ANALOGS OF PYRIMIDINE NUCLEOSIDES.

17.* SYNTHESIS OF 1-[5(2)-FLUOROMETHYLTETRAHYDRO-2-FURYL]URACILS

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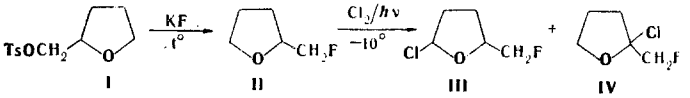
The synthesis of 2-fluoromethyltetrahydrofuran is described, and it is shown that chlorination of the latter gives 2-chloro-5- and 2-chloro-2-fluoromethyltetrahydrofurans in a ratio of 5:1. 2,4-Bis(trimethylsilyl) derivatives of uracil were alkylated by means of the mixture of α-chloro ethers without separation, and a mixture of the cis and trans isomers of 1-(5-fluoromethyltetrahydro-2-furyl)uracils and 1-(2-fluoromethyltetrahydro-2-furyl)uracils were obtained. The reaction products were identified on the basis of the PMR spectra.

In a previous communication [1] we showed that the chlorination of 2-chloromethyl- and 2-bromomethyltetrahydrofurans takes place at both the unsubstituted α-carbon atom and, to a lesser degree, in the substituted α position. The resulting α-chloro ethers were used as alkylating agents in the preparation of 1-[5(2)-halomethyltetrahydro-2-furyl]-5-substituted uracils.

In the present paper we describe for the first time the synthesis of 2-fluoromethyltetrahydrofuran (II) and show that chlorination of the latter (at −10°C) gives 2-chloro-5-fluoromethyl- (III) and 2-chloro-2-fluoromethyltetrahydrofuran (IV) in a ratio of 5:1 (from analysis of the PMR spectra of the reaction mixture). Slight dehydrochlorination of 2-chloro-2-fluoromethyltetrahydrofuran (IV) to give 2-fluoromethyl-4,5-dihydrofuran is possible when the temperature of the reaction mixture is increased. 2-Fluoromethyltetrahydrofuran was obtained by the reaction of 2-(p-tolylsulfonyloxymethyl)tetrahydrofuran (I) with anhydrous potassium fluoride in diethylene glycol at 170-210°C. In view of their instability, the mixture of α-chloro ethers III and IV was used without separation for the alkylation of 2,4-bis(trimethyl-



silyl) derivatives of uracil and 5-substituted uracils V-VII. The reaction takes place at 20-25°C in an aprotic solvent. As a result we obtained a mixture of cis and trans isomers of 2,5-disubstituted tetrahydrofurans VIIIa,b-Xa,b and 2,2-disubstituted tetrahydrofurans XI-XIII. The maximum yield of VIIIa,b-Xa,b was 40% (the sum of the isomers), whereas the yield of XI-XIII did not exceed 9%. The mixture of isomers of 2,5-disubstituted tetrahydrofurans can be separated from the 2,2-disubstituted tetrahydrofurans by fractional crystallization from ethanol or by column chromatography on silica gel. In connection with the fact that the 2,2-disubstitutted tetrahydrofurans are formed as side products in small amounts, they were identified from the PMR spectra; an individual compound (XI) was isolated in only one case (see the experimental section).

*See [1] for communication 16.

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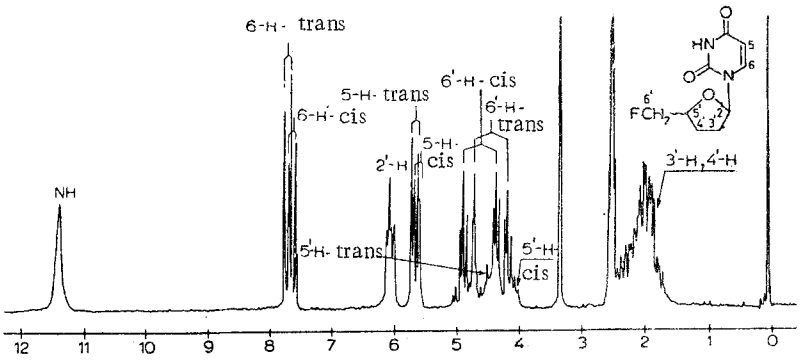
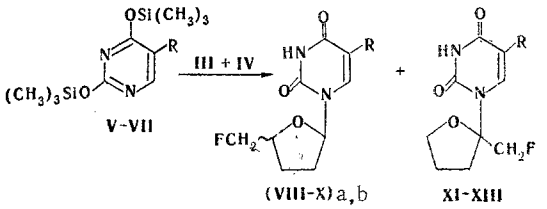


