SYNTHESIS AND CARDIOVASCULAR PROPERTIES OF SALSOLIDINE DERIVATIVES

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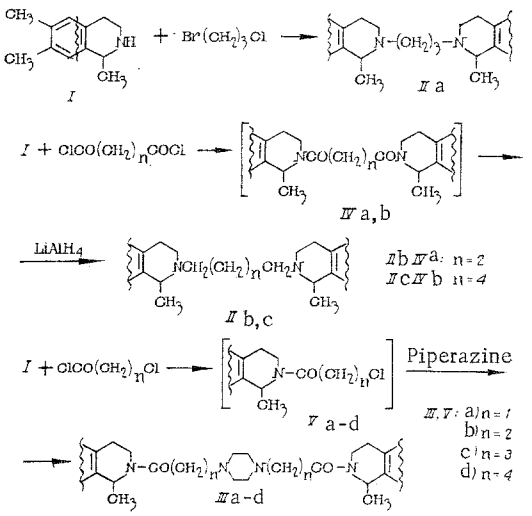
UDC 615.22:547.833.1].012.1

Derivatives of 6,7-dihydroxyisoquinoline (I) have frequently been the subjects of study in the search for cardiovascular drugs [1-5]. A number of compounds with spasmolytic, vasodilating, antianginal, and hypotensive activity carry from one to three aromatic (or heteroaromatic) rings with 6-π-electron systems which often contain electron-donor substituents (HO, CH_3O, CH_3), and less frequently halogens, a fairly long alkyl chain, the same groups or fragments on one or both ends of the extended molecule, or one or two basic nitrogen atoms. This combination of structural features is well exemplified by ditrimine and lidoflazine [2]. Other compounds (verapamil, ganglerone, dilazol, difril, nafiverin, phenbutazine, cinnarizine, etc.) [1, 2] also possess one or other of the structural features listed above.

In view of these considerations, we have synthesized salsolidines in which two of its residues are linked by polymethylene chains of differing lengths (IIa-c), or by aminoacyl chains (IIIa-d).

Compounds (IIa-c) were obtained by two routes: reaction of I with 1,3-chlorobromopropane, or acylation (I) with succinyl or adipoyl chloride followed by lithium aluminohydride reduction of the resulting diamides (IVa, b). Compounds (IIIa-d) were synthesized by acylating (I) with the ω-chloroalkanoyl chloride, and reacting the resulting ω-chloroacyl derivatives (Va-d) with piperazine.

The resulting compounds (II) and (III) were studied for their effects on the arterial pressure and cerebral circulation in comparison with (I). The most active compound was (IIIc), which reduced arterial pressure 16 times more than (I) (at equimolar doses). In order to obtain even more effective hypotensive agents by varying the structural features listed above, it will probably be necessary to increase the symmetry of the terminal moieties of the mole-



cule, to determine the significance of the interatomic distances between the different molecular groupings, and perhaps to evaluate the ability of this type of compound to form molecular or complex compounds with metal ions, primarily Ca^{2+}.

Scientific-Research Institute of Pharmacology, Academy of Medical Sciences of the USSR, Moscow. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 7, pp. 815-817, July, 1982. Original article submitted December 16, 1981.

TABLE 1. N-Substituted Salsolidines

Compound	Yield, %	mp, °C (decomp.)	Found, %				Molecular formula	Calculated, %			
			C	H	Cl	N		C	H	Cl	N
IIa·2HCl	57,3	160	57,65	7,86	12,72	5,14	$C_{27}H_{40}Cl_2N_2O_4 \cdot 2H_2O$	57,54	7,87	12,58	4,97
IIb·2HCl	45	247	63,09	8,26	12,29	5,06	$C_{30}H_{46}Cl_2N_2O_4$	63,27	8,13	12,47	4,92
IIc·2HCl	60	—	61,99	7,79	12,97	5,16	$C_{28}H_{42}Cl_2N_2O_4$	62,09	7,81	13,11	5,17
IIIa·2HCl	40	175	56,49	7,23	10,25	8,29	$C_{32}H_{46}Cl_2N_4O_6 \cdot 1,5H_2O$	56,46	7,26	10,42	8,23
IIIb·2HCl	58	152	59,14	7,44	10,25	8,08	$C_{34}H_{50}Cl_2N_4O_6 \cdot 0,5H_2O$	59,13	7,45	10,27	8,11
IIIc·$2C_4H_4O_4$*	23	—	60,49	7,21		6,50	$C_{44}H_{60}N_4O_{14} \cdot 0,25H_2O$	60,53	6,97		6,41
IIId·$2C_4H_4O_4$*	25	—	61,04	7,32		6,14	$C_{46}H_{64}N_4O_{14} \cdot 0,25H_2O$	61,29	7,21		6,21
VI·HCl	44,3	—	57,60	6,89	9,48	11,11	$C_{18}H_{24}ClN_3O_3 \cdot 0,5H_2O$	57,68	6,72	9,46	11,20

*Crystallized from acetone.

