BRANCHED-CHAIN DERIVATIVES OF ACYCLIC ADENOSINE ANALOGS: ALKYL AND HYDROXYMETHYL DERIVATIVES OF S-ADENOSYL-L-HOMOCYSTEINASE INHIBITORS SUBSTITUTED AT THE 2- AND 3-POSITION OF THE SIDE CHAIN*

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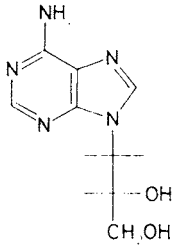
Reaction of 1,3-dichloro-2-propanone (*VII*) with methylmagnesium chloride, followed by alkaline hydrolysis, afforded 2-methylpropane-1,2,3-triol (*VIII*) which on treatment with 2,2-dimethoxypropane and subsequent tosylation gave 4-(*p*-toluenesulfonyloxymethyl)-2,2,4-trimethyl-1,3-dioxolane (*IXb*). Compound *IXb* was condensed with sodium salt of adenine and the intermediate *X* was acid-hydrolysed to give 9-(*RS*)-(2,3-dihydroxy-2-methylpropyl)adenine(*XI*). Oxidation of *XI* with sodium periodate led to 9-(2-oxopropyl)adenine (*XII*). 9-(*RS*)-(2-Hydroxy-2-hydroxymethyloctyl)adenine (*XVI*) was obtained analogously from compound *VII* and hexylmagnesium bromide via triol *XIV*. Methyl 2-bromomethyl-2-propenoate (*XVII*) reacted with sodium salt of adenine and the resulting methyl 2-(adenin-9-ylmethyl)-2-propenoate (*XVIII*) was hydroxylated with sodium perchlorate and osmium tetroxide. The obtained methyl (*RS*)-2-(adenin-9-ylmethyl)-2,3-dihydroxypropanoate (*XIX*) was alkali-hydrolysed to give sodium salt of the acid *XX*. Reduction of ester *XIX* with sodium borohydride furnished 9-(*RS*)-(2,3-dihydroxy-2-hydroxymethylpropyl)adenine (*XXI*). 1-Nonen-3-ol (*XXIII*), obtained by reaction of propenal with hexylmagnesium bromide, was converted by hydroxylation with osmium tetroxide into nonane-1,2,3-triol (*XXIVa*) and further into its 1-O-*p*-toluenesulfonate *XXIVb* which reacted with 2,2-dimethoxypropane to give 2,2-dimethyl-4-hexyl-5-(*p*-toluenesulfonyloxymethyl)-1,3-dioxolane (*XXV*). Compound *XXV* reacted with adenine and the resulting intermediate *XXVI* was converted into 9-(*RS*)-(2,3-dihydroxynonyl)adenine (*XXVII*) by acid hydrolysis. 9-(3-Methyl-2-buten-1-yl)adenine (*XXVIII*), obtained by alkylation of sodium salt of adenine with 1-bromo-3-methyl-2-butene, was oxidized with potassium permanganate in an acid medium to give 9-(3-hydroxy-2-oxo-3-methylbutyl)adenine (*XXIX*). This compound was converted into 9-(*RS*)-(2,3-dihydroxy-3-methylbutyl)adenine (*XXX*) by reduction with sodium borohydride.

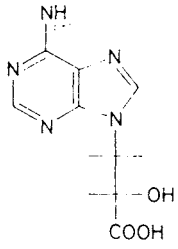
4-C-Hydroxymethyl-1,2-O-isopropylidene-α-D-xylofuranose (*XXXII*) reacted with 2,2-dimethoxypropane under formation of 4-C-hydroxymethyl-1,2:3,5-di-O-isopropylidene derivative *XXXIIIa* whose *p*-toluenesulfonyl derivative *XXXIIIb* on treatment with adenine afforded 4-C-(adenin-9-yl)methyl-1,2:3,5-di-O-isopropylidene-α-D-xylofuranose (*XXXIV*). Acid hydrolysis of this compound, followed by oxidation in an alkaline medium, gave (2*S*,3*R*)-4-(adenin-9-yl)-3-hydroxymethyl-2,3-dihydroxybutanoic acid, isolated as its ethyl ester *XXXVI*.

* Part XVIII in the series Studies on S-Adenosyl-L-homocysteine Hydrolase; Part XVII: Collect. Czech. Chem. Commun. *53*, 1779 (1988).

Our systematic studies of chiral acyclic nucleoside analogs were directed predominantly to the group of adenosine analogs. These studies concern mainly investigation of the structure–activity relationships related to the inhibition of S-adenosyl-L-homocysteinase (SAHase) (for a review see ref.[1]), antiviral and other biological activities which are connected with this effect[2]. Extensive studies[3,4] have revealed three fundamental structural types of compounds that exhibit the most interesting biological effects: 9-(*S*)-(2,3-dihydroxypropyl)adenine[5] (*I*; DHPA) as reversible inhibitor of the enzyme[6], 3-(adenin-9-yl)-2-hydroxypropanoic acid (*II*; AHPA) and its



I



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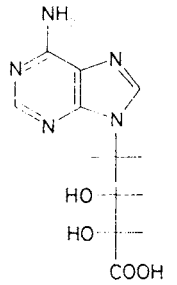
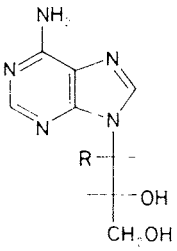


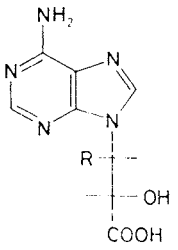
III

esters[7,8], and eritadenine (*III*) and its stereoisomers[9,10], as irreversible SAHase inactivators. The existing variations in the chemical structure of these three types of compounds concerned mainly the heterocyclic base and modifications of the hydroxyl groups in the side chain. Although some 1-alkyl derivatives[7] of compounds *I* and *II* (i.e. *IV* and *V*) as well as some 3-alkyl derivatives[11,12] of DHPA, *VI*, have been prepared, these compounds, in which the mentioned substitution creates another asymmetric center, have not been systematically investigated.



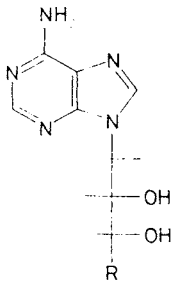
IV

(R = CH_3, C_6H_5)



V

(R = CH_3, C_6H_5)



VI

(R = CH_2, C_6H_5, CH_2OH)

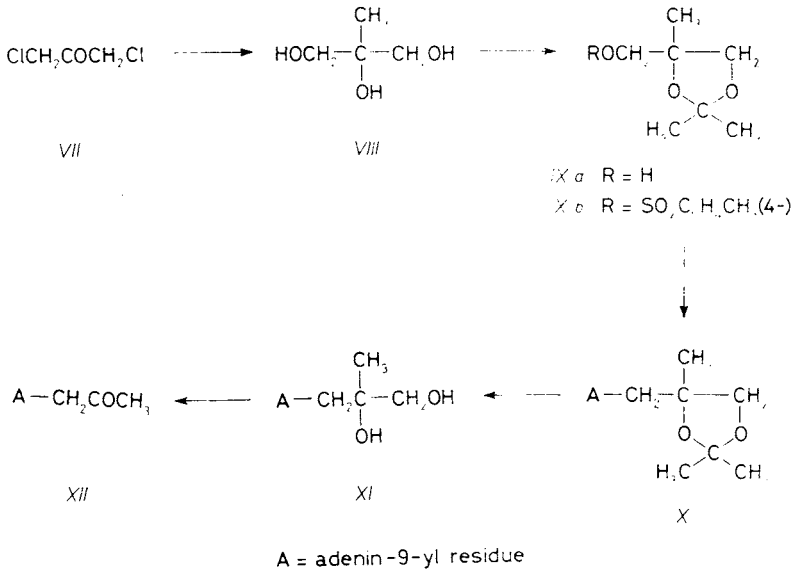
In the analogous series of acyclovir (9-(2-hydroxyethoxymethyl)guanine) derivatives, interesting biologically active compounds have been found among the deriva-

tives which arise from the parent compound by C-alkylation or C-hydroxyalkylation of the side chain[13]. Particularly interesting are compounds which can be regarded as "doubled" structures of the parent type of the side-chain: the so-called DHPG (9-(1,3-dihydroxy-2-propoxymethyl)guanine)[14] and its carba-analog, 9-(3-hydroxymethyl-4-hydroxybutyl)guanine[15].

