NEW ACETENYL ACYCLIC NUCLEOSIDES
SYNTHESIS OF 1-(PROPARGYLOXYMETHYL) DERIVATIVES OF URACIL

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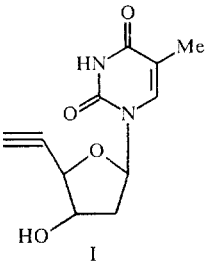
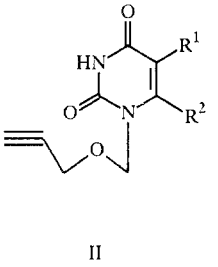
Alkylation of trimethylsilyl derivatives of uracil, thymine, 5-fluorouracil, and 6-methyluracil with propargyloxymethyl chloride afforded the corresponding 1-(propargyloxymethyl) derivatives, new unsaturated acyclic nucleosides having an end carbon–carbon triple bond.

Among the numerous pyrimidine nucleoside analogues is a series of acetylene derivatives containing an ethynyl substituent at position 5 [1, 2] and 6 [3] of the pyrimidine base or in the furanose ring [4]. Some of these derivatives, notably 1-(β-D-arabino-furanosyl)-5-ethynyluracil [5], exhibit pronounced antiviral and antitumor activity. The most interesting of the acetenyl nucleosides is 1-(2′,5′,6′-trideoxy-β-D-erythrohex-5′-inofuranosyl)-5-methyluracil (I), a compound also known as 5′-ethynyl thymidine, which displays considerable inhibiting action with respect to the thymidine kinase produced by various herpes viruses [6].

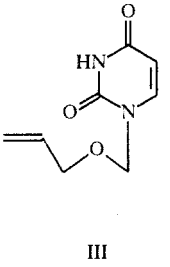
In the search for new, effective inhibitors of virus-specific enzymes and potential antiviral preparations we have synthesized new acyclic analogues of 5′-ethynyl thymidine, namely the 1-(propargyloxymethyl) uracil derivatives (IIa-d), which are also acetenyl analogues of the 1-allyloxyalkylpyrimidines that we obtained in a previous work [7]. Among these, 1-(allyloxymethyl)uracil (III) possesses a marked antiherpetic effect in vitro and in vivo [7].



I



II



III

IIa-d $R^2 = H$, $R^1 = H$,b $R^1 = F$, $R^1 = Me$; IIi $R^1 = H$, $R^2 = Me$

The 1-(propargyloxymethyl) uracil derivatives IIa-d were synthesized in yields of 63.5-72.5% by alkylating the trimethylsilyl derivatives of uracil, thymine, 5-fluorouracil, and 6-methyluracil at room temperature with equimolar amounts of propargyloxymethyl chloride obtained by means of the Henry reaction from propargyl alcohol, paraformaldehyde, and dry hydrogen chloride [8]. As in the case of other sterically unhindered α-halogenated ethers, the alkylation reaction proceeded readily, did not require catalysis by Lewis acids, and even in the case of 6-methyluracil, did not afford significant quantities of 1,3-disubstituted products.

The use of α-halogenated ethers as alkylating agents is always fraught with difficulties due to their low thermal and hydrolytic stability. In a previous work we used allyloxymethyl bromide obtained in situ by treating diallylformal with acetyl bromide as well as allyloxymethyl chloride in synthesizing 1-(allyloxymethyl)uracil III; the yield of end product III was 72.6% in this case. However, an attempt to use dipropargylformal under similar conditions proved unsuccessful, the yield of 1-

Volgograd Medical Institute, Volgograd. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 797-799, June, 1993. Original article submitted October 20, 1992.

0009-3122/93/2906-0684$12.50

TABLE 1. Characteristics of Synthesized Compounds IIa-d

Compound	mp, °C	R_f	PMR spectrum, δ, ppm					
			R^1	R^2	N—CH_2—O, s	O—CH_2—C ≡ C, e (J = 2.5)	O—C—C ≡ CH, t (J = 2.5)	NH, br.s
II	114...115	0,47	5,69 e (J = 8)	7,21 e (J = 8)	5,16	4,19	2,43	10,11
II	127...129	0,56	—	7,43 s (J = 6)	5,13	4,19	2,42	10,31
II	103...105	0,61	1,89 s	7,09 s	5,15	4,18	2,43	9,78
II	125...128	0.54	5,54 s	2,30 s	5,35	4,25	2,39	9,95

(propargyloxymethyl)thymine not exceeding 26.2%. This can be explained by the strong tendency of propargyl derivatives towards addition and isomerization reactions.

