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SYNTHESIS OF UNSATURATED ADENINE DERIVATIVES, POTENTIAL INHIBITORS OF S-ADENOSYL-L-HOMOCYSTEINE HYDROLASE

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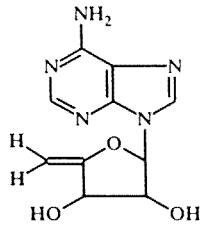
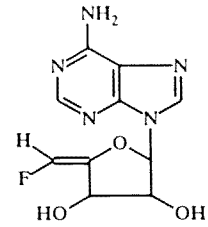
The synthesis of 9-substituted adenine derivatives, containing an unsaturated fragment at the end of the acyclic chain, is described; it consists of the alkylation of adenine salts with unsaturated α-haloethers, tosylates, and epoxides. It was shown that compounds of this series possess moderate antiviral activity.

S-Adenosyl-L-homocysteine hydrolase is a key enzyme in the methylation of nucleic acids. Many viruses are sensitive to inhibitors of S-adenosyl-L-homocysteine hydrolase, as a result of which they can be used as the basis for creating broad-spectrum antiviral agents [1, 2].



I



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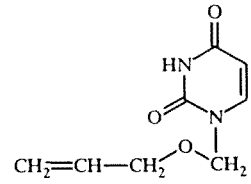

III

S-Adenosyl-L-homocysteine hydrolase catalyzes the hydrolysis of S-adenosyl-L-homocysteine to adenosine and L-homocysteine; one of the intermediates of this process is 4′,5′-didehydro-5′-deoxyadenosine (I) [3]. Its fluorinated analog (Z)-4′,5′-didehydro-5′-deoxy-5′-fluoroadenosine (II) and certain other derivatives of compound II exhibited powerful inhibitory properties toward S-adenosyl-L-homocysteine hydrolase [4-6]. Acyclic inhibitors of this enzyme that contain an unsaturated fragment in the middle of the side chain are known [7-9]. The synthesis of acyclic analogs of adenosine that contain a terminal acetylene fragment — 9-(prop-2-ynyloxymethyl)- and 9-(3-iodoprop-2-ynyloxymethyl)adenines, has recently been described, and their inhibitory properties were studied [10].

Earlier we synthesized N-substituted uracils and cytosines containing a terminal allyl group in the side chain [11-14]. Some of them, for example, 1-(allyloxymethyl)uracil (III), exhibited appreciable antiviral activity *in vitro* and *in vivo* [11].

Continuing investigations in the field of this search for new antiviral agents, we synthesized 9-substituted adenine derivatives containing an unsaturated (ethylene, acetylene) fragment at the end of the acyclic chain, which possesses different lengths and conformational mobilities.

The main way of synthesizing unsaturated adenine derivatives was alkylation of the potassium salt of adenine, produced *in situ* by heating the free adenine base and potassium carbonate in anhydrous DMFA at 80°C for 1-2 h, with unsaturated α-haloethers, tosylates, and epoxides. The use of the sodium salt of adenine as the substrate, produced by treating adenine with a methanol solution of sodium methylate, followed by oxidation with diethyl ether, does not provide any advantages and leads to close yield values for the target compounds. Just as in the case of the alkylation of the trimethylsilyl derivative of uracil [15], the use of allyl bromomethyl ether, produced *in situ* from allylformal and acetyl bromide, gives a yield of 9-(allyloxymethyl)adenine (IV) only a few percent less than the allyl chloromethyl ether, produced by the Henry reaction from allyl alcohol, paraform, and gaseous hydrogen chloride and purified by redistillation under vacuum.

