$S = 2.039$
3170 reflections
388 parameters
All H atoms refined
$w = 1/[\sigma^2(F_o) + 0.00016|F_o|^2]$
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

| | | | |
|---|---|---|---|
| S1—C22 | 1.814 (4) | O5—C24 | 1.206 (4) |
| S1—C24 | 1.756 (3) | N1—C23 | 1.362 (4) |
| O4—C23 | 1.198 (4) | N1—C24 | 1.376 (4) |
| C22—S1—C24 | 93.6 (2) | O4—C23—C22 | 124.3 (3) |
| C23—N1—C24 | 118.9 (3) | N1—C23—C22 | 111.8 (3) |
| S1—C22—C21 | 113.3 (3) | S1—C24—O5 | 125.2 (3) |
| S1—C22—C23 | 105.8 (2) | S1—C24—N1 | 109.9 (2) |
| O4—C23—N1 | 124.0 (3) | O5—C24—N1 | 124.9 (3) |

Table 2. *Hydrogen-bonding geometry (Å, °)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N1—H2···O1$^{i}$ | 0.97 (3) | 1.99 (3) | 2.827 (4) | 143 (3) |
| O1—H1···O5$^{ii}$ | 0.76 (4) | 2.17 (4) | 2.870 (4) | 153 (5) |

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

The structure was solved by direct methods using *SIR*92 (Altomare *et al.*, 1993) and was refined by least-squares procedures. All calculations were performed using *TEXSAN* software (Molecular Structure Corporation, 1995).

Data collection: *MSC/AFC Diffractometer Control Software* (Molecular Structure Corporation, 1994). Cell refinement: *MSC/AFC Diffractometer Control Software*. Data reduction: *TEXSAN*. Program(s) used to solve structure: *SIR*92. Program(s) used to refine structure: *TEXSAN*. Molecular graphics: *TEXSAN*. Software used to prepare material for publication: *TEXSAN*.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE1099). Services for accessing these data are described at the back of the journal.

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# Two absorption furosemide prodrugs

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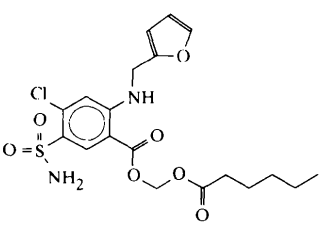
## Abstract

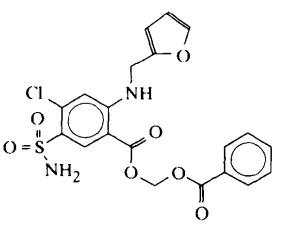
The structures of two absorption furosemide prodrugs, hexanoyloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate ($C_{19}H_{23}ClN_2O_7S$), (I), and benzoyloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate ($C_{20}H_{17}ClN_2O_7S$), (II), are described in this paper and compared with furosemide and four other prodrugs. The molecular conformations of both compounds are similar to those of the other prodrugs; the packing and the crystal system are the primary differences. Compound (I) crystallizes in the trigonal space group $R\bar{3}$ and compound (II) in the monoclinic space group $P2_1/n$. The packing of both structures is stabilized by a three-dimensional hydrogen-bond network.


## Comment

The absorption furosemide prodrugs hexanoyloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate, (I), and benzoyloxymethyl 4-chloro-*N*-furfuryl-5-sulfamoylanthranilate, (II), were synthesized and characterized as acyloxymethyl esters of furosemide (Prandi, Fagiolino, Manta, Llera *et al.*, 1992). The therapeutic activity of these prodrugs has been studied (Prandi, Fagiolino, Manta & Llera, 1992).



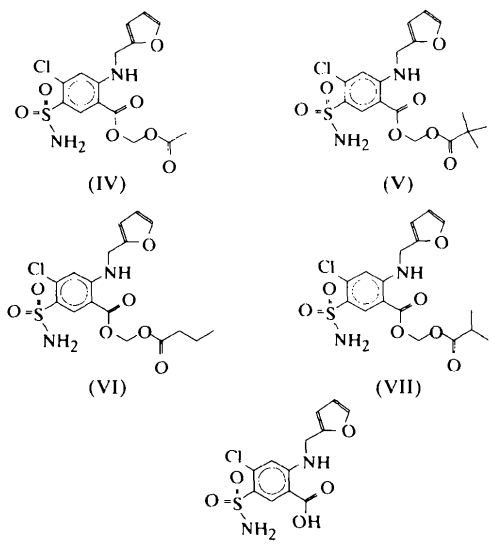
(I)



