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SHORT COMMUNICATIONS

α-Ferrocenylalkylation of Some Biologically Active Compounds*

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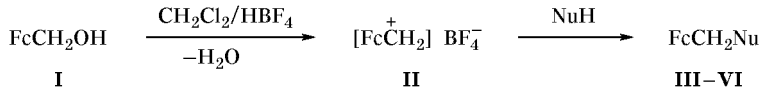
α-Ferrocenylalkylation reactions [1] are used to prepare various ferrocene derivatives exhibiting a wide spectrum of biological activity [2, 3]. With the goal of further search for more efficient compounds of this series, in the present work we effected for the first time α-ferrocenylalkylation of some biologically active compounds [4], such as Cyclophosphan, 5-fluorouracil (as sodium salt), and glycine and phenylalanine ethyl esters, by the action of ferrocenylmethanol (**I**) in the two-phase system CH_2Cl_2–48% aqueous HBF_4 at room temperature under vigorous stirring. It is known [5] that under these conditions α-ferrocenylcarbocation **II** is readily generated from alcohol **I**. Cation **II** reacts with the above nucleophilic substrates at their most electron-rich centers. As a result, we obtained in high yields ferrocene-containing compounds **III**–**VI** (Scheme 1) whose structure was confirmed by the data of elemental analysis, IR and ^{1}H NMR spectroscopy, and mass spectrometry and by chemical transformations.

The IR spectra of compounds **III**–**VI** contain absorption bands typical of vibrations of the ferrocenyl fragment [6] and other functional groups (P=O, C=O, N–H). Their ^{1}H NMR spectra were also consistent with the assumed structures. Compound **VI** showed in the ^{1}H NMR spectrum a double set of signals due to the presence of two isomers (N^1 and and N^3) which we failed to separate by column chromatography on Al_2O_3 (compound **VI** turned out to be unstable). According to the ^{1}H signal intensities, the ratio of the N^1- and N^3-isomers is 65:35. The mass spectra of **III**–**VI** contained low-intense (5–8%) molecular ion peaks; the most abundant ions were $[FcCH_2]^+$ (100%) and $[FcH]^+$ (56–83%).

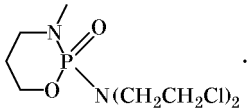
Heating of ferrocenyl-containing esters **IV** and **V** in aqueous–alcoholic alkali resulted in their hydrolysis to the corresponding *N*-ferrocenylmethyl amino acids **VII** and **VIII** (Scheme 2) whose structure was confirmed by elemental analyses and spectral data.

3-Ferrocenylmethyl-2-[bis(2-chloroethyl)amino]-1,3,2λ^5-oxazaphosphinane 2-oxide hydrate (III). To a solution of 0.28 g (1 mmol) of Cyclophosphan hydrate and 0.216 g (1 mmol) of ferrocenylmethanol (**I**) in 2 ml of methylene chloride we added under

Scheme 1.



I **II** **III–VI**

Fc = $C_5H_5FeC_5H_4$; **III**, Nu =  ·H_2O; **IV**, Nu = $EtOCOCH_2NH$; **V**, Nu = $EtOCOCH(CH_2Ph)NH$;

VI, Nu = 5-fluoro-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-1(or 3)-yl.

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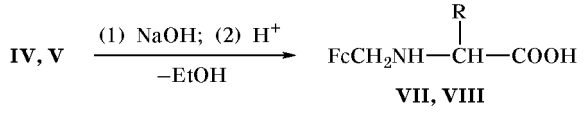
Scheme 2.



