None of the compounds tested, of whatever structure, had any effects on nicotine convulsions or arecoline tremor, i.e., they had no central H- or M-cholinolytic activity.

These hydroxyindolylacetone derivatives have thus shown anticonvulsant activity in respect of antagonism to corazole and electroshock. Of these compounds, one (II) is superior to Zarontin in its anticonvulsant activity and protective index.

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SYNTHESIS AND LOCAL ANESTHETIC ACTIVITY OF 6-[α-AMINO-ω-PHENYLALKYL]CHROMANS

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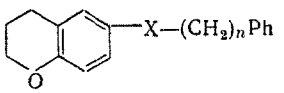
Local anesthetic activity is exhibited by the 6-(ω-amino-ω-phenylalkyl)-1,4-benzodioxanes [3]. Therefore, in order to investigate possible new local anesthetic agents we synthesized and studied previously unknown chroman derivatives whose structures are similar to the indicated derivatives of 1,4-benzodioxane.

We obtained the 4 (α-amine-ω-phenylalkyl)chromans (IIIa-d) by reducing sodium in an n-butanol solution of oximes (IIa-d) synthesized by reacting the previously known 6-(ω-phenylacyl)chromans (Ia-d) [2, 7, 9] with hydroxylamine HCl in a pyridine solution.



Ia-d, IIa-d, IIIa-d

Ia-d; X = C=O; IIa-d: X = C=NOH;
IIIa-d : X = CH—NH_2 a: $n = 0$; b $n = 1$, c: $n = 2$;
d : $n = 3$.

The IIIa-d amines were precipitated in the form of hydrochlorides. Inasmuch as the IIIc amine hydrochlorides turned out to be only slightly water soluble, we also obtained the amine lactates. However, the IIId amine lactate was also only slightly soluble.

Stretch vibrations of the HO-group in the IR spectra of all of the IIa-d oximes were manifested at 3250 cm^{-1}. However, the UV spectrum of the IIa oxime which has both aromatic rings conjugated with a C=NOH bond, was distinctive by a bathochromatic shift in the long-wave absorption band. There were no significant differences between the UV spectra of any of the IIIa-d amine hydrochlorides. The structure of the synthesized eompounds was confirmed by PMR spectral data (Table 1).

The IIIa-c chroman derivatives were found to exhibit the highest degree of local anesthesia activity, but they were also found to be more toxic and more irritating to the tissue than the known derivatives of 1,4-benzodioxane which have a similar structure [3].

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TABLE 1. Compounds IIa-d and IIIa-d

Compound	Yield, %	mp, °C (solvent)	UV spectrum λ_{max}, nm	UV spectrum log ε	PMR spectrum, δ, ppm	Found, % C	Found, % H	Found, % Cl	Found, % N	Empirical formula	Calculated, % C	Calculated, % H	Calculated, % Cl	Calculated, % N
IIa	92	145—6 ethanol	210 244 273	4,48 4,14 4,12	1,99 q (CH_2)[a], 2,72 t ($ArCH_2$)[a], 3,41 t (OCH_2)[a], 6,65 d (8-H)[b], 7,02—7,35 m (5,7-H), 7,30 s (C_6H_5), 9,12 s (OH)	75,68	6,00	—	5,33	$C_{16}N_{15}NO_2$	75,87	5,97	—	5,53
IIb	95	113—4 cyclohexane	212 268	4,52 4,20	1,92 q (CH_2)[a], 2,72 t ($ArCH_2$)[a], 4,07 s ($ArCH_2$), 4,07 t (OCH_2)[a], 6,57 d (8-H)[b], 7,05—7,32 m (ArH), 9,45 s (OH)	76,59	6,75	—	4,94	$C_{17}H_{17}NO_2$	76,38	6,41	—	5,24
IIc	94	90—1 cyclohexane	211 266	4,38 4,04	1,95 q (CH_2)[a], 2,71 t ($ArCH_2$)[a], 2,80—3,10 m (CH_2CH_2), 4,10 t (OCH_2)[a], 6,65 d (8-H)b, 7,00—7,35 m (ArH), 9,95 s (OH)	76,68	7,03	—	4,67	$C_{18}H_{19}NO_2$	76,84	6,81	—	4,98
IId	91	57—8 cyclohexane	212 265	4,43 4,08	1,67—2,05 m (CH_2), 2,45—2,80 m ($ArCH_2$, -C—CH_2), 4,10 t (OCH_2)[a], 6,59 d (8-H)[b], 6,96—7,10 m (5,7-H), 7,02 s (C_6H_5), 8,80 s (OH)	77,33	7,16	—	4,57	$C_{19}H_{21}NO_2$	77,26	7,17	—	4,74
IIIa	90	230—1 ethanol	210 237 285	4,49 4,08 3,37	1,77 t (CH_2)[a], 1,77 s (NH_2), 2,55 t ($ArCH_2$)[a], 3,92 t (OCH_2)[a], 4,85 s (NCH) 6,52 d (8-H)[b], 6,80 d (5-H)[c], 6,95—7,30 m (ArH)[d]	69,71	6,40	12,56	5,36	$C_{16}H_{17}NO$. HCl	69,68	6,58	12,85	5,08
IIIb	91	220—1 ethanol	209 233 281	4,39 4,01 3,32	1,76 s (NH_2), 1,82 q (CH_2)[a], 2,65 t ($ArCH_2$)[a], 2,70 d ($ArCH_2$)[a], 3,92 t (NCH)[a], 3,97 t (OCH_2)[a], 6,55 d (8-H)[b], 6,87 d (5-H)[c], 6,90—7,22 m (7-H), 7,07 s (C_6H_5)[d]	70,22	7,26	11,95	5,08	$C_{17}H_{19}NO$. HCl	70,46	6,96	12,23	4,83
IIIc	85	210—1 n-butanol	210 235 285	4,09 3,87 3,22	1,0—1,3 m (NH_2), 1,58—1,97 m (CH_2), 2,47 t ($ArCH_2$)[a], 2,57 t ($ArCH_2$)[a], 3,12—3,40 m (NCH), 3,92 t (OCH_2)[a], 6,57 d (8-H)[b], 6,72—7,30 m	70,86	7,50	11,91	4,65	$C_{18}H_{21}NO$. HCl	71,16	7,30	11,67	4,61
	—	141—2 acetone	—	—	(5,7-H), 7,17 s (C_6H_5)[d]	70,35	7,39	—	3,70	$C_{18}H_{21}NO$. $C_3H_6O_3$[a]	70,57	7,61	—	3,92
IIId	95	234—5 acetone	207 233 281	4,12 3,80 3,21	1,09 t (NH)[a], 1,55 t (NH)[a], 1,64—2,02 m (CH_2), 2,56 g ($ArCH_2$)[a], 3,14—3,47 m (NCH), 3,97 t (OCH_2)[a] 6,55[d] (8-H)[b], 6,85—7,22 m (5,7-H),	71,52	7,68	10,81	4,35	$C_{19}H_{23}NO$. HCl	71,79	7,60	11,15	4,40
	—	143—4 acetone	—	—	6,99 s (C_6H_5)[d]	71,02	7,98	—	3,84	$C_{19}H_{23}NO$. $C_3H_6O_3$[a]	71,13	7,87	—	3,77

