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NEW SYMMETRIC DIISOPROPYLPHOSPHORYL-S-ALKANEDI YLDIISOTHIUREAS. INVESTIGATIONS ON THEIR SYNTHESIS

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NEW SYMMETRIC DIISOPROPYLPHOSPHORYL-S-ALKANEDI YLDIISOTHIUREAS. INVESTIGATIONS ON THEIR SYNTHESIS

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Symmetric dialkylphosphoryl-S-alkanediyl-diisothiureas $(RO)_2P(O)NHC(=NH)S(CH_2)_nSC(=NH)NHP(O)(OR)_2$ (I, R = isopropyl; n = 2–5) have potential coordination sites involving O, P, N and S as donors atoms. For their synthesis, common two-phase reactions between the corresponding diisothiurea derivatives and diisopropyl phosphonate were unsuccessful. Herein we describe a new synthesis for such compounds using diisopropyl chlorophosphonate. Two new bis-phosphorylated alkanediyl-diisothiureas with increasing carbon chain (I; n = 3, n = 5) were prepared by this method.

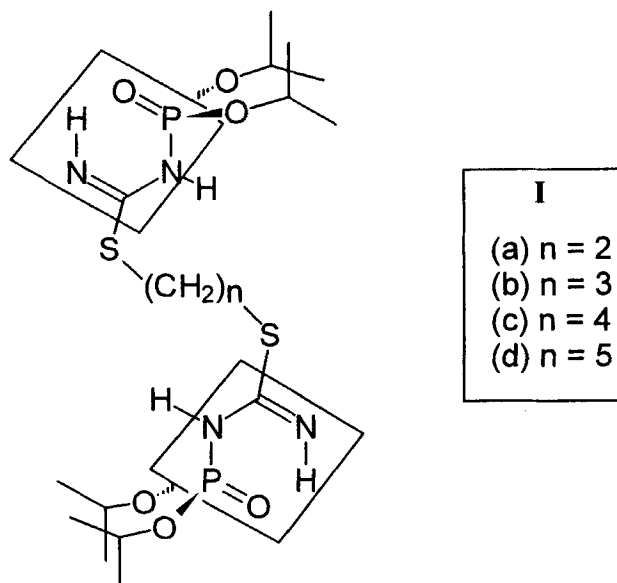
Keywords: symmetric diisopropylphosphoryl-S-alkanediyl-diisothiureas; phosphorylation of S-alkanediyl-diisothiurea; reaction of diisopropyl chlorophosphonate with S-alkanediyl-diisothiurea

INTRODUCTION

Phosphate and amino are naturally occurring groups usually found in several structural and functional combinations. The mechanism of action of such a groups involves directly or indirectly complexation and transportation of metal ions in physiological medium. Creatine phosphate, sphingomyelins, and other phosphoramides are important biological systems where ion complexation takes place.^[1,2] It has been demonstrated that the best

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results to guarantee selectivity of metal-ligand interaction are obtained when both donor atom spatial disposition and nature of the functional groups are considered in the design approaches to the ligand molecules. Lin *et al.* have reported that diisopropylphosphoryl- S-ethanediyldiisothiourea (**1a**) shows a nearly planar arrangement around the moieties containing O=P-N-C-N-H atoms and strong intermolecular hydrogen bonds in its crystal configuration. This finding suggests a very promising site for coordination with metal cations^[3,4] at such positions and makes phosphoryl-S-alkanediyl-diisothioureas interesting systems for investigation as complexing agents.



Chemical structure for **Ia-d**. No caption

In order to obtain more information on the complexation behavior and selectivity of such compounds, we present here preliminary investigations on their synthesis. For a study of the chain size effect on complexation, we synthesized the phosphoryl-S-alkanediyl-diisothioureas (**Ia-d**), where the two binding groups O=P-N-C-N-H are kept apart by n methylene groups. The structural dependence for such open-chain ligands on coordination is now under investigation and will be reported later.

