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Synthesis of Bromine-Substituted Cyclohexenylphosphonates

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Abstract—Bromination of cyclohexa-1,4-dienylphosphonates yields new substituted 4,5-dibromocyclohexene-1-phosphonates. The structure of obtained compounds was confirmed by ^{1}H, ^{13}C and ^{31}P NMR spectra.

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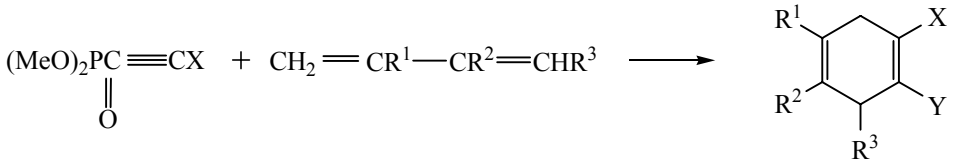
The phosphorus derivatives of cyclohexane are reactive compounds with a broad synthetic opportunites which are also of interest in the study of theoretical problems of organic chemistry. It has been shown that the oxidation of cyclohexa-1,4-diene diphosphonates with $KMnO_4/Al_2O_3$ in acetone leads to the formation of substituted *o*-benzene diphosphonates [1], which are convenient synthons for the corresponding phosphines [2]. The oxidative chlorophosphorylation of cyclohexane allowed us the preparation of cyclohexane- and cyclohexene-1-phosphonic acids dichlorides starting from available materials. The obtained compounds are suitable for the subsequent conversion into other derivatives. In particular, their reactions with ZnF_2 give the highly reactive phosphonic acids difluorides [3]. In continuation of the studies on the synthesis and reactivity of the phosphorus-containing carbocyclic compounds of the cyclohexane series, in this work we performed the bromination of cyclohexa-1,4-diene diphosphonates.

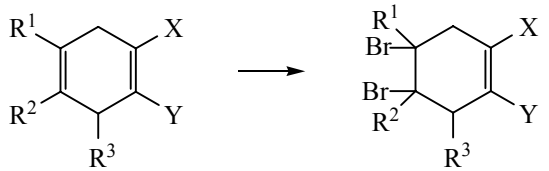
The starting cyclohexa-1,4-diene diphosphonates **Ia**–**If** were obtained via Diels–Alder reaction of acetylene diphosphonates with classical donor 1,3-alkadienes: divinyl, isoprene, piperilene, and 2,3-dimethylbuta-1,3-diene [2].



Ia–**If**

$R^1 = R^2 = Me$, $R^3 = H$, X = Y = PO(OMe) (**a**); $R^1 = R^2 = H$, $R^3 = Me$, X = Y = PO(OMe) (**b**); $R^1 = Me$, $R^2 = R^3 = H$, X = Y = PO(OMe) (**c**); $R^1 = R^2 = Me$, $R^3 = H$, X = PO(OMe), Y = Cl (**d**); $R^1 = R^2 = H$, $R^3 = Me$, X = PO(OMe), Y = Cl (**e**); $R^{1(2)} = Me$, $R^{2(1)} = R^3 = H$, X = PO(OMe), Y = Cl (**f**).

The bromination of cyclohexa-1,4-dienylphosphonates **Ia**–**If** proceeds readily to give the corresponding cyclohex-1-ene-1-phosphonates dibromoderivatives **IIa**–**IIf**. The reaction occurs as a chemoselective electrophilic addition at the electron rich double bond of cyclohexa-1,4-diene.



Ia–**If** **IIa**–**IIf**

$R^1 = R^2 = Me$, $R^3 = H$, X = Y = PO(OMe) (**a**); $R^1 = R^2 = H$, $R^3 = Me$, X = Y = PO(OMe) (**b**); $R^1 = Me$, $R^2 = R^3 = H$, X = Y = PO(OMe) (**c**); $R^1 = R^2 = Me$, $R^3 = H$, X = PO(OMe), Y = Cl (**d**); $R^1 = R^2 = H$, $R^3 = Me$, X = PO(OMe), Y = Cl (**e**); $R^{1(2)} = Me$, $R^{2(1)} = R^3 = H$, X = PO(OMe), Y = Cl (**f**).

