Mannich Reaction with the Exocycle of Methylpheophorbide *a*

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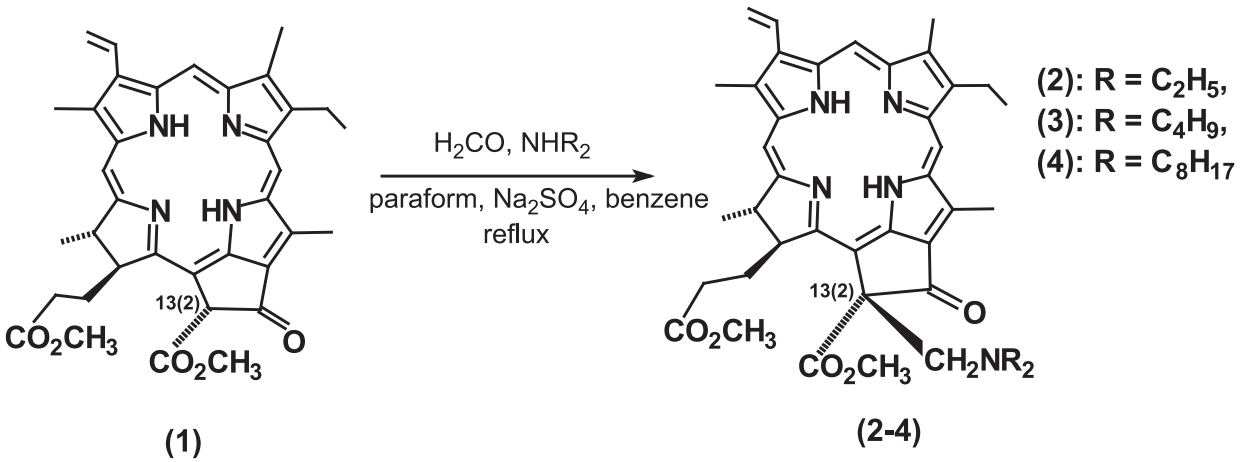
It is shown that the exocycle in methylpheophorbide a can act as a methylene component in the Mannich reaction and the interaction with formaldehyde and dialkylamine leads to the corresponding 13(2)-dialkylaminomethyl derivatives. It was established that aminomethylation proceeds stereoselectively with formation of 13(2)R-diastereoisomers. Stereoselectivity of the reaction and R-configuration of the 13(2) carbon atom are explained by the distortion of the enolic form of the exocycle, arising from the repulsion of the substituents in 13(2) and 17 positions. As a result of such distortion one of the diastereofacing sides of the double bond in the intermediate enol becomes more accessible for the electrophilic attack which leads to formation of 13(2)R-diastereomer.

Keywords: Methylpheophorbide *a*, aminomethylation, Mannich reaction.

It is known that chlorophyll *a* and its derivatives not only play an essential role in the living nature, but may be used as initial substances in the synthesis of practically important compounds, having wide applications in medicine,[1-3] catalysis,[4,5] design of polymeric and nano-materials for photoelectronics,[6-9] *etc*. Practically important properties of the chlorin-type compounds are defined mainly by peripheral substituents. Thus, the most efficient way to influence on the properties of chlorophyll derivatives is peripheral modification of substituents in the chlorin macrocycle. In this connection the development of efficient methods for chemical modification of natural chlorins, especially of the more easily available chlorins of the *a* type, is of great interest. To find new opportunities for modification of chlorophyll *a* and its derivatives we have studied the transformations of methylpheophorbide *a* (**1**)[10] at the conditions of Mannich reaction (Scheme 1).

