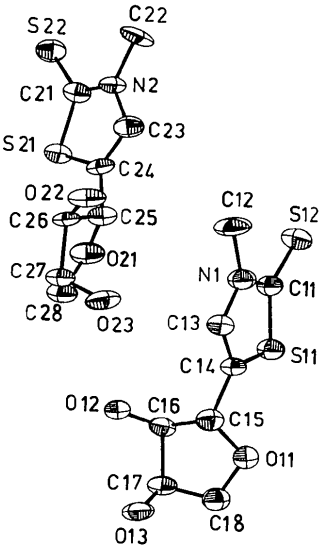

Fig. 1. View along **a** of the independent molecules in the asymmetric unit.

The endocyclic C—O bonds [C(15)—O(11) = 1·452 (15) and O(21)—C(28) = 1·469 (15) Å] are asymmetric, showing the anomeric effect (Jeffrey & French, 1978), a normal feature of this group. The average values of the C—C—C, C—C—O and C—O—C endocyclic angles are 102·3 (10), 106·4 (10) and 107·7 (9)° respectively.

The crystal structure is stabilized by van der Waals contacts with specific interactions between the O(12) and C(13) atoms of one molecule and the O(23) atom of another [O(12)···O(23) = 2·814 (10); O(23)···C(13) = 3·239 (16) Å].

We thank Professor Fernandez-Bolaños for supplying the crystals, and the Comision Asesora de Investigación Científica y Técnica for financial support.

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Structure of 7-Methyl-8-oxo-7,8-dihydroguanosine Monohydrate

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(*Received* 21 *December* 1988; *accepted* 6 *March* 1989)

Abstract. 2-Amino-7-methyl-9-(β-D-ribofuranosyl)-1*H*,9*H*-purine-6,8-dione monohydrate, $C_{11}H_{15}N_5O_6.H_2O$, $M_r = 331{\cdot}29$, orthorhombic, $P2_12_12_1$, $a = 6{\cdot}9811$ (6), $b = 9{\cdot}808$ (2), $c = 20{\cdot}61$ (2) Å, $V = 1411{\cdot}1$ (13) Å^3, $Z = 4$, $D_x = 1{\cdot}559$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1{\cdot}54178$ Å, $\mu = 10{\cdot}825$ cm^{-1}, $F(000) = 696$, $T = 295$ K, $R = 0{\cdot}0296$ for 2472 reflections ($F \geq 4\sigma_F$). The sugar conformation and puckering parameters are ^2E (C2′-*endo*), $P = 161{\cdot}8°$ and $\tau_m = 39{\cdot}2°$. The side chain is *gauche–gauche*. The glycosidic torsion angle is 65·1 (2)° corresponding to the *syn* conformation which is stabilized by the O5′—H···N3 intramolecular hydrogen bond. The purine ring is nearly planar [r.m.s. deviation: 0·014 (2) Å]; the dihedral angle between the pyrimidine and imidazole rings is 1·14 (8)°.

Introduction. Certain ribonucleosides of guanine substituted at C8 have been shown to stimulate the immune system, and have been extensively studied as

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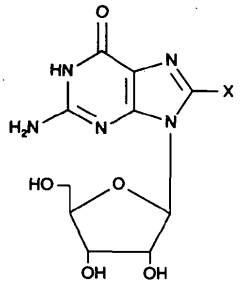
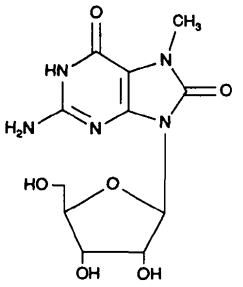
modulators of B-cell activation (Weigle, 1987). The most studied derivatives include 8-bromoguanosine [(1), first prepared in our laboratory by Holmes & Robins (1964)], 8-mercaptoguanosine [(2) (Holmes & Robins, 1964)] and 7-methyl-8-oxo-7,8-dihydroguanosine [(3), first reported from our laboratory by Rizkalla, Robins & Broom (1969)]. These low-molecular-weight compounds have been shown to act as intracellular mitogens in murine splenic B lymphocytes (Goodman & Weigle, 1984) and to augment the proliferation and differentiation of murine T cells in the presence of other stimulating signals (Ahmad & Mond, 1986; Feldbush & Ballas, 1985). 7-Methyl-8-oxo-7,8-dihydroguanosine has been shown to be a more potent B-cell mitogen and a more potent adjuvant for humoral immune responses than either 8-bromo- or 8-mercaptoguanosine (Goodman & Hennen, 1986). More recently, (1) was shown to activate murine natural killer (NK) cells and macrophages by induction of interferon production (Koo, Jewell, Manyak, Sigal & Wicker, 1988). This study investigates the solid-state structure of (3) for comparison with the structures of other 8 substituted guanosines.



