*Chemistry of Heterocyclic Compounds, Vol. 34, No. 5, 1998*

# SYNTHESIS OF 1-(ARYLOXYALKYL)-5-(ARYLAMINO)URACILS

**A. A. Ozerov, M. S. Novikov, A. K. Brel',
and G. N. Solodunova**

*In an attempt to obtain new non-nucleoside inhibitors of the reverse transcriptase HIV-1, we have carried out the synthesis of 1-(benzyloxymethyl)- and 1-[2-(4-R-phenoxy)ethyl]-5-(arylamino)uracils. Indirect alkylation of trimethylsilyl derivatives of 5-(arylamino)uracils with benzyl chloromethyl ether by the Gilbert–Jones method did not affect the exocyclic amino group and gave the corresponding 1-(benzyloxymethyl) derivatives in 58-74% yield. Alkylation of 5-(arylamino)uracils with 1-bromo-2-(4-R-phenoxy)ethane in anhydrous DMF in the presence of potassium carbonate gave a mixture of $N^1$-mono- and $N^1,N^1$-disubstituted products with an overall yield of 46-55%.*

From the initial discovery of the type 1 human immunodepressant virus (HIV-1), which is the causative agent of the acquired immunodepressed syndrome (AIDS) [1, 2], considerable attention has been directed to the study of the life cycle of the virus and the identification of potential targets for chemotherapeutic reactions [3, 4]. Among the many approaches to the discovery of new anti-HIV-1 agents, one of the most promising is inhibition of the reverse transcriptase which catalyzes the transcription of the single chain RNA of the virus into the double chain DNA. Two classes of HIV-1 reverse transcriptases have been identified: nucleoside and non-nucleoside.

The nucleoside inhibitors of HIV-1 reverse transcriptases interfere with the preliminary phosphorylation of the cell enzyme to the corresponding 5'-triphosphates, which simultaneously inhibits the HIV-1 reverse transcriptases and terminates the growth of the viral DNA chain. 3'-Azido-3'-desoxythymidine was the first of these to be used clinically for the alleviation of AIDS. Other 2',3'-didesoxynucleosides (2',3'-didesoxyinosine, 2',3'-didesoxycytidine, 2',3'-didesoxy-2',3'-didehydrothymidine) are currently in clinical use [5, 7]. However, despite the evident selectivity for inhibition of HIV-1 reverse transcriptases, the triphosphates of these nucleoside analogs also inhibit the cellular DNA polymerases and have considerable toxic side effects [8]. Moreover, resistant strains of HIV-1 have arisen with prolonged use of the nucleoside inhibitors [9].

Non-nucleoside inhibitors of HIV-1 reverse transcriptases differ from the nucleoside inhibitors. They do not affect the preliminary phosphorylation, they have high selectivity towards HIV-1, they do not inhibit the activity of cellular DNA-polymerase, and they show considerably smaller toxic effects. One of the basic classes of non-nucleoside inhibitors of HIV-1 reverse transcriptases includes derivatives of pyrimidine bases, in particular 1-[(2-hydroxyethoxy)methyl]-6-(phenylthio)thymine (HERT) (I, $R^1 = CH_3$, $R^2 = CH_2OH$, $R^3 = H$, X = S) [10]. The selectivity index for this compound exceeds 100. Its analogs which lack a hydroxy group in the side chain, for example, 1-(benzyloxymethyl)-6-(phenylthio)thymine (II, $R^1 = CH_3$, $R^2 = C_6H_5$, $R^3 = H$, X = S) and 1-(benzyloxymethyl)-5-ethyl-6-(phenylthio)uracil (III, $R^1 = C_2H_5$, $R^2 = C_6H_5$, $R^3 = H$, X = S) are even more active with respect to HIV-1 reverse transcriptases. The inhibitory properties of HERT analogs increase with the presence of methyl substituents in the *meta*-position ($R^3 = CH_3$) [11-15].

The selenium analog of HERT, 1-[(2-hydroxyethoxy)methyl]-6-(phenylseleno)thymine (IV, $R^1 = CH_3$, $R^2 = CH_2OH$, $R^3 = H$, X = Se), is a highly active inhibitor of HIV-1 reverse transcriptases but its mechanism is different [16]. Similar in structure and inhibitory activity are the 2-alkoxy- and 2-cycloalkoxy-6-benzylpyrimidin-4(3H)-ones (V, $R^1$ and $R^3 = H$, $CH_3$) [17, 18], but the inhibitory activity was greater in compounds containing a cyclic radical $R^2$, e.g., cyclopentyl or cyclohexyl.

