Data collection: *XSCANS* (Siemens, 1994). Cell refinement: *XSCANS*. Data reduction: *SHELXTL* (Sheldrick, 1990*a*). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1990*b*). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *SHELXTL*. Software used to prepare material for publication: *SHELXTL*.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: CF1260). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1998). C**54**, 1911–1915

Three Isostructural Furosemide Prodrugs

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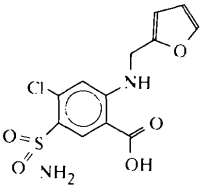
Abstract

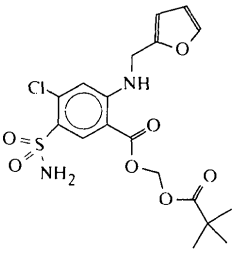
The structures of three furosemide prodrugs, pivaloyloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate, $C_{18}H_{21}ClN_2O_7S$, butyryloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate, $C_{17}H_{19}ClN_2O_7S$, and isobutyryloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate, $C_{17}H_{19}ClN_2O_7S$, have been determined; the crystals have been shown to be isostructural. The crystal structures are described and compared with that of a related prodrug. The dihedral angle between the two planar rings of each prodrug is close to 70°. The space group is $P\bar{1}$ in each case, and the molecules pack as dimers in infinite chains along one of the crystallographic axes.

Comment

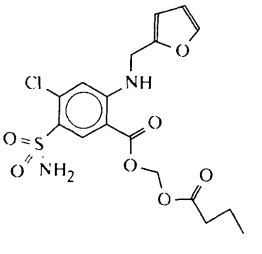
Furosemide (4-chloro-*N*-furfuryl-5-sulfamoylanthranilic acid), (I), is a strong diuretic agent used in hypertensive crisis. The compounds pivaloyloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate, (II), butyryloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate, (III), and isobutyryloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate, (IV), were synthesized and characterized as furosemide prodrugs (Prandi, Fagiolino, Manta, Llera *et al.*, 1992). The therapeutic activity of these prodrugs has been studied (Prandi, Fagiolino, Manta & Llera, 1992).



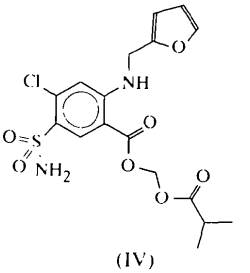
Furosemide (I)



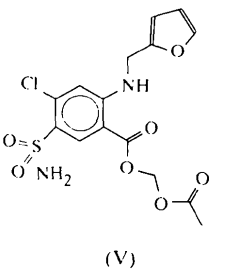
(II)



(III)



(IV)



(V)

The three molecules have the original furosemide skeleton in common, which contains a six-membered aromatic ring (atoms C1 to C6) with coplanar carboxylate and amine substituents (Lamotte *et al.*, 1978). The maximum deviations from this plane are for O1 in

the three molecules, with values of −0.091 (3) in (II), 0.105 (2) in (III) and 0.102 (2) Å in (IV) (Figs. 1, 2 and 3). As in acetyloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate, (V) (González *et al.* 1996), there is an intramolecular hydrogen bond connecting H1 and O1 in each of the three structures, as shown in Table 1.

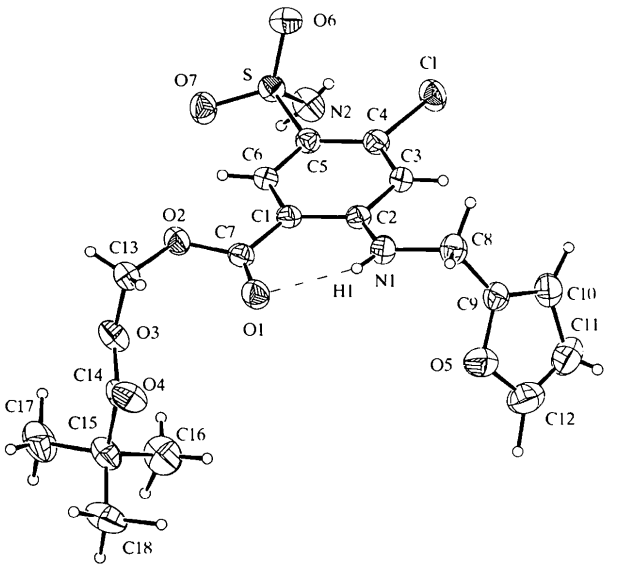


Fig. 1. Drawing of (II) with the intramolecular hydrogen bond depicted as a dashed line. All non-H-atom displacement ellipsoids are drawn at 30% probability.