VII, R = H; **VIII**, R = CH_2Ph.

vigorous stirring at room temperature 0.18 ml of 48% aqueous HBF_4, and the mixture was stirred for 0.5 h. The mixture was then diluted with 15 ml of diethyl ether, 12 ml of 10% aqueous sodium carbonate was added, and the mixture was stirred for 1 h. The organic phase was separated, the aqueous phase was extracted with diethyl ether (3 × 10 ml), the combined extracts were washed with water and dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure at room temperature, and the yellow–brown oily product was washed with 5 ml of hexane. Yield of **III** 0.44 g (93.6%), R_f 0.28. IR spectrum, ν, cm^{-1}: 3560–3160 (H_2O); 3102, 1452, 1096, 1009, 804 (ferrocene); 1240 (P=O). ^1H NMR spectrum, δ, ppm: 4.04 s (5H, C_5H_5), 3.98 m and 4.11 m (4H, C_5H_4), 3.64–3.28 m (8H, CH_2N; 2H, CH_2O; 4H, CH_2Cl), 1.98–2.23 m (2H, CH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 459 (7) $[M-H_2O]^+$, 199 (100) $[FcCH_2]^+$, 186 (56) $[FcH]^+$. Found, %: C 45.64; H 5.33; Cl 14.75; Fe 11.78; N 5.67. $C_{18}H_{25}Cl_2FeN_2O_2P \cdot H_2O$. Calculated, %: C 45.32; H 5.66; Cl 14.88; Fe 11.71; N 5.87.

***N*-Ferrocenylmethylglycine ethyl ester (IV).** Dry ammonia was passed over a period of 2 min through a mixture of 0.1945 g (1.4 mmol) of glycine ethyl ester hydrochloride and 3 ml of methylene chloride. The solvent was removed under reduced pressure, 1.8 ml of methylene chloride and 0.3 g (1.4 mmol) of alcohol **I** were added, and 0.25 ml of 48% aqueous HBF_4 was added under vigorous stirring. The mixture was stirred for 0.5 h and was then treated as described above in the synthesis of compound **III**. Yield of **IV** 0.417 g (99%), yellow oily substance, R_f 0.42. IR spectrum, ν, cm^{-1}: 3340 (N–H); 3100, 1420, 1103, 1000, 819 (ferrocene); 1728 (C=O). ^1H NMR spectrum, δ, ppm: 4.23 q (2H, CH_2O), 4.10 s (5H, C_5H_5), 4.15 m and 4.02 m (2H each, C_5H_4), 3.71 s (2H, CH_2CO), 3.63 d (2H, CH_2N), 1.25 t (3H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 301 (5.8) M^+, 199 (100) $[FcCH_2]^+$, 186 (78) $[FcH]^+$. Found, %: C 59.81; H 6.24; Fe 18.43; N 4.36. $C_{15}H_{19}FeNO_2$. Calculated, %: C 59.85; H 6.31; Fe 18.55; N 4.65.

Ethyl 2-ferrocenylmethylamino-3-phenylpropionate (V) was synthesized in a similar way. Yield 98%, yellow–brown oily substance, R_f 0.34. IR spectrum, ν, cm^{-1}: 3350 (N–H); 3098, 1418, 1100, 1002, 821 (ferrocene); 1722 (C=O). ^1H NMR spectrum, δ, ppm: 7.22 m (5H, C_6H_5), 4.56 m (1H, CH), 4.20 q (2H, CH_2O), 4.08 s (5H, C_5H_5), 4.15 m and 3.98 m (2H each, C_5H_4), 3.64 d (2H, CH_2N), 3.12 d (2H, CH_2Ph), 1.25 t (3H, CH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 391 (8) M^+, 199 (100) $[FcCH_2]^+$, 186 (86) $[FcH]^+$. Found, %: C 67.63; H 6.28; Fe 14.33; N 3.41. $C_{22}H_{25}FeNO_2$. Calculated, %: C 67.56; H 6.39; Fe 14.28; N 3.58.

