STRUCTURE OF THE INTERMEDIATE IN THE ADDITION REACTION OF DIALKYLPHOSPHOROUS ACIDS TO GROSSHEMIN

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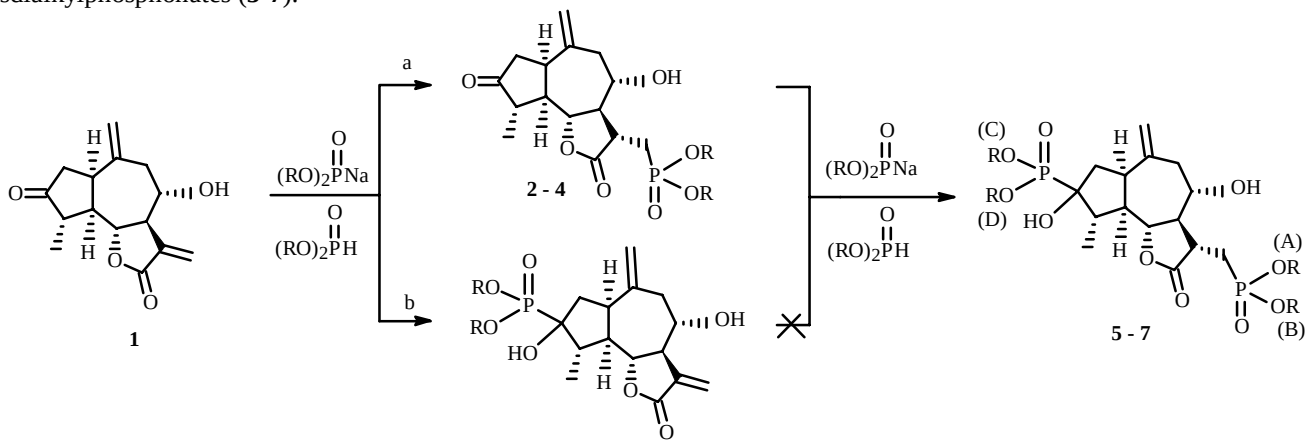
The intermediate in the reaction of grosshemin and dialkylphorphorous acids was isolated and characterized structurally. It has been found that addition of a dialkylphosphite anion occurs under these reaction conditions first at an exomethylene and then at the ketone of grosshemin.

Key words: grosshemin, phosphorylation, PMR, ^{13}C NMR.

In continuation of studies on the composition of the reaction mixture for synthesizing dialkylphosphonate derivatives of the guaianolide grosshemin [1], we prepared new monodialkylphosphonates (**2-4**) in addition to certain bisdialkylphosphonates (**5-7**).



2, 5: R = CH_2CH_3; **3, 6:** R = $CH_2CH_2CH_3$; **4, 7:** R = $CH_2CH_2CH_2CH_3$

The IR spectrum of **2** exhibits characteristic absorption bands for C=O vibrations of a five-membered ring and a γ-lactone at 1772 and 1737 cm^{-1}, respectively; P=O, 1219; and P–O–C, 991.

The PMR spectrum (Table 1) of **2** agrees with that of the bisdialkylphosphonate derivative (**5**). The difference is that the integrated intensities of the methylene signals (–OC$\underline{H}_2$) at 4.12 and methyl signals (–$CH_2C\underline{H}_3$) at 1.33 ppm indicate that **2** contains one dialkylphosphonate. The P-containing functional group adds to the exomethyl double bond of the lactone ring and not to the ketone. This follows from the PMR spectra of **2**, in which the signals for H-13a and H-13b are shifted from weak to strong field compared with the spectrum of starting **1** and appear as a doublet of doublets of doublets at 2.55 ppm with a characteristic SSCC of 20 Hz caused by coupling with ^{31}P. This is also confirmed by the ^{13}C NMR spectrum, in which signals for the C nuclei of the lactone ring, namely C-7, C-11, C-12, and C-13, have the appropriate splittings (SSCCs) caused by coupling with ^{31}P (Table 1).

