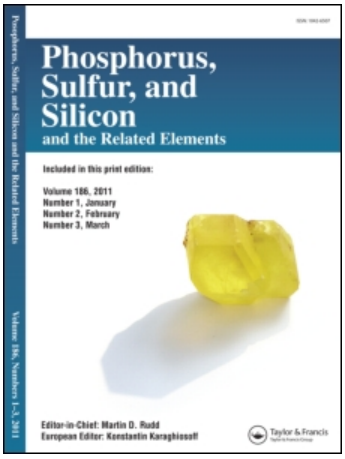

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

A STUDY OF THE REACTION ROUTES UPON BROMINATION OF 1,2-ALKADIENEPHOSPHONIC ESTERS BY SPECTRAL AND CHROMATOGRAPHIC METHODS

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To cite this Article Tancheva, Chonka , Bogilova, Maria and Mondeshka, Diana(2000) 'A STUDY OF THE REACTION ROUTES UPON BROMINATION OF 1,2-ALKADIENEPHOSPHONIC ESTERS BY SPECTRAL AND CHROMATOGRAPHIC METHODS', Phosphorus, Sulfur, and Silicon and the Related Elements, 157: 1, 123 — 138
To link to this Article: DOI: 10.1080/10426500008040517
URL: http://dx.doi.org/10.1080/10426500008040517

Phosphorus, Sulfur, and Silicon, 2000, Vol. 157, pp. 123-138
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A STUDY OF THE REACTION ROUTES UPON BROMINATION OF 1,2-ALKADIENEPHOSPHONIC ESTERS BY SPECTRAL AND CHROMATOGRAPHIC METHODS

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(Received March 18, 1999; In final form July 21, 1999)

By spectral and chromatographic studies, the chemo-, regio- and stereoselectivity of the reaction of 1,2-alkadienephosphonic esters with bromine has been investigated in details. All reaction products were isolated and identified as pure compounds. It has been established that the main reaction pathways – heterocyclisation or 2,3-addition – depend strongly on the degree of substitution at C-3 carbon atom. Unlike to analogous addition reactions with sulfenyl- or selenenylchloride no 1,2-adducts have been detected. It has been proved that the 2,3-addition is highly Z-stereoselective. The probable mechanism of the reaction has been discussed.

Keywords: allenylphosphonates; bromination; electrophilic addition; oxaphospholic heterocyclisation; regioselectivity; stereoselectivity

INTRODUCTION

Studies of the interaction of 1,2-alkadienphosphone esters with a number of electrophiles have shown that the chief reaction route is normally through the oxaphospholic cyclisation.[1-3] However, depending on the nature of the electrophile, and the extent of substitution at the double bonded C-atoms, side reactions do occur. In latter years, we have shown

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by isolation of individual compounds from the reaction mixtures, using chromatographic methods (column and thin-layer chromatography), that besides cyclization, several reactions lead to addition of the reagent to one or both of the double bonds, as well as to secondary reaction products.[4,5]

Chlorination of the 1,2- alkadienephosphonic esters results in exclusive formation of oxaphosphole derivatives[6–8] except for propadienephosphonic esters[9], where the reactions take a different route. Bromination studies have been limited to 3,3-dialkylsubstituted allenephosphonates.[9] In this paper, we report results from the bromination of dialkyl esters of 3,3-dialkylsubstituted, 3-monoalkylsubstituted, and non-substituted 1,2-alkadienephosphonic acids, obtained by chromatographic separation of the products. The isolated pure compounds were analyzed spectroscopically. Main reaction products were also subjected to elemental analysis.

