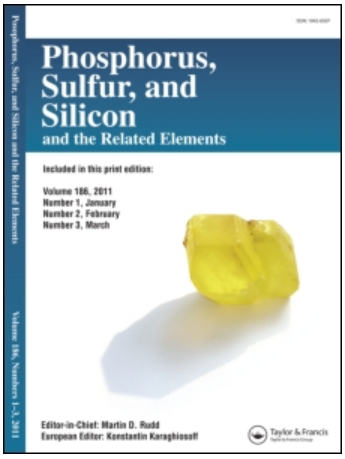

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Formation of Benzooxaphosphole Oxide Heterocyclic System by the Ring-Contractive Arbuzov-Michaelis Isomerization of Alkoxy-Substituted Benzodioxaphosphorins

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FORMATION OF BENZOOXAPHOSPHOLE OXIDE HETEROCYCLIC SYSTEM BY THE RING-CONTRACTIVE ARBUZOV-MICHAELIS ISOMERIZATION OF ALKOXY-SUBSTITUTED BENZODIOXAPHOSPHORINS

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A possibility of the Arbuzov-Michaelis-type isomerization is revealed for the model 2-ethoxy derivative ***4*** *of the six-membered 4H-benzo[1,3,2]dioxaphosphorin heterocycle. The reaction proceeds with ring contraction to give the five-membered 3H-benzo[d][1,2]oxaphosphole 2-oxide heterocyclic system. Some synthetic possibilities of the new reaction disclosed here are demonstrated by introducing a pharmacophoric 5-O-nucleoside to the P(IV) atom leading to the 3H-benzo[d][1,2]oxaphosphole 2-oxide system by this new rearrangement reaction.*

Keywords: 2-hydroxybenzylic alcohol; Arbuzov-Michaelis-type isomerization; benzodioxaphosphorins; benzooxaphosphole oxides; cyclosaligenyl nucleotides; saligenin

INTRODUCTION

For the synthesis of heterocyclic systems in classical organic chemistry two general approaches may be envisaged: ring-containing molecules can be synthesized either by cyclization of a linear (acyclic) precursor

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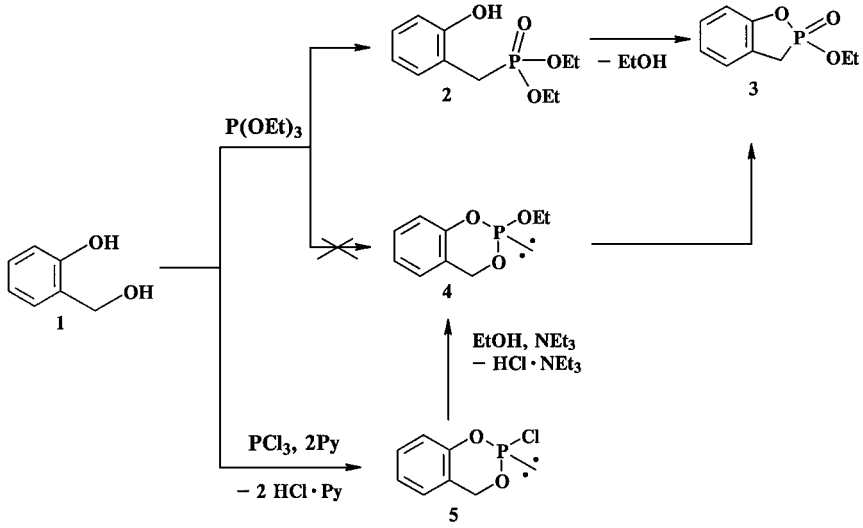
or by modification (expansion or contraction) of a preliminary formed heterocycle. The present work is concerned with one interesting case of the latter type leading to phosphorus containing heterocycles (Scheme 1). Between 1967 and 1969, Ivanov and Ageeva conclusively



SCHEME 1

proved by kinetic and spectral methods that the formation of five-membered benzooxaphosphole oxides **3** in the reactions of ortho-hydroxybenzylic alcohol (saligenin) **1** with $P(OEt)_3$ and $P(OEt)_2Cl$ is due to the cyclization of intermediate *ortho*-hydroxybenzylphosphonate **2**. Alternatively, a possible reaction pathway via the six-membered heterocyclic intermediate **4** was excluded.[1,2,*]

A cyclization pathway leading to the formation of the phosphorus-bearing heterocyclic system **3** is well documented in the literature. So, the reaction of saligenin and $P(OMe)_3$ leads to the formation of the MeO analog of benzyl phosphonate **2**[3] and so confirmed the validity of the approach developed before.[1,2] Then, Chaser thoroughly verified the above results and proved again the formation of **2**.[4] The formation of six-membered heterocyclic intermediate like **4** in both experiments[3,4] was excluded again.

