Russian Chemical Reviews **62** (7) 647 – 659 (1993)
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UDC 547.241

Derivatives of diphosphonic acids: synthesis and biological activity

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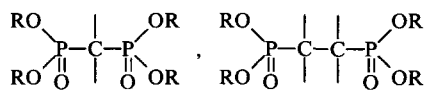
Abstract. The scientific-technical and patent literature on the synthesis of derivatives of diphosphonic acids is surveyed. Various methods of synthesis of diphosphonate, phosphonylphosphinyl, and phosphonophosphate compounds are described. The principal aspects of the use of the above compounds in medicine, biochemistry, and agriculture are examined. The bibliography includes 174 references.

I. Introduction

In recent years, many investigators have shown interest in the method of synthesis and the detection of biological activity of phosphonic acids and their derivatives, which can be regarded as analogues of natural phosphates. Pyrophosphates containing the P–O–P linkage are known to be natural regulators of the metabolism of calcium at the cellular level. Attempts have been made to use inorganic pyrophosphates in the treatment of diseases associated with the breakdown of the calcium metabolism, but the desired results were not achieved owing to the hydrolysis of the above compounds by pyro- and polyphosphatases. Synthetic analogues of pyrophosphates, namely diphosphonates, which are not metabolised because of the presence of P–C–P linkages, attracted the attention of investigators. There exists a series of monographs and reviews in which the methods of synthesis, properties, and the results of biochemical and clinical tests on diphosphonates are considered. However, these studies were devoted as a rule either only to the synthesis of these compounds[1,2] or only to the analysis of their pharmacological properties.[3–10] In a series of investigations attention was devoted merely to the narrow subclass of biphosphoryl substances.[11,12]

The biologically active derivatives of diphosphonic acids known at the present time, which contain two phosphorus atoms in the molecule, can be divided into the following main groups:

1. Compounds with geminal or vicinal phosphonate groups:



2. Polyalkylpolyaminodiphosphonic acids.

3. Phosphonylphosphinyl compounds containing the P–C–P–C linkages.

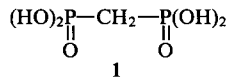
4. The phosphonophosphate compounds P–C–O–P.

The methods of synthesis and biological activities of such compounds are the subject of the present review.

II. Biological activity and synthesis of compounds with geminal phosphonate groups

1. Methylenediphosphonic acid and its halo-derivatives

The closest analogue of inorganic pyrophosphates is methylenediphosphonic acid **1** (MDP), which is capable of forming stable complexes with alkaline earth, transition, and heavy metals. This property of the above compound is used to prevent the deposition of calcium in living tissues.[2]



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Methylenediphosphonic acid forms part of the composition of many disinfecting and radiopharmaceutical preparations.[13] The radioisotopes of certain metals, for example ^{99}Tc, capable of fulfilling the function of a radioactive probe, are used as the main components of such preparations. Chelation of the cations of the above isotopes by MDP makes it possible to increase their toxicological acceptability to the organism, to facilitate their transport, and to ensure the selectivity of their concentration in particular organs.

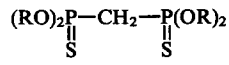
MDP can add to adenosine triphosphate and can also inhibit the incorporation of inorganic phosphate in nucleoside polyphosphates and phosphorolysis;[2,14] MDP acts on the immune system, inhibiting inorganic pyrophosphatase as a consequence of competition for the substrate and a decrease in the concentration of the activator (Mg^{2+}) and the substrate.[15] It has been observed that MDP exerts a mutagenic effect on plants.[16] A review has been devoted to the structure, properties,

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Received 26th January 1993
Uspekhi Khimii **62** (7) 691 – 703 (1973); translated by A K Grzybowski

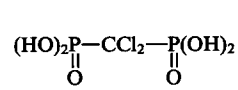
synthesis, and application of MDP and its full and mixed esters.[13] The main reaction leading to the synthesis of MDP and its derivatives is the Arbuzov reaction in its various versions. Another method incorporates the Michaelis–Bekker reaction of a dihaloalkane or a haloalkylphosphonate with a metal dialkyl phosphite in several modifications.[1,13,17] A consecutive method of synthesis using initially the Arbuzov reaction and then the Michaelis–Bekker reaction, which affords the products in an acceptable yield, has also been reported.[2] An exchange reaction between $CH_2(AlCl_2)_2$ and PCl_3, leading to $CH_2(PCl_2)_2$, has been proposed. The acid dichloride of MDP and methylenediphosphonite $CH_2[P(OR)_2]_2$, has been proposed. The acid dichloride of MDP and methylenediphosphonite $CH_2[P(OR)_2]_2$ have been synthesised from the latter and their oxidation in dimethyl sulfoxide (DMSO) afforded the corresponding MDP esters.[13] There exists a method of synthesis of MDP by the oxidation of the readily available methylenediphosphine $CH_2(PH_2)_2$ with nitric acid.[2]

A patent[18] describes a reaction in which the starting materials for the synthesis of MDP esters are white phosphorus, epoxyethane, and sodium alkoxide. MDP esters can also be obtained from tetraalkylmethylenebisphosphonites by a reaction with carbonyl compounds.[19,20] Any phosphonate can be converted into the acid by acid hydrolysis or via trimethylsilyl esters (by reaction with Me_3SiHal). The esters of methylenephosphonodithionic acid **2** are intermediates in the synthesis of biologically active substances. It has been suggested[21] that they can be obtained by the Michaelis–Bekker reaction induced by UV radiation at reduced temperatures in liquid ammonia.

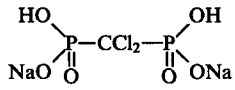


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Dichloromethylenediphosphonic acid **3** (DCMDP) and its disodium salt **4**, known as clodronic acid, are used to prevent the excess resorption of bone and the calcification of soft tissues, to regulate calcium metabolism at the cellular level, and to treat osteoporosis.[3,4,22]



3



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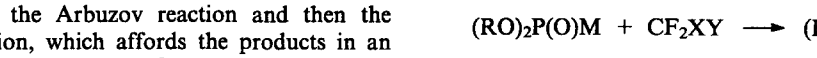
It has been established that DCMDP prevents the spreading of the metastases of bone tumours.[23,24] By regulating the permeability of membranes, this compound also assists in the transport of antitumour drugs into the cell, preventing thereby the disintegration of bone tissue and suppressing the growth of tumours without manifesting toxic properties.[25]

In a study of the effect of dihalomethylenediphosphonates on the activity of alkaline phosphatase and the oxidation of aliphatic acids in cell cultures, it was shown that DCMDP is the most powerful stimulator of the above enzyme compared with the dibromo- and difluoro-derivatives of MDP. The monohalo-derivatives of MDP and the non-halogenated acids are less active in relation to phosphatase and are inactive or inhibit the oxidation of aliphatic acids.[26]

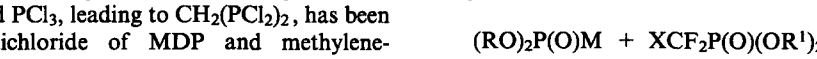
DCMDP can be obtained from trialkyl phosphite, bromotrichloromethane, and an excess of sodium hypochlorite[1] and also as a result of the radical reaction with carbon tetrachloride[27,28] or with $Cl_3CP(O)(OEt)_2$.[29,30]

Difluoromethylenediphosphonic acid (DFMDP) has been proposed as a therapeutic preparation for the treatment of diseases associated with increased desorption of bone. By virtue of the presence of fluorine, this compound can also be used as an experimental means for the investigation of the way in which all diphosphonates act.[31] It has been noted that monofluoro- and difluoro-methylenediphosphonic acids are isopolar analogues of pyrophosphoric acid.[32]

