# SYNTHESIS OF [2-(VINYLOXY)ETHYL]URACIL AND [2-(ALLYLOXY)ETHYL]URACIL

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*A synthesis is reported for $N^1$-mono- and $N^1,N^3$-disubstituted uracil derivatives containing a terminal carbon–carbon double bond in the side-chain. Alkylation of vinyl 2-chloroethyl ether by uracil potassium salts leads to a mixture of 1-[2-(vinyloxy)ethyl] and 1,3-di[2-(vinyloxy)ethyl] derivatives while treatment of 2,4-bis-(trimethylsilyloxy)pyrimidines by vinyl 2-chloroethyl ether leads exclusively to $N^1$-monosubstituted products. Alkylation of cytosine by this chloroether gave 1-[2-(vinyloxy)ethyl]cytosine. The synthesis of 1-[2-(allyloxy)-ethyl]uracil derivatives was carried out by treatment of uracil potassium salts by 1-(allyloxy)-2-(p-toluene-sulfonyloxy)ethane.*

Acyclic analogs of nucleosides similar to acyclovir [1], gancyclovir [2, 3], or 9-[4-hydroxy-3-(hydroxymethyl)butyl]-guanine [4] have high antiviral activity. Despite structural differences, these analogs have hydroxy groups, which imitate the 5′-hydroxyl group of the corresponding natural nucleoside. For this reason, these acyclonucleosides have a similar mechanism of action. These compounds are activated by viral or cellular thymidinekinase and, on the triphosphate level, inhibit viral DNA polymerase [5]. 5′-Ethylthymidine [6], in which the 5′-hydroxyl group is replaced by an unsaturated fragment, has a different mechanism of action based on the inhibition of herpes viral thymidinekinase.

1-(Allyloxyalkyl)-1-uracil derivatives previously synthesized in our laboratory [7] lack hydroxy groups in the side-chain but some of these compounds demonstrated pronounced virus inhibiting action.

In the present work, a synthesis is described for new 1-(allyloxyalkyl)-1-uracil derivatives differing in both the position of the oxygen atom and length of the side-chain.

The synthesis of [2-(vinyloxy)ethyl]uracil and [2-(allyloxy)ethyl]uracil derivatives was carried out by the direct alkylation of potassium salts of uracil (Ia), thymine (Ib), 5-fluorouracil (Ic), 6-methyluracil (Id), as well as cytosine or the corresponding trimethylsilyl derivatives of uracil (IIa) and thymine (IIb) by vinyl 2-chloroethyl ether (III) or 1-(allyloxy)-2-(p-toluenesulfonyloxy)ethane (IV) in accord with the scheme indicated.

The alkylation of sodium and potassium salts of uracils in DMSO or DMF at from 20 to 100°C by alkyl halides [8-11] or tosylates [12-14] leads to a mixture of the products of $N^1$-mono- and $N^1, N^3$-disubstitution products. We also detected formation of a mixture of 1-[2-(vinyloxy)ethyl]uracil derivatives (Va)-(Vd) and 1,3-di[2-(vinyloxy)ethyl]uracil derivatives (VIa)-(VId). Since the chlorine atom in chloroether III has reduced activity [15], achievement of a suitable yield of the desired product required more vigorous reaction conditions (heating in DMF at reflux) and the use of an excess of the alkylating agent, which tends toward tar formation under the reaction conditions (method A).

Products Va-Vc predominated in the mixture of products of the monoalkylation Va-Vc and dialkylation VIa-VIc of uracils Ia-Ic, while a relatively larger amount of the disubstituted product VId is found for 6-methyluracil (Id). This result may be attributed to steric hindrance to alkylation at position 1 from the side of the exocyclic methyl group. The use of a significant excess of Id has virtually no effect on the ratio of the products formed, while the use of excess potassium carbonate shifted this ratio toward disubstituted product VId.

Volgograd Medical Institute, Volgograd 400066. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 393-397, March, 1993. Original article submitted February 10, 1992.

