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

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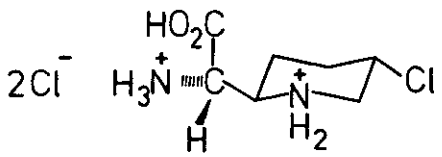
Abstract - Condensations of lactam acetals 2a,b with isocyanacetic esters give 3a,b. The Z-configuration of 3a (R_1=CH_3, R_2=C_2H_5) was determined by X-ray diffraction. Reaction with ethyl N-(ethoxycarbonyl)glycinate gives the protected α,ß-dehydroamino acid derivatives 4. The isocyano group can be 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,ß-unsaturated amino acids and peptides continue unabated [2a-g]. Heterocyclic derivatives of amino acids show interesting pharmacologic properties. Towards our synthesis of streptolutin [9] 1 we planned to check the C-C bond connection of lactam acetals with amino acid derivatives.



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Substituted isocyanacetic esters can be regarded as protected amino acids[3]. 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 unambiqously assigned by a X-ray cristallographic analysis. In not one of the cases the E-isomer could be found. The vinylogous aminoisocyanides cannot be transformed to the α,ß-dehydroamino acid ester derivatives by the conventional procedures with acids[3,+]. Therefore we decided to try the oxidative method with $Tl(OAc)_3$ in methanol[6] 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 5[7].

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

+ For reactions with transitionmetal complexes see lit. 5.

Table 1

R_1	R_2	mp(°C)/bp	IR-spectra, cm^{-1} in KBr			^{13}C-NMR in $CDCl_3$, δ=ppm		
			COO	N=C		ß 	α	N=C
CH_3	CH_3	69[a]	1700	2110	1590	161.0	84.8	167.5
CH_3	C_2H_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_2Ph	CH_3	107-108[b]	1700	2120	1565	160.2	85.8	169.8
CH_2Ph	C_2H_5	63[b]	1690	2120	1565	159.6	85.7	169.4
CH_2Ph	t-Bu	66[a]	1690	2110	1570	159.2	85.1	169.3
CH_3	CH_3	130-135/2·10^{-3} [d]	1690	2110	1580	161.5	87.5	168.0
CH_3	C_2H_5	125-128[b]/5·10^{-3}[d]	1690	2110	1570	162.0	88.4	168.5
CH_2Ph	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 destillation (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.

