Crystal and Molecular Structure of 4-[2-(2-Cyano-3-methyl-3-nitroso-1-guanidino)ethylthiomethyl]-5-methylimidazolium Nitrate (*N*-Nitrosocimetidine Nitrate)

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The crystal and molecular structure of the title compound have been determined from diffraction data using direct methods and least-squares refinement. Recrystallised from ethanol the crystals are monoclinic, space group $P2_1/c$, $Z = 4$, $a = 15.671(9)$, $b = 7.141(2)$, $c = 15.383(7)$ Å, $\beta = 114.73(5)°$. Using 1 573 independent reflections with $I > 3\sigma(I)$ the structure was refined to R 4.0% and R_w 4.8%. The molecule can be described by two planes, one containing the imidazolium ring and the other the nitrosocyanoguanidine residue, which are linked by a large *gauche* five-membered chain. As in previously investigated *N*-nitroso-systems the N(13)–N(14) single bond (1.323 Å) is short whereas the N(14)–O(15) double bond at 1.228 Å is long. The molecules are hydrogen bonded in layers parallel to (100) with adjacent layers related by a 2_1 screw axis along *b*. The crystal structure determines conclusively the primary site of nitrosation in cimetidine.

Certain *N*-nitroso compounds [1] are carcinogenic or mutagenic in animals and there have been suggestions [2] that endogenous concentrations of *N*-nitroso-compounds could be increased by *in vivo* nitrosation of ingested amines and amides in the mammalian stomach. These factors have given rise to the current interest in the nitrosation of foodstuffs, drugs, and environmental chemicals, and recently the nitrosation of the histamine H_2-receptor antagonist cimetidine [3] has been investigated. Previously reported studies include the chemical synthesis [4,5] and kinetics of formation [4] of *N*-nitrosocimetidine, the alkylation of nucleic acid bases by *N*-nitrosocimetidine,[6] and carcinogenicity studies in rats.[7,8] Here we report the structure of *N*-nitrosocimetidine nitrate (1) † both to compare the nitrosocyanoguanidine residue with related nitroso-systems and to determine conclusively the site of nitrosation.

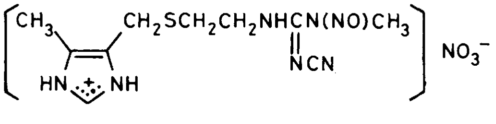
Experimental

The compound was recrystallised from ethanol to give the higher melting (145—147 °C) of the two known polymorphs.[4]

Crystal Data.—$C_{10}H_{16}N_8SO_4$, $M = 344.35$, monoclinic, $a = 15.671(9)$, $b = 7.141(2)$, $c = 15.383(7)$ Å, $\beta = 114.73(5)°$, $U = 1\,563.59$ Å^3, $D_c = 1.46$ g cm^{-3}, $Z = 4$. Space group $P2_1/c$ (C^5_{2h}, No. 14). Mo-K_α radiation $\lambda = 0.71069$ Å, $\mu = 2.4$ cm^{-1}.

The unit cell parameters and their standard deviations were obtained by a least-squares best fit to the setting angles of 25 reflections with values of θ between 10 and 16°. 1 583 Independent reflections with $I > 3\sigma(I)$ were observed with an Enraf–Nonius CAD4-F automated four-circle diffractometer using an ω–2θ scan and Mo-K_α radiation. Lorentz and polarization corrections were applied but no absorption corrections were made.

