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SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF METABOLITES OF 4-(3-DIMETHYLAMINO-PROPIONYL)-1,2-DIMETHOXYBENZENE

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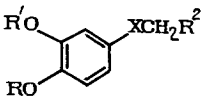
The compound 4-(3-dimethylaminopropionyl)-1,2-dimethoxybenzene (I) shows high antiinflammatory activity (AIA) and has low toxicity [1]. With the object of studying the dependence between the chemical structure and the AIA, as well as seeking new medicinal agents, we investigated the biotransformation of the aminoketone (I) in the rabbit organism and the AIA of its metabolites (II)-(IV), (VIII), and (IX).



I–IX

I–IX: X =CO (I–VIII), CHOH (IX).

I–VI, IX: R^2=H (V, VI), CH_2NMe_2(I–IV,IX);

R=R^1=H (IV), Me(I, IX); R = Me, R^1 = H(II, V): R = H, R^1 = Me(III, VI).

VII, VIII: R = R^1 =Me; R^2 = CH_2Cl (VII), CH_2NHMe (VIII).

The hydrochlorides of the aminoketones (II) and (III) were synthesized by the Mannich reaction using the interaction of the corresponding ketones (V) and (VI) with the formaldehyde and dimethylamine hydrochloride in the solution of 2-propanol. The aminoketone (VIII) was obtained by the action of methylamine on the chloroketone (VII) in benzene solution, and the reduction of the aminoketone (I) with sodium borohydride in methanol gave the aminoalcohol (IX).

The characteristics of the new compounds (II), (III), (VIII), and (IX) synthesized are presented in Table 1.

The structure of the compounds synthesized was confirmed by the data of the PMR spectra (Table 2). In the IR spectra of the aminoketones (II), (III), and (VIII), the stretching vibrations of the carbonyl group appear in the region of 1670-1680 cm^{-1}, and the bands of the hydroxyl group in the spectra of the compounds (II), (III), and (IX) are contained in the region of 3330-3590 cm^{-1}. The UV spectra of the aminoketones (II), (III), and (VIII) are mutually similar and differ from the spectrum of the aminoalcohol (IX), not having absorption bands in the region above 300 nm (see Table 1).

The compounds (IV) [2], (V) and (VI) [3], and (VII) [4] were described previously.

EXPERIMENTAL (CHEMICAL)

The UV spectra were taken on a Specord M40 instrument (Germany) in 95% ethanol. The IR spectra were taken on Specord M80 instrument (Germany) in mineral oil. The PMR spectra were taken on a Tesla BS-487C instrument (Czech Republic, 80 MHz) in deuteromethanol, using TMS as the internal standard.

The characteristics and yields of the new compounds synthesized are presented in the Tables 1 and 2. The values found for the elemental analyses correspond with the calculated values.

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TABLE 1. Characteristics of the New Hydrochlorides of the Compounds (II), (III), (VIII), and (IX) Synthesized

Compound	Yield, %	mp, °C (solvent)	UV spectrum		IR spectrum, ν_{max}, cm^{-1}	Empirical formula
			λ_{max}, nm	log ε		
II	84	183-5	228	3,99	1672(C=O)	$C_{12}H_{17}NO_3 \cdot HCl$
		(2-propanol)	287	3,68	3328 (OH)	
			319	3,65		
III	91	172-4	234	4,17	1680 (C=O)	$C_{12}H_{17}NO_3 \cdot HCl$
		(2-propanol)	282	4,02	3587 (OH)	
			308	3,97		
VIII	44	180-2	230	4,47	1676 (C=O)	$C_{12}H_{17}NO_3 \cdot HCl$
		(2-propanol–acetone, 1:1)	276	4,25		
			305	4,17		
IX	80	130-1	232	4,03	3545 (OH)	$C_{13}H_{21}NO_3 \cdot HCl$
		(2-propanol–acetone, 1;1)	277	3,88		

TABLE 2. PMR Spectral Data (δ, ppm) of the Hydrochlorides of the Compounds (II), (III), (VIII), and (IX)

Compound	CH_2CH_2 CH	CH_3N CH_3O	3-H 5-H 6-H
II	3,57 s	2,98 s	7,46 d[a]
		3,97 s	7,62 dd[a,b]
			7,31 d[b]
III	3,58 s	2,99 s	7,60 d[a]
		3,94 s	7,65 dd[a,b]
			6,90 d[b]
VIII	3,35-3,54 m	2,80 s	7,59 d[a]
		3,92 s	7,75 dd[a,b]
		3,95 s	7,10 d[b]
IX	1,85-1,94 m	2,90 s	6,92 s
	3,18-3,49 m	3,81 s	
	4,26-4,45 m	3,85 s	

[a] J = 2 Hz
[b] J = 9 Hz

Hydrochlorides of 2-Hydroxy-4-(3-dimethylaminopropionyl)-1-methoxybenzene (II) and 1-Hydroxy-4-(3-dimethylaminopropionyl)-2-methoxybenzene (III). The mixture of 35 ml of 2-propanol, 5.0 g (30 mmole) of the ketone (V) or (VI), 2.6 g (32 mmole) of dimethylamine hydrochloride, 2.7 g (90 mmole) of paraformaldehyde (trihydroxymethylene), and 0.1 ml (1 mmole) of concentrated HCl is boiled for 5 h. The mixture is cooled to 0°C, and the resulting residue of the hydrochloride (II) or (III) is filtered off.

