SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF METHYL AND PHENYL DIARYLMETHYL KETONES

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A known method for preparing methyl diarylmethyl ketones is treatment of α-halo-α-phenylacetone with benzene or its homologs in the presence of $AlCl_3$ [1]. The disadvantage of this method is the use of α-chloro-α-phenylacetone, which is a lacrimator that causes unfavorable conditions for the production. We have developed a synthesis of ketones (I-VIII) based on the reaction of arylmagnesium bromides with esters of α-hydroxy acids, followed by addition of ethyl formate or acetyl chloride to the reaction mixture.

$$RCH(OH)COOEt \xrightarrow{ArMgBr} RCOCHAr_2$$

I — VIII

R = Me (I — IV), Ph (V — VIII); Ar = Ph (VIII), C_6H_4Cl-4 (II), C_6H_4OMe-4 (III), C_6H_4OEt-4 (IV), C_6H_4OPr-2 (V), C_6H_4Me-3 (VI), C_6H_4OMe-2 (VII)

Ketones I-VIII are colorless crystalline substances or odorless liquids, which are stable on storage, soluble in DMSO, CCl_4, and alcohol, and insoluble in water (see Table 1).

Stretching vibrations of the carbonyl groups appear at 1730-1680 cm^{-1} in the IR spectra of the ketones taken in a thin layer. There is a singlet of a methine proton in the 4.75-5.77 ppm region in the PMR spectra.

The ketones synthesized were tested for antimicrobial activity.

EXPERIMENTAL (CHEMICAL)

The IR spectra were recorded on a UR-20 spectrophotometer with LiF and NaCl prisms, and the PMR spectra on a Tesla BS-487 c spectrometer (working frequency 80 MHz) for 10% solutions in CCl_4 (internal standard HMDS).

General Method of Preparation of Ketones. A 0.1 mole portion of propyl lactate or 0.1 mole of ethyl mandelate dissolved in ether is added to 0.3 mole of arylmagnesium bromide in ether. After 2 h warming, ethyl formate or AcCl (0.2 mole in each case) is added to the reaction mixture, and the mixture is heated for 2 more h (if ethyl formate is used) or 4 h (if AcCl is added). The subsequent hydrolysis is carried out in 10% HCl. The ether layer is separated from the aqueous layer, washed with a solution of sodium carbonate and water, and dried over Na_2SO_4; after distillation of the solvent, the reaction product is distilled or recrystallized from alcohol.

EXPERIMENTAL (BIOLOGICAL)

The antimicrobial activity of the compounds with respect to *Escherichia coli* (*E. Coli*, strain M-17) and *Staphylococcus aureus* (*S. aureus*, strain 209P) [2], was studied by the method of double serial dilutions in meat peptone broth. The microbial load of the bacteria was $2.5 \cdot 10^5$ cells of an 18 h agar culture in 1 ml of medium containing a given amount of the chemical compound.

The acute toxicity of the preparations was determined on nonpedigree white mice (100 animals) of both sexes with a single intraperitoneal administration.

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TABLE 1. Properties of Ketones I-VIII

Compound	Yield, %	mp, °C	Found, %		Empirical formula	Calculated, %	
			C	H		C	H
I	80	60—1	85,61	6,83	$C_{15}H_{14}O$	85,68	6,71
II	64	184—6/4*	64,70	4,45	$C_{15}H_{12}OCl_2$	64,53	4,33
III	65	69—70	75,4	6,59	$C_{17}H_{18}O_3$	75,53	6,71
IV	71	71—2	76,28	7,51	$C_{19}H_{22}O_3$	76,48	7,43
V	45	148—9	79,95	7,25	$C_{26}H_{28}O_3$	80,38	7,26
VI	59	91—2	87,67	7,01	$C_{22}H_{20}O$	87,96	6,71
VII	40	103—4	79,55	6,12	$C_{22}H_{20}O_3$	79,49	6,06
VIII	66	139—40	88,65	6,19	$C_{20}H_{16}O$	88,20	5,92

*Boiling point is given.

TABLE 2. Antimicrobial Activity of Ketones

Compound	Minimal bacteriostatic concentration, μg/ml		Minimal bactericidal concentration, μg/ml	
	E. coli M-17	S. aureus 209P	E. coli M-17	S. aureus 209P
I	200	50	>200	100
II	25	0,78	200	12,5
III	>200	100	>200	200
IV	—	—	—	—
V	>200	100	>200	200
VI	200	50	>200	200
VII	—	—	—	—
VIII	>200	100	>200	>200

The studies on the antimicrobial activity showed (Table 2) that compounds IV and VIII have no bactericidal action. Compound II has a high activity with respect to *Staphylococcus*. Replacement of a chlorine atom in the benzene ring by a hydrogen atom or an alkoxy radical (compounds I, III, IV) lowers the antimicrobial activity of the ketones. The introduction of a third benzene ring into the molecule of the compounds leads to a still greater decrease in the activity of this group of compounds (V-VIII).

The preparations studied belong to a group of slightly toxic compounds (LD_{50} at a single intraperitoneal administration is 500-1500 mg/kg).

LITERATURE CITED

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