LITERATURE CITED

1. USSR Inventor's Certificate No. 180,605; Otkrytiya, No. 21 (1967).
2. R. Böhm, Pharmazie, 41, 81-87 (1986).
3. A. V. R. Born, Nature, 194, 927-929 (1962).
4. H. Kessler, Angew. Chem., 9, 219-235 (1970).
5. J. A. King and F. H. McMillan, J. Am. Chem. Soc., 68, 1774-1777 (1946).
6. L. P. Kyrides, F. B. Ziently, G. W. Steahly, and H. L. Morril, J. Org. Chem., 12, 577-583 (1947).
7. E. P. Prokof'ev, Zh. A. Krasnaya, and V. F. Kucherov, Org. Magn. Reson., 6, 240-244 (1974).

SYNTHESIS AND CYTOSTATIC ACTIVITY OF XYLOFURANOSYL ANALOGS OF NUCLEOSIDES

É. M. Kaz'mina, I. I. Fedorov, Ya. É. Bezchinskii, N. V. Kiseleva, N. A. Novikov, G. G. Galegov, and A. P. Arzamastsev

UDC 542.91:547.455.526:547.854.4

Among the most widely used antitumor drugs are 5-fluorouracil, its furanidyl derivative (fluorofur [2]), and other biologically active derivatives [4]. Xylofuranosyl analogs of nucleosides are known which possess antitumor and antiviral activity, namely 9-β-D-xylofuranosyladenine [5], 3'-deoxy-3'-haloxylofuranosylcytosine, and 3'-haloxylofuranosyl-5-fluorocytosine [11].

Replacement of the hydrogen in the 3-position of 2'-desoxy-5-substituted uridines by alkyl groups results in a change in thymidine kinase inhibitory activity which correlates with the length of the alkyl chain [6, 7]. This could be due to changes in the lipophilicity of the nucleoside molecule and (when the lipophilicity is at an optimum) the best membrane penetration. The most effective inhibitors of thymidine kinase in this series are compounds which have a pentyl group in the 3-position, further increases in the length of the alkyl chain resulting in a decrease in activity.

On the basis of these observations, we have obtained some 3-substituted 1-(β-D-xylofuranosyl)-5-fluorouracils. Condensation of 1-O-acetyl-2,3,5-tri-O-benzoyl-α-D-xylofuranose [10] with 2,4-bistrimethylsilyl-5-fluorouracil [3] in the presence of $SnCl_4$ as catalyst [11] has given 1-(2',3',5'-tri-O-benzoyl-β-D-xylofuranosyl)-5-fluorouracil (I) [2], which was then alkylated with an equimolar amount of the appropriate alkyl bromide or alkyl iodide in DMSO solution in the presence of anhydrous potassium carbonate as described in [6], to give compounds (III, V, VII, and IX). To obtain the dinucleoside bridged at the 3-position of the 5-fluorouracil moiety by a hexane bridge, namely 1,6-bis-[1-(β-D-xylofuranosyl)-5-fluorouracil-3-yl]hexane (XII), the ratio of (I) to 1,6-dibromohexane used was 2:1. Debenzoylation of (I), (III), (V), (VII), (IX), and (XI) with sodium methoxide in methanol afforded the 1-(β-D-xylofuranosyl)-5-fluorouracils (II), (IV), (VI), (VIII), (X), and (XII) (see Scheme 1).

In our view, this method of preparation of 3-substituted uridine analogs has advantages over the method in which the deblocked nucleoside is alkylated, followed by separation of the products by column chromatography. Alkylation of the benzoylated nucleoside enables the product to be isolated by pouring into cold water. Debenzoylation with sodium methoxide followed by recrystallization gave the pure products.

