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LETTERS TO THE EDITOR

3,3,6-Trimethyl-2-chlorocyclohexeno[1,2-*d*]-1,2-oxaphosphol-4-ene-2-oxide as a Convenient Precursor for the Synthesis of Dimephosphone Analogs

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Abstract—A convenient approach to the synthesis of 3,3,6-trimethyl-2-chlorocyclohexeno[1,2-*d*]-1,2-oxaphosphol-3-ene-2-oxide was developed based on the reaction of the naturally occurring terpenoketone pulegone with methyl dichlorophosphite. Treatment of oxaphospholene-2-oxide with water or ethanol yielded γ-phosphoryl ketones, dimephosphone analogs. The studied hydrolysis and alcoholysis processes differ in stereoselectivity.

Keywords: pulegone, methyl dichlorophosphite, phosphorylation, oxaphospholene, phosphoryl ketones, oxoalkylphosphonates

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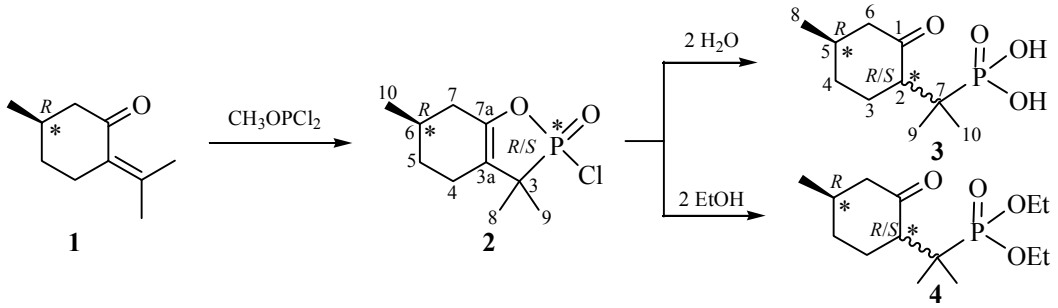
Dimephosphone, (2-methyl-4-oxopent-2-yl)phosphonic acid dimethyl ester, is one of the first organic phosphorus compounds that does not possess anticholinesterase activity and is used as an anti-acidotic agent in the treatment of acidosis of diverse etiology, cerebral circulation disorders, and respiratory system diseases [1]. We have previously obtained P–C analogs of dimephosphone, 4-dialkylphosphoryl-4-methylpentan-2-ones, by reacting oxaphospholenes with Grignard reagents [2]. Their conjugation with a known antituberculosis drug isoniazid led to a decrease in the toxicity of the latter while maintaining the activity [3].

Of the naturally occurring monoterpenoids [4] possessing antitumour [5] and antitubercular activity [6], there are available unsaturated ketones derivatives like pulegone **1**, which is promising for producing terpenoids containing 1,2-oxaphospholene fragment that can be used as precursors for the further synthesis of dimephosphone analogs. Additionally, phosphorylation of natural compounds is one of the approaches that allows modification of their physicochemical and physiological properties [7].

Here we report on a convenient approach to the preparation of such a precursor, 3,3,6-trimethyl-2-chlorocyclohexene[1,2-*d*]-1,2-oxaphosphol-3-ene-2-oxide **2**, and demonstrated its use in the synthesis of γ-phosphoryl ketones, dimephosphone analogs. The reaction of pulegone **1** (*R*-enantiomer) with methyl dichloro-

Scheme 1.



1 **2** **3** **4**

phosphite proceeded easily in the absence of a solvent at a temperature of 95–120°C to form oxaphospholene **2** in a yield of 70–75% (Scheme 1).

Compound **2** is a mixture of two diastereomers in a ratio of 1.06 : 1.0, which have formed due to the presence of two chiral sites in the structure, C^6 and phosphorus atoms. In the $^{31}P–\{^1H\}$ NMR spectrum two singlets were observed at 69–70 ppm. In the $^{13}C–\{^1H\}$ NMR spectrum, a doubling of all signals occurred. The C^{3a} and C^{7a} atoms resonated as doublets at 120 and 145 ppm ($^2J_{PC3a}$ = 11.7, $^2J_{PC7a}$ = 2.9 Hz). The carbon C^3 directly bound to the phosphorus appeared as a doublet at 43 ppm ($^1J_{PC}$ = 101.2 Hz). Doublet of the C^4 atom was registered at 19 ppm ($^3J_{PC}$ = 11.7 Hz).

