CHEMO-, REGIO- AND STEREOSELECTIVITY AND MECHANISM OF THE HETEROCYCLIZATION REACTION OF DIALKYL(5-METHYL-1,3,4-HEXATRIEN-3-YL)PHOSPHONATES WITH METHYLSELENENYL CHLORIDE

Tchonka N. Tancheva[+], Christo M. Angelov*, and Diana M. Mondeshka[+]
*Department of Chemistry, Higher Pedagogical Institute,
9700 Shoumen, Bulgaria
[+]Department of Organic Chemistry, Higher Institute of Chemical Technology, 1156 Sofia, Bulgaria

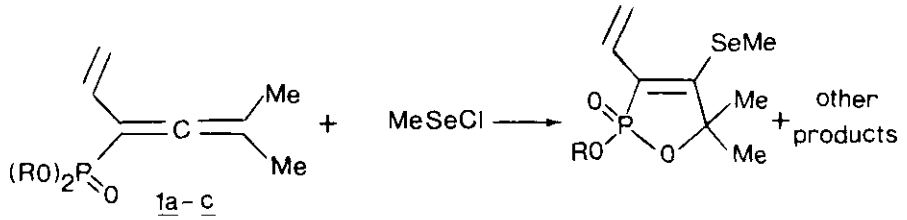
Abstract - The reaction path of dialkyl(5-methyl-1,3,4-hexatrien-3-yl)-phosphonates with methylselenenyl chloride was investigated in details. The spectral and chromatographic studies indicate that alongside the main reaction products - 2,5-dihydro-1,2-oxaphospholes, three different selenophenephosphonates and 1,3-alkadienylphosphonate are obtained too, i.e. the interaction of 1a-c with methylselenenyl chloride is regio-selective but not chemo- and stereoselective reaction.

INTRODUCTION

The accessibility of the dialkyl (5-methyl-1,3,4-hexatrien-3-yl)phosphonates[1] and their rather interesting system of double bonds provided the grounds in recent years for systematic studies on their reactivity with respect to electrophiles. It was shown that depending on the nature of the reagent they afford various classes of heterocyclic compounds[2-4]. We reported recently the preparation in good yields of 3-vinyl-substituted 2,5-dihydro-1,2-oxaphosphole 2-oxides starting from the above triene phosphonates and sulfuryl or selenenyl chlorides[4]. Bearing in mind the fact that selenenyl chlorides are analogous to sulenyl chlorides it seemed reasonable to expect that the thiophene cyclization[2] observed with sulfenyl chlorides should also proseed in this case. Based on this consideration we presently describe the detailed spectroscopic and chromatographic results on the products isolated from the crude reaction mixtures obtained from 1a-c with MeSeCl with the view to investigating the chemo-, regio- and stereoselectivity and mechanism of the reaction*.

RESULTS

The reaction of the dialkyl (5-methyl-1,3,4-hexatrien-3-yl)phosphonates 1a-c with methylselenenyl chloride are conducted according to the procedure described earlier[4] The ^{1}H-NMR spectra of the crude reaction products revealed the presence of signals from the 3-vinyl-2,5-dihydro-1,2-oxaphosphole 2-oxides 2a-c and the signals of other products:



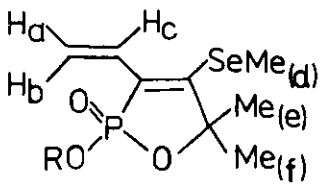
The side products, judged from spectral data, are 10-12% when starting from 1a, 8-10% when starting from 1b and do not exeed 5-7% when starting from 1c. The preliminary results indicate that the interaction between the esters 1a-c and MeSeCl does not proceed in one direction only. This is not surprising bearing in mind the rather complex system of double bonds they possess. With the view to obtaining all products produced by the above reaction in pure form we subjected to column chromatography the crude reaction mixtures. The individual compounds had very close R_f values which rendered their separation very difficult. In most cases were obtained mixed fractions enriched in one of the components which then were divided by preparative TLC. The purity of the individual compounds was monitored by qualitative thin-layer chromatography and spectral methods. We succeeded in isolating and identifying spectrally in pure form all products arising from 1a and enriched in individual selenophenephosphonates fraction from 2b and 2c. First leave the column the oxaphospholes 2a-c. They all exibit spectral characteristics very similar to the ones described in ref. 4 (Table 1). The ^{31}P chemical shifts for 2a-c are typical for this type of compounds[5]. From the remaining four groups of isolated compounds (1c afforded only traces of one of them), three contain a selenophene ring and

*Chemoselectivity will be related to the preference for attack of the one double bond of the comulated dienic system.