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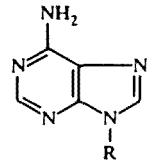
TABLE 1. Physicochemical Properties of 9-Substituted Adenine Derivatives



Compound	Acyclic chain R	mp, °C	R_f*	Yield, %
IV	$CH_2—O—CH_2—CH=CH_2$	178...179	0,37 (A)	48
V	$CH_2—O—CH_2—C\equiv CH$	172...173	0,32 (A)	31
VI	$CH_2—O—CH_2—CH_2—O—CH_2—CH=CH_2$	144...146	0,48 (A)	31
VII	$CH_2—O—CH(CH_2Cl)—CH_2—O—CH=CH_2$	152...156	0,54 (A)	49
VIII	$CH_2—CH_2—O—CH=CH_2$	169...173	0,66 (B)	46
IX	$CH_2—CH_2—O—CH_2—CH=CH_2$	142...143	0,52 (A)	42
X	$CH_2—C(O)—O—CH_2—CH=CH_2$	206...208	0,41 (B)	39
XI	$CH_2—CH(OH)—CH_2—O—CH_2—CH=CH_2$	120...122	0,54 (B)	47

*A) Chloroform—ethanol, 10:1; B) chloroform—methanol, 3:1.

TABLE 2. PMR Spectra of 9-Substituted Adenines IV-IX

Compound	Chemical shifts, δ, ppm
IV	4,28 (2H, d, J = 5 Hz, O—CH_2); 5,42 (2H, m, =CH_2); 5,80 (2H, s, N—CH_2—O); 6,07 (1H, m, —CH=); 7,59 (2H, br. s, NH_2); 8,49 (1H, s, 2-H); 8,59 (1H, s, 8-H)
V	2,75 (1H, t, J = 2,5 Hz, ≡CH); 4,48 (2H, d, J = 2,5 Hz, O—CH_2); 5,83 (2H, s, N—CH_2—O); 7,68 (2H, br. s, NH_2); 8,44 (1H, s, 2-H); 8,50 (1H, s, 8-H)
VI	3,86 (4H, m, O—CH_2—CH_2—O); 4,14 (2H, d, J = 5 Hz, O—CH_2); 5,36 (2H, m, =CH_2); 5,32 (2H, s, N—CH_2—O); 5,88 (1H, m, —CH=); 7,40 (2H, br. s, NH_2); 8,01 (1H, s, 2-H); 8,19 (1H, s, 8-H)
VII	3,46 (4H, m, O—CH_2, CH_2Cl); 3,89 (1H, m, O—CH); 3,82 (2H, dt, J = 1 Hz, O—CH_2); 5,06 (2H, m, =CH_2); 5,16 (1H, m, —CH=); 8,10 (1H, s, 2-H); 8,26 (1H, s, 6-H)
VIII	4,48 (4H, m, O—CH_2, =CH_2); 4,74 (2H, t, J = 5 Hz, N—CH_2); 6,76 (1H, d, d, J = 14 Hz, O—CH=); 7,58 (2H, br. s, NH_2); 8,36 (1H, s, 2-H); 8,43 (1H, s, 8-H)
IX	3,68 (2H, t, O—CH_2); 3,84 (2H, dt, J = 1 Hz, O—CH_2); 5,00 (2H, m, =CH_2); 5,66 (1H, m, —CH=); 7,95 (1H, s, 2-H); 8,04 (1H, s, 8-H)
X	4,86 (2H, d, O—CH_2); 5,47 (2H, m, =CH_2); 5,34 (2H, s, N—CH_2); 6,14 (1H, m, —CH=); 7,51 (2H, br. s, NH_2); 8,39 (2H, s, 2-, 8-H)
XI	3,64 (2H, d, J = 5 Hz, O—CH_2); 4,16 (5H, m, N—CH_2—CH—CH_2—O); 5,32 (2H, m, =CH_2); 6,10 (1H, m, -CH=); 6,95 (2H, br. s, NH_2); 7,99 (2H, s, 2-H); 8,12 (1H, s, 8-H)

*PMR spectra were recorded in DMSO-D_6 (compounds IV, V, VIII, X), methanol-D_4 (IX), or acetone-D_6 (VI, VII, XI).

The use of alkylating agents with different reactivity: increased (α-haloethers, allyl ester of bromoacetic acid), medium (tosylate of 2-allyloxyethanol, allyl glycidyl ether), and reduced (vinyl β-chloroethyl ether), in contrast to alkylation of the pyrimidine bases under analogous conditions [11-14], did not demonstrate any significant influence of the nature of the alkylating agent on the yield of the target compounds (Table 1).

