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Ferrocene Derivatives of Valine and Leucine

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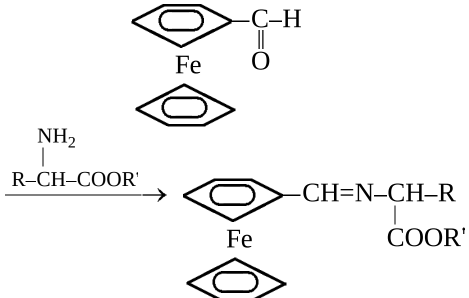
Abstract—Methyl and ethyl esters of valine and leucine were reacted with ferrocenecarbaldehyde to obtain azomethines $(C_5H_5)Fe(C_5H_4CH{=}NCHRCOOR')$ whose reactions with sodium borohydride provide ferrocenylmethyl derivatives $(C_5H_5)Fe(C_5H_4CH_2NHCHR\cdot COOR')$ [R = $(CH_3)_2CH$, $(CH_3)_2CHCH_2$; R' = CH_3, C_2H_5]. The latter compounds react with sodium hydroxide to give, after treatment of the reaction mixtures with acetic acid, N-substituted amino acids $(C_5H_5)Fe(C_5H_4CH_2NHCHRCOOH)$.

Amino acids and their derivatives exhibit physiologic activity and are widely applied as medical substances and biologically active additives. Non-salt derivatives of these compounds, containing biogenic metals, hold much promise as components of such additives. In the present work we report on the synthesis of ferrocene-containing derivatives of valine and leucine.



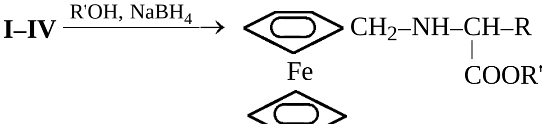
I–IV

R = $(CH_3)_2CH$, R' = CH_3 (**I**), C_2H_5 (**II**);
R = $(CH_3)_2CHCH_2$, R' = CH_3 (**III**), C_2H_5 (**IV**).

Ferrocenecarbaldehyde was reacted with methyl and ethyl esters of valine and leucine in dry methanol in the presence of magnesium sulfate to obtain the corresponding azomethines.

Compounds **I**–**IV** are solid substances soluble in ordinary organic solvents. Their structure was confirmed by ^1H NMR and IR spectroscopy and elemental analysis (Tables 1 and 2).

The reactions of azomethines with sodium borohydrides (reagent ratio 1 : 1.1) in alcohols gave *N*-ferrocenylmethyl derivatives of valine and leucine esters.

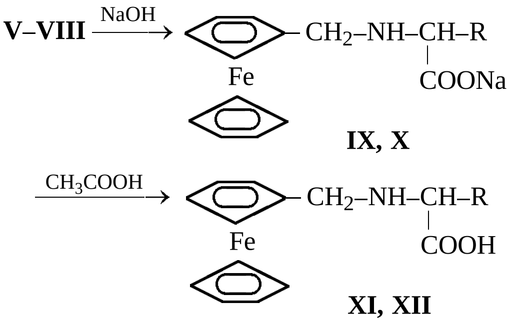


V–VIII

R = $(CH_3)_2CH$, R' = CH_3 (**V**), C_2H_5 (**VI**); R = $(CH_3)_2\cdot CHCH_2$, R' = CH_3 (**VII**), C_2H_5 (**VIII**).

Compounds **V**–**VIII** are oily substances soluble in organic solvents. Their structure was confirmed by ^1H NMR and IR spectroscopy and elemental analysis (Tables 1 and 2).

Compounds **V**–**VIII** were reacted with sodium hydroxide in methanol to obtain salts of *N*-ferrocenylmethyl derivatives of valine and leucine, whose treatment with acetic acid resulted in preparation of N-substituted amino acids **IX**–**XII**. Their structure was confirmed by ^1H NMR and IR spectroscopy and elemental analysis.



XI, XII

R = $(CH_3)_2CH$ (**IX, XI**), $(CH_3)_2CHCH_2$ (**X, XII**).

