3,6-Epithio-5,5-diethyl-6-methyl-1,4,5,6-tetrahydro-1,2,4-triazine (2b). Yield 1.59 g (86%), m.p. 215 °C. Found (%): C, 51.78; H, 8.04; N, 22.62; S, 17.20. $C_8H_{15}N_3S$. Calculated (%): C, 51.89; H, 8.10; N, 22.70; S, 17.29. ^{1}H NMR (DMSO-d_6), δ: 0.68 (t, 6 H, $(CH_3CH_AH_B)_2$, J = 7.0 Hz); 1.42 (m, 4 H, $(CH_3CH_AH_B)_2$); 1.70 (s, 3 H, CH_3); 7.14 (s, 1 H, NH); 10.18 (s, 1 H, NH).

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(4*R*,5*R*)-Bis(*N*,*N*-dimethylaminocarbonyl)-2-chloro-1,3,2-dioxaphospholane: a convenient reagent for control of enantiomeric composition of chiral alcohols by ^{31}P NMR spectroscopy

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The use of enantiomerically pure cyclic chlorophosphite obtained by the reaction of PCl_3 with *N*,*N*,*N*',*N*'-tetramethyldiamide of natural L-(+)-tartaric acid for analysis of the enantiomeric composition of chiral primary and secondary alcohols by ^{31}P NMR spectroscopy is considered.

Key words: chiral alcohols, enantiomeric composition; ^{31}P NMR spectroscopy.

Interest in enantioselective chemical processes is constantly increasing due to the modern requirements of biochemistry, medicine, and technology. Therefore, methods for control of the enantiomeric composition of the final chemical products and reaction mixtures are needed. Polarimetry, chromatography, and NMR spectroscopy are most widely used for this purpose, and each of the methods has both advantages and limitations.[1] Accessibility of standard spectrometers is an advantage of NMR spectroscopy, while the necessity to use expensive enantiomerically pure reagents is its limitation.[2] For the ^{1}H NMR spectroscopy method, additional difficulties appear, which are associated with a narrow interval of change in the chemical shift scale, often making impossible the assignment of signals belonging to different enantiomers. The problem is greatly simplified when NMR on other nuclei is used, in particular, ^{31}P NMR.[3]

As a rule, organophosphorus reagents used for analysis of the enantiomeric composition of chiral alcohols R*OH contain active P—Hal bonds. Reactions with these bonds result in the formation of the R*O—P bonds. These monoadducts with the enantiomeric R*O fragments have different chemical shifts in ^{31}P NMR spectra when the P atom in the starting reagent is either the chiral center or, being achiral, is a part of a chiral molecule. The latter situation is more preferable, because no problems appear related to stoichiometric peculiarities of substitution at the P atom and changes in the initial conformation of the P atom during storage of the reagent. (4*R*,5*R*)-Dialkoxycarbonyl-2-chloro-1,3,2-dioxaphospholanes, cyclic chlorophosphites based on esters of natural tartaric acid, are accessible reagents of this type.[4]

The use of (4*R*,5*R*)-diethoxycarbonyl-2-chloro-1,3,2-dioxaphospholane (**1**) for control of the enantio-

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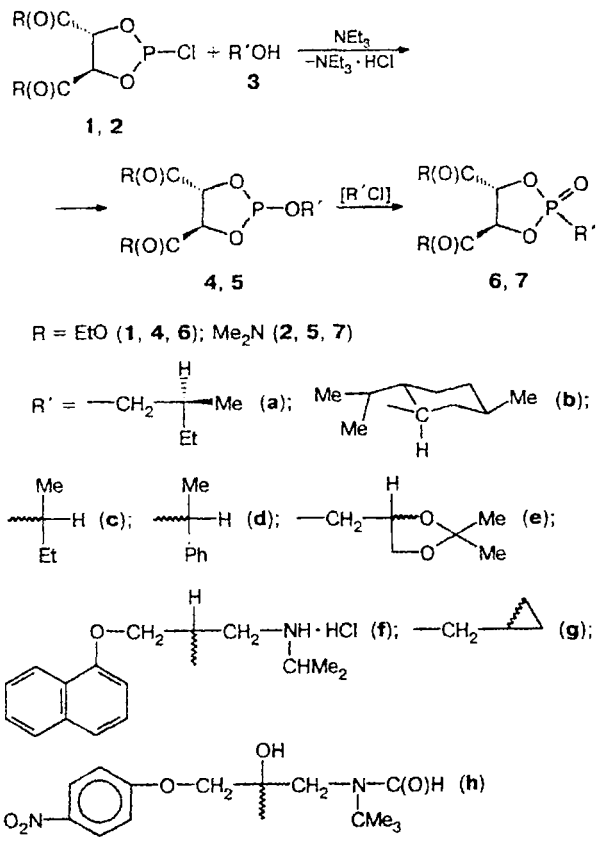
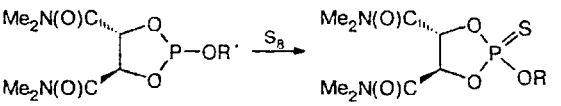
meric purity of various alcohols revealed several disadvantages of this reagent along with advantages (cheapness and simple preparation). In particular, after substitution of a halogen by the alkoxyl R'O fragment (Scheme 1), the ^{31}P-{^{1}H} NMR spectra of the reaction mixtures usually contain signals with δ ^{31}P ~25 with the considerable integral intensity along with signals of desired phosphites **4** in the region of δ ^{31}P ~140. The appearance of admixtures is more characteristic of secondary R'OH alcohols. Probably, along with the main reaction, *i.e.*, the formation of the cyclic phosphite, alkyl halides R'Cl are formed, which initiate the Arbuzov rearrangement resulting in phosphonates **6**.

