Study of the Structure of Droxicam, 5-Methyl-3-(2-pyridyl)-2*H*,5*H*-1,3-oxazino[5,6-*c*][1,2]benzothiazine-2,4(3*H*)-dione 6,6-Dioxide, using *X*-Ray Crystallography and ^{1}H and ^{13}C Nuclear Magnetic Resonance Spectroscopy

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The anti-inflammatory drug Droxicam, 5-methyl-3-(2-pyridyl)-2*H*,5*H*-1,3-oxazino[5,6-*c*]-[1,2]benzothiazine-2,4(3*H*)-dione 6,6-dioxide, has been investigated by n.m.r. spectroscopy, mass spectrometry, and *X*-ray crystallography. The ^{1}H and ^{13}C n.m.r. spectra of this compound have been completely assigned. The single-crystal *X*-ray investigation, $R = 0.0348$ ($R_w = 0.0374$), showed the compound to be monoclinic, space group $P2_1/c$, $a = 8.160(3)$, $b = 15.698(3)$, $c = 12.058(2)$, $\beta = 98.09(2)°$. The three-ring fused system showed an almost planar conformation distorted from coplanarity by the thiazine ring that exhibits a half-chair conformation. The pyridine ring is almost perpendicular to the oxazine ring.

Droxicam,[1] 5-methyl-3-(2-pyridyl)-2*H*,5*H*-1,3-oxazino[5,6-*c*]-[1,2]benzothiazine-2,4(3*H*)-dione-6,6-dioxide (**1**) is a member of a structurally novel family of non-steroidal anti-inflammatory drugs, the oxicams. This compound shows powerful activity in several models of inflammation demonstrating good gastrointestinal tolerance.[2]

The pharmacokinetics and metabolism[3] of droxicam led us to undertake a structural study of droxicam and related compounds. The work reported here describes an investigation of droxicam using ^{1}H and ^{13}C n.m.r. spectroscopy, mass spectrometry, and a single-crystal *X*-ray structure analysis.

Results and Discussion

Nuclear Magnetic Resonance Spectroscopy.—The ^{1}H and ^{13}C n.m.r. chemical shifts and coupling constants of compound (**1**) are shown in Table 1. In describing ^{13}C n.m.r. multiplet patterns, direct refers to strong splittings by directly bonded nuclei, and long-range to small splittings by more remote nuclei. The ^{13}C n.m.r. chemical shifts and ^{1}H n.m.r. chemical shifts and coupling constants of the pyridine ring of compounds (**1**) and (**3**)—(**5**) are shown in Table 2. The ^{13}C n.m.r. chemical shifts of the 1,3-oxazine ring of compounds (**1**)—(**10**) are shown in Table 3. The numbering of all carbon atoms in the Tables is the same as that adopted in the *X*-ray crystallographic structure (Figure 3) in order to provide direct comparison.

Study of the ^{1}H n.m.r. spectrum of the monosubstituted pyridine of droxicam (**1**) allowed immediate assignment of the resonance at δ 8.64 to H(20). Comparison of the spectrum for (**1**) with spectra of compounds (**3**)—(**5**) (disubstituted pyridines) (Table 2) indisputably assigned the resonance of (**1**) at δ 7.66 to H(17) and the resonance at δ 7.58 to H(19). Indeed, the 4-methyl-substituted compound (**4**) showed a singlet at δ 7.47 (−0.19)* assigned to H(17) and a doublet (^3J 5 Hz) at δ 7.40 (−0.18)* assigned to H(19). In contrast, the 6-acetylamino-substituted compound (**5**) exhibited a doublet (^3J 7 Hz) at δ 7.31 (−0.35)* attributed to H(17), and a downfield shift at H(19) was observed (+0.94).*

The ^{13}C n.m.r. of 4-methylpyridyl (**4**), 6-methylpyridyl (**3**), and 6-acetylaminopyridyl (**5**) analogues were also examined and the substituent effects have been compared (Table 2). Acetylamino substitution at C(20) to give compound (**5**) produces an upfield shift at C(17) (−5.5 p.p.m.) and at C(19) (−10.7 p.p.m.); in contrast C(10) (123.6 p.p.m.) and C(13) (125.7 p.p.m.) remained almost unchanged. In spite of the upfield shift observed at C(17) (−3.4 p.p.m.) and at C(19) (−0.9 p.p.m.) for methyl substitution at C(20) in (**3**) the chemical shifts of C(10) (123.4 p.p.m.) and C(13) (125.4 p.p.m.) remained almost unchanged. Methyl substitution at C(18) in (**4**) produces a pronounced (+10.9 p.p.m.) downfield shift at that carbon.

