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N-Benzyl Derivatives of Leucine Esters

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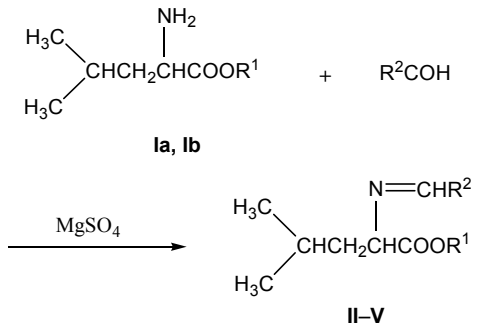
Abstract—Leucine methyl and ethyl esters reacted with 3-bromobenzaldehyde and 4-chlorobenzaldehyde in anhydrous methanol in the presence of magnesium sulfate to afford the coresponding Schiff bases of the general formula $(CH_3)_2CHCH_2CH(COOR^1)N{=}CHR^2$ [R^1 = CH_3, C_2H_5, R^2 = 3-BrC_6H_4, 4-ClC_6H_4]. Their reduction with sodium tetrahydridoborate yielded *N*-benzyl derivatives $(CH_3)_2CHCH_2CH(COOR^1)NHCH_2R^2$, which were converted into *N*-acyl-*N*-benzyl derivatives $(CH_3)_2CHCH_2CH(COOR^1)N(COR^3)CH_2R^2$ [R^3 = CH_3, C_6H_5].

N-Acylated amino acids exhibit versatile biological activity, and they have found wide application as medicines, cosmetic and hygienic agents, and food additives. Some compounds of this series are effective fungicides and pesticides. The presence of an acyl fragment makes their molecules hydrophobic and thus endows them with surfactant properties [1]. Taking into account the above stated, it becomes clear why considerable attention is still given to the synthesis of new *N*-acyl derivatives of amino acids and study of their biological activity, despite a great number of known representatives. From the viewpoint of synthesis of new physiologically active substances, quite promising are *N*-acyl derivatives of *N*-aryl- or *N*-alkyl-substituted amino acids in which the aryl or alkyl moiety contains halogen or phosphorus atoms, nitro groups, etc. In the present communication we report on the preparation of *N*-acyl-*N*-benzylleucine derivatives. While performing this study, specific attention was given to the possibility of synthesizing *N*-benzyl derivatives of leucine by reduction of the corresponding *N*-benzylidene compounds with sodium tetrahydridoborate.

The required initial Schiff bases were prepared by reaction of leucine methyl or ethyl ester with an equimolar amount of 4-chloro- or 3-bromobenzaldehyde in anhydrous methanol in the presence of magnesium sulfate (Scheme 1). Compounds **II**–**V** are high-boiling substances which are soluble in common organic solvents. Their structure was confirmed by the ^{1}H NMR (Table 1) and IR spectra and analytical data (Table 2).

Schiff bases **II**–**V** were reduced with 1.2 equiv of sodium tetrahydridoborate in the corresponding alcohol to obtain *N*-benzyl-substituted leucine esters **VI**–**IX** (Scheme 2). The reduction of ethyl esters **IV** and **V** with sodium tetrahydridoborate in methyl alcohol was accompanied by transesterification; as a result, compounds **VI** and **VII**, respectively, were isolated. In the presence of excess sodium tetrahydridoborate, the reduction process also involves the ester groups, leading to the corresponding amino alcohols **X** and **XI**. Their formation follows from the IR and NMR spectral data and elemental analyses.

Scheme 1.



Ia, **II**, **III**, R^1 = CH_3; **Ib**, **IV**, **V**, R^1 = C_2H_5; **II**, **IV**, R^2 = 3-BrC_6H_4; **III**, **V**, R^2 = 4-ClC_6H_4.

