CONCLUSIONS

1. Methyl phenylphosphinate reacts with tetracyclone in the absence of catalysts according to a scheme involving 1,4 and 1,6 addition of the conjugated cyclone system to form methyl 2,3,4,5-tetraphenyl-4-cyclopenten-1-one-3-phenylphosphinate and 2,3,4,5-tetraphenyl-3-cyclopenten-1-one-2-phenylphosphinate, respectively.

2. Upon heating, the 1,6 adduct is prototropically isomerized to form methyl 2,3,4,5-tetraphenyl-4-cyclopenten-1-one-2-phenylphosphinate and simultaneously dissociates back to the original components, which again react to form the thermodynamically more stable 1,4 adduct.

3. The β- and γ-conjugated keto phosphinates with a cis configuration of the methylidyne proton and the phosphinate group have been isolated in the form of pairs of diastereomers with respect to the asymmetric phosphorus and carbon atoms.

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SYNTHESIS AND MASS SPECTRA OF SOME PHOSPHADIPEPTIDES

V. F. Sizoi, G. Nurgalieva, Yu. S. Nekrasov, A. É. Shipov, M. S. Vaisberg, T. A. Mastryukova, and M. I. Kabachnik

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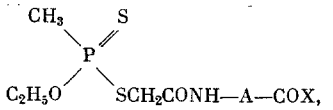
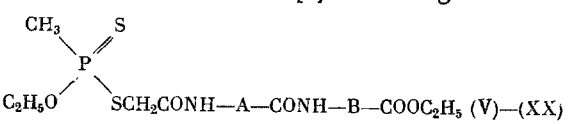
The search for new, highly selective organothiophosphorus insecticides and acaricides has previously [1] led to the synthesis of a number of derivatives of O-ethyl methyldithiophosphonic acid containing residues of amino acids or their esters in the alkanethiol radical with the general formula



$X = OH$ or OC_2H_5, $A = CH_2$ (I), $CH(CH_3)$ (II), $CH(C_3H_7\text{-}i)$ (III), CH_2CH_2 (IV).

In the further development of this investigation we synthesized similar organothiophosphorus derivatives containing dipeptide fragments in the alkanethiol radical [2] with the general formula



where A and B are CH_2, $CH(CH_3)$, $CH(i\text{-}C_3H_7)$, and CH_2CH_2 groups in various combinations. The synthesis of these compounds was carried out by reacting the corresponding O-ethyl methyldithiophosphonates (I-IV, X = OH) [1, 3] with ethyl esters of amino acids in the presence of N,N'-dicyclohexylcarbodiimide (DCCI).

$$CH_3(C_2H_5O)P(S)SCH_2CONH\text{—}A\text{—}COOH + NH_2\text{—}B\text{—}COOC_2H_5 \xrightarrow{DCCI} \rightarrow CH_3(C_2H_5O)P(S)SCH_2CONH\text{—}A\text{—}CONH\text{—}B\text{—}COOC_2H_5$$

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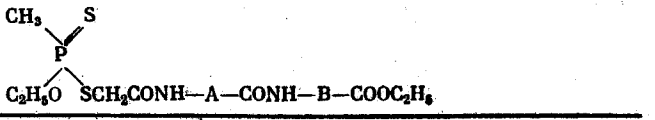
TABLE 1. Constants and Analyses of the Phosphadipeptides



