Crystal and Molecular Structure of Histamine H_2-Receptor Antagonists of the Ranitidine Family. Part 1. 1-(5-Dimethylaminomethyl)-furfurylthiopropan-2-one Thiosemicarbazone and 1-(5-Dimethylaminomethyl)furfurylthiopropan-2-one 1-Methylamino-2-nitroethenylhydrazone

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The crystal and molecular structures of the title compounds have been determined by *X*-ray analysis. The crystals of the thiosemicarbazone derivative (RANTS) are monoclinic, $P2_1/n$, $Z = 4$, $a = 10.455(4)$, $b = 10.973(3)$, $c = 13.512(4)$ Å, $\beta = 92.83(2)°$. Those of the nitroethylene derivative (RANET) are also monoclinic, $C2/c$, $Z = 8$, $a = 27.901(9)$, $b = 9.432(4)$, $c = 13.795(5)$ Å, $\beta = 93.96(3)°$. Both structures were solved, using diffractometer data, by direct methods and refined by least-squares to $R = 4.7\%$ and 3.8%, respectively. The molecules of RANTS are linked together by pairs of S · · · H–N hydrogen bonds connecting two thiosemicarbazone moieties, while in RANET no intermolecular hydrogen bonding was found. The conformation of the two molecules is quite different. The RANTS molecule is folded as a 'pair of tongs' with a pivot at the sulphur atom of the sulphide linkage, but the two limbs are twisted in such a way that no relevant intramolecular interaction is possible. No such folding is present in RANET where the furan ring is oriented, with respect to the sulphide group, in a direction opposite to that found in RANTS.

Ranitidine (I)[1] is a drug which inhibits the histamine-stimulated gastric acid secretion in man and is reported to be four times more active than cimetidine as a histamine H_2-receptor antagonist. Recently Sorba *et al.*[2] have undertaken the study of a series of compounds which are suitable modifications of the ranitidine molecule. They have prepared some thiosemicarbazone, semicarbazone, and nitroethylene derivatives and are investigating their pharmacological activity. Preliminary results show that these compounds are also histamine H_2-receptor antagonists but their activity is markedly lower than that of ranitidine.[2]

The crystal and molecular structures of the title thiosemicarbazone (II) (RANTS) and nitroethylene (III) (RANET) derivatives were determined in order to compare their configuration with that of ranitidine (ranitidine hydrogen-oxalate, RANOX)[3,†] as well as with that of other histamine H_2-receptor antagonists such as burimamide,[4] metiamide,[5] thioburimamide,[5] and cimetidine.[6]

Experimental

RANTS.—$C_{12}H_{20}N_4OS_2$, $M = 300.48$. Monoclinic, $a = 10.455(4)$, $b = 10.973(3)$, $c = 13.512(4)$ Å, $\beta = 92.83(2)°$, $U = 1\,548(1)$ Å^3, $Z = 4$, $D_c = 1.29$ Mg m^{-3}; space group $P2_1/n$ [C_{2h}^5, no. 14, non-standard setting, $\pm(x,y,z;\ \frac{1}{2}-x,\ \frac{1}{2}+y,\ \frac{1}{2}-z)$]; Mo-$K_\alpha$ radiation, $\lambda = 0.710\,69$ Å; $\mu = 0.34$ mm^{-1}; $F(000) = 640$; crystals from ethyl acetate.

Cell dimensions were obtained and refined using diffractometer angular measurements (Cu-K_α radiation, $\lambda = 1.541\,78$ Å) of 25 reflexions.

The crystal employed for the intensity measurements was ground to an almost ellipsoidal shape (0.2 × 0.1 mm in dimensions) and mounted on a Nicolet R3 automatic diffractometer. Reflexions up to $2\theta\ 45°$ were collected using Mo-K_α radiation ($\lambda = 0.710\,69$ Å) and the θ—2θ scanning technique at fixed speed of 1.58° min^{-1}. The intensity of a standard reflexion, remeasured at intervals of 50 observations, did not show significant variations. After checking that the intensity obtained by ψ-scanning of a few reflexions at different 2θ values did not change significantly, the absorption correction was not applied.

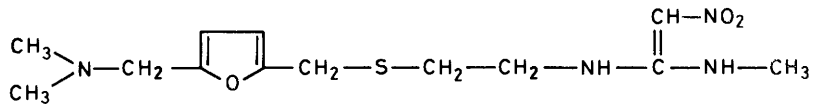
2 044 Independent reflexions were measured, 407 of which, with $I \leqslant 1.96\ \sigma(I)$, were considered as 'unobserved' and not used during the refinement. The data were corrected for background, Lorentz and polarization effects using the XTL programs provided with the diffractometer.[7]

The solution was obtained by direct methods, using the XTL multisolution program (202 reflexions with $E \geqslant 1.68$). The *E*-map corresponding to the set with the best figures of merit revealed all non-hydrogen atoms.

