PREPARATION AND SYNTHETIC UTILIZATION OF 3-(ADENIN-9-YL)-2-HYDROXYALKANOIC ACIDS AND THEIR DERIVATIVES*

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Received January 9th, 1984

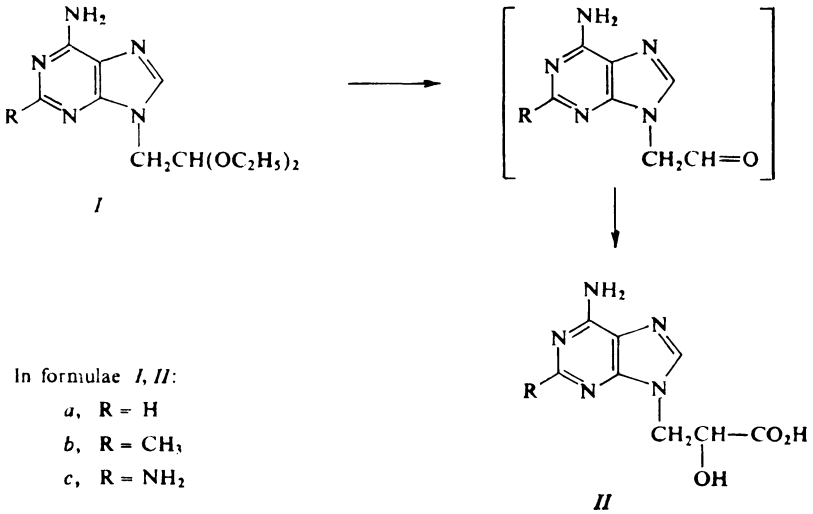
Condensation of adenine and its substituted derivatives with 1,1-dialkoxy-2-bromoalkanes afforded substituted 2-(adenin-9-yl)-1,1-dialkoxyalkanes *I* and *IV*. Acid hydrolysis of *I* or *IV*, followed by reaction with alkali metal cyanides and acid hydrolysis, gave substituted 3-(adenin-9-yl)-2-hydroxyalkanoic acids *II*, *V* and *VI*. Methyl esters of these compounds (*VIII*) were converted into 3-(adenin-9-yl)alkane-1,2-diols *IX* by reduction with sodium borohydride. 3-(Adenin-9-yl)-2-methoxypropanoic acid (*XVII*) was obtained by oxidation of 9-(3-hydroxy-2-methoxypropyl)-adenine (*XVI*) with sodium periodate; 4-(adenin-9-yl)-2-(*S*)-hydroxybutanoic acid (*XXVII*) was synthesized by oxidation of 9-(*S*)-(2-tetrahydropyranyloxy-4-hydroxybutyl)adenine (*XXV*), prepared from diethyl L-malate. Acid hydrolysis of *XXV* afforded 9-(*S*)-(2,4-dihydroxybutyl)adenine (*XXVI*). 4-(Adenin-9-yl)-3-hydroxypentanoic acid (*XXIX*) was obtained by reaction of malonic acid with 2-(adenin-9-yl)-1,1-diethoxypropane (*IVa*) in water.

In one communication of this series we described the marked inactivating effect of the so-called eritadenines, *i.e.* 4-(adenin-9-yl)-2,3-dihydroxybutanoic acids, on S-adenosyl-L-homocysteine hydrolase, a key enzyme for the regulation of methylation processes[1]. This inactivation results in many biological activities, especially in proliferating systems[2]. Within the framework of our systematic studies of structure-activity relationship in the series of hydroxylated 9-(ω-carboxyalkyl)adenines we found a strong enzyme-inhibitory effect also with simpler eritadenine analogues, enantiomeric (*R*)- and (*S*)-3-(adenin-9-yl)-2-hydroxypropanoic acids (*II*) (see ref.[3]); these compounds are formed in low yields as side-products in one of syntheses of *erythro*-isomers of eritadenines[4] or by degradation of 5-(adenin-9-yl)-5-deoxyaldofuranosides[5].

Since compounds *II* and their derivatives are of extraordinary biological interest (see *e.g.* ref.[6]), elaboration of new methods for their synthesis was desirable. The present paper concerns a general method of preparation of racemic 3-(adenin-9-yl)-2-hydroxyalkanoic acids and some aspects of their further preparative utilization.

* Part XII in the series Studies on S-Adenosyl-L-homocysteine Hydrolase; Part XI: This Journal *49*, 1543 (1984).

As starting compounds for preparation of 3-(adenin-9-yl)-2-hydroxypropanoic acid and its analogues substituted in the adenine ring we used the 9-(2,2-diethoxymethyl) derivatives *I*, accessible by condensation of bromoacetaldehyde diethylacetal either with sodium salt of the adenine base or with this base in the presence of potassium carbonate[4,7], preferably in dimethylformamide at elevated temperature. In the presence of dilute aqueous acids, compounds *I* afford the free aldehyde, stable only under acidic conditions, which on reaction with excess of an alkali metal cyanide in a neutral medium is converted into the cyanohydrin derivative. Its acid hydrolysis gives finally the corresponding α-hydroxy acid *II* as the sole reaction product. The assumed cyanohydrin addition compounds have not been isolated and their stability is uncertain: an electrophoretical study of the mixture after reaction with cyanide revealed the presence of acidic products *II* already before the acid hydrolysis (Scheme 1).



I

II

In formulae *I*, *II*:
a, R = H
b, R = CH_3
c, R = NH_2

SCHEME 1

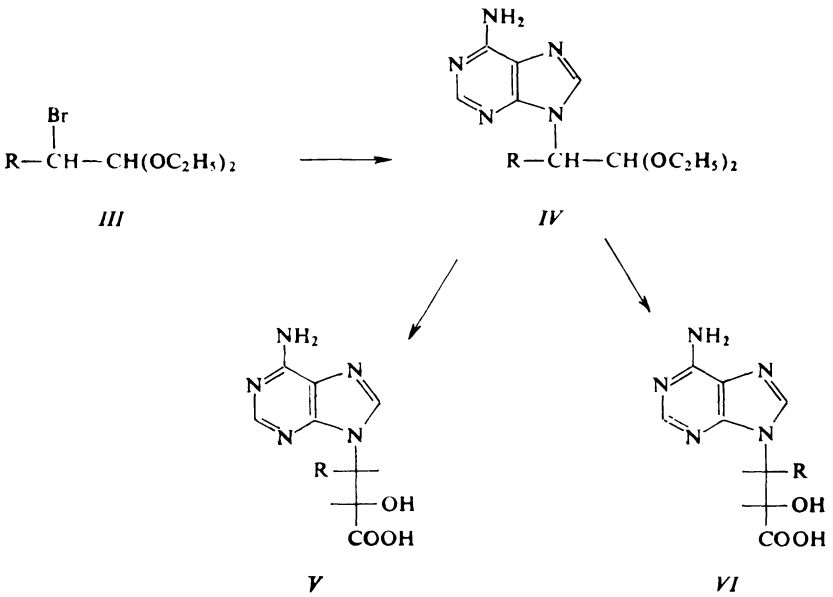
This synthesis can easily be carried out on a large scale as a simple one-flask synthesis. It gives good yields and affords chromatographically (HPLC) pure products *II* which can be isolated either as the free acids by direct crystallization of crude reaction mixture, or by deionization and chromatography on anion-exchange resins (this procedure can be used also for processing of mother liquors after crystallization of the main portion of compound *II* from the reaction mixture).

The mentioned compounds have been characterized by their mass and UV spectra (similar to those of the corresponding 9-alkyladenines). The free acids *II* have a zwitter-ionic character and are sparingly soluble in water, whereas the solubility of their ammonium or alkali metal salts is very good. In weakly alkaline solutions, the

electrophoretic mobility of these compounds corresponds to their dissociation to the carboxylate anion.

An analogous reaction sequence was used also in the preparation of the homologous compounds *V*, derived from higher alkanoic acids. In this case, the starting 2-bromo-1,1-diethoxyalkane *III* was prepared by bromination of the corresponding alkanal and *in situ* reaction with ethanol. The reaction of the compound *III* with adenine proceeds better in the presence of potassium carbonate than with the sodium salt of adenine, generated prior to the reaction. Anyway, the yield of the derivative *IV* is markedly lower than in the reaction of the bromoacetaldehyde derivative, undoubtedly due to a concurrent β-elimination in compound *III*. Attempts to perform this condensation in the phase-transfer arrangement[8,9] completely failed; however, attempted analogous reaction of bromoacetaldehyde diethyl acetal was also unsuccessful.

Further synthetic path is analogous to that shown in Scheme 1: the isolated intermediates *IV* are first cleaved with dilute mineral acid, treated with cyanide and finally subjected to acid hydrolysis to give the corresponding 3-(adenin-9-yl)-2-hydroxyalkanoic acids. Because of substitution in the position 3, the obtained product consists of the racemic *erythro*- and *threo*-isomers (*V*, *VI*). These stereoisomers can be separated by HPLC, in the case of methyl derivatives even by paper chromatography. As shown by ^{1}H NMR spectra, *threo*-isomers *V* predominate in the products (Scheme 2).