The structure was solved by direct methods and refined by full-matrix least-squares analysis first with isotropic and then anisotropic temperature factors. Hydrogen atoms were located from a difference synthesis after the seventh refinement cycle at R 6.6%. Two further cycles of full-matrix anisotropic refinement without hydrogen refinement was followed by refinement to convergence in two blocks, with positional parameters of all atoms in one and non-hydrogen anisotropic temperature factors in the other. The final R value was 4.0% and the weighted R 4.8%. During the final stages of refinement a Chebyshev weighting scheme [9] with $w = [4.28t_0(x) + 2.33t_1(x) - 1.60t_2(x) - 0.14t_3(x) + 1.43t_4(x)]^{-1}$ where $x = F_o/F_{max.}$ was applied. Positional and equivalent isotropic thermal parameters are given in Table 1.‡



(1)

All calculations were carried out on a VAX 11/750 computer with data reduction and structure refinement by CRYSTALS,[10] phase determination by MULTAN 78,[11] and graphics by CHEMGRAF.[12]

Results and Discussion

Interatomic distances and bond angles together with their standard deviations are given in Table 2. The numbering of the atoms corresponds to Figure 1 which shows the molecule projected onto its least-squares best plane.

Nitrosocimetidine's geometry can be described by two planes (Table 3), one containing the imidazolium ring and the other the nitrosocyanoguanidine residue separated by an essentially gauche linkage. The maximum deviation of any atom from the least-squares best plane through the imidazole ring is 0.003 Å. Despite the high level of steric interaction indicated by the short contacts C(10) • • • C(18) and N(14) • • • N(11) [2.918(5) and 2.577(4) Å, respectively] the nitrosocyanoguanidine residue with a maximum deviation of 0.097 Å is remarkably planar.

All the bond lengths and most of the interbond angles of the imidazolium ring and C(7)—N(11) side-chain agree with those for cimetidine [13] to within observational error. The

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† 4-[2-(2-Cyano-3-methyl-3-nitroso-1-guanidino)ethylthiomethyl]-5-methylimidazolium nitrate.

‡ Lists of structure factors and thermal parameters have been deposited as Supplementary Publication No. SUP 23601 (20 pp.) (see *J. Chem. Soc., Perkin Trans. 2*, 1983, Issue 1, for details).

Table 1. Positional parameters and equivalent * isotropic temperature factors for *N*-nitrosocimetidine nitrate with e.s.d.s in parentheses

Atom	x/a	y/b	z/c	U (iso)
C(1)	0.196 8(3)	0.219 4(6)	0.004 5(3)	0.0516
C(2)	0.134 4(3)	0.192 2(5)	0.054 0(2)	0.0361
N(3)	0.041 3(2)	0.247 3(4)	0.014 1(2)	0.0404
C(4)	0.002 5(3)	0.206 8(6)	0.073 9(3)	0.0450
N(5)	0.066 9(2)	0.126 6(5)	0.150 0(2)	0.0415
C(6)	0.150 0(2)	0.115 3(5)	0.140 4(2)	0.0345
C(7)	0.234 5(3)	0.021 9(5)	0.212 2(2)	0.0412
S(8)	0.289 7(1)	0.139 3(2)	0.328 0(1)	0.0428
C(9)	0.361 2(2)	0.313 2(5)	0.305 5(3)	0.0413
C(10)	0.316 7(2)	0.505 9(5)	0.276 1(2)	0.0386
N(11)	0.304 0(2)	0.601 4(4)	0.354 0(2)	0.0352
C(12)	0.370 8(2)	0.688 0(5)	0.426 2(2)	0.0320
N(13)	0.343 6(2)	0.768 8(4)	0.495 3(2)	0.0363
N(14)	0.257 6(2)	0.727 8(5)	0.485 1(2)	0.0473
O(15)	0.235 9(2)	0.795 6(4)	0.546 4(2)	0.0560
C(16)	0.405 4(3)	0.888 2(6)	0.572 8(3)	0.0499
N(17)	0.459 1(2)	0.712 2(4)	0.446 3(2)	0.0420
C(18)	0.503 4(3)	0.653 2(6)	0.394 1(3)	0.0444
N(19)	0.552 2(3)	0.610 5(6)	0.358 9(3)	0.0613
N(20)	−0.053 3(2)	0.084 4(5)	0.282 5(2)	0.0420
O(21)	−0.091 0(2)	0.121 3(5)	0.337 9(2)	0.0549
O(22)	0.032 8(2)	0.062 8(5)	0.314 3(2)	0.0560
O(23)	−0.102 9(2)	0.070 7(5)	0.195 8(2)	0.0574
H(1)	0.259 4(33)	0.182 5(65)	0.042 1(32)	0.0500
H(2)	0.207 1(32)	0.346 4(68)	−0.000 2(32)	0.0500
H(3)	0.171 4(32)	0.151 9(67)	−0.051 9(32)	0.0500
H(4)	0.001 9(32)	0.303 2(65)	−0.047 2(32)	0.0500
H(5)	−0.062 8(33)	0.230 2(67)	0.059 6(32)	0.0500
H(6)	0.060 3(32)	0.087 4(66)	0.201 5(32)	0.0500
H(7)	0.284 1(32)	0.010 8(66)	0.189 3(32)	0.0500
H(8)	0.217 6(31)	−0.102 2(67)	0.224 9(31)	0.0500
H(9)	0.418 4(33)	0.325 9(64)	0.365 1(32)	0.0500
H(10)	0.377 1(33)	0.268 5(69)	0.256 2(33)	0.0500
H(11)	0.252 1(32)	0.490 9(65)	0.227 1(31)	0.0500
H(12)	0.360 7(32)	0.591 0(67)	0.256 7(32)	0.0500
H(13)	0.245 2(31)	0.594 8(65)	0.350 2(31)	0.0500
H(14)	0.463 2(32)	0.925 8(67)	0.567 0(32)	0.0500
H(15)	0.367 9(32)	0.983 7(67)	0.577 4(32)	0.0500
H(16)	0.430 7(34)	0.807 4(65)	0.634 4(33)	0.0500

