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# Structure of a New $H_2$-Receptor Antagonist, 2-(2-{[5-(Dimethylammoniomethyl)-2-furyl]methylthio}ethylamino)-2-methylamino-1-nitroethylene Hydrogen Oxalate (Ranitidine Hydrogen Oxalate)*

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**Abstract.** $C_{13}H_{23}N_4O_3S^+.C_2HO_4^-$, $M_r$ = 404·44, monoclinic, $P2_1/c$, $a$ = 13·642 (7), $b$ = 5·531 (3), $c$ = 26·018 (12) Å, $\beta$ = 103·508 (29)°, $Z$ = 4, $U$ = 1908·84 Å$^3$, $D_c$ = 1·407 Mg m$^{-3}$, Mo $K\alpha$ ($\lambda$ = 0·7107 Å, $\mu$ = 0·217 mm$^{-1}$); final $R$ = 0·048 for 1676 observed reflexions. The ranitidine molecule is protonated at the dimethylamino group. The interatomic distances and angles are in agreement with the given atom type and hybridization with the exception of the 2-ethylamino-2-methylamino-1-nitroethylene residue where electron delocalization occurs. The ranitidine molecule is folded in a head-to-tail orientation with an intramolecular hydrogen bond between the methylamino group and nitro O atom of 2·60 (1) Å. The nitro and methylamino groups are *cis* whereas the ethylamino group carrying the rest of the molecule is *trans* to the nitro group. The crystal structure consists of layers of hydrogen-bonded ranitidine and hydrogen oxalate ions in the *bc* plane.

**Introduction.** Like histamine, conventional $H_2$-receptor antagonists such as burimamide, metiamide and cimetidine contain imidazole rings and this has been regarded as an essential structural feature (Black, Duncan, Durant, Ganellin & Parsons, 1972). Only the side chains were extensively modified. But ranitidine, a substituted amine alkylfuran, is a selective $H_2$-receptor antagonist (Bradshaw, Brittain, Clitherow, Daly, Jack, Price & Stables, 1979; Prous, 1979) and does not contain an imidazole ring. *In vivo* and *in vitro* studies have shown that ranitidine is a competitive $H_2$-antagonist without significant activity at histamine $H_1$-receptors or at cholinergic receptors (Simon & Kather, 1979; Woodings, Dixon, Harrison, Carey & Richards, 1980). Ranitidine is four to five times more potent than cimetidine in inhibiting secretion of gastric acid (Peden, Saunders & Wormsley, 1979). It has also been tested against duodenal ulcer (Langman, Henry, Bell, Burnham & Ogilvy, 1980).

The sample used in this structure determination was prepared by the procedure described by Toso, Decorte, Zonno & Šunjić (1981). Preliminary cell dimensions and the space group were determined from oscillation and Weissenberg photographs recorded with Cu $K\alpha$ radiation. Final cell dimensions were refined from diffractometer measurements. Intensities were collected on a Philips PW 1100 computer-controlled four-circle diffractometer in the $\omega$-scan mode [scan width = 1·20° ($\theta$), scan speed = 0·040°($\theta$) s$^{-1}$] with graphite-monochromated Mo $K\alpha$ radiation. 1676 independent reflexions [$I \geq 2\sigma(I)$] in the range $2 < \theta < 30°$ were recorded and used in the calculations. Three standard reflexions were measured every 2 h. The data were corrected for background, Lorentz and polarization effects. The structure was solved with *MULTAN* 80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980). A subsequent difference synthesis located the H atoms. Refinement was by full-matrix least squares, minimizing $\sum w(|F_o| - |F_c|)^2$ with unit weights. A scale factor, atomic coordinates, anisotropic thermal parameters for the heavier atoms and isotropic thermal parameters for the H atoms (340 variables in all) were refined. Anisotropic thermal parameters are in the usual range: the maximum value is $U_{11}$ for O(7) [0·127 (4) Å$^2$]. The isotropic thermal parameter of H(13), 0·20 (3) Å$^2$, is high but the difference synthesis clearly located its position. The final $R$ = 0·048 for 1676 reflexions with $I \geq 2\sigma(I)$. Scattering factors given by Cromer & Mann (1968) and (for H) Stewart, Davidson & Simpson (1965) were used. An anomalous-dispersion correction was included for S (Cromer & Liberman, 1970).

