SYNTHESIS AND ANTIMICROBIAL ACTION OF AMINOKETONES

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UDC 615.276.212.3:547.572.1

The wide distribution of resistance to many antibiotics and chemical preparations among the pathogens of infectious diseases renders very urgent the search for chemotherapeutic agents, particularly in the series of aminoketones and their salts. With the object of the further (cf. [1-4]) determination of the dependence of the structure–biological activity of aminoketones, we synthesized a series of hydrogen halides of aminoketones (I)-(VII) (Table 1) and carried out the study of their antibacterial action in relation to five reference strains of Gram-positive and Gram-negative microorganisms (Table 2).

EXPERIMENTAL (CHEMICAL)

The melting temperature was determined on a "Boetius" stage (GDR) (Table 1). The PMR spectra were taken on a Tesla-13S 487 instrument.

General Method for the Isolation of the Hydrochlorides of Substituted α-Imidazolylacetophenones (I)-(V). The mixture of 0.02 mole of the corresponding substituted α-bromoacetophenone and 0.04 mole of imidazole in 50 ml of acetone was kept for approximately 12 h. The solvent was then distilled off, and 50 ml of water were added to the residue. The undissolved residue, representing α-imidazolylacetophenone, was separated, dried, and again dissolved in acetone prior to the addition of an equivalent of HCl. The precipitated residue of (I)-(V) was separated, dissolved in alcohol, and precipitated with ether.

1-Methyl-3-phenacylimidazolyl Bromide (VI). The mixture of 0.02 mole of α-bromoacetophenone and 0.02 mole of N-methylimidazole in 100 ml of benzene was held for approximately 12 h. The precipitated residue was separated, washed with acetone, and dried.

β-Imidazolylpropiophenone Hydrochloride (VII). The mixture of 0.02 mole of α-bromopropiophenone and 0.04 mole of imidazole in 50 ml of acetone was kept for approximately 20 h. The further separation of the product was accomplished as described for the compounds (I)-(V).

EXPERIMENTAL (BIOLOGICAL)

The antimicrobial action of the compounds obtained was studied by the method of serial dilutions according to the generally accepted method presented in the instructions of the Ministry of Public Health of the USSR: "On the unification of methods for the determination of the sensitivity of microorganisms to chemotherapeutic preparations."

The majority of the preparations tested [besides (IV) and (V)] was soluble in water. The substances insoluble in water were dissolved in the nutrient medium with the addition of DMSO.

It can be seen from the data presented in Table 2 that some compounds show a marked bacteriostatic action toward both the Gram-positive and the Gram-negative microorganisms. The most active compounds proved to be (II) and (III), which acted bacteriostatically on four bacterial cultures, and also possessed the bactericidal characteristic at higher concentrations. Compound (IV) acted on two cultures, and compounds (V) and (VII) acted on one. Consequently, the introduction of the methyl group of (II) and the chlorine atom of (III) at the position 4 of the benzene ring of α-imidazolylacetophenone hydrochloride (I) increases the activity of the compound significantly. The further increase in the number of the methyl groups in the benzene ring of compound (II) – the substance (IV) – leads to a decrease in the activity. Other variations in the structure of the aminoketone did not give significant changes in the activity of the aminoketones obtained. Thus, the introduction of the methyl

Institute of Physicoorganic Chemistry and Carbon Chemistry, Academy of Sciences of the Ukrainian SSR, Donetsk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 10, pp. 1232-1234, October, 1989. Original article submitted October 11, 1988.

0091-150X/89/2310-0847$12.50

TABLE 1. Characteristics of the Synthesized Aminoketones (I)-(VII)

Compound	Name	Yield, %	mp, °C	Empirical formula†	PMR spectra in CF_3COOH, chemical shifts, ppm			
					CH_2	CH_2	Br	imidazolyl
I	α-Imidazolylacetophenone hydrochloride	80	142—143	$C_{11}H_{11}ClN_2O$	—	6,00s	7,50—7,83 m	8,00s, 8,10s; 8,80 s
II	α-Imidazolyl-(4-methylacetophenone) hydrochloride	83	105—130 with decomp.	$C_{12}H_{13}ClN_2O$	2,53s	6,01 s	7,41—7,50 m	7,93s; 8,03s; 8,81 s
III	α-Imidazolyl-(4-chloroacetophenone) hydrochloride	84	194—207 with decomp.	$C_{11}H_{10}Cl_2N_2O$	—	5,98 s	7,53—7,64 m	7,96 s; 8,06s, 8,81 s
IV	α-Imidazolyl-(2,4,6-trimethylacetophenone) hydrochloride	90	240—255 with decomp.	$C_{14}H_{17}ClN_2O$	2,31s	5,60 s	7,03 s	7,51 s; 7,63 s, 8,91 s
V	α-Imidazolyl-(4-nitroacetophenone) hydrochloride	93	211—216 with decomp.	$C_{11}H_{10}ClN_3O_3$	—	6,09 s	8,25—8,56 s	7,58d; 8,89 s
VI*	1-Methyl-3-phenacylimidazolyl bromide	85	114—120	$C_{12}H_{13}BrN_2O$	3,80s	5,77 s	7,22—7,52 m	7,70 s, 7,90 s, 8,50s
VII	β-Imidazolylpropiophenone hydrochloride	90	174—176	$C_{12}H_{13}ClN_2O$	—	3,88 t; 4,88 t	7,50—7,78 m	7,96s; 8,08 s; 8,93s