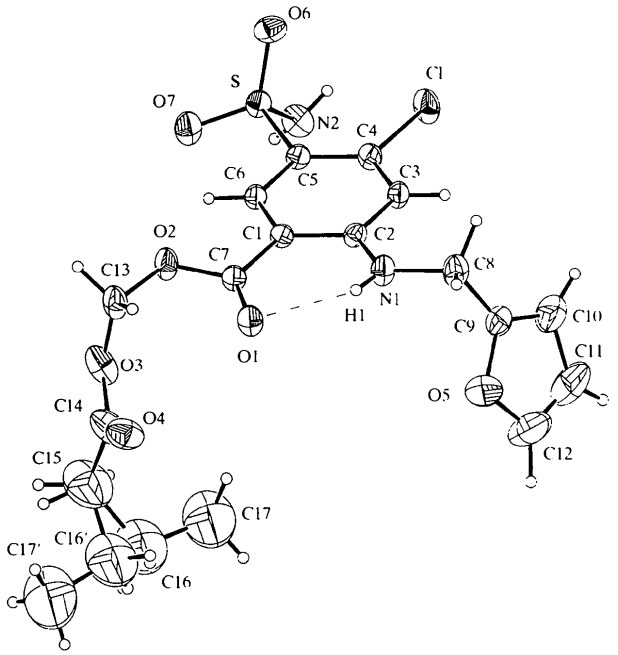


Fig. 2. Drawing of (III) with the intramolecular hydrogen bond depicted as a dashed line. Both disordered positions of the butyl chain are represented. All non-H-atom displacement ellipsoids are drawn at 30% probability.

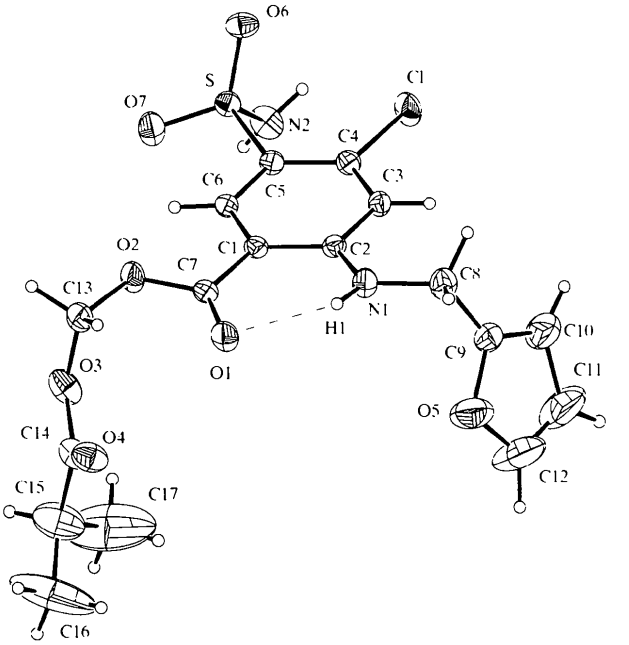


Fig. 3. Drawing of (IV) with the intramolecular hydrogen bond depicted as a dashed line. All non-H-atom displacement ellipsoids are drawn at 30% probability.

The molecules each contain a furan ring. The dihedral angle with the benzene ring has a value of 69.7 (2) in (II), 70.2 (2) in (III) and 71.3 (2)° in (IV). Owing to the rotational freedom around the N1—C8 and C8—C9 bonds, the similarity of these values was unanticipated, but may be related to the packing arrangements common to these structures. However, an equivalent dihedral angle of 67.6° is also seen in (V) (González *et al.*, 1996).

