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# α-Alkenyl Analogs of Phosphorylcholines

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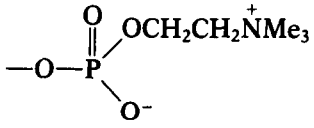
## ABSTRACT

*The new type of α-alkenyl esters of phosphorus acids containing ammonium or phosphonium groups in unsaturated radicals as well as carbonyl or other complexes of Mo, Cr, W, Mn, or Pt with such organophosphorus ligands have been described. The alkenyl phosphates undergo dealkylation upon heating to give betaines. This conversion results in a substantial decrease of an anticholinesterase activity of the compounds and in a sharp rise of their hydrolytic stability. The prototropic rearrangement is observed for the phosphonium betaines.*

## *INTRODUCTION*

Phosphocholines are present in living cells, e.g., in the form of biologically active phospholipid compounds containing betaine fragments:

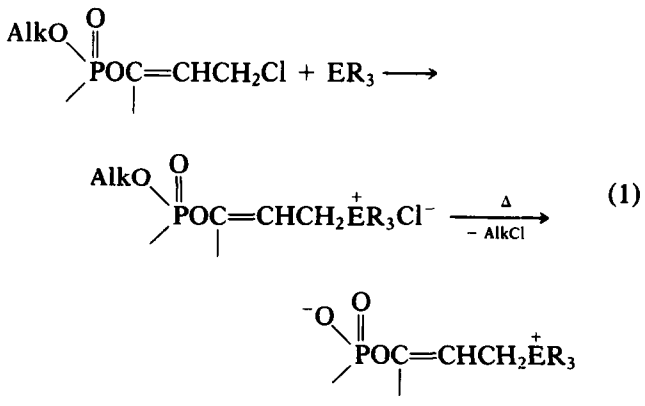


They exhibit high levels of activity in a wide range of physiologically vital regulatory events, including platelet activation and selective tumor cytotoxicity against a number of cancer cells, and are used as potential drugs in chemotherapy (for references see [1]).

In this connection, the development of chemical methods for modification of a choline fragment, e.g., introduction of an unsaturated bond to its α position, variation of substituents or an onium center, is of definite interest. Continuing our investigations on vinyl phosphate chemistry [2] we have looked for synthetic approaches to the betaine structures shown in Eqs. (1) and (2).

## *RESULTS AND DISCUSSION*

The realized method of synthesis consists in alkylation of amines or phosphines by α-alkenyl phosphates containing chlorine atoms at terminal $CH_2$ groups of unsaturated radicals followed by thermal dealkylation of the resulting ester products is shown Eq. (1).



(1)

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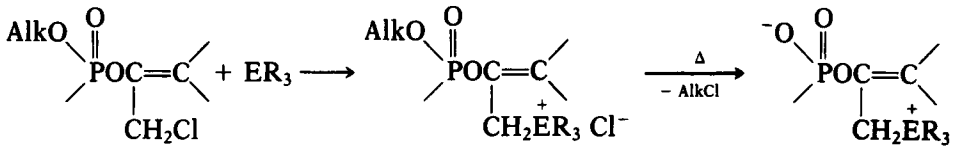
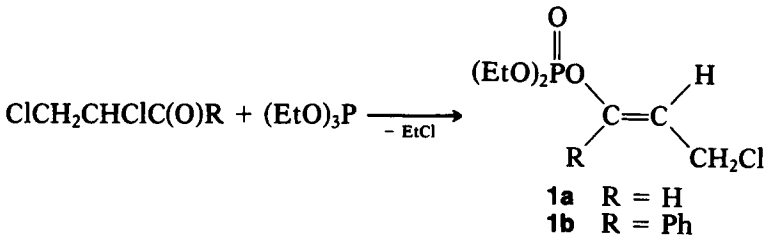


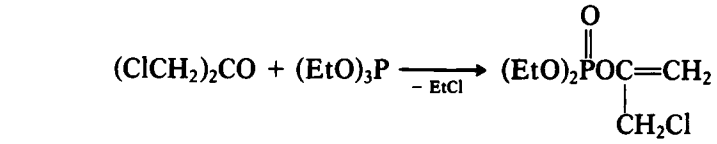
(2)

where E = N or P.



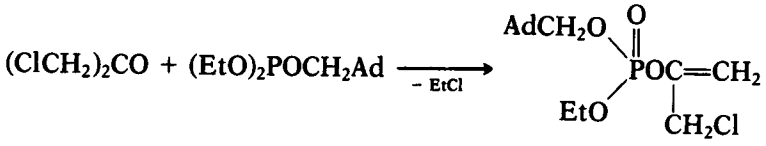
(3)

**1a** R = H
**1b** R = Ph



(4)

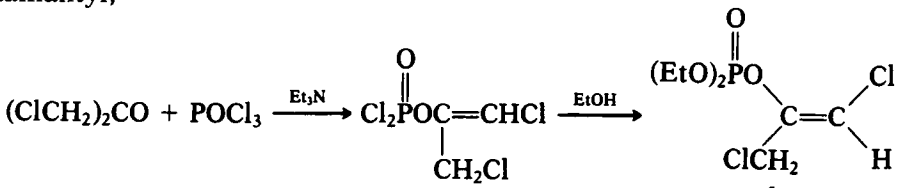
**2**



(5)

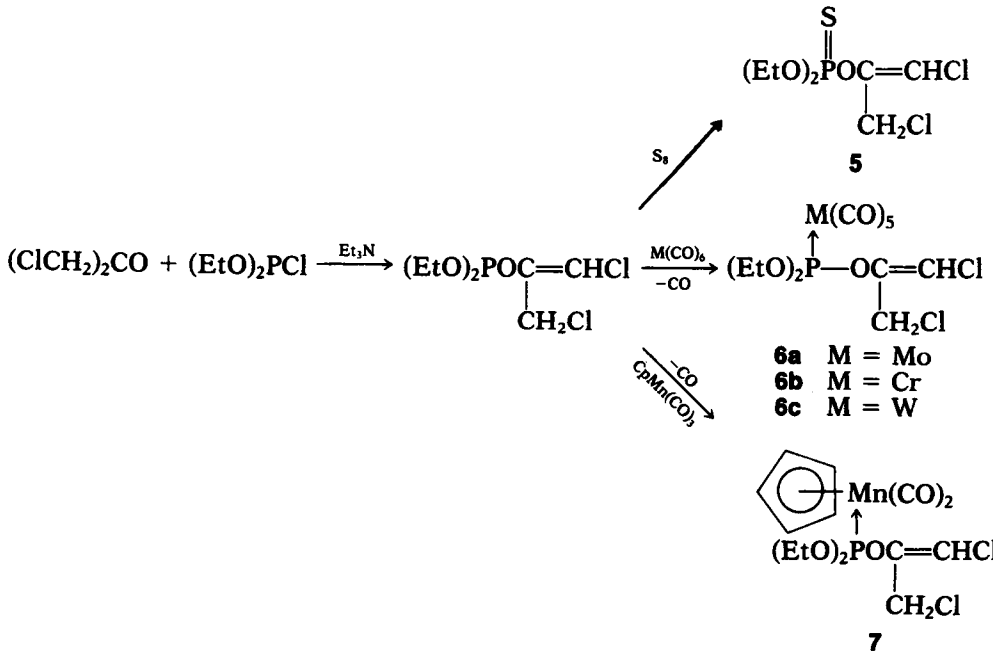
**3**

where Ad = 1-adamantyl;



(6)

**4**

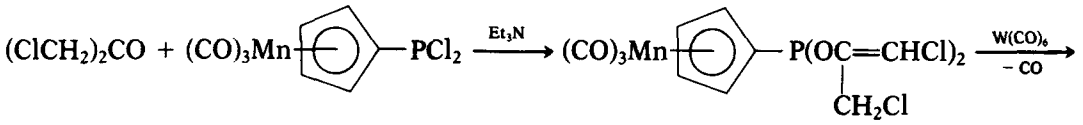


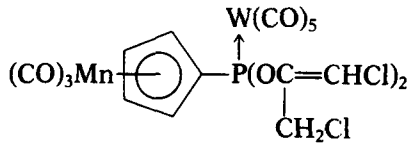
(7)

**5**

**6a** M = Mo
**6b** M = Cr
**6c** M = W

**7**





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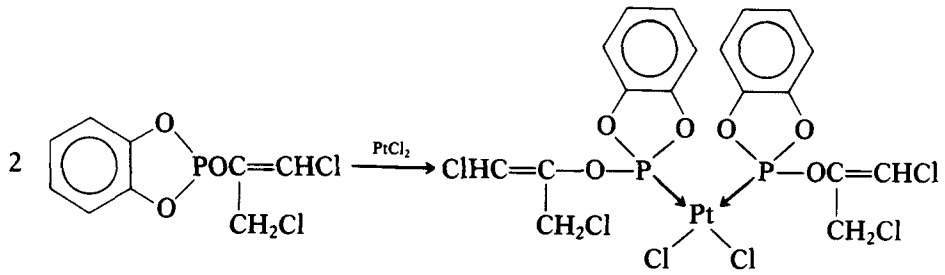
(8)



9

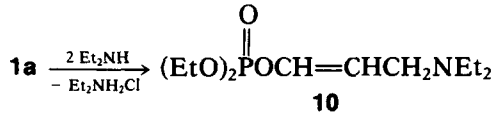
(9)

The starting α-alkenyl phosphates were obtained either by the known Perkow reaction [see Eqs. (3)–(5)] or by condensation of phosphorus chlorides with aldehydes, ketones, or esters bearing readily removable hydrogen atoms in the α-position to the carbonyl group ($pK_a$ ca. 15 or less) in the presence of triethylamine (Eq. 6) [2].