Compound	A	B	Yield, %	mp, °C	Found, %				Empirical formula	Calculated, %			
					C	H	N	P		C	H	N	P
(V)	CH_2	CH_2	86,5	78,5–79,5	37,4	6,0	7,6	8,6	$C_{11}H_{21}N_2O_5PS_2$	37,1	5,9	7,8	9,0
(VI)	CH_2	$CH(CH_3)$	67,1	81–82	38,8	6,1	7,5		$C_{12}H_{23}N_2O_5PS_2$	38,8	6,0	7,6	
(VII)	CH_2	$CH(C_3H_7\text{-}i)$	71,4	Oil				7,8	$C_{14}H_{27}N_2O_5PS_2$				7,8
(VIII)	CH_2	CH_2CH_2	88,0	52–53				8,2	$C_{12}H_{23}N_2O_5PS_2$				8,4
(IX)	$CH(CH_3)$	CH_2	89,6	120–125				8,2	$C_{12}H_{23}N_2O_5PS_2$				8,4
(X)	$CH(CH_3)$	$CH(CH_3)$	84,5	Oil			7,5		$C_{13}H_{25}N_2O_5PS_2$			7,3	
(XI)	$CH(CH_3)$	$CH(C_3H_7\text{-}i)$	93,4	Oil				7,5	$C_{15}H_{29}N_2O_5PS_2$				7,5
(XII)	$CH(CH_3)$	CH_2CH_2	76,0	69,5–70,5	40,6	6,7	7,1	7,7	$C_{13}H_{25}N_2O_5PS_2$	40,6	6,5	7,3	8,0
(XIII)	CH_2CH_2	CH_2	87,5	90–91	39,0	6,0	7,6	8,4	$C_{12}H_{23}N_2O_5PS_2$	38,9	6,0	7,6	8,4
(XIV)	CH_2CH_2	$CH(CH_3)$	54,2	63–68	40,6	6,3	7,4	8,1	$C_{13}H_{25}N_2O_5PS_2$	40,6	6,5	7,3	8,0
(XV)	CH_2CH_2	$CH(C_3H_7\text{-}i)$	55,2	82–83				7,2	$C_{15}H_{29}N_2O_5PS_2$				7,5
(XVI)	CH_2CH_2	CH_2CH_2	72,4	Oil				7,8	$C_{13}H_{25}N_2O_5PS_2$				8,0
(XVII)	$CH(C_3H_7\text{-}i)$	CH_2	75,0	107–108	42,5	6,9	7,1	7,8	$C_{14}H_{27}N_2O_5PS_2$	42,2	6,8	7,0	7,8
(XVIII)	$CH(C_3H_7\text{-}i)$	$CH(CH_3)$	52,8	130–133	43,5	7,1	6,7	7,4	$C_{15}H_{29}N_2O_5PS_2$	43,7	7,1	6,8	7,5
(XIX)	$CH(C_3H_7\text{-}i)$	$CH(C_3H_7\text{-}i)$	66,3*	114–119 144–145	46,5	8,0	6,4		$C_{17}H_{33}N_2O_5PS_2$	46,4	7,6	6,4	
(XX)	$CH(C_3H_7\text{-}i)$	CH_2CH_2	79,7	88–88,5	43,6	7,2		7,4	$C_{15}H_{29}N_2O_5PS_2$	43,7	7,1		7,5

*Total yield of the two diastereomeric fractions.

TABLE 2. Mass Spectra of $Me(EtO)P(S)SCH_2CONHCH(R)COOH$ (I-III)

Ion	(I)	(II)	(III)	Ion	(I)	(II)	(III)
M+	10*	7	18	$Me(EtO)PS_2$+	—	—	11
M—H_2O+	14	9	11	Me(EtO)P(OH)SH+	97	46	33
M—EtO+	—	2	—	Me(EtO)P(O)SH+	33	13	—
M—EtOH+	4	2	8	$Me(OH)PS_2$+	15	32	28
M—H_2O—C_3H_6+	—	—	2	Me(EtO)PS+	56	37	42
M—EtOH—R+	—	2	3	$HSCH_2CONHCHC_3H_7$+	—	—	7
$Me(EtO)P(S)SCH_2CO$+	4	11	13	$Me(HO)_2PSH$+	31	24	11
$Me(EtO)P(S)SCHCO$+	7	9	14	$SCH_2CONHCHC_3H_7$+	—	—	5
M—H_2O—MePSO+	11	10	—	$Me(HO)_2PS$+	42	34	14
M—Me(EtO)PSOH+	9	34	34	$SCH_2CONHCH_2$+	16	—	—
$Me(HO)P(S)SCH_2CO$+	—	3	6	$SCH_2CONHCH$+	—	—	24
$MeP(O)(S)SCH_2CO$+	8	—	8	CONHCHCOOH+	—	15	—
Me(EtO)P(S)SH+	50	30	22	$EtCONHC_2H_3$+	—	17	—
M—$(EtO)P(CH_2)S_2$+	21	11	7	$Me(HO)_2PS$+	100	100	100