Fig. 1. PMR spectrum of a mixture of cis and trans isomers of 1-(5-fluoromethyltetrahydro-2-furyl)uracil (VIIIa,b) (in d_6-DMSO with hexamethyldisiloxane as the standard).

The assignment of the isomers of the 1-(5-fluoromethyltetrahydro-2-furyl)uracils was made on the basis of the chemical shifts of the signals of the 5'-H and 6'-H protons of the substituent of the side chain of the tetrahydrofuran ring. A study of the Overhauser nuclear effect (ONE) between the 6-H proton of the pyrimidine base and the 5'-H protons of the tetrahydrofuran ring in a series of similar compounds, which we presented in a previous communication [1], proved that the resonance of the 5'-H proton of the tetrahydrofuran ring in the cis isomers of the investigated compounds is shifted 0.4-0.5 ppm to strong field as compared with the trans isomers. The signal of the 6'-H protons of the side chain of the tetrahydrofuran ring is a doublet ($^2J_{HCF}$ = 46 Hz) of multiplets as a consequence of coupling with the fluorine nucleus, which in the case of the cis isomers is shifted to weak field under the influence of the anisotropy of the uracil ring (Fig. 1). A doublet of quartets of the protons of the CH_2 group in the tetrahydrofuran ring, which arises as a consequence of H—C—F and H—C—H spin-spin coupling (45.6 and 8.7 Hz), is characteristic for the PMR spectra of 2,2-disubstituted tetrahydrofurans XI-XIII. The UV spectra of the compounds obtained are characteristic for 1-substituted uracils.



V, VIII, XI R=H; VI, IX, XII R=CH_3; VII, X, XIII R=F; VIII—X: a — cis isomer, b — trans isomer

The mixture of isomers Xa,b over a wide range of doses does not display antitumorigenic activity in mice with lympholeucosis L 1210 and adenocarcinoma 755, and we therefore did not separate the mixture to obtain the individual isomers and investigate their antitumorigenic activity.

EXPERIMENTAL

The purity of VIII-XI was monitored by thin-layer chromatography (TLC) on Silufol UV-254 and by elementary analysis. The PMR spectra of solutions of the compounds in d_6-DMSO or CCl_4 were recorded with a Bruker WH-90 DS spectrometer with hexamethyldisiloxane as the internal standard. The UV spectra were recorded with a Unicam SP 1800 spectrophotometer. The course of the separation during column chromatography was monitored by means of a Uvikord flow absorptiometer connected to a recorder. The melting points were determined with a Boëtius microblock.

2-Fluoromethyltetrahydrofuran (II). A mixture of 104.0 g (0.4 mole) of I [2] and 120 g of anhydrous potassium fluoride in 150 ml of freshly distilled diethylene glycol was heated at 170-210°C for 1-2 h with simultaneous distillation of the resulting 2-fluoromethyltetrahydro-

TABLE 1. PMR Spectra of Mixtures of cis and trans Isomers of 1-(5-Fluoromethyltetrahydro-2-furyl)uracils (VIIIa,b-Xa,b) in d_6-DMSO (δ, ppm, Relative to Hexamethyldisiloxane)

Compound	Chemical shifts, δ, ppm												
	NH	6-H		5-H (5-CH_3)		2′-H	3′-H—4′-H	5′-H′		6′-H		cis/trans
		cis	trans	cis	trans			cis	trans	cis	trans	
VIII a,b	11,2	7,64*	7,77*	5,66*	5,68*	6,10	2,4—1,8	4,15	4,45	4,6	4,4	1,2 : 1
IX a,b	11,3	7,46	7,54	(1,84)	(1,84)	6,08	2,4—1,8	4,08	4,48	4,7	4,5	4,9 : 1
X a,b	11,7	7,74†	7,74†	—	—	5,96‡	2,4—1,8	4,05	4,43	4,6	4,4	3,4 : 1

*$^3J_{6-H—5-H}$ = 8.0 Hz. †$^3J_{H_6F}$ = 7.1 Hz. ‡$^5J_{H_2'F}$ = 1.8 Hz.