In the ^{13}C NMR spectrum of compound **X** in $CDCl_3$, signals from the methyl carbon atoms were located at δ_C 22.51 and 22.79 ppm, signals from the methylene groups appeared at δ_C 41.02, 50.24, and 63.06 ppm, methine carbon atoms gave signals at

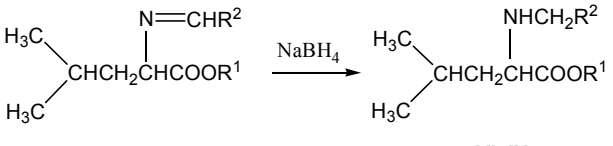
Table 1. ^{1}H NMR spectra of leucine derivatives **II–IX** in $CDCl_3$, δ, ppm (*J*, Hz)

Comp. no.	$(CH_3)_2CHCH_2$	R^1	CH	=CH or CH_2	R^2
II	0.88 d (3H, *J* = 6.0) 0.93 d (3H, *J* = 6.1) 1.19–2.0 m (3H)	3.72 s (3H)	4.08 t (*J* = 7.2)	8.21 s	7.1–8.0 m (4H)
III	0.87 d (3H, *J* = 6.0) 0.92 d (3H, *J* = 6.1) 1.15–1.95 m (3H)	3.70 s (3H)	4.08 t (*J* = 7.0)	8.23 s	7.32 d (2H, *J* = 8.5), 7.69 d (2H, *J* = 8.5)
IV	0.88 d (3H, *J* = 6.0) 0.93 d (3H, *J* = 6.1) 1.30–1.95 m (3H)	1.25 t (3H, *J* = 7.1), 4.18 q (2H, *J* = 7.1)	4.07 t (*J* = 7.0)	8.22 s	7.23–7.96 m (4H)
V	0.90 d (3H, *J* = 6.2) 0.95 d (3H, *J* = 6.2) 1.30–1.96 m (3H)	1.28 t (3H, *J* = 7.2), 4.18 q (2H, *J* = 7.1)	4.09 t (*J* = 7.0)	8.25 s	7.38 d (2H, *J* = 8.6), 7.74 d (2H, *J* = 8.6)
VI[a]	0.83 d (3H, *J* = 6.3) 0.89 d (3H, *J* = 6.3) 1.34–1.85 m (3H)	3.68 s (3H)	3.25 t (*J* = 7.1)	3.66 d (*J* = 11)	7.10–7.50 m (4H)
VII	0.84 d (3H, *J* = 6.2) 0.90 d (3H, *J* = 6.1) 1.20–1.80 m (3H)	3.70 s (3H)	3.26 t (*J* = 7.1)	3.68 d (*J* = 11)	7.25 s (4H)
VIII	0.92 d (3H, *J* = 6.2) 0.98 d (3H, *J* = 6.2) 1.20–2.00 m (3H)	1.33 t (3H, *J* = 7.0), 4.25 q (2H, *J* = 7.1)	3.30 t (*J* = 7.1)	3.75 d (*J* = 10)	7.10–7.60 m (4H)
IX	0.81 d (3H, *J* = 6.2) 0.87 d (3H, *J* = 6.2) 1.32–2.00 m (3H)	1.21 t (3H, *J* = 7.1), 4.12 q (2H, *J* = 7.1)	3.21 t (*J* = 7.3)	3.62 d (*J* = 9.6)	7.20 s (4H)

[a] δ_{NH}, ppm: 1.96 (**VI**), 1.83 (**VII**), 2.44 (**VIII**), 2.26 (**IX**)

δ_C 24.76 and 56.09 ppm, and aromatic carbon signals were observed at δ_C 122.35, 126.48, 129.82, 129.96, 130.91, and 142.58 ppm. The ^{13}C NMR spectrum of **XI** ($CDCl_3$) contained the following signals, δ_C, ppm: 22.10, 22.91 (CH_3); 39.32, 49.21, 62.15 (CH_2); 24.66, 56.15 (CH); 128.47, 129.82, 133.16, 136.05 (C_{arom}). Protons from the methyl groups in compound **X** appeared in the ^{1}H NMR spectrum as two doublets at δ 0.89 (3H, *J* = 6.6 Hz) and 0.91 ppm (3H, *J* = 6.6 Hz); methylene proton signals were located at δ 1.1–1.3 (m, 1H), 1.35–1.45 (m, 1H), 3.29 (d, 1H, *J* = 10.8 Hz), 3.65 (d, 1H, *J* = 10.8 Hz), and 3.77 ppm (d, 2H, *J* = 6.2 Hz); methine protons gave rise to two multiplets at δ 1.56–1.71 and 2.69–2.78 ppm; and the