RESULTS AND DISCUSSION

For the synthesis of diisopropylphosphoryl-S-alkanediyl-diisothiureas (**Ia-d**) we first followed the method described by Lin *et al.*,^[3,4] which consisted of a biphasic reaction between alkanediyl-diisothiurea dihydrobromides **IIa-d** and dialkylphosphonate **III** (R = isopropyl) in carbon tetrachloride and aqueous sodium hydroxide medium (route A, Fig. 1). By such a phosphorylation method we obtained **Ia** in a yield less than 30% after purification and only traces of **Ib-d**.

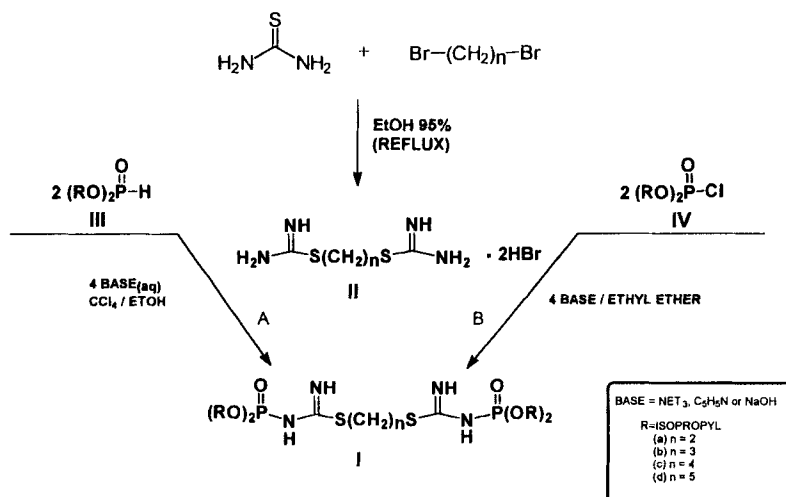
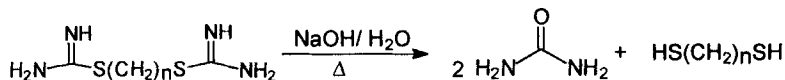


FIGURE 1 Two routes for Phosphorylation of alkanediyl-diisothiurea

In all cases a strong mercaptan odor was evolved as an indication of decomposition of the alkanediyl-diisothiurea, common in strongly alkali and high temperature conditions (Equation 1).^[5]



EQUATION 1. No caption

The reaction was run two times with different bases (NEt_3 and $\text{C}_5\text{H}_5\text{N}$), being also unproductive for **Ia-d**. Only starting material was recovered.

An alternative phosphorylation method was then proposed, which consisted of the homogeneous reaction of **II** with dialkyl chlorophosphonate **IV** (R = isopropyl) in ethyl ether/ NEt_3 or $\text{C}_5\text{H}_5\text{N}$ (route B, Figure 1). In both routes A and B, phosphorylation of the symmetric intermediate alkanediyldiisothioureia dihydrobromides **IIa-d** is necessary. These salts were easily prepared by S-alkylation of thiourea with the appropriate alkyldibromide,^[3,4] and had to be further neutralized and phosphorylated *in situ*. Results from route B are presented in Table I and refer to purified products.

TABLE I Results for preparation of **Ia-d** by route B

| $ \begin{array}{c} \text{(CH}_3\text{)}_2\text{CHO}-\text{P}(=\text{O})-\text{NH}-\text{C}(=\text{NH})-\text{S}(\text{CH}_2)_n-\text{S}-\text{C}(=\text{NH})-\text{NH}-\text{P}(=\text{O})-\text{OCH}(\text{CH}_3)_2 \\ \text{(CH}_3\text{)}_2\text{CHO} \qquad \qquad \qquad \text{H} \qquad \qquad \qquad \text{H} \qquad \qquad \qquad \text{H} \qquad \qquad \qquad \text{OCH}(\text{CH}_3)_2 \\ \text{(I)} \end{array} $ | | | |
|---|----------|-----------|----------------------------------|
| COMPOUND | YIELD(%) | M.P. (°C) | PURIFICATION METHOD |
| Ia (n = 2) | 47 | 180-182 | cryst. from H_2O |
| Ib (n = 3) | 30 | oil | column chrom. (AcOEt) |
| Ic (n = 4) | * | — | — |
| Id (n = 5) | 45 | 93-95 | cryst. from H_2O |

