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SYNTHESIS OF 3-O-ARYL ESTERS OF (*R,S*)-9-(2,3-DIHYDROXYPROPYL)ADENINE AND ITS PYRIMIDINE ANALOGS AS NEW POTENTIAL INHIBITORS OF *S*-ADENOSYL-*L*-HOMOCYSTEINE HYDROLASE

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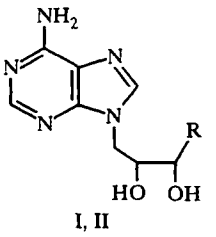
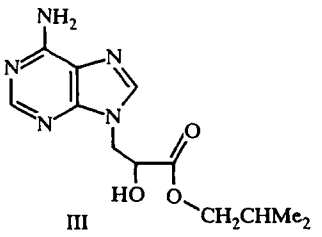
With the aim of searching for new antiviral agents of the acyclonucleoside type, 3-O-aryl esters of (R,S)-9-(2,3-dihydroxypropyl)adenine and its pyrimidine analogs have been synthesized. Alkylation of adenine and cytosine by aryl glycidyl ethers in the presence of potassium carbonate affords 46-76% yields of the corresponding N^9- and N^1-substituted derivatives. The interaction of aryl glycidyl ethers with trimethylsilyl derivatives of uracil and thymine also results in 41-57% yields of N^1-monosubstituted products with identical acyclic chain structure.

S-Adenosyl-*L*-homocysteine hydrolase is the key enzyme in nucleic acid methylation reactions, as this enzyme catalyzes the hydrolysis of *S*-adenosyl-*L*-homocysteine to adenosine and homocysteine. Many viruses are sensitive to inhibitors of *S*-adenosyl-*L*-homocysteine hydrolase, and hence these materials can be used for the basis for developing broad-spectrum antiviral agents [1, 2]. The first *S*-adenosyl-*L*-homocysteine hydrolase inhibitors that were discovered were (*S*)-9-(2,3-dihydroxypropyl)adenine (I, R = H) [3, 4] and (2*R*,3*R*)-4-(adenin-9-yl)-2,3-dihydroxybutyric acid (*D*-eritradenine, II, R = COOH) [5]; however, a more pronounced inhibiting effect was demonstrated by the isobutyl ester of (*R,S*)-3-(adenin-9-yl)-2-hydroxypropionic acid (III) [6]. In comparative studies, compound III was more effective than I or II in the inhibition of *S*-adenosyl-*L*-homocysteine hydrolase and also vesicular stomatitis virus *in vitro* [7].



I, II



III

As a condition for high inhibitor activity of the adenine derivatives I-III and also neplanocin A and its 9-cyclopentene analog, which had demonstrated a powerful inhibiting effect for *S*-adenosyl-*L*-homocysteine hydrolase [8, 9], an important factor is the presence of a free hydroxyl group in position 2′, and also the presence of some sort of oxygen-containing substituent in position 3′ of the side chain. Analysis of the chemical structure of *S*-adenosyl-*L*-homocysteine hydrolase inhibitors also suggests that in the structure of the

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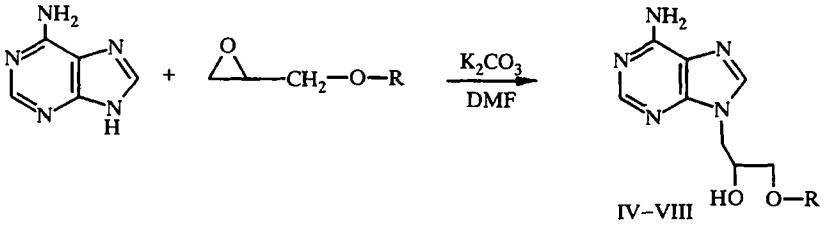
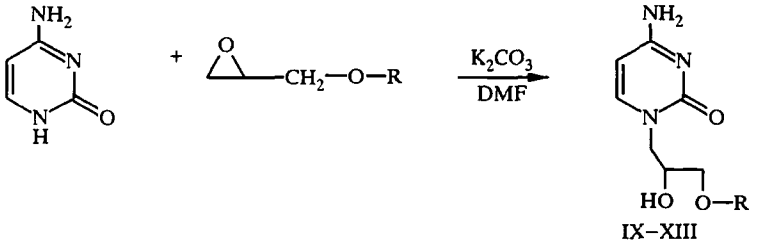
enzyme, in the region of substrate binding corresponding to positions 3′ and 5′ of the ribosyl ring, there is apparently a broad hydrophobic pocket. In this connection, we synthesized a series of new 9-substituted derivatives of adenine in which the acyclic chain has the indicated structural features; we also synthesized the corresponding pyrimidine analogs.