The reaction of oxaphospholene **2** with an excess of *O*-nucleophiles like water and ethanol led to the ring closure resulting in the formation of γ-phosphoryl ketones **3** and **4** with high stereoselectivity. The compounds were obtained as mixtures of diastereomers in a ratio of 1 : 0.17 and 1 : 0.21, respectively, due to the presence of two asymmetric carbon atoms, C^2 and C^5. The $^{31}P–\{^1H\}$ NMR spectra of **3** and **4** contained singlets in the range of 35–36 ppm.

In summary, the reaction of naturally occurring terpenoketone pulegone with methyl dichlorophosphite and subsequent treatment of the resulting oxaphospholene with water or ethanol is a convenient way to obtain γ-phosphoryl ketones, dimephosphone analogs. The hydrolysis and alcoholysis processes differ in stereoselectivity.

3,3,6-Trimethyl-2-chlorocyclohexeno[1,2-*d*]-1,2-oxaphosphol-4-ene-2-oxide (2). Yield 75% (*dr* = 1.06 : 1), colorless solid, mp 43°C, bp 118°C (0.9 mmHg). IR spectrum (KBr), ν, cm^{-1}: 557 br (P–Cl), 1289 br (P=O), 1697 (C=C). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): **diastereomer 2a** (the data given in parentheses are for the $^{13}C–\{^1H\}$ spectra), 42.81 m (d) (C^3, $^1J_{PC}$ = 101.2, $^2J_{HC}$ = 3.7), 120.07 m (d) (C^{3a}, $^2J_{PC}$ = 11.7), 19.55 m (d) (C^4, $^3J_{PC}$ = 11.7, $^1J_{HC}$ = 128.4), 30.03 m (s) (C^5, $^1J_{HC}$ = 124.7), 28.78 m (s) (C^6, $^1J_{HC}$ = 128.4), 31.98 m (s) (C^7, $^1J_{HC}$ = 129.8), 145.85 br.m (d) (C^{7a}, $^2J_{PC}$ = 2.9), 21.55 m (d) (C^8, $^1J_{HC}$ = 129.8), 21.08 m (br.d) (C^9, $^2J_{PC}$ = 0.7, overlapped with the signal of C^{10}), 21.14 m (br.s) (C^{10}, overlapped with the signal of C^9); **diastereomer 2b**, 42.81 m (d) (C^3, $^1J_{PC}$ = 101.2, $^2J_{HC}$ = 3.7), 119.88 m (d) (C^{3a}, $^2J_{PC}$ = 11.4), 19.25 m (d) (C^4, $^3J_{PC}$ = 12.5, $^1J_{HC}$ = 125.4), 29.78 m (s) (C^5, $^1J_{HC}$ = 125.8), 28.72 m (s) (C^6, $^1J_{HC}$ = 128.4), 31.91 m (s) (C^7, $^1J_{HC}$ = 129.8), 145.84 br.m (d) (C^{7a}, $^2J_{PC}$ = 3.3), 21.25 m (d) (C^8, $^1J_{HC}$ = 130.5), 21.90 m (br.d) (C^9, $^2J_{PC}$ = 0.7, overlapped with the signal of C^{10}), 21.01 m (br.s) (C^{10}, overlapped with the signal of C^9). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm (*J*, Hz): 70.1 m ($^3J_{HP}$ = 21.5, **2a**), 69.8 m ($^3J_{HP}$ = 21.5, **2b**). Found, %: C 50.87; H 6.73; Cl 15.24; P 13.07. $C_{10}H_{16}ClO_2P$. Calculated, %: C 51.18; H 6.87; Cl 15.11; P 13.20.

