are to be taken into account in the search for active antiinflammatory preparations among derivatives of indolylacetic acid.

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SYNTHESIS AND DIURETIC ACTION OF SUBSTITUTED 2-BUTENOLIDES-4

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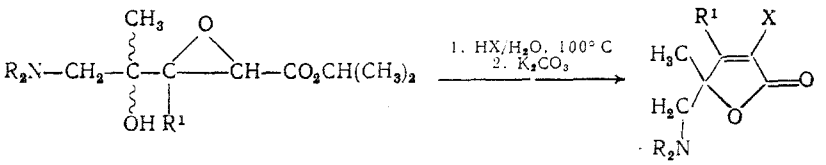
UDC 547.722.724:615.254.3-02:616.63

With the aim of finding new biologically active compounds in the series of functional-substituted unsaturated γ-lactones, we synthesized methyl- and phenyl-substituted 2-halogen-4-aminoethyl-2-butenolides-4 (VIIIa, b-XIVa, b) by heating, in an excess of hydrohalic acid, esters of the corresponding E-5-amino-4-hydroxy-2,3-epoxyvaleric acids (I-VII) obtained by the method we suggested earlier [3].



I — VII VIIIa, b — XIVa, b

HX = HCl, HBr; I, VIIIa,b: R = R′ = Me; II, IXa,b: R = Et, R′ = Me; III, Xa,b: 2R = $=-(CH_2)_4-$, R′ = Me; IV, XIa,b: 2R = $-(CH_2)_6-$, R′ = Me; V, XIIa,b: 2R = $=-(CH_2)_2O(CH_2)_2-$, R′ = Me; VI, XIIIa,b: R = Me, R′ = Ph: VII, XIVa,b. 2R = $=-(CH_2)_2O(CH_2)_2-$, R′ = Ph; VIIIa—XIVa: X = Cl; VIIIb — XIVb. X = Br.

The conversion of esters I-VIII into lactones VIIIa, b-XIVa, b probably takes place by means of a halogen hydride scission of the epoxy ring at the α-carbon lateral to the complex ester group, and by subsequent lactonation and dehydration.

The structure of butenolides VIIIa, b-XIVa, b was confirmed by spectral data as well as element analysis of both the free bases VIIIa, b-XIVa, b and their hydroxychlorides which were obtained in water-soluble forms for the study of biological activity. The IR spectra of compounds VIIIa, b-XIIa, b have a carbonyl group and C=C bond absorption band at 1775-1780 and 1650-1660 cm^{-1}, respectively. These are somewhat higher than the values characteristic of unsaturated γ-lactones, and might be attributed to the influence of the halogen in the α-position [2]. The indicated absorption bands in the spectra of the phenyl-substituted butenolide XIIIa, b and XIVa, b were observed at 1765 and 1633-1640 cm^{-1}. The significant variance in the chemical shifts of the methyl group protons that is characteristic of the PMR of lactones VIIIa, b-XIVa, b, is due to the double bond's descreening effect of the

Minsk Medical Institute. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 20, No. 10, pp. 1213-1216, October 1986. Original article submitted July 10, 1985.

TABLE 1. Properties of Synthesized Compounds

Compound	Yield, %	mp, °C	Found, %		Empirical formula	Calculated, %			Hydrochlorides	
			Hal	N		Hal	N	mp, °C	Cl*, % found	Cl*, % calculated
VIIIa	58	41—2	17,50	6,71	$C_9H_{14}ClNO_2$	17,41	6,87	192	14,59	14,76
VIIIb	58	51—2	32,21	5,70	$C_9H_{14}BrNO_2$	32,20	5,65	216	12,40	12,46
IXa	47	26	15,30	6,14	$C_{11}H_{18}ClNO_2$	15,29	6,04	171	13,35	13,22
IXb	31	37—8	29,15	5,18	$C_{11}H_{18}BrNO_2$	28,93	5,07	150—1	11,57	11,34
Xa	57	74	15,35	6,00	$C_{11}H_{16}ClNO_3$	15,43	6,09	201	13,51	13,32
Xb	59	78	29,30	4,87	$C_{11}H_{16}BrNO_2$	29,14	5.11	207	11,70	11,41
XIa	42	37	13,82	5,30	$C_{13}H_{20}ClNO_2$	13,75	5.43	187—8	12,03	12,05
XIb	40	62	26,35	4,53	$C_{13}H_{20}BrNO_2$	26,43	4,63	184—5	10,60	10,47
XIIa	54	47	14,60	5,54	$C_{11}H_{16}ClNO_3$	14,43	5,70	200	12,81	12,56
XIIb	73	50	27,80	4,75	$C_{11}H_{16}BrNO_3$	27,54	4,82	210	10,81	10,85
XIIIa	84	51—2	13,49	5,10	$C_{14}H_{16}ClNO_2$	13,13	5,27	185—6	11,91	11,73
XIIIb	76	92—3	25,60	4,63	$C_{14}H_{16}BrNO_2$	25,46	4,51	—	—	—
XIVa	75	86—7	11,75	4,35	$C_{16}H_{18}ClNO_3$	11,52	4,55	195—6	10,42	10,29
XIVb	70	94—5	22,84	4,02	$C_{16}H_{18}BrNO_3$	22,69	3,97	—	—	—

*Data given for mercurimetric assay of ion-bound chlorine.