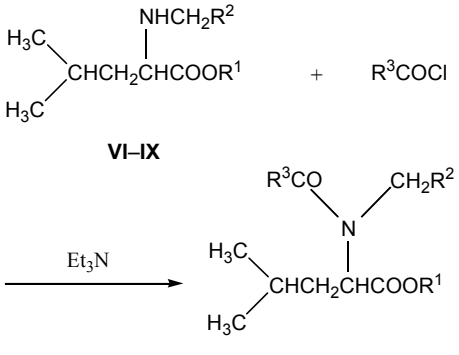
Scheme 2.



II–V **VI–IX**

IV, $R^1 = CH_3$, R^2 = 3-BrC_6H_4; **VII**, $R^1 = CH_3$, R^2 = 4-ClC_6H_4; **VIII**, $R^1 = C_2H_5$, R^2 = 3-BrC_6H_4; **IX**, $R^1 = C_2H_5$, R^2 = 4-ClC_6H_4.

Scheme 3.



XII, $R^1 = CH_3$, R^2 = 3-BrC_6H_4, $R^3 = CH_3$; **XIII**, $R^1 = CH_3$, R^2 = 3-BrC_6H_4, $R^3 = C_6H_5$; **XIV**, R^2 = 4-ClC_6H_4, $R^3 = CH_3$, XV, $R^1 = CH_3$, R^2 = 4-ClC_6H_4, $R^3 = C_6H_5$; **XVI**, $R^1 = C_2H_5$, R^2 = 3-BrC_6H_4, $R^3 = CH_3$; **XVII**, $R^1 = C_2H_5$, R^2 = 3-BrC_6H_4, $R^3 = C_6H_5$; **XVIII**, $R^1 = C_2H_5$, R^2 = 4-ClC_6H_4, $R^3 = CH_3$; **XIX**, $R^1 = C_2H_5$, R^2 = 4-ClC_6H_4, $R^3 = C_6H_5$.

Table 2. Yields, boiling points, refractive indices, IR spectral parameters, and elemental analyses of compounds **II–IX**

Comp. no.	Yield, %	bp, °C (*p*, mm)	n_D^{20}	IR spectrum, ν, cm^{-1}		Found, %			Formula	Calculated, %		
				C=O	C=N	C	H	N		C	H	N
II	84	138–139 (0.03)	1.5391	1743	1643	54.02	5.98	4.33	$C_{14}H_{18}BrNO_2$	53.86	5.81	4.49
III	81	140–141 (0.03)	1.5320	1743	1643	62.97	6.64	4.98	$C_{14}H_{18}ClNO_2$	62.80	6.78	5.23
IV	81	135–136 (0.03)	1.5336	1739	1643	55.47	6.36	4.18	$C_{15}H_{20}BrNO_2$	55.23	6.18	4.29
V	80	126–127 (0.02)	1.5254	1736	1642	64.21	7.36	5.02	$C_{15}H_{20}ClNO_2$	63.94	7.15	4.97
VI	85	125–126 (4)	1.5218	1735	–	53.68	6.71	4.23	$C_{14}H_{20}BrNO_2$	53.51	6.42	4.46
VII	84	119–120 (2)	1.5092	1736	–	62.50	7.54	4.93	$C_{14}H_{20}ClNO_2$	62.33	7.43	5.19
VIII	80	118–120 (3)	1.5196	1731	–	55.02	6.87	4.03	$C_{15}H_{22}BrNO_2$	54.89	6.76	4.27
IX	77	129–130 (2)	1.5075	1731	–	63.60	7.98	4.86	$C_{15}H_{22}ClNO_2$	63.48	7.81	4.94

Table 3. ^{1}H NMR spectra of leucine derivatives $(CH_3)_2CHCH_2CH(COOR^1)NR^3CH_2R^2$ (**XII–XIX**) in $CDCl_3$, δ, ppm (*J*, Hz)

