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Synthesis and Crystal Structure of Dipotassium Salts of *N*-Alkyl-*N*-{[*O*-alkoxy(hydroxy)phosphoryl]methyl}-ditiocarbamic Acids

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Abstract—A one-pot method for the synthesis of dipotassium salts of *N*-alkyl-*N*-{[*O*-alkoxy(hydroxy)phosphoryl]-methyl}dithiocarbamic acids has been elaborated. Dipotassium salts of *N*-isopropyl-, *N*-butyl-, and *N*-cyclohexyl-*N*-{[hydroxy(*O*-ethoxy)phosphoryl]methyl}dithiocarbamic acids as well as *N*-{[*O*-butoxy(hydroxy)phosphoryl]-methyl}-*N*-(2-methoxyethyl)dithiocarbamic acid have been synthesized and isolated. Crystal and molecular structure of the latter compound have been elucidated.

Keywords: dithiocarbamates, aminophosphonic acids, crystal structure

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Compounds containing a dithiocarbamate group NC(S)SH have been widely used in analytical chemistry as reagents for extraction-based separation and photometric detection of chalcophile elements as well as rubber curing agents and incectofungicides [1]. Complexes of natural amino acids dithiocarbamates with Mn(II), Cu(II), Fe(II), Au(III), Sn(IV), or Pd(II) cation exhibit carcinostatic and bactericide properties and have been used in the study of biochemical processes involving nitrogen oxide [2–8].

Herein we prepared organophosphorus derivatives of dithiocarbamates, dipotassium alkyl{[*N*-alkyl-*N*-(carbodithioato)amino]methyl}phosphonates **4a**–**4d**, from the corresponding amines and dialkyl phosphites through the intermediates **1**–**3**, in order to investigate the complex forming properties of the products [9].

It was first found that potassium salt of [(isopropyl-amino)methyl](*O*-ethyl)phosphonic acid **3a** reacted with carbon sulfide in aqueous ethanol medium in the presence of equimolar amount of potassium hydroxide to afford salt **4a** with high yield.

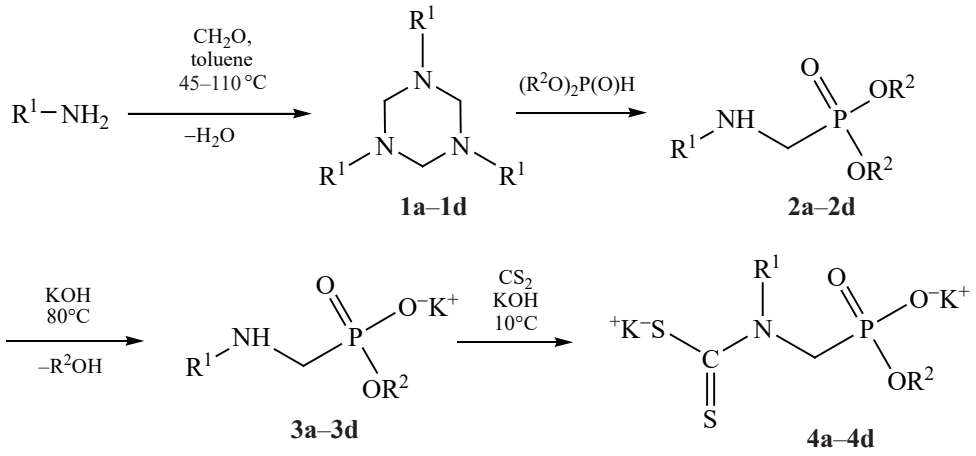
Since the aminophosphonic acids were not commercially available, it was rational to synthesize compounds **4** via a four-stage procedure from the primary amines, paraformaldehyde, dialkyl phosphite, and carbon sulfide without isolation of intermediates **1**–**3** (Scheme 1). Crude products **4** could be obtained with yield exceeding 92% by thorough control of stoichiometric ratios, reactions temperature, and completeness of the single stages (^{31}P NMR data). Losses during recrystallization did not exceed 20%.