* The equivalent isotropic temperature factor is calculated as eq $U[\mathrm{iso}] = (U_1U_2U_3)^{1/3}$, where U_1, U_2, U_3 are the mean square displacements (Å^2) along each of the principal axes of the thermal ellipsoid.

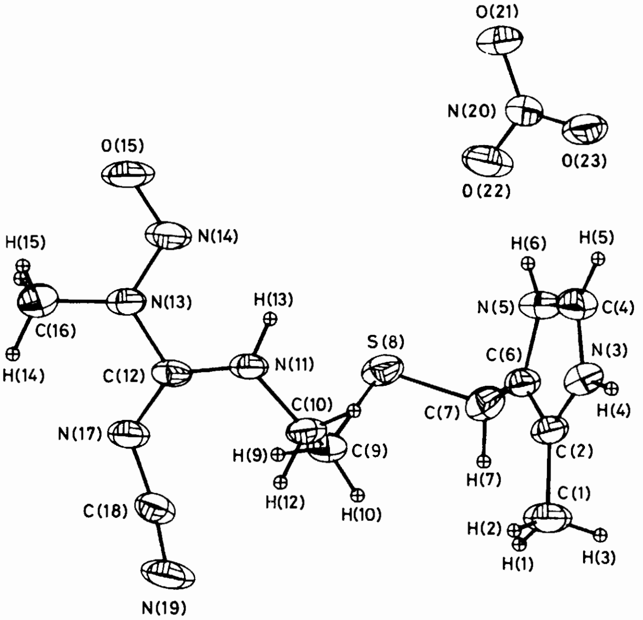
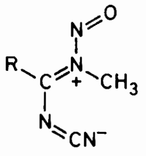


Figure 1. Least-squares best plane view of nitrosocimetidine nitrate. Thermal ellipsoids are drawn at 50% probability level with hydrogens shown as spheres of arbitrary radius



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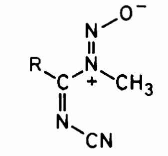

