Crystal and Molecular Structures of Antiarthritica. I. *N*-Acetyl-D,L-penicillamine – $C_7H_{13}NO_3S$

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Bakjord, E. D. and Pedersen, B. F., 1988. Crystal and Molecular Structures of Antiarthritica. I. *N*-Acetyl-D,L-penicillamine – $C_7H_{13}NO_3S$. – Acta Chem. Scand., Ser. A 42: 8–15.

Crystal and experimental data for the title compound are as follows: $C_7H_{13}NO_3S$, M.w. = 191.23, monoclinic, $P2_1/c$, a = 6.054(1), b = 10.096(3), c = 14.963(1) Å, β = 95.78(2)°, V = 909.7 Å^3, Z = 4, D_m = 1.35 Mg m^{-3}, D_x = 1.40 Mg m^{-3}, λ(Mo$K\alpha$) = 0.71069 Å, F(000) = 408, T = 113 K, R = 0.0541 for 1985 unique reflections. There are two planar groups in the molecule, approximately normal to each other. There is some disorder in the structure since sulfur and one methyl group seem to occupy two different sets of positions in the ratio 4:1. Otherwise, distances and angles in this molecule closely resemble the corresponding values found in the related *N*-acetyl-L-cysteine. As usual in *N*-acyl amino acids without *N*-substituents there are N–H···O hydrogen bonds. O–H···O hydrogen bonds are also present and each molecule is hydrogen-bonded to four other ones. No intramolecular hydrogen bonds and no hydrogen bond contacts for sulfur are present.

Dedicated to Professor Olav Foss on his 70th birthday

N-acetylpenicillamine is not yet in use as a drug. In Norway, Cuprimin® is registered officially for use; the active component in this drug is the related compound penicillamine. Penicillamine has several biological effects, being used against Wilson's disease (hepatolenticular degeneration), cystinuria and serious forms of rheumatoid arthritis that do not respond to antiinflammatory or antimalarial drugs. Possible modes of antirheumatic action of the compound will be discussed elsewhere. Here, we report the crystal structure of the title compound.

Experimental

Crystals were grown from a saturated aqueous solution. Film data show the symmetry of the crystals to be monoclinic with systematic absences $h0l$ for l odd and $0k0$ for k odd, giving the space group $P2_1/c$.[1] Unit cell parameters were determined from 16 specially selected reflections and were as follows: a = 6.054(1), b = 10.096(3), c = 14.961(3) Å and β = 95.78(2)°. The density determined by the flotation point method was about 1.35 Mg m^{-3}, giving Z = 4. A crystal of dimensions 0.2×0.15×0.3 mm was used for data collection on a Syntex P$\bar{1}$ automatic diffractometer at a temperature of 113 K, using monochromated Mo$K\alpha$ radiation, ω-2θ scan, scan speed = 4° min^{-1} 2θ(max) = 60° and three test reflections (2 1 −3, 1 2 −3, 0 2 2). The total number of reflections observed with $I > 2.5\sigma(I)$ is 2077. The intensity of one of the test reflections varied somewhat, probably due to the growth of ice, as the values determined after de-icing were again normal. The intensities were normalized and corrected for Lorentz and polarization effects, but not for absorption and extinction.

Structure determination and refinement. The structure was determined by direct methods using MULTAN.[2] The set of phases with the highest FOM was used to calculate an E-map which revealed all non H atoms of the molecule.

