of fluorine atoms in the molecule of 3-perfluoroacyloxypropylsilatranes leads to decrease in the toxicity and a certain intensification of the neurotropic activity.

In contrast to these compounds, 3-fluoro- and 3,3,3-trifluoropropylsilatranes are considerably more toxic (see Table 4). The introduction of three methyl groups at positions 3, 7, and 10 of the silatrane skeleton decrease the toxicity, and is accompanied by the appearance of the hypothermal and potentiating ability (Table 2).

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SYNTHESIS AND LOCAL-ANESTHETIC ACTIVITY OF 6-[ω-AMINO-ω-ARYLALKYL]BENZO-1,4-DIOXANES

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A number of benzo-1,4-dioxane derivatives are known to exhibit local-anesthetic activity [3, 4]. Since ω-aminoalkylbenzene with a phenyl group in the side chain also exhibits activity of this type [11], we have synthesized a number of new benzo-1,4-dioxane analogs and studied their local anesthetic properties.

The 6-(ω-amino-ω-arylalkyl)benzo-1,4-dioxanes (IIa-e) were synthesized by Leuckart's reaction; the 6-(ω-aroylvinyl)benzo-1,4-dioxanes (Ia-e) were heated with ammonium formate, and the N-formyl derivatives then hydrolyzed with acid.

The ketone Ia was synthesized by acylation of benzo-1,4-dioxane (III) with benzoyl chloride, and the ketones Ib-e by hydrogenation of the 6-(2-aroylvinyl)benzo-1,4-dioxanes (V) in the presence of Raney nickel; the latter were obtained by condensation of 6-formylbenzo-1,4-dioxane (IV) [4] with acetophenone or its p-derivative in methanolic potassium hydroxide at 20°C by the usual method [7]. The chalcones Vb and c (An = C_6H_4Cl-p, C_6H_4F-p) were prepared for the first time.

Hydrogenation of the chalcone Vb ($_9$Ar = C_6H_4Cl-p) proceeded more slowly than for the other compounds, and uncontrolled hydrogenation of the chalcone Va (Ar = C_6H_5) gave 6-(3-hydroxy-3-phenylpropyl)benzo-1,4-dioxane (VI).

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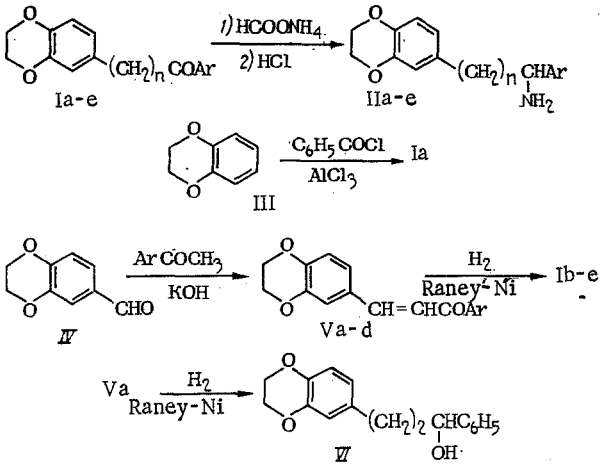

I, II: a) Ar = C_6H_5, n = 0; b) Ar = C_6H_5, n = 2; c) Ar = C_6H_4Cl-p; n = 2; d) Ar = C_6H_4F-p, n = 2; e) Ar = $C_6H_4OCH_3$-p; n = 2.
Va: Ar = C_6H_5; Vb: Ar = C_6H_4Cl-p; Vc: Ar = C_6H_4F-p.
Vd: Ar = $C_6H_4OCH_3$-p

In the spectra of the ketones Ib-e, the stretching vibrations of the carbonyl group occur at higher frequencies (1660-1675 cm^{-1}) than for the corresponding chalcones V (1640-1650 cm^{-1}), and absorption bands in the UV spectra are further displaced toward the long-wave region for the chalcones V which have longer chains compared with the ketones Ib-e.

6-(2-Amino-2-phenylethyl)benzo-1,4-dioxane (IIf), its N,N-dimethyl derivative IIg, and benzene analog 1,2-diphenylethylamine (IIh) were synthesized by the method given in [2, 6]. The structures of the compounds were confirmed by NMR spectral data.

