CHIMIA 43 (1989) Nr. 1–2 (Januar–Februar)

Chimia 43 (1989) 4–5

Diastereoselective Cyclization of a Glycyl-alanine Azomethine to an Imidazolidinone: Determination of the Product Configuration by X-Ray Analysis

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Abstract: Glycyl-(*S*)-alanine-esters **1** and **2** can be condensed to the corresponding 4-oxo-imidazolidin-3-yl-propionates **3** and **4**, respectively. The diastereomers **3a** and **4a** are formed preferentially and the configuration was found to be *u* by single crystal X-ray diffraction of **4a**. The crystal structure shows some quite unusual features.

The Problem

Dipeptide esters of glycylglycine, alanylglycine, and glycylalanine (**1**, **2**) can be converted to imidazolidinones (**3**, **4**) by cyclization of the corresponding azomethines, one diastereomer being formed preferentially from the alanine-containing precursors. Subsequent stereoselective alkylation of the heterocyclic derivatives on the endo- and exocyclic α-carbonyl positions through Li-enolates is a first step of creating stereogenic centres along a peptide backbone[1]. While the configuration of the substituents on the ring of the alanylglycine-derived imidazolidinones can be safely assigned by NMR-spectroscopic comparison with simple analogues[2], this is not possible with the heterocycles **3** and **4**, bearing a stereogenic centre in the exocyclic position. For a discussion of the most surprising effects observed in reactions of Li-enolates generated from these heterocycles[1b, 1c], it was mandatory to know their configuration.

Glycyl-(*S*)-alanine-ethyl-ester·HCl **2** was condensed with pivalaldehyde (i) to a Schiff base, which was cyclized (ii) and protected by treatment with benzyl-chlorocarbonate (iii) to yield the imidazolidinone **4** (see Scheme 1).

The two diastereomers **4a** and **4b** were separated chromatographically. The major diastereomer crystallized to furnish enantiomerically pure (+)-**4a**. It was possible to obtain suitable single crystals for a crystal structure analysis which revealed the configuration of (+)-**4a** to be *u*, the *N*,*N*-acetal carbon atom thus possessing (*R*)-configuration.

Experiments

Preparation of **4**

Preparation of the epimeric esters (+)-1-benzyloxycarbonyl-2-(*R*)-*tert*-butyl-3-(ethoxy-propano-2′-(*S*)-yl)-imidazolidin-4-one **4a** and (−)-1-benzyloxycarbonyl-2-(*S*)-*tert*-butyl-3-(ethoxy-propano-2′-(*S*)-yl)imidazolidin-4-one **4b** was carried out as described for the corresponding methyl esters[1a].

7.71 g (36.6 mmol) glycyl-(*S*)-alanine-ethyl-ester·HCl were suspended in 80 mL CH_2Cl_2 and cooled to 0 °C. Pivalaldehyde (4.50 mL, 41.3 mmol) and 8 g $MgSO_4$ were added and 8 mL (57 mmol) NEt_3 were dropped to the solution at 0 °C. The mixture was allowed to warm up and was stirred at room temperature for 24 h under a drying tube. Filtration and evaporation of the solvent yielded 7.83 g (88%) of the azomethine.

The crude azomethine (7.83 g, 32.3 mmol) was dissolved in 50 mL EtOH, chilled to −10 °C (ice/MeOH), and 2.5 mL (35 mmol) AcCl were added dropwise under argon. The reaction mixture was stirred overnight at room temperature and the solvent was evaporated in vacuo to yield a foamy solid.

The crude cyclized product was dissolved in 100 mL CH_2Cl_2 and combined with 4.6 mL (32.4 mmol) benzylchloroformate. The mixture was then chilled to 0 °C and 14 mL (100 mmol) NEt_3 were added dropwise. The reaction mixture was stirred overnight at room temperature under a drying tube and worked up as in the case of the methyl ester. Chromatography of the resulting product (9.3 g) on a 150 × 50 mm SiO_2 column with 30% EtOAc/hexane yielded 467 mg pure crystalline **4a**, 562 mg pure oily **4b**, and 3.233 g of a mixture (35% overall yield). The mixed fraction was separated once more to yield 1.468 g **4a** (1.935 g total) and 556 mg **4b** (1.118 g total, 3:2 ratio of the two diastereomers).