The structure was refined by full-matrix least-

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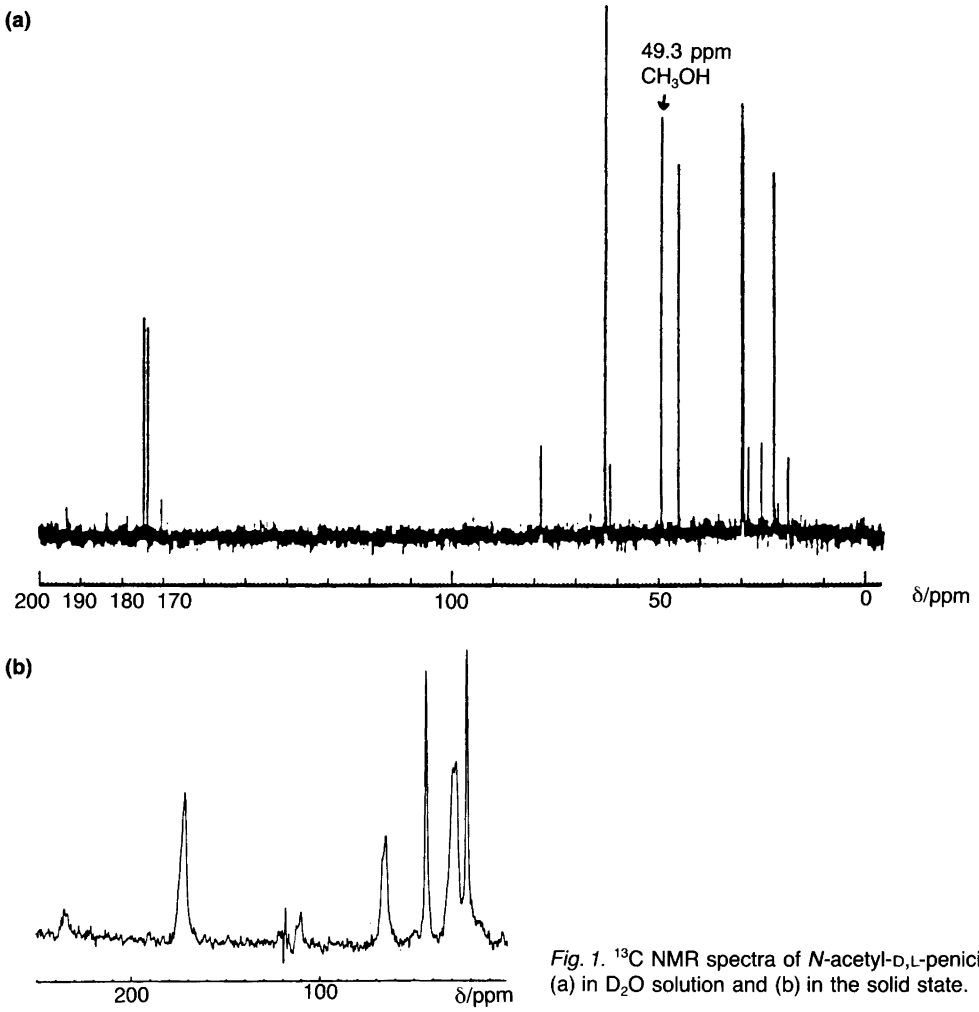

Fig. 1. ^{13}C NMR spectra of *N*-acetyl-D,L-penicillamine (a) in D_2O solution and (b) in the solid state.

squares technique.[3] Most of the hydrogen atoms were located from a Fourier difference map. We had difficulties in refining the parameters for S and C6. The refinement with isotropic temperature factors gave a negative value of B for C6 and fairly large value of B for S, indicating that too much diffracting matter had been placed in the S-position and too little in the C6-position. Refinement of the corresponding multiplicity factors gave 0.80 and 1.55, respectively. We then introduced two sets of positions for S and C6, and anisotropic thermal parameters for the other atoms. The results improved, but we had difficulties in refining carbon ($g = 0.8$) and sulfur ($g = 0.2$) atoms situated only 0.3 Å apart. This led us to believe that we possibly had a combination of two different compounds – with and without a C6 methyl substituent on C3. To obtain more detailed insight into this problem we recorded Guinier powder diffraction patterns of the compound before and after recrystallization, supplementing these measurements with NMR and MS spectroscopic measurements (Figs. 1 and 2, Tables 1 and 2).

The conclusion reached was that the compound under study was *N*-acetyl-D,L-penicillamine, $C_7H_{13}NO_3S$. Further refinement was then carried out on this basis, introducing disorder in

