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# Structure of a Peptide Oxazolone: 2-(1′-Benzyloxycarbonylamino-1′-methylethyl)-4,4-dimethyl-5-oxazolone

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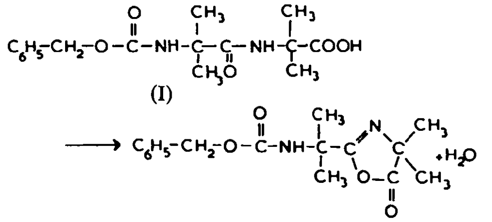
**Abstract.** $C_{16}H_{20}N_2O_4$, monoclinic, $P2_1$, $a = 6{\cdot}270\ (1)$, $b = 11{\cdot}119\ (3)$, $c = 11{\cdot}640\ (4)$ Å, $\beta = 100{\cdot}7\ (2)°$, $D_m = 1{\cdot}27$ (flotation), $D_c = 1{\cdot}26$ Mg m$^{-3}$, $Z = 2$. The structure has been refined to a final $R$ value of 0·041 for 1584 independent counter-measured reflections. The oxazolone ring in the molecule is nearly planar. The exocyclic O atom is 0·065 Å out of the plane defined by the other four atoms in the ring belonging to the lactone group. The difference in length between the two adjacent C—O bonds in the ring is small, but significant. The crystal structure is stabilized by van der Waals interactions and a N—H···N hydrogen bond.

**Introduction.** Oxazolones are believed to be intermediates in the racemization of optically active peptides (Goodman & Levine, 1964; Goodman & McGahren, 1967). However, no crystal structure of a peptide oxazolone has been available until now. Here we report the X-ray analysis of a peptide oxazolone derived from the optically inactive amino acid α-aminobutyric acid. Compound (II) is believed to have formed from benzyloxycarbonyl-α-aminobutyryl-α-aminobutyric acid (I) (P. Balaram, private communication).



(I)

(II)

The X-ray data were collected on a CAD-4 computer-controlled diffractometer from a specimen 0·4 × 0·4 × 0·1 mm using graphite-monochromated Cu $K\alpha$ radiation up to a Bragg angle of 75°. Of the 2010 unique reflections collected in this range, 1584 had $I > 2\sigma(I)$ and were subsequently used for the structure determination and refinement. The data were corrected for Lorentz and polarization factors. In view of the moderate size of the structure, the X-ray analysis turned out to be unexpectedly difficult. Structure solution was attempted by the use of *MULTAN* (Germain, Main & Woolfson, 1971) as well as by the symbolic addition procedure (Karle & Karle, 1966). In both cases three calculations were made, the first with normal $E$ values, the second with $E$ values calculated using spherically averaged group scattering factors for rigid fragments and the third with $E$ values normalized ($\langle E^2 \rangle = 1$) in each parity group. In each of the six calculations, the $E$ map corresponding to the most probable solution was uninterpretable. After a careful examination of $E$ maps corresponding to the second most probable solutions followed by trial structure factor calculations, a fragment containing 12 atoms could be identified. The remaining atoms were located from a subsequent difference Fourier map. The structure was refined, with anisotropic and isotropic thermal

Table 1. *Coordinates* ($\times 10^4$) *and equivalent isotropic thermal parameters* (*Hamilton,* 1959) *of the non-hydrogen atoms*

The standard deviations are given in parentheses.

| | *x* | *y* | *z* | *B* (Å$^2$) |
|---|---|---|---|---|
| C(1) | 7780 (6) | 805 (3) | 1431 (3) | 4·0 (1) |
| C(2) | 6273 (7) | 95 (4) | 709 (3) | 5·4 (2) |
| C(3) | 4185 (7) | 481 (5) | 362 (3) | 5·8 (2) |
| C(4) | 3558 (6) | 1597 (5) | 746 (3) | 5·7 (2) |
| C(5) | 5073 (6) | 2319 (4) | 1455 (3) | 4·4 (1) |
| C(6) | 7193 (5) | 1919 (3) | 1811 (2) | 3·3 (1) |
| C(7) | 8834 (5) | 2691 (3) | 2595 (3) | 3·6 (1) |
| O(8) | 8123 (4) | 2885 (2) | 3700 (2) | 3·7 (1) |
| C(9) | 7247 (4) | 3987 (3) | 3838 (2) | 3·1 (1) |
| O(10) | 7460 (4) | 4858 (2) | 3249 (2) | 4·1 (1) |
| N(11) | 6113 (4) | 3944 (2) | 4705 (2) | 3·3 (1) |
| C(12) | 4941 (5) | 4998 (2) | 5015 (3) | 3·1 (1) |
| C(13) | 6478 (6) | 5875 (3) | 5748 (3) | 4·3 (1) |
| C(14) | 3204 (6) | 4546 (4) | 5677 (3) | 4·4 (1) |
| C(15) | 3759 (4) | 5600 (3) | 3923 (2) | 2·8 (1) |
| N(16) | 3480 (4) | 6716 (2) | 3723 (2) | 3·0 (1) |
| C(17) | 2080 (5) | 6836 (3) | 2576 (2) | 3·1 (1) |
| C(18) | −78 (6) | 7436 (3) | 2682 (3) | 4·6 (1) |
| C(19) | 3238 (7) | 7498 (4) | 1719 (3) | 4·6 (1) |
| C(20) | 1670 (4) | 5536 (3) | 2171 (2) | 3·2 (1) |
| O(21) | 708 (4) | 5132 (2) | 1278 (2) | 4·4 (1) |
| O(22) | 2721 (3) | 4819 (2) | 3064 (2) | 3·2 (1) |

