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The Crystal Structure of 3-Hydroxy-3-isobutyl-2-pyrrolidone-5-carboxylic Acid, Lactam of 4-Hydroxy-4-isobutylglutamic Acid from *Reseda odorata* L.

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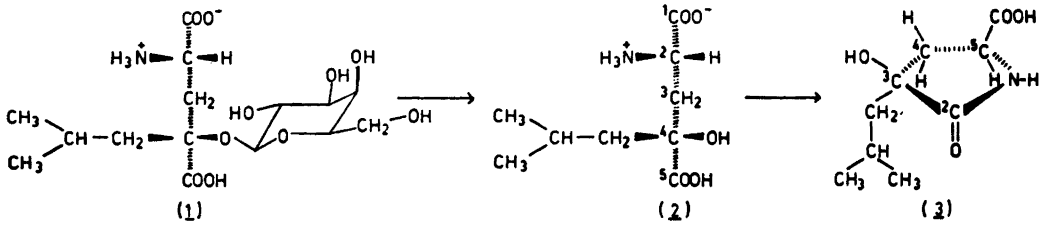
The relative configuration of 3-hydroxy-3-isobutyl-2-pyrrolidone-5-carboxylic acid has been determined by an X-ray crystal structure analysis. The compound crystallized in space group $P2_12_12_1$ with two molecules in the asymmetric unit. $a = 16.023(3)$ Å, $b = 19.349(7)$ Å, $c = 6.9053(16)$ Å. The structure was solved by direct methods using MULTAN and refined by full-matrix least-squares technique to an R of 0.137 for 645 diffractometer-collected intensities. The absolute configurations of the title compounds were deduced; the configuration of the amino acid and the lactam are 2(*S*),4(*S*) and 3(*S*),5(*S*), respectively.

The present structure analysis is part of a series of papers on the 4-substituted glutamic acid derivatives found in nature.[1,2] From inflorescences of *Reseda odorata* L. 4-(β-D-galactopyranosyloxy)-4-isobutylglutamic acid (*1*) has been isolated in appreciable amounts. Acidic hydrolysis of *1* yields the title compounds 4-hydroxy-4-isobutylglutamic acid (*2*) and 3-hydroxy-3-isobutyl-2-pyrrolidone-5-carboxylic acid (*3*).[1] Recently *2* has been identified as a constituent of *Reseda odorata* L. and the structure has been confirmed by synthesis.[3] The configurations of *1*, 2 and *3* have been tentatively proposed on the basis of similarity between ^{1}H NMR spectra of *2* and the diastereoisomeric 4-hydroxy-4-methylglutamic acids.[1]

This paper describes the results obtained from X-ray crystal structure analysis of the lactam *3* produced by acidic hydrolysis of the natural product *1*.

EXPERIMENTAL

The compound used in these investigations was prepared by hydrolysis of the natural product *1*.[1] Most of the crystals from the ether solutions were thin plates. Thicker crystals were composed of several misoriented layers. Even the crystal used for the data collection showed splitting of some reflexions, although its dimensions were only $0.08 \times 0.08 \times 0.43$ mm^3. Other recrystallization methods were tried without improvement of the crystal quality. Photographs showed that $h00$ was absent for $h \neq 2n$, $0k0$ for $k \neq 2n$. As all $00l$ reflexions except 002 were absent, it was not possible at this stage to decide whether the space group was $P2_12_12_1$ or $P2_12_12$. Structure solution showed that the first possibility was correct.



(1) (2) (3)

Crystal data.
Space group $P2_12_12_1$ (No. 19).
$a = 16.023(3)$ Å, $b = 19.349(7)$ Å, $c = 6.9053(16)$ Å
Formula weight 201.22 ($C_9H_{15}NO_4$),
$Z = 8$, $D_m = 1.25(1)$ g cm^{-3}, $D_x = 1.25$ g cm^{-3},
$V = 2141$ Å^3,
$\mu(\mathrm{Mo}K\alpha) = 2.1$ cm^{-1}.

The cell dimensions were obtained from least-squares refinement of a series of diffractometer-measured 2θ angles (Mo$K\alpha$, $\lambda = 0.71069$ Å). The density was measured by flotation in a CsCl-solution at 22 °C. $Z = 8$ corresponds to two molecules in the asymmetric unit.