The prepared salts **4a**–**4d** were white crystalline compounds, readily soluble in water, methanol, and ethanol. In the presence of copper(II) cations, they gave colored water-soluble coordination compounds $[CuL_2]^{2-}$ containing strong charge-transfer band in the electronic absorption spectra ($\lambda = 436$ nm, $\lg\varepsilon = 4.10$ for the complex with compound **4b**).

Crystal structure of compound **4d** was elucidated by means of X-ray diffraction analysis (Figs. 1 and 2). Crystal packing of compound **4d** was manifested by the (0*bc*) layers formed due to ionic interactions. The layers were linked via the C–H···H–C interactions. The methoxy group was disordered between two positions with the refined population of 0.84 and 0.16.

Similar structures of the K^+, Rb^+, and Cs^+ complexes with anion of *N*-carbodithioato-L-proline have been earlier described as per the X-ray diffraction studies [10].

Scheme 1.



R^2 = Et, R^1 = *i*-Pr (**a**), Bu (**b**), *cyclo*-Hex (**c**); R^1 = CH_2CH_2OMe, R^2 = Bu (**d**).

In summary, the suggested single-pot synthesis allowed neutral salts of *N*-alkyl-*N*-{[*O*-alkoxy(hydroxy)-phosphoryl]methyl}dithiocarbamine acids from available precursors. Copper(II) complexes with such ligands will be investigated further, including their antitumor activity.

EXPERIMENTAL

^1H, ^{13}C, and ^{31}P NMR spectra were recorded using a Bruker AVANCE III 400 instrument operating at 400, 100, and 162 MHz, respectively, in deuterated acetonitrile CD_3CN or water D_2O. X-ray diffraction analysis of the $C_{10}H_{20}K_2NO_5PS_2$ **4d** crystal was performed using a Bruker Kappa APEX II diffractometer [MoK_α radiation, λ = 0.71073 Å, at 296(2) K]. The following software packages were used in the processing: APEX3 [11], SAINT [12], SADABS (absorption accounting) [13], SHELXT (structure solving) [14]; the structure was refined via least squares SHELXL method [15] implemented in the Olex2 software package [16].

Dipotassium salts of *N*-alkyl-*N*-{[*O*-alkoxy(hydroxy)-phosphoryl]methyl}dithiocarbamine acids. A mixture of 0.1 mol of the corresponding primary amine and 3.06 g (0.102 mol) of paraformaldehyde in 50 mL of a toluene–hexane (5 : 1) mixture was stirred at 50°C during 1 h until dissolution of paraformaldehyde and then refluxed with a Dean–Stark apparatus until the evolution of water (1.8 mL) was complete. 0.1 mol of the corresponding dialkyl phosphite was added to the obtained solution of triasinane **1**, and the mixture was refluxed until

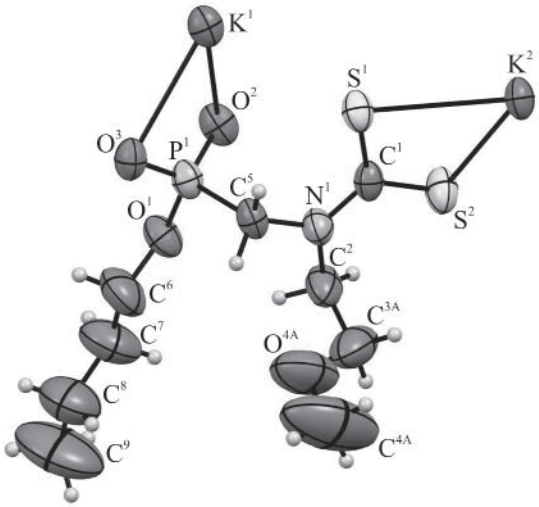


Fig. 1. General view of a molecule of compound **4d** in the crystal.