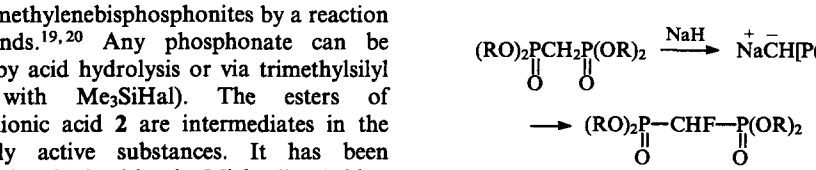
Both symmetrical and asymmetric difluoromethylene-diphosphonates can be obtained by the Michaelis–Bekker reaction[32,33]



or by the reaction



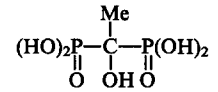
where X, Y = Cl, Br, or I; M = Na or K; and R, R^1 = alkyl. Another version of the synthesis of fluoromethylene-diphosphonates involves the use of methylenediphosphonic acid esters, which are treated with butyllithium, sodium hydride, or potassium *tert*-butoxide,[1,32,34,35] the carbanions $\bar{C}H(PO_3R_2)_2$ formed being subsequently fluorinated by perchloryl fluoride:[32,34,35]



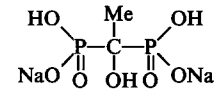
The esters obtained can be hydrolysed to the corresponding acids.

2. Hydroxyethylidenediphosphonic acid

The best known compounds among diphosphonic acids used in medicine are hydroxyethylidenediphosphonic acid **5** (HEDP) and its disodium salt **6**, called etidronate.



5



6

The study of the complex-forming properties of HEDP showed that the combination in the molecule of this compound of two acid phosphono-groups and the hydroxy-group with its comparatively high basicity gives rise to the possibility of the formation by this ligand of stable complexes with alkaline earth, transition, and lanthanide metals. The stability constants of the HEDP complexes of certain metals[12] differ little from the corresponding constants of the MDP complexes. Therefore, by virtue of their ability to reduce the degree of resorption of bone and to diminish the liberation of hydroxyproline, HEDP and etidronate are used as regulators of calcium metabolism at the cellular level in the treatment of Paget's disease.[3,36] In minimal doses, HEDP increases the incorporation of calcium into bone tissue, prevents the development of various types of osteoporosis and myositis and prevents the destruction of the peridontal membrane and of the transplanted bone in animals.[12] HEDP inhibits the formation and growth of calcium oxalate stones in kidneys. The addition of HEDP to dental preparations and toothpastes is an excellent means whereby the formation of plaque and caries can be prevented.[3,11] The use of xydiphone — the potassium sodium salt of HEDP — for the treatment of urinary calculus as an anticalcifying and antiinflammatory agent has been permitted.[37] It has been suggested in the USA that HEDP be used as a pharmaceutical preparation for the treatment of persons suffering from metastatic bone cancer.[38]

The extremely high selectivity of the complex forming capacity of HEDP in relation to beryllium is notewothy.[12] Its introduction into the organism poisoned by Be^{2+} ions eliminates the inhibition of the activity of alkaline phosphates. As stabilisers of cell membranes, HEDP and its salts can be effective prophylactic

agents in diseases such as bronchial asthma and hyperglycemia. By virtue of its ability to reduce to the normal level the concentration of cholesterol and triglycerides in the plasma and also its ability to be incorporated in the phospholipids of cell membranes, HEDP prevents the accumulation of peroxide compounds in erythrocytes.[3,39]

HEDP is widely used for the treatment of rheumatoid diseases. It is particularly effective as an antiarthritic agent in combination with antiinflammatory agents. The antiatherosclerotic effect of HEDP has been described: it was found that it influences the immune system, the genetic apparatus of the cell, the biosynthesis of prostaglandins, the stimulation of the citric acid cycle,[16,40] the metabolism of vitamin D,[2,41] and the embryotropic effect of the latter.[42]

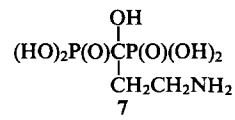
HEDP salts increase the bactericidal activity of phenolic compounds, which permits their use in disinfectants, shampoos, mouth washes, and other similar products. A series of publications have been devoted to the use of HEDP in cosmetics. HEDP esters are employed as pesticides.[11]

Thus comprehensive studies on the properties of HEDP and its salts have led to an extremely wide range of their applications, some of which have been successfully realised in practice.

The practical interest in HEDP is determined primarily also by the ready availability of the starting material and the comparative simplicity of its synthesis, which permitted the industrial manufacture of this product. The reaction of PCl_3 or H_3PO_3 (or their mixture) with acetic acid (or a mixture of acetic acid and acetic anhydride) as well as the reaction of H_3PO_3 with acetic anhydride or carboxylic acid chlorides have been used to synthesise HEDP. Numerous versions of the acylation of phosphorus(III) compounds differ in the reaction conditions, the reactant ratios, and the yields of the target product.[1,11,12,43-51] A method of synthesis of HEDP by the hydrolysis and acidolysis of dimethyl phosphite to H_3PO_3 followed by acetylation with acetic anhydride or acetyl chloride, affording a yield up to 96%, has been developed.[52] It has been suggested that the still residue remaining after the distillation of dimethyl phosphite, which is a waste product in the manufacture of chlorofos, be used as the starting material. An improved version of the synthesis of HEDP from dimethyl phosphite and acetic anhydride in solution in acetic acid has been described.[53] The methods of synthesis of HEDP introduced into industrial production have been considered in detail in a review.[54] A high yield of HEDP (97%) has been achieved in the synthesis based on the interaction of PCl_3 and acetic acid using a zinc catalyst.[55,56] A method has been proposed for the continuous synthesis of HEDP with a purity of 99.2% by the reaction of P_4O_6 with carboxylic acids[57] and also by the reaction of a mixture of phosphorus oxides, obtained as side products in the synthesis of P_4O_6, with acetic acid.[58] If the reaction of P_4O_6 with acetic acid is carried out in the presence of urea under a nitrogen atmosphere,[59] then the yield of HEDP increases to 97%. A procedure has been proposed for the synthesis of HEDP and its analogues by the nitrosation of aminodiphosphonic acid $H_2NC(R)(PO_3H_2)_2$ with nitrous acid or substances forming HNO_2 during the reaction (nitrogen oxides, nitrous fumes, NOCl, $NaNO_2$, and aqua regia).[60] The initial aminoalkylidenediphosphonic acid is obtained by the reaction of PCl_3 with acid amides in the presence of H_3PO_3 and subsequent hydrolysis; HEDP is isolated as the hydrate in yields up to 100%.