The carbon atoms C(10), C(14), and C(17) all appear within the narrow range 123.6, 123.97, and 123.91 p.p.m. The same situation occurs for C(13) and C(19) that appear at 125.6 and 125.2 p.p.m. The assignment of the resonance at 123.97 p.p.m. to C(14) was obvious from an examination of the coupled spectrum. The two-dimensional proton–carbon chemical shift correlation spectrum of (**1**), presented as contour plot (Figure 1), permits assignment of the resonance at 123.91 p.p.m. to C(17), that at 125.2 p.p.m. to C(19), and that at 149.6 p.p.m. to C(20).

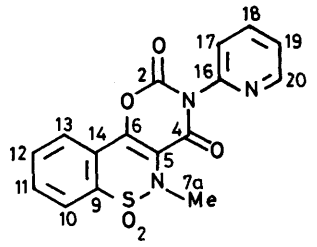
For assignment of the protonated carbons corresponding to the benzene ring the studies of Chauhan and Still[4] on thiochromone, thiochroman-4-one, and the related 1,1-dioxides, and of Whipple[5] on the assignment of ^{13}C resonances in unsymmetrical *ortho*-disubstituted benzene rings applied to 4-hydroxy-1,2-benzothiazine 1,1-dioxides were taken into account. The resonances assigned in these studies exhibit a considerable parallelism to those corresponding to the C(10), C(11), C(12), and C(13) carbon atoms of compound (**1**): 123.1, 133.0, 135.0, and 128.5 for thiochromone 1,1-dioxide, 123.7, 133.3, 134.9, and 128.8 for thiochromane 1,1-dioxide, and 124.5, 132.3, 132.8, and 126.4 p.p.m. for 4-hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide. In contrast, the 2D spectrum showed the correlation between the C(10), C(11), C(12), C(13), and C(18) carbons, and the strongly overlapping multiplets of their corresponding protons.

Examination of the coupled spectrum of (**1**) showed singlets at 158.1 and 146.0 p.p.m. It was then obvious to assign the resonance at 146.0 p.p.m. to C(2). The fact that C(6) was coupled with H(13) and C(16) was coupled with H(17), H(18), and H(20) permitted assignment of the narrow range of resonances at 148.6 and 147.6 p.p.m. The carbon C(5) was split by the protons of the methyl group and showed a quartet in the coupled spectrum at 117.3 p.p.m.

The ten compounds appearing in Table 3 under the generic heading '1,3-oxazine-2,4-dione' strictly include only nine members of this class of compounds. However, the thione (**2**) possesses as a common spectroscopic feature the fact that

* Figures in brackets are Δδ, *i.e.*, δ Droxicam − δ compound for the same proton.

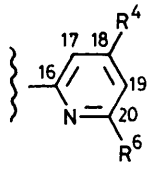
Table 1. N.m.r. data of Droxicam (**1**) in [$^2H_6$]DMSO



Carbon atom	^{13}C N.m.r.[a]	Multiplicity[b] Direct	Multiplicity[b] Long-range	^{1}H N.m.r.[a]	Multiplicity[b] Direct	Multiplicity[b] Long-range
2	146.0	s				
4	158.1	s				
5	117.3	s	q, $^3J_{CH}$ 2.8			
6	148.6	s	d, $^3J_{CH}$ 4.2			
9	134.0	s	m			
10	123.6	d, $^1J_{CH}$ 170	m	8.05	m	
11	133.7	d, $^1J_{CH}$ 166	m	8.01	m	
12	134.2	d, $^1J_{CH}$ 169	d, $^3J_{CH}$ 7.4	8.00	m	
13	125.6	d, $^1J_{CH}$ 167	m	8.14	m	
14	123.97	s	m			
16	147.6	s	ddd, $^3J_{CH}$ 10.3, $^3J_{CH}$ 9.9, $^2J_{CH}$ 1.8			
17	123.91	d, $^1J_{CH}$ 171	d, $^3J_{CH}$ 6.8	7.66	ddd, $^3J_{17,18}$ 7.90, $^4J_{17,19}$ 1.84	
18	139.4	d, $^1J_{CH}$ 167	d, $^3J_{CH}$ 7.3	8.09	m	
19	125.2	d, $^1J_{CH}$ 169	m	7.58	ddd, $^3J_{18,19}$ 7.49, $^3J_{19,20}$ 4.84	
20	149.6	d, $^1J_{CH}$ 179	dd, $^3J_{CH}$ 7.3, $^2J_{CH}$ 3.8	8.64	ddd, $^4J_{18,20}$ 1.88, $^5J_{17,20}$ 0.85	
7a	36.6	q, $^1J_{CH}$ 143.5		3.12	s	