(1) X = Br
(2) X = SH



(3)

Experimental. The title compound (3) was synthesized by the procedure of Kini, Hennen & Robins (1987). A lone crystal cluster formed from an aqueous solution in a capped bottle over an extended period of time. Table 1 summarizes data collection and refinement. All non-H atoms were obtained from *SHELXS*86 (Sheldrick, 1986)]. All H atoms were located in a difference map as peaks of density 0·38–0·78 e Å^{-3} at $R = 0{\cdot}056$. All positional parameters, anisotropic thermal parameters for non-H atoms and isotropic thermal parameters for H atoms were refined with *SHELX*76 (Sheldrick, 1976). Scattering factors and anomalous-dispersion corrections were taken from *International Tables for X-ray Crystallography* (1974) except those of H which were taken from Stewart, Davidson & Simpson (1965). Data were reduced with *SDP-Plus* (Frenz, 1985); least-squares-planes program from Cordes (1983); figures were drawn with *ORTEP*II (Johnson, 1976).*

Table 1. *Crystallographic summary for* (3)

(*a*) Data collection (295 K)[i,ii]	
Mode	ω–2θ scan
Scan range (°)	$0{\cdot}80 + 0{\cdot}15\tan\theta$
Background	Scan 0·25 times scan range before and after scan
Scan rate (° min^{-1})	1·4–16·49
Exposure time (h)	74·6
Stability correction	Not applied
2θ range (°)	3·0–152·0
Range in *hkl*, min.	0, −12, −25
max.	8, 12, 25
Total reflections, measured, unique	6309, 2925
R_{int}	0·0226
Crystal dimensions (mm)	0·38 × 0·145 × 0·025
Crystal volume (mm^3)	0·00138
Crystal faces	{001}; {010}; (100); ($\bar{1}\bar{2}$1); ($\bar{1}$21)
Transmission-factor range	0·791–0·973
(*b*) Structure refinement[iii]	
Reflections used ($F \geq 4\sigma_F$)	2472
No. of variables	277
Extinction parameter	5·7 (8) × 10^{-7}
Goodness of fit, S	1·255
R, wR	0·0296, 0·0374
R for all data	0·0439
Max., av. Δ/σ	0·0045, 0·0004
Max., min. $\Delta\rho$ in ΔF map (e Å^{-3})	0·31, −0·20

Notes: (i) Unit-cell parameters were obtained by least-squares refinement of the setting angles of 25 reflections with $50{\cdot}5 < 2\theta < 54{\cdot}2°$. (ii) Enraf–Nonius CAD-4 diffractometer with a graphite monochromator was used. Data reduction was accomplished with the *SDP-Plus* software (Frenz, 1985). Crystal and instrument stability were monitored by remeasurement of three check reflections (245, 41$\bar{2}$, 1$\bar{5}$4) every hour. A linear fit of the intensities of these reflections was used to correct the data. (iii) Function minimized was $\sum w(|F_o| - |F_c|)^2$, where $w^{-1} = (\sigma_F^2 + 0{\cdot}0004F^2)$. $\sigma_F = F\sigma_I/2I$; $\sigma_I = (N_{pk} + N_{bg1} + N_{bg2})^{1/2}$.

Discussion. The atomic coordinates are listed in Table 2; bond lengths, bond angles and selected torsion angles are listed in Table 3.