The basic method used in synthesizing 3-O-aryl esters of (*R,S*)-9-(2,3-dihydroxypropyl)adenine (IV-VIII) and (*R,S*)-1-(2,3-dihydroxypropyl)cytosine (IX-XIII) consisted of alkylation of the corresponding nucleic bases by aryl glycidyl ethers in anhydrous DMF at 105-110°C in the presence of potassium carbonate, following procedures given in [10].



IV–VIII

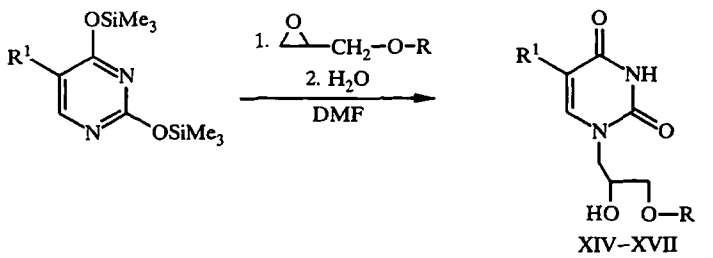


IX–XIII

IV, IX R = Ph; V, X R = *p*-C_6H_4Cl; VI, XI R = *p*-C_6H_4Me;
VII, XII R = α-naphthyl; VIII, XIII R = β-naphthyl

According to data obtained by PMR spectrometry and thin-layer chromatography, the reaction of adenine alkylation by these particular epoxides proceeds under the indicated conditions to give rather high yields (46-69%) of the desired products (IV-VIII); the reaction does not involve the exocyclic amino group, and it does not result in the formation of any 7-substituted derivatives as byproducts.

High selectivity of N^1-monosubstitution was observed in the synthesis of cytosine derivatives (IX-XIII), the yields of which amounted to 58-77% depending on the nature of the aromatic substituent in the side chain. However, under analogous conditions, the alkylation of the potassium salts of uracil and thymine, obtained *in situ* by heating the free pyrimidine bases with potassium carbonate in a dimethylformamide medium, was complicated by the formation of considerable quantities of N^1,N^3-disubstituted products. Because of this problem, we prepared the 3-O-aryl esters of (*R,S*)-1-(2,3-dihydroxypropyl)uracil (XIV, XV) and thymine (XVI, XVII) by a procedure we had developed previously for alkylation of trimethylsilyl derivatives of uracil and thymine by epoxides in anhydrous DMF [11].



XIV–XVII

XIV, XVI R = Ph; XV, XVII R = *p*-C_6H_4Cl; XIV, XV R^1 = H; XVI, XVII R^1 = Me

By refluxing phenyl or *p*-chlorophenyl glycidyl ether with a 10-15% molar excess of the trimethylsilyl derivative of uracil or thymine in anhydrous DMF for 1 h, we obtained the desired products, the N^1-monosubstituted compounds XIV-XVII, in yields of 41-57% after preparative chromatography.