3. Aminohydroxyalkylidenediphosphonic acids

Compounds such as 3-amino-1-hydroxy-1,1-propylidenediphosphonic acid **7** (APD), 4-amino-1-hydroxy-1,1-butylidenediphosphonic acid (ABD), 6-amino-1-hydroxy-1,1-hexylidenediphosphonic acid, and 6-amino-1,1-hexylidenediphosphonic acid are used as regulators of the calcium metabolism for the prevention of the deposition of calcium in the soft tissues and the resorption of bone and for the treatment of poisoning by metal salts and alcohol.[3,4,12]



7

Their complexes with alkaline earth, transition, and lanthanide metals exhibit an enhanced solubility by virtue of the presence in the molecule, together with two acid phosphono-groups, of hydroxy- and amino-groups, which play the role of a basic centre in the molecule.[11] The use of the above compounds in the treatment of Paget's disease is based on this property. It has been established that APD has minimal side effects;[61] ABD is used in the treatment of urinary calculus.[62,63] It has been shown in experiments *in vivo* and *in vitro* that APD is 100–300 times more active than DCMDP as the inhibitor of the resorption of bone.[63] The acid **7** and other diphosphonates having a terminal amino-group are readily incorporated into the structure of cell membranes and into phospholipids. They also prevent the accumulation of peroxide compounds in erythrocytes.[39] APD and ABD participate in the metabolism of dihydroxyvitamin D. They effectively normalise the level of calcium in the blood in patients suffering from malignant hyperglycemia.[63,64] Synergistic compositions containing cytostatic or hormonal antitumour agents (melphalan, chlorambucil, methotrexate, etc.) and geminal diphosphonates such as ABD have been proposed for the treatment of metastatic bone cancer.[65]

Hydroxyalkylidenediphosphonic acids containing an amino-group have been synthesised from the corresponding carboxylic aminoacids by treatment with a mixture of H_3PO_4 and PCl_3 [3,66-71] or a mixture of H_3PO_3 and PCl_3 [63,72] and subsequent hydrolysis. If a sulfonic acid is added in the latter version,[73] then the yield of the product can be increased to 90%. It has also been suggested that P_4O_6,[74] a mixture of H_3PO_4 and P_4O_6,[75] and a mixture of H_3PO_3 and $POCl_3$ [62] be used as the phosphorus-containing reagents.

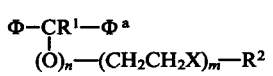
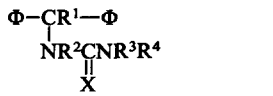
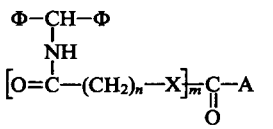
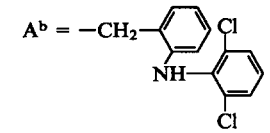
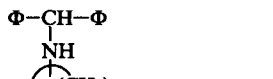
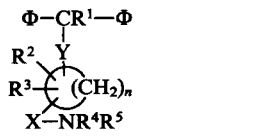
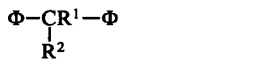
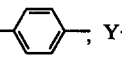
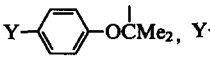
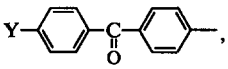
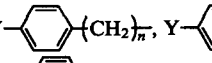
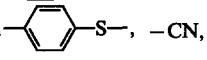
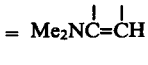
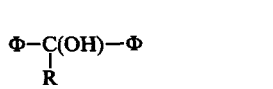
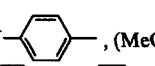
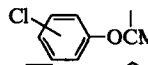
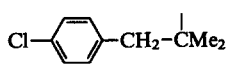
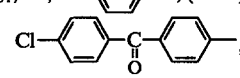
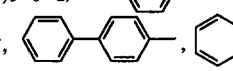
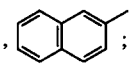
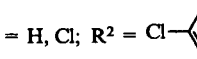
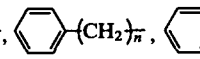
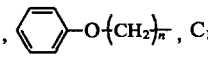
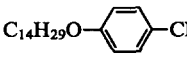
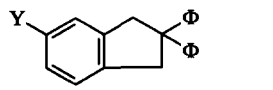
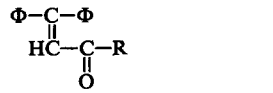
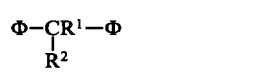
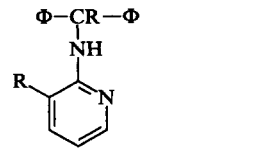
4. Inhibitors of the resorption of bone and antiinflammatory, antiarthritic, and antirheumatoid agents

Because of the ability of diphosphonic acids to form stable complexes with metal ions, they can be used in the treatment of diseases associated with the breakdown of calcium metabolism. A large number of new compounds of this class which can form part of pharmaceutical preparations for the treatment of the above diseases, have been synthesised in recent years. Furthermore, if the diphosphonic acid molecule includes a carboxylic acid residue with antiinflammatory and antipyretic activities, then the use of such a compound as an antiinflammatory agent is particularly effective.

Investigators followed the path leading to an increase in the complexity of the structures of compounds with known pharmacological activities (DCMDP, HEDP, APD, ABD) by introducing into the structure of the given substance all possible cyclic and acyclic hydrocarbon fragments and heterocycles. The synthesis of new compounds are based on the known phosphonylation methods (the Arbuzov and Michaelis–Bekker reactions, addition of di- and tri-alkyl phosphites to unsaturated bonds, phosphonylation of carboxylic acids and their derivatives)[1] in combination with various procedures for the further development of the structure which do not involve the phosphonate groups.

The principal representatives of the geminal diphosphonic acids and their salts and esters obtained during the last 20 years, which exhibit antiresorptive, antiinflammatory, and antiarthritic activities, are presented in Table 1.

Table 1. Geminal diphosphonic acids and their derivatives exhibiting antiresorptive, antiinflammatory, antiarthritic, and antirheumatoid activities.

Formula	Substituents	Ref.
	Compounds without heterocyclic fragments in the molecule	
	R^1 = H, OH, Alk, Hal, arylalkyl; R^2 = Alk, arylalkyl, hydroxyalkyl, alkenyl, arylalkenyl; n = 0, 1; X = CH_2, m = 1–9; O, m = 1, 2	76–79
	R^1, R^2 = H, Alk; R^3 = Alk, Ar, arylalkyl; R^4 = H, Ar; X = O, S	80
	A^b =  X = NH, O; m = 0, 1, n = 1–10	81, 82
	R = H, Alk(C_{1-5}); n = 3–10	83
	R^1 = H, OH, NH_2; R^2, R^3 = H, Alk, alkylene; R^4, R^5 = H, Alk, Ac, arylalkyl; X, Y = bond, alkylene; n = 5–7	84
	R^1 = H, OH, OAc, NH_2; R^2 = Bu^t, Y-, Y-, Y-, Y-, Y-, Cl-, –CN, $-(CH_2)_2CN$, $-(CH_2)_3NH_2$, $-CH_2NMe_2$; R^1+R^2 = 	85–88
	R = n-C_5H_{11}, Bu^t, n-$C_{15}H_{31}$, Ph, Y-, $(MeO)_3C_6H_2$, , Cl-, , , ; Y = Me, Cl, F	89
	R^1 = H, Cl; R^2 = Cl-, , , $C_{14}H_{29}O$-; n = 1–3	89
		90
	Compounds with a heterocycle in their structure[c]	
	R = $CR^1R^2R^3$, cyclo-Alk, Ar, cyclo-Het; R^1, R^2 = Alk(C_{1-3}); R^3 = Alk(C_{1-10})	91
	R^1 = H, Alk; R^2 = $C(X)NHR^3$, $NHC(O)R^3$, $NHSO_2R^3$; X = O, S; R^3 = Alk, Ar, Het {Het = pyridyl, 2-benzo[*b*]thienyl, 2-benzo[*b*]thiophenyl, imidazolyl, pyridyl, thienyl, quinolinyl}	92, 93
	R = H, Me	94

[a] $(O)_n$—$(CH_2CH_2X)_m$—R^2

[b] A = –CH_2–

[c] Y = Me, Cl, F

Table 1 (continued)

