AZACYCLOALKANES VIII. AROMATIC AMIDES OF N-SUBSTITUTED α-PYRROLIDINEDICARBOXYLIC ACIDS

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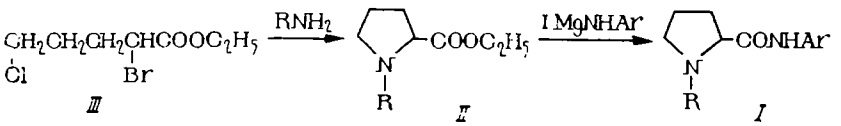
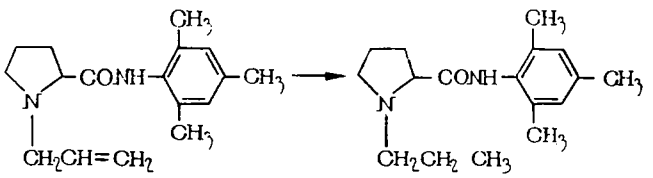
Many aromatic amides of N,N-substituted α-amino acids possess high local anesthetizing activity. Some of the compounds of this group, e.g., xylocaine [1,2], trimecaine [3], carbocaine [4, 5], and others, [6] have been widely applied in medical practice.

In search of new anesthetics and, first of all, for preparations to be used as surface anesthetics, as well as for the study of the dependence of pharmacological activity on the chemical structure, a synthesis was carried out of aromatic amides of N-substituted α-pyrrolidinecarboxylic acids [1]. The intermediate esters of N-substituted α-pyrrolidinecarboxylic acids (II) with R = CH_3 or C_2H_5 were obtained from α,δ-dihalovaleric acids by the method described by us earlier [7]. For the synthesis of esters of amino acids II with heavier residues at the nitrogen atom of the heterocyclic ring, it was found convenient to carry out cyclization of ethyl ester of α-bromo-δ-chlorovaleric acid (III) with primary amines:



The latter variant in the synthesis of esters II has the advantage of amination proceeding under mild conditions with high yields of cyclic products. By using this method, we obtained a series of new esters of N-substituted α-pyrrolidinecarboxylic acids (Table 1; typical experiment, see Experimental part). The reaction of esters II with magnesium halide derivatives of the appropriate aromatic amines [8, 9] yielded amides I (Table 2; typical experiment, see Experimental part).

Mesidide of N-propyl-α-pyrrolidinecarboxylic acid (Ib) was obtained by hydrogenation of N-allyl derivative (Ia) in the presence of palladium on charcoal



The properties of synthesized amides I are given in Table 2. They readily yielded hydrochlorides, in the form of white crystalline substances, readily soluble in water. With the increase in the length of N-alkyl residue the solubility of hydrochlorides in water decreases; substances with a residue heavier than hexyl are sparingly soluble in water.

As a result of the study of pharmacological properties of hydrochlorides of amides I, it has been established that they produce infiltration and conduction anesthesia, while some of them also possess

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TABLE 1. Esters of N-Substituted α-Pyrrolidinecarboxylic Acids (II)

R	Yield, %	Boiling point, deg	n_D^{20}	d_4^{20}	Found, %		Empirical formula	Calculated, %	
					C	H		C	H
iso-C_3H_7	40,5	93—5 (12 mm)	1,4455	0,9735	64,45 64,49	10,09 10,29	$C_{10}H_{19}NO_2$	64,8	10,33
n-C_4H_9*	65	62—3 (1mm)	1,4460	0,9594	66,02 65,98	10,54 10,47	$C_{11}H_{21}NO_2$	66,28	10,62
iso-C_4H_9	79,5	72—3 (2mm)	1,4427	—	66,54 66,55	10,58 10,70	$C_{11}H_{21}NO_2$	66,28	10,62
iso-C_5H_{11}	54,7	96—9 (3mm)	1,4440	0,9399	67,24 67,37	10,81 10,83	$C_{12}H_{23}NO_2$	67,56	10,86
C_6H_{13}	68	101—2 (2mm)	1,4463	—	68,39 68,34	10,98 11,09	$C_{13}H_{25}NO_2$	68,69	11,09
C_7H_{15}	65	106—7 (2mm)	1,4478	—	70,04 70,01	11,38 11,45	$C_{14}H_{27}NO_2$	69,66	11,28
$C_{10}H_{21}$	60	146—8 (4mm)	1,4501	—	72,44 72,49	11,82 11,98	$C_{17}H_{33}NO_2$	72,04	11,73
$C_{14}H_{29}$	83	182—3 (2mm)	1,4554	—	74,29 74,42	12,27 12,24	$C_{21}H_{41}NO_2$	74,29	12,17
CH_2=CH =CH_2	69,3	95—6 (12mm	1,4540	0,9809	65,80 65,91	9,40 9,53	$C_{10}H_{17}NO_2$	65,54	9,35
Cyclo-pentyl	77,8	86—7 (1,5 mm)	1,4712	1,0242	67,90 67,81	9,82 9,92	$C_{12}H_{21}NO_2$	68,21	10,00
Cyclohexyl	83	107—9 (2mm)	1,4784	1,009	69,29 69,54	10,52 10,52	$C_{13}H_{23}NO_2$	69,29	10,28
$CH_2C_6H_5$†	75,3	126—8 (4mm)	1,5108	1,0536	71,94 71,98	8,33 8,43	$C_{14}H_{19}NO_2$	72,06	8,21
C_6H_5‡	60	125—6 (2mm)	1,5421		70,80 70,96	7,64 7,65	$C_{13}H_{17}NO_2$	71,19	7,82