*Here and in the following tables the values given are the relative intensities of the ions (%).

TABLE 3. Mass Spectra of $Me(EtO)P(S)SCH_2CONHCH(R)CONHCH(R')$-COOEt (V, VI, XVII-XIX)

Ion	(V) R=H R'=H	(VI) R=H R'=Me	(XVII) R=i-Pr R=H	(XVIII) R=i-Pr R'=Me	(XIX) R=i-Pr R'=i-Pr
M+	5	9	2	2	3
M—Me+	—	0,5	—	0,5	1
M—H_2O+	0,5	0,3	0,5	0,5	1
M—EtO+	3	3	3	4	3
M—EtOH+	1	3	—	—	2
M—COOEt+	—	2	—	—	1
M—NHCH(R')COOEt+	14	22	5	12	19
M—$NH_2CH(R')COOEt$+	3	5	3	4	5
M—CONHCH(R')COOEt+	2	4	12	16	27
M—Me(EtO)PS+	1	3	—	—	1
M—Me(EtO)PSOH+	100	100	45	50	70
M—$(EtO)P(CH_2)S_2$+	12	14	3	4	5
M—Me(EtO)PSOH—SH+	14	2	9	14	23
M—Me(EtO)PSOH—R'+	1	—	—	—	5
M—Me(EtO)PSOH—EtOH+	10	5	2	—	—
$Me(EtO)P(S)SCH_2CO$+	22	40	100	100	100
$Me(HO)P(S)SCH_2CO$+	7	8	12	8	17
$Me(EtO)P(SH)_2$+	7	19	3	—	3
Me(EtO)P(S)SH+	8	12	9	11	12
$Me(EtO)PS_2$+	11	10	15	9	23
Me(EtO)P(OH)SH+	11	10	9	10	11
$Me(HO)PS_2$+	16	19	10	—	14
Me(EtO)PS+	36	38	23	8	29
$Me(HO)_2PSH$+	6	7	10	9	24
$Me(HO)_2PS$+	5	7	8	6	7
Me(HO)PS+	59	49	32	12	35
MeCONHCH(R')COOEt+	14	18	—	—	—
$CH_2CONHCH(R')COOEt$+	11	—	—	—	—
$C_5H_8NO_2$+	—	—	12	20	25
$NH_3CH(R')COOEt$+	37	34	18	12	24
NHCH(R')COOEt+	—	—	—	—	12

The constants of the compounds, the yields, and the data from the elemental analysis are given in Table 1. In all cases their purity was determined by TLC and $^{31}P-\{^1H\}$ NMR. The compounds obtained contain one, two, or three asymmetric atoms and can appear as mixtures of diastereomers in the last two cases.

In connection with the investigation of the physiological action of these compounds [1,4] and their metabolism [5] we studied their mass-spectrometric fragmentation. It was found that all the compounds produce a fairly intense peak of the molecular ion (M^+). This makes it possible to identify such compounds with certainty. Tables 2 through 5 present the mass spectra of compounds I-III, V, VI, XII-XIV, and XVII-XX. The main paths for the fragmentation of the compounds studied are presented in Scheme 1 in the example case of N-[S-(methylethoxythiophosphinyl)thioglycolyl]-O-ethylglycylglycine (V).