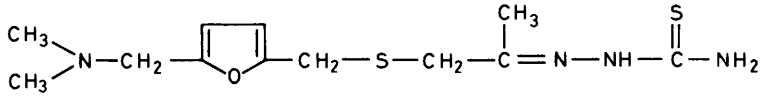
Refinement of the positional and anisotropic thermal parameters by full-matrix least-squares cycles (unit weights) using the SHELX 76 program[8] led to $R = 0.073$. A subsequent difference Fourier map clearly showed 15 out of the 20 hydrogen atoms. In the environment of the C(6) methylene and C(8) methyl carbon atoms (*cf.* Figure 1) several peaks were found. These peaks were left out of the subsequent refinement which converged to $R = 0.056$. The ΔF map at this stage showed three peaks around C(6) and four around C(8); on the basis of geometrical considerations it was possible to select the most likely hydrogen atoms, although the remaining peaks somehow persisted until completion of the refinement (on the final ΔF map the highest residual peak was 0.45 e Å^{-3}). Hydrogen atoms were refined constraining their distances and angles toward the standard values [distance between hydrogen and the nearest atom, 1.01(2) Å]. The isotropic temperature factors of hydrogen atoms belonging to the same chemical groups were refined as a single variable parameter. Five such values were assigned to CH_3, CH_2, CH, NH_2, and NH groups, respectively.

In the final steps of the refinement the weighting function $w = 1/(\sigma_F^2 + qF_o^2)$ was applied; σ_F is the standard deviation of the observed amplitude estimated from counting statistics and q is a parameter, chosen so as to maintain $w\Delta F^2$ as constant as possible over all ranges of $|F_o|$ and $\sin\theta/\lambda$ (in our

† The crystal structure of the free ranitidine base is not known and the only possible comparison is with the oxalate salt. This should be kept in mind, since the influence of the anion on the structure could be relevant.



(I)



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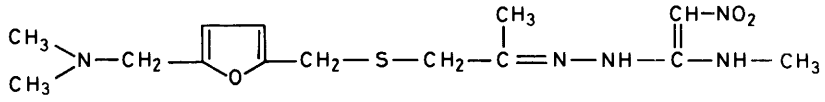

(III)

Table 1. RANTS: atom co-ordinates (× 10^4) and temperature factors (Å² × 10^3)

Atom	*x*	*y*	*z*	*U*
S(1)	7 240(1)	−1 043(1)	2 549(1)	53(1) *
S(2)	3 500(1)	3 781(1)	547(1)	51(1) *
O(1)	8 685(3)	1 155(3)	1 185(2)	51(1) *
N(1)	8 847(3)	2 559(3)	−643(2)	48(1) *
N(2)	5 689(3)	938(2)	888(2)	39(1) *
N(3)	4 641(3)	1 715(2)	860(2)	41(1) *
N(4)	5 963(3)	3 220(3)	222(2)	47(1) *
C(2)	8 866(4)	936(3)	2 174(3)	44(1) *
C(3)	10 097(4)	1 199(4)	2 358(3)	63(2) *
C(4)	10 691(4)	1 629(4)	1 465(3)	61(2) *
C(5)	9 816(3)	1 581(3)	769(3)	51(1) *
C(6)	9 842(4)	1 722(4)	−332(3)	62(2) *
C(7)	9 176(5)	3 809(4)	−364(4)	83(2) *
C(8)	8 768(5)	2 500(5)	−1 712(4)	95(2) *
C(9)	7 746(4)	525(3)	2 773(2)	48(1) *
C(10)	6 639(4)	−906(3)	1 315(3)	45(1) *
C(11)	5 492(3)	−111(3)	1 289(2)	39(1) *
C(12)	4 239(4)	−570(3)	1 715(3)	58(1) *
C(13)	4 805(3)	2 878(3)	538(2)	38(1) *

* Equivalent isotropic *U* defined as one-third of the trace of the orthogonalised U_{ij} tensor.