Scheme 1



We have established that an insignificant modification of the reagent, namely, the use of diamide **2** instead of ester **1** decreases substantially the amount of undesirable admixtures. The comparative parameters of the spectra of cyclic phosphites **4** and **5** synthesized from ester **1** and diamide **2** are presented in Table 1. Along with the data for the P^{III} derivatives, phosphites of chiral alcohols **5a—h**, the values of δ ^{31}P for the P^{IV} derivatives, thiophosphates **8a—h** obtained by the action of sulfur on phosphites **5**, are given.



The difference in chemical shifts of nuclei-probes (in the given case, $\Delta\delta$ ^{31}P) induced by diastereomerism of the adducts is the most important characteristics determining the outlook of using the reagent for analysis of the enantiomeric purity of the chiral substrate by NMR spectroscopy. The greater the difference, the lower the requirements for quality of the NMR experiment (approaching routine in the limiting case) and the higher the reliability of the determination of integral peaks belonging to individual diastereomers. As can be seen from Table 1, the $\Delta\delta$ ^{31}P value for diastereomeric phosphites **4** is lower, as a rule, than that for phosphites **5**. For thiophosphates **8**, the $\Delta\delta$ ^{31}P values are still lower, which, in general, is typical of the P^{IV} derivatives.

In the ^{31}P NMR spectra of the products of the reactions of enantiomerically pure (*S*)-(−)-2-methylbutanol (**3a**) and L-menthol (**3b**) with both reagents studied, only one signal belonging to the corresponding phosphites **4a,b** and **5a,b** appears. Like compound **1**, reagent **2** does not possess pronounced kinetic diastereoselectivity, and the determination of the enantiomeric excess (*ee*) of undoubted racemic alcohols **3c—g** results in the *ee* values ≤0.1% (**c**,**d**,**g**), 2.2% (**f**), and 3.7% (**e**), *i.e.*, the average deviation of its true *ee* (0%) is ≤1.25%. For the same series of racemic alcohols, under similar conditions of recording the spectra for the determination of *ee* using compound **1**, the average deviation of experimental values is 3.25%. This can be reasonably

Table 1. Chemical shifts (δ) and $\Delta\delta$ values in ^{31}P NMR spectra of adducts of chiral dioxaphospholanes **1** and **2** with chiral alcohols **3**

Alcohol	Phosphites **4**		Phosphites **5**		Thiophosphates **8**	
	δ ^{31}P	$\Delta\delta$ ^{31}P	δ ^{31}P	$\Delta\delta$ ^{31}P	δ ^{31}P	$\Delta\delta$ ^{31}P
3a	141.2	0	136.1	0		
3b	144.6	0	136.9	0		
3c	143.3 143.0	0.3	138.1 137.2	0.9	79.13	~0
3d	143.1 142.0	1.1	138.5 130.6	7.9	78.7 77.8	0.9
3e	142.1 141.7	0.4	137.3 136.8	0.5	80.2 80.0	0.2
3f	144.6 140.8	3.8	141.6 138.3	3.3	80.1 78.2	1.9
3g	142.6 141.4	1.2	136.9 135.0	1.9	80.6 80.2	0.4
3h	144.8 143.0	1.8	143.3 141.4	1.9	80.0 79.1	0.9

related to the lower $\Delta\delta$ ^{31}P values for diastereomeric phosphites **4**.

For the quantitative analysis of the enantiomeric composition of nonracemic substrates by reagent **2**, we used glycidol (**3g**) and 2-hydroxy-1-(4-nitrophenoxy)-3-(*N*-formyl-*N*-*tert*-butyl)aminopropane (**3h**). The sample of nonracemic (*S*)-glycidol was synthesized by the enantioselective epoxidation of allyl alcohol by cumyl hydroperoxide according to Sharpless.[5] According to the published data, glycidol obtained by this method is characterized by the enantiomeric excess ~90%. The *ee* values for the samples synthesized in two independent experiments were 87.2 and 91.5%.

