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SYNTHESIS OF 1-(3-HALOTETRAHYDRO-2-FURYL) DERIVATIVES OF URACIL, 5-SUBSTITUTED URACILS, AND CYTOSINE

L. T. Kaulinya and M. Yu. Lidak

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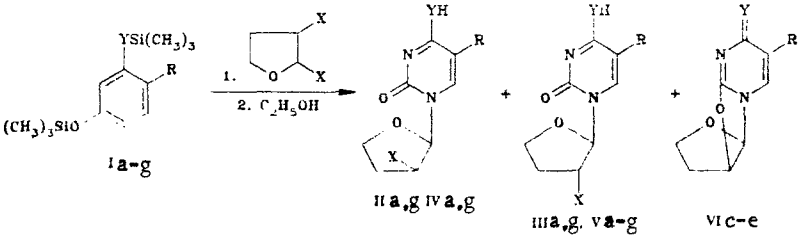
The cis and trans isomers of 1-(3-halotetrahydro-2-furyl) derivatives of uracil, 5-substituted uracils, and cytosine were obtained by alkylation of 2,4-bis(trimethylsilyl) derivatives of uracil, 5-substituted uracils, and cytosine with 2,3-dihalotetrahydrofurans. 2,3'-Anhydro compounds are also formed in the alkylation of 5-halouracil derivatives. The physicochemical properties of the compounds obtained and the antineoplastic activities of the 5-fluorouracil derivatives were studied.

Some analogs of nucleosides that contain a halogen atom in the glycoside part of the molecule have antineoplastic [1, 2] and antiviral [3] activity. It seemed of interest to synthesize analogs of the well-known antineoplastic preparation fluorafur [4] that contain a chlorine or bromine atom in the 3 position of the tetrahydrofuran ring. The introduction of halogen increases the lipophilicity of the compounds, thereby changing their ability to penetrate through the cell membranes and the overall biological effect in the organism.

To synthesize the 1-(3-halotetrahydro-2-furyl) derivatives of the pyrimidine bases we used alkylation of silyl derivatives of uracil, 5-substituted uracils, and cytosine, as well as our previously developed method for the alkylation of nucleic acid bases in the presence of triethylamine [5]. A preliminary communication regarding the synthesis of these compounds has been published [6]. 2,3-Dihalotetrahydrofurans, which are formed by the addition of chlorine or bromine to 2,3-dihydrofuran and have a trans structure [7, 8], served as the alkylating agents. In the course of the reactions we obtained mixtures of cis (IIa-g, IVa-g) and trans (IIIa-g, Va-g) isomers of 1-(3-halotetrahydro-2-furyl)uracils and cytosine. A side product, which is formed in maximum amounts in the alkylation of Ic, was detected chromatographically in the alkylation of silyl derivatives Ic-f of 5-halouracils. We isolated side product VIc of the reaction of the silyl derivative of 5-fluorouracil and 2,3-dihalotetrahydrofurans and proved its structure to be that of a 2,3'-anhydro compound on the basis of PMR spectroscopy and the results of elementary analysis. Compounds VId,e are formed in very small amounts, and their presence in the mixtures of reaction products was detected by means of PMR spectroscopy.



I—VI a, g R=H, b R=CH_3, c R=F, d R=Cl, e R=Br, f R=I; II, III X=Cl, IV, V X=Br; I—VI a—f, Y=O, g Y=NH

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006.
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TABLE 1. The cis Isomers of 1-(3-Halotetrahydro-2-furyl)-uracil, 5-Substituted Uracils, and Cytosine (IIa-g, IVa-g)

