6-OXA-3-PHOSPHABICYCLO[3.1.0]HEXANE 3-OXIDE DERIVATIVES

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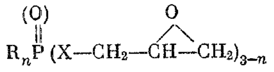
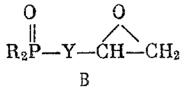
A large number of papers on the synthesis, properties, and practical applications of epoxy compounds have appeared recently. The first organophosphorus compound containing an epoxy group was synthesized in 1952 [1]. Phosphorylated α-epoxides are now being applied for the preparation of thermally stable copolymers, as hydraulic liquids, as stabilizers and plasticizers for vinyl resins, as auxiliaries in the textile industry, and as lubricants [2-6]. Despite the rapid increase in the scope of application of phosphorus-containing epoxides and the large number of investigations on these compounds, the number of their structural variants remains small and can be represented by the following three typical formulas



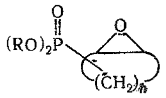
$R_n\overset{(O)}{\overset{\|}{P}}(X-CH_2-\overset{O}{CH-CH_2})_{3-n}$

A

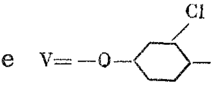


$R_2\overset{O}{\overset{\|}{P}}-Y-\overset{O}{CH-CH_2}$

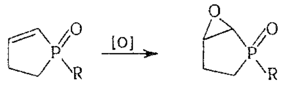
B



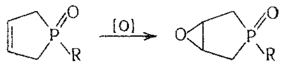
C

Most of the compounds have the structure A, in which the oxirane ring forms part of a 2,3-epoxypropyl group. The latter may be linked directly to the phosphorus atom [1, 7-10], or may be separated from it by the bridge group X (X= $-C_6H_4O-$ [11], $-N(CH_3)-$ [12], $-O-$ [3, 4, 6, 10, 13, 14], $-OCH_2CH(CH_2Cl)O-$ [15], $-CH_2O-$ [16, 17]). In compounds of type B the oxirane ring may be linked directly to the phosphorus atom [18-23], or it may be separated from it by the group Y, which may, for example, be  [24]. In the series of substances of type C two groups of compounds with n = 3 and 4 are known [25]. Other structural variants, and in particular epoxy derivatives of phosphorus-containing heterocycles, have been unknown until recently.

This paper is concerned with a new group of phosphorus-containing epoxides, which are bicyclic systems consisting of condensed phospholane and oxirane rings. Their synthesis is based on the oxidation of phospholene 1-oxide derivatives with peroxy acids [26]. We had at our disposal phospholene 1-oxide derivatives with the double bond in the 2- and in the 3-position. In the oxidation of these compounds we could expect to prepare epoxyphospholane oxides with structures D and E respectively:



D



E

However, the experiments showed that the ease of epoxidation depends greatly on the position of the double bond in the ring. 3-Phosphole 1-oxide derivatives readily react with peroxy acids at room temperature

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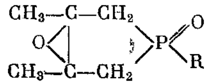
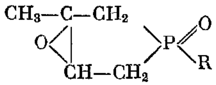
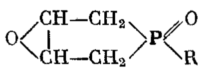
TABLE 1


(A)


(B)


(C)