The present work describes the methods, used to synthetize the C-alkyl derivatives of the three structural types of acyclic adenosine analogs, *I*–*III*, in which the alkyl group is introduced into the positions 2 and 3 of the side chain. This modification retains the fundamental structural features of the molecule except the character of the hydroxyl groups which change from primary to secondary or tertiary and from secondary to tertiary one. The structural change is accompanied by formation of new asymmetric centers. Save some exceptions, the synthesis was aimed at the preparation of racemates which were sufficient for preliminary biological evaluations. Our model studies involved three types of C-alkyl groups: the methyl, hexyl and hydroxymethyl groups. A comparison of the methyl with the hydroxymethyl derivative may give important information on the role of a hydrophobic or hydrophilic substituent in the side-chain. Moreover, introduction of a hexyl group into the molecule of an acyclic adenosine analog may give rise to adenosine aminohydrolase inhibitors analogous to EHNA[1,16] with important biological aspects.

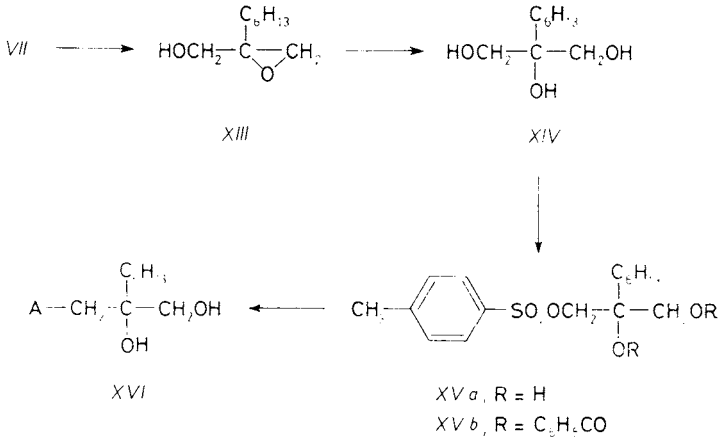
The simplest general synthesis of 2-C-methyl and 2-C-hexyl derivatives of DHPA (*I*) started from the corresponding 2-C-alkylglycerols prepared by reaction of 1,3-dichloro-2-propanone[17] with the corresponding alkylmagnesium halide. The reaction was performed at −20°C and afforded an unstable intermediate which in the case of the methyl derivative was converted by treatment with an aqueous alkali directly into the desired 2-C-methylglycerol (2-hydroxymethylpropane-1,2-diol, *VIII*), probably via a double epoxide formation and hydrolysis. This compound reacted with 2,2-dimethoxypropane to give the corresponding 1,3-dioxolane *IXa*, which was tosylated at the only free hydroxyl function. The obtained *p*-toluenesulfonyl ester *IXb* reacted smoothly with sodium salt of adenine in dimethylformamide, affording 2',3'-O-isopropylidene derivative *X*: the reaction gave exclusively the 9-isomer. Acid hydrolysis of the intermediate *X* furnished the 2-C-methyl derivative of (*RS*)-DHPA, i.e. 9-(*RS*)-(2,3-dihydroxy-2-methylpropyl)adenine (*XI*). The structure of this compound was confirmed not only by mass and NMR spectra (and NMR spectra of the intermediates), but also by degradation with sodium periodate leading to 9-(2-oxopropyl)adenine (*XII*) as the only product (Scheme 1).

Also the preparation of 2-C-hexyl-(*RS*)-DHPA (*XIV*) followed the same reaction scheme (Scheme 2). The alkaline hydrolysis of the primary Grignard product from compound *VII* afforded oxirane *XIII* which was alkali-resistant. The compound *XIII* gave the typical reaction with N-(*p*-nitrobenzyl)pyridinium bromide in an alkaline medium. It was the only reaction product and was readily converted into the 1,2,3-triol *XIV* by treatment with dilute aqueous trifluoroacetic acid. The primary hydroxyl



SCHEME 1

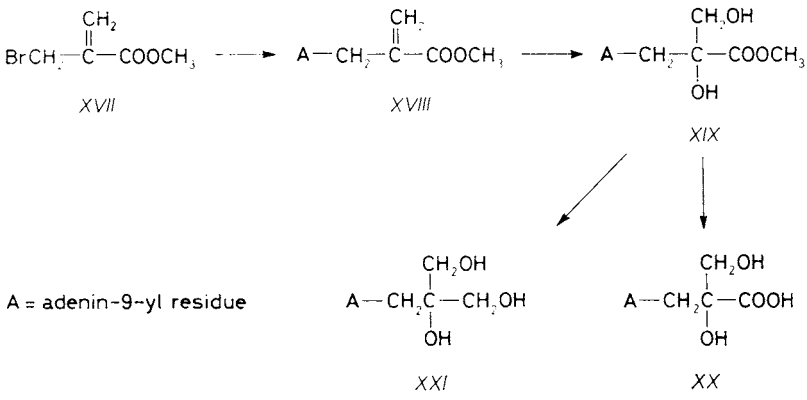
in triol *XIV* was then selectively tosylated with equimolar amount of tosyl chloride and the remaining hydroxy groups in the obtained tosyl derivative *XVa* were benzoylated with benzoyl chloride in pyridine. The resulting 2,3-di-O-benzoyl derivative



SCHEME 2

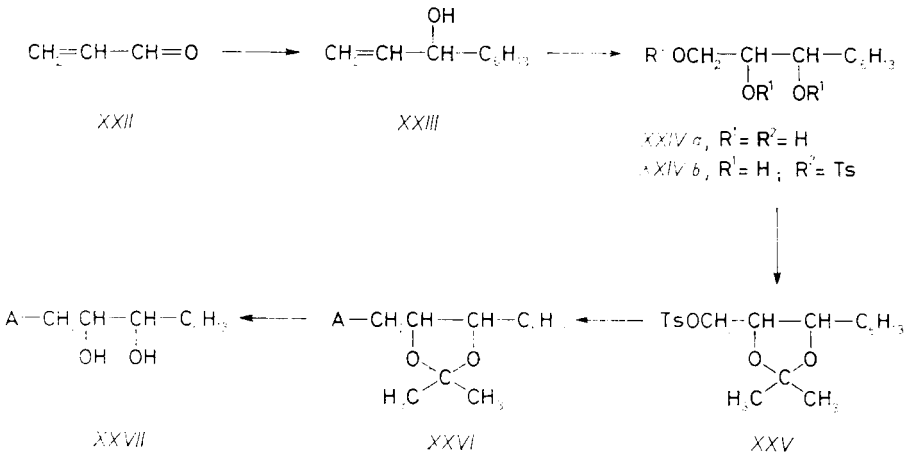
XVb was condensed with sodium salt of adenine prepared in situ. The crude reaction product was debenzoylated and compound *XVI* was purified by chromatography on silica gel. The prepared 9-(*RS*)-(2-hydroxy-2-hydroxymethyloctyl)adenine (*XVI*) exhibited characteristic mass spectrum containing molecular ion and typical fragments compatible with the expected structure.

This approach, i.e. reaction of compound *VII* with Grignard reagent, was not suitable for the preparation of the 2-C-hydroxymethyl derivative of glycerol, i.e. tris(hydroxymethyl)carbinol. Therefore, the 2-C-hydroxymethyl derivative of DHPA, *XXI*, was prepared by another route (Scheme 3): methyl 2-bromomethyl-2-propenoate (*XVII*), relatively easily accessible from diethyl malonate[18], alkylated sodium salt of adenine under formation of the 2-methoxycarbonyl derivative *XVIII*. The product was unequivocally characterized by the presence of a double bond, mass spectrum (molecular ion and the corresponding fragments) and ^{1}H NMR spectrum exhibiting two singlets of protons on a double bond at 5·47 and 6·24 ppm. Hydroxylation of *XVIII* with osmium tetroxide in the presence of sodium chlorate led to methyl 2-(adenin-9-ylmethyl)-2,3-dihydroxypropanoate (*XIX*). Its isolation from the excess of inorganic salts was easily performed by chromatography on octadecylsilica gel. The ester *XIX* was saponified to give salt of the acid *XX* (which is the 2-hydroxymethyl derivative of compound *II* (AHPA)). Similarly as other α-hydroxy esters[7], the ester *XIX* was reduced easily with sodium borohydride. 9-(*RS*)-(2,3-Dihydroxy-2-hydroxymethylpropyl)adenine (*XXI*) obtained in this reaction was isolated in high yield as the hydrate by chromatography on an ion-exchanger and on octadecylsilica gel. It had the expected mass spectrum with molecular peak and fragments arising by loss of H_2O and CH_2OH, as well as fragments typical for acyclic analogs of the mentioned type (BCH_2, BCH_3). Compound *XXI* can be regarded as a 2-C-hydroxymethyl derivative of DHPA (*I*) and at the same time as a "double" molecule of this compound (for the analogous relationship between acyclovir and DHPG vide supra).



