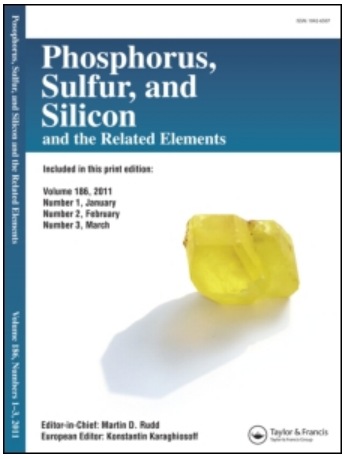

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SYNTHESIS OF TETRAALKYLDIAMIDOPHOSPHITES

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SYNTHESIS OF TETRAALKYLDIAMIDOPHOSPHITES

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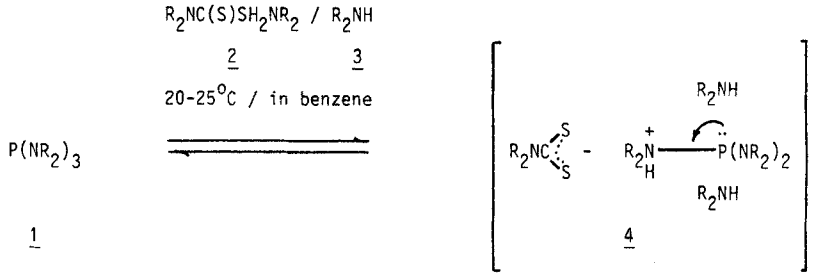
A method for the synthesis of monoester amidophosphites at room temperature is proposed. The tris-(*N,N*-diethyl)-amide of phosphorous acid activated by the *N,N*-diethylammonium salt of *N,N*-diethyldithiocarbamic acid, in the presence of diethylamine, is used as a reagent. The synthesis of thiophosphate derivatives of 1-0-stearoylethane-2-ol, cholesterol and R,S-α-tocopherol is described.

It is known that the tris-(*N,N*-dialkyl)-amides of phosphorous acid are used as reagents for the phosphorylation of organic compounds containing a free hydroxyl group.[1] In general, a mixture of the reagent and the substrate is heated in a molar ratio of 3:1 to give the corresponding monoester derivative.[1–6] The necessity of extended heating, as well as the occurrence of disproportionation under the reaction conditions (reaction time: up to 10 h; heating: up to 160°C) have to be pointed out as considerable disadvantages. As a result, this type of reagents would not be feasible if thermally labile compounds are to be phosphorylated.

We now describe the synthesis of tetraalkyldiamidophosphites of some biologically active lipids with the general formula: $R^1OP(NR_2)_2/R$ = Ethyl; R^1 = 1-0-Stearoylethyl, Cholesteryl, R,S-α-Tocopheryl/at room temperature by means of new phosphorylating reagent. In this case, the tris-(*N,N*-diethyl)-amide of phosphorous acid, **1**, activated by the *N,N*-diethylammonium salt of *N,N*-diethyldithiocarbamic acid, **2**, in the presence of diethylamine, **3** in a molar ratio 1:1:1, was used, **4**.



SCHEME 1 For **1**, **2**, **3**, and **4**: R = C_2H_5

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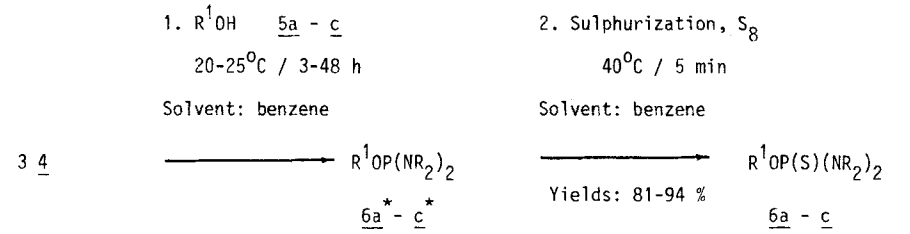
RESULTS AND DISCUSSION

1-0-Stearoylethane-2-ol, **5a**, cholesterol, **5b** and R,S-α-tocopherol, **5c** were selected as model substrates containing primary, secondary and sterically hindered phenolic hydroxyl functions.