All X-ray data were obtained on a Nonius three-circle automatic diffractometer with graphite-monochromated Mo$K\alpha$ radiation. The crystal was mounted on a glass rod and oriented with c along the ϕ-axis of the goniometer. Each reflexion was scanned over a range of 0.6° in both ω and $\theta/2\theta$ scanning mode. Scan speed was 0.3° min^{-1}. Background was measured between the axial reflexions and plotted against θ. The background count for each reflexion was interpolated on this curve. A standard reflexion was remeasured after every 25 reflexions. Each of the 1192 independent reflexions in the range $2.5° < \theta < 20.0°$ was measured twice (*hkl* and $\bar{h}\bar{k}\bar{l}$). The intensities were taken as a sum of four counts (both ω and $\theta/2\theta$ for each of the symmetry related reflexions) corrected for background. 645 reflexions had intensities greater than 2.5 times their corresponding standard deviations obtained from counting statistics and were considered observed. No absorption correction was applied.

Determination and refinement of the structure. The structure was solved by direct methods using MULTAN,[4] which after several attempts gave 24 of the 28 non-hydrogen atoms. Positional and isotropic temperature parameters for the non-hydrogen atoms were refined by full-matrix least-squares technique. For the hydrogen atoms calculated positions were used and isotropic temperature factors were set equal to those of the atoms to which they are bonded. The hydrogen atoms of the hydrogen bonds were placed on the line connecting the bonded atoms. Most of the hydrogen atoms could be detected from a difference electron density map and all hydrogen positions were at points with positive density.

The final R was 0.137 [$R = \sum(||F_o| - |F_c||)/\sum|F_o|$]. (645 reflexions with unit weight were used.) A difference electron density map showed peaks around the non-hydrogen atoms, as if the temperature factors were anisotropic, but all atoms would have the largest value correspond-

Table 1. Final atomic parameters (and e.s.d.'s). Fractional coordinates are $\times 10^3$ and temperature factors Å$^2 \times 10$.

	MOLECULE A				MOLECULE B			
	X	Y	Z	U	X	Y	Z	U
C1	411(2)	603(2)	700(5)	47(9)	20(2)	938(2)	-243(6)	49(10)
C2	230(2)	515(1)	642(4)	24(7)	216(2)	947(1)	-121(5)	31(8)
C3	185(2)	585(1)	680(5)	40(9)	176(2)	895(2)	46(5)	41(9)
C4	259(2)	629(2)	723(5)	53(11)	111(2)	852(1)	-83(5)	37(9)
C5	330(2)	596(2)	637(5)	38(9)	95(2)	900(1)	-259(4)	28(8)
C6	142(2)	604(1)	485(4)	25(8)	236(2)	857(2)	174(6)	55(11)
C7	104(3)	680(2)	476(7)	88(16)	282(3)	797(2)	73(6)	69(12)
C8	37(4)	693(3)	611(10)	183(29)	327(4)	753(3)	232(9)	142(21)
C9	69(4)	682(3)	250(9)	155(24)	340(3)	817(3)	-76(8)	119(19)
N1	305(2)	522(1)	617(4)	29(6)	170(2)	939(1)	-276(4)	39(7)
O1	461(1)	548(1)	719(3)	56(7)	-48(1)	907(1)	-215(3)	54(7)
O2	443(2)	661(1)	753(4)	85(9)	18(1)	1008(1)	-240(4)	65(7)
O3	129(1)	580(1)	839(3)	44(6)	124(1)	944(1)	158(3)	38(6)
O4	187(1)	457(1)	647(3)	44(6)	280(1)	977(1)	-97(3)	36(6)
H(C4)1	267	632	866	52	58	845	-8	37
H(C4)2	250	676	663	53	138	808	-128	37
H(C5)	331	614	500	38	90	871	-376	28
H(C6)1	183	597	377	25	279	889	226	55
H(C6)2	98	569	455	25	207	839	291	55
H(C7)	149	715	494	90	238	767	12	69
H(C8)1	17	741	595	184	358	714	167	140
H(C8)2	-10	660	584	184	369	783	300	140
H(C8)3	58	686	745	184	286	735	326	140
H(C9)1	43	728	222	154	367	775	-133	120
H(C9)2	117	674	158	154	310	843	-180	120
H(C9)3	27	644	230	154	385	847	-18	120
H(N1)	325	491	532	29	186	966	-377	39
H(O1)	518	550	762	56	-102	926	-189	54
H(O3)	79	556	806	44	157	972	242	38