*Described by us in [5].

†The data of the elemental analysis satisfy the calculated values.

TABLE 2. Antimicrobial Activity of the Aminoketones (I)-(VII)

Compound	Antibacterial activity of (I)-(VII)									
	St. aureus № 56		S. typhimurium 353		E. coli M-17		B. anthracoides		Ps. aeruginosa	
	MIC, μg/ml	MBcC, μg/ml	MIC, μg/ml	MBcC, μg/ml	MIC, μg/ml	MBcC, μg/ml	MIC, μg/ml	MBcC, μg/ml	MIC, μg/ml	MBcC, μg/ml
I	>500	>500	500	>500	250	>500	>500	>500	>500	>500
II	4	500	16	64	125	500	32	>500	>500	>500
III	16	500	8	64	125	500	32	>500	>500	>500
IV	64	>500	125	>500	250	>500	250	>500	>500	>500
V	64	>500	500	>500	250	>500	250	>500	>500	>500
VI	500	>500	500	>500	250	>500	500	>500	>500	>500
VII	125	>500	>500	>500	>500	>500	>500	>500	>500-	<500

group into the imidazole fragment in (VI) and the nitro group into the benzene ring of (V), and the increase in the separation of the carbonyl group and the imidazole fragment by the CH_2 unit in (VII) do not lead to a noticeable increase of activity.

Therefore, it can be concluded on the basis of the data presented that the bacteriostatic properties of the aminoketones investigated are basically determined by the structure of the aryl fragment of the aminoketone molecule. The utilization of the investigated aminoketones as analogs in the further search for new antibacterial preparations is of interest.

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SYNTHESIS AND ANTIALLERGIC ACTIVITY OF 7-SUBSTITUTED THEOPHYLLINE DERIVATIVES

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UDC 615.31:547.288.4.012.1

The search for preparations for the treatment of allergic reactions is developing in the direction of creating materials selectively influencing the different stages of the allergic reaction, such as immunomodulators, preparations of the type of Intal (cromolyn), inhibiting the release of mediators of allergin from the fat cells and basophilic leucocytes, as well as antagonists of H_1-histaminic receptors and others.

Effective application in medical practice of preparations of Ketotifen [synonym for zaditen; 4,9-dihydro-4-(1-piperidinylidine)-10H-benzo(4,5)cycloheptal(1,2-6-thiophen-1-on-oxyfumarate)] and preparations of Oksatomid {1-[3,4-(diphenylmethyl)-1-piperazinylpropyl]-1,3-dihydro-2H-benzimidazol-2-one}, the pharmaceutical spectra of which combine the properties of Intal and blockers of the H_1-histaminic receptor, increased the interest to create preparations with a polyfunctional mechanism of action.

Theophylline, which is widely used in therapy for allergic bronchial asthma, possesses a polyfunctional mechanism: it shows spasmolytic, bronchial dilating action, and, in addition, inhibits the release of mediators of allergy. We have shown earlier that several 7,8-substituted theophyllines [1] exceed theophylline in their inhibitory influence on the release of mediators but not in their broncholytic (antihistaminic) activity. In continuing these studies we synthesized 12 original 7-substituted theophyllines (I and II) and studied their characteristic pharmacological properties as well as their bronchiodilating (antihistaminic) activity, antianaphylactic action, and toxicity upon single injection.

Compound I was synthesized from 7-cyanoalkyltheophylline II through the intermediate iminoester (III), which was obtained by the action of gaseous HCl on a suspension of 7-cyanoalkyltheophylline II in a mixture of dichloroethane and alcohol. It should be noted that, for successful formation of IIIa and IIIb the temperature of the reaction mass was 22-25°C; it was 40-45°C for IIIc. The iminoesters III were used after drying without purification.

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 10, pp. 1235-1237, October, 1989. Original article submitted December 8, 1988.

0091-150X/89/2310-0849$12.50