CONCLUSIONS

1. Diphenylborylimidoylamidinates and dialkylborylimidoylamidinates substituted at the nitrogen atom were synthesized.

2. The hydrochloride and perchlorate salts of dialkylborylimidoylamidinates, which are a variant of boronium salts, were prepared. Complexes in which a donor–acceptor interaction is accomplished between the boron atom of a boron halide and the trigonal nitrogen atom of the chelate ring were prepared by reacting boron halides with the dialkylborylimidoylamidinates.

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SYNTHESIS OF α-KETOPHOSPHONIC ACIDS

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A general method of synthesis of α-ketophosphonic acids (KPA), notwithstanding isolated approaches [1-3], until now has not been worked out. In addition, α-ketophosphonic acids as analogs of α-ketocarboxylic acids present definite interest for investigation of the mechanism of homologous enzymes.

For the production of KPA it was necessary to solve the problem of the selection of shielding groups which would not inhibit the formation of C(O)–P bonds and which would be removed without affecting the C–P bonds and C=O groups. The production of the diacid chloride of acetophosphonic acid was described by us earlier [4], and it follows that hydrolysis of such acid chlorides could be one of the unique methods of synthesis of KPA on the strength of the drastic conditions of obtaining acid chlorides and the low yields. Thus, under these conditions one cannot obtain the diacid chloride of phenylacetophosphonic acid from its diethyl ester. The utilization of tertiary butoxy groups in a shielding capacity, which earlier [5] allowed the synthesis of the antibiotic phosphomycin, also did not lead to desirable results.

Phosphonic acids with a labile C–P bond were earlier obtained by hydrogenation of the corresponding benzyl esters [6], but the possibility of utilizing this shielding in the case of α-ketophosphonates is complicated by the fact that dibenzyl esters of KPA are now known and the carbonyl group could be affected during hydrogenation. During testing of the method in the stage of removal of benzyl groups, which was used in the chemistry of nucleotides, one was able to obtain KPA (I) according the scheme

$$RCOCl + P(OCH_2C_6H_5)_3 \rightarrow \underset{(II)}{RCOP(O)(OCH_2C_6H_5)_2} \xrightarrow{H_2/Pd} \underset{(I)}{RCOP(O)(OH)_2}$$

$$\downarrow \qquad \uparrow H_2/Pd$$

$$RCOP(O)(ONa)(OCH_2C_6H_5)$$

$$(III)$$

R = CH_3 (a), $(CH_3)_2CH$ (b), $(CH_3)_2CHCH_2$ (c), $C_6H_5CH_2$ (d), $CH_3OCOCH_2CH_2$ (e), $HOCOCH_2CH_2$ (f)

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TABLE 1. IR (for the Na salt) and PMR Spectra of α-Ketophosphonic Acids and Their Esters

Compound	IR spectrum ν, cm^{-1}			PMR spectrum δ, ppm (J, Hz)						
	C=O	P=O	P—O—C	CH_3	CH_2	OCH_2	CH	CH=	C_6H_5	OH
(IIa)	1695	1255	995	2,26 (5,5)		5,00 (8,5)			7,22	–
(IIb)	1685	1250	990	1,07 (7,0)		5,02 (8,5)	3,01 (7,0)		7,25	–
(IIc)	1690	1255	995	0,87 (6,5)	2,55 (6,5)	5,05 (8,0)	2,22 (6,5)		7,25	–
(IId)	–	1185	990			5,08 (8,0)		6,21 (12,5)	7,31	–
(IIe)	1695	1255	995		2,47 9,97	5,02 (8,0)			7,25	–
(IIIa)	1660	1240	1030–1095	2,38 (4,5)		4,96 (8,0)		7,43		
(IIIb)	1660	1230	1010–1090			4,94 (8,0)	3,13 (7,0)		7,39	–
(IIIc)	1660	1225	1030–1090		2,75 (6,5)	4,97 (8,0)			7,47	–
(IIId)	1675	1235	1030–1105		4,06	4,97 (8,0)		7,46		–
(Ia)	1665	1120	–	2,44 (5,0)						10,20
(Ib)	1665	1190	–	1,14 (6,5)			3,27 (6,5)			8,80
(Ic)	1660	1140	–	0,95 (6,5)	2,75 (7,0)		3,20			9,17
(Id)	1665	1125	–		4,22			6,25 (13,0)	7,20	9,81
(Ie)	1660	1160	–	3,62	2,65					9,35