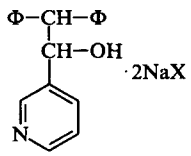
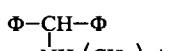
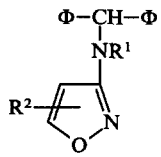
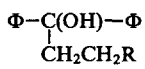
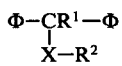
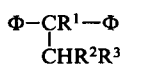
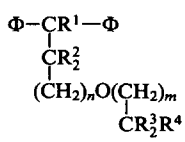
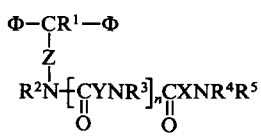
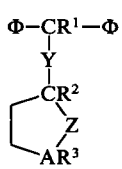
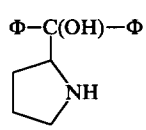
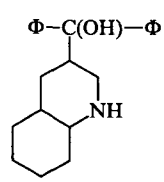
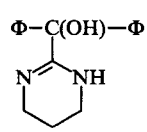
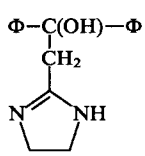
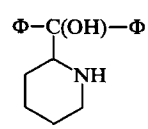
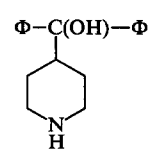
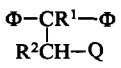
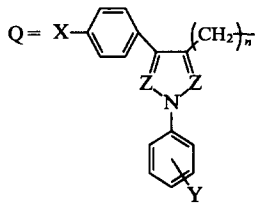
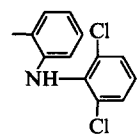
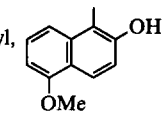
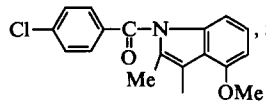
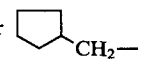
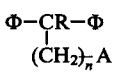
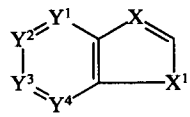
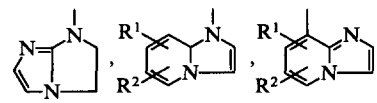
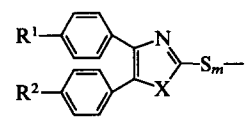
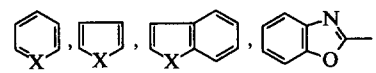
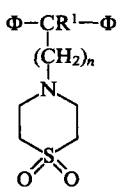
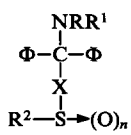
Formula	Substituents	Ref.
 (NE-58095)		95–97
	A = cycloalkyl (C_{5-8}), bicycloheptyl, bicycloheptenyl, saturated heterocycle (C_{4-7}) with O, S, SO, SO_2 groups; $m = 0-4$	98
	R^1 = H, Alk; R^2 = H, Alk, cyclo-Alk, Ph, alkenyl, phenylalkenyl, phenylalkyl, alkoxyphenylalkyl	99
	R = piperidinyl, morpholinyl	66
	X = alkylene (C_{2-8}); R^1 = H, OH, AcO, R^3N; R^2 = Het (Het = imidazole, oxazole, isoxazole, thiazole, pyridine, 1,2,3-triazole, 1,2,4-triazole, benzimidazole, alkyl-substituted), OAlk, Hal, OH, COOH, NH_2, NO_2, Ph, $PhCH_2$, CN, AlkOC(O), SAlk	100
	R^1 = H, OH, NH_2, R^4NH; R^2 = H, Alk; R^3 = Het	101
	R^1 = H, OH, NH_2; R^2, R^3 = H, Alk(C_{1-5}); R^4 = Het; m, n = 0–2	102
	R^1 = H, OH; R^2–R^5 = H, Alk; X, Y, Z = alkylene; n = 0–2 (R^2NZ, R^3NY, and R^4NX may be heterocycles)	103
	R^1 = H, OH, NH_2; R^2, R^3 = H, Alk; $R^2 + R^3$ = alkylene; Y = alkylene or bond; Z = heteroalkylene substituted or unsubstituted by an alkyl, benzyl, or cyclohexylmethyl group; A = N, CR^3; $Z + R^2$ = bond Examples:      	104

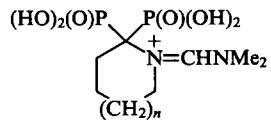
Table 1 (continued)

Formula	Substituents	Refs
	R^1 = H, Cl, OH, AcO, NH_2, $RCH_2C(O)O-$; R^2 = H; $R^1 + R^2$ = bond;	105, 106
	Q =  n = 0–2; X, Y = H, Cl, F; Z = CH, N, RC	
	For R^1 = OH: R^2 = H, Alk; Q^d = Ph (unsubstituted or substituted by Cl or F), biphenyl,	107–110
	1,2-naphthyl, 2-thienyl,  , $(CH_2)_n$Ar, 11-oxo-2-dibenzo[*b*,*f*]oxepinyl,  ,	
	 , 5-R^3,6-R^4-indan-1-yl, (R^3 =  or  ; R^4 = H, Cl);	
	R^5R^6CH, (R^5 = H, Me, Et; R^6 = phenoxyl, Ph, heteroaryl, etc.)	
	R = H, OH; n = 0, 1;	111–113
	A =  X, X^1 = N, CH; X = X^1 ≠ CH; one of the Y^1–Y^4 = N, others are CH groups,	
	 R^1, R^2 = H, OH, Alk, Hal,	
	A = 	114
	R^1, R^2 = H, OH, OAlk, Hal; X = O, S, NH; m = 0, 1; n = 0–6	
	A = SR^3 (R^3 = H, Alk, Ph, $-C(X)NZ^1Z^2$,  ; X = O, S; Z^1, Z^2 = H, Alk); n = 0–10	115
	R^1 = H, Me, Ph, OH; n = 0, 2, 5, 10	116, 117
	R = H, Alk(C_{1-5}), $CONH_2$; R^1 = H, Alk(C_{1-6}), CH_2Ph, Cl, MeC_6H_4, Ph; RR^1 = $(CH_2)_m$ (m = 4, 5); R^2 = Alk(C_{1-6}), cyclo-Alk(C_{5-7}), Ph, CF_3, 5-6-membered heterocycle with 1 or 2 heteroatoms (N, S); n = 0–2; X = $(CH_2)_{1-6}$	118, 119

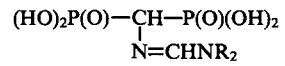
[a] Φ = $P(O)(OH)_2$.
[b] A = groups with antiinflammatory properties.
[c] Alkyl, aryl, and cycloalkyl groups can also be used instead of a heterocycle.
[d] Aromatic or heteroaromatic carboxylic acid residue with antiinflammatory and antipyretic properties.

5. Bactericidal, antiviral, and antitumour agents

Diphosphonic acids are capable of acting also upon bacteria. Thus the amidinodiphosphonic acids **8** and **9**, which possess bacteriostatic activity, have been patented.[120]



8, n = 0, 1;

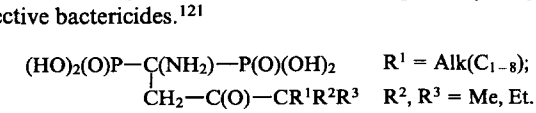


9, R = H, Me, Et.

They were obtained by the reaction of aminomethylenediphosphonates with formamides and $POCl_3$.

$$H_2NCH(PO_3H_2)_2 + HCONH_2 + POCl_3 \longrightarrow$$
$$\longrightarrow H_2N{-}CH{=}N{-}CH(PO_3H_2)_2$$

Compounds with the structure **10**, obtained by the phosphonylation of the 3-oxonitrile $R^1R^2R^3CC(O)CH_2CN$ with a mixture of H_3PO_3 and PBr_3 and subsequent hydrolysis, are effective bactericides.[121]

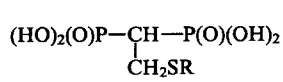


10

R^1 = Alk(C_{1-8}); R^2, R^3 = Me, Et.

