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PHOSPHATE DERIVATIVES OF NATURAL LACTONES. I. SYNTHESIS OF NOVEL ISOALANTOLACTONE DIALKYLPHOSPHONATES

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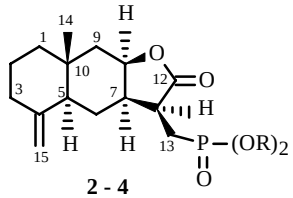
Novel isoalantolactone dialkylphosphonates were synthesized in 70-87% yields by reacting this eudesmanolide with dialkylphosphites. Their structures were proved by spectral analysis using IR, PMR, ^{13}C and ^{31}P NMR, and two-dimensional $^{1}H—^{1}H$ (COSY) spectroscopy. The reaction of isoalantolactone with dialkylphosphites is highly stereoselective.

Key words: isoalantolactone, phosphorylation, PMR, ^{13}C and ^{31}P NMR, 2D $^{1}H—^{1}H$ NMR (COSY).

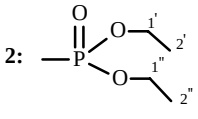
Interest in the synthesis of various derivatives of phosphonic acids has recently risen markedly [1-4]. Compounds that are analogs of natural phosphates are attracting attention because they, as a rule, are chemically more stable than the phosphates themselves and, consequently, may possess prolonged action in vivo. To the best of our knowledge, data on the synthesis of P-containing derivatives of sesquiterpene lactones have not been published. The preparation of such derivatives may become a promising direction for the chemical modification of this class of available natural compounds.

The starting isoalantolactone (**1**) has a high biological activity. Therefore, we phosphorylated this compound. We synthesized **2-4** under conditions analogous to those for the synthesis of phosphonates of monoterpenes [1, 2].



2 - 4

-P(O)(OR)$_2$



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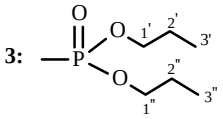

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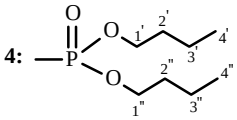

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The IR spectra of **2-4** exhibit characteristic absorption bands at 1760 and 1770 cm^{-1}, corresponding to C=O vibrations of the γ-lactone, 1225, P=O; and 1034, 970 and 1028, 990, P–O–C.

The NMR spectra (Tables 1 and 2) of **2-4** were interpreted using two-dimensional (2D) $^{1}H—^{1}H$ NMR (COSY).

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TABLE 1. PMR (500.13 MHz, $CDCl_3$, δ, ppm, J/Hz) Spectra of Isoalantolactone Dialkylphosphonates **2-4**

H atom	**2**	**3**	**4**
7	2.63 dddd (12.0; 6.3; 6.1; 4.0)	2.65 dddd (12.0; 6.2; 6.0; 4.0)	2.60 dddd (11.5; 6.1; 6.0; 3.5)
8	4.50 m	4.50 m	4.50 m
9a	2.18 dd (15.4; 1.7)	2.15 dd (15.0; 1.8)	2.15 dd (15.5; 1.5)
9b	1.47 dd (15.4; 4.2)	1.49 dd (15.0; 4.0)	1.48 dd (15.5; 3.5)
11	**3.04 dddd (12.0; 6.3; 2.6, $^3J_{PH}$ = 13.0)**	**3.05 dddd (12.0; 6.2; 2.5, $^3J_{PH}$ = 13.0)**	**3.05 dddd (12.0; 6.1; 2.6, $^3J_{PH}$ = 13.0)**
13a	**2.37 ddd (16.0; 2.6, $^2J_{PH}$ = 16.0)**	**2.35 ddd (16.0; 2.5, $^2J_{PH}$ = 16.0)**	**2.35 ddd (16.0; 2.6, $^2J_{PH}$ = 16.0)**
13b	**1.92 ddd (16.0; 12.0, $^2J_{PH}$ = 16.0)**	**1.90 ddd (16.0; 12.0, $^2J_{PH}$ = 16.0)**	**1.90 ddd (16.0; 12.0, $^2J_{PH}$ = 16.0)**
14	0.80 s (3H)	0.80 s (3H)	0.80 s (3H)
15a	4.75 br.s	4.76 br.s	4.75 br.s
15b	4.45 br.s	4.45 br.s	4.45 br.s
1′	**4.10 m (4H)**	**4.00 m (4H)**	**4.00 m (4H)**
(1″)			
2′	1.35 t (6H, 7.0)	1.70 m (4H)	1.65 m (4H)
(2″)			
3′	-	0.95 t (6H, 7.0)	1.40 m (4H)
(3″)			
4′	-	-	0.95 t (6H, 7.0)
(4″)			

Signals of protons coupling with ^{31}P are shown in bold.