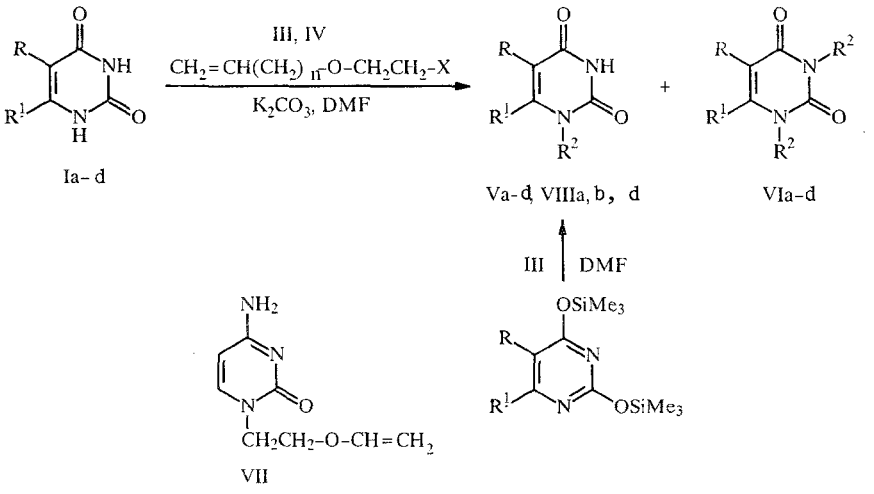


0009-3122/93/2903-0330$12.50 

TABLE 1. Structure and Physicochemical Properties of N-Alkyluracils with a C=C Bond in the Side Chain

| Compound | n | R | $R^1$ | Chemical formula | mp $_{20}$, °C ($n_D$) | $R_f$* | Yield, % (method) |
|---|---|---|---|---|---|---|---|
| Va | 0 | H | H | $C_8H_{10}N_2O_3$ | 101...103 | 0,29 (a) | 40(A); 22 (B) |
| Vb | 0 | Me | H | $C_9H_{12}N_2O_3$ | 112...114 | 0,34 (a) | 41(A); 24 (B) |
| Vc | 0 | F | H | $C_8H_9FN_2O_3$ | (1,5260) | 0,36 (a) | 41 (A) |
| Vd | 0 | H | Me | $C_9H_{12}N_2O_3$ | 118...119 | 0,26 (a) | 28 (A) |
| VIa | 0 | H | H | $C_{12}H_{16}N_2O_4$ | (1,5325) | 0,64 (a) | 32 (A) |
| VIb | 0 | Me | H | $C_{13}H_{18}N_2O_4$ | (1,5162) | 0,76 (a) | 30 (A) |
| VIc | 0 | F | H | $C_{12}H_{15}FN_2O_4$ | (1,5156) | 0,79 (a) | 28 (A) |
| VId | 0 | H | Me | $C_{13}H_{18}N_2O_4$ | 78...79 | 0,59 (a) | 48 (A) |
| VII | 0 | — | — | $C_8H_{11}N_3O_2$ | 179...181 | 0,20 (b) | 57 (A) |
| VIIIa | 1 | H | H | $C_9H_{12}N_2O_3$ | 60...62 | 0,40 (c) | 72 (C) |
| VIIIb | 1 | Me | H | $C_{10}H_{14}N_2O_3$ | 110...113 | 0,51 (c) | 69 (C) |
| VIIId | 1 | H | Me | $C_{10}H_{14}N_2O_3$ | 109...111 | 0,44 (c) | 56 (C) |

*a) 1:1 Chloroform–ethyl acetate, b) 9:1 chloroform–ethanol, c) ethyl acetate.




Ia-d, V, VIa-d, VIIIa, b, d R=H, R=F, R=Me, $R^1$=H, $R^1$=Me; V, VIa-d, VIIIa, b, d $R^2$= $=CH_2CH_2-O-(CH_2)_nCH=CH_2$; III, IV, V, VIa-d, VIIIa, b, d n=0,1, X=Cl, X=OTs

The alkylation of the potassium salt of cytosine, which has an exocyclic amino group, by chloroether III according to method A gives 1-[2-(vinyloxy)ethyl]cytosine (VII) in 57% yield.

Methods have been developed for the selective preparation of $N^1$-monosubstituted uracils based on the alkylation of 2,4-bis(trimethylsilyloxy)pyrimidines using highly reactive alkyl halides such as alkoxymethyl chlorides and bromides [13,16-18], methyl iodide [19, 20], benzyl chloride [21], and 1,4-dichloro-2-butyne [11]. However, alkyl halides with low reactivity were not employed in such reactions.

Trimethylsilyl derivatives IIa and IIb do not react with chloroether III in nonpolar solvents even in the case of excess alkylating agent as described for reactive alkyl halides [11, 13, 16-20].

However, the alkylation of IIa and IIb by an equimolar amount of chloroether III in a polar medium at elevated temperature (in DMF at reflux, method B) leads to the desired $N^1$-monosubstituted products Va and Vb in 22 and 24% yield, respectively. In this case, formation of $N^1$, $N^3$-disubstituted products in significant amounts was not observed. The use of DMF as the solvent facilitated this reaction, probably due to greater polarization of the carbon–halide bond in chloroether III. An attempt to alkylate the trimethylsilyl derivative of 6-methyluracil was unsuccessful. This failure was not unexpected in light of the results of Wittenburg [22]. Attempts to synthesize VII under analogous conditions were also unsuccessful.