The only difference between the reported molecules is in the esterification. The unit cells of the three molecules are isostructural and their volumes are influenced by the ester groups. Molecule (II) exhibits the largest volume and (IV) the smallest. The previously studied compound, (V) (González *et al.*, 1996), has the smallest unit-cell volume in the series, having the small acetyl group as substituent.

Interatomic distances and angles in the common parts of (II), (III) and (IV) are very similar to those in (I) and (V). Table 2 shows selected geometric parameters of the three molecules.

The molecules pack as dimeric units about inversion centres, with the dimers stabilized by two symmetry-equivalent intermolecular hydrogen bonds between N1 and O6; stacking and overlap of the aromatic rings in planes separated by 3.786 (1) in (II), 3.757 (1) in (III) and 3.772 (1) Å in (IV) also appear to play a key role in the dimerization. The dimers are linked by hydrogen bonds between N2 and O6, and between N2 and O4, the latter relating molecules by a pure translation along **a** (Fig. 4). It is interesting that in the crystal structure of

the related prodrug (V) (González *et al.*, 1996), dimers also form about inversion centres, but in this case the stabilizing hydrogen bonds are between N2 and O1.

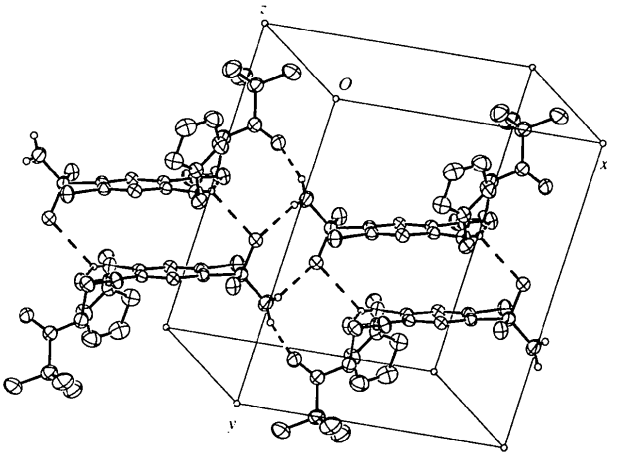


Fig. 4. Packing diagram for (II), showing the hydrogen-bonding scheme and the unit cell. Note that double chains are directed along the *x* axis. H atoms not involved in hydrogen bonds are omitted for clarity.

Experimental

The three title compounds were obtained as described previously by Prandi, Fagiolino, Manta, Llera *et al.* (1992); crystallization was performed by vapour diffusion (ethyl acetate/hexane) at room temperature.

Compound (II)

Crystal data

$C_{18}H_{21}ClN_2O_7S$
M_r = 444.88
Triclinic
$P\bar{1}$
a = 10.677 (2) Å
b = 12.374 (2) Å
c = 8.946 (2) Å
α = 110.41 (2)°
β = 107.90 (2)°
γ = 99.50 (2)°
V = 1003.8 (3) Å^3
Z = 2
D_x = 1.472 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 12.5–25.0°
μ = 0.338 mm^{-1}
T = 293 (2) K
Prismatic
0.9 × 0.5 × 0.4 mm
Colourless

Data collection

Rigaku AFC-7*S* diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (Molecular Structure Corporation, 1993)
T_{min} = 0.825, T_{max} = 0.874
4853 measured reflections
4608 independent reflections

2978 reflections with $I > 2\sigma(I)$
R_{int} = 0.039
θ_{max} = 27.5°
$h = 0 \rightarrow 13$
$k = -16 \rightarrow 15$
$l = -11 \rightarrow 11$
3 standard reflections
every 150 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.194
S = 1.041
4608 reflections
346 parameters
All H atoms refined
$w = 1/[\sigma^2(F_o^2) + (0.1162P)^2 + 0.2728P]$
where $P = (F_o^2 + 2F_c^2)/3$

$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.614 e Å^{-3}
$\Delta\rho_{min}$ = −0.310 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Compound (III)