[a] Chemical shifts (δ) are measured in p.p.m. from the central solvent line and corrected to Me_4Si using an offset of 39.7 p.p.m. for ^{13}C and 2.50 p.p.m. for ^{1}H n.m.r. spectroscopy. [b] Coupling constant values in Hz.

Table 2. N.m.r. data[a] of the pyridine ring of 5-methyl-3-(4- or 6-substituted-2-pyridyl)-2*H*,5*H*-1,3-oxazino[5,6-*c*][1,2]benzothiazine-2,4(3*H*)-dione 6,6-dioxide derivatives



Compd.	R^4	R^6	Carbon atom 16	17	18	19	20	Hydrogen atom 17	19
(**1**)	H	H	147.6	123.91	139.4	125.2	149.6	7.66 (ddd, ^3J 7.9 Hz)	7.58 (ddd, ^3J 7.5 and ^3J 4.8 Hz)
(**3**)	H	Me	146.6	120.5	139.3	124.3	158.5	7.42 (d, ^3J 7.6 Hz)	7.45 (d, ^3J 7.5 Hz)
(**4**)	Me	H	147.5	124.0	150.3	125.7	149.0	7.47 (s)	7.40 (d, ^3J 5.0 Hz)
(**5**)	H	NHCOMe	145.5	118.4	141.2	114.5	152.2	7.31 (d, ^3J 7.0 Hz)	8.52 (d, ^3J 7.5 Hz)

[a] Solvent [$^2H_6$]DMSO. See footnotes of Table 1.

chemical shifts of C(4), C(5), and C(6) are in the same range as those of the corresponding diones. Comparison of the chemical shifts reveals a general similarity in the carbonyl and thione systems. Indeed, in the dione (**1**) and thione (**2**) pair the only significant change is a downfield shift of +34.1 p.p.m. in the C(2) resonance on going from the carbonyl to the thione. This gives excellent corroboration of the correctness of the C(4) assignment of compound (**1**) (158.1 p.p.m.).

Further evidence in support of the assignments of the oxazino ring comes from the detection and measurement of direct selective heteronuclear ^{13}C {^{1}H} nuclear Overhauser enhancements by use of the recently described[6] HETNOE technique. On weak irradiation at 3.12 p.p.m. compound (**1**) showed positive n.O.e. enhancements on quaternary carbons located three [C(5)] and four [C(4), C(6), and C(9)] bonds away from the methyl protons. The percentage of n.O.e. enhancements

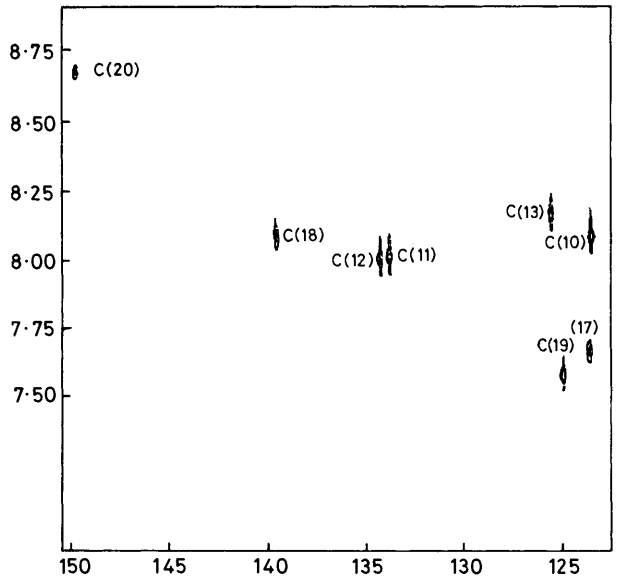
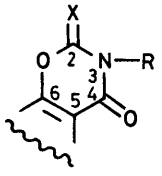


Figure 1. Heteronuclear ^{1}H-^{13}C chemical shift correlated spectrum of (**1**). Assignments are given