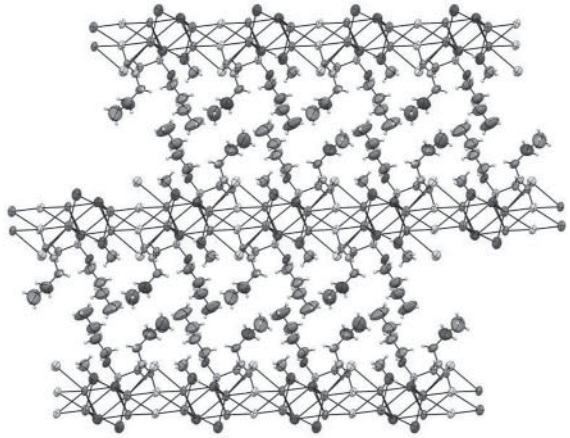


Fig. 2. Part of crystal packing of compound **4d** (view along the *b* axis).

disappearance of the ^{31}P NMR signals of the dialkyl phosphite (about 7 ppm). The solvent was removed under vacuum, and the obtained alkylaminomethyl phosphonate **2** was dissolved in 20 mL of ethanol; 6.0 g of potassium hydroxide and 2 mL of water were added, the mixture was refluxed during 4 h until hydrolysis was complete (disappearance of the ^{31}P NMR signal of the alkylaminomethyl phosphonate **2** at 18–20 ppm), and ethanol was removed under vacuum. The mixture was cooled on an ice bath, 6.0 g of KOH and 40 mL of water were added at temperature not exceeding 10°C with stirring during 1 h, 6.54 mL (0.11 mol) of freshly distilled carbon sulfide was added, and the mixture was stirred during 4 h at room temperature. Water and other volatile substances were removed under reduced pressure and the residue was dried in a vacuum dessicator over calcined $CaCl_2$. The product was recrystallized from a 1,4-dioxane–ethanol mixture (**4a**, **4b**, **4d**) or ethanol (**4c**) and dried in a vacuum oven at 60°C (5 mmHg)

Dipotassium ethyl{[isopropyl(carbodithioato)-amino]methyl}phosphonate (4a). Yield 27.01 g (81%), white crystals, decomp. 197°C (dioxane–ethanol). ^1H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 0.91 d (6H, C**H**$_3$CH, $^3J_{HH}$ = 6.9), 0.93 m (3H, C**H**$_3$CH$_2$O), 3.67 d. t (2H, OC**H**$_2$CH$_3$, $^3J_{HP}$ = 14.0, $^3J_{HH}$ = 7.1), 4.14 d (2H, PCH$_2$N, $^2J_{HP}$ = 13.4), 5.53 septet (1H, CH$_3$C**H**, $^3J_{HH}$ = 6.7). $^{13}C\{^1H\}$ NMR spectrum (D_2O), δ_C, ppm (*J*, Hz): 16.0 d (**C**H$_3$CH$_2$O, $^3J_{CP}$ = 6.3), 19.2 (**C**H$_3$CH), 46.3 d (PCH$_2$N, $^1J_{CP}$ = 148.7), 55.0 (CH$_3$**C**H), 60.9 d (POCH$_2$, $^2J_{CP}$ = 5.9), 208.9 (CSSK). $^{31}P\{^1H\}$ NMR spectrum (D_2O): δ_P 18.3 ppm. Found K, %: 23.53. $C_7H_{14}K_2NO_3PS_2$. Calculated K, %: 23.45.

Dipotassium ethyl{[butyl(carbodithioato)amino]-methyl}phosphonate (4b). Yield 26.76 g (77%), white crystals, decomp. 195°C (dioxane–ethanol). ^1H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 0.83 t (3H, C**H**$_3$CH$_2$CH$_2$, $^3J_{HH}$ = 7.4), 1.15 t (3H, C**H**$_3$CH$_2$O, $^3J_{HH}$ = 7.1), 1.18–1.27 m (2H, CH$_3$C**H**$_2$CH$_2$), 1.56–1.64 m (2H, CH$_3$CH$_2$C**H**$_2$), 3.83–3.90 m (2H, OC**H**$_2$CH$_3$), 4.09 t (2H, CH$_2$C**H**$_2$N, $^3J_{HH}$ = 7.1), 4.53 d (2H, PCH$_2$N, $^2J_{HP}$ = 12.3). $^{13}C\{^1H\}$ NMR spectrum (D_2O), δ_C, ppm (*J*, Hz): 13.2 (**C**H$_3$CH$_2$CH$_2$), 16.2 d (**C**H$_3$CH$_2$O, $^3J_{CP}$ = 5.8), 19.5 (CH$_3$**C**H$_2$CH$_2$), 27.5 (CH$_3$CH$_2$**C**H$_2$), 59.3 d (PCH$_2$N, $^1J_{CP}$ = 144.6), 53.7 (CH$_2$**C**H$_2$N), 61.6 d (O**C**H$_2$CH$_3$, $^2J_{CP}$ = 5.7), 208.9 (CSSK). $^{31}P\{^1H\}$ NMR spectrum (D_2O): δ_P 17.5 ppm. Found K, %: 22.41. $C_8H_{16}K_2NO_3PS_2$. Calculated K, %: 22.50.

