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SYNTHESIS AND PHARMACOLOGICAL ACTIVITY OF STEREOISOMERIC DERIVATIVES OF trans-DECAHYDROQUINOLINE

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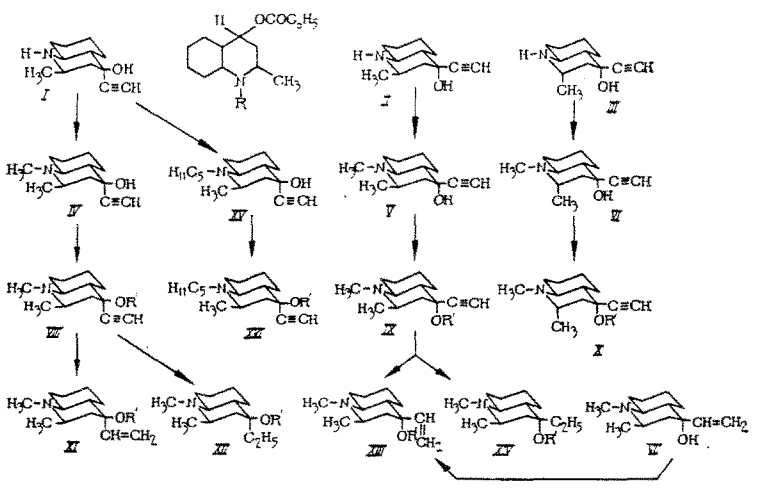
Compounds with high anesthetizing activity have been detected among oxygen derivatives of decahydroquinoline [8]. A number of stereoisomeric benzoic acid esters of 1-R-2-methyl-decahydroquinoline-4-ol (R = C_1-C_5 alkyl, allyl, etc.) have clearly expressed local-anesthetic activity [10]. However, they, like the anesthetics being used in practice, do not fully meet the modern requirements of practical medicine, chiefly because of their toxicity and irritating properties. The problem of the search for and creation of new effective local anesthetics therefore continues to remain an extremely urgent matter.

The simple and practicable methods that we have developed for obtaining three geometrical isomers of 2-methyl- (I-III) and 1,2-dimethyl-4-ethynyl-trans-decahydroqunolin-4-ol (IV-VI) [6,9] have created favorable possibilities for the synthesis of anesthetics of the decahydroquinoline series with ethynyl, vinyl, and ethyl groups attached to $C_{(4)}$, which have not been studied in a pharmacological respect. These studies make it possible to trace the dependence of the pharmacological properties of the compounds on the spatial orientation and nature of the substituents attached to $C_{(2)}$ and $C_{(4)}$.

In this connection, in the present research we obtained previously undescribed decahydroquinoline derivatives and studied their pharmacological properties.

Stereoisomeric acetylenic alcohols IV-VI [6, 9], which were obtained by N-methylation of noramino alcohols I-III, served as the starting substances.



R = alkyl C_1 - C_5 , allyl et al.; R'=COC_6H_5.

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TABLE 1. Decahydroquinoline Derivatives VIII-XIV and XVI and Their Properties