Glycosidic linkage. The molecular conformation and atom labeling are illustrated in Fig. 1. The aglycon is *syn* to the ribose ring with $\chi = 65{\cdot}1\ (2)°$ (O4′—C1′—N9—C4) and is stabilized by the O5′—HO5′···N3 intramolecular hydrogen bond. These features have been observed in other 8-substituted guanosines such as 8-chloro (Birnbaum, Lassota & Shugar, 1984), 8-bromo- (Tavale & Sobell, 1970) and 8-methylguanosine (Hamada, Honda, Fujii, Fujiwara & Tomita, 1985). In 2-oxo-1-(β-D-ribofuranosyl)-4-imidazoline-4-carboxylic acid

* Lists of anisotropic thermal parameters, bond lengths and angles involving H atoms, torsion angles, least-squares planes and structure-factor amplitudes have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 52008 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. *Positional and isotropic thermal parameters* (Å^2) *for all atoms in* (3)

For non-H atoms, $U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij}a_i^*a_j^*\mathbf{A}_{ij}$, where $\mathbf{A}_{ij}$ is the dot product of the ith and jth direct-space unit-cell vectors.

	x	y	z	U_{eq}/U
N1	0·3524 (3)	0·2084 (2)	0·52105 (6)	0·0343 (4)
C2	0·3486 (3)	0·1774 (2)	0·45630 (8)	0·0312 (5)
N3	0·3478 (2)	0·27081 (13)	0·40995 (6)	0·0308 (4)
C4	0·3617 (3)	0·3995 (2)	0·43294 (7)	0·0288 (4)
C5	0·3679 (3)	0·4389 (2)	0·49692 (8)	0·0327 (5)
C6	0·3606 (3)	0·3405 (2)	0·54653 (8)	0·0332 (5)
N7	0·3816 (3)	0·5811 (2)	0·49846 (7)	0·0393 (5)
C8	0·3833 (3)	0·6305 (2)	0·43680 (9)	0·0363 (5)
N9	0·3733 (2)	0·51584 (13)	0·39551 (6)	0·0319 (4)
N10	0·3440 (3)	0·0452 (2)	0·43959 (9)	0·0445 (5)
O11	0·3617 (3)	0·35643 (15)	0·60634 (5)	0·0478 (5)
C12	0·3907 (5)	0·6672 (2)	0·55614 (11)	0·0552 (8)
O13	0·3928 (3)	0·74976 (13)	0·41944 (7)	0·0513 (5)
C1′	0·3533 (3)	0·5280 (2)	0·32570 (8)	0·0311 (4)
C2′	0·4805 (3)	0·4342 (2)	0·28526 (8)	0·0305 (5)
C3′	0·3688 (3)	0·4302 (2)	0·22150 (8)	0·0345 (5)
C4′	0·1596 (3)	0·4301 (2)	0·24440 (8)	0·0330 (5)
C5′	0·0688 (3)	0·2905 (2)	0·24983 (10)	0·0401 (5)
O2′	0·6711 (2)	0·4803 (2)	0·28101 (6)	0·0418 (4)
O3′	0·4200 (2)	0·5511 (2)	0·18704 (7)	0·0470 (5)
O4′	0·1625 (2)	0·49244 (13)	0·30877 (5)	0·0349 (3)
O5′	0·1877 (2)	0·19530 (13)	0·28306 (6)	0·0420 (4)
O*W*	0·3633 (2)	−0·01500 (15)	0·60215 (6)	0·0420 (4)
H1	0·349 (3)	0·129 (2)	0·5522 (11)	0·046 (6)
H10*A*	0·372 (4)	0·027 (2)	0·4009 (12)	0·051 (7)
H10*B*	0·360 (5)	−0·019 (3)	0·467 (2)	0·079 (9)
H12*A*	0·470 (5)	0·629 (3)	0·586 (2)	0·072 (9)
H12*B*	0·407 (5)	0·762 (4)	0·5411 (14)	0·085 (10)
H12*C*	0·277 (6)	0·671 (4)	0·578 (2)	0·113 (14)
H1′	0·376 (3)	0·622 (2)	0·3150 (9)	0·034 (5)
H2′	0·485 (3)	0·343 (2)	0·3048 (10)	0·031 (5)
H3′	0·403 (3)	0·344 (2)	0·1944 (10)	0·034 (5)
H4′	0·087 (3)	0·486 (2)	0·2171 (10)	0·038 (5)
H5′*A*	−0·068 (4)	0·299 (2)	0·2752 (11)	0·050 (6)
H5′*B*	0·042 (3)	0·254 (2)	0·2059 (10)	0·040 (6)
HO2′	0·679 (4)	0·547 (3)	0·2568 (14)	0·058 (7)
HO3′	0·337 (4)	0·578 (3)	0·1630 (13)	0·053 (7)
HO5′	0·194 (4)	0·215 (3)	0·3265 (12)	0·057 (7)
HO*WA*	0·289 (7)	0·002 (5)	0·635 (2)	0·122 (14)
HO*WB*	0·488 (6)	−0·017 (4)	0·627 (2)	0·091 (10)