(II)

Both molecules share the original furosemide [(4-chloro-*N*-furfuryl-5-sulfamoylanthranilic acid), (III)] framework, which contains a six-membered aromatic ring (atoms C1 to C6) with the carboxylate and amine

groups coplanar. There is an intramolecular hydrogen bond between H1 and O1 in both compounds, as in the other four previously studied prodrugs [acetyloxymethyl (IV) (González *et al.*, 1996); pivaloyloxymethyl (V), butyryloxymethyl (VI) and isobutyryloxymethyl (VII), esters of furosemide (Suescun *et al.*, 1998)] (see Tables 2 and 4).




In both molecules the furan ring is planar. Its dihedral angle with the phenyl ring shows similar values in all the prodrugs and in furosemide. The rotational freedom of the N1—C8—C9 linkage, differences in the ester group of each prodrug and the different packing environments may explain the small variations in the observed values in (I) and (II) [61.0 (3) and 75.4 (3)°, respectively] with respect to the other compounds [68° in (III) (Lamotte *et al.*, 1978), 67.6 (3) in (IV), 69.7 (2) in (V), 70.2 (3) in (VI) and 71.3 (3)° in (VII)]. Bond distances and angles of common fragments of both compounds are equal, within experimental error, to those of (III), (IV), (V), (VI) and (VII).

The final substituent of the ester group is an *n*-hexanoyl group in (I) and a benzoyl group in (II). These two groups are appreciably larger than the equivalent groups in the other prodrugs; this may explain the different packing arrangements. In both compounds the packing is directed by hydrogen bonds forming a fully three-dimensional network, while in the other four prodrugs, hydrogen bonds form only linear chains of translationally related molecules.

Compound (I) crystallizes in trigonal space group $R\bar{3}$. The other furosemide prodrugs studied crystallize in space groups of considerably lower symmetry. The *n*-hexanoyl group of (I) is disordered and was modelled by two equally probable positions with restrained distances and angles. Compound (II) crystallizes in the monoclinic

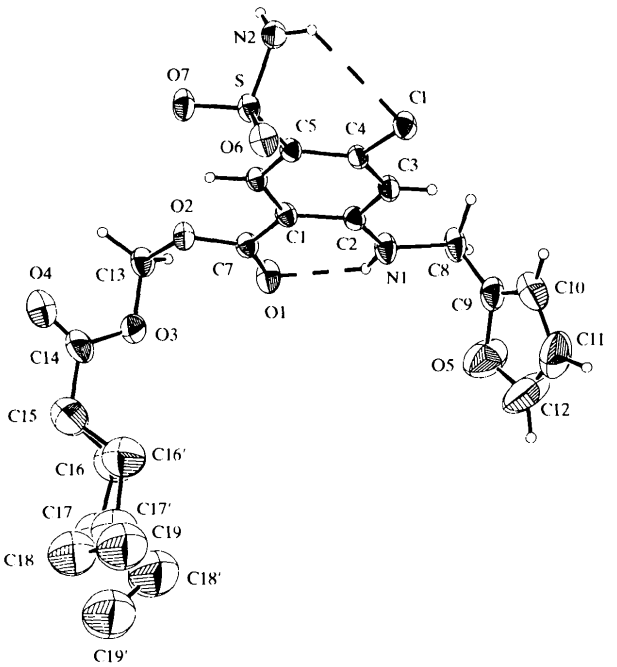



Fig. 1. *ZORTEP* (Zsolnai & Pritzkow, 1995) drawing of (I). Intramolecular hydrogen bonds are marked as dashed lines. Displacement ellipsoids are drawn at the 30% probability level for non-H atoms. Both positions of the disordered group are represented. H atoms belonging to this group are omitted for clarity.