Compound	Benzoylation time, h	Yield, %	mp, °C	R_f	Found, %				Empirical formula	Calc., %				IR Spectra, cm^{-1}		
					C	H	Cl	N		C	H	Cl	N	νC=O	νC≡C	ν≡CH
VIII	3	86,6	174—5	0,71	77,61	8,29	—	4,66	$C_{20}H_{25}NO_2$	77,14	8,09	—	4,49	1730	2115	3320
VIII·HCl	—		205—6		69,15	7,68	10,56	4,18	$C_{20}H_{26}NO_2Cl$	69,05	7,63	10,20	4,02			
IX	13	61,5	126—7	0,60	76,98	8,21	—	4,35	$C_{20}H_{25}NO_2$	77,14	8,09	—	4,49	1725	2110	3320
IX·HCl	—		249		69,18	7,59	10,66	3,95	$C_{20}H_{26}NO_2Cl$	69,05	7,63	10,20	4,02			
X	25	50	154—5	0,55	77,28	8,14	—	4,59	$C_{20}H_{25}NO_2$	77,14	8,09	—	4,49	1730	2115	3280
X·HCl	—		217—8		69,17	7,73	9,88	4,13	$C_{20}H_{26}NO_2Cl$	69,05	7,63	10,20	4,02			
XI	—	80	138—9	0,62	76,13	8,52	—	4,63	$C_{20}H_{27}NO_2$	76,64	8,68	—	4,47	1735	—	—
XI·HCl	—		180—1		68,93	7,95	...	4,06	$C_{20}H_{28}NO_2Cl$	68,65	8,07	...	3,98			
XII	—	46	118—9		76,75	9,10	—	4,56	$C_{20}H_{29}NO_2$	76,66	9,27	—	4,74	1735	—	—
XII·HCl	—		oil	0,41	...	...	...	...	$C_{20}H_{30}NO_2Cl$	...	...	...	...			
XIII	11	63,6	136—7	0,55	77,11	8,91	—	4,13	$C_{20}H_{27}NO_2$	76,64	8,68	—	4,47	1730		
XIII·HCl	—		172—3		68,03	8,12	...	3,98	$C_{20}H_{28}NO_2Cl$	68,65	8,07		3,98			
XIV	—	81	106—7	0,20	76,21	9,12	—	4,68	$C_{20}H_{29}NO_2$	76,66	9,27	—	4,44	1725	—	—
XIV·HCl	—		oil		...	...	...	...	$C_{20}H_{30}NO_2Cl$	...	...	...				
XVI	11	49	111—2	0,49	78,26	9,08	—	3,92	$C_{24}H_{33}NO_2$	78,43	9,08	—	3,81	1730	2115	3300
XVI·HCl	—		208—9		71,61	8,29	...	3,59	$C_{24}H_{34}NO_2Cl$	71,35	8,48	...	3,47			

Notes. 1. Compounds VIII, X, and XI were recrystallized from acetone, and the remaining compounds were recrystallized from petroleum ether; VIII·HCl-XIV·HCl and XVI·HCl were recrystallized from ethanol or a mixture of ethanol with ether. 2. Nazarov and co-workers [5] described the production of VIII in low yield on the basis of an unseparated mixture of isomers of 1,2-dimethyl-4-ethynyldecahydroquinolin-4-ol; however, they could not obtain VIII·HCl, and its pharmacological properties therefore were not studied.

The corresponding stereoisomers (VIII-X) of 1,2-dimethyl-4-ethynyl-4-benzoxy-trans-decahydroquinoline were obtained by the reaction of the hydrochlorides of stereoisomeric amino alcohols IV-VI with PhCoCl in refluxing pyridine solutions. The 1-n-amyl derivative (XVI) was synthesized under similar conditions starting from the hydrochloride of acetylenic alcohol XV, which was obtained by alkylation of noramino alcohol I with n-amyl iodide in ethyl acetate in the presence of potassium carbonate. The benzoylation reaction times and yields of products vary as a function of the three-dimensional structures of the starting alcohols (Table 1). Thus in the case of the epimeric pair IV and V, alcohol IV, with an equatorial hydroxy group, under identical conditions is acylated approximately four times faster than its axial epimer V. These results are in conformity with one of the rules of conformational analysis [3] and constitute yet another confirmation of the correctness of the previously assigned configurations of alcohols IV and V [9]. The corresponding 1,2-dimethyl-4-vinyl-4-benzoxy-trans-decahydroquinolines XI and XIII were obtained by selective hydrogenation of the triple bond of the hydrochlorides of VIII and IX on a palladium catalyst applied to $CaVO_3$. However, the yield of benzoate XIII obtained via this method does not exceed 22%. Compound XIII was therefore synthesized in 63.6% yield by another method, viz., by benzolylation of 1,2-dimethyl-4-vinyl-trans-decahydroquinolin-4-ol VII under the conditions described above [6]. 1,2-Dimethyl-4-ethyl-4-benzoxy-trans-decahydroquinolines XII and XIV were synthesized by exhaustive hydrogenation of the triple bond of the hydrochlorides of the same amino esters VIII and IX in the presence of Raney nickel. According to the results of thin-layer chromatography (TLC), the exhaustive and selective hydrogenation of the triple bond of benzoate X·HCl under the conditions described above proceeds completely with the formation in each case of a single reaction product. However, workup of the reaction mixture even under mild conditions (with ammonium hydroxide in the cold) leads to saponification of the ester group of the desired products with the formation of the corresponding isomers of 1,2a-dimethyl-4e-vinyl (ethyl)-trans-decahydroquinolin-4a-ol; this is confirmed by the absence of depression of the melting points of the latter in mixtures with genuine samples [7] and by the complete coincidence of their IR spectra.

