

HETEROCYCLIC SUBSTITUTED AMINO ACIDS VIA α,β -DEHYDROAMINO ACID DERIVATIVES.
 STUDIES ON AMINO ACIDS III ¹

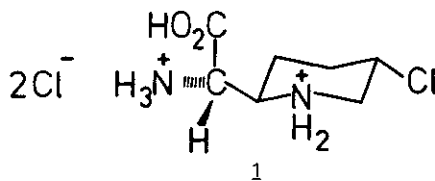
 Claus Herdeis*^a and Ulrich Nagel^b

 Institut für Pharmazie und Lebensmittelchemie^a und Institut für Anorganische Chemie der Universität München^b

Abstract - Condensations of lactam acetals 2a,b with isocyanacetic esters give 3a,b. The Z-configuration of 3a ($R_1=CH_3$, $R_2=C_2H_5$) was determined by X-ray diffraction. Reaction with ethyl N-(ethoxycarbonyl)glycinate gives the protected α,β -dehydroamino acid derivatives 4. The isocyano group can be converted to the carbamate group via the isocyanates 5.

Catalytic hydrogenation of the double bond and deprotection of the functional groups give the amino acids 11a,b and 10.

Efforts towards the synthesis of α,β -unsaturated amino acids and peptides continue unabated ^{2a-g}. Heterocyclic derivatives of amino acids show interesting pharmacologic properties. Towards our synthesis of streptoludin ⁹⁾ 1 we planned to check the C-C bond connection of lactam acetals with amino acid derivatives.





Substituted isocyanacetic esters can be regarded as protected amino acids³. The condensation of the lactam acetals with isocyanacetic esters in stoichiometric amounts at ambient temperature yield the condensation products 3a,b (Table 1)*. The Z-configuration of 3a ($R_1=CH_3$, $R_2=C_2H_5$) was unambiguously assigned by a X-ray crystallographic analysis. In not one of the cases the E-isomer could be found. The vinyllogous aminoisocyanides cannot be transformed to the α,β -dehydroamino acid ester derivatives by the conventional procedures with acids^{3,+)}. Therefore we decided to try the oxidative method with $Tl(OAc)_3$ in methanol⁶ to get the methyl carbamate group. The yields were 40-50%. With the isoelectronic $Hg(OAc)_2$ in chloroform/ H_2O we can isolate the isocyanates 5⁷.

* Condensation with formamide acetals see lit. 4a,b.

+ For reactions with transitionmetal complexes see lit. 5.


Table 1

R ₁	<u>3a</u>	R ₂	mp (°C) / bp	IR-spectra, cm ⁻¹ in KBr			¹³ C-NMR in CDCl ₃ , δ = ppm		
				COO	N=C		β 	α	N=C
CH ₃		CH ₃	69 ^a	1700	2110	1590	161.0	84.8	167.5
CH ₃		C ₂ H ₅	82 ^a	1695	2120	1590	161.3	85.8	167.9
CH ₃		t-Bu	72 ^c	1690	2110	1580	160.5	85.9	168.8
CH ₂ Ph		CH ₃	107-108 ^b	1700	2120	1565	160.2	85.8	169.8
CH ₂ Ph		C ₂ H ₅	63 ^b	1690	2120	1565	159.6	85.7	169.4
CH ₂ Ph		t-Bu	66 ^a	1690	2110	1570	159.2	85.1	169.3
<u>3b</u>									
CH ₃		CH ₃	130-135/2·10 ⁻³ d	1690	2110	1580	161.5	87.5	168.0
CH ₃		C ₂ H ₅	125-128 ^b /5·10 ⁻³ d	1690	2110	1570	162.0	88.4	168.5
CH ₂ Ph		CH ₃	150/5·10 ⁻³ d	1700	2115	1565	162.5	88.2	168.3

^a colourless crystals from ether, ^b colourless crystals from EtOH, ^c colourless crystals from hexane/ether 9+1, ^d bulb to bulb distillation (Büchi-Kugelrohr)

Without purification the crude isocyanates can be treated with alcohols furnishing the carbamates. In the case of benzyl alcohol this method is an easy way to transform the isocyanide group into the Cbz-group.

