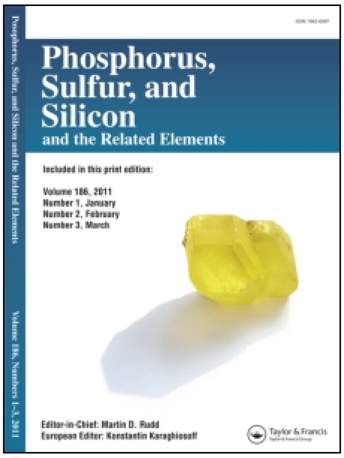

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REACTION OF DIMETHYL ESTERS OF 3-METHYL-1,2-ALKADIENEPHOSPHONIC ACIDS WITH METHYLSULFENYL CHLORIDE—ORIENTATION AND STEREOCHEMISTRY

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REACTION OF DIMETHYL ESTERS OF 3-METHYL-1,2-ALKADIENEPHOSPHONIC ACIDS WITH METHYLSULFENYL CHLORIDE—ORIENTATION AND STEREOCHEMISTRY

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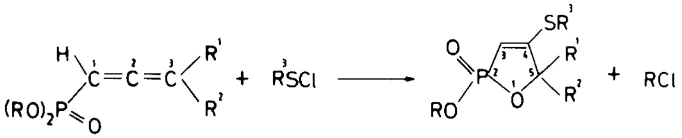
The reaction of 3-methyl-1,2-alkadienephosphonic acid (i.e. 3-alkyl-3-methylsubstituted allenephosphonic) dimethyl esters **1** with methylsulfenyl chloride **2** is oriented mainly to the 1,2-oxaphosphol-3-ene ring products **3a–d** (as diastereoisomeric mixtures when alkyl ≠ CH_3). In low extent common 1,2-adducts **4a–d** as E,Z-mixtures are also formed. The ratio **3**:**4** and, in particular the E:Z ratio rises by increase of the size of the alkyl group at the allenic C^3-atom of **1**. Lowering the temperature of the reaction of **1** and **2** leads to an increase of the annulation stereoselectivity although it remains not very high in the studied temperature interval (−45° – +15°C).

INTRODUCTION

In previous communications[1,2] we have described the reaction of esters of 3,3-dialkyl-substituted allenephosphonic acids with alkyl (aryl)sulfenyl chlorides giving 1,2-oxaphosphol-3-enes, monocyclic or spiro-cyclic at C^5 with cyclohexane ring:



Scheme 1

On the base of ^1H NMR data we have assumed,[1] that in the cases of different alkyl substituents at C^5 ($R^1 \neq R^2$) mixtures of diastereoisomers are formed (chirality of C^5 and P^2), but no attempts for their separation and isolation in individual compounds were made.

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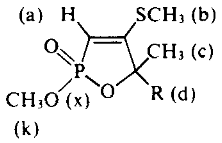
RESULTS

In the present paper we report our detailed investigation on the products of the interaction of dimethyl esters of 3-methyl-substituted 1,2-butadiene, 1,2-pentadiene, 1,2-hexadienephosphonic as well as of 3,4-dimethyl-1,2-pentadienephosphonic acids **1a**, **1b**, **1c** and **1d**, respectively, with methylsulfenyl chloride **2** in order to elucidate the orientation, stereochemistry and mechanism of the reaction.

The qualitative TLC analysis as well as the ^{1}H NMR spectra of the crude reaction mixtures obtained from **1** and **2** show, that besides 1,2-oxaphosphol-3-ene derivatives **3** certain amounts of other products are formed (see Scheme 2 below). By column chromatography using distilled† reaction mixtures the 1,2-oxaphosphol-3-enes **3a–d** (**3b**, **3c** and **3d** as separated pure diastereoisomers and some mixtures of them) were obtained in 46–61% total yields. The ^{1}H NMR, IR and TLC data characterizing the pure diastereoisomers are given in Table I. In the cases of the reaction mixtures containing **3c** and **3d** it was possible to achieve almost complete separation and to determine directly the ratio of diastereoisomers. This is illustrated by ^{1}H NMR spectra of the mixture containing **3c** before and after chromatographic sepa-