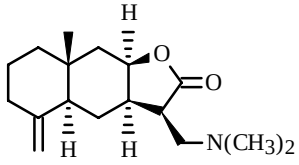
TABLE 2. ^{13}C NMR (75.47 MHz, $CDCl_3$, δ, ppm, J/Hz) Spectra of **2-4**

C atom	**2**	**3**	**4**
4	149.0 s	148.9 s	148.9 s
8	78.4 d	78.3 d	78.4 d
12	**177.3 d ($^3J_{CP}$ = 23.1)**	**177.3 d ($^3J_{CP}$ = 23.7)**	**177.3 d ($^3J_{CP}$ = 23.0)**
13	**21.1 dt ($^1J_{CP}$ = 146.6)**	**21.5 dt ($^1J_{CP}$ = 146.6)**	**21.0 dt ($^1J_{CP}$ = 146.5)**
14	17.8 q	17.8 q	17.8 q
15	106.5 t	106.5 t	106.5 t
1′	**62.05 dt ($^2J_{CP}$ = 6.5)**	**67.54 dt ($^2J_{CP}$ = 6.6)**	**65.81 dt ($^2J_{CP}$ = 6.6)**
(1″)	**61.83dt ($^2J_{CP}$ = 6.6)**	**67.30 dt ($^2J_{CP}$ = 6.6)**	**65.51 dt ($^2J_{CP}$ = 6.6)**
2′	**16.44 dq ($^3J_{CP}$ = 3.0)**	**23.94 dt ($^3J_{CP}$ = 3.0)**	**32.63 dt ($^3J_{CP}$ = 3.5)**
(2″)		**23.86 dt ($^3J_{CP}$ = 3.0)**	**32.55 dt ($^2J_{CP}$ = 3.5)**
3′	-	-	13.63 q
(3″)			

Signals of C atoms coupling with ^{31}P are shown in bold.

The PMR (Table 1) of **2-4** contain signals for protons of the eudesmane skeleton and multiplets for H-11 (J_{P11_H} = 13.0 Hz) and H-13a and H-13b (J_{P13_H} = 16.0 Hz), the signals of which are complicated by additional splitting by the P of the dialkylphosphonate. The spin—spin coupling constant (SSCC) J_{PH} agrees well with those reported [2]. The signals of the methylene protons have different chemical shifts as a result of the diastereotopic nature of the alkoxy groups induced by the introduction of an additional chiral center on C-11. The splitting of these protons by the P leads to additional complications for these protons (protons on C-1′, C-1″, C-2′, D-2″, C-3′, C-3″, C-4′, C-4″, Tables 1 and 2). Signals at 29.70, 29.82, and 29.83

ppm of the dialkylphosphonate appear in the ^{31}P spectrum as a symmetric multiplet. Atom C-11 has the *S* configuration in all phosphonate derivatives of **2**-**4**, i.e., the protons on C-7 and C-11 are *cis*-oriented. The proton positions agree with the PMR spectra, in which a small SSCCs (6.3 Hz for **2**; 6.2, **3**; 6.1, **4**) (Table 1) are observed for H-7 and H-11. The configuration of C-11 is analogous after amination of isoalantolactone by a Michael reaction. This was proven by an x-ray structure analysis of the dimethylamino derivative **5** [5].



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The presence of a direct C-13–P bond, i.e., formation of a organophorphorus derivative of isoalantolactone is consistent with the ^{13}C NMR. For example, the signal for C-13 in the ^{13}C NMR of **2** is observed as a doublet with a large SSCC, 146.6 Hz. This is in excellent agreement with the J_{CP} SSCC previously reported [2]. Signals of other C atoms are also further split in the ^{13}C NMR spectrum owing to the effect of the dialkylphosphonate ^{31}P. For example, the signal of the C atom of the C=O γ-lactone ring of **2** at 177.3 ppm is split into a doublet with SSCC 23.1 Hz (Table 2). The signals of the methylene C atoms of the dialkylphosphonate are also split because of coupling with ^{31}P with SSCC 6.5 and 6.6 Hz for C-1′ and C-1″, respectively, and 3.0 and 3.5 Hz for C-2′ and C-2″, respectively (Table 2).

Thus, three novel dialkylphosphonate derivatives based on the eudesmane sesquiterpene lactone isoalantolactone are isolated for the first time from the aerial part of tall elecampane. Their structures are unambiguously established using PMR, ^{13}C and ^{31}P NMR, and 2D ^{1}H—^{1}H NMR (COSY). The phosphorylation reaction of this compound is highly chemo- and stereoselective.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus. IR spectra were recorded on a Vector 22 instrument.

