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Reactions of C-Phosphorylated Acetamidines with Dialkylchlorophosphates

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Abstract—The reactions of the C-phosphorylated acetamidines sodium derivatives with dialkylchlorophosphates were studied. They occur selectively to afford N^1,N^1-dialkyl-N^2-benzoylbis(dialkoxyphosphoryl)-acetamidines. Based on the CH-acid properties of C-phosphorylated acetamidines, we developed a convenient method for the synthesis of new diphosphorylated amidines.

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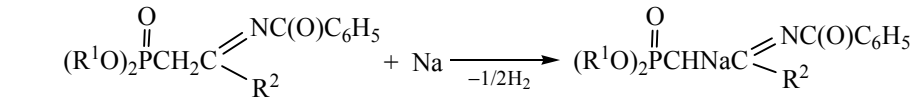
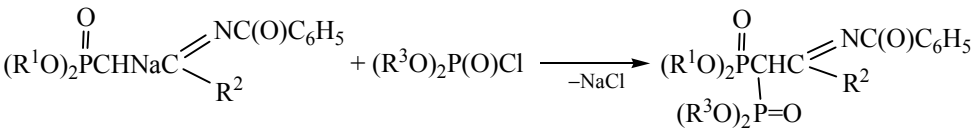
Interest in the chemistry of amidines is due to their unique structure and versatile properties [1, 2]. Amidines exhibit the biological activity of various kinds, and they are widely used in medicine and agriculture. Therefore the synthesis of new structures of amidines is very important.

So far, the methods of obtaining phosphorus amidines based on the use of CH-acid properties of the activated methylene group were poorly described in the literature. But we believe these methods to be promising. It was found that the methylene group of C-phosphorylated acetamidines connected with the electron-withdrawing phosphonate and amidine groups possesses acidic properties. The reaction of these compounds with sodium proceeds via the substitution of one of the methylene hydrogen atom to form the sodium derivative [3]. Aiming to synthesize new structures of amidines we carried out phosphorylation of the sodium derivatives of C-phosphorylated acetamidines. The starting C-phosphorylated acetamidines do not contain NH-bond in their structures and therefore no interference occurs in the studying and using the CH-acid properties of these compounds. Dimethyl chlorophosphate and diethyl chlorophosphate were used as phosphorylating reagents.

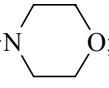
Sodium derivatives were obtained by the action of metallic sodium on the C-phosphorylated acetamidines in dioxane. Reaction (1) was carried out at heating to 40–50°C and vigorous stirring until complete conversion of sodium. Since the yield of the sodium derivative is close to quantitative, the second stage of the process, the phosphorylation [reaction (2)], was performed without isolation of the sodium derivative. For this purpose, to the reaction mixture obtained as described above was added dropwise the required amount of dialkyl chlorophosphate in dioxane under stirring at 20–30°C. Then the temperature was raised to 50°C, and the stirring was continued for 3 h. The



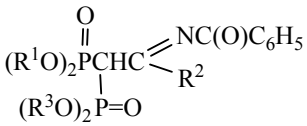
(1)



(2)

R^1 = *i*-C_3H_7, C_4H_9; R^2 = $N(C_2H_5)_2$, $N(C_3H_7)_2$, $N(C_4H_9)_2$,  ; R^3 = CH_3, C_2H_5.

Physicochemical properties of diphosphorylated acetamidines



Comp. no.	R^1	R^2	R^3	Yield, %	n_D^{20}	d_4^{20}	MR_D found	MR_D calculated	Found, % N	Found, % P	Formula	Calculated, % N	Calculated, % P
I	C_4H_9	$N(C_4H_9)_2$	C_2H_5	89	1.4875	1.0753	161.15	160.98	4.80	10.52	$C_{29}H_{52}O_7N_2P_2$	4.65	10.30
II	C_4H_9	$N(C_2H_5)_2$	CH_3	87	1.4625	1.0402	133.85	133.09	5.64	12.36	$C_{22}H_{40}O_7N_2P_2$	5.53	12.25
III	C_4H_9	$N(C_4H_9)_2$	CH_3	86	1.4915	1.0925	156.01	155.04	4.81	10.61	$C_{28}H_{50}O_7N_2P_2$	4.76	10.54
IV	*i*-C_3H_7	$N(C_3H_7)_2$	C_2H_5	84	1.4865	1.0409	111.28	110.52	5.35	11.54	$C_{25}H_{44}O_7N_2P_2$	5.13	11.35
V	C_4H_9	$N(C_2H_5)_2$	C_2H_5	87	1.4918	1.1388	139.12	138.22	5.04	11.18	$C_{25}H_{44}O_7N_2P_2$	5.13	11.35
VI	C_4H_9	$N(CH_2CH_2)_2O$	CH_3	85	1.4975	1.1709	133.07	132.66	5.33	11.59	$C_{23}H_{32}O_8N_2P_2$	5.26	11.65