RESULTS AND DISCUSSION

In agreement with earlier reports for chlorination, bromination of the esters of 3,3-dialkylsubstituted allenephosphonic acids results almost exclusively in formation of cyclic products.[6] However, chromatographic investigation showed traces of other compounds, but in insufficient quantities to be isolated and/or spectroscopically identified. The reaction can therefore be considered chemo- and regiospecific. Unlike the chlorination of 3-monosubstituted, 1,2-alkadienephosphonic esters, the bromination of the compounds *1a-d* leads to formation of complex product mixtures. When subjected to chromatographic separation, the main product (approx. 60 %, Table I) was found to be 2,5- dihydro-1,2-oxaphospholes *2a-d* isolated as pure (E) and (Z) isomers or as a mixture of (E)/(Z) diastereomers. In addition considerable amount of the 2,3- adducts *3a-d* is formed, where the (Z)-isomer is strongly prevailing (Tables I,III). Very small amounts of the (E)- and (Z)- isomers of the alkenephosphonates *4a-d* were also isolated (Tables I,IV), presumably formed by 1,3- prototropic rearrangement of the 2,3- adducts *3a-d*. 1,2- Adducts were not formed in any of the reactions.

On the basis of the above data the reaction of 3-monoalkylsubstituted allenephosphonic esters with bromine is assumed to proceed according to the following scheme (Scheme 1)

TABLE I Content (%) omtographically isolated compounds from the reaction mixtures obtained by interaction of 1a-f and bromine

Comp. Nr	R^1	R^2	*Config.*	*Oxaphospholes 2a-d*	*2,3-Adducts 3a-f*	*Isomeric alkenephosphonates 4a-f*	*Alkynphosphonates 5e,f*	*Alkenephosphonates 6e,f*	*Alkanephosphonates 7e,f*
			E		5	1			
1 a	Me	Me		61			–	–	–
			Z		29	4			
			E	34	6	–			
1 b	Me	Pr^n					–	–	–
			Z	25	32	3			
			E	33	10	–			
1 c	Et	Me					–	–	–
			Z	24	29	4			
			E		9	–			
1 d	Et	Pr^n		56			–	–	–
			Z		32	3			
			E		10	8			
1 e	Me	H		–			4	3	2
			Z		60	13			
			E		9	7			
1 f	Et	H		–					
			Z		61	13	4.5	3.5	2

TABLE II TLC and ^{1}H-NMR data of 2-alkoxy-5-alkyl-4-bromo-2,5-dihydro-1,2-oxaphosphole-2-oxides 2 a-d

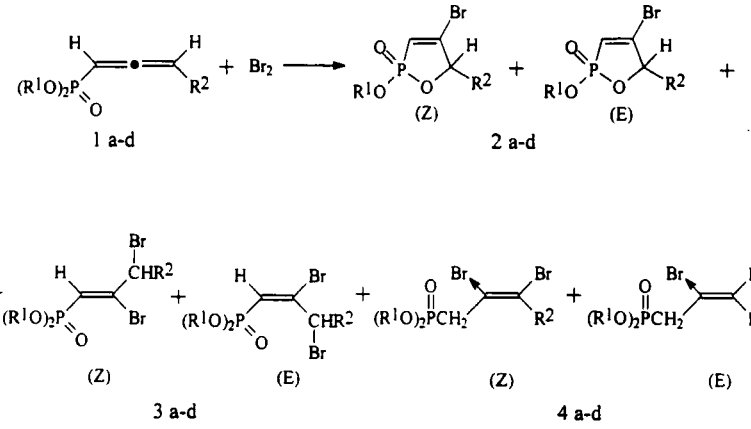
(E)

(Z)