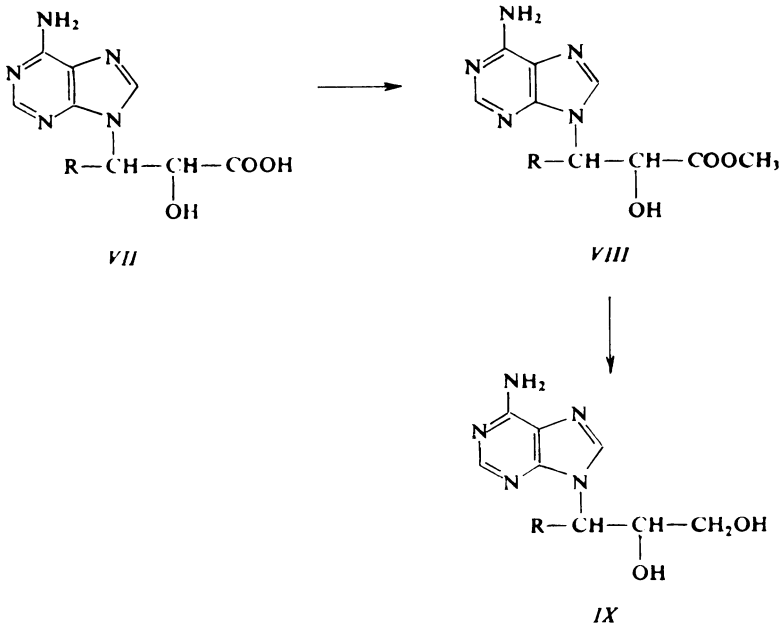
In formulae *III*—*VI*; *a*, R = CH_3; *b*, R = $CH_3(CH_2)_4CH_2$.

SCHEME 2

Electrophoretic properties and UV spectra of the obtained homologous 3-(adenin-9-yl)-2-hydroxyalkanoic acids *V* and *VI* are similar to those of the parent compound *II*. Moreover, their structure was confirmed by mass and ^{1}H NMR spectra.

We can thus conclude that the cyanohydrin synthesis, starting from 2-(adenin-9-yl)-1,1-dialkoxyalkanes, represents a general method of synthesis of 3-(adenin-9-yl)-2-hydroxyalkanoic acids *VII* (*V*, *VI*).

One of the possible synthetic utilizations of these compounds consists in their transformation into 3-(adenin-9-yl)alkane-1,2-diols *IX* (Scheme 3). Sulfuric acid-



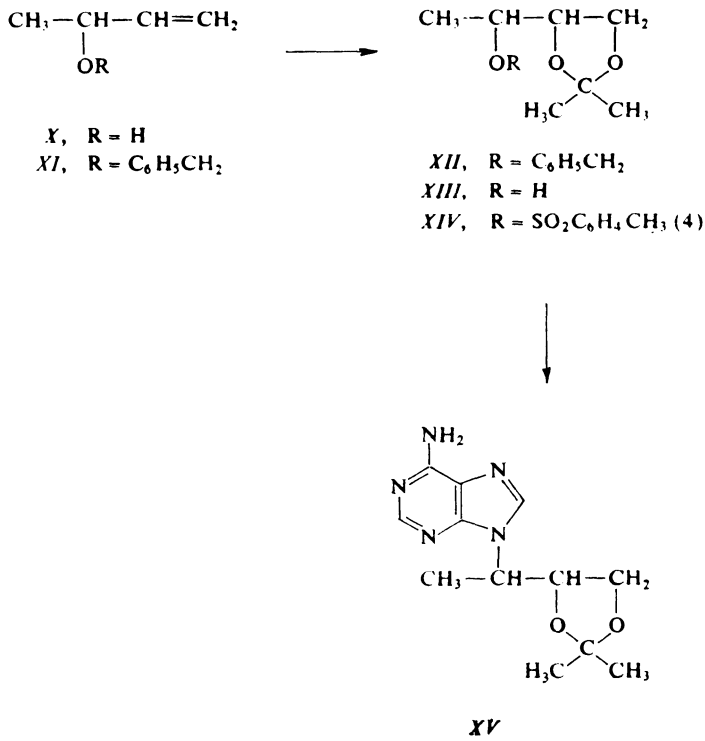
In formulae *VII*—*IX*; *a*, R = H; *b*, R = CH_3; *c*, R = $CH_3(CH_2)_4CH_2$.

SCHEME 3

-catalyzed esterification of free carboxylic acids *VII* with methanol affords smoothly the corresponding methyl esters *VIII*; the inorganic acid can be removed from the reaction mixture *e.g.* by a weakly alkaline anion-exchange resin; however, neutralization with triethylamine followed by desalting by chromatography on a column of octadecyl-silica gel proved to be the method of choice. In ethanolic or aqueous-ethanolic solution, the obtained methyl esters *VIII* are converted into the corresponding substituted alkane-1,2-diols *IX* by reduction with sodium borohydride. Thus, compound *VIIa* (*IIa*) was transformed into 9-(*RS*)-(2,3-dihydroxypropyl)-adenine (*IXa*), identical with an authentic[10] material, compounds *VIIb* and *VIIc*

were converted into the homologues *IXb* and *IXc*. Structures of these compounds and the intermediates *VIII* were verified by mass and ^{1}H NMR spectroscopy. The ratio of the *erythro* and *threo* isomers in compounds *IXb* and *IXc* corresponds to the ratio of the carboxylic acids *V* and *VI* or their methyl esters *VIII*. The substituted *erythro*-butane-1,2-diol derivative *IXb* was recently synthesized by building the adenine base from 3-amino-1,2-butanediol[11]; our synthesis represents thus an alternative preparation of this compound as well as of its *threo*-isomer.

In order to find another way leading to compounds *IX* (R ≠ H) (possibly resulting in another ratio of their diastereoisomers) we investigated also the synthetic route, depicted in Scheme 4. 1-Buten-2-ol (*X*) was converted into the benzyl ether *XI*



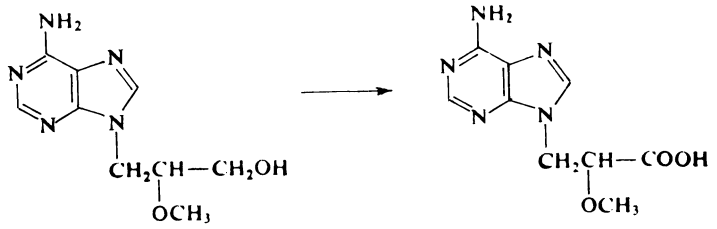
XV

SCHEME 4

which then upon hydroxylation with osmium tetroxide and reaction with acetone gave the dioxolane derivative *XII*. After hydrogenolytic removal of the benzyl protecting group in a neutral medium, the obtained 2,2-dimethyl-4-(2-hydroxyethyl)-1,3-dioxolane (*XIII*) was transformed into the 4-toluenesulfonyl derivative *XIV*. However, nucleophilic substitution reaction of *XIV* with sodium adenate

in dimethylformamide gave only very poor yields of product. This route was therefore abandoned, although it would lead to a product rich in the *erythro*-isomer *IXb*, since the compound *XV* (and therefore also the *p*-toluenesulfonate *XIV*) represents a 1 : 2 *erythro-threo* mixture and the nucleophilic substitution of the *p*-toluenesulfonate *XIV* proceeds with configurational inversion.

For the investigations of structure-activity relationships we prepared further analogues of the carboxylic acids *II* and *VII*, modified in the aliphatic chain. 9-(*RS*)-(3-Hydroxy-2-methoxypropyl)adenine[5] (*XVI*) was oxidized with sodium periodate in the presence of ruthenium catalyst to give 3-(adenin-9-yl)-2-methoxypropanoic acid (*XVII*) (Scheme 5).

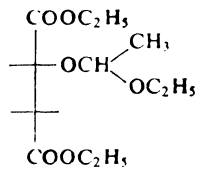


XVI *XVII*

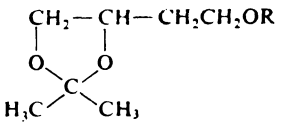
SCHEME 5

The homologous 4-(adenin-9-yl)-3-hydroxybutanoic acid (*XXVII*) was prepared in one of its enantiomeric forms by the reaction sequence shown in Scheme 6: (4*S*)-2,2-dimethyl-4-(2-hydroxyethyl)-1,3-dioxolane *XIX*, prepared from diethyl L-malate[5] *via* its 2-O-(1-ethoxyethyl) derivative *XVIII* by a modified procedure, was benzoylated and the obtained derivative *XX* was subjected to acid hydrolysis to give (2*S*)-4-O-benzoyl-1,2,4-butanetriol (*XXI*). Its reaction with *p*-toluenesulfonyl chloride, followed by protection of the remaining hydroxyl by addition of 3,4-dihydropyrane, afforded the completely protected derivative *XXIII*. Condensation of this compound with sodium adenate gave 9-(2*S*)-(4-benzoyloxy-2-tetrahydropyranyloxybutyl)adenine (*XXIV*) the structure of which was proved by the ^{1}H NMR spectrum and also by methanolysis leading to the monosubstituted 9-(2*S*)-(2,4-dihydroxybutyl)adenine (*XXV*). Acid hydrolysis of *XXV* gave 9-(2*S*)-(2,4-dihydroxybutyl)adenine (*XXVI*) whereas its ruthenium-catalyzed oxidation with sodium periodate followed by acid hydrolysis led to 4-(adenin-9-yl)-3-(*S*)-hydroxybutanoic acid (*XXVII*) (Scheme 6).

