SYNTHESIS AND PHARMACOLOGICAL PROPERTIES OF 3,4-DIOXYPIPERIDINE DERIVATIVES

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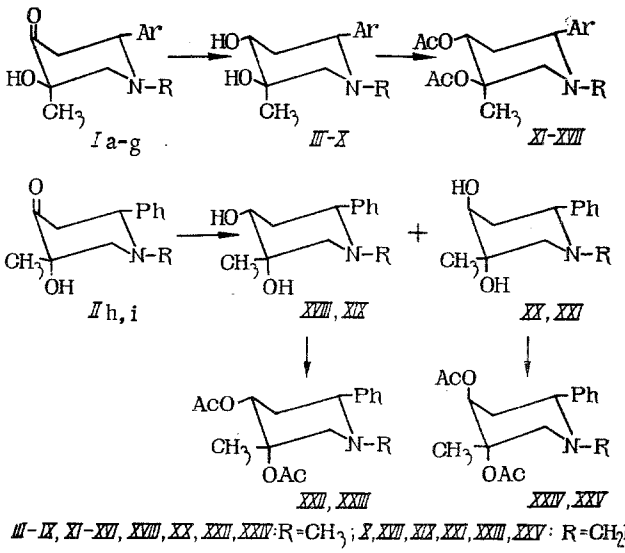
In search for new biological active substances in the oxypiperidine series, using a known method [1], we have synthesized a series of aryl-substituted stereoisomeric 3,4-dioxypiperidines (III-X, XVIII-XXI) and their diacetates (XI-XVII, XXII-XXV). Their structures were confirmed by elemental analysis and spectral data.



III-IX, XI-XVI, XVIII, XX, XXII, XXIV: R=CH3; I, XVII, XIX, XXI, XXIII, XXV: R=CH2Ph

The PMR spectra of diacetates XI and XVII show the 4-H proton signals at 5.20 and 5.25 ppm, and those of diacetates XXII and XXIII show the corresponding signals at 4.58 and 4.56, respectively, as 17 Hz wide quartets due to their axial orientation. On the contrary, the PMR spectra of acetates XXIV and XXV show the 4-H proton signals at 4.88 and 4.94 ppm, respectively, as 8 Hz wide triplets, indicating their equatorial orientation [2]. All the prepared dioxypiperidines, III-X and XVIII-XXI, as well as their diacetates, XI-XVII and XXII-XXV, were obtained as hydrochlorides well soluble in water.

EXPERIMENTAL

Chemical

PMR spectra were recorded in carbon tetrachloride solutions on a Varian NA-100 D-15 instrument using tetramethylsilane as an internal standard (ppm scale). Stereoisomeric 3-oxy-4-piperidines (Ia-g and IIh, i) were prepared as described earlier [3]. Data for these compounds are presented in Table 1.

1e,3a-Dimethyl-6e-aryl-(III-IX) and 1e-Benzyl-3a-methyl-6e-phenyl-3e,4e- (X)-dioxypiperidines. To a solution of compounds Ia-g (0.04 moles) in isopropyl alcohol (40 ml) was

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TABLE 1. Data for Compounds III-XXV