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TABLE 1. PMR (500.13 MHz) and ^{13}C NMR (125.76 MHz) Data for the Diethylphosphonate Derivative of Grosshemin (**2**)

Atom	PMR, δ, ppm, J/Hz	^{13}C NMR, δ, ppm, J/Hz
1	3.11 ddd (J = 8.0, 8.0, 4.0)	43.34 d
2	2.20-2.30 (overlaps with other signals H-2a, H-2b)	39.49 t
3	-	201 s
4	2.45-2.55 (overlaps with other signals)	51.08 d
5	2.20-2.30 (overlaps with other signals)	47.13 d
6	3.97 dd ($^3J_{6/5}$ = 10.0, $^3J_{6/7}$ = 10.0)	83.31 d
7	2.63 ddd ($^3J_{7/11}$ = 12.0, $^3J_{7/6}$ = 10.0, $^3J_{7/8}$ = 10.0)	**40.84 dd ($^3J_{CP}$ = 3.3)***
8	3.69 ddd ($^3J_{8/7}$ = 10.0, $^3J_{8/9b}$ = 10.0, $^3J_{8/9a}$ = 6.0)	74.77 d
9	2.85 dd (13.0, 6.0, H-9a)	48.07 t
	2.20-2.30 (overlaps with other signals H-9b)	
10	-	144.09 s
11*	**2.81 dddd ($^3J_{PH-11}$ = 27.0, $^3J_{11/7}$ = 12.0, $^3J_{11/13a}$ = 5.0, $^3J_{11/13b}$ = 5.0)**	**53.93 dd ($^2J_{CP}$ = 4.8)**
12	-	**175.80 d ($^3J_{CP}$ = 8.0)**
13	**2.55 ddd ($^2J_{PH-13}$ = 20.0, $^2J_{13a/13b}$ = 16.0, $^3J_{13a/11}$ = 5.0, H-13a)**	**24.84 dt ($^1J_{CP}$ = 141.7)**
	2.20-2.30 (overlaps with other signals H-13b)	
14	5.06 br.s (H-14a)	114.67 t
	4.74 br.s (H-14b)	
15	1.21 d (J = 7.0)	14.33 q
16	**4.12 m (4H, -OC<u>H</u>$_2$-A(B)**)**	**62.62 dt ($^2J_{CP}$ = 6.9, -O<u>C</u>H$_2$-A(B))**
17	**1.33 t (6H, -OC<u>H</u>$_2$CH$_3$A(B))**	**16.22 dq ($^3J_{CP}$ = 5.0, - O<u>C</u>H$_2$CH$_3$A(B))**

*Signals of H and C atoms coupled to ^{31}P are shown in bold.

**A and D are diastereotopic groups (NMR parameters in the table refer to underlined H and C nuclei).

TABLE 2. Physicochemical Constants of Dialkylphosphites

Dialkylphosphites	bp, °C/mm	Index of refraction, n_D^{20}	Density
Diethylphosphite	72-73/9	1.4060	1.072
Dipropylphosphite	203/9	1.4170	1.018
Dibutylphosphite	118-119/11	1.4230	0.995

The C-11 in all phosphonate derivatives of grosshemin (**2-4**) has the *S*-configuration based on PMR data, in which the SSCC is large (12.0 Hz), indicating the *trans*-orientation of H-7 and H-11 (Table 1).

It is interesting that the initial attack is at the exomethyl of the lactone ring (route a) and not at the ketone (route b) because, according to previously published work on the kinetics of the Pudovik reaction of cinnamic esters and other compounds, the phosphorylation reaction rate of ketones is much greater than that of analogous reactions at a C=C bond conjugated with an ester [2].

Thus, the reaction of the guaianolide grosshemin with dialkylphosphorous acids produces intermediate monodialkylphosphonates. It has been found that products of addition at the exomethyl double bond of the lactone are formed first.

EXPERIMENTAL

Grosshemin (**1**, mp 200-202°C, $[\alpha]_D^{20}$ +159.9°, *c* 1.14, $CHCl_3$) was isolated from the aerial part of *Chartolepis intermedia* Boiss [3] and used as starting material for chemical modifications.

Dialkylphosphites were synthesized by the literature method [4]. Table 2 lists physicochemical constants.

The course of the reactions and the purity of the products were monitored by TLC using Silufol plates and development

by spraying with vanillin (1%) in H_2SO_4 and aqueous $KMnO_4$ (1%).

The products were purified by column flash-chromatography over silica gel (Chemapol 40/100) with elution by mixtures of petroleum ether and ethylacetate with increasing content (from 0 to 100%) of the latter.