Crystal data

$C_{17}H_{19}ClN_2O_7S$
M_r = 430.85
Triclinic
$P\bar{1}$
a = 10.494 (2) Å
b = 12.679 (2) Å
c = 8.606 (2) Å
α = 107.08 (2)°
β = 107.39 (2)°
γ = 103.77 (2)°
V = 975.7 (3) Å^3
Z = 2
D_x = 1.467 Mg m^{-3}
D_m not measured

Mo $K\alpha$ radiation
λ = 0.71069 Å
Cell parameters from 25 reflections
θ = 12.5–25.0°
μ = 0.345 mm^{-1}
T = 293 (2) K
Prismatic
0.4 × 0.2 × 0.1 mm
Colourless

Data collection

Rigaku AFC-7*S* diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (Molecular Structure Corporation, 1993)
T_{min} = 0.876, T_{max} = 1.000
4730 measured reflections
4484 independent reflections

3567 reflections with $I > 2\sigma(I)$
R_{int} = 0.017
θ_{max} = 27.48°
$h = 0 \rightarrow 13$
$k = -16 \rightarrow 15$
$l = -11 \rightarrow 10$
3 standard reflections
every 150 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.157
S = 1.035
4484 reflections
308 parameters
Only coordinates of H atoms refined

$w = 1/[\sigma^2(F_o^2) + (0.0842P)^2 + 0.4822P]$
where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.693 e Å^{-3}
$\Delta\rho_{min}$ = −0.469 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Compound (IV)

Crystal data

$C_{17}H_{19}ClN_2O_7S$
M_r = 430.85

Mo $K\alpha$ radiation
λ = 0.71069 Å

Triclinic
$P\bar{1}$
a = 10.580 (2) Å
b = 12.471 (2) Å
c = 8.643 (3) Å
α = 107.78 (2)°
β = 107.76 (2)°
γ = 102.863 (14)°
V = 969.4 (4) Å^3
Z = 2
D_x = 1.476 Mg m^{-3}
D_m not measured

Cell parameters from 25 reflections
θ = 12.5–25.0°
μ = 0.347 mm^{-1}
T = 293 (2) K
Prismatic
1.0 × 0.5 × 0.4 mm
Colourless

Data collection

Rigaku AFC-7*S* diffractometer
$\theta/2\theta$ scans
Absorption correction: ψ scan (Molecular Structure Corporation, 1993)
T_{min} = 0.752, T_{max} = 0.870
4701 measured reflections
4459 independent reflections

3668 reflections with $I > 2\sigma(I)$
R_{int} = 0.027
θ_{max} = 27.52°
$h = 0 \rightarrow 13$
$k = -16 \rightarrow 15$
$l = -11 \rightarrow 10$
3 standard reflections every 150 reflections
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)]$ = 0.058
$wR(F^2)$ = 0.180
S = 1.089
4458 reflections
289 parameters
Only coordinates of H atoms refined

$w = 1/[\sigma^2(F_o^2) + (0.0896P)^2 + 0.8658P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.550 e Å^{-3}
$\Delta\rho_{min}$ = −0.622 e Å^{-3}
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Hydrogen-bonding geometry (Å, °) for (II), (III) and (IV)*

D—H···A	D—H	H···A	D···A	D—H···A
(II)				
N1—H1···O1	0.76 (4)	2.11 (4)	2.717 (4)	137 (4)
N1—H1···O6′	0.76 (4)	2.60 (4)	3.125 (4)	128 (4)
N2—H2*A*···O6^{ii}	0.62 (5)	2.56 (5)	3.160 (5)	164 (6)
N2—H2*B*···O4^{iii}	0.95 (6)	2.09 (6)	3.015 (5)	164 (5)
(III)				
N1—H1···O1	0.72 (4)	2.11 (4)	2.729 (3)	145 (4)
N1—H1···O6′	0.72 (4)	2.67 (4)	3.100 (3)	121 (4)
N2—H2*A*···O6^{ii}	0.83 (4)	2.34 (4)	3.157 (4)	170 (4)
N2—H2*B*···O4^{iii}	0.79 (4)	2.19 (4)	2.976 (4)	171 (4)
(IV)				
N1—H1···O1	0.76 (4)	2.12 (4)	2.717 (4)	136 (4)
N1—H1···O6′	0.76 (4)	2.56 (4)	3.096 (4)	129 (4)
N2—H2*A*···O6^{ii}	0.89 (5)	2.25 (5)	3.131 (4)	172 (4)
N2—H2*B*···O4^{iii}	0.80 (5)	2.18 (5)	2.956 (5)	164 (5)

Symmetry codes: (i) $1-x, 1-y, -z$; (ii) $-x, 1-y, -z$; (iii) $x-1, y, z$.