Compound	mp, °C	R_f	Found, %			Empirical formula	Calculated, %			Yield, %
			C	H	N		C	H	N	
IIa	152—154	0,89	42,2	4,1	12,6	$C_8H_9ClN_2O_3$	41,4	4,2	12,9	60
IIb	198—199	0,80	46,4	4,5	11,5	$C_8H_{11}ClN_2O_3$	46,9	4,8	12,1	56
IIc	196—198	0,90	41,0	3,5	11,8	$C_8H_8ClFN_2O_3$	41,0	3,4	11,9	55
IId	220—222	0,81	38,0	3,3	10,7	$C_8H_9ClN_2O_3$	38,3	3,2	11,1	13
IIe	237—238	0,84	32,5	2,7	9,2	$C_8H_8BrClN_2O_3$	32,5	2,7	9,5	11
IIf	219—251	0,81	28,1	2,3	8,3	$C_8H_8ClIN_2O_3$	28,1	2,3	8,2	6
IIg	213—215	0,27	45,0	4,8	18,9	$C_8H_{10}ClN_5O_2$	44,6	4,7	19,5	27
IVa	187—188	0,73	36,8	3,5	10,7	$C_8H_9BrN_2O_3$	36,0	3,4	10,6	70
IVb	216—217	0,73	39,0	3,9	10,6	$C_9H_{11}BrN_2O_3$	39,3	4,0	10,2	69
IVc	179—180	0,72	34,7	2,9	10,8	$C_8H_8BrFN_2O_3$	34,4	2,9	10,0	66
IVd	213—215	0,68	32,1	2,8	9,5	$C_8H_8BrClN_2O_3$	32,5	2,7	9,5	12
IVe	236—237	0,75	27,5	2,3	8,0	$C_8H_8Br_2N_2O_3$	27,1	2,3	7,9	10
IVf	229—230	0,75	24,6	2,0	7,9	$C_8H_8BrIN_2O_3$	24,8	2,1	7,2	6
IVg	207—208	0,69	36,8	3,7	16,0	$C_8H_{10}BrN_3O_2$	36,9	3,9	16,2	26

The ratios of the alkylation products depend both on substituent R in the pyrimidine ring and on the reaction conditions. Derivatives IIa-g and IVa-g are the most kinetically favorable reaction products and, at low temperatures (20-50°C), are the principal products (~60% yields); trans derivatives IIIa-g and Va-g and anhydro compounds VIc-e are formed in only trace amounts. The yields of the trans isomers increase when the reaction temperature is raised to 120-150°C, and the development of anhydro compounds VIc-d is observed. Thus 2,3'-anhydro compound VIc (34% yield), cis isomer IVc (22% yield), and trans isomer Vc (7% yield) were obtained in the alkylation of 2,4-bis(trimethylsilyl)-5-fluorouracil with 2,3-dibromotetrahydrofuran at 130-140°C with removal of the trimethylbromosilane formed during the reaction by distillation.

The alkylation of a silyl derivative of 5-fluorouracil by 2,3-dihalotetrahydrofurans in dichloroethane in the presence of stannic chloride at 20°C, as a result of which the cis (IIc, IVc) and trans (IIIc, Vc) isomers in a ratio of 1:1 were obtained, has been previously described [9]. The formation of an anhydro compound was not observed. In the alkylation of 5-fluorouracil with an equimolar amount of 2,3-dihalotetrahydrofuran in the presence of excess triethylamine at room temperature we obtained cis isomers IIc and IVc as the prinicpal products in ~50% yield. The trans isomers IIIc and Vc are formed in trace amounts, and an anhydro compound was not detected.

Compound VIc was obtained by treatment of mixtures of the cis and trans isomers of 1-(3-halotetrahydro-2-furyl)-5-fluorouracils (IIc, IIIc and IVc, Vc) with 0.2 N NaOH at room temperature for 15-20 h by the method in [9]; the cis isomer does not undergo the reaction and can be isolated from the reaction mixture. This reaction is an indirect confirmation of the structure of the 2,3'-anhydro compound.

Alkylation of 5-bromo- and 5-iodouracil derivatives at 130-140°C leads to partial elimination of halogen with the formation of uracil derivatives. For this reason, IIe, IIf and IVe, IVf were obtained in high yields by halogenation of the corresponding uracil derivatives by the method proposed for other 1-substituted uracils [10].

Small amounts of 1,3-disubstituted uracils, which we did not specially isolate, with the exception of 1,3-bis(3-chlorotetrahydro-2-furyl)-5-fluorouracil (see the Experimental section), are formed along with 1-substituted uracils in the alkylation of silyl derivatives of 5-fluorouracil.

The reaction products can be separated by fractional crystallization from ethanol. The properties of the cis isomers of the compounds obtained are presented in Tables 1 and 2.

The signal of the anomeric proton in the PMR spectra of the cis isomers of the synthesized compounds IIa-g and IVa-g is a doublet of doublets (dd) with spin—spin coupling constants (SSCC) 4.6 and 1.8 Hz, whereas in the spectra of trans isomers IIIa-g and Va-g it is a pseudotriplet (5.83 ppm) with SSCC 1.5 Hz; this corresponds to the data for the cis and trans isomers of 1-(3-hydroxytetrahydro-2-furyl)-5-fluorouracil [11, 12]. The signal of the anomeric proton of VIc is a doublet (6.32 ppm) with SSCC 5.3 Hz (Fig. 1). The spectrum of