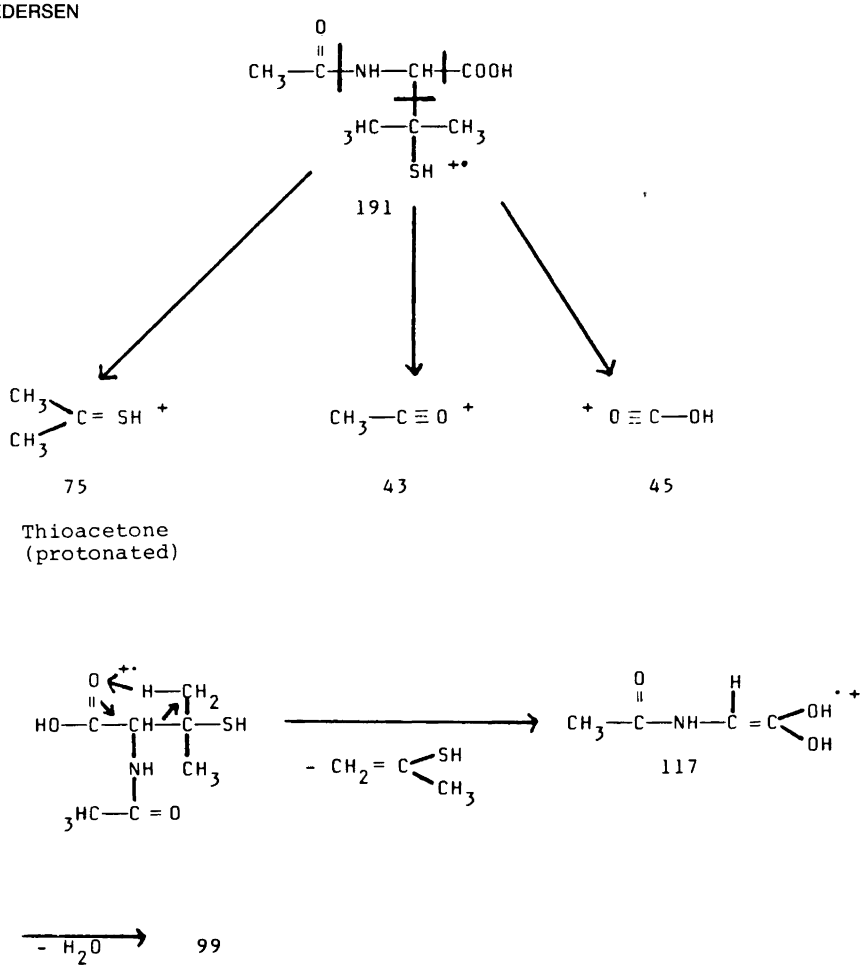

Fig. 2. Mass spectrometric fragmentation of *N*-acetyl-D,L-penicillamine.

the positions of sulfur and C6 and using isotropic thermal parameters for C6 and for sulfur in the position with occupancy of 0.2. As the C6 atom with $g = 0.2$ has a diffracting power approximately equal to that of hydrogen, it is unlikely to be properly refined here. The temperature factors could not be refined simultaneously with the g-factors, and one set was therefore kept constant while the other set was refined. The hydrogen atoms on the methyl groups and on sulfur were

Table 1. ^{13}C NMR signals (δ/ppm) and their assignments.

Solution in D_2O	Solid state	Assignment
22.07	22.14	CH_3 in acetyl
29.52, 29.74	29.50, 27.78	$(CH_3)_2$ in $(CH_3)_2$–C–SH
45.13	43.77	C in $(CH_3)_2$–C–SH
62.80	64.98	CH in C2–H10
173.62, 174.55	171.43	C=O in acetyl and COOH