The reactions presented in these equations proceed stereoselectively, with preferential formation of (*E*)-isomeric propenyl phosphates **1** and (*Z*)-vinyl phosphate **4**. According to X-ray data [3], their stereoconfiguration remains unchanged in subsequent conversions with participation of terminal $CH_2Cl$ groups.

Syntheses shown in Eqs. (7) and (8) possess the obvious advantage of providing alkenyl phosphites that can be transformed into various tetracoordinate phosphorus derivatives.

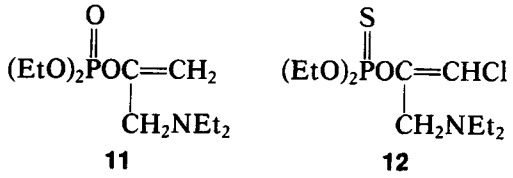
The chlorine atoms in $CH_2Cl$ groups of the compounds obtained are easily substituted for nitrogen in reactions with secondary or tertiary amines. The reaction (10) with secondary amines leads to free bases, which give the corresponding hydrochlorides upon treatment with gaseous HCl [3].



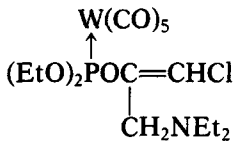
10

(10)

In a similar way, the diethylamino derivatives **11–13** were obtained from esters **2, 5,** and **6c**.



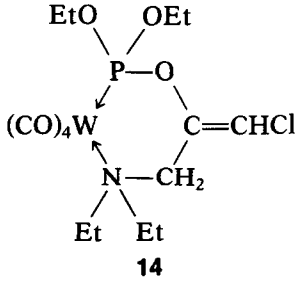
11 12



13

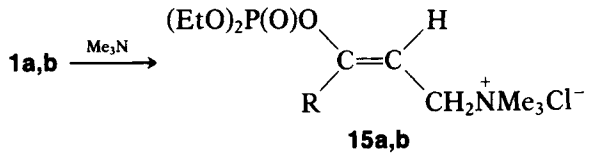
The bases **10–12** are liquids distillable in vacuum, whereas their hydrochlorides are crystalline compounds.

It is noteworthy that irradiation transforms **13** into chelate complex **14**.



14

Being treated with tertiary amines under mild conditions, the propenyl phosphates give hygroscopic crystalline ammonium chlorides:

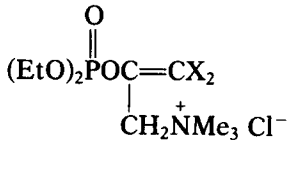


15a,b

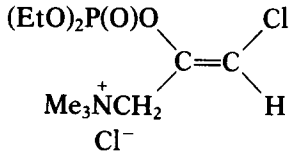
(11)

where R = H (a), Ph (b).

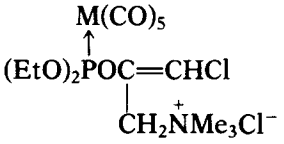
By analogy, ammonium salts **16–18** have been prepared from esters **2, 4,** and **6** (and in addition **37**, which is the 3,3-dichloro derivative of **16**).



**16** X = H
**37** X = Cl



**17**



**18a** M = Mo
**18b** M = Cr
**18c** M = W

It should be mentioned that in such reactions only highly basic, sterically unhindered amines are active. Pyridine, acridine, dimethylaniline, and even triethylamine react with the chloro-substituted alkenyl phosphates very slowly.

The hydrochlorides of the amino derivatives **10–12** are readily dealkylated on heating or prolonged storing to give betaines **19–21**. They were first synthesized representatives of this class of organophosphorus compounds [3].

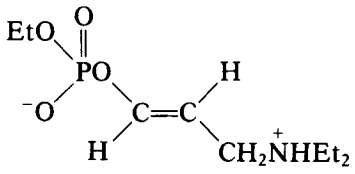
Similar dealkylation is also characteristic for ammonium salts **15–17**. When heated in vacuum for several hours, they convert almost quantitatively into betaines **22–24**.

The compounds **19–24** are stable, water-soluble crystalline products. Their structures have been confirmed by IR and NMR spectra and in some cases by X-ray analysis [3]. All attempts to obtain betaines from metal–carbonyl complexes **13** and **18** under the above-mentioned conditions failed.

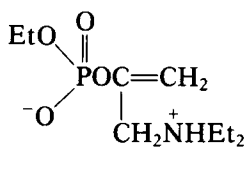
The alkylation of diamines with chloroalkenyl phosphates gives new interesting preparative opportunities. For example, from **4** and triethylenediamine or N,N,N′,N′-tetramethylethylenediamine, new bisbetaine structures **25** and **26** were obtained.

The synthetic strategy developed for ammonium betaines proved valid as well for preparing their phosphonium analogs. Since trialkyl phosphines are more nucleophilic than trialkyl amines, their alkylation proceeds more easily. The resulting phosphonium salts are smoothly dealkylated into corresponding betaines. This conversion is illustrated by Eqs. (12)–(15).

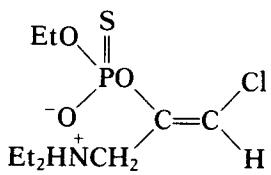
In contrast to ammonium betaines, the phosphonium analogs have more flexible structures and participate in some specific rearrangements. Betaines **31c** and **34** having unsubstituted terminal methylene groups undergo a 1,3-prototropic shift



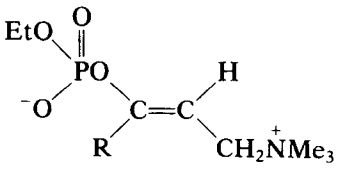
**19**



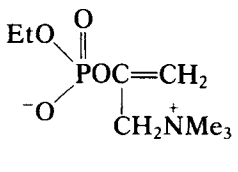
**20**



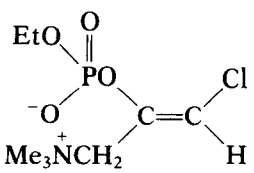
**21**



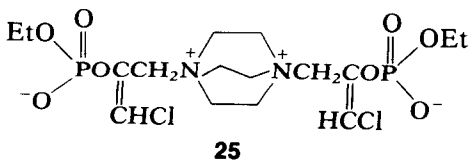
**22a** R = H
**22b** R = Ph



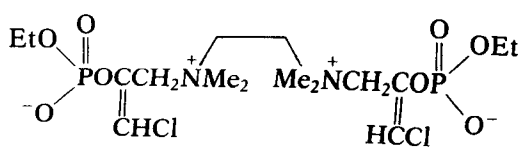
**23**



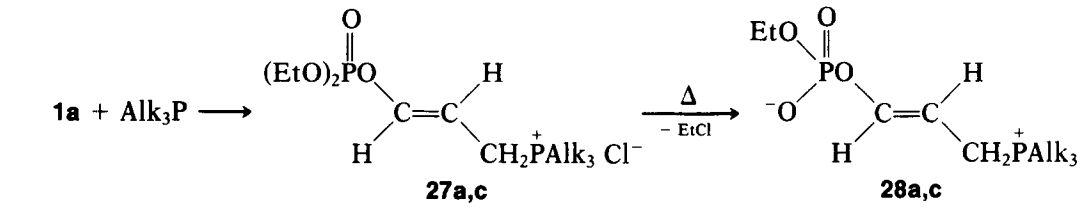
**24**



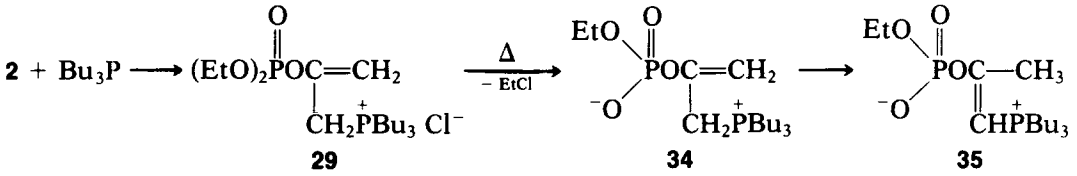
**25**



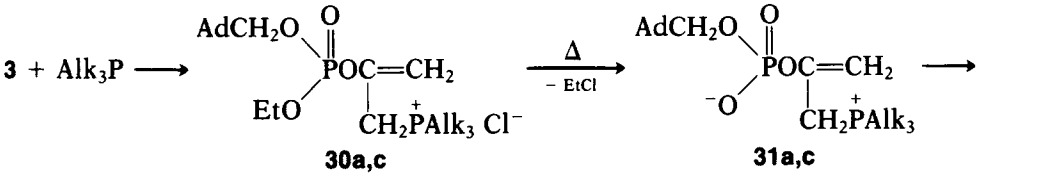
**26**



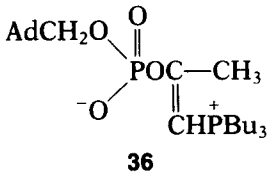
(12)

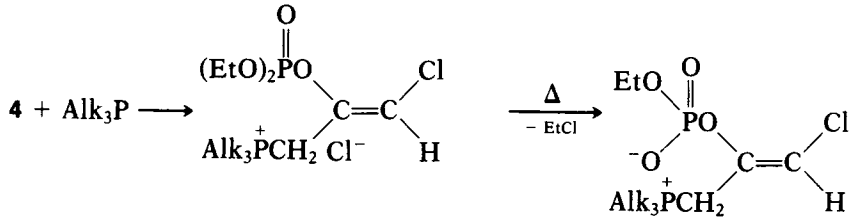


(13)



(14)





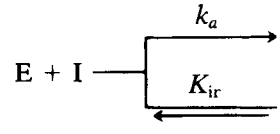
(15)

where Alk = Me (A), Pr (B), Bu (C)

which accompanies the thermal dealkylation of starting esters. The rearranged products **35** and **36** were isolated and characterized.