The structures of the synthesized compounds were confirmed by the results of elementary analysis and IR spectroscopy (see Table 1). Intense absorption bands at 1725-1735 cm^{-1}, which are characteristic for an ester carbonyl group, are observed in the IR spectra of benzoates VIII-XIV and XVI. Absorption bands of hydroxy groups are absent. Absorption bands of the stretching vibrations of the C≡C and ≡C—H bonds of VIII-X and XVI lie at 2110-2115 and 3280-3320 cm^{-1}, respectively.

The synthesized benzoic acid esters (VIII-XI, XIII, and XVI) of decahydroquinolin-4-ols were subjected to pharmacological study in the form of the hydrochlorides, which are readily soluble in water (see Table 1).

EXPERIMENTAL CHEMICAL

The course of the reactions and the purity of the synthesized compounds were monitored by thin-layer chromatography (TLC) on alkaline activity III aluminum oxide with elution with diethyl ether—petroleum ether (2:1) and development with iodide vapors. The IR spectra of KCl pellets of the hydrochlorides and KBr pellets and CCl_4 solutions of the bases were recorded with a Zeiss UR-20 spectrometer (East Germany). The starting acetylenic alcohols I-VII were obtained by previously described methods [6, 7, 9].

1-n-Amyl-2-methyl-4-ethynyl-trans-decahydroquinolin-4-ol (XV). A mixture of 10 g (0.051 mole) of I, 10.3 g (0.051 mole) of n-amyl iodide, 7.2 g (0.051 mole) of K_2CO_3, and 200 ml of $CH_3COC_2H_5$ was heated at 75-80°C for 24 h, after which it was cooled and treated with a saturated solution of K_2CO_3. This mixture was extracted with diethyl ether, and the combined extracts were dried over K_2CO_3. The solvents were evaporated, and the residue was recyrstallized from ether to give 10.4 g (76%) of XV in the form of an oil. Found, %: C 77.68; H 11.01; N 4.98. $C_{17}H_{29}NO$. Calculated, %: C 77.92, H 11.26, N 5.04.

Hydrochloride XV·HCl. This compound was obtained in quantitative yield by treatment of an alcohol solution of XV with an ether solution of hydrogen chloride. Workup gave fine colorless crystals with mp 103-104°C (alcohol—ether). Found, %: 68.71; H 10.02; Cl 11.01; N 4.72. $C_{17}H_{29}NO·HCl$. Calculated,%: C 68.97, H 10.27; Cl 11.29; N 4.46.

General Method for the Benzolylation of Alcohols IV-VII and XV. Preparation of Benzoic Acid Esters VIII-X, XIII, and XVI. A mixture of 0.02 mole of the hydrochloride of the corresponding amino alcohol, 0.07 mole of PhCOCl, and 10 ml of dry pyridine was heated at 115-120°C until the reaction was complete. The end of the reaction was determined by means of TLC from

TABLE 2. Activity of the Compounds in Various Forms of Anesthesia and Their Toxicities

Compound	Solution concn., %	Topical anesthesia		Infilt. anesthesia		Conductor anesthesia		LD_{50}, mg/kg	
		A	B	A	B	A	B	SC	IP
VIII·HCl	0,25	580±31	7	34±8,0	15				
	0,5	665±66	12	32±3	115			458	196
	1	869±54	17	36+0	150				
	2	1084±118	42			100±50			
IX·HCl	0,5	225±18		20±0,5	10				
	1	187±13		25±2	10	No anesthesia		255	...
X·HCl	0,5			28±4					
	1			36+0	30	12±0		>1000	...
	2			36±0	50				
XI·HCl	0,25	488±69	5	34±2	25				
	0,5	673±88	7	36±0	120	170±41		317	183
	1	596±34	12			503±27	30		
	2					589±19	60		
XIII·HCl	0,5	125±36		18±2					
XVI·HCl	0,25	1002±56	25					...	...
Dicain	0,5	1104±32	40	26±3	5			500	488
	0,25	1175±45	17						
Novocain	0,5	1183±60	27					41,5	57
	0,5			31±1,6	10				
	1			35±0,5	20			490±10	170±5
	2					292±43	15		

