SYNTHESIS, ANTIMICROBIAL AND MUTAGENIC ACTIVITY OF β-HYDROXYKETONES

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UDC 615.281:547.451.5].012.1+
615.281:547.451.5].065:612.5.
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Methods of obtaining β-hydroxyketones of the arylaliphatic series by condensation of alkylaryl ketones with formaldehyde in methanol are known [7]. However, the indicated method suffers from the low yield of product (20%). Extending our work in the area of organotin compounds [1], we obtained β-hydroxyketones which were evaluated comparatively for antibacterial and mutagenic properties as the subject of this investigation.

A parallel study of the antimicrobial and mutagenic activity of β-hydroxyketones allows a test of the possibility of using the compounds either as chemotherapeutic agents or as sterilization and disinfection materials. The synthesis was accomplished by the interaction of α-bromoisopropylphenyl ketone with aliphatic and aromatic aldehydes in the presence of zinc.

$$C_6H_5COCBr(CH_3)_2 + RCHO + Zn \xrightarrow{H_2O} C_6H_5COC(CH_3)_2CH(OH)R,$$

where R = CCl_3 (I); 2,4-$Cl_2C_6H_3$ (II); 2-ClC_6H_4 (III); C_6H_5 (IV); 4-Br-C_6H_4 (V); 4-$(CH_3)_2NC_6H_4$ (VI); 4-ClC_6H_4 (VII); iso-Pr (VIII); 4-$CH_3OC_6H_4$ (IX); 3-ClC_6H_4 (X).

EXPERIMENTAL CHEMICAL SECTION

These compounds are colorless crystalline materials or odorless liquids, stable to storage, soluble in DMSO and alcohols, insoluble in water (Cf. Table 1).

The IR spectra of the β-hydroxyketones, obtained in thin films, showed low-frequency stretching vibrations of the hydroxyl group at 30-120 cm^{-1} as a result of intramolecular hydrogen bonding between the hydroxyl group and the π-electrons of the carbonyl group conjugated with the six-membered ring.

Stretching vibrations of the β-hydroxyketone carbonyl group appeared in the IR at 1710-1675 cm^{-1}. Intense absorption bonds also were observed in the 1220-1230 cm^{-1} region as a result of the in-plane deformation of the OH group.

TABLE 1. Properties of the β-Hydroxyketones I-X

Compound	Yield, %	mp, °C	Found, %			Empirical formula	Calculated, %		
			C	H	Cl (Br)		C	H	Cl (Br)
I	76	93—94	—	—	33,46	$C_{12}H_{13}Cl_3O_2$	—	—	33,62
II	93	92—93	—	—	21,29	$C_{17}H_{16}Cl_2O_2$	—	—	21,05
III	83	71—72	—	—	12,18	$C_{17}H_{17}ClO_2$	—	—	12,13
IV	79	115—116	80,56	7,23	—	$C_{17}H_{18}O_2$	80,31	7,07	—
V	83	74—75	—	—	24,21	$C_{17}H_{17}BrO_2$	—	—	24,02
VI	67	138—140	(%N 4,94)			$C_{19}H_{23}NO_2$	(%N 4,71)		—
VII	90	136—137	—	—	12,02	$C_{17}H_{17}ClO_2$	—	—	12,13
VIII	62	84—88/4*	76,43	9,02	—	$C_{14}H_{20}O_2$	76,32	9,15	—
IX	64	86—88/2*	76,26	7,01	—	$C_{18}H_{20}O_3$	76,03	7,09	—
X	88	57—58	—	—	12,27	$C_{17}H_{17}ClO_2$	—	—	12,13

*Indicates bp.

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0091-150X/85/1901-0041$09.50

TABLE 2. Antimicrobial Activity of β-Hydroxyketones

Compound	Toxicity, LD_{50}, mg/kg	Minimum bacteriostatic concentration, μg/ml		Minimum bactericidal concentration, μg/ml	
		E. coli, M17	S. aureus, 209P	E. coli M17	S. aureus, 209P
I	500	250	500	500	500
II	1500	1000	1000	1000	1000
III	1000	125	125	500	500
IV	1500	—	—	—	—
V	500	250	250	500	500
VI	1200	—	—	—	—
VII	1000	3,9	3,9	62,5	62,5
VIII	800	62,5	62,5	250	250
IX	1000	250	250	1000	1000
X	1000	7,8	7,8	62,5	62,5
Standard (Chloramine-T)		1000	1000	4000	4000

TABLE 3. Mutagenic Effect of β-Hydroxyketones (bone marrow cells)