The bromination was carried out in a methylene chloride medium by stirring equimolar amounts of the starting materials at 0°C.

The reaction progress was monitored by NMR spectroscopy. Thus, in the ^{13}C NMR spectra, the most informative for this type of compounds, after the reaction completion the singlet signals of sp^2-hybridized carbon atoms C^4 and C^5 of the initial cyclohexa-1,4-dienylphosphonates at δ_C ~ 115–120 ppm were not found. The appearance of intensive signals shifted upfield to δ_C ~ 54–68 ppm indicated the formation of the assumed adduct. Note that the ^1H and ^{13}C NMR spectra of the reaction mixtures contain the signals of aromatic ring atoms indicating that the minor oxidation product is the product of cyclohexa-1,4-dienylphosphonate aromatization.

The structure of dibromoderivatives **IIa**–**IIf** obtained was confirmed by the ^1H, ^{13}C, and ^{31}P NMR spectra. Thus, in the ^{13}C NMR spectrum of **IIa** shown in Fig. 1 the carbon atoms C^1 and C^2 at the double bond bound directly with the phosphorus atoms resonate as a doublet signal at δ_C 137.81 ppm with a large coupling constant $^1J_{CP}$ 190.8 Hz. The magnetically equivalent carbon atoms C^3 and C^6 give rise to a triplet signal at δ_C 46.81 ppm ($^2J_{CP} = {}^3J_{CP} = 12.2$ Hz). The carbon atoms C^4 and C^5 bound with the bromine atoms resonate as singlets of high intensity at δ_C 67.54 ppm.

A single intensive signal of two equivalent methyl carbon atoms is shifted upfield to δ_C 8.29 ppm. The carbon atoms of methoxy groups at the phosphorus atoms appear as broad signal at δ_C 53.19 ppm, the constant of the spin–spin coupling with the phosphorus nucleus $^2J_{CP}$ cannot be determined probably due to the insufficient resolution.

In the ^1H NMR spectrum of **IIa** (Fig. 2) there are two signals of the methylene protons of cyclohexene ring as an AB-system ($^2J_{HH}$ 2.19 Hz). The components of the AB system are broadened due to the weak interaction of the protons with the phosphorus nucleus.

The methoxy protons resonate in the expected region at δ 3.66 ppm, an integral intensity of this signal confirms the presence of 12 protons. Unfortunately, we failed to detect the coupling constant with the phosphorus nucleus $^3J_{HP}$ due to the signal broadening.

An intensive singlet signal in a strong field at δ 1.84 ppm corresponds to the protons of methyl groups at the quaternary carbon atoms of the cyclohexene ring.

The ^{31}P NMR spectrum of tetramethyl 4,5-dibromo-4,5-dimethylcyclohex-1-ene-1,2-diylbisphosphonate **IIa** contains a singlet signal at δ_P 14.40 ppm.

Note that in the case of bromine addition to the unsymmetrically substituted cyclohexa-1,4-dienylphosphonates the formation of two or more stereoisomers was observed, which leads to the considerable complication of the spectral pattern. In some cases it was impossible to interpret the NMR spectra of the adducts in detail.

In the case of the bromination of methyl-substituted 2-chloro-1,4-hexadienylphosphonate **IIe** existing as a mixture of two regioisomers we also observed the formation of two isomers, 4- and 5-methyl-substituted 4,5-dibromo-2-chlorohex-1-ene phosphonates, in a ratio of 2:1.