Nr	R^1	R^2	*Config.*	R_f	*Chemical shifts, δ ppm*				*Coupling constants, J (Hz)*					
					H_a	H_b	R^1	R^2	$^2J_{Ha,P}$	$^3J_{R1,P}$	$^3J_{Hb,P}$	$^4J_{R2,P}$	$^3J_{R2,Hb}$	$^4J_{Ha,Hb}$
2 a	Me	Me	E/Z mixture	0.32	6.41 dd	4.96 m	3.80 d	1.49 dd	24.0	11.8	4.5	3.9	6.5	1.8
			E	0.32	6.40 dd	4.82 ddt	3.61 d	0.99 t	23.8	11.8	4.6	4.2	6.5	1.7
2 b	Me	Pr^n						1.59 m						
								1.92 m						
			Z	0.30	6.38 dd	4.84 ddt	3.78 d	0.97 t	23.4	12.0	4.2	4.0	6.5	1.3
								1.57 m						
								1.89 m						
			E	0.30	6.45 dd	4.85 ddq	1.32 t	1.52 dd	24.2	11.7	4.4	4.6	6.5	1.6
2 c	Et	Me					4.03 qd							
			Z	0.28	6.42 dd	4.88 ddq	1.30 t	1.47 dd	23.7	12.1	3.9	4.3	6.5	1.1
							4.05 qd							
2 d	Et	Pr^n	E/Z mixture	0.31	6.48 dd	4.90 m	1.34 t	0.99 t	24.0	11.8	4.6	4.2	6.5	1.7
							4.05 qd	1.62 m						
								1.94 m						

IR-spectra (film, cm^{-1}): 983 – 965 (R^2 -O -P), 1280 – 1265 (P = O), 1610 – 1590 (C = C)

Bromination of esters of the propadienephosphonic acid *1e,f* affords complex mixtures of products, which according to preliminary data, in contrast to chlorination, contain no cyclic compounds. The main reaction products, separated by column chromatography, are the (Z)-2,3-adducts *3e,f* together with a much smaller amount of the (E)-2,3- adducts *3e,f* and the products *4e,f* presumably formed by 1,3-prototropic rearrangement of *3e,f*.



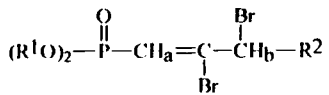
1a, 2a, 3a, 4a	R^1 = Me	R^2 = Me
1b, 2b, 3b, 4b	R^1 = Me	R^2 = Pr^n
1c, 2c, 3c, 4c,	R^1 = Et	R^2 = Me
1d, 2d, 3d, 4d	R^1 = Et	R^2 = Pr^n

SCHEME 1

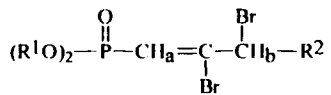
Tiny amounts of the alkynphosphonates *5e,f* are also isolated, as well as compounds *6e,f* and *7e,f* (Tables I,V), formed by secondary reactions. (Scheme 2)

The structure and configuration of the isolated compounds were determined spectroscopically, mainly by analysis of their ^{1}H-NMR spectra. (Tables II–V)

TABLE III TLC and 1H-NMR data of dialkyl-2,3-dibromo-1-alkenylphosphonates 3 a-f



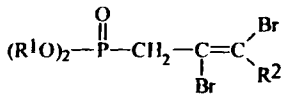
Nr	R^1	R^2	*Config.*	R_f	*Chemical shifts, δ ppm*			*Coupling constant, J (Hz)*		
					CH_a	CH_b	R^2	$^2J_{Ha,P}$	$^4J_{Hb,P}$	$^4J_{Ha,Hb}$
3 a	Me	Me	E	0.59	6.05 d	5.75 qd	1.58 d	8.05	1.75	<0.7
			Z	0.52	6.50 d	4.55 bq	1.66 d	9.6	1	<1.2
			E	0.58	6.10 d	5.17 td	0.88 t	8.0	1.8	<0.7
3 b	Me	Pr^n					1.28 m			
							1.85 m			
			Z	0.51	6.46 d	4.50 t	0.90 t	9.5	0.9	<0.7
							1.35 m			
							1.96 m			
3 c	Et	Me	E	0.60	6.00 d	5.70 qd	1.60 d	8.1	1.7	< 0.7
			Z	0.50	6.35 d	4.45 bq	1.78 ddd	9.6	0.9	<0.7
			E	0.58	6.12 d	5.70 td	0.89 t	8.0	1.8	<0.7
3 d	Me	Pr^n					1.29 m			



