TABLE I

ADDITION PRODUCTS FROM ALKENES AND ALKYNES WITH DIMETHYLMETHYLTHIOSULFONIUM TRINITROBENZENESULFONATE

Substrate	Decompn. point, °C.	Yield, %	Calcd. % C	Calcd. % H	Calcd. % N	Found[a] % C	Found[a] % H	Found[a] % N
cis-2-Butene	134–136	94	34.14	4.19	9.18	34.51	4.42	9.56
trans-2-Butene	136–138	95	34.14	4.19	9.18	33.87	4.53	9.46
1-Pentene	141–142	93	35.66	4.49	8.91	35.68	4.59	9.13
Cyclopentene	139.5–140	89	35.81	4.08	8.95	36.11	4.05	9.26
Cyclohexene	141–143	99	37.26	4.38	8.69	37.01	4.32	8.45
Cyclooctene	122–123	74	39.91	4.93	8.21	39.42	5.06	7.95
3-Hexyne	134.5–135	89	37.26	4.38	8.69	36.87	4.39	8.51
Phenylacetylene	147–147.5	77	40.55	3.40	8.35	40.77	3.49	8.58
Diphenylacetylene	200–200.5	..	47.66	3.66	7.25	47.49	4.03	7.40

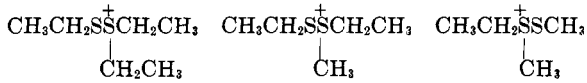
[a] Analyses were by C. F. Geiger, Ontario, Calif., and A. Elek, Torrance, Calif.

TABLE II

ADDITION PRODUCTS FROM 1-PENTENE AND ALKYLATED DISULFIDES

Addend	Yield, %	Product m.p., °C.	Calcd. % C	Calcd. % H	Calcd. % N	Found[a] % C	Found[a] % H	Found[a] % N
6	66	114.5–115.5	39.75	5.30	8.18	39.73	5.59	8.47
7	94	105.5–106.5	38.46	5.04	8.41	38.83	5.25	8.44
8	68	130.5–131	37.10	4.77	8.65	36.74	4.69	8.66

[a] Analyses were by C. F. Geiger, Ontario, Calif.



6 **7** **8**

(the anion in each case is 2,4,6-trinitrobenzenesulfonate)

The stereochemical course of the addition reaction involving alkenes is most likely *trans*. The evidence arises from the identity of the cyclooctene addition product **5** as described by eq. 4 with that arising from the cyclooctene episulfide. The principal assumption involved is simply that nucleophilic opening of the episulfonium ring is *trans*, for alkylation of the episulfide should not involve bonds between sulfur and the carbocyclic ring.[10]

Experimental

1-Dimethylsulfonio-2-methylthiocyclooctane 2,4,6-Trinitrobenzenesulfonate.—As a typical example of the addition of an alkylated disulfide to an alkene, 2.50 g. (0.00625 mole) of dimethylmethylthiosulfonium trinitrobenzenesulfonate was suspended in 7 ml. of nitromethane and 1.10 g. (0.00100 mole) of cyclooctene was added in one portion. When the mixture was swirled, the undissolved solid quickly disappeared. After 20 min., 50 ml. of absolute ether was added. A light yellow oil separated which quickly crystallized. The solid was isolated by filtration, washed with 20 ml. of ether and 20 ml. of pentane, and air dried for a few minutes. After drying the product at reduced pressure, 2.80 g., m.p. 119–121°, was obtained. One crystallization from nitromethane–ether gave 2.35 g. (74%) of white crystals, m.p. 122–123°.

Identical reaction, isolation, and purification conditions were used for the addition of the sulfonium compound to alkynes.

(10) It should be noted at this point that the reaction of episulfonium salts with nucleophiles does not invariably result in ring opening and the formation of β-substituted sulfonium salts.[1] As examples of other situations, iodide ion yields the original alkene, iodine, and a disulfide, and mercaptide ion yields the original alkene and a disulfide.[11]

(11) D. J. Pettitt and G. K. Helmkamp, *J. Org. Chem.*, **29**, 2702 (1964).