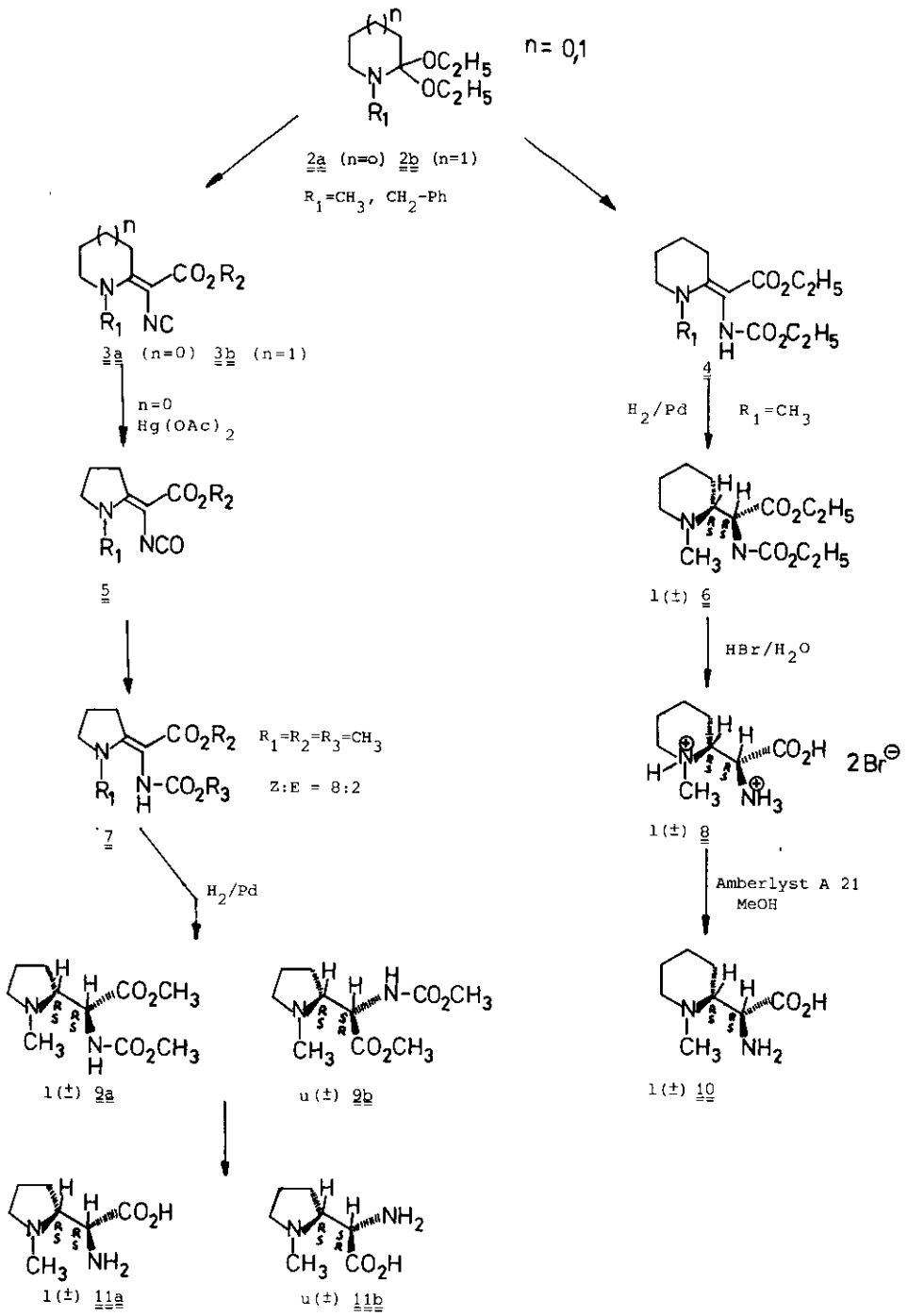
Table 2

R_1	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_2H_5	98-99[b]	3255	1720	1570
CH_3	C_2H_5	CH_3	74[b]	3250	1720	1580
CH_3	C_2H_5	C_2H_5	78-79[b]	3240	1700	1580
CH_2Ph	CH_3	CH_3	124-125[c]	3280	1730	1560
CH_2PH	CH_3	CH_2Ph	94[b]	3260	1700	1580
CH_2Ph	C_2H_5	CH_2Ph	93[b]	3270	1710	1560
CH_3	C_2H_5	CH_2Ph	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 ^{13}C-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 ß.

Scheme 1


n= 0,1
2a (n=o) 2b (n=1)
R1=CH3, CH2-Ph
3a (n=0) 3b (n=1)
n=0
Hg(OAc)2
5
7
R1=R2=R3=CH3
Z:E = 8:2
H2/Pd
4
H2/Pd
R1=CH3
1(±) 6
HBr/H2O
1(±) 8
2 Br⊖
Amberlyst A 21
MeOH
1(±) 10
1(±) 9a
u(±) 9b
1(±) 11a
u(±) 11b

In the case of 7 (R_1,R_2,R_3=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 $NaBH_4$/EtOH[8a,b] or $NaCNBH_3$ in acidic media was unsatisfactory. Only catalytic hydrogenation with Pd/C/H_2 under pressure and temperature (80°C/80 bar) gave a diastereomeric mixture of 9a,b in a ratio of 8:2. Now the diastereomers could be seperated with low pressure liquid chromatography (Lobar Merck column, $CHCl_3$/MeOH 95+5, Silicagel). Deprotection of the functional groups with HBr/H_2O and ion-exchange on Amberlyst A 21 resin (MeOH) gave the amino acids 11a,b. [mp 173-174°C (n-propanol) and mp 134-136°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 176-177°C (n-propanol)].

For the X-ray structure determination of 3a (R_1=CH_3, R_2=C_2H_5) a colourless needle (ether) was cut to 0.2 x 0.2 x 0.5 mm. The compound $C_{10}H_{14}N_2O_2$ belonged to the centrosymmetric monoclinic space group P 2_1/c. The cell constants, a=9.00 (3) Å, b=16.448 (5) Å, c=14.695 (4) Å, and ß=105.45 (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 Mo-Kα-radiation. A total of 2911 independent reflexions ($2\vartheta < 46°$) 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 A. 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 Å).

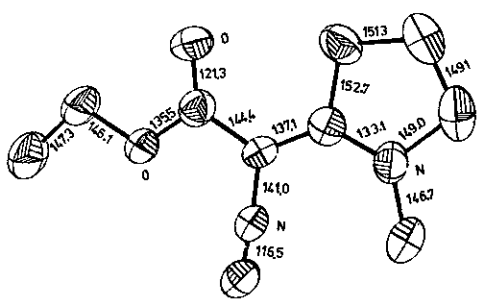


Fig. A stereoview of the molecular structure of 3a (R_1=CH_3, R_2=C_2H_5), bond distances in pm.

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