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REACTION OF BORYLOXYALKYLPHOSPHINES WITH AMINES

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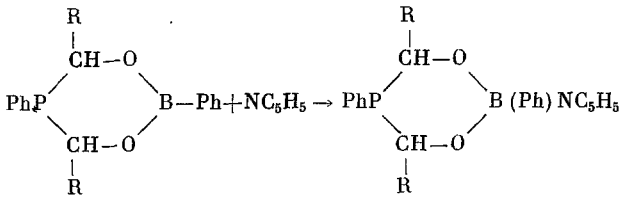
Boryloxyalkylphosphines form aminomethylphosphines with primary and secondary amines. In this way 1,3,5-diazaphosphorinanes [1] and 1,5-diaza-3,7-diphosphacyclooctanes [2] were obtained from 1,3,2,5-dioxaboraphosphorinanes. From the reaction of 5-thio(seleno)-1,3,2,5-dioxaboraphosphorinanes with pyridine, complexes are formed [3]. An attempt was made to obtain pyridine complexes with 1,3,2,5-dioxaboraphosphorinanes. However, in contrast with their sulfides and selenides, the reaction did not proceed. This is explainable by the strong electron-acceptor properties of thio- and selenophosphoryl groups. It was of interest to carry reactions of pyridine with 1,3,2,5-dioxaborophosphorinanes having pronounced acceptor substituents at the C atom attached to the P atom. Trichloromethyl and p-nitrophenyl were introduced as such substituents



R = CCl_3 (I); $C_6H_4NO_2$-*p*.(II)

4,6-Dichloromethyl- and 4,6-di-p-nitrophenyl-2,5-diphenyl-1,3,2,5-dioxaboraphosphorinanes formed stable crystalline complexes (I) and (II) with pyridine. The IR spectra of the complexes differed from the spectra of the initial compounds. In the PMR spectra the ratio of the integral intensities of the aromatic and pyridine protons confirmed the addition of pyridine. The chemical shifts (CS) of the signals of the P atom nuclei in the ^{31}P NMR spectrum were −32 ppm, and the signals of the methine protons in the PMR spectrum and also the SSCC $^2J_{PH}$ of (I) coincide with those obtained for the initial compound. The equivalence of the protons indicates that the compound is present in a chair conformation, while the value of the constant indicates an equatorial orientation of the phenyl attached to the P atom [4]. The initial compound for (II) is a mixture of stereoisomers with CS of −12 and −24 ppm in the ^{31}P NMR spectrum, one of which has nonequivalent protons according to the PMR spectra. The CS of the signals of (II) in the ^{31}P NMR spectrum lies close to the weak field of the initial compound, while the methine protons in its PMR spectrum are nonequivalent. The signal in the weak field in the ^{31}P NMR spectrum and the nonequivalence of the protons in the PMR spectra shows that the p-nitrophenyl groups in (II) occupy different positions in the chair conformation, or the molecule is present in the twist conformation [5]. The twist conformation with equatorial substituents on the C atoms attached to the P atom was proved

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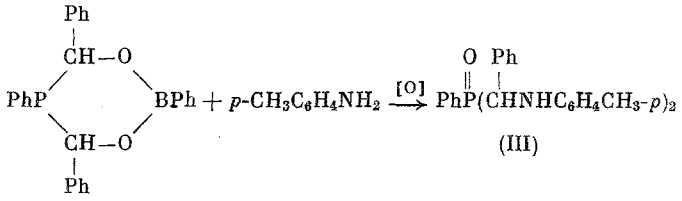
by the X-ray diffraction analysis of one of the stereoisomers of 5-phenyl-5-thio-2,4,6-triisopropyl-1,3,5-dioxaphosphorinane [6].

The difference in the influence of the substituents on the course of the reaction shows that the donor substituents hinder, and the acceptor substituents promote the complexation at the B atom. The thiophosphoryl group exhibits a pronounced acceptor character. The phosphino group has no such property.