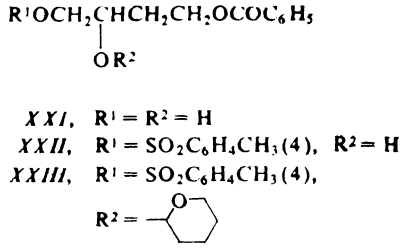
(*RS*)-4-(Adenin-9-yl)-3-hydroxypentanoic acid (*XXIX*), which is a homologue of the acid *XXVII*, was obtained from the acetal *IVa* by reaction with malonic acid in water (Scheme 7). In this case, malonic acid reacts with 2-(adenin-9-yl)propanal to give primarily 4-(adenin-9-yl)-2-pentanoic acid (*XXVIII*) which on addition of wa-



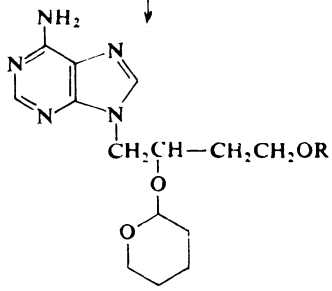
XVIII



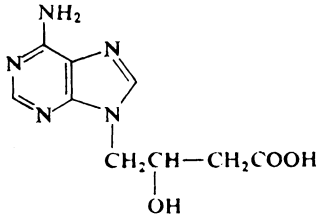
XIX, R = H
XX, R = C_6H_5CO



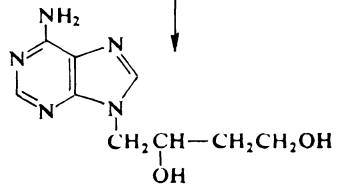
XXI, $R^1 = R^2 = H$
XXII, $R^1 = SO_2C_6H_4CH_3(4)$, $R^2 = H$
XXIII, $R^1 = SO_2C_6H_4CH_3(4)$,



XXIV, R = C_6H_5CO
XXV, R = H

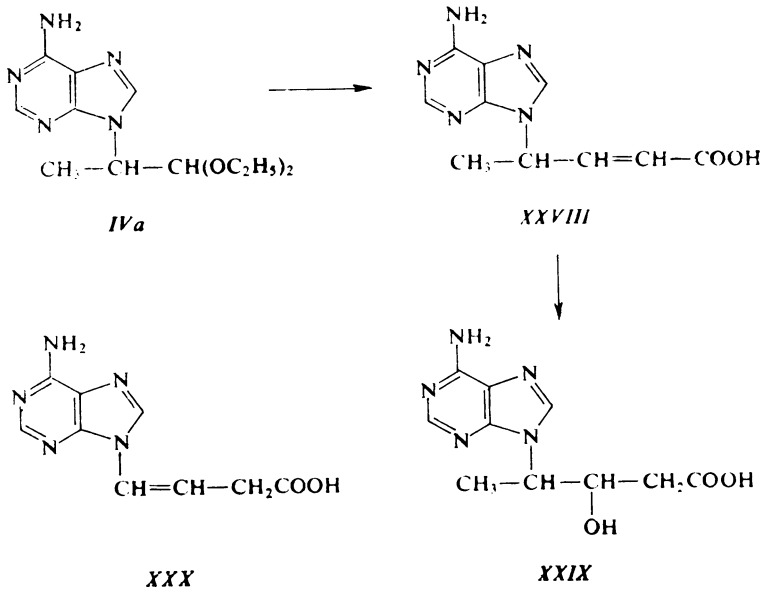


XXVII



XXVI

SCHEME 6



SCHEME 7

ter is converted into the β-hydroxy acid *XXIX*. The structure of *XXIX* was confirmed by the presence of the corresponding molecular peak in its mass spectrum and by the absence of a double bond in the product. In the light of this finding we can interpret also the previously described[4] anomalous condensation of malonic acid with 9-(2,2-diethoxyethyl)adenine, leading to 4-(adenin-9-yl)-3-butenoic acid (*XXX*). It cannot be excluded that also in this case the normal condensation product (2-butenoic acid derivative) may temporarily add water to form an adduct which may subsequently undergo a β,γ-elimination reaction leading to the insoluble compound *XXX*, or an α,β-elimination to give 2-butenoic acid which returns into the reaction cycle. Since in the case of compound *XXVIII* the equilibrium is not shifted by separation of one of the products from the reaction mixture, we can isolate the product of water addition *i.e.* the compound *XXIX*, as the sole reaction product.

EXPERIMENTAL

Melting points were determined on a Kofler block and are uncorrected. Unless otherwise stated, the solutions were evaporated at 40°C/2 kPa and the compounds were dried at 13 Pa over phosphorus pentoxide. Paper chromatography was carried out on a paper Whatman No 2 in the system S1 2-propanol–conc. aqueous ammonia–water (7 : 1 : 2), thin-layer chromatography on silica gel (Silufol UV 235, Kavalier, Czechoslovakia) in system S2 chloroform, S3 chloroform–methanol (9 : 1), S4 chloroform–methanol (17 : 3), S5 chloroform–methanol (4 : 1), S6 chloro-

form–ethanol (9 : 1), S7 benzene, S8 benzene–ethyl acetate (9 : 1), S9 benzene–ethyl acetate (7 : 3). Electrophoresis was performed on a paper Whatman No 3MM in the system E1, 0·05 mol . $.l^{-1}$ triethylammonium hydrogen carbonate, pH 7·5, at 20 V/cm (1 h). The electrophoretical mobilities are related to uridine 3′-phosphate. Preparative chromatography on silica gel (Silpearl, Kavalier, Czechoslovakia) was carried out either on columns or on loose layers (40 × 15 × × 0·3 cm), preparative chromatography on a column (80 × 4 cm) of Macheray & Nagel microcrystalline cellulose in the system S1 (20 ml/h); continuous detection with a Uvicord apparatus (LKB, Sweden). The adenine derivatives were deionized on columns of Dowex 50X8 (H^+-form) by washing with water to disappearance of conductivity and UV-absorption, and subsequent elution with 2% aqueous ammonia.

UV absorption spectra were taken in aqueous solutions on a Specord UV-VIS (Carl Zeiss, Jena, GDR) spectrometer, ^1H NMR spectra on a Varian 200 instrument in deuteriochloroform or hexadeuteriodimethyl sulfoxide (with hexamethyldisiloxane as internal standard); chemical shifts are given in ppm and coupling constants in Hz. High performance liquid chromatography was carried out on 3·3 × 150 mm columns of Separon SIX C18 (5 μ) (Laboratorní přístroje, Prague) in 0·1 mol l^{-1} triethylammonium hydrogen carbonate, pH 7·5, containing following amounts of methanol (wt/wt): S10, 5%; S11, 50%. Flow rate 0·4 ml/min at room temperature, detection at 254 nm by an LCD 254 instrument with EZ 11 recorder (Laboratorní přístroje, Prague).

9-(2,2-Diethoxyethyl)adenine (*Ia*) was prepared according to a previously described procedure[4]; R_F = 0·80 (S1), 0·60 (S4), 0·70 (S5).

9-(2,2-Diethoxyethyl)-2-methyladenine (*Ib*)

Sodium hydride (0·24 g; 10 mol) was added to a suspension of 2-methyladenine (1·50 g; 10 mmol) in dimethylformamide (50 ml) and the mixture was stirred at 80°C for 1 h under calcium chloride protecting tube. After addition of bromoacetaldehyde diethyl acetal (2·5 ml), the clear solution was heated to 100°C for 6 h. Another portion of the bromo acetal (1 ml) was added and the heating was continued for further 4 h. The mixture was taken down at 60C°/13 Pa, the residue extracted with boiling chloroform (4 × 100 ml), the extract filtered through Celite and the filtrate evaporated *in vacuo*. The residue was purified by chromatography on two plates of silica gel in the system S3, the product bands (R_F 0·65 in S4) were eluted with methanol (300 ml), and after evaporation the product was crystallized from ethyl acetate (light petroleum added until turbid). Yield 1·05 g (39·5%) of *Ib*, m.p. 155°C. For $C_{12}H_{19}N_5O_2$ (265·3) calculated: 54·32% C, 7·22% H. 26·40% N; found: 54·47% C, 7·28% H, 26·27% N. Mass spectrum: 265 (M^+), 236 ($M-C_2H_5$), 221 ($M-C_2H_4O$), 220 ($M-C_2H_5O$), 162 (BCH_2)*, 149 (BH). UV spectrum (methanol): λ_{max} 264 nm (ε_{max} 13 100); λ_{min} 230 nm. R_F = 0·65 (S4).