Regioselectivity is related to the relative positions of nucleophile and electrophile on the reacting double bond.

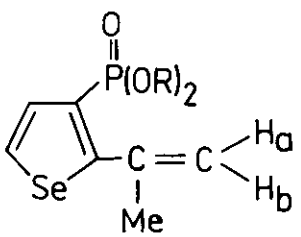
Stereoselectivity refer to the type of the chemical transformation of the reaction's intermediate.

Table 1. TLC and ^{1}H- and ^{31}P-NMR data of 2a-c obtained by column chromatography



No	R	R_f	Chemical shifts, δ (ppm)						Coupl. Constants J Hz		
			^{31}P	Ha	Hb	Hc	Hd	He,f	a-b a-c	b-c P-a	P-b P-c
2a	Me	0.58	31.7	5.57ddd	5.90ddd	6.53ddd	2.26s	1.54s 1.63s	1.0 11.6	17.8 2.1	1.0 28.2
b	Et	0.60	30.0	5.50ddd	5.81ddd	6.54ddd	2.23s	1.50s 1.59s	1.0 10.9	17.6 2.0	0.8 28.0
c	Pr^i	0.61	29.2	5.46ddd	5.82ddd	6.51ddd	2.20s	1.47s 1.56s	0.8 11.0	17.8 2.0	1.0 28.2

Table 2. TLC and ^{1}H- and ^{31}P-NMR data of 3a-c obtained by colmn chromatography



No	R	R_f	Chemical shifts, δ (ppm)						Coupl. Constants, J Hz			
			^{31}P	H-4	H-5	Ha	Hb	Me	H^4-H^5 Ha-Hb	H^4-P H^4-Se	H^5-P H^5-Se	Me-Ha Me-Hb
3a	Me	0.41	16.6	7.43dd	7.83dd	5.25dd	5.20dd	2.14dd	6.0 (0.8)	4.3 (8.8)	3.0 (46.1)	1.2 (1.5)
b	Et	0.43	14.4	7.40dd	7.85dd	5.18dd	5.15dd	2.12dd	5.9 (0.6)	4.1 (8.6)	2.9 (46.3)	1.0 (1.5)
c	Pr^i	0.42	14.1	7.44dd	7.76dd	5.24dd	5.16dd	2.15dd	5.8 (0.8)	4.3 (8.7)	3.0 (46.3)	1.1 (1.6)

are formed in various ratios depending on 1a-c. On the basis in their ^{1}H- and ^{31}P-NMR spectra we ascribe to them the following structures. Compound 1a with MeSeCl except 2a affords as main product 2-isopropenyl-3-dimethoxyphosphonyl-selenophene 3a

(Table 2). The esters 3b and 3c are present in lesser amounts. The structure of 3a-c are assigned on the following grounds: i) The ^{1}H-NMR signals for aromatic protons appear in the 7.40 - 7.85 ppm region and are assigned to the C-4 and C-5 of the selenophene ring forming a part of an ABX system because of their interaction with phosphorus. ii) Protons typical for isopropenyl group[6] are observed too. The spin-spin interaction between the methyl group protons and the Ha, a trans-allylic interaction, is small and the the signal for Ha is narrower. Conversely, the spin-spin