---

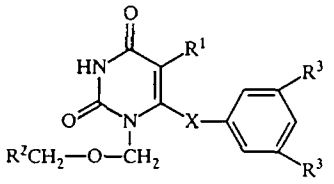
Pharmacology Scientific Research Institute, Volgograd Medical Academy, Volgograd 400066, Russia. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 5, pp. 691-697, May, 1998. Original article submitted April 14, 1997; revision submitted December 20, 1997.

0009-3122/98/3405-0611$20.00 

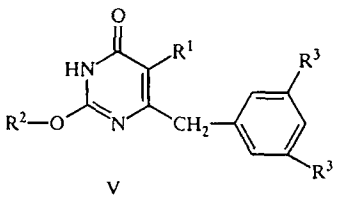
TABLE 1. Characteristics of the Compounds Synthesized

| Compound | Molecular formula | (Found, %) / (Calculated, %) C | H | N | mp, °C | $R_f$* | Yield, % |
|---|---|---|---|---|---|---|---|
| XIV | $C_{18}H_{17}N_3O_3$ | 66,30 / 66,86 | 5,27 / 5,30 | 13,29 / 13,00 | 154...156 | 0,21 | 73 |
| XV | $C_{19}H_{19}N_3O_3$ | 67,83 / 67,64 | 5,35 / 5,68 | 12,84 / 12,46 | 110...113 | 0,28 | 58 |
| XVI | $C_{19}H_{19}N_3O_3$ | 67,77 / 67,64 | 5,46 / 5,68 | 12,49 / 12,46 | 136...139 | 0,26 | 74 |
| XVII | $C_{19}H_{19}N_3O_3$ | 68,20 / 67,64 | 5,58 / 5,68 | 12,00 / 12,46 | 168...171 | 0,28 | 68 |
| XVIII | $C_{18}H_{16}BrN_3O_3$ | 53,91 / 53,75 | 4,12 / 4,01 | 10,96 / 10,45 | 179...182 | 0,28 | 60 |
| XIX | $C_{19}H_{19}N_3O_3$ | 67,49 / 67,64 | 5,73 / 5,68 | 12,65 / 12,46 | 172...175 | 0,24 | 41 |
| XXI | $C_{18}H_{17}N_3O_3$ | 66,61 / 66,86 | 5,44 / 5,30 | 13,21 / 13,00 | 164...166 | 0,16 | 29 |
| XXII | $C_{18}H_{16}ClN_3O_3$ | 60,96 / 60,42 | 4,57 / 4,51 | 11,32 / 11,74 | 206...209 | 0,12 | 24 |
| XXIII | $C_{19}H_{19}N_3O_3$ | 67,03 / 67,64 | 5,82 / 5,68 | 12,87 / 12,46 | 192...194 | 0,18 | 31 |
| XXIV | $C_{19}H_{19}N_3O_3$ | 67,24 / 67,64 | 5,45 / 5,68 | 12,88 / 12,46 | 142...145 | 0,17 | 27 |
| XXV | $C_{26}H_{25}N_3O_4$ | 70,58 / 70,41 | 5,79 / 5,68 | 9,79 / 9,47 | 125...128 | 0,71 | 21 |
| XXVI | $C_{26}H_{23}Cl_2N_3O_4$ | 60,31 / 60,95 | 4,61 / 4,52 | 8,58 / 8,42 | 159...162 | 0,64 | 22 |
| XXVII | $C_{28}H_{29}N_3O_4$ | 71,07 / 71,32 | 6,46 / 6,20 | 8,86 / 8,91 | 140...142 | 0,77 | 22 |
| XXVIII | $C_{27}H_{27}N_3O_4$ | 71,15 / 70,88 | 5,89 / 5,95 | 9,04 / 9,18 | 100...103 | 0,81 | 36 |
| XXIX | $C_{27}H_{27}N_3O_4$ | 70,99 / 70,88 | 6,11 / 5,95 | 9,05 / 9,18 | 107...109 | 0,74 | 28 |

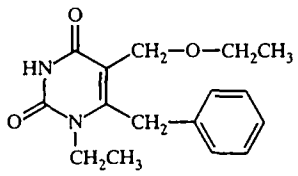
*Chloroform–ethyl acetate (3:1).