Table 3. ^{13}C N.m.r. chemical shifts[a] of 1,3-oxazino-2,4-dione ring of 5-methyl-3-substituted-2*H*,5*H*-1,3-oxazino[5,6-*c*][1,2]benzothiazine-2,4(3*H*)-dione 6,6-dioxide derivatives



Compd.	X	R	Carbon atom 2	4	5	6
(**1**)	O	2-Pyridyl	146.0	158.1	117.3	148.6
(**2**)	S	2-Pyridyl	180.1	155.3	119.4	150.7
(**3**)	O	6-Methyl-2-pyridyl	145.9	157.9	117.1	148.4
(**4**)	O	4-Methyl-2-pyridyl	145.7	157.9	117.1	148.4
(**5**)	O	6-Acetylamino-2-pyridyl	145.9	158.0	117.1	148.7
(**6**)	O	H	145.8	158.9	117.0	148.6
(**7**)	O	Methyl	146.4	158.0	116.6	147.2
(**8**)	O	Phenyl	146.4	158.2	117.4	147.8
(**9**)	O	5-Methyl-3-isoxazolyl	145.0	157.3	117.0	148.6
(**10**)	O	2-Pyrimidinyl	145.4	157.6	116.9	149.3

[a] Solvent [$^{2}H_6$]DMSO. See footnotes of Table 1.

were 59% at 117.3 p.p.m., 38% at 158.1 p.p.m., 28% at 148.6 p.p.m., and only 4% at 134.0 p.p.m.

Mass Spectrometry.—The electron impact (e.i.) spectra showed the molecular ions of compounds (**1**) (*m/z* 357), (**2**) (*m/z* 373), and (**6**) (*m/z* 280) (Table 4). The fragmentation mode of the 1,3-oxazino[5,6-*c*][1,2]benzothiazine-2,4-diones may be explained by elimination of the corresponding isocyanate.

The fragmentation pattern of compounds (**1**), (**2**), and (**6**) (Figure 2) revealed intense ions at *m/z* 237, corresponding to a loss of 120 a.m.u. (2-pyridyl isocyanate), 136 a.m.u. (2-pyridyl isothiocyanate), and 43 a.m.u. (isocyanic acid) respectively.

The molecular ion at *m/z* 237 can lose SO_2[7–9] to yield *m/z* 173 which either undergoes further loss[10] of CO and HCN leading to *m/z* 117 or loses 69 a.m.u. (C_3H_3NO) to give the base peak *m/z* 104. A loss of C_3H_3NO from the ion at *m/z* 237 leading to *m/z* 168 followed by the loss of SO_2 offers an alternative route to fragment *m/z* 104.

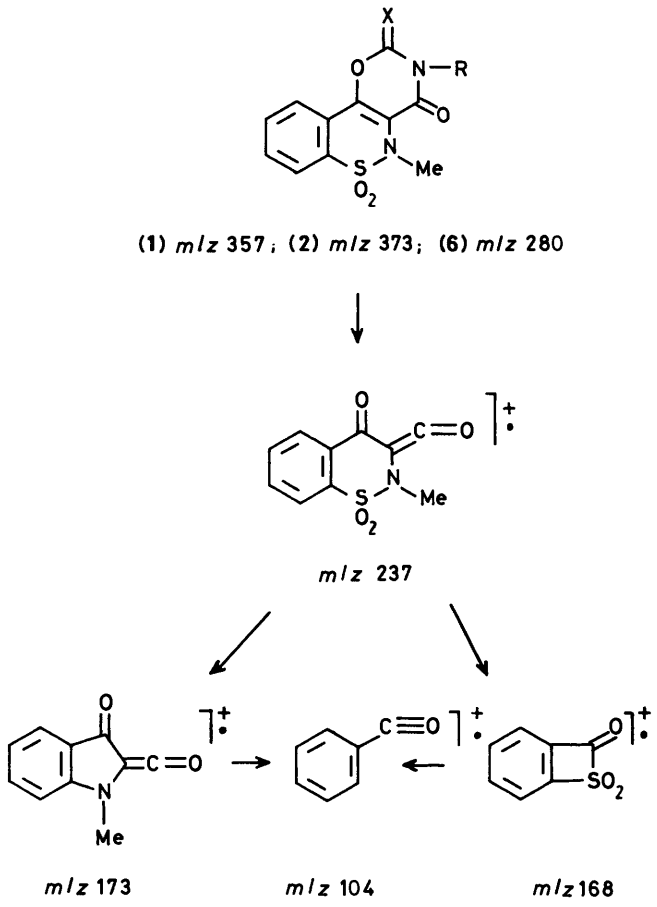


Figure 2. The mass spectrometric fragmentation pattern of compounds (**1**), (**2**), and (**6**)

X-Ray Results.—A diagram of one molecule of Droxicam with the relevant atom numbering scheme and principal ring torsion angles is shown in Figure 3. In the perspective view of the unit-cell contents, including hydrogen atoms, there are no indications of any intermolecular association forming hydrogen-bonded dimers. The final fractional atomic co-ordinates are given in Table 5, and bond lengths and angles in Table 6.