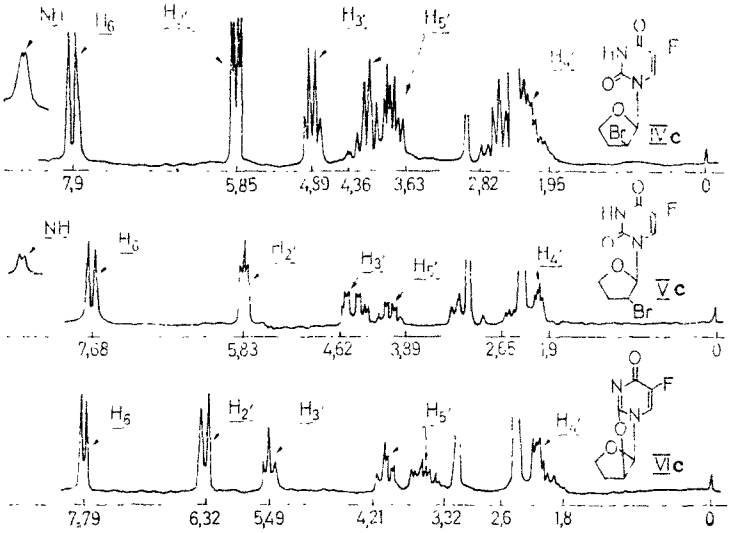


Fig. 1. PMR spectra of the cis (IVc) and trans (Vc) isomers of 1-(3-bromotetrahydro-2-furyl)-5-fluorouracil and 2,3'-anhydro-1-(tetrahydro-2-furyl)-5-fluorouracil (VIc) [d_6-dimethyl sulfoxide (d_6-DMSO); hexamethyldisiloxane (HMDS)].

TABLE 2. UV Spectra of the cis Isomers of IIa-g and IVa-g

Compound	UV spectrum, λ_{max}, nm (log ε)			Compound	UV spectrum, λ_{max}, nm (log ε)		
	pH 2.0	pH 7.0	pH 12.0		pH 2.0	pH 7.0	pH 12.0
IIa	264 (11,8)	262 (7,8)	263 (8,8)	IVa	264 (9,2)	264 (10,0)	263 (7,2)
IIb	268 (10,4)	269 (7,2)	268 (7,2)	IVb	269 (9,0)	269 (9,8)	268 (7,4)
IIc	271 (9,2)	273 (7,4)	269 (7,9)	IVc	269 (13,2)	269 (12,0)	268 (10,6)
IId	278 (8,7)	278 (9,4)	276 (7,0)	IVd	276 (10,0)	276 (14,0)	274 (7,7)
IIe	281 (10,2)	284 (9,6)	278 (7,8)	IVe	281 (9,0)	281 (9,3)	277 (6,8)
IIf	290 (6,4)	290 (6,4)	283 (4,8)	IVf	289 (7,3)	289 (9,8)	281 (6,1)
IIg	282 (8,8)	273 (7,0)	282 (5,0)	IVg	281 (13,4)	272 (10,9)	272 (9,1)

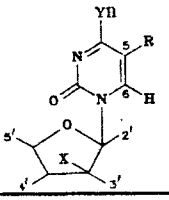
this compound is in agreement with the data presented in [9]. The PMR spectra of the cis isomers of the compounds obtained are presented in Table 3.

The IR spectra of 1-(3-halotetrahydro-2-furyl) derivatives of uracil and cytosine contain $\nu_{C=O}$ absorption bands at 1620-1720 cm^{-1} for the uracil derivatives and ν_{NH_2} bands at 3000-3400 cm^{-1} for the cytosine derivatives. The band of symmetrical vibrations of the —C—O—C— bond is shifted to 1060-1100 cm^{-1} as compared with 1-(tetrahydro-2-furyl)uracils [4], for which it lies at 1017-1027 cm^{-1}.

A bathochromic shift of 2-3 nm as compared with the spectra of 1-(tetrahydro-2-furyl)-uracils [4, 13, 14] and an increase in the extinction coefficients are observed in the UV spectra of the synthesized compounds. For 1-(3-halotetrahydro-2-furyl)-5-halouracils there is a bathochromic shift as compared with 1-(3-halotetrahydro-2-furyl)uracil, which increases in the order F < Cl < Br < I.

The antineoplastic activity was investigated with respect to two strains of implanted tumors of mice, viz., leucosis L 1210 and the dense tumor of adenocarcinoma 755. We investigated the cis isomers of 1-(3-chlorotetrahydro-2-furyl)-5-fluorouracil (IIc) and 1-(3-bromotetrahydro-2-furyl)-5-uracil (IVc). Compounds IIc and IVc were introduced intraperitoneally 1, 2, 3, 4, and 7 days after transplantation of the tumor. A broad range of doses up to toxic levels was investigated, and the dose—effect curve was constructed. The maximum therapeutic effect that can be achieved by means of a given preparation was determined. It was found that IIc increases the lifetime of mice with lympholeucosis L 1210 by 64% and reduces the growth of the AC-755 tumor by 38%, as compared with 45% and 25%, respectively, for IVc. With respect to their antineoplastic activity, these compounds are similar to the preparation fluorafur but do not surpass it.