9-(2,2-Diethoxyethyl)-2-aminoadenine (*Ic*)

The reaction was performed with 2-aminoadenine (1·5 g; 10 mmol) as described for compound *Ib*. Purification by chromatography on silica gel and crystallization from ethyl acetate–light petroleum gave 1·60 g (60%) of compound *Ic*, m.p. 147–149°C. For $C_{11}H_{18}N_6O_2$ (266·3) calculated: 49·61% C, 6·81% H, 31·56% N; found: 49·80% C, 6·84% H, 31·37% N. Mass spectrum: 266 (M^+), 237 ($M-C_2H_5$), 222 ($M-C_2H_4O$), 221 (C_2H_5O), 163 (BCH_2), 150 (BH). UV spectrum (methanol): λ_{max} 256 nm (ε_{max} 7 600); 282 nm (ε_{max} 8 600); λ_{min} 238, 267 nm. R_F = 0·44 (S4).

* B denotes the heterocyclic base residue.

(*RS*)-3-(Adenin-9-yl)-2-hydroxypropanoic Acid (*IIa*)

A mixture of compound *Ia* (60 g; 0·24 mol), water (1 200 ml) and conc. hydrochloric acid (32 ml) was heated under reflux for 4 h until the reaction was complete (S4). After cooling to −5°C (ice–salt mixture), sodium cyanide (60 g; 1·224 mol) was added under stirring, the mixture was rapidly adjusted to pH 6—6·5 with acetic acid and stirred at 0°C for 5 h and at room temperature overnight. Concentrated hydrochloric acid (800 ml) was added, the mixture was refluxed for 6 h, cooled, and taken down *in vacuo*. The residue was codistilled with water (5 × 300 ml), mixed with water (300 ml) and filtered. The solid was washed with ice-cold water, acetone and dried *in vacuo*, yielding 40·3 g (74·7%) of compound *IIa*, chromatographically (S1, S9) as well as electrophoretically (E1) homogeneous, purity >95%. An analytical sample was crystallized from water and did not melt below 260°C. For $C_8H_9N_5O_3$ (223·2) calculated: 43·05% C, 4·06% H, 31·38% N; found: 43·25% C, 4·11% H, 31·40% N. UV spectrum (pH 2): λ_{max} 261 nm (ε_{max} 13 500), λ_{min} 232 nm. The product is identical (S1, S9, E1) with an authentic[4,5] sample; $R_F = 0·39$ (S1), $E_{Up} = 0·58$ (E1).

(*RS*)-3-(2-Methyladenin-9-yl)-2-hydroxypropanoic Acid (*IIb*)

A solution of compound *Ib* (1 g; 3·77 mmol) in 0·25M-H_2SO_4 (40 ml) was heated to 70°C for 6 h till the reaction was complete (S4), cooled with ice and neutralized with 4M-LiOH. Sodium cyanide (1 g) was added under cooling with ice, the mixture was immediately adjusted with acetic acid to pH 6—6·5, stirred at 0°C for 2 h and at room temperature overnight and refluxed with concentrated hydrochloric acid (10 ml) for 3 h. After evaporation *in vacuo*, the residue was codistilled with water (3 × 100 ml), dissolved in water (20 ml) and deionized on a column of Dowex 50 (300 ml; *vide supra*). The ammonia eluate was taken down *in vacuo*, the residue was dissolved in water (20 ml), the solution was adjusted to pH 9 with ammonia and applied on a column of Dowex 1X2 (acetate, 100 ml). The column was washed with water until the UV-absorption and conductivity of the eluate dropped, the ion-exchange resin was suspended in 1M formic acid (500 ml), filtered off and washed with boiling water (1 litre). The combined filtrates were taken down *in vacuo* and the residue was again chromatographed on a column (25 ml) of the same ion exchanging resin with a gradient (0—1 mol l^{-1}; à 1 litre) of acetic acid. The product-containing fraction was evaporated, the residue codistilled three times with water, with ethanol, and crystallized from 50% aqueous ethanol (ether added to turbidity), yielding 0·65 g (72·7%) of *IIb*, m.p. 260°C (dec.). For $C_9H_{11}N_5O_3$ (237·2) calculated: 45·56% C, 4·67% H, 29·53% N; found: 45·70% C, 4·71% H, 29·67% N. UV spectrum (pH 2, pH 7): λ_{max} 263 nm (ε_{max} 12 600); (pH 12): λ_{max} 264 nm (ε_{max} 13 200). $R_F = 0·42$ (S1), $E_{Up} = 0·54$ (E1).

(*RS*)-3-(2-Aminoadenin-9-yl)-2-hydroxypropanoic Acid (*IIc*)

The title compound was prepared from compound *Ic* (1·07 g; 4 mmol) as described for compound *IIb*. Chromatography on Dowex 1X2 followed by crystallization from 50% aqueous ethanol gave 0·65 g (68%) of *IIc*, m.p. 235°C. For $C_8H_{10}N_6O_3$ (238·2) calculated: 40·33% C, 4·23% H, 35·29% N; found: 40·60% C, 4·17% H, 35·08% N. UV spectrum (pH 2): λ_{max} 246 (ε_{max} 9 000), 290 nm (7 600); (pH 12): λ_{max} 256 nm (8 000), 278 nm (8 400). $R_F = 0·20$ (S1), $E_{Up} = 0·46$ (E1).

2-Bromo-1,1-diethoxypropane (*IIIa*)

Bis-azaisobutyronitrile (0·1 g) was added to a solution of freshly distilled propanal (162·5 g; 2·8 mol) in dry ethyl acetate (800 ml). A solution of bromine (126 ml; 2·47 mol) in ethyl acetate

(200 ml) was added under stirring and cooling (ice–salt mixture) at such a rate to maintain the temperature between −3° and 0°C. After further stirring at −5°C for 15 min, 99% ethanol (1 200 ml) was added dropwise so as to keep the temperature below +5°C. The mixture was stirred at 0°C for 2 h, set aside overnight, concentrated to 1 litre and poured into a solution of potassium carbonate (500 g) in water (500 ml). The organic layer was taken up in ether (1 litre), washed with saturated solution of sodium hydrogen carbonate (2 × 100 ml), water (2 × 100 ml), and dried over magnesium sulfate. After evaporation of the solvent *in vacuo*, the product *IIIa* was distilled, b.p. 68–70°C/2 kPa (reported[12,13] b.p. 78–79°C/2·6 kPa); yield 307 g (52%).

2-Bromo-1,1-diethoxyoctane (*IIIb*)

A solution of bromine (34 ml; 0·66 mol) in ethyl acetate (100 ml) was added dropwise to a cooled (ice) and stirred solution of octanal (87 g; 0·68 mol) in ethyl acetate (300 ml), the temperature being maintained below +4°C (about 1 h). After stirring for 30 min at 0°C, absolute ethanol (300 ml) was added at a temperature below 5°C. After stirring overnight at room temperature, the mixture was diluted with water (1200 ml) and extracted with ether (1 litre). The ethereal solution was washed with water, saturated sodium hydrogen carbonate solution, and again with water, dried over magnesium sulfate and taken down *in vacuo*. Distillation at 124–128°C : : 2 kPa gave 130 g (68%) of *IIIb*. For $C_{12}H_{25}BrO_2$ (281·3) calculated: 51·24% C, 8·96% H, 28·43% Br; found: 51·32% C, 9·02% H, 28·16% Br. Mass spectrum: 280 (M^+), 251 ($M-C_2H_5$), 235 ($M-C_2H_5OH$), 200 ($M-HBr$), 155 (235 − HBr), 103 ($(C_2H_5O)_2CH^+$).

(*RS*)-2-(Adenin-9-yl)-1,1-diethoxypropane (*IVa*)

A solution of compound *IIIa* (25·3 g; 0·12 mol) in dimethylformamide (20 mol) was added during 1 h at 150°C to a magnetically stirred mixture of adenine (13·5 g; 0·1 mol), potassium carbonate (15 g; 0·11 mol) and dimethylformamide (200 ml). After refluxing for 14 h with stirring, compound *IIIa* (5 g) was added and the refluxing was continued for 6 h. The mixture was filtered while hot, the salts were washed with dimethylformamide (50 ml) and the filtrate was taken down *in vacuo*. The residue was extracted with chloroform (1 litre total), the extract was filtered through Celite, taken down and the residue was applied on a column of silica gel (150 g) in chloroform (*vide supra*). After washing with chloroform (1 litre), the product was eluted with chloroform–ethanol (95 : 5). The combined product fractions were taken down and the product was crystallized from ethyl acetate–light petroleum; yield 4·6 g (19·6%) of *IVa*; m.p. 125°C. For $C_{12}H_{19}N_5O_2$ (265·3) calculated: 54·32% C, 7·22% H, 26·40% N; found: 54·50% C, 7·30% H, 26·52% N. UV spectrum (methanol): λ_{max} 261 nm (ε_{max} 13 400). R_F = 0·60 (S5).

