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Reaction of (2-Nitro- and 2-Bromo-2-nitroethenyl)phosphonates with 1,3-Cyclohexadiene

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Abstract — Specific features of the reactions of bis(chloroethyl) 2-nitro- and 2-bromo-2-nitroethenylphosphonates with 1,3-cyclohexadiene were studied. It was found that the reaction with 2-nitroethenylphosphonate occurs stereoselectively and provides bis(2-chloroethyl) *endo*-(3-nitrobicyclo[2.2.2]oct-5-en-2-yl)phosphonate. 2-Bromo-2-nitroethenylphosphonate under the same conditions gives a mixture of the *endo* and *exo* isomers of the corresponding nitrobicyclooctenes. Enhanced tendency of adducts derived from *gem*-bromonitroethenylphosphonates for intramolecular transformations, such as dehydrohalogenation and aromatization, under the cycloaddition conditions was revealed.

We have previously shown that nitro- and halonitroethenylphosphonates act as highly active dienophiles in the Diels–Alder reaction with aliphatic dienes, cyclopentadiene, and furan [1–3]. In the present work we have studied reactions of nitro- and *gem*-bromonitroethenylphosphonates **I** and **II** with cyclohexadiene, aiming at revealing specific features of these reactions compared with similar reactions with cyclopentadiene. Such reactions are interesting to study in terms of development of convenient synthetic approaches to polyfunctional bicyclooctenes, important intermediates in the synthesis of fragments of natural compounds, such as hormones, vitamin D_3, etc. [4, 5].

It is known that cyclopentadiene reacts with nitroethenylphosphonate **I** in benzene under reflux for 1 h to give a mixture of the *endo* and *exo* diastereomers of the corresponding phosphorylated norbornene in 80% yield [1]. Unlike cyclopentadiene, 1,3-cyclohexadiene reacts under more rigid conditions, viz. in benzene under reflux for 36 h. The reaction results in exclusive formation of the *endo* isomer of bis(2-chloroethyl) (3-nitrobicyclo[2.2.2]oct-5-en-2-yl)phosphonate (**IIIa**) in 69% yield (see table).

Yields, R_f values, and IR and ^{1}H and ^{31}P NMR spectral parameters of phoshorylated nitrobicyclooctenes **IIIa, IVa,** and **IVb**

Comp. no.	Yield, %	R_f	IR spectrum ($CHCl_3$), ν, cm^{-1}			^{1}H NMR spectrum ($CDCl_3$), δ, ppm (J, Hz)								^{31}P NMR spectrum, δ_P, ppm
			NO_2	P=O	POC	C^1H	C^2H	C^3H	C^4H	C^5H	C^6H	C^7H_2	C^8H_2	
IIIa	69	0.64	1375, 1555	1250	1030, 1080	2.62 ($J_{1,2}$ 2.5, ($J_{1,6}$ 7.0)	3.22 ($^2J_{HP}$ 0, ($J_{2,3}$ 5.2, ($J_{1,2}$ 2.5)	4.69 ^{3}(J_{HP} 19.5, ($J_{2,3}$ 5.2, ($J_{3,4}$ 4.0)	2.90 ($^1J_{3,4}$ 4.0, ($J_{4,5}$ 6.0)	6.33 ($J_{5,6}$ 5.5, ($J_{4,5}$ 6.0)	5.89 ($J_{5,6}$ 5.5, ($J_{1,6}$ 7.0)	1.10 m	1.95 m	28.0
IVa[a]	49	0.28	1355, 1555	1265	1030, 1090	3.19 m	3.50	–	3.19 m	6.48 ($J_{5,6}$ 0, ($J_{4,5}$ 5.8)	6.10 ($J_{5,6}$ 6.0, ($J_{1,6}$ 6.0)	1.50 m	2.20 m	23.0
IVb[a]	49	0.54	1350, 1560	1263	1030, 1092	2.90 m	3.95	–	3.10 m	6.25 ($J_{5,6}$ 5.6, ($J_{4,5}$ 6.0)	6.10 ($J_{5,6}$ 5.6, ($J_{1,6}$ 5.8)	1.65 m	2.25 m	23.5

[a] The *endo/exo* isomer ratio in the mixture of **IVa** and **IVb** is 1 : 1. The chloroethoxy groups in compounds **IIIa, IVa,** and **IVb** appear as two multiplets at 3.51–3.72 and 4.10–4.33 ppm.