SCHEME 3

The group of 3-C-substituted derivatives of the parent structure *I* comprises the 3-C-methyl derivatives, i.e. 9-(2,3-dihydroxybutyl)adenines[11] (*VI*; R = CH_3), the 3-C-phenyl derivative, i.e. 9-(2,3-dihydroxy-3-phenylpropyl)adenine[11] (*VI*; R = = C_6H_5) and the 3-C-hydroxymethyl derivatives, i.e. 9-(2,3,4-trihydroxybutyl)-adenines[11,12] (*VI*; R = CH_2OH). Two other types of compounds are described in the present work. The hydrophobic 2,3-dihydroxynonyl derivative *XXVII* was obtained according to Scheme 4. Reaction of propenal (*XXII*) with hexylmagnesium bromide afforded 1-nonen-3-ol (*XXIII*) which was without purification hydroxylated with osmium tetroxide to give nonane-1,2,3-triol (*XXIVa*). Tosylation of the primary hydroxyl, followed by reaction of the tosyl derivative *XXIVb* with 2,2-dimethoxy-propane, afforded the protected tosyl derivative *XXV*. It was purified by chromatography on silica gel, reacted with sodium salt of adenine in dimethylformamide and the obtained 2',3'-O-isopropylidene derivative *XXVI* was converted into 9-(2,3-dihydroxynonyl)adenine (*XXVII*). Although the reaction sequence led very probably to a mixture of erythro- and threo-isomers of *XXVII*, their attempted analytical separation was unsuccessful.

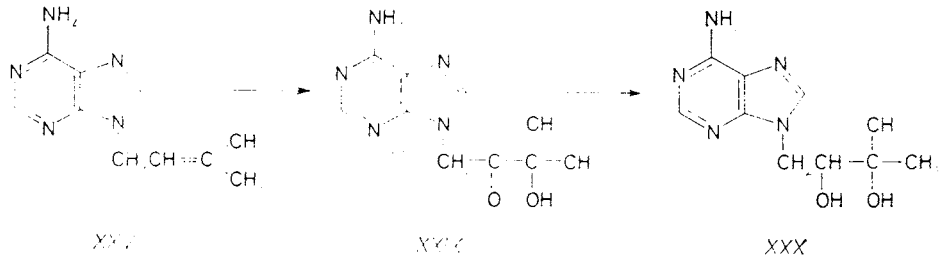


A = adenin-9-yl, Ts = *p*-toluenesulfonyl residue

SCHEME 4

Compound *XXX*, i.e. the 3-C-dimethyl derivative of DHPA (*I*), represents a new type of 3-C-alkylated derivatives of compound *I*: 3-C-dialkyl derivatives that are characterized by the presence of a tertiary hydroxyl in position 3 of the side chain. Its preparation started from compound *XXVIII*, accessible by alkylation of adenine with isopentenyl bromide (Scheme 5). The structure of *XXVIII* was confirmed by the UV spectrum (9-isomer) as well as by the mass spectrum. The N(3)-isomer,

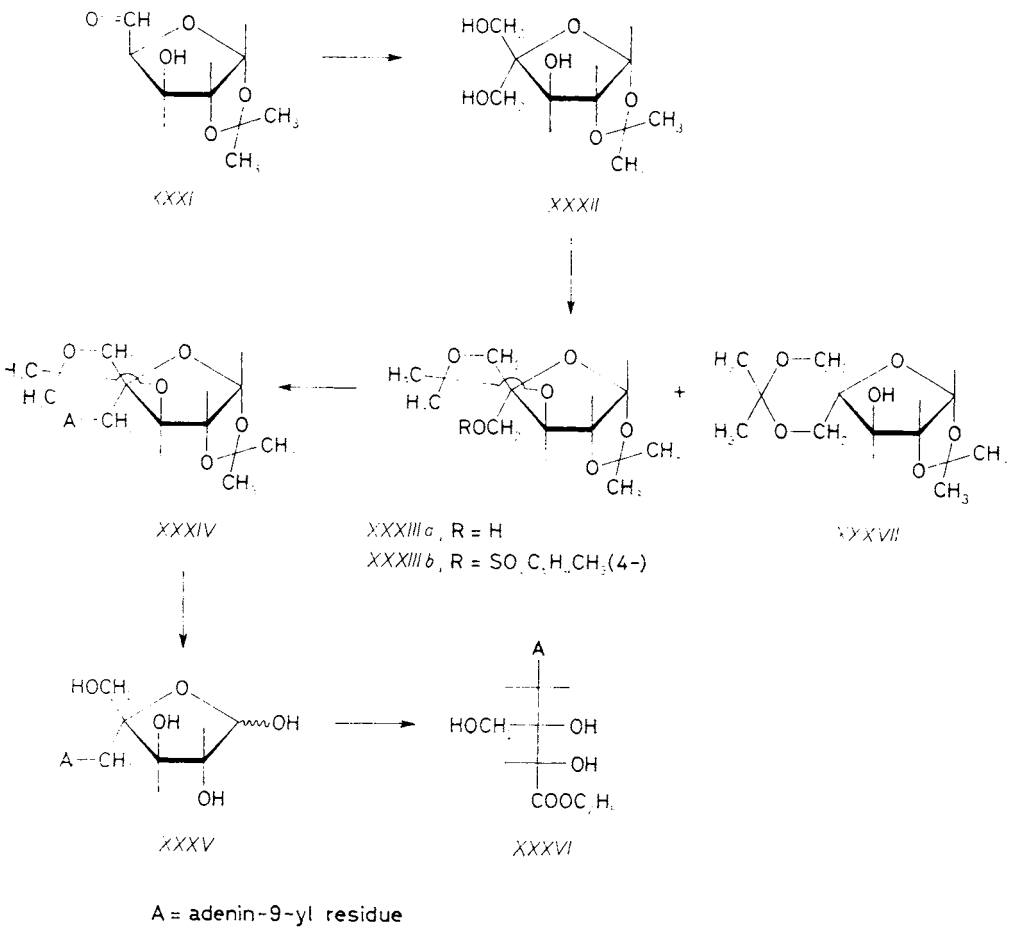
arising as the minor reaction product, was also characterized. Attempted *cis*-hydroxylation of the double bond in *XXVIII* with potassium permanganate in acidic aqueous solution gave, instead of the desired diol *XXX*, the α-hydroxy ketone *XXIX* as product of further oxidation. Under the given conditions the compound *XXIX* was formed quantitatively and the reaction was so fast that the intermediary diol *XXX* was not detected at all. The α-hydroxy ketone *XXIX* is the first representative of this type of compounds among acyclic adenosine analogs. Its structure was proven by molecular ion 235 in its mass spectrum, C—OH and C=O signals in the ^{13}C NMR spectrum and the presence of only one hydroxyl in the ^{1}H NMR spectrum. As expected, compound *XXIX* formed a stable hydrate. Its reduction was accomplished with borohydride bound to a basic ion-exchanger[19]. This procedure did not require deionization during the work-up simplifying thus substantially the isolation. The obtained 9-(*RS*)-(2,3-dihydroxy-3-methylbutyl)adenine (*XXX*) was characterized unequivocally by its mass spectrum (molecular ion) and by the ^{1}H NMR spectrum containing signals due to two different methyl groups, one CH(2′) in the side chain, a hydroxyl and two protons of the 1′-CH_2 group. The UV spectrum agreed with the proposed N(9)-alkyladenine structure.



XXIX *XXX*

SCHEME 5

The last type of 2-C-alkyl analogs, studied in this communication, are 2-C-alkyl analogs of eritadenines. Eritadenines (*III*) exhibit an extraordinarily high activity in various in vitro as well as in vivo systems[1,2] and this activity depends to a considerable extent on the configuration (the natural D-erythro compounds *III* have invariably the highest activity). Therefore, the preparation of their derivatives should employ enantioselective reactions; the best starting material are sugar derivatives with suitable leaving groups. These compounds are converted into adenin-9-yl substituted deoxy sugars and degraded further to the substituted 4-(adenin-9-yl)--2,3-dihydroxybutanoic acid[9]. This approach was used in the preparation of 2-C--hydroxymethyl derivative *XXXVI*. Because of better accessibility, we prepared the derivative derived from L-eritadenine, the second most active of the four geometric isomers[4,10] (Scheme 6).