The calculations were carried out on a Univac 1110 computer at the University Computing Centre in

* This structure determination was presented at the Symposium on Biologically Active Molecules, August 1981, Buffalo, NY, USA.

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Table 1. *Final atomic coordinates* ($\times 10^4$, *for* S $\times 10^5$) *and equivalent isotropic thermal parameters* ($\times 10^2$)

For non-hydrogen atoms $U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$. Atoms of the hydrogen oxalate anion are denoted by daggers.

| | *x* | *y* | *z* | $U_{eq}$ (Å$^2$) |
|---|---|---|---|---|
| S | 99988 (11) | 17610 (31) | 94469 (6) | 5·81 (14) |
| C(1) | 6441 (4) | 4694 (9) | 9287 (1) | 3·8 (3) |
| C(2) | 6714 (4) | 6495 (9) | 8950 (2) | 4·5 (3) |
| N(3) | 5491 (3) | 4364 (8) | 9305 (1) | 4·5 (3) |
| C(4) | 5162 (4) | 2502 (11) | 9623 (2) | 6·0 (4) |
| N(5) | 6040 (4) | 7970 (8) | 8634 (1) | 5·2 (3) |
| O(6) | 5098 (3) | 7863 (7) | 8621 (1) | 6·9 (3) |
| O(7) | 6355 (3) | 9486 (7) | 8344 (1) | 7·5 (3) |
| N(8) | 7146 (3) | 3341 (8) | 9582 (1) | 4·6 (3) |
| O(9)† | 2613 (2) | −2560 (5) | 8413 (1) | 5·3 (3) |
| O(10)† | 2745 (3) | −4103 (6) | 9211 (1) | 5·7 (3) |
| C(11)† | 2675 (3) | −2390 (8) | 8882 (2) | 3·5 (3) |
| C(12)† | 2666 (3) | 142 (8) | 9141 (1) | 3·3 (3) |
| O(13)† | 2581 (2) | 1868 (5) | 8798 (1) | 4·8 (2) |
| O(14)† | 2747 (2) | 381 (5) | 9610 (1) | 5·0 (2) |
| O(1′) | 8918 (2) | 5974 (6) | 8336 (1) | 5·0 (3) |
| C(2′) | 9686 (4) | 4364 (11) | 8517 (2) | 5·2 (4) |
| C(3′) | 9836 (4) | 3025 (13) | 8117 (2) | 6·6 (4) |
| C(4′) | 9126 (4) | 3787 (12) | 7653 (2) | 6·6 (4) |
| C(5′) | 8585 (4) | 5606 (11) | 7800 (2) | 4·9 (3) |
| C(6′) | 10178 (4) | 4447 (11) | 9086 (2) | 5·4 (3) |
| C(7′) | 8642 (4) | 1670 (10) | 9326 (2) | 5·1 (4) |
| C(8′) | 8232 (4) | 3525 (10) | 9651 (2) | 4·8 (3) |
| C(9′) | 7775 (4) | 7256 (10) | 7532 (2) | 4·8 (3) |
| N(10′) | 6849 (3) | 5940 (7) | 7247 (1) | 4·1 (4) |
| C(11′) | 6046 (4) | 7714 (11) | 7023 (2) | 4·9 (4) |
| C(12′) | 6462 (5) | 4160 (11) | 7587 (2) | 5·5 (4) |