The alkali metal salts of compound **10** exhibited an antimicrobial activity.[122]

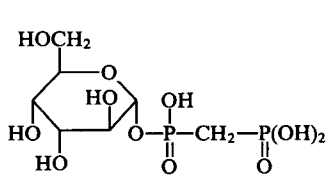
It is believed[123] that compounds with the structure **11** are potential inhibitors of the replication of the influenza A virus. They have been obtained by adding S-nucleophiles, such as thiophenol, 2-mercaptoethanol, ethanethiol, propane-1-thiol, and dodecane-1-thiol, to tetralkyl ethenylidenediphosphonates.



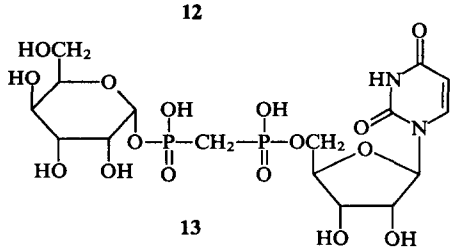
11

R = Et, Pr, Ph.

A series of geminal α-amino- and α-hydroxy-propylidene-α,α-diphosphonic acids derived from purines and pyrimidines (thymine, uracil, 6-methyluracil, and 5-fluorouracil) have been synthesised. They showed a low antiviral and a moderate antitumour activity on certain strains of tumours.[124] The synthesis and the results of biochemical studies on potential substrate inhibitors of glycosyltransferase on the surfaces of the membranes of cancer cells — the phosphonate analogues of nucleoside diphosphate sugars — have been described.[125] It was shown that, among all the intermediate and final products of synthesis, compound **12** exhibits a weak activity against the rhinovirus, while compound **13** inhibits competitively glycoproteingalactosyltransferase.

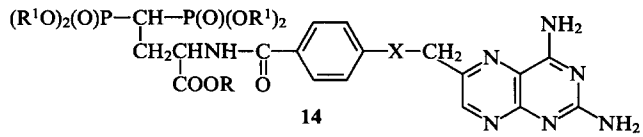


12



13

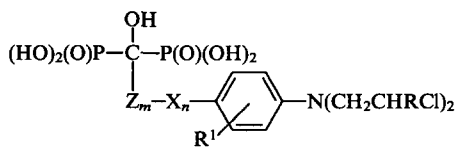
Geminal diphosphonic analogues of aminopterin (methotrexate) **14**, derivatives of 10*H*-deazamethopterin, and pharmaceutical compositions based on them have been proposed for the treatment of bone carcinomas, rheumatic psoriasis, different types of polymyositis, Reiter's disease, and rheumatic polyarthritis.[126]



14

X = NR or CHR^2; R, R^1 = Alk; R^2 = H, Alk.

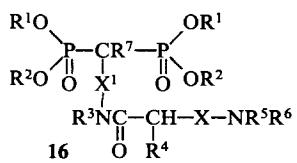
On the basis of the analysis of the structures of active diphosphonic acids, the authors of a patent application[127] proposed compounds **15**, containing two geminal phosphonate groups, a hydroxy-group, and a terminal amino-group in the hydrocarbon chain, as in ABD and APD [as antitumour agents? (Ed. of Translation)].



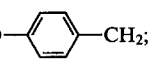
15

R = H, Me; R^1 = H, Hal, NH_2, OAlk, Alk;
Z = alkylene, aminoalkylene;
X = O, S, NH;
m, n = 0, 1.

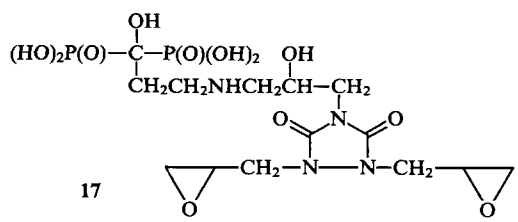
It was established that, as a result of their accumulation in bone tumours and metastases, compounds **15** induce a significant inhibition of the growth of tumours and increase the survival rate among rats. The rapid calcification of osteosarcoma and lung metastases was confirmed.[38] A patent has also been obtained for a method of synthesis of compounds **15** and pharmaceutical preparations based on them for the treatment of bone tumours.[128] It was shown that joint therapy using compounds **15**, APD, and melphalan yields the best results.[129] Compounds **16**, with an analogous structure, which are also inhibitors of malignant neoplasms, have been patented.[130]



16

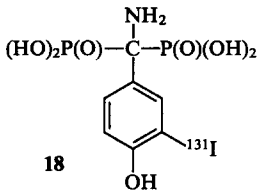
R^1, R^2 = H, Alk; R^3 = H, Alk, cyclo-Alk, Bn, Ph, MeO--CH_2;
R^4 = H, Alk, NH_2; R^5, R^6 = HalCH_2CH_2;
NR^5R^6 = aziridinyl; R^7 = H, Hal, OH, Alk;
X = alkylene, phenylene, arylalkylene;
X^1 = bond, alkylene, cycloalkylalkylene, arylalkylene.

It has been reported[131] that compound **17** also exhibits an appreciable antitumour activity and that the best results in the treatment of osteolytic metastases in rats were achieved by preliminary treatment with APD.



17

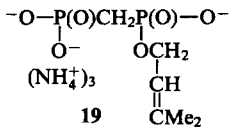
α-Amino-[3-^{131}I]-4-hydroxybenzylidenediphosphonate **18** was synthesised[132] in order to analgise and treat bone metastases. It proved to be the most effective among a series of analogues.[133,134] It has been noted that compound **18** accumulates in bone tissues and that its content is higher in diseased tissues than in healthy tissues. The β-emission from the compound has a smaller effect on bone marrow than the radiopharmaceutical preparations used previously.



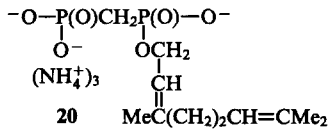
18

6. Artificial substrates and inhibitors of various enzymes

The search for synthetic substrates and inhibitors of various enzymes has continued. Thus the synthesis, properties, and the results of biochemical studies of dimethylallyl- and geranylmethylenediphosphonates **19** and **20**, which can serve as artificial substrates for prenyltransferase, have been described.[135]



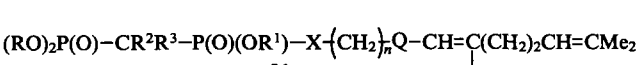
19



20

The ammonium salts of compounds **19** and **20** were synthesised by the reaction of $[HOPO_2CH_2PO_3]^{3-}(NBu_4^+)_3$ with $Me_2C{=}CHCH_2Br$ or geranyl chloride, which is obtained by treating geraniol with *N*-chlorosuccinamide and dimethyl sulfide. It has been established with the aid of compounds **19** and **20** that the presence of the high-energy O–P–O linkage is not important for enzymic reactions, but the structure containing two phosphorus atoms is topologically important for them. The behaviour of geranyl- and geranyldifluoro-methylenediphosphonates in reactions with various enzymes has been investigated.[136]

The synthesis of compounds **21**, used as inhibitors of squalene synthetase, has been described.[137]



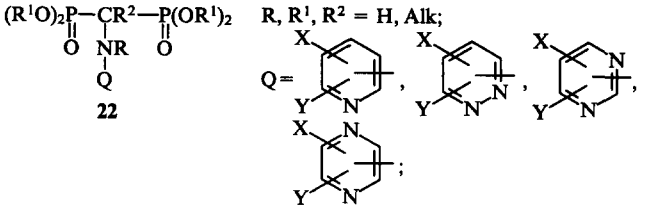
21

R, R^1 = M, H, Alk, alkenyl; R^2, R^3 = H, Hal; X = O, NH, NR^4; R^4 = Alk; Q = $-CH_2CH_2C(Me)=CH-$, bond; *n* = 1–4; when X = O, *n* = 2–4.

