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LETTERS TO THE EDITOR

To the 85th Anniversary of birthday of late Yu.G. Gololobov

Synthesis of 4-[3,4-Di-(2,3,4-tri)methoxyphenyl]benzo[*e*]-1,2-oxaphosphorines

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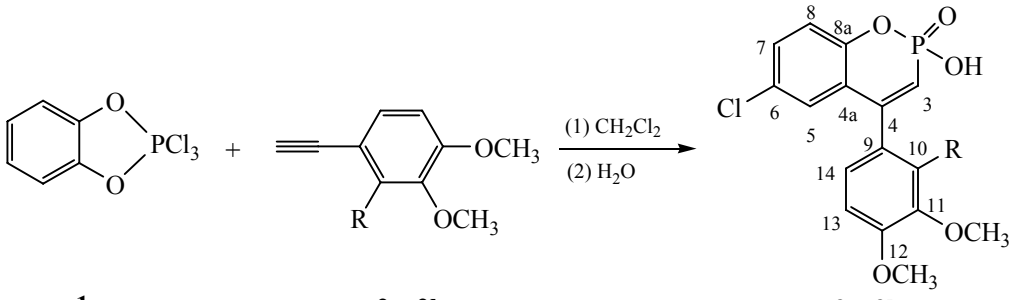
Polymethoxyaryl derivatives are widespread in nature; the corresponding fragments are part of the class of natural compounds like alkaloids, flavanoids, coumarins and others [1, 2]. Due to the presence of hydroxy and methoxy moieties these natural compounds exhibit antioxidant properties. In some cases, the antitumor activity of some arenopyrones and coumarin derivatives is attributed to the presence of such structural fragments [3].

Previously, the reaction of 2,2,2-trihalo-1,3,2-dioxaphospholes with terminal acetylenes has been shown to be one of the most convenient methods for the synthesis of areno-1,2-oxaphosphorine derivatives, which are *P*-analogs of natural chromenes and coumarins [4]. One of the features of this reaction is the migration of one of the halogen atoms from the phosphorus atom preferably to the sixth position of the aromatic ring of oxaphosphorines (*para*-position with respect to the endocyclic oxygen atom of the oxaphosphorine ring) [5]. In further studies it was shown that the nature of substituents (for example, 4-nitro- and 4-metoxyphenylacetylenes) in the aromatic ring of arylacetylenes has no significant effect on the regiochemistry of halogenation of oxaphosphorine arylene moiety, but affects the reaction rate [6]. In the case of reacting trihalophospholes with arylacetylenes with donor substituents the reaction rate increased significantly. In addition, the presence of donor substituents in the position 4 of the aryl moiety of oxaphosphorine scaffold increases its resistance to hydrolysis [7].

In this work, the behavior of 2,2,2-trichlorobenzo-1,3,2-dioxaphospholes **1** in the reactions with 3,4-dimethoxy-2,3,4-trimetoxyphenylacetylenes **2a** and **2b** containing several donor substituents was studied with the aim to develop a convenient method for the synthesis of polymethoxylated areno-1,2-oxaphospholes. As in the case of the reaction of 2,2,2-trichlorobenzo-1,3,2-dioxaphosphole with 4-metoxyphenylacetylene, arylacetylenes **2a** and **2b** containing donor methoxy groups in the aromatic ring reacted with 1,3,2-dioxaphosphole **1** to afford the corresponding areno-1,2-oxaphosphorine derivatives. In this case the halogenation of arenooxaphosphorine scaffold occurred regularly in the position 6 to form 4-[di(tri)methoxyphenyl]-2,6-dichlorobenzo[*e*]-1,2-oxaphosphorine 2-oxides, whose hydrolysis afforded phosphonic acids **3a** and **3b** (Scheme 1).

The presence of a halogen atom in the 6 position of molecules **3a** and **3b** was unambiguously confirmed by ^{1}H and ^{13}C NMR spectroscopy. Thus, in ^{1}H NMR spectra of compounds **3a** and **3b** there were the signals

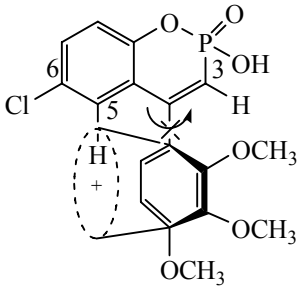
Scheme 1.