IR spectra were recorded on a Vector 22 instrument.

NMR spectra were recorded on a Bruker DRX-500 spectrometer (working frequency 500.13 MHz for ^1H; 125.76, ^{13}C). Signals were assigned using ^{13}C NMR spectra recorded in the J-modulation regime (zero decoupling from protons, opposite phase for signals of atoms with even and uneven numbers of bound protons with tuning at J = 135 Hz).

Preparation of Dialkylphosphonates (2-4) (General Method). Metallic sodium (22.8 mg) was dissolved in dialkylphosphite (2.5 mL). The solution was cooled to 0°C, stirred, treated with grosshemin (**1**, 200 mg, 0.76 mol) dissolved in dialkylphosphite (2 mL), held at room teperature for 40 min, treated with water, and extracted with ethylacetate. The organic layer was washed with NaOH (30%) and saturated NaCl solution, dried over Na_2SO_4, and filtered. Solvent was vacuum distilled. The solid was chromatographed over a column of SiO_2 (6 g) with elution by mixtures of petroleum ether and ethylacetate with the content of the latter increasing to 100%.

(1*R*,4*S*,5*R*,6*R*,7*R*,8*S*,11*S*)-3-Oxo-8-hydroxyguai-10(14)-en-12,6-olid-13-ylphosphonic Acid Diethylester (2). Oily product, yield 30 mg (10.0%).

IR spectrum (KBr, cm^{-1}): 3350 (OH), 2956, 2923, 2852, 1772, and 1737 (C=O and γ-lactone C=O), 1717, 1700, 1650, 1457, 1376, 1219 (P=O), 1166, 991 (P–O–C), 966.

Table 1 lists the PMR and ^{13}C NMR spectra.

(1*R*,4*S*,5*R*,6*R*,7*R*,8*S*,11*S*)-3-Oxo-8-hydroxyguai-10(14)-en-12,6-olid-13-ylphosphonic Acid Dipropylester (3). Oily product, yield 27 mg (8.4%).

IR spectrum (KBr, cm^{-1}): 3341 (OH), 2926, 2854, 1775 and 1740 (C=O and γ-lactone C=O), 1643, 1457, 1377, 1235 (P=O), 1171, 1166, 998 (P–O–C), 908, 856, 723, 700, 665, 514.

PMR spectrum (500.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.13 (ddd, J = 8.0, 8.0, 5.0, H-1), 2.20-2.32 (overlaps with other signals, H-2a), 2.20-2.32 (overlaps with other signals, H-2b), 2.48-2.56 (overlaps with other signals, H-4), 2.20-2.32 (overlaps with other signals, H-5), 3.98 (dd, $^3J_{6/5}$ = 10.0, $^3J_{6/7}$ = 10.0, H-6), 2.66 (ddd, $^3J_{7/11}$ = 12.0, $^3J_{7/6}$ = 10.0, $^3J_{7/8}$ = 10.0, H-7), 3.70 (ddd, $^3J_{8/7}$ = 10.0, $^3J_{8/9b}$ = 10.0, $^3J_{8/9b}$ = 6.0, H-8), 2.87 (dd, $^2J_{9a/9b}$ = 13.0, $^3J_{9a/8}$ = 5.5, H-9a), 2.20-2.32 (overlaps with other signals, H-9b), **2.82 (dddd, $^3J_{PH-11}$ = 27.0, $^3J_{11/7}$ = 12.0, $^3J_{11/13a}$ = 5.0, $^3J_{11/13b}$ = 5.0, H-11*), 2.58 (ddd, $^2J_{PH-13}$, = 20.0, $^2J_{13a/13b}$ = 16.0, $^3J_{13a/11}$ = 5.0, H-13a), 2.20-2.32 (overlaps with other signals, H-13b)**, 5.08 (br.s, H-14a), 4.77 (br.s, H-14b), 1.23 (d, 3H, $^3J_{15/4}$ = 7.0, H-15), **4.05 (m, 4H, –OC<u>H</u>$_2$-A(B)**), 1.71 (m, 4H, –OCH$_2$C<u>H</u>$_2$-A(B))**, 0.96 (t, 6H, J = 7.0, –O(CH$_2$)$_2$C<u>H</u>$_3$ A(B)).

