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SYNTHESIS AND STUDY OF THE ANTIVIRAL ACTIVITY OF PROPANOLAMINE DERIVATIVES

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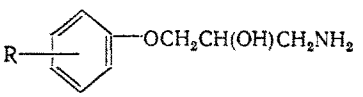
UDC 615.281.8:547.562].012.1

The process of developing new preparations for viral infection chemotherapy has shown that the oxyethyl [7] or propandiolamine [3] fragment is frequently encountered among the various chemical groups that enhance antiviral action. On the other hand, it is generally recognized that quaternary derivatives are active against certain viruses [3, 4]. However, there has been no special study of the effect that the oxyalkylammonium fragment has on the antiviral activity of the ammonium derivatives, and there is no information about the activity of its simplest derivatives. For that purpose we employed a method we previously developed [9] to synthesize the series 1-aryloxy-2-oxypropylamines, having the general formula:



(I — IX),

where R = H (I); 4-CH_3 (II); 4-Br (III); 2-Cl (IV); 3-CH_3 (V); 4-CH_3O (VI); 2-Br (VII); 2,4-Cl_2 (VIII); 3-CH_3-4-iso-C_3H_7 (IX).

We also synthesized the N-phthalimide (compounds XIV-XVII and N-acyl (XVIII-XXI) derivatives of aryloxypropylamines. There has been particular interest [5] in obtaining the substituted thioureas:

$$ArXCH_2CH(OH)CH_2NH_2 + S{=}C{=}NC_6H_5 \longrightarrow \underset{XXII - XXVII}{ArXCH_2CH(OH)CH_2NHC(=S-)NHC_6H_5},$$

where (enumerated compounds, Ar, X): XXII, C_6H_5, O; XXIII, C_6H_5, NC_6H_5; XXIV, $C_6H_4CH_3$-2, NH; XXV, $C_6H_3(CH_3)_2$-2,4, NH; XXVI, $C_6H_3(CH_3)_2$-2,5, NH; XXVII, C_6H_4Br-2, NH.

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0091-150X/87/2103-0217$12.50

TABLE 1. N-Phthalimide Derivatives of Glycine Esters

Compound	Yield, %	mp, °C	R_f	R_M^0	Found N, %	Empirical formula	Calculated, %
XIV	64	113—3,5	0,26	2,34	3,44	$C_{24}H_{19}NO_5$	3,49
XV	68	162—2,5	0,31	2,18	3,90	$C_{21}H_{17}NO_4$	4,13
XVI	76	175—6,5	0,29	2,16	7,95	$C_{17}H_{14}N_2O_6$	8,19
XVII	63	175—6	0,35	2,77	7,43	$C_{23}H_{18}N_2O_3$	7,57

The following quaternary derivative 1-aryloxy- and 1-arylamino-2-oxypropylamines XXVIII-LVI which we synthesized earlier were tested for antiviral activity:

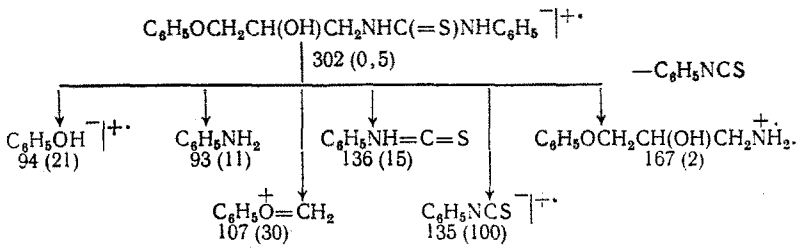
$$ArYCH_2CH(OH)CH_2\overset{+}{N}(CH_3)_2R\cdot X^-,$$

XXVIII — LVI

where Ar = $C_{10}H_7$-1 (XXVIII — XXXV); $C_6H_3(CH_3)_2$-2,6 (XXXVI — XXXVII); $C_{10}H_7$-2 (XXXVIII—XL); $C_6H_4CH_2CH{=}CH_2$-2 (XLI—XLIV); p-C_4H_9 (XLV); furfuryl (XLVI); C_6H_5 (XLVII — XLIX); C_6H_4Cl-2 (L — LIII); $C_6H_2(CH_3)_3$-2,4,6 (LIV — LVI); Y = O (XXVIII — XLVI); C_6H_5N (XLVII — XLIX); NH (L — LVI); R = $CH(CH_3)_2$ (XXVIII, XXXVII, XXXVIII, XLII, XLVIII, L, LIV); $CH_2CONHC_6H_3(CH_3)_2$-2,6 (XXIX); $CH_2CONHC_6H_4Cl$-2 (XXX); $CH_2COC_6H_4Br$-4 (XXXI, XXXVI, XLI, XLV—XLVII, LI, LVI); $CH_2COOC_2H_5$ (XXXII); $CH_2C_6H_4Br$-2 (XXXIII, XXXIX); $CH_2CH{=}CH_2$ (XXXIV, LX, XLIV, LII); $CH_2CONHC_6H_2(CH_3)_3$-2,4,6 (XXXV); $CH_2C_6H_4Cl$-2 (XLIII, XLIX, LIII, LV); X = Cl (XXIX, XXX, XXXV); Br (XXXI — XXXIV, XXXVI, XXXIX — XLI, XLIII — XLVII, XLIX, LI — LIII, LV, LVI); I (XXVIII, XXXVII, XXXVIII, XLII, XLVIII, L, LIV).

