EXPERIMENTAL (PHARMACOLOGY)

Antibacterial activity was studied by means of twofold batch cultures in a liquid culture medium corresponding to the microorganisms followed by inoculation of a pathogenic culture [2]. Lines of Staphyloccocus, Streptococcus, E. coli, Proteus, and Shigella were used in the study.

The experimental data obtained from the studies on antimicrobial activity indicated that the inhibitory activity of beroline was considerably strengthened by replacement of the methoxy group by hydroxyl at the 9-position of the isoquinoline ring (see Table 1).

The acute toxicity of the compounds was studied in white mice of weight 18-23 g. The LD_{50} values were calculated by the method of Kerber [1]. Agents were introduced in increasing doses.

It was shown from the experiments carried out that the inhibitory properties of the modified alkaloid were more pronounced and the acute toxicity had decreased substantially.

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SYNTHESIS AND RADIOPROTECTIVE ACTIVITY OF 2-PHENYLETHYLAMINE DERIVATIVES

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UDC 615.849.1.015.25:547.568].012.1

It has previously been shown [1, 2] that the radioprotective activity of 1-(m-hydroxyphenyl)-2-aminoethanol (I) is very dependent on the substituent at the nitrogen atom; it was found that compound I, and also its N-methyl (II) and N-ethyl (III) derivatives are very effective.

It was of interest to evaluate the role of the substituent at the β-carbon atom of the hydrocarbon chain in compounds of this type in the manifestation of the radioprotective effect, and hence to clarify whether the presence of a hydroxyl group in this position was necessary for obtaining this effect. For this purpose we synthesized a series of derivatives of I – II and III, and also the unsubstituted benzene ring analog, 1-phenyl-2-aminoethanol (IV).

We chose the corresponding chlorides (V-VII) as the starting materials, since it has been reported [6] that the hydroxyl group at the β-position of amine (IV) is readily replaced by chlorine by the action of $SOCl_2$. It has been also reported [8] that during the substitution of the OH group by halogen in compounds with phenolic hydroxyls, the latter have to be protected by an acyl group. However, the hydrochloride of (III), similarly as that of IV, reacts readily with $SOCl_2$ with the formation of chloride VII. In the case of the methyl analog milder conditions are required.

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 11, pp. 1349-1355, November, 1988. Original article submitted August 14, 1987.

0091-150X/88/2211-0857$12.50

$3\text{-}RC_6H_4CHR^1CH_2NR^2R^3$

I—XIX

R = OH (I—III, VI, VII, IX, XI, XIII—XVII, XIX), H (IV, V, VIII, X, XII), AcO (XVIII); R^1 = OH (I—IV, XIV), Cl (V—VII, XV), SSO_3H (VIII, IX), SPO_3NaH (X), SPO_3H_2 (XI), SH (XII), H (XIII), OMe (XVI), AcO (XVII, XVIII), PhCOO (XIX); R^2 = H (I—XIII, XVI—XIX); $R^2 + R^3 = HCC_6H_4OMe\text{-}4$ (XIV, XV), R^3 = H (I, IV, V, VIII, X, XII, XVI, XIX), Me (II, VI, XIII, XVII, XVIII), Et (III, VII, IX, XI).

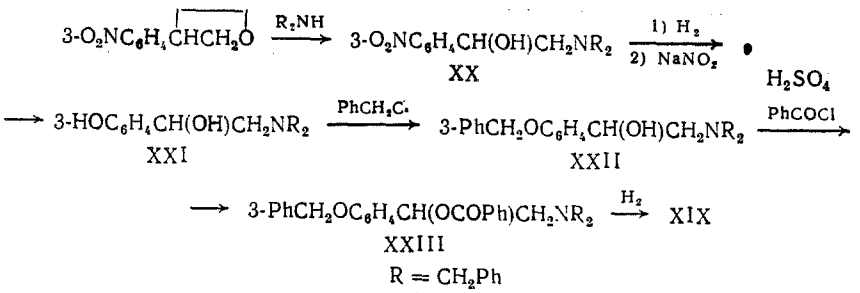
Despite variation of the reaction conditions, we did not succeed in preparing the corresponding chloride from a substituted amine I by this method. The corresponding thiosulfates (VIII, IX) and thiophophates (X, XI) were obtained by the action of sodium thiosulfate and thiophosphate on chlorides V and VII. Similar derivatives could not be obtained from chloride VI. Acid hydrolysis of thiosulfate VIII gave mercaptan (XII). An attempt was made to replace the chlorine by alkoxy groups in chloride VI by the action of sodium alcoholate. Although the reaction conditions were varied, the corresponding β-alkoxy derivatives could not be obtained. It was found that the corresponding aziridine is thus formed, which polymerizes readily.