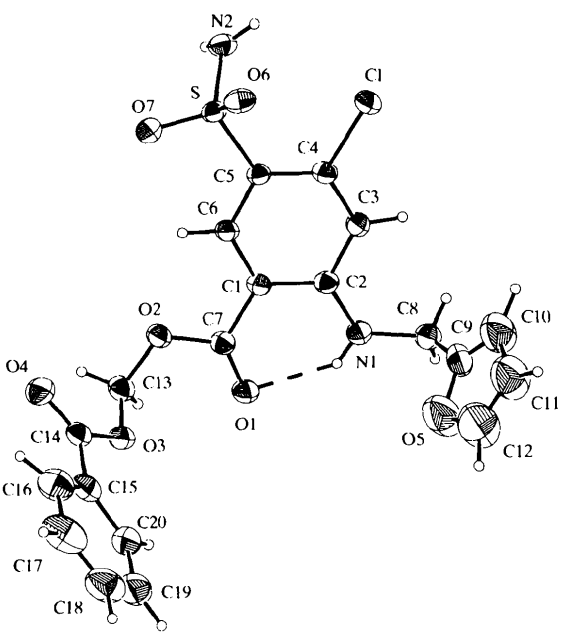



Fig. 2. *ZORTEP* drawing of (II). The intramolecular hydrogen bond is marked as a dashed line. Displacement ellipsoids are drawn at the 50% probability level for non-H atoms.

space group $P2_1/n$ with the rigid phenyl ring of the ester moiety forming an angle of 74.4 (1)° with the phenyl ring of the furosemide moiety and 77.9 (3)° with the furan ring. There is an extra intramolecular hydrogen bond connecting N2 and Cl in (I) that is neither present in (II) nor has been observed in (III), (IV), (V), (VI) or (VII).

## Experimental

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

### Compound (I)

*Crystal data*

$C_{19}H_{23}ClN_2O_7S$
$M_r$ = 458.90
Trigonal
$R\bar{3}$
$a$ = 36.925 (4) Å
$c$ = 8.256 (2) Å
$V$ = 9749 (3) Å$^3$
$Z$ = 18
$D_x$ = 1.407 Mg m$^{-3}$
$D_m$ not measured

Mo $K\alpha$ radiation
$\lambda$ = 0.71069 Å
Cell parameters from 25 reflections
$\theta$ = 10.84–13.50°
$\mu$ = 0.316 mm$^{-1}$
$T$ = 273 (2) K
Hexagonal prism
1.00 × 0.30 × 0.30 mm
Yellow

*Data collection*

Rigaku AFC-7*S* diffractometer
$\theta/2\theta$ scans
Absorption correction: $\psi$ scan (*MSC/AFC Diffractometer Control Software*; Molecular Structure Corporation, 1993)
$T_{min}$ = 0.743, $T_{max}$ = 0.911
5437 measured reflections

4973 independent reflections
2995 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.028
$\theta_{max}$ = 27.50°
$h = -40 \rightarrow 40$
$k = 0 \rightarrow 47$
$l = 0 \rightarrow 10$
3 standard reflections every 150 reflections
intensity decay: none

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.056
$wR(F^2)$ = 0.199
$S$ = 1.039
4973 reflections
336 parameters
H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.1136P)^2 + 9.3355P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$ = 0.001
$\Delta\rho_{max}$ = 0.581 e Å$^{-3}$
$\Delta\rho_{min}$ = −0.520 e Å$^{-3}$
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °) for (I)*

| | | | |
|---|---|---|---|
| N1—C8 | 1.462 (4) | C17—C18 | 1.520 (5) |
| C8—C9 | 1.477 (7) | C18—C19 | 1.522 (5) |
| C14—C15 | 1.473 (4) | C16′—C17′ | 1.529 (5) |
| C15—C16 | 1.501 (5) | C17′—C18′ | 1.522 (5) |
| C15—C16′ | 1.510 (4) | C18′—C19′ | 1.528 (5) |
| C16—C17 | 1.535 (5) | | |
| C2—N1—C8 | 123.7 (3) | C15—C16—C17 | 113.8 (7) |
| N1—C8—C9 | 114.6 (4) | C18—C17—C16 | 114.3 (7) |
| O5—C9—C8 | 118.0 (4) | C17—C18—C19 | 113.5 (8) |
| O3—C14—C15 | 116.0 (5) | C15—C16′—C17′ | 112.8 (6) |
| C14—C15—C16 | 117.7 (6) | C18′—C17′—C16′ | 113.1 (7) |
| C14—C15—C16′ | 118.2 (5) | C17′—C18′—C19′ | 111.5 (7) |