(a)				(b)	
Mass	% Ht. mod.	Mass	% Ht. mod.	Mass	% Ht. mod.
27.2	5.0	82.0	0.5	86.1	0.1
28.1	32.6	83.0	0.6	87.0	0.3
29.0	3.0	84.1	0.2	88.0	0.1
29.8	3.7	85.0	0.5	89.0	0.1
30.9	0.3	86.0	0.4	98.0	0.7
32.0	5.7	87.0	5.6	98.9	1.7
33.0	0.9	88.0	1.4	99.9	0.2
34.1	1.5	89.0	0.6	104.0	1.6
35.1	0.2	89.9	0.2	112.0	2.2
36.1	1.3	91.0	0.5	113.0	0.7
37.1	0.3	92.0	0.1	114.0	5.5
38.0	0.8	95.1	0.1	115.0	0.7
38.9	7.0	96.1	0.1	116.0	2.1
39.8	1.1	97.0	0.5	117.0	7.8
40.9	24.9	98.0	1.2	118.0	1.1
42.0	4.7	98.9	31.2	127.0	0.2
43.1	47.2	99.9	2.3	129.9	1.1
44.1	2.9	100.9	0.3	130.9	0.1
45.1	3.9	102.0	0.7	132.9	0.1
46.1	0.7	103.0	0.3	139.9	6.7
47.1	5.0	104.0	4.3	140.9	0.3
48.0	0.1	105.0	0.4	142.0	0.4
48.9	0.2	106.0	0.2	146.0	13.7
49.9	0.3	111.0	0.1	147.0	0.9
50.9	0.6	112.0	2.1	147.9	0.9
52.0	0.6	113.0	2.2	149.9	4.4
53.1	2.5	114.0	2.9	150.9	0.1
54.1	1.9	115.0	1.0	156.0	0.1
55.1	3.3	116.0	2.0	157.9	10.6
56.1	7.9	117.0	37.2	158.9	0.8
57.1	13.5	118.0	2.3	159.9	3.6
58.0	1.0	118.9	0.3	161.0	0.1
58.9	8.8	124.0	0.1	172.9	0.1
59.9	1.5	127.9	0.6	173.9	15.5
60.9	0.7	128.9	0.5	174.9	1.5
62.0	0.2	129.9	0.4	175.9	0.8
64.0	0.3	130.9	0.6	187.9	0.1
65.1	0.0	131.9	0.9	189.9	0.2
66.0	0.2	134.0	0.1	191.9	100.0
67.1	0.2	138.9	0.3	192.9	8.3
68.0	1.6	139.9	1.5	193.9	5.1
69.0	2.7	140.9	0.1	194.9	0.2
69.9	18.0	145.0	0.1	197.9	0.4
71.0	9.6	146.0	0.9	205.9	1.3
72.0	5.1	148.9	0.3	231.9	0.3
73.0	1.1	157.0	0.1	382.8	0.7
74.0	8.8	157.9	0.2		
75.1	100.0	172.9	0.4		
76.1	4.2				
77.0	4.1				
78.0	0.2				
79.0	0.0				
79.8	0.2				
80.8	0.1				
81.0	0.2				

Table 3. Coordinates and thermal parameters for S, N, O and C multiplied by 10^4. Standard deviations in parentheses.[a]

Atom	*x*	*y*	*z*	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
S	8193(4)	3713(2)	4283(1)	156(7)	210(7)	174(6)	−35(6)	14(5)	37(5)
N	8055(4)	3446(3)	6323(2)	113(11)	200(14)	168(12)	−4(9)	5(9)	−30(10)
O1	5584(3)	1406(2)	6807(2)	174(11)	311(14)	246(12)	5(10)	9(9)	114(10)
O2	6173(4)	4640(2)	7258(1)	228(11)	286(13)	224(12)	34(10)	14(9)	−90(10)
O3	2494(3)	2287(2)	6111(2)	136(10)	328(14)	295(12)	4(10)	9(9)	−7(11)
C1	4499(5)	2235(3)	6246(2)	132(13)	210(16)	161(13)	5(11)	17(10)	−34(12)
C2	6029(5)	3144(3)	5756(2)	119(13)	169(14)	164(14)	8(11)	−6(10)	−13(11)
C3	6510(5)	2568(3)	4831(2)	142(13)	194(15)	167(13)	−4(11)	17(10)	2(12)
C4	7988(5)	4187(3)	7062(2)	152(13)	199(15)	165(14)	−34(12)	23(10)	6(12)
C5	10142(5)	4424(4)	7630(2)	223(16)	403(22)	174(16)	−67(15)	−19(12)	−51(15)
C7	4318(5)	2445(3)	4205(2)	202(15)	275(18)	148(14)	13(13)	−23(11)	−19(13)

[a]The form of the anisotropic temperature factor is:
$\exp[-2\pi^2(U_{11}a^{*2}h^2 + U_{22}b^{*2}k^2 + U_{33}c^{*2}l^2 + 2U_{12}a^*b^*hk + 2U_{13}a^*c^*hl + 2U_{23}b^*c^*kl)]$.

not recognizable in the difference maps. The final value of g for S was 0.79, with $1\text{-}g = 0.21$ for S′.