Compound	Ar	Yield, %	mp, °C	Found, %		Molecular formula	Calculated, %	
				N	Cl		N	Cl
III·HCl	C_6H_5	94	235—7	5,64	13,72	$C_{13}H_{19}NO_2 \cdot HCl$	5,43	13,79
IV	4-$CH_3C_6H_4$	85	174—5	5,69	—	$C_{14}H_{21}NO_2$	5,95	—
IV·HCl	4-$CH_3C_6H_4$	90	235—6	5,08	13,30	$C_{14}H_{21}NO_2 \cdot HCl$	5,15	13,07
V	4-$CH_3OC_6H_4$	79	131—2	5,43	—	$C_{14}H_{21}NO_3$	5,57	—
V·HCl	4-$CH_3OC_6H_4$	86	208—9	5,01	12,28	$C_{14}H_{21}NO_3 \cdot HCl$	4,87	12,35
VI	2-ClC_6H_4	82	142—3	5,34	13,70	$C_{13}H_{16}ClNO_2$	5,48	13,89
VI·HCl	2-ClC_6H_4	92	215—6	4,83	24,46	$C_{13}H_{16}ClNO_2 \cdot HCl$	4,79	24,32
VII	4-ClC_6H_4	88	153—4	5,41	13,84	$C_{13}H_{16}ClNO_2$	5,48	13,89
VII·HCl	4-ClC_6H_4	95	240—2	4,90	24,38	$C_{13}H_{16}ClNO_2 \cdot HCl$	4,79	24,32
VIII	2-FC_6H_4	84	130—1	5,94	—	$C_{13}H_{16}FNO_2$	5,86	—
VIII·HCl	2-FC_6H_4	94	235—7	4,90	13,14	$C_{13}H_{16}FNO_2 \cdot HCl$	5,08	12,89
IX	4-BrC_6H_4	86	176—7	4,83	26,50*	$C_{13}H_{16}BrNO_2$	4,67	26,67
IX·HCl	4-BrC_6H_4	90	242—4	4,28	10,40	$C_{13}H_{16}BrNO_2 \cdot HCl$	4,16	10,55
X·HCl	C_6H_5	94	215—7	4,06	10,53	$C_{19}H_{23}NO_2 \cdot HCl$	4,20	10,64
XI	C_6H_5	80	115—6	4,42	—	$C_{17}H_{23}NO_4$	4,13	—
XI·HCl	C_6H_5	88	223—4	4,27	10,38	$C_{17}H_{23}NO_4 \cdot HCl$	4,10	10,40
XII	4-$CH_3C_6H_4$	76	120—1	4,56	—	$C_{18}H_{25}NO_4$	4,39	—
XII·HCl	4-$CH_3C_6H_4$	91	221—3	4,12	9,72	$C_{18}H_{25}NO_4 \cdot HCl$	3,94	9,99
XIII	2-ClC_6H_4	78	109—10	4,18	10,30	$C_{17}H_{22}ClNO_4$	4,12	10,46
XIII·HCl	2-ClC_6H_4	85	217—8	3,60	19,07	$C_{17}H_{22}ClNO_4 \cdot HCl$	3,72	16,90
XIV	4-ClC_6H_4	82	76—7	3,88	10,41	$C_{17}H_{22}ClNO_4$	4,12	10,46
XIV·HCl	4-ClC_6H_4	90	193—4	3,66	18,84	$C_{17}H_{22}ClNO_4 \cdot HCl$	3,72	18,90
XV	2-FC_6H_4	74	84—5	4,54	—	$C_{17}H_{22}FNO_4$	4,33	—
XV·HCl	2-FC_6H_4	86	220—1	3,83	9,16	$C_{17}H_{22}NFO_4 \cdot HCl$	3,62	9,04
XVI	4-BrC_6H_4	85	73—4	3,60	21,06*	$C_{17}H_{22}BrNO_4$	3,65	20,83
XVI·HCl	4-BrC_6H_4	94	208—10	3,16	8,33	$C_{17}H_{22}BrNO_4 \cdot HCl$	3,31	8,45
XVII	C_6H_5	80	94—5	3,82	—	$C_{23}H_{27}NO_4$	3,67	—
XVII·HCl	C_6H_5	89	202—4	3,40	8,70	$C_{23}H_{27}NO_4 \cdot HCl$	3,31	8,50
XVIII·HCl	—	75	208—10	5,31	13,63	$C_{13}H_{19}NO_2 \cdot HCl$	5,43	13,79
XIX·HCl	—	78	193—4	4,18	10,82	$C_{19}H_{23}NO_2 \cdot HCl$	4,20	10,64
XX·HCl	—	70	201—3	5,60	13,90	$C_{13}H_{19}NO_2 \cdot HCl$	5,43	13,79
XXI·HCl	—	81	187—8	4,06	10,68	$C_{19}H_{23}NO_2 \cdot HCl$	4,20	10,64
XXII	—	77	87—8	4,24	—	$C_{17}H_{23}NO_4$	4,59	—
XXII·HCl	—	84	227—8	3,92	10,50	$C_{17}E_{23}NO_4 \cdot HCl$	4,10	10,40
XXIII	—	81	67—8	3,77	—	$C_{23}H_{27}NO_4$	3,67	—
XXIII·HCl	—	90	197—9	3,56	8,83	$C_{23}H_{27}NO_4 \cdot HCl$	3,31	8,50
XXIV	—	73	52—3	4,40	—	$C_{17}H_{23}NO_4$	4,59	—
XXIV·HCl	—	87	223—4	4,19	10,14	$C_{17}H_{23}NO_4 \cdot HCl$	4,10	10,40
XXV	—	70	68—9	3,58	—	$C_{23}H_{27}NO_4$	3,67	—
XXV·HCl	—	74	192—4	3,13	8,66	$C_{23}H_{27}NO_4 \cdot HCl$	3,31	8,50

*Analyzed on Br.

added portions of sodium borohydride (7.5g). The reaction mixture was kept at 20-25°C for 2 h, acidified with acetic acid, the solvent removed, and the residue dissolved in water (50 ml) and made alkaline with potassium carbonate. The product was filtered, dried in air, and crystallized from a mixture of heptane:dioxane (3:1).