Note. A pertains to the index of anesthesia (M ± m), and B pertains to the total anesthesia time (in minutes).

the disappearance of the spot of the starting alcohol. The cooled mixture was treated with 40 ml of a saturated solution of K_2CO_3, and the acylation product was extracted repeatedly with ether. The extract was dried, the solvents were removed, and the crystalline residue was recrystallized to give the corresponding benzoic acid ester (see Table 1).

Hydrochlorides VIII·HCl-X·HCl, XIII·HCl, and XVI·HCl. These compounds were obtained in quantitative yields from the corresponding bases as described above.

Stereoisomeric 1,2-Dimethyl-4-vinyl-4-benzoxy-trans-decahydroquinolines XI and XIII. These compounds were obtained by hydrogenation of 0.007 mole of the hydrochlorides of the corresponding amino alcohols VIII and IX in anhydrous alcohol (125 ml) in the presence of 0.25 g of a 5% Pd catalyst applied to $CaCO_3$. After absorption of the theroetically necessary amount of H_2 (1 mole), hydrogenation was discontinued, and the catalyst was removed by filtration. The solvent was removed, and the residue was recrystallized until its melting point was constant (one to two recrystallizations). This procedure gave XI·HCl and XIII·HCl, which were converted to the bases by the usual method.

Stereosiomeric 1,2-Dimethyl-4-ethyl-4-benzoxy-trans-decahydroquinolines XII and XIV. These compounds were obtained from 0.007 mole of the hydrochlorides of acetylenic decahydroquinolols VIII and IX by complete catalytic hydrogenation in anhydrous alcohol (100 ml) in the presence of 2.5 g of Raney nickel catalyst. After absorption of the theoretically necessary amount of H_2 (2 moles), hydrogenation was discontinued. The reaction products were isolated as described above.

The yields, constants, results of elementary analysis, and data from the IR spectra of the synthesized substances are presented in Table 1.

EXPERIMENTAL PHARMACOLOGICAL

In experiments on laboratory animals we studied the acute toxicity and local-anesthetic activity (in the case of various forms of anesthesia) of the crystalline and water-soluble hydrochlorides VII·HCl-XI·HCl, XIII·HCl, and XVI·HCl. In addition, we investigated the m-cholinolytic, papaverinelike, and antihistamine activity of XI·HCl.

The acute toxicity was determined in the case of subcutaneous (SC) and intraperitoneal (IP) administration in white mongrel mice of both sexes with masses of 18-21 g. The LD_{50} values were calculated by the method of Litchfield and Wilcoxon [12], and the death rate in the course of 24 h was taken into account.

TABLE 3. m-Choline-blocking, Papaverinelike, and Antihistamine Activity of XI·HCl

Compound	Acetylcholine-induced spasm		Barium chloride-induced spasm		Histamine-induced spasm	
	A	B	A	B	A	B
XI·HCl	$4 \cdot 10^{-5}$	$4 \cdot 10^{-5}$	$3 \cdot 10^{-5}$	$3 \cdot 10^{-5}$	$8 \cdot 10^{-6}$	$4 \cdot 10^{-5}$
Atropine	$4 \cdot 10^{-7}$	$5 \cdot 10^{-6}$				
Papaverine			$3 \cdot 10^{-5}$	$9 \cdot 10^{-5}$		
Dimedrol					$1 \cdot 10^{-7}$	$2 \cdot 10^{-7}$

Note. The lowest concentrations that eliminate (A) and prevent (B) spasm of the smooth musculature are presented.