The ammonium- and phosphonium-substituted alkenyl phosphates presented here, being to a certain extent the structural analogs of acetylcholine, $AcOCH_2CH_2\overset{+}{N}Me_3$ (the natural mediator in the transmission of action potentials across nerve–nerver and neuromuscular synapses), can reveal an anticholinesterase activity. It is also known that the introduction of double bonds into alkyl phosphates increases their phosphorylating potency with respect to cholinesterases. However, it is difficult to predict in what measure these activating factors, that is, the presence of a C=C bond and an onium center in a leaving group, would be manifested in betaines where the electrophilic phosphorus is shielded by a negatively charged oxygen atom. Of no small importance for a potential biologically active compound is hydrolytic stability, which has never been previously evaluated for these structures. In this connection, we have studied the kinetic aspects of inhibition of human erythrocyte acetylcholinesterase (AChE) by some alkenyl phosphates (see Table 1) and determined the rate constants for their alkaline hydrolysis.

The kinetic investigation of the reactions with AChE was performed by the pH titration method [4] based on potentiometric control of a residual activity of the enzyme, E, with respect to its substrate, acetylcholine iodide, after incubation of E with an inhibitor, I. This method allows ascertaining the type of inhibition process, which, in general, can proceed via an irreversible (Eq. 16a), a reversible (Eq. 16b), or the combined scheme. In reaction (16a), in contrast to (16b), the enzyme active site undergoes the phosphorylation and completely loses its activity in the $(EI)_p$ complex.



(16a)

(16b)

The competing processes in this scheme are characterized, respectively, by a bimolecular rate con-

**TABLE 1** Kinetic Parameters for Combined Inhibition of Human Erythrocyte AChE by Alkenyl Phosphates (25°C, pH 7.8) and Rate Constants for Alkaline Hydrolysis of Alkenyl Phosphates (25°C)

| Compound | $k_a$ ($M^{-1}$ $min^{-1}$) | $K_{ir}$ (M) | $k_{OH}$ ($M^{-1}s^{-1}$) |
|---|---|---|---|
| **15a** | | | $(2.4 \pm 0.4) \times 10^{-2}$ |
| **15b** | | | $(4.2 \pm 0.2) \times 10^{-3}$ |
| **22a** | | | $(7.0 \pm 2.5) \times 10^{-7}$[b] |
| **16** | $(7.7 \pm 0.1) \times 10^{2}$ | $(1.5 \pm 0.2) \times 10^{-3}$ | $(7.3 \pm 0.4) \times 10^{-3}$ |
| **17** | $(1.05 \pm 0.01) \times 10^{5}$ | $(9.5 \pm 0.1) \times 10^{-5}$ | $(6.0 \pm 0.3) \times 10^{-2}$ |
| **37** | $(5.6 \pm 0.4) \times 10^{5}$ | —[a] | |
| **32a** | $(8.4 \pm 0.3) \times 10^{4}$ | $(5.0 \pm 0.1) \times 10^{-5}$ | |
| **23** | $3.5 \pm 0.1$ | $(1.7 \pm 0.1) \times 10^{-2}$ | |
| **24** | $(1.1 \pm 0.04) \times 10^{2}$ | $(2.1 \pm 0.1) \times 10^{-3}$ | |
| **33a** | $(5.5 \pm 0.4) \times 10^{2}$ | —[a] | |
| **27a** | $(2.3 \pm 0.1) \times 10^{3}$ | $(7.2 \pm 0.2) \times 10^{-4}$ | |
| **28a** | $11.3 \pm 0.2$ | $(1.4 \pm 0.5) \times 10^{-2}$ | |

[a] The scattering of experimental points makes the evaluation of $K_{ir}$ impossible.
[b] At 20°C.

stant $k_a$ and an equilibrium dissociation constant $K_{ir}$ for enzyme–inhibitor complex $(EI)_r$.

The distinguishing feature of inactivation of AChE by the compounds studied here is the combined character of the inhibition (Table 1); i.e., the onium center, probably because of its molecular structural peculiarities, can reversibly associate with the enzyme irrespective of the two-centered (P . . . $\overset{+}{N}$) binding of I to E preceding the phosphorylation of the active site.

In the file of phosphorus triesters **16, 17,** and **37,** the activating influence of ammonium substituents and terminal chlorine atoms in vinyloxyl radicals is distinctly observed. The ester **37** phosphorylates AChE about 560 times faster than vinyl phosphate $(EtO)_2P(O)OC(Me)=CCl_2$, which does not contain an onium center ($k_a$ $1.0 \times 10^3$ $M^{-1}$ $min^{-1}$) [5]. The effect of the phosphonium group, in this sense, resembles that of the ammonium group (cf. **32a** and **17**). The introduction of the first Cl atom into the alkenyl group is accompanied by a 136-fold increase of $k_a$, while the second chlorine atom gives rise to an additional 5.3-fold acceleration (cf. **16, 17,** and **37**). Similar trends can be seen in reversible inhibition, where the increase in antiesterase activity is exhibited by strengthening of the enzyme–inhibitor complex, i.e., by decrease in its dissociation constant $K_{ir}$.

The inhibitory activity of betaines is less by ca. $10^2$–$10^3$ times than that of the corresponding triesters. In fact, they react with AChE as weak reversible inhibitors.

The transformation into a betaine form also results in the pronounced rise of resistance to alkaline hydrolysis (see Table 1). For example, betaine **22a** is hydrolyzed in aqueous NaOH ca. 30,000 times slower than the corresponding triester **15a**. The hydrolysis of triesters is accelerated by an electron-withdrawing chlorine substituent (cf. **16** and **17**) and retarded by steric hindrance of an electrophilic phosphorus center (cf. **15a** and **15b**).

The reasons for the reduced anti-AChE activity of betaines are not clear. It is quite possible that the substituent $O^-$, besides blocking the nucleophilic attack on phosphorus (see data on alkaline hydrolysis), hinders the two-centered associative addition of an inhibitor to AChE's esteratic and anionic loci. However, the registrated suppression of AChE inhibition potency on "betainization" can be used as an empirical method for regulation of the biological activity in this class of organophosphorus compounds.

## *EXPERIMENTAL*

Proton, $^{13}C$, and $^{31}P$ NMR spectra were recorded with a Bruker WP 200SY spectrometer. Chemical shifts in parts per million are quoted relative to external tetramethylsilane ($\delta_H$, $\delta_C$) or 85% $H_3PO_4$ ($\delta_P$). The IR spectra were obtained on an UR-20 instrument in KBr tablets or Nujol unless otherwise indicated.

All the operations with carbonyl derivatives of Cr, Mn, Mo, and W were carried out under argon.

The synthesis and properties of triesters **2, 4, 5, 10–12** and betaines **19–21** have been described earlier [3].

### Trans-*3-Chloroprop-1-enyl Diethyl Phosphate* (**1a**)

This compound was obtained by the known method [6] and isolated from the mixture of geometric isomers by repeated vacuum distillation in 25% yield; bp 83–84°C at 0.05 mmHg; $n_D^{20}$ 1.4450; $\nu_{max}$ (neat) 1275 (P=O), 1680 $cm^{-1}$ (C=C); $\delta_H$ ($CDCl_3$), 1.31 (6H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 1.0 Hz, $CH_3$), 4.14 (4H, m, $J_{HP}$ 8.6 Hz, $CH_2O$), 4.20 (2H, ddd, $J_{HH}$

8.0, 1.0 Hz, $J_{HP}$ 0.7 Hz, $CH_2Cl$), 5.63 (1H, dtd, $J_{HH}$ 12.1, 8.0 Hz, $J_{HP}$ 1.2 Hz, CCH=), 6.86 (1H, dtd, $J_{HH}$ 12.1, 1.0 Hz, $J_{HP}$ 6.9 Hz, OCH=); $\delta_P$ (neat), −4.0; $\delta_C$ (neat), 15.6 (2C, d, $J_{Cp}$ 6.1 Hz, $CH_3$), 40.6 (1C, s, $CH_2Cl$), 64.2 (2C, d, $J_{Cp}$ 5.7 Hz, $CH_2O$), 112.8 (1C, d, $J_{Cp}$ 10.7 Hz, CC=), 140.6 (1C, d, $J_{Cp}$ 5.0 Hz, OC=). Analysis found, Cl, 15.39; P, 13.37; $C_7H_{14}ClO_4P$ requires Cl, 15.51; P, 13.55%.