(3)

major difference is the angle C(4)–N(5)–C(6) (109.8°) which, due to the protonation at N(5), is several degrees larger than the corresponding angle in cimetidine. In the nitrosocyanoguanidine group the N(13)–N(14) bond (1.323 Å) is shorter than a typical single-bond value of 1.37—1.44 Å and the N(14)–O(15) bond (1.228 Å) lies at the top end of the range normally attributed to N=O double bonds. This partial double-bond character of the N–N and N–O bonds has been observed spectroscopically for a number of *N*-nitroso-compounds.[14,15] The presence of the *N*-nitroso-group in the nitrosocyanoguanidine residue has a profound effect upon the electronic distribution within the moiety. The planar nitrosocyanoguanidine has two extreme resonance forms, (2) and (3). The effect of these resonance species is particularly illustrated by the large differences between the C(12)–N(13) and C(12)–N(17) bond lengths in nitrosocimetidine [1.423(4) and 1.296(4) Å] and their equivalents in cimetidine [1.330(2) and 1.348(2) Å]. Although the bond lengths and angles around C(12) in nitrosocimetidine differ from those in cimetidine they do agree well with the equivalent parameters found in many other *N*-nitroso-compounds such as *N*-methyl-*N*-nitrosourea and *NN'*-dimethyl-*N*-nitrosourea.[16]

Due to the electron distribution in the *N*-nitroso-group there is restricted rotation about N(13)–N(14) and the possibility of two isomers. Only the *E*-form of the nitroso-group is found in the crystal structure. The *Z*-isomer may be obtained by changing the C(12)–N(13)–N(14)–O(15) torsion angle from 178.6 to 0°. This would produce an N(11)–O(15) separation of *ca.* 2.0 Å, a value far below the normal van der Waals contact distance. This therefore makes formation of the *Z*-form sterically unfavourable. In the *E*-isomer the C(16) • • • • O(15) distance of 2.600(5) Å suggests that there may be some interaction between the methyl and nitroso-group. However the O(15) • • • • C(16)–H(15) and O(15) • • • •C(16)–H(16) angles of 63.8 and 88.6° do not favour hydrogen bonding.

The torsion angles of the C(6)—C(12) chain are given in Table 4. These values are considerably different from those in cimetidine causing a straightening of the chain and a removal of the two terminal residues from each other. In nitrosocimetidine, as in many previous cases where a sulphur has been introduced into an alkyl chain, we obtain the characteristic folded *gauche*-conformation around the sulphur rather than the extended *trans*-conformation frequently observed for an unsubstituted polymethylene chain.

The crystal structure is built up from nitrosocimetidine cations and nitrate anions linked by a complex network of three different N–H • • • O hydrogen bonds (Figure 2). The N(5)–H(6) • • • O(22) bond (2.830 Å) and N(3)–H(4) • • • O(21) bond (2.797 Å) link the molecules into ribbon-like arrangements down the *c* axis, where each molecular group, consisting

Table 2. Interatomic distances (Å) and interbond angles (°) with estimated standard deviations in parentheses

(i) Distances

C(1)–C(2)	1.484(5)	N(20)–O(21)	1.251(4)
C(2)–N(3)	1.382(5)	N(20)–O(22)	1.238(4)
N(3)–C(4)	1.329(5)	N(20)–O(23)	1.236(4)
C(4)–N(5)	1.314(5)	C(1)–H(1)	0.94(5)
N(5)–C(6)	1.374(4)	C(1)–H(2)	0.93(5)
C(6)–C(2)	1.362(5)	C(1)–H(3)	0.92(5)
C(6)–C(7)	1.481(5)	N(3)–H(4)	0.97(4)
C(7)–S(8)	1.826(4)	C(4)–H(5)	0.97(5)
S(8)–C(9)	1.800(4)	N(5)–H(6)	0.89(4)
C(9)–C(10)	1.524(5)	C(7)–H(7)	0.98(4)
C(10)–N(11)	1.462(4)	C(7)–H(8)	0.97(5)
N(11)–C(12)	1.318(4)	C(9)–H(9)	0.98(5)
C(12)–N(13)	1.423(4)	C(9)–H(10)	0.95(4)
N(13)–N(14)	1.323(4)	C(10)–H(11)	0.98(5)
N(13)–C(16)	1.456(5)	C(10)–H(12)	1.05(5)
N(14)–O(15)	1.228(4)	N(11)–H(13)	0.90(4)
C(12)–N(17)	1.296(4)	C(16)–H(14)	0.98(5)
N(17)–C(18)	1.331(5)	C(16)–H(15)	0.92(5)
C(18)–N(19)	1.148(5)	C(16)–H(16)	1.04(5)