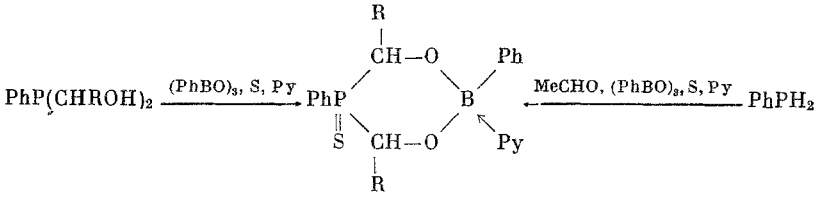
The influence of the substituents at the C atom attached to the P atom is also revealed in the reactions of 1,3,2,5-dioxaboraphosphorinanes with primary amines. While in the absence of substituents, even in excess of p-toluidine, 1.5-di-p-tolyl-3,7-diphenyl-1,5-diaza-3,7-diphosphacyclooctane is formed in almost quantitative yield [7], in the case of phenyl substituents, a complex mixture is obtained, from which bis(p-toluidinobenzyl)phenylphosphine oxide (III) was isolated



(III)

The structure of (III) has been established from the data of IR and ^{31}P NMR spectra.

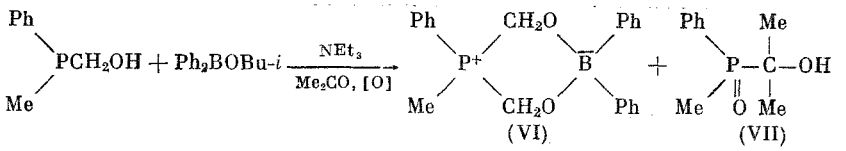
In [3], a synthesis is described of the complexes of sulfides and selenides of 1,3,2,5-dioxaboraphosphorinanes by simultaneous action of sulfur selenium and pyridine on 1,3,2,5-dioxaboraphosphorinanes. However, the preparation of these complexes can be carried out starting from bis(α-hydroxyalkyl)phenylphosphine and phenylboric acid anhydride or phenylphosphine and a mixture of the aldehyde and phenylboric acid anhydride and sulfur or selenium and pyridine



R = H, (IV); Me (V).

This method substantially simplifies the preparation of complexes, since there is no need to isolate 1,3,2,5-dioxaboraphosphorinane or bis(α-hydroxyalkyl)phenylphosphines. The CS of the signals in the ^{31}P NMR spectra of the reaction mixtures and the products isolated coincide.

In the reaction of bis(α-hydroxyalkyl)phenylphosphines with isobutyl ester of diphenylboric acid, after the addition of sulfur and pyridine or Et_3N, ammonium 5-thio(seleno)-1,3,2,5-dioxaboraphosphorinanes were isolated [8]. The reason for the formation of the products in the form of salts is the presence of the hydroxyalkyl group. It might be expected that also other hydroxyalkylphosphines will react with isobutyl ester of diphenylboric acid at a 2:1 ratio of the hydroxyalkyl groups to the boron atoms to give salt-like products. We therefore carried out the reaction of methyl(phenyl)hydroxymethylphosphine with isobutyl ester of diphenylboric acid at a 2:1 ratio in the presence of trimethylamine. However, instead of the expected salt compound, 2,2,5-triphenyl-5-methyl-1,3,2,5-dioxaboraphosphorinane was isolated after washing with acetone, and methyl(α-hydroxyisopropyl)phenylphosphine oxide was obtained from the filtrate



(VI) (VII)

The structure of (VII) was confirmed by the PMR spectrum. The source of formaldehyde for the formation of (VI) is methyl(phenyl)hydroxymethylphosphine, which is confirmed by the formation of (VII), which is a product of the addition of acetone to methylphenylphosphine.

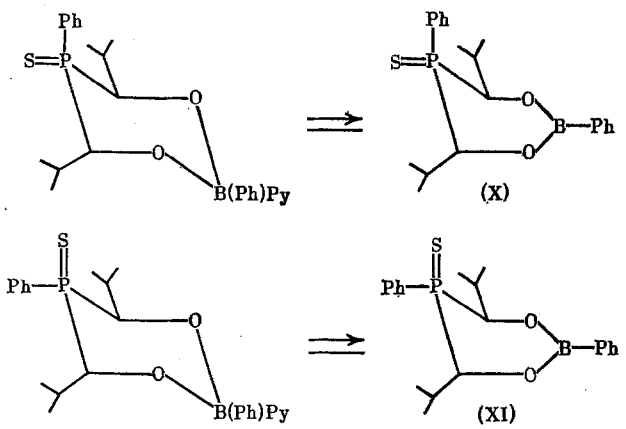
The formation of salt-type compounds from 1,3-propanediols, isobutyl ester of diphenylboric acid and several amines was shown in [3]. In the solid state, the absorption characteristic for the hydroxyl groups wasnot present in the IR spectra.