The only substitution reaction of chlorine in compound VI which could be accomplished was dechlorination by catalytic reduction to the chain-unsubstituted derivative (XIII).

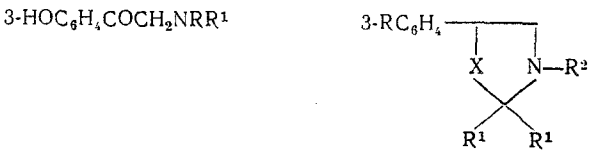
It was earlier shown that direct substitution of the hydroxyl by chlorine in amine I could not be accomplished, and therefore it was decided to protect the amino group in this compound by an arylidene group. The corresponding chloride (XV) is readily formed from N-(4-methoxybenzylidene) derivative of I (XIV) by the action of $SOCl_2$, which after treatment with MeONa in MeOH and subsequent hydrolysis gives 2-methoxy-2-(3-hydroxyphenyl)ethylamine (XVI).

The β-monoacetate of amine II (XVII) was obtained by selective hydrolysis of diacetate (XVIII) according to [9].

The synthesis of the benzoate (XIX) was carried out starting from m-nitrostyrene oxide according to the following scheme:



The doubtlessly interesting β-carbonyl analog of amine II (XXIV) was synthesized by debenzylation of 3-hydroxyphenyl-ω-methylbenzylaminoacetophenone (XXV), obtained according to [4], and also a similar derivative of I, 3-hydroxy-ω-aminoacetophenone (XXVI), was also synthesized according to [11].



XXIV—XXVI XXVII, XXIX—XXXII

R = H (XXIV, XXVI, XXVII, XXXI), CH_2Ph (XXV), OH (XXIX, XXX, XXXII); R′ = H (XXVI), Me (XXIV, XXV, XXVII, XXIX, XXXI); $R^1 + R^1 = (CH_2)_5$ (XXX), NH (XXXII); R^2 = Me (XXVII), H (XXIX—XXXI), Et (XXXII), X = O (XXVII, XXIX, XXX), S (XXXI, XXXII).

The synthesis of several derivatives of amines I-IV was also carried out by a method in which the β-carbon atom in the chain and the amino group are incorporated in a heterocyclic ring. Oxazolidine XXVII was obtained by a known method [5] from II and acetone. The corresponding oxazolidines (XXIX and XXX), unsubstituted at the nitrogen atom were synthesized by the reaction of O,O'-N-tris(trimethylsilyl) derivative of I (XXVIII) with acetone and cyclo-

hexanone. Thiazolidine XXXI was obtained by the action of acetone on mercaptan XII, while iminothiazolidine XXXII was obtained by the action of potassium thiocyanate on chloride VI.

EXPERIMENTAL (CHEMISTRY)

The purity of the compounds obtained was monitored on Silufol UV-254 plates. The IR spectra were run in KBr tablets on a Perkin-Elmer 398 spectrophotometer (Sweden). The PMR spectra were recorded in $(CD_3)_2SO$ on a Varian 100 spectrometer, using TMS as a standard.

