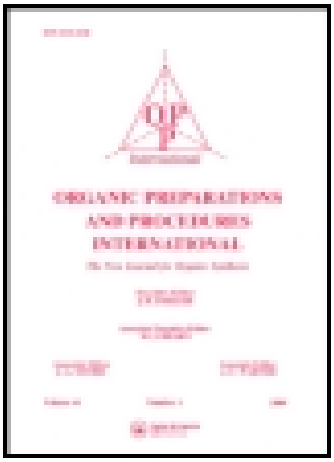

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N-ACETYL-α,β-DEHYDROAMINO ACID N'-METHYLAMIDES AND N',N'-DIMETHYLAMIDES

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N-ACETYL-α,β-DEHYDROAMINO ACID *N'*-METHYLAMIDES AND *N',N'*-DIMETHYLAMIDES†

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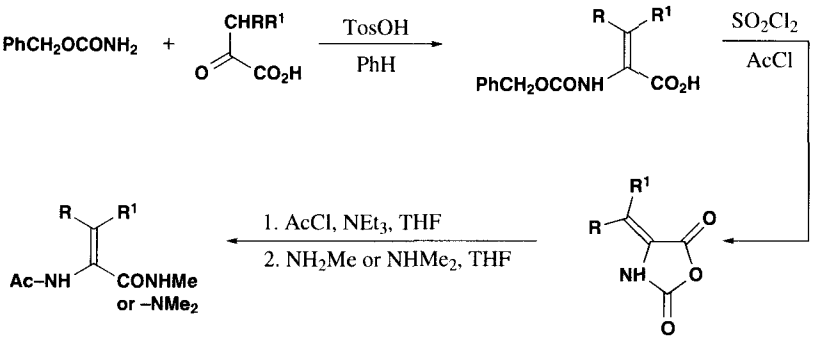
α,β-Dehydroamino acids belong to a large group of nonstandard amino acids, which occur in a number of entities of microbial, plant and animal origin. They are a focus of enormous interest due to their applicability to peptide and protein engineering. An α,β-dehydroamino acid incorporated into a peptide chain forms the system involving three rigid groups located on atom C^{α}: the α,β-double bond flanked by two adjacent amide bonds. As a consequence, these amino acids provide conformational constraint to the peptide backbone and restrict the orientation of the side chain β-substituent(s), and hence generate often specific peptide secondary structures (for recent reviews on α,β-dehydropeptides, see Ref. 1-3). However, relatively little effort has been directed to explore the stereoelectronic interactions of bond $C^{\alpha}=C^{\beta}$ with neighboring peptide bonds.[4] To address this question, we prepared *N*-acetyl-α,β-dehydroamino acid *N'*-methylamides and report herein the synthesis of Ac-(*Z*)-ΔAbu-NHMe, Ac-(*Z*)-ΔLeu-NHMe and Ac-ΔVal-NHMe,[5] the new members of the unsaturated amide series, whose conformational preferences and electronic density perturbation we recently investigated.[4] We also

describe the synthesis of the analogous unsaturated *N',N'*-dimethyl amides, useful models in this[4] as well as other studies on the basic properties of α,β-dehydropeptides.



(*Z*)-ΔAbu: R = Me, R^1 = H (*Z*)-ΔLeu: R = $CHMe_2$, R^1 = H ΔVal: R = R^1 =Me

The title compounds were obtained by adopting Shin's methods for the generation of the $C^{\alpha}=C^{\beta}$ bond and the incorporation of α,β-dehydroamino acids into a peptide chain.[6-8] Benzyl carbamate was condensed in the presence of *p*-toluenesulfonic acid as a catalyst, with an appropriate α-oxo acid with azeotropic removal of water.[6] The resulting N^{α}-benzyloxycarbonyl-α,β-dehydroamino acid wad cyclized by treatment with SO_2Cl_2 to an α,β-dehydroamino acid *N*-carboxy anhydride,[7] which gives in two consecutive one-pot reactions, first with acetyl chloride and then with an appropriate amine, the final product.[8] Yields and analytical data of the compounds synthesized are summarized in Table 1. Tables 2 and 3 list ^1H and ^{13}C selected chemical shifts, respectively. All the amides obtained have sharp melting points, satisfactory elemental analyses, ^1H and ^{13}C NMR spectra as expected and are of 98.8-99.8% purity as determined by HPLC. Their IR characteristic is also correct.[4]