Preparative chromatography and subsequent recrystallization of the substances obtained make it possible to obtain individual (according to the data of thin-layer chromatography and PMR spectroscopy) 9-substituted adenine derivatives that contain virtually no 7-isomers.

Preliminary investigations of the antiviral action of compounds IV-XI *in vitro*, conducted at the Belarus Scientific Research Institute of Epidemiology and Microbiology (Minsk), showed moderate activity of the unsaturated adenine derivatives

obtained with respect to vaccinia virus (VII) and Venezuelan equine encephalitis virus (IV, V) in concentrations of 5...25 μg/ml.

EXPERIMENTAL

The PMR spectra were recorded on a Tesla BS-567 A spectrometer (100 MHz) in the FT system, with internal standard HMDS. The characteristics of the PMR spectra and the solvents used are presented in Table 2. Plates of Silufol UV-254 were used for thin-layer chromatography.

The data of elementary analysis for C, H, and N for compounds IV-XI correspond to the calculated values.

9-(Allyloxymethyl)adenine (IV). A. A suspension of 1.0 g (7.4 mmoles) of adenine and 1.15 g (8.3 mmoles) of freshly calcined potassium carbonate in 25 ml of anhydrous DMFA was mixed for 1 h at 80°C, cooled, and a solution of 1.3 g (8.6 mmoles) of allyl chloromethyl ether in 15 ml of DMFA was added. The reaction mixture was mixed for 20 h at room temperature, filtered, the filtrate evaporated under vacuum, the residue extracted with 50 ml of boiling chloroform, and the extract filtered and evaporated. The crystalline residue was chromatographed on a column with silica gel (20 × 1.5 cm); eluent chloroform—methanol, 9:1. Fractions that according to the TLC data contained compound IV were combined and evaporated. The residue was recrystallized from isopropyl alcohol, and 0.75 g of a light-beige fine-crystalline compound IV was obtained in a yield of 48%.

B. To a suspension of 1.9 g (12.1 mmoles) of the sodium salt of adenine in 25 ml of DMFA at room temperature over a period of 10 min, a solution of 1.4 g (13.1 mmoles) of allyl chloromethyl ether in 10 ml of DMFA was added; the mixture was mixed for 20 h, filtered, the filtrate was evaporated under vacuum, and compound IV was isolated as described in method A; yield 1.05 g (42%).

C. A mixture of 2.0 g (14.8 mmoles) of adenine and 2.1 g (15.2 mmoles) of freshly calcined potassium carbonate was mixed in 25 ml of DMFA at 80°C for 1 h, cooled to room temperature, and a mixture of 2.7 g (18.8 mmoles) of diallylformal and 1.1 ml (14.9 mmoles) of acetyl bromide, preliminarily kept at room temperature for 2 h, was added. The reaction mass was mixed at room temperature for 24 h, filtered, and the filtrate was evaporated under vacuum. Compound IV was isolated as described in method A; yield 1.25 g (41%).

9-(Propargyloxymethyl)adenine (V). A suspension of 1.8 g (13.0 mmoles) of adenine and 2.0 g (15.0 mmoles) of freshly calcined potassium carbonate in 25 ml of DMFA was mixed at 80°C for 2 h, cooled, 1.7 g (16.0 mmoles) of propargyl chloromethyl ether was added, and the mixture was mixed at room temperature for 24 h. The reaction mass was filtered, the filtrate was evaporated under vacuum, the residue was recrystallized twice from 10 ml of 95% aqueous ethanol, and 0.85 g of the light-yellow crystalline compound V was obtained; yield 31%.

9-{[2-(Allyloxy)ethoxy]methyl}adenine (VI). A suspension of 1.0 g (7.4 mmoles) of adenine and 1.15 g (8.3 mmoles) of freshly calcined potassium carbonate in 25 ml of DMFA was mixed for 1 h at 80°C, cooled, a solution of 1.3 g (8.6 mmoles) of 2-(allyloxy)ethoxymethyl chloride in 15 ml of DMFA was added, the mixture was mixed for 20 h at room temperature, filtered, the filtrate was evaporated under vacuum, and compound VI was isolated according to method A. The residue was recrystallized from 95% aqueous ethanol, yielding 0.55 g (31%) of compound VI.