Note. [a]J = 6 Hz, [b]J = 9 Hz, [c]J = 2 Hz. [d]Free base. [e]Lactate.

TABLE 2. Acute Toxicity, Local Anesthetic Action, and Local Irritant Action of IIIa, b Amine Hydrochlorides and IIIc Amine Lactate

Compound	LD_{50}, mg/kg	Infiltration anesthesia	Surface anesthesia	Conduction anesthesia			Local irritant action		
				minimum concentration for blocking nerve conductivity, mM	time required to reduce action potential to 50% of 10 mM solution, min	time required to reduce action potential from 50 to 100% of 10 mM solution, min	degree of irritation by a 1% solution	average tissue-irritating concentration, %	threshold tissue-irritating concentration, %
IIIa	226 (189 — 270)	1,9	0	0,05	6,5	29	1,9	1,2	0,1
IIIb	174 (112 — 270)	3,4	0,04	0,07	10,0	30	1,3	2,3	0,2
IIIc)	76 (45 — 129)	3,3	0	0,01	7,5	>15 h	1,7	1,4	0,2
Novocaine	570 (539 — 602)	1,0	0	0,75	12,5	25	0,0	6,6	1,9
Trimecaine	391 (372 — 410)	2,9	0	0,75	6,5	23	1,2	3,6	0,1
Lidocaine	270 (204 — 356)	1,9	0,03	0,85	50,0	38	0,3	6,9	0,7
Pyromecaine	300 (287 — 313)	2,5	0,18	0,25	5,6	49	1,9	1,2	0,6
Dicaine	44 (35 — 55)	5,6	1,00	0,02	1,5	>15 h	2,6	0,6	0,1

The acute toxicity of compounds IIIa-c was in direct proportion to a 0 to 2 increase in (n) methylene groups in their side chain. However, a symbatic increase in all types of local anesthetic and local irritant action did not occur. The local anesthetic properties of the IIIc amine hydrochloride differed little from those of local anesthetic agents used in medicine (Table 2).

The investigations undertaken indicate that the type of compounds examined represents a potential source of new local anesthetics.

EXPERIMENTAL CHEMICAL

UV spectra were recorded on a Specord UV-VIS instrument (GDR) in ethanol. IR spectra were recorded on a UR-20 instrument (GDR) in petroleum jelly. PMR spectra were recorded on a Tesla BS487C instrument (Czechoslovakia) with an operating frequency of 80 MHz in CCl_4. The PMR spectrum of the oxime IIa was recorded in $CDCl_3$. TMS was used as the internal standard.

The characteristics and yields of the new compounds are listed in Table 1.

6-(ω-phenylacyl)chroman Oximes (IIa-d). A mixture of 0.04 moles of the ketones of Ia-d [2, 7, 9], 11.6 g (0.16 mole) of hydroxylamine HCl, and 120 ml of pyridine was heated for 4 h at 100°C, cooled, and decanted into water. This was followed by ether extraction and distillation of the ether from the dried extract.

6-(α-Amino-ω-phenylalkyl)chromans (IIIa-d). A 4.6 g (0.2 mole) portion of metallic sodium was added in pieces to a solution of 0.025 mole of IIa-d oximes in 70 ml of n-butanol at the solution's bp temperature. After the sodium was dissolved the mixture was cooled, acidified with HCl, and concentrated in a vacuum. The residue was made alkaline with an aqueous solution of NaOH, extracted by ether and passage through gaseous anhydrous HCl (or by the addition of lactic acid). The hydrochlorides (or lactates) of the IIIa-d amines precipitated into the dried ether extract.

EXPERIMENTAL PHARMACOLOGICAL

The IIIa, b amines were studied in the form of their hydrochlorides and the IIIc amine was examined in the form of a lactate. Acute toxicity upon subcutaneous injection in white mice was determined by the Litchfield and Wilcoxon method as modified by Roth [1]. Infiltration anesthesia was studied in guinea pigs by the method in [5]. Surface anesthesia was tested on rabbit cornea by the method in [4], and conduction anesthesia was tested on isolated frog sciatic nerve by recording the action potential and minimum concentrations needed to block nerve conductivity [10]. Local irritant properties were tested on white rats by method [6] as modified in [8].

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