Most of the mass spectra contain common ions with m/e 197, 169, 155, 141, 127, 123, 113, 112, and

TABLE 4. Mass Spectra of $Me(EtO)P(S)SCH_2CONHCH(R)CONHCH_2CH_2COOEt$ (XII, XX)

Ion	(XII) R=Me	(XX) R=i-Pr	Ion	(XII) R=Me	(XX) R=i-Pr
M+	2	2	$Me(EtO)P(S)SH^+$	13	11
M—Me+	—	0,3	$Me(EtO)PS_2^+$	16	12
M—EtO+	5	5	$Me(EtO)P(OH)SH^+$	8	7
$M—NHCH_2CH_2COOEt^+$	2	1	$Me(HO)PS_2^+$	15	10
$M—NH_2CH_2CH_2COOEt^+$	3	2	$Me(EtO)PS^+$	29	20
$M—Me(EtO)PS^+$	2	1	$Me(HO)_2PSH^+$	5	11
$M—Me(EtO)PSOH^+$	59	39	$Me(HO)_2PS^+$	18	9
$M—CONHCH_2CH_2COOEt^+$	11	14	$Me(HO)PS^+$	48	38
$M—(EtO)P(CH_2)S_2^+$	8	3	$EtCONHCH_2CH_2COOEt^+$	12	—
$M—Me(EtO)PSOH—SH^+$	19	9	$CONHCH_2CH_2COOEt^+$	6	5
$Me(EtO)P(S)SCH_2CO^+$	100	100	$C_3H_5NO_2^+$	—	18
$Me(HO)P(S)SCH_2CO^+$	15	9	$NH_3CH_2CH_2COOEt^+$	22	11
$Me(EtO)P(SH)_2^+$	8	—			

TABLE 5. Mass Spectra of $Me(EtO)P(S)SCH_2CONHCH_2CH_2CONHCH(R')COOEt$ (XIII, XIV)

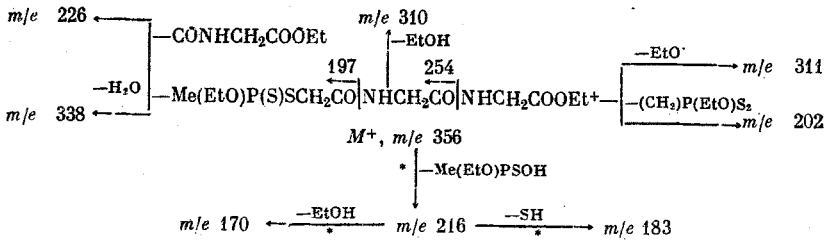
Ion	(XIII) R'=H	(XIV) R'=Me	Ion	(XIII) R'=H	(XIV) R'=Me
M+	27	8	$Me(EtO)P(S)SH^+$	42	13
M—Me+	1	0,1	$Me(EtO)PS_2^+$	—	8
M—Me—Et+	3	1	$Me(EtO)P(OH)SH^+$	16	25
M—EtO+	5	2	$Me(EtO)P(S)OH^+$	15	8
M—EtOH+	2	3	$Me(HO)_2PS_2^+$	24	19
M—COOEt+	—	1	$Me(EtO)PS^+$	42	33
$M—NHCH(R')COOEt^+$	17	4	$Me(HO)_2PSH^+$	49	25
$M—Me(EtO)PS^+$	8	5	$Me(HO)_2PS^+$	31	34
$M—Me(EtO)PSOH^+$	100	35	$Me(HO)PS^+$	99	100
$M—(EtO)P(CH_2)S_2^+$	29	13	$MeCONHCH(R')COOEt^+$	15	6
$M—Me(EtO)PSOH—SH^+$	—	6	$CH_2CONHCH(R')COOEt^+$	24	6
$M—Me(EtO)PSOH—EtOH^+$	20	9	$CH_2CH_2CONHCH(R')COOEt^+$	51	20
$M—Me(EtO)P(S)SCH_2CO^+$	11	6	$CONHCH(R')COOEt^+$	10	20
$Me(EtO)P(S)SCH_2CO^+$	18	11	$NH_3CH_2CH_2CONHCH(R')COOEt^+$	5	3
$Me(HO)P(S)SCH_2CO^+$	—	8	$NH_3CH(R')COOEt^+$	60	37
$Me(EtO)P(SH)_2^+$	12	5			