In the reaction of 1,3-propanediol with isobutyl ester of diphenylboric acid in the presence of higher aliphatic amines, compounds were obtained having an absorption in the IR spectra, characteristic for the hydroxyl groups (3220 cm^{-1}, a broad band) and for the $\overset{+}{N}$–H groups bound by a coordination bond (2150, 2400, 2500 cm^{-1}). This shows that the compounds are present in a complex form

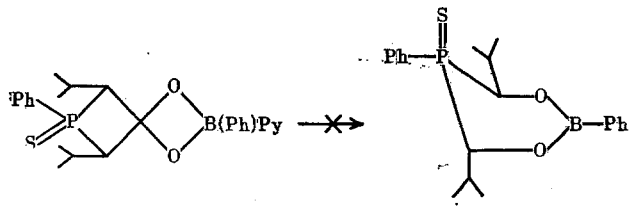
$$HOCH_2CH_2CH_2OH + Ph_2BOBu\text{-}i + RNH_2 \rightarrow \underset{\text{(VIII),(IX)}}{HOCH_2CH_2CH_2O\overset{\overset{RNH_2}{\downarrow}}{B}Ph_2}$$

$R = C_8H_{17}$ (VIII); $C_{10}H_{21}$ (IX).

On heating, the pyridine complexes of 1,3,2,5-dioxaboraphosphorinanes split off pyridine and give 1,3,2,5- dioxaboraphosphorinanes. The splitting off of pyridine can also occur on evaporation of the solutions of the complexes of sulfides in dioxane. Thus, the individual stereoisomers (X) and (XI) could be isolated from the pyridine complexes of the individual stereoisomers of 2,5-diphenyl-5-thio-2,4,6-triisopropyl-1,3,2,5-dioxaboraphosphorinanes with a CS of 23 and 28 ppm in the ^{31}P NMR spectra, present in a chair conformation with equatorial isopropyl groups and with axial and equatorial phenyl groups, respectively.



The isolated stereoisomers differ in their melting points and IR and PMR spectra from the initial complexes. The constants of (X) coincide with those given in [9]. Compound (XI) was not isolated in individual state previously. When pyridine is split off, the same isomer is formed from which the pyridine complex was obtained. This indicates that the P atom in the pyridine complex has the same configuration as in the initial stereoisomer. The pyridine complex of the stereoisomer of 2,5-diphenyl-5-thio-4,6-diisopropyl-1,3,2,5-dioxaborophosphorinane with a CS of 49 ppm with nonequivalent protons in the PMR spectrum, does not split off pyridine, even on boiling in dioxane for several hours.



In contrast to 1,3,2,5-dioxaboraphosphorinanes with alkyl or phenyl substituents or without substituents, which readily add sulfur in pyridine with the formation of sulfide complexes, compounds (I) and (II) do not add sulfur.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer. The PMR spectra were run on a Varian T-60 spectrometer (60 MHz) at 34.5°C and at a 10% concentration of the solutions. The ^{31}P NMR spectra were obtained on a KGU-4 spectrometer (10.2 MHz) with protons decoupling at a frequency of 25.2 MHz. The CS are given with reference to 85% H_3PO_4 and the positive values refer to weak fields.

Complex of 2,5-Diphenyl-4,6-ditrichloromethyl-1,3,2,5-dioxaborophosphorinane with Pyridine (I). A 4.9 g portion of 4,6-ditrichloromethyl-2,5-diphenyl-1,3,2,5-dioxaboraphosphorinane [4] was dissolved in 7 ml of pyridine. After 3 h, pyridine was removed in vacuo (0.1 mm, 40°C), and the residue was crystallized from acetone. Yield, 4.3 g (75%), mp 182°C, $\delta^{31}P$—32 ppm (C_6H_6). Found, %: C 44.63; H 2.98; P 5.22; N 2.62. $C_{21}H_{17}PO_2BNCl_6$. Calculated, %: C 44.21; H 2.98; P 5.44; N 2.46.