Table 2. *Final positional* ($\times 10^3$) *and isotropic thermal* ($\times 10^2$) *parameters for hydrogen atoms*

| | *x* | *y* | *z* | *U* (Å$^2$) |
|---|---|---|---|---|
| H(2) | 737 (3) | 658 (8) | 893 (2) | 4 (1) |
| H(3) | 504 (4) | 517 (10) | 911 (2) | 7 (2) |
| H(4)1 | 524 (4) | 108 (10) | 949 (2) | 8 (2) |
| H(4)2 | 560 (3) | 263 (9) | 1002 (2) | 7 (2) |
| H(4)3 | 444 (4) | 262 (10) | 960 (2) | 7 (2) |
| H(8) | 695 (3) | 241 (8) | 981 (2) | 5 (1) |
| H(13)* | 281 (5) | 291 (15) | 893 (3) | 20 (3) |
| H(3′) | 1031 (4) | 206 (11) | 814 (2) | 8 (2) |
| H(4′) | 900 (4) | 319 (10) | 727 (2) | 7 (2) |
| H(6′)1 | 1096 (4) | 474 (9) | 914 (2) | 7 (2) |
| H(6′)2 | 989 (3) | 583 (9) | 921 (2) | 5 (1) |
| H(7′)1 | 848 (4) | 32 (11) | 945 (2) | 7 (2) |
| H(7′)2 | 830 (3) | 172 (9) | 891 (2) | 6 (1) |
| H(8′)1 | 843 (3) | 501 (9) | 956 (2) | 5 (1) |
| H(8′)2 | 855 (3) | 310 (9) | 1003 (2) | 6 (1) |
| H(9′)1 | 754 (3) | 823 (9) | 780 (2) | 5 (1) |
| H(9′)2 | 804 (3) | 817 (9) | 726 (2) | 6 (1) |
| H(10′) | 705 (4) | 508 (10) | 696 (2) | 7 (2) |
| H(11′)1 | 574 (4) | 831 (10) | 731 (2) | 6 (2) |
| H(11′)2 | 636 (4) | 878 (11) | 680 (2) | 6 (2) |
| H(11′)3 | 547 (3) | 707 (9) | 679 (2) | 3 (1) |
| H(12′)1 | 628 (5) | 511 (13) | 790 (2) | 10 (2) |
| H(12′)2 | 578 (5) | 344 (12) | 734 (2) | 11 (2) |
| H(12′)3 | 701 (5) | 342 (13) | 775 (2) | 6 (2) |

* Hydrogen oxalate anion.

Zagreb with the XRAY system (Stewart, Machin, Dickinson, Ammon, Heck & Flack, 1976). Atomic coordinates are listed in Tables 1 and 2.*

**Discussion.** The structural formula with the atom numbering is shown in Fig. 1. Bond lengths and angles for non-hydrogen atoms are in Table 3. The molecular packing is illustrated in Figs. 2 and 3.

Bond lengths and angles are in agreement with the given atom type and hybridization with the exception of the 2-ethylamino-2-methylamino-1-nitroethylene residue (Table 3). The lengthening of C(1)=C(2) to

* Lists of structure factors, anisotropic thermal parameters and bond lengths and angles involving H have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36649 (22 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

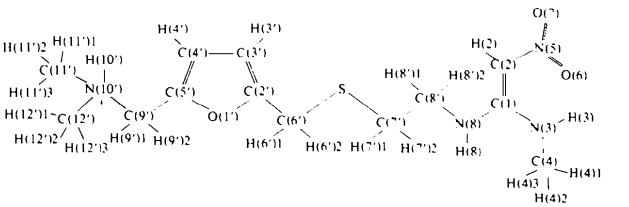

Fig. 1. Structural formula with the atom numbering.