### *Adamant-1-ylmethyl 1-Chloromethylvinyl Ethyl Phosphate* (**3**)

A solution of triethylamine and adamant-1-ylmethanol (each 33 mmol) in dry benzene (50 mL) was added to an equimolar amount of diethyl chlorophosphite in the same solvent (50 mL) at room temperature. The mixture was stirred for 8 h and then filtered; the filtrate was evaporated in vacuum to give adamant-1-ylmethyl diethyl phosphite (80%), $\delta_P$ 138.8. A solution of 1,3-dichloroacetone (30 mmol) in anhydrous ether (30 mL) was added to a stirred solution of the phosphite (25 mmol) in ether (50 mL) at room temperature. After 2 h the solvent was distilled off and the residue was kept in vacuum without heating. The resulting phosphate **3** (85%, $\delta_P$ −6.0) was used further without any purification as it decomposes upon distillation.

### *Pentacarbonyl[2-chloro-1-chloromethylvinyl-(diethyl)phosphite]molybdenum* (**6a**)

A solution of hexacarbonylmolybdenum (15 mmol) and 2-chloro-1-chloromethylvinyl diethyl phosphite (15 mmol) in diglyme (1.5 mL) was heated in a sealed tube at 100°C for 14 h then chromatographed on silica gel (L 40–100 μ) using, at first, hexane to elute unreacted $Mo(CO)_6$ then benzene–hexane (v/v 1 : 4) to obtain the yellowish viscous liquid, **6a** (31%); $\nu_{max}$ (neat) 1625 (C=C), 1955, 1995, 2080 $cm^{-1}$ (C≡O); $\delta_H$ ($C_6D_6$), 0.98 (6H, t, $CH_3$), 3.59 (2H, s, $CH_2Cl$), 3.88 (4H, m, $CH_2$), 5.23 (1H, s, HC=); $\delta_P$ ($C_6H_6$), 156.4. Analysis, found, C 30.16; H, 2.70; P, 6.45; $C_{12}H_{13}Cl_2MoO_8P$ requires C, 29.84; H, 2.71; P, 6.41%.

### *Pentacarbonyl[2-chloro-1-chloromethylvinyl-(diethyl)phosphite]chromium* (**6b**)

A solution of hexacarbonylchromium (5–15 mmol) in anhydrous THF (100 mL) was irradiated by mercury lamp (375 W) for 5 h; then equimolar 2-chloro-1-chloromethylvinyl diethyl phosphite was added and the mixture was kept overnight under an intensive stream of argon. After removal of the solvent the residue was separated by chromatography, as above, to give the colorless viscous liquid **6b** (18%); $\nu_{max}$ 1650 (C=C), 1960, 2005, 2085 $cm^{-1}$ (C≡O); $\delta_H$ ($CDCl_3$), 1.41 (6H, t, $CH_3$), 4.23 (6H, m, $CH_2$), 6.07 (1H, d, $J_{HP}$ 1.5 Hz, HC=); $\delta_P$ ($C_6D_6$), 173.6.

### *Pentacarbonyl[2-chloro-1-chloromethylvinyl-(diethyl)phosphite]tungsten* (**6c**)

This complex was prepared in 27% yield from hexacarbonyltungsten in a manner analogous to that described for **6b**; $\delta_H$ ($CDCl_3$), 1.39 (6H, t, $CH_3$), 4.22 (6H, m, $CH_2$), 6.10 (1H, d, $J_{HP}$ 2.0 Hz, HC=); $\delta_P$ ($C_6H_6$), 133.3. Analysis, found, C, 25.63; H, 2.31; P, 5.21; $C_{12}H_{13}Cl_2O_8PW$ requires C, 25.24; H, 2.29; P, 5.42%).

### *Dicarbonyl[2-chloro-1-chloromethylvinyl-(diethyl)phosphite] (η-cyclopentadienyl)-manganese* (**7**)

This compound was prepared by the method used for synthesis of **6b** and **6c**. The reaction mixture was heated in vacuum (0.1 mmHg, 50°C, 2 h) to remove the unreacted cymantrene then eluted with benzene on silica gel to yield bright yellow viscous liquid **7** (21%); $\nu_{max}$ (neat) 1650 (C=C), 1900, 1960 (C≡O); $\delta_H$ ($CDCl_3$), 1.28 (6H, t, $CH_3$), 4.07 (4H, m, $CH_2O$), 4.17 (2H, s, $CH_2Cl$), 4.52 (5H, s, $H_{Cp}$), 5.85 (1H, s, HC=); $\delta_P$ ($C_6H_6$), 202. Analysis, found P, 6.92; $C_{14}H_{18}Cl_2MnO_5P$ requires P, 7.32%).

### *Pentacarbonyl[di(2-chloro-1-chloromethylvinyl)-cymantrenylphosphonite]tungsten* (**8**)

A solution of triethylamine (9.6 mmol) in dry ether (3 mL) was slowly added to a stirred mixture of dichlorocymantrenylphosphine (4.4 mmol) and 1,3-dichloroacetone (8.8 mmol) in ether (20 mL) at 0°C. The mixture was stirred for 1 h at 0°C, then filtered. The filtrate was evaporated and the residue was kept in vacuum for some hours. The resulting di(2-chloro-1-chloromethylvinyl)cymantrenylphosphonite ($\delta_P$ 160.2) in anhydrous THF (5 mL) was added to a solution of $W(CO)_5$(THF) [from 4.4 mmol of $W(CO)_6$] in 100 mL of anhydrous THF and the mixture was left for 12 h under a brisk stream of argon. Evaporation of the solvent gave the crude product **8**, which was purified by chromatography on silica gel [L 40/100 μ, eluant hexane or benzene for $W(CO)_6$ or the product, respectively], mp 134–134.5°C (decomp; from hexane); $\nu_{max}$ ($CH_2Cl_2$) 1640 (C=C), 1945, 2030 (MnC≡O), 1950, 1970, 1995, 2085 $cm^{-1}$ (WC≡O); $\delta_H$ ($CDCl_3$), 4.29 (4H, s, $CH_2$), 4.87 (2H, m, $J_{HH}$ = $J_{HP}$ 2.1 Hz, β-$H_{Cp}$), 5.47 (2H, m, $J_{HH}$ = $J_{HP}$ 2.1 Hz, α-$H_{Cp}$), 6.17 (2H, d, $J_{HP}$ 2.3 Hz, HC=); $\delta_P$ ($C_6H_6$), 154.4 ($J_{PW}$ 400 Hz). Analysis, found P, 3.87; $C_{19}H_{10}Cl_4MnO_{10}PW$ requires P, 3.82%.

### cis-*Dichlorobis[2-(2-chloro-1-chloromethylvinyloxy)benzo-1,3,2λ³-dioxaphosphole]-platinum* (**9**)

A solution of 2-(2-chloro-1-chloromethylvinyloxy)benzo-1,3,2λ³-dioxaphosphole (5.4 mmol) in chloroform (3 mL) was added dropwise to a stirred

solution of $PtCl_2$ (2.9 mmol) in the same solvent (20 mL). The mixture was boiled under reflux for 3 h with continuous stirring, cooled, and filtered to give a light yellow solid, **9** (92%), mp 158–159°C (from benzene); $\delta_H$ ($CDCl_3$), 4.37 (4H, s, $CH_2$), 6.13 (2H, s, HC=), 7.18–7.26 (8H, m, $C_6H_4$); $\delta_P$ ($CHCl_3$), 91.1 ($J_{PPt}$ 5915 Hz). Analysis, found, P, 7.55; $C_{18}H_{14}Cl_6O_6P_2Pt$ requires P, 7.78%).

### *Pentacarbonyl[2-chloro-1-diethylaminomethylvinyl(diethyl)-phosphite]tungsten* (**13**)

A mixture of complex **6c** (1.57 mmol) and diethylamine (6.3 mmol) was heated in a sealed tube at 55°C for 8 h. After addition of ether, the mixture was filtered and the filtrate was evaporated to give **13** (50%); $\delta_H$ ($CDCl_3$), 1.02 (6H, t, $\underline{CH_3}CH_2N$), 1.41 (6H, t, $\underline{CH_3}CH_2O$), 2.56 (4H, q, $CH_2N$), 3.20 (2H, s, $CH_2N$), 4.17 (4H, m, $CH_2O$), 5.98 (1H, s, HC=). Hydrochloride of **13**: $\delta_H$ ($CDCl_3$), 1.37 (6H, t, $\underline{CH_3}CH_2N$), 1.47 (6H, t, $\underline{CH_3}CH_2O$), 3.21 (4H, m, $CH_2N$), 4.10 (6H, m, $CH_2$), 6.73 (1H, d, $J_{HP}$ 2.3 Hz, HC=); $\delta_P$ ($CHCl_3$), 138.8 ($J_{PW}$ 396 Hz). Analysis, found, C, 29.92; H, 3.83; N, 2.34; P, 4.72; $C_{16}H_{24}Cl_2NO_8PW$ requires C, 29.84; H, 3.76; N, 2.17; P, 4.81%.