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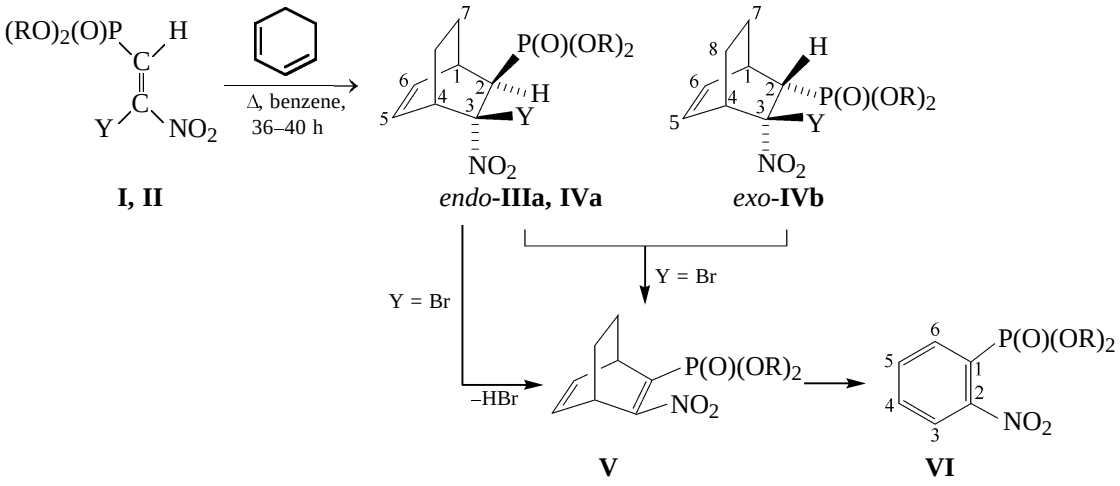


R = CH_2CH_2Cl, Y = H (**I, IIIa**), Br (**II, IVa, IVb**); R = CH_2CH_2Cl (**V, VI**).

The *endo*-stereoselectivity of the Diels-Alder reaction involving cyclohexadienes and vicinally substituted nitroalkenes containing electron-acceptor subtituents β to the NO_2 group was noted in [6–9]. Such differences in the activity and stereoselectivity of the diene synthesis with cyclopenta- and cyclohexadienes is evidently connected with the structural features of these two reagents and agrees with published data.