*According to literature data [10], bp 116-118° (20 mm), n_D^{20} 1.4465.
†According to literature data [11], bp 104-105° (0.07 mm), n_D^{20} 1.5120.
‡With methyl ester of α-bromo-δ-chlorovaleric acid, the yield in cyclization increased by 68-70%.

surface anesthetizing activity (Table 2). The structure of the aromatic portion of amides I affects the activity in a manner similar to that observed for aromatic amides of aliphatic amino acids [3], i.e., with the increase in the number of methyl groups the activity increases. Derivatives of aniline and o-toluidine produced no surface anesthesia; conduction and infiltration anesthetics were active for a short time. In the series of mesidides of N-substituted α-pyrrolidinecarboxylic acids, the ability of producing infiltration anesthesia increases with the increase of residue R at the nitrogen atom of the hydrocyclic ring (from CH_3 to C_4H_9). The derivatives of N-butyl- and N- isobutyl-α-pyrrolidinecarboxylic acid possess well defined activity at all kinds of anesthesia and show relatively low toxicity. Compound I (R = C_6H_{13}) produces all kinds of anesthesia with the surface anesthesia in very low concentrations (0.05-0.1%); however, they exert a well defined stimulating action on tissues. Compound I (R = C_7H_{15}) is sparingly soluble in water; it also exerts an anesthetizing effect, the exact characteristic of which is difficult to give because of the sharply expressed stimulating action. Compound I (R = $CH_2C_6H_5$) produces no surface anesthesia, and its action in infiltration anesthesia is of brief duration. Among the substances under study the most interesting were the mesidides of N-butyl- and N-cyclohexyl-α-pyrrolidinecarboxylic acids which are a subject of a separate investigation.

EXPERIMENTAL

Esters of N-Substituted α-Pyrrolidinecarboxylic Acids (II) (typical experiment) [12]. A solution of 1 mole of ethyl ester of α-bromo-δ-chlorovaleric acid and 3.5 moles of primary amine in benzene or toluene was refluxed for 6 h. Upon cooling, ether was added to the reaction mixture to precipitate completely amine hydrohalides; the precipitate was filtered off, and an excess of saturated aqueous solution of potassium carbonate was added to the filtrate. The benzene–ether solution was separated, the solvents distilled off, and the residue fractionated in vacuo. Appropriate amides of N-substituted α-pyrrolidinecarboxylic acids were obtained in some cases in a yield of 15-35% as high-boiling byproducts [12].

TABLE 2. Amides of N-Substituted α-Pyrrolidinecarboxylic Acids (I)