In the follow-up of our systematic study on the phosphorylation of polyfunctional organic compounds by various phosphorus(III) reagents

*The authors also presumed the formation of another acyclid intermediate (*o*-chloromethylphenylphosphite) in the reaction of saligenin with $P(OEt)Cl_2$.

(see for example[5,6]), in this work we examined the possible formation of heterocyclic system **3** described in[1,2,4] by ring contraction of the six-membered precursor phosphite **4**. Phosphite **4** was synthesized independently and its structure has been proven by spectroscopic means.

RESULTS AND DISCUSSION

In order to verify the new strategy proposed for the synthesis of heterocyclic benzooxaphosphole oxide systems, we prepared the starting six-membered cyclic chlorophosphite **5** by the treatment of saligenin with PCl_3 in the presence of pyridine by the literature method.[7] The dioxaphosphorin ring structure of this compound was unambiguously proved by the characteristic values of chemical shift in the ^{31}P NMR spectrum (δ_p 140.72 ppm), chemical shifts of benzyl protons in the ^{1}H and ^{13}C NMR spectra (4.86 ppm and 5.31 ppm; 60.66 ppm respectively), and coupling constants ($^{3}J_{HP}$ 9.6 Hz and 2.3 Hz, $^{2}J_{CP}$ 1.8 Hz).[8] The product of the second step was the ethoxy phosphite **4**, which we first obtained by a substitution of the chlorine atom in **5** by an ethoxy group in a solution of ethanol in petroleum ether in the presence of triethylamine (NEt_3). Phosphite **4** was isolated by vacuum distillation and proved to be stable when stored in the absence of solvent at 0°C for at least one month. The presence of a six-membered dioxaphosphorin heterocyclic structure of compound **4** was confirmed by the characteristic resonance signals and coupling constants ^{3}J in ^{31}P and ^{1}H NMR spectra, as for the above-mentioned six-membered chlorophosphite **5**: δ_p 118.17 ppm; $\delta_{H(benzyl)}$ 4.71 ppm and 5.16 ppm; $^{3}J_{H(benzyl)P}$ 2.8 Hz and 9.6 Hz, respectively.

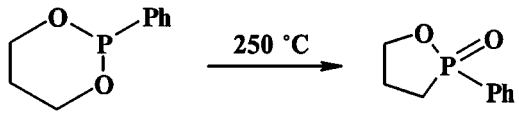
However, we found that when **4** was dissolved in $CDCl_3$ at room temperature, a new set of signals resulting from the formation of a new compound **3** appeared while those from the initial compound **4** decreased in the ^{31}P and ^{1}H NMR spectra. Clearly, compound **3** is the result of a rearrangement reaction of starting material **4**. The rearrangement reaction proceeded in 10 min to an extent of 6% and is completed in 3 days at 20°C. Moreover, a simplification of the above procedure can be applied: The reaction mixture leading to compound **4** in petroleum ether was filtered and concentrated to a small volume and was used directly for the rearrangement.

From ^{31}P and ^{1}H NMR data, the discovered rearrangement corresponds to the ring contraction of a six-membered ring to a five-membered one, which is unambiguously proved by the following facts: A C—P bond appears in the new product **3** (δ_p 46.12 ppm; $^{1}J_{CP}$ 123.8 Hz);

the benzyl —CH_2— group enters into the phosphonate fragment, rather than the ethyl —CH_2— group ($\delta_{H(benzyl)}$ 3.04 and 3.13 ppm, $\delta_{H(ethyl)}$ 3.95 and 3.98 ppm, $\delta_{C(benzyl)}$ 23.55 ppm, and $\delta_{C(ethyl)}$ 62.54 ppm). Additionally, this conclusion can be made because the methylene group attached to the phosphorus atom did not show $^1H,^1H$-couplings to the methyl group. This would be observed if the ethoxy-group would be involved in the rearrangement. All NMR and mass-spectral characterisitics of the final product **3** are identical to those reported earlier for this compound obtained using the classical cyclization method (**2** into **3**, Scheme 1).[1,2,4]

^{31}P NMR monitoring showed that the six-membered chlorophosphite precursor **5** of the ethoxy derivative **4** did not show ring contraction of the heterocycle either during synthesis, vacuum distillation, storage without solvent at room temperature for at least 1 week or during the substitution of the chlorine atom into the EtO group. Therefore, all experimental data lead to the conclusion that the rearrangement reaction discovered here is due to a transformation of the isolated ethoxy-substituted phosphite **4**, and that product **3** is not a result of a trivial ethanolysis of the P—Cl bond of the possible five-membered acid chloride that may have been formed starting from the cyclic chlorophosphite **5**. However, we cannot exclude a principal possibility for the isomerization of six-membered chlorophosphites to five-membered chlorophosphonates under more rigid conditions.