Table 3. *Bond lengths* (Å) *and angles* (°)

Ranitidine

| | | | |
|---|---|---|---|
| C(1)–C(2) | 1·433 (8) | C(6′) C(2′) | 1·476 (8) |
| C(1) N(3) | 1·321 (7) | C(2′) O(1′) | 1·372 (7) |
| C(1)–N(8) | 1·315 (6) | C(2′)– C(3′) | 1·332 (9) |
| C(2) N(5) | 1·353 (7) | C(3′) C(4′) | 1·423 (8) |
| N(3) C(4) | 1·456 (8) | C(4′)–C(5′) | 1·354 (9) |
| N(5) O(6) | 1·280 (8) | C(5′) O(1′) | 1·377 (6) |
| N(5) O(7) | 1·270 (7) | C(5′) C(9′) | 1·477 (8) |
| N(8) C(8′) | 1·454 (7) | C(9′) N(10′) | 1·495 (6) |
| C(8′)–C(7′) | 1·517 (8) | N(10′) C(11′) | 1·484 (7) |
| C(7′)–S | 1·804 (6) | N(10′)– C(12′) | 1·500 (8) |
| C(6′)–S | 1·804 (6) | | |

| | | | |
|---|---|---|---|
| C(2)–C(1)–N(3) | 120·9 (4) | C(3′) C(2′)– O(1′) | 109·7 (5) |
| C(2)–C(1)–N(8) | 119·7 (5) | C(6′) C(2′) O(1′) | 117·1 (5) |
| N(3) C(1) N(8) | 119·4 (5) | C(6′)–C(2′)– C(3′) | 133·2 (5) |
| C(1) C(2) N(5) | 123·6 (5) | C(2′) C(3′) C(4′) | 107·4 (6) |
| C(1)–N(3)–C(4) | 123·5 (4) | C(3′) C(4′) C(5′) | 106·8 (5) |
| C(2) N(5) O(6) | 121·6 (5) | C(4′) C(5′) O(1′) | 108·8 (5) |
| C(2)– N(5)– O(7) | 118·9 (5) | C(4′) C(5′) C(9′) | 136·2 (5) |
| O(6) –N(5)– O(7) | 119·5 (4) | O(1′)– C(5′) C(9′) | 114·9 (5) |
| C(1) N(8)–C(8′) | 128·0 (5) | C(2′) O(1′) C(5′) | 107·3 (4) |
| N(8) C(8′) C(7′) | 112·5 (4) | C(5′) C(9′) N(10′) | 112·7 (4) |
| C(8′) C(7′) S | 112·4 (4) | C(9′) N(10′) C(11′) | 109·5 (4) |
| C(7′) –S –C(6′) | 101·0 (3) | C(9′) N(10′) C(12′) | 113·6 (4) |
| S C(6′)– C(2′) | 114·3 (4) | C(11′)– N(10′)–C(12′) | 109·6 (5) |

Hydrogen oxalate anion

| | | | |
|---|---|---|---|
| O(9)–C(11) | 1·209 (6) | O(9)– C(11)– O(10) | 126·9 (4) |
| O(10)– C(11) | 1·264 (6) | O(9) C(11) C(12) | 120·2 (4) |
| C(11) –C(12) | 1·556 (7) | O(10) C(11)– C(12) | 112·9 (4) |
| C(12)– O(13) | 1·294 (6) | C(11) C(12) O(13) | 111·9 (4) |
| C(12)– O(14) | 1·204 (6) | C(11) C(12) O(14) | 121·9 (4) |
| | | O(13) C(12)– O(14) | 126·2 (4) |

1·433 (8) Å and the shortening of C(1)–N(3) to 1·321 (7), C(2)–N(5) to 1·353 (7), and C(1)–N(8) to 1·315 (6) Å can be explained by a delocalized bonding system. The atoms involved in this system are almost coplanar (Table 5). Bond lengths in the $HC_2O_4^-$ ion, C(12)–O(14) 1·204 (6) and C(12)–O(13) 1·294 (6) Å, typify a double and a single bond respectively, whereas the C(11)–O(9) and C(11)–O(10) distances [1·209 (6) and 1·264 (6) Å] resemble bond distances found in structures containing infinite chains of hydrogen-bonded oxalate ions (Thomas & Renne, 1975).