TABLE 1. Charasteristics of Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %			Nucleic base	R	Bp (mm Hg) or mp, °C	R_f (and system)	Yield, %
		C	H	N					
IV	$C_{14}H_{15}N_5O_2$	58,35 / 58,94	5,44 / 5,30	24,81 / 24,55	Adenine	Phenyl	169...172	0,60 (A)	69
V	$C_{14}H_{14}ClN_5O_2$	52,24 / 52,59	4,68 / 4,41	22,20 / 21,90	Adenine	*p*-Chlorophenyl	202...204	0,60 (A)	64
VI	$C_{15}H_{17}N_5O_2$	59,97 / 60,19	5,92 / 5,72	23,01 / 23,40	Adenine	*p*-Tolyl	176...181	0,61 (A)	62
VII	$C_{18}H_{17}N_5O_2$	64,71 / 64,47	5,34 / 5,11	20,38 / 20,88	Adenine	α-Naphthyl	209...211	0,62 (A)	55
VIII	$C_{18}H_{17}N_5O_2$	64,25 / 64,47	4,86 / 5,11	20,59 / 20,88	Adenine	β-Naphthyl	216...219	0,62 (A)	46
IX	$C_{13}H_{15}N_3O_3$	60,00 / 59,76	5,98 / 5,79	15,51 / 16,08	Cytosine	Phenyl	142...145	0,39 (A)	77
X	$C_{13}H_{14}ClN_3O_3$	53,03 / 52,80	4,94 / 4,77	14,03 / 14,21	Cytosine	*p*-Chlorophenyl	207...211	0,39 (A)	71
XI	$C_{14}H_{17}N_3O_3$	60,97 / 61,08	6,04 / 6,22	15,49 / 15,26	Cytosine	*p*-Tolyl	200...203	0,41 (A)	58
XII	$C_{17}H_{17}N_3O_3$	65,32 / 65,58	5,66 / 5,50	13,08 / 13,50	Cytosine	α-Naphthyl	228...230	0,33 (A)	73
XIII	$C_{17}H_{17}N_3O_3$	65,78 / 65,58	5,27 / 5,50	13,72 / 13,50	Cytosine	β-Naphthyl	240...243	0,40 (A)	68
XIV	$C_{13}H_{14}N_2O_4$	59,64 / 59,53	5,30 / 5,38	10,49 / 10,68	Uracil	Phenyl	150...153	0,57 (B)	51
XV	$C_{13}H_{13}ClN_2O_4$	52,67 / 52,62	4,66 / 4,42	9,16 / 9,44	Uracil	*p*-Chlorophenyl	162...165	0,62 (B)	45
XVI	$C_{14}H_{16}N_2O_4$	61,07 / 60,86	5,01 / 5,84	9,82 / 10,14	Thymine	Phenyl	155...158	0,67 (B)	57
XVII	$C_{14}H_{15}ClN_2O_4$	54,34 / 54,11	4,94 / 4,87	8,89 / 9,02	Thymine	*p*-Chlorophenyl	127...130	0,71 (B)	41