Crystal structure analyses of two benzothiazines have been determined previously.[11,12] We now report the first crystallographic study of a 1,3-oxazinobenzothiazine-2,4-dione. A salient feature of the molecule of droxicam is the almost planar conformation of the three-ring fused system (angles between normals to planes: benzene–thiazine 15.86°, thiazine–oxazine 13.05° benzene–oxazine 17.79°) and that the pyridine ring is almost perpendicular to the oxazine ring (angle between the normal to planes = 86.17°). The torsion angles along the bonds connecting this part of the molecule are C(2)–N(3)–C(16)–N(15) 95.89°, C(2)–N(3)–C(16)–C(17) 83.95°, C(4)–N(3)–C(16)–N(15) 87.20°, and C(4)–N(3)–C(16)–C(17) 92.97°.

Some small, but significant, deviations from planarity are nevertheless observed. The thiazine ring exhibits a half-chair conformation as in the case of 4-hydroxy-2-methyl-*N*-(2-pyridyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide.[11] The conformation of the ring skeleton described by the

Table 4. Mass spectrometric fragmentation of compounds (**1**), (**2**), and (**6**)[a]

m/z	(1)	(2)	(6)
373		12	
357	5		
280			13
237	35	49	12
173	8	5	2
168	21	25	12
117	59	64	57
104	100	100	100

[a] Intensity of some of the more important fragments expressed as a percentage of the base peak.

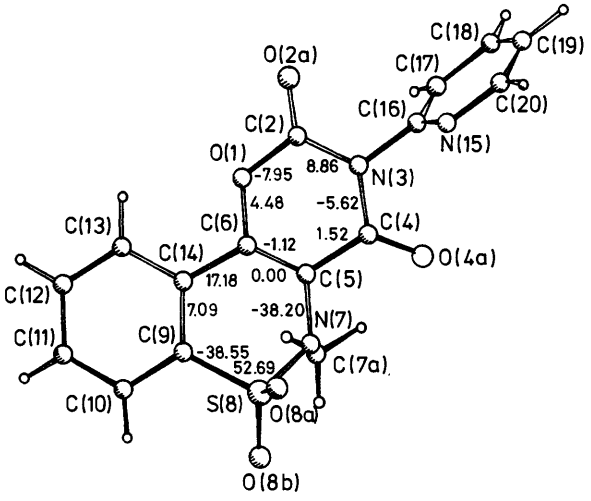


Figure 3. *X*-Ray crystallographic structure of droxicam showing the numbering used in the crystal analysis and principal ring torsion angles in degrees

deviations of the atoms from the least-squares plane shows that S(8) and N(7) are displaced −0.362 Å and 0.324 Å respectively while carbon atoms are displaced −0.062 Å (C5), −0.172 Å (C6), 0.139 Å (C9), and 0.079 Å (C14). The torsion angles in the ring (Figure 3) also provide evidence for a half-chair conformation.

The oxazine and the pyridine rings are planar with a mean value departure of the atoms from the plane of the ring of 0.019 and 0.011 Å respectively.

With regard to molecular geometry of the phenyl ring, Table 6 shows that bond lengths C(11)–C(12) and C(10)–C(11) are shortened to 1.373(4) Å, and in the thiazine ring C(9)–S(8) (1.751 Å) and S(8)–N(7) (1.651 Å) are in the range common to heterocyclic sulphamides.[13]

The average angle around the nitrogen atoms was found to have the following values: for N(3) 120.0° and for N(7) 114.9°. These results indicate that the nitrogen N(3) of the oxazine ring should be considered as close to an sp^2 hybridization state.