To execute the Mannich reaction methylpheophorbide *a* (**1**) (20-50 mg, 0.032-0.08 mmol), paraform (50-100 mg, corresponding to 1.67-3.34 mmol of formaldehyde) and dialkylamine (diethylamine, dibutylamine, dioctylamine, 5-15 mmol) were dissolved in benzene (30 ml). After addition of anhydrous Na_2SO_4 (300 mg) the mixture was refluxed for 1.5-3 hours until the full conversion of compound **1** (TLC control). The reaction mixture was diluted by chloroform (50-70 ml) and washed with water until neutrality. The obtained solution was dried over unhydrous Na_2SO_4 and evaporated under reduced pressure. The residue after evaporation of the solvent was recrystallized from a chloroform-hexane mixture. Rerystallization is the only suitable method for purification because the aminomethylation products **2** - **4** are easily destroyed upon chromatography both on silica and Al_2O_3. Since application of chromatography was not possible it was important to achieve full conversion of the initial methylpheophorbide by use of amine and paraform in large excesses. The relatively low yields of the target products (40-60 %) obtained under these conditions are most likely due to the side reactions of these species competing with aminomethylation.

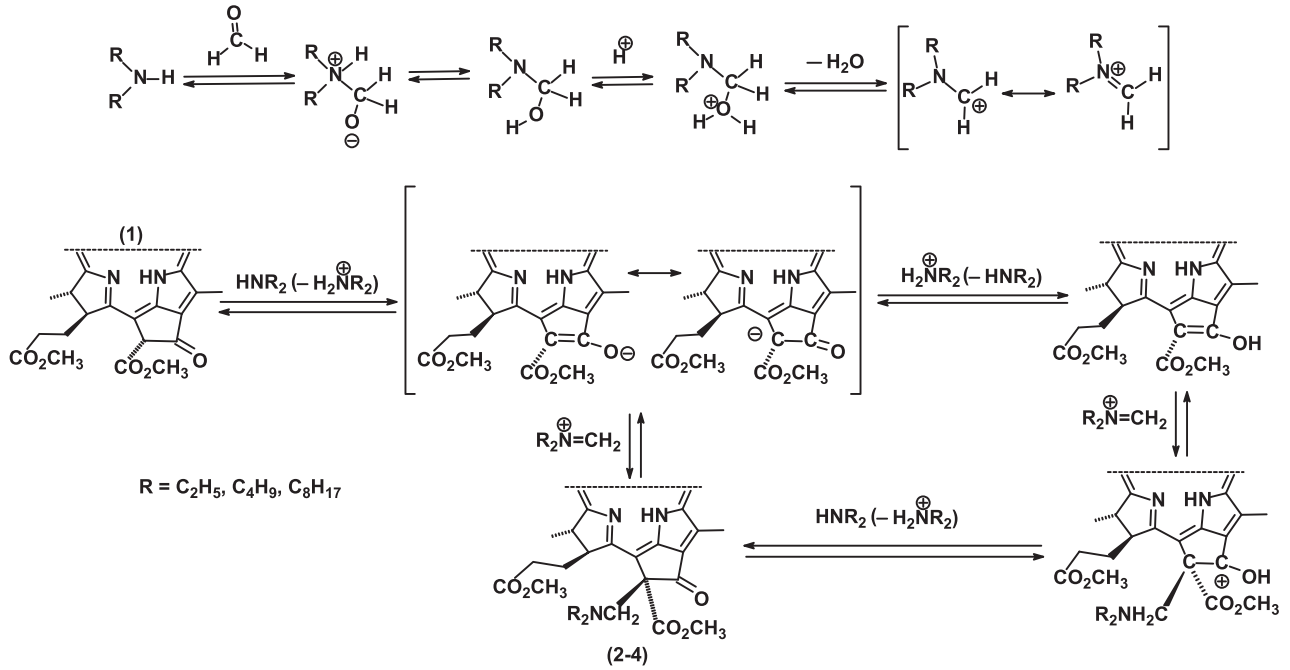


Scheme 1.

The formation of aminomethylation products **2-4** was confirmed by ^{1}H NMR spectroscopy and mass-spectrometry.[#] The signal of exocycle proton at 13(2) position is absent in the ^{1}H NMR spectra of the products, whereas the AB multipletes of the methylene group of the dialkylaminomethyl fragment are observed at ~ 4.0 – 4.5 ppm along with multipletes of the neighbouring alkyl groups. In the mass spectra the peaks corresponding to the molecular and protonated molecular ions of aminomethylation products **2**-**4** were observed.