1e,3e-Dimethyl- (XVIII), 1e-Benzyl-3e-methyl-6e-phenyl-3a, 4e-Dioxypiperidines (XIX), and 1e,3e-Dimethyl-(XX), 1e-Benzyl-3e-methyl-6e-phenyl-3a, 4a-Dioxypiperidine (XXI). These compounds were prepared by reduction of compound IIh as described above, but with the following difference: After the alkalinization the reaction products were extracted with ether, the ether was removed, and the residual stereoisomeric diols were separated by preparative chromatography on a column of aluminum oxide (activity grade II) at a ratio of adsorbent: substance = 100:1, and using hexane:ether (1:1) for the separation of diols XVIII and XIX, and ether:methanol (1:1) for the separation of diols XX and XXI.

Hydrochlorides of dioxypiperidines III-IX and XVIII-XXI were obtained by treating the solutions of the corresponding bases, in methylethylketone, with gaseous hydrogen chloride and a subsequent crystallization from a mixture of methylethylketone-isopropyl alcohol.

3,4-Dioxypiperidines Diacetates (XI-XVII and XXII-XXV). To a solution of diols III-X and XVIII-XXI (0.05 moles) in acetic acid (10-15 ml) was added acetyl chloride (15 ml). The reaction mixture was kept at 20-25°C for 20 h and then diluted with anhydrous ether. Compounds XI·HCL-XVII·HCl and XXII·HCl-XXV·HCl were filtered and crystallized from a mixtures of methylethylketone—isopropyl alcohol. Diacetates XI-XVII and XXII-XXV were obtained by treating aqueous solutions of the hydrochlorides with a small excess of sodium hydroxide,

TABLE 2. Toxicity and Some Pharmacological Effects of 3,4-Dioxypiperidine Derivatives

Compound	Toxicity (intraperitoneally)		Radioprotective effect				Antihypoxic effect		Surface anesthesia (Rene index)
	LD_{16} $LD_{50} \pm m$ LD_{84} mg/kg	general activity	number of animals	dose, mg/kg	survival rate, %	life duration in days	life duration in min (experiment/control)	protection index	
III·HCl	264		20	K	0	9,0±0,8			
	340±32	S	10	132	0	11,1±0,9	2,4±0,2	1,33	—
	440		10	33	0	11,4±1,5	1,6±0,3		
IV·HCl	765		40	K	2,5	9,1±0,5	2,4±0,3		
	805±16,3	D	30	383	7	8,2±0,5	2,4±0,7	1,0	15
	855		10	96	10	7,2±0,8			
V·HCl	643		20	K	0	9,8±0,5	4,2±0,6		
	753±52,8	D	10	321	10	12,6±2,4	1,8±0,3	2,33	15
	880		10	80	10	10,8±0,8			
VI·HCl	166		20	K	0	8,0±0,5	3,6±0,7		
	233±26,0	D	10	83	0	7,5±1,3	2,4±0,7	1,41	15
	330		10	21	0	6,5±0,8			
VII·HCl	216		20	K	20	11,1±1,9			
	276±24,5	D	10	108	10	12,4±1,1	3,1±0,3	1,29	—
	350		10	27	0	7,9±0,6	2,4±0,7		
VIII·HCl	240		40	K	0	8,5±0,4			
	300±24,6	S	10	120	0	12,5±2,1	4,4±1,9	1,2	15
	375		30	30	7	8,7±0,6	3,7±1,0		
X·HCl	105		20	K	0	8,6±0,9			
	141±15,3	S	10	52	0	9,9±0,4	2,9±0.4	1,61	864,0±64,5
	189		10	13	0	10,4±1,0	1,8±0,3		
XI·HCl	568		70	K^1	20	12,5±0,7	1,0±0,2		
	590±8,54	S	40	284	35	11,7±0,8	0,7±0,2	1,14	15
	615		30	71	13,3	12,1±1,2			
XII·HCl	584		20	K	10	11,7±1,4	1,5±0,3		
	880±82,2	D	10	292	38	13,0±2,4	0,9±0,2	1,67	—
	1134		10	73	0	10,2±1,4			
XIII·HCl	436		20	K	10	11,7±1,4	1,2±0,1		
	483±18,1	D	10	218	10	13,6±1,8	0,7±0,2	1,71	—
	535		10	55	0	12,4±0,8			
XV·HCl	400		50	K	12	10,9±0,6	7,9±1,3*	1,97	—
	542±62	D	10	200	10	11,3±1,7	4,0±1,1		
	750		50	50	16	12,9±0,8			
XVII·HCl	537		40	K	5	9,8±0,8	1,8±0,3*	2,44	15
	687±6,36	D	30	269	7	7,40±1,1	0,7±0,2		
	885		70	67	0	9,4±1,0			
XXIII·HCl	188		50	K	4	11,9±0,8			
	233±18,2	D	10	94	0	11,2±1,6	2,5±0,6*	2,78	15
	288		40	23	5	11,3±0,9	0 9±0,2		
XXIV·HCl	292		20	K	10	11,2±1,1			
	346±22,6	D	10	146	0	13,3±2,1	1,0±0,2	1,43	15
	420		10	36	10	12,0±0,5	0,7±,02		
XXV·HCl	420		40	K	7,5	12,4±0,9			
	485±26,5	D	10	210	20	10,9±1,1	1,8±0,8	0,85	—
	565		30	52	10	11,6±1,1	2,1±1,0		