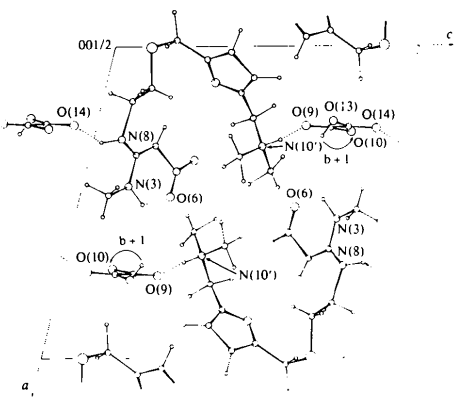


Fig. 2. Molecular packing viewed along **b**. Hydrogen bonds are indicated by dotted lines. The positive direction of **b** is away from the viewer.

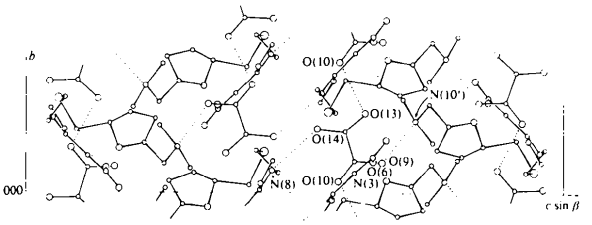


Fig. 3. A view of the crystal structure along **a** showing the waved layers of hydrogen-bonded ranitidine and hydrogen oxalate molecules in the *bc* plane. For the sake of clarity H atoms are omitted.

The conformation of the molecule is described by the torsion angles (Table 4) and for planar parts of the molecule by the deviations from the best least-squares planes (Table 5). The furyl moiety is planar within the limits of the experimental errors (Tables 4 and 5); the mean value of the ring torsion angles is 0·68°. The conformation around C(1)=C(2) is such that the nitro and methylamino groups are *cis* [torsion angle 0·5 (8)°] whereas the ethylamino group carrying the rest of the molecule and the nitro group are *trans* [torsion angle −179·8 (5)°]. The hydrogen oxalate anion is planar within the limits of experimental error (Table 5). The torsion angles around C(11)–C(12) are 0·4 (6) and 1·9 (7)°.

The ranitidine molecule is folded in a head-to-tail orientation (Fig. 2) with an intramolecular hydrogen bond N(3)–H(3)···O(6), 2·598 (6) Å (Table 6). A hydrogen oxalate anion is hydrogen bonded to two ranitidine molecules by $N(10')^+$–H···O(9), 2·797 (6) and N(8)–H···O(14), 2·921 (6) Å, forming an infinite chain along **c**. The hydrogen oxalate anions are connected by O(13)–H···O(10), 2·461 (5) Å, in an infinite chain along **b** (Fig. 3). Thus, waved layers of hydrogen-bonded ranitidine and oxalate ions appear in the *bc* plane.

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Table 5. *Displacements* (Å) *of atoms from least-squares planes*

Atoms included in calculations of the planes are denoted by asterisks.

| Furyl ring | | Ethylenediamine residue | | Hydrogen oxalate anion | |
|---|---|---|---|---|---|
| O(1')* | 0·003 (6) | C(1)* | 0·009 (7) | O(9)* | 0·011 (4) |
| C(2')* | 0·010 (10) | C(2)* | 0·033 (8) | O(10)* | 0·011 (4) |
| C(3')* | 0·004 (11) | N(3)* | 0·035 (6) | C(11)* | 0·002 (5) |
| C(4')* | 0·005 (11) | N(5)* | 0·022 (6) | C(12)* | 0·005 (5) |
| C(5')* | 0·005 (10) | N(8)* | 0·025 (6) | O(13)* | 0·009 (4) |
| C(6') | 0·012 (10) | H(2)* | 0·054 (6) | O(14)* | 0·013 (4) |
| C(9') | 0·053 (9) | | | | |