SCHEME 6

Its synthesis started from 1,2-O-isopropylidenedialdehydo-α-D-xylofuranose (*XXXI*), readily accessible from D-glucose[20]. Compound *XXXI* was hydroxymethylated with formaldehyde to give derivative *XXXII* (ref.[20]). The key reaction step was the reaction of *XXXII* with 2,2-dimethoxypropane, which yielded the 3,5-O-isopropylidene derivative *XXXIIIa* as the main product. The isomeric isopropylidene derivative *XXXVII* was formed in only minor quantities (*XXXIIIa* : *XXVII* 8 : 1) and was separated by chromatography on silica gel. The structure of both compounds follows unequivocally from their ^{1}H NMR spectra: the spectrum of *XXXIIIa* exhibits a free primary hydroxyl signal and a multiplet of CH_2—O protons with a significant shift on addition of trichloroethyl isocyanate (TEI) (proof of free CH_2OH group); on the other

hand, the doublet of secondary 3-OH group in the spectrum of *XXXVII* disappeared after addition of TEI while the multiplet of O—CH_2 (2×) did not change.

In the next step, the free primary hydroxyl was tosylated. Proton NMR spectrum of the obtained crystalline tosyl derivative *XXXIIIb* exhibited all the characteristic signals of a sugar and a tosyl group. It was condensed with sodium salt of adenine under usual conditions to give compound *XXXIV* as the main reaction product. Chromatography on silica gel afforded pure 4-C-(adenin-9-ylmethyl)-1,2 : 3,5-di-O--isopropylidene-α-D-xylofuranose (*XXXIV*) the ^{2}H NMR spectrum of which proved the presence of an adenine ring, two different isopropylidene groups and all the expected sugar protons in positions 1, 2 and 3. The methylene groups in positions 5 and 6 appeared as two pairs of doublets of markedly different chemical shifts. Compound *XXXIV* was converted into the C-substituted derivative of L-eritadenine by degradation of the free aldose with oxygen in an alkaline medium[9]: first the protecting groups were removed by acid hydrolysis of *XXXIV* and the formed free aldose *XXXV* was, without isolation, oxidized with oxygen in aqueous alkaline solution. After deionisation, the carboxylic acid was isolated by chromatography on a basic anion-exchanger. The obtained product was almost pure; to remove remaining impurities, it was esterified with ethanol and the ethyl ester *XXXVI* was isolated by chromatography on octadecyl silica gel. The product had the expected mass and UV spectrum and was chromatographically homogeneous. The structure of the key intermediate *XXXIV* determines unequivocally the absolute configuration (2*S*, 3*R*) of the side chain.

The described example illustrates the potential use of the method for the preparation of C-alkyl derivatives of erythro- and threo-configuration, substituted in position 2 of the side chain in compound *III*. The variability of the method is limited by additional transformation of the hydroxymethyl group, introduced into the position 4 by hydroxymethylation, or by transformation of the hydroxymethyl group of the original aldofuranose.

The inhibitory effect of the prepared compounds toward S-adenosyl-L-homocysteinase, as well as other biological activity data, will be published elsewhere.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Unless stated otherwise, the solutions were evaporated at 40°C/2 kPa and the compounds dried over phosphorus pentoxide at 13 Pa. Thin-layer chromatography (TLC) on silica gel was performed on Silufol UV 254 sheets (Kavalier, Votice, Czechoslovakia) in the following systems: S1 chloroform, S2 chloroform–methanol (9 : 1), S3 chloroform–methanol (4 : 1), S4 benzene. Paper chromatography was carried out on a paper Whatman No 1 in the system S5 2-propanol–conc. aqueous ammonia–water (7 : 1 : 2). Analytical liquid chromatography (HPLC) was performed on 4 × × 250 mm columns of Separon SGX C18 (5 μ) in 0·05M triethylammonium hydrogen carbonate containing: S6 5% methanol, S7 15% methanol; detection at 254 nm; $k = (t_R - t_0)/t_0$ where t_R

is the retention time and t_0 is the column dead time. NMR spectra were measured on a Varian XL-200 spectrometer in hexadeuteriodimethyl sulfoxide (unless stated otherwise) with tetramethylsilane as internal standard. The chemical shifts are given in ppm, the coupling constants J in Hz. Mass spectra were measured on AEI MS 902 spectrometer (ion source temperature 120°C, electron energy 70 eV). UV spectra were taken in aqueous solutions on a Specord UV-VIS (Zeiss, Jena, G.D.R.) spectrometer. Column chromatography was carried out on silica gel (30—40 μ) prepared in the Service Laboratories of the Institute. Ionex chromatography was continuously monitored at 254 nm using a Uvicord instrument (LKB, Uppsala, Sweden).

4-Hydroxymethyl-2,2,4-trimethyl-1,3-dioxolane (*IXa*)

A solution of 1,3-dichloro-2-propanone (*VII*; 0·5 mol) in ether (500 ml) was added dropwise under argon at −20°C to a solution of methylmagnesium iodide (0·6 mol) in ether (400 ml) and the mixture was stirred at 0°C for 2 h. A solution of ammonium chloride (80·0 g) in water (300 ml) was added, the mixture was filtered through Celite, washed with ether (300 ml) and the ethereal layer was separated. The aqueous phase was saturated with sodium chloride and extracted with ether (4 × 200 ml). The combined ethereal extracts were dried over magnesium sulfate and the solvent was removed at 30°C/2 kPa. Distillation of the residue in vacuo afforded 56·3 g of a reddish oil (0·394 mol, 79% for 1,3-dichloro-2-methyl-2-propanol), b.p. 42°C/13 Pa, which was immediately added dropwise to an ice-cold solution of sodium hydroxide (59·0 g; 1·476 mol) in water (500 ml) so as the temperature did not exceed 10°C. After stirring at room temperature overnight, the mixture was saturated with potassium carbonate and extracted with a benzene–ethanol mixture (2 : 1; 3 × 200 ml) and ethanol, the combined extracts were dried over potassium carbonate overnight and taken down. The residue in acetone (500 ml) was dried over magnesium sulfate and the solvent was evaporated. The remaining compound *VIII* was mixed with acetone (200 ml) and 2,2-dimethoxypropane (100 ml) and a solution of hydrogen chloride in dimethylformamide was added to acid reaction. After standing at room temperature for 2 days, the mixture was made alkaline with triethylamine and taken down in vacuo. The residue was dissolved in ether (200 ml), washed with water (3 × 50 ml), the aqueous extract was washed with ether (3 × 50 ml) and the combined ethereal extracts were dried over magnesium sulfate. Evaporation of the solvent and distillation of the residue in vacuo afforded 31·2 g (43%) of *IXa*, b.p. 107—110°C/2 kPa. For $C_7H_{14}O_3$ (146·2) calculated: 57·51% C, 9·65% H; found: 57·31% C, 9·36% H.

4-(*p*-Toluenesulfonyloxymethyl)-2,2,4-trimethyl-1,3-dioxolane (*IXb*)

A solution of *IXa* (29·2 g; 0·2 mol) in pyridine (100 ml) was added dropwise to a stirred and ice-cooled solution of *p*-toluenesulfonyl chloride (46·0 g; 0·24 mol) and 4-dimethylaminopyridine (0·4 g) in pyridine (200 ml) and the mixture was stirred at 0°C for 4 h and then at room temperature for 20 h. Water (40 ml) was added and after 1 h the mixture was concentrated in vacuo to a half, diluted with ethyl acetate (1 l) and washed with water (3 × 200 ml). The solvent was evaporated, the residue was codistilled with toluene (2 × 100 ml) and stirred with light petroleum (200 ml) in an ice bath for 1 h. The crystalline product was collected, washed with light petroleum and dried in vacuo; yield 43·2 g (72%) of *IXb*, m.p. 66°C; R_F 0·30 (S1). For $C_{14}H_{20}O_5S$ (300·4) calculated: 55·98% C, 6·71% H, 10·67% S; found: 56·12% C, 6·48% H, 10·65% S. ^{1}H NMR spectrum ($CDCl_3$): 1·27 s, 3 H (4-CH_3); 1·30 s, 3 H + 1·34 s, 3 H (2-CH_3); 2·45 s, 3 H (Ar—CH_3); 3·91 d + 3·76 d, 2 H (CH_2—OSO_2); 3·94 d + 3·66 d, 2 H, J = 9·1 (C—CH_2O); 7·35 d, 2 H + 7·79 d, 2 H, M = 8·0 (arom.).