The resultant compounds' structure and uniformity were confirmed by element and chromatographic analysis, and in the case of a few representatives, by UV and mass spectral analysis as well.

In comparison to the thioureas with a simpler structure [1], the UV-spectra of the N,N'-substituted thioureas XXIV-XXVII were observed to have two absorption bands — a very intensive shortwave band in the 208-210 nm region and a less intensive band in the 248-250 nm region. Mass spectrum of thiourea XXII fully confirmed the following structure:



Compound XXV exhibits an analogous decomposition pattern with the formation of the characteristic ions: m/z (relative intensity, %) 329 (6), 121 (4), 134 (100), 72 (14), 60 (18), -, 135 (42), 105 (8).

Mass spectrum analysis of compound XXVIII confirmed its structure. The characteristic ions were formed during decomposition m/z (relative intensity, %): 273 (1.2), 258 (0.1), 256 (0.3), 187 (0.1), 170 (0.4), 144 (1.5), 142 (37.0), 127 (15.0), 115 (4.2), 86 (100), 58 (7.2), 44 (52.5). In comparison to the arylamines, the mass spectra of the aryloxy derivatives were characterized by low-intensity fragment peaks, including the aromatic residue, and very intensive peaks of the nitrogen-containing ions. This is connected to the positive charge's primary localization on the nitrogen atom due to the lesser degree of nitrogen-containing fragment ionization [14].

Compounds I-IX and XIV-LVI were tested for antiviral activity, but only compound XXVIII exhibited the ability to inhibit the formation of variola vaccine patches. A reduction in the virus titer was observed within the range of 1.6-1.2 log BOE/ml when the concentration of the test substance corresponded to the maximum tolerable concentration (MTC), 1/2 and 1/4 MTC. The remaining compounds were not able to suppress the reproduction of the tested viruses in tissue cultures.

Representatives of the examined series of substances (XII, XIII, XVII, XVIII, XXII, XXIII, XXIV, XXIX-XXXI, XXXIII-XXXV, XLIX, XLI, LII, LIII, and LVI) exhibited some viricidal

TABLE 2. N-Benzoyl Derivatives of 1-Phenoxy-2-oxy-3-aminopropanes

Compound	Yield, %	mp, °C	R_f^*	R_M^0	Found N, %	Empirical formula	Calculated, %
XVIII	51	138—9	0,46	1,58	8,74	$C_{16}H_{16}N_2O_5$	8,87
XIX	80	127—8	0,58	0,66	9,59	$C_{16}H_{18}N_2O_3$	9,76
XX	86	120—1	0,44	1,38	4,20	$C_{18}H_{19}NO_5$	4,25
XXI	52	87—8	0,50	2,87	4,46	$C_{19}H_{20}NO_3$	4,52

*Compounds XVIII and XX were recrystallized from benzene, XIX from water, and XXI from a mixture of CCl_4 and benzene (1:1).

activity in experiments with herpes simplex virus. The most active viricides which neutralize the infectious activity of 100 viral BOE at a concentration of 50 μg/ml (XXIX-XXXI, XXXV, XLIX, and LVI) and 5 μg/ml (XXXVI and XLI) were found to be among the quaternary derivatives of 1-aryloxy- and 1-arylamino-2-oxypropylamines. The contact inhibition capability in the latter two substances was combined with toxic activity for FÉK cultures at concentrations over 500 μg/ml.

EXPERIMENTAL CHEMICAL PART

TLC for N,N'-substituted thiourea derivatives and N-benzoyl derivatives was performed on a loose layer of grade II activity aluminum oxide in a benzene-ethanol (10:1) solvent system. The same system at 20:1 was used for the N-phthalimide derivatives. Spots were developed on iodine vapors. Lipid affinity was determined by reverse phase TLC [12]. UV spectra were recorded on a Specord UV-VIS instrument in 95% ethanol at a concentration of 10^{-4} mole/liter. Mass spectra were recorded on a MAT-112S and MAT-212 (Varian) mass spectrometer at an ionization energy of 70 eV with a direct feed of the substance into the ion source.

The starting glycine esters were obtained by method [6] for p-benzoylphenol (X), mp 81°C yield 37%: by method [8] for 2-naphthol (XI), mp 178-180°/2-3 mm, yield 75%: by method [8] for n-nitrophenol (XII), mp 67°C, yield 40%: in a similar manner by method [6] for N-(2,3-epoxypropyl)-carbazole (XIII), mp 112-113°C, yield 70%.