Nonracemic (*R*)-**3h** was obtained as an intermediate product when racemic 1,2-dihydroxy-3-*tert*-butylaminopropane was cleaved to the enantiomers according to the previously described procedure.[6] The samples of the formyl derivative with different enantiomeric purity were isolated by fractional crystallization. We determined the enantiomeric composition of these samples by two methods. First, we eliminated the formyl protection and transformed the samples into (2*R*)-hydroxy-1-(4-nitrophenoxy)-3-*tert*-butylaminopropane hydrochloride, which was analyzed by polarimetry (according to the published data,[6] the enantiomerically pure (2*R*)-isomer is characterized by the value $[\alpha]_{546}^{20}$ +17.75 (*c* 4, MeOH)). Second, the samples were transformed into phosphites **5h**, and the corresponding signals in their ^{31}P NMR spectra were integrated. For two samples of **3h**, the optical purity determined polarimetrically was 79.4 and 82.0%. For the same samples, the enantiomeric excess determined by reagent **2** was 78.8 and 81.4%, respectively.

Thus, the results allow us to recommend (4*R*,5*R*)-bis(*N*,*N*-dimethylaminocarbonyl)-2-chloro-1,3,2-dioxaphospholane **2** as an available, cheap, and convenient reagent for control of the enantiomeric composition of chiral alcohols by ^{31}P NMR spectroscopy.

Experimental

^{31}P-{^{1}H} NMR spectra were recorded on a Bruker MSL-400 spectrometer (161.92 MHz) using H_3PO_4 as the external standard and THF as the solvent.

***N*,*N*,*N*′,*N*′-Tetramethyldiamide of L-(+)-tartaric acid** was obtained from the corresponding diethyl tartrate and Me_2HN by a known procedure.[7]

(4*R*,5*R*)-Diethoxycarbonyl-2-chloro-1,3,2-dioxaphospholane (1) was synthesized according to the previously described procedure:[4] diethyl tartrate (5 g, 24 mmol) in THF (25 mL) was added to PCl_3 (2.1 mL, 24 mmol) in THF (25 mL). ^{31}P NMR spectrum of compound **1**: δ 174.2.

(4*R*,5*R*)-Bis(*N*,*N*-dimethylaminocarbonyl)-2-chloro-1,3,2-dioxaphospholane (2). A solution of PCl_3 (1.7 mL, 19.4 mmol) in THF (20 mL) was added dropwise to a suspension of *N*,*N*,*N*′,*N*′-tetramethyldiamide of L-(+)-tartaric acid in anhydrous THF (60 mL) in an argon atmosphere at ~20 °C, and the mixture was refluxed for 40 min. As the reaction passed, the amide was dissolved. The mixture was cooled to ~20 °C. The ^{31}P NMR spectrum of the reaction mixture contained the only signal of chlorophosphite **2**: δ 173.5. The total volume of the solution was measured, and the approximate content of dioxaphospholane **2** in 1 mL was calculated, accepting the yield to be quantitative.

A solution of dioxaphospholane **2** in THF thus prepared was stored in a refrigerator and used for analysis when necessary.

Analysis of the enantiomeric composition of the alcohol under study (general procedure). A solution (2.0 mL) of dioxaphospholane **1** (~0.2 g, 0.8 mmol with the concentration of ~0.1 g mL^{-1}) or a solution (4.0 mL) of dioxaphospholane **2** (~0.2 g, 0.8 mmol with the concentration of ~0.05 g mL^{-1}) was placed in an atmosphere of dry argon in a flask with a magnetic stirrer, and triethylamine (0.3 mL, 2.3 mmol) was added at 5—10 °C. The reaction mixture was stirred for 10 min, and a solution of the alcohol analyzed (0.8 mmol) in THF (2 mL) was slowly added dropwise. The mixture was stirred for 10 min, its temperature was brought to room temperature, and the solution was filtered and placed in an ampule with a diameter of 10 mm for recording the ^{31}P NMR spectrum. The enantiomeric excess was calculated by the formula $ee = (I_1 - I_2)/(I_1 + I_2)$, where I_1 and I_2 are the integral intensities of the signals of the corresponding diastereomeric phosphites **4** or **5**.

(4*R*,5*R*)-Bis(*N*,*N*-Dimethylaminocarbonyl-2-alkoxy-2-thio-1,3,2-dioxaphospholanes (8c—h). Finely powdered elemental sulfur (0.05 g, 15 mmol) was added to solutions of phosphites **5c—h** (0.8 mmol) prepared according to the procedure presented above. The reaction mixture was stirred for 2 h and allowed to stand overnight. Excess sulfur was removed by filtration, and the filtrate was analyzed by ^{31}P NMR spectroscopy.

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