TABLE 2. Physicochemical Properties of 1-(5-Fluoromethyltetrahydro-2-furyl)uracils

Compound	UV spectrum, λ_{max}, nm (ε·10⁻³)			R_f*	Found, %			Empirical formula	Calc., %			Yield, %
	pH 2	pH 7	pH 12		C	H	N		C	H	N	
VIIIa,b	264 (9,3)	264 (8,8)	264 (7,0)	0,63	50,9	5,3	12,8	$C_9H_{11}FN_2O_3$	50,1	5,2	13,1	15,2
IXa,b	269 (10,5)	270 (9,7)	268 (8,9)	0,74	51,9	5,6	11,9	$C_{10}H_{13}FN_2O_3$	52,6	5,7	12,3	65,0
Xa,b	271 (9,3)	271 (8,8)	270 (6,8)	0,72	47,0	4,7	11,9	$C_9H_{10}F_2N_2O_3$	46,5	4,3	12,1	30,2

*In a chloroform—ethanol system (9:1).

furan. The product was purified by vacuum distillation with collection of the fraction with bp 32-35°C (22 mm) and n_D^{20} 1.405 to give 24.5 g (58%) of II with bp 110°C. PMR spectrum (in CCl_4): 1.5-2.1 (m, 4, 3-H—4-H), 4.2 (m, 2, CH_2), 4.1 (m, 1, 2-H), and 4.5 ppm (m, 2, 5-H). Found: C 57.5; H 8.5; F 18.4%. C_5H_9FO. Calculated: C 57.7; H 8.7; F 18.3%.

2-Chloro-5- and 2-Chloro-2-fluoromethyltetrahydrofurans (III, IV). A solution of 10.4 g (0.1 mole) of II in 100 ml of dry CCl_4 was placed in a quartz flask, the flask was cooled to —15°C, and a mixture of dry nitrogen and 8.5 g (0.12 mole) of chlorine was fed into the mixture in the course of 1.5 h with stirring and irradiation with a PRK-4 mercury lamp (400 W; the distance from the lamp to the flask was 30-40 cm) while maintaining the temperature at —15 to —10°C. Irradiation was then continued for another hour while nitrogen was blown through the mixture to remove the hydrogen chloride, after which NaA molecular sieves were added, and the mixture was stirred for 30 min and filtered. The mixture was concentrated *in vacuo* to half its original volume and used in the next reaction. The yield of chlorination products was determined from the PMR spectrum of the reaction mixture. It contained 18.5% unchanged starting II, 62% III, and 13.5% IV.

1-(5-Fluoromethyltetrahydro-2-furyl)uracil (VIIIa,b) and 1-(2-Fluoromethyltetrahydro-2-furyl)uracil (XI). A mixture of 2.8 g (0.025 mole) of uracil, 20 ml of hexamethyldisilazane, and 1.0 ml of trimethylchlorosilane was heated at 150-170°C until the uracil had dissolved completely, after which the solution was heated for another 2 h. The excess hexamethyldisilazane was removed by distillation *in vacuo*, 10 ml of dry acetonitrile was added to the resulting 2,4-bis(trimethylsilyl)uracil, and 3.42 g (0.025 mole) of the mixture of ethers III and IV was added slowly dropwise. The mixture was stirred at room temperature for 4 h, after which 10 ml of ethanol was added in such a way that the temperature did not rise above 40°C. The mixture was stirred at room temperature for 1 h, and the resulting precipitate was separated and extracted with chloroform. The chloroform-insoluble part of the precipitate was unchanged uracil (1.2 g). The chloroform solution was evaporated, and the residue was combined with the mother liquor and purified with a column filled with silica gel [elution with ethanol—chloroform (1:9)]. The separation was monitored by means of a flow absorptiometer. The compounds obtained were recrystallized from ethanol to give 0.8 g of a mixture of isomers VIIIa,b (Tables 1 and 2), 0.1 g of trans isomer VIIIb, with mp 143-145°C, and 0.25 g of XI with mp 198-199°C. UV spectrum, λ_{max} (ε): 264 (9400), at pH 2, 264 (8800) at pH 7, and 264 (7000) at pH 12. PMR spectrum (d_6-DMSO): 1.7-2.4 (m, 4, 3′-H—4′-H); 4.00 (m, 2, 5′-H); 4.56, 4.78 (dq, 2, CH_2, J_{HCF} = 45.6 Hz, J_{HCH} = 8.7 Hz); 5.57 (d, 1, 6-H, $^3J_{6-H—5-H}$ = 8.0 Hz); 7.74 (d, 1, 6-H, $^3J_{6-H—5-H}$ = 8.0 Hz); 11.3 ppm (s, 1, NH).