EXPERIMENTAL SECTION

Benzyl carbamate, sulfuryl chloride, acetyl chloride, methylamine and dimethylamine were purchased from Fluka and α-oxo acids were prepared by our previous procedure.[9] Purified solvents (Polskie Odczynniki Chemiczne) were stored over drying agents. Organic solutions were dried over anhydrous Na_2SO_4. The solvents from reaction mixtures and column chromatographic separations were removed *in vacuo* on a rotatory evaporator at bath temperatures not exceeding 30°. Reactions were monitored and preliminary checking of product homogeneity was performed on silica gel plates (DC Alufolien Kieselgel 60 No 5553 Merck) in $CHCl_3$-MeOH (5:1). Spots were visualized with bromine-fluorescein. Mps. were determined on a Boetius heating block and are uncorrected. HPLC analyses were performed on a Beckman "System Gold" chromatograph for Methods Development consisting of a Model 126 programmable module, a Model 168 diode array detector, a Model 210A injection valve with a 5 µl loop, a PC386SX (Wearnes) with "System Gold" version 5.1 software for data collection and controller function. An Alltech Alltima, C_{18}, 5µ, 150 x 4.6 mm column and solvent systems given in Table 1 with a flow rate 1 mL/min were applied. Elemental analyses were performed on a Perkin-Elmer analyzer.

TABLE 1. Yields and Analytical Data of N-Acetyl-α,β-dehydroamino Acid N'-Methylamides and N',N'-Dimethylamides

Amide	Yield (%)	mp. (°C) Crystallization System	HPLC Purity (%)	tR (min) (A:B)[a]	Analysis (Found) C	H	N
Ac-(Z)-ΔAbu-NHMe	58	139-141 AcOEt/Hex	98.9	3.02[b] (95:5)	53.82 (53.40)	7.75 (8.00)	17.94 (17.63)
Ac-(Z)-ΔLeu-NHMe	76	194.5-196 Sublimed	98.8	3.72 (85:15)	58.67 (58.65)	8.75 (8.90)	15.21 (15.17)
Ac-ΔVal-NHMe	46	209-211 $CHCl_3$/Hex	98.8	2.92 (90:10)	56.45 (56.28)	8.29 (8.40)	16.46 (16.55)
Ac-(Z)-ΔAbu-NMe_2	23	123-124.5 Et_2O/Hex	99.8	12.60 (95:5)	55.85[c] (55.81)	8.32 (8.44)	16.28 (16.02)
Ac-(Z)-ΔLeu-NMe_2[d]	71	183-185 Sublimed	98.6	11.47 (85:15)	60.58 (60.72)	9.15 (9.35)	14.13 (14.20)
Ac-ΔVal-NMe_2	48	176-178[d] $CHCl_3$/Hex	99.6	8.10 (90:10)	–[e]	–[e]	–[e]

a) A = 0.1% trifluoroacetic acid, B = acetonitrile; b) tR for the (*E*)-isomer = 3.32 min in the same solvent system; c) Analyzed for 0.1 H_2O in sample; d) This coumpond itself is known, but yield and the above analytical data are lacking[15]; e) Lit.[16] mp. 175-176, correct analysis

TABLE 2. ^1H NMR Spectra (δ, ppm, ^3J <Hz>) of N-Acetyl-α,β-Dehydroamino Acid N'-Methyl-amides and N',N'-Dimethylamides

Amide	CH_3CO	NH	CH	CH	N'H	N'CH_3 or N'$(CH_3)_2$
1	1.94 (s,3H)	8.89 (s,1H)	6.27 (q,1H <7.5>)	1.58 (d,3H <7.5>)	7.69 (q,1H <4.7>)	2.62 (d,3H <4.7>)
2	1.92 (s,3H)	8.92 (s,1H)	6.03 (d,1H <10.1>)	2.46 (m,1H)	7.68 (q,1H <4.5>)	2.58 (d,3H <4.5>)
3	1.87 (s,3H)	8.84 (s,1H)	-	1.62 (s,3H) 1.85 (s,3H)	7.53 (q,1H <4.7>)	2.58 (d,3H <4.7>)
4	1.90 (s,3H)	9.27 (s,1H)	5.18 (q,1H <7>)	1.62 (d,3H <7.0>)	–	2.78 (bs,3H) 2.92 (bs,3H)
5[a]	1.88 (s,3H)	9.32 (s,1H)	4.88 (d,1H <9.8>)	2.63 (m,1H)	–	2.76 (s,3H) 2.94 (s,3H)
6	1.85 (s,3H)	9.06 (s,1H)	–	1.58 (s,3H) 1.61 (s,3H)	–	2.80 (s,3H) 2.91 (s,3H)

