(13)–C(15)–H(153)	111·4(2)	C(24)–C(25)–H(25)	118·9(3)
H(151)–C(15)–H(152)	110·4(4)	C(26)–C(25)–H(25)	121·2(2)
H(151)–C(15)–H(153)	105·1(4)	C(25)–C(26)–H(26)	119·9(2)
H(152)–C(15)–H(153)	107·9(4)	C(27)–C(26)–H(26)	120·0(3)
C(13)–C(16)–H(161)	108 1(3)	C(26)–C(27)–H(27)	123·6(3)
C(13)–C(16)–H(162)	109·8(3)	C(28)–C(27)–H(27)	116·5(3)
C(13)–C(16)–H(163)	100·9(3)	C(27)–C(28)–H(28)	122·9(2)
H(161)–C(16)–H(162)	107·6(3)	C(23)–C(28)–H(28)	116·1(3)
H(161)–C(16)–H(163)	111·7(4)		

TABLE 4

Displacements (Å) from their mean planes of the atoms belonging to:

(*a*) The thiamorpholine ring
S(4) 0·316, N(1) −0·118, C(2) 0·195, C(3) −0·298, C(5) −0·286, C(6) 0·190

(*b*) The β-lactam system
N(4) −0·005, C(6) 0·004, C(7) −0·004, C(8) 0·003, O(9) 0·001

(*c*) The benzene ring
C(23) 0·005, C(24) −0·004, C(25) 0·000, C(26) 0·003, C(27) −0·002, C(28) −0·002

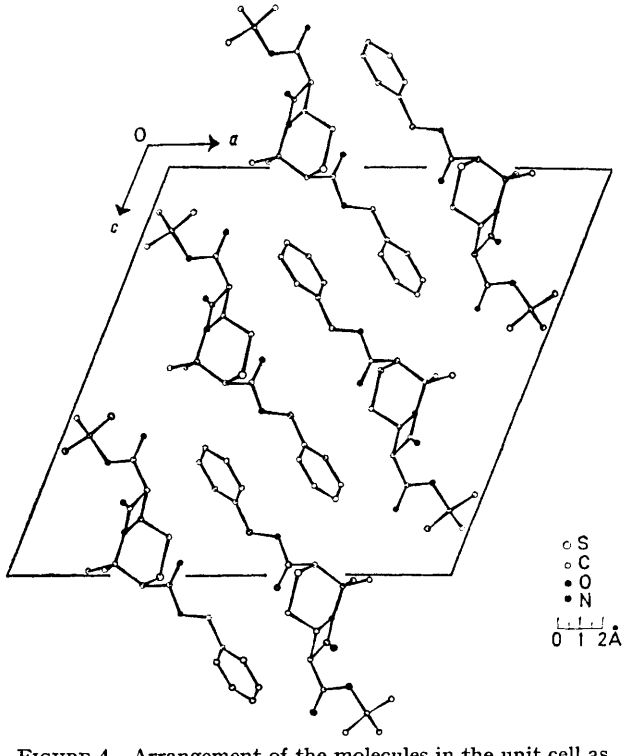


FIGURE 4 Arrangement of the molecules in the unit cell as seen along the [010] direction

View Article Online

Published on 01 January 1973. Downloaded by Michigan State University on 19/01/2016 02:17:25.

ance.[17] Sweet and Dahl have recently suggested that there is a correlation between biological activity and the hybridisation state of the ring nitrogen atoms N(1). In the five biologically active compounds so far studied at all accurately, N(1) is the apex of a pyramid raised 0·2—0·4 Å above the atoms attached to it. In our compound, N(1) is in a more nearly planar environment, only 0·067 Å above the attached atoms, very similar to the distance, 0·065 Å, found by Sweet and Dahl in the inactive Δ2 cephalosporin derivative they studied. However the number of structures so far measured in the active and inactive groups is too small for any firm statistically significant deduction to be made.

Figure 4 shows the arrangement of the molecules in the crystal as seen along the [010] direction. The molecule is essentially linear and lies nearly parallel to one of the diagonals of the *ac* plane, thus accounting for the short *b* axis dimension. Calculation of the intermolecular contact distances showed that none of them is significantly shorter than the sum of the van der Waal's radii of the corresponding atoms.

We thank O. J. R. Hodder for help in carrying out computations and for many useful discussions, and Mrs. S. Cutfield for help with the diagrams.

[2/1058 *Received*, 10*th May*, 1972]

[17] J. Donohue, L. R. Lavine, and J. S. Rollett, *Acta Cryst.*, 1956, **9**, 655.