TABLE 2. Chemical Shifts in the PMR Spectra of N-Alkyluracils Va-Vd, VIa-VId, VII, VIIIa, VIIIb, and VIIId

| Compound | Chemical shift δ, ppm (J, Hz) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | $NCH_2$ | $CH_2O$ | $OCH_2C=$ | $-HC=$ | $=CH_2$ | R | $R^1$ | NH(br) |
| Va | 3,69...4,22 m | | — | 6,34 d.d (14,7) | 3,69...4,22 m | 5,62 d (7,5) | 7,21 d (7,5) | 9,96 |
| Vb | 3,64...4,36 m | | — | 6,51 d.d (14,7) | 3,64...4,36 m | 1,90 s | 7,18 s | 9,83 |
| Vc | 3,68...4,20 m | | — | 6,40 d.d (14,7) | 3,68...4,20 m | — | 7,68 d | 10,09 |
| Vd | 3,86...4,26 m | | — | 6,43 d.d (14,7) | 3,86...4,26 m | 5,56 s | 2,29 s | 10,09 |
| VIa | 3,56...4,39 m | | — | 6,36 d.d (14,7) 6,38 d.d (14,7) | 3,56...4,39 m | 5,69 d (8) | 7,54 d (8) | — |
| VIb | 3,45...4,35 m | | — | 6,50 d.d (14,7) 6,53 d.d (14,7) | 3,45...4,35 m | 1,83 s | 7,17 s | — |
| VIc | 3,63...4,21 m | | — | 6,41 d.d (14,7) 6,44 d.d (14,7) | 3,63...4,21 m | — | 7,70 d (7) | — |
| VId | 3,65...4,21 m | | — | 6,42 d.d (14,7) 6,44 d.d (14,7) | 3,65...4,21 m | 5,58 s | 2,28 s | — |
| VII | 4,10...4,16 m | | — | 6,78 d.d (14,7) | 4,18...4,60 m | 5,94 d | 7,82 d | 7,38* |
| VIIIa | 3,54 t (5) | 3,74 t (5) | 3,86 d.t (5, 2) | 5,51...5,94 m | 4,86...5,22 m | 5,40 d (7,5) | 7,38 d | 9,95 |
| VIIIb | 3,51 t (5) | 3,77 t (5) | 3,86 d.t (5, 2) | 5,49...5,94 m | 4,85...5,22 m | 1,71 s | 7,19 s | 9,78 |
| VIIId | 3,50 t (5) | 3,73 t (5) | 3,83 d.t (5, 2) | 5,49...5,93 m | 4,84...5,27 m | 5,37 s | 2,25 s | 9,98 |

*Values for the exocyclic amino group are given.

The synthesis of previously reported [14] and new 1-[2-(allyloxy)ethyl] derivatives VIIIa, VIIIb, and VIIId was carried out by treating potassium salts of the corresponding uracils Ia, Ib, and Id with tosylate IV, obtained by the tosylation of 2-(allyloxy)ethanol, in DMF (method C). In order to increase the yield of the desired $N^1$-monosubstitution products, we used 1.4-1.5 equivalents of uracil (Ia) or thymine (Ib) and 2.0 equivalents 6-methyluracil (Id) relative to potassium carbonate and tosylate IV. In all cases, however, the desired products contained traces of the 1,3-disubstitution products.

Harvey et al. [23] have shown that tosylates have much higher reactivity than the corresponding chlorides. Thus, tosylate alkylation may be employed under milder conditions and this, in turn, permits greater selectivity. In contrast, an increase in temperature, as in the case of using III, markedly reduces the selectivity of uracil alkylation. The yield and physicochemical properties of the products are given in Table 1.

The two methylene groups and terminal protons at the C=C double bond in the side chain in the PMR spectra of [2-(vinyloxy)ethyl]pyrimidines Va-Vd, VIa-VId, and VII are seen as a six-proton multiplet at 3.45-4.35 ppm, while the vinyl proton appears as a one-proton doublet of doublets at 6.34-6.53 ppm (depending on the nature of the heterocycle) with coupling constants 14 and 7 Hz. The hydrogen atoms of the allyl fragment in the PMR spectra of 1-[2-(allyloxy)ethyl]uracils VIIIa, VIIIb, and VIIId are seen as a doublet of triplets of the methylene groups at 3.83-3.86 ppm (J 5 and 1 Hz) and two characteristic multiplets for the hydrogen atoms at the C=C double bond at 4.85-5.27 and 5.49-5.94 ppm with the expected integral intensity ratio. The multiplicity, chemical shifts, and integral intensities of the protons of the heterocyclic rings are also in accord with the proposed substitution (Table 2).