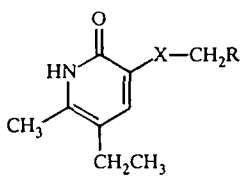

I–IV




V




VI




VII

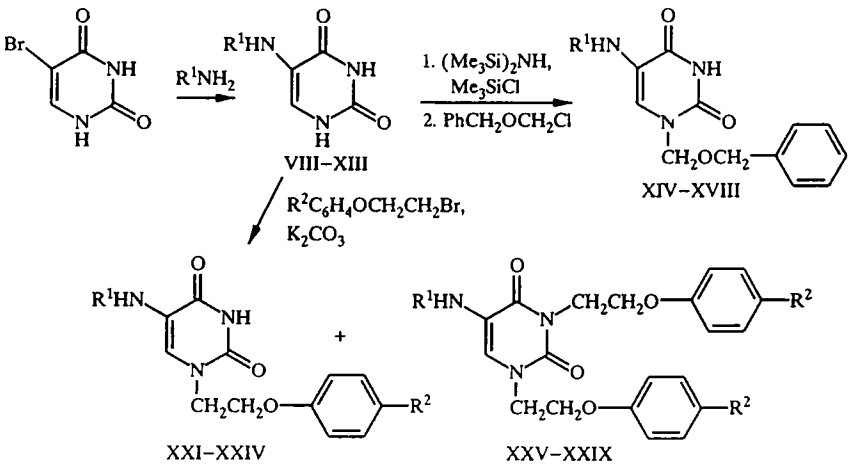
The regioisomeric analog of the pyrimidinones V and HERT, 6-benzyl-5-ethoxymethyl-1-ethyluracil (VI) [19], and various derivatives of pyridine-2(1H)-ones (VII, X = NH, $CH_2$; R = aryl, heteroaryl) [20-22] also have inhibitory properties towards HIV-1 reverse transcriptases.

The structural characteristics of all the cited non-nucleoside inhibitors of HIV-1 reverse transcriptases are the presence in position 5 or 6 of the azine of an unsubstituted or substituted (preferably containing a halogen, an alkyl or an alkoxy substituent) aryl residue separated from the heterocycle by a nitrogen, sulfur or selenium atom or a short carbon chain. In this connection, the synthesis of 5-arylsubstituted derivatives of uracil seemed a promising direction for the discovery of new highly selective inhibitors of HIV-1 replication.

In this paper we report the synthesis of some 1-(benzyloxymethyl)- and 1-[2-(4-R-phenoxy)ethyl]-5-(arylamino)uracils. It has been shown previously that 5-bromouracil can be aminated by various aromatic amine in ethylene glycol to give 5-(arylamino)uracils [23]. Under these conditions, the products of 6-substitution, which had been described for stronger nucleophiles [24], were not observed. We have found that amination of 5-bromouracil without a solvent by aromatic and arylaliphatic amines which are sufficiently stable to oxidation, for example, aniline, *o*-, *m*- and *p*-toluidines and benzylamine, proceeds with the formation 5-(phenylamino)- (VIII), 5-(*o*-tolylamino)- (IX), 5-(*m*-tolylamino)- (X), 5-(*p*-tolylamino)- (XI) and 5-(benzylamino)- (XII) uracils in 56-78% yield by boiling with a 3-5-fold excess of the corresponding amine. Subsequent bromination of uracil VIII in a mixture of acetic acid and dioxane gave a 78% yield of 5-(4-bromophenylamino)uracil (XIII) which demonstrated that electrophilic substitution can be used for the further functionalization of the synthesized 5-(arylamino)uracils VIII-XII.

Subsequent alkylation of the silylated bases VIII-XI and XIII with benzyl chloromethyl ether gave the corresponding 1-(benzyloxymethyl)-5-(arylamino)uracils XIV-XVIII in yields of 58-73% (Scheme 1). It should be noted that silylation of the uracils VIII-XII with hexamethyldisilazane in the presence of trimethylchlorosilane did not affect the exocyclic amino groups, according to $^1$H NMR spectroscopy, but gave exclusively the 2,4-bis(trimethylsiloxy)-5-(arylamino)uracil. In the case of uracils VIII and X, these products crystallized readily on cooling their solutions in excess of the silylating agent. However, an attempt to synthesize 1-(benzyloxymethyl)-5-(benzylamino)uracil (XIX) by alkylation of the trimethylsilyl derivative of uracil XII with benzyl chloromethyl ether was unsuccessful and gave a resinous product.