(*RS*)-2-(Adenin-9-yl)-1,1-diethoxyoctane (*IVb*)

Compound *IIIb* (81·7 g; 0·29 mol) was added dropwise at 120°C during 1 h to a stirred mixture of adenine (33·8 g; 0·25 mol), potassium carbonate (45 g; 0·33 mol) and dimethylformamide (500 ml). After stirring at 120–130°C for 17 h, the hot mixture was filtered, the salts were washed with dimethylformamide (100 ml) and the filtrate was taken down at 60°C *in vacuo*. The residue was codistilled with toluene (3 × 200 ml), extracted with boiling chloroform (1 litre total) and the extract was filtered through Celite. Evaporation of the filtrate, purification on a silica gel column (300 g) as described for *IVa* and crystallization from ethyl acetate–light petroleum afforded 8 g (9·5%) of *IVb*, m.p. 108–111°C. For $C_{17}H_{29}N_5O_2$ (335·5) calculated: 60·86% C, 8·72% H, 20·88% N; found: 61·04% C, 8·77% H, 21·02% N. Mass spectrum: 335 (M^+), 290 ($M-C_2H_5O$), 239 ($M-C_2H_5OH$), 260 (289 − C_2H_5), 244 (289 − C_2H_5O), 136 (BH), 135 (B). UV spectrum (methanol): λ_{max} 261 nm (ε_{max} 13 500). R_F = 0·40 (S6).

Attempted phase-transfer reaction: A solution of compound *IIIb* (1·55 g; 5·5 mmol) in 1,2-dimethoxyethane (50 ml) was added with stirring to a boiling mixture of adenine (0·67 g; 5 mmol); tetrabutylammonium phosphate (0·50 g) and 50% aqueous potassium hydroxide (50 ml). Chromatography in S3 did not detect any *IVb* even after 8 h.

(*RS*)-3-(Adenin-9-yl)-2-hydroxybutanoic Acid (*Va*, *VIa*)

A mixture of compound *IVa* (13 g; 55 mmol), water (275 ml) and conc. hydrochloric acid (7·5 ml) was stirred at 90°C till the reaction was complete (S3). After cooling with ice, sodium cyanide (15 g; 0·31 mol) was added, the mixture was neutralized with acetic acid and stirred at 0°C for 4 h and (in stoppered bottle) at room temperature overnight. The mixture was refluxed with conc. hydrochloric acid (150 ml) for 6 h, evaporated, the residue was codistilled with water *in vacuo* (4 × 200 ml), dissolved in water (100 ml) and applied on a column of Dowex 50X8 (H^+-form, 1 litre). After deionization (*vide supra*) the ammonia eluate was taken down, applied in water (pH 9) on a column of Dowex 1X2 (acetate; 400 ml) which was then washed with water until the eluate lost its UV absorption and conductivity. The Dowex was stirred with 2M formic acid (1 litre) for 2 h, filtered, washed with boiling water (1 litre) and the combined filtrates were taken down. The residue was codistilled with water (3 × 200 ml) and crystallized from water, affording 9·9 g (75·9%) of compound *Va*, *VIa*, melting point higher than 260°C. According to spectrophotometric measurement of the spots in chromatography in S1 and HPLC in S10, *Va* : *VIa* = = 3 : 2. For $C_9H_{11}N_5O_3$ (237·2) calculated: 45·56% C, 4·67% H, 29·53% N; found: 45·79% C, 4·68% H, 29·41% N. Mass spectrum: 237 (M^+), 192 (M−COOH), 162 (M−CH(OH)COOH), 136 (BH), 135 (B). UV spectrum (pH 2): λ_{max} 261 nm (ε_{max} 14 200), *Va*, R_F = 0·41 (S1), E_{Up} = = 0·57 (E1); *VIa*, R_F = 0·55 (S1), E_{Up} = 0·57 (E1).

(*RS*)-3-(Adenin-9-yl)-2-hydroxynonanoic Acid (*Vb*, *VIb*)

A mixture of compound *IVb* (6·5 g; 19·4 mmol), dioxane (70 ml) and 1M-H_2SO_4 (70 ml) was heated to 70°C till the reaction was complete (24 h; detection by chromatography in S3). After neutralization with 5M-LiOH to pH 4 and cooling with ice, sodium cyanide (6 g) was added, followed by acetic acid (to pH 6—6·5). The mixture was stirred in a stoppered bottle at room temperature overnight, boiled with conc. hydrochloric acid (100 ml) for 7 h and taken down *in vacuo*. The residue was codistilled with water (4 × 200 ml) and applied on a column of Dowex 50X8 (H^+-form; 400 ml). The column was washed with 20% aqueous methanol (2 l) and the resin was suspended in 20% aqueous methanol (600 ml). The suspension was made alkaline (pH 10) with triethylamine and stirred for 1 h the pH being kept between 9—10 with triethylamine. The resin was filtered off, washed with 20% aqueous methanol (2 l) and the filtrate was taken down *in vacuo*. A solution of the residue in 20% methanol (50 ml) was adjusted to pH 10 with triethylamine and applied on a column of Dowex 1X2 (acetate; 250 ml). After washing with 20% aqueous methanol until the UV-absorption disappeared, the Dowex was suspended in 1M formic acid (500 ml), the suspension was stirred for 1 h, filtered and washed with boiling 0·25M formic acid (1 litre) and methanol (500 ml) and the combined filtrates were taken down *in vacuo*. The residue was codistilled with water (3 × 100 ml) and crystallized from water, affording 3·8 g (63·8%) of the compound *Vb*, *VIb*, m.p. 234—235°C. For $C_{14}H_{21}N_5O_3$ (307·4) calculated: 54·70% C, 6·89% H, 22·79% N; found: 54·75% C, 6·92% H, 22·93% N. Mass spectrum: 307 (M^+), 262 (M−COOH), 232 (M−CH(OH)COOH), 178 (M−COOH−C_6H_{12}), 162 (232 − C_5H_{10}), 136 (BH_2), 135 (BH). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide: *Vb*: 4·47 (d, 1 H, $J_{2',3'}$ = 4·7) $H_{2'}$; 8·14 (s, 1 H) H_8; *VIb*: 4·29 (d, 1 H, $J_{2',3'}$ = 4·7) $H_{2'}$; 8·16 (s, 1 H) H_8; for both isomers: 4·82 (pent, 1 H, $J_{3',4'}$ = 4·7, $J_{3',4''}$ = 9·4) $H_{3'}$; 7·21 (br, 1 H)

NH_2; 8·12 (s, 1 H) H_2; 1·75—2·10 (m, 2 H); 1·15 (center, m, 8 H); 0·79 (center, m, 3 H). Ratio *Vb* : *VIb* = 73 : 27. UV spectrum (pH 2, 7, 12): λ_{max} 262 nm (ε_{max} 13 800). *Vb*, R_F = 0·63 (S1), E_{Up} = 0·50 (E1); *VIb*, R_F = 0·74 (S1), E_{Up} = 0·50 (E1).

Methyl (*RS*)-3-(Adenin-9-yl)-2-hydroxypropanoate (*VIIIa*)

A mixture of compound *IIa* (6·7 g; 30 mmol), methanol (300 ml) and conc. sulfuric acid (3 ml) was refluxed for 4 h under calcium chloride protecting tube, cooled with ice, neutralized with triethylamine and taken down *in vacuo*. The residue was dissolved in water (100 ml), applied on a column of silica gel SI C18 (500 ml) and eluted with water (5 ml/min), the elution course being followed by monitoring the conductivity and UV-absorption. After removal of salts (first part of the eluate), water eluted the chromatographically pure ester *VIIIa*. The eluate was taken down *in vacuo*, the residue was codistilled with methanol, mixed with acetone, filtered, washed with acetone and dried *in vacuo*, affording 5·7 g (80%) of compound *VIIIa*, m.p. 196—198°C, identical (S4, S6) with an authentic material[4]. For $C_9H_{11}N_5O_3$ (237·2) calculated: 45·56% C, 4·67% H, 29·53% N; found: 45·72% C, 4·70% H, 29·62% N. UV-spectrum (methanol): λ_{max} 262 nm (ε_{max} 13 700). Mass spectrum: 237 (M^+), 178 (M—CH_3OCO), 148 (M—CH(OH).$COOCH_3$), 135 (BH). R_F = 0·32 (S5), 0·12 (S6).