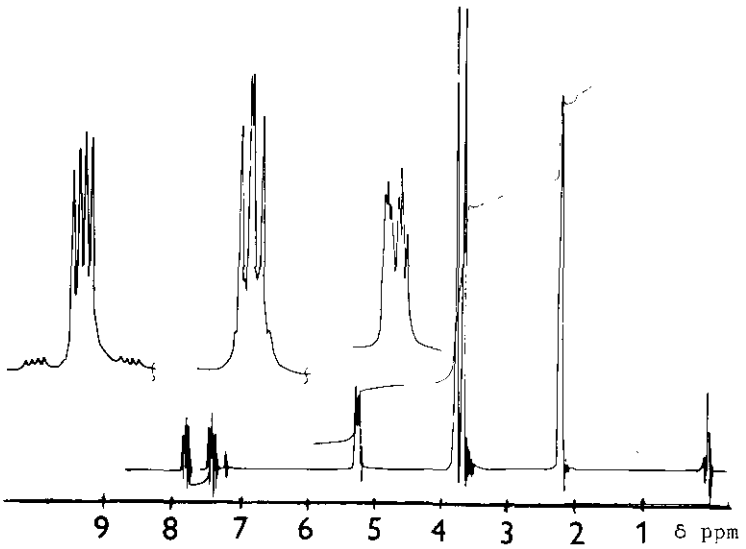
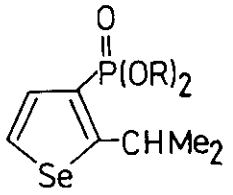


Fig. 1 ^{1}H-NMR Spectrum of 2-isopropenyl-3-dimethoxyphosphonylselenophene (3a).

Table 3. TLC and ^{1}H- and ^{31}P-NMR data of 4a-c obtained by column chromatography



No	R	R_f	Chemical shifts δ (ppm)					Coupl. Constants J Hz					
			^{31}P	H-4	H-5	CH	2Me	H^4-H^5	H^4-P	H^5-P	H^4-Se	H^5-Se	H-Me
4a	Me	0.51	17.4	7.38dd	7.86dd	3.95qq	1.35d	5.8	4.1	2.8	9.3	48.2	7.0
b	Et	0.54	15.6	7.24dd	7.8dd	3.88qq	1.30d	5.6	4.0	3.1	9.0	48.0	6.9
c	Pr^i	0.55	15.0	7.29dd	7.75dd	3.90qq	1.34d	5.7	4.2	2.9	9.1	47.8	7.0

d - doublet, q - quartet.

interaction between the methyl group protons and Hb, a cis-allylic interaction, is

greater and leads to a wider signal for Hb. The peak of the methyl protons is broader; on expansion they appear as a quartet clealy reflecting the multiplcities of Ha and Hb thus allowing the exact determinaton of the size of the vicinal and geminal constants. iii) The ^{31}P chemical shift appear in a region typical for phosphnate structure[7]. On Fig. 1 the spectrum of 3a is shown.

The selenophene 4a-c are present in a lesser amount than 3a-c. They have very close R_f values to the ones of 2a-c and are eluted from the column together with their last fractions and another product with a higher R_f value. This compounds were isolated in pure form by means of preparative TLC. They are structurally similar to 3a-c with the exception that they have an isopropyl group in position 2 (Table 3). The ^1H-NMR spectra of 4a (Fig. 2) and of 4b, 4c are very similar to these of analoguous thiophene phosphonates[2]. The structure of compounds 5a-c is especially interesting.

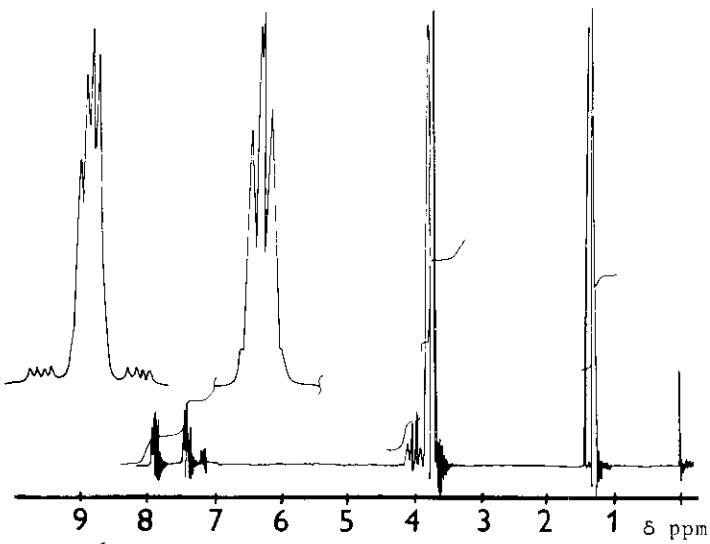
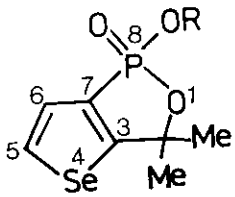


Fig. 2 ^1H-NMR Spectrum of 2-isopropyl-3-dimethoxyphosphonylselenophene (4a).