Generally, phospite-phosphonate transformations are classified into two groups.[9] One group is characterized by a relatively clear role of the reagent or catalyst and is called classical Arbuzov-Michaelis rearrangement. The second group, where the mechanisms and the role of a possible promoter/activator/catalyst remains still unclear, is called Arbuzov-Michaelis isomerizations. All presently known processes of the second type require elevated temperatures, such as 160°C for tribenzylphosphite[10] or diethyl-3-oxobutylphosphite[11] and 175°C for allyl diethylphosphite,[12] 250°C for trimethylphosphite[13] and 2-phenyl-[1,3,2]dioxaphosphorin-2-yl (which also undergoes ring contraction (Scheme 2),[14] or even 320°C for triphenylphosphite in the presence of PhBr and Raney's nickel.[15]



SCHEME 2

In contrast to these data, the disclosed cyclophosphite-phosphonate transformation of compound **4** proceeds under extremely mild conditions (already at room temperature), and are comparable to the

photochemical isomerization of benzylphosphites[16–18] or the ion-radical rearrangement of dialkylphenylphosphonite[19] under anodic oxidation conditions which are both known for their radical mechanisms (see also).[20–24*]

The driving force of the isomerization described here and other probably related Arbuzov-Michaelis-type isomerizations remains unclear. We did not perform a detailed study of this mechanism in this work and restricted ourselves to an assumption that the reaction may be activated by residual phosphoryl compounds[13] probably present in **4** or triethylammonium chloride ($Et_3NH^+Cl^-$), whose trace amounts are frequently found even in carefully distillated phosphites.[25]

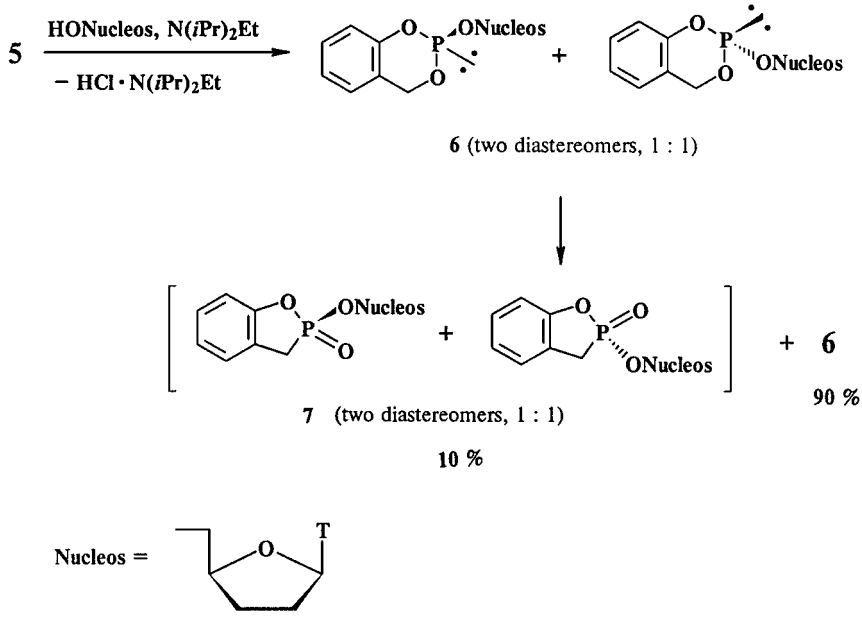
The new three-step procedure including a ring-contractive rearrangement for the synthesis of heterocyclic benzooxaphosphole oxides has two main advantages:

1. The exclusion of toxic and dangerous lower phosphorous acid esters as reagents in the step of saligenin phosphorylation and the use of more suitable and less expensive PCl_3.
2. Many options for the introduction of not only simple alkoxy residues like OMe, OEt but also other alkoxy groups that are derivatives of natural compounds in the exocyclic position of a heterocyclic molecule in the step of chlorine substitution at the phosphorus atom.