TABLE I

Yields, TLC and spectral data of **3a–d**,



obtained by column chromatography of distilled reaction mixtures of **1** and **2** at the reaction temperature −15°C

3	R	Yield %	R_f	Chemical shifts (ppm) H_a	H_b	H_c	H_d	H_k	J (Hz) PH_a	PH_b
3a	CH_3	46	0.20	5.64d	2.44s	1.47s	1.51s	3.67d	25.4	11.6
3b	C_2H_5 (**3b₁**)	50	0.24	5.59d	2.41s	1.49s	0.85t(CH_3) 1.70q(CH_2)	3.72d	26.5	11.5
	C_2H_5 (**3b₂**)		0.26	5.65d	2.41s	1.42s	0.85t(CH_3) 1.70q(CH_2)	3.67d	26.0	11.8
3c	*n*-C_3H_7 (**3c₁**)	55	0.21	5.58d	2.41s	1.48s	0.88t(CH_3) 1.58m(CH_2CH_2)	3.72d	26.5	11.2
	n-C_3H_7 (**3c₂**)		0.27	5.69d	2.45s	1.42s	0.88t(CH_3) 1.58m(CH_2CH_2)	3.67d	26.0	10.5
3d	*i*-C_3H_7 (**3d₁**)	61	0.22	5.44d	2.38s	1.52s	0.92d(CH_3) 1.86m(CH)	3.79d	26.4	11.2
	i-C_3H_7 (**3d₂**)		0.26	5.50d	2.44s	1.51s	1.00d(CH_3) 1.86m(CH)	3.78d	26.8	11.8

3a–d IR(CCl_4): 1540–1562 ($\nu_{C=O}$); 1235–1275 ($\nu_{P=O}$).

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† Collected in a large temperature interval after removal of low-boiling impurities (which made chromatographic separation difficult).