Hydrochloride of 4-(3-Methylaminopropionyl)-1,2-dimethoxybenzene (VIII). The solution of 4.0 g (25 mmole) of the chloroketone (VII) and 2.0 g (65 mmole) of methylamine in 50 ml of dry benzene is maintained for 7 days at 20°C prior to the washing with a saturated aqueous solution of sodium carbonate. The mixture is concentrated *in vacuo*, and the residue is dissolved in 25 ml of acetone. Dry HCl gas is passed into the solution, and the residue of the hydrochloride (VIII) is filtered off.

Hydrochloride of 4-(1-Hydroxy-3-dimethylaminopropyl)-1,2-dimethoxybenzene (IX). The hydrochloride of the aminoketone (I) (3.0 g, 11 mmole) is dissolved in 30 ml of methanol. Sodium borohydride (0.64 g, 16 mmole) is added in small portions with stirring at 2-5°C, and the mixture is stirred for 3 h more at 20°C. The mixture is concentrated *in vacuo*, and the residue is dissolved in benzene. The solution is washed with a saturated aqueous solution of sodium carbonate, and it is concentrated *in vacuo*. The residue is dissolved in 20 ml of acetone. Dry HCl gas is passed into the solution, and the residue of the hydrochloride (IX) is filtered off.

EXPERIMENTAL (PHARMACOLOGICAL)

The investigated compounds (hydrochlorides) were introduced sc in the form of the 1% solution in the sterile 0.9% aqueous solution of sodium chloride. Male mice of the line BALB/c having the mass 18-22 g, male rats of the Wistar line having the mass 180-220 g, and rabbits of the chinchilla breed of both sexes having the mass of 2.5-3.5 kg were utilized.

TABLE 3. AIA and Acute Toxicity of the Hydrochlorides (I)-(IV), (VIII), and (IX) with the sc method of Introduction

Compound	Inhibition of inflammation (by comparison with the control), ED_{50}, mg/kg		LD_{50}, mg/kg
	carragenin edema	bentonite edema	
I	37.2	40.3	541 (492-583)
II	27.3	17.6	253 (238-269)
III	40.0	22.0	26.6 (23.2-30.1)
IV	47.6	29.8	1596 (1492-1689)
VIII	57.2	60.4	332 (296-362)
IX	Inactive	Inactive	1632 (1390-1815)
LAS	150	130	1000 (890-1130)
Voltaren	11.5	11.0	208 (165-262)

Note. Limits of variations are shown in brackets for the $p \leq 0.05$.

Acute toxicity for mice was determined by the method of Litchfield and Wilcoxon, modified by Roth [5]. The AIA was studied using models of experimental carragenin [6] and bentonite [7] edema of the foot of the rat. The Table 3 presents values of the ED_{50} for the decrease in the edema (by comparison with the control), measured at 1, 2, 3, and 5 h after the introduction of the investigated compounds.

The biotransformation of the aminoketone (I) was studied in rabbits using the investigation of the composition of the urine collected in the course of 2 days (until the cessation of the elimination of metabolites) after the single sc introduction of the hydrochloride (I) at the dose of 54 mg/kg (0.1 LD_{50} for mice), and incubated with β-glucuronidase–arylsulfatase at 37°C and the pH 5 for 1 day [8] prior to acidification with HCl to the pH 1, the extraction with ether to remove natural metabolites, and neutralization with NaOH to the pH 7. The method of TLC on plates of Alufol (Germany) led to the identification of six compounds which are not natural metabolites. The R_f values (the development in iodine vapor) indicated are as follows: 0.35 (III) and 0.50 (II) in the 3:1:1 system of ethanol–benzene–concentrated NH_4OH, and 0.51 (IV) and 0.71 (II, III) in the 10:1 system of ethanol–concentrated NH_4OH. The urine was then rendered alkaline with NaOH to the pH 10 and extracted with ether. The compounds (VIII), (IX), and (I), with the corresponding R_f values of 0.41, 0.51, and 0.64 in the 10:1 system of ethanol–concentrated NH_4OH, were identified in the concentrated ether extract by the same method. The compounds (II) and (IX) are the main metabolites. Compound (VIII) was detected in a small amount, and the compounds (III) and (IV) were identified in the form of traces.

It was established that the aminoketone (I), which undergoes reduction in the rabbit organism, forms the aminoalcohol (IX) of low toxicity which does not show AIA. When (I) is subjected to O- or N-dealkylation, it forms the aminoketones (II)-(IV) or correspondingly (VIII) which do not differ significantly in their AIAs from the initial compound (I), but they are more toxic with the exception of the aminoketone (IV) which is threefold less toxic than the compound (I). The methylaminoketone (VIII) is less active and more toxic by comparison with the dimethyl analog (I). The most active new compound – the metabolite (II) – surpasses the aminoketone (I) in its AIA by an average of twofold, and surpasses lysine acetylsalicylate (LAS) by sixfold, but it is inferior to voltaren by twofold, being somewhat less toxic than voltaren but more toxic than compound (I) (by twofold) and LAS (by fourfold) (see Table 3).

The directions established for the biotransformation of the aminoketone (I) correspond with those for the previously investigated β-dialkylaminoketones [9].

The investigation carried out shows the promise of the search for new antiinflammatory agents among aminoketones of the type considered.

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