To demonstrate the second option, we tested the applicability of the strategy by introducing a nucleoside as an alkoxy-substituent (Scheme 3). (About biological activity of cyclosaligenyl nucleotides see in).[8,26–38] The corresponding nucleoside phosphite **6** for the expected rearrangement reaction was readily obtained with an almost quantitative yield by the treatment of chlorophosphite **5** with nucleoside 2′,3′-dideoxy-2′,3′-didehydrothymidine (d4T) in the presence of Hünig's base (diisopropylethylamine, DIPEA) at 0°C. Two diastereomeric trivalent-phosphorus derivatives **6a**,**b** (at a ratio of 1:1) were formed, as was confirmed by ^{31}P NMR study of the reaction mixture in a CH_3CN solution at 0°C.

Subsequently, a NMR-study showed that these compounds undergo the expected rearrangement reaction under extremely mild conditions (only warming up to room temperature and storing the obtained solution of **6** in CH_3CN for 30 min followed by evaporation in the high vacuum and resolution in $CDCl_3$ to give the target 2-*O*-nucleoside derivative of 3*H*-benzo[*d*][1,2]oxaphosphole 2-oxide **7** (with a 10% yield

*It should be noted that the known phosphite-phosphonate isomerization of dialkylpropargylphosphites, which proceeds easily and gives similar products, should be classified as sigmatropic Claisen rearrangements rather than among Arbuzov-Michaelis ones.



SCHEME 3

at a 1:1 ratio of diastereomers), whose structure was supported by ^{31}P NMR data.

The described reaction can be considered as the first example of the phosphite-phosphonate Arbuzov-Michaelis-type isomerization (involving the contraction of the six-membered ring) in the synthetic chemistry of nucleotides. We continue to study similar transformations for biomedically important dialkylamide groups (to be published).

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were determined using a Bruker AMX 400 spectrometer. ^{31}P spectra were recorded with Bruker AMX 400 and Bruker DRX 500 spectrometers. Mass-spectra were determined using MS 890 spectrometer.

All syntheses were performed using dry solvents under an argon atmosphere.

2-Chloro-4*H*-benzo[1,3,2]dioxaphosphorin-2-yl (5)

Was obtained by the literature method.[7] ^{1}H, ^{13}C, and ^{31}P NMR data for **5** see in.[8]

2-Ethoxy-4*H*-benzo[1,3,2]dioxaphosphorin-2-yl (4)

To a solution of 3.69 g (0.020 mol) of chlorophosphite **5** in 70 mL of light petroleum at −10°C was added dropwise with intensive stirring a solution of 0.99 g (1.25 mL, 0.022 mol) of ethanol and 2.18 g (3.00 mL, 0.022 mol) of triethylamine in 20 mL of petroleum over 1 h. The mixture was then stirred at room temperature for 5 h and then storred overnight. ^{31}P-NMR of the solution (80.96 MHz, petroleum), δ, ppm: 118.07. The mixture was filtered under argon, the precipitate of triethylamine hydrochloride was thoroughly washed by petroleum, and the solvent was removed in vacuo from the combined filtrates. The residuary oil was distilled (0.5 mm Hg, 66–67°C) giving 1.52 g (44 %) of phosphite **4** as a colourless liquid.

^{1}H-NMR (400.13 MHz, $CDCl_3$), δ, ppm: 7.19 *ddd* (1H, $^{3}J_{1H\text{-}1H}$ 7.7 Hz, $^{3}J_{1H\text{-}1H}$ 7.7 Hz, $^{4}J_{1H\text{-}1H}$ 1.8 Hz), 6.93 *ddd* (1H, $^{3}J_{1H\text{-}1H}$ 7.7 Hz, $^{3}J_{1H\text{-}1H}$ 7.7 Hz, $^{4}J_{1H\text{-}1H}$ 1.2 Hz), and 6.91 *m* (2H) (aryl), 5.16 *dd* (1H, $^{2}J_{1H\text{-}1H}$ 13.6 Hz, $^{3}J_{1H\text{-}1H}$ 2.8 Hz) and 4.71 *dd* (1H, $^{2}J_{1H\text{-}1H}$ 13.6 Hz, $^{3}J_{1H\text{-}1H}$ 9.6 Hz) (benzyl), 3.97 *ddk* (1H, $^{2}J_{1H\text{-}1H}$ 9.2 Hz, $^{3}J_{1H\text{-}1H}$ 7.2 Hz, $^{3}J_{31P\text{-}1H}$ 9.2 Hz) and 3.95 *ddk* (1H, $^{2}J_{1H\text{-}1H}$ 9.2 Hz, $^{3}J_{1H\text{-}1H}$ 7.2 Hz, $^{3}J_{1H\text{-}1H}$ 9.2 Hz) (CH_2-ethyl), 1.26 *t* (3H, $^{3}J_{1H\text{-}1H}$ 7.2 Hz) (CH_3-ethyl).