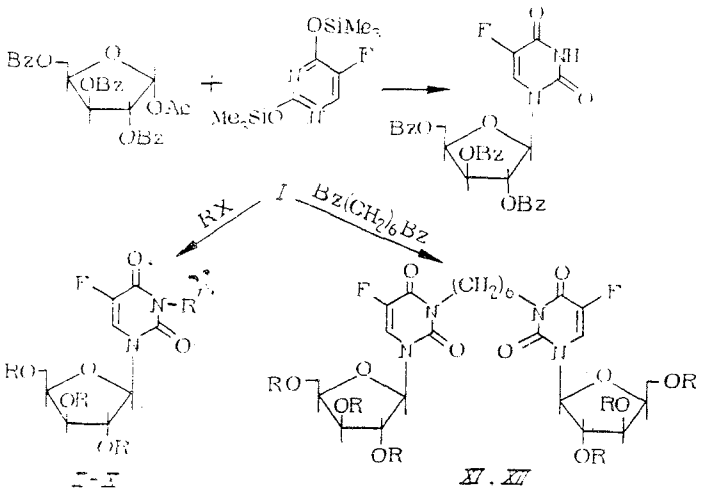
The lipophilicity of the nucleosides can also be enhanced by introducing hydrophobic substituents into the carbohydrate moiety of the molecule. Specifically, it was found that

No. 1 I. M. Sechenov Moscow Institute of Medicine. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 23, No. 10, pp. 1217-1223, October, 1989. Original article submitted December 5, 1988.

 0091-150X/89/2310-0830$12.50

an adamantylcarbonyl group in the 5'-position of several ribo- and 2'-desoxyribonucleosides substantially increased their antitumor activity [4, 8].

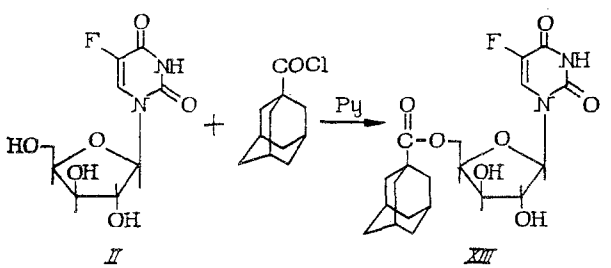
Scheme 1



II: R = R¹ = H; III: R = Bz, R¹ = Me; IV: R = H, R¹ = Me; V: R = Bz, R¹ = Et; VI: R = H, R¹ = Et; VII: R = Bz, R¹ = C_5H_{11}; VIII: R = H, R¹ = C_5H_{11}; IX: R = Bz, R¹ = $C_{15}H_{31}$; X: R = H, R¹ = $C_{15}H_{31}$; XI: R = = Bz; XII: R = H.

Treatment of the xylofuranosyl compound (II) with an equimolar amount of adamantylcarbonyl chloride in dry pyridine at room temperature gave 1-[5'-O-(1-adamantylcarbonyl)-β-D-xylofuranosyl]-5-fluorouracil (XIII) (Scheme 2).

Scheme 2



The nucleoside analogs (II, IV, VI, VIII, XII) are soluble in water and DMSO. Compounds (X) and (XIII) are insoluble in water, but soluble in ethanol and DMSO. The physicochemical properties of the compounds obtained are given in Table 1.

In recent years, the attention of investigators has again been attracted to 9-β-D-xylofuranosyladenine, which has been found quite recently to possess antiviral activity. For this reason, it was important to develop convenient methods for its synthesis, since the known methods require protected xylofuranose compounds which are difficult to obtain, and the yields are relatively poor.

9-β-D-Xylofuranosyladenine (XIV) has been obtained by condensation of 1-O-acetyl-2,3,5-tri-O-benzoyl-α-D-xylofuranose with 6,9-bis(trimethylsilyl)-N^6-benzoyladenine in the presence of trimethylsilyl trifluoromethanesulfonate, followed by deblocking the intermediate 9-(2'-3',5'-tri-O-benzoyl-β-D-xylofuranosyl)-N^6-benzoyladenine with ammonia in methanol, in 68.3% yield.

The cytostatic activity of these analogs was assessed from the change in the number of cells using the "vero" cell line (a culture of cells from the kidneys of the green marmoset). The cells were inoculated into flasks at an initial concentration of 10^5/ml on medium 199, containing 5% of bovine serum and 280 μg/ml of L-glutamine. The cells were counted in a Goryachev chamber after 72 h.

