ANALOGS OF PYRIMIDINE NUCLEOSIDES.

14.* SYNTHESIS AND ANTITUMORIGENIC ACTIVITY OF ALKOXYALKYL DERIVATIVES OF 5-FLUOROURACIL

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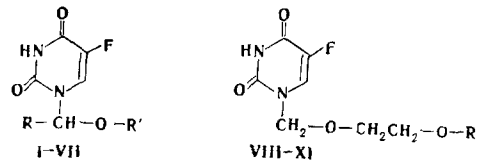
A number of alkoxyalkyl derivatives of 5-fluorouracil were synthesized by alkylation of 2,4-bis(trimethylsilyl)-5-fluorouracil with α-chloro ethers or by the addition of 5-fluorouracil to vinyl ethers. It was established that the synthesized compounds are capable of increasing the lifetimes of mice with L-1210 leukemia and La hemocytoblastosis. The UV and NMR spectra of the synthesized compounds are presented.

1-(2-Tetrahydrofuryl)-5-fluorouracil has high antitumorigenic activity and low toxicity and is widely used in clinical practice under the name ftorafur [1, 2].

The present paper is devoted to the synthesis of structural analogs of ftorafur, viz., 5-fluorouracil alkoxyalkyl derivatives I-XI. A comparison of the physicochemical and biological properties of ftorafur and its acyclic analogs is necessary to shed some light on the problem as to whether the tetrahydrofuran ring is the specific fragment responsible for the antitumorigenic activity of ftorafur or whether it can be replaced by an acyclic ether grouping with a definite length and structure that ensures a lipophilicity that is close to that of the original compound.



I—IV R=H; V—VII R=CH_3; I R′=CH_3; II, V R′=C_2H_5; III, VI R′=C_3H_7; IV, VII R′=C_4H_9; VIII R=$COCH_3$; IX R=H; X R=CH_3; XI R=C_2H_5

Derivative IX was obtained by deacetylation of VIII. The characteristics of I-XI are presented in Tables 1 and 2.

A study of the biochemical properties and biological activity of the acyclic analogs of ftorafur is of great significance for an understanding of the mechanism of the action of ftorafur and may also serve as a basis for an efficient search for new antitumorigenic preparations.

The synthesis of alkoxyalkyl derivatives of 5-fluorouracil (I-VII) was realized by alkylation of 2,4-bis(trimethylsilyl)-5-fluorouracil with aliphatic α-chloro ethers (method A). Compounds V-VII were also obtained by the addition of 5-fluorouracil to vinyl ethers in the presence of acetic acid as the catalyst (method B). α-Chloro ethers of the CH_2ClOR type were obtained by chloromethylation of the corresponding alcohols [3], while compounds of the CH_3CHCl—OR type were obtained by the addition of hydrogen chloride to vinyl ethers [4]. α-Chloro ethers with the general formula $ClCH_2OCH_2CH_2OR$ (R = CH_3, C_2H_5) were synthesized by

*See [9] for Communication 13.

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TABLE 1. Alkoxyalkyl Derivatives of 5-Fluorouracil (I-XI)

Compound	R_f	mp, °C	UV spectrum, λ max, nm (log ε)			Yield, %*
			pH 2	pH 7	pH 12	
I	0,69	132—134	269 (8100)	269 (7900)	269 (5900)	70
II	0,70	129—131	268 (8400)	268 (8300)	268 (6000)	87
III	0,73	72—74	269 (6200)	269 (6400)	269 (4500)	75
IV	0,73	67—69	270 (8100)	270 (8100)	270 (6000)	72
V	0,80	116—118	271 (8600)	271 (9100)	272 (6200)	97
VI	0,82	104—106	271 (8600)	271 (8500)	271 (6700)	80
VII	0,82	57—59	270 (7800)	270 (7600)	270 (5400)	90
VIII	0,47	142—144	270 (8000)	270 (7700)	270 (5800)	90
IX	0,17	153—155	269 (8300)	269 (7700)	270 (6000)	80
X	0,64	105—107	268 (7600)	268 (7400)	269 (5500)	78
XI	0,68	75—77	268 (9400)	268 (9800)	268 (7200)	84

*Based on the converted 5-fluorouracil.