Scheme 1

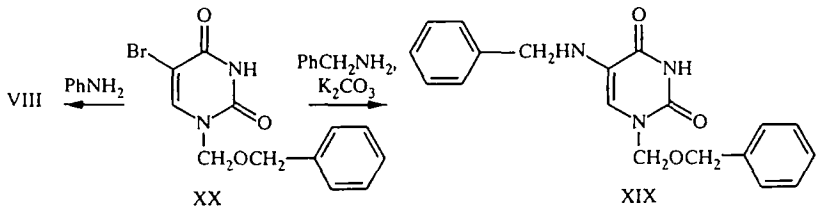



VIII, XIV, XXI—XXIII, XXV—XXVII $R^1$ = Ph; IX, XV, XXVIII $R^1$ = *o*-$MeC_6H_4$; X, XVI, XXIV, XXIX $R^1$ = *m*-$MeC_6H_4$; XI, XVII $R^1$ = *p*-$MeC_6H_4$; XII $R^1$ = $CH_2Ph$; XIII, XVIII $R^1$ = *p*-$BrC_6H_4$; XXI, XXIV, XXV, XXVIII, XXIX $R^2$ = H; XXII, XXVI $R^2$ = Cl; XXIII, XXVII $R^2$ = Me

The expected uracil XIX was obtained from 1-(benzyloxymethyl)-5-bromouracil (XX), synthesized by a known method [25], by amination with a 4-fold excess of benzylamine in anhydrous DMF in the presence of potassium carbonate at 105-110°C. Aromatic amines, which are considerably less basic and nucleophilic, did not react with the bromide XX under these conditions. Uracil VIII was obtained in 66% yield under more vigorous conditions (boiling bromide XX with an excess of aniline for 1 h). The observed degradation of the intermediate 1-(benzyloxymethyl)-5-(phenylamino)uracil (XIV) agrees with the mechanism described for 5-(arylamino)derivatives of nucleophiles [26] (Scheme 2).

Incorporation of the 4-R-phenoxyethyl substituent was achieved by alkylation of the 5-(arylamino)uracils VIII-X in the presence of potassium carbonate in DMF at 80-85°C (Scheme 1). 1-Bromo-2-(4-R-phenoxy)ethanes, prepared by alkylation of aqueous solutions of the potassium salts of the corresponding 4-R-phenols with 1,2-dibromoethane at 95-100°C in the presence of a catalytic amount of dibenzo-18-crown-6 [25], were used as the alkylating agents. Mixtures of the $N^1$-mono- (XXI-XXIV) and $N^1$,$N^3$-disubstituted products (XXV-XXIX), separated chromatographically, were obtained in 46-55% overall yield by alkylation of the potassium salts of the 5-(arylamino)uracils VIII-X with the bromides mentioned. It is interesting to note

Scheme 2



that only the $N^1$,$N^3$-disubstituted product (XXVIII) was isolated on alkylation of 5-(*o*-tolylamino)uracil (IX) with 1-bromo-2-phenoxyethane. Only traces of 1-(2-phenoxyethyl)-5-(*o*-tolylamino)uracil were observed by TLC.

## EXPERIMENTAL

$^1$H NMR spectra were recorded with Bruker WP-200 and Tesla BS-567A spectrometers with HMDS as internal standard. Thin layer chromatography was carried out on Silufol UV-254 strips with development with iodine vapor. Silica gel L 40/100 was used for preparative chromatography. Melting points were determined in glass capillaries and are uncorrected.

**5-(Phenylamino)uracil (VIII).** A mixture of 5-bromouracil (5.0 g, 26.2 mmol) and aniline (25 cm$^3$, 274.3 mmol) was heated for 1 h in a nitrogen atmosphere on a 195-200°C heating bath. Complete solution of the 5-bromouracil occurred after 15 min, then separation of a crystalline product began and the reaction mixture had become completely solid at the end of the reaction period. The mixture was cooled, water (25 cm$^3$) and carbon tetrachloride (25 cm$^3$) were added, the mixture was stirred for 15 min, filtered, and the residue was washed on the filter with water (50 cm$^3$) and 95% ethanol (25 cm$^3$). The product was dissolved with 5% sodium hydroxide solution (100 cm$^3$), filtered, and the filtrate brought to pH 5-6 with acetic acid. The precipitate was filtered off, washed with water, air dried and recrystallized from anhydrous DMF to give product VIII (4.1 g, 77%) as light beige crystals, m.p. 314-319°C (m.p. 317-319°C, 76% yield [23]). $^1$H NMR spectrum (DMSO-$D_6$): 6.71 (3 H, m, phenyl), 6.90 (1 H, s, $C_{(5)}$–NH), 7.10 (2 H, m, phenyl), 7.30 (1 H, s, H-6), 10.64 (1 H, br s, $N_{(3)}$H), 11.26 ppm (1 H, br s, $N_{(1)}$H).