9-(2,2,4-Trimethyl-1,3-dioxolan-4-ylmethyl)adenine (*X*)

Adenine (18·9 g; 0·14 mol) was added to a suspension of sodium hydride (0·14 mol) in dimethylformamide (500 ml) and the stirred mixture was heated to 80°C for 1 h under exclusion of moisture. Compound *IXb* (40·0 g) was added and the mixture was stirred at 100°C for 45 h. The solvent was evaporated at 50°C in vacuo, the residue was codistilled with toluene (3 × 200 ml) and extracted with boiling chloroform (1 l; boiling for 10 min). After filtration and washing the solid with boiling chloroform (1 l), the filtrate was taken down and the residue was crystallized from ethanol affording 17·6 g (56%) of chromatographically pure *X*, m.p. 223—224°C; R_F 0·40 (S2). An analytical sample was crystallized from methanol. For $C_{12}H_{17}N_5O_2$ (263·3) calculated: 54·73% C, 6·51% H, 26·60% N; found: 55·02% C, 6·37% H, 26·34% N. Mass spectrum, *m/z*: 263 (M^+), 248 (M — CH_3), 205 (base peak, M — $(CH_3)_2CO$), 188, 149, 148 (B + CH_2), 135 (BH). ^{1}H NMR spectrum: 1·13 s + 1·21 s + 1·29 s, 2 H (3 × CH_3); 3·74 d + 4·05 d, 2 H, *J*(gem) = 8·9 (NCH_2); 4·23 s, 2 H (OCH_2); 7·20 br, 2 H (NH_2); 8·03 s, 1 H (H-2_{Ad}); 8·16 s, 1 H (H-8_{Ad}).

9-(2,3-Dihydroxy-2-methylpropyl)adenine (*XI*)

A solution of compound *X* (8·8 g; 33·5 mmol) in a mixture of water (150 ml) and conc. sulfuric acid (2 ml) was allowed to stand at room temperature overnight. The mixture was diluted with water (100 ml), neutralized with saturated barium hydroxide solution, filtered through Celite while hot and the Celite was washed with boiling water (500 ml). The filtrate was taken down in vacuo and the dry residue was crystallized from ethanol (ether added to turbidity) to give 6·4 g (86%) of *XI*, m.p. 209°C. R_F 0·80 (S5). For $C_9H_{13}N_5O_2$ (223·2) calculated: 48·42% C, 5·87% H, 31·38% N; found: 48·65% C, 5·64% H, 31·58% N. UV spectrum (pH 2): λ_{max} 260 nm, ε_{max} 16 400 ^{1}H NMR spectrum: 0·96 s, 3 H (CH_3); 3·23 m, 2 H (OCH_2); 4·12 2 d, 2 H, *J*(gem) = 14·0 (NCH_2); 4·85 s, 1 H (OH); 5·04 t, *J* = 6·0, 1 H (OH); 7·20 br, 2 H (NH_2); 8·02 s, 1 H (H-2_{Ad}); 8·14 s, 1 H (H-8_{Ad}). Mass spectrum, *m/z*: 223 (M^+), 205 (M — H_2O), 192 (M — CH_2OH), 188 (205 — OH), 148 (base peak) (B–CH_2), 135 (BH).

9-(2-Oxopropyl)adenine (*XII*)

Compound *XI* (1·15 g; 5 mmol), followed by an aqueous solution of ruthenium oxychloride (from 10 mg of RuO_2; 0·5 ml), was added to a solution of sodium periodate (3·6 g; 16·7 mmol) in 70% acetone (75 ml). The mixture was stirred at room temperature for 3 h (the reaction was quantitative according to TLC in S3) and diluted with acetone (100 ml). The precipitate was filtered, washed with acetone (200 ml) and the filtrate was taken down in vacuo. The remaining aqueous solution was made slightly alkaline with ammonia and taken down. The dry residue was dissolved in water (50 ml), acidified with Dowex 50X8 (H^+ form) and the suspension was applied onto a column (100 ml) of the same ion-exchanger. After washing with water to loss of UV absorption and drop of conductivity of the eluate, the Dowex was suspended in water (250 ml), the mixture was adjusted to pH 9·5 with ammonia, filtered, the resin was washed with water (200 ml) and the filtrate was taken down in vacuo. The residue was dissolved in hot ethanol, mixed with twice the volume of ether, the separated impurities were removed by filtration through Celite and the solvents were evaporated. The crystalline residue was crystallized from ethanol (light petroleum added to turbidity) at 0°C. Yield 0·70 g (73%) of *XII*, m.p. 240—245°C; R_F 0·33 (S3), 0·64 (S5). For $C_8H_9N_5O$ (191·2) calculated: 50·25% C, 4·74% H, 36·64% N; found: 50·33% C, 4·54% H, 36·48% N. Mass spectrum, *m/z*: 191 (M^+), 149 (M — CH_2CO), 148 (base peak, M — CH_3CO), 135 (BH). UV spectrum (pH 2): λ_{max} 259 nm, ε_{max} 14 300.

9-(2-Hydroxy-2-hydroxymethyloctyl)adenine (*XVI*)

A solution of 1,3-dichloro-2-propanone (*VII*; 0·29 mol) in ether (230 ml) was added at −20°C to a stirred solution of hexylmagnesium bromide (0·34 mol) in ether (270 ml). After stirring for 2 h at 0°C, a solution of ammonium chloride (46·0 g) in water (170 ml) was added dropwise, the precipitate was filtered off and washed with ethyl acetate (200 ml). The aqueous layer was saturated with sodium chloride, extracted with ether (2× 200 ml), and all the organic phases were combined. After drying over magnesium sulfate and evaporation at 30°C/2 kPa, the crude 2-chloromethyl-2-hydroxyoctyl chloride (51·5 g; 84%) was dissolved in dioxane (250 ml) and added dropwise under stirring to 4M sodium hydroxide (250 ml). After the exothermic reaction had ceased, the mixture was stirred overnight at room temperature, diluted with water (1 l), and extracted with ether (3× 300 ml). The extract was washed with water (3× 100 ml) and the solvent was evaporated. The resulting 2-hydroxymethyl-2-octyloxirane (*XIII*; R_F 0·67 in S4) was heated with 80% dioxane (250 ml) and trifluoroacetic acid (12 ml) to 100°C for 8 h (according to TLC in S4 the reaction was quantitative; the product did not react with N-(*p*-nitrobenzyl)pyridinium bromide) and the mixture was made alkaline with ammonia. After evaporation, the residue was extracted with ether (200 ml), the extract was washed with water (50 ml), dried over magnesium sulfate and taken down in vacuo, yielding 25·4 g (0·144 mol; 50% from *VII*) of 2-hydroxymethyloctane-1,2-diol (*XIV*), homogeneous according to TLC in S4 (R_F 0·35).

To a solution of this product in pyridine (150 ml) a solution of *p*-toluenesulfonyl chloride (27·5 g; 0·144 mol) in pyridine (100 ml) was added under stirring and ice-cooling. 4-Dimethylaminopyridine (0·2 g) was added, the mixture was stirred at 0°C for 4 h and at room temperature for 20 h and decomposed with water (10 ml). After stirring for 30 min the mixture was diluted with ethyl acetate (1·5 l), washed with water (3× 200 ml), taken down in vacuo and the residue was codistilled with toluene (4× 100 ml) and dried in vacuo, affording 36·7 g (0·111 mol) of the *p*-toluenesulfonyl derivative *XVa*, homogeneous according to TLC in S4. This compound was dissolved in pyridine (150 ml) and benzoyl chloride (50 ml; 0·344 mol) was added dropwise during 30 min under stirring and cooling with ice. The mixture was stirred at 0°C for 2 h and at room temperature overnight. Water (20 ml) was added, followed after 1 h by ethyl acetate (1 l), and the organic solution was successively washed (à 200 ml) with water (3×), 1M hydrochloric acid (to acid reaction), water, saturated solution of sodium hydrogen carbonate (3×), again with water, and dried over magnesium sulfate. After evaporation, the residue was stirred at 0°C with light petroleum (200 ml), the solid was filtered off, washed with light petroleum and discarded. The filtrate was taken down and chromatographed on a silica gel column (500 ml) in benzene to give the dibenzoyl derivative *XVb* as a colourless oil (R_F 0·70 in S4) which was dried in vacuo; yield 27·0 g (50 mmol).

The crude *XVb*, obtained above, was dissolved in dimethylformamide (50 ml) and added to a suspension of sodium salt of adenine (50 mmol) in dimethylformamide (150 ml), prepared as described in the preparation of *X*. The mixture was heated to 100°C for 24 h under stirring and exclusion of moisture and the solvent was evaporated at 50°C/2 kPa. The residue was codistilled with toluene (4 × 100 ml), extracted with boiling chloroform (4 × 250 ml), filtered, the filtrate taken down in vacuo and the residue was briefly boiled with 0·1M sodium methoxide in methanol (100 ml). After standing at room temperature for 2 h, the mixture was neutralized with Dowex 50X8 (H^+ form), made alkaline with triethylamine, filtered and the Dowex was washed with methanol (300 ml). The filtrate was taken down and the residue chromatographed on a column of silica gel (400 ml) in chloroform. Compound *XVI* was eluted with chloroform–methanol (95 : 5). The combined fractions were stripped of solvents and the residue was crystallized from ethanol (light petroleum added tu turbidity) to give 6·5 g (44% from *XVb*) of *XVI*, m.p. 178°C; R_F 0·40 (S2). For $C_{14}H_{23}N_5O_4$ (293·4) calculated: 57·31% C, 7·91% H, 23·88% N; found:

57·02% C, 7·79% H, 23·65% N. Mass spectrum, *m/z*: 293 (M^+), 276 (M − OH), 275 (M − H_2O), 262 (M − CH_2OH), 250 (M − C_3H_7), 246 (275 − C_2H_5), 236 (M − C_4H_9), 218 (275 − C_4H_9), 208 (M − C_6H_{13}), 204 (275 − C_5H_{11}), 148 (B + CH_2), 136 (base peak) (BH_2), 135 (BH).