Complex of 4,6-di-p-Nitrophenyl-2,5-diphenyl-1,3,2,5-dioxaboraphosphorinane with Pyridine (II). A 5 g portion of 4,6-di-p-nitrophenyl-2,5-diphenyl-1,3,2,5-dioxaboraphosphorinane [4] was dissolved in 10 ml of a benzene—pyridine mixture (3:1). The solution acquired a red color. After 1 h, the solvent was removed in vacuo (0.1 mm, 40°C) and the residue was crystallized from acetone. Yield, 4.4 g (77%), mp 192°C, $\delta^{31}P$—26 ppm (C_6H_6). Found, %: C 63.45; H 4.67; P 5.14; N 7.05%. $C_{31}H_{27}PO_6BN_3$. Calculated, %: C 64.25; H 4.66; P. 5.35; N 7.25.

Bis(p-toluidinobenzyl)phenylphosphine Oxide (III). A solution of 0.8 g (7.5 mmoles) of p-toluidine in 5 ml of ethanol was added to 3.06 g (7.5 mmoles) of 2,4,5,6-tetraphenyl-1,3,2,5-dioxaboraphosphorinane [10], and the mixture was heated to dissolution. After 3 h, the precipitate was filtered and recrystallized from MeCN. Yield, 1 g (26%), mp 182°C, $\delta^{31}P$—16 ppm (DMFA). IR spectrum (ν, cm^{-1}): 3300, 3400 (oil). Found, %: C 80.34; H 6.30; P 6.50; N 5.72. $C_{34}H_{33}PON_2$. Calculated, %: C 79.07; H 6.40; P 6.14; N 5.43%.

Complex of 2,5-Diphenyl-5-thio-1,3,2,5-dioxaboraphosphorinane with Pyridine (IV). A 2.1 g (20 mmole) portion of phenylboric acid anhydride was added to 3.4 g (20 mmole) of bis(hydroxymethyl)phenylphosphine, the mixture was heated to the dissolution of the anhydride, and an excess of sulfur and 8 ml of pyridine were added. On the next day, pyridine was removed in vacuo (0.1 mm, 40°C), the residue was dissolved in MeCN and excess sulfur was filtered. On evaporation of the filtrate a precipitate separated, which was recrystallized from acetone. Yield, 3.3 g (45%), mp 134°C, δ^{31} 29 ppm (C_6H_6) (cf. [3]).

Complex of 4,6-Dimethyl-2,5-diphenyl-5-thio-1,3,2,5-dioxaboraphosphorinane with Pyridine (V). A solution of 2.1 g (20 mmoles) of phenylboric acid anhydride in 30 ml of MeCHO and 5 ml of pyridine was gradually added at 0°C to 2.2 g (20 mmoles) of phenylphosphine. The mixture was heated to 20°C and an excess of sulfur was added. On the next day, the volatile components were removed in vacuo (0.1 mm, 40°C), and the residue was recrystallized from acetone. Yield, 4.8 g (61%), mp 97°C, $\delta^{31}P$ 51 ppm (DMFA) (cf. [3]).

2,2,5-Triphenyl-5-methyl-1,3,2,5-dioxaboraphosphorinane (VI) and Methyl(α-hydroxyisopropyl)phenylphosphine Oxide (VII). A 1 ml portion of Et_3N and then 2.39 g (10 mmoles) of isobutyl ester of diphenylboric acid were added to 1.57 g (10 mmoles) of methyl(phenyl)-hydroxymethylphosphine. After 2 days, the precipitate that separated was filtered and washed with acetone. The yield of (VI) was 1.5 g (85%), mp 151°C, $\delta^{31}P$ 1 ppm (DMFA) (cf. [11]). Crystals precipitated from the filtrate. The yield of (VII) was 0.4 g (40%), mp 148°C, $\delta^{31}P$ 42 ppm. (C_6H_6 + DMFA). IR spectrum (ν, cm^{-1}): 3400 (oil). Found, %: C 59.97; H 7.86; P 15.88. $C_{10}H_{15}PO_2$. Calculated, %: C 60.60; H 7.57; P 15.66.