Compounds IX-XII were prepared analogously. The characteristics of the compounds synthesized agreed with literature data [23].

**5-(*p*-Bromophenyl)uracil (XIII).** Bromine (0.7 cm$^3$, 13.6 mmol) was added over 5 min at room temperature to a stirred suspension of 5-(phenylamino)uracil VIII in anhydrous acetic acid (15 cm$^3$) and dioxane (15 cm$^3$). The mixture was stirred for 3 h, filtered, and the precipitate was washed with dioxane, dried in air, and recrystallized from anhydrous DMF (20 cm$^3$) to give compound XIII (2.7 g, 78%) as white crystals, m.p. 277-280°C.

**1-Benzyloxymethyl-5-(phenylamino)uracil (XIV).** A mixture of 5-(phenylamino)uracil VIII (2.0 g, 5.8 mmol), hexamethyldisilazane (50 cm$^3$) and trimethylchlorosilane (0.5 cm$^3$) was boiled for 8 h with the exclusion of moisture, the solution was then cooled to −5°C and kept for one day. The precipitate was filtered off, washed with hexamethyldisilazane (10 cm$^3$) and dried in vacuum to give colorless needles of 2,4-di(trimethylsilyloxy)-5-(phenylamino)pyrimidine (2.6 g, 73%), m.p. 109-113°C. The filtrate was concentrated to 10 cm$^3$ and a further 0.6 g (17%) of the trimethylsilyl derivative of VIII was isolated. $^1$H NMR spectrum ($CCl_4$): 0.26 (9 H, s, $Si(CH_3)_3$), 0.28 (9 H, s, $Si(CH_3)_3$), 6.40 (3 H, m, phenyl), 6.50 (1 H, $C_{(5)}$–NH), 6.74 (2 H, m, phenyl), 7.68 ppm (1 H, s, H-6).

A solution of benzyl chloromethyl ether (0.9 g, 5.7 mmol) in methylene chloride (5 cm$^3$) was added to a solution of 2,4-di(trimethylsilyloxy)-5-(phenylamino)pyrimidine (2.0 g, 5.5 mmol) in anhydrous methylene chloride (20 cm$^3$), the mixture was stirred for one day with the exclusion of moisture, isopropanol (5 cm$^3$) was added, and the mixture was cooled to −5°C for one day. The precipitate was filtered off and recrystallized from 95% ethanol (25 cm$^3$) to give product XIV (1.35 g, 73%) as white crystals, m.p. 154-156°C. $^1$H NMR spectrum (DMSO-$D_6$): 4.76 (2 H, s, $CH_2$), 5.37 (2 H, s, $CH_2$), 6.95 (3 H, m, phenyl), 7.16 (1 H, s, $C_{(5)}$–NH), 7.28 (2 H, m, phenyl), 7.45 (5 H, s, phenyl), 7.73 (1 H, s, H-6), 10.36 ppm (1 H, br s, $N_{(3)}$-H).

Compounds XV-XVIII were prepared analogously.

**1-Benzyloxymethyl-5-(*o*-tolylamino)uracil (XV).** $^1$H NMR spectrum (acetone-$D_6$): 2.15 (3 H, s, $CH_3$), 4.53 (2 H, s, $CH_2$), 5.17 (2 H, s, $CH_2$), 7.00 (5 H, m, aryl, $C_{(5)}$–NH), 7.16 (1 H, s, H-6), 7.25 (5 H, s, phenyl), 10.38 ppm (1 H, br s, $N_{(3)}H$).