Compound			Yield, %	bp, °C (p, mm)	mp, °C	n_D^{20}	d_4^{20}	Found/Calculated					Molecular formula
No.	type	R						*MR*	C, %	H, %	P, %	Epoxide O, %	
I	A	C_6H_5	80		155	—	—	—	64,90 64,86	6,92 6,80	13.90 13,94	6,83 7,20	$C_{12}H_{15}O_2P$
II	A	OC_2H_5	66	—	79—80	—	—	—	50,91 50,52	7,73 7,89	15,95 16,28	8,24 8,41	$C_8H_{15}O_3P$
III	A	OC_4H_9-*n*	90	111—112 (0,025)	—	1,4681	1,0888	55,68 55,37	55,20 55,04	9,01 8,71	14,24 14,20	7,24 7,34	$C_{10}H_{19}O_3P$
IV	B	OCH_3	65	87 (0,03)	53—56	1,4811	1,2432	37,13 36,90	44,53 44,44	6,94 6,78	18,66 19,06	9,81 9,87	$C_6H_{11}O_2P$
V	B	OC_2H_5	82,7	94—95 (0,03)	—	1,4748	1,1768	42,12 41,53	47,78 47,73	7,69 7,44	17,52 17,59	8,72 9,09	$C_7H_{13}O_3P$
VI	B	OC_3H_7	69,5	108—109 (0,023)	—	1,4721	1,1432	46,54 46,15	50,74 50,53	8,01 7,89	16,19 16,26	8,06 8,42	$C_8H_{15}O_3P$
VII	B	OC_3H_7-*i*	70,5	91 (0,03)	—	1,4697	1,1375	46,48 46,15	50.32 50,52	7,96 7,89	15,78 16,26	8,13 8,42	$C_8H_{15}O_3P$
VIII	B	OC_4H_9	88,7	118 (0,03)	—	1,4701	1,1132	51,15 50,75	53,38 52,94	8,48 8,33	14,76 15,18	7,44 7,84	$C_9H_{17}O_3P$
IX	C	OC_2H_5	75	87—88 (0,03)	—	1,4820	1,2466	37,05 36,91	44,22 44,44	7,15 6,79	19,45 19,11	9,80 9,88	$C_6H_{11}O_3P$
Xa	C	OC_6H_5	55,2	131—132 (0,04)	46—49	1,5578	1,2988	52,16 51,76	57,49 57,14	5,43 5,24	14.90 14,75	7,17 7,62	$C_{10}H_{11}O_3P$
Xb	C	OC_6H_5	31,2	—	65—66	—	—	—	57,24 57.14	5,58 5,24	14.40 14,75	7,57 7,62	$C_{10}H_{11}O_3P$
XI	A	OC_5H_5	35	140—142 (0,01)	93—95	—	—	—	60,73 60,50	6,58 6,30	13,36 13,03	—	$C_{12}H_{15}O_3P$

with formation in high yields of 6-oxa-3-phospha[3.1.0]hexane 3-oxide derivatives (type E). The compounds obtained are listed with their physicochemical characteristics in Table 1.

Attempts to oxidize 2-phosphole 1-oxide derivatives with peroxy acids and obtain epoxyphospholane oxides of type D were unsuccessful. In all cases unchanged phospholene oxides were obtained in the fractionation of the reaction mixture. It is probable that the inertness of the double bond of 2-phospholene 1-oxides toward electrophilic peroxy acids is to be attributed to the reduction in their nucleophilicity as a result of the proximity of the P=O group. The enhanced electrophilicity of the double bond of noncyclic vinylphosphonic compounds was observed earlier in reactions with a number of nucleophilic reagents [27, 28]. The attempt which we made to oxidize 3-methyl-1-phenyl-2-phospholene 1-oxide with hydrogen peroxide in presence of benzonitrile led to the formation of an epoxide in extremely low yield (5%). However, we are not certain that the product was a 2,3-epoxyphospholane 1-oxide, and not the 3,4-isomer, which could be formed by the oxidation of the product of the isomerization of the original phospholene oxide. The NMR spectrum supported the latter view.

In view of the fact that in the oxidation of unsaturated compounds as well as epoxides isomeric ketones and unsaturated alcohols can be formed, for the identification of the compounds listed in Table 1 we carried out analysis for epoxide oxygen and determined IR and NMR spectra. The epoxyphospholane structure is supported by the absence of IR absorption bands in the regions 1570-1660, 1680-1760, and above 3300 cm^{-1}, characteristic for a double bond, carbonyl group, and hydroxy group respectively, and also by the presence of absorption bands in the regions 800-840 and 3000-3050 cm^{-1}, characteristic for an oxirane ring and for a C – H bond in it, respectively. On transition from the phospholene to the epoxyphospholane there are also characteristic changes in the NMR spectra. The doublet at 5-6 p.p.m. characteristic for an ethylene proton disappears, and a doublet appears at 3.2-3.7 p.p.m., typical of a proton at an oxirane ring.

As regards the question of the stereospecificity of the epoxidation reaction and the configuration of the products we will only mention here that in most of the cases studied only one isomer, or a mixture with a decided predominance of one of the isomers, was formed. Only in the case of the compound (X) did we succeed in isolating two products of identical composition, but with different constants. The question of the absolute configuration of the products and the steric direction of the reaction, which is of great interest, is being studied by us, and the results of these investigations will be reported separately.