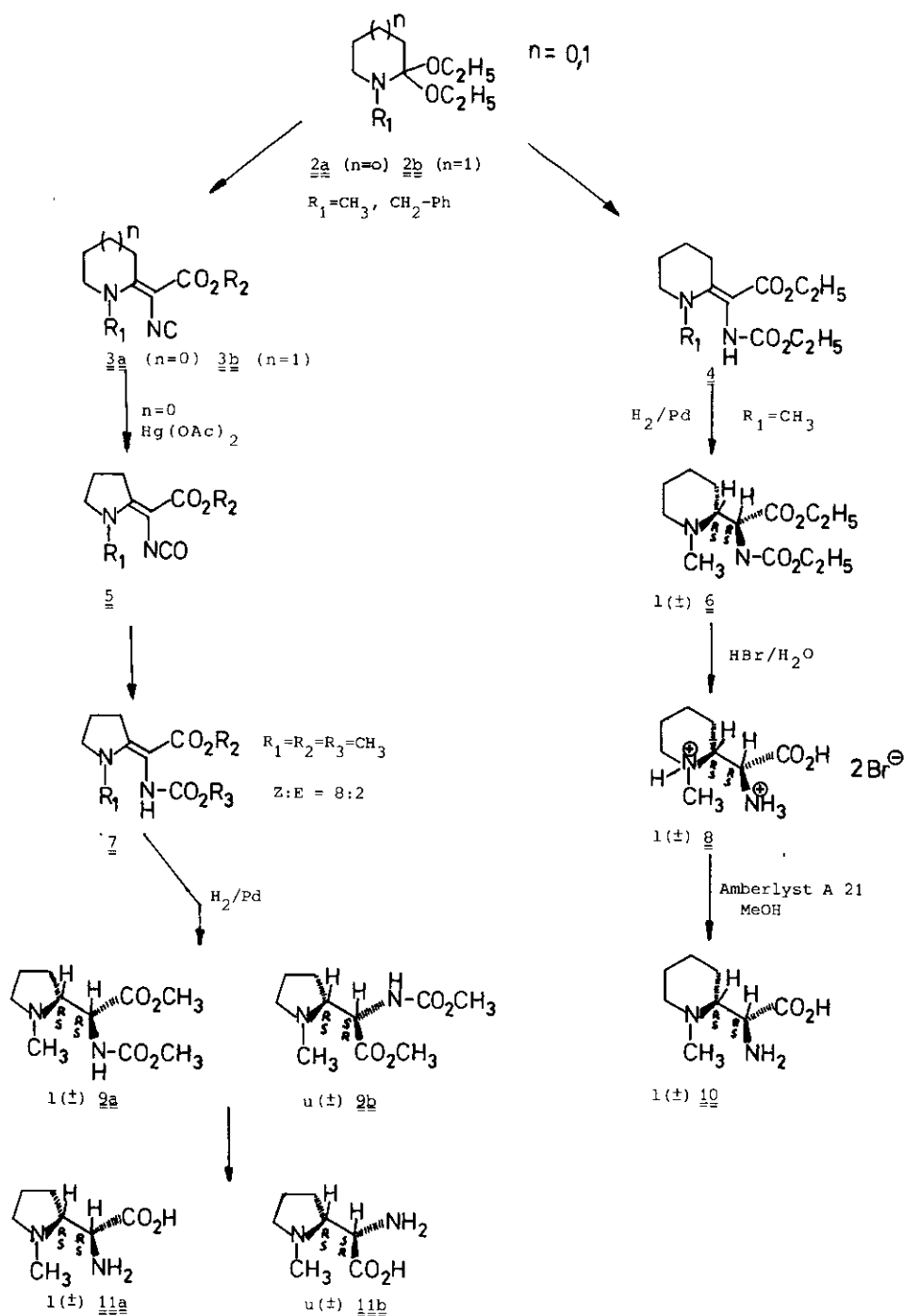
Table 2

R ₁	<u>7</u>	R ₂	R ₃	mp (°C)	IR-spectra, cm ⁻¹ in KBr		
					NH	COO	
CH ₃		CH ₃	CH ₃	114-115 ^a	3280	1720	1570
CH ₃		CH ₃	C ₂ H ₅	98-99 ^b	3255	1720	1570
CH ₃		C ₂ H ₅	CH ₃	74 ^b	3250	1720	1580
CH ₃		C ₂ H ₅	C ₂ H ₅	78-79 ^b	3240	1700	1580
CH ₂ Ph		CH ₃	CH ₃	124-125 ^c	3280	1730	1560
CH ₂ Ph		CH ₃	CH ₂ Ph	94 ^b	3260	1700	1580
CH ₂ Ph		C ₂ H ₅	CH ₂ Ph	93 ^b	3270	1710	1560
CH ₃		C ₂ H ₅	CH ₂ Ph	49-52 ^b	3240	1700	1585

^a diastereomeric mixture of Z:E = 8:2 from Etac, ^b colourless crystals from ether, ^c colourless crystals from EtOH.