molar ratio sodium–C-phosphorylated acetamidine–dialkyl chlorophosphate was 1:1:(1–1.05). To isolate the target product the reaction mixture was cooled to 20°C, sodium chloride was filtered off, and the solvent was removed by distillation in a vacuum. The yield of the reaction products was 84–89%. N^1,N^1-Dialkyl-N^2-benzoylbis(dialkoxyphosphoryl)acetamidines are the target compounds of the phosphorylation reaction. Physicochemical properties of the compounds **I–VI** are listed in the table.

The compounds obtained were purified by column chromatography using silica gel LC 5/40μ. The composition and the structure of the synthesized compounds were confirmed by the elemental analysis, molecular refraction, ^{1}H NMR and IR spectra.

The obtained compounds are viscous pale orange liquids, well soluble in organic solvents and poorly soluble in water.

The screening for biological activity of the obtained N^1,N^1-dialkyl-N^2-benzoylbis(dialkoxyphosphoryl)acetamidines performed by means of PASS program predicted with high probability anticancer, anti-inflamatory activity. They can be used as regulators of calcium metabolism and hypolipidemic drugs.

Thus, the reaction of sodium derivatives of *C*-phosphorylated acetamidines with dialkylchlorophosphates affords N^1,N^1-dialkyl-N^2-benzoylbis(dialkoxyphosphoryl)acetamidines in high yield.

EXPERIMENTAL

N^1,N^1-Dibutyl-N^2-benzoyl-(2-diethoxyphosphoryl-2-dibutoxyphosphoryl)acetamidine (I). To a solution of 2 g (0.0043 mol) of N^1,N^1-dibutyl-N^2-benzoyl(dibutoxyphosphoryl)acetamidine in 4 ml of anhydrous dioxane was added by portions 0.1 g (0.0043 mol) of sodium under stirring at the temperature 20–30°C. The reaction mixture was stirred to complete conversion of sodium. To a solution of the resulting acetamidine sodium derivative was added dropwise 0.74 g (0.0043 mol) of diethyl chlorophosphate in 2 ml of dioxane at stirring at 20–30°C. The molar ratio N^1,N^1-dibutyl-N^2-benzoyl-(dibutoxyphosphoryl)acetamidine–sodium–diethylchlorophosphate was 1:1:1. The temperature was raised to 40°C, and the stirring was continued for 3 h. Sodium chloride was filtered off; the solvent was removed by distillation in a vacuum at 15–20 hPa. The residue was evacuated for 1 h at 50°C and 2–4 hPa. Yield 2.3 g (89%). IR spectrum, ν, cm^{-1}: 952–1026 (POC), 1212–1236 (P=O), 1686 (C=N), 1720 (C=O), 1630 (C⎓C). ^{1}H NMR spectrum (CCl_4), δ, ppm: 0.89 t (18H, CH_3), 1.33 m (16H, CH_2), 2.76 d (1H, CHP), 3.48 t (4H, NCH_2), 3.97 m (8H, CH_2OP), 7.24 m (5H, C_6H_5).

N^1,N^1-Diethyl-N^2-benzoyl-(2-dimethoxyphosphoryl-2-dibutoxyphosphoryl)acetamidine (II) was prepared similarly from 1.50 g (0.0037 mol) of N^1,N^1-diethyl-N^2-benzoyl(dibutoxyphosphoryl)acetamidine, 0.08 g (0.0037 mol) of sodium and 0.56 g (0.0039 mol) of dimethyl chlorophosphate. The molar ratio N^1,N^1-diethyl-N^2-benzoyl(dibutoxyphosphoryl)acetamidine–sodium–dimethylchlorophosphate was 1:1:1.05. Yield 1.63 g (87%). IR spectrum, ν, cm^{-1}: 992–1061 (POC), 1215–1237 (P=O), 1655 (C=N), 1725 (C=O), 1626 (C⎓C). ^{1}H NMR spectrum (CCl_4), δ, ppm: 0.90 t (12H, CH_3), 1.37 m (8H, CH_2), 2.77 d (1H, CHP), 3.31 q (4H, NCH_2), 3.62 d (6H, CH_3OP), 3.89 m (4H, CH_2OP), 7.32 m (5H,C_6H_5).

