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SYNTHESIS AND ANTI-INFLAMMATORY ACTIVITY OF 1-ALKYL-2-[3-DIMETHYLAMINOPROPIONYL]-4,5-DIMETHOXYBENZENES

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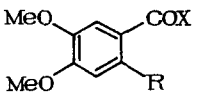
4-(3-Dimethylaminopropionyl)-1,2-dimethoxybenzene displays anti-inflammatory activity and has low toxicity [1]. In order to study the relationship between chemical structure and pharmacological properties and to search for new pharmaceutical preparations, we have synthesized and investigated new derivatives of the above aminoketone (IIa-c) that contain alkyl substituents in the aromatic ring.

Aminoketone hydrochlorides IIa-c were obtained by means of the Mannich reaction from the interaction between the appropriate ketones (Ia-c), dimethylamine hydrochloride, and formaldehyde.



I a-c, *II* a-c

I, *II*: X = Me (*I*), $CH_2CH_2NMe_2 \cdot HCl$ (*II*)

I a-c, *II* a-c: R = Me (a), Et (b), Bu (c)

Ketones Ia and Ib used initially have been described in earlier communications [2, 3], while the new ketone Ic was synthesized by acetylating 4-butyl-1,2-dimethoxybenzene [4] with acetyl chloride in the presence of anhydrous $SnCl_4$.

Physical properties and spectral data for the newly synthesized compounds Ic and IIa-c are shown in Tables 1 and 2. Elemental analysis data was in line with calculated values.

The structure of the synthesized substances was corroborated by UV, IR, and PMR spectral data. Similarities were seen in the UV spectra of compounds IIa-c, the UV absorption bands of aminoketone hydrochloride IIc being shifted somewhat toward the longwave region and being more intense than the corresponding UV bands of starting ketone Ic (see Table 1).

EXPERIMENTAL (CHEMICAL)

UV spectra were recorded on a Specord UV-VIS (Germany) in ethanol; IR spectra on a UR-20 instrument (Germany) in petroleum jelly; and PMR spectra on a Tesla BS-487C (Czechoslovakia, 80 MHz) in deuteromethanol, internal standard TMS.

1-Acetyl-2-butyl-4,5-dimethoxybenzene (Ic). A 135 g sample (0.5 mole) of anhydrous $SnCl_4$ was added at 20°C to a solution of 97 g (0.5 mole) of 4-butyl-1,2-dimethoxybenzene and 39 g (0.5 mole) of acetyl chloride in 400 ml of dry dichloroethane. After stirring for 3 h at 30-40°C, the mixture was cooled and poured out onto ice. The organic layer was separated off, washed with 10% HCl solution and water, dried over $MgSO_4$ and distilled.

1-Alkyl-2-(3-dimethylaminopropionyl)-4,5-dimethoxybenzene Hydrochlorides (IIa-c). A mixture of 50 mmoles of the corresponding ketone Ia-c, 2.3 g (75 mmoles) of paraform (trioxymethylene), 4.9 g (60 mmoles) of $Me_2NH \cdot HCl$, 30 ml

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TABLE 1. Physical Properties and Spectral Data of the Newly Synthesized Compounds

Compound	Yield, %	mp, °C	UV spectrum		IR spectrum, $\nu_{C=O}$, cm^{-1}	Empirical formula
			λ_{max}, nm	lg ε		
Ic	62	—	230	3,22	1670	$C_{14}H_{20}O_3$
			273	3,14		
			307	arm		
IIa	67	161—2	231	4,21	1680	$C_{14}H_{21}NO_3 \cdot HCl$
			276	3,90		
			312	3,72		
IIb	56	172—3	232	4,31	1680	$C_{15}H_{23}NO_3 \cdot HCl$
			277	3,97		
			310	3,79		
IIc	52	63—4	231	4,15	1660	$C_{17}H_{27}NO_3 \cdot HCl$
			276	3,79		
			310	3,63		

Note. Compound Ic had a bp of 144-145°C at 1 mm Hg, n_D^{20} 1.5429.

TABLE 2. PMR Spectral Data (δ, ppm) for Compounds Ic and IIa-c

Compound	CH_2 CH_2Ar CH_3Ar	CH_2CH_2 $COCH_2CH_2N$	CH_3N CH_3CO (s)	CH_3O (s)	3-H 6-H (s)
Ic	0,86 t[a]	1,1—1,6 m	2,21	3,63	6,50[b]
	2,71 t[a]			3,68	7,04
IIa	2,45 s	3,84 s	2,86	3,80	6,79
					7,41
IIb	1,18 t[a]	3,50 s	2,88	3,83	6,83
	2,80 q[a]				7,40
IIc	0,89 t[a]	1,2—1,5 m	2,89	3,84	6,78
	2,64 t[a]	3,49 s			7,36

[a] J = 6 Hz.

[b] In CCl_4 solution.

of ethanol and 0.1 ml of concentrated HCl was boiled for 10 h, cooled to 0°C, and the resultant precipitate was recrystallized from 2-propanol.

EXPERIMENTAL (PHARMACOLOGICAL)

The test compounds were injected subcutaneously as 1% aqueous solutions into male BALB/c line mice weighing 18-22 g and male Wistar line rats weighing 150-220 g.

Toxicity in the case of the mice was determined using a modified Litchfield and Wilkinson method [5]. Anti-inflammatory activity was investigated using the following models: carragenin-induced edema [6], bentonite edema [7], and traumatic edema [8] of the rat's paw. Table 3 shows the mean arithmetic values of percentage reduction in edema (compared to the control), measured 1, 2, 3, and 5 hours after administration of the test compounds, and graphically calculated values of ED_{50}, the dosage causing a 50% reduction in the edema. Each of the 5 dosages of the test compounds was administered to groups of 10 animals.

It was found that aminoketones IIa-c were of low toxicity. In terms of their anti-inflammatory activity they were superior to 4-(3-dimethylaminopropionyl)-1,2-dimethoxybenzene [1] (the structural analogue without alkyl substituents in the ring) and significantly superior to lysine acetylsalicylate (LAS, water-soluble aspirin). The most active compound, namely ethyl derivative IIb, proved considerably superior to LAS in terms of anti-exudative effect (studied using mice with peritonitis induced by intraperitoneal injection of acetic acid [9]) with ED_{50} values of 64 and 185 mg/kg, respectively. It also surpassed LAS as regards

TABLE 3. Toxicity and Anti-Inflammatory Activity of Compounds IIa-c for Hypodermic Injection

Compound (50 mg/kg dose)	LD_{50}, mg/kg	Mean inflammation inhibition percentage (compared to the control)		
		C	B	T
IIa	311 (276—346)	74,0	57,4	58,4
IIb	369 (357—393)	69,0 45,8*	53,0 29,7*	72,2 38,0*
IIc	328 (276—354)	52,2	41,9	50,6
LAS	1000 (890—1130)	22,4 150*	8,6 130*	10,1 102*

Notes. Median lethal dose fluctuation range for $p < 0.05$ is shown in brackets. C) Carragenin-induced paw edema; B) bentonite edema; T) traumatic edema. *) ED_{50}, mg/kg.

analgesic activity, investigated using a model of spasms induced by acetic acid in mice [10] (ED_{50} of 131 and 320 mg/kg, respectively), and in terms of antipyretic effect for hyperthermia induced by hypodermic injections of baker's yeast suspensions in rats [9] (ED_{50} of 12 and 38 mg/kg, respectively, when determining doses causing a 1°C reduction in the rectal temperature).

It is clear from these investigations that it is worthwhile pursuing the search for new medicinal preparations among aminoketones of this type.

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