Table 2. RANTS: hydrogen co-ordinates (× 10^4) and temperature factors (Å² × 10^3)

Atom	*x*	*y*	*z*	*U*
H(1)	3 830(22)	1 441(29)	1 144(29)	79(13)
H(2)	6 082(30)	4 074(18)	−4(26)	65(8)
H(3)	6 697(22)	2 673(25)	175(27)	65(8)
H(4)	10 492(33)	1 059(33)	3 022(16)	76(8)
H(5)	11 554(23)	1 963(35)	1 321(29)	76(8)
H(6)	9 565(27)	960(19)	−741(19)	63(4)
H(7)	10 690(18)	2 028(27)	−573(20)	63(4)
H(8)	9 996(28)	4 051(34)	−702(30)	130(6)
H(9)	8 501(31)	4 411(27)	−598(31)	130(6)
H(10)	9 352(42)	3 760(33)	388(13)	130(6)
H(11)	9 563(28)	2 749(37)	−2 059(27)	130(6)
H(12)	8 045(31)	3 070(32)	−1 952(27)	130(6)
H(13)	8 523(36)	1 627(18)	−1 872(26)	130(6)
H(14)	6 997(20)	1 097(21)	2 709(23)	63(4)
H(15)	7 991(27)	563(26)	3 509(12)	63(4)
H(16)	7 309(21)	−585(26)	870(18)	63(4)
H(17)	6 392(26)	−1 756(16)	1 113(20)	63(4)
H(18)	3 784(34)	66(28)	2 093(29)	130(6)
H(19)	4 351(36)	−1 282(29)	2 174(28)	130(6)
H(20)	3 645(30)	−820(40)	1 145(21)	130(6)

case $q = 0.0006$). Convergence was achieved with $R = 0.047$ (weighted $R = 0.049$) for 237 variables and 1 637 observations (goodness of fit = 1.713).

RANET.—$C_{14}H_{23}N_5O_3S$, $M = 341.48$. Monoclinic, $a = 27.901(9)$, $b = 9.432(4)$, $c = 13.795(5)$ Å, $\beta = 93.96(3)°$, $U = 3\,644(2)$ Å³, $Z = 8$, $D_c = 1.24$ Mg m^{-3}; space group $C2/c$ (C_{2h}^6, no. 15); Mo-K_α radiation, $\lambda = 0.710\,69$ Å; $\mu = 0.20$ mm^{-1}; $F(000) = 1\,456$; crystals from di-isopropyl ether (90%)–ethyl acetate (10%).

Cell dimensions were obtained and refined using the angular settings of 22 reflexions measured on the diffractometer (Mo-K_α radiation). The intensities were measured with the Nicolet R3 diffractometer using a crystal with dimensions 0.15 × 0.25 × 0.40 mm. Reflexions up to 2θ 40° were collected using Mo-K_α radiation and the ω-scan technique with variable speed ranging from 1 to 15° min^{-1}. The intensities of two standard reflexions, remeasured at intervals of 50 observations, did not show significant variations and in this case also the absorption correction was negligible. Out of a total of 1 694 independent reflexions, 302, with $I \leqslant 1.96\,\sigma(I)$, were not employed in the refinement. The data reduction was performed as for RANTS.

The solution was achieved by direct methods, using the multi-solution routine of the SHELXTL [9] system (254 reflexions with $E \geqslant 1.5$). The *E*-map computed with the best set of phases revealed all but one non-hydrogen atoms. The missing C(8) atom was located after a single Fourier cycle and the subsequent refinement was by full-matrix least-squares, using the SHELXTL [9] system, leading to $R = 0.079$ (anisotropic thermal parameters and unit weights). A difference Fourier map computed at this stage revealed all 23 hydrogen atoms. They were refined by constraining their distance from the nearest atom toward the standard value and with isotropic temperature factors assuming three different variable values for the hydrogens in CH_3, CH_2, and CH or NH groups.

In the last cycles of refinement the same weighting scheme used for RANTS was introduced and the *q* value converged to 0.0004. The final *R* value was 0.039 (weighted $R = 0.041$) for 280 variables and 1 394 observation (two strong low-angle reflexions were eliminated because they were affected by severe extinction), with a goodness of fit of 1.761.

For both structures the scattering factors were computed with the analytical expression of Cromer and Waber.[10]

Refined co-ordinates and equivalent isotropic temperature factors [11] for non-hydrogen atoms are given in Table 1 for RANTS and in Table 3 for RANET. The co-ordinates and isotropic temperature factors of the hydrogen atoms are listed in Tables 2 and 4, respectively. Anisotropic thermal parameters of the non-hydrogen atoms and of the observed amplitudes

Table 3. RANET: atom co-ordinates ($\times 10^4$) and temperature factors ($Å^2 \times 10^3$)