Complex of 1-Hydroxy-3-diphenylboryloxypropane with Tertiary Octylamine (VIII). A 2.19 g (9 mmole) portion of isobutyl ester of diphenylboric acid and 1.18 g (9 mmole) of tert.-octylamine are added to 0.7 g (9 mmole) of 1,3-propanediol. Warming up of the reaction mixture was observed and a precipitate separated. After 2 h, 10 ml of acetone were added, and the precipitate was filtered. Yield, 2.8 g (77%), mp 116°C. Found, %: C 74.89; H 9.60; N 4.19. $C_{23}H_{36}BO_2N$. Calculated, %: C 74.80; H 9.76; N 3.79.

Complex of 1-Hydroxy-3-diphenylboryloxypropane with Decylamine (IX). A 1.2 g (6.4 mmole) portion of isobutyl ester of diphenylboric acid and 1 g (6.4 mmole) of decylamine were added to 0.5 g (6.4 mmole) of 1,3-propanediol. A warming up of the reaction mixture was observed. The volatile components were removed in vacuo (0.1 mm, 40-60°C). The residue was a viscous liquid. Yield 2.2 g (97%). Found, %: C 75.27; H 9.76; N 3.67. $C_{25}H_{40}BO_2N$. Calculated, %: C 75.57; H 10.08; N 3.53.

Stereoisomers of 2,5-Diphenyl-5-thio-4,6-diisopropyl-1,3,2,5-dioxaboraphosphorinanes (X) and (XI). A 0.4 g portion of complex (XI) with pyridine with $\delta^{31}P$ 24 ppm [3] was dissolved in 50 ml of dioxane. After a few days, dioxane was evaporated at 20°C, and the residue was crystallized from C_6H_6. The yield of (X) was 0.2 g (50%), mp 164°C, $\delta^{31}P$ 23 ppm (cf. [10]). Compound (XI) was obtained in a similar way from the corresponding complex with pyridine, having $\delta^{31}P$ 29 ppm [3]. Yield 58%, mp 130°C, $\delta^{31}P$ 28 ppm (C_6H_6). Found, %: C 63.80; H 6.60; N is absent. $C_{20}H_{26}POBS$. Calculated, %: C 64.52; H 6.99.

CONCLUSIONS

1. Electron-acceptor substituents on the carbon atoms attached to the phosphorus atom increase the ability of 1,3,2,5-dioxaboraphosphorinanes to form complexes at the boron atom with tertiary amines.

2. When dissolved in dioxane, the pyridine complexes of stereoisomers of 2,5-diphenyl-4,6-diisopropyl-5-thio-1,3,2,5-dioxaboraphosphorinanes split off pyridine to form stereosiomers of 2,5-diphenyl-4,6-diisopropyl-5-thio-1,3,2,5-dioxaboraphosphorinanes with the retention of the configuration.

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INHIBITION OF CHOLINESTERASES BY S-β-ARYL(BENZYL)MERCAPTOETHYL ESTERS OF PHOSPHORUS THIOACIDS

V. M. Kuzamyshev, L. G. Grineva, D. G. Duda, M. Kh. Berkhamov, and N. N. Godovikov

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Earlier it was shown [1] that S-β-arylmercaptoethyl esters of monothioacids of P(V) have an anticholinesterase activity substantially surpassing that of the known analogous compounds containing aliphatic radicals at the sulfide S atom [2] and exhibiting a combined type of inhibition of cholinesterases.

For a more detailed study of the effects found [1] we synthesized a series of compounds of the type (see scheme at top of following page).

The synthesis of most of the compounds was published earlier [1, 3]. The undescribed compounds were synthesized by alkylation of the salts of the corresponding bioacids of phosphorus with β-chloroethylbenzyl and β-chloroethylaryl sulfides analogously to [1, 3]; the properties of these substances are cited in Table 1.

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