R	Ar	Yield, %	Base						Hydrochloride				Surface anesthesia (1% solution)		Infiltration anesthesia (0.25% solution)	
			melting point, deg	found, %		empirical formula	calc., %		melting point, deg	found, %	empirical formula	calc., %	Renier index	duration†	depth	duration, ‡
				C	H		C	H								
CH_3	Phenyl	89	—	—	—	—	—	—	214—6	14,77 14,79	$C_{12}H_{16}N_2O \cdot HCl$	14,73	—	—	2	2
CH_3	o-Tolyl	89	—	—	—	—	—	—	195—6	14,09 14,07	$C_{13}H_{18}N_2O \cdot HCl$	13,92	—	—	2	2
H	Mesityl	50	—	—	—	—	—	—	135—7 (decomp.)	12,92 12,95	$C_{14}H_{20}N_2O \cdot HCl$		—	—	—	—
CH_3	»	89	79—80	73,15 73,31	8,91 9,08	$C_{15}H_{22}N_2O$	73,16	9,05	241—2	12,51 12,38	$C_{15}H_{22}N_2O \cdot HCl$	12,54	—	—	2	2
C_2H_5	»	84	51,5—52,5	73,63 73,84	9,26 9,28	$C_{16}H_{24}N_2O$	73,79	9,29	241,5—242,5	11,49 11,52	$C_{16}H_{24}N_2O \cdot HCl$	11,95	—	—	0,5	0,5
C_3H_7	»	85	64—5	74,00 74,13	9,46 9,32	$C_{17}H_{26}N_2O$	74,40	9,55	260—2	11,25 11,26	$C_{17}H_{26}N_2O \cdot HCl$	11,40	401	—	1	2
iso-C_3H_7	»	73	83,5—84,5	74,14 74,16	9,58 9,60	$C_{17}H_{26}N_2O$	74,40	9,55	253—4	11,24 11,33	$C_{17}H_{26}N_2O \cdot HCl$	11,40	566	—	1	2
C_4H_9	»	89	73—5	75,26 75,38	10,00 10,01	$C_{18}H_{28}N_2O$	74,98	9,79	261—2	11,24 11,37	$C_{18}H_{28}N_2O \cdot HCl$	10,91	1 300	1	2	4
iso-C_4H_9	»	73	82—3	74,81 74,82	9,81 9,87	$C_{18}H_{28}N_2O$	74,98	9,79	252—3	10,84 10,96	$C_{18}H_{28}N_2O \cdot HCl$	10,91	1 300	0,8	2	4
iso-C_5H_{11}	»	66	75—6	75,17 75,05	10,02 10,03	$C_{19}H_{30}N_2O$	75,56	10,00	251—3	10,05 10,31	$C_{19}H_{30}N_2O \cdot HCl$	10,46	1 266**	—	1	5
C_6H_{13}	»	76	220—1 (40 mm)*	75,82 75,92	9,90 10,12	$C_{20}H_{32}N_2O$	75,90	10,20	211—2	9,64 9,70	$C_{20}H_{32}N_2O \cdot HCl$	10,05	1 300**	1	—	—
C_7H_{15}	»	78	219—1 (2mm)*	75,93 76,05	10,36 10,42	$C_{21}H_{34}N_2O$	76,32	10,37	216—7	9,47 9,54	$C_{21}H_{34}N_2O \cdot HCl$	9,66	††	—	—	—
$CH_2=CH=CH_2$	»	88	56—7	74,91 74,71	8,83 8,77	$C_{17}H_{24}N_2O$	74,96	8,88	243,5—244,5	11,48 11,34	$C_{17}H_{24}N_2O \cdot HCl$	11,48	671**	0,6	1	2
Cyclopentyl	»	87	109—10	75,98 76,24	9,39 9,31	$C_{19}H_{28}N_2O$	75,97	9,39	284—5	10,56 10,47	$C_{19}H_{28}N_2O \cdot HCl$	10,52	1 134**	0,7	0,5	1
Cyclohexyl	Mesityl	83	126,5—127,5	76,76 76,79	9,63 9,70	$C_{20}H_{30}N_2O$	76,38	9,62	267—8	9,99 9,91	$C_{20}H_{30}N_2O \cdot HCl$	10,10	1 300	1	2	6
$CH_2C_6H_5$	»	77	28—30	—	—	—	—	—	203—5	10,07 10,16	$C_{21}H_{26}N_2O \cdot HCl$	9,88	—	—	2	2
C_6H_5	»	68	—	—	—	—	—	—	195—6	9,92 10,06	$C_{20}H_{24}N_2O \cdot HCl$	10,28	††			

*Boiling point.

†A comparison was made between 1% solution of the substance with 1% dicaine solution, for which the Renier index was equal to 1300, duration of action (60 min) was taken as equal to 1.

‡A comparison was made between 1% solution of the substance with 1% novocaine, the action of which in depth (40%) and duration (0.5 h) was taken as equal to 1.

**Has a stimulating action.

††Sparingly soluble in water.

Amides of N-Substituted α-Pyrrolidinecarboxylic Acids (I) (typical experiment). To an ether solution of 0.1 mole of methyl magnesium iodide was carefully added dropwise 0.1 mole of aromatic amine in absolute ether. On the completion of the reaction, to the aminomagnesium iodide was added dropwise the ether solution of 0.05 mole of ester of N-substituted α-pyrrolidinecarboxylic acid, and the mixture was refluxed for 1 h. After cooling, the mixture was acidified with diluted hydrochloric acid to pH 5.0-6.0, the aqueous layer was separated and extracted several times with ether, and the aqueous solution was made alkaline by concentrated ammonia. The base was extracted with ether. After the solvent was distilled off, dilute hydrochloric acid was added to the residue to an acid reaction; the solution was boiled with activated carbon and made alkaline with 40% aqueous potassium hydroxide solution, and the amide was extracted with ether. The ether solution was dried over magnesium sulfate and the ether distilled off to yield the appropriate amides.

The Hydrochlorides were obtained by mixing the ether solution of hydrogen chloride and base. Crystallization was carried out from a mixture of alcohol and ether.

Mesidide of N-Propyl-α-pyrrolidinecarboxylic Acid (1b).* A solution of 1 g of mesidide of N-allyl-α-pyrrolidinecarboxylic acid in 50 ml of alcohol was hydrogenated over palladium on charcoal at atmospheric pressure and room temperature. The theoretical amount of hydrogen was absorbed in 1.5 h. The catalyst was filtered off, the alcohol distilled off, and the residue crystallized on standing.

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*G. I. Gurevich participated in the synthesis of this compound.