Atom	*x*	*y*	*z*	*U*
S	1 316(1)	836(1)	−120(1)	68(1) *
O(1)	1 938(1)	3 707(2)	−802(2)	71(1) *
O(2)	471(1)	1 765(2)	4 353(1)	63(1) *
O(3)	383(1)	3 243(2)	5 548(2)	72(1) *
N(1)	2 618(1)	5 462(3)	−1 927(2)	89(1) *
N(2)	660(1)	2 736(2)	1 653(2)	46(1) *
N(3)	593(1)	2 757(2)	2 640(2)	49(1) *
N(4)	607(1)	5 183(2)	2 522(2)	53(1) *
N(5)	445(1)	3 029(2)	4 661(2)	53(1) *
C(2)	1 714(1)	3 555(4)	59(2)	63(1) *
C(3)	1 531(1)	4 795(4)	302(3)	75(2) *
C(4)	1 642(1)	5 796(4)	−413(3)	80(2) *
C(5)	1 885(1)	5 102(4)	−1 077(3)	72(1) *
C(6)	2 094(1)	5 505(4)	−2 008(3)	90(2) *
C(7)	2 799(2)	5 638(6)	−2 902(4)	153(3) *
C(8)	2 817(2)	6 538(5)	−1 620(4)	123(2) *
C(9)	1 722(1)	2 128(4)	493(2)	75(1) *
C(10)	740(1)	1 534(3)	183(2)	54(1) *
C(11)	675(1)	1 508(3)	1 252(2)	46(1) *
C(12)	635(1)	100(3)	1 746(2)	71(1) *
C(13)	560(1)	4 029(3)	3 067(2)	43(1) *
C(14)	477(1)	4 152(3)	4 057(2)	47(1) *
C(15)	632(2)	6 622(4)	2 896(3)	74(2) *

* Equivalent isotropic *U* defined as one-third of the trace of the orthogonalised U_{ij} tensor.

Table 4. RANET: hydrogen co-ordinates ($\times 10^4$) and temperature factors ($Å^2 \times 10^3$)

Atom	*x*	*y*	*z*	*U*
H(1)	556(10)	1 995(29)	3 023(20)	84(4)
H(2)	623(10)	5 073(32)	1 890(20)	84(4)
H(3)	1 353(10)	5 021(31)	797(20)	84(4)
H(4)	1 561(10)	6 840(30)	−424(21)	84(4)
H(5)	1 980(10)	6 537(30)	−2 217(19)	83(4)
H(6)	1 971(10)	4 834(32)	−2 549(20)	83(4)
H(7)	2 632(13)	6 576(39)	−3 073(25)	128(4)
H(8)	3 140(13)	5 633(37)	−2 679(25)	128(4)
H(9)	2 628(13)	4 903(40)	−3 364(26)	128(4)
H(10)	3 178(12)	6 514(39)	−1 323(25)	128(4)
H(11)	2 700(13)	7 488(40)	−1 563(26)	128(4)
H(12)	2 685(13)	6 279(40)	−635(25)	128(4)
H(13)	1 649(10)	2 160(29)	1 191(20)	83(4)
H(14)	2 011(10)	1 641(30)	445(19)	83(4)
H(15)	709(9)	2 498(31)	−60(19)	83(4)
H(16)	510(10)	895(29)	−165(20)	83(4)
H(17)	684(13)	−652(26)	1 304(27)	128(4)
H(18)	345(14)	79(41)	2 043(26)	128(4)
H(19)	860(14)	35(41)	2 288(27)	128(4)
H(20)	458(10)	5 064(32)	4 367(19)	84(4)
H(21)	682(15)	7 136(45)	2 369(30)	128(4)
H(22)	925(14)	6 738(44)	3 302(30)	128(4)
H(23)	335(15)	6 871(42)	3 263(31)	128(4)

and calculated structure factors are listed in Supplementary Publication No. SUP 23668 (23 pp.).*

Discussion

RANTS.—Interatomic distances and angles with their standard deviations are given in Table 5 and the more relevant torsion angles in Table 6. In Figure 1 a view of the molecule, with the unconventional numbering scheme adopted for the atoms, is shown.

* For details of Supplementary Publications see *J. Chem. Soc., Perkin Trans. 2*, 1983, Issue 1.