TABLE 2. PMR Spectra of Alkoxyalkyl Derivatives of 5-Fluorouracil (I-XI)

Compound	NH*	δ, ppm (J, Hz)	
		6H (J_{HF})	other signals
I	11,9	8,07 (6,4)	5,09 (2H, s, CH_2); 3,42 (3H, s, CH_3)
II	11,9	8,05 (6,2)	5,09 (2H, s, CH_2); 3,64 (2H, q, J=6,4, CH_2CH_3); 1,26 (3H, t, J=6,4, CH_3)
III	11,5	7,55 (5,5)	5,02 (2H, s, CH_2); 3,44 (2H, t, J=6,4, OCH_2CH_2—); 1,60 (2H, sext, J=6,4, CH_2CH_3); 0,91 (3H, t, J=6,4, CH_3)
IV	11,9	7,98 (6,5)	5,09 (2H, s, CH_2); 3,57 (2H, t, J=6,4, OCH_2CH_2—); 1,67 (4H, m, CH_2CH_2); 0,84 (3H, t, J=6,4, CH_3)
V	11,5	7,35 (5,8)	5,73 (1H, o, J=6,5; J_{HF}=1,0, CH); 3,44 (2H, q, J=6,5, CH_2); 1,35 (3H, d, J=6,5, $CHCH_3$); 1,11 (3H, t, J=6,5, CH_2CH_3)
VI	11,6	7,39 (5,9)	5,83 (1H, o, J=6,5; J_{HF}=2,0, CH); 3,44 (2H, t, J=6,5, OCH_2); 1,62 (2H, sext, J=6,5, CH_2); 0,93 (3H, t J=6,5, CH_3)
VII	11,8	7,26 (5,5)	5,72 (1H, o, J=6,5; J_{HF}=2,0, CH); 3,49 (2H, t, J=6,5, OCH_2); 1,40 (3H, d, J=6,6, $CHCH_3$); 1,39 (4H, m, CH_2CH_2); 0,92 (3H, t, J=6,5, CH_2CH_3)
VIII	12,4	7,91 (6,0)	4,80 (2H, s, CH_2); 3,44 (2H, m, CH_2CH_2); 3,07 (2H, s, CH_2CH_2); 1,94 (3H, s, CH_3)
IX	11,6	7,85 (6,3)	4,76 (2H, s, CH_2); 3,84 (2H, s, CH_2CH_2); 2,97 (2H, s, CH_2CH_2)
X	11,6	7,82 (6,2)	5,04 (2H, s, CH_2); 3,65 (2H, m, CH_2CH_2); 3,44 (2H, m, CH_2CH_2); 3,27 (3H, s, OCH_3)
XI	11,8	7,85 (6,7)	4,98 (2H, s, CH_2); 3,55 (6H, m, CH_2CH_2, CH_2CH_3); 1,11 (3H, t J=6,5, CH_3)

*A broad signal in all cases.

chloromethylation of methyl- and ethylcellosolves and were used as the alkylating agents for the synthesis of X and XI. 1-Acetoxy-2-chloromethoxyethane, which has been previously used for the alkylation of adenine and cytosine [5], served as the alkylating agent for the preparation of VIII [5] ; the use of 1-benzoxy-2-chloromethoxyethane is also possible [6].

The antitumorigenic activity of the synthesized compounds was studied with respect to two strains of transplanted tumors, viz., L-1210 leukemia and La hemocytoblastosis. It is apparent from Table 3 that II, III, and V have the greatest activity; this is possibly associated with the definite lipophilic properties of these compounds [7].

EXPERIMENTAL

The UV spectra of solutions of the compounds in water were recorded with a Specord UV-vis spectrophotometer. The PMR spectra of solutions of the compounds in a mixture of CCl_4 and d_6-DMSO were obtained with a Perkin-Elmer R-12A spectrometer (60 Hz) with hexamethyldi-

TABLE 3. Effect of 1-Substituted 5-Fluorouracils on the Lifetimes of Mice with L-1210 Lymphatic Leukemia and La Hemocytoblastosis in the Case of Intraperitoneal Injection

Compound	Increase in the lifetime, %	
	L-1210	La
I	21	26
II	58	46
III	43	65
IV	15	15
V	58	85
VII	10	40
VIII	0	0
IX	0	10
X	0	24
XI	0	18

siloxane as the internal standard. Chromatography was carried out on Silufol UV-254 plates (Czechoslovakian SSR) in a chloroform–ethanol system (9:1).