1 **2a**, **2b** **3a**, **3b**

R = H (**a**), OCH_3 (**b**).

of H^{5-7} protons in the area of the signals of aromatic protons of benzo moiety fused with oxaphosphorine ring, which is typical for 1,2,4-trisubstituted benzenes. The presence of additional methoxy group in the *position 10* of the molecule **3b** led to an upfield shift of the protons H^{5-7} signals (compared with those signals in the spectrum of compound **3a**). It should be noted that the most significant shift ($\Delta\delta$ = 0.68 ppm) was observed in the case of the signal of H^5, which was apparently due to shielding this proton in compound **3b** owing to anisotropy of phenyl substituent in the position *4* of oxaphosphorine ring. This is possible only in the case of existence of atropisomers in compound **3b** (due to hindered rotation around the C^4–C^9 bond, like *ortho*-substituted biphenyls [8]). In the case of compound **3a** there are no obstacles to the free rotation around the C^4–C^9 bond, and an averaging effect of the magnetic anisotropy of the phenyl substituent occurs. As a result, the H^5 proton resonates in the weaker field of the ^{1}H NMR spectrum.



In summary, the presence of several donor substituents in the aromatic ring does not prevent the reaction between arylacetylenes and areno-1,3,2-dioxaphospholes derivatives to form oxaphosphorine scaffold. Basically 2,6-dichlorobenzo[*e*]-1,2-2-oxaphosphorine 2-oxides are formed. The reaction of 2,2,2-trihalo-1,3,2-dioxaphospholes with methoxyphenylacetylenes can be used as a convenient approach towards the synthesis of 1,2-methoxylated arenooxaphosphorine 2-oxides, which are structurally related to the natural compounds.

3,4-Dimethoxy- and 2,3,4-trimetoxyphenylacetylenes **2a** and **2b** were prepared by reacting the corresponding iodobenzenes with dimethylethynylcarbinol [9].

Compound 3a. To a solution of 0.76 g (3.1 mmol) of phosphorane **1** in 7 mL of CH_2Cl_2 were added 0.4 mL (0.26 g, 3.1 mmol) of hex-1-ene and a solution of 0.5 g (3.1 mmol) of 3,4-dimetoxyphenylacetylene in 2 mL CH_2Cl_2. After one day, the solvent and volatiles were removed in a vacuum (12 Torr). To the brown oily residue were added 7 mL of CH_2Cl_2 and 15 mL of water. After a few days, the resulting white precipitate was filtered off and dried. Yield 61%, mp 282°C. IR spectrum, ν, cm^{-1}: 3053, 3003, 2952, 2908, 2836, 2523, 2269, 1667, 1599, 1580, 1549, 1515, 1464, 1416, 1325, 1286, 1245, 1219, 1180, 1142, 1112, 1015, 932, 885, 852, 822, 802, 781, 767, 741, 648, 602, 549, 470, 453, 420. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.79 s ($C^{11}OCH_3$), 3.82 s ($C^{12}OCH_3$), 6.38 d (H^3, $^2J_{PH}$ 17.6), 6.89 d.d (H^{14}, $^3J_{HH}$ 8.5, $^4J_{HH}$ 2.0), 6.97 d (H^{10}, $^4J_{HH}$ 2.0), 7.06 d (H^{13}, $^3J_{HH}$ 8.5), 7.15 d (H^5, $^4J_{HH}$ 2.5), 7.32 d (H^8, $^3J_{HH}$ 8.5), 7.48 d.d (H^7, $^3J_{HH}$ 8.5, $^4J_{HH}$ 2.5). ^{13}C NMR spectrum, δ_C, ppm (*J*, Hz) (^{13}C–{^{1}H}): 150.53 m (d) (C^4, $^2J_{PC4}$ 1.8), 150.38 m (d) (C^{8a}, $^2J_{PC}{}^{8a}$ 17.0, $^3J_{HC}{}^{8a}$ 11.0, $^3J_{HC}{}^{8a}$ 7.6, $^2J_{HC}{}^{8a}$ 3.7), 149.63 m (s) (C^{12}), 148.94 m (s) (C^{11}, $^3J_{HC11}$ 7.3, $^3J_{HC11}$ 3.7), 130.60 d.d (s) (C^7, $^1J_{HC7}$ 170.2, $^3J_{HC7}$ 6.6), 130.24 m (d) (C^9, $^3J_{PC9}$ 18.3, $^3J_{HC9}$ 8.8, $^3J_{HC9}$ 6.6, $^2J_{HC9}$ 1.5), 127.93 d.d (s) (C^5, $^1J_{HC5}$ 165.1, $^3J_{HC5}$ 5.9), 127.16 d.d.d (s) (C^6, $^3J_{HC6}$ 8.1, $^2J_{HC6}$ 4.7, $^2J_{HC6}$ 4.7), 123.95 m (d)