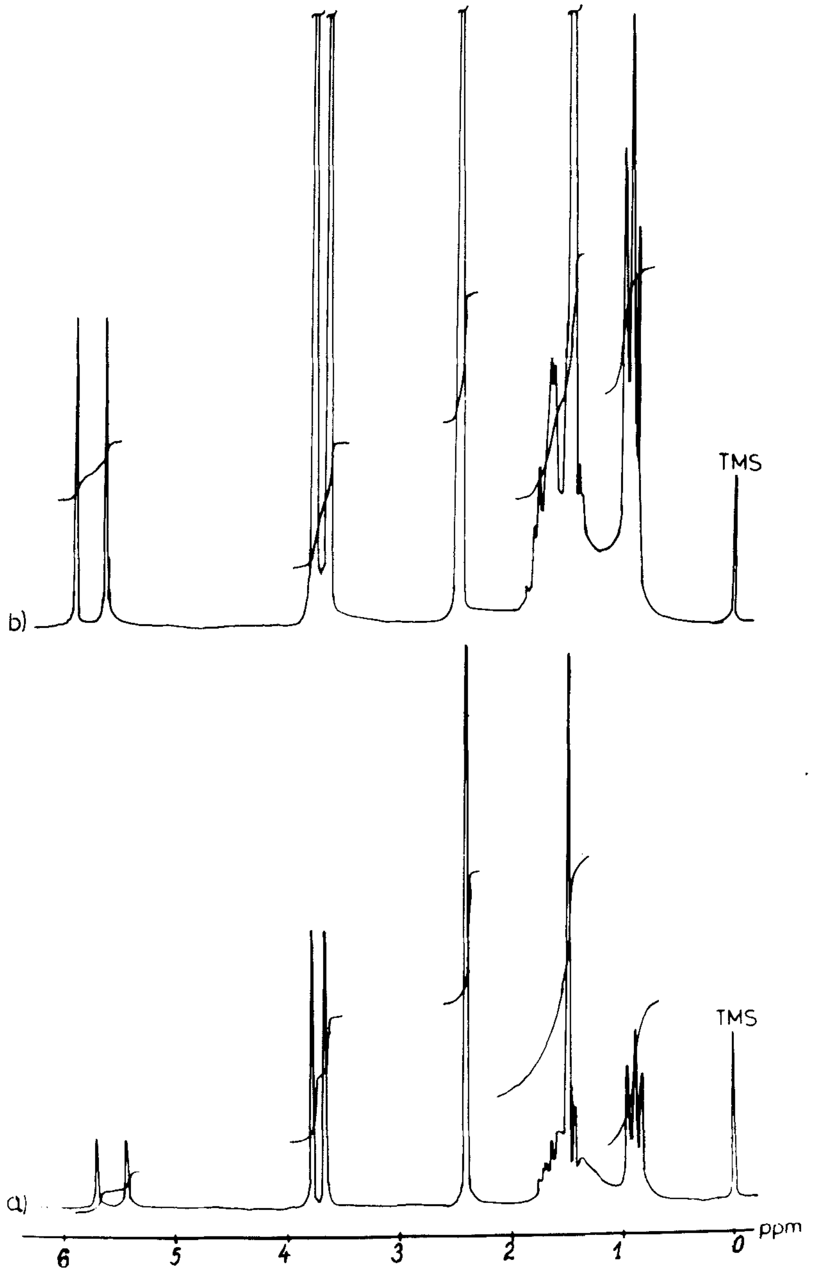


FIGURE 1 ^{1}H NMR spectra of 1,2-oxaphosphol-3-enes: (a) **3c**$_1$ $R_f = 0.21$; (b) **3c**$_2$ $R_f = 0.27$.

ration (absence of double signals at δ (ppm) 5.7, 3.7 and 1.5 for the protons H_a, H_b and H_c in the spectra of the separated pure diastereoisomers **3c**$_1$ and **3c**$_2$; see Table I, Figures 1a, 1b and Figure 2a).

In all cases common 1,2-adducts of **1** and **2**, i.e. 1-chloro-2-methylthio-2-alkenephosphonic esters **4a–d** as E,Z-mixtures were isolated in 8–15% total yields along

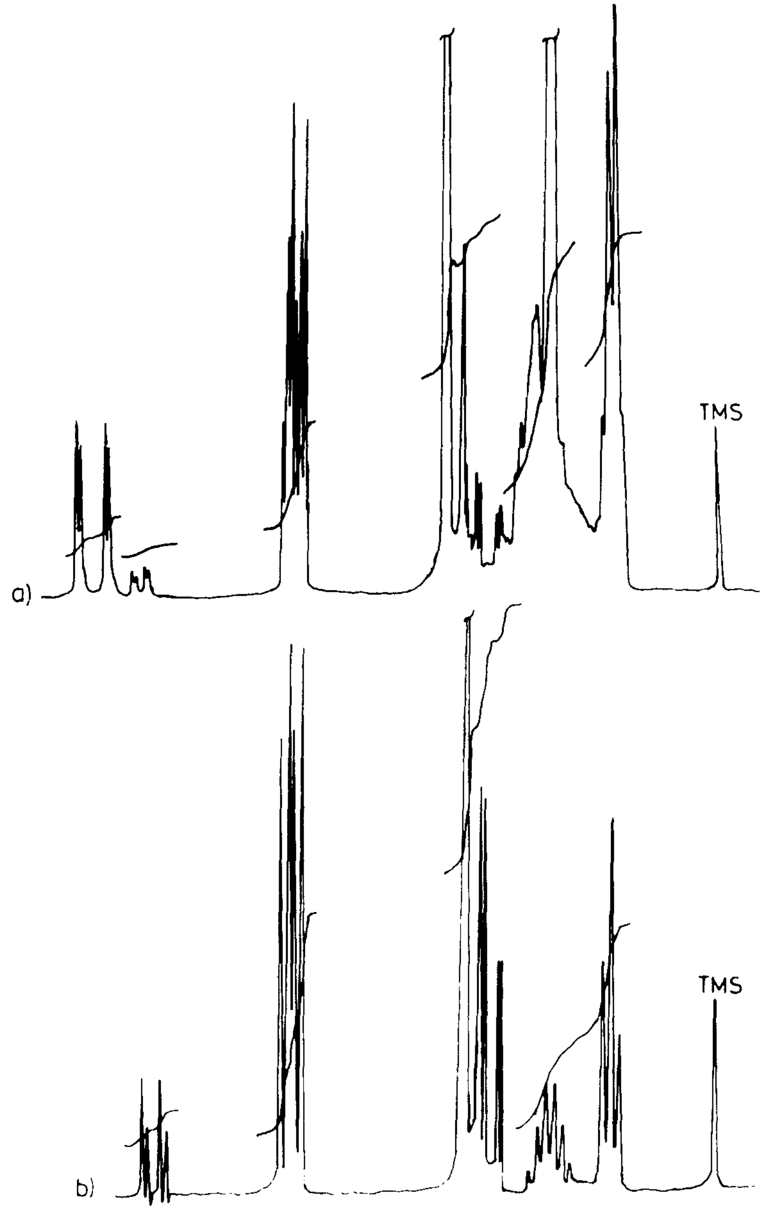
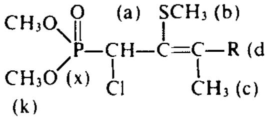