1(3)-Ferrocenylmethyl-5-fluorouracil (VI). To a mixture of 0.152 g (1 mmol) of 5-fluorouracil sodium salt and 0.216 g (1 mmol) of alcohol **I** in 2 ml of methylene chloride we added under vigorous stirring at room temperature 0.18 ml of 48% aqueous HBF_4. The mixture was stirred for 2 h and was then treated as described above in the synthesis of compound **III**. Yield of **VI** 0.138 g (42%), brown crystals, mp 216–220°C (from aqueous ethanol, 1:1). IR spectrum, ν, cm^{-1}: 3480–3430 (N–H); 3100, 1418, 1101, 1000, 818 (ferrocene); 1687–1642 (C=O). ^1H NMR spectrum, δ, ppm: 11.18 s and 11.04 s (1H, NH), 8.07 m and 8.03 m (1H, CH), 6.05 s and 5.88 s (2H, CH_2), 4.28 m and 4.12 m (2H each, C_5H_4), 4.18 s (5H, C_5H_5). Mass spectrum, *m*/*z* (I_{rel}, %): 328 (5.5) M^+, 199 (100) $[FcCH_2]^+$, 186 (64) $[FcH]^+$. Found, %: C 54.63; H 4.02; Fe 17.08; N 8.56. $C_{15}H_{13}FFeN_2O_2$. Calculated, %: C 54.92; H 3.96; Fe 17.03; N 8.54.

***N*-Ferrocenylmethylglycine (VII).** A mixture of 0.19 g (4.75 mmol) of NaOH and 0.21 g (0.7 mmol) of ester **IV** in 6 ml of aqueous ethanol (1:1) was stirred for 1 h on heating under reflux. The mixture was filtered, and the filtrate was neutralized with hydrochloric acid to pH 7 and was left to stand for 20 h in a refrigerator at 5–6°C. The yellow–brown precipitate was filtered off, washed with 5 ml of cold water, and dried to a constant weight. Yield of **VII** 0.16 g (84%), mp 208–210°C (from ethanol). IR spectrum, ν, cm^{-1}: 3425–3320 (N–H); 3098, 1418, 1100, 1003, 821 (ferrocene); 1698, 1631 (COOH). ^1H NMR spectrum, δ, ppm: 4.92 s (1H, COOH), 4.32 d (1H, NH), 4.20 m and 4.10 m (2H each, C_5H_4), 4.15 s (5H, C_5H_5), 3.78 d (2H, CH_2CO), 3.67 d (2H, CH_2N). Mass spectrum, *m*/*z* (I_{rel}, %): 273 (6.2) M^+, 199 (100) $[FcCH_2]^+$, 186 (73) $[FcH]^+$. Found, %: C 57.02; H 5.44; Fe 20.31; N 5.04. $C_{13}H_{15}FeNO_2$. Calculated, %: C 57.19; H 5.49; Fe 20.46; N 5.13.

2-Ferrocenylamino-3-phenylpropionic acid (VIII) was synthesized in a similar way. Yield 65%, yellow–brown crystals, mp 183–184°C (from ethanol–

water, 3 : 1). IR spectrum, ν, cm^{-1}: 3420–3352 (N–H); 3100, 1420, 1100, 1002, 820 (ferrocene); 1702, 1632 (COOH); 1608, 1572 (C–C_{arom}). ^{1}H NMR spectrum, δ, ppm: 7.31 m (5H, C_6H_5) 4.92 s (1H, COOH), 4.58 m (1H, CH), 4.30 d (1H, NH), 4.18 m and 4.07 m (2H each, C_5H_4), 4.14 s (5H, C_5H_5), 3.72 d (2H, CH_2N), 3.14 d (2H, CH_2Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 361 (5.4) M^+, 199 (100) $[FcCH_2]^+$, 186 (63) $[FcH]^+$, 91 (42) $[C_6H_5CH_2]^+$. Found, %: C 66.31; H 5.24; Fe 15.19; N 3.75. $C_{20}H_{19}FeNO_2$. Calculated, %: C 66.54; H 5.26; Fe 15.47; N 3.88.

The purity of the products was checked by TLC on Silufol UV-254 plates using diethyl ether as eluent; development with iodine vapor. The IR spectra were obtained on a UR-20 instrument in KBr. The ^{1}H NMR spectra were measured on a Bruker WP-200 spectrometer (200.13 MHz) using acetone-d_6 (compounds **III**–**V**, **VII**, and **VIII**) and DMSO-d_6 (**VI**) as solvents and TMS as internal reference. The mass spectra (70 eV) were run on a Kratos MS-890 instrument.

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