^{31}P-NMR (161.98 MHz, $CDCl_3$), δ, ppm: 118.17.

The Isomerization of 2-Ethoxy-4*H*-benzo[1,3,2]-dioxaphosphorin-2-yl (4) into 2-Ethoxy-3*H*-benzo[*d*][1,2] oxaphosphole 2-oxide (3)

A 2 M solution of phosphite **4** in $CDCl_3$ was kept under argon at room temperature. Reaction solution:

1. For 1 day:
   ^{31}P-NMR (161.98 MHz, $CDCl_3$), δ, ppm: 117.88 (35%) and 45.94 (65%).
2. For 3 days:
   ^{1}H-NMR (400.13 MHz, $CDCl_3$), δ, ppm: 6.98 *m* (2H) and 6.78 *m* (2H) (aryl), 3.98 *ddk* (1H, $^{2}J_{1H\text{-}1H}$ 10.4 Hz, $^{3}J_{1H\text{-}1H}$ 7.0 Hz, $^{3}J_{31P\text{-}1H}$ 10.4 Hz) and 3.95 *ddk* (1H, $^{2}J_{1H\text{-}1H}$ 10.4 Hz, $^{3}J_{1H\text{-}1H}$ 7.0 Hz, $^{3}J_{31P\text{-}1H}$ 10.4 Hz) (CH_2-ethyl), 3.13 *ddd* (1H, $^{2}J_{1H\text{-}1H}$ 18.5 Hz, $J_{1H\text{-}1H}$ 3.8 Hz, $^{2}J_{31P\text{-}1H}$ 15.4 Hz) and 3.04 *ddd* (1H, $^{2}J_{1H\text{-}1H}$ 18.5 Hz, $J_{1H\text{-}1H}$ 3.4 Hz, $^{2}J_{31P\text{-}1H}$ 15.0 Hz) (benzyl), 1.12 *td* (3H, $^{3}J_{1H\text{-}1H}$ 7.0 Hz, $^{4}J_{31P\text{-}1H}$ 2.0 Hz) (CH_3-ethyl).

^{13}C-NMR (100.61 MHz, $CDCl_3$), δ, ppm (J_{CP}, Hz): 152.31 (11.9), 128.22, 126.56 (18.8), 122.57, 121.82 (3.6), and 112.31 (12.4) (aryl), 62.54 (6.8) (CH_2-ethyl), 23.55 (123.8) (benzyl), 15.55 (5.6) (CH_3-ethyl).

^{31}P-NMR (161.98 MHz, $CDCl_3$), δ, ppm: 46.12.

Mass-spectrum (70 eV, m/z (I, %)): 198 $[M]^+$ (65), 170 $[M-C_2H_4]^+$ (100).

All spectral data for the product of the conversion observed are in full agreement with those for **3**.[1,2,4]

The Isomerization of Diastereomeric 2-(2′,3′-*di*deoxy-2′,3′-didehydro-thymydin-5-O-yl)-4*H*-benzo[1,3,2]dioxaphosphorin-2-yles (6) into *d*iastereomeric 2-(2′,3′-dideoxy-2′,3′-didehydro-thymydin-5-*O*-yl)-3*H*-benzo[*d*][1,2]oxaphosphole 2-oxide (7)

To a solution of 20 mg (0.089 mmol) of 2′,3′-dideoxy-2′,3′-didehydro-thymydine in 2 mL of acetonitrile at 0°C was added with intensive stirring 16.80 mL (0.098 mmol) of diisopropylamine (DIPEA) and 18.48 mg (0.098 mmol) of chlorophosphite **5**. After 30 min the solvent was evaporated and the residue was resolved in $CDCl_3$. Reaction solution: ^{31}P-NMR (202.40 MHz, $CDCl_3$), δ, ppm:117.95 and 116.65 (1:1, two diastereomers of **6**, 90%), 48.09 and 47.70 (1 : 1, two diastereomers of **7**, 10%).

Keeping the mixture in the NMR-tube at room temperature for 7 days lead to complete decomposition of the reaction products.

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