## EXPERIMENTAL

The PMR spectra were taken on a Tesla BS-567A spectrometer at 100 MHz in the FT mode in deuteroacetone for Va-Vd, VIa-VId, VIIIa, VIIIb, and VIIId and dimethylsulfoxide-$d_6$ for VII with HMDS as the internal standard. Thin-layer chromatography was carried out on Silufol UV-254 plates. Silica gel L40/100 manufactured in Czechoslovakia was used for column chromatography. The melting points were determined in a glass capillary and were not corrected.

**1-(Allyloxy)-2-(p-toluenesulfonyloxy)ethane (IV, $C_{12}H_{16}O_4S$).** A solution of 25.0 g (0.131 mole) p-toluenesulfonyl chloride in 25 ml pyridine was added dropwise with stirring over 45 min to a solution of 10.8 g (0.106 mole) 2-(allyloxy)-ethanol in 30 ml anhydrous pyridine at −5°C and the mixture was stirred at 0°C for an additional 20 h. Then, 150 ml chloroform was added to the reaction mixture. The organic layer was washed with two 50-ml portions of 10% hydrochloric acid, two 50-ml portions of saturated aqueous $NaHCO_3$, and 100 ml water, dried over $Na_2SO_4$, filtered, and evaporated in vacuum to give 14.4 g (53%) IV as a light (yellow viscous liquid, $R_f$ 0.73 (2:1 hexane−ethyl acetate).

**General Method for the Preparation of 1-[2-(Vinyloxy)ethyl]uracils Va-Vd and 1,3-Di[2-(vinyloxy)ethyl]uracils VIa-VId (Method A).** A mixture of 0.025 mole 5- or 6-substituted uracil Ia-Id and 3.5 g (0.025 mole) $K_2CO_3$ in 50 ml anhydrous DMF was stirred in a nitrogen atmosphere at 85°C for 1.5 h. Then, 2.86 ml (0.028 mole) chloroether III was added and the mixture was heated at reflux for 10 h. After cooling, the mixture was filtered and the filtrate was evaporated in vacuum. The residue was treated with 80 ml water and extracted with five 50-ml chloroform portions. The extract was dried over $Na_2SO_4$ and filtered. The filtrate was evaporated and the residue was subjected to a 50 × 1.6-cm silica gel column. Elution with chloroform first gave the 1,3-disubstituted derivative VIa-VId and then elution with 1:1 chloroform−ethyl acetate gave the 1-[2-(vinyloxy)ethyl] derivative Va-Vd.

**1-[2-(Vinyloxy)ethyl]uracil (Va) and 1-[2-(Vinyloxy)ethyl]thymine (Vb) (Method B).** A sample of 1.6 ml (0.016 mole) chloroether III was added to a solution of 0.017 mole trimethylsilyl derivative IIa or IIb in 50 ml anhydrous DMF and heated at reflux in a nitrogen treated with 25 ml of ethanol, filtered, and the filtrate atmosphere for 20 h with protection from atmospheric moisture. The solvent was dissolved in vacuum and the residue was treated with 25 ml of ethanol, filtered, and the filtrate placed onto a 30 × 1.5-cm silica gel column and eluted with 1:1 chloroform−ethyl acetate. The fractions containing product were combined and evaporated to give 1-[2-(vinyloxy)ethyl] derivatives Va and Vb.

**1-[2-(Vinyloxy)ethyl]cytosine (VII, Method A)** was obtained analogously to Va-Vd and VIa-VId.

**1-[2-(Allyloxy)ethyl]uracil (VIIIa, Method B).** A mixture of 2.8 g (0.025 mole) uracil and 2.5 g (0.018 mole) $K_2CO_3$ in 50 ml DMF was stirred at 80°C for 2 h. Then, 4.7 g (0.018 mole) tosylate IV was added and the reaction mixture was stirred for 20 h at 100°C. After cooling, the mixture was filtered and the filtrate was evaporated in vacuum. The residue was treated with 100 ml water and extracted with five 50-ml chloroform portions. The extract was dried over $Na_2SO_3$* and evaporated. The residue was subjected to chromatography on a 30 × 1.6-cm silica gel column with elution by 1:1 chloroform−ethyl acetate. Product VIIIa was obtained upon crystallization from 2:1 ethyl acetate−hexane.

**1-(2-Allyloxy)ethyl]thymine (VIIIb).** A mixture of 2.6 g (0.021 mole) thymine and 2.0 g (0.0145 mole) $K_2CO_3$ in 50 ml DMF was treated with 5.3 g (0.021 mole) tosylate IV. The separation was carried out as described for VIIIa.

**1-[2-(Allyloxy)ethyl]-6-methyluracil (VIIId).** A mixture of 2.4 g (0.019 mole) 6-methyluracil and 1.3 g (0.009 mole) $K_2CO_3$ in 40 ml DMF was treated with 2.4 g (0.009 mole) tosylate IV. The separation was carried out as described for VIIIa.

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*This is probably a typographical error and should be $Na_2SO_4$ − Translator.

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