Synthesis of Ethyl *p*-Nitrophenyl α-Methoxyalkylphosphonates

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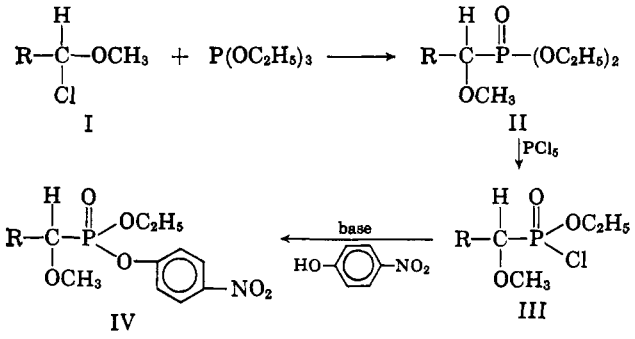
Synthesis of a new class of organophosphorus compounds, ethyl *p*-nitrophenyl α-methoxyalkylphosphonates, is reported. The compounds were prepared *via* the Michaelis–Arbuzov reaction of diethyl *p*-nitrophenyl phosphite and α-chloroalkyl methyl ethers. Confirmation of structure of the compounds was ascertained by hydrolysis to the known crystalline α-hydroxybenzylphosphonic acid, isolated as the aniline salt.

We are reporting the chemistry of some new ethyl *p*-nitrophenyl α-methoxyalkylphosphonates (IV), which were synthesized as part of a program for the preparation of novel organophosphonates that should have enhanced antienzymatic activity and decreased mammalian toxicity, and be applicable for possible therapeutic use.[1]

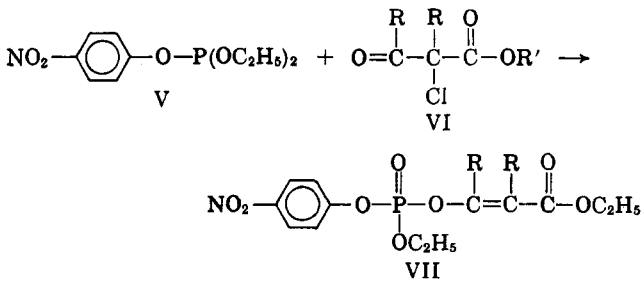
The initial preparation of these compounds *via* the Michaelis–Arbuzov reaction of triethyl phosphite and α-chloroamyl methyl ether was as follows. Although II was easily prepared using the above routine, III was synthesized with difficulty. For example, the treatment with phosphorus pentachloride, at times, proceeded too far, and, in addition to III, the dichloridate resulted which was not easily separable from III. Occasionally, for unknown reasons, reaction of II with phosphorus pentachloride did not yield III, or the dichloridate, but rather an unworkable sirupy residue.

(1) E. L. Becker, T. R. Fukuto, B. Boone, D. C. Canham, and E. Boger, *Biochemistry*, **2**, 72 (1963); B. H. Alexander, L. S. Hafner, M. V. Garrison, and J. E. Brown, *J. Org. Chem.*, **28**, 3499 (1963).

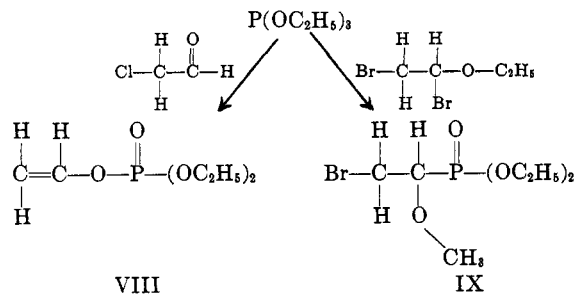


The preparation of IV from III furthermore was not a smooth reaction and the yields were quite low. For these reasons, another route for the preparation of the desired compounds (IV) was sought.

Stiles[2] previously had prepared diethyl *p*-nitrophenyl phosphite (V) and treated it with an "α-chloro-β-chalcogen fatty acid" (VI), to give the phosphate VII.