Methyl (*RS*)-3-(Adenin-9-yl)-2-hydroxybutanoate (*VIIIb*)

A mixture of compound *VIIb* (3·5 g; 15 mmol; stereoisomeric mixture of *Va* + *VIa*), methanol (200 ml) and conc. sulfuric acid (2 ml) was refluxed for 3 h, poured into a suspension of Amberlite IR 45 (50 ml) in methanol (200 ml), stirred until neutral and filtered. The resin was washed with methanol, the filtrate taken down *in vacuo* and the residue chromatographed on a column of silica gel (200 g) in chloroform–methanol (95 : 5). The product fractions were evaporated and the residue was crystallized from ethyl acetate–light petroleum; yield 2·8 g (74%) of *VIIIb*, m.p. 143—144°C. For $C_{10}H_{13}N_5O_3$ (251·3) calculated: 47·80% C, 5·21% H, 27·88% N; found: 47·95% C, 5·20% H, 28·10% N. Mass spectrum: 251 (M^+), 236 (M—CH_3), 220 (M—OCH_3), 192 (M—$COOCH_3$), 162 (M—CH(OH)$COOCH_3$), 136 (BH_2), 135 (BH). ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): *threo* 1·54 (d, 3 H, $J_{CH_3,2'}$ = 7·5) 4′-CH_3; 3·54 (s, 3 H) $COOCH_3$; 4·55 (dd, 1 H; $J_{2',3'}$ = 5·1, $J_{2',OH}$ = 5·5) $H_{2'}$; 4·92 (dq, 1 H, $J_{2',3'}$ = 5·1, $J_{3',4'}$ = 7·4) $H_{3'}$; 6·16 (d, 1 H) OH; *erythro* 1·51 (d, 3 H, $J_{CH_3,2'}$ = 7·3) 4′-CH_3; 3·61 (s, 3 H) $COOCH_3$; 4·46 (dd, 1 H, $J_{2',3'}$ = 5·0, $J_{2',OH}$ = 6·2) $H_{2'}$; 4·95 (dq, 1 H, $J_{2',3'}$ = 5·4, $J_{3',4'}$ = 7·2) $H_{3'}$; 6·12 (d, 1 H) OH; common: 7·21 (br, 2 H) NH_2; 8·12 (s, 1 H) H_2; 8·15 (s, 1 H) H_8; *threo* : *erythro* = 3 : 2. UV spectrum (pH 2): λ_{max} 261 nm (ε_{max} = 13 700). R_F = 0·40 (S5), 0·17 (S6).

Methyl (*RS*)-3-(Adenin-9-yl)-2-hydroxynonanoate (*VIIIc*)

A mixture of compound *VIIc* (mixture of *Vb* + *VIb*) (1·40 g; 4·56 mmol), methanol (100 ml) and sulfuric acid (1 ml) was processed as described for the preparation of compound *VIIIb*. The residue after evaporation of the eluate was purified on two plates of silica gel in the system S5, the product bands were eluted with methanol (500 ml) and the residue was crystallized from methanol and ether, yielding 1·20 g (82%) of *VIIIc*, m.p. 201—202°C. For $C_{15}H_{23}N_5O_3$ (321·4) calculated: 56·05% C, 7·21% H, 21·80% N; found: 56·12% C, 7·25% H, 21·87% N. ^{1}H NMR spectrum (deuteriochloroform + hexadeuteriodimethyl sulfoxide): *threo* 3·49 (s, 3 H) $COOCH_3$; 4·54 (brt, 1 H, $J_{2',3'}$ = 4·0, $J_{2',OH}$ = 5·0) $H_{2'}$; *erythro* 3·65 (s, 3 H) $COOCH_3$; 4·41 (brt, 1 H, $J \sim 5{\cdot}0$) $H_{2'}$; common 0·82 (m, 3 H); 1·20 (m, 8 H); 1·80—2·20 (m, 2 H); 4·85 (dq, 1 H, $J_{2',3'}$ = = 3·7; $J_{3',4'}$ = 5·6, $J_{3',4''}$ = 9·8) $H_{3'}$; 6·16 (d, 1 H, $J_{2',OH}$ = 6·3) OH; 7·09 (brd, 2 H) NH_2; 8·12 (s, 1 H) H_2; 8·17 (s, 1 H) H_8. After reaction with deuterioacetic acid: *threo* 3·50 (s, 3 H)

$COOCH_3$; 4·56 (d, 1 H, $J_{2',3'} = 3·7$) $H_{2'}$; 4·92 (dq, 1 H) $H_{3'}$; *erythro*: 3·66 (s, 3 H) $COOCH_3$; 4·43 (d, 1 H, $J_{2',3'} = 4·5$) $H_{2'}$; 4·92 (dq, 1 H) $H_{3'}$; *threo* : *erythro* = 85:15. UV spectrum (pH 2): λ_{max} 261 nm (ε_{max} 13 100). $R_F = 0·48$ (S4), 0·74 (S5).

9-(*RS*)-(2,3-Dihydroxypropyl)adenine (*IXa*)

A solution of sodium borohydride (1·2 g) in ethanol (60 ml) was added dropwise at −5°C to a stirred suspension of compound *VIIIa* (2·0 g; 8·44 mmol) in ethanol (120 ml) the temperature being kept below 0°C. The mixture was stirred at 0°C for 2 h and at room temperature overnight and the excess reagent was decomposed by addition of Dowex 50X8 (H^+-form). The mixture was filtered, the resin was washed with methanol (100 ml) and the filtrate was taken down. The residue was dissolved in water (50 ml) and, together with the used Dowex, applied on a column (150 ml) of the same ion exchange resin. The column was washed with water until the conductivity dropped and the product was eluted with 2·5% ammonia. The UV-absorbing eluate was taken down *in vacuo* and the residue was crystallized from water, affording 1·57 g (88·9%) of compound *IXa*, m.p. 207—208°C, identical (S1, S4, S9) with an authentic material[10]. $R_F = 0·57$ (S1), 0·13 (S5).

9-(*RS*)-(1,2-Dihydroxy-3-butyl)adenine (*IXb*)

A suspension of compound *VIIIb* (3·0 g; 12 mmol) in ethanol (150 ml) was treated with a solution of sodium borohydride (1·8 g) in ethanol (100 ml). A work-up procedure, analogous to that for the compound *IXa*, followed by crystallization from 80% aqueous ethanol (ether added to turbidity), afforded 1·90 g (71%) of compound *IXb*, m.p. 216—218°C. For $C_9H_{13}N_5O_2$ (223·2) calculated: 48·42% C, 5·87% H, 31·38% N; found: 48·70% C, 5·96% H, 31·64% N. Mass spectrum: 223 (M^+), 206 (M−OH), 205 (M−H_2O), 192 (M−CH_2OH), 162 (M−$CH(OH)CH_2$.OH), 136 (BH_2), 135 (BH). UV spectrum (pH 2): λ_{max} 262 nm (ε_{max} = 13 200). $R_F = 0·65$ (S1), 0·20 (S5).

9-(*RS*)-(1,2-Dihydroxy-3-nonyl)adenine (*IXc*)

A solution of sodium borohydride (2 g) in ethanol (100 ml) was added dropwise at 0°C to a stirred solution of compound *VIIIc* (2·0 g; 6·2 mmol) in ethanol (100 ml) and the mixture was worked up as described for the preparation of compound *IXa*. The column of the ion exchange resin was washed first with 30% aqueous methanol and the product was eluted with 2·5% ammonia in 30% aqueous methanol. The UV-absorbing ammonia eluate was taken down and the residue was purified by chromatography on 2 plates of silica gel in the system S4. Elution with methanol (500 ml), evaporation of solvent and crystallization from ethanol gave 1·16 g (64%) of compound *IXc*, m.p. 161—163°C. For $C_{14}H_{23}N_5O_2$ (293·4) calculated: 57·31% C, 7·90% H, 23·88% N; found: 57·50% C, 7·48% H, 23·70% N. Mass spectrum: 293 (M^+), 276 (M−OH), 275 (M−H_2O), 262 (M−CH_2OH), 250 (M−C_3H_7), 232 (M−$CH(OH)CH_2OH$), 209 (M−C_6H_{12}), 191 (209−H_2O), 178 (209−CH_2OH), 136 (BH_2), 135 (BH). ^1H NMR spectrum (deuteriochloroform): *erythro*: 3·26 (t, 2 H, $J = 5·6$), $H_{1'}$; 3·82 (br pent, 1 H, $J = 5·9$) $H_{2'}$; 4·70 (t, 1 H, $J_{OH,H_{1'}} = 5·6$) 1′-OH; 5·30 (d, 1 H, $J_{OH,H_{2'}} = 5·6$) 2′-OH; 8·12 (s, 1 H) H_2; *threo*: 3·14 (brt, 2 H) $H_{1'}$; 3·87 (m, 1 H) $H_{2'}$; 4·67 (t, 1 H, $J \sim 6·0$) 1′-OH; 5·27 (d, 1 H, $J \sim 6·0$) 2′-OH; 8·09 (s, 1 H) H_2; common for both isomers: 0·78 (t, 3 H, $J_{8',9'} = 6·8$) $H_{9'}$; 1·14 (m, 8 H) H_5—$H_{8'}$; 2·00 (m, 2 H) $H_{4'}$; 4·57 (m, 1 H) $H_{3'}$; 7·29 (br, 2 H) NH_2; 8·15 (s, 1 H) H_8. UV spectrum (pH 2): λ_{max} 261 nm (ε_{max} 13 500). $R_F = 0·90$ (S1), 0·08 (S3), 0·43 (S4), 0·51 (S5).

2-Benzyloxy-3-butene (*XI*)

A solution of 3-buten-2-ol (*X*; 29·9 g; 0·415 mol) in dimethylformamide (50 ml) was added dropwise at −10°C to a stirred suspension of sodium hydride (10 g; 0·416 mol) in dimethylformamide (250 ml) and the stirring was continued for 1 h at −5°C. Benzyl chloride (52 ml; 0·43 mol) was added dropwise at temperature lower than −5°C, the mixture was stirred at −10°C for 4 h and at room temperature overnight (with exclusion of moisture). After standing for 2 days, the salts were filtered off and washed with dimethylformamide (100 ml). The filtrate was diluted with water (1 litre), extracted with ether (3 × 400 ml), the extract was washed with water (3 × × 100 ml), dried over magnesium sulfate, filtered and taken down. Distillation of the residue at 74−76°C/2 kPa gave 42 g (62·4%) of compound *XI*. For $C_{11}H_{14}O$ (162·2) calculated: 81·44% C, 8·70% H; found: 81·52% C, 8·75% H. Mass spectrum: 162 (M^+). R_F = 0·46 (S7), 0·85 (S8).

