ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 10, pp. 1930–1933. © Pleiades Publishing, Ltd., 2014.
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Synthesis and Bactericidal Activity of Substituted Cyclic Acetals

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Received April 24, 2014

Abtract—A series of substituted cyclic acetals were synthesized and tested for their bactericidal activity against bacteria strain *Azospirillum brasilense* Sp245.

Keywords: biological activity, biotoxicity, *gem*-dichlorocyclopropanes, cyclic acetals, *Azospirillum* bacteria

DOI: 10.1134/S1070363214100119

Substituted cyclic acetals are important intermediates in organic synthesis and are widely used as solvents, plasticizers, surfactants, etc. [1]. 1,3-Dioxacyclo-alkyl moiety is often present in complex molecules having biological activity [2].

Efficiency and prospects of using substituted cyclic acetals as plant protection chemicals have been lately found [3, 4]. Continuing these studies, we examined biotoxicity of some simplest cyclic acetals with respect to the strain *A. brasilense* Sp245.

Bacteria of the genus *Azospirillum* are among the most studied bacteria, stimulating the growth of plants and capable of associative interaction with many higher plants. They have a high adaptive potential to the negative external influences, like the lack of nutrients, salinity, lack of moisture. Compared with other rhizosphere microorganisms, *Azospirillum* have sufficiently high resistance to heavy metals [5]. They are capable of transforming selenium and gold compounds, changing their oxidation state and transferring them from soluble to insoluble less toxic forms [6, 7]. In recent years, it was shown that the use of *Azospirillum* in bioremediation improves the process and allows for better extraction of harmful substances [8].

Substituted cyclic acetals **I–V** were obtained in a yield of 90% by condensation of the corresponding di(tri)ols with formaldehyde and isobutyraldehyde (Scheme 1).

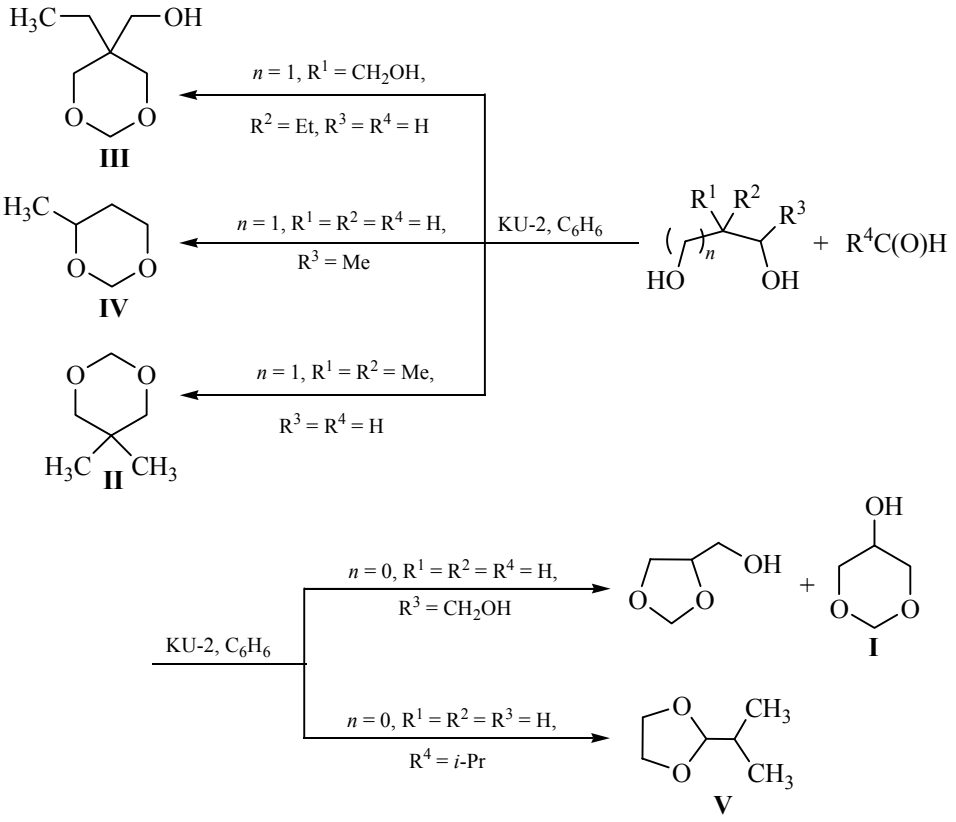
The derivative **VI** was synthesized from epichlorohydrin and formaldehyde as described in [9]. 5,5-Disubstituted 1,3-dioxane **VII** was prepared by condensation of 3,3-bis(chloromethyl)oxetane with formaldehyde followed by reacting the resulting 5,5-dichloromethyl-1,3-dioxane with *n*-butanol [10] (Scheme 2).