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parameters for the heavy atoms and the H atoms respectively, using the modified version of a block-diagonal least-squares program originally written by R. Shiono. The refinement converged at $R = 0{\cdot}041$. The weighting scheme was of the form $1/(a + bF_o + cF_o^2)$, where $a = 1{\cdot}05$, $b = 0{\cdot}158$ and $c = 0{\cdot}004$. The scattering factors for the non-hydrogen atoms and the H atoms were taken from Cromer & Waber (1965) and Stewart, Davidson & Simpson (1965) respectively. The final coordinates of the non-hydrogen atoms are given in Table 1.*

**Discussion.** The bond lengths and angles in the molecule and the crystal structure are shown in Figs. 1 and 2 respectively.

The molecule can be considered as being made up essentially of three planar groupings, namely the five-membered ring, the peptide-like fragment O(8), C(9), O(10), N(11), C(12), and the phenyl ring. The values of the five dihedral angles necessary to define the geometrical relationships among them are given in Table 2. The five-membered ring and the peptide-like group are inclined with respect to each other at 68·8° whereas the plane of the phenyl ring makes an angle of 82·5° with that of the peptide-like group.

The displacements of the atoms in the five-membered ring from its mean plane vary from −0·011 Å to 0·012 Å. Two of these displacements, namely those of C(20) and O(22), are statistically significant ($\Delta > 3\sigma$), though small. The two methyl carbons, C(18) and C(19), are displaced by nearly equal amounts on the opposite sides of the plane of the five-membered ring. The exocyclic O(21), and C(12) deviate from the plane by 0·068 and −0·078 Å respectively. The length of the N(16)—C(15) bond is appropriate for a C—N double bond. Thus it does not appear to be conjugated with the lactone group C(15), O(22), C(20), O(21), C(17).

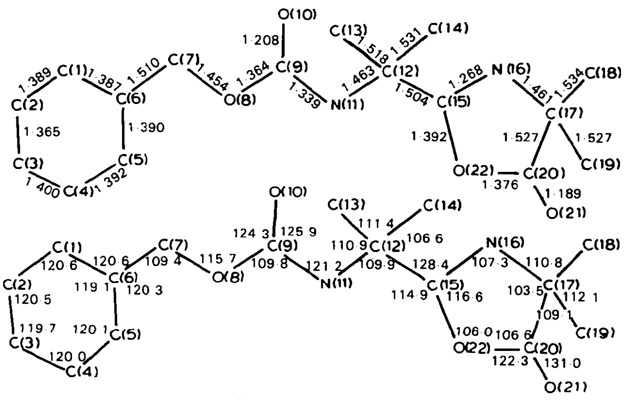

Fig. 1. Bond lengths (Å) and angles (°) in the molecule. The standard deviations in bond lengths and angles range from 0·003 to 0·007 Å and from 0·2 to 0·5° respectively. The respective average values are 0·005 Å and 0·3°.

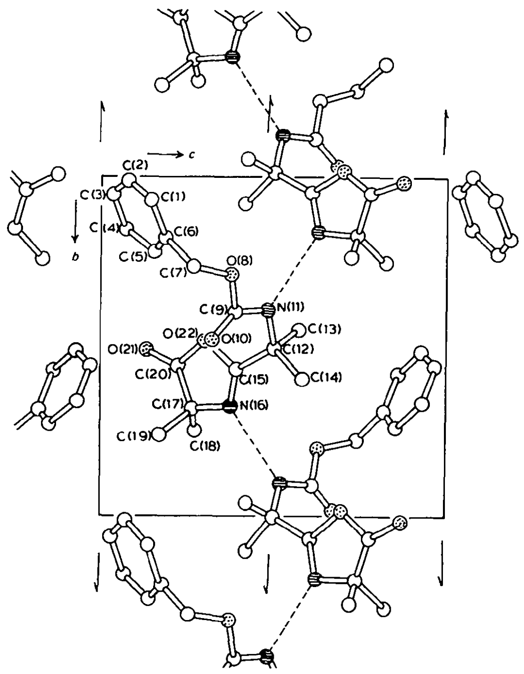

Fig. 2. Crystal structure as viewed along the *a* axis. The broken lines indicate hydrogen bonds.

