

Ethyl 2-Amino- $\alpha$ -(*E*-methoxyimino)-4-thiazoleacetate

BY G. LAURENT, F. DURANT\* AND G. EVRARD

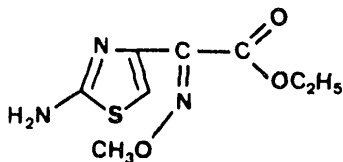
Laboratoire de Chimie Moléculaire Structurale, Facultés Universitaires de Namur, 61 rue de Bruxelles, B-5000 Namur, Belgium

(Received 1 November 1980; accepted 1 December 1980)

**Abstract.**  $C_8H_{11}N_3O_3S$ ,  $M_r = 229.3$ , triclinic,  $P\bar{1}$ ,  $a = 8.344$  (5),  $b = 10.476$  (5),  $c = 8.246$  (5) Å,  $\alpha = 103.41$  (5),  $\beta = 124.03$  (5),  $\gamma = 94.56$  (5)°,  $D_m = 1.35$  (2),  $D_c = 1.36$  Mg m<sup>-3</sup>,  $Z = 2$ ,  $T = 294$  K.  $R = 0.074$  for 1703 reflexions. The aminothiazolyl and methoxyimino groups are nearly coplanar and perpendicular to the carboxyl group. The molecules form centrosymmetric dimers linked through the aminothiazolyl groups; moreover, each molecule is hydrogen bonded to two neighbours through the exocyclic amine and carbonyl groups.

**Introduction.** Cephalosporins characterized by an oxyimino group in the C<sub>7</sub> side chain exhibit potent antibiotic activity when in the *syn* configuration while the *anti* isomers display very low antibacterial power (10 to 100 less active). This is the case, among others, for cefuroxime (O'Callaghan, Sykes, Ryan, Foord & Muggleton, 1976) and cefotaxime (Bucourt, Heymès, Lutz, Pénasse & Perronnet, 1977, 1978) now commercially available.

To disclose the conformational differences between the two isomers, we have undertaken an X-ray crystallographic study of both *syn* and *anti* oxyimino cephalosporins. On account of the difficulties encountered in the crystallization of such cephalosporins, we began by the study of the opposite side chains with the cephem nucleus excluded. In this work, we report the structural features of the title compound corresponding to the *anti* inactive isomer of cefotaxime:



and we compare them with those of the *syn* derivative (Laurent, Durant & Evrard, 1981).

Crystals were obtained by evaporation of an ether solution. The space group was determined from photographs. Final cell dimensions and intensities were

\* To whom correspondence should be addressed.

Table 1. Instrumental settings for the data collection

Crystal size: 0.32 × 0.25 × 0.18 mm  
Source: Cu K $\alpha$ ;  $\lambda = 1.54178$  Å  
Graphite monochromator  
 $2 \leq \theta \leq 72^\circ$   
 $\Delta 2\theta = 0.60 + 0.30 \operatorname{tg} \theta$  (°)  
Aperture = 2.5 + 0.5 tg  $\theta$  (mm)  
Confidence level: 2.5 $\sigma$ , where  $\sigma^2 = S + B + (0.03S)^2$ ,  $S$  being the scan and  $B$  the background count  
Number of independent reflexions: 2213  
Total observed: 1703

Table 2. Final coordinates ( $\times 10^4$ , for H  $\times 10^3$ ) with e.s.d.'s in parentheses and  $U_{eq}$  values ( $\text{\AA}^2 \times 10^4$ , for H  $\times 10^3$ )

