SYNTHESIS AND ANTIBACTERIAL PROPERTIES OF 1,3-DIOXOLANES

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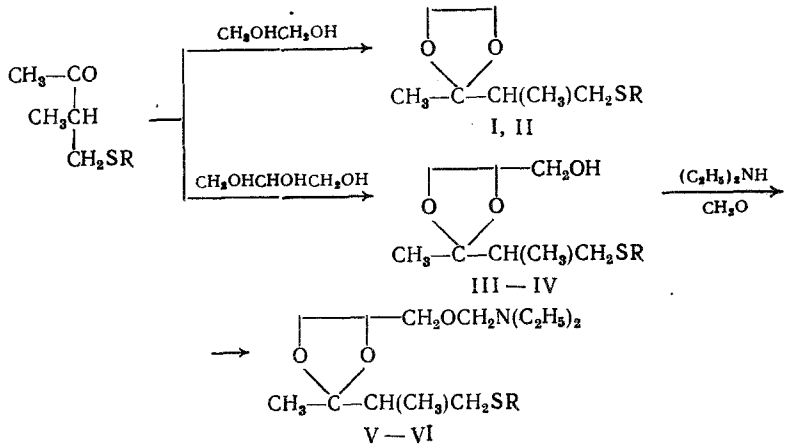
1,3-Dioxolanes and their derivatives have a wide spectrum of biological activity (local anaesthetic, antibacterial, spasmolytic, and neuropharmacological) [3-5]. It was of interest to carry out the synthesis and to study the antibacterial properties, of some novel thioalkyl substituted 1,3-dioxolanes and also those with various substituents in the 4-position of the heterocycle. The synthesis of these compounds was based on ketosulfides as shown in the scheme.



I, III, V: R = C_2H_5; II, IV, VI: R = C_3H_7.

Ketalizations of the ketosulfides with ethylene glycol and with glycerol were carried out in refluxing toluene. p-Toluene sulfonic acid was used as catalyst and water was removed from the reaction medium by azeotropic distillation. The products were insoluble in water but freely soluble in organic solvents. Their structures were confirmed by elemental analytical data and PMR and IR spectroscopic absorption data. Bands were observed in the IR spectrum at 1065-1077 cm^{-1} (—O—C—O—), 3450 cm^{-1} (O—H), and 2820 cm^{-1} (C—N).

Only one of the two possible (cis or trans) stereoisomers was observed according to the spectral data and to TLC. This is probably due to the existence of only one stabilized form.

EXPERIMENTAL (CHEMICAL)

IR spectra were obtained on a UR-20 instrument for thin layers (10-15μm). PMR spectra were recorded on a Tesla-487 spectrometer at 80 MHz using CCl_4 solvent and related to HMDS.

The starting ketosulfide was obtained by method [1].

2-Methyl-2-(1-methyl-2-alkylthioethyl)-1,3-dioxolanes (I, II). Into a flask fitted with reflux condenser and attachment for azeotropic distillation of water there were added toluene (100 ml), ethylene glycol (0.22 mole), freshly distilled 2-methyl-1-alkylthio-3-butanone (0.2 mole), and p-toluenesulfonic acid catalyst (100-150 mg). The mixture was refluxed until no further water was collected in the measuring arm of the apparatus, cooled, and neutralized with saturated sodium carbonate solution (60 ml) at 0°C over 30 min. The organic layer was separated, dried ($MgSO_4$), toluene distilled off, and the product fractionated *in vacuo*. The yields and physical constants for I and II are given in Table 1.

2-Methyl-2-(1-methyl-2-alkylthioethyl)-4-hydroxymethyl-1,3-dioxolanes (III, IV). Prepared analogously from glycerol (0.22 mole) and 2-methyl-1-alkylthio-3-butanone (0.2 mole) in toluene (100 ml) to give III and IV (see Table 1).