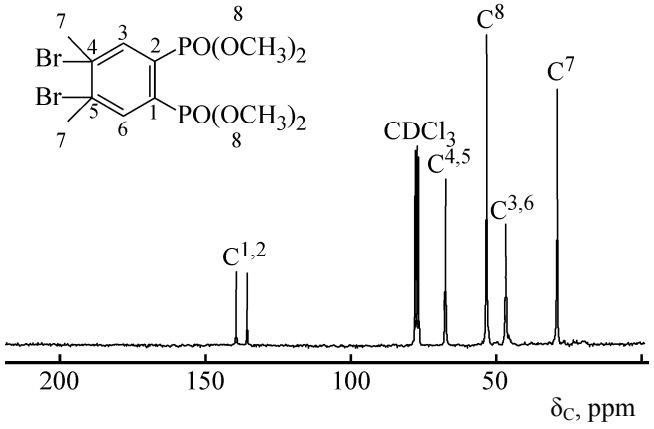


Fig. 1. ^{13}C NMR spectrum of tetramethyl (4,5-dibromo-4,5-dimethylcyclohex-1-ene-1,2-diyl)bisphosphonate (**IIa**).

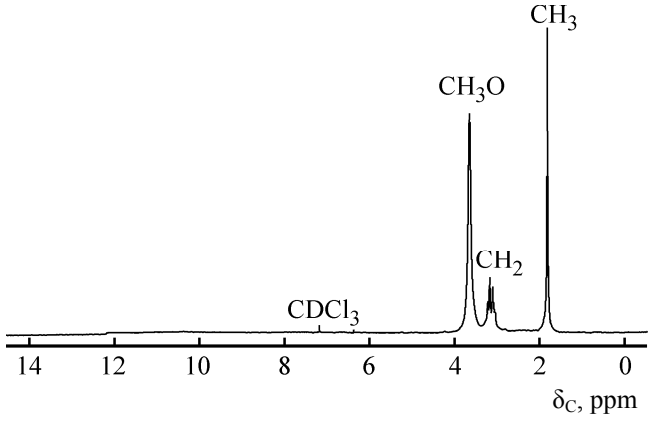


Fig. 2. ^1H NMR spectrum of tetramethyl (4,5-dibromo-4,5-dimethylcyclohex-1-ene-1,2-diyl)bisphosphonate (**IIa**).

EXPERIMENTAL

The NMR spectra were recorded on a Bruker AC-200 [200.132 (^{1}H), 50.328 (^{13}C) and 81.014 MHz (^{31}P)], Bruker AC-400 [400.133 MHz (^{1}H)], and Tesla BS-497 (100 MHz) spectrometers, in the last case with ^{1}H–{^{31}P} double magnetic resonance experiments. Hexamethyldisiloxane (HMDS) was used as an internal reference for ^{1}H NMR spectra, the chemical shifts were recalculated to TMS. The phosphorus chemical shifts were determined relative to external 85% phosphoric acid (Bruker AC-200) and trimethyl phosphate (Tesla BS-497). The ^{13}C NMR spectra were referenced to the internal $CDCl_3$ and recalculated to TMS.

The organic solvents and reagents were purified using standard laboratory techniques [4, 5].

General procedure for preparation of compounds IIa–IIf. To a solution of the corresponding cyclohexa-1,4-diene phosphonate **I** in dichloromethane was added dropwise under cooling and stirring a solution of an equimolar amount of Br_2 in dichloromethane. After complete addition, the reaction mixture was stirred for 1 h at room temperature. Then the solvent was distilled off in a vacuum. The residue, a yellowish viscous oil, is the target 4,5-dibromocyclohex-1-ene phosphonates **IIa**–**IIf**.

Tetramethyl (4,5-dibromo-4,5-dimethylcyclohex-1-ene-1,2-diyl)bisphosphonate (IIa) was prepared from tetramethyl (4,5-dimethylcyclohexa-1,4-diene-1,2-diyl)bisphosphonate **Ia**. ^{1}H NMR spectrum, δ, ppm: 1.84 s (6H, CH_3), 3.12 d (2H, CH_2, $^2J_{HH}$ 19.2 Hz), 3.18 d (2H, CH_2, $^2J_{HH}$ 19.2 Hz), 3.66 br. s (12H, OCH_3). ^{13}C NMR spectrum, δ_C, ppm: 29.08 (CH_3), 46.81 t ($C^{3,6}$, $^2J_{CP}$ 12.2 Hz), 53.40 br. s (CH_3OP), 67.54 ($C^{4,5}$), 137.81 d ($C^{1,2}$, $^1J_{CP}$ 190.8 Hz). ^{31}P NMR spectrum: δ_P 14.39 ppm.