The phosphorylation was performed at 20–25°C for 3–48 h, according to the following reaction scheme:



SCHEME 2 For **5a**, **6a*** and **6a:** R^1 = 1-0-Stearoylethyl; **5b**, **6b*** and **6b**: R^1 = Cholesteryl; **5c**, **6c*** and **6c**: R^1 = R,S-α-Tocopheryl. For **6a*–c*** and **6a–c**: R = C_2H_5.

The structure of the P^{III} derivatives (**6a*–c***) was proven indirectly after chemical transformations to the corresponding thiophosphates (**6a–c**).

We assume that the phosphorylation ability of the reagent (Scheme 1) is due to the initial formation of an activated complex, **4** in equilibrium with the phosphorous acid triamide, **1** and the *N,N*-diethylammonium salt of *N,N*-diethyldithiocarbamic acid, **2**. As a result of quaternization one of the amido groups of the phosphorylating reagent is functioning a good leaving group and may readily be substituted by nucleophilic attack of the substrate on phosphorus. The last stage, which is irreversible, will result in a displacement of the equilibrium to the right.

As expected[7,8] the *N,N*-diethyldithiocarbaminate anion reacts to a certain extent with the activated reagent to give bis(*N,N*-diethyldithiocarbamoyl)-(*N,N*-diethylamido)-phosphite (^{31}P NMR: δ 57.7 ppm, s). By preliminary model studies we have established that this compound does not possess phosphorylating ability under the experimental conditions employed, and its generation is inhibited by the diethylamine added. This side reaction, however, does not hinder the main phosphorylating process at the specific molar ratio-reagent/substrate 3/1 chosen.

EXPERIMENTAL

The tris-(*N,N*-diethyl)-amide of phosphorous acid, **1**, was prepared according to ref.[9] 1-0-Stearoylethane-2-ol, **5a**, was prepared according to ref.[10] All other reagents were GR, or of purity in excess of 98% (Merck). Solvents were dried prior to use. Reaction conditions were kept strictly anhydrous.

Preparative thin-layer chromatography (TLC) was performed on 20 × 20 cm plates and stationary phase of silica gel G (Merck) with a layer thickness of 2 mm; after 1 h activation at 120°C. As mobile phases were used: chloroform (system A); n-hexane/diethyl ether 95/5, v/v (system B).

The melting points were determined on a Kofler melting point apparatus and are uncorrected.

^{1}H NMR spectra were recorded on a Bruker WH-360 spectrometer at 360.13 MHz. ^{1}H chemical shifts are reported in ppm relative to tetramethylsilane (TMS). ^{31}P NMR spectra were recorded on a Bruker WH-90 spectrometer at 36.46 MHz. ^{31}P chemical shifts are reported in ppm relative to 85%

phosphoric acid (external), where a positive sign is downfield from the standard. IR spectra were recorded on a Perkin–Elmer 337 spectrometer. Peak positions are reported in cm^{-1}.

Elemental analyses were performed by the Microanalytical Service Laboratory, University of Plovdiv.

1-0-Stearoylethane-2-0-bis(N,N-diethylamido)-thiophosphate, **6a** Typical procedure: To a solution of the tris-(*N,N*-diethyl)-amide of phosphorous acid (**1**; 0.741 g; 3 mmol) the *N,N*-diethylammonium salt of *N,N*-diethyldithiocarbamic acid (**2**; 0.667 g; 3 mmol) and diethylamine (**3**; 0.219 g; 3 mmol) in benzene (25 mL), 1-0-stearoylethane-2-ol (**5a**; 0.329 g; 1 mmol) was added. After homogenization, the reaction mixture was kept at 20–25°C for 3 h. Then sulphur (0.096 g; 3 mmol) was added and the system was heated at 40°C for 5 min to give the thiophosphate derivative, **6a**. The solvent was removed under vacuum and the compound was extracted from the residue with *n*-hexane (2 × 50 mL). After filtration, part of the solvent was distilled off and the product was isolated by TLC using system A as a mobile phase, and then diethyl ether for eluting the thiophosphate derivative from the silica gel adsorbent.

Yield of **6a**: 0.49 g (91%); n_D^{50}: 1.4617; Rf: 0.62 (system A).

