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LOCAL ANESTHETIC ACTIVITY OF TROPINE ESTERS OF 5-ARYLFURAN-2-CARBOXYLIC ACIDS

N. I. Koretskaya, T. K. Trubitsyna, M. D. Mashkovskii, and A. F. Oleinik

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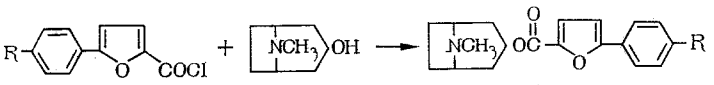
In continuation of work on the preparation and pharmacological examination of tropine esters of organic acids [1, 2], we have synthesized some tropine esters of 5-arylfuran-2-carboxylic acids and examined their biological activity.

The newly synthesized esters were investigated primarily from the point of view of their local anesthetic activity, since the chemical structure of the compounds were similar to that of cocaine and other local anesthetics (presence in the molecule of an aromatic ring, an ester grouping, and a tropine residue [3, 4]).

The synthesis of the tropine esters of 5-arylfuran-2-carboxylic acids was carried out by the reaction of the 5-arylfuran-2-carbonyl chlorides [5] with a twofold excess of tropine. The excess of tropine served as an acceptor for the hydrogen chloride evolved, thus shifting the direction of the equilibrium in the direction of the formation of the tropine esters of the 5-arylfuran-2-carboxylic acids (Ia-f). The reaction was carried out in an inert organic solvent at the boiling point of the reaction mixture.



I

a) R=H; c) R=Br; e) R=OCH_3
b) R=Cl; d) R=CH_3; f) R=NO_2

EXPERIMENTAL

Pharmacology

The local anesthetic activity, local irritant effects, and the acute toxicity of the tropine esters of 5-arylfuran-2-carboxylic acids were examined in comparison with dicaine, novocaine, and cocaine.

The degree of terminal anesthesia was determined in experiments using rabbits by introducing solutions of the compounds into the conjunctival sac, the activity being estimated by Renier's index. Infiltration anesthesia was investigated in guinea pigs by the method of Bülbring and Wajda [6], taking into account and adding up the number of painful stimuli of the skin which did not react following intracutaneous administration of the drugs over a period of 30 min.

Conduction anesthesia was investigated in frogs by the method of Bülbring and Wadja.

Local irritant effects were investigated visually by subcutaneous administration of the drugs to white rats, and in rabbits by introduction of solutions of the compounds into the

S. Ordzhonikidze All-Union Scientific-Research Institute for Pharmaceutical Chemistry, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 4, pp. 33-36, April, 1977. Original article submitted October 27, 1976.

TABLE 1. Anesthetic Properties of Tropine Esters of 5-Arylfuran-2-carboxylic Acids

R	Terminal anesthesia (Renier's index)*		Infiltration anesthesia index (number of nonresponding stimuli after 30 min ±standard error)	Conduction anesthesia (time of disappearance of frog reflexes, min ±standard error)			LD_{50}, mg/kg	
	concentration of solutions						intravenous	subcutaneous
	0,1%	0,5%	0,1%	0,1%	0,25%	0,5%		
H	1159 (1053 - 1264) n=3	1300 n=8	36 n=5	5±0,6 n=5	6,2±0,6 n=5	3,2±0,6 n=5	26,5	142
Cl	1124 n=5	1298 n=3	4±6 n=4	—	—	—	31,5	124
Br	980 (850 - 1110) n=6	1300 n=3	0 n=3	—	—	—	27,7	—
CH_3	1138 (1150 - 1226) n=7	1293 n=4	30±2 n=5	—	—	—	33,5	136
OCH_3	809 (465 - 1153) n=8	1300 n=4	25±3 n=5	—	—	—	21,5	87,5
NO_2	127 (27 - 227) n=5	1300 n=4	10±3 n=5	—	—	—	23,5	—
Cocaine	13 n=4	625 (452 - 797) n=10	—	—	—	5,3±0,3 n=4	23,5	185
Dicaine	726 (621 - 830) n=8	1127 (1029 - 1225) n=8	35±1 n=4	2,7±0,2 n=5	1,2±0,6 n=4	—	10,7	53
Novocaine	13 n=3	—	27±7 n=5	7±0,6 n=5		—	—	—

Note: n) number of experiments.
*Mean values with confidence intervals (P = 0.05).