(ii) Angles

C(1)–C(2)–N(3)	122.4(3)	C(10)–N(11)–C(12)	125.2(3)
C(1)–C(2)–C(6)	131.7(3)	N(11)–C(12)–N(13)	116.1(3)
C(2)–N(3)–C(4)	109.5(3)	N(11)–C(12)–N(17)	131.0(3)
N(3)–C(4)–N(5)	108.0(3)	N(13)–C(12)–N(17)	113.0(3)
C(4)–N(5)–C(6)	109.8(3)	C(12)–N(13)–N(14)	115.5(3)
N(5)–C(6)–C(2)	106.8(3)	C(12)–N(13)–C(16)	123.0(3)
N(5)–C(6)–C(7)	122.5(3)	N(13)–N(14)–O(15)	114.6(3)
C(6)–C(2)–N(3)	105.9(3)	C(16)–N(13)–N(14)	121.5(3)
C(2)–C(6)–C(7)	130.5(3)	C(12)–N(17)–C(18)	126.0(3)
C(6)–C(7)–S(8)	115.6(2)	N(17)–C(18)–N(19)	171.0(4)
C(7)–S(8)–C(9)	102.0(2)	O(21)–N(20)–O(22)	120.3(3)
S(8)–C(9)–C(10)	115.8(2)	O(22)–N(20)–O(23)	120.4(3)
C(9)–C(10)–N(11)	112.4(3)	O(23)–N(20)–O(21)	119.3(3)

(iii) Intermolecular contacts *

N(5)I ··· O(22)I	2.830(4)
N(3)II ··· O(21)I	2.797(4)
N(11)III ··· O(23)I	2.924(4)

* Roman numerals denote the following equivalent positions relative to the reference molecule at x, y, z:

I $x, -\frac{1}{2} - y, z - \frac{1}{2}$
II $-x, y - \frac{1}{2}, \frac{1}{2} - z$

Table 3. The displacement (Å) of the specified atoms from the least-squares best plane