$C_{28}H_{59}N_2O_3PS$	calc.	C 62.86	H 11.14	H 5.24	P 5.79	S 6.00
(535.0)	found	C 62.48	H 11.10	N 5.24	P 5.86	S 6.05

^1H NMR (C_6D_6); $\delta = 0.93$ (m, 3H, CH_3—); 1.06 (t, 12H, CH_3CH_2N, $J = 7.0$ Hz); 1.38 (m, 30H, —$(CH_2)_{15}$—); 2.18 (t, 2H, CH_2CO, $J = 7.5$ Hz); 3.28 (m, 8H, CH_2N, $J = 7.0$ Hz); 3.98 ppm (m, 4H, OCH_2CH_2O).
^{31}P NMR – $\{^1H\}(C_6D_6)$: $\delta = 77.8$ ppm (s).
IR (KBr): $\nu = 1750$ (CO); 1020, 790 (PO—C, P—OC); 720 (P—N); 695 cm^{-1} (P=S).

Cholesteryl-3-0-bis(N,N-diethylamido)-thiophosphate, **6b:** Using cholesterol (**5b**; 0.387 g; 1 mmol) this derivative was synthesized at room temperature (12 h) and then purified (system B), as described for **6a**.

Yield of **6b**; 0.48 g (81%); m.p. 74–75°C (from diethyl ether); Rf: 0.51 (system B).

$C_{35}H_{65}N_2OPS$	calc.	C 70.87	H 11.07	N 4.72	P 5.23	S 5.41
(593.1)	found	C 70.32	H 11.00	N 4.76	P 5.19	S 5.44

^1H NMR (C_6D_6): $\delta = 0.79$ (s, 3H, CH_3-18); 1.03 (s, 3H, CH_3-26); 1.05 (s, 3H, CH_3-27); 1.09 (s, 3H, CH_3-19); 1.13 (d, 3H, CH_3-21, $J = 6.5$ Hz); 1.16 (t, 12H, CH_3CH_2N, $J = 7.0$ Hz); 3.19 (m, 8H, CH_2N, $J = 7.0$ Hz); 4.83 (m, 1H, CH—O—); 5.53 ppm (m, 1H, =CH—).
^{31}P NMR – $\{^1H\}(C_6D_6)$: $\delta = 77.2$ ppm (s).
IR (KBr): $\nu = 1015$, 790 (PO—C, P—OC); 730 (P—N); 695 cm^{-1} (P=S).

R,S-α-Tocopheryl-6-0-bis(N,N-diethylamido)thiophosphate, **6c.** Using *R,S*-α-tocopherol (**5c**; 0.431 g; 1 mmol), the derivative was synthesized within 48 h at room temperature and purified (system A), as described for **6a**.

Yield of **6c**: 0.60 g (94%); n_D^{20}: 1.5131; Rf: 0.88 (system A).

$C_{37}H_{69}N_2O_2PS$	calc.	C 69.74	H 10.94	N 4.40	P 4.87	S 5.03
(637.2)	found	C 69.39	H 11.00	N 4.37	P 4.80	S 5.09

^1H NMR (C_6D_6): $\delta = 1.03$, 1.06 (each *d*, 12H, CH_3—, $J = 6.5$ Hz); 1.16 (t, 12H, CH_3CH_2N; $J = 7.0$ Hz); 1.20–1.37 (m, 9H, —$(CH_2)_3$—, CH_3—); 1.37–1.50(m, 6H, —$(CH_2)_3$—); 1.50–1.80 (m, 8H, —$(CH_2)_3$—, CH_2C—$_{ring}$); 2.42 (s, 6H, CH_3—$_{nucleus}$); 2.45 (s, 3H, CH_3—$_{nucleus}$); 2.65(m, 2H, CH_2CH_2—$_{ring}$); 3.32 ppm (m, 8H, CH_2N, $J = 7.0$ Hz).
^{31}P NMR – $\{^1H\}(C_6D_6)$: $\delta = 72.6$ ppm (s).
IR (KBr): $\nu = 1245$, 835 (PO—C, P—OC_{aryl}); 725(P—N); 690 cm^{-1} (P=S).

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