Table 4. TLC and ^1H- and ^{31}P-NMR data of 5a-c obtained by column chromatography



No	R	R_f	Chemical shifts, δ (ppm)				Coupling Constants, J Hz				
			^{31}P	Ha	Hb	2Me	a-b	a-P	b-P	a-Se	b-Se
5a	Me	0.38	35.4	8.02dd	7.21dd	1.66s,1.70s	5.2	3.9	2.6	43.8	8.0
b	Et	0.40	33.6	8.03dd	7.29dd	1.65s,1.72s	5.3	3.5	2.5	44.0	8.2
c	Pr^i	0.39	32.8	8.04dd	7.10dd	1.68s,1.72s	5.1	4.0	2.7	44.1	8.2

These phosphonates contain two heterocycles one of which is a selenophene and the other a 2,5-dihydro-1,2-oxaphosphole (Table 4). They are formed in lesser amounts than 3a-c but in greater amounts than 4a-c. The substances 5a-c are eluted from the column last. Their structure is based on the following considerations: i) Typical proton signals for a selenophene ring are present in the ^{1}H-NMR spectra[8]. ii) Two oxaphosphole ring methyl proton signals are seen as nonequivalent because of their different interactions with the substitents at phosphorus. Their chemical shifts are in a region typical for compounds with oxaphosphole structure[9-11]. iii) The chemical shift of phosphorus is characteristic for oxaphosphole compounds[4]. iv) The integral intensity for the alkoxy group at phosphorus corresponds to one ester function. On Fig. 3 the ^{1}H-NMR spectrum of 5a is shown. The obtained selenophosphonates contain about 8% the isotope ^{77}Se which is magnetically active and interacts with other nuclei. This interaction becomes evident with the protons at the α and β carbons of the selenophene ring[16] which exhibit symmetric satelite signals on enhancement of the main signal (Fig. 1, 2 and 3). The dialkyl 1-chloro-4-methylseleno-5-methyl-2,4-hexadiene-3-phosphonates 6a-c were isolated in the smallest amounts on chromatographic separation. The compound 6a was isolated in pure state, while 6b and 6c were obtained as a mixture with 2b, 2c and 4b, 4c. The ^{1}H-NMR spectrum of 6a (Fig. 4) suppors unequivocally its structure since it contains two doublets for the two methyl groups at C-5. The spin-spin interaction of these protons corresponds to their Z and E position with respect to the P=O group[12]. The C-2 proton signal appears downfield and has a spin-spin coupling constant with phosphorus of 19.8 Hz characteritic for the two trans nuclei, while the chloromethylene group protons resonate as two doublet with a $J_{H,P}$ of 2.1Hz which speaks in favour of a cis-allylic interaction[14]. These spectral characteristics determine the configu-

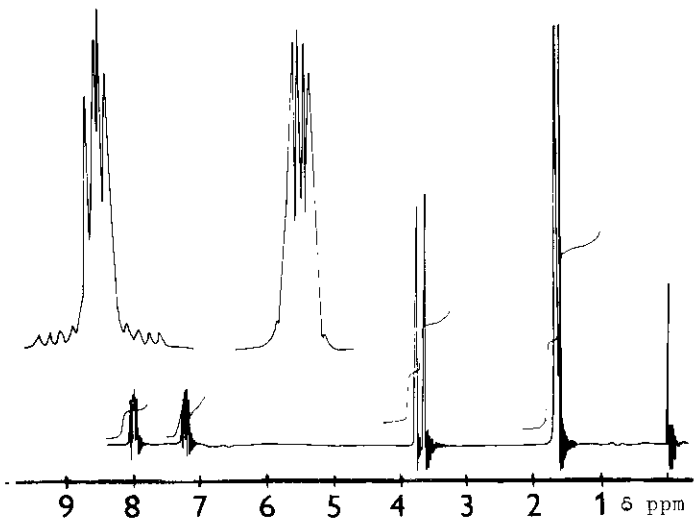


Fig. 3 ^{1}H-NMR Spectrum of 8-methoxy-2,2-dimethyl-1-oxa-8-phospha-4-selena-bicyclo- 3,3,0 -3,5-octadiene 8-oxide (5a).

