SYNTHESIS AND ANTIBACTERIAL PROPERTIES OF SOME 2-[1-METHYL-2-ALKYLTHIOETHYL]-1,3-DIOXOLANES

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In earlier work [3, 4], we showed that 1,3-dioxolanes and some of their derivatives possess considerable physiological activity. The present communication is a continuation of the preceding work and involves the synthesis of some new 2-methyl-2-(1-methyl-2-alkylthioethyl)-1,3-dioxolanes (I-V) and an investigation of their antimicrobial effects. Sulfur containing ketones — ketosulfides — were used as starting materials for the synthesis. New 1,3-dioxolanes were obtained by the ketalization of the ketosulfides with ethyleneglycol in boiling toluene. The reaction was catalyzed by TsOH. Water was removed from the reaction by azeotropic distillation.

$$\underbrace{\overline{O(CH_2)_2OC}(CH_3)CH(CH_3)CH_2SR}_{\text{I—V}}\quad \text{I}:R = Et,\ \text{II}:R = Pr,\ \text{III}:R = Bu,\ \text{IV}:R = Am\text{-}iso,\ \text{V}:R = Am$$

The compounds were liquids, insoluble in water, and readily soluble in organic solvents. The structures of the substances synthesized were confirmed by elemental analysis and IR spectral data. The IR spectra contained bands at 1065-1077 cm^{-1} (—O—C—O—), characteristic of dioxolanes.

EXPERIMENTAL (CHEMICAL)

Infrared spectra were obtained on a UR-20 (GDR) instrument using the thin-film (10-15 μm) method. The starting ketosulfides were obtained by the method given in [1].

2-Methyl-2(1-methyl-2-alkylthioethyl)-1,3-dioxolanes (I-V). In a reaction vessel, fitted with a reflux condenser and attachment for the azeotropic distillation of water, was placed 100 ml of toluene, 0.22 mole of ethylene glycol, 0.2 mole of freshly-prepared 1-alkylthio-2-methyl-2-butanone and 100-150 mg of TsOH. The mixture was refluxed until no more water collected in the calibrated attachment. The solution was cooled to 0°C, and neutralized with 60 ml of saturated sodium carbonate solution for 30 minutes. The organic layer was separated and dried with $MgSO_4$. After distillation of the toluene, the product was fractionated in vacuo. Yields and physical constants of the products are given in Table 1.

TABLE 1. Physical Data for the 1,3-Dioxolanes (I-V)

Compound	Yield, %	bp, °C (mm mercury)	Found, %			Empirical formula	Calculated, %		
			C	H	S		C	H	S
I	92	86—8(2)	56,99	9,45	16,75	$C_9H_{18}O_2S$	56,84	9,47	16,83
II	70	109—10 (3)	58,97	9,87	15,64	$C_{10}H_{20}O_2S$	58,82	9,80	15,70
III	80	124—25 (1,5)	60,59	10,25	14,63	$C_{11}H_{22}O_2S$	60,55	10,09	14,67
IV	89	114—15 (1)	62,17	10,39	13,75	$C_{12}H_{24}O_2S$	62,06	10,34	13,79
V	87	117—18 (0,5)	62,24	10,46	13,69	$C_{12}H_{24}O_2S$	62,06	10,34	13,79

EXPERIMENTAL (PHARMACOLOGICAL)

The antibacterial activity of the 1,3-dioxolanes was studied by the method of double serial dilution [5]. Strains of staphylococcus, streptococcus, pyogenes bacillus, *E. coli*, and anthrax were used in the work. The acute toxicity of the compounds was determined on white mice weighing 20-24 g; the LD_{50} was calculated by Kerber's method [2]. The preparations were administered in increasing doses in 10% Tween-80. The tests showed that all the compounds had low toxicity and exhibited some bacteriostatic action against pathogenic

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TABLE 2. Antibacterial Activity and Toxicity of the 1,3-Dioxolanes (I-V)

Compound	MIC, μg/ml					LD$_{50}$ mg/kg
	staphylococcus	streptococcus	anthrax	E. coli	pyogenes bacillus	
I	12,5	12,5	50	50	50	799,5
II	25,0	25,0	100	100	100	1005,0
III	25,0	25,0	100	100	100	987,9
IV	12,5	12,5	50	50	50	687,3
V	50,0	50,0	100	100	100	1116,5

microflora. Their activity increases with decreasing sulfide content of the compound. It was noted compound IV, with a branched chain, had a lower minimum inhibiting concentration (MIC) and therefore a greater antibacterial effect (Table 2).

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SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF ALKYLTHIOALKYLMALONIC ESTERS

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In the literature two methods are described for the preparation of alkylthioalkylmalonic esters: by heating of acetyldimethyl sulfide or α-chlorodialkyl sulfide with sodium-malonic ester for several hours, giving a yield of not more than 10-35% [3]. The disadvantages of these methods are the duration of the process, low yield, and the formation of a large amount of side products. In continuation of our study of organizing compounds [1], we have developed a new and more effective method for the synthesis of alkylthioalkylmalonic esters by reaction of bromozinc-malonic ester with α-chloro-thioethers in an ethyl acetate medium in the presence of $HgCl_2$ as catalyst.

$$\mathrm{BrZnCH(COOEt)_2 + RCHClSR' \longrightarrow \underset{I-VI}{R'SCH(R)CH(COOEt)_2}}$$

I: R = H, R' = Et: II: R = H, R' = Pr; III: R = Me, R' = Pr-i; IV: R = Pr-i; R' = Et;
V: R = H, R' = allyl VI: R = H, R' = Bu.

Diesters (I-VI) were obtained by the new method, and their physicochemical characteristics are shown in Table 1.

The structure of (I-VI) was confirmed by elemental analysis and IR spectroscopy. The IR spectra of I-VI, taken in a thin layer, show intense absorption of the stretching vibrations of the carbonyl groups in the 1750-1730 cm^{-1} region and absorption of the ether group in the 1120-1040 cm^{-1} region. The stretching vibrations of the RS group are observed at 640-600 cm^{-1}.

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