Experimental

N.m.r. Spectroscopy.—N.m.r. spectra were carried out in the pulsed Fourier transform mode with an internal deuterium lock, at 100 MHz (^{1}H) and 25.1 MHz (^{13}C) on a Bruker-AM-100 and at 200 MHz (^{1}H) and 50.3 MHz (^{13}C) on a Varian-XL-200. Simultaneous acquisition of blank and irradiated spectra for observation in difference mode was employed in order to minimize drift errors. The spectra were recorded in [$^2H_6$]-dimethyl sulphoxide (DMSO) at concentrations of 14—18% w/v except for compound (**2**), the concentration of which was of 3% w/v. Operating temperature was 310 K. The heteronuclear ^{1}H-^{13}C shift-correlated experiment for (**1**) was performed using the standard Varian pulse program XCOR.[14] The measurement of long-range selective heteronuclear ^{13}C {^{1}H} n.O.e. enhancements was achieved by means of the microprogram previously described.[6] N.O.e. enhancements factors were calculated from peak height ratios. The reference chosen was the central peak of [$^2H_6$]DMSO. Thus $\eta_\delta = [(I/I\text{ref})_N/(I/I\text{ref})_B] - 1$, where the subscripts N and B refer to the n.O.e. spectrum and base spectrum, respectively.

Table 5. Fractional atomic co-ordinates ($\times 10^4$) with their e.s.d.s

	x	*y*	*z*
O(1)	5 526(2)	577(1)	11 389(1)
C(2)	6 862(3)	494(2)	12 216(2)
O(2a)	6 804(3)	−34(1)	12 924(2)
N(3)	8 192(3)	1 025(1)	12 144(2)
C(4)	8 204(3)	1 709(2)	11 393(2)
O(4a)	9 369(2)	2 186(1)	11 435(2)
C(5)	6 685(3)	1 765(2)	10 592(2)
C(6)	5 436(3)	1 222(2)	10 622(2)
N(7)	6 574(2)	2 455(1)	9 813(2)
C(7a)	6 187(4)	3 283(2)	10 297(3)
S(8)	5 578(1)	2 192(1)	8 573(1)
O(8a)	5 505(2)	1 527(2)	8 153(2)
O(8b)	5 252(3)	2 957(2)	7 939(2)
C(9)	3 728(3)	1 769(2)	8 915(2)
C(10)	2 221(3)	1 907(2)	8 241(2)
C(11)	826(3)	1 522(2)	8 523(3)
C(12)	917(3)	1 017(2)	9 459(3)
C(13)	2 406(3)	888(2)	10 152(2)
C(14)	3 845(3)	1 273(2)	9 890(2)
N(15)	10 804(3)	402(3)	12 587(2)
C(16)	9 672(3)	886(2)	12 958(2)
C(17)	9 796(4)	1 239(2)	13 995(3)
C(18)	11 190(4)	1 049(2)	14 748(3)
C(19)	12 380(4)	539(2)	14 410(3)
C(20)	12 164(4)	247(2)	13 324(3)
H(7a1)	5 301(16)	3 277(13)	10 588(14)
H(7a2)	6 098(15)	3 712(13)	9 732(14)
H(7a3)	7 127(15)	3 410(12)	10 982(14)
H(10)	2 237(15)	2 253(12)	7 577(14)
H(11)	−205(16)	1 599(13)	8 071(14)
H(12)	−96(15)	729(13)	9 639(14)
H(13)	2 458(15)	563(13)	10 859(14)
H(17)	8 974(15)	1 593(13)	14 139(14)
H(18)	11 275(15)	1 302(12)	15 517(14)
H(19)	13 436(16)	373(12)	14 926(14)
H(20)	13 011(15)	−98(13)	13 042(14)

Mass Spectrometry.—Mass spectra were determined with a Hewlett Packard 5895 spectrometer using the direct insertion method and electron-impact at an ionizing voltage of 70 eV.

Crystal Data.—$C_{16}H_{11}N_3O_5S$, M = 357.34. Monoclinic, a = 8.160(3), b = 15.698(3), c = 12.058(2) Å, α = 90.0°, β = 98.09(2)°, γ = 90.0°, V = 1 529.2(6) Å^3 (by least-squares refinement on diffractometer angles for 25 automatically centred reflections), λ = 0.710 69 Å, space group $P2_1/c$, Z = 4, D_x = 1.56 g cm^{-3}. Colourless single crystals were grown from acetone by slow evaporation of the solvent. Crystal dimensions: 0.32 × 0.45 × 0.60 mm, μ(Mo-K_α) = 2.35 cm^{-1}.