a) ^1H NMR in $CDCl_3$ (a 6% solution) ppm, <Hz>: 0.91 (d, 6H <6.6> $(CH_3)_2C$), 1.92 (s, 3H, CH_3), 2.65 (m, 1H, $C^{\gamma}H$), 2.94 and 3.13 (2 bs, 6H, $N(CH_3)_2$,), 4.95 (dd, 1H <9.8> ^4J <0.9> $C^{\beta}H$), 9.45 (d, 1H ^4J <0.9> NH). There are two sets of signals in the literature ^1H NMR spectrum of this compound in $CDCl_3$ solution,[15] ascribed to (*Z*) (major) and (*E*) (minor) conformers being in slow equilibrium. However we did not observed any change in the spectrum after 24 h standing of the measured solution of this sample.

^1H and ^{13}C NMR spectra were recorded with a Brucker Avance DRX 300 spectrometer in DMSO-d_6 with internal Me_4Si. Assignment of proton and carbon resonances was based on DEPT, (^1H,^1H)-COSY and (^1H,^{13}C)-COSY techniques and in the case of quaternary carbon atoms on the HMBC experiment. For *Z/E* configuration assignment, resonances C$^{\gamma}$*H*, C$^{\beta}$*H* and N*H* compared in a series of compounds as measured in a given solvent can be of the diagnostic values.[10,11] The respective values in DMSO-d_6[12] for the series of compounds below are as follows:

(*E*)-Ac-Pro-Abu-NHMe[13]	1.85 (d, 3H <7.5>)	5.76 (q, 1H <7.5>)	9.25 (s, 1H)
(*Z*)-Ac-Pro-Abu-NHMe[13]	1.59 (d, 3H <7.5>)	6.49 (q, 1H <7.5>)	9.06 (s, 1H)
(*E*)-Ac-Abu-NHMe[14]	1.75 (d, 3H <7.5>)	5.61 (q, 1H <7.5>)	9.13 (bs, 1H)
(*Z*)-Ac-Abu-NHMe (in Table 2)	1.58 (d, 3H <7.5>)	6.27 (q, 1H <7.5>)	8.89 (s, 1H)

The long range coupling constant ^4J between N*H* and *trans* C$^{\beta}$*H* is also diagnostic for *Z* configuration assignment, as seen in the spectra of Ac-(Z)-Leu-NMe_2 in $CDCl_3$ [a) in Table 2]. The configuration of the remaining compounds was assumed to be Z on the basis of derivation of all the Abu and Leu amides from (*Z*)- α,β-dehydroamino acid *N*-carboxy anhydrides.

TABLE 3. ^{13}C NMR Spectra (δ, ppm) of N-Acetyl-α,β-Dehydroamino Acid N'-Methylamides and N',N'-Dimethylamides

Amide	$\underline{C}H_3CO$	$CH_3\underline{C}O$	C$^{\alpha}$	C$^{\beta}$H	C$^{\gamma}$H	C$^{\alpha}\underline{C}$O	N'CH_3 or N'$(CH_3)_2$
1	22.71	168.37	131.47	126.31	12.85	164.85	25.86
2	23.57	169.87	129.23	139.40	27.13[a]	165.84	26.86
3	22.48	168.29	125.79	133.71	20.09 20.76	165.90	25.62
4	23.02	168.72	132.30	117.11	12.77	168.66	35.42 39.51
5	22.97	168.91	129.02	129.10	26.09[b]	168.91	34.91 39.30
6	23.05	168.55	126.17[c]	124.31[c]	19.56 19.94	168.13	34.71 38.32

a) $CH(CH_3)_2$: ^1H: 0.91 (d,6H <6.6>), ^{13}C: 22.68; b) $CH(CH_3)_2$: ^1H: 0.93 (d,6H <6.6>), ^{13}C: 22.97; c) These assignments may be reversed.