Note: TLC on grade II alumina, basic form. Eluents: dichloroethane—acetone (system A), benzene—acetone (system B). Compound, R_f, and eluent system: IIa (grade IV alumina), 0.35, A (3:1); IIb, 0.58, B (5:1); IIc, 0.65, B (2:1); IIIa, 0.17, A (3:1); IIIb, 0.27, A (3:2); IIIc, 0.31, A (3:1); IIId, 0.33, A (3:1); VI, 0.2, a (3:2).

EXPERIMENTAL CHEMICAL PART

The purity of the compounds was checked (as the mono- or dihydrochlorides, and the dimaleates) by TLC on grade II or grade IV basic alumina. All the novel compounds, and the known intermediates (Va-d), gave a single spot on the chromatogram. The compounds were dried in vacuo over P_2O_5 at 80 °C for 2 h.

1,4-Bis(salsolidinyl-2-oxoethylpiperazine) Dihydrochloride (IIIa). To 2.07 g (0.01 mole) of (I) and 1.7 ml (0.012 mole) or triethylamine in 20 ml of dichloroethane was added dropwise with stirring at a temperature of 0-4°C 1.21 g (0.012 mole) of chloroacetyl chloride in 10 ml of dry dichloroethane. The mixture was stirred at this temperature for 30 min, and kept at room temperature for 1 h. The suspension was washed with dilute hydrochloric acid, water, sodium carbonate solution, and again with water. The organic layer was dried over magnesium sulfate, the filtrate evaporated in vacuo, and to the residue of crude Va was added 0.97 g (0.005 mole) of piperazine hexahydrate and 10 ml of toluene. The mixture was boiled for 10 h, and the reaction mixture treated with dilute sodium carbonate solution and dichloroethane. The organic layer was separated, dried over magnesium sulfate, filtered, and the solvent removed in vacuo. The residue was washed by decantation with dry ether, dissolved in dry dichloroethane, treated with ether saturated with hydrogen chloride, and an equal volume of ether. Filtration gave 1.35 g of the crystalline hydrochloride IIIa. Similarly, via the crude compounds (Vb-d) were obtained (IIIb-d), the last two compounds being isolated as the dimaleates.

1,3-Bis(salsolidin-2-yl)propane Dihydrochloride (IIa). A mixture of 2.07 g (0.01 mole) of (I), 2.01 g (0.02 mole) of sodium carbonate, 0.79 g (0.005 mole) of 1,3-bromochloropropane, and 10 ml of toluene was boiled for 12 h. The solvent was distilled off in vacuo, the residue treated with water and ether, and the aqueous layer extracted with ether. The combined ethereal extracts were dried over magnesium sulfate, filtered, and the filtrate treated with saturated ethereal hydrogen chloride. The solid was filtered off, washed with ether and acetone, dissolved with warming in dichloroethane, and the dihydrochloride (IIa) precipitated by adding twice the volume of acetone.

Succinic acid bis(salsolidin-2-yl)amide (IVa) and adipic acid bis(salsolidin-2-yl)amide (IVb) were obtained as for (V) in yields of 83 and 72% (0.015 mole of triethylamine and 0.015 mole of succinyl or adipyl chloride respectively were taken per 0.025 mole of (I)).

1,4-Bis(salsolidin-2-yl)butane Dihydrochloride (IIb). A suspension of 1 g (0.025 mole) of lithium aluminohydride in 50 ml of absolute ether was stirred for 1 h, then a solution of 2.5 g (0.005 mole) of the diamide (IVa) in 10 ml of dry tetrahydrofuran was added dropwise. The mixture was boiled with stirring for 8 h, and the mixture after cooling was worked up in the usual way. The ether layer was separated, washed with water, extracted with dilute hydrochloric acid, the acid extract washed with ether, basified with sodium hydroxide solution, extracted with ether, the extract dried with magnesium sulfate, and the filtrate treated with saturated ethereal hydrogen chloride. The precipitate was filtered off, washed with dry ether, and crystallized from absolute alcohol to give 1.2 g of the dihydrochloride (IIb).