N^1,N^1-Dibutyl-N^2-benzoyl-(2-dimethoxyphosphoryl-2-dibutoxyphosphoryl)acetamidine (III) was prepared similarly from 2 g (0.0043 mol) of N^1,N^1-dibutyl-N^2-benzoyl(dibutoxyphosphoryl)acetamidine, 0.099 g (0.0043 mol) of sodium and 0.63 g (0.0044 mol) of dimethylchlorophosphate. The molar ratio N^1,N^1-dibutyl-N^2-benzoyl(dibutoxyphosphoryl)acetamidines–sodium–dimethylchlorophosphate was 1:1:1.03. Yield 2.17 g (86%). IR spectrum, ν, cm^{-1}: 992–1062 (POC), 1215–1240 (P=O), 1684 (C=N), 1734 (C=O), 1636 (C≡C). ^{1}H NMR spectrum (CCl_4), δ, ppm: 0.93 t (12H, CH_3), 1.27 m (16H, CH_2), 2.77 d (1H, CHP), 3.23 t (4H, NCH_2), 3.91 d (6H, CH_3OP), 4.65 m (4H, CH_2OP), 7.30 m (5H, C_6H_5).

N^1,N^1-Dipropyl-N^2-benzoyl-(2-diethoxyphosphoryl-2-diisopropoxyphosphoryl)acetamidine (IV) was prepared similarly from 2 g (0.0049 mol) of N^1,N^1-dipropyl-N^2-benzoyl(diisopropoxyphosphoryl)acetamidine, 0.11 g (0.0049 mol) of sodium and 0.84 g (0.0049 mol) of diethylchlorophosphate. The molar ratio N^1,N^1-dipropyl-N^2-benzoyl(diisopropoxyphosphoryl)acetamidine–sodium–diethylchlorophosphate was 1:1:1. Yield 2.25 g (84%). IR spectrum, ν, cm^{-1}: 998–1064 (POC), 1217–1245 (P=O), 1677 (C=N), 1740 (C=O), 1625 (C≡C). ^{1}H NMR spectrum (CCl_4), δ, ppm: 0.92 d (18H, CH_3), 1.05 t (6H, CH_3), 1.23 m (4H, CH_2), 2.80 d (1H, CHP), 3.23 t (4H, NCH_2), 4.46 m (6H, CHOP), 7.29 m (5H, C_6H_5).

N^1,N^1-Diethyl-N^2-benzoyl-(2-diethoxyphosphoryl-2-dibutoxyphosphoryl)acetamidine (V) was prepared similarly from 1.8 g (0.0044 mol) of N^1,N^1-diethyl-N^2-benzoyl(dibutoxyphosphoryl)acetamidine, 0.11 g (0.0044 mol) of sodium and 0.84 g (0.0049 mol) of diethylchlorophosphate. The molar ratio N^1,N^1-diethyl-N^2-benzoyl(dibutoxyphosphoryl)acetamidine–sodium–diethylchlorophosphate was 1:1:1.Yield 2.1 g (87%). IR spectrum, ν, cm^{-1}: 998–1054 (POC), 1223–1245 (P=O), 1682 (C=N), 1740 (C=O), 1635 (C≡C). ^{1}H NMR spectrum (CCl_4), δ, ppm: 0.92 t (18H, CH_3), 1.26 m (8H, CH_2), 2.75 d (1H, CHP), 3.25 q (4H, NCH_2), 4.61 m (8H, CH_2OP), 7.32 m (5H, C_6H_5).

N^1-Morpholino-N^2-benzoyl-(2-dimethoxyphosphoryl-2-dibutoxyphosphoryl)acetamidine (VI) was prepared similarly from 1.38 g (0.0033 mol) of N^1-morpholino-N^2-benzoyl(dibutoxyphosphoryl)acetamidine, 0.07 g (0.0033 mol) of sodium and 0.49 g (0.0034 mol) of dimethylchlorophosphate. The molar ratio N^1-morpholino-N^2-benzoyl(dibutoxyphosphoryl)-acetamidines–sodium–dimethylchlorophosphate was 1:1:1.03. Yield 1.5 g (85%). IR spectrum, ν, cm^{-1}: 996–1072 (POC), 1210–1230 (P=O), 1676 (C=N), 1725 (C=O), 1627 (C≡C). ^{1}H NMR spectrum (CCl_4), δ, ppm: 0.84 t (6H, CH_3), 1.31 m (8H, CH_2), 2.83 d (1H, CHP), 3.45 q (4H, NCH_2), 3.65 t (4H, CH_2O), 3.85 d (6H, CH_3OP), 4.01 m (4H, CH_2OP), 7.34 m (5H, C_6H_5).

The ^{1}H NMR spectra were recorded on a Varian Mercury 300 BB spectrometer operating at 300 MHz.

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