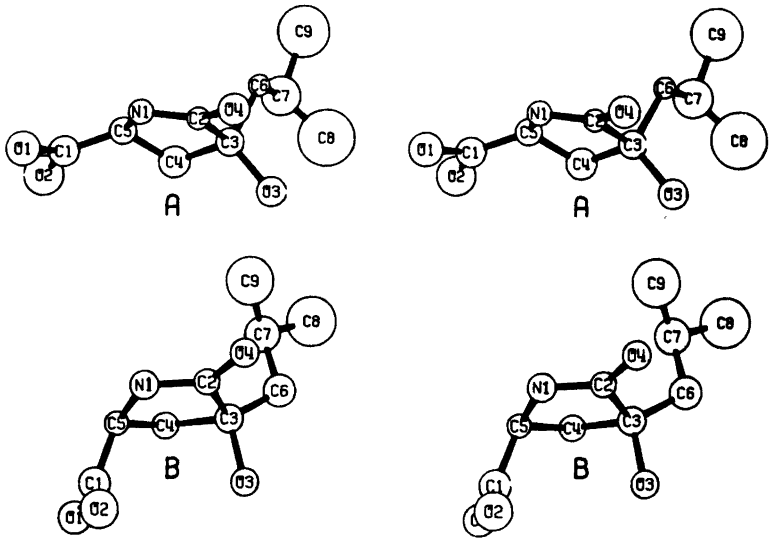


Fig. 1. Stereoscopic drawing of the two crystallographically independent molecules. The hydrogen atoms have been omitted. The thermal ellipsoids enclose 50 % probability. The molecules have been placed individually to allow comparison of the conformations.

ing to vibration in the same direction. The phenomenon is probably due to crystal defects.

The final atomic parameters are listed in Table 1.*

The input tapes for the diffractometer were produced on an IBM 1130 computer by INDIFF.[5] The remaining calculations were performed on the IBM 370/165 computer at NEUCC, Lundtofte, Denmark. The N.R.C.2. A Picker data reduction programme,[6] MULTAN,[4] and the X-RAY System [7] were used. The drawings were prepared by ORTEP [8] and the tables by POSTER.[9]

DISCUSSION

The accuracy in the molecular parameters found is low and does not allow a detailed discussion of the structure. The two crystallographically independent molecules named A and B are shown in Fig. 1.

The packing of the molecules in the unit cell is shown in Fig. 2. Six different hydrogen bonds, which involve all NH and OH groups hold the molecules together in double layers perpendicular to *b*, while the non-polar isobutyl groups lay alongside each other. The distances between layers are all greater than the sum of

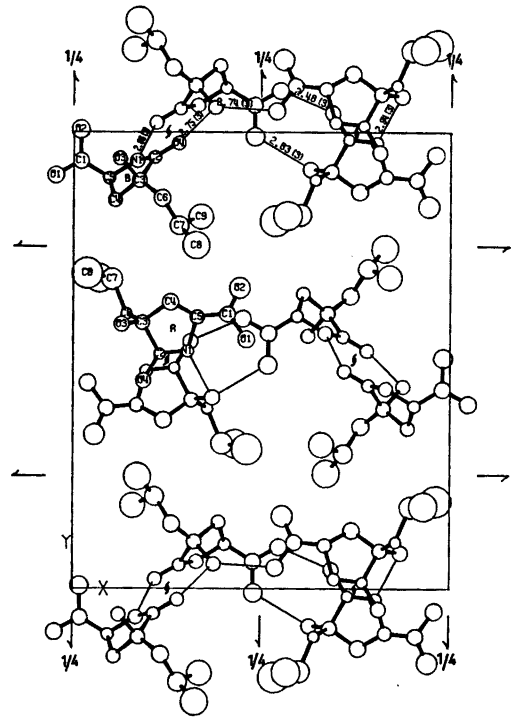


Fig. 2. The crystal structure as seen along the *c* axis. Hydrogen bonds are indicated and their length given.

* Copies of the structure factor table can be obtained from the author on request.

Table 2. Interatomic distances (Å) and angles (°).