95, which form as a result of the fragmentation of the S-(methylethoxythiophosphinyl)thioglycolic residue. Scheme 2 shows the possible paths for the formation of the ion with m/e 95, which has the maximum intensity in most of the mass spectra. Two probable structures, viz., PS_2^+ (A) and $Me(HO)PS^+$ (B), may be proposed for this fragment; however, the high-resolution mass spectra suggest that this peak is a singlet and corresponds to structure B (m_{found} = 94.9726, m_{calc} = 94.9721). This structure is also supported by the metastable ions with m/e 145.0 and 53.4 (Table 6), which correspond to the successive elimination of C_2H_4 and SCH_2CO from the $Me(EtO)P(S)SCH_2CO^+$ ion (m/e 197).

Another characteristic feature of all the mass spectra is the presence of an intense peak of a rearranged ion which corresponds to the elimination of 140 mass units from M^+. The measured exact mass of the ejected particle (140.0061) corresponds to the elimination of Me(EtO)PSOH (m_{calc} = 140.0061). The ejection of such a fragment requires the migration of O and H atoms to the methylethoxythiophosphinylthiol residue. The O atom of the amide group then migrates to the P atom. Another possible hypothesis includes the migration of the O atom of the carboxyl group (acids) or the carbethoxy group (esters). If this were so, the mass spectrum of $Me(EtO)P(S)SCH_2CONH$-sec-Bu [6], which has no carboxyl oxygen, should not show a peak of M^+ with m = 140; however, in its mass spectrum the peak due to the ejection of 140 mass units from M^+ has the maximum intensity, and the O atom of the amide group, therefore, participates in this rearrangement.

All the mass spectra we studied contain peaks which correspond to the splitting of the amide linkages to form ions with m/e 197 (I-III, V, VI, XII-XIV, and XVII-XX), 254 (V and VI), 268 (XII-XIV), 295 (XX), and 296 (XVII-XIX), which are unequivocally related to the sequence of amino acid residues in the molecule. An interesting feature of the mass spectra of the carbethoxy derivatives (V, VI, XII-XIV, and XVII-XX) is the presence of intense peaks of the ions $H_3NCH(R')COOEt^+$ (R' = H, Me, i-Pr; m/e 104, 118, 146, respectively), which characterize the terminal amino acid. Thus, there is a possibility of mass-spectrometrically monitoring the metabolic conversions of phosphadipeptides which are accompanied by the splitting off of the amino acid residues.

Scheme 1



*Here and in the following, the asterisks denote fragmentation paths that have been confirmed by the corresponding metastable peaks (see Table 6).

