SYNTHESIS AND PHARMACOLOGICAL INVESTIGATION OF SOME DERIVATIVES OF 1,2,3,4-TETRAHYDROPYRIMIDINE-5-CARBOXYLIC ACID

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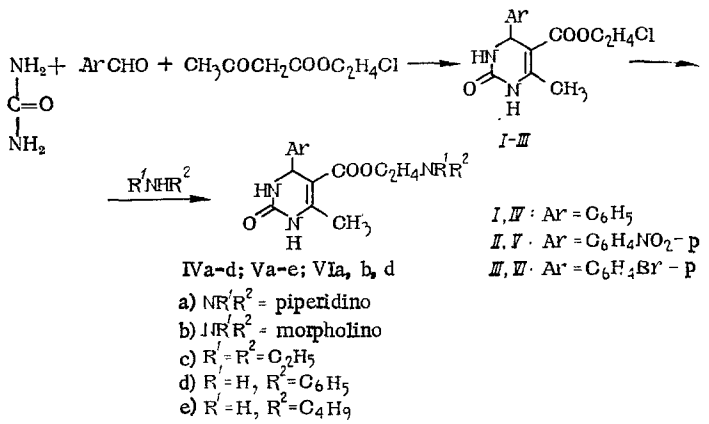
Derivatives of 2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid exhibit antitumor and antiviral activity [1-3]. We first discovered that amides of that acid have hypotensive and coronary dilatation properties [4]. In order to extend the search for substances which affect the blood circulation system, we synthesized new β-aminoethyl esters of 2-oxo-4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid. Those compounds were obtained through a nucleophilic substitution reaction of the chlorine atom in the corresponding β-chloroethyl esters I-III by an amine residue. The β-chloroethyl esters of 2-oxo-4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid were obtained by a modification of the Bidzhinelli condensation [5] from urea, benzaldehyde or its derivative, and the β-chloroethyl ester of acetoacetic acid.



The structure of the compounds obtained was established by a combination of UV and IR spectra (Table 1).

The chlorine of compound I-III has a comparatively low activity in reactions with amines, and for that reason the amination is carried out in the presence of potassium iodide. Dimethylformamide is used as a solvent, which as a result of its high solvating ability shows catalytic activity in nucleophilic substitution reactions [6].

Compounds IVa-d were investigated pharmacologically, and the results of those studies are shown in Table 2. In acute experiments on narcotized cats it was shown that all of the investigated substances lower the arterial pressure, but their hypotensive action is less than that of papaverine. In doses of 1 to 5 mg/kg these substances have no effect on the hemodynamic effects of epinephrine, acetylcholine and serotonin. Compound IVa lowers the hypotensive reaction to the stimulation of the peripheral end of the vagus nerve. ED_{50} is 5.4 (3.1 to 7.7) mg/kg.

The effect of these substances on coronary blood circulation was investigated by the method of N. A. Kaverina [7] on cats, and by the flowmetric method [8] in experiments on dogs. In doses of 1 to 5 mg/kg these substances do not alter the coronary blood flow. The method of Papp and Szekeres [9] was used to determine the effect of these substances on the pituitrin spasm of coronary vessels. In a series of experiments compound

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TABLE 1. Derivatives of 2-Oxo-4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid

Compound	Yield, %	Melting point, °C	Found, %				Calculated, %				Empirical formula	UV Spectrum		IR Spectrum
			C	H	N	Hal	C	H	N	Hal		λ_{max}, nm	lg ε	$\nu_{C=O}$, cm^{-1}
I	49	178—80	57,12	5,40	12,87	9,90	57,05	5,13	12,08	9,50	$C_{14}H_{15}N_2O_3Cl$	205, 218 sh. 286	4,3; 4,1; 4,1	1730,1710
II	60	203—5	50,18	4,25	13,01	10,79	49,71	4,15	12,97	10,44	$C_{14}H_{14}N_3O_5Cl$	205, 218 sh. 274	4,2; 4,0; 4,2	1740,1718
III	44	204—6	43,29	3,89	7,93	31,12	43,18	3,90	7,75	30,90	$C_{13}H_{14}N_2O_3ClBr$	203, 234, 292	4,0; 4,2; 4,1	1730,1700
IVa	71	131—3	66,50	7,34	12,53	—	66,45	7,34	12,24	—	$C_{19}H_{25}N_3O_3$	205, 218 sh. 298	4,8; 4,1; 4,0	1730,1710
IVb	59	146—7	62,42	6,80	11,81	—	62,59	6,71	12,17	—	$C_{18}H_{24}N_3O_4$	205,218 sh. 288	4,3; 4,1; 4,0	1720,1695
IVc	90	105—7	65,41	7,95	12,17	—	65,23	7,60	12,69	—	$C_{18}H_{25}N_3O_3$	205, 218 sh. 288	4,4; 4,2; 4,2	1730,1710
IVd	87	148—50	68,32	6,23	11,59	—	68,36	6,02	11,96	—	$C_{20}H_{21}N_3O_3$	205, 244, 289	4,0; 3,9; 3,8	1720,1710
Va	75	151—3	58,49	6,25	14,79	—	58,74	6,23	14,43	—	$C_{19}H_{24}N_4O_5$	203, 215 sh. 275	4,3; 4,1; 4,2	1730,1710
Vb	42	124—6	55,65	5,71	14,05	—	55,38	5,68	14,35	—	$C_{18}H_{22}N_4O_6$	203, 215 sh. 275	4,3; 4,2; 4,2	1740,1720
Vc	63	172—4	57,23	6,64	14,60	—	57,44	6,43	14,85	—	$C_{18}H_{24}N_4O_5$	203, 218 sh. 279	4,3; 4,1; 4,2	1740,1720
Vd	85	144—6	60,75	5,08	14,19	—	60,60	5,08	14,13	—	$C_{20}H_{20}N_4O_5$	203, 253, 275	4,3; 4,3; 4,3	1740,1720
Ve	53	112—4	57,23	6,64	14,60	—	57,44	6,43	14,85	—	$C_{18}H_{24}N_4O_5$	203, 218 sh. 275	4,3; 4,1; 4,2	1740,1720
Va	87	145—7	53,06	5,54	9,86	19,01	52,69	5,90	10,34	19,47	$C_{19}H_{24}N_3O_3Br$	203, 230, 286	4,4; 4,2; 4,0	1730,1710
Vb	61	135—7	50,50	5,27	9,80	18,60	50,95	5,23	9,90	18,83	$C_{18}H_{22}N_3O_4Br$	203, 230, 286	4,4; 4,1; 4,0	1730,1710
Vc	68	129—31	55,64	4,49	9,47	18,20	55,82	4,68	9,76	18,57	$C_{20}H_{20}N_3O_3Br$	203, 234, 286	4,3; 4,2; 4,0	1730,1710

TABLE 2. Effect of Compounds IVa-d on the Cardiovascular System and Their Acute Toxicity

Compound	ED_{30} hypotensive effect, mg/kg	Effect on the spasm of rabbit's ear produced by epinephrine	LD_{50} for white mice with intraperitoneal administration, mg/kg
IVa	4,9 (1,8÷8,0)	No change (10^{-6}—10^{-5}) *	260 (240—325)
IVb	9,0 (5,5÷12,4)	Reduced (10^{-5}) *	250
IVc	0,5	—	500
IVd	3—5	Reduced (10^{-5}) *	1000
Papaverine	0,27	Reduced (10^{-5}) *	91 (82—101) [10]

*Concentration of substance (in g/liter).

IVa in doses of 0.5 to 1.0 mg/kg and compound IVb in doses of 5 mg/kg reduced the ECG changes produced by pituitrin. In experiments on isolated vessels of rabbit's ear compounds IVb and IVd, in concentrations of 10^{-5} g/liter, reduced the vessel spasm produced by epinephrine. In this respect these compounds do not differ from papaverine, but they are considerably less toxic (compound IVd is more than 10 times less toxic).

The finding in compounds IVa-d of hypotensive and spasmolytic properties provides the basis for further investigation of compounds of this type.

EXPERIMENTAL

Chemical

UV spectra were obtained on a Specord UV-Vis spectrophotometer in ethanol, at concentrations of 5×10^{-5} mmole. IR spectra were recorded on the UR-20 instrument in mineral oil mulls.

2-Oxo-4-phenyl-5-(β-chloroethoxycarbonyl)-6-methyl-1,2,3,4-tetrahydropyrimidine (I). To a solution of 0.6 g (0.01 mole) of urea in 30 ml of absolute ethanol we added 1.65 g (0.01 mmole) of β-chloroethyl ester of acetoacetic acid and 1.05 g (0.1 mmole) of benzaldehyde. The mixture was acidified with concentrated hydrochloric acid and refluxed for 5 h. Compound I separated upon cooling. Compounds II and III were obtained by the same method (see Table 1).

2-Oxo-4-phenyl-5-(β-piperidinoethoxycarbonyl)-6-methyl-1,2,3,4-tetrahydropyrimidine (IVa). To a solution of 1.4 g (0.05 mmole) of compound I in 25 ml of dimethylformamide, we added 0.85 g (0.1 mmole) of piperidine and potassium iodide in an equimolar ratio. The mixture was boiled, cooled, and diluted with water. A colorless residue was obtained, which was crystallized from benzene. When hydrogen chloride was bubbled through, we obtained hydrochloride IVa. Compounds IVb-d, Va-e, and VIa, b, d were obtained by similar reaction.

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