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SYNTHESIS AND ANTIINFLAMMATORY ACTIVITY OF 5-HALO-1-(3-DIMETHYLAMINOPROPIONYL)-2,3-DIMETHOXYBENZENES

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Among halogen substituted 3-dimethylaminopropionyl derivatives of 1,2-dimethoxybenzene [3] are found compounds that have antiinflammatory activity. In connection with this we have synthesized and studied the hydrochlorides of hitherto unknown 5-halo-1-(3-dimethylaminopropionyl)-2,3-dimethoxybenzenes (IVa, b).

Alcohols IIa, b, prepared by reaction of aldehydes Ia, b [2] with MeMgI, were oxidized with CrO_3 to ketones IIIa, b, which were reacted with $Me_2NH \cdot HCl$ to yield ketones IVa, b.

$$\underset{\text{Ia, b}}{ArCHO} \longrightarrow \underset{\text{IIa, b}}{ArCHOHCH_3} \longrightarrow \underset{\text{IIIa, b}}{ArCOCH_3} \longrightarrow \underset{\text{IVa, b}}{ArCOCH_2CH_2NMe_2 \cdot HCl}$$

$Ar = C_6H_2(OMe)_2\text{-}2,3\text{-}X\text{-}5$; X = Br (a), Cl (b).

In the UV spectra of chloro derivatives IIb-IVb the absorption bands are shifted to the long-wave side in comparison with the corresponding bands of bromo derivatives IIa-IVa.

EXPERIMENTAL CHEMICAL

UV spectra were taken on a Specord UV-VIS spectrometer (GDR) in ethanol. IR spectra were recorded on a UR-20 spectrometer (GDR) in paraffin oil. PMR spectra were taken on a Tesla BS-487C instrument (Czechoslovakia) at 80 MHz, using TMS as internal standard.

Characteristics and yields of the novel compounds synthesized are listed in Table 1.

5-Halo-1-(1-hydroxyethyl)-2,3-dimethoxybenzenes (IIa, b). A solution of 0.12 mole of aldehyde Ia, b [2] in a mixture of 200 ml of dry ether and 10 ml of dry benzene is added dropwise to a solution of MeMgI, prepared from 3.6 g (0.15 mole) of metallic Mg and 21.3 g (0.15 mole) of MeI. The mixture is refluxed with stirring for 6 h and cooled. After addition of 100 ml of 10% HCl it is filtered, the ethereal layer is separated, and the aqueous layer is extracted with ether. The ethereal extract is washed with water, $NaHCO_3$, and water, and dried over Na_2SO_4. The ether is evaporated and the residue is filtered through a column with a diameter of 3 cm filled with silica gel (15 g of silica gel per gram of compound). The column is washed out with a mixture of $CHCl_3$ and ethyl acetate (9:1) and the fraction with R_f 0.45-050 (Silufol, Czechoslovakia) is collected. Evaporation of that fraction yields compounds IIa, b, which on distillation under a vacuum of 1 mm decompose to a considerable extent.

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TABLE 1. Compounds IIa, b, IIIa, b, and IVa, b

Compound	Yield, %	mp, °C (n_D^{20})	UV spectrum		IR spectrum, ν C=O, cm⁻¹	PMR spectrum, δ, ppm				Found, %			Empirical formula	Calculated, %		
			λmax, nm	lg ε		OCH₃	ArH	other protons	solvent	C	H	Hal		C	H	Hal
II a	98	(1,5620)	220 280	sh 3,24	—	s 3,68 s 3,73	d* 6,75 d* 7,03	d ** 1,30 (CH_3) s 2,96 (OH) q ** 4,93 (CH)	CCl_4	46,0	5,1	30,9	$C_{10}H_{13}BrO_3$	46,0	5,0	30,6
II b	90	(1,5336)	225 283	3,92 3,25	—	s 3,80 s 3,85	d* 6,71 d* 6,96	d ** 1,40 (CH_3) s 2,15 (OH) q * 5,00 (CH)	CCl_4	55,2	5,9	16,0	$C_{10}H_{13}ClO_3$	55,4	6,0	16,4
III a	86	65—6	219 248 313	4,42 sh 3,39	1 670	s 3,78 s 3,80	d* 7,00 d* 7,19	s 2,48 ($COCH_3$)	CCl_4	46,4	4,5	30,6	$C_{10}H_{11}BrO_3$	46,4	4,3	30,8
III b	85	53—4	222 250 316	4,31 3,64 3,36	1 680	s 3,95 s 3,99	d* 7,00 d* 7,23	s 2,64 ($COCH_3$)	CCl_4	55,9	5,2	16,5	$C_{10}H_{11}ClO_3$	55,7	5,4	16,4
IV a	70	146—7	221 252 318	4,34 3,69 3,34	1 665	s 3,55 s 3,64	s 7,00 s 7,08	s 2,70 (NCH_3) s 3,28 (CH_2CH_2)	CD_3OD	44,4	5,4	32,7	$C_{13}H_{18}BrNO_3 \cdot HCl$	44,3	5,4	32,7
IV b	65	145—6	222 256 318	4,57 3,97 3,60	1 665	s 3,55 s 3,65	s 7,01 s 7,08	s 2,70 (NCH_3) s 3,30 (CH_2CH_2)	CD_3OD	50,8	6,3	23,1	$C_{13}H_{18}ClNO_3 \cdot HCl$	50,7	6,2	23,0