Tetramethyl (4,5-dibromo-3-methylcyclohex-1-ene-1,2-diyl)bisphosphonate (IIb) was prepared from tetramethyl (3-methylcyclohexa-1,4-diene-1,2-diyl)bisphosphonate **Ib**. ^{1}H NMR spectrum, δ, ppm: 1.10–1.70 m (3H, CH_3), 2.80–3.47 m (2H, CH_2; 1H, CH; 3H, CH_3), 3.74–3.90 m (12H, CH_3OP), 4.46 br. s (1H, CHBr), 4.71 br. s (1H, CHBr). The ^{13}C and ^{31}P NMR spectra contain the signals sets of the stereoisomers mixture, which assignment was impossible.

Tetramethyl (4,5-dibromo-4-methylcyclohex-1-ene-1,2-diyl)bisphosphonate (IIc) was prepared from tetramethyl (4-methylcyclohexa-1,4-diene-1,2-diyl)bisphosphonate **Ic**. ^{1}H NMR spectrum, δ, ppm: 1.87 s (3H, CH_3), 3.05–3.35 m (4H, CH_2), 3.71 d (3H, CH_3OP, $^3J_{HP}$ 12.0 Hz), 3.82 d (3H, CH_3OP, $^3J_{HP}$ 12.0 Hz), 4.51 br. s (1H, CHBr). ^{13}C NMR spectrum, δ_C, ppm: 32.65 (CH_3), 39.51 d (C^3, $^2J_{CP}$ 12.2 Hz), 42.16 d (C^6, $^2J_{CP}$ 12.5 Hz), 53.12 br. s (CH_3OP), 54.79 d (C^5, $^3J_{CP}$ 7.5 Hz), 61.25 d (C^4, $^3J_{CP}$ 8.6 Hz), 140.74 d (C^1, $^1J_{CP}$ 188.9 Hz), 140.61 d (C^2, $^1J_{CP}$ 187.3 Hz). ^{31}P NMR spectrum: δ_P 14.09 ppm.

Dimethyl (4,5-dibromo-4,5-dimethyl-2-chlorocyclohex-1-en-1-yl)phosphonate (IId) was prepared from dimethyl (4,5-dimethyl-2-chlorocyclohexa-1,4-dien-1-yl)phosphonate **Id**. ^{1}H NMR spectrum, δ, ppm: 1.83 s and 1.85 s (6H, CH_3), 3.01 d (1H, CH_2CP, $^2J_{HH}$ 19.6 Hz), 3.10 d (1H, CH_2CP, $^2J_{HH}$ 19.6 Hz), 3.08 d (1H, CH_2, $^2J_{HH}$ 20.0 Hz), 3.31 d (1H, CH_2, $^2J_{HH}$ 20.0 Hz), 3.65 d. d (6H, CH_3OP, $^3J_{HP}$ 11.2 Hz). ^{13}C NMR spectrum, δ_C, ppm: 29.10 and 28.86 (CH_3), 46.14 d (C^6, $^2J_{CP}$ 8.86 Hz), 51.97 d (C^3, $^3J_{CP}$ 12.3 Hz), 52.53 (OCH_3), 68.25 (C^5), 68.56 (C^4), 120.84 d (C^1, $^1J_{CP}$ 185.9 Hz), 140.45 (C^2). ^{31}P NMR spectrum: δ_P 15.60 ppm.