**1-Benzyloxymethyl-5-(*m*-tolylamino)uracil (XVI).** $^1$H NMR spectrum (acetone-$D_6$): 2.13 (3 H, s, $CH_3$), 4.55 (2 H, s, $CH_2$), 5.18 (2 H, s, $CH_2$), 6.87 (5 H, m, aryl, $C_{(5)}$–NH), 7.19 (5 H, s, phenyl), 7.38 (1 H, s, H-6), 10.36 ppm (1 H, br s, $N_{(3)}H$).

**1-Benzyloxymethyl-5-(*p*-tolylamino)uracil (XVII).** $^1$H NMR spectrum (DMSO-$D_6$): 2.11 (3 H, s, $CH_3$), 4.50 (2 H, s, $CH_2$), 5.12 (2 H, s, $CH_2$), 6.96 (5 H, m, aryl, $C_{(5)}$–NH), 7.17 (5 H, s, phenyl), 7.33 (1 H, s, H-6), 10.15 ppm (1 H, br s, $N_{(3)}H$).

**1-Benzyloxymethyl-4-(*p*-bromophenylamino)uracil (XVIII).** $^1$H NMR spectrum (DMSO-$D_6$): 4.56 (2 H, s, $CH_2$), 5.18 (2 H, s, $CH_2$), 6.98 (5 H, m, aryl, $C_{(5)}$–NH), 7.21 (5 H, s, phenyl), 7.48 (1 H, s, H-6), 10.30 ppm (1 H, br s, $N_{(3)}H$).

**1-Benzyloxymethyl-5-(benzylamino)uracil (XIX).** 1-Benzyloxymethyl-5-bromouracil XX (2.0 g, 6.4 mmol), anhydrous potassium carbonate (1.0 g, 7.2 mmol) and benzylamine (3.0 $cm^3$, 27.5 mmol) in anhydrous DMF (20 $cm^3$) were stirred at 105-110°C for 2 h, cooled, filtered, the filtrate evaporated in vacuum and the residue treated with 5% acetic acid. The precipitate was filtered off, washed with water, dried in air, and recrystallized from acetone (50 $cm^3$) to give compound XIX (0.9 g, 41%), m.p. 172-175°C. $^1$H NMR spectrum (DMSO-$D_6$): 4.10 (2 H, s, $CH_2$), 4.34 (2 H, s, $CH_2$), 5.01 (2 H, s, $CH_2$), 6.37 (1 H, s, $C_{(5)}$–NH), 7.13 (5 H, s, phenyl), 7.19 (6 H, m, phenyl, H-6), 10.10 ppm (1 H, br s, $N_{(3)}H$).

**1-(2-Phenoxyethyl)-5-(phenylamino)uracil (XXI) and 1,3-Di(2-phenoxyethyl)-5-(phenylamino)uracil (XXV).** A suspension of uracil VIII (2.5 g, 12.3 mmol) and freshly calcined potassium carbonate (1.7 g, 12.3 mmol) in anhydrous DMF (80 $cm^3$) was stirred at 80-85°C for 1 h, a solution of 1-bromo-2-phenoxyethane (2.5 g, 12.4 mmol) in DMF (10 $cm^3$) was added and the mixture was stirred for a further 6 h at the same temperature. The mixture was cooled, filtered, the filtrate evaporated in vacuum, the residue extracted with boiling isopropanol (50 $cm^3$) and the extract evaporated in vacuum. Crystalline solid obtained (3.7 g) was dissolved in the minimum of chloroform, placed on a silica gel column (80 × 1.6 cm), eluted with chloroform, the eluate evaporated in vacuum, and the residue recrystallized from carbon tetrachloride to give compound XXV (1.15 g, 21%), m.p. 125-128°C. $^1$H NMR spectrum (DMSO-$D_6$): 4.14 (8 H, m, $CH_2$), 6.91 (16 H, m, phenyl, $C_{(5)}$–NH), 7.54 ppm (1 H, s, H-6).

After separation of the disubstituted product XXV, the column was eluted with 10:1 chloroform–isopropanol, the eluate was evaporated in vacuum, and the residue was recrystallized from 3:1 acetone–isopropanol to give compound XXI (1.15 g, 29%, m.p. 164-166°C. $^1$H NMR spectrum (DMSO-$D_6$): 4.10 (4 H, m, $CH_2$), 6.88 (11 H, phenyl, $C_{(5)}$–NH), 7.50 (1 H, s, H-6), 11.14 ppm (1 H, br. s, $N_{(3)}H$).

Compounds XXII-XXIV and XXVI-XXIX were prepared analogously.