Dipotassium ethyl{[(carbodithioato)cyclo-hexylamino]methyl}phosphonate (4c). Yield 31.37 g (84%), white crystals, decomp. 213°C (ethanol). ^1H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 0.78–1.06 m (5H, C**H**^{a}H^e), 0.92 t (3H, C**H**$_3$CH$_2$O, $^3J_{HH}$ = 7.1), 1.16–1.58 m (5H, CH^a**H**^{e}), 3.65 d. t (2H, OC**H**$_2$CH$_3$, $^3J_{HP}$ = 14.2, $^3J_{HH}$ = 7.0), 4.17 d (2H, PCH$_2$N, $^2J_{HP}$ = 10.8), 5.14 m (1H, *cyclo*-C^{1}H). $^{13}C\{^1H\}$ NMR spectrum (D_2O), δ_C, ppm (*J*, Hz): 16.1 d (**C**H$_3$CH$_2$O, $^3J_{CP}$ = 6.1), 25.0 (*cyclo*-C^{2}H$_2$, *cyclo*-C^{6}H$_2$), 25.5 (*cyclo*-C^{3}H$_2$, *cyclo*-C^{5}H$_2$), 29.9 (*cyclo*-C^{4}H$_2$), 47.2 d (PCH$_2$N, $^1J_{CP}$ = 148.4), 60.9 d (POCH$_2$, $^2J_{CP}$ = 5.7), 63.5 (*cyclo*-C^{1}H), 208.7 (CSSK). $^{31}P\{^1H\}$ NMR spectrum (D_2O): δ_P 18.2 ppm. Found K, %: 20.82. $C_{10}H_{18}K_2NO_3PS_2$. Calculated K, %: 20.93.

Dipotassium butyl{[(carbodithioato)(2-methoxyethyl)amino]methyl}phosphonate (4d). Yield 28.31 g (75%), white crystals, decomp. 177°C (dioxane–ethanol). ^1H NMR spectrum (CD_3CN), δ, ppm: 0.89 m (**C**H$_3$CH$_2$CH$_2$), 1.34 m (CH$_3$**C**H$_2$CH$_2$), 1.56 m (CH$_3$CH$_2$**C**H$_2$), 3.38 s (CH$_3$O), 3.82 m (POCH$_2$), 4.37 m (OCH$_2$**C**H$_2$N), 4.65 m (O**C**H$_2$CH$_2$N), 4.75 m (PCH$_2$N). $^{13}C\{^1H\}$ NMR spectrum (CD_3CN), δ_C, ppm (*J*, Hz): 13.6 (**C**H$_3$CH$_2$CH$_2$), 19.1 (CH$_3$**C**H$_2$CH$_2$), 33.1 (CH$_3$CH$_2$**C**H$_2$), 51.7 d (PCH$_2$N, $^1J_{CP}$ = 143.4), 52.3 (OCH$_2$**C**H$_2$N), 58.5 (O**C**H$_2$CH$_2$N), 64.6 d (POCH$_2$, $^2J_{CP}$ = 6.2), 69.9 (CH$_3$O), 212.5 (CSSK). $^{31}P\{^1H\}$ NMR spectrum (CD_3CN): δ_P 16.8 ppm. Found K, %: 20.80. $C_{10}H_{18}K_2NO_3PS_2$. Calculated K, %: 20.71.