The ¹³C-absorption of the olefinic carbon atoms of 7 are in the range of 91.0 - 91.9 ppm for α and 156.5 - 157.0 ppm for β.

Scheme 1



In the case of 2 ($R_1, R_2, R_3 = \text{CH}_3$) we isolated a mixture of Z/E stereoisomers in a ratio of 8:2. At this stage a separation of the stereoisomers could not be achieved. Reduction of the double bond in the usual way with $\text{NaBH}_4/\text{EtOH}$ ^{8a,b} or NaCNBH_3 in acidic media was unsatisfactory. Only catalytic hydrogenation with $\text{Pd/C}/\text{H}_2$ under pressure and temperature ($80^\circ\text{C}/80\text{ bar}$) gave a diastereomeric mixture of 9a,b in a ratio of 8:2. Now the diastereomers could be separated with low pressure liquid chromatography (Lobar Merck column, $\text{CHCl}_3/\text{MeOH } .95+5$, Silicagel). Deprotection of the functional groups with $\text{HBr}/\text{H}_2\text{O}$ and ion-exchange on Amberlyst A 21 resin (MeOH) gave the amino acids 11a,b. [mp $173\text{--}174^\circ\text{C}$ (n-propanol) and mp $134\text{--}136^\circ\text{C}$ (n-propanol)]. On the other hand condensation of the 6-ring lactam acetals with ethyl N-(ethoxycarbonyl)glycinate gave 4 as the only stereoisomer. The same procedure as above yields the amino acid 10 [mp $176\text{--}177^\circ\text{C}$ (n-propanol)].

For the X-ray structure determination of 3a ($R_1 = \text{CH}_3$, $R_2 = \text{C}_2\text{H}_5$) a colourless needle (ether) was cut to $0.2 \times 0.2 \times 0.5\text{ mm}$. The compound $\text{C}_{10}\text{H}_{14}\text{N}_2\text{O}_2$ belonged to the centrosymmetric monoclinic space group $\text{P } 2_1/c$. The cell constants, $a = 9.00\text{ (3) \AA}$, $b = 16.448\text{ (5) \AA}$, $c = 14.695\text{ (4) \AA}$, and $\beta = 105.45\text{ (2) deg}$, gave a calculated density of 1.23 g/cc (measured 1.25 (3) g/cc) for $z = 8$ molecules in the unit cell. Data were collected on a Synthex R3 diffractometer in ω -scan technique using graphite monochromated $\text{Mo-K}\alpha$ -radiation. A total of 2911 independent reflexions ($2\sqrt{h^2 + k^2} < 46^\circ$) were measured, of which 2233 (77 %) were considered to be observed ($I > 2\sigma(I)$). The structure was refined to $R = 0.094$, $R_w = 0.056$ ($w = \frac{1}{\sigma^2(F)}$) anisotropically for all heavy atoms with the hydrogen atoms "riding" in idealized positions on their carbon atoms. The two independent molecules of 3 in the unit cell showed a maximum bond length difference of 0.02 \AA . The bond distances show a great amount of delocalisation of the lone pair electrons at the nitrogen into the ester carbonyl group. There is a remarkable shortening of the C-N bond in the pyrrolidine ring (1.33 \AA).

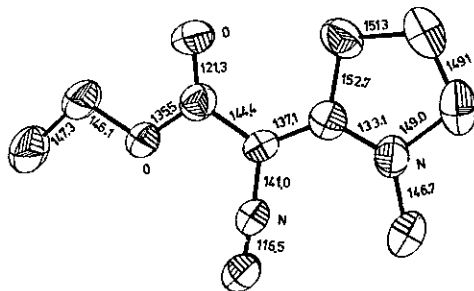


Fig. A stereoview of the molecular structure of 3a ($R_1 = \text{CH}_3$, $R_2 = \text{C}_2\text{H}_5$), bond distances in pm.

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