### *Tetracarbonyl[2-chloro-1-diethylaminomethylvinyl(diethyl)phosphite-N,P]tungsten* (**14**)

A solution of **13** (0.8 mmol) in dry benzene (100 mL) was irradiated with a mercury lamp (375 W) for 6 h. The reaction mixture was filtered and the filtrate was evaporated. The residue was extracted into hexane. Evaporation of the solvent gave the yellow solid, **14** (63%); mp 82–83°C (from hexane at −78°C); $\nu_{max}$ ($C_6H_6$) 1890, 1905, 1930, 2030 $cm^{-1}$ (C≡O) $\delta_H$ ($CDCl_3$), 1.08 (6H, t, $\underline{CH_3}CH_2N$), 1.31 (6H, t, $\underline{CH_3}CH_2O$), 2.80 (2H, m, $CH_2N$), 3.00 (2H, m, $CH_2N$), 3.55 (2H, d, $J_{HP}$ 1.4 Hz, $CH_2N$), 4.12 (4H, m, $CH_2O$), 5.49 (1H, s, HC=); $\delta_P$ ($C_6H_6$), 143.3. Analysis, found, C, 31.20; H, 3.84; N, 2.15; P, 5.13; $C_{15}H_{23}ClNO_7PW$ requires C, 31.08; H, 4.00; N, 2.42; P, 5.34%.

### (E)-*3-Diethoxyphosphoryloxyprop-2-enyl(trimethyl)ammonium Chloride* (**15a**)

Trimethylamine (14 mmol) dried over sodium metal was added to a solution of phosphate **1a** (13 mmol) in anhydrous ether (5 mL) at 0°C. The mixture was cooled in a refrigerator for a day then filtered. The resulting solid was repeatedly washed with dry ether and kept in vacuum for some hours to give hygroscopic crystalline **15a** (79.5%), mp 64–65°C; $\nu_{max}$ 1280 (P=O), 1680 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.37 (6H, td, $J_{HH}$ 7.0 Hz, $J_{HP}$ 1.2 Hz, $CH_3$), 3.11 (9H, s, $CH_3$), 3.97 (2H, d, $J_{HH}$ 8.2 Hz, $CH_2N$), 4.29 (4H, m, $J_{HP}$ 8.6 Hz, $CH_2O$), 5.80 (1H, dtd, $J_{HH}$ 12.0, 8.2 Hz, $J_{HP}$ 1.1 Hz, CCH=), 6.99 (1H, dd, $J_{HH}$ 12.0 Hz, $J_{HP}$ 7.0 Hz, OCH=); $\delta_P$ ($D_2O$), −5.5. Analysis, found, Cl, 12.18; N, 5.15; P, 10.75; $C_{10}H_{23}ClNO_4P$ requires Cl, 12.32; N, 4.87; P, 10.76%.

### (E)-*3-Diethoxyphosphoryloxy-3-phenylprop-2-enyl(trimethyl)ammonium Chloride* (**15b**)

Triethyl phosphite (120 mmol) was slowly mixed with an equimolar amount of 2,3-dichloro-1-phenylpropan-1-one. Next day a solution of triethylamine (100 mmol) in ether was added and after 24 h the mixture was filtered, and the filtrate was diluted with pentane, decanted and evaporated. The residue was treated with trimethylamine in ether, and next day the resulting crystalline precipitate was filtered off and recrystallized from acetone to give **15b** (25%), colorless needles, mp 120–121°C; $\nu_{max}$ 1275 (P=O), 1660 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.21 (6H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 1.1 Hz, $CH_3$), 3.51 (9H, s, $CH_3$), 4.04 (4H, m, $J_{HP}$ 8.2 Hz, $CH_2O$), 4.59 (2H, dd, $J_{HH}$ 8.2 Hz, $J_{HP}$ 1.1 Hz, $CH_2N$), 5.98 (1H, td, $J_{HH}$ 8.2 Hz, $J_{HP}$ 1.9 Hz, HC=), 7.43–7.66 (5H, m, $C_6H_5$), $\delta_P$ ($D_2O$), −6.5. Analysis, found, Cl, 9.47; N, 4.57; P, 7.84; $C_{16}H_{27}ClNO_4P$ requires Cl, 9.74; N, 3.85; P, 8.51%.

### *2-Diethoxyphosphoryloxyprop-2-enyl(trimethyl)-ammonium Chloride* (**16**)

This product was prepared from phosphate **2**, in the same way as **15a**, as hygroscopic low-melting crystals (82%), $\nu_{max}$ 1260 (P=O), 1640 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.35 (6H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.8 Hz, $CH_3$), 3.50 (9H, s, $CH_3$), 4.20 (4H, m, $J_{HP}$ 8.3 Hz, $CH_2O$), 4.69 (2H, s, $CH_2N$), 5.52, 5.68 (2H, m, $H_2C$=); $\delta_P$ ($D_2O$), −5.1. Analysis, found, Cl, 11.43; N, 5.40; P, 10.67; $C_{10}H_{23}ClNO_4P$ requires Cl, 12.32; N, 4.87; P, 10.76%.

### (Z)-*3-Chloro-2-diethoxyphosphoryloxyprop-2-enyl(trimethyl)ammonium Chloride* (**17**)

This product was prepared from phosphate **4** in the same way as **15a**, as hygroscopic colorless crystals (75%), mp 99–100°C; $\nu_{max}$ 1280 (P=O), 1650 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.40 (6H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.8 Hz, $CH_3$), 3.24 (9H, s, $CH_3$), 4.29 (2H, s, $CH_2N$), 4.38 (4H, m, $J_{HP}$ 8.2 Hz, $CH_2O$), 6.80 (1H, d, $J_{HP}$ 2.5 Hz, HC=); $\delta_P$ ($D_2O$), −6.6. Analysis, found, Cl, 21.54; N, 4.12; P, 9.49; $C_{10}H_{22}Cl_2NO_4P$ requires Cl, 22.01; N, 4.35; P, 9.61%).

### *General Procedure for Preparing Pentacarbonyl[3-chloro-2-diethoxyphosphinyloxyprop-2-enyl(trimethyl)ammonium chloride]metals* (**18a–c**)

The mixture of an appropriate complex **6** (2 mmol) and trimethylamine (20 mmol) was kept in a sealed ampule for 120 h at room temperature; then the excess of the amine was evaporated and the residue was washed with dry benzene to give the products

**18a–c** (80–90%), $\delta_H$ ($CDCl_3$), 1.35 (6H, t, $CH_3$), 3.45 (9H, s, $CH_3$), 4.05 (4H, m, $CH_2O$), 4.95 (2H, s, $CH_2N$), 7.10 (1H, d, $J_{HP}$ 2.5 Hz, HC=).

**18a:** $\delta_P$ ($CHCl_3$), 162.4.

**18b:** Hygroscopic crystals, $\delta_P$ ($CHCl_3$), 184.8. Analysis, found, P, 6.08; $C_{15}H_{22}Cl_2CrNO_8P$ requires P, 6.22%.

**18c:** $\delta_P$ ($CHCl_3$), 140.8 ($J_{PW}$ 400 Hz). Analysis, found, C, 28.38; H, 3.53; N, 2.16; P, 4.32; $C_{15}H_{22}Cl_2NO_8PW$ requires C, 28.59; H, 3.52; N, 2.22; P, 4.92%.

### (E)-(*3-Trimethylammonio-1-propenyl) Ethyl Phosphate* (**22a**)

The ester **15a** was heated in high vacuum at 50–70°C for 10 h to yield colorless stable crystals of **22a** (100%), mp 180–181°C; $\nu_{max}$ 1285 (P=O), 1675 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.28 (3H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.8 Hz, $CH_3$), 3.08 (9H, s, $CH_3$), 3.92 (2H, d, $J_{HH}$ 8.3 Hz, $CH_2N$), 4.00 (2H, m, $J_{HP}$ 8.2 Hz, $CH_2O$), 5.53 (1H, dtd, $J_{HH}$ 12.2, 8.3 Hz, $J_{HP}$ 1.0 Hz, CCH=), 6.89 (1H, dd, $J_{HH}$ 12.2 Hz, $J_{HP}$ 7.8 Hz, OCH=); $\delta_P$ ($D_2O$), −3.6. Analysis, found, N, 6.42; P, 14.02; $C_8H_{18}NO_4P$ requires N, 6.28; P, 13.88%.