$$U_{eq} = (U_{11} \cdot U_{22} \cdot U_{33})^{1/3}$$

	x	y	z	$U_{eq}$
S(1)	5771 (2)	1488 (1)	8311 (3)	663
C(2)	5361 (7)	3077 (5)	8880 (9)	561
N(3)	6714 (8)	4217 (5)	9524 (11)	874
N(4)	3689 (6)	3060 (4)	8679 (7)	527
C(5)	2652 (7)	1728 (5)	8050 (8)	474
C(6)	3547 (8)	768 (5)	7797 (9)	572
C(7)	715 (7)	1534 (5)	7692 (8)	498
N(8)	-426 (7)	484 (4)	7432 (7)	599
O(9)	377 (6)	-623 (4)	7486 (7)	672
C(10)	-976 (12)	-1750 (7)	7192 (13)	766
C(11)	-205 (8)	2719 (5)	7589 (10)	581
O(12)	-225 (6)	3396 (4)	8946 (7)	859
O(13)	-990 (7)	2891 (5)	5780 (8)	888
C(14)	-2014 (14)	4025 (9)	5353 (14)	1192
C(15)	-4107 (17)	3414 (11)	3981 (18)	1535
H(31)	653 (8)	499 (6)	1007 (9)	72
H(32)	752 (9)	414 (6)	941 (9)	72
H(61)	311 (7)	-8 (5)	741 (8)	57
H(101)	-114 (9)	-152 (6)	847 (9)	80
H(102)	-218 (9)	-197 (2)	598 (10)	80
H(103)	-25 (8)	-258 (6)	745 (9)	80

measured on a Nonius CAD-4 four-circle computer-controlled diffractometer. The instrumental settings are given in Table 1. No corrections were made for absorption.

The structure was solved with *MULTAN* (Germain, Main & Woolfson, 1971). All heavy atoms were found in the most probable *E* map. Refinement was by

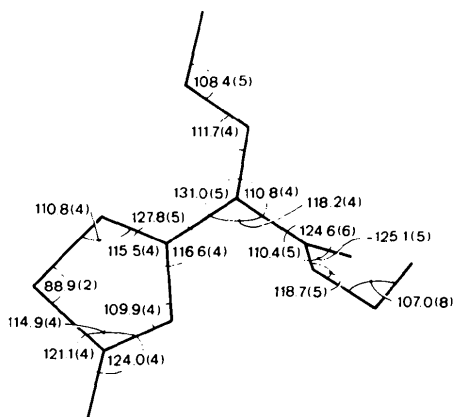
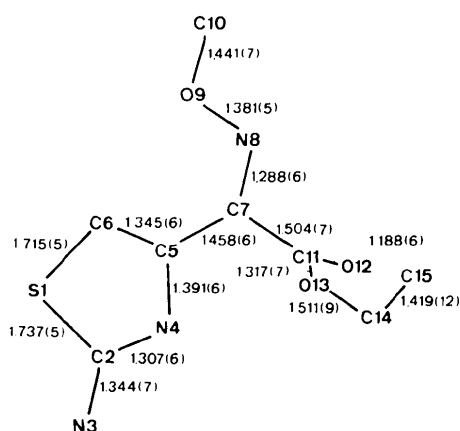


Fig. 1. Atom numbering, bond lengths (Å) and angles (°) with e.s.d.'s in parentheses, H atoms excepted.

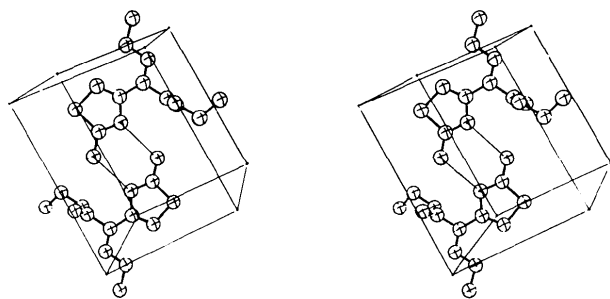


Fig. 2. Stereoview of the unit cell.