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Table 1. ^1H NMR spectra of compounds **I**–**VIII**, δ, ppm (solvent $CDCl_3$)

Comp. no.	R	R'	C_5H_5	C_5H_4	CH	CH=N
I	0.95 d (3H, *J* 6.6 Hz), 0.97 d (3H, *J* 6.6 Hz), 2.10–2.62 m (1H)	3.73 s (3H)	4.15 s (5H)	4.38 t (2H, *J* 2 Hz), 4.6–4.8 m (2H)	3.50 d (*J* 8 Hz)	8.12 s
II	0.95 d (3H, *J* 6.6 Hz), 0.98 d (3H, *J* 6.6 Hz), 2.04–2.60 m (1H)	1.29 t (3H, *J* 7.1 Hz), 4.19 q (2H, *J* 6.3 Hz)	4.18 s (5H)	4.38 t (2H, *J* 1.9 Hz), 4.6–4.8 m (2H)	3.48 d (*J* 7.8 Hz)	8.13 s
III	0.92 d (3H, *J* 5.8 Hz), 0.97 d (3H, *J* 5.8 Hz), 1.46–2.10 m (3H)	3.73 s (3H)	4.19 s (5H)	4.41 t (2H, *J* 1.9 Hz), 4.61–4.78 m (2H)	3.96 t (*J* 7 Hz)	8.16 s
IV	0.91 d (3H, *J* 5.8 Hz), 0.96 d (3H, *J* 5.9 Hz), 1.48–2.05 m (3H)	1.29 t (3H, *J* 7.2 Hz) 4.18 q (2H, *J* 6.6 Hz)	4.19 s (5H)	4.39 t (2H, *J* 1.9 Hz), 4.62–4.80 m (2H)	3.92 t (*J* 7 Hz)	8.16 s
V	0.94 d (6H, *J* 6.6 Hz), 1.82–2.19 m (1H)	3.67 s (3H)	4.12 s	4.09 t (2H, *J* 1.9 Hz), 4.20–4.31 m (2H)	3.04 d (*J* 5.9 Hz)	
VI	0.95 d (6H, *J* 6.6 Hz), 1.81–2.30 m (1H)	1.28 t (3H, *J* 7.1 Hz), 4.05 q (2H, *J* 6.3 Hz)	4.14 s	4.10 t (2H, *J* 1.9 Hz), 4.18–4.31 m (2H)	3.04 d (*J* 5.8 Hz)	
VII	0.88 d (3H, *J* 6.1 Hz), 0.93 d (3H, *J* 6.1 Hz), 1.36–1.94 m (3H)	3.72 s (3H)	4.13 s	4.08 t (2H, *J* 1.8 Hz), 4.16–4.27 m (2H)	3.18–3.28 m	
VIII	0.85 d (3H, *J* 6.2 Hz), 0.89 d (3H, *J* 6.2 Hz), 1.35–2.02 m (3H)	1.25 t (3H, *J* 7.1 Hz), 4.03 q (2H, *J* 6.3 Hz)	4.14 s	4.08 t (2H, *J* 1.8 Hz), 4.18–4.30 m (2H)	3.15–3.26 m	

Table 2. Physicochemical characteristics and elemental analyses of compounds **I**–**VIII**

Comp. no.	Yield, %	mp, °C	IR spectrum, ν, cm^{-1}		Found, %			Formula	Calculated, %		
			CO	C=N	C	H	N		C	H	N
I	82	90–92	1736	1636	62.54	6.62	4.19	$C_{17}H_{21}FeNO_2$	62.40	6.47	4.28
II	80	84–86	1717	1636	63.48	7.01	3.96	$C_{18}H_{23}FeNO_2$	63.36	6.79	4.10
III	80	75–77	1729	1633	63.14	6.52	3.87	$C_{18}H_{23}FeNO_2$	63.36	6.79	4.10
IV	79	51–52	1728	1637	64.43	7.19	4.12	$C_{19}H_{25}FeNO_2$	64.24	7.09	3.94
V	75	–	1732		62.31	7.18	4.07	$C_{17}H_{23}FeNO_2$	62.02	7.04	4.25
VI	70	–	1729		63.08	7.26	4.12	$C_{18}H_{25}FeNO_2$	62.99	7.34	4.08
VII	74	–	1736		63.16	7.41	4.01	$C_{18}H_{25}FeNO_2$	62.99	7.34	4.08
VIII	70	–	1731		64.01	7.85	3.81	$C_{19}H_{27}FeNO_2$	63.87	7.62	3.92