Table 5. RANTS: bond lengths (Å) and bond angles (°)

S(1)–C(9)	1.821(4)	S(1)–C(10)	1.759(4)
S(2)–C(13)	1.687(4)	O(1)–C(2)	1.361(5)
O(1)–C(5)	1.413(5)	N(1)–C(6)	1.435(5)
N(1)–C(7)	1.459(5)	N(1)–C(8)	1.444(6)
N(2)–N(3)	1.388(4)	N(2)–C(11)	1.293(4)
N(3)–C(13)	1.361(4)	N(4)–C(13)	1.357(5)
C(2)–C(3)	1.330(6)	C(2)–C(9)	1.524(5)
C(3)–C(4)	1.462(6)	C(4)–C(5)	1.281(5)
C(5)–C(6)	1.497(6)	C(10)–C(11)	1.482(5)
C(11)–C(12)	1.541(5)		

C(9)–S(1)–C(10)	99.5(2)	C(2)–O(1)–C(5)	111.8(3)
C(6)–N(1)–C(7)	111.6(3)	C(6)–N(1)–C(8)	105.6(3)
C(7)–N(1)–C(8)	107.6(4)	N(3)–N(2)–C(11)	114.6(3)
N(2)–N(3)–C(13)	118.2(3)	O(1)–C(2)–C(3)	103.3(3)
O(1)–C(2)–C(9)	120.1(3)	C(3)–C(2)–C(9)	136.6(3)
C(2)–C(3)–C(4)	111.3(4)	C(3)–C(4)–C(5)	106.0(4)
O(1)–C(5)–C(4)	107.6(3)	O(1)–C(5)–C(6)	119.1(3)
C(4)–C(5)–C(6)	132.7(4)	N(1)–C(6)–C(5)	108.0(3)
S(1)–C(9)–C(2)	114.6(2)	S(1)–C(10)–C(11)	108.9(2)
N(2)–C(11)–C(10)	112.8(3)	N(2)–C(11)–C(12)	127.1(3)
C(10)–C(11)–C(12)	120.0(3)	S(2)–C(13)–N(3)	115.7(3)
S(2)–C(13)–N(4)	125.1(2)	N(3)–C(13)–N(4)	119.2(3)

Table 6. Torsion angles (°)

	RANTS	RANET
C(3)–C(2)–C(9)–S(1)	−109.1	105.0
O(1)–C(2)–C(9)–S(1)	73.0	−74.2
C(10)–S(1)–C(9)–C(2)	−67.1	−70.0
C(9)–S(1)–C(10)–C(11)	−66.1	−63.6
S(1)–C(10)–C(11)–C(12)	−70.6	−67.6
S(1)–C(10)–C(11)–N(2)	109.5	112.3
O(1)–C(5)–C(6)–N(1)	58.8	−68.7
C(4)–C(5)–C(6)–N(1)	−131.2	111.7
C(7)–N(1)–C(6)–C(5)	73.1	170.9
C(8)–N(1)–C(6)–C(5)	−170.3	−66.1

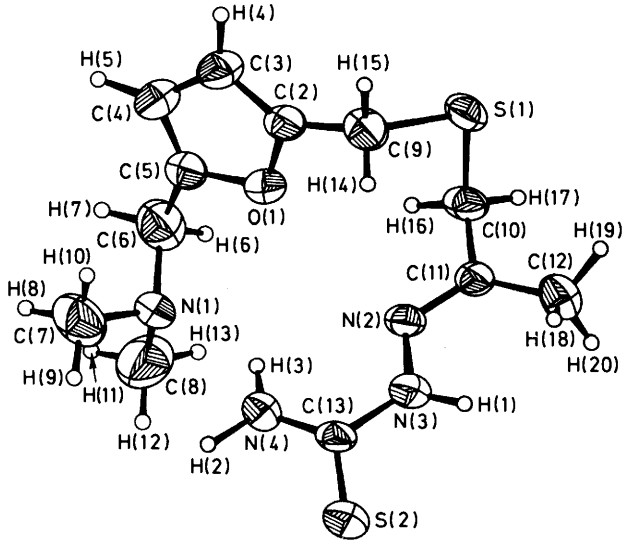

Figure 1. RANTS: view of the molecule obtained with the ORTEP II program. Thermal ellipsoids drawn at 50% probability level

The main feature of the molecular configuration is the folding which takes place at the S(1) atom allowing a ' tongs ' or ' hairpin ' [12] shape (Figure 2a). The two limbs of the tongs are not parallel but twisted in opposite directions with respect