Compound	Dose, mg/kg	Exposure, h	Quantity of studied metaphase	% Metaphase with aberrations	Mitotic index	Degree of mutagenic effect
II	500	6	200	2,5±0,9	3,1±0,2	0
	500	24	200	4,0±1,0	3,0±0,9	1
	500	48	200	8,5±0,5	2,9±0,5	1
III	500	6	200	5,0±1,2	2,1±0,5	1
	500	24	200	6,0±0,8	1,6±0,7	1
	500	48	200	3,0±0,5	2,0±0,3	1
VII	500	6	200	2,5±0,5	3,0±0,4	0
	500	24	200	10,0±0,9	2,5±0,4	1
	500	48	200	16,0±0,8	2,3±0,4	1
VIII	500	6	200	13,0±0,7	2,2±0,5	1
	500	24	200	5,0±0,9	1,5±0,7	1
	500	48	200	10,0±1,2	2,4±0,5	1
Control (starch paste)		6	200	1,5±0,5	2,6±0,5	—
		24	200	1,88±0,7	2,2±0,9	—
		48	200	1,87±0,6	2,0±0,4	—

General Method for Preparation of β-Hydroxyketones. Zinc in the form of thin shavings (0.15 mole) was introduced into a flask and covered with diethyl ether. A mixture of α-bromoketone (0.15 mole) and aldehyde (0.15 mole) was slowly added to the mixture. The reaction mixture was cooled, washed with water, $NaHCO_3$ solution, again with water, and dried with sodium sulfate. After removal of the solvent, the reaction product was distilled or recrystallized from ethanol.

IR spectra were determined on an UR-20 instrument (GDR) with LiF and NaCl prisms.

EXPERIMENTAL BIOLOGICAL SECTION

The antimicrobial activity of the compounds was studied by double serial dilution in beef-peptone broth with *Escherichia coli* (strain M17) and *Staphylococcus aureus* (strain 209P) [2]. The bacteria cell content was 2.5×10^5 cells in 18-h agar culture in 1 ml of medium containing a known quantity of the chemical.

The acute toxicity of the preparations was determined on randomly-bred white mice of both sexes (180 animals) by a single intraperitoneal injection [3]. The LD_{50} of the compounds is presented in Table 2, where it can be seen that these compounds are nontoxic.

The mutagenic activity was studied in epxeriments on lymphocyte cultures, bone marrow cells of mice of the CBA line, and indicator strains of *S. typhimurium* TA 1535, TA 1538, TA 98, and TA 100. Calculation of the chromosomal abberations in the cell cultures was carried out at the metaphase stage. The activity in the microbe tests was studied in direct contact experiments and with metabolic activation *in vitro* [4-6]. The positive controls used were nitrosomethylurea, cytophosphan (cyclophosphamide), diethylnitrosamine, and 2-acetaminofluorene.

Data were worked up using Student's T-test and the nonparametric criteria of Wilcoxon–Mann–Whitney.

Study of the antimicrobial activity of the β-hydroxyketones showed that compounds IV and VI did not possess bactericidal action. The highest antimicrobial activity was shown by preparations with one chlorine atom (compounds VII, X); replacement of the chlorine atom by bromine in the para-position, and introduction of a second and third chlorine atom into the aromatic and aliphatic radicals (compounds I, II, and V) lowered the antimicrobial activity.

The studied materials are of low toxicity: LD_{50} by single intraperitoneal injection ranged from 500 to 1500 mg/kg.

In experiments on themutagenic activity, it was established that compounds II, III, VII, and X showed weak mutagenic action. In doses of 100 to 1000 μg per dish, they increased the level of reversal 3-5 times in strains TA 1535 and TA 100. The effect was observed in direct contact experiments and in experiments with metabolic activation *in vitro*.

The methods used for evaluation of mutagenic activity varied with the differences in sensitivity, so they focused on different types of mutations.

Analysis of the results obtained in tests of the mutagenic activity of the β-hydroxyketones II, III, VII, and VIII show that the indicated preparations produced an authentic increase in the percent aberration in cells of the bone marrow (Cf. Table 3).

Comparative analysis of the results of the study of the antimicrobial and mutagenic properties of these β-hydroxyketones indicates that the antibacterial activity is correlated with the mutagenic effect for compounds II, VII, VIII, and X (single manifestation of two effects).

The data obtained in this study of antimicrobial and mutagenic activity and toxicity indicate the advisability of further study of compounds in the β-hydroxyketone series.

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