EXPERIMENTAL CHEMISTRY

Ultraviolet spectra of the compounds in ethanol were taken on a Specord UV-VIS (GDR) instrument, infrared spectra of the compounds in mineral oil on a UR-20 (GDR) instrument, and NMR spectra on a Tesla BS 487C (ChSSR) (80 MHz) instrument using tetrachloromethane as solvent.

Physical data and yields for the compounds prepared are given in Table 1.

6-Benzoylbenzo-1,4-dioxane (Ia). Benzoyl chloride (17.6 g, 0.125 mole) was added at 5-10°C to a mixture of 50 ml of anhydrous 1,2-dichloroethane, 16.2 g (0.12 moles) of III [3], and 19 g (0.14 moles) of anhydrous aluminum chloride, the mixture stirred for 10 h at 20°C, poured onto ice, and acidified with hydrochloric acid. The organic layer was separated, washed with water, dried and evaporated.

6-(2-Aroylethyl)benzo-1,4-dioxanes (Ib-e). Raney nickel (5 g) was added to a solution of 0.02 moles of V in 50 ml of dioxane in a long-necked hydrogenation flask in an atmosphere of hydrogen. The flask was shaken until 0.02 moles of hydrogen had been absorbed, the catalyst filtered off, and the solvent evaporated.

6-(ω-Amino-ω-arylalkyl)benzo-1,4-dioxanes (IIa-e). A mixture of 0.1 moles of Ia-e and 0.3 moles of ammonium formate was heated for 6 h at 200°C (thermometer in bath), cooled, and washed with water. The insoluble residue was boiled for 3 h with 100 ml of concentrated hydrochloric acid, diluted with water, the solution separated from the the insoluble residue, made alkaline with potassium hydroxide, extracted with ether, and the dried extract evaporated. The hydrochlorides were obtained by passing gaseous hydrogen chloride into a solution of the bases IIa-e in anhydrous ether.

6-(3-Hydroxy-3-phenylpropyl)benzo-1,4-dioxane (VI). The chalcone Va (Ar = C_6H_5) was hydrogenated in the same way as V, but hydrogen was introduced until absorption was complete.

EXPERIMENTAL PHARMACOLOGY

The amines IIa-h were studided as the hydrochlorides. The acute toxicity, from subcutaneous injections of the compounds into white mice, was determined by the method of Litch-

TABLE 1. Data for Synthesized Compounds (Ia-e, IIa-e, Vb and c, and VI)