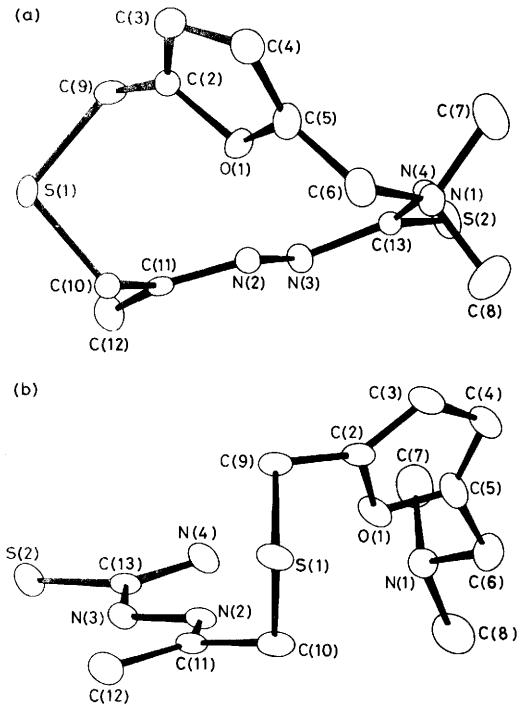

Figure 2. a RANTS: projection of the molecule on the C(9)–S(1)–C(10) plane. b RANTS: projection of the molecule on the plane normal to the C(9)–S(1)–C(10) plane

Table 7. RANET: bond lengths (Å) and bond angles (°)

S–C(9)	1.829(3)	S–C(10)	1.813(3)
O(1)–C(2)	1.387(4)	O(1)–C(5)	1.375(4)
O(2)–N(5)	1.269(3)	O(3)–N(5)	1.264(3)
N(1)–C(6)	1.457(5)	N(1)–C(7)	1.479(6)
N(1)–C(8)	1.455(6)	N(2)–N(3)	1.387(3)
N(2)–C(11)	1.285(4)	N(3)–C(13)	1.343(3)
N(4)–C(13)	1.335(4)	N(4)–C(15)	1.451(4)
N(5)–C(14)	1.354(4)	C(2)–C(3)	1.329(5)
C(2)–C(9)	1.472(5)	C(3)–C(4)	1.416(5)
C(4)–C(5)	1.346(5)	C(5)–C(6)	1.496(5)
C(10)–C(11)	1.499(4)	C(11)–C(12)	1.501(4)
C(13)–C(14)	1.406(4)		
C(9)–S–C(10)	100.5(1)	C(2)–O(1)–C(5)	106.8(2)
C(6)–N(1)–C(7)	109.3(3)	C(6)–N(1)–C(8)	111.5(3)
C(7)–N(1)–C(8)	110.9(4)	N(3)–N(2)–C(11)	116.5(2)
N(2)–N(3)–C(13)	117.5(2)	C(13)–N(4)–C(15)	124.5(2)
O(2)–N(5)–O(3)	119.3(2)	O(2)–N(5)–C(14)	121.4(2)
O(3)–N(5)–C(14)	119.3(2)	O(1)–C(2)–C(3)	109.2(3)
O(1)–C(2)–C(9)	116.6(3)	C(3)–C(2)–C(9)	134.2(3)
C(2)–C(3)–C(4)	107.8(3)	C(3)–C(4)–C(5)	107.1(3)
O(1)–C(5)–C(4)	109.1(3)	O(1)–C(5)–C(6)	116.0(3)
C(4)–C(5)–C(6)	134.9(3)	N(1)–C(6)–C(5)	112.1(3)
S–C(9)–C(2)	115.5(2)	S–C(10)–C(11)	112.9(2)
N(2)–C(11)–C(10)	114.8(2)	N(2)–C(11)–C(12)	126.6(3)
C(10)–C(11)–C(12)	118.6(2)	N(3)–C(13)–N(4)	117.9(2)
N(3)–C(13)–C(14)	121.4(2)	N(4)–C(13)–C(14)	120.6(2)
N(5)–C(14)–C(13)	123.8(2)		

to the C(9)–S(1)–C(10) plane (Figure 2b). A similar molecular conformation is also assumed by RANOX[3] and by other histamine H_2-receptor antagonists containing a sulphide linkage,[5,6] but not by burimamide[4] where the S atom is

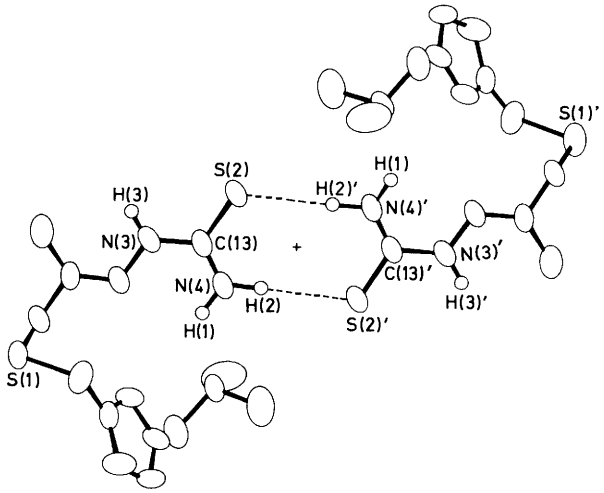

Figure 3. RANTS: scheme of the intermolecular hydrogen bonds

two chains departing from S(1), this being a feature found in all the quoted sulphides with the exception of RANOX.