Data Collection and Processing.—Enraf–Nonius CAD4 diffractometer, ω–2θ mode, graphite-monochromated Mo-K_α radiation; 2 938 reflections measured ($-9 \geqslant h \geqslant 9$, $0 \geqslant k \geqslant$

Table 6. Bond lengths (Å) and bond angles (°) with their e.s.d.s

Bond	Length	Bond	Length
C(2)–O(1)	1.376(3)	C(13)–C(12)	1.390(4)
C(6)–O(1)	1.366(3)	C(14)–C(13)	1.396(3)
O(2a)–C(2)	1.195(3)	C(16)–N(15)	1.321(3)
N(3)–C(2)	1.381(3)	C(20)–N(15)	1.344(3)
C(4)–N(3)	1.405(3)	C(17)–C(16)	1.359(4)
C(16)–N(3)	1.462(3)	C(18)–C(17)	1.384(4)
O(4a)–C(4)	1.205(3)	C(19)–C(18)	1.364(4)
C(5)–C(4)	1.464(3)	C(20)–C(19)	1.375(4)
C(6)–C(5)	1.333(3)	H(7a1)–C(7a)	0.874(14)
N(7)–C(5)	1.427(3)	H(7a2)–C(7a)	0.953(18)
C(14)–C(6)	1.466(3)	H(7a3)–C(7a)	1.064(14)
C(7a)–N(7)	1.476(4)	H(10)–C(10)	0.969(18)
S(8)–N(7)	1.651(2)	H(11)–C(11)	0.944(13)
O(8a)–S(8)	1.423(2)	H(12)–C(12)	0.993(15)
O(8b)–S(8)	1.427(2)	H(13)–C(13)	0.989(17)
C(9)–S(8)	1.751(2)	H(17)–C(17)	0.906(16)
C(10)–C(9)	1.392(3)	H(18)–C(18)	1.002(17)
C(14)–C(9)	1.402(3)	H(19)–C(19)	1.023(13)
C(11)–C(10)	1.373(4)	H(20)–C(20)	0.976(16)
C(12)–C(11)	1.373(4)		

Bond	Bond angle	Bond	Bond angle
C(6)–O(1)–C(2)	121.5(2)	C(9)–S(8)–N(7)	102.3(1)
O(2a)–C(2)–O(1)	118.5(2)	C(9)–S(8)–O(8a)	108.9(1)
N(3)–C(2)–O(1)	116.5(2)	C(9)–S(8)–O(8b)	110.1(1)
N(3)–C(2)–O(2a)	125.0(2)	C(10)–C(9)–S(8)	121.6(2)
C(4)–N(3)–C(2)	125.4(2)	C(14)–C(9)–S(8)	116.6(2)
C(16)–N(3)–C(2)	116.7(2)	C(14)–C(9)–C(10)	121.7(2)
C(16)–N(3)–C(4)	117.8(2)	C(11)–C(10)–O(9)	118.8(3)
O(4a)–C(4)–N(3)	121.7(2)	C(12)–C(11)–C(10)	120.5(2)
C(5)–C(4)–N(3)	112.9(2)	C(13)–C(12)–C(11)	121.3(3)
C(5)–C(4)–O(4a)	125.4(2)	C(14)–C(13)–C(12)	119.5(2)
C(6)–C(5)–C(4)	121.5(2)	C(9)–C(14)–C(6)	119.1(2)
N(7)–C(5)–C(4)	116.7(2)	C(13)–C(14)–C(6)	122.8(2)
N(7)–C(5)–C(6)	121.7(2)	C(13)–C(14)–C(9)	118.0(2)
C(5)–C(6)–O(1)	121.6(2)	C(20)–N(15)–C(16)	115.6(2)
C(14)–C(6)–O(1)	114.0(2)	N(15)–C(16)–N(3)	114.2(2)
C(14)–C(6)–C(5)	124.3(2)	C(17)–C(16)–N(3)	120.3(2)
C(7a)–N(7)–C(5)	113.9(2)	C(17)–C(16)–N(15)	125.5(2)
S(8)–N(7)–C(5)	112.6(2)	C(18)–C(17)–C(16)	117.6(3)
S(8)–N(7)–C(7a)	118.2(2)	C(19)–C(18)–C(17)	119.0(3)
O(8a)–S(8)–N(7)	106.7(1)	C(20)–C(19)–C(18)	118.6(3)
O(8b)–S(8)–N(7)	107.8(1)	C(19)–C(20)–N(15)	123.6(3)
O(8b)–S(8)–O(8a)	119.7(1)		

18, $0 \geqslant l \geqslant 14$), 1 658 reflections observed with $I > 2.5\sigma(I)$. No absorption corrections were made. The monitor reflections were measured after every 50 reflections; these intensities dropped by an average of 0.9% over the period of data collection.

