ANALOGS OF PYRIMIDINE NUCLEOSIDES.

20.* AMINOMETHYLATION OF 5-FLUOROURACIL AND THYMINE

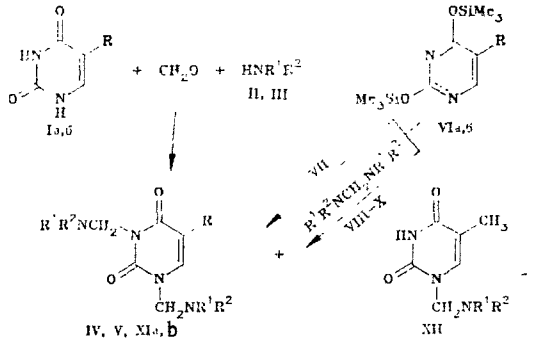
R. A. Zhuk, A. S. Ludzisha,
and R. G. Kostyanovskii

UDC 547.853.4'233.07:
542.953.7:543.422.25

Reactions were studied of 5-fluorouracil and thymine with formaldehyde and secondary amines (piperidine, morpholine) and also of their 2,4-bis(trimethylsilyl) derivatives with N-methoxymethylmorpholine and bis(amino)methanes. The N-aminomethylation products are slightly stable and in aqueous solutions decompose readily to the starting components; their structure was confirmed by PMR spectra.

It is known that aminomethylation of uracil proceeds at the 5-position [2, 3]. Several 5-aminomethyluracils, including the azacyclo-analog of pseudouridine, 5-[N-(2-hydroxyethyl)-N-methyl]-aminomethyluracil [3], were obtained by the Mannich reaction [3]. The aminomethylation of 5-substituted uracils has not yet been investigated. According to [2], the aminomethylation of thymine proceeds at the nitrogen atom at the 3-position, but this finding was not sufficiently substantiated. The aminomethylation of 5-fluorouracil by the Mannich reaction has not been described in the literature. Derivatives of 5-fluorouracil, aminomethylated at the $N_{(1)}$ atom were obtained in [4] by the reaction of 2,4-bis(trimethylsilyl)-5-fluorouracil with 2-methoxy-N-methoxy-N-methoxymethylcaprolactam. N-aminomethyl derivatives, which, in contrast to the corresponding derivatives at the $C_{(5)}$ atom, are appreciably less stable towards hydrolysis, were obtained by aminomethylation of 1,2,4-triazines, including 6-azauracil [5, 6]. (5-Flurouracil-1-yl)azacycloalkanes, (5-fluorouracil-1-yl)-lactams, and (5-fluorouracil-1-yl)amino acids, with a geminal diamine structure, are considered as potential antitumor agents [4, 7, 8]. Therefore, the N-aminomethyl derivatives of 5-fluorouracil are also of interest from the standpoint of their antitumorigenic activity.

In the present work, we studied the reactions of 5-fluorouracil (Ia) and thymine (Ib) with formaldehyde and secondary amines (piperidine, morpholine) and also of 2,4-bis(trimethylsilyl) derivatives of 5-fluorouracil (VIa) and of thymine (VIb) with N-methoxymethylmorpholine (VII) and bis(amino)methanes VIII-X.



I, IV—VI, XI a R=F, b R=CH_3; II, IV, VIII R^1R^2=$-(CH_2)_5-$, III, V, IX R^1R^2=$-(CH_2)_2O(CH_2)_2-$, X—XII $R^1=CH_3$, $R^2=C_6H_5$

When 5-fluorouracil or thymine are boiled with a 3-5-fold excess of piperidine or morpholine and formaldehyde in ethanol, 1,3-bis-Mannich bases IV and V are formed in a yield up

*For Communication 19, see [1].

Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR, Riga 226006. Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow 117334. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 90-93, January, 1987. Original article submitted January 27, 1986; revision submitted June 13, 1986.