FIGURE 2 (a) ^{1}H NMR spectrum of the reaction mixture obtained from **1c** and **2**. (b) ^{1}H NMR spectrum of (E, Z)—**4c**, isolated after chromatographic separation of the reaction mixtures of **1a** and **2**.

with the main reaction products **3**. The structure and configuration of the adducts were confirmed by their ^{1}H NMR and IR spectra (see data in Table 3 and Figure 2b). They were found to be similar to those of analogous compounds, obtained by other authors.[3] We determined also the E : Z ratio in the cases of **4c** and **4d** with the purpose to clarify its dependence on the size of substituent *R* (see Table 3).

TABLE II

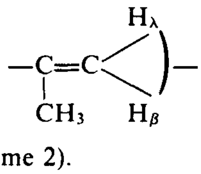
Yields, TLC and spectral data of **4a–d**,  $(CH_3O)_2P(O)-CH(Cl)-C(SCH_3)=C(CH_3)-R$,

obtained by column chromatography of
distilled reaction mixtures of **1** and **2** at the reaction temperature −15°C

4	R	Yield[a] %	R_f[a]	Config.[b]	Chemical shifts (ppm) H_a	H_b	H_c	H_d	H_k	J (Hz) PH_a	PH_k	PH_c
4a	CH_3	15	0.35	—	5.06d	2.21s	1.99d	2.15d	3.79d	15.4	10.9	2.4
4b	C_2H_5	12	0.38	E	5.03d	2.22s	2.10d	1.04t (CH_3) 1.20q (CH_2)	3.74d	15.0	10.0	3.6
				Z	4.99d	2.25s	1.92d	1.04t (CH_3) 1.20q (CH_2)	3.80d	15.6	10.0	2.6
4c	*n*-C_3H_7	13	0.37	E	5.05d	2.24s	2.10d	0.95t (CH_3) 1.45m (CH_2CH_2)	3.67d	15.1	9.3	3.0
				Z	5.00d	2.26s	1.94d	0.95t (CH_3) 1.45m (CH_2CH_2)	3.84d	15.7	9.2	2.2
4d	*i*-C_3H_7	8	0.45	E	5.17d	2.21s	1.99d	1.02d (CH_3) 3.00m (CH)	3.76s	16.0	9.6	3.6
				Z	5.07d	2.25s	1.76d	1.02d (CH_3) 3.00m (CH)	3.83s	16.0	9.4	2.0

4a–d IR (CCl_4): 1260–1261 ($\nu_{P=O}$); 1600–1602 ($\nu_{C=C}$).

