SYNTHESIS AND LOCAL ANESTHETIC ACTIVITY OF α-AMINO-2-(2-CYCLOPENTENYL)ACETANILIDES

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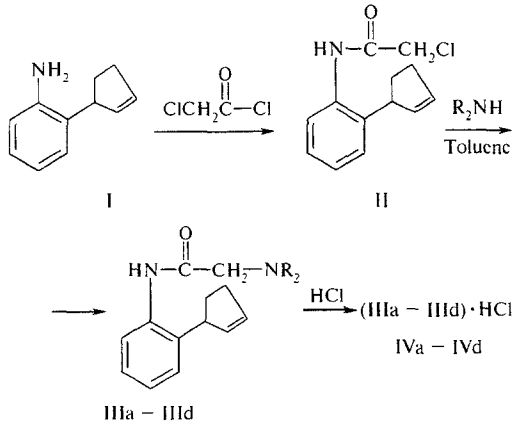
Aminoacetic acid alkylanilide hydrochlorides are known to possess pronounced local anesthetic properties. A convenient initial reagent for the synthesis of cycloalkenyl analogs of these compounds is offered by 2-cyclopentenylaniline, which can be synthesized by the Claisen rearrangement [1]. With the purpose of expanding the circle of potential local anesthetics belonging to this group of arylamines, we have synthesized and characterized a series of cyclopentenylacetanilides.

First, the interaction of 2-cyclopentenylaniline (I) with chloroacetyl chloride in the presence of K_2CO_3 on heating in benzene or toluene led to a high yield of N-(2-chloroacetyl)-2-(2-cyclopenten-1-yl)aniline (II). The subsequent condensation of anilide (II) with secondary amines led to aminoacetic acid anilides (IIIa – IIId). The latter compounds were converted into hydrochlorides (IVa – IVd) and pharmacologically tested.



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EXPERIMENTAL CHEMICAL PART

The ^1H NMR spectra were measured on a Bruker AM 300 spectrometer (working frequencies 300 and 75 MHz) using $CDCl_3$ as the solvent and TMS as the internal standard. The purity of the reaction products was checked by TLC on Silufol UV-254 plates eluted with a CH_2Cl_2 – MeOH (95 : 5) mixture. The data of elemental analyses for C, H, Cl, and N agree with the results of analytical calculations. Yields and physicochemical characteristics of the synthesized compounds are listed in Table 1.

N-(2-Chloroacetyl)-2-(2-cyclopenten-1-yl)aniline (II). To a mixture of 48 g K_2CO_3, 15.9 g (0.1 mole) cyclopentenylaniline (I), and 100 ml dry benzene in a three-neck flask equipped with a mechanical stirrer, dropping funnel, and reflux cooler was gradually added with stirring 22.6 g (0.2 mole) of freshly distilled chloroacetyl chloride. Upon completely adding chloroacetyl chloride, the mixture was heated to boiling for 2 h and filtered hot. Then the solvent was evaporated to dryness at a reduced pressure and the residue recrystallized from benzene.

Aminoacetic acid cyclopentenylanilides (IIIa – IIId). To 4.71 g (0.02 mole) of compound II in a round-bottom flask with reflux cooler was added 75 ml toluene and the mixture was heated to 80°C. To this mixture was added 0.2 mole of the corresponding cyclic amine and the heating was continued for 4 h. The precipitate of amine hydrochloride was separated by filtration. The filtrate was evaporated to dryness and the residue recrystallized from a minimum amount of toluene.

Cyclopentenylanilide hydrochlorides (IVa – IVd). A solution of the corresponding anilide (IIIa – IIId) in hexane was bubbled with dry HCl until the reaction product ceased to precipitate. The precipitated crystals were filtered, washed with hexane, and dried in vacuum. Compound IVd is highly hygroscopic and we failed to determine its melting point.

TABLE 1. Yields and Physicochemical Characteristics of the Synthesized Compounds

Compound	Yield, %	M.p., °C	Empirical formula	^{1}H NMR spectrum, δ, ppm				
				CONH	$OCCH_2$	C = CCH	HC = CH	Other signals
II	90	103 – 104	$C_{13}H_{14}NClO$	8.35 s	4.10 s	3.90 m	5.69 – 5.95 m	1.61 – 2.49 (m, $2CH_2$), 7.0 – 7.75 (m, H arom.)
IIIa	90	65	$C_{18}H_{24}N_2O$	9.52 s	3.12 s	4.01 m	5.80 – 6.10 m	1.5 – 2.6 (m, $7CH_2$), 7.05 – 8.10 (m, H arom.)
IIIb	90	65	$C_{17}H_{22}N_2O_2$	9.25 s	3.12 s	3.90 m	5.71 – 5.98 m	1.63 – 3.68 (m, $6CH_2$), 7.05 – 8.05 (m, H arom.)
IIIc	87	63	$C_{17}H_{23}N_3O$	9.40 s	3.11 s	3.95 m	5.78 – 6.09 m	1.65 – 2.90 (m, $6CH_2$), 5.20 (s, NH), 7.50 – 8.05 (m, H arom.)
IIId	61	50	$C_{15}H_{20}N_2O$	9.40 s	3.10 s	4.00 m	5.80 – 6.05 m	2.38 (s, $2CH_2$), 1.70 – 2.49 (m, $2CH_2$), 7.05 – 8.12 (m, H arom.)
IVa	98	233	$C_{18}H_{24}N_2O \cdot HCl$					
IVb	98	185	$C_{17}H_{22}N_2O_2 \cdot HCl$					
IVc	98	155	$C_{17}H_{23}N_3O \cdot HCl$					
IVd	97		$C_{15}H_{20}N_2O \cdot HCl$					