Structure Analysis and Refinement.—The structure was resolved by direct methods applying the MULTAN 11/84[15] system, the E-map based on the phase set with highest figure of merit established positions for all non-hydrogens atoms. The refinement of the structural model was performed by anisotropic full-matrix least-squares methods (SHELX-76).[16] All hydrogen atoms were located from a difference Fourier synthesis and refined with global isotropic temperature factors. In the final difference Fourier map calculated after the last cycle there were no peaks >0.17 e Å^{-3}. The weighting scheme $w = 1/[\sigma^2(F_o) + 0.000\,868F_o^2]$, with $\sigma(F_o)$ from counting statistics gave satisfactory agreement analyses. Final R and R_w values are 0.0348 and 0.0374. Scale factor 1.420(3). Atomic scattering factors and corrections for anomalous dispersion were taken from the International Tables for *X*-Ray Crystallography.[13] Geometrical calculations were performed with XANADU[17] and the perspective stereoscopic view with PLUTO.[18] The anisotropic thermal parameters have been deposited *

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* *Supplementary data* (see section 5.6.3 of Instructions for Authors in *J. Chem. Soc., Perkin Trans. 2*, 1987, Issue 1). Thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

References

1 *Drug of the Future*, 1986, **11**, 835; J. Esteve Soler, Fr. Demande FR 2.528.433, 1982 (*Chem. Abstr.*, 1984, **100**, 191893j); J. Esteve Soler, Eur. Pat. Appl. EP 99 770/1986; J. Esteve Soler, U.S. P. 4 563 452/1986.
2 A. J. Farré, M. Colombo, M. Fort, B. Gutiérrez, L. Rodriguez, and R. Roser, *Methods Find. Exp. Clin. Pharmacol.*, 1986, **8**, 407.
3 A. Esteve, L. Martínez, R. Roser, and R. Sagarra, *Methods Find. Exp. Clin. Pharmacol.*, 1986, **8**, 423.
4 M. S. Chauhan and I. W. J. Still, *Can. J. Chem.*, 1975, **53**, 2880.
5 E. B. Whipple, *Org. Magn. Reson.*, 1977, **10**, 23.
6 F. Sánchez-Ferrando, *Magn. Reson. Chem.*, 1985, **23**, 185; C. Cativiela and F. Sánchez-Ferrando, *ibid.*, p. 1072.
7 G. Heyes, G. Holt, and A. Lewis, *J. Chem. Soc., Perkin Trans. 1*, 1972, 2351.
8 C. R. Rasmussen, *J. Org. Chem.*, 1974, **39**, 1554.
9 D. C. Hobbs, and T. M. Twomey, *Drug. Metab. Dispos.*, 1981, **9**, 114.
10 M. Mihalic, H. Hofman, F. Kajfez, J. Kuftinec, N. Blazevic, and M. Zinic, *Acta. Pharm. Jugosl.*, 1982, **32**, 13.
11 B. Kojić-Prodić and Z. Ružić-Toroš, *Acta Crystallogr., Sect. B*, 1982, **38**, 2948.
12 C. P. Norris, H. Berke, and J. G. Lombardino, *J. Heterocycl. Chem.*, 1985, **22**, 837.
13 'International Tables for *X*-Ray Crystallography,' Kynoch Press, Birmingham, 1974.
14 The XCOR sequence written by D. L. Foxal, Varian, Palo Alto, USA, 1982, was used.
15 P. Main, G. Germain, and M. M. Woolfson, 'MULTAN 11/84. A System of Computer Programs for the Automatic Solution of Crystal Structures from *X*-Ray Diffraction Data,' University of York, England, 1984.
16 G. M. Sheldrick, 'SHELX 76. Program for Crystal Structure Determination,' University of Cambridge, England, 1976.
17 P. Roberts and G. M. Sheldrick, 'XANADU. Program for Crystallographic Calculations,' University of Cambridge, England, 1975.
18 W. D. S. Motherwell and W. Clegg, 'PLUTO. Program for Plotting Molecular and Crystal Structures,' University of Cambridge, England, 1978.

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