### (E)-[*1-Phenyl-3-trimethylammonio-1-propenyl*] *Ethyl Phosphate* (**22b**)

The ester **15b** was heated in vacuum at 100°C for 10 h. The resulting yellow glassy product was washed with chloroform several times and crystallized from acetone to give colorless **22b** (90%), mp 166–166.4°C; $\nu_{max}$ 1250 (P=O), 1665 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.06 (3H, td, $J_{HH}$ 7.0 Hz, $J_{HP}$ 1.0 Hz, $CH_3$), 3.11 (9H, s, $CH_3$), 3.82 (2H, m, $J_{HP}$ 8.2 Hz, $CH_2O$), 4.17 (2H, dd, $J_{HH}$ 8.2 Hz, $J_{HP}$ 1.1 Hz, $CH_2N$), 5.78 (1H, td, $J_{HH}$ 8.2 Hz, $J_{HP}$ 1.7 Hz, HC=); $\delta_P$ ($D_2O$), −4.8. Analysis, found, N, 4.14; P, 8.98; $C_{14}H_{22}NO_4P$ requires N, 4.68; P, 10.35%.

### *Ethyl 1-(Trimethylammoniomethyl)ethenyl Phosphate* (**23**)

Compound **16** was heated in vacuum at 100°C for 2 h to give colorless powdered **23** (100%), mp 170–171°C; $\nu_{max}$ 1280 (P=O), 1650 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.28 (3H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.8 Hz, $CH_3$), 3.20 (9H, s, $CH_3$), 4.01 (2H, m, $J_{HP}$ 8.3 Hz, $CH_2O$), 4.02, (2H, s, $CH_2N$), 5.09, 5.33 (2H, m, $H_2C$=); $\delta_P$ ($D_2O$), −5.1. Analysis, found, N, 6.04; P, 13.25; $C_8H_{18}NO_4P$ requires N, 6.28; P, 13.88%.

### (Z)-[*2-Chloro-1-(trimethylammoniomethyl)-ethenyl*] *Ethyl Phosphate* (**24**)

Compound **17** was treated as above to yield colorless stable crystalline **24** (100%), mp 173–174°C; $\nu_{max}$ 1260 (P=O), 1640 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.45 (3H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.8 Hz, $CH_3$), 3.37 (9H, s, $CH_3$), 4.30 (2H, m, $J_{HP}$ 8.3 Hz, $CH_2O$), 4.40 (2H, s, $CH_2N$), 6.67 (1H, d, $J_{HP}$ 2.0 Hz, HC=); $\delta_P$ ($D_2O$), −5.2. Analysis, found, Cl, 13.23; N, 5.17; $C_8H_{17}ClNO_4P$ requires Cl, 13.76; N, 5.44%.

### *Compound* (**25**)

The mixture of phosphate **4** (10 mmol) and triethylenediamine (5 mmol) in benzene (5 mL) was kept at 20°C for 2 d then heated in vacuum at 100°C to give the solid product **25** (70%) crystallized from ethanol, mp 180°C (decomp.); $\nu_{max}$ 1265 (P=O), 1645 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.20 (6H, t, $CH_3$), 4.13 (16H, m, $CH_2$), 4.51 (4H, s, $CH_2C$=), 6.60 (2H, d, $J_{HP}$ 2.3 Hz, HC=); $\delta_P$ ($D_2O$), −4.9. Analysis, found, Cl, 13.39; N, 5.95; P, 11.78. $C_{16}H_{28}Cl_2N_2O_8P_2$ requires Cl, 13.92; N, 5.50; P, 12.16%.

### *Compound* (**26**)

This product was prepared from phosphate **4** and *N,N'*-tetramethylethylenediamine, in a manner analogous to that described for **25**, in 63% yield, mp 220°C (decomp.); $\nu_{max}$ 1260 (P=O), 1640 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.26 (6H, t, $CH_3$), 3.28 (12H, s, $CH_3$), 4.07 (8H, m, $CH_2$), 4.32 (4H, s, $CH_2C$=), 6.56 (2H, d, $J_{HP}$ 2.4 Hz, HC=); $\delta_P$ ($D_2O$), −5.0; M 526, calculated 513. Analysis, found, Cl, 13.38; N, 5.80; P, 11.79; $C_{16}H_{32}Cl_2N_2O_8P_2$ requires Cl, 13.81; N, 5.46; P, 12.07%.

### (E)-(*3-Diethoxyphosphoryloxyprop-2-enyl*)-*trimethylphosphonium Chloride* (**27a**)

Trimethylphosphine (13 mmol) was added to a solution of phosphate **1a** (13 mmol) in anhydrous ether (3 mL) at 0°C and the mixture was left in a refrigerator for 12 h. The resulting crystalline product was washed with ether, dissolved in chloroform, and precipitated with ether to give hygroscopic, low-melting, colorless, crystalline **27a** (82%); $\nu_{max}$ 1285 (P=O), 1680 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.28 (6H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.9 Hz, $CH_3$), 2.13 (9H, d, $J_{HP}$ 11.1 Hz, $CH_3$), 3.54 (2H, dd, $J_{HH}$ 8.3 Hz, $J_{HP}$ 16.2 Hz, $CH_2P$), 4.11 (4H, m, $J_{HP}$ 8.2 Hz, $CH_2O$), 5.32 (1H, m, CCH=), 6.72 (1H, dd, $J_{HH}$ 12.1 Hz, $J_{HP}$ 7.1 Hz, OCH=); $\delta_P$ ($D_2O$), 27.9 ($J_{PP}$ 3.8 Hz, $P^+$), −5.4 (P=O). Analysis, found, Cl, 11.65; P, 19.89; $C_{10}H_{23}ClO_4P_2$ requires Cl, 11.64; P, 20.33%.

### (E)-*Tributyl*(*3-diethoxyphosphoryloxyprop-2-enyl*)*phosphonium Chloride* (**27c**)

This product was prepared from phosphate **1a** and tributylphosphine, in the same way as **27a**, as a light yellow oil; $\nu_{max}$ (neat) 1280 (P=O), 1650 $cm^{-1}$ (C=C); $\delta_H$ ($CDCl_3$), 0.94 (9H, t, $CH_3$), 1.35 (6H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.8 Hz, $CH_3$), 1.53 (12H, m, $CH_2$), 2.40 (6H, m, $CH_2P$), 3.60 (2H, dd, $J_{HH}$ 8.3 Hz, $J_{HP}$ 15.1 Hz, $CH_2P$), 4.16 (4H, m, $CH_2O$), 5.37 (1H, m, $J_{HH}$ 12.3, 8.3 Hz, $J_{HP}$ 1.2 Hz, CCH=), 6.83 (1H, m, $J_{HH}$

12.3 Hz, $J_{HP}$ 7.0 Hz, OCH=); $\delta_P$ ($CDCl_3$) 32.7 ($J_{PP}$ 4.5 Hz, $P^+$), −5.5 (P=O).

### *(E)-Ethyl 3-Trimethylphosphonio-1-propenyl Phosphate* (**28a**)

The compound **27a** was heated at 100°C in vacuum for 1 h, washed with hot methyl ethyl ketone, filtered off, and dried in vacuum to give betaine **28a** (100%), mp 210–212°C; $\nu_{max}$ 1250, 1320 (P=O), 1660 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.10 (3H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 1.0 Hz, $CH_3$), 1.70 (9H, d, $J_{HP}$ 11.1 Hz, $CH_3$), 3.54 (2H, dd, $J_{HH}$ 8.3 Hz, $J_{HP}$ 15.6 Hz, $CH_2P$), 3.78 (2H, m, $J_{HP}$ 8.2 Hz, $CH_2O$), 5.10 (1H, m, CCH=), 6.45 (1H, dd, $J_{HH}$ 12.1 Hz, $J_{HP}$ 6.7 Hz, OCH=); $\delta_P$ ($D_2O$), 26.2 ($P^+$), −3.0 (P=O). Analysis, found P, 25.22; $C_8H_{18}O_4P_2$ requires P, 25.79%.

### (E)-*Ethyl 3-Tributylphosphonio-1-propenyl Phosphate* (**28c**)

The compound **27c** was heated at 80–90°C in vacuum for 3 h, the resulting solid was crystallized from methyl ethyl ketone to give colorless crystalline **28c**, mp 82–83°C; $\nu_{max}$ 1280 (P=O), 1640 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 0.93 (9H, t, $CH_3$), 1.27 (3H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 1.0 Hz, $CH_3$), 1.51 (12H, m, $CH_2$), 2.14 (6H, m, $CH_2P$), 2.99 (2H, m, $J_{HP}$ 15.3 Hz, $J_{HH}$ 8.7 Hz, $CH_2P$), 3.97 (2H, m, $CH_2O$), 5.26 (1H, m, $J_{HH}$ 12.3, 8.7 Hz, $J_{HP}$ 6.2 Hz, CCH=), 6.72 (1H, m, $J_{HH}$ 12.3, 1.2 Hz, $J_{HP}$ 6.8 Hz, OCH=); $\delta_P$ ($D_2O$), 33.0 ($P^+$), −3.0 (P=O). Analysis, found, P, 16.44; $C_{17}H_{36}O_4P_2$ requires P, 16.91%.