full-matrix least squares (Sheldrick, 1976). All H atoms except those on C(14) and C(15) were located on a difference synthesis. With anisotropic temperature factors for all non-H atoms and isotropic for H (equal to those of the parent atom), the final  $R = \sum |F_o| - |F_c| / \sum |F_o| = 0.074$  for the observed reflexions. The final coordinates are given in Table 2. Fig. 1 gives the

atom numbering, bond lengths and angles. A stereoview of the cell contents is shown in Fig. 2.\*

**Discussion.** Within experimental deviations, each aminothiazolyl, oxyimino and carboxyl group is planar (Table 3). Moreover the first two groups are nearly coplanar; the angle between their mean planes is  $13.4^\circ$  and C(5)–C(7) is shortened [1.458 (6) Å] suggesting conjugation between the thiazolyl ring and the methoxyimino group as in the *syn* isomer [1.456 (3) Å]. An intramolecular hydrogen-bond-like interaction [C(6)–H(61)···O(9)] seems to stabilize the molecule in a conformation different from that found in the *syn* derivative. In the latter, the oxyimino and carboxyl groups are inverted by rotation of  $180^\circ$  around C(5)–C(7) (Table 4); therefore, such an interaction cannot be allowed from C(6)–H(61) to O(13) or O(12) because the steric hindrance around O(9) prevents the carboxyl from being coplanar with the thiazolyl group.

The molecules are held together by hydrogen bonds (Table 5) and form centrosymmetric dimers (Fig. 2):

\* Lists of structure factors and anisotropic thermal parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35827 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 3. Deviations from mean planes and angles between these planes

Deviations (Å)

(1) Plane through S(1), C(2), N(3), N(4), C(5) and C(6): aminothiazolyl group

S(1)	−0.010	N(4)	−0.008
C(2)	−0.012	C(5)	0.002
N(3)	0.015	C(6)	0.013

(e.s.d. 0.012 Å)

(2) Plane through C(5), C(7), N(8), O(9) and C(11): oxyimino group

C(5)	0.001	O(9)	−0.007
C(7)	0.003	C(11)	−0.006
N(8)	0.009		

(e.s.d. 0.006 Å)

(3) Plane through C(7), C(11), O(12) and O(13): carboxyl group

C(7)	−0.001	O(12)	−0.001
C(11)	0.002	O(13)	−0.001

(e.s.d. 0.001 Å)

Angles (°)

Planes	This work	<i>syn</i> derivative
1–2	13.4	18.3
2–3	77.1	78.4
1–3	82.3	67.2

(e.s.d.  $<0.4^\circ$ )

Table 4. Mean torsion angles compared with those of the *syn* derivative

	E.s.d.'s are < 0.8°.	
	This work	<i>syn</i> derivative*
N(4)–C(5)–C(7)–N(8)	–167.6°	16.5°
N(4)–C(5)–C(7)–C(11)	12.5	–163.7
C(6)–C(5)–C(7)–N(8)	14.2	–161.1
C(6)–C(5)–C(7)–C(11)	–165.8	18.8
C(5)–C(7)–N(8)–O(9)	–1.0	177.4
C(5)–C(7)–C(11)–O(12)	–103.3	101.7
C(5)–C(7)–C(11)–O(13)	77.0	–76.8
N(8)–C(7)–C(11)–O(12)	76.7	–78.5
N(8)–C(7)–C(11)–O(13)	–103.0	103.0
O(9)–N(8)–C(7)–C(11)	179.0	–2.5
C(7)–N(8)–O(9)–C(10)	180.0	–176.4

The difference results from the inversion of the methoxyimino and carboxyl groups by rotation ( $\sim 180^\circ$ ) around C(5)–C(7).

\* Laurent, Durant & Evrard (1981).

N(3)–H(31)···N(4) [N(3)···N(4)( $-x + 1, -y + 1, -z + 2$ ) 3.032 (6) Å]. Moreover, the carbonyl groups are connected through the exocyclic amines of neighbouring dimers: O(12)···H(32)–N(3) [O(12)···N(3)( $x + 1, y, z$ ) 3.002 (6) Å].