N-[3-(p-Benzoylphenoxyl)-2-oxypropyl]phthalimide (XIV). A melt of 44.45 g (175 mmoles) of X and 18.7 g (175 mmoles) of phthalimide was kept for 5 h at 160-190°C. After cooling, pulverization, and recrystallization from ethanol, the yield of XIV was 51.4 g. In the same manner, compounds XV-XVII were obtained from XI-XIII respectively (Table 1).

N-(p-Nitrobenzoyl)-3-phenoxy-2-oxypropylamine (XVIII). A 16.71 portion (100 mmoles) of 1-phenoxy-2-oxy-3-aminopropane was dissolved with heating in 400 ml of benzene. A 101.1 g (100 mmoles) of triethylamine was added to the mixture, followed by the dropwise addition while stirring of a solution of 18.55 g (100 mmoles) of n-nitrobenzoylchloride in 100 ml of benzene. The mixture was stirred for 2 h at room temperature and left overnight. The residue was suctioned off and washed with water. Following recrystallization from benzene, the yield of XVIII was 29 g.

In a similar manner, compounds XX and XXI (Table 2) were obtained from 1-(2-methoxyphenoxy)-2-oxy-3-aminopropane or 1-(2-allylphenoxy)-2-oxy-3-aminopropane with benzoylchloride or n-methoxybenzoylchloride.

N-(p-Aminobenzoyl)-3-phenoxy-2-oxypropylamine (XIX). A mixture of 6.32 g (20 mmoles) of XVIII, 48 ml of acetic acid, 175 ml of water, and 7 g of zinc powder was heated for 2 h at 120°C and filtered in a hot state for the removal of sludge. A white precipitate separated from the filtrate upon cooling. After recrystallization from water the yield of XIX was 4.9 g (see Table 2).

N-3-Phenoxy-2-oxypropyl)-N'-phenylthiourea (XXII). A 2.7-g portion (20 mmoles) of phenylisothiocyanate was added to a solution of 3.34 g (20 mmoles) of 1-phenoxy-2-oxy-3-aminopropane in 30 ml of benzene. The mixture was then heated to boiling and left overnight. The residue was suctioned off and washed with benzene. After recrystallization from ethanol, a yield of 5.6 g of pure XXII was obtained. In a similar manner, compounds XXIII-XXVII (Table 3) were obtained from various arylaminopropanolamines (obtained by method [10]).

TABLE 3. N,N'-Substituted Thioureas

Compound	Yield, %	mp, °C	R_f^*	R_M^0	Found, %		Empirical formula	Calculated, %		λ_{max}, nm (lg ε)
					N	S		N	S	
XXII	82	143—5	0,60	1,31	9,80	10,76	$C_{16}H_{18}N_2O_2S$	9,62	10,96	—
XXIII	72	101—2	0,59	2,25	11,00	8,36	$C_{22}H_{23}N_3OS$	11,12	8,46	—
XXIV	93	111—2	0,60	1,80	10,91	8,33	$C_{16}H_{18}BrN_3OS$	11,05	8,42	208 (4,66); 248 (4,44)
XXV	80	136,5—7	0,35	2,17	12,38	9,22	$C_{17}H_{22}N_2O_2S$	12,65	9,63	210 (4,61); 250 (4,41)
XXVI	88	137,5—8,5	0,41	2,29	12,55	9,50	$C_{18}H_{23}N_3OS$	12,76	9,72	209 (4,65); 248 (4,42)
XXVII	61	130—1	0,36	2,67	12,51	9,35	$C_{18}H_{23}N_3OS$	12,76	9,72	210 (4,63); 250 (4,42)

*Compound XXII was recrystallized from ethanol, XXIII from CCl_4, XXIV from benzene, and XXV-XXVII from toluene.

EXPERIMENTAL BIOLOGICAL PART

Antiviral properties were experimentally assayed in tissue cultures inoculated by primary screening [15] with viruses of the following categories: variola, Type 1 herpes simplex, classic avian plague, Newcastle disease, vesicular stomatitis, Venezuelan equine encephalitis and echovirus-6. This was followed by a quantitative analysis of antiviral activity by the patch reduction method under an agar cover which we have described earlier [2].

The echovirus was examined on multilayer cultures of passivated musculocutaneous human embryo cells. The other viruses were investigated on multilayer cultures of primary trypsinized chick embryo fibroblasts.

Prior to the quantitative analysis of the antiviral effect's characteristics, the MTC was found for the substances under examination for non-infected tissue cultures after a 96-hour incubation period.

Viricidal properties were assayed by titrating the infectious capacity of Type I herpes simplex virus after a 24-hour contact with various concentrations of the substances under study.

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