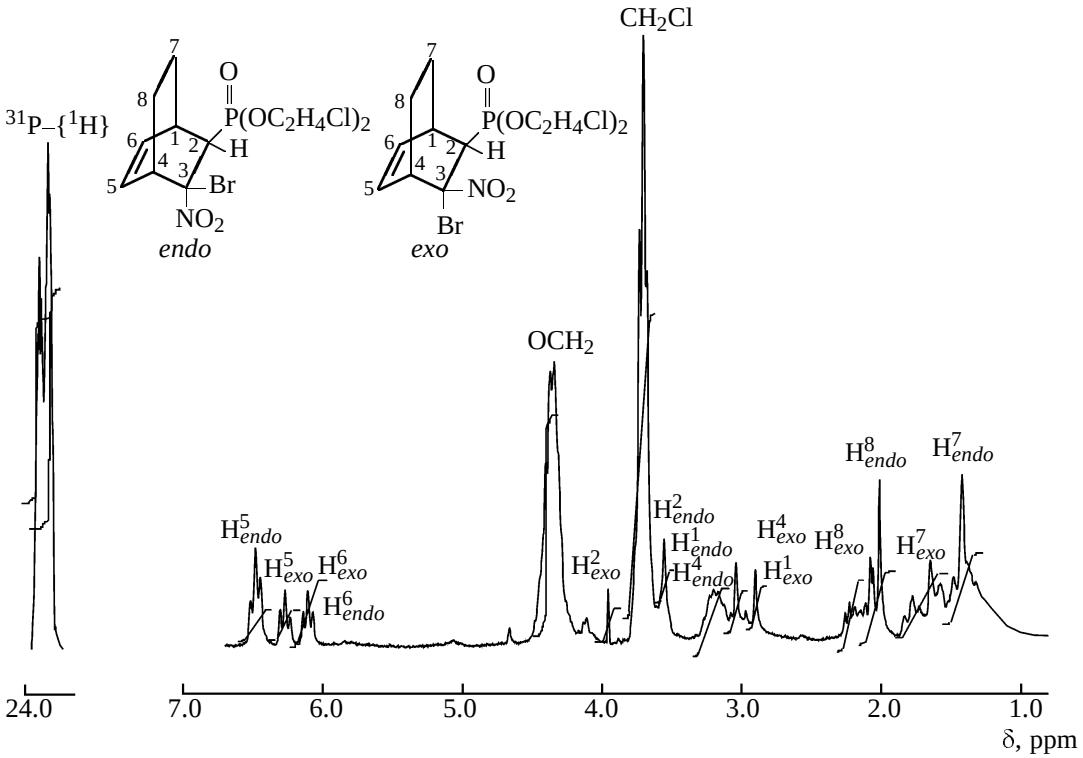
Bromonitroethenylphosphonate **II** reacted with cyclohexadiene under analogous conditions (benzene, 80°C, 40 h) to give a hardly separable mixture of products, whose column chromatography gave a 1:1 mixture of the *endo* and *exo* isomers of bis(2-chloroethyl) [3-bromo-3-nitrobicyclo[2.2.2]oct-5-en-2-yl]-phosphonate (**IVa**, **IVb**), as well as intramolecular transformations products, viz. bis(2-chloroethyl) [3-nitrobicyclo[2.2.2]octa-2,5-dien-2-yl]phosphonate (**V**) and nitroarylphosphonate **VI**. By repeated chromatography of the mixture of bicyclooctene **IVa** and **IVb** we could obtain a pure *endo* isomer **IVa** in 20% yield.

The lower yield of bicyclooctenes **IVa** and **IVb** (49%) as compared to bicyclooctene **IIIa** (69%) is evidently explained by stronger steric strain of the unsaturated bicyclic system with three electron-acceptor substituents [$P(O)(OR)_2$, NO_2, and Br] and stronger tendency of compound **IV** for intermolecular transformations under rigid conditions. The presence of an easily leaving nucleofugal halogen in the *gem*-position to the nitro group and a mobile hydrogen atom at the $P(O)(OR)_2$ group evidently favors dehydrohalogenation and formation of bicyclooctadiene **V**. Note that the possibility of preparing substituted bicyclooctadienes from adducts of diene synthesis was considered in the works [10, 11] devoted to synthesis of benzene derivatives. The instability of compound **V** is evidently connected with the *cisoid* location of the phosphoryl and nitro groups (steric factor) [12]; as a result, cleavage of the ethylene bridge and formation of arene **VI** occurs. The presence of compound **VI** in the mixture is confirmed by the presence of characteristic signals in the downfield region of the ^1H NMR spectrum (δ 6.40–8.20 ppm).

The formation of aromatic products in high yields (80–92%) under [4 + 2]-cycloaddition conditions was also observed in [9–11, 13], for example, in reactions of cyclohexadiene with acetylenic dienophiles. The formation of the benzene ring has been explained [11, 14] by bridge cleavage in the intermediate bicyclooctene via ethylene elimination.