1-Phenyl-2-aminoethylthiosulfuric Acid (VIII). A solution of 2 g (0.0104 mole) of 1-chloro-1-phenyl-2-aminoethane hydrochloride (V·HCl) [6] and 2.36 g of $Na_2S_2O_3 \cdot 5H_2O$ in 20 ml of water is heated for 1 h at 90°C, and the precipitate that separates is filtered to yield 1.4 g of acid VIII. The physicochemical characteristics of VIII and other compounds obtained are given in Table 1.

Sodium 1-Phenyl-2-aminoethylthiophosphate (X). A 10.3 g portion (0.026 mole) of sodium thiophosphate in 20 ml of water is added to a solution of 6 g (0.031 mole) of V·HCl in 40 ml of water and 20 ml of DMFA. The mixture is heated at 40°C for 3 h, cooled, and the precipitate is separated. The filtrate is added dropwise, with stirring and cooling, to a twofold volume of ethanol, and 4.1 g of sodium salt X are isolated from the precipitate.

1-Phenyl-2-aminoethylmercaptan Hydrochloride (XII·HCl). A mixture of 2 g (0.008 mole) of VIII with 25 ml of 15% HCl is heated for 30 min at 90°C in a nitrogen current, and then evaporated in vacuo, and 150 ml of alcohol are added to the residue. The precipitate that separates is filtered, the filtrate is evaporated to dryness, and dry ether is added to the residue. Yield 1.25 g of XII·HCl.

2,2-Dimethyl-4-phenylthiazolidine Hydrochloride (XXXI·HCl). A 2 g portion (0.0104 mole) of mercaptan XII·HCl is boiled for 4 h with 30 ml of dry acetone, the mixture is cooled, the precipitate is filtered, and washed with cold acetone to yield 1.7 g of thiazolidine hydrochloride XXXI·HCl.

N-Ethyl-2-chloro-2-(3-hydroxyphenyl)ethylamine Hydrochloride (VII·HCl). A suspension of 3.0 g (0.014 mole) of amine III·HCl in a mixture of 20 ml of $SOCl_2$ and 15 ml of benzene is heated for 1 h at 40-45°C. The reaction mixture is evaporated (35-40°C) in vacuo to dryness, 40 ml of dry benzene are added, and the mixture is evaporated again. The precipitate is washed with two 30 ml portions of benzene, and then dissolved in isopropanol. The solution is treated with activated carbon, and after filtration, precipitated with ether. The precipitate that separates is filtered, washed with ether, and reprecipitated from isopropanol with acetone, to yield 1.5 g of the hydrochloride of compound VII.

The hydrochloride of VI is synthesized in a similar way.

1-(3-Hydroxyphenyl)-2-ethylaminoethylthiosulfuric Acid (IX). A solution of 4.7 g (0.02 mole) of VII·HCl and 4.45 g (0.018 mole) of $Na_2S_2O_3 \cdot 5H_2O$ in 15 ml of water is stirred for 3 h at 40°C and 4 h at 60°C, and then acetone is added. The precipitate that separates is filtered, the filtrate is evaporated in vacuo, and the residue is dissolved in isopropanol. The solution is treated with activated carbon, and, after filtration, evaporated to yield 3.6 g of compound IX.

1-(3-Hydroxyphenyl)-2-ethylaminoethylthiophosphoric Acid (XI). A solution of 4.0 g (0.02 mole) of $Na_3SPO_3 \cdot 12H_2O$ is added to a solution of 5.9 g (0.025 mole) of VII·HCl in 20 ml of water. The reaction mixture is stirred for 4 h, and then evaporated (up to 35°C) in vacuo to dryness. The precipitate is dissolved in 100 ml of methanol, the solution is treated with activated carbon, evaporated after filtration to a volume of 20 ml, and precipitated with absolute ethanol. After three reprecipitations, 1.3 g of acid XI is obtained.

2-(3-Hydroxyphenyl)-methylaminoethane Hydrochloride (XIII·HCl). A 3.1 g portion of VI·HCl in 100 ml of ethanol is hydrogenated at 20°C over Pd-black. After the removal of the catalyst, 1.76 g of hydrochloride of amine XIII is obtained, mp 86-88°C (according to the literature data, mp 89°C [10]).