4-(1-Benzyloxyethyl)-2,2-dimethyl-1,3-dioxolane (*XII*)

A solution of compound *XI* (42 g; 0·259 mol) in ethanol (150 ml), followed by osmium tetroxide (0·5 g), was added to a solution of sodium chlorate (50 g; 0·47 mol) in water (100 ml) and the mixture was stirred overnight at room temperature. Ethanol was removed *in vacuo* and the residue was extracted with ethyl acetate (3 × 100 ml). The extract was washed with water, dried over magnesium sulfate and taken down *in vacuo*. The residue was codistilled with toluene under diminished pressure (3 × 50 ml), taken up in acetone (150 ml) and mixed with ethyl orthoformate (45 ml). The mixture was acidified with 6M-HCl in dimethylformamide (2 ml) and left to stand overnight at room temperature. The mixture was then made alkaline with triethylamine and taken down *in vacuo*. The residue was dissolved in ether, the solution washed with water (3 × 100 ml) and dried over magnesium sulfate. After evaporation of the solvent the residue was distilled *in vacuo*. The product *XII* was present in the main fraction, b.p. 142−145°C/2 kPa; yield 26·5 g (43·3% related to *XI*). For $C_{14}H_{20}O_3$ (236·3) calculated: 71·16% C, 8·53% H; found: 71·22% C, 8·57% H. Mass spectrum: 236 (M^+). ^{1}H NMR spectrum (deuteriochloroform): *threo*: 1·25 (d, 3 H, J = 6·24) CH_3 (ethyl); 1·35 + 1·41 (2 × s, 2 × 3 H) $(CH_3)_2C$; 3·53 (pent, 1 H, J = 6·3) CH (ethyl); 4·03 (q, 1 H, $J \sim$ 6·0) H_5; *erythro*: 1·12 (d, 3 H, J = 6·35) CH_3 (ethyl); 1·37 + 1·42 (2 × s, 2 × 3 H) $(CH_3)_2C$; 3·60 (pent, 1 H, J = 6·4) CH (ethyl); 4·17 (q, 1 H, J = 6·7) H_5; common for both isomers: 3·70−4·20 (m, 4 H) 2 H_4 + OCH_3; 4·57 (AB-system, J_{gem} = 11·8) $C_6H_5CH_2$; 7·32 (m, 5 H) arom. protons; *threo* : *erythro* ≈ 2 : 1. R_F = 0·40 (S2), 0·13 (S7), 0·52 (S8).

4-[1-(Adenin-9-yl)ethyl]-2,2-dimethyl-1,3-dioxolane (*XV*)

Compound *XII* (26 g; 0·11 mol) in 80% aqueous methanol (500 ml) was hydrogenated over 10% palladium on carbon (1 g) at room temperature and 0·1 MPa overpressure overnight. The suspension was filtered through Celite which was then washed with methanol (200 ml) and the filtrate was taken down. The thus-obtained compound *XIII* (R_F = 0·05, S2; 0·25, S8) was dissolved in pyridine (150 ml) and to the stirred solution *p*-toluenesulfonyl chloride (27 g; 0·14 mol) was added in two portions under cooling with ice. The mixture was stirred at 0°C for 4 h and at room temperature overnight, decomposed with water (10 ml) and after 30 min diluted with ethyl acetate (500 ml). The solution was washed with water (3 × 200 ml) and taken down *in vacuo*. The residue was codistilled with toluene (several 100 ml portions) to remove all the pyridine, and purified by chromatography on a column of silica gel (200 g) in chloroform, yielding 14·7 g (44·5% based on *XII*) of the derivative *XIV* as a yellowish oil, R_F = 0·12 (S2), 0·18 (S8).

This product (14·7 g; 49 mmol) in dimethylformamide (60 ml) was added to a mixture of adenine (6·75 g; 50 mmol) and sodium hydride (1·2 g; 50 mmol) in dimethylformamide (75 ml), which had been stirred for 1 h at 80°C prior to the addition. The mixture was heated to 100°C for 15 h, filtered through Celite, the solvent was evaporated at 60°C/13 Pa and the residue was extracted with hot chloroform until all the product was removed from the solid. The solvent was removed *in vacuo* and the residue was purified by chromatography on 1 plate of silica gel in the system S6. Elution of the product band ($R_F = 0{\cdot}32$ in S6) with methanol (500 ml) and crystallization from ethanol–ether gave 0·40 g (3·8% related to *XIV*) of compound *XV*, m.p. 174–175°C. For $C_{12}H_{17}N_5O_2$ (263·3) calculated: 54·73% C, 6·51% H, 26·60% N; found: 54·92% C, 6·54% H, 26·80% N. Mass spectrum: 263 (M^+). $R_F = 0{\cdot}32$ (S6).

Hydrolysis of the compound *XV* (50 mg) in 1M-H_2SO_4 at 37°C for 24 h gave quantitative yield of *IXb*, identical with an authentic material (*vide supra*) (S1, S5, S9 (HPLC)).

(*RS*)-3-(Adenin-9-yl)-2-methoxypropanoic Acid (*XVII*)

Sodium periodate (6·4 g; 30 mmol) was added in two portions during 3 h to a solution of 9-(*RS*)-(2-methoxy-3-hydroxypropyl)adenine (*XVI*, see ref.[5]; 1·67 g; 7·5 mmol) in 70% aqueous acetone (150 ml), containing ruthenium oxychloride (from 20 mg of ruthenium) and the mixture was stirred at room temperature for 20 h. According to chromatography in S6, the reaction was quantitative ($R_F = 0$; *XVI*, $R_F = 0{\cdot}19$). After filtering and washing the precipitate with acetone (100 ml), the filtrate was taken down and the residue was deionized on a column of Dowex 50 (100 ml) as described above. The ammonia eluate was taken down and the residue was applied on a column of silica gel SI C18 (50 ml) and eluted with 5% methanol in 0·05M formic acid. Evaporation of the UV-absorbing part of the eluate and codistillation of the residue with water (3 × 20 ml) gave the pure (S9) product which was crystallized from water; yield 0·47 g (26·4%) of *XVII*, m.p. 258–260°C. For $C_9H_{11}N_5O_3$ (237·2) calculated: 45·56% C, 4·67% H, 29·53% N; found: 45·80% C, 4·71% H, 29·34% N. Mass spectrum: 237 (M^+). UV spectrum (pH 2): λ_{max} 261 nm (ε_{max} 14 200). $R_F = 0{\cdot}50$ (S1), $E_{Up} = 0{\cdot}54$ (E1).

Diethyl (2*S*)-O-(1-Ethoxyethyl)ethane-1,4-dicarboxylate (*XVIII*)

A mixture of diethyl L-malate (228 g; 1·2 mol), ethyl vinyl ether (130 ml; 98 g; 1·36 mol) and conc. hydrochloric acid (0·5 ml) was stirred under calcium chloride protecting tube in an ice bath and then at room temperature overnight. Silver oxide (20 g) was added, the mixture was stirred for 1 h, filtered through Celite which was then washed with ether (100 ml) and the solvent was evaporated *in vacuo*. Distillation of the residue at 116–118°C/40 Pa afforded 292 g (92·8%) of compound *XVIII*. For $C_{12}H_{22}O_6$ (262·3) calculated: 54·94% C, 8·45% H; found: 54·59% C, 8·56% H.

(4*S*)-2,2-Dimethyl-4-(2-hydroxyethyl)-1,3-dioxolane (*XIX*)

A solution of compound *XVIII* (188·9 g; 0·72 mol) in ether (350 ml) was added dropwise to a stirred solution of Synhydride (469 g) in ether (1 400 ml) so as to keep a gentle boil. After stirring for 2 h, water (235 ml) was added, the suspension was filtered and the solid on the filter was washed with dioxane (1·5 l). The filtrate was taken down *in vacuo*, the residue was taken up in ether (1·5 l) dried over magnesium sulfate for 24 h, filtered and the solvent was evaporated *in vacuo*. Distillation of the residue gave 121·7 g (95%) of (2*S*)-2-O-(1-ethoxyethyl)butane-1,2,4-triol, b.p. 126°C : : 27 Pa. This product was dissolved in 90% aqueous methanol (1 litre), the solution was stirred with Dowex 50X8 (H^+-form; 100 ml) at room temperature overnight, filtered and the solvent was evaporated *in vacuo*. The residue was coevaporated with toluene (3 × 100 ml), mixed with acetone (400 ml) and ethyl orthoformate (100 ml), and 6M-HCl in dimethylformamide was added

to acid reaction. After standing overnight, the mixture was made alkaline with triethylamine and taken down *in vacuo*. The residue was dissolved in ether (500 ml), the solution washed with water (4 × 50 ml) and dried over magnesium sulfate. Evaporation of the solvent and distillation *in vacuo* afforded 72·4 g (72·5%) of compound *XIX*, b.p. 92°C/2 kPa (reported[12] b.p. 100°C/2 kPa).