The function minimized in the refinement was $\Sigma w(|F_o|-|F_c|)^2$, w being the reciprocal of the variance. The final R-factor was 0.0541, with $R_w = 0.0769$ and goodness of fit $S = 3.7$. Final atomic coordinates and standard deviations are given in Tables 3 and 4.

Discussion

The numbering of the atoms is shown in Fig. 3, and bond distances and angles are given in Table 5, all with e.s.d.'s. The crystal packing is shown in Fig. 4. The principal thermal vibrational ellipsoids for the non-hydrogen atoms correspond to r.m.s. amplitudes of between 0.106 Å and 0.207 Å, the smallest amplitudes being found in the middle of the molecule, as one would expect.

The distances and angles found in *N*-acetyl-D,L-penicillamine (Table 6) closely resemble those reported[4] for *N*-acetyl-L-cysteine with one exception, viz. the C2–C3 distance, which is significantly longer in the present compound [1.555 (4) Å compared to 1.532(2) Å]. This may be related to the presence of two methyl substituents in *N*-acetyl-D,L-penicillamine which are not present in *N*-acetyl-L-cysteine. The bond angles are fairly similar in the two compounds.

According to Chen and Parthasarathy,[5] the formation of a fairly short, specific, intermolecular hydrogen bond between the carboxyl −OH and the oxygen atom of the acyl group is characteristic of *N*-acyl aminoacids and *N*-acyl peptides. Furthermore, *N*-acyl aminoacids with unsubstituted N are likely to form weaker N(acyl)–H···O=C hydrogen bonds. In the present compound both of these kinds of hydrogen bonds are found, with distances of 2.56 Å and 2.98 Å, respectively (Table 7). No hydrogen bonds involving sulfur are present here, but they are found in the related *N*-acetyl-L-cysteine,[4] in which sulfur acts both as hydrogen bond donor and acceptor. In a neutron diffraction study of L-cysteine by

Table 4. Coordinates and isotropic thermal parameters for S′, C6 and C6′ multiplied by 10^4, and for hydrogen by 10^3.

Atom	*x*	*y*	*z*	*B*
S′	7701(10)	1018(7)	4873(4)	1.7(1)
C6′	8715(47)	3634(35)	4379(21)	5.8(10)
C6	7715(17)	1138(11)	4964(7)	2.3(2)
H1	1150(16)	421(11)	732(7)	0.4(30)
H2	1029(7)	529(4)	791(3)	8.8(9)
H3	1044(8)	406(5)	807(3)	14.6(11)
H4	320(10)	173(6)	451(4)	1.4(14)
H5	338(10)	335(6)	412(4)	3.0(14)
H6	497(9)	200(5)	363(3)	5.0(12)
H10	473(8)	383(5)	572(3)	4.9(10)
HN	972(8)	307(5)	623(3)	3.5(12)
HO1	451(3)	86(2)	718(1)	2.3(3)

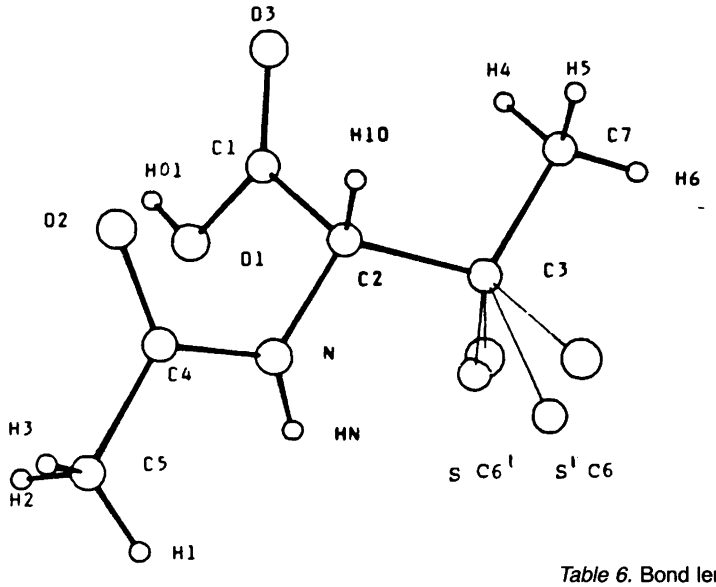

Fig. 3. Numbering of atoms in *N*-acetyl-D,L-penicillamine.