 0009-3122/87/2301-0074$12.50

TABLE 1. Characteristics of 1-Mono- and 1,3-Bis(aminomethyl) Derivatives of 5-Fluorouracil and Thymine IV, V, XI, XII

Compound	mp, °C	Calculated, %			Empirical formula	Found, %			Yield, %	
		C	H	N		C	H	N	A	Б
IVa	150—152 (dec.)	59,2	7,8	17,3	$C_{15}H_{25}FN_4O_2$	59,4	7,9	17,2	65	50
IVb	175—177 (dec.)	63,7	8.8	17,5	$C_{17}H_{28}N_4O_2$	63,5	9,0	17,4	90	73
Va	128—130	51.2	6.5	17,1	$C_{14}H_{21}FN_4O_4$	51,1	6.6	17,0	72	61
Vb	123—125	55,6	7.5	17,3	$C_{15}H_{24}N_4O_4$	55.5	7.8	17,4	74	57
XIa	103—105	65,2	5,8	15.2	$C_{20}H_{21}FN_4O_2$	65,1	5,6	15,1	—	52
XIb	104—106	69,2	6.7	15,4	$C_{21}H_{24}N_4O_2$	69.3	6,8	15,2	—	23
XII	130—132 (dec.)	63,6	6,2	17,1	$C_{13}H_{15}N_3O_2$	63,9	6,0	17,3	—	58

to 90%. At a twofold excess of the amine, the yield of the products decreases to 45%. Compounds IV and V are white crystalline substances, which decompose during recrystallization from ethanol or chloroform with the formation of the initial bases Ia,b. However, they can be purified by recrystallization from a 1:3 mixture of ethyl acetate and hexane. The characteristics of products IV and V are given in Tables 1 and 2. The reaction could not be obtained with N-methylaniline and dimethylamine.

It is known that during the alkylation of 2,4-bis(trimethylsilyl) derivatives of 5-fluorouracil and thymine (VIa,b) by glycosyl halides [9] and α-chloroethers [10], 1-substituted pyrimidine bases are formed. Therefore, to obtain N-mono-substituted derivatives of 5-fluorouracil and thymine, we used the silyl derivative method. As aminomethylating reagents, we used N-methoxymethylmorpholine (VII), bis(piperidino)methane (VIII), bis(morpholino)methane (IX), and bis(methylanilino)methane (X). The reaction was carried out in anhydrous medium without a solvent, and also in acetonitrile or dichloroethane at a temperature of 20-50°C. The reaction of the silyl derivative VIa with amine VII (in a 1:2 ratio) at 20°C is completed after a few minutes with the formation of a Mannich base Va, identical to that described above. At a 1:1 ratio of the reagents, compound Va is also formed, but with a lower yield. Product Va was also obtained by using amine IX. Compounds IVa,b and XIa were synthesized in a similar way, while in the reaction of the silyl derivative VIb with amine X, not only the bis-Mannich base XIb, but also a mono-substituted derivative, 1-methylanilinomethylthymine (XII), could be isolated. In the PMR spectra, the NCH_2N signals at the $N_{(1)}$ and $N_{(3)}$ atoms were assigned on the basis of comparison with the data for 1-mono- and 1,3-bishydroxymethyluracils [11]. Aminomethylation of compounds VIa,b by the action of bis(dimethylamino)methane could not be accomplished.

The N-Mannich bases of 5-fluorouracil and thymine decompose in polar solvents with the liberation of the starting pyrimidine. In water, at room temperature, they decompose in the course of a few minutes. The synthesized compounds may find application in organic synthesis as reactive bifunctional derivatives of 5-fluorouracil and thymine.

EXPERIMENTAL

The melting points were determined on a Boetius microblock. The PMR spectra were obtained on a Bruker WH-90 spectrometer in $CDCl_3$, relative to HMDSO as internal standard.