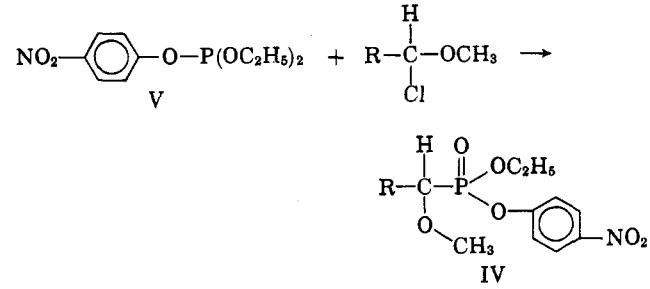


Allen and Johnson[3] had treated triethyl phosphite somewhat similarly with chloroacetaldehyde, and the phosphate VIII resulted.

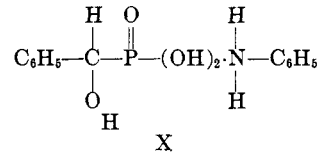


We considered the possibility that the α-chloroalkyl methyl ether (I) might react differently from the fatty acid VI or the aldehyde with a phosphite and yield a phosphonate rather than a phosphate. This was based upon the report of Abramov and Karp[4] who treated triethyl phosphite with α-haloalkyl ethers and obtained a normal Michaelis–Arbuzov reaction; that is, a phosphonate IX was the end product.

The following reaction was tried, and a synthesis was found for a class of phosphonates that has been previously extremely difficult to prepare.

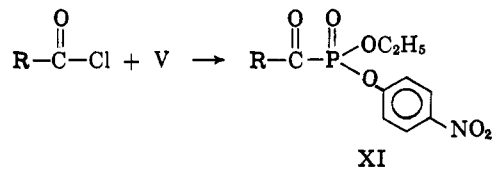


Infrared spectra of the product IV obtained from III and those obtained from V were identical. Confirmation that IV was a phosphonate was ascertained as follows: hydrolysis of IV (R = C_6H_5) with hydrochloric acid and the isolation of the resultant product as the crystalline aniline salt gave the known phosphonate X.



A comparison of the two routes of syntheses (III or V → IV) shows this. Ethyl *p*-nitrophenyl α-methoxypentylphosphonate (IV, R = n-C_4H_9) was isolated in 10% yield from triethyl phosphite (II → IV). The same compound was obtained in 69% yield from diethyl *p*-nitrophenyl phosphite (V → IV). However, the yields of some arylalkyl compounds synthesized by this latter route were as low as 9%. IV *via* the latter reaction was also easier to prepare in a pure state and the prerequisite intermediates were more simply made.

Based on the knowledge that acyl halides will react with triethyl phosphite to yield keto compounds,[5] we tried the following reaction.



In all cases when an alkyl acyl halide was treated with diethyl *p*-nitrophenyl phosphite, an exothermic reaction occurred; the products isolated, however, could not be purified. Infrared spectra determined on the crude products indicated peaks for the carbonyl, nitro, and P=O groups, and the spectra were somewhat similar to the curves of the ethyl *p*-nitrophenyl α-methoxyalkylphosphonates.

Experimental

α-Chloroalkyl Methyl Ethers (1).—The α-chloro straight-chain alkyl methyl ethers were prepared, essentially as described by Klages and Muhlbauer[6] with the exception that isopropyl chloride was used as the solvent. Methylene chloride as a solvent is inferior to isopropyl chloride because the water–hydrochloric acid phase formed in the reaction mixture is lighter than the methylene chloride–product phase.

Attempts to prepare the α-chloroarylalkyl methyl ethers by the above route failed; they were, however, synthesized by con-

(2) A. R. Stiles, U. S. Patent 2,895,982 (July 21, 1959).

(3) J. F. Allen and O. H. Johnson, *J. Am. Chem. Soc.*, **77**, 2871 (1955).

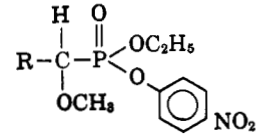
(4) V. S. Abramov and G. S. Karp, *Dokl. Akad. Nauk. SSSR*, **91**, 1095 (1953); *Chem. Abstr.*, **48**, 9906*g* (1954).

(5) M. I. Kabachnik and P. A. Rossliskaya, *Bull. Acad. Sci. URSS, Classe sci. chim.*, 364 (1945); *Chem. Abstr.*, **40**, 4688[8] (1946).