TABLE 1. Physicochemical Properties of Xylofuranosyl Derivatives of Fluorouracil and Adenine

Compound	Yield, %	mp, °C	Empirical formula	R_f*
I	189—90	80,5	$C_{30}H_{23}FN_2O_9$	0,40
II	150—1	73,5	$C_9H_{11}FN_2O_6$	(0,16)
III	125—6	84,8	$C_{31}H_{25}FN_2O_9$	0,57
IV	204—5	63,5	$C_{10}H_{13}FN_2O_6$	(0,25)
V	153	91,5	$C_{32}H_{27}FN_2O_9$	0,62
VI	208—9	82,3	$C_{11}H_{15}FN_2O_6$	0,33
VII	112—3	83,6	$C_{14}H_{21}FN_2O_6$	0,51
VIII	161—2	95,8	$C_{35}H_{33}FN_2V_9$	(0,74)
IX	79—80	90,6	$C_{45}H_{53}FN_2O_9$	(0,88)
X	124—5	86,4	$C_{24}H_{41}FN_2O_6$	(0,73)
XI	109—11	71,5	$C_{66}H_{56}F_2N_4O_{18}$	0,45
XII	208—9	85,5	$C_{24}H_{29}F_2N_4O_{12}$	(0,06)
XIII	99—101	52,9	$C_{20}H_{26}FN_2O_7$	(0,74)
XIV	144—6	68,3	$C_{10}H_{12}N_5O_4$	—

*In the system ethyl acetate—hexane (25:30); ethyl acetate in brackets.

TABLE 2. IR and UV Spectral Properties of Compounds Obtained

Compound	IR spectrum, cm^{-1}					UV spectrum, in ethanol, λ_{max}, m ($\varepsilon \cdot 10^{-3}$)
	ν_{OH}	$\nu_{C=O}$	ν_{C-F}	σ_{CH}(ring)	σ_{CH} (av.)	
I		1720*, 1678	1700,1260	762	712	
II	3400 (br.)	1705	1685,1260	860; 784		209 (10,44)
III		1720*, 1660	1690,1263	765	714	
IV	3450 3360	1699	1669,1250	844; 777		208 (10,00)
V		1720*, 1665	1690,1265	760	712	
VI	3350 (br.)	1700	1676,1269	850; 769		208 (9,59) 270 (9,26)
VII		1725*, 1675	1705,1260	762	713	
VIII	3400 3480	1701	1665,1265	854; 772		208 (10,20) 271 (9,78)
IX		1720*, 1670	1705,1262	762	710	
X	3520 3430	1703	1640,1262	865; 770		209 (10,44) 271 (10,50)
XI		1725*, 1660	1685,1260	766	718	
XII	3450 (br.)	1702	1672,1272	860; 778		207 (21,36) 270 (19,29)
XIII	3450 (br.)	1730*, 1685	1706,1265	845; 780		209 (10,44) 270 (10,79)

*Absorption attributed to the benzoyl group (in I, III, V, VII, IX, and XI), or to the adamantylcarbonyl group (in XIII).

The ability of the nucleoside analogs to inhibit the growth of cells was assessed over a period of 48 h. The controls were cell cultures which did not contain the test compounds.

The test compounds were introduced into the medium 24 h after the cells were introduced, and the cells were counted in a Goryachev chamber. The time of contact of the test compounds with the cells was 48 h.

Cytostatic activity was assessed by finding the concentration of the test compound which inhibited the growth of the cells by 50% (IG_{50}).

The compounds were tested in a range of concentrations from 1.5-3200 μg/ml (II, IV, VI, XI), 15-1600 μg/ml (VIII), and 1.5-80 μg/ml (X).