Chloromethyl-*gem*-dichlorocyclopropane **VIII** was synthesized by dichlorocarbenilation of allyl chloride under the Makosza conditions [11] (Scheme 3).

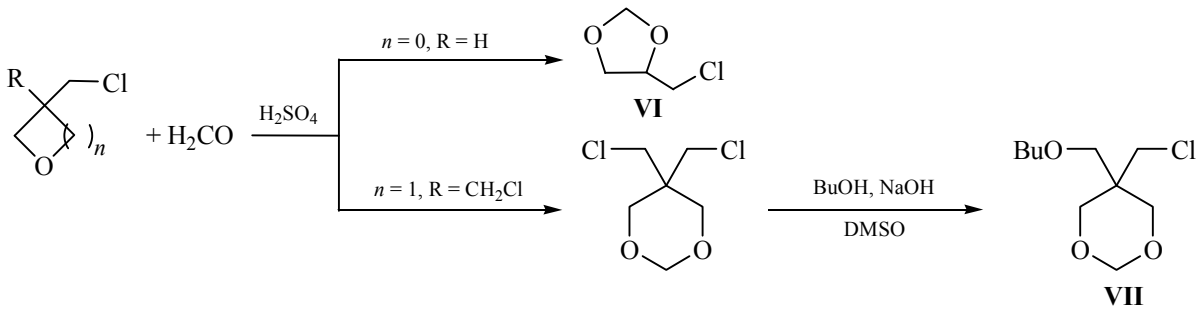
We estimate biotoxicity of compounds **I–VIII** against *Azospirillum brasilense* Sp245 bacterial strain (Collection of rizosphere microorganisms, Institute of Biochemistry and Physiology of Plants and Microorganisms, Russian Academy of Sciences). The culture was grown under aerobic conditions (forced aeration, 140 rpm) at 28°C in a liquid synthetic malate medium modified to the following composition (g/L): K_2HPO_4 3.0; KH_2PO_4 2.0; NaCl 0.1; malic acid 3.76; NaOH 2.24; NH_4Cl 0.5; $MgSO_4·7H_2O$ 0.2; $CaCl_2$ 0.02; $FeSO_4·7H_2O$ 0.02 (introduced as a chelate with nitrilotriacetic acid); $Na_2MoO_4·2H_2O$ 0.002 (pH 6.8–7.0). Inhibition of culture growth in the presence of **I–VIII** was determined by the change in optical density (λ 595 nm, Spekol 221 spectrophotometer) after 18–20 h of growth. Mass concentrations of the test substances (liquids) were calculated at ρ 0.85–0.88 g/cm.

When using cyclic acetals **I–III** at a concentration range of 0.5–1%, growth of the strain *A. Brasilense* Sp245 was almost completely suppressed. Therefore the biotoxicity of the reagents **I–VIII** was studied at smaller concentrations. It has been found (see figure) that oxyalkyl- and alkylformals **I–IV** showed low toxicity. Acetal **V** and 4-chloromethyl-1,3-dioxolane

Scheme 1.

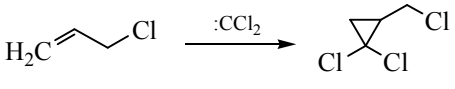


Scheme 2.



VI inhibit the bacteria growth by >50% at a concentration of 0.1%. When replacing the OH-group by Cl in 5,5-disubstituted 1,3-dioxolane, the ability to inhibit bacterial growth increases sharply (**III**, **VII**). Compound **VIII**, whose molecule contains *gem*-dichlorocyclopropane fragment instead of cycloacetyl moiety, was one of the most active reagents with respect to the used bacterial strains.

Scheme 3.