TABLE 3. PMR Spectra of the cis Isomers of the Compounds IIa-g and IVa-g



Compound	Chemical shifts,* δ, ppm							SSCC, J, Hz	
	NH (NH_2)	H_6 ($^3J_{H_6H_5}$=8,0 Hz)	H_5 ($^3J_{H_6H_5}$=8,0 Hz)	H_2 ($^3J_{H_{2'}H_{3'}}$=4,6 Hz)	$H_{3'}$	$H_{5'}$	$H_{4'}$	$^3J_{H_{3'}H_{2'}}$ = $^3J_{H_{3'}H_{4'}}$	$^3J_{H_{3'}H_{4'}}$
IIa	11,30	7,54	5,60	5,95	4,83	4,32—3,82	2,78—1,98	4,6	5,7
IIb	11,30	7,40	—	5,95	4,85	4,43—3,80	2,80—1,96	4,6	5,8
IIc	11,90	7,90 ($^3J_{FH_6}$=7,0 Hz)	—	5,96 ($^5J_{H_{2'}F}$=1,8 Hz)	4,84	3,24—3,78	2,84—2,02	4,6	5,8
IId	11,90	7,90	—	5,91	4,84	4,35—3,44	2,61—1,91	4,6	5,8
IIe	11,80	7,90	—	5,94	4,85	4,36—3,82	2,82—1,96	4,8	5,4
IIf	11,70	7,91	—	5,88	4,84	4,34—3,82	2,88—2,00	4,2	5,6
IIg	(7,10)	7,52	5,72	5,88	4,88	4,18—3,91	3,81—2,71	4,2	5,6
IVa	11,30	7,51	5,53	5,87	4,91	4,31—3,82	2,98—2,01	4,6	5,6
IVb	11,30	7,41	—	5,86	4,89	4,37—3,78	2,94—1,97	4,6	5,8
IVc	11,90	7,90 ($^3J_{FH_6}$=7,0 Hz)	— ($^5J_{H_{2'}F}$=1,8 Hz)	5,85	4,89	4,36—3,63	2,82—1,95	4,7	5,7
IVd	11,90	7,90	—	5,85	4,91	4,40—3,84	2,88—2,01	4,6	5,6
IVe	11,90	7,90	—	5,85	4,91	4,37—3,82	2,89—2,01	4,4	5,6
IVf	11,70	7,84	—	5,88	4,91	4,36—3,82	2,89—3,82	4,4	5,6
IVg	(7,10)	7,51	5,46	5,76	4,91	4,27—3,80	2,91—2,00	4,2	5,6

*1-(trans-3-Chlorotetrahydro-2-furyl)-5-fluorouracil, δ, ppm: 5.77 (1H, d, C_2'—H, J = 12 Hz), 7.74 (1H, d, C_6—H, J = 7.0 Hz). 1-(cis-3-Chlorotetrahydro-2-furyl)-5-fluorouracil, δ, ppm: 5.98 (1H, dd, C_2'—H, J = 4.2; 2.0 Hz), 7.84 (1H, d, C_6—H, J = 7.0 Hz). 2,3'-Anhydro-1-(cis-3-hydroxytetrahydro-2-furyl)-5-fluorouracil, δ, ppm: 5.33 (1H, t, C_3'—H, J = 5.2 Hz), 6.17 (1H, d, C_2—H, J = 5.2 Hz), 8.12 (1H, d, C_6—H, J = 4.6 Hz).

EXPERIMENTAL

The purity of the synthesized compounds was monitored by means of thin-layer chromatography (TLC) on Silufol UV-254 plates in a chloroform—ethanol system (9:1). The melting points were determined with a Boetius microblock. The UV spectra were recorded with a Specord UV-Vis spectrophotometer. The IR spectra of suspensions of the compounds in mineral oil or hexachlorobutadiene were recorded with a UR-20 spectrometer. The PMR spectra of solutions of the compounds in d_6-DMSO were obtained with a Bruker WH-90 spectrometer with hexamethyldisiloxane (HMDS) as the internal standard. The 2,3-dihalotetrahydrofurans were synthesized by the method in [7, 8].