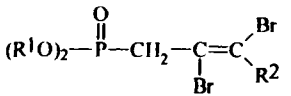
Nr	R^1	R^2	Config.	R_f	Chemical shifts, δ ppm			Coupling constant, J (Hz)		
					CH_a	CH_b	R^2	$^2J_{Ha,P}$	$^4J_{Hb,P}$	$^4J_{Ha,Hb}$
							1.87 m			
			Z	0.52	6.50 d	4.55 td	0.91 t	9.5	0.9	< 0.7
							1.36 m			
							1.99 m			
3 e	Me	H	E	0.60	6.26 d	4.84 d	4.84 d	7.5	1.8	< 0.7
			Z	0.46	6.78 d	4.46 dd	4.46 dd	8.2	1.0	< 0.7
3 f	Et	H	E	0.61	6.24 d	4.82 d	4.82 d	7.6	1.7	< 0.7
			Z	0.48	6.75 d	4.42 dd	4.42 dd	8.2	1.0	< 0.7

IR-spectra (film, cm^{-1}): 983 – 965 (R^2 – O – P), 1280 – 1265 (P = O), 1610 – 1590 (C = C)

TABLE IV TLC and ^{1}H-NMR data of dialkyl-2,3-dibromo-2-alkenylphosphonates 4 a-f



Nr	R^1	R^2	*Config.*	R_f	*Chemical shift, δ ppm*		*Coupling constant, J (Hz)*			
					CH_2	R^2	$^2J_{H,P}$	$^4J_{H,P}$	$^5J_{H,P}$	$^5J_{H,H}$
4 a	Me	Me	E	0.68	3.07 d	2.38 d	21.7	–	5.5	–
			Z	0.58	2.89 d	2.25 d	21.0	–	3.8	–
			E	0.70	3.05 d	0.92 t	21.5	–	3.2	–
4 b	Me	Pr^n				1.72 m				
						2.25 m				
			Z	0.60	2.92 d	0.90 t	21.0	–	2.5	–
						1.68 m				
						2.19 m				
4 e	Et	Me	E	0.68	3.20 d	2.40 d	22.0	–	5.2	–
			Z	0.59	2.80 d	2.25 d	21.5	–	3.7	–
			E	0.70	3.00 d	0.90 t	22.0	–	3.3	–
4 d	Et	Pr^n				1.70 m				



Nr	R^1	R^2	Config.	R_f	Chemical shift, δ ppm		Coupling constant, J (Hz)			
					CH_2	R^2	$^2J_{H,P}$	$^4J_{H,P}$	$^5J_{H,P}$	$^5J_{H,H}$
						2.24 m				
			Z	0.60	2.90 d	0.88 t	21.5	–	3.0	–
						1.70 m				
						2.16 m				
4 e	Me	H	E	0.61	3.16 d	5.96 br.d	21.8	4.1	–	<0.7
			Z	0.55	2.95 d	5.31 dt	21.0	5.1	–	~ 1.0
4 f	Et	H	E	0.60	3.18 d	5.92 br.d	21.5	4.0	–	<0.7
			Z	0.56	2.94 d	5.46 dt	21.2	5.3	–	1.2

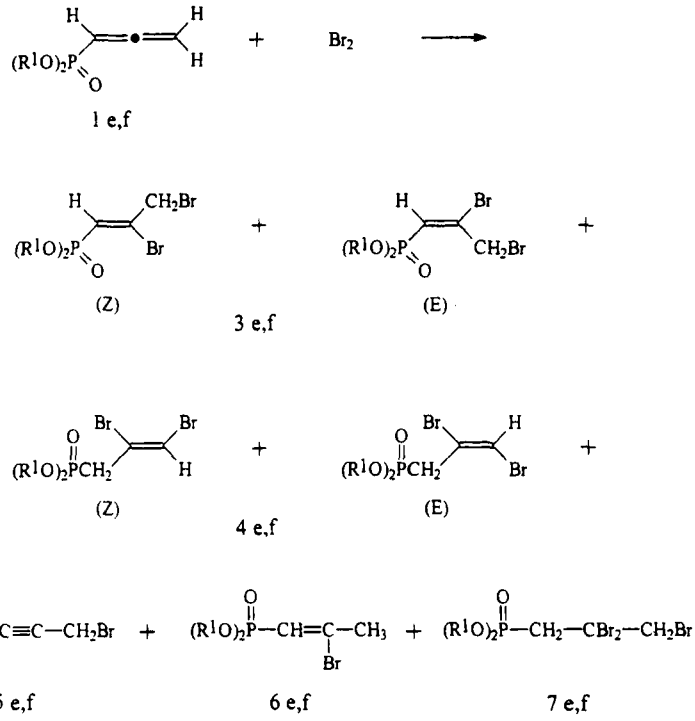
IR-spectra (film, cm^{-1}): 990 – 975 (R^2 – O – P), 1280 – 1260 (P = O), 1605 – 1588 (C = C)