[a] Yields and R_f values of the mixtures of isomers E-**4** and Z-**4**.
[b] The ratio E-**4c**:Z—**4c** is 1.7:1; E-**4d**:Z-**4d** is 5.0:1 (from NMR data).

Only in the case of the reaction mixture containing **3a** an additional by-product—3-methyl-2-thiomethyl-1,3-butadienephosphonic ester **5a** (NMR (CCl_4) δppm 2.25(3H, s, SCH_3), 5.71(1H, d, C^1H, $^2J_{HP}$ 15.0 Hz), 5.17 1H, 5.0 1H, 2.01 3H for H_α, H_β and CH_3, typical[4] for  $-\underset{CH_3}{C}=C\begin{smallmatrix}H_\alpha\\ H_\beta\end{smallmatrix}$)— was also isolated in 4% yield (probably formed as shown in Scheme 2).

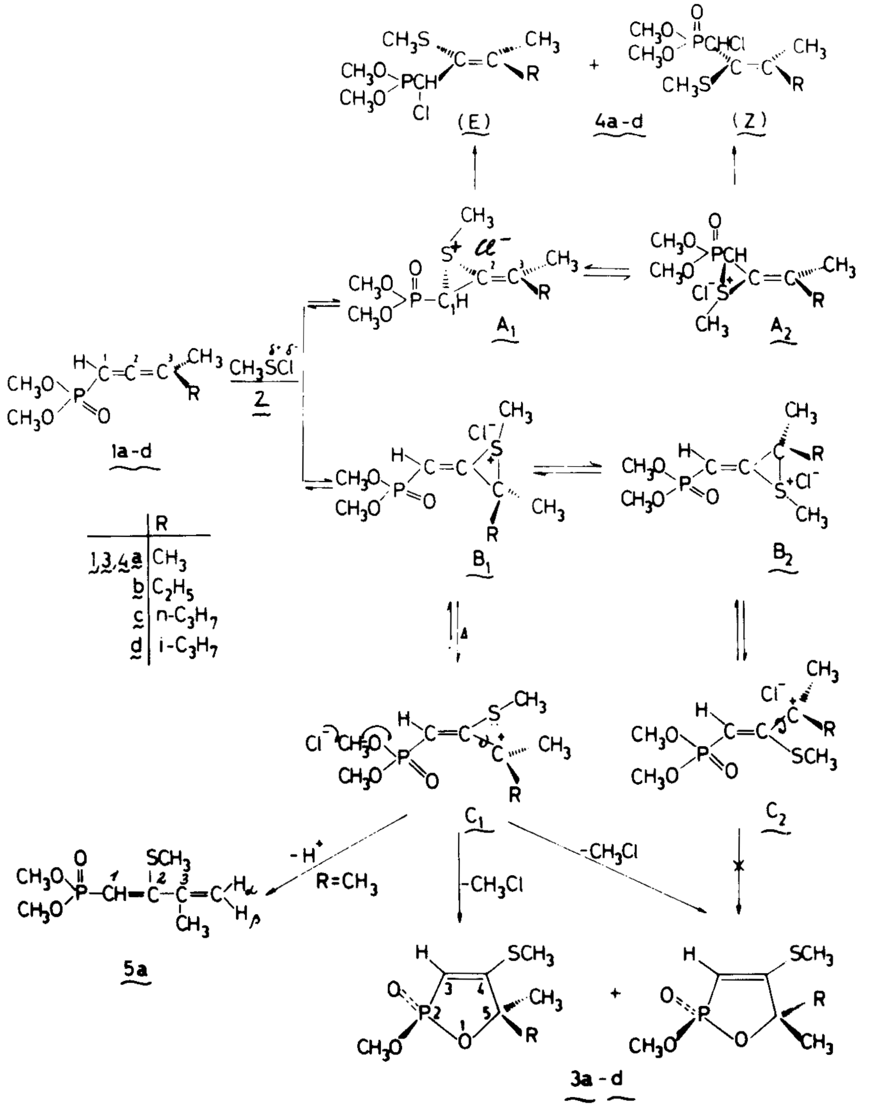
The ratio of the diastereoisomers **3b**$_1$:**3b**$_2$, **3c**$_1$:**3c**$_2$ and **3d**$_1$:**3d**$_2$, determined on the basis of the ^1H NMR spectra of the corresponding reaction mixtures, obtained at −15°C, was found to be in the range 4:1 to 7.7:1.