The study of aminomethylation products by ^{1}H NMR spectroscopy shows that in all cases only one of all possible diastereoisomers is formed. According to the ROESY data the carbon atom in the 13(2) position of the reaction products **2-4** has *R*-configuration. Stereoselectivity of the reaction and the formation of 13(2)*R*-stereoisomers may be explained by the suggestion that enolic form of the exocycle in methylpheophorbide *a* is not strictly planar due to repulsion of substituents in the 13(2) and 17 positions). Attack of the enolic fragment by a bulky dialkylaminomethyl cation predominantly occurs on the side opposite to that in which the ester group in the 13(2) position is deflected (Scheme 2).

So, it was shown here, that the exocycle of methylpheophorbide *a* may serve as methylene component in the Mannich reaction and the corresponding



Scheme 2.

[#] ^{1}H NMR spectra were recorded in $CDCl_3$ on «Bruker Avance II» spectrometer at 300 MHz. Mass-spectra were obtained on «Thermo Finnigan LSQ Fleet» chromatomass spectrometer (ESI, direct probe inputting). UV-vis spectra were recorded on UV–1700 (PharmaSpec) spectrometer (SHIMADZU) at 200–1100 nm in 10 mm quartz cuvettes using chloroform as reference solvent. Reaction was controlled by TLC on Silufol plates, eluent - CCl_4-acetone (1:4 by volume).

13(2)-(N,N-Dimethylaminomethyl)pheophorbide a methyl ester (2). The compound **1** (20 mg, 0.033 mmol) gave derivative **2** (10.3 mg, 45% yield) as gray-blue powder. *m/z* (ESI): 692.1 (MH^+). UV-vis ($CHCl_3$) λ nm (relative intensity, %): 665(40), 610(8), 537(12), 506(15), 410(100). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.63 s (1H, H^{10}), 9.47 s (1H, H^5), 8.62 s (1H, H^{20}), 8.04 dd (1H, 3-(C*H*=CH_2), *J* = 17.6 and 11.0 Hz), 6.35 dd (1H, 3-(CH=CHH_{trans}), *J* = 17.8 and 1.6 Hz), 6.19 dd (1H, 3-(CH=CHH_{cis}), *J* = 11.6 and 1.6 Hz), 4.24 d (1H, 13(2)-CHH_AN(C_2H_5)$_2$, *J* = 16.8 Hz), 4.12 d (1H, 13(2)-CHH_BN(C_2H_5)$_2$, *J* = 16.8 Hz), 4.41-4.51 m (2H, H^{17}, H^{18}), 3.48-3.73 m (2H, 8-C$H_2$$CH_3$), 3.74 s (3H, 13(2)-$CO_2CH_3$), 3.63 s (3H, 12-$CH_3$), 3.55 s (3H, 17-$CH_2CH_2$COOC$H_3$), 3.45 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 3.04 q (4H, 13(2)-$CH_2$N(C$H_2$$CH_3$)$_2$, *J* = 7.0 Hz), 2.19-2.70 m (4H, 17-CH_2CH_2COOCH_3), 1.81 d (3H, 18-CH_3, *J* = 7.6 Hz), 1.74 t (3H, 8-CH_2CH_3, *J* = 7.6 Hz), 0.33 t (6H, 13(2)-CH_2N(CH_2CH_3)$_2$, *J* = 7.0 Hz), 0.48 brs (1H, I-NH), -1.69 brs (1H, III-NH).