N-(4-Methoxybenzylidene)-2-chloro-2-(3-hydroxyphenyl)ethylamine Hydrochloride (XV·HCl). A 19.34 g portion (0.0615 mole) of Schiff base XIV, obtained according to [14] is gradually added to 50 ml of a freshly distilled $SOCl_2$. Then 0.5 ml of DMFA is added, and the mixture is held for 2 h at room temperature. It is evaporated to dryness in vacuo and absolute ethanol is added to the residue to yield 17.7 g of XV·HCl.

TABLE 1. Physicochemical Properties of Synthesized Compounds

Compound	Yield, %	mp, °C	Found, %					Empirical formula	Calculated, %				
			C	H	Cl	N	S		C	H	Cl	N	S
VII·HCl	46	145—6	50,89	6,51	—	5,90	—	$C_{10}H_{14}ClNO \cdot HCl$	50,86	6,40	—	5,93	—
VI·HCl	62	124—7[b]	48,50	6,05	16,10	6,33	—	$C_9H_{12}ClNO \cdot HCl$	48,67	5,90	15,96	6,31	—
VIII	56,5	202—3[b]	41,45	4,66	—	5,97	26,92	$C_8H_{11}NO_3S_2$	41,19	4,75	—	6,00	27,48
IX	57	162[a]	43,33	5,48	—	—	22,85	$C_{10}H_{15}NO_4S_2$	43,30	5,45	—	—	23,12
X	44	162[a]	32,29	4,71	—	4,68	10,68	$C_8H_{11}NO_3PSNa \cdot 2,5H_2O$	32,07	5,37	—	4,66	10,68
XI	18	130—4[a]	43,17	6,11	—	4,75	—	$C_{10}H_{16}NO_4PS \cdot H_2O$	43,01	6,16	—	4,79	—
XII·HCl	82	156—7[c]	49,80	6,24	18,45	7,47	16,35	$C_8H_{11}NS \cdot HCl$	50,65	6,38	18,68	7,38	16,90
XV·HCl	76	180—[c]	58,80	5,55	21,77	4,50	—	$C_{16}H_{16}ClNO_2 \cdot HCl$	58,91	5,25	21,73	4,29	—
XVI·adipate	22	193—5[c]	59,50	7,38	—	5,75	—	$C_9H_{13}NO_2 \cdot 0,5C_6H_{10}O_4$	59,98	7,75	—	5,83	—
XVII·HCl	27	158—61[d]	53,68	6,74	14,85	5,92	—	$C_{11}H_{15}NO_3 \cdot HCl$	53,77	6,56	14,42	5,70	—
XIX·HCl	33	188—91[d]	61,24	5,56	12,18	—	—	$C_{15}H_{15}NO_3 \cdot HCl$	61,33	5,49	12,07	4,77	—
XX·HCl	88	208—10[d]	66,06	5,77	—	6,84	—	$C_{22}H_{22}N_2O_3 \cdot HCl$	66,24	5,81	8,89	7,02	—
XXI·HCl	94	177—9[d]	71,28	6,61	—	3,62	—	$C_{22}H_{23}NO_2 \cdot HCl$	71,43	6,54	9,58	3,79	—
XXII·HCl	55	182—6	75,31	6,70	7,90	—	—	$C_{29}H_{29}NO_2 \cdot HCl$	75,72	6,57	7,70	3,04	—
XXIII·HCl	61,5	178—80	76,43	6,02	6,50	—	—	$C_{36}H_{33}NO_3 \cdot HCl$	76,65	6,07	6,28	—	—
XXIX	55	103—6[e]	68,15	7,67	—	7,29	—	$C_{11}H_{15}NO_2$	68,37	7,82	—	7,25	—
XXXI	85	160—1	57,80	7,11	15,10	6,08	13,93	$C_{11}H_{15}NS \cdot HCl$	57,50	7,11	15,42	6,09	13,95
XXXII	60	180[a]	59,06	6,32	—	12,72	—	$C_{11}H_{14}N_2OS$	59,43	6,35	—	12,60	—

Note. a) With dec.; b) recryst. from water; c) from alcohol; d) from isopropanol; e) from acetone–hexane.