(C^{4a}, $^3J_{PC4a}$ 15.4, $^3J_{HC4a}$ 8.1, $^3J_{HC4a}$ 6.6), 121.41 d.d (d) (C^8, $^1J_{HC8}$ 167.3, $^3J_{PC8}$ 7.0), 120.99 d.d (d) (C^{14}, $^1J_{HC14}$ 162.1, $^3J_{HC14}$ 6.6), 116.62 d.d (d) (C^3, $^1J_{PC3}$ 168.7, $^1J_{HC3}$ 163.6), 112.15 d.d (s) (C^{10}, $^1J_{HC10}$ 158.5, $^3J_{HC10}$ 7.3), 111.75 d (s) (C^{13}, $^1J_{HC13}$ 161.4), 55.76 q (s) ($C^{12}OCH_3$, $^1J_{HC}$ 144.5), 55.70 q (s) ($C^{11}OCH_3$, $^1J_{HC}$ 144.5). ^{31}P NMR spectrum: δ_P 4.80 ppm (d, $^1J_{PH}$ 17.6 Hz). Found, %: C 53.87; H 4.64; Cl 9.75; P 8.12. $C_{16}H_{14}ClO_5P$. Calculated, %: C 54.48; H 4.0; Cl 10.05; P 8.78.

Compound 3b was obtained similarly from 0.64 g (2.6 mmol) of phosphorane **1**, 0.33 mL (0.22 g, 2.6 mmol) of hex-1-ene, and 0.5 g (2.6 mmol) of 2,3,4-trimethoxyphenylacetylene **2b**. Yield 57%, mp 219°C. IR spectrum, ν, cm^{-1}: 3435, 3058, 2980, 2944, 2840, 2524, 2267, 1595, 1547, 1494, 1466, 1436, 1413, 1340, 1296, 1254, 1230, 1203, 1171, 1156, 1121, 1100, 1041, 1011, 975, 933, 908, 882, 851, 828, 795, 751, 736, 687, 673, 660, 646, 614, 570, 539, 522, 459, 420. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.60 s ($C^{11}OCH_3$), 3.78 s ($C^{10}OCH_3$), 3.85 s ($C^{12}OCH_3$), 6.31 d (H^3, $^2J_{PH}$ 17.6), 6.83 d (H^5, $^4J_{HH}$ 2.5), 6.91 d (H^{13}, $^3J_{HH}$ 8.5), 6.93 d.d (H^{14}, $^3J_{HH}$ 8.5), 7.28 d (H^8, $^3J_{HH}$ 8.5), 7.45 m (H^7, $^3J_{HH}$ 8.5, $^4J_{HH}$ 2.5, $^5J_{PH}$ 1.0). ^{13}C NMR spectrum, δ_C, ppm (*J*, Hz): 154.45 m (s) (C^{12}, $^3J_{HC}$ 12 11.0, $^2J_{HC}$ 12 3.9), 150.51 m (s) (C^{10}, $^3J_{HC10}$ 6.6, $^2J_{HC10}$ 3.7), 149.57 m (d) (C^{8a}, $^2J_{PC8a}$ 17.0, $^2J_{HC8a}$ 3.7), 148.12 m (d) (C^4, $^2J_{PC4}$ 1.8), 141.68 m (s) (C^{11}, $^3J_{HC11}$ 8.8, $^3J_{HC11}$ 4.4), 130.37 d.d (s) (C^7, $^1J_{HC7}$ 170.2, $^3J_{HC7}$ 5.9), 127.51 d.d (s) (C^5, $^1J_{HC5}$ 165.1, $^3J_{HC5}$ 5.1), 127.04 d.d.d (s) (C^6, $^3J_{HC6}$ 11.7, $^2J_{HC6}$ 3.6–3.8, $^2J_{HC6}$ 3.7), 124.40 d (s) (C^{14}, $^1J_{HC14}$ 162.9), 124.38 m (d) (C^9, $^3J_{PC9}$ 18.7, $^3J_{HC9}$ 5.9, $^3J_{HC9}$ 5.9, $^2J_{HC9}$ 2.2), 124.08 m (d) (C^{4a}, $^3J_{PC4a}$ 16.1, $^3J_{HC4a}$ 8.0, $^3J_{HC4a}$ 8.0, $^2J_{HC4a}$ 5.1), 121.06 d.d (d) (C^8, $^1J_{HC8}$ 167.3, $^3J_{PC8}$ 6.6), 118.07 d.d (d) (C^3, $^1J_{PC3}$ 165.8, $^1J_{HC3}$ 164.3), 108.30 d (s) (C^{13}, $^1J_{HC13}$ 162.9), 61.05 q (s) ($C^{12}OCH_3$, $^1J_{HC}$ 145.3), 60.64 q (s) ($C^{10}OCH_3$, $^1J_{HC}$ 145.3), 56.07 q (s) ($C^{11}OCH_3$, $^1J_{HC}$ 145.3). ^{31}P NMR spectrum: δ_P 4.10 ppm (d, $^1J_{PH}$ 17.6 Hz). Found, %: C 52.67; H 4.89; Cl 9.02; P 7.70. $C_{17}H_{16}ClO_6P$. Calculated, %: C 53.35; H 4.21; Cl 9.26; P 8.09.