Attempted synthesis of bicyclooctadiene by dehydrobromination of *gem*-bromonitrobicyclooctene **IVa** in benzene under reflux (30 min) in the presence of pyridine failed. The major reaction product was nitrophenylphosphonate **VI**. It was isolated pure in 55% yield. Here, too, bicyclooctadiene **V** was detected by spectroscopy only. Its presence in the reaction mixture is confirmed by the fact that the corresponding ^{31}P NMR signal appears at 9 ppm, which is characteristic of phosphorylated nitroalkenes [15]. Moreover, the ^1H NMR spectra of bicyclooctadiene **V** display multiplets of protons at the bridgehead C^1 and C^4 atoms (δ 3.3 and 3.5 ppm, respectively), that are shifted downfield as compared to starting bicyclooctene **IVa**.

The structure of phosphorylated nitrobicyclooctenes **IIIa, IVa,** and **IVb** and arene **VI** was established on the basis of spectral data and their com-



^{31}P and ^{1}H NMR spectra of the mixture of bis(2-chloroethyl) *endo*- and *exo*-[3-bromo-3-nitrobicyclo[2.2.2]oct-5-en-2-yl]-phosphonates **IVa** and **IVb** in $CDCl_3$.

parison with published data for structurally related compounds [7]. The ^{1}H and ^{31}P NMR spectra of compound **IV**, unlike that of compound **III**, show doubled signals of all ring protons and phosphorus nuclei, implying that this compound exists as a mixture of the *endo* and *exo* diastereomers **IVa** and **IVb** (see figure).

According [16–18], criteria used for stereochemical assessment of bicycloheptenes can also be applied to bicyclooctenes. One of such criteria for substituted bicyclooctenes relates to the chemical shifts of the C^5H and C^6H olefin protons. In the *endo* isomers, the difference in the chemical shifts of the C^5H and C^6H signals is larger because of the steric proximity to these protons to the back-side substituent (in our case NO_2). In the *exo* isomer, the effect of the NO_2 group is attenuated, and, therefore, the difference in the chemical shifts of the C^5H and C^6H signals is smaller, as exemplified by the corresponding parameters of *endo*- and *exo*-bicyclooctenes **IVa** and **IVb**. Hence, the C^4H and C^6H signals of *exo* isomer **IVb** are close to each other (Δδ 0.15 ppm). The respective signals of *endo* isomer **IVa** are more distant from each other (Δ 0.38 ppm) (see table). Stereohomogeneous nitrobicyclooctenylphosphonate **IIIa**, as judged from the value of this parameter (Δδ 0.44 ppm), has *endo* configuration (see table). Analysis of the integral intensities of nonoverlapping signals in the ^{1}H NMR spectra of the mixture of compounds **IVa** and **IVb** in the range characteristic of olefin protons (δ 6.10–6.48 ppm) and of upfield signals of bridge protons allowed us to conclude that the ratio of *endo* and *exo* stereoisomers **IVa** and **IVb** is 1 : 1.

The ^{1}H NMR spectra of compound **VI** characteristically display aromatic proton signals at 6–9 ppm [15, 19]. The C^6H proton signal appears at 6.31 ppm, whereas the signal of the C^3H proton that is the strongest influenced by the electron-acceptor nitro group is observed at 8.20 ppm. Both proton signals are multiplets due to coupling with the phosphorus nucleus. The C^4H and C^5H proton signals are at 7.35 and 7.50 ppm, respectively. The signal of **VI** in the ^{31}P NMR spectrum is observed at 15 ppm, which is evidence showing that the phosphoryl group is attached to an sp^2-carbon atom [15, 19].

EXPERIMENTAL

The IR spectra were obtained on an InfraLUM FT 02 instrument in $CHCl_3$ (*c* 0.1-0.001 M). The ^{1}H and

^{31}P NMR spectra were registered on a Bruker AC-200 spectrometer (200 MHz) in $CDCl_3$ against internal HMDS with an accuracy of ±0.5 Hz. The ^{31}P NMR spectra were measured against external 85% phosphoric acid.