TABLE 3. ^{1}H NMR Spectral Data for Compounds Obtained

Compound	Chemical shift, δ; coupling constants, Hz									
	H (1′)	H (2′)	H (3′)	H (4′)	H (5′) d	H (6) d	N—CH_2	N—CH_2CH_2— m	—CH_2— m	—CH_3
II	5,82 d.d. $J_{1,2}$=1,6 $J_{1,F}$=1,2	4,29 m $J_{2,3}$=1,6	4,25 m $J_{3,4}$=3,6	4,43 t.d $J_{4,5}$=5,4	4,00	8,06 $J_{6,F}$=6,6	— — —	— — —	— — —	— — —
IV	5,85 s	4,24 ———	4,32 m	4,44 m $J_{4,5}$=4,7	4,02	8,06 $J_{6,F}$=6,5	— — —	— — —	— — —	3,34 s
VI	5,84 s	4,26 ———	4,34 m $J_{3,4}$=3,9	4,36—4,51 m $J_{4,5}$=5,3	4,01	8,04 $J_{6,F}$=6,2	3,98 q J=7,1	— — —	— — —	1,21 t J=7,1
VIII	5,83 s	4,27 ———	4,38 m $J_{3,4}$=3,1	4,36—4,53 m $J_{4,5}$=5,3	4,01	8,04 $J_{6,F}$=6,2	3,94 t J=7,9	1,70	1,34 4H	0,88 t J=7,1
X*	5,85 s	4,15		4,43 m $J_{4,5}$=4,0	4,04	8,14 $J_{6,F}$=6,8	3,97 t J=7,3	...	1,07— 1,55 m 24H	0,88 t J=7,1
XII	5,83 d.d. $J_{1,2}$=1,5 $J_{1,F}$=1,2	4,26 ——— $J_{2,3}$=3,2	4,30 m $J_{3,4}$=3,2	4,42 t.d. $J_{4,5}$=5,6	4,04	8,04 $J_{6,F}$=6,4	3,94 t J=7,1 4H	1,70 4H	1,33 m 4H	— — —
XIII†	5,67 s	4,37		4,50 m $J_{4,5}$=5,4	4,25	8,02 $J_{6,F}$=7,3				

*Spectrum obtained in $(CD_3)_2CO$. Internal standard TMS. The signal for the NCH_2CH_2 group overlapped with that for the solvent.

†Spectrum obtained in DMSO-D_6 + TMS. The signals for the adamantyl group were: CH 1.99 m (3H), CH_2 1.91 m (6H), CH_2 1.73 m (6H).

Compound (II) showed no appreciable cytostatic activity in concentrations up to 3200 μg/ml. For (IV), (VI), and (XII) the ID_{50} (the concentration causing the deaths of 50% of the cells as compared with the controls) was 1500, 1280, and 2210 μg/ml, respectively.

A linear relationship between the inhibition of cell growth and concentration was found only with (VIII) and (X), their ID_{50} values being 280 and 20 μg/ml, respectively.

Significant cytostatic activity was therefore observed in compounds bearing at least a pentyl substituent in the 3-position. The high activity of the pentadecyl compound (X) was unexpected. It could be due to a second rise in biological activity at high lipophilicity, such as is sometimes seen in homologous series.

The structures of the nucleoside analogs were confirmed by IR and UV spectroscopy (Table 2), ^1H NMR spectroscopy (Table 3), elemental analysis, and in the cases of (II) and (XII), ^{13}C NMR spectroscopy.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were obtained on a Bruker WM-250 instrument (West Germany) in D_2O, using 2,2-dimethyl-2-silapentane-5-sulfonic acid as internal standard. IR spectra were obtained on a Perkin–Elmer-457 spectrometer (Sweden) as suspensions in Vaseline oil, and UV spectra on a Hitachi EPS 3T spectrometer, in water. Melting points were measured on a Boetius micro-hot plate. The purity of the compounds was checked by chromatography on Silufol UV-254 plates in the system ethyl acetate–hexane (25:30) and ethyl acetate. The elemental analyses were in agreement with the calculated values.

1-(2',3',5'-Tri-O-benzoyl-β-D-xylofuranosyl-5-fluorouracil (I). A mixture of 2.74 g (10 mmole) of 2,4-bistrimethylsilyl-5-fluorouracil, 4.30 g (8.5 mmoles) of 1-O-acetyl-2,3,5-tri-O-benzoyl-α-D-xylofuranose, and 1.5 ml (12.8 mmoles) of freshly distilled $SnCl_4$ was stirred in 150 ml of dry dichloroethane for 2 h with protection from atmospheric moisture. The mixture was neutralized with saturated sodium bicarbonate solution, stirred for 1 h, filtered through kieselguhr, and the solid washed with dichloroethane (2 × 20 ml). The organic layer was separated, washed with water (2 × 50 ml), dried over anhydrous sodium sulfate, and evaporated under reduced pressure at 40-50°C. The residue was dissolved in 40 ml of dichloroethane, filtered, and again evaporated to give 4.76 g (97%) of a foam, which was dissolved in 20 ml of chloroform, and hexane added until a strong opalescence was obtained. After cooling, 3.95 g of finely crystalline solid (I) was filtered off.