2-Methoxy-2-(3-hydroxyphenyl)ethylamine Adipate (XVI·adipate). A solution of MeONa (prepared from 0.6 g of Na and 20 ml of CH_3OH) is added to a suspension of 4.3 g (0.13 mole) of XV·HCl in 30 ml of methanol. The mixture is boiled for 2 h, the precipitate is filtered, and the filtrate is evaporated to dryness. The residue is boiled for 1 h with dilute HCl (1:1), and washed with ether. The aqueous layer is evaporated to dryness, the residue is dissolved in absolute alcohol, and the solution is treated with an alcoholic ammonia solution. The precipitate that separates is filtered, the filtrate is evaporated to dryness, to the residue 5 ml of hexamethyldisilazane and 3 ml of absolute toluene are added, and the solution is heated at 110-120°C. The solvent is evaporated and the residue is evaporated at 125-130°C/1 mm to give 1.1 g of the bistrimethylsilyl derivative in the form of a colorless liquid, with n_D^{20} 1.4762. The solution of this compound in ethanol is treated with 0.5 g of adipic acid to yield 0.6 g of XVI·adipate.

N-Methyl-2-(3-hydroxyphenyl)-2-acetoxyethylamine Hydrochloride (XVII·HCl). Wet ether is added to a solution of 2.6 g (0.00906 mole) of the diacetyl derivative of XVIII, obtained according to [7], in methanol saturated with HCl, and the mixture is held for several days at room temperature. The precipitate that separates is filtered to yield 0.6 g of XVII·HCl. IR spectrum, ν_{max}, cm^{-1}: 1745 (C=O).

1-(3-Hydroxyphenyl)-2-dibenzylaminoethanol Hydrochloride (XXI·HCl). A 24.8 g portion (0.15 mole) of m-nitrostyrene oxide is boiled for 4 h with 29.3 g (0.15 mole) of dibenzylamine in ethanol. The mixture is evaporated to yield 48 g of 1-(3-nitrophenyl)-2-dibenzylaminoethanol (XX). A solution of 27 g of this compound in methanol is hydrogenated over Raney Ni at room temperature and at atmospheric pressure. To the residue after the filtration and evaporation to dryness, 110 ml of 20% H_2SO_4 are added, and a solution of 4.95 g (0.72 mole) of $NaNO_2$ in 50 ml of water is added dropwise at 0°C. The solution obtained is gradually added to 120 ml of boiling water. After cooling, the mixture is made alkaline with ammonia to pH 9.0 and extracted with ether. The extract is dried, an ether solution of HCl is added to yield 26 g of XXI·HCl.

1-(3-Benzyloxyphenyl)-2-dibenzylaminoethanol Hydrochloride (XXII·HCl). A solution of NaOEt (prepared from 1.2 g of Na and 50 ml of EtOH) and 3.3 g of benzyl chloride are added to a solution of 9.7 g (0.0262 mole) of XXI·HCl in 100 ml of absolute ethanol. The mixture is boiled for 6 h and filtered. The filtrate is evaporated to a volume of 40 ml, an ether solution of HCl is added to yield 6.6 g XXII·HCl.

N-Dibenzyl-2-(3-benzyloxyphenyl)-2-benzoyloxyethylamine Hydrochloride (XXIII·HCl). A 2.5 ml portion of benzoyl chloride is added to a solution of 2.7 g (0.006 mole) of XXII·HCl in 15 ml of dry pyridine. The mixture is heated for 2 h at 90°C, poured onto ice, and extracted with ethyl acetate. The extract is washed with an HCl solution, evaporated to dryness, and the residue is dissolved in ether. An ether solution of HCl is added to yield 2 g of XXIII·HCl. IR spectrum, ν_{max}, cm^{-1}: 1730 (COO).