*not isolated

Replacement of diisopropyl phosphonate by diisopropyl chlorophosphonate influences markedly the nature of the base required. Mild experimental conditions and less risk of degradation for the alkanediyldiisothiureas was observed when diisopropyl chlorophosphonate and NEt_3 or $\text{C}_5\text{H}_5\text{N}$ were used. No mercaptan odor was detected. Two new diisopropylphosphoryl-S-alkanediyldiisothiureas **Ib** and **Id** were so synthesized, but curiously **Ic** was not obtained. We conclude that the increment in alkyl chain within the series **IIa-d** is size-limited for $n=4$ (**Ic**) and did not transfer any difficulty to their bis-phosphorylation, as derivatives with $n = 2$, $n = 3$ and $n = 5$ (**Ia**, **Ib** and **Id**) were obtained in increasing to similar yield. This intriguing result is still under investigation against their complexing properties. The compounds synthesized and the intermediates were characterized by usual techniques.

EXPERIMENTAL

All experiments were carried out in standard laboratory glassware without an inert gas atmosphere. Uncorrected melting points were taken on

Fischer-Johns apparatus. Chemicals were obtained from commercial suppliers and purified by suitable techniques. Solvents and PCl_3 were distilled before use. ^1H , ^{13}C and ^{31}P NMR spectra were measured on a Varian UP-300 spectrometer in CDCl_3 with TMS as internal standard or 85% H_3PO_4 as external standard; IR spectra were recorded as KBr discs or films on a Perkin-Elmer spectrometer. Mass spectra (EI-70eV) were recorded on VG Auto Spec instrument.

Diisopropyl phosphonate (III) and diisopropyl chlorophosphonate (IV)

Prepared as described in reference 6.

Alkanediyldiisothiurea dihydrobromides IIa-d^[3,4]

Prepared by reaction of thiourea with the corresponding alkanediyl dibromide and recrystallized in ethyl alcohol. **IIa**) 84%; m.p. 224–226 °C. **IIb**) 91%; m.p. 202–206 °C. **IIc**) 76%; m.p. 218–221 °C. **IId**) 73%; m.p. 168–170 °C.

Phosphorylation of alkanediyldiisothiureas by route B – General Procedure

Appropriate alkanediyldiisothiurea dihydrobromide **IIa-d** (0.005mol) was added to a solution of triethylamine or pyridine (3 ml) in 15 ml of ethyl ether. After 15 minutes, the mixture was cooled to 0–5 °C and 0.01mol of diisopropyl chlorophosphonate (**IV**) was added dropwise. The mixture was stirred at room temperature for 4 hours, keeping a basic pH by adding triethylamine if necessary. Triethylamine hydrobromide was filtered off and the solvent was removed in vacuum to give the crude product.

Ia: crude product was recrystallized from water to afford a solid, 47%; m.p. 179–180 °C. **IV**(cm^{-1}): 3363, 3275, 3200, 3101 (ν_{NH}); 1630 ($\nu_{\text{C=NH}}$); 1565 (ν_{NH}); 1202 ($\nu_{\text{P=O}}$); 975, 1010 ($\nu_{\text{C-O-P}}$). **^{31}P -NMR**: δ = 3.44. **^1H -NMR**: δ = 1.32 (24 H, $-\text{CH}_3$, 2 d, J_{HCCH} = 6.0 Hz); 4.57 (4 H, $-\text{HCO}$, m, J_{HCCH} = 6.0 Hz, J_{POCH} = 7.5 Hz); 3.16 (4 H, $-\text{CH}_2\text{S}$, s). **^{13}C -RMN**: δ = 23.63, 23.69, 23.75 ($-\text{CH}_3$); 70.85 ($-\text{HCO}$, d, J_{POC} = 6.0 Hz); 30.67 ($-\text{CH}_2\text{S}$); 168.13 (C=NH , d, J_{PNC} = not calculated). **EI-MS**: m/z (%): 506 (0.7) [M] $^+$; 300 (86); 267 (69); 156 (46); 123 (100).