PMR spectra were recorded on Bruker DRX-500, AM-300, and AC-200 spectrometers (working frequencies 500.13 MHz for ^{1}H; 75.47, ^{13}C; 81.02, ^{31}P, external standard 80% H_3PO_4, δ_P 0.0 ppm). Standard Bruker programs were used to record 2D ^{1}H—^{1}H and ^{13}C—^{1}H (7 Hz) COSY spectra.

Column flash chromatography over silica gel (Chemapol 40/100) with elution by petroleum ether—ethylacetate mixtures of increasing (from 0 to 60% of the latter) polarity were used. Silufol plates were used for TLC with development by spraying with vanillin solution in H_2SO_4 (1%) and aqueous $KMnO_4$ (1%).

Starting **1** with mp 111-113°C was isolated from *Inula helenium* (elecambane) for the chemical modifications [6].

(5*S*,7*R*,8*R*,10*R*,11*S*)-Eudesm-4(15)-en-12,8-olide-13-ylphosphonic Acid Diethyl Ester (2). Diethylphosphite (1.5 mL) was treated with sodium (24.8 mg, 1.07 mmole). After the metal dissolved completely, the reaction mixture was cooled to 0°C, treated with isoalantolactone (**1**, 200 mg, 0.86 mmole), left at room temperature for 1 h, and diluted with water. The product was extracted with ethylacetate (3×50 mL). The organic layer was washed with NaOH (30%, 3×5 mL) and saturated NaCl solution and dried over Na_2SO_4. The solvent was evaporated. The solid (300 mg) was chromatographed over a silica-gel (6 g) column (eluent petroleum ether—ethylacetate, 2:3). Yield 0.27 g (87%), R_f 0.12 (petroleum ether—ethylacetate, 4:1). Oily product.

IR spectrum (KBr, cm^{-1}): 1760 (C=O γ-lactone), 1225 (P=O), 1034, 970 (P–O–C).

^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 29.70.

(5*S*,7*R*,8*R*,10*R*,11*S*)-Eudesm-4(15)-en-12,8-olide-13-ylphosphonic Acid Dipropyl Ester (3). Dipropylphosphite (1.33 mL) was treated with metallic sodium (12.4 mg, 0.5 mmole). The reaction mixture was cooled to 0°C and treated with **1** (100 mg, 0.43 mmole). The reaction was carried out at room temperature for 2 h. The reaction mixture was diluted with water and extracted with ethylacetate (3×50 mL). The organic layer was washed with NaOH (30%, 3×5 mL) and saturated NaCl solution and dried over Na_2SO_4. The solvent was evaporated. The solid (200 mg) was purified by column chromatography over silica gel (6 g) (eluent petroleum ether—ethylacetate, 3:1). Yield 0.12 g (70%), R_f 0.23 (hexane—ethylacetate, 4:1). Oily product.

IR spectrum (KBr, cm^{-1}): 1770 (C=O γ-lactone), 1225 (P=O), 1028, 990 (P–O–C).

Certain cross-peaks in the 2D ^1H—^1H (COSY) NMR: H-8/H-9b, H-7/H-11, H-6a/H-6b, H-7/H-6a, H-7/H-6b, H-11/H-13b, H-13a/H-13b, H-9a/H-9b, H-2a, H-2b, H-1′/H-2′ (H-1″/H-2″), H-2′/H-3′ (H-2″/H-3″).

^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 29.82.

(5*S*,7*R*,8*R*,10*R*,11*S*)-Eudesm-4(15)-en-12,8-olide-13-ylphosphonic Acid Dibutyl Ester (4). Dibutylphosphite (3 mL) was treated with sodium (24.8 mg, 1.07 mmole). After the metal dissolved completely, the reaction mixture was cooled to 0°C and treated with **1** (200 mg, 0.86 mmole). The reaction was carried out at room temperature for 1 h. The reaction mixture was diluted with water. The product was extracted with ethylacetate (3×50 mL). The organic layer was washed with NaOH (30%, 3×5 mL) and saturated NaCl solution and dried over Na_2SO_4. The solvent was evaporated. The solid (300 mg) was chromatographed over a silica-gel (6 g) column (eluent petroleum ether—ethylacetate, 2:3). Yield 0.25 g (70%), R_f 0.12 (petroleum ether—ethylacetate, 4:1). Oily product

IR spectrum (KBr, cm^{-1}): 1770 (C=O γ-lactone), 1225 (P=O), 1028, 990 (P–O–C).

^{31}P NMR spectrum ($CDCl_3$, δ, ppm): 29.83.

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