### *Tributyl[2-(diethoxyphosphoryloxy)-2-propenyl]-phosphonium Chloride* (**29**)

A solution of tributylphosphine (43 mmol) in anhydrous ether (3 mL) was added to an equimolar amount of phosphate **2**. The mixture was kept in a refrigerator for a day, then decanted, and the precipitate was repeatedly washed with dry ether and kept in vacuum without heating to give a light yellow oil, $\delta_H$ ($CDCl_3$), 0.91 (9H, t, $CH_3$), 1.26 (6H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.8 Hz, $CH_3$), 1.43 (12H, m, $CH_3$), 2.38 (6H, m, $CH_2P$), 3.94 (2H, d, $J_{HP}$ 15.3 Hz, $CH_2P$), 4.14 (4H, m, $J_{HP}$ 8.1 Hz, $CH_2O$), 5.10, 5.30 (2H, m, $H_2C$=); $\delta_P$ ($CDCl_3$), 31.4 ($P^+$), −6.7 (P=O); $\delta_C$ ($CDCl_3$), 12.6 (3C, s, $CH_3$), 15.4 (2C, d, $J_{CP}$ 5.9 Hz, $CH_3$), 18.5 (3C, d, $J_{CP}$ 46.6 Hz, $CH_2P$), 22.9 (3C, d, $J_{CP}$ 16.0 Hz, 2-C in Bu), 23.2 (3C, d, $J_{CP}$ 3.7 Hz, 3-C in Bu), 26.1 (1C, dd, $J_{CP}$ 46.5, 4.8 Hz, $CH_2P$), 64.3 (2C, d, $J_{CP}$ 5.6 Hz, $CH_2O$), 104.0 (1C, d, $J_{CP}$ 6.4 Hz, $H_2C$=), 143.5 (1C, dd, $J_{CP}$ 10.9, 8.6 Hz, OC=).

### *2-[Adamant-1-ylmethyloxy(ethoxy)phosphoryloxy]prop-2-enyl(tri-*n*-butyl)phosphonium Chloride* (**30c**)

Tributylphosphine (15 mmol) was added to a solution of phosphate **3** (13 mmol) in anhydrous ether (3 mL). Next day the resulting oil was thoroughly washed with dry ether and kept in vacuum without heating to give chloride **30c** (85%), $\nu_{max}$ (neat) 1280 (P=O), 1650 $cm^{-1}$ (C=C); $\delta_H$ ($CDCl_3$), 0.93 (9H, t, $CH_3$), 1.25 (3H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.9 Hz, $CH_3$), 1.53 (27H, m, Ad + $C_2H_4$), 2.12 (6H, m, $CH_2P$), 3.09 (2H, m, $AdCH_2$), 3.35 (2H, d, $J_{HP}$ 11.3 Hz, $CH_2P$), 3.52 (2H, m, $CH_2O$), 4.29, 4.47 (2H, m, $H_2C$=); $\delta_P$ ($CDCl_3$), 31.4 ($J_{PP}$ 3.3 Hz, $P^+$), −6.3 (P=O). Analysis, found, Cl, 6.40; P, 10.66; $C_{28}H_{53}ClO_4P_2$ requires Cl, 6.43; P, 11.24%.

### *1-Adamantylmethyl 1-(trimethylphosphoniomethyl)ethenyl Phosphate* (**31a**)

Trimethylphosphine (13 mmol) was added to a solution of phosphate **3** (13 mmol) in anhydrous ether (3 mL) at 0°C and the mixture was kept in a refrigerator for 2 d. The resulting precipitate was repeatedly rinsed with ether and crystallized from methyl ethyl ketone to give colorless crystalline betaine **31a** (40%), mp 199–201°C; $\nu_{max}$ 1280 (P=O), 1655 $cm^{-1}$ (C=C); $\delta_H$ ($CDCl_3$), 1.70 (15H, m, Ad), 2.23 (9H, d, $J_{HP}$ 14.5 Hz, $CH_3$), 3.63 (2H, d, $J_{HP}$ 4.8 Hz, $CH_2O$), 3.88 (2H, d, $J_{HP}$ 15.9 Hz, $CH_2P$), 4.18 (2H, m, $H_2C$=); $\delta_P$ ($CDCl_3$), 25.7 ($J_{PP}$ 3.5 Hz, $P^+$), −6.1 (P=O).

### (Z)-*3-Chloro-2-diethoxyphosphoryloxyprop-2-enyl(trimethyl)phosphonium Chloride* (**32a**)

Trimethylphosphine (39 mmol) was added to a solution of phosphate **4** (39 mmol) in anhydrous ether (3 mL) at 0°C and left for 12 h at this temperature. The precipitated crystals were washed with ether and kept in vacuum without heating to give colorless hygroscopic **32a** (100%), mp 74–75°C; $\nu_{max}$ 1280, 1310 (P=O), 1660 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.40 (6H, td, $J_{HH}$ 7.0 Hz, $J_{HP}$ 1.2 Hz, $CH_3$), 1.97 (9H, d, $J_{HP}$ 14.4 Hz, $CH_3$), 3.53 (2H, dd, $J_{HP}$ 15.0, 0.9 Hz, $CH_2P$), 4.35 (4H, m, $J_{HP}$ 8.5 Hz, $CH_2O$), 6.36 (1H, dd, $J_{HP}$ 5.0, 2.3 Hz, HC=); $\delta_P$ ($D_2O$), 26.7 ($J_{PP}$ 6.6 Hz, $P^+$), −6.4 (P=O). Analysis, found, Cl, 20.06; P, 17.78; $C_{10}H_{22}Cl_2O_4P_2$ requires Cl, 20.91; P, 18.27%.

### (Z)-*Tributyl(3-chloro-2-diethoxyphosphoryloxyprop-2-enyl)phosphonium Chloride* (**32c**)

Tributylphosphine (50 mmol) was added to a solution of phosphate **4** (40 mmol) in anhydrous ether (3 mL) at room temperature and the mixture was kept in a refrigerator overnight. The resulting

product was precipitated from chloroform with ether to give oily **32c** (60%), $\nu_{max}$ (neat) 1275 (P=O), 1650 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 0.85 (9H, t, $CH_3$), 1.26 (6H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 1.3 Hz, $CH_3$), 1.45 (12H, m, $CH_2$), 2.32 (6H, m, $CH_2P$), 4.12 (4H, m, $J_{HP}$ 8.3 Hz, $CH_2O$), 4.27 (2H, d, $J_{HP}$ 15.6 Hz, $CH_2P$), 6.84 (1H, dd, $J_{HP}$ 4.9, 1.8 Hz, HC=); $\delta_P$ ($D_2O$), 32.1 ($J_{PP}$ 5.4 Hz, $P^+$), −7.1 (P=O). Analysis, found, Cl, 17.17; P, 12.40; $C_{19}H_{40}Cl_2O_4P_2$ requires Cl, 15.24; P, 13.31%.

### (Z)-[*2-Chloro-1-(trimethylphosphoniomethyl)-ethenyl*] *Ethyl Phosphate* (**33a**)

The compound **32a** was heated in vacuum at 100°C for 2 h to give nonhygroscopic crystalline betaine **33a** (100%), mp 163–164°C; $\nu_{max}$ 1280, 1300 (P=O), 1655 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.30 (3H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.9 Hz, $CH_3$), 1.95 (9H, d, $J_{HP}$ 14.4 Hz, $CH_3$), 3.47 (2H, d, $J_{HP}$ 15.1 Hz, $CH_2P$), 4.10 (2H, m, $J_{HP}$ 8.2 Hz, $CH_2O$), 6.08 (1H, dd, $J_{HP}$ 5.1, 2.2 Hz, HC=); $\delta_P$ ($D_2O$), 26.1 ($P^+$), −5.1 (P=O). Analysis, found, Cl, 13.06; P, 22.11; $C_8H_{17}ClO_4P_2$ requires Cl, 12.91; P, 22.56%.

### (Z)-[*2-Chloro-1-(tripropylphosphoniomethyl)-ethenyl*] *Ethyl Phosphate* (**33b**)

Tripropylphosphine (16 mmol) was added to phosphate **4** (14 mmol) at 20°C. The mixture was left for 6 d at room temperature then heated at 80–90°C for 5 h. The colored solid product was washed with acetone to give colorless betaine **33b** (30%), mp 157–158°C; $\nu_{max}$ 1260, 1280 (P=O), 1650 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 1.04 (9H, td, $J_{HH}$ 7.2 Hz, $J_{HP}$ 0.9 Hz, $CH_3$), 1.27 (3H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 1.0 Hz, $CH_3$), 1.62 (6H, m, $CH_2$), 2.22 (6H, m, $CH_2P$), 3.40 (2H, d, $J_{HP}$ 13.7 Hz, $CH_2P$), 4.06 (2H, m, $J_{HP}$ 8.2 Hz, $CH_2O$), 6.06 (1H, dd, $J_{HP}$ 4.3, 2.3 Hz, HC=); $\delta_P$ ($D_2O$), 31.3 ($J_{PP}$ 5.3 Hz, $P^+$), −5.1 (P=O). Analysis, found, Cl, 9.55; P, 16.69; $C_{14}H_{29}ClO_4P_2$ requires Cl, 9.88; P, 17.27%.