Notes. 1) ν_{OH} in the IR spectrum of IIa, b 3450 and 3400 cm^{-1}. 2) For compound IVa found %: N 4.0; calculated %: N 4.0. 3) For compund IVb found %: N 4.5; calculated %: N 4.5 4) Asterisk: J = 2-3 Hz; two asterisks: J = 6 Hz.

TABLE 2. Toxicity and Antiinflammatory Activity of Compounds IVa, b

Compound	LD_{50}, mg/kg	Dose, mg/kg	Percentage oppression of the inflammation caused by		
			carrageenin	bentonite	trauma
IV a	286 (253—311)	50	82,3	56,3	23,2
IV b	364 (312—396)	50	76,6	53,8	30,9
Lysine acetylsalicylate	1000 (890—1130)	50	22,4	8,6	10,1
		200	73,1	23,2	28,3

Note. In parentheses: limits of the fluctuations; the data are statistically reliable ($P < 0.05$).

1-Acetyl-5-halo-2,3-dimethoxybenzenes (IIIa, b). Six grams (0.06 mole) of Cr_2O_3 is added to a mixture of 9.5 g (0.12 mole) of dry pyridine and 150 ml of dry CH_2Cl_2. The mixture is shaken for 15 min and 0.01 mole of alcohols IIa, b, dissolved in the minimal volume of CH_2Cl_2, is added. The mixture is shaken vigorously several times, transferred to another flask, shaken for 15 min, and transferred to another flask. The first two flasks are washed with 50 ml of CH_2Cl_2, which is added to the reaction mixture. The mixture is extracted in turn three times with 100 ml of 5% NaOH, 100 ml of a saturated $NaHCO_3$ solution, and water, dried over Na_2SO_4, and concentrated. The residue is dissolved in ether and filtered, the filtrate is concentrated, and the residue is crystallized from a CCl_4–pentane mixture.

Hydrochlorides of 5-Halo-1-(3-dimethylaminopropionyl)2,3-dimethoxybenzenes (IVa, b). A mixture of 10 mmoles of ketones IIIa, b, 0.5 g (16 mmole) paraform, 1 g (12 mmole) of $Me_2NH \cdot HCl$, 10 ml of ethanol, and 0.1 ml of conc. HCl is refluxed for 10 h, concentrated to half the volume, cooled to 5°C, and the precipitate formed is crystallized from ethanol.

EXPERIMENTAL PHARMACOLOGICAL

The acute toxicity in white mice was determined by the method of Litchfield and Wilcoxon, modified by Roth [1]. The antiinflammatory activity was studied with the models of experimental carrageenin [6], bentonite [5], and traumatic [4] edemas of the foot of white rats. The compounds were administered subcutaneously as aqueous solutions. We used mongrel mice weighing 18-25 g and rats weighing 150-250 g of both sexes. In Table 2 are listed the average arithmetic values of the percentage decrease of the edema, measured 1, 2, 3, and 5 h after administering the compounds investigated.

Aminoketones IVa, b have low toxicity and their antiinflammatory activity surpasses that of lysine acetylsalicylate (water-soluble aspirin), but among them there are only minor differences in pharmacological parameters.

The investigations carried out open up new perspectives in the search for new antiinflammatory compounds among compounds of the type studied.

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