*asterisk denotes the confidence.

Note. K-control, S-convulsions, D-depression, K^1-irradiation 10 R/min.

extracting with ether, drying the extracts over anhydrous magnesium sulfate, removing the ether, and crystallizing the residue from hexane.

EXPERIMENTAL

Pharmacological

The study of pharmacological properties of the 3,4-dioxypiperidine derivatives was carried out on 2,190 mongrel mice weighing 20-22 g, 15 cats, and 30 rabbits (isolated intestines and eye cornea). Acute toxicity at a single intraperitoneal administration was studied with mice [4], as well as the antihypoxic (decompression chamber SBK-48M at the height of 10,000 m for 15 min), radiation-protective (^{60}Co, 1,000 R, 70 R/min), local-anesthetic [5], and analgesic activities. The effect on mobility was studied using an Actometer (an electronic instrument measuring small capacity changes caused by the moving animal). The effect of these compounds on muscular tonus was also studied [7], as well as their effect on body temperature and Phenamine (10 mg/kg, intraperitoneally), reserpine (2.5 mg/kg, intraperitoneally), 5-oxytryptophane (50 mg/kg, intraperitoneally), apomorphine (10 mg/kg, intraperitoneally), Corazole (150 mg/kg, intraperitoneally), strychnine (1.5 mg/kg, subcutaneously), and arecholine (2.5 mg/kg, intraperitoneally) activities on arterial pressure, breathing, and choline receptors (in experiments on cats) using isolated rabbit intestines.

On single intraperitoneal administration, the LD_{50} indicator varied from 141 ± 15.3 to 805 ± 16.3 mg/kg. The most toxic of the 3e,4e-dioxypiperidine derivatives was X (141 mg/kg). On substituting the benzyl radical with methyl in position 1 (III, VI-VIII), the toxicity decreased by 1.6-2.5 times. Among the latter compounds, the least toxic was III with an unsubstituted phenyl in position 6. When p-methoxyphenyl (V) or p-tolyl (IV) radicals were introduced into position 6, the LD_{50} amounted to 753 and 805 mg/kg, respectively. The same relationship between the LD_{50} values and the chemical composition was found in 3,4-dioxypiperidine derivatives as in the dioxypiperidines, but the latter compounds were more toxic. All the investigated compounds, with the exception of III, VIII, X, and XI, when administered at LD_{50}, caused a depression of the central nervous system in mice.

In the experiments on mice, the "phenylpiperidine" derivatives (Table 2) decreased mobility (XI, XV, and XXV), decreased the tonus of the skeletal musculature and body temperature (XI and XVII), increased the pain sensitivity threshold (XI and XXV), prolonged life of the animals poisoned with strychnine and Corazole (XI, XVII, and XXIII), interfered with the central and peripheral effects of arecholine (XVII), decreased exophthalmos and the body temperature elevation on Phenamine administration (XI and XV), retarded the development of hypothermic effects of reserpine and apomorphine (XVII, XXIII, and XXV), and did not affect the intensity of the "head shaking" symptom caused by the administration of 5-oxytryptophane. In acute experiments with narcotized cats, compound XI caused a temporary curtailment of breathing, a decrease in blood pressure, and a brief disturbance in the cardiac vagus. Thereby, the functional state of the upper sympathetic ganglion was not altered.