Methyl 2-(Adenin-9-ylmethyl)-2-propenoate (*XVIII*)

A mixture of methyl 2-bromomethyl-2-propenoate[19] (*XVII*; 43·2 g; 0·43 mol) and dimethylformamide (100 ml) was added dropwise at 80°C during 1 h to a stirred suspension of sodium salt of adenine (0·25 mol) in dimethylformamide (700 ml; prepared as described for compound *X*). The mixture was stirred at 80°C for 16 h under exclusion of moisture, the solvent was evaporated in vacuo and the residue was codistilled with toluene (3× 100 ml) and extracted with boiling chloroform (3× 250 ml). The chloroform-insoluble residue was dissolved in methanol (100 ml), adsorbed on silica gel (50 g), the solvent was evaporated in vacuo and the residue was codistilled with toluene (100 ml). The silica gel with the adsorbed material was slurried in chloroform and applied onto a column of silica gel (500 ml) in chloroform. Dilution with chloroform–methanol (95 : 5) afforded the product which was crystallized from methanol (light petroleum added to turbidity); yield 20·0 g (36%) of *XVIII*, m.p. 213°C, R_F 0·52 (S3). For $C_{10}H_{11}N_5O_2$ (233·2) calculated: 51·49% C, 4·75% H, 30·03% N; found: 51·26% C, 4·77% H, 29·94% N. Mass spectrum, *m/z*: 233 (M^+), 218 (M − CH_3), 202 (M − OCH_3), 174 (M − $COOCH_3$), 136 (BH_2), 135 (BH). ^{1}H NMR spectrum: 3·72 s, 3 H (OCH_3); 5·00 bs, 2 H (NCH_2); 5·47 bs, 1 H + 6·24 bs, 1 H (CH_2=C); 7·23 bs, 2 H (NH_2); 8·09 s, 1 H (H-2_{Ad}); 8·12 s, 1 H (H-8_{Ad}).

Methyl 2-(Adenin-9-ylmethyl)-2,3-dihydroxypropanoate (*XIX*)

Compound *XVIII* (13·4 g; 57·6 mmol), followed by osmium tetroxide (1 g), was added to a mixture of sodium perchlorate (18·6 g; 175 mmol), water (200 ml) and methanol (1 l). The mixture was refluxed with stirring for 5 h (TLC in S3 showed a quantitative reaction), the methanol was evaporated in vacuo, the residue was concentrated to about 50 ml and chromatographed on an octadecylsilica gel column (200 ml) in water. Water eluted (5 ml/min) first the salts and then the product. The product (UV-absorbing) fraction was taken down, the residue was codistilled with ethanol and crystallized from methanol (light petroleum added to turbidity). Yield 11·7 g (76%) of compound *XIX*, m.p. 193°C. R_F 0·25 (S3). For $C_{10}H_{13}N_5O_4$ (267·3) calculated: 44·94% C, 4·90% H, 26·21% N; found: 45·07% C, 5·03% H, 26·16% N.

2-(Adenin-9-ylmethyl)-2,3-dihydroxypropanoic Acid (*XX*)

A suspension of compound *XIX* (1·33 g; 5 mmol) in water (40 ml) and 1M methanolic sodium methoxide (10 ml) was stirred until it became homogeneous and then left overnight at 40°C. The mixture was neutralized with Dowex 50X8 (H^+ form) to pH 7·0, the Dowex was filtered off, washed with water (20 ml) and the filtrate was taken down in vacuo. The residue was codistilled with ethanol and the sodium salt was precipitated with ether from ethanol; yield 1·0 g (72%) of sodium salt of *XX*. Purity (HPLC in S7) 99·5%, k 0·53. For $C_9H_{10}N_5O_4Na$ (275·2) calculated: 39·27% C, 3·66% H, 25·45% N; found: 39·55% C, 3·44% H, 25·77% N.

9-(2,3-Dihydroxy-2-hydroxymethylpropyl)adenine (*XXI*)

Sodium borohydride (11 g; 290 mmol) was gradually added during 90 min to an ice-cooled and stirred suspension of *XIX* (10·6 g; 40 mmol) in 96% ethanol (800 ml) at such a rate that tempera-

ture did not exceed 10°C. The mixture was stirred at 0°C for 6 h and then at room temperature for 20 h. According to TLC in S3 the reduction was quantitative. The mixture was neutralized with Dowex 50X8 (H^+ form), filtered, the Dowex was washed with water (300 ml) and added to a column of the same fresh ion-exchanger (200 ml). The filtrate was concentrated to about 20 ml in vacuo, applied onto this column which was then washed with water (5 ml/min) to drop of conductivity and UV absorption of the eluate to the original values. Elution with 2·5% aqueous ammonia afforded a UV-absorbing fraction which was taken down in vacuo, the residue was codistilled with ethanol and crystallized from 70% aqueous ethanol (ether added to turbidity). Yield 9·0 g (88%) of monohydrate of *XXI*, m.p. 218–220°C, *k* 5·95 in S6, R_F 0·45 (S5). For $C_9H_{15}N_5O_4$ (257·2) calculated: 42·01% C, 5·87% H, 27·23% N; found: 42·25% C, 5·53% H, 27·44% N. Mass spectrum, *m/z*: 239 (M^+), 221 (M − H_2O), 208 (M − CH_2OH), 192 (M − CHOH—OH), 191, 149 (B + CH_3), 148 (B + CH_2), 136 (BH_2), 135 (BH).

2,3-O-Isopropylidene-9-(2,3-dihydroxynonyl)adenine (*XXVI*)

A solution of propenal (*XXII*; 11·8 g; 0·21 mol) in ether (100 ml) was added dropwise at −20°C to a stirred solution of hexylmagnesium bromide (0·2 mol) in ether (250 ml). After stirring at 0°C for 2 h a solution of ammonium chloride (40 g) in water (150 ml) was added dropwise. The ethereal layer was separated, washed with water (50 ml) and dried over magnesium sulfate. Evaporation of the solvent and drying in vacuo afforded 24·5 g (172 mmol; 86%) of chromatographically homogeneous (R_F 0·60 in S1) 1-nonen-3-ol (*XXIII*). This product, followed with osmium tetroxide (0·2 g), was added to a solution of sodium chlorate (50 g) in 50% aqueous ethanol (200 ml). The stirred mixture was heated to 50°C for 6 h under reflux condenser (the reaction was quantitative according to TLC in S1). Ethanol was evaporated in vacuo, the remaining emulsion was extracted with ethyl acetate (3× 100 ml), the organic phase was washed with water (3× 25 ml), dried over magnesium sulfate and taken down. Drying in vacuo gave 21·3 g (70% from *XXIII*) of nonane-1,2,3-triol (*XXIVa*); R_F 0·24 (S1).

A solution of this compound (0·12 mol) in pyridine (100 ml) was cooled in ice and *p*-toluenesulfonyl chloride (24·0 g; 0·126 mol) was added over 30 min in four portions with stirring. The mixture was stirred at 0°C for 2 h, allowed to stand overnight and diluted with water (200 ml). After 1 h ethyl acetate (500 ml) was added, the solution was washed with water, 5% hydrochloric acid (to acid reaction), water, saturated sodium hydrogen carbonate and water (200 ml of each), and dried over magnesium sulfate. The solvent was evaporated and the residue (chromatographically homogeneous *p*-toluenesulfonyl derivative *XXIVb*; R_F 0·32 in S1) was dried in vacuo. This compound was dissolved in a mixture of acetone (100 ml) and 2,2-dimethoxypropane (150 ml), acidified with hydrogen chloride in dimethylformamide and allowed to stand at room temperature for 24 h. The mixture was made alkaline with triethylamine, taken down in vacuo, the residue was mixed with ethyl acetate (300 ml) and the mixture was washed with water (3× 100 ml). After drying with magnesium sulfate the solvent was evaporated in vacuo and the residue was chromatographed on a silica gel column (300 ml) in benzene; the yield of *XXV* was 24·0 g (54% from *XXIVa*), colourless oil; R_F 0·24 (S4).