9-{[1-(Allyloxy)-3-chloro-2-propoxy]methyl}adenine (VII). A suspension of 2.0 g (14.8 mmoles) of adenine and 2.1 g (15.2 mmoles) of freshly calcined potassium carbonate in 40 ml of DMFA was mixed for 1 h at 80°C, cooled, a solution of 3.0 g (15.1 mmoles) of 1-(allyloxy)-3-chloro-2-propoxymethyl chloride in 20 ml of DMFA was added, the mixture was mixed for 20 h at room temperature, filtered, the filtrate was evaporated under vacuum, and compound VII was isolated analogously to the preceding. After recrystallization from isopropyl alcohol, 2.15 g of compound VI was obtained, yield 49%.

9-[2-(Vinyloxy)ethyl]adenine (VIII). A suspension of 5.0 g (37.0 mmoles) of adenine and 4.5 g (32.6 mmoles) of freshly calcined potassium carbonate in 100 ml of DMFA was mixed at 80°C for 1 h, 3.4 g (33.5 mmoles) of vinyl β-chloroethyl ether was added, the reaction mixture was boiled for 6 h, cooled, and filtered, the filtrate was evaporated at reduced pressure, the residue was extracted with 100 ml of boiling chloroform, and the extract was filtered and evaporated under vacuum. The residue was chromatographed on a column with silica gel (35 × 2.5 cm), eluent chloroform—methanol, 9:1. Fractions containing the end product according to TLC data were combined and evaporated. The residue was recrystallized from methanol, and 3.50 g of compound VIII was obtained, yield 46%.

9-[2-(Allyloxy)ethyl]adenine (IX). A suspension of 1.2 g (8.9 mmoles) of adenine and 1.3 g (9.4 mmoles) of freshly calcined potassium carbonate in 25 ml of DMFA was mixed at 80°C for 1 h, 2.25 g (8.8 mmoles) of 2-(p-toluenesulfonyloxy)-

1-(allyloxy)ethane in 15 ml of DMFA was added, the mixture was mixed for 12 h at 95-100°C, cooled, and filtered, and the filtrate was evaporated under vacuum. Compound IX was isolated according to method A and recrystallized from 95% aqueous ethanol; 0.80 g of compound IX was obtained, yield 42%.

9-[(Allyloxy)carbonylmethyl]adenine (X). A suspension of 1.5 g (11.1 mmoles) of adenine and 1.5 g (10.9 mmoles) of freshly calcined potassium carbonate in 25 ml of DMFA was mixed for 2 h at 95-100°C, 2.0 g (11.2 mmoles) of the allyl ester of bromoacetic acid was added, and the mixture was mixed at the same temperature for 6 h. The hot solution was filtered, evaporated under vacuum, the residue was extracted with 25 ml of boiling 95% aqueous ethanol, the hot extract was filtered and exposed for 24 h at −5-0°C, the precipitate formed was filtered off and repeatedly recrystallized from ethanol; 1.0 g of compound X was obtained in the form of yellow lamellar crystals, yield 39%.

9-[3-(Allyloxy)-2-hydroxypropyl]adenine (XI). A suspension of 1.5 g (11.1 mmoles) of adenine and 1.5 g (10.9 mmoles) of freshly calcined potassium carbonate in 25 ml of DMFA was mixed for 2 h at 95-100°C, 1.25 g (11.0 mmoles) of allyl glycidyl ether was added, and the mixture was mixed at the same temperature for 12 h. It was cooled, filtered off, the filtrate was evaporated under vacuum, the residue was extracted with 50 ml of boiling chloroform, the extract was filtered, evaporated under vacuum, the residue was chromatographed as described in method A, it was recrystallized from isopropyl alcohol, and 1.3 g of compound XI was obtained, yield 47%.

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