1-Ethoxy-3-chloromethoxyethane. A stream of hydrogen chloride was passed through a mixture of 13.9 ml (0.51 mole) of formalin and 22 ml (0.23 mole) of ethylene glycol monoethyl ether at −20°C for 2 h. The temperature was gradually raised to room temperature, and the mixture was extracted with ether. The ether solution was dried with calcium chloride, and the the calcium chloride was removed by filtration and washed with 40 ml of dry ether. The combined filtrates were evaporated *in vacuo* to give 24.96 g (39%) of 1-ethoxy-3-chloromethoxyethane with bp 68°C (21 mm) and n_D^{20} 1.428 [bp 43°C (3 mm), d_4^{20} 1.0534, and n_D^{20} 1.4280 [8]].

1-Methoxy-3-chloromethoxyethane was similarly obtained in 48% yield and had n_D^{20} 1.423 and bp 84-87°C (16 mm).

General Method for the Synthesis of Alkoxyalkyl Derivatives of 5-Fluorouracil (I-VII). A) By Means of α-Chloro Ethers. A mixture of an aliphatic α-chloro ether (0.11-0.14 mole) and 2,4-bis(trimethylsilyl)-5-fluorouracil, obtained from 0.1 mole of 5-fluorouracil, was stirred at 30°C for 1 h, after which it was cooled to 20°C and treated with 50 ml of absolute ethanol. The precipitated 5-fluorouracil was removed by filtration and washed with chloroform (two 10-ml portions). The combined filtrates were evaporated *in vacuo*, and 50 ml of chloroform was added to the residue. The 5-fluorouracil was removed by filtration and washed with chloroform (two 10-ml portions). The filtrates were evaporated, and the residue was recrystallized from hexane–ethanol (1:1).

B) General Method for the Synthesis of V-VII by Means of Vinyl Ethers. 5-Fluorouracil (0.1 mole) was dissolved in 100 ml of dimethylformamide (DMF), 0.2 mole of the vinyl ether and 0.05 mole of glacial acetic acid were added, and the mixture was heated at 100°C for 5 h. The DMF was removed by vacuum distillation, and the residue was dissolved in chloroform. The 5-fluorouracil was removed by filtration, and the residue was evaporated in vacuo and recrystallized from ethanol–hexane (1:1).

The yields calculated on the basis of the converted 5-fluorouracil and the characteristics of the substances obtained are presented in Tables 1 and 2.

1-(2-Acetoxyethoxymethylene)-5-fluorouracil (VIII). 2,4-Bis(trimethylsilyl)-5-fluorouracil, obtained from 0.1 mole of 5-fluorouracil, was added to 0.11 mole of 1-acetoxy-2-chloromethoxyethane, and the mixture was stirred at 30°C for 3 h. It was then cooled to room temperature and treated with 100 ml of ethanol–chloroform (1:1). The unchanged 5-fluorouracil was removed by filtration and washed with chloroform. The filtrate was evaporated *in vacuo*, and the residue was recrystallized from ethanol–water (9:1).

1-(2-Hydroxyethoxymethylene)-5-fluorouracil (IX). A 0.1-mole sample of VIII was dissolved in 10 ml of a methanol solution of ammonia, and the solution was allowed to stand at 20°C for 6 h. It was then evaporated *in vacuo*, and the residue was recrystallized from ethanol–ethyl acetate (1:1).

1-(2-Methoxyethoxymethylene)-5-fluorouracil (X) and 1-(2-Ethoxyethoxymethylene)-5-fluorouracil (XI). These compounds were obtained by method A and were purified by recrystallization from chloroform–hexane (1:1).

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SYNTHESIS OF 5-NITRO-N,N-DIPHENYLHYDRAZINOPYRIMIDINES AND INVESTIGATION OF THEIR FREE RADICALS

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A number of 5-nitro-N,N-diphenylhydrazinopyrimidines were synthesized. Free radicals were obtained by oxidation of these compounds with PbO_2. The stabilities of 5-nitro-4-pyrimidinylhydrazyl radicals are close to the stability of the α,α-diphenyl-β-2,4-dinitrophenylhydrazyl radical. The structures of the compounds obtained were confirmed by the UV, IR, PMR, and EPR spectra.

The introduction of heterocyclic substituents in stable radicals has a substantial effect on their electronic and three-dimensional structures, and this gives rise to a change in the spectral characteristics and reactivities and to the manifestation of the specific properties of these radicals [1].

No reports regarding the effect of a pyrimidine ring on the properties of free radicals have appeared in the literature. At the same time, information of this sort may be of value for obtaining quantitative data on the electronic nature and chemical peculiarities of pyrimidine derivatives.

The aim of the present research was to synthesize N,N-diphenyl-N'-pyrimidinylhydrazines that contain diverse substituents in the pyrimidine ring, to generate the corresponding hy-

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