(2*S*)-3-O-Benzoyl-1-O-*p*-toluenesulfonylbutane-1,2,4-triol (*XXII*)

Triethylamine (4 ml) was added to a solution of compound *XIX* (29·2 g; 0·2 mol) and benzoyl cyanide (27·8 g; 0·21 mol) in 1,2-dichloromethane (300 ml). After 2 h ethanol (20 ml) was added, the solvent was removed *in vacuo* and the residue was chromatographed on a column of silica gel (600 g) in chloroform. The obtained chromatographically pure (R_F = 0·32 in S2, 0·67 in S3) product *XX* was stirred overnight with Dowex 50X8 (H^+-form; 50 ml) in 50% aqueous methanol (500 ml), the suspension was filtered, the resin washed with methanol and the filtrate was taken down *in vacuo*, leaving the chromatographically pure (R_F = 0·30 in S3) product *XXI*. This was codistilled with toluene (4 × 100 ml) and pyridine (2 × 100 ml) *in vacuo* and taken up in pyridine (200 ml). The solution was cooled with ice and stirred with *p*-toluenesulfonyl chloride (40 g; 0·21 mol) and 4-dimethylaminopyridine (0·2 g) at 0°C for 4 h and at room temperature for 20 h. After decomposition with water (20 ml) and standing for 1 h, the mixture was diluted with ethyl acetate (1 litre), washed successively with water (4 × 100 ml), 0·25M-H_2SO_4 (to acid reaction), saturated sodium hydrogen carbonate and water and dried over magnesium sulfate. The solvent was evaporated *in vacuo* and the residue chromatographed on a silica gel column (500 g) in chloroform, affording oily compound *XXII*; yield 34 g (46·8%); R_F = 0·23 (S2), 0·72 (S3). This product was immediately used in the next reaction step.

9-(*S*)-(4-Benzoyloxy-2-tetrahydropyranyloxybutyl)adenine (*XXIV*)

To a solution of compound *XXII* (34 g; 93·7 mmol) in 1,2-dichloromethane (150 ml) was added 3,4-dihydropyran (36 ml), followed after cooling to −30°C by 6M-HCl in dimethylformamide (3 ml). The mixture was stirred at 0°C for 6 h and at room temperature overnight, mixed with silver carbonate (30 g), stirred for 2 h and filtered through Celite which was then washed with chloroform (100 ml). Evaporation of the filtrate *in vacuo* and drying at 13 Pa afforded the oily compound *XXIII*, R_F = 0·42 (S2). A solution of this product in dimethylformamide (120 ml) was added to a mixture of adenine (13·5 g; 0·1 mol) and sodium hydride (2·4 g; 0·1 mol) in dimethylformamide (300 ml) which had been stirred for 1 h at 80°C under calcium chloride protecting tube prior to the addition. After stirring for 15 h at 100°C, the mixture was taken down at 13 Pa, the residue was extracted with boiling chloroform (1 litre total), the extract was filtered through Celite and the solvent was evaporated *in vacuo*. The residue was applied on a silica gel column (300 g) and, after washing with chloroform, the product was eluted with ethanol–chloroform (1 : 9) and crystallized from ethyl acetate–light petroleum. Yield 15·7 g (40·8% from *XXII*) of compound *XXIV*, m.p. 109°C; $[\alpha]_D^{20}$ −18·8° (*c* 0·4, dimethylformamide). For $C_{21}H_{25}N_5O_4$ (411·5) calculated: 61·30% C, 6·12% H, 17·02% N; found: 61·16% C, 6·16% H, 16·74% N. R_F = = 0·43 (S3).

9-(*S*)-4-Hydroxy-(2-tetrahydropyranyloxybutyl)adenine (*XXV*)

A solution of compound *XXIV* (12·3 g; 30 mmol) in 0·1M methanolic sodium methoxide (150 ml) was set aside at room temperature overnight, neutralized with Dowex 50X8 (H^+-form), filtered, the resin was washed with methanol and the solvent was evaporated *in vacuo*. The crystalline residue was crystallized from ethyl acetate–ether, affording 9·0 g (97·3%) of the title compound, m.p. 159–161°C. For $C_{14}H_{21}N_5O_3$ (307·4) calculated: 54·70% C, 6·89% H, 22·79% N; found: 55·18% C, 7·11% H, 22·47% N. R_F = 0·47 (S5). Mass spectrum: 307 (M^+).

9-(*S*)-(2,4-Dihydroxybutyl)adenine (*XXVI*)

A solution of compound *XXV* (3·1 g; 10 mmol) in 0·25M-H_2SO_4 was kept at 40°C for 24 h, diluted with water (200 ml) and exactly neutralized with barium hydroxide. The mixture was heated to 80°C, filtered through Celite which was then washed with hot water (500 ml) and the filtrate was taken down *in vacuo*. Crystallization of the residue from 80% aqueous ethanol (ether added until turbid) afforded 1·6 g (71·7%) of compound *XXVI*, m.p. 212–214°C. $[\alpha]_D^{20}$ +2·6° (*c* 0·5; 0·1M-HCl). For $C_9H_{13}N_5O_2$ (223·2) calculated: 48·42% C, 5·87% H, 31·38% N; found: 48·02% C, 5·63% H, 31·12% N. R_F = 0·65 (S1), 0·28 (S5). UV spectrum (pH 2): λ_{max} 261 nm (ε_{max} 14 200). Mass spectrum: 223 (M^+).

(2*S*)-4-(Adenin-9-yl)-3-hydroxybutanoic Acid (*XXVII*)

To a stirred solution of sodium periodate (1·7 g; 8 mmol) in 70% aqueous acetone (50 ml) was added the compound *XXV* (1·08 g; 3·5 mmol) and, after dissolution, a solution of ruthenium oxychloride (1 ml, corresponding to 20 mg of ruthenium). The mixture was stirred with a glass stirrer for 3 h, filtered through Celite which was then washed with acetone, and taken down. The residue in water (25 ml) was deionized on a column of Dowex 50 (100 ml, *vide supra*) and the ammonia eluate was evaporated *in vacuo*. After warming the residue with 0·25M-H_2SO_4 (25 ml) to 40°C for 20 h, the solution was exactly neutralized with barium hydroxide, heated to 80°C, filtered through Celite which was then washed with hot water (300 ml), and the filtrate was taken down *in vacuo*. The residue was dissolved in water (20 ml), the solution was adjusted to pH 9 with ammonia and applied on a column of Dowex 1X2 (acetate, 100 ml). After washing with water to drop of UV absorption and conductivity, the product was eluted with a linear gradient of acetic acid (0–1 mol l^{-1}, 2 l each) and crystallized from water, yielding 500 mg (60·3%) of compound *XXVII*, not melting under 260°C. For $C_9H_{11}N_5O_3$ (237·2) calculated: 45·56% C, 4·67% H, 29·53% N; found: 45·72% C, 4·80% H, 29·48% N. Mass spectrum: 237 (M^+). UV spectrum (pH 2): λ_{max} 260 nm (ε_{max} 13 400). R_F = 0·43 (S1), E_{Up} = 0·51 (E1),

(*RS*)-4-(Adenin-9-yl)-3-hydroxypentanoic Acid (*XXIX*)

A mixture of compound *IVa* (2·4 g; 10 mmol), malonic acid (4·2 g; 40 mmol) and water (100 ml) was refluxed with stirring for 40 h (according to E1 the reaction was nearly quantitative). The clear solution was cooled, deionized on a column of Dowex 50 (300 ml) and the ammonia eluate was taken down *in vacuo*. The residue was dissolved in water (40 ml), the solution was made alkaline with ammonia and applied on a column of Dowex 1X2 (acetate; 150 ml). After washing with water to disappearance of UV-absorption and conductivity of the eluate, elution with a linear gradient of acetic acid (0–1 mol l^{-1}, 2 l each) afforded the product (fractions 0·8–1M) which, after evaporation and codistillation with water (3×) *in vacuo*, was crystallized from water. Yield 1·15 g (42·8%) of compound *XXIX*, m.p. above 260°C. For $C_{10}H_{13}N_5O_3.H_2O$ (269·3) calculated: 44·60% C, 5·62% H, 26·01% N; found: 44·65% C, 5·72% H, 26·18% N. Mass spectrum: 251 (M^+), 233 ($M-H_2O$), 192 ($M-CH_2CO_2H$), 188 ($233-CH_2CO_2H$), 136 (BH_2), 135 (BH). UV spectrum (pH 2): λ_{max} 260 nm (ε_{max} 14 500). R_F = 0·29 (S1), E_{Up} = 0·42 (E1).

The author is indebted to Dr M. Masojídková for measurement and analysis of the NMR *spectra, to Dr J. Kohoutová for the mass spectra measurements and to Dr I. Rosenberg for the* HPLC *analyses. The excellent technical assistance of Mrs B. Nováková is gratefully acknowledged.*

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Translated by M. Tichý.