The IR spectra are in accordance with the structure of the compounds, determined by NMR-analysis, but the IR-spectra of the isomeric couples are too similar to allow interpretation of their configurations (Tables II–IV). The ^{1}H-NMRspectra of compounds *2a-d* (Table II) are typical for oxaphosphole derivatives and very similar to analogous 5,5-dialkylsubstituted oxaphospholes[4,5] The ^{1}H-NMR spectra of the isomers of the 2,3-adducts *3a-f* (Table III) differ considerably from each other. The difference in the chemical shift of the CH = proton of both isomers is smaller when compared to analogous methyl (phenyl) sulphenyl and selenenyl derivatives.[4,5] This might be due to the presence of a bromine atom in cis-position both in (E) and (Z)-isomers. Nevertheless, in the case also the CH = proton of the (Z)- isomer appears in a lower field and the higher stereospecific value of $2J_{HP}$ constant is still retained.[4,5,10] The protons in CHBr are observed at quite different fields. The field of the (E)- isomer is weaker, resulting in a greater $4J_{HP}$ constant. Trans- $4j_{HP}$ has a smaller value, giving rise to broadening of the CHBr signal of the (Z)- isomer only. The configuration of the isomeric alkenephosphonates *4a-f* (Table IV) was determined on the basis of the chemical shift of the CH_2 P group, taking into consideration also some parameters discussed in details in the selenium analogues.[4]

The published data concerning the reaction of allenes with nonacidic electrophiles are in favor of an A_E2 mechanism. As first step here the bromonium ions A-1, A-2 or carbenium ions B-1, B-2 are formed. In the second stage mainly two reaction directions are realized : a) nucleophilic attack of the phosphoryl group at the allenic C-3 atom with the formation of the cyclic phosphonium ion *C* and further the 1,2-oxaphosphole-2-oxides *2a-d*; b) nucleophilic trans attack of the bromine anion at C-3 of bromonium ions *A-1*, *A-2*, leading to the 2,3-adducts *3a-f* (Scheme 3).

The structure of the alkynephosphonates *5e,f* isolated in small amounts, was resolved by their IR- and NMR spectra. Certain proton signals in the NMR spectrum of the reaction mixture have justified the assumption that the same type of compounds are formed in an analogous reaction with chlorine[3]. The presence of *5e,f* in the reaction mixtures could be accounted for through the formation, in the case of a propadienephosphonates of a carbene ion at the C-2 atom, *D*