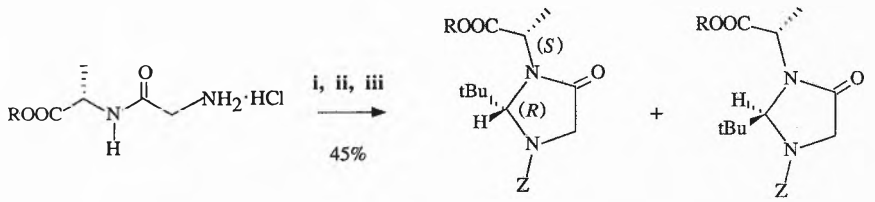
(+)-**4a**: *m.p.* = 84–85 °C; $[\alpha]_D = +18.1°$ (*c* = 1.37, EtOAc); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.36 (dist. s, 5H, aromatic); 5.17 (s, 2H, benzyloxy CH_2); 5.07 (br s, 1H, H-C acetal); 4.24 and 4.23 (2 × q, *J* = 7 Hz, 2H, -OC*H*$_2$CH$_3$); 4.18 (A of AX system, *J* = 16 Hz, 1H, *H*-C(5)H); 4.02 (q, *J* = 7 Hz, 1H, CH$_3$C*H*COOCH$_2$CH$_3$); 3.80 (X of AX system, *J* = 16 Hz, 1H, HC(5)-*H*); 1.49 (d, *J* = 7 Hz, 3H, C*H*$_3$CHCOOCH$_2$CH$_3$); 1.28 (t, *J* = 7 Hz, 3H, -OCH$_2$C*H*$_3$); 1.04 (s, 9H, (CH$_3$)$_3$C); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 169.9, 169.5, 155.2, 135.7, 128.6, 128.5, 128.2, 81.0, 68.0, 61.6, 54.1, 49.8, 40.2, 25.5, 14.6, 14.1; Anal. calc. for $C_{20}H_{28}N_2O_5$: C 63.81, H 7.50, N 7.44, O 21.25; found C 63.75, H 7.60, N 7.28.

(−)-**4b**: $[\alpha]_D = -38.0°$ (*c* = 1.76, EtOAc); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 7.35 (dist. s, 5H, aromatic); 5.20 and 5.13 (AB system, *J* = 12 Hz, 2H, benzyloxy CH_2); 5.08 (br s, 1H, H-C acetal); 4.12 and 4.10 (2 × q, *J* = 7 Hz, 2H, -OC*H*$_2$CH$_3$); 4.20 (A of AX system, 1H, *H*-C(5)H); 3.96 (m, 1H, CH$_3$C*H*COOCH$_2$CH$_3$); 3.83 (X of AX system, *J* = 16 Hz, 1H, HC(5)-*H*); 1.77 (d, *J* = 7 Hz, 3H, C*H*$_3$CHCOOCH$_2$CH$_3$); 1.13 (t, *J* = 7 Hz, 3H, -OCH$_2$C*H*$_3$); 1.00 (s, 9H, (CH$_3$)$_3$C); ^{13}C-NMR ($CDCl_3$, 75 MHz) δ 172.4, 170.2, 155.5, 135.9, 128.6, 128.4, 128.2, 83.3, 67.8, 61.7, 55.7, 50.4, 39.4, 25.5, 15.1, 14.0; Anal. calc. for $C_{20}H_{28}N_2O_5$: C 63.81, H 7.50, N 7.44, O 21.25; found C 64.02, H 7.50, N 7.15.

X-ray analysis of **4a**

Single crystals were grown from ethanol. A cube of dimensions 0.5 × 0.4 × 0.4 mm was chosen for the measurement. The ester crystallizes in the monoclinic space group $P2_1$ with cell dimensions *a* = 6.135(2) Å, *b* = 39.770(27) Å, *c* = 8.937(4) Å, β = 110.28(3)°, *V* = 2045.4 Å^3, *Z* = 4, $\rho_{calc.}$ = 1.22 g cm^{-3}, $C_{20}H_{28}N_2O_5$, 376.46 g mol^{-1}. 2897 unique reflections (2324 with $I > 3\sigma(I)$) were measured by ω-scan on a four-circle diffractometer Enraf Nonius CAD-4 at room temperature to a maximum θ of 23° ($Mo_{K\alpha}$ radiation, λ = 0.71069 Å). The structure was solved by Direct Methods[3]. All atoms were found in the first run except for the ester group atoms of molecule 2. Their positions were determined from a difference Fourier map after two isotropic least-squares cycles. All hydrogens were calculated and the positions were treated with constraints (C-H distances 1.08 Å) during full-matrix least-squares analysis[4]. The refinement (C-, N- and O-atoms anisotropically and H-atoms riding on C-atoms, their isotropical displacement parameters being restricted to 120% of $(U_{11} + U_{22} + U_{33})/3$ of the corresponding carbon atom) with unit weights converged to *R* = 0.08[5]. The ester group of molecule 2 shows disorder, no geometrical constraints were used to correct for it.