***N*$^{\alpha}$-Benzyloxycarbonyl-α,β-dehydroamino Acids** were synthesized according to Ref. 6. and were of 90.0-99.8% purity, determined by HPLC. $PhCH_2OCO$-(*Z*)-ΔAbu contained 5% of the (*E*)-isomer as seen in ^1H NMR spectra.

α,β-Dehydroamino acid *N*-carboxy Anhydrides were obtained according to Ref. 7. (*Z*)-ΔAbuNCA on crystallization from chloroform/*n*-hexane melted at 139-141.5° (lit. mp. 136-138°). (*Z*)-ΔLeuNCA on crystallization from benzene/*n*-hexane melted at 93-95° (lit. mp. 91-92°) and was so stable that its HPLC analysis was feasible to indicate its 100% purity. ΔValNCA on crystallization from benzene melted at 150-152° (lit. mp. 145-146°).

N*-Acetyl-α,β-dehydroamino Acid *N'*-Methylamides and *N',N'*-Dimethylamides.** ***General Procedure. To a vigorously stirred solution of an α,β-dehydroamino acid *N*-carboxy anhydride (0.13 g of (*Z*)-ΔAbuNCA, 0.16 g of (*Z*)-ΔLeuNCA or 0.14 g of ΔValNCA, 1.0 mmol each) in tetrahydrofuran (5 mL), cooled to -15°, AcCl (0.08 mL, 1.1 mmol) and NEt_3 (0.15 mL, 1.1 mmol) were added. Stirring was continued at 20° for 40 min, the reaction mixture recooled to -15° and NH_2Me or $NHMe_2$ (2.0 mmol) in tetrahydrofuran added (0.60 mL of 3.4 M solution of the former or 0.62 mL of 3.2 M solution of the latter). Stirring was continued at 20° overnight and the solvent evaporated.

Ac-(Z)-ΔAbu-NHMe (**1**), *Ac-(Z)-ΔAbu-NMe*$_2$ (**4**), *Ac-(Z)-ΔLeu-NHMe* (**2**) and *Ac-(Z)-ΔLeu-NMe*$_2$ (**5**). The above respective postreaction residue, dissolved in ethyl acetate was applied to a silica gel column (Kieselgel 60H Merck, 20 g) equilibrated with this solvent. The column was eluted with a mixture of ethyl acetate-ethanol (5:1) and 15 mL fractions were collected. The fractions containing the amide synthesized (TLC) were evaporated and dried at 20° over P_2O_5 at 1 mm Hg. Two former amides were crystallized from solvents given in Table 1. The remainder were crystallized from methanol-chloroform (1:4)/*n*-hexane and sublimed at 1 mm Hg using a bath of temperature 125-145°. Yields and analytical and NMR data are collected in Tables 1-3.

Ac-ΔVal-NHMe (**3**) and *Ac-ΔVal-NMe*$_2$ (**6**). The respective postreaction residue dissolved in chloroform was applied to a silica gel column (Kieselgel 60H Merck, 17 g) equilibrated with this solvent. The column was eluted with chloroform and then with a mixture of chloroform-methanol (3:1). Fractions of 5 mL were collected and these containing the amide synthesized (TLC) were evaporated, dried at 20° over P_2O_5 at 1 mm Hg and crystallized. Yields and analytical and NMR data are cited in Tables 1-3.

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5. Abbreviations used: ΔAbu = α,β-dehydrobutyrine, ΔLeu = α,β-dehydroleucine, ΔVal = α,β-dehydrovaline, ΔNCA = α,β-dehydroamino acid *N*-carboxy anhydride, Hex = *n*-hexane, THF = tetrahydrofuran.

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A FACILE SYNTHESIS FOR RACEMIC AND OPTICALLY ACTIVE 1-AMINOINDANS

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In the course of development work for new central nervous system drugs, we found that a key intermediate, 1-aminoindan and particularly optically active 1-aminoindan, is not readily available in commercial quantities. We therefore developed a facile synthesis suitable for both racemic and enantiomerically pure 1-aminoindans.[1] 1-Aminoindan has previously been prepared by reduction of indanone oxime either with metal,[2] metal-hydride[3] or catalytic hydrogenation.[4] The disadvantage of