A number of concomitant effects may contribute to preventing the formation of intramolecular hydrogen bonds; the formation of the antagonist N(4)–H(2)···S(2)′ intermolecular hydrogen bond, the steric hindrance due to the two CH_3 groups attached to N(1), and finally the decrease of conformational flexibility of the side chain due to the presence of the C(11)=N(2) double bond. The closest intramolecular approach between atoms of the two chains departing from S(1) are N(2)···O(1) = 3.147(4), N(4)···O(1) = 3.816(4) Å.

The furan ring is planar (r.m.s. deviation of the atoms from their least-squares plane, 0.007 Å) and the comparison with the structure of furan,[13,14] illustrated in Table 8, shows some noticeable distortions of the geometry of the ring. In particular the distances C(3)–C(4) and C(5)–O(1) and the angles C(2)–C(3)–C(4) and C(2)–O(1)–C(5) are increased, while the angle C(3)–C(2)–O(1) is narrowed.

The group =N(2)–N(3)–C(13)[=S(2)]–N(4) is also planar (r.m.s. deviation = 0.009 Å) with C(11) at 0.119 Å from the least-squares plane. Bond distances and angles of the thiosemicarbazone moiety compare well with those of other thiosemicarbazones;[15] the only noteworthy feature is the lengthening of the N(4)–C(13) bond (1.357 Å, while the largest value found in the literature is 1.344 Å for acetone thiosemicarbazone[15]).

The plane through the three atoms of the sulphide link, C(9)–S(1)–C(10), is almost perpendicular to both the planes of the adjacent furan ring and thiosemicarbazone group, as shown in Figure 2b and indicated by the values of the torsion angles given in Table 6.

The packing of the molecules is characterized by the formation of pairs of symmetry-related hydrogen bonds (Figure 3) between S(2) and N(4)′ (at $1-x$, $1-y$, $-z$) through H(2)′. Also, in the other histamine H_2-receptor antagonists containing the imidazole ring, the molecules are linked by a couple of hydrogen bonds related by an inversion centre, but the atoms involved are different. In the case of burimamide, metiamide, and thiaburimamide the thiourea sulphur is hydrogen bonded to N(3) instead of N(4) (*cf.* Figure 3). In cimetidine, where the S atom is substituted by an *N*-cyano-group, the hydrogen bond is between the NH group closer to

Table 8. Comparison of the geometry of the furan ring in the title compounds and in renitidine oxalate with that of furan

	O(1)–C(2) (Å)	O(1)–C(5) (Å)	C(2)–C(3) (Å)	C(4)–C(5) (Å)	C(3)–C(4) (Å)
RANTS	1.361	1.413	1.330	1.281	1.462
RANET	1.387	1.377	1.328	1.345	1.415
RANOX	1.372	1.377	1.332	1.354	1.423
Furan *a*	1.368	1.368	1.322	1.322	1.428
b	1.362	1.362	1.361	1.361	1.431
	C(2)–O(1)–C(5) (°)	O(1)–C(2)–C(3) (°)	O(1)–C(5)–C(4) (°)	C(2)–C(3)–C(4) (°)	C(3)–C(4)–C(5) (°)
RANTS	111.8	103.3	107.6	111.3	106.0
RANET	106.8	109.1	109.1	107.9	107.1
RANOX	107.3	109.7	108.8	107.4	106.8
Furan *a*	106.2	110.1	110.1	106.8	106.8
b	106.3	110.4	110.4	106.3	106.3

[a] *X*-Ray study. [b] Spectroscopic study.

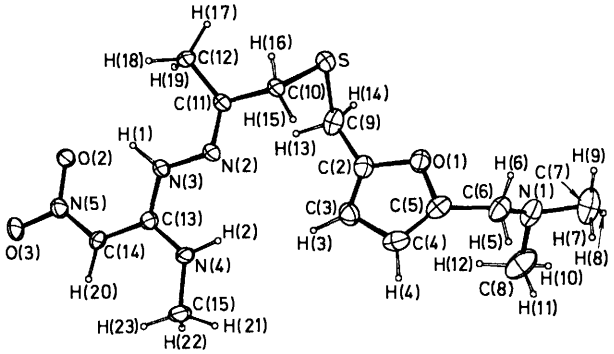

Figure 4. RANET: ORTEP II view of the molecule (as for Figure 1)