Table 5. Bond lengths (Å) and angles (°) for *N*-acetyl-D,L-penicillamine.

Bond lengths			
S–C3	1.793(3)		
S'–C3	1.722(7)		
N–C2	1.452(4)		
N–C4	1.338(4)		
O1–C1	1.313(4)		
O2–C4	1.252(3)		
O3–C1	1.212(3)		
C1–C2	1.541(4)		
C2–C3	1.555(4)		
C4–C5	1.502(4)		
C3–C7	1.551(4)		
C3–C6	1.621(11)		
C3–C6'	1.892(33)		
Angle			
C2–N–C4	120.4(2)	S'–C3–C7	106.2(3)
O1–C1–O3	124.2(3)	S'–C3–C6'	102.8(10)
O1–C1–C2	113.4(2)	C2–C3–C7	110.0(2)
O3–C1–C2	122.3(3)	C2–C3–C6	110.3(4)
N–C2–C1	111.1(2)	C2–C3–C6'	107.9(10)
N–C2–C3	112.1(2)	C7–C3–C6	110.5(4)
C1–C2–C3	112.1(2)	C7–C3–C6'	114.9(9)
S–C3–C2	109.4(2)	N–C4–O2	119.8(3)
S–C3–C7	105.4(2)	N–C4–C5	117.4(3)
S–C3–C6	111.1(4)	O2–C4–C5	122.8(3)
S'–C3–C2	115.0(3)		

Table 6. Bond lengths (Å) and angles (°) (a) for *N*-acetyl-L-cysteine and (b) for *N*-acetyl-D,L-penicillamine. Standard deviations for bonds in (a) are 0.002 Å or less.

	(a)	(b)
Bond lengths		
C4–C5	1.498	1.502(4)
C4–O2	1.247	1.252(3)
C4–N	1.337	1.338(4)
N–C2	1.452	1.452(4)
C2–C1	1.522	1.541(4)
C1–O1	1.315	1.313(4)
C1–O3	1.213	1.212(3)
C2–C3	1.532	1.555(4)
C3–S	1.808	
C3–S		1.793(3)
C3–S'		1.722(7)
Angle		
C2–N–C4	120.8	120.4(2)
O1–C1–O3	124.8	124.2(3)
O1–C1–C2	115.1	113.4(2)
O3–C1–C2	120.1	122.3(3)
N–C2–C1	112.3	111.1(2)
N–C2–C3	112.6	112.1(2)
C1–C2–C3	109.5	112.1(2)
S–C3–C2	113.9	
S–C3–C2		109.4(2)
S'–C3–C2		115.0(3)
N–C4–O2	120.6	119.8(3)
N–C4–C5	117.4	117.4(3)
O2–C4–C5	122.0	122.8(3)

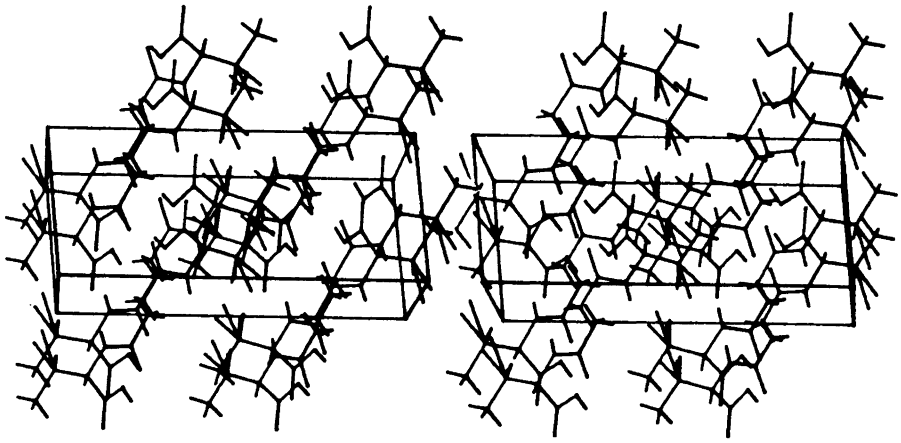

Fig. 4. Packing of *N*-acetyl-D,L-penicillamine as viewed along *b*.