ration of the synthesized diene phosphonate. The chemical shift of phosphorus (δ 12.7 ppm) is in agreement with literature data[15]. The quantities of the described side products in the reaction mixtures of the ethyl and isopropyl esters 1b, c decreases, as was already mentioned above, a trend that renders their separation difficult and not always possible. Regrdless of the small amounts of reaction mixtures obtained from MeSeCl and 1b,c the ^{31}P-NMR spectra indicate the presence of all mentioned above structures.

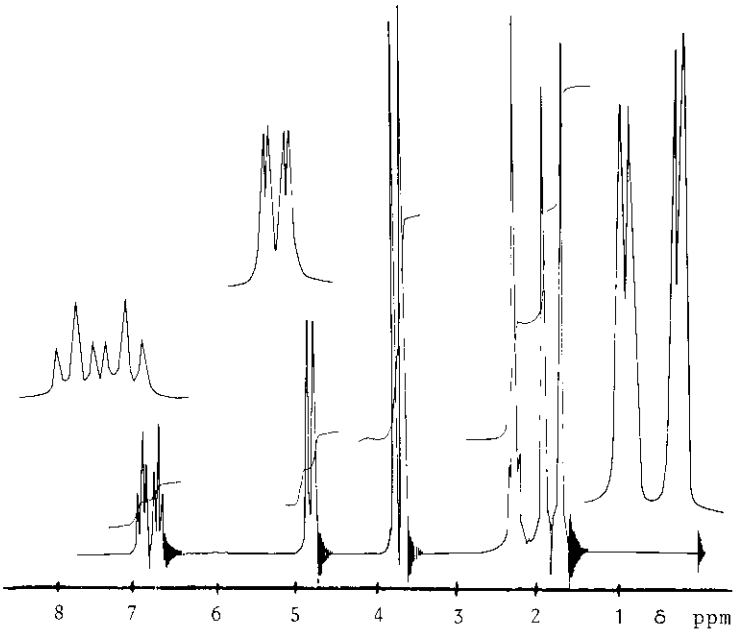
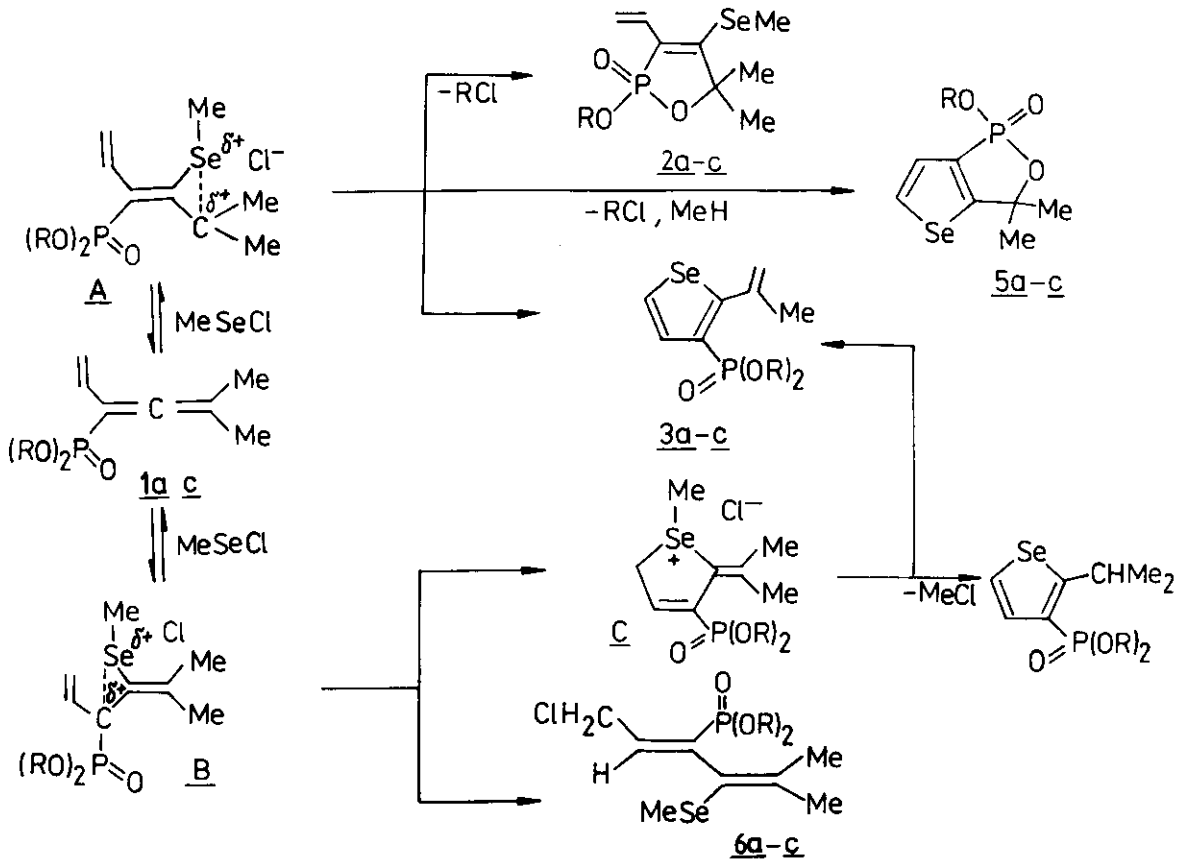