In the cases of **3c** and **3d** the diastereoisomeric ratio determined both directly by column chromatographic separation or by ^{1}H NMR spectra of the reaction mixtures shows values close to each other (Table II).

In order to elucidate the influence of the reaction temperature on the stereoselectivity of the 1,2-oxaphosphol-3-ene annulation the reaction of **1b** and **1c** with **2** at different temperatures in the range −45°C to +15°C were carried out. The diastereomeric ratios data from these experiments are given in Table II.

DISCUSSION

The results obtained show that the reaction of 3-methyl-3-alkyl-substituted allenephosphonates **1** with **2** leads to the formation mainly of diastereoisomeric mixtures



Scheme 2

TABLE III

Ratio of the diastereomeric oxaphospholenes **3b–d** in the crude reaction mixture (as determined by their ^{1}H NMR spectra)

Crude product	Reaction temperature °C	Diastereomer ratio ($\mathbf{3b_1}$–$\mathbf{d_1}$: $\mathbf{3b_2}$–$\mathbf{d_2}$)
3b	15	3.3 : 1
3b	0	3.8 : 1
3b	−15	4.0 : 1
3b	−45	6.0 : 1
3c	15	2.4 : 1
3c	0	3.5 : 1
3c	−15	7.7 : 1 (6.0 : 1)[a]
3d	−15	4.0 : 1 (3.3 : 1)[a]

[a] Ratio of the isomers obtained by column chromatography of the distilled reaction mixtures. In these cases a small fraction of diastereomeric mixture was isolated.

of five-membered annulenes **3** and in low extent—of common 1,2-adducts **4**. The data for the **3**:**4** ratio also indicate, that by augmentation of the size of the alkyl substituent R at the allenic C^3 of **1** (see the scheme below) the orientation of the reaction of **1** and **2** is shifted partially to the 1,2-addition pathway. Analogous dependence, but in greater extent, is observed for the E:Z ratio of the adducts **4** in the favor of E-isomers. Thus, when *n*-propyl group at the same allenic C^3 is replaced by isopropyl group the ratio **3**:**4** increases 1.8 times, while the increase of the E:Z ratio for the corresponding adducts **4** rises 3 times (compare Table I and III).

The above results are consistent with the following possible mechanism of the reaction of **1** and **2**:

It is well known that the first step of the reaction of allenes with sulfenyl chlorides is the formation of episulfonium ion.[5,6] Its stabilization depends on the ability of sulfur to localize positive charge rather than on the electronic effects of the substituents at the episulfonium ring.[6,7] Therefore in our case four episulfonium ions $\mathbf{A_1}$, $\mathbf{A_2}$ (attack at the allenic C^1–C^2) and $\mathbf{B_1}$, $\mathbf{B_2}$ (attack C^2–C^3) might be formed in principle. The last attack is evidently favored by a stronger stabilizing electronic effects of the substituents CH_3 and R in $\mathbf{B_1}$ and $\mathbf{B_2}$ compared with $\mathbf{A_1}$ and $\mathbf{A_2}$. For this reason 1,2-addition reaction of **1** and **2** proceeds in low extent. This idea is confirmed by further experiments involving compounds with reduced member of alkyl substituents at the same allenic C^3 of **1**[8] where 1,2-addition is the main direction of the reaction. On the other hand by increase of the bulk of *R* the equilibrium $\mathbf{A_1} \rightleftharpoons \mathbf{A_2}$ is obviously shifted towards the ion $\mathbf{A_1}$ leading in this way to an increase of E:Z ratio of the 1,2-adducts **4**.