(6) F. Klages and E. Muhlbauer, *Ber.*, **92**, 1819 (1959).

TABLE I

ETHYL p-NITROPHENYL α-METHOXYALKYLPHOSPHONATES



IV

R	Purification[a]	$n^{25}D$	Yield, %	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	P, % Calcd.	P, % Found
C_3H_7	B	1.516	66	$C_{12}H_{20}NO_6P$	49.2	48.6	6.4	6.3	4.4	4.4	9.8	9.1
C_4H_9	B	1.514	10 or 69[b]	$C_{14}H_{22}NO_6P$	50.8	50.6	6.7	7.1	4.2	4.6	9.4	8.6
C_5H_{11}	B	1.512	15	$C_{15}H_{24}NO_6P$	52.2	52.6	7.0	7.0	4.1	4.1	9.0	8.4
C_6H_{13}	B	1.503	64	$C_{16}H_{26}NO_6P$	53.5	54.1	7.3	7.6	3.9	3.9	8.6	8.4
C_7H_{15}	C	1.503	21	$C_{17}H_{28}NO_6P$	54.7	54.9	7.6	7.6	3.8	3.5	8.3	8.0
C_6H_5	B	1.557	52	$C_{16}H_{18}NO_6P$	54.7	54.7	5.2	5.2	4.0	3.6	8.8	8.6
$C_6H_5CH_2$	C	1.553	9	$C_{17}H_{20}NO_6P$	55.0	55.0	5.5	5.6	3.8	3.8	8.5	8.5
$C_6H_5C_2H_4$	C	1.548	21	$C_{18}H_{22}NO_6P$	57.0	56.9	5.9	5.9	3.7	3.8	8.2	8.2

[a] B = Kontes molecular still, first toluene then xylene; C = same, first xylene then DMF. [b] Route A, 69%; route B, 10%.

verting the aldehydes to the acetals by Langvad's procedure.[7] Boiling points, refractive indices, and yields of once-distilled dimethyl acetals are as follows: from 2-phenylethanal, 42–44° (0.05 mm.), $n^{21}D$ 1.4938, and 67%; from 3-phenylpropanal, 125–135° (25 mm.), $n^{24}D$ 1.4890, and 60%.

The acetals that resulted were chlorinated according to the directions of Strauss and Heinze,[8] with the exception that we used equimolar quantities of materials. Boiling points, refractive indices, and yields of once-distilled products are as follows: 1-chloro-2-phenylethyl methyl ether, 64° (0.3 mm.), $n^{24}D$ 1.5272, and 30%; 1-chloro-3-phenylpropyl methyl ether, 66° (0.1 mm.), $n^{27}D$ 1.5126, and 71%.

Diethyl p-Nitrophenylphosphite (V).—V was prepared according to the directions of Stiles.[2] The yield of diethyl phosphorochloridite was 50%, b.p. 52–55° (16 mm.), $n^{23}D$ 1.4366. Triethylamine was used in place of diethylaniline as the acid acceptor to prepare V, yield 79%, $n^{24}D$ 1.5317.

Ethyl p-Nitrophenyl α-Methoxypentylphosphonate (IV, R = n-C_4H_9).—The procedures for the preparation of ethyl p-nitrophenyl α-methoxyalkylphosphonates are illustrated by the following syntheses of IV (R = n-C_4H_9) (see Table I).

Method A.—α-Chloroamyl methyl ether (13.7 g., 0.1 mole) was placed in a three-necked 50-ml. round-bottom flask equipped with a magnetic stirrer, air condenser, drying tube, and dropping funnel at room temperature. While stirring, diethyl p-nitrophenyl phosphite (26 g., 0.1 mole) was added dropwise and the reaction mixture became quite warm; it was set aside at room temperature for several hours and kept overnight at 5°.

The ester was purified by passing it through a falling-film molecular still at a pressure of 0.03 mm. using toluene initially, then xylene, as the heating solvent.

Method B.—Approximately 58 g. (0.42 mole) of α-chloroamyl methyl ether was added to triethyl phosphite (70.5 g., 0.42 mole) with stirring. The mixture was heated for 2 hr. on a water bath at 55° and then distilled. The main portion was fractionated through a 12-in. helices-packed column.