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TABLE 1. 1,3-Dioxolane Physical Constants for I-VI

Compound	Yield, %	bp °C/mm Hg	Found, %				Empirical formula	Calculated, %			
			C	H	S	N		C	H	S	N
I	92	86—88/2	56,99	9,45	16,75	—	$C_9H_{18}O_2S$	56,84	9,47	16,83	—
II	70	109—110/3	58,97	9,87	15,64	—	$C_{10}H_{20}O_2S$	58,82	9,80	15,70	—
III	80	121—122/0,5	54,60	9,11	14,48	—	$C_{10}H_{20}O_3S$	54,54	9,09	14,54	—
IV	85	146—148/0,5	56,49	9,47	13,61	—	$C_{11}H_{22}O_3S$	56,41	9,40	13,68	—
V	93	153—155/2	59,11	10,30	10,53	4,67	$C_{15}H_{31}NO_3S$	59,01	10,16	10,47	4,58
VI	98	148—149/0,5	60,30	10,43	10,09	4,44	$C_{16}H_{33}NO_3S$	60,18	10,34	10,01	4,37

TABLE 2. Antibacterial Activity and Acute Toxicity of 1,3-Dioxolanes I-VI

Compound	Minimum inhibitory concentration, μg/ml					LD_{50}, mg/kg
	streptococci	staphylococci	B. pyocyaneus	E. coli	anthracoid	
I	12,5	12,5	50	50	50	799,5
II	25	25	100	100	100	1005,0
III	25	25	100	100	100	812,5
IV	25	25	100	100	100	912,0
V	0,15	0,15	0,62	0,62	0,62	521,0
VI	0,15	0,15	0,62	0,62	0,62	591,0

2-Methyl-2-(1-methyl-2-alkylthioethyl)-4-dimethylaminomethoxymethyl-1,3-dioxolanes (V, VI). Into a flask fitted with reflux condenser and a Dean and Stark attachment there were added III (0.05 mole), diethylamine (0.05 mole), paraformaldehyde (0.05), and p-toluenesulfonic acid (100-150 mg) in toluene (50 ml). The mixture was refluxed until water (0.9 ml) had collected. After drying the solution ($MgSO_4$) the solvent was distilled off and the product fractionated *in vacuo*. The yields and physical constants for V and VI are given in Table 1.

EXPERIMENTAL (PHARMACOLOGICAL)

The antibiotic activity of 1,3-dioxolanes was determined by the method of progressive dilution. The strains used in this work were: staphylococci, streptococci, *B. pyocyaneus*, *E. coli*, and anthracoids. The data obtained points to a sharp increase in the antibacterials' V and VI activity upon introduction of a tertiary nitrogen atom at position 4 of the heterocycle.

The acute toxicity of the compounds was studied in white mice and the LD_{50} claculated according to Kerber [2]. Preparations were introduced in increasing doses in 10% Tween-80. These experiments showed that all compounds were of low toxicity but that the toxicity was highest when the diethylamino group was introduced into the 1,3-dioxolane ring (Table 2).

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SYNTHESIS AND ANTIFUNGAL ACTIVITY OF SOME γ-IODOPROPARGYL ESTERS OF MONO- AND DICARBAMATES

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Data on the pharmacological activity of carbamate derivatives is given in the literature [1, 3]. Related preparations used in medical practice include meprotan (meprobamate), isoprotan, etc.

In a further search for biologically active carbamate derivatives, we synthesized previously-unknown γ-iodopropargyl esters of carbamic acids. They were prepared not by the hypohalide method [4], but directly by the substitution of metals by halogen in acetylides in dry ether solution according to the following scheme:

$$RNHC(O)OCH_2C{\equiv}CCu + I_2 \xrightarrow{\text{ether}} RNHC(O)OCH_2C{\equiv}CI$$

I: $R = C_6H_5$; II: $R = 2,4\text{-}Cl_2C_6H_4$; III: $R = \alpha\text{-}C_{10}H_7$; IV: $R = CH_3(CH_2)_{17}$; V: $R = IC{\equiv}CCH_2OC(O)NH(CH_2)_6$; VI: $R = IC{\equiv}CCH_2OC(O)NHC_6H_3(CH_3)\text{-}4$

The γ-iodopropargyl carbamates I-VI (cf. Table 1) are stable under ordinary conditions and are crystalline substances, easily soluble in organic solvents and insoluble in water.

The composition and structure of the compounds obtained were supported by data from elemental analysis and IR spectroscopy. The IR spectra of the γ-iodopropargyl carbamates showed absorption bands characteristic of the C≡C oscillation in the 2210 cm^{-1} region, of the N–H bond in the 3310 cm^{-1} region, and of the carbamate group in the 1710 cm^{-1} region.

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