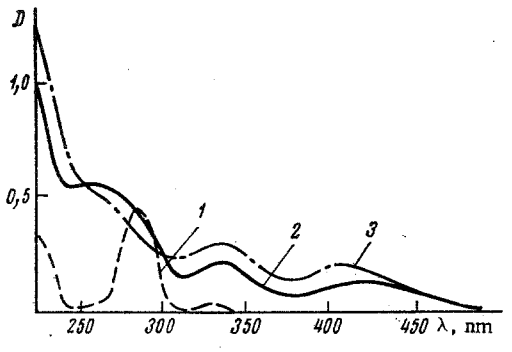


Fig. 1

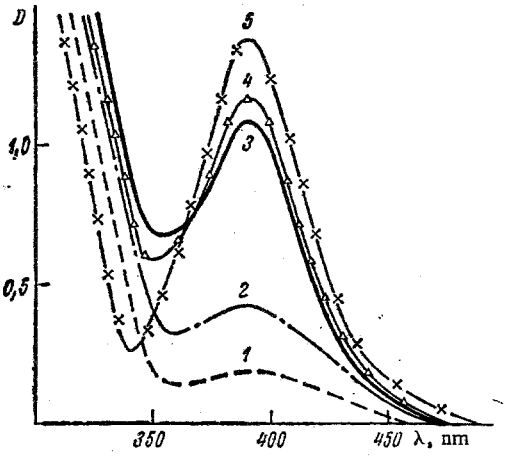


Fig. 2

Fig. 1. UV spectrum of diacid chloride of pyridoxamine in the presence of the Na salt of (Ia) and pyruvic acid in methanol over 27 h after the start of the reaction: 1) 10^{-4} M diacid chloride of pyridoxamine; 2) the same, $+4 \cdot 10^{-4}$ M Na salt of (Ia) $+2 \cdot 10^{-4}$ M NaOH; 3) the same, $+4 \cdot 10^{-4}$ M Na salt of pyruvic acid $+2 \cdot 10^{-4}$ M NaOH.

Fig. 2. The formation of pyridoxal during nonenzymatic transamination of the Na salt of (Ia): 1-3) 30 min, 4 h, 48 h; 4) the same, for the Na salt of pyruvic acid (incubated 48 h); 5) pyridoxal acid chloride (10^{-4} M). All spectra were taken in 0.1 N NaOH.

The reaction of acid chlorides with purified tribenzyl phosphite under conditions close to those described in [7] led to a good yield of the ketoesters (II), which are oily [with the exception of one crystalline product, (IId)]. The substances which are distilled under high vacuum are sufficiently stable without the introduction of moisture. There are intense absorption bands in IR spectra of these compounds in the areas 1250-1255 and 990-995 cm^{-1} which correspond to P=O groups and P—O—C esters of phosphonic acids [7]. The α-ketoesters (II) obtained by us, with the exception of (IId), exist in ketone form as is indicated by intense absorption in the 1685-1695-cm^{-1} region corresponding to the C=O group, and also the presence of proton signals of $CH_nC(O)$

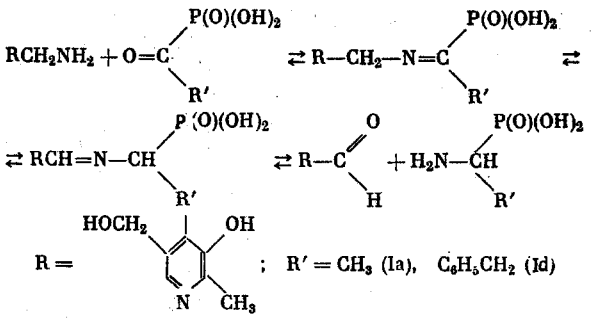
groups in PMR spectra of these compounds. The (IId) ester probably exists in enol form, since absorption in the C–O group range is absent, and there is a signal at 6.21 ppm in the PMR spectrum which corresponds to an olefin proton of enol form. All diesters (II) under normal conditions give 2,4-dinitrophenylhydrazones.

Monodebenzylation of (II) occurs easily upon action of NaI in acetone giving the crystalline Na salts of the monobenzyl esters (III), which can be used for the introduction of an α-ketophosphonyl residue into more complex structures giving various KPA derivatives.

Certain difficulties were encountered during the production of (I) which were connected with their instability. Hydrogenation of pure (II) in the presence of Pd-black led to (I) with 10-20% of unidentified foreign matter. Attempts to purify individual KPA compounds by various methods invariably were accompanied by their decomposition, although fresh preparations of (I) could be used with success for various syntheses, for example, the production of α-aminophosphonic acids. Hydrogenation of the Na salt of (III) proceeded more smoothly; however, multiple reprecipitations of the Na salt of (I) from cold water–alcohol solutions were required to obtain satisfactory analyses.