EXPERIMENTAL

The IR spectra were measured on a Protege-460 FT–IR instrument in KBr. The ^1H NMR spectra were obtained on a Tesla BS-567A instrument in $CDCl_3$, reference ™MS. The starting methyl and ethyl esters of valine [1, 2] and leucine [3, 4] were prepared by conventional procedures.

Azomethines I–**IV.** Ferrocenecarbaldehyde, 51 mmol, and 10 g of calcined magnesium sulfate was added to a solution of 50 mmol of valine or leucine ester in 120 ml of dry methanol. The mixture was stirred at room temperatures for 48 h, the precipitate was filtered off, and the solvent was removed at reduced pressure. The reaction product was extracted from the residue with hexane, and the hexane extracts were filtered and concentrated at reduced pressure. The crystals that formed were separated, washed with cold hexane, and dried in a vacuum.

***N*-Ferrocenylmethyl derivatives of valine and leucine esters.** Sodium borohydride, 44 mmol, was added to a solution of 40 mmol of azomethine **I**–**IV** in 50 ml of the corresponding dry alcohol at –30°C. The reaction mixture was stirred for 3 h at –30°C and then for 10 h at room temperature, after which 44 mmol of glacial acetic acid was added to it dropwise. The reaction mixture was stirred for 2 h and filtered. The solvent was removed at reduced pressure. The reaction product was extracted from the residue with hexane, the extract was filtered, the solvent was removed by distillation, and the reaction product was dried in a vacuum.

Sodium salt of *N*-(ferrocenylmethyl)valine (IX). A solution of 0.4 g of sodium hydroxide in 30 ml of methanol was added to a solution of 3.29 g of methyl ester of *N*-(ferrocenylmethyl)valine in 30 ml of methanol. The reaction mixture was stirred at 50°C for 12 h and left to stand for 2 days. The precipitate that formed was filtered off, washed in succession with methanol, acetone, and ether, and dried at reduced pressure to obtain 2.90 g (86%) of compound **IX**, mp 242–244°C (decomp.). Found, %: C 56.88; H 6.11; N 4.02. $C_{16}H_{20}FeNNaO_2$. Calculated, %: C 57.00; H 5.98; N 4.15.

Sodium salt of *N*-(ferrocenylmethyl)leucine (X) was prepared in a similar way from 3.43 g of methyl ester of *N*-(ferrocenylmethyl)leucine and 0.4 g of sodiumhydroxide. Yield 2.95 g (84%), mp 239–241°C (decomp.). Found, %: C 57.95; H 6.27; N 4.01. $C_{17}H_{22}FeNNaO_2$. Calculated, %: C 58.14; H 6.31; N 3.99.

***N*-(Ferrocenylmethyl)valine (XI).** Trifluoroacetic acid, 0.57 g, was added to a solution of 1.69 g of sodium salt of *N*-(ferrocenylmethyl)valine in 50 ml of water. The mixture was stirred for 3 h. The precipitate that formed was filtered off, washed in succession with acetone and ether, and dried in a vacuum to obtain 1.26 g (80%) of compound **XI**, mp 198–200°C. Found, %: C 61.16; H 6.89; N 4.29. $C_{16}H_{21}FeNO_2$. Calculated, %: C 60.97; H 6.72; N 4.44.

***N*-(Ferrocenylmethyl)leucine (XII)** was prepared in a similar way from 1.76 g of sodium salt of *N*-(ferrocenylmethyl)leucine and 0.57 g of trifluoroacetic acid. Yield 1.35 g (77%), mp 192–194°C. Found, %: C 62.23; H 7.14; N 4.18. $C_{17}H_{23}FeNO_2$. Calculated, %: C 62.02; H 7.04; N 4.25.

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