$$(RO)_2P - CH = C - CH_2Br, \quad (D),$$



1e, 3e, 4e, 5e, 6e, 7e $R^1 = Me$

1f, 3f, 4f, 5f, 6f, 7f $R^1 = Et$

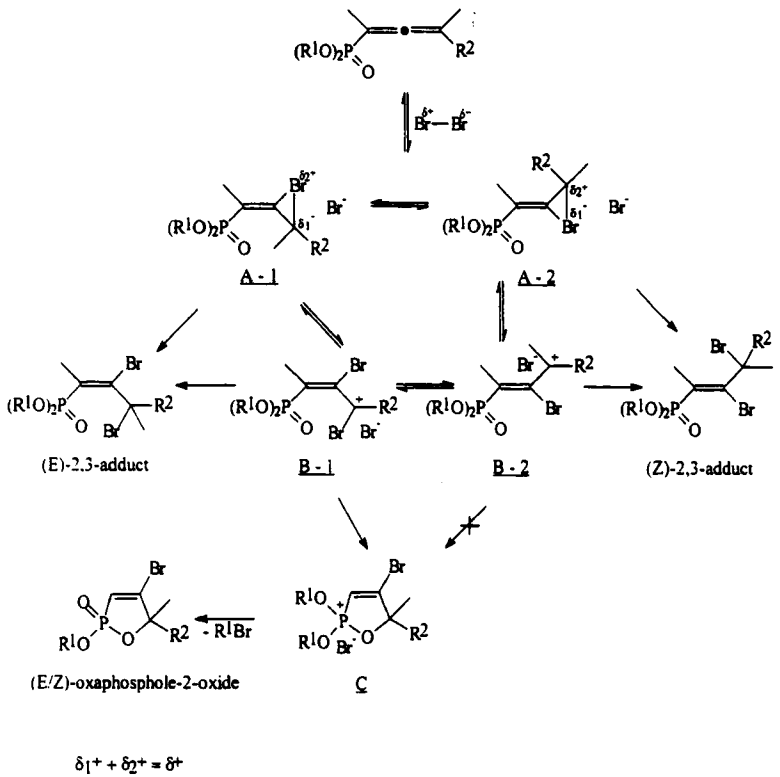
SCHEME 2

which besides addition of a bromide anion to give *3e,f* can also be stabilized by elimination of a proton to give *5e,f*. The charge at the C-3 atom of the carbene ion *E*

$$(RO)_2P - CH = CBr - CH_2, \quad (9)(E)$$

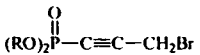
is obviously insufficient to attack the nucleophilic phosphorus atom, thus explaining the absence of cyclic products. The fact, that mainly a (Z)-2,3-adduct is formed points to the conclusion that the chief intermedi-

ates of the reaction are cyclic bromonium ions which, upon trans-attack of the bromide anion on the C-3 atom, give a (Z)-adduct. Minor amounts of other compounds were also isolated from the reaction mixtures. Their IR-and NMR spectra showed them to be esters of the 2-bromo-1-propenephosphonic acid, *6d,e*. These compounds could only be result of secondary reactions by addition of HBr, formed during the reaction, to the start compound, or by reaction with other reaction products. Alkynes or other side products were not observed by bromination of the esters of 3,3-di- and 3-monosubstituted-1,2-alkadienephosphonic acids. The lack of alkynes, together with high degree of cyclisation, can be understood from the greater stabilization of the type *E*, carbene ions by alkyl substituents.

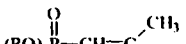


SCHEME 3

TABLE V IR and ^{1}H-NMR data of dialkyl-3-bromo-1-propinylphosphonates 5 e, f, 2-bromo-1-propenylphosphonates 6 e, f and dialkyl-3-bromopropyl-phosphonates 7 e, f



5 e, f



6 e, f

7 e, f

Nr	R	R_f	*Chemical shift, δ ppm*				*Coupling constant, J (Hz)*		*IR-spectra, (cm^{-1})*
			CH_2P	CH-P	CH_2Br	CH_3	^{2J}HP	^{4J}HP	
5 e	Me	0.40	–	–	3.90 d	–	–	3.8	1270 (P = O)
									2223 (C ≡ C)
5 f	Et	0.42	–	–	3.93 d	–	–	4.0	1268 (P = O)
									2225 (C ≡ C)
6 e	Me	0.69	–	5.92 d	–	2.50 d	9.8	3. 1	1265 (P = O)
									1620 (C = C)
6 f	Et	0.70	–	5.86 d	–	2.48 d	9.6	3.2	1263 (P = O)
									1618 (C = C)
7 e	Me	0.75	3.20 d	–	4.50 m	–	19.2	–	1255 (P = O)
					(AB)				
7 f	Et	0.76	3.19 d	–	4.45 m	–	19.0	–	1256 (P = O)
					(AB)				

The present results confirm that bromination of allenephosphonic esters is a highly chemo- and regioselective reaction which, depending on the structure of the allene, can take one and/or several reaction routes. In comparison with other electrophilic reactions, bromination has a higher (Z)-stereoselectivity. A possible explanation is the nature of the bromine atom.