Dimethyl (4,5-dibromo-3-methyl-2-chlorocyclohex-1-en-1-yl)phosphonate (IIe) was prepared from dimethyl (3-methyl-2-chlorocyclohexa-1,4-dien-1-yl)phosphonate **Ie**. The first isomer, content 75%. ^{1}H NMR spectrum, δ, ppm: 1.09 d (3H, CH_3, $^3J_{HH}$ 7.6 Hz), 2.88–3.30 m (1H, CH; 2H, CH_2), 3.66 d (3H, CH_3OP, $^3J_{HP}$ 6.8 Hz), 4.30–4.40 m (1H, CHBr), 5.45–5.60 m (1H, CHBr). ^{13}C NMR spectrum, δ_C, ppm: 22.44 (CH_3), 35.34 d (C^3, $^3J_{CP}$ 8.9 Hz), 43.50 d (C^6, $^2J_{CP}$ 10.1 Hz), 52.63 (CH_3OP), 54.34 d (C^5, $^3J_{CP}$ 11.4 Hz), 56.69 (C^4), 125.47 d (C^1, $^1J_{CP}$ 184.3 Hz), 139.54 (C^2). ^{31}P NMR spectrum: δ_P 15.12 ppm. The second isomer, content 25%. ^{1}H NMR spectrum, δ, ppm: 1.50 d (3H, CH_3, $^3J_{HH}$ 7.6 Hz), 2.88–3.30 m (1H, CH; 2H, CH_2), 3.63 d (3H, CH_3OP, $^3J_{HP}$ 6.5 Hz), 4.54–4.88 m (1H, CHBr), 5.45–5.60 m (1H, CHBr). ^{13}C NMR spectrum, δ_C, ppm: 22.44 (CH_3), 36.16 d (C^3, $^3J_{CP}$ 10.8 Hz), 42.12 d (C^6, $^2J_{CP}$ 12.3 Hz), 44.81 (C^4), 52.41 d (CH_3OP, $^2J_{CP}$ 5.1 Hz), 53.42 d (C^5, $^3J_{CP}$ 5.8 Hz), 126.81 d (C^1, $^1J_{CP}$ 184.3 Hz), 142.57 (C^2, $^3J_{CP}$ 10.1 Hz). ^{31}P NMR spectrum: δ_P 16.86 ppm.

Dimethyl [4,5-dibromo-4(5)-methyl-2-chlorocyclohex-1-en-1-yl)phosphonate IIf was prepared from dimethyl [4(5)-methyl-2-chlorocyclohexa-1,4-dien-1-yl)phosphonate **If** as a mixture with isimer **If'**. Content of **If** 65%. ^{1}H NMR spectrum, δ, ppm: 1.90 s

(3H, CH_3), 3.00 d (1H, C^3H_2, $^2J_{HH}$ 19.6 Hz), 3.07 d. d (1H, C^6H_2, $^2J_{HH}$ 19.6, $^3J_{HP}$ 1.0 Hz), 3.22–3.55 m (1H, C^3H_2, $^2J_{HH}$ 19.2 Hz), 3.72 d (6H, CH_3OP, $^3J_{HP}$ 15.0 Hz), 4.46 br. s (1H, C^5HBr). ^{13}C NMR spectrum, δ_C, ppm: 32.67 (CH_3), 38.57 d (C^6, $^2J_{CP}$ 8.8 Hz), 47.52 d (C^3, $^3J_{CP}$ 12.0 Hz), 52.68 br. s (CH_3OP), 53.41 d (C^5, $^3J_{CP}$ 10.2 Hz), 62.30 (C^4), 118.84 d (C^1, $^1J_{CP}$ 187.6 Hz), 139.98 (C^2). ^{31}P NMR spectrum: δ_P 15.47 ppm.

Dimethyl [4,5-dibromo-5-methyl-2-chlorocyclohex-1-en-1-yl)phosphonate (IIf'), content 35%. ^1H NMR spectrum, δ, ppm: 1.91 s (3H, CH_3), 2.97–3.55 m (2H, C^3H_2; 2H, C^6H_2), 3.74 d (6H, CH_3OP, $^3J_{HP}$ 13.8 Hz), 4.41 br. s (1H, C^5HBr). ^{13}C NMR spectrum, δ_C, ppm: 32.69 (CH_3), 41.40 d (C^6, $^2J_{CP}$ 7.2 Hz), 44.84 d (C^3, $^3J_{CP}$ 11.9 Hz), 52.68 br.s (CH_3OP), 53.92 (C^4), 61.87 d (C^5, $^3J_{CP}$ 9.9 Hz), 120.18 d (C^1, $^1J_{CP}$ 187.7 Hz), 139.98 (C^2). ^{31}P NMR spectrum: δ_P 15.19 ppm.

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