For epoxidation we took 3-phospholene 1-oxide derivatives differing in the number of substituents at the double bond. As would be expected, reaction went most readily with 3,4-dimethyl-3-phospholene 1-oxide derivatives, and 3-methyl-3-phospholene 1-oxide derivatives were not greatly different in reactivity. Phospholene oxides with an unsubstituted double bond were considerably more inert. In this case reaction was conducted practically without solvents and at elevated temperature. After we had carried out a series of experiments with monoperphthalic or peracetic acid as epoxidizing agent we found that it is more expedient to use the latter. Unlike phthalic acid, the separation of which is difficult because of its slow precipitation, the acetic acid formed is readily removed in a vacuum. After the examination of several solvents we found that diethyl ether is the most convenient. It is readily removed from the reaction mixture at the end of the reaction, and it is completely inert, in which respect it differs from chloroform, which is not so readily removed and often contains appreciable admixture of hydrogen chloride and phosgene, which react with the epoxide ring and cause undesirable complications in the reaction.

In conducting analyses for epoxide oxygen we found that methods [29] based on the use of titrated solutions of hydrogen chloride in ether, dioxane, or pyridine do not ensure reproducible results. Good results are obtained only by the use of a titrated solution of hydrogen bromide in glacial acetic acid [29].

EXPERIMENTAL

The phospholene oxide derivatives required for the reactions were synthesized by previously described methods [30-31]. Oxidation was conducted with peracetic acid (PAA) or monoperphthalic acid (MPPA) in diethyl ether or chloroform. The reaction vessel was a three-necked flask fitted with dropping funnel, thermometer dipping in the reaction mixture, and calcium chloride tube. Agitation was effected by periodic shaking of the flask. The reaction conditions are stated in Table 2. Typical variants of the syntheses are described below.

Preparation of 3-Butoxy-1,5-dimethyl-6-oxa-3-phosphabicyclo[3.1.0]hexane 3-oxide (III). To 23.6 g of 1-butoxy-3,4-dimethyl-3-phospholene 1-oxide in 300 ml of dry ether 13.2 g

TABLE 2

Compound	Peroxyacid	Solvent	T, °C	Time, h	Yield, %	Compound	Peroxyacid	Solvent	T, °C	Time, h	Yield, %
I	PAA	Ether	21	49	80,0	V	MPPA	Ether	21	240	55,0
II	»	»	21	75	66,0	VI	PAA	$CHCl_3$	21	65	69,5
III	»	»	21	96	90,0	VII	»	$CHCl_3$	21	48	70,5
IV	»	$CHCl_3$	21	39	65,0	VIII	»	»	21	48	88,7
V	»	$CHCl_3$	21	69	82,7	IX	»	—	35—40	96	75,0
						Xa + Xb	»	—	60—80	240	86,4
						XI	»	$CHCl_3$	20—25	60	35,0

of PAA (80%) was added. No liberation of heat was observed. After 4 days volatile products were removed in a vacuum, and the residue was fractionated. We isolated 22.7 g (90%) of (III). Its constants and analysis are given in Table 1.

The epoxyphospholane oxides (I) and (II) were synthesized analogously. Volatile products were removed, and the desired products crystallized and were recrystallized from CCl_4 or ether.

Preparation of 1,5-Dimethyl-3-phenoxy-6-oxa-3-phosphabicyclo[3.1.0]hexane 3-oxide (I). To 40 g of 3,4-dimethyl-1-phenoxy-3-phospholene 1-oxide in 200 ml of $CHCl_3$ 22 g of PAA (94%) in 150 ml of $CHCl_3$ was added. The temperature of the mixture rose by 5°. After 60 h the pH of the reaction mixture was brought to 8 by the addition of dilute NaOH solution, and the chloroform layer was separated and dried with K_2CO_3. Volatile products were removed in a vacuum, and the residue was boiled in ethereal solution with active charcoal and then crystallized from ether. We obtained 32 g (74%) of (I). In a similar way we prepared (II) in 63% yield; bp 150-155° (9 mm). Under similar conditions (XI) was synthesized.