TABLE 2. Hydrochlorides of Tropine Esters of 5-Arylfuran-2-carboxylic Acids (I)

Compound	R	Melting point, deg	R_f	Yield, %	Found, %			Calculated, %			Molecular formula
					C	H	Cl	C	H	Cl	
Ib	Cl	244—6	0,45	57,6	59,60	5,65	18,71	59,70	5,54	18,55	$C_{19}H_{20}ClNO_3 \cdot HCl$
Ic	Br	244—5	0,47	47,0	53,56	5,04	7,92	53,48	4,96	8,31	$C_{19}H_{20}BrNO_3 \cdot HCl$
Id	CH_3	242—3	0,44	37,3	66,37	6,63	9,84	66,38	6,69	9,80	$C_{20}H_{23}NO_3 \cdot HCl$
Ie	OCH_3	232—3	0,34	29,8	60,71	6,46	8,88	60,69	6,62	8,96	$C_{20}H_{23}NO_4 \cdot HCl \cdot H_2O$ *
If	NO_2	275—7	0,20	25,3	56,77	5,62	8,69	56,79	5,52	8,82	$C_{19}H_{20}N_2O_5 \cdot HCl \cdot 1/2H_2O$ †

*Calculated, %: H_2O 4.55. Found, %: 4.29.
†Calculated, %: H_2O 2.24. Found, %: H_2O 1.69.

ocular conjunctival sacs.

Acute toxicity was determined in white mice by intravenous and subcutaneous administration. The LD_{50} was estimated by Kerber's method.

It was found that all the compounds possessed pronounced local anesthetic properties (Table 1). Determination of terminal anesthesia showed that the analgetic activity of 0.5% solutions of all these compounds was greater then that of a solution of cocaine of the same concentration, and was not inferior to that of dicaine. The duration of the anesthetic effect was 60-90 min.

The infiltration activity of Ia, Id, and Ie was found to be close to or somewhat greater than that of novocaine.

The most active compound was the tropine ester of 5-phenylfuran-2-carboxylic acid. In a concentration of 0.1% this compound caused complete anesthesia of the cornea of the rabbit eye, being 10 times more active than cocaine and twice as active as dicaine. Intracutaneous administration of a 0.1% solution of the drug to guinea pigs gave complete infiltration anesthesia and was as active as novocaine. In experiments on frogs to determine the ability to produce conduction anesthesia, the drug was better than cocaine and novocaine, but was inferior to dicaine.

The drug was half as toxic as dicaine, but was more toxic than cocaine by subcutaneous administration (LD_{50} figures are given in Table 1).

A limiting factor in the practical utilization of Ia and the other compounds in this series is their irritant effect, which is expressed in the form of edema and hyperemia of the tissues on subcutaneous administration to white rats, or irritation of the cornea of the eye and mucous membranes of the eyelid in rabbits following instillation of the 0.5 and 1% solutions.

Chemistry

The chromatographic system used for the tropine esters was isopentyl alcohol—5% acetic acid (1:1), developer Dragendorf's reagent, paper M-20 slow filtration from the Leningrad plant.

Tropine Ester of 5-Phenylfuran-2-carboxylic Acid (Ia). To a solution of 4.13 g (0.02 mole) of 5-phenylfuran-2-carbonyl chloride [3] in 40 ml of xylene, a solution of 5.65 g (0.04 mole) of tropine in 40 ml of xylene was added. The mixture was boiled with stirring for 5 h, cooled to room temperature, and the tropine hydrochloride filtered off and washed with xylene. The xylene was removed from the filtrate under reduced pressure, and the residue was treated with 40 ml of 1 N sodium hydroxide and extracted with ether. The extract was dried over anhydrous sodium sulfate, the ether was distilled off, and the residue was dissolved in 6 ml of anhydrous alcohol, cooled in ice-water, and treated with a 25% alcoholic solution of hydrogen chloride (pH 3.0-4.0). The hydrochloride was precipitated with dry ether to give 2.32 g (33.3%) of Ia hydrochloride, mp 228-230° (from alcohol—ether), R_f 0.42. Found, %: C 65.43; H 6.49; Cl 10.06. $C_{19}H_{21}NO_3 \cdot HCL$. Calculated, %: C 65.61; H 6.38; Cl 10.19.