Compound	Yield, %	bp, °C (mm mercury)	mp, °C (solvent)	UV spectrum		IR spectrum	Found, %				Empirical formula	Calculated, %			
				λ_{max}, nm	log ε	$\nu_{C=O}$, cm^{-1}	C	H	Cl	N		C	H	Cl	N
Ia	88	172—4 (1)	68—9 (ethanol)	208 243 285 313	4,46 4,20 4,03 3,92	1640	75,29	5,01	—	—	$C_{15}H_{12}O_3$	74,99	5,03	—	—
Ib	92	—	64—5 (ethanol)	206 243 287	4,81 4,12 3,58	1660	76,42	5,76	—	—	$C_{17}H_{16}O_3$	76,10	6,01	—	—
Ic	95	226—8 (4)	—	207 253 280	4,61 4,20 Shoulder	1675	67,70	5,08	11,42	—	$C_{17}H_{15}ClO_3$	67,44	4,96	11,57	—
Id	92	—	43—4 (ethanol)	205 243 283	4,79 4,15 3,54	1670	71,42	5,32	—	—	$C_{17}H_{15}FO_3$	71,32	5,28	—	—
Ie	91	246—8 (4)	—	206 219 280 330	4,30 3,98 3,93 Shoulder	1665	72,71	6,15	—	—	$C_{18}H_{18}O_4$	72,46	6,08	—	—
IIa	59	187—9 (3)	—	—	—	—	74,83	6,33	—	5,98	$C_{15}H_{15}NO_2$	74,66	6,27	—	5,81
—	—	—	250—1 (acetone—ether)	210 235 284	4,65 Shoulder 3,46	—	64,89	5,78	12,74	4,74	$C_{15}H_{15}NO_2 \cdot HCl$	64,87	5,81	12,76	5,04
IIb	70	197—9 (1)	—	—	—	—	75,71	7,19	—	5,42	$C_{17}H_{19}NO_2$	75,81	7,11	—	5,20
—	—	—	120—1 (acetone—ethanol)	206 225 286	4,71 Shoulder 3,52	—	66,63	6,52	11,86	4,48	$C_{17}H_{19}NO_2 \cdot HCl$	66,77	6,59	11,59	4,58
IIc	66	213—5 (1)	—	—	—	—	67,37	5,81	11,55	4,78	$C_{17}H_{18}ClNO_2$	67,21	5,97	11,67	4,61
—	—	—	207—8 (acetone—ethanol)	206 222 286	4,71 4,25 3,49	—	60,22	5,80	20,97	3,88	$C_{17}H_{18}ClNO_2 \cdot HCl$	60,01	5,63	20,84	4,12
IId	77	202—4 (1)	—	—	—	—	71,31	6,49	—	4,97	$C_{17}H_{18}FNO_2$	71,06	6,31	—	4,88
—	—	—	188—9 (acetone)	207 227 287	4,70 Shoulder 3,49	—	63,39	6,16	—	4,22	$C_{17}H_{18}FNO_2 \cdot HCl$	63,06	5,91	—	4,33
IIe	67	227—9 (1)	—	—	—	—	72,38	7,09	—	4,75	$C_{18}H_{21}NO_3$	72,21	7,07	—	4,68
—	—	—	190—1 (ethanol—ether)	207 223 285	4,75 3,81 3,49	—	64,46	6,73	10,41	3,96	$C_{18}H_{21}NO_3 \cdot HCl$	64,38	6,60	10,56	4,17
Vb	44	—	124—5 (ethanol)	215 268 360	4,35 4,17 4,28	1650	68,18	4,40	12,06	—	$C_{17}H_{13}ClO_3$	67,89	4,36	11,79	—
Vc	48	—	134—5 (ethanol)	210 264 358	4,48 4,23 4,13	1640	72,16	4,54	—	—	$C_{17}H_{13}FO_3$	71,82	4,61	—	—
VI	96	—	50—1 (hexane)	209 235 285	4,45 Shoulder 3,47	3290 (OH)	75,80	6,32	—	—	$C_{17}H_{18}O_3$	75,55	6,66	—	—

TABLE 2. Toxicity, Local-Anesthetic, and Local-Irritant Action of the Hydrochlorides of the Amines IIa-h

Compound	LD_{50}, mg/kg	Local-anesthetic activity in infiltration anesthesia	Local irritant action		
			degree of irritation from 1% solution	mean concentration causing irritation, %	threshold concentration causing irritation, %
IIa	—	0,4	1,2	2,7	0,2
IIb	250 (208—300)	3,1	1,7	1,4	0,1
IIc	450 (265—765)	2,6	2,0	1,0	0,1
IId	275 (227—333)	2,0	1,8	1,3	0,1
IIe	278 (192—403)	2,3	1,2	2,8	0,2
IIf	640 (538—761)	1,6	0,8	3,0	0,5
IIg	1050 (724—1522)	0,4	1,2	2,5	0,3
IIh	250 (189—330)	1,5	1,2	2,6	0,2
Novocaine	570 (539—602)	1,0	0,0	6,6	1,9
Trimecaine	391 (372—410)	2,9	1,2	3,6	0,1
Pyrromecaine	300 (287—313)	2,5	1,9	1,2	0,6
Dicaine	44 (35—55)	3,0	2,6	0,6	0,1

Note. Range given in parentheses.

field and Wilcoxon, Roth modification [1]. Infiltration anesthesia was studied on guinea pigs by the method given in [8]; topical anesthesia, on the cornea of a rabbit using the method described in [5], and local-irritant properties on white rats by the method given in [9] (modified as in [10]).

