DERIVATIVES OF PYRIMIDINE.

XLVIII. SYNTHESIS AND BIOLOGICAL PROPERTIES OF SOME N_1-SUBSTITUTED 5-FLUOROURACILS

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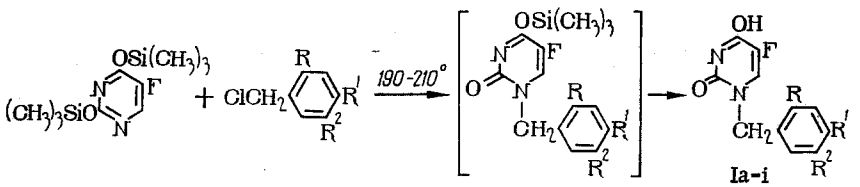
In spite of the fact that 5-fluorouracil is widely used in oncological practice, ac- according to the data of clinicians it frequently produces serious toxic reactions [1 - 3].

In order to investigate the effect of the alkoxybenzyl group on the antitumor activity and toxicity of 5-fluorouracil, we carried out the synthesis of a series of N_1-substituted 5-fluorouracils (I), according to the following scheme:

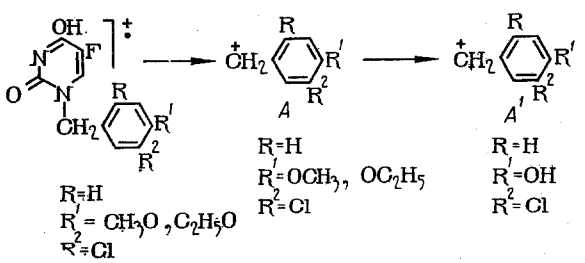


The benzylchlorides used as starting materials were obtained by a method previously described [4 - 6].

We synthesized compounds I by heating bis-trimethylsilyl-oxy-5-fluorouracil [7] with the appropriate benzyl chlorides at 190 - 210°C (Table 1). The structure of I was confirmed by NMR and mass spectroscopy data.

The aromatic protons N_1-(3-chloro-, 3-bromo-4-alkoxybenzyl)-5-fluorouracils produce a group of lines characteristic of 1, 3, 4-substituted benzenes (quartet at 7.15 ppm and singlet at 7.4 ppm). The methylene protons appear as a singlet in the region of 4.8 ppm. The proton in position 6 of the pyrimidine ring appears as a doublet in the region of 7.80 - 7.85 ppm as a result of interaction with the fluorine nucleus.

The peaks of molecular ions in the mass spectra of compounds I are of medium intensity. The most intense peaks are those due to the simple cleavage of the pyrimidine—benzene N—C bond, with localization of the positive charge on the alkoxybenzilic fragment (ions A and A^1).



In the mass spectrum of Ia the maximum is the peak due to ion A, and in the spectrum of Ib, the peak of ion A^1 (m/e 141, 143). Of noticeable intensity are also the peaks of the ion with m/e of 105, which in the case of Ia is formed from the ion $[A-CH_3]^+$ through the loss

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TABLE 1. N_1-substituted Benzyl-5-fluorouracils (Ia-i)

Compound	R	R_1	R_2	Yield, %	Melting point, °C	R_f	Found, %				Molecular formula	Calculated, %			
							C	H	N	Cl		C	H	N	Cl
Ia	H	CH_3O	Cl	73,8	185—6	0,62	50,32	3,83	9,53	12,74	$C_{12}H_{10}ClN_2O_3$	50,63	3,54	9,84	12,46
Ib	H	C_2H_5O	Cl	73,1	169—70	0,69	52,57	4,37	9,64	11,55	$C_{13}H_{12}FClN_2O_3$	52,27	4,05	9,38	11,87
Ic	H	C_3H_7O	Cl	70,4	175—6	0,75	53,45	4,82	8,64	11,85	$C_{14}H_{14}FClN_2O_3$	53,77	4,51	8,96	11,34
Id	H	iso C_3H_7O	Cl	73,6	132—3	0,67	53,47	4,82	8,75	11,75	$C_{14}H_{14}FClN_2O_3$	53,77	4,51	8,96	11,34
Ie	H	C_4H_9O	Cl	58,2	173—4	0,78	55,43	4,63	8,84	10,52	$C_{15}H_{16}FClN_2O_3$	55,14	4,94	8,58	10,85
If	H	CH_3O	Br	50,1	186—7	0,77	44,01	3,42	8,21	—	$C_{12}H_{10}BrFN_2O_3$	43,78	3,06	8,51	—
Ig	H	C_2H_5O	Br	51,4	179—80	0,80	45,10	3,48	8,44	—	$C_{13}H_{12}BrFN_2O_3$	45,21	3,52	8,17	—
Ih	CH_3O	H	Br	48,6	196—7	0,79	43,51	3,36	8,83	—	$C_{12}H_{10}BrFN_2O_3$	43,79	3,06	8,51	—
Ii	C_2H_5O	H	Br	70,0	186—7	0,86	45,50	3,82	8,42	—	$C_{13}H_{12}BrFN_2O_3$	45,21	3,52	8,17	—