(a) The imidazolium ring

Equation of plane $1.5664x + 6.404\,25y + 5.408\,80z = 1.725$

C(2)	0.001
N(3)	−0.003
C(4)	0.003
N(5)	−0.002
C(6)	0.000

(b) The nitrosocyanoguanidine residue

Equation of plane $1.249\,15x - 5.664\,72y + 7.921\,28z = 0.038$

C(12)	−0.097	C(16)	−0.026
N(13)	−0.041	N(17)	0.036
N(14)	0.003	C(18)	0.011
O(15)	0.078	N(19)	0.035

Table 4. Selected torsion angles (°) in nitrosocimetidine

C(6)–C(7)–S(8)–C(9)	−82.78
C(7)–S(8)–C(9)–C(10)	94.10
S(8)–C(9)–C(10)–N(11)	68.15
C(9)–C(10)–N(11)–C(12)	78.62

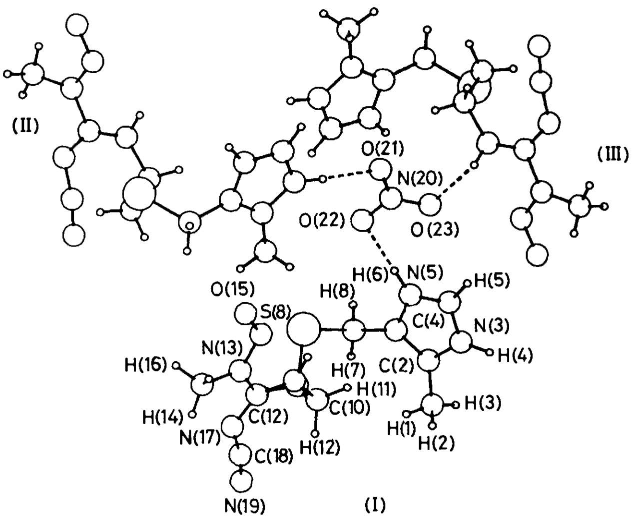

Figure 2. Least-squares best-plane view of three nitrosocimetidine cations hydrogen bonded to a nitrate anion. The cation (I) and the nitrate anion lie at x, y, z and are related to (II) and (III) which lie at the equivalent positions $x, -\frac{1}{2} - y, z - \frac{1}{2}$ and $-x, y - \frac{1}{2}, \frac{1}{2} - z$, respectively

of a nitrosocimetidine and nitrate ion, is related to the next by a *c* glide perpendicular to the *b* axis. The other N(11)–H(13) ··· O(23) bond links adjacent ribbons to form a series of layers of molecules parallel to (100). Adjacent layers are related by a 2_1 screw axis along *b* and bonded by normal van der Waals interactions.

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References

1 P. N. Magee, R. Montesano, and R. Preussmann, 'N-Nitroso-compounds and Related Carcinogens,' A. C. S. Monograph, 1976, No. 173, p. 491.
2 S. S. Mirvish, *Toxicol. Appl. Pharmacol.*, 1975, **31**, 325.
3 R. W. Brimblecombe, W. A. M. Duncan, G. J. Durant, J. C. Emmett, C. R. Ganellin, G. B. Leslie, and M. E. Parsons, *Gastroenterology*, 1978, **74**, 339.
4 P. M. G. Bavin, G. J. Durant, P. D. Miles, R. C. Mitchell, and E. S. Pepper, *J. Chem. Res.* (*S*), 1980, 212.
5 A. B. Foster, M. Jarman, and D. Manson, *Cancer Lett.*, 1980, **9**, 47.
6 D. E. Jensen and C. T. Gombar, 'Factors which influence the *in vivo* Methylating Potential of Nitrosocimetidine,' Nitrosamines and Human Cancer, Banbury Centre Report, No. 12, 1982, p. 379.
7 W. Lijinsky, 'Carcinogenesis Studies with *N*-Nitrosocimetidine, I,' Nitrosamines and Human Cancer, Banbury Centre Report, No. 12, 1982, p. 397.
8 M. Habs, D. Schmähl, G. Eisenbrand, and R. Preussmann, 'Carcinogenesis Studies with *N*-Nitrosocimetidine, II,' Nitrosamines and Human Cancer, Banbury Centre Report, No. 12, 1982, p. 403.
9 J. R. Carruthers and D. J. Watkin, *Acta Crystallogr.*, 1979, **A35**, 698.

10 D. J. Watkin and J. R. Carruthers, ' CRYSTALS User Guide,' Chemical Crystallography Laboratory, University of Oxford, 1981.
11 P. Main, S. J. Fiske, S. E. Hull, L. Lessinger, G. Germain, J.-P. Declercq, and M. M. Woolfson, ' MULTAN 80, A System of Computer Programs for the Automatic Solution of Crystal Structures from *X*-Ray Diffraction Data,' Department of Physics, University of York, 1980.
12 E. K. Davies, ' CHEMGRAF User Guide,' Chemical Crystallography Laboratory, University of Oxford, 1981.
13 S. R. Critchley, D.Phil. Thesis, Oxford, 1978, vol. 1, ch. 3.
14 R. N. Haszeldine and B. J. H. Mallinson, *J. Chem. Soc.*, 1955, 4172.
15 C. E. Looney, W. D. Phillips, and E. L. Reilly, *J. Am. Chem. Soc.*, 1957, **79**, 6136.
16 K. Prout, P. Lowe, and F. M. Miao, *Cryst. Struct. Commun.*, 1982, **11**, 147.

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