2-(3-Hydroxyphenyl)-2-benzoyloxyethylamine Hydrochloride (XIX·HCl). A solution of 2 g of XXIII·HCl in 100 ml of ethanol is hydrogenated at 50°C over activated Pd-black to yield 0.3 g of XIX·HCl. IR spectrum, ν_{max}, cm^{-1}: 1720 (COO).

3-Hydroxyphenyl-ω-methylaminoacetophenone Hydrochloride (XXIV·HCl) is obtained by hydrogenation of XXV·HCl, mp 225°C (dec.) under similar conditions; according to literature data, mp 234°C [12]. IR spectrum, ν_{max}, cm^{-1}: 1690 (CO).

3-Ethyl-5-(3-hydroxyphenyl)-2-iminothiazolidine (XXXII). A solution of 2.0 g of KCNS in 5 ml of water is added to a solution of 3.6 g (0.015 mole) of chloride VII in 10 ml of water. The mixture is heated for 1 h at 90°C, cooled, and 30 ml of water are added. The oily precipitate is washed with 2 N aqueous ammonia, and reprecipitated from alcohol with water to yield 2.1 g of thiazolidine XXXII.

1-(3-Trimethylsilyloxyphenyl)-1-trimethylsiloxy-2-trimethylsilalaminoethane (XXVIII). A mixture of 18.9 g (0.1 mole) I·HCl and 30 ml of hexamethyldisilazane in 30 ml of absolute toluene is heated at 120-130°C, the filtrate is distilled in vacuo to yield 27.8 g (75%) of the trisilyl derivative XXVIII, bp 128-130°C/1 mm, n_D^{20} 1.4720, d_4^{20} 0.8160.

5-(3-Hydroxyphenyl)-2,2-dimethyloxazolidine (XXIX). A solution of 4.5 g (0.0116 mole) of XXVIII in 200 ml of acetone is boiled with 5 g of CaC_2, the filtrate is evaporated, and the residue is crystallized from acetone to yield 1.3 g of oxazolidine (XXIX). PMR spectrum, δ, ppm: 8.3 br. s (1 H, NH), 7.12 t (1H, H arom.), 6.85-6.66 m (3H, H arom.), 4.77 t (1H, CH,

TABLE 2. Toxicity and Radioprotective Properties of the Compounds

Compound	Method of administration	LD_{50}, mg/kg	ED, mg/kg	% survival ratio at the 30th day
I	s/c	1668	9,3	83±6 [2]
II	s/c	1076	5	88±4 [2]
III	s/c	1428	10,7	80±13 [2]
VI	s/c	210	23,5[a] 93[b]	60±16; 60±16
VIII	s/c	325	30; 119	0; 0
IX	s/c	1008	87; 350	0+10; 0+10
X	s/c	375	40; 160	10±10; 50±17
XI	s/c	900	76,3; 350	50±17; 10±10
XII	s/c	263	27; 108	20±13; 60±11
XIII	s/c	1500	9,2; 92	0+10; 60±16
XIV	s/c	2500	12; 120	30±13; 40±11
XVII	s/c	2000	12,3; 123	31±9; 90±10
XIX	s/c	160	15,3[a]; 61[b]	0+10; 60±16
XXIV	s/c	927	104,5[a]; 417,5[b]	20±13; 100±10
XXVI	s/c	1445	9,2; 92	20±13; 10±10
XXVII	s/c	108	10,2; 27,5[b]	20±13; 60±11.
XXIX	s/c	61	9,5	0+10
XXX	i/p	352	11,45; 40,6[a] 162,5[b]	70±10; 90±10 100—10
XXXII	i/p	42	4,25[a]; 17[b]	0+10; 0+10

a) 1/8 LD_{16}, b) 1/2 LD_{16}.
Note. s/c — subcutaneously, i/p — intraperitoneally.