1-(2',3',5'-Tri-O-benzoyl-β-D-xylofuranosyl)-3-methyl-5-fluorouracil (III). A mixture of 1.15 g (2 mmoles) of the tribenzoate (I), 0.31 g (2.2 mmoles) of methyl iodide, 5 ml of DMSO, and 0.25 g of finely ground potassium carbonate was stirred for 6 h at room temperature. About 10 g of crushed ice was then added, and the mixture kept for 1 h. The solid was isolated by centrifugation, washed with water, and air-dried. Crystallization from ethanol gave 1 g of (III).

1-(2',3',5'-Tri-O-benzoyl-β-D-xylofuranosyl)-3-ethyl-5-fluorouracil (V). A mixture of 1.15 g (2 mmoles) of (I), 5.34 g (2.2 mmoles) of EtI, 5 ml of DMSO, and 0.25 g of K_2CO_3 was stirred for 6 h. It was then worked up as described for (III). Crystallization from ethanol gave 1.11 g (91.5%) of finely crystalline (V).

1-(2',3',5'-Tri-O-benzoyl-β-D-xylofuranosyl)-3-pentyl-5-fluorouracil (VII). A mixture of 1.15 g (2 mmoles) of (I), 0.44 g (2.2 mmoles) of pentyl iodide, 5 ml of DMSO, and 0.25 g of K_2CO_3 was stirred for 6 h, and worked up as described for (III). Crystallization from a mixture of 10 ml of ethanol, 12 ml of chloroform, and 4 ml of hexane gave 1.24 g of (VII).

1-(2',3',5'-Tri-O-benzoyl-β-D-xylofuranosyl)-3-pentadecyl-5-fluorouracil (IX). A mixture of 1.15 g (2 mmoles) of (I), 0.64 g (2.2 mmoles) of pentadecyl bromide, 10 ml of DMSO, and 0.25 g of K_2CO_3 was stirred for 1 day. Ice water (25 ml) was then added, and the mixture kept for 1 h. The solid which separated was filtered off, and washed without compaction on the filter with 200 ml of water. The solid was dissolved in 25 ml of chloroform, and the solution dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was triturated with 10 ml of hexane, and the hexane discarded. This operation was repeated twice. Drying in vacuo gave 1.42 g of amorphous (IX).

1,6-Bis-[1-(2',3',5'-tri-O-benzoyl-β-D-xylofuranosyl)-5-fluorouracil-3-yl]hexane (XI). To a solution of 2.3 g of K_2CO_3 was added with stirring 15 ml of a solution containing 0.54 g (2.2 mmoles) of 1,6-dibromohexane in 20 ml of DMSO, and the mixture stirred for 1 day.

The remaining 5 ml of solution was added dropwise as slowly as possible over 8 h to the reaction mixture, heated to 40-50°C. After stirring for 1 day at room temperature, 30 g of crushed ice was added, and after 1 h the solid was isolated by centrifugation, washed with water, and dried in air. Crystallization from ethanol gave 1.76 g of (XI).