The structure of the acids (I) is confirmed by IR and PMR spectral data (Table 1), and also by conversion into already known α-aminophosphonic acids.*

For further investigation of the action of KPA with enzymes, in particular with transaminases, of which pyridoxal 5'-phosphate is a coenzyme, we studied the behavior of compounds (Ia) and (Id) in reaction conditions of model transamination [8]



In alcohol solutions KPA, similar to the corresponding α-ketocarboxylic acid, quickly formed ketimines with pyridoxamine (Fig. 1), the prototropic rearrangement of which proceeded normally into aldimines (Fig. 2) and was not accompanied by rupture of the C–P bond, insofar as corresponding α-aminophosphonic acid in amounts, for example, equivalent to the pyridoxal formed were discovered in the reaction mixture.

EXPERIMENTAL

The IR, UV, and PMR spectra were taken on "Spekord IR," "Spekord UV-VIS," and "Tesla-80" instruments, respectively. For TLC Silufol UV-254 and the following systems were used: for (II), benzene + ethyl acetate (9 : 1), for (I) and (III), isopropanol + NH_3 + H_2O (7 : 1 : 2). Compounds (II) and (III) were identified by absorption in the UV region and by reaction with $(NH_4)_2MoO_4$. In addition, for the manifestation of (II) a color reaction during successive treatment of a chromatogram with 2,4-dinitrophenylhydrazine and triethylamine was used. Compound (I) was identified by reaction with $(NH_4)_2MoO_4$.

Dibenzyl Esters of α-Ketophosphonic Acids (II). An ether solution of 11 mmole of the freshly prepared acid chloride was added to 10 mmole of pure tribenzyl phosphite during mixing and cooling. The mixture was held for 12 h at 20°C, protected from the introduction of air, the volatile products were distilled in vacuum, and the remaining oil was purified by molecular distillation (100-120°C and $5 \cdot 10^{-4}$ to $1 \cdot 10^{-3}$ mm), with a 50% yield† of 2,4-dinitrophenylhydrazones with melting points (from alcohol): (IIa) 148-150°C; (IIc) 111-113°C; (IId) (two isomers) 107-109, 126-128°C.

Monobenzyl Esters of α-Ketophosphonic Acids (III). A solution of 10 mmole of the diester (II) and 10 mmole of anhydrous NaI in 15 ml of absolute acetone was boiled several hours, cooled, the crystalline mono-Na salt (III) was filtered off, washed with cold acetone, and crystallized from alcohol containing water. The

*This reaction will be described in a separate communication.

†In the case of (IId) the residue was recrystallized from CCl_4 with a 40% yield and a mp of 118-119°C.

yield of (III) was 60%. For the isolation of free (III) a solution of 10 mmole of the Na salt in a minimal amount of cold H_2O was acidified to a pH=1 by cold 20% HCl, (III) was quickly extracted with dichloroethane, and after removal of the solvent in vacuum, the oil forming (III) was obtained.

Hydrogenation of Dibenzyl Esters (II). We hydrogenated 1 mmole (II) in 3 ml of ethanol over 10-20 mg of Pd-black. After completion of the reaction (1-2 h) the catalyst was filtered off and washed with ethanol, the filtrate was evaporated in a vacuum, and a viscous oil was obtained containing 80-90% (I).

Sodium Salts of α-Ketophosphonic Acids (I). We suspended 1.5 mmole of the Na salt (III) in 20 ml of methanol, dissolved in H_2O, and hydrogenated over 10-20 mg of Pd-black. After completion of the reaction the catalyst was filtered off and washed with H_2O, the filtrate was evaporated in a vacuum at 25-30°C and the residue was reprecipitated several times from alcohol containing water. The yield was 70%.

Nonenzymatic Transamination of α-Ketophosphonic Acids. We dissolved 0.03 mmole of diacid chloride of pyridoxamine, 0.12 mmole of Na salt (Ia), and 0.06 mmole of NaOH in 3 ml of absolute methanol, removed aliquots after 15 min, 4 h, and 27 h, diluted with methanol, and took UV spectra (see Fig. 1). From this same mixture we removed aliquots after 30 min, 4 h, and 48 h, dissolved in 0.1 N NaOH, and took UV spectra (see Fig. 2). After 120 h part of the reaction mixture was chromatographed in an isopropanol–25% NH_4OH–water (7 : 1 : 2) system and the amount of α-aminoethylphosphonic acid was determined by a color reaction with ninhydrin.

Reactions for Na salt (I) pyruvic acid, and phenylpyruvic acid were carried out in an analogous manner.

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CONCLUSIONS

1. α-Ketophosphonic acids are synthesized by hydrogenation of their benzyl esters.

2. The possibility of nonenzymatic transamination of α-ketophosphonic acids without rupure of the C–P bond is shown.

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