TABLE 2. Summary of Data on the Toxicity and Antitumor Activity of N_1-substituted Benzyl-5-fluorouracils (Ia-i)

Compound	Toxicity for mice with single injection			Dose, mg/kg	Antitumor activity in rats				
								mice	
	LD_{100}	LD_{50}	MPD		sarcoma 45	Svec Leukemia	Pliss lymphosarcoma	sarcoma 180	ascitic Ehrlich carcinoma
	mg/kg								
Ia	631	526	431	50	+	++	+	0	0
Ib	666	579	500	50	+	++	+	0	0
Ic	1400	1190	1051	50/100	+	++	+	0	0
Id	600	500	444	50	+	+	+	0	0
Ie	1500	1200	1000	50/100	+	+	++	0	0
If	550	400	350	30	0	0		0	0
Ig	550	400	350	35	+	0		0	0
Ih	400	350	300	30	0	0		0	0
5-fluorouracil	210	125	62	25/10	+	+++	+++	+	+++

Note: 0 — no effect; (+) — inhibition of tumor growth up to 30-59%; (++) — up to 60 - 79%; (+++) — up to 80 - 95%.

of a chlorine atom, and in the case of Ib, from ion A^1 through the loss of a molecule of hydrochloric acid.

The purity and identification of I were established by means of thin-layer chromatography.

EXPERIMENTAL

Biological

The investigation of antitumor properties of these preparations was conducted according to previously described methods [8]. The toxicity was investigated on unbred white male mice by a single intraperitoneal injection. The chemotherapeutic experiments were conducted on unbread rats and mice with various transplanted tumors (sarcoma 45, Svec leukemia, Pliss lymphosarcoma, sarcoma 180, and ascitic Ehrlich carcinoma).

The data obtained (shown in Table 2) indicate that all the synthesized derivatives of 5-fluorouracil (I) have a considerably lower toxicity as compared with 5-fluorouracil. We have also noticed that against rat sarcoma 45, the majority of the compounds investigated (except Nos. 6 and 8) show an antitumor activity approximately equal to that of 5-fluorouracil; against Svec leukemia and Pliss lymphosarcoma these compounds have a lower activity than 5-fluorouracil. These compounds differ from 5-fluorouracil in that they have no effect on the mice tumors investigated.

In conclusion, the introduction of the alkoxybenzylic group into the N_1-position of 5-fluorouracil lowers not only the toxicity but also the antitumor activity of this parent compound.

EXPERIMENTAL

Chemical

NMR spectra were obtained on the Varian T-60 instrument (7% solution in hexadeuteroethanol). The mass spectra were taken on the MKh-1303 instrument with direct introduction of the sample into the ion source. Thin-layer chromatography was carried out on microplates (SiO_2, G, ether–acetone 49:1, development with iodine vapor).

N_1-(3-chloro-3-bromo-4-alkoxy- and 2-Alkoxy-5-bromobenzyl)-5-fluorouracils (I). A mixture of 2.74 g (0.01 mole) of bis-trimethylsilyloxy-5-fluorouracil and 0.01 mole of the appropriately substituted benzyl chloride was heated in a Claissen flask at 190 - 210°C for 30 min. During this time about 1 g of trimethylchlorosilane was distilled off. To the hot mixture was added 30 ml of carbon tetrachloride. The warm solution was rapidily filtered, and 5 ml of absolute methanol were added to the mother liquor. The crystals were filtered, washed with carbon tetrachloride, and recrystallized from ethanol (see Table 1).

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