Fig. 4 ^{1}H-NMR Spectrum of dimethyl 1-chloro-4-methyl-seleno-5-methyl-2,4-hexadiene-3-phosphonate (6a).

DISCUSSION

The spectral and chromatographic studies conducted on crude reaction mixtures obtained from 1a-c and MeSeCl indicate that together with the main reaction - oxaphosphole heterocycliztion - four other reaction courses are observed. Since selenenyl chlorides are polar reagens we assume the first step of the reaction to be an electrophilic attack of the selenium atom upon the allene double bond system (see Scheme). The C-4 and C-5 double bond is obviously of higer electron density which should favour the reaction and the formation of the unsymmetric episelenium ion A, which explains the formation of oxaphospholes as the main reaction products. Moreover the intermediate ion A simultaneously leading to selenophene and oxaphosphole heterocyclizaions affording the bicyclic compounds 5a-c. The unsymmetric ion B which gives further the intermediate C can also be assumed to exist, albeit in minor amount. Compounds 3a-c and 4a-c arise from the intermediate C. The 1,3-diene phosphonates 6a-c arising as a result of 1,4-addition of the MeSeCl also support the formation of ion B. The selenophenes 3a-c can take place via ion A as well with the simultaneous elimination of hydrogen chlride and methane. The decreased yields of the side products obtained from 1b and 1c and selenenyl chloride can be


-RCl
2a-c
-RCl, MeH
5a-c
A
MeSeCl
1a c
MeSeCl
B
3a-c
C
-MeCl
6a-c

explained with the positive inductive effect of the alkyl groups which increase the electron density of the phosphoryl oxygen and facilitate in this manner oxaphosphole cyclization.

It is worth noting that regardless of the existing analogy between selenenyl chlorides and sulfenyl chlorides, the interaction between MeSCl and the above esters does not afford the thiophene analogues of compounds 3a-c and 5a-c. On the other hand thiophene cyclization to the analogues of 4a-c proceeds to a greater extent[2]. A possible explanation lies in the different stabilities of the episelenonium and episulfenium ions.

EXPERIMENTAL

Analytical Methods. ^{1}H- and ^{31}P-NMR Spectra were recorded on JNM-PS-100 (100 MHz) FX 90 (90 MHz) and Brucker (250 MHz) spectrometrs at normal probe temperatures in $CDCl_3$. The chemical shifts of ^{1}H and ^{31}P are relative to internal TMS or HMDSO and 85% H_3PO_4.

Starting Materials. The crude reaction mixtures of 1a-c with MeSeCl were obtained according literature data[4].