3-CH_3 group. Thus, the spectrum of compound VIIIa contains singlets of methyl and N-dimethyl groups at 1.33, 2.00, and 2.20 ppm respectively as well as a quartet of the methylene group with doublet centers at 2.37 and 2.68 ppm (J_{hem} = 14 Hz).

EXPERIMENTAL CHEMICAL SECTION

The IR spectra were read on a Specord 75IR spectrophotometer, and the PMR spectra on a Tesla BS-467 instrument (60 MHz), HMDS was the internal standard. Data on the synthesized compounds are given in Table 1.

2-Chloro-3,4-dimethyl-4-dimethylaminomethyl-2-butenolide-4 (VIIIa). A solution of 7.35 g (0.03 mole) of ester I in 12.6 ml (0.15 mole) of concentrated HCl (d = 1.18) was boiled for 5 h, then saturated with HCl (gas) and boiled for 5 h more. The mixture was then treated with a potash solution and extracted with ether. The ether extracts were dried with Na_2SO_4. The ester was concentrated in a vacuum, and the residue was crystallized from a 10:1 hexane/isopropyl alcohol mixture. Yield 3.5 g of compound VIIIa.

Compounds VIIIa, b-XIXa, b were obtained in a similar fashion.

Hydrochlorides of butenolides VIIIa, b-XIVA, b were obtained by treating solutions of the corresponding bases in dry ether with HCl gas followed by crystallization from a 2:1 acetone/methanol mixture.

EXPERIMENTAL (PHARMACOLOGICAL SECTION)

The acute toxicity of the synthesized compounds was tested on white mice by the Dixon and Mood method [4]. The LD_{50} iv doses were determined for the animals.

The effect of the compounds on renal diuretic function was studied in water load tests on white rats weighing from 180-240 g. The water was administered through a gastric tube in an amount equal to 2.5% of the animals' body weight. The animals were placed into individual metabolism cages for the collection of urine. The amount of urine voided by each rat over a 3-h period was measured and expressed as a percentage of the water load. The diuretic action of the compounds under study was compared to the activity of the widely used diuretic furosemide (5 mg/kg intraabdominally) and urea (960 mg/kg) administered abdominally [1]. The compounds were administered to the rats intraabdominally at doses of 10 and 20% of the LD_{50} 15 min before the water load.

The experimental results showed that the index of acute toxicity, the LD_{50}, of the synthesized butenolide hydrochlorides VIIIa, b-XIVa, b fell in the iv dose range of 66.0-306.9 mg/kg (Table 2). As a whole, the compounds that had a chlorine atom (VIIIa, IXa, and XIIa) were found to be more toxic than the analogous compounds containing bromine (VIIIb, IXb, XIb, and XIIb). Brief (20-50 sec) tonic-clonic spasms were observed in the mice when

TABLE 2. Acute Toxicity and Diuretic Action of Synthesized Compounds

Compound	Acute toxicity for white mice LD_{50}, mg/kg iv	Diuretic action in white rats		
		intraabdominally administered dose of compounds, mg/kg	amount of urine voided in 3 h $(\bar{X}\pm S_{\bar{x}})$	effect, % of water load
	control	—	51,68±1,58	100
VIIIa	130,6 (111,2—153,5)	26,0	72,03±6,46*	139,36
VIIIb	278,6 (257,6—301,3)	55,7	91,29±2,66*	176,64
IXa	102,8 (95,1—111,2)	20,0	99,89±6,77*	193,28
		10,0	62,57±14,87	121,07
IXb	133,7 (127,9—139,6)	26,8	73,92±7,76*	143,03
Xb	197,2 (188,4—206,5)	39,4	73,32±2,49*	141,87
XIa	66,8 (61,7—72,4)	13,4	78,25±2,11*	151,41
		6,7	68,40±3,25*	132,35
XIb	82,2 (74,3—90,9)	16,4	79,54±10,44*	153,90
XIIa	250,0 (238,1—262,5)	50,0	94,17±1,41*	182,22
XIIb	306,9 (295,1—318,4)	61,4	70,15±5,60*	135,74
		30,7	57,29±11,86	110,85
XIIIa	129,4 (119,8—139,8)	12,9	72,35±1,27*	139,99
XIVa	238,0 (207,8—272,5)**	23,8	9,72±2,49*	18,81
Furosemide	. . .	5,0	108,67±10,83*	210,87
Urea	. . .	960,0	62,67±6,51*	121,26

*Statistically reliable changes ($P < 0.05$).
**Gastric administration.

the administered doses of the compounds under study approached the lethal levels. As a rule, the animals died 25-60 sec after respiratory arrest. In the case of compound VIIIb, they died 25-60 sec after initial cardiac arrest.

All of the examined compounds exhibited diuretic action when they were administered to rats intraabdominally at doses ranging from 10-20% of the LD_{50} (see Table 2). In these tests too, the compounds containing a chlorine atom were more active than those with a bromine atom. The most intensive diuresis was noted in rats following the administration of compounds IXa and XIIa which caused an increase in diuresis that was 82-93% greater than that in the control animals. The diuretic effect of the indicated compounds exceeded the diuretic action of urea, but was comparable to the action of furosemide when administered intraabdominally at a dose of 5 mg/kg, as recommended by many investigators.

Thus, the synthesized butenolide derivatives can be classified among the diuretics with moderate to low toxicity.

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