The structure of compounds IIa-d was verified by means of PMR spectroscopy. In the spectra of 1-(propargyloxymethyl) uracil derivatives IIa-d propargyl fragment protons appeared as a two-proton doublet with coupling constant of 2.5 Hz at 4.18-4.25 ppm and a single-proton triplet with coupling constant of 2.5 Hz and chemical shift of 2.39-2.43 ppm. The singlet corresponding to the exocyclic methylene group at the nitrogen atom, which had a chemical shift of 5.13-5.16 ppm for the uracil derivative IIa, the 5-fluorouracil derivative IIb, and the thymine derivative IIc, moved 0.20 ppm downfield in the case of 6-methyluracil derivative IId, which confirmed that substitution had taken place at position 1 of the pyrimidine ring.

EXPERIMENTAL

PMR spectra were recorded in $CDCl_3$ on a Tesla BS-487 C (80 MHz), internal standard HMDS. The purity and individuality of the compounds was monitored by means of TLC using silica gel LS 5/40 in a fixed layer, with chloroform–ethanol eluent (10:1) and iodine vapor development.

Elemental analysis data for C, H, and N was in line with calculated values.

Propargyloxymethyl Chloride (C_4H_5ClO). A suspension of 13.0 g (0.43 mole) of paraformaldehyde in 20 ml (0.34 mole) of propargyl alcohol and 50 ml of dry chloroform was saturated with dry hydrogen chloride by stirring vigorously for 2 h at 0-5°C. After filtering, the organic layer was separated and kept over dry magnesium sulfate at 0-5°C for 12 h. The solution was then filtered and double distilled in vacuum, taking off the 55-60°C bp fraction (75 mm Hg); n_D^{20} 1.4470; d_4^{20} 1.1110; found MR_D 25.140; calculated MR_D 25.180. Yield 17.8 g (49.6%).

1-(Propargyloxymethyl)-5-fluorouracil (IIb, $C_8H_7FN_2O_3$). A sample of 1.4 g (13.4 mmoles) of propargyloxymethyl chloride was added to a solution of 3.7 g (13.5 mmoles) of 2,4-di(trimethylsiloxy)-5-fluoropyrimidine in 25 ml of dry tetrachloromethane. After stirring at room temperature under moistureproof conditions for 24 h, 10 ml of water was added to the mixture, which was then stirred vigorously for a further 15 min. The resultant precipitate was filtered off and twice crystallized from 10 ml of 95% ethanol to give 1.85 g of IIb in the form of white needles. Yield 69.8%.

1-(Propargyloxymethyl)thymine (IIc, $C_9H_{10}N_2O_3$). A. A sample of 1.1 g (10.5 mmoles) of propargyloxymethyl chloride was added to a solution of 2.8 g (10.4 mmoles) of 2,4-di(trimethylsiloxy)-5-methylpyrimidine in 25 ml of dry chloroform. After stirring at room temperature under moistureproof conditions for 24 h, 10 ml of water was added to the mixture, which was then stirred vigorously for a further 15 min. Following filtration the organic layer was separated and the aqueous layer extracted with chloroform (3 × 20 ml). The combined chloroform solution was dried using magnesium sulfate, then filtered and evaporated. After triturating the residue with 25 ml of diethyl ether and cooling for 24 h at between −10 and −5°C, the resultant precipitate was filtered off and twice crystallized from 10 ml of 95% ethanol. Yield 1.35 g of IIc (72.5%) in the form of white needles.

B. After adding 0.8 ml (10.8 mmoles) of freshly distilled acetyl bromide to 1.5 g (12.1 mmoles) of dipropargylformal at −20°C, the mixture was kept at −20°C for 15 min and then at room temperature for 2 h. The resultant yellow reaction mass was added to a solution of 3.1 g (11.5 mmoles) of 2,4-di(trimethylsiloxy)-5-methylpyrimidine in 25 ml of dry chloroform. After stirring at room temperature for 24 h compound IIc was isolated in the same way as for method A. Yield 0.55 g (26.2%).

Compounds IIa ($C_8H_8N_2O_3$) and IId ($C_9H_{10}N_2O_3$) were obtained in the same way as IIc (method A) in yields of 67.5 and 63.5%, respectively.

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