The presence of two alkyl groups at the episulfonium ring of the ions $\mathbf{B_1}$ and $\mathbf{B_2}$ is evidently a reason for the existence of equilibrium between these ions and the corresponding tertiary carbenium ions $\mathbf{C_1}$ and $\mathbf{C_2}$. The intramolecular P=O attack on the positively charged tertiary C atom in $\mathbf{C_2}$ (or on the same atom in $\mathbf{B_2}$) is sterically extremely unfavored, and therefore the 1,2-oxaphosphol-3-ene annulation proceeds exclusively via ion $\mathbf{B_1}$ and $\mathbf{C_1}$ under elimination of CH_3Cl in an Arbuzov second-step process. Increasing the reaction temperature the equilibrium $\mathbf{B_1} \rightleftharpoons \mathbf{C_1}$ is evidently shifted towards the ion $\mathbf{C_1}$ thus lowering the stereoselectivity of the 1,2-oxaphosphol-3-ene annulation pathway of the reaction of **1** and **2**. The stronger the stabilizing effect of R in $\mathbf{C_1}$, resp. $\mathbf{B_1}$, the greater extent of annulation is observed as compared with the 1,2-addition pathway of the reaction (increase of the yields of **3** and decrease those of **4**, see Tables 1 and 3). Another possibility for stabilization of the carbenium ion C_1 is a proton elimination leading in the case $R{=}CH_3$ to the formation of the 1,3-alkadienephosphonic ester **5a**.

EXPERIMENTAL

The qualitative TLC investigations were carried out on silicagel "Merck" 60 F_{254} pre-coated aluminium sheets, using ethylacetate-heptane 2:1 as a mobile phase, threefold development.

The column chromatographic separation was performed on silicagel "Merck" 60 0.060–0.200 mm.

The ^1H NMR spectra were measured on a JEOL JNM-PS-100 spectrometer at 100 MHz, in some cases on spectrometer TESLA BS 487C at 80 MHz at normal probe temperature in $CDCl_3$ or CCl_4, or mixture of them. The chemical shifts are relative to internal TMS or (in a few cases) HMDSO $(Me_3Si)_2O$.

The starting dimethyl esters of 3-methyl-1,2-alkadienephosphonic acids **1a–d** were obtained by the procedure described in the literature.[9]

Experiments on the Orientation of the Reaction of 1a–d with 2 and Temperature Dependence of the Stereoselectivity of the 1,2-Oxaphosphol-3-ene Annulation. *General procedure:* The reaction of 3-methyl-1,2-alkadienephosphonic dimethyl esters **1a–d** was carried out by the procedure described earlier,[1] but at temperatures −45°, −15°, 0° and +15°C as shown in Table I. Samples of the obtained crude reaction mixtures were used for ^1H NMR determination of the diastereoisomeric ratio **3b**, **3c** and **3d**. The reaction mixtures were then distilled and after removal of the solvent and low-boiling impurities (as CH_3Cl formed and unreacted starting CH_3SCl) all volatile products were collected in vaccuo in a large temperature interval. The mixtures of reaction products were then separated by column chromatography.

Column Chromatographic Separation of the Reaction Mixtures. *General procedure:* 0.50–0.70 g of the reaction mixture, absorbed on silicagel were inserted into a column (height 100 cm, diameter 3 cm) containing 75–100 g silicagel in heptane. Then heptane/ethylacetate mixtures with increased polarity were used as an eluent, the last portion being a pure ethylacetate. Fractions of each 80 ml were collected at a rate 420 drops/min. Fractions nos. 20–30 contained 1,2-adducts **4a–d** (**4b, c, d** as E and Z isomers). The 1,2-oxaphospholene **3a** was collected in fractions nos. 40–65. In the case of **3b**, **3c** and **3d** the higher R_f-value diastereoisomers $\mathbf{3b_2}$, $\mathbf{3c_2}$ and $\mathbf{3d_2}$ were isolated from the fractions nos. 40–45, the diastereoisomers with lower R_f values—from the fractions nos. 60–65. The 3-methyl-2-thiomethyl-1,3-butadienephosphonic ester **5a** was isolated from fractions nos. 35–40.

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