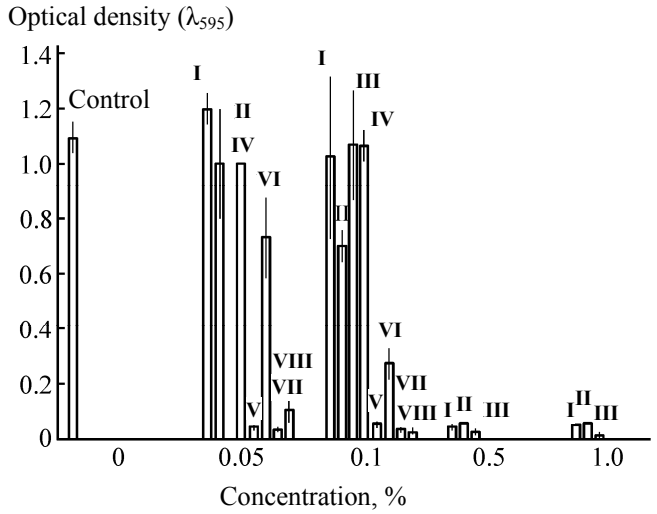


VIII

These data demonstrate that cyclic formals free of chlorine atoms in the side chain, are not harmful to living organisms, while 2-alkyl- and 4(5)-chloromethyl-1,3-dioxacycloalkanes are of interest as promising antiseptics and bactericidal components. The substituted polychlorocyclopropanes can be also used for these purposes.

EXPERIMENTAL

Synthesis of cyclic acetals I–V. A mixture of 1.1 mol of the corresponding diol or glycerol, 1.1 mol of paraformaldehyde or isobutyraldehyde, 20 g of cationite KU-2 in 200 mL of benzene was vigorously



Toxicity of compounds **I–VIII** with respect to the strain *A. Brasilense* Sp245.

stirred under reflux using a Dean–Stark trap. After cooling, the catalyst was filtered off. The filtrate was washed with 5% $NaHCO_3$ solution and water. The organic layer was dried over $MgSO_4$ and fractionated. Physicochemical constants and parameters of the NMR spectra of the obtained compounds were similar to those described previously [12–14].

4-Hydroxymethyl-1,3-dioxolane and 5-hydroxy-1,3-dioxane (I). Yield 93%, mp 190–195°C. According to gas chromatography-mass spectrometry data, glycerol formal **I** consist of an equimolar mixture of 5-hydroxy-1,3-dioxane and 4-hydroxymethyl-1,3-dioxolane.

5,5-Dimethyl-1,3-dioxane (II). Yield 77%, mp 125°C.

5-Ethyl-5-hydroxymethyl-1,3-dioxane (III). Yield 97%, bp 85°C (4 mmHg).

4-Methyl-1,3-dioxane (IV). Yield 69%, bp 114°C.

2-Isopropyl-1,3-dioxolane (V). Yield 92%, bp 121°C.

4-Chloromethyl-1,3-dioxolane (VI). A mixture of 2 mol of epichlorohydrin, 360 mL of water, and 1 mL of sulfuric acid was vigorously stirred at 90–100°C for 2 h. Then to the mixture was added 1.8 mol of paraformaldehyde, and heating was continued until the mixture became transparent. After adding 10% Na_2CO_3 solution, the resulting mixture was distilled. Fraction with bp 100–145°C was extracted with chloroform, dried with $MgSO_4$, and distilled. Yield 92%, bp 148°C. Physicochemical constants and parameters of the NMR spectra were consistent with the previously described [9].

5-Butoxymethyl-5-chloromethyl-1,3-dioxane (VII). To a mixture of 0.1 mol of 3,3-bischloromethyloxetane and 0.1 mol of paraformaldehyde in 80 mL of 1,4-dioxane was added dropwise 2 mL of conc. sulfuric acid. The mixture was stirred at 90–100°C for 5 h. After cooling a solution of Na_2CO_3 was added. Then the solvent was evaporated, and the residue was distilled in a vacuum to give 5,5-bischloromethyl-1,3-dioxane in 70% yield, bp 120°C (12 mmHg) [10].

To a mixture of 0.012 mol of butanol, 0.012 mol of NaOH, 0.03 g of catamine AB, and 15 mL of DMSO was added 0.012 mol of 5-chloromethyl-1,3-dioxane under vigorous stirring and heating (65–70°C). Then the mixture was washed with water and extracted with chloroform. The organic layer was dried with $MgSO_4$ and concentrated. The residue was distilled in a vacuum. Yield 80%, bp 144°C (12 mmHg) [10].

2-(Chloromethyl)-1,1-dichlorocyclopropane (VIII). To a solution of 0.1 mol of 3-chloroprop-1-ene, 0.2 g of triethylbenzylammonium chloride in 300 mL of chloroform at vigorous stirring and heating at 40–45°C was added dropwise 320 g of 50% aqueous solution of NaOH within 2 h. Then the mixture was washed with water, and the organic layer was dried over $MgSO_4$. After removing chloroform, the residue was distilled in a vacuum. Yield 98%, bp 58°C (5 mmHg). Physicochemical constants and parameters of the NMR spectra were consistent with the previously described [11].

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