The characteristics of the cis isomers of the compounds obtained are presented in Tables 1-3. The PMR spectra of IVc, Vc, and VIc are presented in Fig. 1.

1-(3-Chlorotetrahydro-2-furyl)uracil cis Isomer (IIa). A mixture of 11.9 g (107 mmole) of uracil, 40 ml of hexamethyldisilazane, and 1.5 ml of trimethylchlorosilane was heated at 150-170°C until dissolving was complete, after which the solution was heated for another 1 h. The excess hexamethyldisilazane was removed by distillation at reduced pressure, 40 ml of dry acetonitrile and 18.0 g (128 mmole) of 2,3-dichlorotetrahydrofuran were added to the residue, and the reaction mixture was stirred at 50-60°C for 4 h. It was then cooled and treated with 15 ml of ethanol, and the mixture was stirred for another 20 min. The resulting precipitate was separated and recrystallized from chloroform to give 13.7 g (60%, based on uracil) of a product with mp 152-154°C.

1-(3-Chlorotetrahydro-2-furyl)-5-fluorouracil (cis Isomer IIc compound IIa and trans isomer IIIc),2,3'-Anhydro-1-(tetrahydro-2-furyl-5-fluorouracil (VIc), and 1,3-Bis(3-chlorotetrahydro-2-furyl)-5-fluorouracil. A mixture of 2.6 g (20 mmole) of 5-fluorouracil, 20 ml of hexamethyldisilazane, and 1.3 ml of trimethylchlorosilane was treated as described above. After removal of the solvent by distillation, 3.4 g (24 mmole) of 2,3-dichlorotetrahydrofuran was added to the residue, and the temperature was raised slowly to 138°C (the trimethylchloro-

silane liberated in the reaction began to be removed by distillation). The reaction was continued for 20 min, after which the mixture was cooled and treated with 20 ml of ethanol, and the resulting mixture was stirred for 20 min. The precipitate (3.5 g) was removed by filtration and recrystallized from chloroform to give 1.2 g (21.5%, based on 5-fluorouracil) of IIC, with mp 196-198°C, and 1.9 g (34%) of VIc with mp 133-135°C. UV spectrum (water), $\lambda_{max}(\varepsilon)$: 218 (5000), 277 nm (7800). Found, %: C 48.6, H 3.4, N 14.0. $C_8H_8ClPN_2O_3$. Calculated, %: C 48.5, H 3.6, N 14.1.

The mother liquor was concentrated in vacuo to give 0.6 of a substance, recrystallization of which from ethanol gave 10.36 g (6.5%) of IIc with mp 165-167°C.

The mother liquor was evaporated to a syrupy residue, which was cooled to 4°C. In the course of several days, 0.6 g of 1,3-bis(3-chlorotetrahydro-2-furyl)-5-fluorouracil precipitated. Recrystallization from ethanol gave 0.53 g (8%) of a substance with mp 143-145°C. PMR spectrum: 1.8-2.87 (4H, m, H_4'H_4"), 3.67-4.4 (4H, m, H_5'H_5"), 4.4-5.16 (2H, m, H_3'H_3"), 5.96; 5.77 (2H, dd, H_2'H_2", J = 1.6 Hz), 7.87; 7.75 ppm (2H, dd, H_6H_6, J = 6.3 Hz). Found, %: C 42.0, H 3.9, N 8.1. $C_{12}H_{13}Cl_2FN_2O_4$. Calculated, %: C 42.5, H 3.9, N 8.3.

1-(3-Bromotetrahydro-2-furyl)-5-fluorouracil (cis Isomer IVc and trans Isomer Vc). A mixture of 3.25 g (25 mmole) of 5-fluorouracil, 11.5 g (50 mmole) of 2,3-dibromotetrahydrofuran, and 5.07 g (50 mmole) of triethylamine in 100 ml of dry acetonitrile was stirred at room temperature for 6 h, after which the precipitated triethylamine hydrochloride was separated. The filtrate was concentrated in vacuo to a syrupy residue, which was dissolved in 200 ml of chloroform. The chloroform solution was washed with water (two 20-ml portions), and the precipitate was separated and recrystallized from ethanol to give 4.05 g (58%) of IVc with mp 179-180°C.

The mother liquor was concentrated in vacuo to give 0.9 g of a substance, recrystallization of which from ethanol—ethyl acetate (1:1) gave 0.5 (7%) of Vc with mp 161-163°C.

Compounds IIb, IId-g, IVa,b, and IVd-g. These compounds were obtained by a procedure similar to that used for IIa.

Compounds IId-f were also synthesized by halogenation of IIa in analogy with the method in [10].

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