DISTANCES	A	B	ANGLES	A	B
C1-C5	1.37(5)	1.41(4)	C5-C1-01	121(3)	120(3)
C1-01	1.35(4)	1.26(4)	C5-C1-02	123(3)	122(3)
C1-02	1.28(4)	1.34(4)	01-C1-02	115(3)	118(3)
C2-C3	1.56(4)	1.65(4)	C3-C2-N1	113(2)	106(2)
C2-N1	1.22(4)	1.31(4)	C3-C2-04	119(2)	122(3)
C2-04	1.33(3)	1.19(4)	N1-C2-04	127(3)	131(3)
C3-C4	1.51(5)	1.60(5)	C2-C3-C4	99(2)	100(2)
C3-C6	1.55(4)	1.51(5)	C2-C3-C6	105(2)	117(3)
C3-03	1.42(4)	1.48(4)	C2-C3-03	112(2)	102(2)
C4-C5	1.43(5)	1.56(4)	C4-C3-C6	113(3)	119(3)
C5-N1	1.51(4)	1.42(4)	C4-C3-03	112(3)	105(2)
C6-C7	1.60(5)	1.53(5)	C6-C3-03	114(3)	112(3)
C7-C8	1.45(9)	1.56(7)	C3-C4-C5	107(3)	103(2)
C7-C9	1.65(8)	1.45(7)	C1-C5-C4	125(3)	113(3)
			C1-C5-N1	112(3)	117(3)
TORSIONAL ANGLES IN THE RING			C4-C5-N1	105(2)	104(2)
N1-C2-C3-C4	-14(3)	11(3)	C3-C6-C7	115(3)	115(3)
C2-C3-C4-C5	22(3)	-23(3)	C6-C7-C8	115(4)	108(4)
C3-C4-C5-N1	-23(3)	29(3)	C6-C7-C9	101(3)	115(3)
C4-C5-N1-C2	14(3)	-25(3)	C8-C7-C9	111(5)	110(4)
C5-N1-C2-C3	0(3)	9(3)	C2-N1-C5	111(2)	118(3)

van der Waals radii. The hydrogen bond from the carboxy group in one B molecule to the carbonyl group of an A molecule is rather short, 2.48(3) Å.

The bond lengths and angles together with the torsion angles of the rings are given in Table 2. The rings adopt two different envelope conformations, both with C(4) at the flap of the envelope. The angles between the two planes of the envelope are 25 and −26°, respectively. Consequently, in the molecule A the isobutyl group at C(3) is in axial position, and the C(3)-hydroxy and C(5)-carboxy groups are in equatorial positions. In the molecule B the isobutyl group is in equatorial position and the hydroxy and carboxy groups are in axial positions. The absolute configuration is either 3(*S*),5(*S*) or 3(*R*),5(*R*).

By combination of this result with the knowledge of the 2(*S*)-configuration for *2* the relationship between *3* and *2* reveals that the absolute configuration for *3* is 3(*S*),5(*S*)-3-hydroxy-3-isobutyl-2-pyrrolidone-5-carboxylic acid. Correspondingly *2* has the absolute configuration 2(*S*),4(*S*)-4-hydroxy-4-isobutylglutamic acid and the natural product *1* from *R. odorata* has the configuration 2(*S*),4(*S*)-4-(β-D-galactopyranosyloxy)-4-isobutylglutamic acid. These results differ from the previous tentatively proposed absolute configurations.[1]

The previous proposal was made on the basis of comparison of ^{1}H NMR spectra of *2* and published values for two diastereoisomers of 4-hydroxy-4-methylglutamic acid.[10] The result obtained now raises the question of the validity of this comparison. Another possible explanation for the new result is, however, that the configurations assigned to the diastereoisomeric 4-hydroxy-4-methylglutamic acids should be reversed. Originally 2(*S*),4(*S*) configuration was assigned to optically active 4-hydroxy-4-methylglutamic acid isolated from *Phyllitis scolopendrium* (Aspleniaceae).[11] The amino acid was reduced to 4-methylglutamic acid and the configuration assumed to be retained. However, the reduced product was a 9:1 mixture of the two diastereoisomers of 4-methylglutamic acid thus raising doubt on the retention of configuration. The doubt is enhanced since unpublished investigations[12] have demonstrated that both diastereoisomers of 4-hydroxy-4-methylglutamic acid are present in *P. scolopendrium*, and because the rotation reported for the first isolation of 4-hydroxy-4-methylglutamic acid ($[\alpha]_D^{18}$ −18.5 (6 N HCl))[11] is different from those later found for both diastereoisomers ($[\alpha]_D^{23}$ −8.3 (0.2 N HCl) and $[\alpha]_D^{23}$ +23.2 (0.2 N HCl)),[10] respectively. Later assignment of configuration to the two diastereoisomers were done on basis of ^{1}H NMR data and assumptions

about preferred conformations.[10] This method, however, may lead to erroneous results, as the configuration of the diastereoisomers of 3-hydroxy-4-methylglutamic acid which was first proposed on basis of ^{1}H NMR,[13] later had to be changed when an X-ray analysis was made.[14]

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