NMR spectra were recorded on an Avance-400 spectrometer [400.0 (^{1}H), 162.0 (^{31}P), 100.6 MHz (^{13}C)] using as internal reference the signals of residual proton or carbon nuclei of DMSO-d_6 or HMDS (^{1}H and ^{13}C) or external reference H_3PO_4 (^{31}P). IR spectra were obtained on a Bruker-Tenzor 27 instrument from KBr pellets.

REFERENCES

1. *Flavonoids. Chemistry, Biochemistry and Applications*, Andersen, Q.M. and Markham, K.R., Eds., Boca Raton; London; New York: CRC Press, Taylor & Francis group, LLC, 2006.
2. *Introduction to Natural Product Chemistry*, Xu, R., Ye, Y., and Zhao. W., Eds., Boca Raton; London; New York: CRC Press, Taylor & Francis group, LLC, 2012.
3. Wu, J., Peng, T., Chen, F., Leng, Y., Tong, L., Li, M., Qu, R., Xie, H., Ding, J., and Duan, W., *Lett. Drug Design & Discovery*, 2015, vol. 12, no. 5, p. 366. DOI: 10.2174/1570180812666141111235026.
4. Mironov, V.F., Zyablikova, T.A., Konovalova, I.V., Khanipova, M.G., Petrov, R.R., and Musin, R.Z., *Rus. J. Gen. Chem*., 1997, vol. 67, p. 646.
5. Mironov, V.F. and Nemtarev, A.V., *Rev. J. Chem*., 2011, vol. 1, p. 27. DOI: 10.1134/S2079978011010067.
6. Aniskin, A.S., Nemtarev, A.V., Baranov, D.S., Mironov, V.F., and Vasilevskii, S.F., *Russ. J. Gen. Chem*., 2014, vol. 83, no. 5, p. 1010. DOI: 10.1134/S1070363213050253.
7. Nemtarev, A.V., Mironov, V.F., Aniskin, A.S., Baranov, D.S., Mironova, E.V., Krivolopov, D.B., Musin, R.Z., Vasilevskii, S.F., Druzhkov, N.O., and Cherkasov, V.K., *Russ. Chem. Bull*., 2013, vol. 62, no. 1, p. 55. DOI: 10.1007/s11172-013-0008-2.
8. Allinger, N.L., Eliel, E.L., and Wilen, S.H., *Topics in Stereochemistry*, 2007, vol. 14, p. 1. DOI: 10.1002/9780470147238.ch1.
9. Nguyen, P., Yuan, Z., Agocs, L., Lesley, G., and Marder, T.B., *Inorg. Chim. Acta*, 1994, vol. 220, nos. 1–2, p. 289. DOI: 10.1016/0020- 1693(94)03881-3.