### (Z)-[*2-Chloro-1-(tributylphosphoniomethyl)-ethenyl*] *Ethyl Phosphate* (**33c**)

Compound **32c** was heated in vacuum at 80–90°C for 5 h. The resulting product was repeatedly washed with dry ether and kept in vacuum to give betaine **33c** (100%), mp 128.5–129°C; $\nu_{max}$ 1275 (P=O), 1645 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 0.94 (9H, t, $CH_3$), 1.30 (3H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 0.8 Hz, $CH_3$), 1.55 (12H, m, $CH_2$), 2.28 (6H, m, $CH_2P$), 3.42 (2H, d, $J_{HP}$ 13.9 Hz, $CH_2P$), 4.08 (2H, m, $J_{HP}$ 8.2 Hz, $CH_2O$), 6.08 (1H, dd, $J_{HP}$ 4.7, 2.4 Hz, HC=); $\delta_P$ ($D_2O$), 32.7 ($J_{PP}$ 5.3 Hz, $P^+$), −5.1 (P=O). Analysis, found, Cl, 9.83; P, 15.41; $C_{17}H_{35}ClO_4P_2$ requires Cl, 8.84; P, 15.45.

### *Ethyl 1-Methyl-2-tributylphosphonioethenyl Phosphate* (**35**)

A solution of phosphate **2** (10 mmol) and tributylphosphine (12 mmol) in anhydrous ether (5 mL) was kept for 2 d at room temperature. Then the ether solution was poured off and the oily residue was rinsed with ether, precipitated from chloroform, dissolved in THF (20 mL), and boiled under reflux for 25 h. After cooling with Dry Ice, the hygroscopic crystalline betaine **35** was separated (30%), mp 116–117°C; $\nu_{max}$ 1100 (P=O), 1620 $cm^{-1}$ (C=C); $\delta_H$ ($D_2O$), 0.93 (9H, t, $CH_3$), 1.31 (3H, t, $\underline{CH_3}CH_2$), 1.49 (12H, m, $CH_2$), 2.21 (6H, m, $CH_2P$), 2.33 (3H, s, $CH_3C$=), 4.04 (2H, m, $CH_2O$), 4.92 (1H, dd, $J_{HP}$ 14.8, 3.4 Hz, HC=); $\delta_P$ ($D_2O$), 22.5 ($P^+$), −6.9 (P=O). Analysis, found, P, 16.13; $C_{17}H_{36}O_4P_2$ requires P, 16.91%.

### *1-Adamantylmethyl 1-Methyl-2-tributylphosphonioethenyl Phosphate* (**36**)

The compound **30c** was heated in vacuum at 100°C for 6 h, the resulting product was rinsed with THF to yield white powdered **36** (60%), mp 182–183°C (from methyl ethyl ketone); $\nu_{max}$ 1280, 1310 (P=O), 1635 $cm^{-1}$ (C=C); $\delta_H$ ($CDCl_3$), 0.86 (9H, t, $CH_3$), 1.57 (27H, m, Ad + $C_2H_4$), 2.09 (6H, m, $CH_2P$), 2.38 (3H, s, $CH_3$), 3.43 (2H, d, $J_{HP}$ 4.9 Hz, $CH_2O$), 4.22 (1H, dd, $J_{HP}$ 18.4, 1.9 Hz, HC=); $\delta_P$ ($CDCl_3$), 21.9 ($P^+$), −5.4 (P=O); $\delta_C$ ($CDCl_3$), 13.3 (3C, s, $CH_3$), 20.2 (3C, d, $J_{CP}$ 52.4 Hz, $CH_2P$), 22.6 (1C, d, $J_{CP}$ 10.6 Hz, $CH_3$), 23.6 (3C, d, $J_{CP}$ 6.5 Hz, 2-C in Bu), 23.8 (3C, d, $J_{CP}$ 4.5 Hz, 3-C in Bu), 28.1 (3C, s, Ad), 33.6 (1C, d, $J_{CP}$ 8.5 Hz, Ad), 37.0 (3C, s, Ad), 39.1 (3C, s, Ad), 76.2 (1C, d, $J_{CP}$ 6.9 Hz, $CH_2O$), 78.3 (1C, dd, $J_{CP}$ 87.1, 8.1 Hz, HC=), 176.6 (1C, m, OC=). Analysis, found, P, 12.56; $C_{26}H_{48}O_4P_2$ requires P, 12.73%.

### *3,3-Dichloro-2-diethoxyphosphoryloxyprop-2-enyl(trimethyl)ammonium Chloride* (**37**)

Triethyl phosphite (20 mmol) was mixed with a solution of 1,1,1,3-tetrachloroacetone (20 mmol) in ether (30 mL) at −30°C. When the reaction was complete the solvent was partially evaporated and trimethylamine (20 mmol) in ether (5 mL) was added to the residue at 0°C. After 12 h the precipitated crystals were separated, washed with ether and dried in vacuum to give colorless hydroscopic crystalline **37** (25%), mp 81–82°C; $\nu_{max}$ 1280 (P=O), 1630 $cm^{-1}$ (C=C); $\delta_H$ ($CDCl_3$), 1.32 (6H, td, $J_{HH}$ 7.1 Hz, $J_{HP}$ 1.2 Hz, $CH_3$), 3.54 (9H, s, $CH_3$), 4.19 (4H, m, $J_{HP}$ 8.5 Hz, $CH_2O$), 4.76 (2H, s, $CH_2N$); $\delta_P$ ($CDCl_3$), −7.1. Analysis, found, Cl, 29.32; N, 4.80; P, 8.12; $C_{10}H_{21}Cl_3NO_4P$ requires Cl, 29.82; N, 3.93; P, 8.68%.

### *Kinetic Measurements*

Kinetic studies on inhibition of human erythrocyte AChE were carried out in phosphate buffer (pH 7.8) containing KCl (0.1 *M*) according to the known pH-state method [4]. The mixture of the enzyme and an inhibitor was incubated at 25°C for a time $t$ (0.5–30 min); then acetylcholine iodide (final concentration $2 \times 10^{-3}$ *M*) was added to it and the residual enzymic activity, $V_t$, was determined by titration of the liberated acetic acid with 0.05 *N* NaOH solution over a period of 5 min using the autotitrator BAT-15 (USSR). From a plot of ln $(V_0/V_t)$ vs $t$ the observed rate constants, $k_0$, were obtained according to Eq. (17)

$$\ln (V_0/V_t) = k_0[I]_0 t + a \qquad (17)$$

where $V_0$ is the AChE activity in the absence of an inhibitor, $[I]_0$ is the initial inhibitor concentration, and $a$ is a constant. The kinetic parameters $k_a$ and $K_{ir}$ were deduced from a plot of $1/k_0$ vs $[I]_0$ in accordance with Eq. (18):

$$1/k_0 = 1/k_a + [I]_0/(k_a \cdot K_{ir}) \qquad (18)$$

The extremes of variation of the inhibitor concentration (in general, 4–6 points) differed by 5–10 times.

The alkaline hydrolysis was carried out in a thermostatted cell at 25°C. Four milliliters of aqueous solution of a hydrolyzable ester (final concentration $2 \times 10^{-2}$ *M*) was added to 21 mL of NaOH solution in water (final concentration $4.8 \times 10^{-2}$ *M*). Samples of the mixture (2 mL) were withdrawn at appropriate intervals, $t$, and potentiometrically titrated with 0.1 *N* HCl to determine the residual base concentration $[B]_t$. The hydrolysis rate constants, $k_{OH}$, were graphically deduced using Eq. (19):

$$\frac{1}{[B]_0 - [P]_0} \ln \frac{[P]_0([B]_0 - x)}{[B]_0([P]_0 - x)} = k_{OH} t \qquad (19)$$

where $[B]_0$ and $[P]_0$ are the initial base or phosphate concentrations, repectively, and $x = [B]_0 - [B]_t$. Phosphate **17** requires 2 equiv of base for hydrolysis.

### *References*

[1] S.K. Bhatia, J. Hajdu, J. Org. Chem., 53, 1988, 5034.
[2] Yu.G. Gololobov, Yu.V. Balitskii, M.N. Danchenko, T.V. Kim, E.I. Kiseleva, T.V. Kolodka, V.P. Lysenko, D.M. Malenko, N.K. Maidanovich, L.I. Nesterova: Proceedings of the VIIth Conference on Chemistry of Organophosphorus Compounds. Leningrad, USSR, p. 72 (1987).
[3] T.V. Kim, E.I. Kiseleva, Yu.T. Struchkov, M.Yu. Antipin, A.N. Chernega, Yu.G. Gololobov, Zh. Obsch. Khim., 54, 1984, 2486; Yu.G. Gololobov, T.V. Kim, E.I. Kiseleva, Dokl. Akad. Nauk (USSR), 272, 1983, 1388.
[4] A.P. Brestkin, I.L. Brik, R.I. Volkova, N.N. Godovikov, Ch.Ch. Gurdaliev, M.I. Kabachnik, N.A. Kardanov, Dokl. Adad. Nauk (USSR), 200, 1971, 103.
[5] Yu.G. Gololobov, L.F. Kasukhin, G.V. Pesotskaya, V.S. Petrenko, T.V. Kim, Zh.M. Ivanova, Zh. Obsch. Khim., 48, 1978, 1974.
[6] W. Perkow, E.W. Krockow, K. Knoevenagel, Chem. Ber., 88, 1955, 662.