Starting nitro- and *gem*-bromonitroethenylphosphonates **I** and **II** were obtained according to the procedures in [20, 21].

Purification and isolation of individual compounds was carried out by column chromatography on silica gel (Chemapol 100/200) or alumina using the Trappe solvent series [22]. Purity control and reaction monitoring were performed by TLC on Silufol-254 plates using a 3:1 hexane–acetone mixture, development in iodine vapor.

Bis(2-chloroethyl) [3-nitrobicyclo[2.2.2]oct-5-en-2-yl]phosphonate (IIIa). To a solution of 1.00 g of bis(2-chloroethyl) (2-nitroethenyl)phosphonate (**I**) in 15 ml of anhydrous benzene, 0.61 g of 1,3-cyclohexadiene was added, and the resulting mixture was refluxed with stirring for 36 h. The solvent was removed on a rotary evaporator, and the residue was subjected to column chromatography. *endo*-**IIIa** was isolated from the ethereal fraction, yield 0.89 g (69%), oil, R_f 0.64. Found, %: C 40.26, 40.36; H 5.06, 5.11; N 3.98, 4.00; P 8.62, 8.63. $C_{12}H_{18}Cl_2NO_5P$. Calculated, %: C 40.22; H 5.03; N 3.91; P 8.66.

Bis(2-chloroethyl) [3-bromo-3-nitrobicyclo-[2.2.2]oct-5-en-2-yl]phosphonate (IVa, IVb), bis-(2-chloroethyl) [3-nitrobicyclo[2.2.2]octa-2,5-dien-2-yl]phosphonate (V), and bis(2-chloroethyl) 2-(nitrophenyl)phosphonate (VI). To a solution of 1.00 g of bis(2-chloroethyl) (2-bromo-2-nitroethenyl)-phosphonate (**II**) in 10 ml of absolute benzene, 0.48 g of 1,3-cyclohexadiene was added, and the resulting mixture was refluxed with stirring for 40 h. The solvent was removed on a rotary evaporator, and the residue was subjected to column chromatography. A 1:4 mixture of compounds **V** and **VI** was isolated from the benzene fraction, yield 0.34 g, yellow oil. Compound **IV** was isolated from the chloroform fraction as a 1:1 mixture of the *endo* and *exo* isomers **IVa** and **IVb**, yield 0.60 g (49%), R_f 0.54 and 0.28.

endo Isomer **IVa** was isolated pure by repeated chromatography of the mixture of **IVa** and **IVb**, eluent chloroform; yield 0.24 g (20%), R_f 0.54. Found, %: C 32.93, 32.92; H 3.87, 3.94; N 3.15, 3.16; P 6.95, 6.94. $C_{12}H_{17}BrCl_2NO_5P$. Calculated, %: C 32/95; H 3.89; N 3.20; P 7.09.

Bis(2-chloroethyl) (2-nitrophenyl)phosphonate (VI). To a solution of 0.42 g of compound **IVa** in 10 ml of absolute benzene, 0.78 g of pyridine was added, and the resulting mixture was refluxed for 68 h. Pyridinium bromide was filtered off, the filtrate was evaporated on a rotary evaporator, and the residual oil was subjected to chromatography on alumina to obtain 0.29 g of a yellow oil containing compounds **V** and **VI** in a ~2:5 ratio (eluent chloroform). Repeated chromatography of this mixture gave 0.17 g (60%) of compound **VI** from the benzene fraction, R_f 0.38. Found, %: C 36.55, 36.50; H 3.21, 3.25; N 4.30, 4.31; P 9.58, 9.62. $C_{10}H_{12}Cl_2NO_5P$. Calculated, %: C 36.58; H 3.66; N 4.27; P 9.45.

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