EXPERIMENTAL

1. Spectral methods of analysis ^{1}H-NMR spectra were recorded on a JEOL-PS-100 or Brucker CW-250 spectrometers in a chloroform solution at room temperature. Chemical shifts were measured against HMSO (0,05 ppm as compared to TMS) as internal standard, δ ppm.

   IR spectra were recorded on a UR-10 or IR-72 spectrophotometer (Carl Zeiss Jena, GDR), using thin layer or tablet.
2. A general method for preparation of the reaction mixtures

   A chloroform solution of 0,03 moles bromine is slowly added to a solution of 0,03 moles dialkyl ester of 1,2-alkadienephosphonic acid in 30 ml dry chloroform of tetrachloromethane at 5–10°C.

   After half an hour the temperature is brought up to ambient temperature, and the reaction mixture is left for another two hours. The solvent is then removed (in vacuum), and the mixture is distilled in vacuum through a broad temperature range.
3. Chromatographic separation of the reaction mixtures:

   General method

   Separation was achieved by column and preparative thin layer chromatography. Qualitative TLC analysis and determination of the R_f-values of isolated compounds were performed on kieselgel "Merck" $60F_{254}$ pre-coated sheets, mobile phase hexane : ethyl acetate = 1:2,1. The chromatographic sheets were developed by exposure to UV light (F_{254}). Column chromatographic separation was performed on silicagel "Merck" 60 (0,063–0,200 nm). 0,5 to 1,0 g of the reaction mixture was subjected to separation on 50 to 100 g silicagel in hexane by the wet method. Eluation is carried out with a mixture of hexane-ethyl acetate, ratio 5:1 to 1:2 and finally with pure ethyl acetate. Fractions of 50–70 ml each were withdrawn during the separation at a flow rate of about 100 drops per minute.

A. Chromatographic separation of the reaction mixture, obtained by interaction of the dimethyl ester of 1,2- hexadienephosphonic acid, *1b* and bromine.

Starting with a mixture of 0,982 g the following products were isolated:

FRACTIONS	*COMPOUNDS*	*G*	*%*
12 – 15	(E)-3b	0,040	4
16–23	(E)-3b + (Z)-3b	0,069	7
24–29	(Z)-3b	0,245	25
30–34	(Z)-3b + (Z)-4b	0,049	5
37–41	(E)-2b	0,088	9
42–47	(E)-2b + (Z)-2b	0,421	43
48–52	(Z)-2b	0,078	7

Applying preparative TLC on the mixed fractions pure compounds were obtained.

B. Chromatographic separation of the reaction mixture obtained by interaction of the dimethyl ester of 1,2-propadienephosphonic acid and bromine.

Starting with a mixture of 0,870 g the following products were isolated:

FRACTIONS	*COMPOUNDS*	*G*	*%*
5 – 6	7e	0,017	2
8 – 9	(E)-3e	0,070	8
10 – 11	(E)-3e + (Z)-4e	0,035	4
12 – 14	(Z)-4e	0,096	11
15 – 17	6e + (E)-4e	0,051	6
18 – 19	(E)-4e	0,035	4
20 – 21	5e + (Z)-3e	0,052	6
22 – 30	(Z)-3e	0,450	57

The compounds from the mixed fractions were separated by preparative TLC.

Applying similar procedure, from the reaction mixtures obtained by interaction of 1a, 1b, 1c and 1f with bromine the pure compounds were also isolated (Tables I–5).

Acknowledgements

The authors thank to "National Fund of Science" for the financial support.

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