*Acta Cryst.* (1981). **B37**, 974–976

## Ethyl 2-Amino- $\alpha$ -(*E*-methoxyimino)-4-thiazoleacetate Hydrobromide

BY G. LAURENT, C. PARMENTIER, G. EVRARD AND F. DURANT\*

Laboratoire de Chimie Moléculaire Structurale, Facultés Universitaires de Namur, 61 rue de Bruxelles, B-5000 Namur, Belgium

(Received 27 October 1980; accepted 1 December 1980)

**Abstract.** C<sub>8</sub>H<sub>12</sub>N<sub>3</sub>O<sub>3</sub>S<sup>+</sup>.Br<sup>–</sup>,  $M_r = 310.2$ , monoclinic,  $P2_1/c$ ,  $a = 10.812$  (5),  $b = 8.895$  (5),  $c = 13.385$  (5) Å,  $\beta = 109.34$  (5)°,  $D_m = 1.71$  (2),  $D_c = 1.70$  Mg m<sup>–3</sup>,  $Z = 4$ ,  $T = 294$  K;  $R = 0.048$  for 2093 reflexions. The three characteristic groups, amino-thiazolyl, oxyimino and carboxyl, are nearly coplanar. The molecules are linked to each other by hydrogen bonds through exocyclic amines and Br<sup>–</sup> ions.

**Introduction.** An X-ray crystallographic study of the title compound was undertaken to disclose any conformational change which might have occurred in the change from the free base (Laurent, Durant & Evrard, 1981) to the thiazolium salt.

\* To whom correspondence should be addressed.

0567-7408/81/040974-03\$01.00

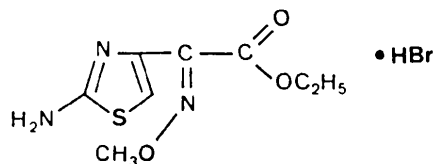
Table 5. Hydrogen-bond lengths (Å) and angles (°) with e.s.d.'s

N(3)–H(31)	0.90 (6)	H(32)–N(3)–C(2)	117 (5)
N(3)–H(32)	0.74 (6)	H(32)–N(3)–H(31)	128 (6)
C(6)–H(61)	0.84 (5)	H(61)–C(6)–S(1)	122 (4)
H(31)–N(3)–C(2)	115 (4)	H(61)–C(6)–C(5)	127 (4)

We thank Dr J. Perronnet (Roussel–Uclaf, Romainville, France) for providing the sample.

### References

- BUCOURT, R., HEYMÈS, R., LUTZ, A., PÉNASSE, L. & PERRONNET, J. (1977). *C. R. Acad. Sci. Paris Sér. D.* **284**, 1847–1849.
- BUCOURT, R., HEYMÈS, R., LUTZ, A., PÉNASSE, L. & PERRONNET, J. (1978). *Tetrahedron*, **34**, 2233–2243.
- GERMAIN, G., MAIN, P. & WOLFSON, M. M. (1971). *Acta Cryst.* **A27**, 368–376.
- LAURENT, G., DURANT, F. & EVRARD, G. (1981). *Cryst. Struct. Commun.* In the press.
- O'CALLAGHAN, C. H., SYKES, R. B., RYAN, D. M., FOORD, R. D. & MUGGLETON, P. W. (1976). *J. Antibiot.* **29**, 29.
- SHELDRIK, G. M. (1976). *SHELX 76* system of computing programs. Univ. of Cambridge, England.



Suitable crystals were obtained from different solutions: methanol/water, *n*-butanol/water/methanol, ethanol/water/acetone and ethyl acetate. They all have the same lattice parameters. The space group was determined from photographs. Final cell dimensions and intensities were measured on a Nonius CAD-4 four-circle computer-controlled diffractometer. No absorption corrections were made. Table 1 lists the instrumental settings for the data collection.

© 1981 International Union of Crystallography