Table 3. *Bond lengths* (Å), *bond angles* (°) *and selected torsion angles* (°) *in* (3)

1	2	3	1—2	1—2—3
C2	N1	C6	1·369 (2)	124·89 (14)
N3	C2	N10	1·323 (2)	118·9 (2)
N3	C2	N1		123·4 (2)
N10	C2	N1	1·342 (2)	117·7 (2)
C4	N3	C2	1·352 (2)	113·15 (14)
C5	C4	N9	1·375 (2)	107·59 (14)
C5	C4	N3		126·93 (14)
N9	C4	N3	1·379 (2)	125·49 (14)
C6	C5	N7	1·407 (2)	132·1 (2)
C6	C5	C4		120·2 (2)
N7	C5	C4	1·398 (2)	107·71 (14)
O11	C6	N1	1·242 (2)	119·2 (2)
O11	C6	C5		129·4 (2)
N1	C6	C5	1·400 (2)	111·35 (15)
C8	N7	C12	1·360 (3)	123·7 (2)
C8	N7	C5		109·57 (14)
C12	N7	C5	1·459 (3)	126·7 (2)
N9	C8	O13	1·412 (2)	126·0 (2)
N9	C8	N7		106·18 (15)
O13	C8	N7	1·225 (2)	127·9 (2)
C1′	N9	C4	1·450 (2)	128·11 (13)
C1′	N9	C8		122·47 (14)
C4	N9	C8		108·94 (14)
C2′	C1′	O4′	1·527 (2)	105·28 (13)
C2′	C1′	N9		115·82 (14)
O4′	C1′	N9	1·421 (2)	108·29 (13)
C3′	C2′	O2′	1·529 (3)	115·92 (14)
C3′	C2′	C1′		100·80 (14)
O2′	C2′	C1′	1·408 (2)	112·97 (14)
C4′	C3′	O3′	1·534 (3)	113·06 (15)
C4′	C3′	C2′		102·79 (13)
O3′	C3′	C2′	1·427 (2)	106·19 (15)
C5′	C4′	O4′	1·513 (3)	108·49 (14)
C5′	C4′	C3′		114·9 (2)
O4′	C4′	C3′	1·461 (2)	105·44 (14)
O5′	C5′	C4′	1·425 (2)	112·6 (2)
C1′	O4′	C4′		109·79 (13)

χ	C4	N9	C1′	O4′	65·1 (2)	θ_3	C2′	C1′	O4′	C4′	−24·0 (2)
χ'	C8	N9	C1′	O4′	−106·0 (2)	θ_4	O4′	C1′	C2′	C3′	38·1 (2)
θ_0	C1′	C2′	C3′	C4′	−37·2 (2)	φ_{OO}	O4′	C4′	C5′	O5′	−70·5 (2)
θ_1	C2′	C3′	C4′	O4′	24·2 (2)	φ_{CO}	C3′	C4′	C5′	O5′	47·2 (2)
θ_2	C3′	C4′	O4′	C1′	−0·3 (2)						