^{13}C NMR spectrum (125.76 MHz, $CDCl_3$, δ, ppm): 43.27 (d, C-1), 38.23 (t, C-2), 202 (s, C-3), 53.24 (d, C-4), 46.67 (d, C-5), 78.23 (d, C-6), **42.25 (d, C-7***)**, 69.99 (d, C-8), 48.87 (t, C-9), 139.23 (s, C-10), **59.44 (dd, $^3J_{CP}$ = 5.0, C-11), 174.93 (d, $^3J_{CP}$ = 8.0, C-12), 24.07 (dt, $^1J_{CP}$ = 142.8, C-13)**, 109.81 (t, C-14), 14.41 (q, C-15), **63.07 (dt, $^2J_{CP}$ = 7.0, –O<u>C</u>H$_2$-A(B))****, 24.68 (dt, $^3J_{CP}$ = 3.0, –OCH$_2$<u>C</u>H$_2$-A(B))**, 8.98 (q, –O(CH$_2$)$_2$<u>C</u>H$_3$ A(B)).

(1*R*,4*S*,5*R*,6*R*,7*R*,8*S*,11*S*)-3-Oxo-8-hydroxyguai-10(14)-en-12,6-olid-13-ylphosphonic Acid Dibutylester (4). Oily product, yield 27 mg (7.8%).

IR spectrum (KBr, cm^{-1}): 3361 (OH), 2956, 2923, 2852, 1772 and 1741 (C=O and γ-lactone C=O), 1644, 1458, 1377, 1217 (P=O), 1115, 989 (P–O–C), 909, 721, 668.

PMR spectrum (500.13 MHz, $CDCl_3$, δ, ppm, J/Hz): 3.14 (ddd, J = 8.0, 8.0, 5.0, H-1), 2.20-2.32 (overlaps with other signals, H-2a), 2.20-2.32 (overlaps with other signals, H-2b), 2.50-2.58 (overlaps with other signals, H-4), 2.20-2.32 (overlaps with other signals, H-5), 3.98 (dd, $^3J_{6/5}$ = 10.0, $^3J_{6/7}$ = 10.0, H-6), 2.67 (ddd, $^3J_{7/11}$ = 12.0, $^3J_{7/6}$ = 10.0, $^3J_{7/8}$ = 10.0, H-7), 3.71 (ddd, $^3J_{8/7}$ = 10.0, $^3J_{8/9b}$ = 10.0, $^3J_{8/9a}$ = 6.0, H-8), 2.87 (dd, $^2J_{9a/9b}$ = 13.0, $^3J_{9a/8}$ = 5.5, H-9a), 2.20-2.32 (overlaps with other signals, H-9b), **2.82 (m, H-11*), 2.56 (m, H-13a), 2.20-.232 (overlaps with other signals, H-13b)**, 5.08 (br.s, H-14a), 4.77 (br.s, H-14b), 1.23 (d, 3H, $^3J_{15/4}$ = 7.0, H-15), **4.07 (m, 4H, –OC<u>H</u>$_2$-A(B)****), 1.66 (m, 4H, –OCH$_2$C<u>H</u>$_2$-A(B))**, 1.41 (m, 4H, –O(CH$_2$)$_2$C<u>H</u>$_2$-A(B)), 0.95 (t, 6H, J = 7.0, –(CH$_2$)$_3$C<u>H</u>$_3$ A(B)).

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*Signals for protons coupled to ^{31}P are in bold.

**A and B are diasterotopic groups (NMR aprameters refer to the underlined protons).

***Signals for C atoms coupled to ^{31}P are in bold.

****A and B are diastereotopic groups (NMR parameters refer to underlined C atoms).

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REFERENCES

1. R. I. Dzhalmakhanbetova, S. A. Ivasenko, A. T. Kulyyasov, B. B. Khasenov, N. B. Kurmankulov, and S. M. Adekenov, *Khim. Prir. Soedin.*, 311 (2004).
2. V. I. Galkin, A. B. Khabibullina, E. R. Gaifutdinova, I. V. Bakhtiyarova, and R. A. Cherkasova, *Dokl. Akad. Nauk SSSR*, **296**, 107 (1987).
3. S. M. Adekenov, Doctoral Dissertation in Chemical Sciences, IBOC, RAS, Moscow (1992).
4. L. F. Fieser and M. Fieser, *Reagents for Organic Synthesis*, Wiley, New York (1967).