5-Methyl-2-(dihydroxyphosphorylprop-2-yl)-cyclohexanone (3). Yield 94% (*dr* = 1.0 : 0.17), colorless solid, mp 70°C. IR spectrum (nujol), ν, cm^{-1}: 1195–1229 br (P=O), 1682, 1717 (C=O). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): **diastereomer 3a**, 215.19 br.m (br.s) (C^1), 55.77 d.m (s) (C^2, $^1J_{HC}$ = 126.9), 29.43 t.m (d) (C^3, $^3J_{PC}$ = 4.0, $^1J_{HC}$ = 128.4), 34.23 t.m (s) (C^4, $^1J_{HC}$ = 123.4), 36.76 br.d.m (br.s) (C^5, $^1J_{HC}$ = 124.0), 51.82 t.m (s) (C^6, $^1J_{HC}$ = 126.9), 35.51 d.m (d) (C^7, $^1J_{PC}$ = 134.2), 22.14 q.m (br.s) (C^8, $^1J_{HC}$ = 126.9), 20.17 q.m (d) (C^9, $^2J_{PC}$ = 2.9, $^1J_{HC}$ = 129.1), 19.97 q.m (d) (C^{10}, $^2J_{PC}$ = 1.8 $^1J_{HC}$ = 129.9); **diastereomer 3b**, 215.95 br.m (br.s) (C^1), 55.87 m (s) (C^2, overlapped with the signal of C^2 of **3a**), 25.19 br.t.m (d) (C^3, $^3J_{PC}$ = 4.0, $^1J_{HC}$ = 128.4), 31.01 br.t.m (br.s) (C^4, $^1J_{HC}$ = 123.0), 32.54 br.d.m (br.s) (C^5, $^1J_{HC}$ = 124.0), 49.97 t.m (s) (C^6, $^1J_{HC}$ = 126.9), 35.98 m (d) (C^7, $^1J_{PC}$ = 134.6, overlapped with the signal of C^7 of diastereomer **3a**), 18.68 q.m (d) (C^8, $^2J_{PC}$ = 2.2, $^1J_{HC}$ = 129.7). ^{31}P NMR spectrum ($CDCl_3$), δ_P, ppm (*J*, Hz): 36.5 m ($^3J_{HP}$ = 15.7, $^3J_{HP}$ = 15.7, **3a**), 36.4 m (**3b**, overlapped with the signal of **3a**). Found, %: C 51.14; H 8.29; P 13.18. $C_{10}H_{19}O_4P$. Calculated, %: C 51.28; H 8.18; P 13.22.

5-Methyl-2-(diethoxyphosphorylprop-2-yl)cyclohexanone (4). Yield 87% (*dr* = 1.0 : 0.21), colorless oil. IR spectrum (nujol), ν, cm^{-1}: 1200–1227 br (P=O), 1735 (C=O). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): **diastereomer 4a**, 211.20 br.m (br.s) (C^1), 54.06 d.m (br.s) (C^2, $^1J_{HC}$ = 127.0), 29.47 t.m (br.s) (C^3, $^1J_{HC}$ = 127.8), 34.44 t.m (s) (C^4, $^1J_{HC}$ = 127.2), 36.77 d.m (s) (C^5, $^1J_{HC}$ = 125.6), 52.34 t.m (s) (C^6, $^1J_{HC}$ = 127.0), 35.84 br.m (br.s) (C^7), 22.23 q.m (br.s) (C^8, $^1J_{HC}$ = 125.8), 21.17 m (br.s) (C^9), 19.51 m (br.s) (C^{10}), 30.27 t.m (br.s) (OCH_2, $^1J_{HC}$ = 127.4), 14.20 br.q (s) ($OCH_2\underline{CH_3}$, $^1J_{HC}$ = 127.2); **diastereomer 4b**, 211.85 br.m (br.s) (C^1), 53.67 d.m (s) (C^2, overlapped with the signal of C^2 of **4a**), 25.95 t.m (br.s) (C^3, $^1J_{HC}$ = 127.9), 31.19 t.m (br.s) (C^4, $^1J_{HC}$ = 127.2), 32.53 d.m (br.s) (C^5, $^1J_{HC}$ = 125.6), 50.34 t.m (s) (C^6, $^1J_{HC}$ = 127.0), 35.8–36.2 br.m (br.s) (C^7, overlapped with the signal of C^7 of **4a**), 18.76 q.m (s) (C^8, $^1J_{HC}$ = 125.8), 30.12

t.m (br.s) (OCH_2, $^1J_{HC}$ = 127.4), 14.20 br.q (s) ($OCH_2\underline{CH_3}$, $^1J_{HC}$ = 127.2). ^{31}P NMR spectrum (C_2H_5OH), δ_P, ppm (J, Hz): 35.4 m ($^3J_{HP}$ = 16.8, $^3J_{HP}$ = 9.0, **4a**), 34.5 m ($^3J_{HP}$ = 16.8, $^3J_{HP}$ = 7.8, **4b**). Found, %: C 58.02; H 9.43; P 10.39. $C_{14}H_{27}O_4P$. Calculated, %: C 57.92; H 9.37; P 10.67.

^1H, ^{13}C, ^{13}C–{^1H}, ^{31}P NMR spectra were recorded on a Bruker Avance 400 instrument. IR spectra were registered on a Bruker Tensor-27 spectrometer.

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