$(MeO)_2P(O)CH_2P(O)(OMe)OH$ in methylene chloride and ethyldiisopropylamine are treated with diphenylphosphoric acid chloride, after which farnesylamine is added and compounds **21** are obtained.

7. Herbicides

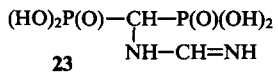
Diphosphonic acids exhibit also a herbicidal activity. Thus the syntheses and herbicidal properties of 46 compounds having the structure **22** have been described in patent applications.[138,139] The synthesis of compounds **22** is based on the reaction between the amino-derivatives of a N-containing heterocycle, $R^2C(OR^3)_3$, and dialkyl phosphite followed by the hydrolysis of the intermediates. (*N*-Pyridyl)aminomethylenediphosphonic acids **22** (R = R^1 = R^2 = H; Q = 3-X-2-pyridyl, X = H, alkyl, Hal; Y = H) and their salts are particularly effective in the fight against perennial weeds.[140]



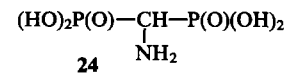
22

X, Y = H, Alk, Hal, NO_2, AcNH, CO_2H, CO_2Me, OH, OMe.

The formamidino- and aminomethylene-diphosphonic acids **23** and **24**, obtained from P_4O_6, anhydrous H_3PO_3, and $HCONH_2$ and by subsequent hydrolysis of the reaction mixture, are suitable as herbicides.[141]



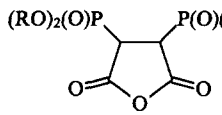
23



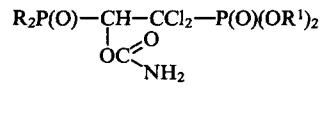
24

III. Vicinal diphosphonic acids

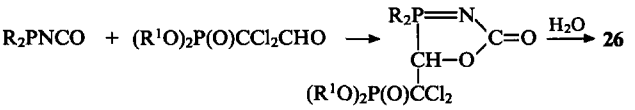
Among the biologically active diphosphonic acids, compounds with a vicinal structure occupy a modest place. Nevertheless, several representatives of substances of this class, which exhibit various types of activity, have been synthesised in recent years. Thus, 3,4-bis(dialkylphosphono)tetrahydrofuran-2,5-diones **25**, used as insecticides and acaricides, have been described in a patent.[142] The synthesis of compounds **26**, which, for R = BuO or Ph and R^1 = Et, exhibit weak pesticidal properties and affect the rate of plant growth, has been reported.[143] These compounds were synthesised by the reaction of phosphorus (III) acid isocyanates with phosphorylated acetaldehydes.



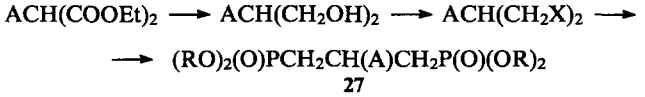
25



26



Specific inhibition of calcium metabolism at the celullar level is induced by the 1,3-diphosphonates **27**, synthesised in accordance with the following scheme;[144,145]

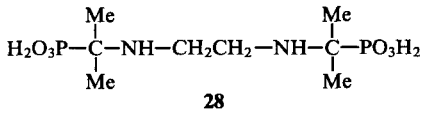


27

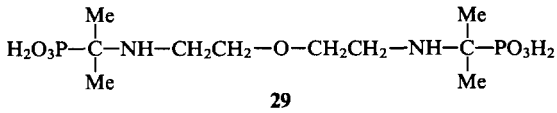
X = Hal, OTs; A = alkyl, arylalkyl, aryloxyalkyl; R = alkyl.

IV. Polyalkylpolyaminodiphosphonic acids

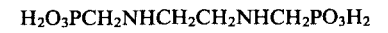
This group includes organophosphorus compounds containing a nitrogen atom in the alkylene chain adjoining the two PO_3H_2 groups. They are capable of activating certain enzymes. Nitrogen-containing diphosphonic acids such as ethylenediaminebisisopropylidenephosphonic acid **28** (phosphicine), 3-oxapentylenediamine-*N*,*N*′-bisisopropylidenephosphonic acid **29**, ethylenediamine-*N*,*N*′-bismethylenephosphonic acid **30**, ethylenediamine-*N*,*N*′-diacetic-*N*,*N*′-bismethylenephosphonic acid **31**, and 3-thiapentylenediamine-*N*,*N*′-bisisopropylidenephosphonic acid **32** possess this property.[12]



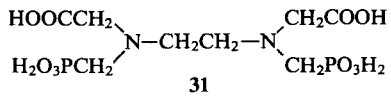
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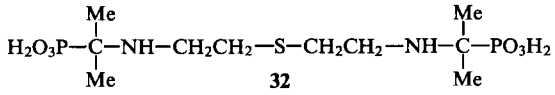
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30



31

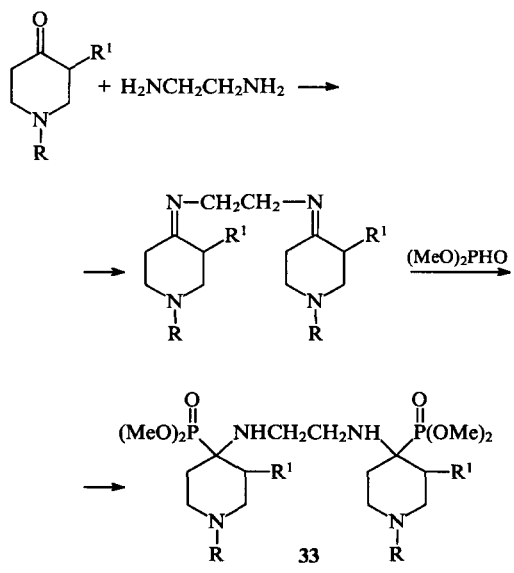


32

A systematic study of the biological properties of alkylenediaminebisalkylenephosphonic acids led to the discovery of the possibility of using substances of this type for the removal from the organism of incorporated toxic metals and also made it possible to discover the influence of these compounds on the removal of certain biologically important elements and on the state of metal complexes in the organism.

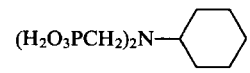
A characteristic feature of organophosphorus ligands containing a nitrogen atom in the alkylene chain linking the two PO_3H_2 groups is the preferential formation of complexes with cations having a small (Be, Fe) or large (lanthanides) radius but not with alkaline earth metals.[12] A unique property of substances of this group is the virtual absence of toxicity. By virtue of their ability to remove copper from the organism, they are used for the treatment of hepatocerebral dystrophy. Phosphicine is particularly effective for the removal of beryllium from the organism, without affecting calcium metabolism, and also for the removal of lead and uranium[11] and for the treatment of poisoning with alcohol.[4]

Phosphicine and its analogues have been synthesised by condensing the corresponding amine with the carbonyl group in aldehydes, ketones, piperidinones, etc. and with trivalent phosphorus compounds.[3] For example, treatment of alkylpiperidinones with ethylenediamine in benzene afforded[146] the corresponding bis-Schiff bases, which are made to react with dimethyl phosphite, whereby bis(phosphonylpiperidinyl)-ethylenediamines **33** are obtained.