Table 2. *Dihedral angles and hydrogen-bond parameters*

The primed atoms are related to the unprimed by $-x$, $\frac{1}{2} + y$, $-z$. H(N11) is the H atom attached to N(11).

| | |
|---|---|
| C(5)—C(6)—C(7)—O(8) | 61·8 (3)° |
| C(6)—C(7)—O(8)—C(9) | −103·2 (3) |
| C(7)—O(8)—C(9)—N(11) | 162·3 (3) |
| C(9)—N(11)—C(12)—C(15) | 43·7 (3) |
| N(11)—C(12)—C(15)—N(16) | −142·5 (3) |
| N(11)···N(16)′ | 3·063 (3) Å |
| N(11)—H(N11) | 0·85 (4) |
| N(16)′···N(11)—H(N11) | 8 (3)° |

The lactone group in the molecule is nearly planar, as in the case of other structures containing this group. In the present structure that part of the lactone group which forms part of the five-membered ring, namely C(15), O(22), C(20) and C(17), forms a plane with atomic deviations from the mean plane varying between −0·012 and 0·011 Å. The exocyclic O atom deviates from this plane by 0·065 Å. Yet another feature of the geometry of the lactone group observed earlier by many workers is the difference in lengths between the two

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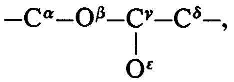
* Lists of structure factors, thermal parameters and H-atom positional parameters have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 35081 (10 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

C—O bonds in the ring. If the atoms in the lactone are numbered as



$$-C^{\alpha}-O^{\beta}-\underset{\substack{|\\ O^{\varepsilon}}}{C^{\gamma}}-C^{\delta}-,$$

it is found that in most of the structures analysed so far, $C^{\alpha}$ is $sp^3$ hybridized. In these structures, the length of the $C^{\alpha}$—$O^{\beta}$ bond is, on average, greater than that of the $C^{\gamma}$—$O^{\beta}$ bond by about 0·1 Å. It has been proposed that this difference can be explained by two factors, namely the difference in hybridization state of $C^{\alpha}$ and $C^{\gamma}$, and the electron delocalization along the $C^{\gamma}$—$O^{\beta}$ and $C^{\gamma}$—$O^{\varepsilon}$ bonds (Kalyani & Vijayan, 1969). In the present structure, as well as in the structure of a lactone oxime (Jones & Chaney, 1972), $C^{\alpha}$ is $sp^2$ hybridized and hence the difference in the two C—O lengths could only be due to electron delocalization. The $C^{\alpha}$—$O^{\beta}$ and $C^{\gamma}$—$O^{\beta}$ lengths in the present structure are 1·392 (3) and 1·376 (3) Å respectively. The corresponding values in the lactone oxime are 1·402 (5) and 1·369 (5) Å. Thus the effect of electron delocalization is small though significant. The third geometrical feature associated with the lactone group is the inequality of the exocyclic angles about the carbonyl group. In the present structure, the two angles differ by 8·7°, a value comparable with those observed in other similar structures.

The crystal structure is stabilized by van der Waals interactions and an intermolecular N—H···N hydrogen bond. The dimensions of this hydrogen bond are given in Table 2.

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# Structure du Chlorhydrate de Procaïne *N*-D-Glucoside Monohydraté

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**Abstract.** $C_{19}H_{31}N_2O_7^+ . Cl^- . H_2O$, monoclinic, $C2$, $Z = 4$, $a = 15{\cdot}757$ (3), $b = 8{\cdot}442$ (2), $c = 18{\cdot}694$ (3) Å, $\beta = 111{\cdot}88$ (2)°, $D_c = 1{\cdot}329$ Mg m$^{-3}$, $V = 2307{\cdot}6$ Å$^3$. The structure was solved by direct methods and refined by least-squares calculations to a final $R$ of 0·049. The N atom of the *p*-aminobenzoate group links together the procaine and glucose molecules. All bond distances and angles are in good agreement with expected values. The molecules are linked by a complex hydrogen-bond system and short van der Waals interactions.

**Introduction.** La disparition du pouvoir anesthésique de la procaïne en présence de sucres aldoses a déjà été signalée (Saunier & Vincent, 1948). La procaïne continue cependant d'être utilisée en présence d'aldoses dans des préparations pharmaceutiques dont il reste à déterminer la durée de validité.

Cannell (1951) a fait réagir en solution aqueuse et à chaud la procaïne et le glucose pour obtenir un dérivé cristallin dont il donne les constantes physiques et la composition centésimale. Il attribue à ce dérivé la formule d'un N-hétéroside, en se basant sur le fait qu'il ne possède plus le pouvoir réducteur du glucose et qu'il ne donne plus les réactions des amines primaires aromatiques comme le fait la procaïne. Nous avons des raisons de croire que ce dérivé est un de ceux qui se forment dans les préparations pharmaceutiques.

Les cristaux nécessaires à l'étude radiocristallographique ont été obtenus sous forme de chlorhydrate à partir d'une solution éthanolique.

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