**1-[2-(*p*-Chlorophenoxy)ethyl]-5-(phenylamino)uracil (XXII).** $^1$H NMR spectrum (DMSO-$D_6$): 4.10 (4 H, m, $CH_2$), 6.88 (10 H, m, phenyl, aryl, $C_{(5)}$–NH), 7.50 (1 H, s, H-6), 11.40 ppm (1 H, br s, $N_{(3)}H$).

**1-[2-(*p*-Methylphenoxy)ethyl]-5-(phenylamino)uracil (XXIII).** $^1$H NMR spectrum (DMSO-$D_6$): 2.13 (3 H, s, $CH_3$), 4.08 (4 H, m, $CH_2$), 6.81 (10 H, m, phenyl, aryl, $C_{(5)}$–NH), 7.47 (1 H, s, H-6), 11.21 ppm (1 H, br s, $N_{(3)}H$).

**1-(2-Phenoxyethyl)-5-(*m*-methylphenylamino)uracil (XXIV).** $^1$H NMR spectrum (DMSO-$D_6$): 2.12 (3 H, s, $CH_3$), 4.12 (4 H, m, $CH_2$), 6.83 (10 H, m, phenyl, aryl, $C_{(5)}$–NH), 7.49 (1 H, s, H-6), 11.18 ppm (1 H, br s, $N_{(3)}H$).

**1,3-Di[2-(*p*-chlorophenoxy)ethyl]-5-(phenylamino)uracil (XXVI).** $^1$H NMR spectrum (DMSO-$D_6$): 4.13 (8 H, m, $CH_2$), 6.88 (14 H, m, phenyl, aryl, $C_{(5)}$–NH), 7.58 ppm (1 H, s, H-6).

**1,3-Di[2-(*p*-methylphenoxy)ethyl]-5-(phenylamino)uracil (XXVII).** $^1$H NMR spectrum (DMSO-$D_6$): 2.11 (3 H, s, $CH_3$), 2.13 (3 H, s, $CH_3$), 4.14 (8 H, m, $CH_2$), 6.84 (14 H, m, phenyl, aryl, $C_{(5)}$–NH), 7.55 ppm (1 H, s, H-6).

**1,3-Di(2-phenoxyethyl)-5-(*o*-methylphenylamino)uracil (XXVIII).** $^1$H NMR spectrum (DMSO-$D_6$): 2.17 (3 H, s, $CH_3$), 4.17 (8 H, m, $CH_2$), 6.94 (15 H, m, phenyl, aryl, $C_{(5)}$–NH), 7.40 ppm (1 H, s, H-6).

**1,3-Di(2-phenoxyethyl)-5-(*m*-methylphenylamino)uracil (XXIX).** $^1$H NMR spectrum (DMSO-$D_6$): 2.12 (3 H, s, $CH_3$), 4.17 (8 H, m, $CH_2$), 6.85 (15 H, m, phenyl, aryl, $C_{(5)}$–NH), 7.55 ppm (1 H, s, H-6).

## REFERENCES

1. F. Barre-Sinoussi, J. Chermann, F. Rey, M. T. Nugeyre, S. Chamaret, J. Gruest, C. Daguet, C. Axler-Blin, F. Vezinet-Brun, C. Rouzioux, W. Rozenbaum, and L. Montagnier, Science, **220**, 868 (1983).