In dilution of $3 \cdot 10^{-5}$ to $1 \cdot 10^{-5}$ compound XIV blocked the reaction of the isolated rabbit intestine on acetylcholine, while in dilution of $5 \cdot 10^{-4}$, compound XI depressed the action of histamine.

The compound 3a-methyl-1e-benzyl-6e-phenyl-3e,4e-dioxypiperidine (X) exhibited a local-anesthetic activity comparable with that of dicaine (Rene index 807.6 × 37.3 at full anesthesia 30-45 min and 50-60 min), while other compounds (IV-VI, VIII, IX, XVII, and XXIII) were inactive.

Among the investigated compounds the best radio-protective effect (38%) was exhibited by 1e,3a-dimethyl-6e-p-tolyl-3e,4e-dioxypiperidine diacetate hydrochloride (XII), while the other compounds (III-VIII, X, XIII, XV, XVII, XXIII-XXV) did not show it.

Antihypoxic activity was shown by compounds XXIII, XVII, V, XV, XIII, XII, and X.

LITERATURE CITED

1. L. S. Stanishevskii, I. G. Tishchenko, A. Ya. Guzikov, et al., Zh. Org. Khim., 11, 643 (1975).
2. N. S. Bkhakka and D. G. Williams, The Application of NMR in Organic Chemistry, Moscow (1966), p. 103.

3. L. S. Stanishevskii, I. G. Tishchenko, and A. Ya. Guzikov, Zh. Org. Khim., 7, 2612 (1971).
4. M. L. Belen'kii, Elements of the Quantitative Estimation of the Pharmacological Effect [in Russian], Leningrad (1963), p. 81.
5. J. L. Regnier, Methods for Measuring the Activity of General Anesthetics, Paris (1929), p. 12.
6. V. V. Gatsura, Methods for Primary Pharmacological Investigations of Biologically Active Compounds [in Russian], Moscow (1974), p. 142.
7. N. Dunham and T. Mija, J. Am. Pharm. Ass., Sci. Ed., 46, 208 (1957).

QUATERNARY SALTS OF D-(—)-1-(p-NITROPHENYL)-2-DIMETHYLAMINO-PROPANDIOL-1,3

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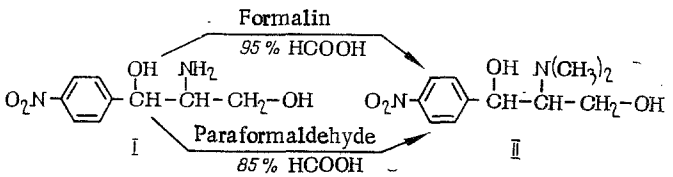
Compounds containing a quaternary ammonium group are of interest as physiologically active substances. Some of them show antifungal and antibacterial activities [1-4].

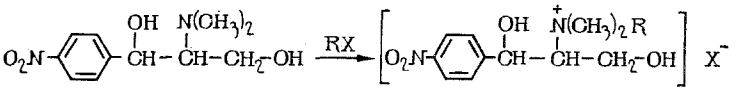
We have synthesized a series of quaternary salts starting with D-(—)-1-(p-nitrophenyl)-2-aminopropandiol-1,3 (I), an intermediate in the synthesis of levomycetin (chloramphenicol).

Primary amine I was first converted into tertiary D-(—)-1-(p-nitrophenyl)-2-dimethylaminopropandiol-1,3 (II) by the action of formic acid in the presence of formalin or paraformaldehyde according to the Leuckart-Wallach reaction [5].



The use of 85% formic acid in the presence of formalin did not produce the tertiary amine. The latter compound was produced by using 95% acid and formalin, or 85% acid and paraformaldehyde.

Quaternization of the tertiary amine II was carried out with the aid of n-alkyl halides containing 1-16 carbon atoms.



where R = C_1 – C_{16}, X = Br, I

It was established that the reaction with alkyl halides (with the exception of methyl iodide) did not take place in nitromethane and acetonitrile at 20-60°C for several days. The quaternary salts were formed in tetrahydrofurane under the given conditions, but in insignificant yields. Better yields were obtained by using a mixture of solvents at 37°C. The quaternary salts were precipitated from the solution with a fivefold volume of diethyl ether.

The quaternary salts are high-melting substances and are well soluble in water.

Their structure was confirmed by IR, UV, and argentometric titration data.

Some data for the prepared quaternary compounds are presented in Table 1.

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