1-(β-D-Xylofuranosyl)-5-fluorouracil (II). To a suspension of 2.0 g (3.5 mmoles) of (I) in 20 ml of absolute methanol was added with stirring 5 ml of 1 M sodium methoxide in methanol. After 2 h, 10 ml of methanol and 1 ml of the sodium methoxide solution were added, and the mixture stirred for 0.5 h at 30-40°C. After cooling, the pH of the solution was brought to 5 by adding Dowex-50 (H^+), filtered, and the residue washed on the filter with methanol (2 × 5 ml). The solution was evaporated under reduced pressure, and the residue treated with 10 ml of water and 20 ml of dichloroethane. After shaking the mixture in a separatory funnel, the aqueous layer was separated and again extracted with 20 ml of dichloroethane. The operation was repeated three times. The aqueous layer was evaporated under reduced pressure at a temperature not exceeding 35°C, and the residue treated with 5 ml of benzene and 1 ml of absolute ethanol, and again evaporated. This operation was repeated until the oil solidified to a porous foam. This was dissolved in 4 ml of absolute ethanol, and 2-3 drops of hexane added carefully, followed by ethyl acetate until a slight opalescence appeared. After 1 day, the solution with the crystals which had separated was again treated with ethyl acetate until opalescence appeared, and kept for 1 day in the refrigerator. Hexane (0.5 ml) was then added, and after 1 day 0.67 g (73.5%) of large crystals of (II) were filtered off. ^{13}C NMR spectrum, δ, ppm: 160.45 q ($C_{(4)}$, J_{C-C-F} = 25.9 Hz), 151.1 s ($C_{(2)}$), 141.4 q ($C_{(5)}$, J_{C-F} = 231.2 Hz), 127.2 q ($C_{(6)}$, J_{C-C-F} = 35.1 Hz), 92.3 s ($C_{(1')}$), 84.5 s ($C_{(4')}$), 81.4 s ($C_{(2')}$), 75.75 s ($C_{(3')}$), 60.75 s ($C_{(5')}$).

1-(β-D-Xylofuranosyl)-3-methyl-5-fluorouracil (IV). To a suspension of 0.88 g (1.5 mmoles) of (II) in 10 ml of dry methanol was added with stirring 2 ml of a 1 M solution of sodium methoxide in methanol. After 2 h, 5 ml of methanol was added, and the mixture stirred at 30-40°C for 0.5 h, then worked up as for (I). Crystallization from 3 ml of methanol and 0.5 ml of ethyl acetate gave 0.26 g of (IV).

Similarly obtained was 1-(β-D-xylofuranosyl)-3-ethyl-5-fluorouracil (VI), from (V). Crystallization from 2 ml of methanol and 0.5 ml of ethyl acetate gave 0.36 g of product.

1-(β-D-Xylofuranosyl)-3-pentyl-5-fluorouracil (VIII) was obtained from (VII). The product was crystallized from 5 ml of ethyl acetate, to which was added hexane until a slight opalescence was obtained. After keeping for 1 day, more hexane was added until a strong opalescence appeared, and the mixture kept in the refrigerator for 1 day. The solution was decanted from the crystals, washed with hexane (3 × 10 ml), and kept for a week in a flask in a vacuum desiccator over NaOH and paraffin wax, to give 0.42 g of (VIII).

1-(β-D-Xylofuranosyl)-3-pentadecyl-5-fluorouracil (X) was obtained from (IX). After cooling, the reaction mixture was neutralized by adding Dowex-50 (H^+), filtered, and the solid on the filter washed with ethyl acetate (3 × 10 ml) and methanol (2 × 5 ml). The solution was evaporated under reduced pressure, 10 ml of water and 20 ml of ethyl acetate added, shaken in a separatory funnel, and the aqueous layer discarded. The organic layer was dried over sodium sulfate, and evaporated under reduced pressure to a volume of 3-5 ml. On cooling crystals of (X) separated, and were filtered off, washed with hexane, and recrystallized from ethyl acetate to give 0.61 g of (IX).

1,6-Bis-[1-(β-D-xylofuranosyl)-5-fluorouracil-3-yl]hexane (XII) was obtained from (XI). It was crystallized from 2 ml of ethanol and 7 ml of ethyl acetate. On cooling, there was obtained 0.74 g of the dinucleoside (XII). ^{13}C NMR spectrum, δ, ppm: 159.85 d ($C_{(4)}$, J_{C-C-F} = 25.9 Hz), 151.0 s ($C_{(2)}$), 141.0 d ($C_{(5)}$, J_{C-F} = 229.3 Hz), 125.3 d ($C_{(6)}$, J_{C-C-F} = 35.1 Hz), 93.1 s C(1'), 84.8 s C(4'), 81.5 s C(2'), 75.7 s C(3'), 60.7 s C(5'), 43.0 s (NCH_2), 27.5 s (NCH_2CH_2), 26.7 s ($NCH_2CH_2CH_2$).