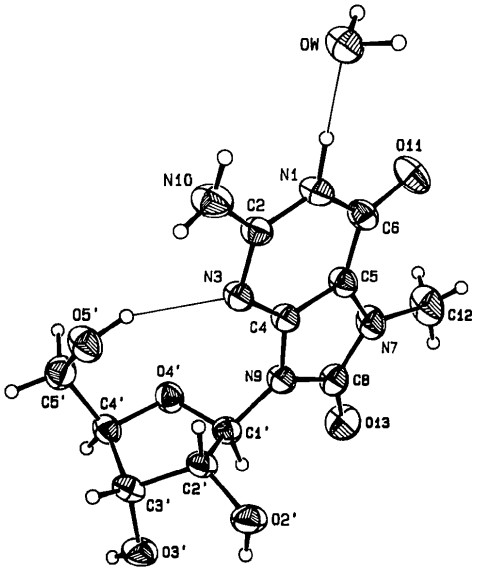


Fig. 1. Thermal-ellipsoid plot of (3) illustrating atom labeling, molecular conformation and intramolecular hydrogen bonding. The ellipsoids are drawn at the 50% probability level.

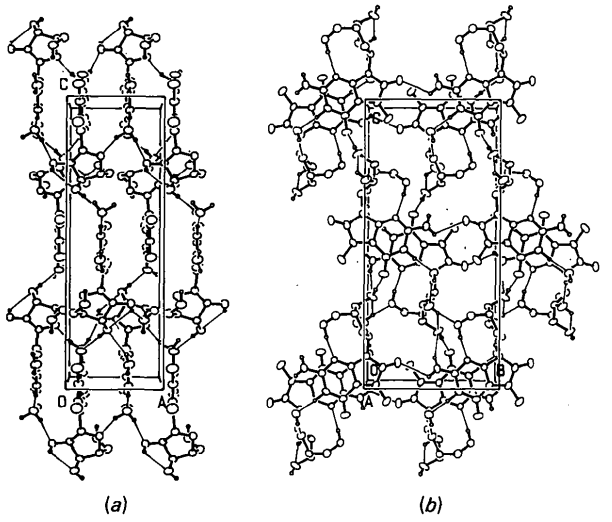
(Larson, Cottam & Robins, 1988) a similar conformation [χ = 55·1 (2)°] is observed without the benefit of an O5′-to-base intramolecular hydrogen bond. Thus, even the small size of the 8-oxo group is sufficient to favor the *syn* conformation. It has been suggested that the B-cell activity of 8-bromoguanosine is a result of its confinement to the *syn* conformation (Katze, 1985) and the parallel of activity and conformation of (3) to (1) supports this hypothesis. The glycosyl bond length [1·450 (2) Å] is not significantly different from those observed in the 8-chloro, 8-methyl and 8-bromo derivatives [1·458 (3), 1·458 (5) and 1·474 (9) Å] or in the imidazoline [1·449 (2) Å].

The aglycon moiety. The imidazole ring is planar [r.m.s.d.: 0·005 (1) Å]; the pyrimidine ring possesses a slight boat conformation [r.m.s.d.: 0·012 (1) Å; N3 and C6 are up]. The dihedral angle between these planes is 1·14 (8)°; the overall r.m.s.d. of the purine ring is 0·014 (1) Å. Atom C1′ is 0·128 (2) Å above the imidazole plane suggesting some sp^3 hybridization of N9, whereas C12 is in the plane [0·001 (2) Å deviation] suggesting only sp^2 character for N7. In the imidazoline structure (Larson *et al.*, 1988), C1′ is

in the imidazole plane and the N1—C2 bond [corresponding to N9—C8 in (3)] is 0·03 Å shorter than in (3). The bond lengths in the aglycon are within two e.s.d.'s of those observed in the structure of the cationic molecule of 7-methylguanosine (Yamagata, Fukumoto, Hamada, Fujiwara & Tomita, 1983); however, that structure exhibited average e.s.d.'s of 0·024 Å. The principal effect of the 8-oxo substituent is the elongation of the C8—N9 bond and the reduction of the N7—C8—N9 angle when compared to 7-methylguanosine. Annular and substituent bond angles are within two e.s.d.'s (average e.s.d.'s in 7-methylguanosine were 1·5°) except for those of the ribose which differ by 4 and 6°. These differences probably result from the glycosidic conformation. In the two molecules of 7-methylguanosine, the N1-protonated molecule is *anti* while the non-protonated molecule is *syn*. The latter is very similar to (3) and the bond angles at N9 are likewise very similar.