Table 2. *Selected geometric parameters (Å, °) for (II), (III) and (IV)*

	(II)	(III)	(IV)
C14—C15	1.520 (5)	1.494 (4)	1.503 (5)
C15—C16	1.529 (6)	1.534 (5)	1.477 (10)
C15—C16′		1.533 (5)	
C16—C17		1.531 (5)	
C16′—C17′		1.520 (6)	
C15—C18	1.516 (7)		
C15—C17	1.540 (7)		1.423 (11)
O4—C14—C15	126.3 (3)	128.2 (4)	126.2 (4)
O3—C14—C15	110.6 (3)	106.9 (4)	109.9 (3)
C14—C15—C16	108.2 (3)	110.1 (5)	112.5 (5)
C18—C15—C14	109.2 (3)		
C18—C15—C16	110.0 (5)		
C18—C15—C17	111.9 (4)		
C14—C15—C17	108.8 (4)		112.4 (6)
C16—C15—C17	108.7 (4)		110.2 (7)
C14—C15—C16′		111.6 (5)	
C17—C16—C15		108.1 (5)	
C17′—C16′—C15		108.8 (5)	
C7—O2—C13—O3	−89.0 (3)	−88.7 (3)	−88.6 (3)
O2—C13—O3—C14	126.2 (3)	124.1 (3)	125.2 (3)
C13—O3—C14—O4	4.0 (5)	2.6 (6)	4.7 (5)
O3—C14—C15—C16	64.9 (5)	134.6 (6)	−169.5 (7)
O3—C14—C15—C18	−175.4 (4)		
O3—C14—C15—C17	−53.1 (4)		65.4 (8)
O3—C14—C15—C16′		165.6 (6)	
C14—C15—C16—C17		−69.7 (10)	
C14—C15—C16′—C17′		99.2 (11)	
C2—N1—C8—C9	−80.8 (4)	−81.2 (4)	−80.2 (4)
N1—C8—C9—C10	116.1 (5)	113.7 (5)	114.7 (5)

For all compounds, a collimator of 1.0 mm diameter was used for data collection. The three structures were solved by direct methods, locating all non-H atoms except the disordered atoms of (III). Conformational restraints were applied to disordered atoms of (III) to improve bond distances and angles. The occupancy of both positions of the disordered groups were refined and converged to 0.538 (8) for C16 and C17. The displacement parameters of C16 and C17 of (IV) were restrained to be similar to those of C15. All H atoms, except those belonging to the disordered group of (III) and to the final atoms of the ester group and the furan ring in (IV), were located by difference Fourier maps and were refined. In these cases, H atoms were refined as riding with U_{iso}(H) = 1.2U_{eq}(parent atom).

For all compounds, data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1993); cell refinement: *MSC/AFC Diffractometer Control Software*; data reduction: *MSC/AFC Diffractometer Control Software*; program(s) used to solve structures: *SHELXS*86 (Sheldrick, 1990); program(s) used to refine structures: *SHELXL*93 (Sheldrick, 1993); molecular graphics: *ZORTEP* (Zsolnai & Pritzkow, 1995); software used to prepare material for publication: *PLATON* (Spek, 1990).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: SX1045). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1998). C**54**, 1915–1917

The Antifungal Agent 8-Ethyl-5,8-dihydro-5-oxo-2-(1-pyrrolidinyl)pyrido[2,3-*d*]-pyrimidine-6-carboxylic Acid (Piromidic Acid)