Column and TLC Chromatography. The qualitative TLC investigations were carried out on silicagel "Merck" 60 F_{254} precoated aluminium sheets, using hexane/ethyl acetate 2.3:1 as a mobile phase, two- or threefold developement. The column chromatographic separation was performed on silica gel "Merk" 60 (0.063 - 0.200 mm).

A.General Procedure for the Column Chromatograhic Separation of the Reaction Mixtures. The reaction mixtures (0.90 - 1.10 g) absorbed on silica gel were inserted into a column (high 140 cm, diameter 2.5 cm) containing 110 - 130 g silica gel in hexane. Hexane/ethyl acetate mixtures with increased polarity were used as eluant, the last portion being pure ethyl acetate. Fractions 70 ml each were collected at a rate of elution about 360 drops/min. Fractions nos. 22-31 (20-32; 19-33) contained pure 1,2-oxaphosphole 2a (2b, 2c resp.), fractions nos. 32-49 (33-45; 34-46) contained a mixture of 2a, 4a and 6a (2b, 4b and 6b; 2c, 4c and 6c resp.), fractions nos. 50-54 (46-49; 47-51) a mixture of the 4a and 3a (4b, 3b and 4c,3c resp.), fractions nos. 54-58 (46-48; 47-49) pure 3a (3b, 3c resp.) and fractions nos 66-74 (64-68; 63-66) the bicyclic compound 5a (5b, 5c resp.).

B. Preparative TLC Separaion. The fraction mixtures 32-49 and 50-54 (46-49; 47-51 resp.) were subsequently subjected to TLC on precoated silica gel "Merck" 60 F_{254} plates (200/200 mm) using ethyl acetate/hexane (2.3:1) as eluant. Compounds 2a

4a, 6a and 3a, 4a (3b and 4b; 3c and 4c resp.) were isolated in pure state after a two-fold development. The purity of the compouns was followed by TLC.

ACKNOWLEDGMENT

The authors are indebted to Dr. Otto Dahl (The H. C. Ørsted Institute, University of Copenhagen, Denmark) for the ^{31}P-NMR spectra.

REFERENCES

1. Ch. M. Angelov, M. Kirilov and B. I. Ionin, Zh. Obshch. Khim., 1979, 49, 1960.

2. Ch. M. Angelov and K. V. Vachkov, Tetrahedron Lett., 1981, 22, 2517.

3. Ch. M. Angelov, N. M. Stojanov and B. I. Ionin, Zh. Obshch. Khim., 1982, 52, 178.

4. Ch. M. Angelov and Ch. Zh. Christov, Synthesis, 1984, 664.

5. Ch. M. Angelov, Heterocycles, 1983, 20 791.

6. A. V. Dogadina, B. I. Ionin and A. A. Petrov, Zh. Obshch. Khim., 1972, 42, 1919.

7. D. W. Allen, B. G. Hutley and M. I. Mellor, J. Chem. Soc., Perkin II, 1972, 63.

8. Ch. M. Angelov and Ch. Zh. Christov, Phosphorus and Sulfur, 1983, 15, 373.

9. Ch. M. Angelov and Ch. Zh. Christov, Zh. Obshch. Khim., 1980, 50, 1891.

10. Ch. M. Angelov and Ch. Zh. Christov, Phosphorus and Sulfur, 1983, 15, 205.

11. R. S. Macomber, G. A. Krudy, K. Seff and L. E. Rendon-Dizmiron, J. Org. Chem., 1983, 48, 1425.

12. Ch. M. Angelov, K.V. Vachkov, J. Petrova and M. Kirilov, Phosphorus and Sulfur, 1982, 14, 7.

13. A. V. Dogadina, K. S. Migaleva, B. I. Ionin and A. A. Petrov, Zh. Obshch. Khim., 1972, 42, 2186.

14. A. M. Shekhade, V. I. Zakharov, V. M. Ignat'ev, B. I. Ionin and A. A. Petrov, Zh. Obshch. Khim., 1978, 48, 55.

15. V. K. Brel', A. V. Dogadina, B. I. Ionin and A. A. Petrov, Zh. Obshch. Khim., 1980, 50, 1246.

16. M. P. Simonin, M. J. Pauet, J. M. Gense and C. Paumier, Org. Magn. Resonance, 1976, 8, 508.

Received, 29th October, 1984