Diethyl[(isopropylamino)methyl]phosphonate (2a) was prepared as described elsewhere [17]. Yield 19.04 g (91%) colorless oil, bp 57°C (3.7×10^{-3} mm Hg), n_D^{20} 1.4321. ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.94 d (6H, C**H**$_3$CH, $^3J_{HH}$ = 6.5), 1.27 t (6H, C**H**$_3$CH$_2$O, $^3J_{HH}$ = 7.0), 2.95 d (2H, PCH$_2$N, $^2J_{HP}$ = 11.3), 3.44 septet (1H, CH$_3$C**H**, $^3J_{HH}$ = 6.5), 4.10 d. t (1H, CH$_3$C**H**, $^3J_{HP}$ = 12.1, $^3J_{HH}$ = 7.0). $^{13}C\{^1H\}$ NMR spectrum ($CDCl_3$), δ_C, ppm (*J*, Hz): 16.4 d (**C**H$_3$CH$_2$O, $^3J_{CP}$ = 6.2), 17.4 (**C**H$_3$CH), 46.2 d (PCH$_2$N, $^1J_{CP}$ = 165.4), 52.0 d (POCH$_2$, $^2J_{CP}$ = 11.3), 62.0 d (CH$_3$**C**H, $^3J_{CP}$ = 6.7). $^{31}P\{^1H\}$ NMR spectrum ($CDCl_3$): δ_P 25.2 ppm.

Potassium ethyl[(isopropylamino)methyl]phosphonate (3a). Yield 17.56 g (88%), white hygroscopic powder. ^1H NMR spectrum (D_2O), δ, ppm (*J*, Hz): 0.97 d (6H, C**H**$_3$CH, $^3J_{HH}$ = 6.4 Hz), 1.18 t (3H, C**H**$_3$CH$_2$O, $^3J_{HH}$ = 7.1 Hz), 2.68 d (2H, PCH$_2$N, $^2J_{HP}$ = 13.4 Hz), 2.80 septet (1H, CH$_3$C**H**, $^3J_{HH}$ = 6.3 Hz), 3.84 d. t (2H, OC**H**$_2$CH$_3$, $^3J_{HP}$ = 14.2, $^3J_{HH}$ = 7.1 Hz). $^{13}C\{^1H\}$ NMR spectrum (D_2O), δ_C, ppm (*J*, Hz): 15.9 d (**C**H$_3$CH$_2$O, $^3J_{CP}$ =

5.9 Hz), 20.9 (**C**H_3CH), 42.0 d (PCH_2N, $^1J_{CP}$ = 142.8 Hz), 49.4 d (POCH_2, $^2J_{CP}$ = 12.8 Hz), 60.8 (CH_3**C**H). $^{31}P\{^1H\}$ NMR spectrum (D_2O): δ_P 22.4 ppm. Found K, %: 18.08. $C_6H_{15}KNO_3P$. Calculated K, %: 17.83.

X-ray diffraction analysis of crystals of compound 4d. The crystals were monoclinic $C_{10}H_{22}K_2NO_5PS_2$, crystal size 0.388 × 0.253 × 0.162 mm^3, M 409.57 g/mol, space group $P2_1/c$, $Z = 4$, $a = 16.973(2)$ Å, $b = 7.5769(8)$ Å, c = 16.6439(19) Å, β = 113.976(6)°, V = 1955.8(4) Å^3, d_{calc} = 1.391 g/cm^3, μ = 0.795 mm^{-1}, 24196 reflections were collected ($-21 \le h \le 21$, $-9 \le k \le 9$, $-20 \le l \le 20$), 4.916° ≤ 2θ 52.892°, 4001 reflections were independent (R_{int} 0.1002), 205 parameters were refined, $R_1 = 0.0509$, $wR^2 = 0.1211$ [$I \ge 2\sigma(I)$], peak residual electronic density 0.25 (–0.36) e/Å^3. The crystallographic data were deposited at the Cambridge Crystallographic Data Centre (CCDC 1942246).

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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