| | |
|---|---|
| C1—C2—N1—C8 | 169.8 (4) |
| C2—N1—C8—C9 | 87.4 (5) |
| N1—C8—C9—O5 | 66.9 (5) |
| C13—O3—C14—C15 | 177.6 (5) |
| O3—C14—C15—C16 | −3.9 (12) |
| O3—C14—C15—C16′ | 51.4 (13) |
| C14—C15—C16—C17 | −175.4 (10) |
| C15—C16—C17—C18 | −40 (2) |
| C16—C17—C18—C19 | −65 (2) |
| C14—C15—C16′—C17′ | −162.8 (11) |
| C15—C16′—C17′—C18′ | −158.3 (14) |
| C16′—C17′—C18′—C19′ | 115 (2) |

Table 2. *Hydrogen-bonding geometry (Å, °) for (I)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N1—H1···O1 | 0.82 (6) | 2.07 (5) | 2.680 (5) | 131 (4) |
| N2—H2*A*···Cl | 0.83 (5) | 2.77 (5) | 3.297 (4) | 123 (5) |
| N2—H2*A*···O6$^{i}$ | 0.83 (5) | 2.23 (5) | 2.988 (6) | 151 (5) |
| N2—H2*B*···O1$^{ii}$ | 0.83 (5) | 2.51 (5) | 3.125 (6) | 132 (4) |
| N2—H2*B*···O4$^{iii}$ | 0.83 (5) | 2.47 (5) | 3.129 (7) | 137 (4) |

Symmetry codes: (i) $\frac{2}{3} - y, x - y - \frac{2}{3}, \frac{1}{3} + z$; (ii) $1 - x, -y, 1 - z$; (iii) $1 - x, -y, -z$.

### Compound (II)

*Crystal data*

$C_{20}H_{17}ClN_2O_7S$
$M_r$ = 464.87
Monoclinic
$P2_1/n$
$a$ = 7.836 (2) Å
$b$ = 17.605 (10) Å
$c$ = 15.4951 (18) Å
$\beta$ = 94.026 (16)°
$V$ = 2132.4 (13) Å$^3$
$Z$ = 4
$D_x$ = 1.448 Mg m$^{-3}$
$D_m$ not measured

Mo $K\alpha$ radiation
$\lambda$ = 0.71070 Å
Cell parameters from 25 reflections
$\theta$ = 18.79–21.31°
$\mu$ = 0.322 mm$^{-1}$
$T$ = 293 (2) K
Rhombohedral
0.8 × 0.4 × 0.4 mm
Colourless

*Data collection*

Rigaku AFC-7*S* diffractometer
$\theta/2\theta$ scans
Absorption correction: $\psi$ scan (*MSC/AFC Diffractometer Control Software*; Molecular Structure Corporation, 1993)
$T_{min}$ = 0.783, $T_{max}$ = 0.882
6393 measured reflections

4886 independent reflections
3298 reflections with $I > 2\sigma(I)$
$R_{int}$ = 0.054
$\theta_{max}$ = 27.49°
$h = 0 \rightarrow 10$
$k = -4 \rightarrow 22$
$l = -20 \rightarrow 20$
3 standard reflections every 150 reflections
intensity decay: none

*Refinement*

Refinement on $F^2$
$R[F^2 > 2\sigma(F^2)]$ = 0.063
$wR(F^2)$ = 0.216
$S$ = 1.041
4886 reflections
323 parameters

$w = 1/[\sigma^2(F_o^2) + (0.1355P)^2 + 0.4781P]$ where $P = (F_o^2 + 2F_c^2)/3$
a$(\Delta/\sigma)_{max}$ = 0.000
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.680 e Å$^{-3}$