2. M. Popovic, M. G. Sarngadharan, E. Read, and R. C. Gallo, Science, **224**, 497 (1984).
3. H. Mitsuya, R. Yarchoan, and S. Broder, Science, **249**, 1533 (1990).
4. E. De Clercq, Trends Pharmacol. Sci., **11**, 198 (1990).
5. H. Mitsuya, K. J. Weingold, P. A. Furman, M. H. St. Clair, S. Nusinoff-Lerman, R. C. Gallo, D. P. Bolognesi, D. W. Barry, and S. Broder, Proc. Nat. Acad. Sci. USA, **82**, 7096 (1985).
6. H. Mitsuya and S. Broder, Proc. Nat. Acad. Sci. USA, **83**, 1911 (1986).
7. P. S. Kedar, J. Abbotts, T. Kovacs, K. Lesiak, P. Torrence, and S. H. Wilson, Biochemistry, **29**, 3603 (1990).
8. W. B. Parker, E. L. White, S. C. Shaddix, L. J. Ross, R. W. Bucheit, J. M. Germany, J. A. Secrist, R. Vince, and W. M. Shannon, J. Biol Chem., **266**, 1754 (1991).
9. D. D. Richman, Antimicrob. Agents Chemother., **37**, 1207 (1993).
10. T. Miyasaka, H. Tanaka, M. Baba, H. Hayakawa, R. T. Walker, J. Balzarini, and E. De Clercq, J. Med. Chem., **32**, 2507 (1989).
11. M. Baba, E. De Clercq, H. Tanaka, M. Ubasawa, H. Takashima, K. Sekiya, I. Nitta, K. Umeza, H. Nakashima, S. Mori, S. Shigeta, R. T. Walker, and T. Miyasaka, Proc. Nat. Acad. Sci. USA, **88**, 2356 (1991).
12. H. Tanaka, M. Baba, M. Ubasawa, H. Takashima, K. Sekiya, I. Nitta, S. Shigeta, R. T. Walker, E. De Clercq, and T. Miyasaka, J. Med. Chem., **34**, 1394 (1991).
13. H. Tanaka, M. Baba, S. Saito, T. Miyasaka, H. Takasma, K. Sekiya, M. Ubasawa, I. Nitta, R. T. Walker, H. Nakashima, and E. De Clercq, J. Med. Chem., **34**, 1508 (1991).
14. H. Tanaka, H. Takashima, M. Ubasawa, K. Sekiya, I. Nitta, M. Baba, S. Shigeta, R. T. Walker, E. De Clercq, and T. Miyasaka, J. Med. Chem., **35**, 337 (1992).
15. H. Tanaka, H. Takashima, M. Ubasawa, K. Sekiya, I. Nitta, M. Baba, S. Shigeta, R. T. Walker, E. De Clercq, and T. Miyasaka, J. Med. Chem., **35**, 4713 (1992).
16. N. M. Goudgaon and R. F. Shinazi, J. Med. Chem., **34**, 3305 (1991).
17. E. Tramontano, M. E. Marongiu, A. De Montis, A. G. Loi, M. Artico, S. Massa, A. Mai, and P. La Colla, Microbiologiya, **17**, 269 (1994).
18. S. Massa, A. Mai, M. Artico, G. Sbardella, E. Tramontano, A. G. Loi, P. Scano, and P. La Colla, Antiviral Chem. Chemother., **6**, 1 (1995).
19. H. Tanaka, M. Baba, H. Takashima, K. Matsumoto, A. Kittaka, R. T. Walker, E. De Clercq, and T. Miyasaka, Nucleosides Nucleotides, **13**, 155 (1994).
20. W. S. Saari, J. M. Hoffman, J. S. Wai, T. E. Fisher, C. S. Rooney, A. M. Smith, C. M. Thomas, M. E. Goldman, J. A. O'Brien, J. H. Nunberg, J. C. Quintero, W. A. Schleif, E. A. Emini, A. M. Stern, and P. S. Anderson. J. Med. Chem., **34**, 2922 (1991).
21. W. S. Saari, J. S. Wai, T. E. Fisher, C. M. Thomas, J. M. Hofman, C. S. Rooney, A. M. Smith, J. H. Jones, D. I. Bamberger, M. E. Goldman, J. A. O'Brien, J. H. Nunberg, J. C. Quintaro, W. A. Schleif, E. A. Emini, and P. S. Anderson, J. Med. Chem., **35**, 3793 (1992).
22. J. S. Wai, T. M. Williams, D. L. Bamberger, T. E. Fisher, J. M. Hofman, R. J. Hudcosky, S. C. McTough, C. S. Rooney, W. S. Saari, C. M. Thomas, M. E. Goldman, J. A. O'Brien, E. A. Emini, J. H. Nunberg, J. C. Quintero, W. A. Schleif, and P. S. Anderson, J. Med. Chem., **36**, 249 (1993).
23. F. R. Gerns, A. Perrotta, and G. H. Hitching, J. Med. Chem., **9**, 108 (1966).
24. T. K. Bradshaw and D. W. Hutchinson, Chem. Soc. Rev., **6**, 43 (1977).
25. M. S. Novikov, A. A. Ozerov, A. K. Brel', G. N. Solodunova, and T. P. Ozerova, Khim. Geterotsikl. Soedin., No. 3, 380 (1966).
26. A. M. Bobst, A. J. Ozinkas, and E. De Clercq, Helv. Chim. Acta, **66**, 534 (1983).