Preparation of Bis(amino)methanes. Bis(dimethylamino)methane was obtained according to [12]. Compounds VIII-X were obtained in a similar way. Bis(piperidino)methane (VIII), bp 114-116°C (22 mm), n_D^{20} 1.4820 (according to the data in [13], bp 59.5-61°C (0.6-0.7 mm), n_D^{20} 1.4830). PMR spectrum ($CDCl_3$): 2.82 (2H, s, NCH_2N), 2.38 (8H, d, J = 6.0 Hz, CH_2CH_2), 1.47 ppm (12H, s, CH_2). Bis(morpholino)methane (IX), bp 97-100°C (7 mm), n_D^{20} 1.4570. PMR spectrum ($CDCl_3$): 3.73 (8H, t, CH_2OCH_2), 2.96 (2H, s, NCH_2N), 2.56 ppm (8H, t, CH_2NCH_2). Bis(methylanilino)methane (X), bp 192-195°C (10 mm), n_D^{20} 1.6145. PMR spectrum ($CDCl_3$): 7.33-7.09 (5H, m, Ph), 6.93-6.64 (5H, m, Ph), 4.96 (2H, s, NCH_2N), 2.87 ppm (6H, s, CH_3).

Methoxymethylmorpholine (VII) was obtained by a method described in [14].

1,3-Bis(aminomethyl) Derivatives of 5-Fluorouracil and Thymine (IV, Va,b, XIa). A. A 5 ml portion of a 31% solution of formaldehyde and 0.06-0.10 mole of the corresponding amine II or III are added with stirring to a suspension of 0.02 mole of Ia or Ib in 50 ml of

TABLE 2. PMR Spectra of 1-Mono- and 1,3-Bis(aminomethyl) Derivatives of 5-Fluorouracil and Thymine IV, V, XI, XII

Compound	Chemical shift, δ, ppm (J, Hz)			
	$C_{(6)}H$, 1H, d	$N_{(3)}CH_2$, 2H, s	$N_{(1)}CH$, 2H, s	other signals
IVa	7,40 (5,8)	4,93	4,49	2,60 (8H, m, CH_2NCH_2); 1,52 [12H, m, $(CH_2)_3$]
IVb	7,09 (0,9)	4,93	4,49	2,58 (8H, m, CH_2NCH_2); 1,93 (3H, d, J = =0,9 Hz, CH_3); 1,49 [12H, m, $(CH_2)_3$]
Va	7,38 (5,8)	4,97	4,51	3,67 (8H, q, CH_2OCH_2); 2,67 (8H, m, CH_2NCH_2)
Vb	7,09 (0,9)	4,96	4,50	3,69 (8H, q, CH_2OCH_2); 2,67 (8H, m, CH_2NCH_2); 1,96 (3H, d, J=0,9 Hz CH_3)
XIa	—	5,60	5,29	7,40—6,69 (11H, m, Ph, 6-H; 3,13 (3H, s, NCH_3); 3,04 (3H, s, NCH_3)
XIb	—	5,62	5,31	7,40—6,73 (11H, m, Ph, 6-H); 3,13 (3H, s, NCH_3); 3,04 (3H, s, NCH_3); 1,82 (3H, d, J=0,9 Hz, CH_3)
XII	—	—	5,33	8,91 (1H, s, NH); 7,42—7,18 (5H, m Ph); 7,00—6,78 (5H, m Ph); 3,07 (3H, s, NCH_3); 1,84 (3H, d, J=0,9 Hz, CH_3)

ethanol. The reaction mixture is boiled for 2 h, then cooled, and the precipitate that separates is filtered. The filtrate is evaporated, and 10 ml of hexane is added to the residue. The precipitate that separates is filtered. The combined precipitate is recrystallized from a hexane—ethyl acetate (3:1) mixture. Compounds IVa,b and Va,b are obtained.

B. A 0.02 mole portion of VII (or IX) is added slowly, with stirring, to 0.01 mole of VIa, and the mixture is stirred for 1 h at 20°C. A 10 ml portion of hexane is added, the precipitate is filtered, and extracted by 10-15 ml of ethyl acetate. The solvent is evaporated, and the residue is recrystallized from a hexane—ethyl acetate (3:1) mixture. Compound Va is obtained.

Compounds IVa and XIa are obtained in a similar way using amines VIII and X.