H atoms treated by a mixture of independent and constrained refinement

$\Delta\rho_{min} = -0.603$ e Å$^{-3}$
Extinction correction: none
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 3. *Selected geometric parameters (Å, °) for (II)*

| | | | |
|---|---|---|---|
| N1—C8 | 1.456 (5) | C16—C17 | 1.416 (8) |
| C8—C9 | 1.473 (7) | C17—C18 | 1.390 (11) |
| C14—C15 | 1.477 (5) | C18—C19 | 1.347 (10) |
| C15—C16 | 1.359 (7) | C19—C20 | 1.391 (7) |
| C15—C20 | 1.402 (7) | | |
| C2—N1—C8 | 125.2 (3) | C15—C16—C17 | 120.7 (6) |
| N1—C8—C9 | 114.2 (3) | C18—C17—C16 | 118.0 (6) |
| O5—C9—C8 | 117.3 (5) | C19—C18—C17 | 121.6 (6) |
| O3—C14—C15 | 111.5 (3) | C18—C19—C20 | 120.5 (6) |
| C16—C15—C14 | 118.9 (4) | C19—C20—C15 | 119.3 (6) |
| C20—C15—C14 | 121.2 (4) | | |
| C1—C2—N1—C8 | −174.5 (3) | O3—C14—C15—C20 | −10.7 (5) |
| C2—N1—C8—C9 | 84.6 (5) | C14—C15—C16—C17 | −177.0 (4) |
| N1—C8—C9—O5 | 57.7 (7) | C16—C17—C18—C19 | −1.2 (10) |
| C13—O3—C14—C15 | −177.8 (3) | C18—C19—C20—C15 | −0.4 (8) |
| O3—C14—C15—C16 | 167.8 (4) | | |

Table 4. *Hydrogen-bonding geometry (Å, °) for (II)*

| *D*—H···*A* | *D*—H | H···*A* | *D*···*A* | *D*—H···*A* |
|---|---|---|---|---|
| N1—H1···O1 | 0.82 (3) | 2.01 (4) | 2.689 (4) | 140 (4) |
| N1—H1···O4$^{i}$ | 0.82 (3) | 2.49 (4) | 3.079 (5) | 129 (3) |
| N2—H2A···O1$^{ii}$ | 0.83 (3) | 2.30 (4) | 3.004 (4) | 143 (4) |
| N2—H2A···O4$^{iii}$ | 0.83 (3) | 2.51 (4) | 3.105 (5) | 129 (4) |
| N2—H2B···O6$^{iv}$ | 0.83 (4) | 2.20 (4) | 3.006 (4) | 162 (4) |

Symmetry codes: (i) $x-1, y, z$; (ii) $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$; (iii) $x-\frac{1}{2}, \frac{1}{2}-y, \frac{1}{2}+z$; (iv) $-x, 1-y, 2-z$.

A 1 mm collimator was used for both data collections. The structures were solved by direct methods, locating all non-H atoms, except those disordered in (I) which were located in difference Fourier maps. All atoms of the disordered group were refined with restrained bond distances, angles and displacement parameters to improve convergence. Occupancy of both positions of disordered groups was refined and converged to 0.5 within experimental error. The refinement was then concluded with this occupancy fixed at 0.5. The displacement parameters of furan ring atoms of (I) were restrained to reduce anisotropy to acceptable values. In compound (I), all H atoms, except those belonging to the disordered group and the furan ring, were located in difference Fourier maps and freely refined. The rest were calculated at geometrical positions and refined riding with $U_{iso} = 1.2U_{eq}$ of the parent atom. In compound (II), H atoms belonging to C3, C6, C8, C13, C16, C20, N1 and N2 were located in a difference Fourier map. Those belonging to C3, C6, C16, C20 and N1 were freely refined and the others were refined with restrained distances. Those belonging to C10, C11, C12, C17, C18 and C19 were placed at calculated positions and refined riding on the atom to which they are bonded. All H-atom isotropic displacement parameters were fixed at $U_{iso} = 1.2U_{eq}$ of the parent atom.

For both 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*97 (Sheldrick, 1997*a*); program(s) used to refine structures: *SHELXL*97 (Sheldrick, 1997*b*); 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: SX1070). Services for accessing these data are described at the back of the journal.

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*Acta Cryst.* (1999). C**55**, 416–419

# Two new spiro lactam-lactones

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## Abstract

In 3-methyl-2-oxa-6-azaspiro[4.5]decane-1,7-dione, (1) ($C_9H_{13}NO_3$), and 3-methyl-2-oxa-6-azaspiro[4.6]undecane-1,7-dione, (2) ($C_{10}H_{15}NO_3$), the lactone rings are in an envelope conformation. The lactam rings are in a distorted half-chair conformation in compound (1) and in a chair conformation in (2). Molecules are joined through hydrogen bonds in both compounds.