Comp. no.	$(CH_3)_2CHCH_2$	NCH	NCH_2	R^1	R^2, R^3
XII	0.79 d (3H, *J* = 6.1), 0.87 d (3H, *J* = 6.0), 1.20–1.95 m (3H)	4.81 t (*J* = 7.2)	4.54 s	3.57 s (3H)	7.05–7.53 m (4H), 2.05 s (3H)
XIII	0.68 d (3H, *J* = 6.1), 0.75 d (3H, *J* = 6.1), 1.15–1.95 m (3H)	4.41 t (*J* = 7.0)	4.52 s	3.53 s (3H)	7.01–7.62 m (9H)
XIV	0.67 d (3H, *J* = 6.1), 0.76 d (3H, *J* = 6.2), 1.02–1.82 m (3H)	4.74 t (*J* = 7.2)	4.42 s	3.46 s (3H)	7.03–7.21 m (4H), 1.95 s (3H)
XV	0.66 d (3H, *J* = 6.1), 0.74 d (3H, *J* = 6.1), 1.15–1.92 m (3H)	4.44 t (*J* = 7.3)	4.54 s	3.55 s (3H)	7.08–7.43 m (9H)
XVI	0.65 d (3H, *J* = 6.1), 0.72 d (3H, *J* = 6.1), 1.15–1.72 m (3H)	4.63 t (*J* = 7.2)	4.35 s	1.04 t (3H, *J* = 7.1) 3.86 q (2H, *J* = 7.2)	6.90–7.42 m (4H), 1.88 s (3H)
XVII	0.66 d (3H, *J* = 6.1), 0.73 d (3H, *J* = 6.1), 1.35–1.92 m (3H)	4.33 t (*J* = 7.2)	4.54 s	1.21 t (3H, *J* = 7.2) 4.04 q (2H, *J* = 7.2)	7.0–7.58 m (9H)
XVIII	0.63 d (3H, *J* = 6.1), 0.71 d (3H, *J* = 6.1), 1.15–1.78 m (3H)	4.57 t (*J* = 7.1)	4.41 s	1.02 t (3H, *J* = 7.1) 3.82 q (2H, *J* = 7.0)	6.90–7.32 m (4H), 1.81 s (3H)
XIX	0.66 d (3H, *J* = 6.1), 0.74 d (3H, *J* = 6.1), 1.25–1.90 m (3H)	4.34 t (*J* = 7.2)	4.56 s	1.12 t (3H, *J* = 7.1) 3.89 q (2H, *J* = 7.1)	7.05–7.48 m (9H)

Table 4. Yields, IR spectral parameters, and elemental analyses of *N*-acyl-*N*-benzylleucine esters **XII–XIX**

Comp. no.	Yield, %	IR spectrum, ν, cm^{-1}		Found, %			Formula	Calculated, %		
		C=O ester	C=O amide	C	H	N		C	H	N
XII	80	1740	1656	54.12	6.43	3.77	$C_{16}H_{22}BrNO_3$	53.93	6.22	3.93
XIII	81	1742	1644	60.41	5.94	3.38	$C_{21}H_{24}BrNO_3$	60.29	5.78	3.35
XIV	78	1741	1655	61.77	7.25	4.33	$C_{16}H_{22}ClNO_3$	61.63	7.11	4.49
XV	79	1742	1644	67.38	6.54	3.88	$C_{21}H_{24}ClNO_3$	67.46	6.47	3.75
XVI	79	1737	1653	55.32	6.69	3.65	$C_{17}H_{24}BrNO_3$	55.14	6.53	3.78
XVII	79	1738	1643	61.23	6.18	3.08	$C_{22}H_{26}BrNO_3$	61.12	6.06	3.24
XVIII	78	1736	1655	62.83	7.55	4.45	$C_{17}H_{24}ClNO_3$	62.67	7.42	4.30
XIX	79	1737	1644	68.04	6.82	3.65	$C_{22}H_{26}ClNO_3$	68.12	6.76	3.61

singlet at δ 1.98 ppm was assigned to the NH proton. The following signals were found in the ^{1}H NMR spectrum of **XI**, δ, ppm: 0.84 d (3H, CH_3, J = 6.6 Hz), 0.87 d (3H, CH_3, J = 6.3 Hz), 1.24–1.41 m (2H, CH_2), 3.33 d (1H, J = 11.1 Hz), 3.65 d (1H, CH_2, J = 11.1 Hz), 3.79 d (2H, CH_2, J = 12.1 Hz); 1.54–1.63 m (1H, CH), 2.68–2.81 m (1H, CH), 1.98 s (NH).