Preparation of 3-Methoxy-1-methyl-6-oxa-3-phosphabicyclo[3.1.0]hexane 3-oxide (IV). To 29.3 g of 1-methoxy-3-methyl-3-phospholene 1-oxide in 150 ml of chloroform 24 g of PAA (90%) was added. The temperature of the mixture rose by 12°. After 39 h volatile products were removed in a vacuum, and the residue was fractionated. We isolated 21.5 g (65%) of (IV), which crystallized when allowed to stand. (V)-(VIII) were prepared similarly.

Preparation of 3-Ethoxy-1-methyl-6-oxa-3-phosphabicyclo[3.1.0]hexane 3-oxide (V). 1-Ethoxy-3-methyl-3-phospholene 1-oxide (8.8 g) in 10 ml of ether was mixed with 160 ml of an ethereal solution of MPPA with an active-oxygen concentration of 0.06216 g/ml. After 10 days volatile products were removed in a vacuum, and the residue was mixed with $CHCl_3$ and heated to the boil. The precipitated phthalic acid was filtered off, $CHCl_3$ was vacuum-evaporated, and the residue was fractionated. We obtained 5.3 g (55%) of (V); bp 82-84° (0.018 mm); n_D^{20} 1.4755; d_4^{20} 1.1790.

Preparation of 3-Ethoxy-6-oxa-3-phosphabicyclo[3.1.0]hexane 3-oxide (IX). To 38.1 g of 1-ethoxy-3-phospholene 1-oxide in 300 ml of diethyl ether 35 ml of PAA (85%) was added. After 1 day the concentration of active oxygen had scarcely changed. Ether was driven off, the reaction mixture was kept at 35-40° for 4 days, volatile products were removed, and the residue was fractionated. We isolated 14.7 g of unchanged phospholene oxide and 16.2 g (74% based on the phospholene oxide that reacted) of (IX).

Preparation of 3-Phenoxy-6-oxa-3-phosphabicyclo[3.1.0]hexane 3-oxide (X). To 21.3 g of 1-phenoxy-3-phospholene 1-oxide in 15 ml of ether 15.9 g of PAA (60%) was added. The temperature of the mixture rose by 9°. As the active-oxygen concentration changed very little, ether was driven off, and the reaction mixture was heated for 48 h at 60-80°. In view of the appreciable resinification, the products were dissolved in ether, and the solution was boiled with active charcoal and then distilled. The main product came over at 124-125° ($7 \cdot 10^{-4}$ mm) and had n_D^{20} 1.5568 and d_4^{20} 1.2904. Epoxide oxygen was determined qualitatively. After a time, part of the product crystallized out. The crystalline product was separated and recrystallized from diethyl ether; this gave (Xb). Fractional distillation of the mother liquor gave the liquid product (Xa).

Oxidation of 3-Methyl-1-phenyl-2-phospholene 1-oxide. A solution of 1.08 g of $KHCO_3$, 7.0 g of benzonitrile, 5 ml of 47% hydrogen peroxide, and 12 g of 3-methyl-1-phenyl-2-phospholene

1-oxide in 120 ml of methanol was left for 19 h at room temperature, then heated at 45° for 4 h, and again left at room temperature for 1 day. Methanol was removed in a vacuum, and the benzamide formed (mp 123-125°) was precipitated by the addition of CCl_4. The yellow oil remaining after the removal of CCl_4 was fractionated. We obtained 0.7 g (5%) of a substance with bp 148-149° (0.04 mm). After a time it crystallized, and after recrystallization from benzene it had mp 102°. Found %: C 63.80; H 6.70; P 14.78. $C_{11}H_{13}O_2P$. Calculated %: C 63.40; H 6.25; P 14.89. A qualitative reaction for epoxide oxygen was positive.

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CONCLUSIONS

1. A new group of organophosphorus epoxides with bicyclic systems consisting of condensed phospholane and oxirane rings was prepared.

2. Organic peroxy acids react smoothly with the double bonds of 3-phospholene 1-oxides, but not with those of 2-phospholene 1-oxides.

3. The behavior of phospholene 1-oxides in reactions with electrophilic peroxy acids shows that the nucleophilicity of the double bond in these substances greatly depends on its position in the ring.

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