Ib: the residual oil was purified by silica gel column chromatography (silica gel MERCK-60, 70–230 mesh; ethyl acetate) to afford a clear oil, 30%. **IV** (cm^{-1}): 3350, 3283, 3210, 3126 (ν_{NH}); 1630 ($\nu_{\text{C=NH}}$); 1560 (ν_{NH}); 1200 (broad, $\nu_{\text{P=O}}$); 970 (broad, $\nu_{\text{C-O-P}}$). **^{31}P -NMR:** $\delta = 3.00$. **^1H -NMR:** $\delta = 1.31$ (24 H, $-\text{CH}_3$, 2 d, $J_{\text{HCCH}} = 6.0$ Hz); 4.57 (4 H, $-\text{HCO}$, m, $J_{\text{HCCH}} = 6.0$ Hz, $J_{\text{POCH}} = 7.5$ Hz); 3.05 (4 H, $-\text{CH}_2\text{S}$, t, $J_{\text{HCCH}} = 6.9$ Hz); 1.98 (2 H, $\text{C}-\text{CH}_2-\text{C}-\text{S}$, qui, $J_{\text{HCCH}} = 6.9$ Hz). **^{13}C -NMR:** $\delta = 23.64$, 23.70, 23.74, 23.80 ($-\text{CH}_3$); 70.85 ($-\text{HCO}$, d, $J_{\text{POC}} = 6.0$ Hz); 29.64 ($-\text{CH}_2\text{S}$); 29.59 ($-\text{CH}_2-\text{C}-\text{S}$); 168.06 ($\text{C}=\text{NH}$, d, $J_{\text{PNC}} = 3.5$ Hz).

Ic: not isolated.

Id: crude product was precipitated and recrystallized from water to afford a solid, 45%; m.p. 93–95 °C. **IV** (cm^{-1}): 3360, 3280, 3210, 3150 (ν_{NH}); 1635 ($\nu_{\text{C=NH}}$); 1560 (ν_{NH}); 1202 ($\nu_{\text{P=O}}$); 975, 1005 ($\nu_{\text{C-O-P}}$). **^{31}P -NMR:** $\delta = 3.31$. **^1H -NMR:** $\delta = 1.31$ (24 H, $-\text{CH}_3$, 2 d, $J_{\text{HCCH}} = 5.7$ Hz); 4.56 (4 H, $-\text{HCO}$, m, $J_{\text{HCCH}} = 6.3$ Hz, $J_{\text{POCH}} = 7.8$ Hz); 2.97 (4 H, $-\text{CH}_2\text{S}$, t, $J_{\text{HCCH}} = 7.2$ Hz); 1.64 (4 H, $-\text{CH}_2-\text{C}-\text{S}$, m); 1.47 (2 H, $-\text{CH}_2-\text{C}-\text{C}-\text{S}$, m). **^{13}C -NMR:** $\delta = 23.63$, 23.69, 23.73, 23.80 ($-\text{CH}_3$); 70.75 ($-\text{HCO}$, d, $J_{\text{POC}} = 6.1$ Hz); 30.68 ($-\text{CH}_2\text{S}$); 29.09 ($-\text{CH}_2-\text{C}-\text{S}$); 27.65 ($-\text{CH}_2-\text{C}-\text{C}-\text{S}$); 168.53 ($\text{C}=\text{NH}$, d, $J_{\text{PNC}} = \text{not calculated}$). **El-MS :** m/z (%): 548 (7) $[\text{M}]^+$; 342 (15); 309 (11); 240 (100); 156 (23); 123 (83).

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