Compound IIf was found to be more active as an infiltration anesthetic and less toxic than the benzene analog IIh or novocaine (Table 2). Removal of the methylene group from the side chain, or N,N-dimethylation of the amino group decreased both activity and toxicity (amines IIa and g), while lengthening the side chain on the methylene group increased both the activity and toxicity. Thus, the amine IIb is more active than trimecaine, pyrromecaine, and dicaine, and is more toxic than trimecaine and pyrromecaine, but less toxic than dicaine. The introduction of a chlorine, fluorine, or methoxy group into the p-position of the benzene ring of the amine IIb gave amines with lower activity (IIc-e).

The topical anesthetic activity of the amines IIb, c, and e was, respectively, 4, 54, and 5% of the activity of dicaine; the remaining amines were practically inactive.

The local irritant action of the amines IIa-h was greater than that of novocaine or trimecaine but weaker than that of pyrromecaine or dicaine. The amine IIf showed less irritant action than the benzene analog IIh. N,N-dimethylation of the amine IIf, elimination of the methylene group, or introduction of another methylene group into the side chain increased the local irritant action as did also the introduction of p-chloro and p-fluoro substituents into the benzene ring; introduction of a p-methoxy group, however, decreased the local irritant action.

This investigation has shown that derivatives of benzo-1,4-dioxane of this type do show some local anesthetic activity.

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THE SERIES OF 3H-QUINAZOL-4-ONE.

XIV. SYNTHESIS AND PROPERTIES OF 1-ETHOXALYL(METHOXYSUCCINYL)-3-ARYL-1,2,3,4-TETRAHYDROQUINAZILIN-3-ONES

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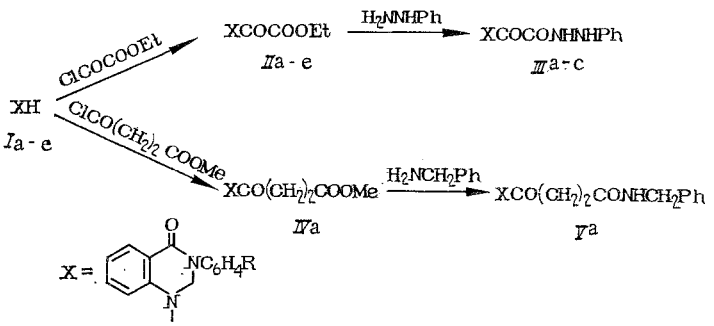
In a search for biologically active compounds, and in continuation of the investigation in [2], we obtained a series of derivatives of 1-ethoxalyl(methoxysuccinyl)-3-aryl-1,2,3-4-tetrahydroquinazolin-4-ones according to the following scheme:



I — V: R = H (a), Me = 2 (b), Br = 4 (c), Me = 4 (d), OMe = 4 (e)

In the reaction of 3-aryl-1,2,3,4-tetrahydroquinazolin-4-ones (Ia-e) with oxalic acid monoester chloride or β-carbomethoxypropionyl chloride, 1-ethoxalyl-3-aryl-1,2,3,4-tetrahydroquinazolin-4-ones (IIa-e) and 1-methoxysuccinyl-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (IVa) respectively, were obtained. The reaction of compounds IIa-c with phenylhydrazine leads to the formation of 4-phenylhydrazooxalyl-3-aryl-1,2,3,4-tetrahydroquinazolin-4-ones (IIIa-c). In the reaction of IVa with benzylamine, 1-benzylaminosuccinyl-3-phenyl-1,2,3,4-tetrahydroquinazolin-4-one (Va) was obtained.

The compounds obtained (see Table 1) are crystalline substances, slightly basic in character. They are insoluble in water, but are soluble in ethanol, benzene, toluene, and dioxane. The structure of the compound was confirmed by IR, UV, and PMR spectra, and also by the data of elemental analysis. In the IR spectra of all the compounds there are bands characteristic of the quinazolone ring: at 1650-1660, 1600-1610, 1490-1520 cm^{-1} [4]. In the IR spectra of compounds IIa-e and IVa, intense absorption bands have been observed, due to the presence of an ester group, while for compounds IIIa-c and Va, absorption bands at

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