Table 4. *Hydrogen bonding in* (3)

D—H···*A*			Symmetry of *A* relative to *D*	*d*(*D*···*A*) (Å)	*d*(H...*A*) (Å)	∠(*D*—H ···*A*) (°)
N1	H1	*OW*	*x*, *y*, *z*	2·757 (2)	1·75 (2)	174· (2)
N10	H10*A*	O3′	1·0 − *x*, *y* − 0·5, 0·5 − *z*	3·087 (2)	2·33 (2)	149· (2)
N10	H10*B*	O13	*x*, *y* − 1·0, *z*	2·948 (2)	2·49 (3)	115· (2)
O2′	HO2′	O5′	1·0 − *x*, 0·5 + *y*, 1·0 − *z*	2·677 (2)	1·91 (3)	154· (3)
O2′	HO2′	O3′	*x*, *y*, *z*	2·704 (2)	2·31 (3)	110· (2)
O3′	HO3′	O11	0·5 − *x*, 1·0 − *y*, *z* − 0·5	2·731 (2)	1·92 (3)	180· (3)
O5′	HO5′	N3	*x*, *y*, *z*	2·939 (2)	2·10 (3)	151· (2)
OW	*HOWA*	O2′	*x* − 0·5, 0·5 − *y*, 1·0 − *z*	2·778 (2)	1·92 (5)	166· (4)
OW	*HOWB*	O4′	*x* + 0·5, 0·5 − *y*, 1·0 − *z*	2·790 (2)	1·81 (4)	161· (3)



(*a*) (*b*)

Fig. 2. Crystal packing diagrams of (3) with water molecules included, C—H H atoms omitted and hydrogen bonds drawn as thin lines. (*a*) View along the *b* axis, illustrating the base stacking and the hydrogen-bond linking of molecules through the water along the *a* axis. (*b*) View along the *a* axis showing the partial base overlap.

The sugar moiety. The sugar is in the C2′-*endo* (^2E) conformation having phase angle of pseudorotation $P = 161·8°$ and amplitude of pucker $\tau_m = 39·2°$ (Altona & Sundaralingam, 1972), which are characteristic of *syn* nucleosides including those cited above (Hamada *et al.*, 1985). The C5′—O5′ side chain is in the requisite *gauche*$^-$–*gauche*$^+$ orientation to form the O5′···N3 intramolecular hydrogen bond. The bond lengths in the ribose moiety are normal as are the bond angles.

Packing. The hydrogen bonding is detailed in Table 4 and illustrated in the packing diagram of Fig. 2. The O5′···N3 intramolecular hydrogen bond is moderately strong in light of its geometrical parameters [*d*(O5′···N3) = 2·939 (2) Å], but apparently weaker than those found in 8-bromo- (Tavale & Sobell, 1970), 8-chloro- (Birnbaum *et al.*, 1984), 8-methyl- (Hamada *et al.*, 1985) and 7-methylguanosine (Yamagata *et al.*, 1983) (2·860, 2·845, 2·839 and 2·79 Å, respectively). The base moieties are nearly parallel to the *bc* plane [dihedral angle: 3·50 (2)°] and stacked around the 2_1 screw axes parallel to the *a* axis. The purine rings are only partially overlapped, pyrimidine-to-pyrimidine, with minimum interplanar contacts of 3·412 (3) Å on one side and 3·580 (3) Å on the other. The dihedral angle between stacked planes is 6·99 (3)°. The water molecule, which is a proton acceptor for N1, links molecules translated one unit along **a**. O4′, which infrequently participates in hydrogen bonding, acts as an acceptor for the water molecule. There is possibly a weak intramolecular hydrogen bond, O2′—HO2′···O3′, which results in bifurcation of the HO2′ hydrogen bonding. The very weak head-to-tail amino (N10) to 8-oxo (O13) interaction along the *b* axis is the only interbase hydrogen bonding in the structure.