TABLE 2. Infiltration Anesthetic Activity of the Arylamine Derivatives Studied

Compound	Solution concentration, %	Anesthesia onset time, min	Percentage increase in latent period to first pain reaction (relative to initial level, 30 min after injection)			Anesthesia duration, min
			Hot plate	Skin irritation	Tail irritation	
IVa	0.5	14.2 ± 1.2	400.0 ± 20.9	200.0 ± 20.4	200.0 ± 17.0	80.7 ± 7.0*
IVa	1	12.7 ± 1.0	425.0 ± 23.5	200.0 ± 22.6	220.0 ± 17.5	83.5 ± 7.5*
IVb	0.5	14.8 ± 1.0	400.0 ± 20.5	180.0 ± 17.0	140.0 ± 8.5	80.3 ± 9.0
IVb	1	13.5 ± 0.8	420.9 ± 28.5	160.0 ± 20.0	160.0 ± 9.8	80.5 ± 8.0*
IVc	0.5	15.5 ± 1.7	188.3 ± 17.0	60.0 ± 4.5	66.0 ± 3.4	65.2 ± 3.4
IVd	0.5	1.5 ± 1.2	12.8 ± 17.0	60.5 ± 5.3	62.0 ± 17.0	60.0 ± 4.7
Novocaine	0.5	11.3 ± 1.2	428.3 ± 24.8	240.0 ± 20.4	200.0 ± 17.0	60.9 ± 5.7
Lidocaine	1	9.7 ± 0.8	785.7 ± 50.3	560.0 ± 41.0	360.0 ± 32.2	110.3 ± 9.5

* $p < 0.05$ relative to the novocaine test.

EXPERIMENTAL PHARMACOLOGICAL PART

Methods of investigation. The local infiltration anesthesia was studied on white mongrel mice (weighing 20 – 25 g) and white rats (180 – 200 g) as described in [2]. The analgesiometric data were obtained using the hot-plate test and tests involving electric irritation of the skin and tail base.

For the hot-plate test, the animals were placed into a chamber with the floor heated to 55°C and the time to first licking of the hind paws was measured. The electric irritation of skin was studied in a chamber with a conductive floor (ac electric current: strength, 5.0 mA; frequency, 50 Hz). The nociceptive irritation of the tail was produced via subcutaneous needle electrodes (single rectangular pulses: duration, 5 sec; repetition period, not less than 30 sec). The pain reaction was evaluated by determining the time to first defensive drawing back of the hind paw or tail, respectively.

The compounds studied were injected at a dose of 0.05 ml (mice) or 0.1 ml (rats) into the hind foot aponeurosis (on the plantar side) in the region of distal branches of the tibial and peroneal nerves. The local anesthetic activity was assessed by the increase in the latent period before the nociceptive reaction. Each compound was studied in a group of six animals.

The conduction anesthesia was studied in a group of 80 urethane-narcotized rats by applying the test compounds (using a cotton impregnated with solutions of various concentrations) onto exposed sciatic nerve. The nerve was irritated with electric current pulses every 10 min at a point shifted from the test site to the periphery. The anesthetic effect was evaluated by measuring the latent period to the pain reaction. The reference preparations were 0.5 – 1% novocaine and 1 – 2% lidocaine solutions.

The experimental data were statistically processed to determine the arithmetic mean (M) and its confidence interval (m). The reliability of differences was evaluated using the Student t-criterion.

RESULTS AND DISCUSSION

It was found that all the synthesized compounds are capable of increasing more or less significantly the pain reaction threshold.

TABLE 3. Conduction Anesthetic Activity of the Arylamine Derivatives Studied

Compound	Solution concentration, %	Anesthesia onset time, min	Percentage increase in latent period to first pain reaction (relative to initial level, 30 min after application)	Anesthesia duration, min
IVa	0.5	15.0 ± 0.6	75.1 ± 6.2	83.7 ± 6.7
IVa	1	17.3 ± 1.3	75.5 ± 4.3	79.7 ± 6.0
IVa	0.5	15.2 ± 1.2	60.8 ± 5.3	69.5 ± 5.5
IVb	1	13.7 ± 1.3	78.3 ± 3.9	60.0 ± 5.3
IVc	0.5	13.5 ± 1.6	65.2 ± 3.4	66.5 ± 3.4
IVd	0.5	1.4 ± 1.3	60.3 ± 17.0	64.0 ± 3.5
Novocaine	0.5	12.5 ± 0.8	70.8 ± 6.3	70.3 ± 6.1
	1	13.0 ± 1.17	95.3 ± 9.7	85.0 ± 6.3
Lidocaine	1	10.0 ± 0.6	100.3 ± 8.9	90.5 ± 8.5
	2	10.0 ± 1.17	128.0 ± 8.0	120.0 ± 8.1

For the infiltration anesthesia studied by the hot-plate test, the effect of compounds IVa – IVd at a concentration of 0.5 or 1% is comparable to that of 0.5% novocaine with respect to the anesthesia onset time and the strength of action. As for the duration of the anesthetic affect, the action of compounds IVa and IVb exceeded that of novocaine by approximately 20 min (Table 2). In the case of electric skin irritation, the anesthetic effect of compounds IVa – IVd was somewhat less pronounced compared to that of novocaine and was markedly lower than the effect of lidocaine. In the test with electric irritation of the tail, compounds IVa – IVd are also less effective than novocaine and especially than lidocaine. As for the conduction anesthesia, all the compounds studied were somewhat less effective than novocaine and markedly inferior to lidocaine with respect to both strength and duration of action (Table 3).

Thus, all the compounds studied in this work possess the properties of weak local anesthetics.

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