TABLE 2. PMR Spectra of Synthesized Compounds, δ, ppm

Compound	Nucleic base	N—CH_2—CH(OH)—CH_2—O	Aromatic substituent
IV	7,01 br. s (2H, NH_2); 7,95 s (1H, 8-H); 8,05 s (1H, 2-H)	3,77...4,48 m (5H, CH_2-CH-CH_2); 5,43 br. s (1H, OH)	6,67...7,28 m (5H, phenyl)
V	7,03 br. s (2H, NH_2); 7,96 s (1H, 8-H); 8,04 s (1H, 2-H)	3,79...4,38 m (5H, CH_2-CH-CH_2); 5,50 br. s (1H, OH)	6,76...7,28 m (4H, *p*-chlorophenyl)
VI	6,93 br. s (2H, NH_2); 7,99 s (1H, 8-H); 8,09 s (1H, 2-H)	3,73...4,48 m (5H, CH_2-CH-CH_2); 5,52 br. s (1H, OH)	2,17 s (3H, CH_3); 6,56...7,22 m (4H, *p*-tolyl)
VII	7,00 br. s (2H, NH_2); 8,00 s (1H, 8-H); 8,04 s (1H, 2-H)	4,01...4,51 m (5H, CH_2-CH-CH_2); 5,51 br. s (1H, OH)	6,74...6,88 m (1H, 4'-H); 7,22...7,47 m (4H, 3'-H, 5'-H, 6'-H, 7'-H); 7,63...7,79 m (1H, 8'-H); 8,10...8,28 m (1H, 2'-H)
VIII	7,01 br. s (2H, NH_2); 7,98 s (1H, 8-H); 8,05 s (1H, 2-H)	3,88...4,50 m (5H, CH_2-CH-CH_2); 5,52 br. s (1H, OH)	6,94...7,51 m (5H, 1'-H, 3'-H, 6'-H, 7'-H, 8'-H); 7,60...7,80 m (2H, 4'-H, 5'-H)
IX	5,63 d (7 Hz, 1H, 5-H); 6,97 br. s (2H, NH_2); 7,37 d (7 Hz, 1H, 6-H)	3,38...3,70 m (1H, CH); 3,78...4,20 m (4H, CH_2); 5,29 br. s (1H, OH)	6,67...7,24 m (5H, phenyl)
X	5,58 d (7 Hz, 1H, 5-H); 6,81 br. s (2H, NH_2); 7,36 d (7 Hz, 1H, 6-H)	3,43...3,68 m (1H, CH); 3,78...4,17 m (4H, CH_2); 5,26 br. s (1H, OH)	6,77...7,21 m (4H, *p*-chlorophenyl)
XI	5,60 d (7 Hz, 1H, 5-H); 6,97 br. s (2H, NH_2); 7,37 d (7 Hz, 1H, 6-H)	3,37...3,68 m (1H, CH); 3,74...4,15 m (4H, CH_2); 5,29 br. s (1H, OH)	2,14 s (3H, CH_3); 6,61...7,08 m (4H, *p*-tolyl)
XII	5,59 d (7 Hz, 1H, 5-H); 6,95 br. s (2H, NH_2); 7,37 d (7 Hz, 1H, 6-H)	3,47...3,77 m (1H, CH); 3,95...4,31 m (4H, CH_2); 5,43 br. s (1H, OH)	6,75...6,90 m (1H, 4'-H); 7,16...7,51 m (4H, 3'-H, 5'-H, 6'-H, 7'-H); 7,61...7,85 m (1H, 8'-H); 8,08...8,30 m (1H, 2'-H)
XIII	5,59 d (7 Hz, 1 H, 5-H); 6,82 br. s (2 H, NH_2); 7,36 d (7 Hz, 1 H, 6-H)	3,41...3,72 m (1H, CH); 3,89...4,25 m (4H, CH_2); 5,35 br. s (1H, OH)	6,98...7,50 m (5H, 1'-H, 3'-H, 6'-H, 7'-H, 8'-H); 7,60...7,83 m (2H, 4'-H, 5'-H)
XIV	5,44 d (8 Hz, 1H, 5-H); 7,36 d (8 Hz, 1H, 6-H)	3,42...3,80 m (1H, CH); 3,84...4,22 m (4H, CH_2); 4,32 br. s (1H, OH)	6,68...7,28 m (5H, phenyl)
XV	5,42 d (8 Hz, 1H, 5-H); 7,47 d (8 Hz, 1H, 6-H)	3,46...3,76 m (1H, CH); 3,86...4,14 m (4H, CH_2); 4,35 br. s (1H, OH)	6,82...7,30 m (4H, *p*-chlorophenyl)
XVI	1,73 s (3H, CH_3); 7,22 s (1H, 6-H)	3,37...3,70 m (1H, CH); 3,79...4,12 m (4H, CH_2); 4,30 br. s (1H, OH)	6,67...7,38 m (5H, phenyl)
XVII	1,75 s (3H, CH_3); 7,41 s (1H, 6-H)	3,41...3,68 m (1H, CH); 3,75...4,17 m (4H, CH_2); 4,29 br. s (1H, OH)	7,01...7,45 m (4H, *p*-chlorophenyl)