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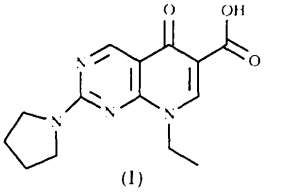
Abstract

The structure of the title compound, $C_{14}H_{16}N_4O_3$, was determined by single-crystal X-ray methods. The molecule is planar within ±0.15 Å except for the C atoms of the pyrrolidine ring and the *N*-ethyl group, which is displaced by −1.246 (3) Å from the mean plane. There is a significant difference between the two N—C bond lengths in the pyridine ring with the N1—C10 bond to the ring junction being longer by 0.039 (4) Å than N1—C2. The N—C bond lengths in the pyrimidine ring range from 1.306 (4) to 1.373 (3) Å; similar structural features have been reported for pipemidic acid. The *N*-ethyl group is approximately perpendicular to the plane of the pyrido–pyrimidinone moiety; the C2—N1—C11—C12 torsion angle is −93.2 (3)°. A single intramolecular hydrogen bond is observed between the H atom of the carboxylic acid group and the O atom of the ketone [O16···H—O15 2.525 (3) Å and 154 (1)°].

Comment

The title compound has been used as an antimicrobial agent in the treatment of urinary tract infections suspected to be caused by gram negative bacteria. Although the mechanism is not known exactly, it is known that the quinolones inhibit a subunit of DNA gyrase in bacteria (Timmers & Sternglanz, 1978). The crystal structures of the antibacterial quinoline agents nalidixic acid (Achari & Neidle, 1976), aminooxolinic acid (Czugler *et al.*, 1976), oxolinic acid (Cygler & Huber, 1985), pipemidic acid (Fonseca *et al.*, 1986) and cinoxacin (Rosales *et al.*, 1985) have been determined by X-ray analysis. We report here the structure of the title compound, (I).



(I)

The molecule contains a pyrrolidine ring joined to a pyrido–pyrimidine ring system. The dihedral angle between the least-squares planes is 7.46 (8)°. The substituents on the pyridine ring at N1, C3 and C4 are the same as those supported by the pyridine rings in nalidixic acid (Huber *et al.*, 1980), oxolinic acid (Cygler & Huber, 1985), aminooxolinic acid (Czugler *et al.*, 1976), pipemidic acid (Fonseca *et al.*, 1986), cinoxacin (Rosales *et al.*, 1985) and silver pefloxacin (Baenziger *et al.*, 1986). The geometric parameters for these substituents in the title compound are similar to those observed in the antibacterial quinolone compounds. The C4=O16 bond length of 1.261 (3) Å is in good agreement with that observed in oxolinic acid [1.259 (3) Å], nalidixic acid [1.261 (8) Å] and pefloxacin [1.254 (5) Å], while it is longer than that observed in pipemidic acid [1.237 (3) Å] and cinoxacin [1.248 (3) Å].

The pyrido–pyrimidinone moiety in the title compound is practically planar with a dihedral angle of 1.09 (6)° between the pyrimidine and pyridine rings. The N—C bond lengths in the pyrimidine ring range from 1.306 (4) to 1.373 (3) Å; this significant difference is also observed in pipemidic acid. The *N*-ethyl substituent in the title compound is almost perpendicular to the pyridine ring, and is slightly rotated about the C—N bond away from the carboxylic acid group. The C2—N1—C11—C12 torsion angle is −93.2 (3)°, in good agreement with values of −102.3 (2), −97.5, −97.3 (3) and −90.0° in oxolinic, aminooxolinic, pipemidic and nalidixic acid, respectively.

Cygler & Huber (1985) have presented a report on a group of highly active antibacterial agents, all presenting a strong intramolecular hydrogen bond between an O atom of the carboxylic acid group and the O atom of an adjacent carbonyl group. Timmers & Sternglanz (1978) suggested that oxolinic and nalidixic acid may exert their antibacterial activity by forming a complex *in situ* involving the 4-keto O atom and the ionized 3-carboxylic acid with a divalent cation in the metalloprotein involved in DNA replication. All members in this quinolone family have the 4-oxopyridine-3-carboxylic