J_{HC-CH_2} 6.7), 3.16 m (2H, CH_2, J_{CH_2-CH} 6.7, J_{C}^{H} 11.8), 1.42 s (3H, CH_3), 1.38 s (3H, CH_3).

When XXVIII is heated with cyclohexanone in alcohol, 5-(3-hydroxyphenyl)-2-spirocyclohexanoxazolidine XXX is obtained, mp 128-130°C (according to literature data, mp. 132°C [13]).

EXPERIMENTAL (BIOLOGY)

The acute toxicity and radioprotective activity was studied on CBA × $C_{57}Bl/F_1$ female hybrid mice. The compounds were administered subcutaneously and intraperitoneally 15 min before the irradiation. The irradiation was carried out on a RUM-17 x-ray apparatus in a dose of 7.5 Gy and a dose rate of 4.5 Gy/min. The method of irradiation and chemical dosimetry was earlier described in [1]. The survival ratio of the mice was determined at the 30th day after the irradiation. The survival ratio in the control was about 5%.

The data in Table 2, where the characteristics of compounds I-III are also given, show that the replacement of the hydroxyl at β-carbon atom in the chain by other substituents leads to increase in the toxicity (except for XVI and XVII) and to decrease in the radioprotective effect (RPE). When the hydrogen is substituted by methyl, benzoyl and acetyl groups, the RPE substantially decreases, although the last of these derivatives is fairly active. Only the dehydroxylated compound XIII in a large dose exhibits a pronounced RPE, while the chloro derivative VI is effective in both small and large doses. The carbonyl analogs XXIV and XXVI have a weak RPE, which can be sharply increased for XXIV by increasing the dose to 1/2 LD_{16}. A pronounced RPE can also be obtained also for certain sulfur-containing compounds, if they are introduced in large doses.

For the heterocyclic derivatives, a high RPE was observed only in spirocyclohexanoxazolidine XXX. It is possible that in this case, as in the case of the benzoyl and acetyl derivative, the activity is exhibited because of the hydrolysis of these compounds, proceeding in the organism with the formation of I and II.

From the results obtained it can be concluded that the hydroxyl group at the β-carbon atom in the hydrocarbon chain in compounds of type I-III is not a "unique" specific grouping ensuring the interaction with α_1-receptors, while other substituents, though to a lesser extent, cause a receptor effect because, as has already been shown in [3], a radioprotective effect is realized with compounds of this type. In this respect not only the chemical nature

of the substituents, but also their steric effect exerted on the β-carbon atom is of definite importance.

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ELECTRON TOPOLOGY INVESTIGATION OF THE STRUCTURE–ACTIVITY RELATIONSHIP IN THE SERIES OF α-CHYMOTRYPSIN INHIBITORS

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UDC 615.355:577.152.344.042.2].011.5

In studies of the relationship between the structure and biological activity of chemical compounds, different languages are used for describing the chemical structure, based on a vector or matrix representation of the structure (a qualitative level), and also various physicochemical characteristics, used in the correlational analysis (the qualitative level). In the study of structure–activity relationship (SAR), the use of electronic structure parameters is very important for describing the structure and properties of compounds.

In [3], one of us proposed a compositional method for studying the electronic structure of large molecular systems, designed for the examination of the SAR. The electronic characteristics thus obtained are further used for constructing electron-topological contiguity matrixes (ETCM). The information contained in the ETCM characterizes, on one hand, the electronic state of the molecule, and on the other hand, its real geometry in the space. The electron-topological method of analysis of SAR that was developed is based on the use of ETCM and on both qualitative and quantitative aspects of the chemical structure.

We have shown earlier [2, 5] that electronic factors must be taken into account in the examination of SAR and their role in the complex investigation together with logical-structural, regression and other approaches. By introducing the electronic factors, the possibilities of predicting the activity, based on SAR method can be substantially extended, and compounds of various series (and classes) can be included in the sequences studied. Further-

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Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 22, No. 11, pp. 1355-1361, November, 1988. Original article submitted May 5, 1987.

0091-150X/88/2211-0863$12.50