Dihydrochloride (IIc) was obtained from diamide (IVb).

2-[β-(1-Imidazolyl)propionyl]salsolidine Dihydrochloride (VI). Crude (Vb) was prepared, and to the residue after removal of the dichloroethane was added 1.76 g (0.02 mole) of imidazole and 10 ml of toluene. The mixture was boiled for 10 h, cooled, treated with water, extracted with dichloroethane, and the organic layer washed with water. The subsequent workup was as for (IIIa). The compound was purified by solution in dichloroethane followed by precipitation with ether.

Data on (IIa-c), (IIIa-d), and (VI) are given in Table 1.

EXPERIMENTAL PHARMACOLOGICAL PART

Experiments were carried out on cats under general anesthesia (urethane and chloralose), with artificial pulmonary ventilation. The blood flow to the brain through the internal maxillary artery was measured with a "Nikhon koden" electromagnetic flowmeter. At the same time, the EEG of the parietal region, the ECG in II leads, and the arterial pressure in the femoral artery were recorded. Recording was carried out on a Mingograph-81 apparatus.

In a dose of 10 mg/kg, (IIIc) on intravenous administration to cats caused a reduction in arterial pressure by on average 36 ± 2.7% (29-43). The compound reduced the volume flow rate of the cerebral blood supply by 17 ± 2.2% (11-23). The effect was noted immediately following administration of the compound, and continued for 10 min.

Intravenous administration of a dose of 10 mg/kg of (IIId) to cats reduced the arterial pressure by only 14 ± 0.4% (13-15), and the cerebral blood flow decreased by 28 ± 8.1%. The effect lasted for 10 min. For comparison, the effects of salsolidine on the arterial pressure and cerebral blood flow were examined. In a dose of 20 mg/kg intravenously, salsolidine had no marked effect on the arterial pressure and the cerebral circulation. In a dose of 50 mg/kg, salsolidine reduced the arterial pressure and decreased the cerebral blood flow to the same extent as (IIIc) at 10 mg/kg, i.e., by 36 and 12% respectively.

Thus, these compounds possess hypotensive properties, and reduce the cerebral blood supply, apparently as a result of the hypotension.

Compounds (IIIa, b) and (VI) [compound (VI) was obtained for purposes of comparison, since the imidazole residue is known to have pharmcoproperties] in doses of 5-10 mg/kg had weak hypotensive effects, and had no advantages over salsolidine.

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ANALOGS OF ACETYLCHOLINE AND DIACETYLCHOLINE CONTAINING ADAMANTYL RADICALS

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UDC 615.216.5+615.217.3]:577.175.822].015.11

Earlier it was shown [1] that when a methyl group is replaced by a highly lipophilic adamantyl radical, cholinomimetics lose their depolarizing properties and are converted to cholinolytics. This phenomenon is evidently associated with a change in the conditions of fixation of the substances on the synaptic membrane on account of hydrophobic interactions. The pattern found has been confirmed on a large series of compounds, primarily in the comparison of acetylcholine (Ia) and diacetylcholine (succinylcholine, ditilin, IIa) with their adamantyl analogs (Ib and IIb) [2]. The latter possessed the properties of cholinolytics; moreover, the adamantyl analog of diacetylcholine (IIb), called diadonium, has been approved for use in anesthesiological practice as a nonpolarizing myorelaxant [3].

We were interested in tracing the influence of different localization of the adamantyl radical on the magnitude and nature of the cholinergic activity of adamantyl derivatives of acetylcholine and diacetylcholine. Information on the role of individual fragments of the structure of curare-like substances in the mechanism, activity, and duration of their action may be useful for an approach to the understanding of the structure of the cholinoreceptors of the skeletal muscles and the mechanism of neuromuscular block, as well as for planning means of directed synthesis of myorelaxants with set properties. For this purpose we synthesized a series of analogs of I and II, in which the adamantyl radical is bounded directly to a quaternary nitrogen atom, separated from it by one or two methylene groups, or is found in the amino alcohol or acid portion of the molecule.

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 16, No. 7, pp. 818-822, July, 1982. Original article submitted June 18, 1981.

0091-150X/82/1607-0542$07.50