Scheme 1



1 (R = CH_3)

2 (R = C_2H_5)

3a (R = CH_3) (*ca.* 2:1) **3b** (R = CH_3)

4a (R = C_2H_5) (*ca.* 3:2) **4b** (R = C_2H_5)

i: $Me_3CCHO/CH_2Cl_2/NEt_3/MgSO_4$; **ii**: AcCl/EtOH or MeOH; **iii**: Z-Cl/DMAP/NEt_3/CH_2Cl_2

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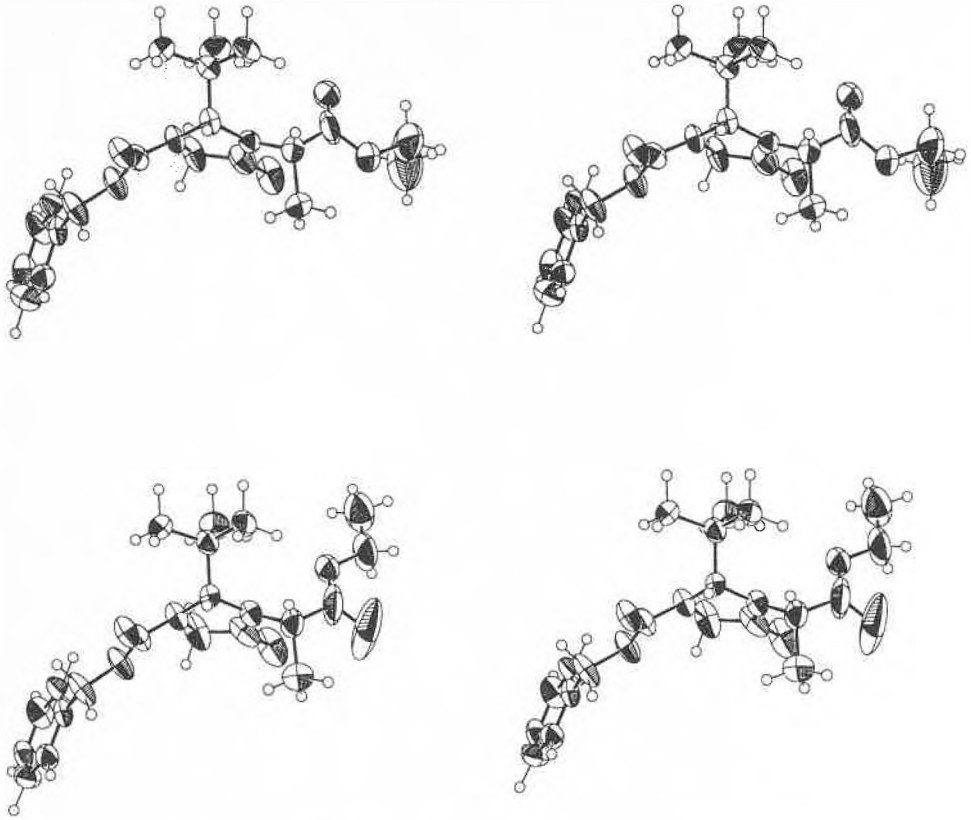

Fig. 1. ORTEP stereoviews of molecules 1 (top) and 2. Ellipsoids are drawn at the 50% probability level.