A solution of this compound (65 mmol) in dimethylformamide (90 ml) was added at 80°C to a stirred suspension of sodium salt of adenine (75 mmol) in dimethylformamide (200 ml) (prepared as described in the preparation of *X*) and the mixture was stirred at 100°C for 15 h under exclusion of moisture. The solvent was evaporated at 50°C/2 kPa, the residue was codistilled with toluene (3× 200 ml) and extracted with boiling chloroform (3× 300 ml). After filtration and evaporation in vacuo, the residue was purified by chromatography on silica gel (300 ml) in chloroform. The product fractions were combined, taken down in vacuo and the product was crystallized from ethyl acetate (light petroleum added to turbidity) to give 12·6 g (58%)

of *XXVI*, m.p. 181–182°C; R_F 0·50 (S2). For $C_{17}H_{27}N_5O_2$ (333·4) calculated: 61·23% C, 8·16% H, 21·01% N; found: 61·60% C, 8·08% H, 20·95% N.

9-(2,3-Dihydroxynonyl)adenine (*XXVII*)

A mixture of *XXVI* (6·7 g; 20 mmol), methanol (150 ml) and 0·1M sulfuric acid was kept at 40°C for 20 h, neutralized with a solution of barium hydroxide and the same volume of ethanol was added. After heating to 80°C the suspension was filtered through Celite which was then washed with boiling water (1 l) and methanol (200 ml). The combined filtrates were taken down in vacuo and the residue was crystallized from 80% ethanol (ether added to turbidity); yield 5·0 g (85%) of *XXVII*, m.p. 208–209°C; R_F 0·20 (S2). For $C_{14}H_{23}N_5O_2$ (293·4) calculated: 57·31% C, 7·91% H, 23·88% N; found: 57·43% C, 7·74% H, 24·12% N.

9-(3-Methyl-2-buten-yl)adenine (*XXVIII*)

1-Bromo-3-methyl-2-butene (17·5 g; 177 mmol) was added to a suspension of sodium salt of adenine (0·1 mol) in dimethylformamide (300 ml) (prepared as described in the preparation of *X*). The stirred mixture was heated to 100°C for 12 h under exclusion of moisture. After evaporation at 50°C/2 kPa and codistillation with toluene (2× 100 ml) the mixture was extracted with boiling chloroform (1 l total), the solvent was evaporated and the residue chromatographed on a silica gel column (400 ml) in chloroform. The product fractions were combined, the solvent was evaporated and the product crystallized from ethyl acetate (light petroleum added to turbidity); yield 9·0 g (45%) of *XXVIII*, m.p. 165–166°C, R_F 0·55 (S2). For $C_{10}H_{13}N_5$ (203·2) calculated: 59·09% C, 6·45% H, 34·46% N; found: 59·37% C, 6·46% H, 34·32% N. Mass spectrum, *m/z*: 203 (M^+), 188 (M – CH_3), 135 (BH). UV spectrum (pH 2): λ_{max} 262 nm, ε_{max} 15 300.

Further elution afforded (after crystallization from ethyl acetate–light petroleum) 3·5 g (17%) of the N^3-isomer of *XXVIII*, m.p. 225–226°C; R_F 0·25 (S2). For $C_{10}H_{13}N_5$ (203·2) calculated: 59·09% C, 6·45% H, 34·46% N; found: 59·39% C, 6·25% H, 34·40% N. Mass spectrum, *m/z*: 203 (M^+), 188 (M – CH_3), 135 (BH). UV spectrum (pH 2): λ_{max} 275 nm, ε_{max} 13 700.

9-(3-Hydroxy-2-oxo-3-methylbutyl)adenine (*XXIX*)

Potassium permanganate (0·05M, 800 ml total) was gradually added to a solution of *XXVIII* (5·1 g; 25 mmol) in 0·25M sulfuric acid (400 ml) until the reaction was complete (TLC in S2). The mixture was filtered through Celite, the filtrate was neutralized with ammonia, concentrated in vacuo to about 200 ml, Dowex 50X8 (H^+ form) was added to dissolution (about 100 ml) and the mixture was poured on a column of the same ion exchanger (300 ml). After washing with water to drop of conductivity and UV absorption to the original values, elution with 2·5% aqueous ammonia afforded a UV-absorbing fraction which was taken down in vacuo, mixed with water (100 ml), made alkaline with triethylamine, and applied onto a column of Dowex 1X2 (HCO_3^- form, 200 ml). The UV-absorbing eluate, obtained by elution with water, was evaporated in vacuo and the residue crystallized from water, affording 3·2 g (56%) of *XXIX* as a monohydrate, m.p. 207°C; R_F 0·24 (S2), 0·50 (S3). For $C_{10}H_{15}N_5O_3$ (253·3) calculated: 47·42% C, 5·97% H, 27·67% N; found: 47·68% C, 6·17% H, 27·82% N. Mass spectrum, *m/z*: 235 (M^+), 220 (M – CH_3), 218 (M – OH), 207 (M – CO), 149 (base peak) (B–CH_2), 136 (BH_2), 135 (BH). ^{1}H NMR spectrum: 1·31 s, 6 H (2× CH_3); 5·45 s, 2 H (NCH_2); 5·76 s, 1 H (OH); 7·23 br, 2 H (NH_2); 8·03 s, 1 H (H-2_{Ad}); 8·11 s, 1 H (H-8_{Ad}). ^{13}C NMR spectrum: 26·74 (CH_3); 47·92 (C–OH); 76·06 (NCH_2); 209·28 (C=O); adenine 118·52 (C-5); 141·81 (C-8); 149·95 (C-4); 152·62 (C-2); 156·07 (C-6).

9-(2,3-Dihydroxy-3-methylbutyl)adenine (*XXX*)

A solution of *XXIX* (2·53 g; 10 mmol) in methanol (250 ml) was cooled with ice and stirred at 0°C with Dowex 1X2 (BH_4^- form; 10 ml) for 1 h. The reaction was quantitative (TLC in S3). The suspension was filtered, the resin was washed with methanol (200 ml) and water (200 ml), the filtrates were combined and taken down in vacuo. The residue was codistilled with ethanol and crystallized from ethanol (ether added to turbidity) to yield 1·86 g (79%) of the product, m.p. 113–114°C; R_F 0·37 (S3). For $C_{10}H_{15}N_5O_2$ (237·3) calculated: 50·62% C, 6·37% H, 29·52% N; found: 50·35% C, 6·20% H, 29·35% N. Mass spectrum, *m/z*: 237 (M^+), 218 (M – H_2O), 178, 148 (B + CH_2), 136 (BH_2), 135 (BH). ^{1}H NMR spectrum: 1·14 s, 3 H + 1·16 s, 3 H (2 × CH_3); 3·54 m, 1 H (2-CH); 3·91 dd, 1 H, *J*(1b, 2) = 9·7 (1-CHb); 4·48 br d, 1 H, *J*(1a, 2) = 2·0, *J*(gem) = 13·5 (1-CHa); 4·55 s, 1 H (3-OH); 7·18 br, 2 H (NH_2); 8·05 s, 1 H ($H\text{-}2_{Ad}$); 8·15 s, 1 H ($H\text{-}8_{Ad}$).

4-C-Hydroxymethyl-1,2-O-isopropylidene-β-L-threo-pentofuranose (*XXXII*; see ref.[20])

To an ice-cooled solution of 1,2-O-isopropylidenedialdehydo-α-D-xylofuranose[20] (*XXXI*; 72·6 g; 0·33 mol) in water (450 ml) was added 38% aqueous formaldehyde (100 ml) and 1M sodium hydroxide (700 ml) during 30 min under stirring. The mixture was stirred at 0°C for 6 h and then at room temperature for 6 h. After neutralization with Dowex 50X8 (H^+ form) the suspension was filtered, the Dowex was washed with water (200 ml), the filtrate was taken down and the residue was codistilled with ethanol (2× 200 ml) and extracted with boiling ethyl acetate (1 l). The extract was filtered, the solvent evaporated in vacuo and the residue chromatographed on a silica gel column (500 ml) in chloroform. The product fractions were taken down in vacuo and the product was crystallized from acetone in a refrigerator; yield 35·0 g (48%) of *XXXII*, m.p. 103°C (ethyl acetate–light petroleum) (reported[22] m.p. 103–104°C); R_F 0·23 (S2). For $C_9H_{16}O_6$ (220·2) calculated: 49·08% C, 7·32% H; found: 49·30% C, 7·64% H. ^{1}H NMR spectrum ($CDCl_3$): 1·32 s + 1·54 s, 2 H (2 × CH_3); 2·30 + 2·60 m, 2 H (2× OH-5); 3·50–3·95 m, 4 H (2× OCH_2); 3·74 d, 1 H (OH-3); 4·24 d, 1 H, *J*(3, OH) = 4·8 (H-3); 4·65 dd, 1 H, *J*(2, 3) = 0·6 (*trans*-H-2); 6·01 d, 1 H, *J*(1, 2) = 4·0 (H-1).