Table 7. Hydrogen bonds in *N*-acetyl-D,L-penicillamine.

A–H···B	A	B	A···B /Å	H···B /Å	A–H /Å	∠A–H–B /°
N–HN···O3	*x,y,z*	*x*+1,*y*,*z*	2.98	1.88	1.09	171
O1–HO1···O2	$-x,{}^1/_2+y,{}^1/_2-z$	*x*+1,*y*−1,*z*+1	2.56	1.60	1.05	153

Kerr *et al.*,[6] S–H···S and S–H···O hydrogen bonds are believed to be present, and disorder in the positions of both sulfur and hydrogen atoms had to be postulated.

Two planes were calculated, one defined by the amide group and C2 and C5:

$$(-0.0234a - 0.0813b + 0.0360c)R - 1.431 = 0$$

and the other defined by the carboxyl group:

$$(-0.0030a + 0.0670b + 0.0491c)R - 8.149 = 0.$$

All the atoms N, HN, C4, O2, C2 and C5, defining the amide plane, are coplanar. The carboxyl group is also planar and the hydrogen atom HO is located in the carboxyl plane. *N*-acyl aminoacids seem to prefer that these two planes are either normal to each other or that they are parallel.[5] In the present compound the planes are about normal to each other, the angle being 98.2°, whereas in *N*-acetyl-L-cysteine they are closer to parallel, making an angle of 16.6°.

The conformation about C2–C3 is staggered, and N and S are *gauche*, both in *N*-acetyl-D,L-penicillamine and in *N*-acetyl-L-cysteine. According to the refinement, sulfur and C1 seem to prefer being *anti*, the conformation found in about 70 % of the molecules.

Table 8. Mean distances (Å) and angles (°) for the acyl group taken from Ref. 5, and corresponding values for *N*-acetyl-D,L-penicillamine.

	N-acetyl-D,L-penicillamine	Mean values (Ref. 5)
Bond		
C2–N	1.452(4)	1.455(5)
C4–N	1.338(4)	1.332(5)
C4–O2	1.252(3)	1.243(4)
C4–C5	1.502(4)	1.510(4)
Angle		
C2–N–C4	120.4(2)	121.9(3)
N–C4–O2	119.8(3)	121.5(3)
N–C4–C5	117.4(3)	116.6(3)
O2–C4–C5	122.8(3)	121.9(4)

The angle O1–C1–C2–N in *N*-acetyl-D,L-penicillamine is markedly greater than in *N*-acetyl-L-cysteine, due to the difference in the angle between the two planar parts of the respective molecules. When plotted in a Ramachandran plot,[7] *N*-acyl aminoacids and *N*-acyl peptides fall in the region at the upper left, $\psi \approx 300°$ and $\varphi \approx 60°$, in contrast to peptides in general, which cover a much wider region. We have found a *trans* planar conformation of the acyl group with respect to the rest of the molecule, as normally found when there are no bulky substituents on nitrogen.

Chen and Parthsarathy[5] have compared the dimensions of several *N*-acyl aminoacids. The dimensions found here compare very well and there are no significant differences between our values and their mean values (Table 8).

The packing in the crystal is shown in Fig. 4. One molecule is connected by four hydrogen bonds, i.e. two N–HN···O3 and two O1–HO1···O2 (see Table 7), to four different molecules, thus making a three-dimensional network. No natural hydrogen bonding contacts occur for sulfur.

In conclusion, we find that the possibility of disorder in the sulfur and C6 positions provides a plausible explanation of the long C3–C6 distances found, viz. 1.89 Å and 1.62 Å, as compared to the expected value of about 1.54 Å as normally found for C–C bonds. The position of C6 is very poorly determined owing to the low scattering power of 20 % of a C atom and the close vicinity of a sulfur atom. The different spectroscopic analyses performed support the conclusion that only one species is present.

Acknowledgements. We would like to thank several persons at The Department of Chemistry of this University for analytical assistance, S. Furuseth for Guinier patterns, G. Hvistendal for MS spectra, B. Pedersen for NMR spectra and B. Klewe for help during the X-ray study. Finally, we would like to thank Dr. E. Munthe, Diakonhjemmet Sykehus, who introduced us to this field.

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Received May 4, 1987.