Topical anesthesia was established on the corneas of the eyes of rabbits by the method of Regnier and Valette [2]; infiltration anesthesia was established by subcutaneous administration to guinea pigs by the method of Bulbring and Wajda [11], and conductor anesthesia was established in the sciatic nerve of frogs [1]. The anesthetizing activity of the compounds was compared with the standard preparations dicain in the case of topical anesthesia and novocain in the case of inflitration and conductor anesthesia.

The m-choline-blocking and papaverinelike activity were studied on isolated sections of the small intestines of rabbits, and the antihistamine activity was studied on isolated sections of the small intestines of guinea pigs. For comparison, similar experiments were set up where the standard preparations were compared with respect to the lowest concentrations that eliminated the spasm of the smooth musculature of the intestines induced by acetylcholine, barium chloride, and histamine. The results of the investigation of the local-anesthetic activity and toxicity of the compounds are presented in Table 2.

The LD_{50} values of the synthesized substances ranged from 255 to 100 mg/kg (see Table 2).

Benzoate XVI·HCl with an n-amyl radical attached to the nitrogen atom proved to be the most effective compound in topical anesthesia; it approaches dicain with respect to anesthesia strength but surpasses it significantly with respect to total anesthesia time. Despite its overall toxicity, XVI·HCl has a pronounced local-irritant effect, which is manifested in hyperemia of the conjuctiva and blepharospasm in rabbits and the development of necrosis at the sites of subcutaneous administration in guinea pigs. Compounds VIII·HCl and XI·HCl, which have only different radicals attached to the $C_{(4)}$ atom, differ little from one another with respect to activity in topical and infiltration anesthesia. Slight irritant properties develop with an increase in the concentration in the case of XI·HCl, and this leads to a decrease in the index of topical anesthesia; these undesirable properties are less pronounced in the case of VIII·HCl.

Attention is directed to the long times of infiltration anesthesia induced by these compounds. Thus, for example, the time of total anesthesia induced by a 0.5% solution of XI·HCl exceeds that of novocain by a factor of 12. Anesthesia of almost the same duration is induced by VIII·HCl; however, in one of the six experimental guinea pigs sensitivity was restored sooner than 0.5 h from the moment of its administration, and this led to a decrease in the index. In 11 cases, 1% solutions of this benzoate induced total anesthesia for up to 2.5 h.

A significant difference in the activity of the preparations was displayed in conductor anesthesia: whereas 2% solutions of VIII·HCl virtually did not induce anesthesia, solutions of XI·HCl of the same concentrations led to profound and prolonged disruption of conductivity via the sciatic nerve of frogs. In this respect, XI·HCl surpasses novocain by a factor of two. The X·HCl isomer did not induce conductor anesthesia, and infiltration anesthesia of sufficient depth was achieved only the use of 1% and 2% solutions; however, with respect to duration, its anesthesia was inferior to that of the corresponding concentrations of VIII·HCl and XI·HCl.

Compound IX·HCl was ineffective in all forms of anesthesia, and XIII·HCl was ineffective in topical and infiltration anesthesia and had virtually no local-anesthetic activity.

All of the investigated substances have m-choline-blocking, papaverinelike, and antihistamine activity; this is reflected in Table 3. These effects are most pronounced for XI·HCl.

An analysis of the results of the pharmacological tests makes it possible to draw the following conclusions.

The toxicities and pharmacological activities of the investigated compounds depend to a significant extent on a number of steric factors. Benzoate X·HCl with an axial methyl group attached to the $C_{(2)}$ atom of the decahydroquinoline ring has very low toxicity. Shifting the indicated methyl group from an axial to an equatorial orientation (IX·HCl) leads to a sharp increase in the toxicity. Replacement of the methyl radical attached to the nitrogen atom in VIII by an n-amyl radical promotes the manifestation of strong topical anesthetizing activity (XVI·HCl). In the series of epimeric pairs VIII and IX and XI and XIII isomers VIII and XI with an equatorial orientation of the benzoxy group have the highest local-anesthetic activity and longest total anesthesia time, as well as the lowest toxicity. A similar principle was previously observed [4] in a series of cocaine isomers.

In contrast to the 4-ethynyl homolog VIII, the 4-vinyl derivative XI has pronounced papaverinelike activity.

It is expedient to continue the synthesis of compounds that induce prolonged infiltration anesthesia in this series.

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