13(2)-(N,N-Dibutylaminomethyl)pheophorbide a methyl ester (3). The compound **1** (50 mg, 0.082 mmol) gave derivative **3** (37.0 mg, 60% yield) as gray-blue powder. *m/z* (ESI): 748.3 (MH^+), 692.3 (MH-C_4H_8)$^+$. UV-vis ($CHCl_3$) λ nm (relative intensity, %): 667(44), 612(8), 539(10), 506(14), 412(100). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.61 s (1H, H^{10}), 9.46 s (1H, H^5), 8.61 s (1H, H^{20}), 8.02 dd (1H, 3-(C*H*=CH_2), *J* = 17.8 and 11.2 Hz), 6.33 dd [1H, 3-(CH=CHH_{trans}), *J* = 17.8 and 1.6 Hz), 6.17 dd (1H, 3-(CH=CHH_{cis}), *J* = 11.4 and 1.6 Hz), 4.24 d (1H, 13(2)-CHH_AN(C_4H_9)$_2$, *J* = 16.2 Hz), 4.12 d (1H, 13(2)-CHH_BN(C_4H_9)$_2$, *J* = 16.2 Hz), 4.41-4.51 m (2H, H^{17}, H^{18}), 3.50-3.70 m (2H, 8-C$H_2$$CH_3$), 3.73 s (3H, 13(2)-$CO_2CH_3$), 3.62 s (3H, 12-$CH_3$), 3.55 s (3H, 17-$CH_2CH_2$COOC$H_3$), 3.45 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 2.19-2.70 m (4H, 17-C$H_2CH_2$COOC$H_3$), 1.81 d (3H, 18-$CH_3$, *J* = 7.6 Hz), 1.74 t (3H, 8-CH_2CH_3, *J* = 7.6 Hz); 13(2)-CH_2N(CH_2CH_2C$H_2$$CH_3$)$_2$: 2.18-2.06 m 4H, 0.80-0.58 m 4H, 0.44-0.17 m 4H; 0.05 t (6H, 13(2)-CH_2N($CH_2CH_2CH_2$CH_3)$_2$, *J* = 7.5 Hz), 0.40 brs (1H, I-NH), -1.71 brs (1H, III-NH).

13(2)-(N,N-Dioctylaminomethyl)pheophorbide a methyl ester (4). The compound **1** (30 mg, 0.049 mmol) gave derivative **4** (17.0 mg, 40% yield) as gray-blue powder. *m/z* (ESI): 860.3 (M^+). UV-vis ($CHCl_3$) λ nm (relative intensity, %): 665(42), 611(8), 538(10), 507(15), 412(100). ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 9.62 s (1H, H^{10}), 9.48 s (1H, H^5), 8.62 s (1H, H^{20}), 8.04 dd (1H, 3-(C*H*=CH_2), *J* = 17.6 and 11.6 Hz), 6.35 dd [1H, 3-(CH=CHH_{trans}), *J* = 17.6 and 1.6 Hz), 6.17 dd (1H, 3-(CH=CHH_{cis}), *J* = 11.6 and 1.6 Hz), 4.24 d (1H, 13(2)-CHH_AN(C_8H_{17})$_2$, *J* = 16.8 Hz), 4.12 d (1H, 13(2)-CHH_BN(C_8H_{17})$_2$, *J* = 16.8 Hz), 4.41-4.51 m (2H, H^{17}, H^{18}), 3.50-3.70 m (2H, 8-C$H_2$$CH_3$), 3.73 s (3H, 13(2)-$CO_2CH_3$), 3.61 s (3H, 12-$CH_3$), 3.57 s (3H, 17-$CH_2CH_2$COOC$H_3$), 3.46 s (3H, 2-$CH_3$), 3.28 s (3H, 7-$CH_3$), 2.20-2.71 m (4H, 17-C$H_2CH_2$COOC$H_3$), 1.81 d (3H, 18-$CH_3$, *J* = 7.6 Hz), 1.73 t (3H, 8-CH_2CH_3, *J* = 7.2 Hz); 13(2)-CH_2N((CH_2)$_7$$CH_3$)$_2$: 2.18-2.06 m 4H, 0.80-0.40 m 8H, 0.44-0.15 m 16H; 0.11 t (6H, 13(2)-CH_2N((CH_2)$_7$CH_3)$_2$, *J* = 7.2 Hz), 0.40 brs (1H, I-NH), -1.71 brs (1H, III-NH).

13(2)-dialkylamonpmethylene derivatives were synthesized. It was established that aminomethylation proceeds stereoselectively with formation of 13(2)*R*-stereoisomers and the possible explanation is proposed.

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