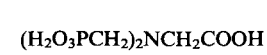


33

The syntheses of complexones **34** and **35** by the reaction of PCl_3 with glycine or cyclohexylamine in the presence of water followed by the interaction of the resulting intermediate with an aldehyde have been described.[147]

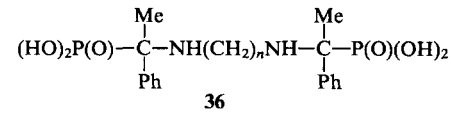


34

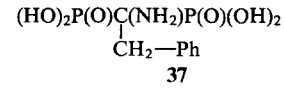


35

The alkylenediaminediphosphonic acids **36** (n = 2, 6), used to inhibit calcium salts, have been synthesised via the intermediate sodium ammonium salts.[148] It has been suggested[149] that 1-amino-2-phenylethylidenediphosphonic acid **37**, obtained by the reaction of $PhCH_2CN$ with PCl_3 and H_3PO_3, be used for the removal of toxic elements from the organism.

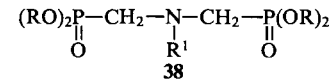


36



37

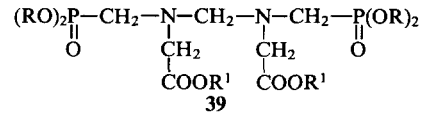
Phosphorus-containing complexones **38** have found extensive applications in medicine.[150-153]



38

R = H, M; R^1 = H, Alk, Ph, Bn, cyclo-C_6H_{11}.

Compounds **39**, which exhibit a herbicidal activity, have been patented.[154]

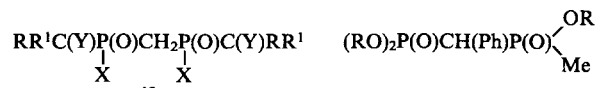


39

R = Ph; R^1 = Alk, arylalkyl.

V. Phosphonophosphinates and diphosphinates

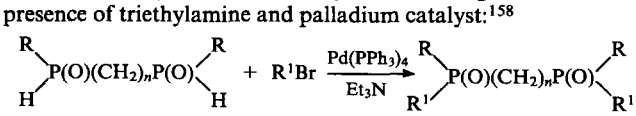
The reaction of esters of methylenediphosphonous acids with carbonyl compounds, which lead (after the hydrolysis) to the corresponding bis[α-hydroxyalkyl(aryl)]methylenediphosphinic acids **40**, has been investigated.[155,156] Compounds **40** are obtained also in the reaction of trialkylmethylenediphosphonite with benzaldehyde in the presence of a base. α-Phosphorus-substituted benzylphosphonate **41** is also formed in this reaction as an addition product.[155]



40 41

X = Cl, Alk, OAlk, OH; Y = Cl, OH; R = H, Me, Et;
R^1 = Alk(C_{2-6}), Ph.

Systematic study of the pesticidal activity of the derivatives of methylenediphosphorus acids showed that they can exhibit growth regulating, herbicidal, and fungicidal activities.[157] It has been suggested that diphosphonates with tetra- and hexamethylene bridges be obtained by the following reaction in the presence of triethylamine and palladium catalyst:[158]

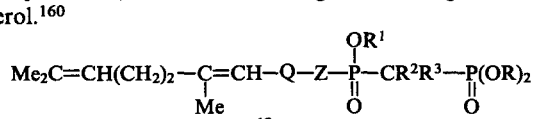


R = EtO, Ph; R_1 = Ph, 4-ClC_6H_4, 4-$Me_2NC_6H_4$, 4-$NO_2C_6H_4$, 4-AcC_6H_4, 2-naphthyl, etc.

Compounds **42**, which strengthen the bone tissue and can be used in stomatology, have been described.[159] They are synthesised by the reaction of $Ph_2P(O)CF_2Br$ with PCl_3 in the presence of zinc dust followed by hydrolysis and the oxidation of the intermediate with distilled water.

$$Ph_2P(O)—CF_2—P(O)(OH)_2$$
42

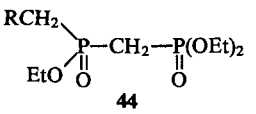
Alkenylphosphinylmethylphosphonates **43** are inhibitors of squalene synthetase, which are used as agents reducing the level of cholesterol.[160]



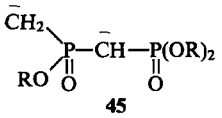
43

R, R^1 = H, Alk, M; R^2, R^3 = H, Hal; Z = $(CH_2)_n$, $(CH_2)_pCH=CH(CH_2)_m$; Q = $CH_2CH_2C(Me)=CH_2$, bond; n = 1–5, m,p = 0–2.

It has been suggested that the phosphinylphosphonyl compounds **44**, obtained by the Arbuzov reaction involving $(EtO)_2PCH_2P(O)(OEt)_2$ and the corresponding alkyl halides RCH_2Br [R = $CH_2CH_2C(Me)=CH_2$ or $Me_2C=CHCH_2$] be used as analogues of natural isoprenoids—isopentenyl and dimethylallyl diphosphates. The ammonium salts of both analogues are competitive inhibitors of the [1′,4]-condensation of isopentenyl diphosphate and geranyl diphosphate catalysed by diphosphate synthetase.[161] Furthermore, it has been reported[162] that the phosphinylphosphonyl dianion **45** is capable of undergoing the alkylation reaction with a multiplicity of electrophiles such as ethyl iodide, geranyl bromide, benzyl bromide, etc., which permits its use in the synthesis of analogues of natural diphosphates.

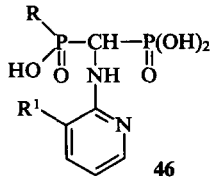


44



45

It has been established[94] that, in contrast to pyridylaminomethylenediphosphinates and the corresponding diphosphonates, pyridylaminomethylenephosphonoalkylphosphinates **46** exhibit a satisfactory antiresorptive activity.



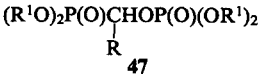
R = Me, Bu, $Ph(CH_2)_4$; R^1 = H, Me.

46

The synthesis of compounds **46** is based on the reaction of equimolar amounts of $(EtO)_2P(O)CH(OEt)_2$, EtO(R)P(O)H, and 2-aminopyridine (or 2-amino-3-methylpyridine) and subsequent hydrolysis.

VI. Phosphonophosphates

Nguyen Lan et al.[89] synthesised and investigated the medical and biological properties of geminal diphosphonates and phosphonophosphates **47**. It was established that, in relation to plasma lipids, these compounds exhibit the maximum pharmacological activity among all the substances of a similar type obtained and they are therefore potential antiatherosclerotic agents.



47

R^1 = H, Alk; R = Alk, Ph, $PhCMe_2$, $PhOCMe_2$, $PhCH_2CMe_2$, $ClC_6H_4C(O)C_6H_4$, cyclo-C_6H_{11}, 2-naphthyl, biphenylyl.

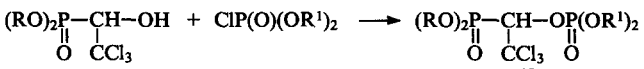
These compounds increase the concentration of the high density lipoprotein cholesterol, the amount of phospholipids, and the ratio of α-cholesterol to β-cholesterol. Compound **47** (R^1 = Me, R = 4-ClC_6H_4) was selected for further pharmacological and clinical studies.

Two methods were used to obtain these compounds, each of which begins with the formation of acylphosphonates $RC(O)P(O)(OR^1)_2$ via the reaction of RCOCl with trialkyl phosphite at 0 °C without a solvent.

The interaction of acylphosphonate with dialkyl phosphites in the presence of 80–100 mol% of dialkylamine at 0 °C in diethyl ether leads to geminal phosphonophosphates,[163] while in the presence of the catalytic amount (~5%) of an amine it affords geminal hydroxyldiphosphonates $RC(OH)[P(O)(OR^1)_2]_2$, which isomerise to phosphonophosphates on refluxing in alcohol.