Compounds Ib, d, e, and f were obtained similarly (Table 2).

Free Base of Ia. This was obtained by treatment of the hydrochloride with aqueous ammonia followed by extraction with ether, mp 68-70° (from heptane). Found, %: C 73.03; H 6.64. $C_{19}H_{21}NO_3$. Calculated, %: C 73.29; H. 6.80.

Citrate of Ia. This was obtained with mp 176-177° (from alcohol). Found, %: C 59.75; H 6.01. $C_{19}H_{21}NO_3 \cdot C_6H_8O_7$. Calculated, %: C 59.64; H 5.81.

Tartrate of Ia. This was obtained with mp 58-60° (from dimethylformamide—ether). Found, %: C 59.16; H 6.16. $C_{19}H_{21}NO_3 \cdot C_4H_6O_6 \cdot {}^1/_2\, H_2O$. Calculated, %: C 58.72; H 6.00.

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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF SOME 1,4-BIFUNCTIONAL DERIVATIVES OF ADAMANTANE

L. N. Lavrova, N. V. Klimova,
M. I. Shmar'yan, D. N. Ibadova,
D. A. Kharkevich, and A. P. Skoldinov

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It has previously been shown that monoquaternary salts of esters of δ-dimethylaminobutanol with certain substituted benzoic and cinnamic acids have a high curare-like activity [1, 2]. In this connection, it was of interest to investigate the pharmacological action of corresponding derivatives of stereoisomeric esters of 1-hydroxy-4-dimethylaminoadamantane, where the δ-dimethylaminobutanol fragment is sterically secured by its inclusion in a cyclic system; therefore, data on the dependence of their physiological activity on structure could be useful in ascertaining the structure of the corresponding receptor formations.

We have previously shown that 2-aminoadamantane and its N-substituted derivatives can be prepared in high yield from 2-adamantanone by reaction with the appropriate formamides or amine formates [3]. In a continuation of these studies we have investigated the reaction of 1-hydroxy-4-adamantanone and its esters with dimethylformamide (DMF). It has been shown that in this case replacement of the carbonyl group by an amino group via the Leuckart reaction takes place smoothly. As a result, 1-hydroxy-4-dimethylaminoadamantane (I) has been synthesized in high yield from 1-hydroxy-4-adamantanone (II); and the corresponding amino esters IV, from esters of the hydroxyketone III, with acetic, phenylacetic, and diphenylacetic acids.

The starting 1-hydroxyadamantone was prepared by oxidation of adamantanone with 100% nitric acid [4]. 1-Acetoxy-4-adamantanone (IIa) was synthesized by heating the hydroxyketone I with acetic anhydride, without a solvent; the esters of the hydroxyketone with phenylacetic (IIIb) and diphenylacetic acid (IIIc) were prepared by heating the hydroxyketone I with the appropriate acid chloride in benzene solution, in the presence of metallic magnesium (Table 1).

The Leuckart reaction was effected by heating hydroxyketone I in formic acid with an excess of DMF at 130-160°C; the hydroxyamine formed in 70-80% yield was separated from unreacted hydroxyketone by conversion to the hydrochloride. The reaction with esters of the hydroxyketone III, was carried out similarly; under these conditions no hydrolysis of the ester group was observed. The esters of 1-hydroxy-4-dimethylaminoadamantane which were isolated were identical in properties to the substances prepared by acylation of 1-hydroxy-4-dimethylaminoadamantane (II). The amino esters IV, were converted further into the methiodides V, by boiling the appropriate bases in acetone with methyl iodide.

The stereoisomeric forms (A and B) were isolated in individual state.

1-Hydroxy-4-dimethylaminoadamantane and its esters can exist in the form of stereoisomers which differ in the steric location of the amino group with respect to the hydroxy or acyloxy group. By thin-layer chromatography on Silufol it was shown that the compound II

Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-Farmatsevticheskii Zhurnal, Vol. 11, No. 4, pp. 36-42, April, 1977. Original article submitted October 20, 1976.