4-C-Hydroxymethyl-1,2:3,5-di-O-isopropylidene-β-L-arabinofuranose (*XXXIIIa*)

A solution of *XXXII* (30·0 g; 0·136 mol) in a mixture of acetone (60 ml) and 2,2-dimethoxypropane (60 ml) was acidified with 4M hydrogen chloride in dimethylformamide. After standing at room temperature for 1 h (the reaction was quantitative according to TLC in S2), the mixture was made alkaline with triethylamine and the solvents were evaporated in vacuo. The residue was dissolved in ethyl acetate (200 ml), the solution washed with water (2 × 50 ml) and dried over magnesium sulfate. The solvent was evaporated and the product was purified by column chromatography on silica gel (200 ml) in chloroform. The product-containing fractions were combined, the solvent evaporated and the product crystallized from ether–light petroleum, affording 26·0 g (74%) of *XXXIIIa*, m.p. 108°C; R_F 0·12 (S1), 0·55 (S2). For $C_{12}H_{20}O_6$ (260·3) calculated: 55·37% C, 7·75% H; found: 55·18% C, 7·42% H. R_F 0·52 (S2). ^{1}H NMR spectrum ($CDCl_3$): 1·30 s, 3 H + 1·37 s, 6 H + 1·54 s, 3 H (4× CH_3); 2·20 m, 1 H (OH-6); 3·50–4·05 m, 4 H (2× OCH_2); 4·00 s, 1 H (H-3); 4·58 d, 1 H, *J*(2, 3) ≦ 0·5 (H-2); 6·02 d, 1 H, *J*(1, 2) = 4·0 (H-1); + TEI: 3·78 dd, 2 H, (2× H-5); 4·48 s, 2 H (2× H-6).

The chromatography further afforded 3·2 g (9%) of the isomeric 4-C-hydroxymethyl-1,2:5,6-di-O-isopropylidene-β-L-threo-pentofuranose (*XXXVII*) as an oil; R_F 0·45 (S2). ^{1}H NMR spectrum ($CDCl_3$): 1·28 s, 3 H + 1·39 s, 3 H + 1·49 s, 6 H (4× CH_3); 3·15 d, 1 H, *J* = 4·5

(OH-3); 3·60—4·20 m, 4 H (2× OCH_2); 4·53 d, 1 H, J(3, OH) = 4·5 (H-3); 4·58 d, 1 H, $J(2, 3) \leqq$ $\leqq$ 0·5 (H-2); 5·89 d, 1 H, $J(1, 2) = 4·0$ (H-1); +TEI: 3·60—4·20 m, 4 H (2× OCH_2); 4·68 d, 1 H, $J(2, 3) \leqq 0·5$ (H-2); 5·63 s, 1 H; 5·92 d, 1 H (H-1).

4-C-(*p*-Toluenesulfonyloxymethyl)-1,2:3,5-di-O-isopropylidene-β-L-arabinofuranose (*XXXIIIb*)

A solution of *p*-toluenesulfonyl chloride (22·0 g; 115 mmol) in 1,2-dichloroethane (120 ml) was added to a stirred and ice-cooled solution of *XXXIIIa* (23·4 g; 90 mmol) and triethylamine (20 ml) in 1,2-dichloroethane (240 ml). The mixture was stirred at 0°C for 4 h, set aside for 20h at 0°C, mixed with methanol (20ml) and, after standing at 0°C for 1 h, diluted with chloroform (1 l). The mixture was washed (à 200 ml) with water, saturated sodium hydrogen carbonate solution, three times with water, and dried over magnesium sulfate. The solvent was evaporated and the residue chromatographed on a silica gel column (400 ml) in chloroform. The product fractions were combined, the solvent was evaporated and the product was crystallized from ethyl acetate (light petroleum added to turbidity); yield 26·7 g (72%) of *XXXIIIb*, m.p. 118°C; R_F 0·25 (S1). For $C_{19}H_{26}O_8S$ (414·5) calculated: 55·06% C, 6·32% H, 7·74% S; found: 54·83% C, 6·16% H, 7·58% S. ^{1}H NMR spectrum ($CDCl_3$): 2·44 s, 3 H (CH_3); 3·59 d + 3·92 d, 2 H, J(gem) = 12·7 (2× H-5); 4·22 br s, 1 H (H-3); 3·98 d + 4·30 d, 2 H, J(gem) = 9·9 (2× H-5′); 4·53 d, 1 H, $J(2, 3) \leqq 0·5$ (H-2); 5·95 d, 1 H, $J(1, 2) = 3·7$ (H-1); 7·34 d + 7·81 d, 4 H, $J = 8·0$ (arom).

4-C-(Adenin-9-ylmethyl)-1,2:3,5-di-O-isopropylidene-α-D-xylofuranose (*XXXIV*)

Compound *XXXIIIb* (18·7 g; 45 mmol) was added at 80°C to a stirred suspension of sodium salt of adenine (50 mmol) in dimethylformamide (200 ml) (see the preparation of *X*) and the mixture was stirred at 110°C for 15 h under exclusion of moisture. Dimethylformamide was evaporated at 60°C/2 kPa, the residue was coevaporated with toluene (3× 200 ml), dissolved in boiling chloroform (1 l total), filtered and the solvent was evaporated in vacuo. The residue was chromatographed on a column of silica gel (300 ml) in chloroform, the product was eluted with chloroform–methanol (95 : 5) and crystallized from ethanol (light petroleum added to turbidity) to give 6·8 g (40%) of *XXXIV*, m.p. 239—240°C. For $C_{17}H_{23}N_5O_5$ (377·4) calculated: 54·10% C, 6·14% H, 18·56% N; found: 53·97% C, 6·15% H, 18·38% N. ^{1}H NMR spectrum ($CDCl_3$): 1·35 s + 1·39 s + 1·44 s + 1·64 s, 12 H (4× CH_3); 3·31 d, 1 H + 3·81 d, 1 H, J(gem) = 12·6 (2× H-5); 4·27 br s, 1 H (H-3); 4·42 d, 1 H + 4·75 d, 1 H, J(gem) = 14·6 (2× H-6); 4·73 d, 1 H, $J(2, 3) \leqq 0·5$ (H-2); 6·17 d, 1 H, $J(1, 2) = 4·5$ (H-1); 6·18 br, 2 H (NH_2); 8·22 s, 1 H (H-2_{Ad}); 8·39 s, 1 H (H-8_{Ad}).

Ethyl (2*S*,3*R*)-4-(Adenin-9-yl)-3-hydroxymethyl-2,3-dihydroxybutanoate (*XXXVI*)

A solution of *XXXIV* (3·8 g; 10 mmol) in water (50 ml) and sulfuric acid (0·8 ml) was stirred at 70°C for 7 h (the reaction was quantitative according to TLC in S3). After neutralization with conc. sodium hydroxide solution, solid sodium hydroxide (1·2 g; 30 mmol) was added, the mixture was made up with water to 200 ml and stirred in an atmosphere of oxygen for 20 h. Dowex 50X8 (H^+ form) was added to neutrality, the mixture was made alkaline with triethylamine, the resin was filtered off and washed with water (200 ml). The combined filtrates were taken down in vacuo, dissolved in water (50 ml, made alkaline with ammonia) and applied onto a column (200 ml) of Dowex 1X2 (acetate form). After washing with water until the UV absorption dropped to the original value, the column was eluted with a linear gradient (à 1 l) of 0—1M acetic acid. The product was eluted with 0·8—1·0M acetic acid. After evaporation in vacuo and

codistillation with ethanol (3× 100 ml) the residue was refluxed under stirring with a mixture of ethanol (70 ml) and sulfuric acid (0·7 ml) for 3 h, cooled with ice, neutralized with triethylamine and the solvent was evaporated in vacuo. The residue in water (20 ml) was chromatographed on a column of octadecylsilica gel (200 ml) in water (5 ml/min). The product was eluted with water and crystallized from ethanol (with ether added to turbidity); yield 1·4 g (45%) of *XXXVI*, m.p. 208°C; R_F 0·19 (S3). For $C_{12}H_{17}N_5O_5$ (311·3) calculated: 46·29% C, 5·51% H, 22·50% N; found: 46·54% C, 5·31% H, 22·37% N. Mass spectrum, *m/z*: 265 (M − C_2H_5OH), 245 (265 − OH), 230, 208, 192, 149 (B + CH_3), 148 (B + CH_2), 136 (BH_2), 135 (BH).

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