The interaction of acylphosphonate with dialkyl phosphites at 80 °C without a solvent leads to geminal phosphonophosphates.[89]

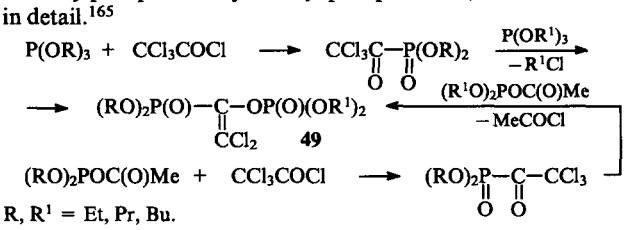
The synthesis of esters of α-(dialkylphosphono)-β,β,β-trichloroethylphosphoric acid **48** from the esters of α-hydroxy-β,β,β-trichloroethylphosphonic acid and the chlorides of dialkylphosphoric acids in the presence of triethylamine were described as early as 1958.[164]



48

R, R^1 = Alk(C_{1-4}).

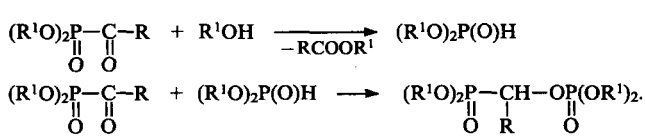
The esters showed strong insecticidal properties and also acted on certain species of stinging insects. The mechanism of the reactions of trialkyl phosphites and dialkyl acetyl phosphites with the chlorides of chloroacetic acids, leading to the formation of α-dialkylphosphonovinyl dialkyl phosphates **49**, has been studied in detail.[165]



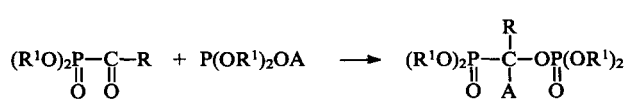
49

R, R^1 = Et, Pr, Bu.

It has been noted[166] that dialkyl α-dialkylphosphonoalkyl phosphates **47** are formed in the reaction of esters of α-ketophosphonic acids with alcohols and amines in 55% yield.

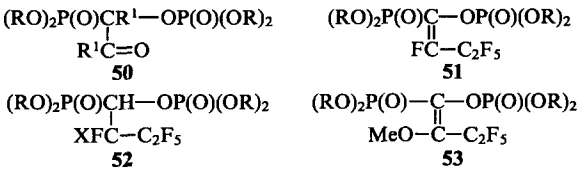


In a review devoted to esters of α-ketophosphonic acids,[167] the latter compounds are regarded as the most convenient initial reagents for the synthesis of phosphonophosphates in accordance with the following scheme:



A = Alk, C(O)Me.

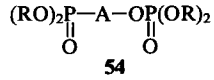
Yet another method of synthesis of phosphonophosphates in yields of above 50% from the esters of α-ketophosphonic acids involves the interaction of the latter with $LiN(CPr^i)_2$ or NaH in tetrahydrofuran.[168] A method of synthesis of phosphonophosphates by the reaction of trialkyl phosphite and R'C(O)X (X = Hal, Ac, NH_2, alkylamino-group, or alkoxy-group) below 45 °C, involving treatment of the intermediate with dialkyl phosphite in the presence of an organic base (NMe_3, NEt_3, Py) in a catalytic amount, has been patented.[169] The yield of the phosphonophosphates reaches 96% in this process. It has been suggested[170] that the reaction of tetraalkyl pyrophosphites $(RO)_2POP(OR)_2$ (R = Pr, Et) or dialkyl acyl phosphite with trifluoroacetic acid in acetonitrile be used for the synthesis of fluorinated phosphonophosphates. The synthesis of fluorine-containing phosphonophosphates **50** in yields in excess of 60% by the reaction of dialkyl phosphites with perfluorinated carboxylic acid anhydrides $(R^1CO)_2O$ ($R^1 = CF_3$, C_2F_5, C_3F_7) has been described.[171] The synthesis of the fluorinated phosphono-phosphates **51**, **52** (X = F, OMe), and **53** has also been investigated.[172]



50 **51**

52 **53**

The halogenated phosphonophosphates **54** have been obtained from PCl_3 and epoxyethane in the presence of $TiCl_4$ and by subsequent treatment of the intermediate with the chloride of monochloroacetic acid.[173]



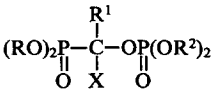
54

R = haloalkyl, for example CH_2CH_2Cl; A = CR^1R^2, $HC=CR^1$; R^1 = H, Hal, Alk; R^2 = H, Hal.

The phosphonates **55** have been obtained in yields of about 92% in two ways.

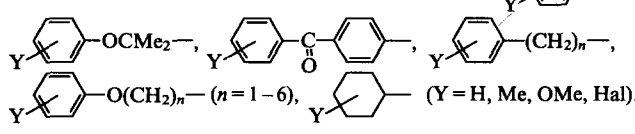
1. By the reaction of dialkyl phosphite with the corresponding acyl chloride in the presence of dialkylamine and the subsequent interaction of the resulting acylphosphonate with a phosphonite.

2. By the reaction of the corresponding aryl or aroyl halide with methylenediphosphonate and subsequent treatment of the resulting aryl or aroyl diphosphonate.



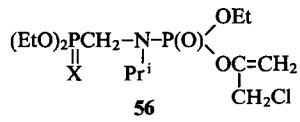
55

X = H, OH, OAc, NH_2; R, R^2 = H, Alk; R^1 = Bu^t, ,

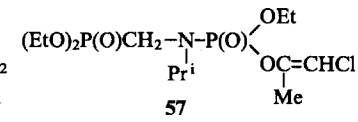


(Y = H, Me, OMe, Hal).

These compounds act on lipids and the lipid metabolism, lower the level of free aliphatic acids and triglycerides in the serum, increase the amount of phospholipids, and regulate the concentration of cholesterol. The acids **55** and their salts diminish the amount of calcium in the rat serum. Some of the derivatives are antiatherosclerotic and hypoglycemic agents.[85,86] The effect of compounds **56** and **57** on the enzymes of the Colorado beetle has been reported.[174]



56



57

X = O, S.

The above compounds inhibit arylesterase, carboxylesterase, acetylcholinesterase, and butyrylcholinesterase of insects, inducing 50% – 100%, mortality in 24 h.

* * *

Analysis of the scientific-technical and patent literature for the last two decades has shown that derivatives of phosphonic acids containing two phosphorus atoms (MDP, HEDP, diphosphonic analogues of amethopterin, phosphicine) have found extensive applications in medicine. These compounds are used as radiopharmaceutical preparations for the treatment of bone diseases and malignant tumours. The practical interest attaching to the physiological properties of compounds containing two phosphorus atoms has led to a vigorous search for ways of synthesising them. Although the syntheses of new preparations are usually based on known phosphonylation methods (the Arbuzov, Michaelis – Bekker, Kabachnik – Fields, Todd – Atherton, etc. methods), an expansion of the range of the initial reagents and the optimisation of the conditions in the above reactions are to be expected in the next few years. This is because the mechanisms and modes of many phosphonylation reactions depend to a considerable extent on the initial conditions. Furthermore, the use of organophosphorus compounds containing specific groups (formyl, amino-, epoxy-, etc.) is promising, which will permit a wider employment of 'non-phosphorus' reactions for the synthesis of diphosphonates and phosphonophosphates.

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