Synthesis of IX and X. The synthesis of these compounds in the form of a mixture of cis and trans isomers was carried out similarly. The PMR spectra and physicochemical characteristics are presented in Tables 1 and 2.

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SYNTHESIS OF ACYLATED (2'-HYDROXYETHYL)AMINO- AND (2'-AMINOETHYL)AMINO-1,3,5-TRIAZINES

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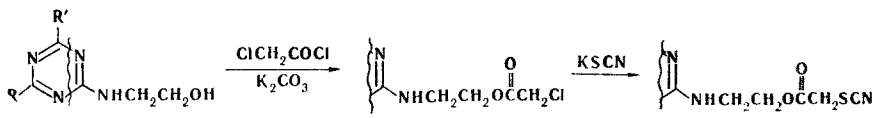
The acylation of (2'-hydroxyethyl)amino-1,3,5-triazines with chloroacetyl chloride with subsequent reaction of the resulting (2'-chloroacetoxyethyl)aminotriazines with potassium thiocyanate is described. Acylated derivatives of substituted (2'-aminoethyl)aminotriazines were obtained by the reaction of the chlorotriazines with monoacylethylenediamines.

1,3,5-Triazines are finding wide application as herbicides. The disadvantages of this class of compounds include their high persistence in environmental objects and the low selectivity of their herbicidal action. The introduction of labile (2'-hydroxyethyl)amino and (2'-aminoethyl)amino groupings in the triazine molecule makes it possible to obtain compounds that have selectivity with respect to their action and more rapid detoxication in the soil and plants.

In order to obtain biologically active compounds and in a continuation of our earlier research [1, 2] on the chemical behavior of (2'-hydroxyethyl)amino- and (2'-aminoethyl)aminotriazines in reactions with electrophilic reagents we accomplished the synthesis of their acylated derivatives.

Chloroacetyl chloride was used as the acylating agent in reactions with (2'-hydroxyethyl)-aminotriazines (I). (2'-Chloroacetoxyethyl)amino-1,3,5-triazines (II) were obtained by the reaction of triazines I with chloroacetyl chloride in acetone in the presence of potassium carbonate.

Starting triazines I contain two reaction centers that are capable of undergoing acylation, viz., the NH and OH groups.



I a-i II a-i III a-d, f

I a-h, II a-h, III a-d, f R=Cl; I i, II i R=OCH_3; I—III a R'=NHC_2H_5; b R'=NHC_3H_7-*n*; c R'=NHC_4H_9-*i*; d R'=NHC_6H_{13}-*n*; e R'=$NHC_{12}H_{25}$-*n*; f R'=$NHCH_2CH{=}CH_2$; g R'=OC_2H_5; h R'=SCH_3; i R'=NHC_3H_7-*i*

The absence in the IR spectra of II of an absorption band of an OH group and the presence of an absorption band of an ester carbonyl group at 1740-1750 cm^{-1}, as well as the absence in the PMR spectra of signals of one or two NH protons (depending on substituent R') at 6-7.8 ppm, confirm that acylation takes place at the OH group. A comparision of data from the PMR spectra of II with the data in [3] makes it possible to conclude that the acyl chloride chlorine atom participates in acylation. The triplet of the most characteristic $CH_2OC(O)$ group in the investigated compounds appears at 4.2-4.3 ppm, while the singlet of the $ClCH_2$ group is observed at 4.2 ppm.

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