Table 4. *Torsion angles* (°)

| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| N(8) | C(1) | C(2) | H(2) | 8 (3) | C(8') | C(7') | S | C(6') | −75·5 (4) | C(4')–C(5') | O(1') | C(2') | 0·8 (7) |
| N(8) | C(1) | C(2) | N(5) | −179·8 (5) | C(7') | S | C(6') | C(2') | −59·0 (5) | C(5') | O(1') | C(2') | C(3') | −0·2 (6) |
| N(3) | C(1) | C(2) | N(5) | 0·5 (8) | S | C(6') | C(2') | O(1') | 114·8 (5) | C(2') | O(1') | C(5') | C(9') | −177·9 (5) |
| C(1) | C(2) | N(5) | O(6) | 0·7 (8) | S | C(6') | C(2') | C(3') | −66·2 (9) | O(1') | C(5') | C(9') | N(10') | −122·7 (5) |
| C(1) | C(2) | N(5) | O(7) | 179·0 (5) | C(6') | C(2') | O(1') | C(5') | 179·1 (5) | C(5') | C(9') | N(10') | C(11') | 175·7 (5) |
| C(2) | C(1) | N(3) | C(4) | 177·4 (5) | O(1') | C(2') | C(3') | C(4') | −0·5 (7) | C(5') | C(9') | N(10') | C(12') | 52·8 (6) |
| C(2) | C(1) | N(8) | C(8') | 5·2 (8) | C(2') | C(3') | C(4') | C(5') | 0·9 (8) | O(9) | C(11) | C(12) | O(13) | 0·4 (6) |
| C(1) | N(8) | C(8') | C(7') | 101·0 (6) | C(3') | C(4') | C(5') | O(1') | −1·0 (7) | O(10) | C(11) | C(12) | O(14) | 1·9 (7) |
| N(8) | C(8') | C(7') | S | −175·9 (4) | | | | | | | | | | |

Table 6. *Hydrogen-bond distances* (Å) *and angles* (°)

| $X$–H···$Y$ | $X$···$Y$ | $X$–H | H···$Y$ | $X$–H···$Y$ | Symmetry operation on $Y$ |
|---|---|---|---|---|---|
| N(3)–H(3)···O(6) | 2·598 (6) | 0·82 (5) | 1·98 (5) | 131 (5) | $x,y,z$ |
| N(8)–H···O(14) | 2·921 (6) | 0·88 (5) | 2·13 (4) | 150 (4) | $1-x,-y,2-z$ |
| N(10′)$^+$–H···O(9) | 2·797 (6) | 0·98 (5) | 1·87 (5) | 158 (5) | $1-x,\frac{1}{2}+y,\frac{1}{2}-z+1$ |
| O(13)–H···O(10) | 2·461 (5) | 0·71 (8) | 1·81 (8) | 152 (8) | $x,1+y,z$ |

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# Structure of 2,4,6-Triaminopyrimidine*

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**Abstract.** $C_4H_7N_5$, $M_r = 125{\cdot}1$, monoclinic, $P2_1/n$, $a = 10{\cdot}348$ (3), $b = 9{\cdot}551$ (2), $c = 12{\cdot}464$ (9) Å, $\beta = 112{\cdot}27$ (4)°, $U = 1140{\cdot}0$ Å$^3$, $Z = 8$, $D_c = 1{\cdot}46$, $D_m = 1{\cdot}45$ g cm$^{-3}$, $\mu$(Cu $K\alpha$) = 8·75 cm$^{-1}$, final $R = 0{\cdot}107$ for 995 independent reflections. Transparent crystals grow from aqueous ethanol/acetone solution as twinned needles with the **c** repeat parallel to the needle axis. The two independent molecules are nearly planar but deviate up to 0·03 (1) Å from the expected local $C_{2v}$ symmetry. Molecules are joined into ribbons by N–H···N bonds linking 4- and 6-amino groups to ring nitrogen atoms. Two ribbons associate by $\pi$–$\pi$ interactions between equivalent molecules to form an infinite antiparallel double ribbon; the 2-amino substituents of different molecules approach each other in a manner which suggests they both donate and accept hydrogen bonds.

**Introduction.** Antifolate drugs are found to associate in the crystalline state *via* dimeric N–H···N interactions with exocyclic amino groups as proton donors and ring nitrogen atoms as proton acceptors. An additional mode of N–H···N hydrogen bonding between tetra-

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