II (R = n-C_4H_9) was treated with phosphorus pentachloride essentially as previously described[9] with these modifications: phosphorus pentachloride (27 g., 0.13 mole) was added through an addition tube (closed to the atmosphere) to 31 g. (0.13 mole of diethyl α-methoxypentylphosphonate dissolved in 150 ml. of dry carbon tetrachloride at 50°. The reaction was maintained at 50° for 7 hr., after which the carbon tetrachloride was removed and the chloridate distilled, yield 44%, b.p. 73° (0.1 mm.), $n^{24}D$ 1.4359.

Approximately 9 ml. of triethylamine was added dropwise to 13 g. (0.064 mole) of distilled III (R = n-C_4H_9) and p-nitrophenol (8.9 g., 0.064 mole) in 100 ml. of dry ether, similarly to the directions of Razumov and co-workers.[10] After refluxing 3 hr., the mixture was cooled and filtered. The filtrate was washed with cold water, 5% aqueous hydrochloric acid, cold water, saturated sodium bicarbonate, cold water, and saturated sodium chloride, and was dried over anhydrous sodium sulfate. After filtering and removing the solvent, the residue was distilled in a falling-film molecular still using toluene, then xylene, as the boiling solvent.

Diethyl α-Methoxybenzylphosphonate (II, R = C_6H_5).—α-Chlorobenzyl methyl ether (33.6 g., 0.21 mole) was added dropwise (caution, vigorous reaction), while stirring, to triethyl phosphite (35.7 g., 0.21 mole), heated at 80 to 100° for 40 min., and distilled through a 12-in. helices-packed column, yield 37 g. (67%), b.p. 128° (0.4 mm.), $n^{20}D$ 1.4940.

Anal. Calcd. for $C_{12}H_{19}O_4P$: C, 55.8; H, 7.4; P, 12.0. Found: C, 55.7; H, 7.5; P, 11.8.

Hydrolysis of Ethyl p-Nitrophenyl α-Methoxybenzylphosphonate (IV, R = C_6H_5).—IV (R = C_6H_5) (7 g., 0.02 mole) and 50 ml. of concentrated hydrochloric acid were refluxed for 10 hr., cooled, and stored overnight at 25°. A solid (p-nitrophenol) was removed, the filtrate was concentrated and extracted with ether, and the extracts were dried over anhydrous sodium sulfate. Removal of the ether yielded an oil which crystallized when dissolved in a minimum amount of cold ethanol, ether, and 0.02 mole of aniline. Recrystallization of the aniline salt from methanol produced crystals which melted at 200–203° (lit.[11] m.p. 201–202°); crude yield was 3 g. (56%); a mixture melting point with an authentic sample prepared according to the directions of Kharasch and co-workers[12] was not depressed.

Anal. Calcd. for $C_{13}H_{16}NO_4P$: C, 55.5; H, 5.7; N, 5.0; P, 11.0. Found: C, 55.2; H, 6.1; N, 5.0; P, 11.2.

Acknowledgment.—Thanks are due Mr. Joseph P. Bingham and Dr. Elmer L. Becker for valuable assistance.

(7) T. Langvad, *Acta Chem. Scand.*, **8**, 336 (1954); *Chem. Abstr.*, **49**, 5277c (1954).

(8) F. Strauss and H. Heinze, *Ann.*, **493**, 191 (1932); *Chem. Abstr.*, **26**, 2449 (1932).

(9) A. I. Razumov, O. A. Mukhacheva, and I. V. Zaikonnikova, *Zh. Obshch. Khim.*, **27**, 754 (1957); *Chem. Abstr.*, **51**, 16332f (1957).

(10) A. I. Razumov, E. A. Markovich, and A. D. Reshetnikova, *Zh. Obshch. Khim.*, **27**, 2394 (1957); *Chem. Abstr.*, **52**, 7194a (1958).

(11) J. B. Conant and A. D. MacDonald, *J. Am. Chem. Soc.*, **42**, 2343 (1920).

(12) M. S. Kharasch, R. A. Mosher, and I. S. Bengelsdorf, *J. Org. Chem.*, **25**, 1000 (1960).