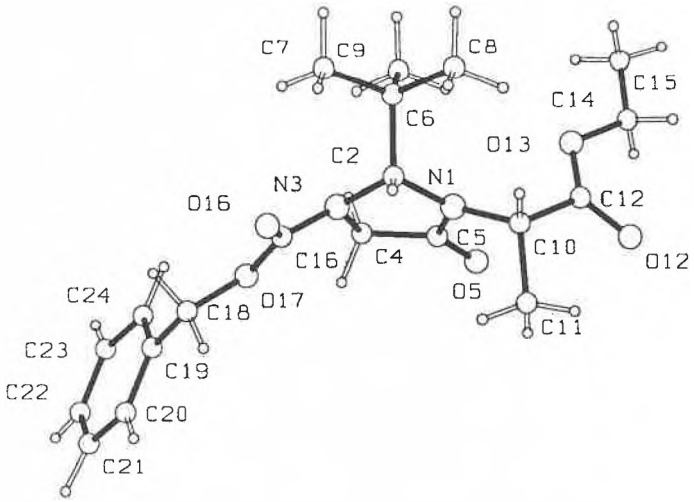

Fig. 2. Numbering scheme for the two molecules.

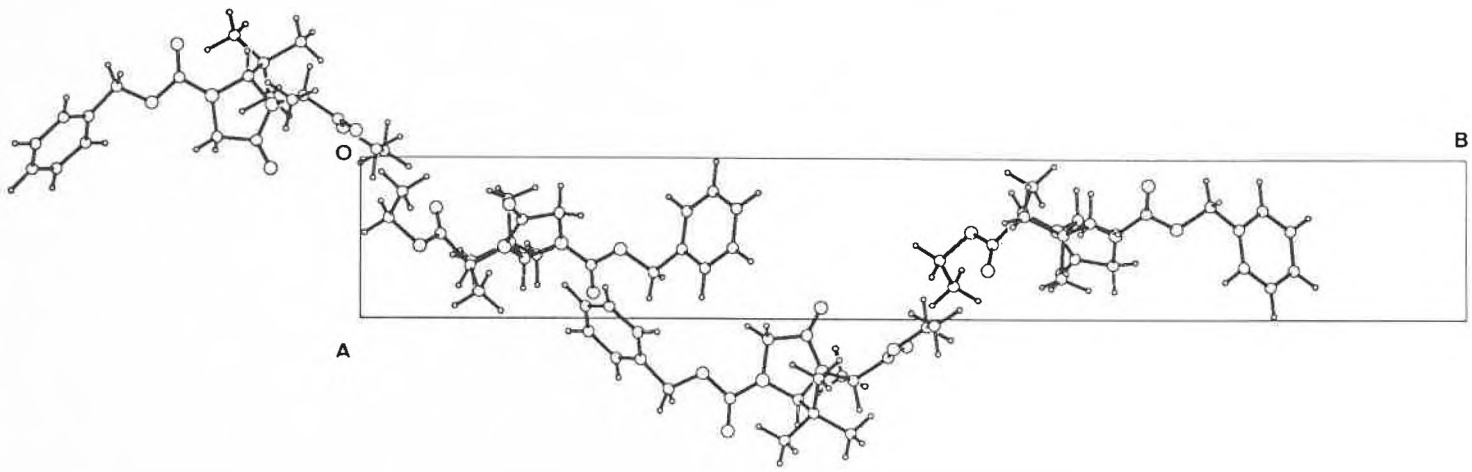

Fig. 3. Projection of the packing along the normal to the xy-plane.

Discussion

The carbon chains of the ethyl ester groups in the two independent molecules adopt different conformations (see Fig. 1): In molecule 1 the chain possesses an unusual *syn*-conformation[6] (torsion angle (C12-O13-C14-C15) = −90.2°) and in molecule 2 it has the energetically favoured *anti*-conformation (torsion angle (C12-O13-C14-C15) = −167.0°, see atom numbering in Fig. 2). This arrangement represents the only published example of a crystal structure where a primary alcohol shows two alternative conformations[7]. Also a structure with two ester groups having different conformations in the same molecule has not been reported until now. Fig. 3 shows a projection of the crystal structure along the normal to the xy-plane which demonstrates the orientation of molecules related over twofold screwaxes along the extremely long monoclinic axis.

Knowing the sense of chirality and configuration of the ethyl esters **4a** and **4b** we can also assign the corresponding methyl esters **3a** and **3b** by NMR-spectroscopic comparison and thus discuss the steric course of their alkylations as done in an independent full paper[1c].

Received: January 25, 1989 [FC 158]

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