1-[5'-O-(1-Adamantylcarbonyl)-β-D-xylofuranosyl]-5-fluorouracil (XIII). To a solution of 0.52 g (2 mmoles) of (II) in 5 ml of dry pyridine was added dropwise with stirring over 2 h at 0°C a solution of 0.41 g (2.2 mmoles) of freshly distilled adamantylcarbonyl chloride in 5 ml of dry pyridine. The solution was kept for 1 day at room temperature, then evaporated under reduced pressure. The residue was treated with 20 ml of water and 20 ml of ethyl acetate, shaken, the organic layer separated, washed with water (2 × 20 ml), dried over sodium sulfate, evaporated under reduced pressure, 5 ml of toluene added, and again evaporated. The oily residue was dissolved in 2 ml of ethyl acetate, and the solution placed on a column

(40 × 0.5 cm, silica gel L, 40/100 μm). Elution was carried out with a mixture of ethyl acetate and hexane (20:1). The first 10 ml of eluate were discarded, and the next 50 ml collected, evaporated to dryness under reduced pressure, and the residue dissolved in 2 ml of hot benzene. After 1 day, the crystals of the adamantylcarbonyl compound (XIII) which had separated were filtered off and washed with hexane to give 0.45 g of product.

9-β-D-Xylofuranosyladenine (XIV). A mixture of 2.39 g (10 mmoles) of $N_{(6)}$-benzoyladenine, 20 ml of HMDS, and 100 mg of ammonium sulfate was heated with protection from moisture for 2 h. The mixture was then evaporated under reduced pressure at 70°C, and the residue treated with 4.81 g (9.5 mmoles) of 1-O-acetyl-2,3,5-tri-O-benzoyl-α-D-xylofuranose, 2.22 g (10 mmoles) of trimethylsilyl trifluoromethanesulfonate, and 50 ml of dry 1,2-dichloroethane, and the mixture heated with stirring and protection from moisture for 0.5 h. It was then cooled and neutralized with sodium bicarbonate solution, and filtered through silica gel L (40 × 100 μm, Czechoslovakian SSR), the silica gel being washed with dichloroethane (2 × 20 ml). The organic layer was separated, washed with water (2 × 50 ml), dried over sodium sulfate, and evaporated under reduced pressure at 45-50°C. The residue was dissolved in 40 ml of dichloroethane, filtered, and again evaporated under reduced pressure. The resulting yellowish foam was treated with 50 ml of a solution of ammonia in methanol, saturated at 0°C, hermetically stoppered, and kept for 48 h at room temperature. The solution was cautiously evaporated under reduced pressure, and the residue treated with 20 ml of water and extracted with chloroform (10 × 10 ml). The aqueous layer was evaporated under reduced pressure at 40°C, and the residue treated with 1 ml of absolute ethanol and 5 ml of benzene, and again evaporated. This operation was repeated three times. The residue was dissolved in 5 ml of methanol, and 25 ml of ethyl acetate added. The product which separated after keeping for 24 h at 5°C was filtered off, washed with ethyl acetate, and dried to give a yield of 1.73 g.

LITERATURE CITED

1. A. A. Zidermane, Fluoropyrimidines in the Chemotherapy of Tumors [in Russian], Riga (1982).
2. É. Ya. Lukevits and A. E. Zabolotskaya, The Silyl Methods for the Synthesis of Nucleosides [in Russian], Riga (1985).
3. M. N. Preobrazhenskaya and S. Ya. Mel'nik, Science and Technology Summaries, Bioorganic Chemistry Series [in Russian], Moscow (1984), pp. 36, 55, 77-120.
4. K. Gerson and D. Kau, J. Med. Chem., 10, 189 (1967).
5. R. Glazer, K. Hartman, and O. Cohen, Biochem. Pharmacol., 30, 2697 (1981).
6. A. Hampton, F. Kappler, and R. R. Chawla, J. Med. Chem., 22, 621 (1979).
7. A. Hampton, F. Kappler, and R. R. Chawla, ibid., 1524 (1979).
8. J. Montgomery and H. Thomas, ibid., 15, 116 (1972).
9. U. Niedballa and H. Vorbrüggen, Anew. Chem., 82, 449 (1970).
10. T. Tkaczynski, J. Smejkal, and F. Sorm, Coll. Czech. Chem. Commun., 29, 1736 (1964).
11. K. A. Watanabe, U. Reichman, C. K. Chu, et al., J. Med. Chem., 23, 1088 (1980).