Compounds **XII–XIX** were synthesized by treatment of *N*-benzyl derivatives **VI–IX** with benzoyl or acetyl chloride in the presence of triethylamine (Scheme 3). *N*-Acyl-*N*-benzylleucine esters **XII–XIX** are oily substances, which are soluble in organic solvents. Their structure was confirmed by the IR and ^{1}H NMR spectra and elemental analyses (Tables 3, 4).

EXPERIMENTAL

The IR spectra were recorded on a Protege-460 Fourier spectrometer from samples prepared as KBr pellets. The ^{1}H and ^{13}C NMR spectra were obtained on Tesla BS-567A and Bruker DPX-300 spectrometers from solutions in $CDCl_3$; the chemical shifts were measured relative to TMS. Initial leucine methyl and ethyl esters were prepared by standard procedures [2, 3].

Schiff bases II–V (*general procedure*). To a solution of 50 mmol of leucine methyl or ethyl ester in 120 ml of anhydrous methanol we added 51 mmol of the corresponding aldehyde and 10 g of calcined magnesium sulfate. The mixture was stirred for 48 h at room temperature, the precipitate was filtered off, and the filtrate was evaporated under reduced pressure. The residue was extracted with hexane, the extract was filtered, and the solvent was removed. The products were purified by vacuum distillation. Their yields and some physical parameters are given in Table 2.

***N*-Benzylleucine esters VI–IX (*general procedure*).** To a solution of 40 mmol of Schiff base **II–V** in 50 ml of the corresponding anhydrous alcohol we added at –30°C 44 mmol of sodium tetrahydridoborate. The mixture was stirred first for 3 h at –30°C and then for 10 h at room temperature, 44 mmol of glacial acetic acid was added, and the mixture was stirred for 1 h and filtered. The solvent was removed under reduced pressure, the residue was extracted with hexane, the extract was filtered, and the solvent was distilled off from the filtrate. The products were purified by vacuum distillation. Their yields and some physical parameters are given in Table 2.

2-(*m*-Bromobenzylamino)-4-methylpentan-1-ol (X). To a solution of 6.24 g (20 mmol) of compound **II** in 70 ml of anhydrous methanol we added at –30°C 2.28 g (60 mmol) of sodium tetrahydridoborate. The mixture was allowed to warm up to room temperature, stirred for 8 h, and left overnight. Glacial acetic acid, 3.6 g (60 mmol), was then added, the mixture was stirred for 2 h and filtered, and the filtrate was evaporated under reduced pressure. The residue was extracted with diethyl ether, the extract was filtered and evaporated, and the residue was recrystallized from hexane. Yield 2 g (70%), mp 57–58°C. Found, %: C 54.72; H 7.25; N 4.77. $C_{13}H_{20}BrNO$. Calculated, %: C 54.56; H 7.04; N 4.89.

2-(*p*-Chlorobenzylamino)-4-methylpentan-1-ol (XI) was synthesized in a similar way from 5.64 g (20 mmol) of compound **V** and 2.28 g (60 mmol) of sodium tetrahydridoborate in anhydrous ethanol. Yield 1.57 g (65%), mp 65–67°C. Found, %: C 64.72;

H 8.56; N 5.63. $C_{13}H_{20}ClNO$. Calculated, %: C 64.59; H 8.34; N 5.79.

***N*-Acyl-*N*-benzylleucine esters XII–XIX (*general procedure*).** To a solution of 5 mmol of compound **VI–IX** in 50 ml of dry diethyl ether we added 5.1 mmol of triethylamine, and a solution of 5.1 mmol of acetyl or benzoyl chloride was then added dropwise under vigorous stirring. The mixture was stirred for 7 h at room temperature, the precipitate was filtered off, and the solvent was removed from the filtrate under reduced pressure. The residue was extracted with hot hexane, the extract was filtered and cooled to –20°C, and the precipitate was separated and dried under reduced pressure. The yields, IR spectra, and elemental analyses of the products are given in Table 4.

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