Compounds IVb and Vb are obtained by reacting compounds VIb with amine VII (or VIII, IX) in 5 ml of dry dichloroethane at 30-50°C.

1,3-Bis(methylaminomethyl)thymine (XIb) and 1-Methylanilinothymine (XII). A 0.02 mole portion of amine X is added to a solution of 0.01 mole of VIb in 5 ml of dry dichloroethane, and the mixture is stirred for 1 h at 30-50°C. A 10 ml portion of hexane is added, and the precipitate is filtered and recrystallized from a hexane—ethyl acetate (3:1) mixture. Compound XII is obtained. Evaporation of the filtrate and treatment of the residue by ethyl acetate (7 ml) and hexane (10 ml) gives crystalline XIb, which is purified by recrystallization from a hexane—ethyl acetate (3:1) mixture.

LITERATURE CITED

1. R. A. Zhuk, A. S. Ludzisha, E. G. Shpaer, M. Yu. Lidak, A. A. Zidermane, and D. V. Meirena, Khim. Geterotsikl. Soedin., No. 10, 1406 (1985).
2. E. I. Besyadetskaya, V. G. Zubenko, and L. V. Lozyuk, Zh. Fiz. Khim., No. 7, 42 (1980).
3. H. Griengl, W. Hayden, W. Kalchauer, and E. Wanek, Arch. Pharmacol., 317, 193 (1984).
4. T. Nishitani, H. Horikawa, T. Iwasaki, K. Matsumoto, and M. Miyoshi, J. Org. Chem., 47, 1706 (1982).
5. A. Mustafa, A. K. Mansour, and H. A. Zaher, Ann. Chem., 733, 177 (1970).
6. S. Asano, J. Kitamura, and K. Takatori, J. Pharm. Soc. Jpn., 92, 1162 (1972).
7. T. Nishitani, T. Iwasaki, Y. Mushika, and M. Miyoshi, J. Org. Chem., 44, 2019 (1979).
8. T. Nishitani, T. Iwasaki, Y. Mushika, I. Inoue, and M. Miyoshi, Chem. Pharm. Bull., 28, 1137 (1980).
9. É. Ya. Lukevits and A. E. Zablotskaya, Silyl Derivative Method for Synthesis of Nucleosides [in Russian], Zinatne, Riga (1985), p. 30.
10. M. Ya. Karpeiskii, S. N. Mikhailov, A. S. Tsieminya, A. A. Ziderman, I. M. Kravchenko, M. Yu. Lidak, and R. A. Zhuk, Khim. Geterotsikl. Soedin., No. 11, 1541 (1980).
11. P. C. Bansal, I. H. Pitman, J. N. S. Tam, M. Mertes, and J. J. Kaminski, J. Pharm. Sci., 70, 850 (1981).

12. Synthesis of Organic Preparations [Russian translation], Coll. 12, Mir, Moscow (1964), p. 74.
13. R. G. Kostyanovskii and O. A. Pan'shin, Izv. Akad. Nauk SSSR, Ser. Khim., 1, 182 (1963).
14. Ch. M. McLeod and G. M. Robinson, J. Chem. Soc., 119, 1470 (1921).

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

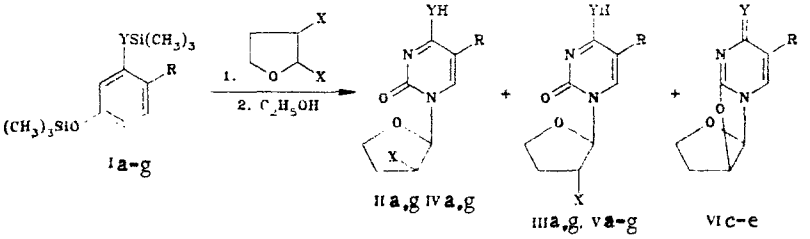
L. T. Kaulinya and M. Yu. Lidak

UDC 547.854.4'722.4:542.94.944

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.
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 94-99, January, 1987. Original article submitted June 12, 1986.