In the PMR spectra of the synthesized compounds, the protons of the three-carbon acyclic fragment are manifested in the form of a complex multiplet in the 3.37-4.51 ppm region; for the adenine derivatives IV-VIII, the signal of the CH group proton is shifted downfield by an average of 0.70 ppm relative to the corresponding signals for the pyrimidine analogs IX-XVII. The secondary hydroxyl group is represented by a one-proton broad singlet with a chemical shift of 4.29-5.52 ppm, depending on the nature of the deuterated solvent that is used. The chemical shifts, multiplicities, and integral intensities of the signals of protons in the heterocyclic and aromatic fragments are generally consistent with the calculated values (Table 2).

EXPERIMENTAL

The PMR spectra were registered on a Tesla BS-567A spectrometer (100 MHz) in a 1:1 mixture of acetone-d_6 and DMSO-d_6 in the case of compounds IV-XIII, and in acetone-d_6 in the case of compounds XIV-XVII, with hexamethyldisiloxane as internal standard. In interpreting the PMR spectra, we used a program licensed from Advanced Chemistry Development Inc., ACD/HNMR Predictor 3.0 Pro; the calculations were performed on a computer with a Pentium II-MMX (233 MHz). The thin-layer chromatography was performed on Silufol UV-254 plates in solvent system A (4:1 mixture of chloroform and methanol) or system B (ethyl acetate), with development in iodine vapor.

The original aryl glycidyl ethers were obtained by alkylating the corresponding phenols and naphthols with an equimolar quantity of the epichlorohydrin in an aqueous medium in the presence of caustic at 90-95°C. The physicochemical characteristics of the synthesized products (Table 1) matched the values reported in the handbook literature.

(*R,S*)-9-(3-Phenoxy-2-hydroxy-1-propyl)adenine (IV). A mixture of 1.5 g (11.1 mmoles) of adenine and 1.6 g (11.6 mmoles) of freshly calcined potassium carbonate was stirred 1 h at 105-110°C in 40 ml of anhydrous DMF. Then a solution of 1.7 g (11.3 mmoles) of phenyl glycidyl ether in 10 ml of DMF was added, and stirring was continued at this same temperature for 2 h. After cooling and filtering, the filtrate was evaporated under vacuum, and the residue was recrystallized twice from 2-propanol, obtaining 2.2 g (69%) of IV in the form of a white crystalline substance, mp 169-172°C.

Compounds V-XIII were obtained analogously.

(*R,S*)-1-(3-Phenoxy-2-hydroxy-1-propyl)uracil (XIV). A mixture of 3.0 g (26.8 mmoles) of uracil, 50 ml of hexamethyldisilazane and 0.5 ml of trimethylchlorosilane was refluxed with protection from moisture, until the solid material had completely dissolved; then the excess hexamethyldisilazane was removed under vacuum. Obtained 5.7 g (83%, 22.2 mmoles) of 2,4-bis(trimethylsilyloxy)pyrimidine. Next, 2.9 g (19.3 mmoles) of phenyl glycidyl ether in 50 ml of anhydrous DMF was added, and the solution was refluxed 1 h. The solvent was removed under vacuum, and the residue was hydrolyzed by refluxing 10 min in 50 ml of 95% ethanol. The unreacted uracil (0.7 g) was filtered off, the filtrate was vacuum-evaporated, and the residue was chromatographed in a column with silica gel (40×1.5 cm), eluent 10:1 chloroform–methanol. The fractions containing the desired product were combined and evaporated. The residue was recrystallized twice from acetone, obtaining 2.6 g (51%) of XIV in the form of a white crystalline substance, mp 150-153°C.

Compounds XV-XVII were obtained analogously.

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