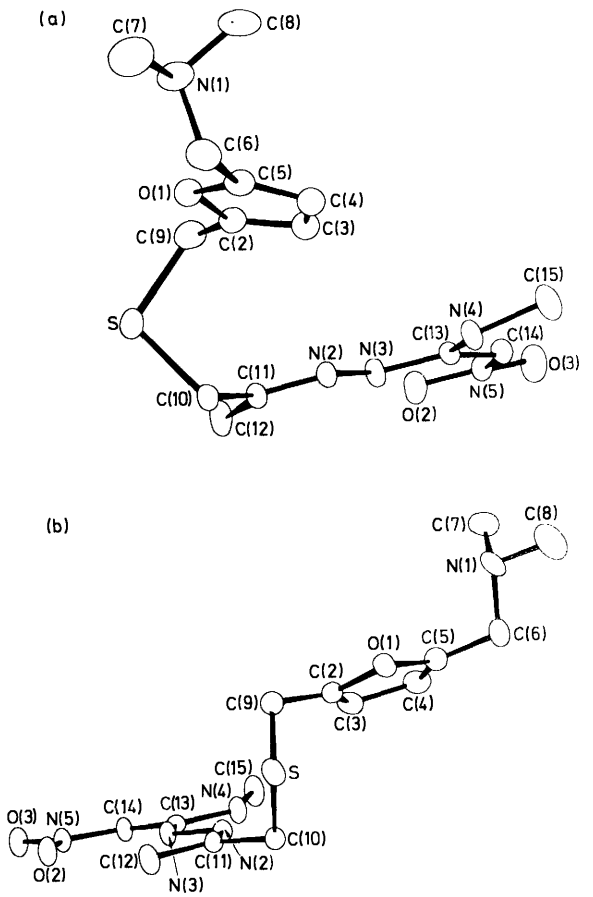

Figure 5. a RANET: projection of the molecule on the C(9)–S–C(10) plane. b RANET: projection of the molecule on the plane normal to the C(9)–S–C(10) plane

RANOX where hydrogen links are present between the base and the oxalate ion.

RANET.—Table 7 gives the interatomic distances and angles while the more relevant torsion angles are reported in Table 6. Figure 4 shows the RANET molecule with the atomic labelling, while in Figure 5 the projection on the C(9)–S–C(10) plane and the view normal to this plane are illustrated.

The two chains departing from sulphur do not come close to one another but extend in opposite directions. The molecular configuration is therefore open as in burimamide. This open configuration is assumed also as a consequence of the fact that the furan ring faces the hydrazone chain with its hydrophobic side [atoms C(3) and C(4)]. With respect to RANTS the ring is rotated around bond C(2)–C(9) by almost 180°. This and other conformational differences are evidenced by the comparison of torsion angles in Table 6.

The furan ring is planar (r.m.s. deviations = 0.004 Å) and, as can be seen from Table 8, its geometry is less distorted than that of the same ring in RANTS and compares well with that found in RANOX. As in this latter compound, also in RANET the nitro-group is involved in an intramolecular hydrogen bond, but in our case the bond is with nitrogen N(3) [O(2) $\cdots$ N(3) = 2.579(4) Å] and not with the methylamino-nitrogen N(4). In fact the stereoisomerism around the C(11)=C(12) double bond is different in the two compounds: the NO_2 and the $NH(CH_3)$ groups are *trans* in RANET and *cis* in RANOX.

The insertion of the double bond C(11)=N(2) reduces the delocalization in the adjacent $NH–C(NHCH_3)=CH–NO_2$ group with respect to that found in RANOX. Finally, as far as the sulphide group is concerned, the values of bond distances and angles are closer to those in RANOX than to those in RANTS.

The molecules of RANET are not linked by any intermolecular hydrogen bond, the closest approach being between O(3) and H′(2)–N′(4) at x, $1-y$, $\frac{1}{2}+z$, with O(3) $\cdots$ N′(4) = 3.127(4) Å, O(3) $\cdots$ H′(2) = 2.45(4) Å, and the angle O(3) $\cdots$ $\widehat{H'(2)}$–N′(4) = 128(2)°.

An overall comparison of the structures of the two title compounds and that of ranitidine oxalate shows great

conformational differences between these derivatives, not only for the molecular fragments which are different but also for the dimethylaminofurfuryl group which is common to the three molecules. It is impossible to draw any conclusion just from the analysis of three derivatives but we intend to continue this work in order to have a better understanding of the conformational behaviour of these histamine H_2-receptor antagonists.

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