Scheme 2

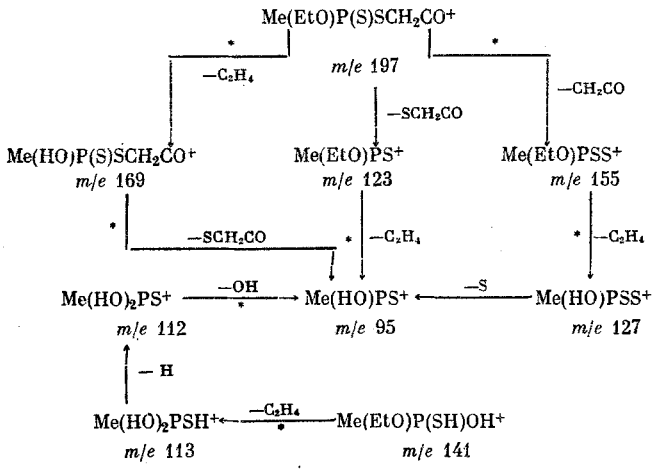


TABLE 6. Metastable Peaks in the Mass Spectra of I-XX

m	Process	Neutral fragment	(I)	(II)	(III)	(V)	(XIII)	(VI)	(XIV)
283,7	370→324	EtOH						×	
210,0	272→239	SH							
179,6	412→272	Me(EtO)PSOH							
155,5	216→183	SH				×			
147,2	230→184	EtOH					×	×	
145,0	197→169	C_2H_4							
144,8	268→197	NHCHPr							
143,0	370→230	Me(EtO)PSOH						×	
133,8	216→170	EtOH				×			
131,1	356→216	Me(EtO)PSOH				×			
122,0	197→155	CH_2CO			×	×			
90,6	141→113	C_2H_4	×	×	×			×	×
80,6	112→95	OH	×	×				×	
73,4	123→95	C_2H_4	×	×	×	×	×	×	×
53,4	169→95	SCH_2CO				×			

m	Process	Neutral fragment	(XII)	(XVII)	(XX)	(XVIII)	(XIX)
283,7	370→324	EtOH					
210,0	272→239	SH			×	×	
179,6	412→272	Me(EtO)PSOH			×		
155,5	216→183	SH					
147,2	230→184	EtOH					
145,0	197→169	C_2H_4		×	×		
144,8	268→197	NHCHPr		×	×		
143,0	370→230	Me(EtO)PSOH					
133,8	216→170	EtOH					
131,1	356→216	Me(EtO)PSOH					
122,0	197→155	CH_2CO		×	×	×	×
90,6	141→113	C_2H_4					
80,6	112→95	OH	×				
73,4	123→95	C_2H_4	×		×		×
53,4	169→95	SCH_2CO	×				×

EXPERIMENTAL

Introduction of Dipeptide Fragment (Synthesis of V-XX). A solution of DCCI in $CHCl_3$ was added to a $CHCl_3$ solution of equimolar amounts of the ethyl ester of an amino acid ($NH_2-B-COOEt$) and a derivative of O-ethyl methyldithiophosphonic acid containing an amino acid residue with a free carboxylic group [1,3]. The mixture was shaken for 10-15 min. Self-heating of the mixture then occurred, and N,N'-dicyclohexylurea precipitated. The reaction mixture was left to stand overnight in a refrigerator for the more complete precipitation of the dicyclohexylurea. The precipitate was filtered, and the filtrate was evaporated in a vacuum. The residue (a viscous syrupy substance) was dissolved in an ether – chloroform mixture. In some cases the solution became cloudy, and a crystalline product precipitated. The crystalline material was recrystallized to a constant melting point. The thick syrupy substances were purified by freezing them out from solutions in a mixture of ether with hexane at −78°C. The purity of the products was monitored by TLC on a free layer of KSK silica gel containing 10% water in a 3:2 hexane – acetone system.

The $^{31}P-\{^1H\}$ NMR spectra were recorded on a Bruker HX-90 spectrometer at a frequency of 36.43 MHz under pulsed conditions, the external reference being 85% phosphoric acid. The low-resolution mass spectra were obtained on an MX-1303 mass spectrometer, which was equipped with a system for the direct introduction of the sample into the ion source [7], with an energy of the ionizing electrons equal to 50 eV. The temperature of the source was 150°C, and that of the introduction system was 50-150°C. The exact masses of the ions were measured on an AEI MS-30 mass spectrometer with a DS-50 data-processing system.

CONCLUSIONS

The mass-spectrometric fragmentation of several phosphadipeptides has been investigated. The mass spectra show peaks which are unequivocally related to the sequence of amino acid residues in the molecule, as well as peaks which correspond to the C-terminal amino acids. These peaks can be utilized for the mass-spectrometric identification of metabolites of the compounds studied.

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