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Structure d'un Nouvel Antibactérien: l'Acide Chloro-2 Dihydro-4,7 Éthyl-7 Oxo-4 Thiéno[2,3-*b*]pyridine Carboxylique-5

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(*Reçu le* 14 *décembre* 1988, *accepté le* 28 *mars* 1989)

Abstract. $C_{10}H_8ClNO_3S$, $M_r = 257{\cdot}7$, triclinic, $P\bar{1}$, $a = 18{\cdot}110\ (4)$, $b = 9{\cdot}076\ (2)$, $c = 7{\cdot}271\ (2)$ Å, $\alpha = 111{\cdot}29\ (2)$, $\beta = 100{\cdot}10\ (2)$, $\gamma = 94{\cdot}75\ (2)°$, $V = 1082$ Å^3, $Z = 4$, $D_m = 1{\cdot}57$, $D_x = 1{\cdot}583$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, Ni filter, $\mu = 4{\cdot}793$ mm^{-1}, $F(000) = 528$, $T = 298$ K, $R = 0{\cdot}049$ for 3451 observed reflections. The title compound, a powerful antibacterial agent, belongs to the well known quinolone family; bond lengths differ somewhat from those of oxolinic acid, another antibacterial agent, with the same 7-ethyl-4-oxopyridine-5-carboxylic acid moiety. The two independent molecules (I) and (II) of the title compound are very similar as far as bond lengths and angles are concerned. They give head-to-tail dimers with significant overlapping of their π clouds. Other intermolecular interactions are of the van der Waals type.

Introduction. L'acide oxolinique et, dans une moindre mesure, l'acide nalidixique ainsi que de nombreuses autres molécules possédant un noyau dihydro-4,7 éthyl-7 oxo-4 pyridine carboxylique-5, désignées sous le nom générique de quinolones, sont de puissants agents antibactériens mais présentent un spectre d'activité limité.

Ces composés causent un arrêt réversible de la synthèse de l'ADN par inhibition de l'ADN girase (Sugino, Peebles, Kreuzer & Cozzarelli, 1977; Gellert, Mizuuchi, O'Dea, Itoh & Tomizawa, 1977).

L'étude intensive entreprise sur les quinolones afin d'améliorer leur spectre d'activité a permis de développer plusieurs familles de composés (GESA XVIII, 1988; Crumplin, 1988). Nous nous sommes particulièrement intéressés à des dihydro-4,7 éthyl-7 oxo-4 thiéno[2,3-*b*]pyridines carboxylique-5 diversement substituées en position 2, en α de l'atome de soufre (Bompart, Giral, Malicorne & Puygrenier, 1987; Bompart, Giral & Malicorne, 1989).

Dans cette série, le dérivé chloré en position 2 du cycle thiényle se révèle être l'un des plus actifs par:

(*a*) Son activité bactéricide: la concentration minimale inhibitrice (CMI) vis-à-vis d' *E. coli*, de 1,56 μg ml^{-1}, est plus élevée que celle de l'acide nalidixique mais sensiblement moins que celle de l'acide oxolinique.

(*b*) Son inhibition de la biosynthèse de l'ADN (DI 50 = 42 μg ml^{-1}) est plus forte que celle des autres composés de la série et de l'acide nalidixique.

(*c*) Son activité vis-à-vis de l'ADN girase (DI 50 = 0,5 μg ml^{-1}) est plus grande que cells des autres composés de la série et presque autant que celle de l'acide nalidixique.

Ceci nous a conduits à aborder l'étude des relations structure–activité de cette famille de quinolones. Un de ses aspects réside dans l'étude des structures cristallines de cette série pour laquelle aucun résultat n'est disponible actuellement. Dans

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