SYNTHESIS OF NEW MONO- AND DISUBSTITUTED HYDROXYALKYL AND AMINOALKYL DERIVATIVES OF HETEROCYCLIC BASES

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Addition of adenine to methyl acrylate afforded 3-(adenin-9-yl)propionic acid (*I*) and 3-(adenin-3-yl)propionic acid (*IV*). Esterification of *I* with diazomethane gave the methyl ester *II* which was reduced with sodium borohydride to 9-(3-hydroxypropyl)adenine (*III*). Reduction of 9-bis-(ethoxycarbonyl)methyladenine (*VI*) under analogous conditions led to 2-(adenin-9-yl)propane-1,3-diol (*VIIb*). 1-O-*p*-Toluenesulfonyl-3,4-O-isopropylidene-(*S*)-butane-1,3,4-triol (*IX*) on reaction with sodium salt of adenine and subsequent acidic hydrolysis afforded 9-(*S*)-(3,4-dihydroxybutyl)-adenine (*XI*). Ethyl (DL)-*erythro*-2,3-dihydroxybutyrate (*XVI*) reacted with dihydropyran to give the compound *XVII*. Reduction of *XVII* with lithium aluminium hydride, followed by reaction with *p*-toluenesulfonyl chloride, afforded the *p*-toluenesulfonyl derivative *XIX* which on reaction with sodium salt of adenine and acidic hydrolysis gave 9-(*RS*)-*erythro*-(2,3-dihydroxybutyl)-adenine (*XXI*). Pentane-1,3,5-triol (*XXV*) was tosylated to a mixture of mono-(*XXVI*) and di-*p*-toluenesulfonyl (*XXVII*) derivatives. The compound *XXVI* reacts with sodium salt of adenine and uracil to give the respective 9- and 1-(*RS*)-3,5-dihydroxypentyl derivatives *XXVIIIa,b*. 1-O-Benzyl-sn-glycerol (*XXIX*) on successive tritylation, methylation, acidic hydrolysis and tosylation was converted to the compound *XXXII* which on reaction with sodium salt of adenine followed by hydrogenolysis afforded 9-(*RS*)-(2-methoxy-3-hydroxypropyl)adenine (*XXXIV*). 9-(*RS*)-(2,3-Dimethoxypropyl)adenine (*XXXVII*) was obtained in an analogous manner. 9-(*RS*)-(2-Hydroxy-3-benzyloxypropyl)adenine (*XXXVIII*) was transformed by tosylation, reaction with azide and subsequent hydrogenolysis to 9-(*RS*)-(2-amino-3-hydroxypropyl)adenine (*XLI*). Hydrogenation of 3-azido-2-hydroxypropyl derivative *XLVII* led to 9-(*RS*)-(3-amino-2-hydroxypropyl)adenine (*XLVIII*). Analogously, 9-(*RS*)-(2,3-diaminopropyl)adenine (*LII*) was prepared from 9-(*RS*)-(2,3-dihydroxypropyl)adenine (*XLIX*) *via* the di-*p*-toluenesulfonyl derivative *L*.

In connection with the recently discovered[1] antiviral activity of 9-(*S*)-(2,3-dihydroxypropyl)adenine it was important to investigate the biological activity of further compounds of this type, modified in the heterocyclic base moiety as well as in the aliphatic chain attached in the position 9 of the purine nucleus. The present paper describes the preparation of some new types of aliphatic derivatives with one or two hydroxy, amino or methoxy groups and also some derivatives of the corresponding carboxylic acids. All these types of compounds contain the adenine moiety; several analogues containing other heterocycles were also prepared. This series of compounds is complementary to the set of derivatives described in one of previous communications of this series[2].

Reaction of adenine with methyl acrylate afforded 3-(adenin-9-yl)propionic acid (*I*) which was esterified with diazomethane to give the methyl ester *II*; this on reduction with sodium borohydride was converted to 9-(3-hydroxypropyl)adenine (*III*), which had been synthesized previously by building up the adenine ring from 3-aminopropan-1-ol[3]. The reaction of adenine with acrylate afforded also the N^3--isomer *IV*, which is formed by addition at the position N^3 of adenine. Its structure was confirmed by the UV spectrum, which was typical for N^3-alkyladenines and different from those of the compounds *I*–*III*, characteristic for N^9-alkyladenines.

Analogously to adenine also cytosine adds to the acrylate, affording 3-(cytosin-1-yl)-propionic acid (*V*); the preparation of *V* by this procedure seems to be more advantageous than the hydrolysis of 1-(2-cyanoethyl)cytosine, obtained by addition of cytosine to acrylonitrile[4].

2-(Adenin-9-yl)propane-1,3-diol (*VIIb*) was prepared already previously by building up the heterocyclic nucleus from the corresponding amino alcohol[6]. In the present work, 9-bis(ethoxycarbonyl)methyladenine (*VI*), prepared by condensation of adenine with diethyl bromomalonate according to ref.[5], was reduced with sodium borohydride in methanol to give the diol *VIIb* which was isolated as the acetyl derivative *VIIa*. This was then transformed back to the diol *VIIb* by methanolysis.

$R—CH_2CH_2COOH$

I, R = adenin-9-yl
IV, R = adenin-3-yl
V, R = cytosin-1-yl

$A—CH_2CH_2R$

II, R = $COOCH_3$
III, R = CH_2OH
A = adenin-9-yl

$A—CH(COOC_2H_5)_2$

VI

$A—CH(CH_2OR)_2$

VIIa, R = $COCH_3$
VIIb, R = H

In contrast to the analogous reduction of 1-bis(ethoxycarbonyl)methyluracil with borohydride in aqueous methanol[7], the reaction of the adenine derivative afforded no side-products arising by partial decarboxylation. The product *VIIb* was characterised by its UV spectrum, typical for N^9-alkyladenines.

The preparation of racemic 3′,4′-dihydroxybutyl derivatives of heterocyclic bases has already been described in the previous communication[2]. This synthetic procedure has been now used for an asymmetric synthesis, starting with 3,4-O-isopropylidene-L--butane-1,3,4-triol (*VIII*). This compound was prepared from diethyl L-malate by blocking the secondary hydroxyl as the tetrahydropyranyl derivative, reduction with lithium aluminium hydride[8] and subsequent protection of the vicinal 3,4-hydroxy

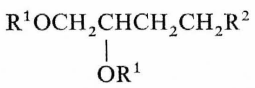
groups by transformation to the dioxolane derivative. Reaction of the compound *VIII* with *p*-toluenesulfonyl chloride in pyridine afforded the 1-O-p-toluenesulfonyl derivative *IX* which was condensed with sodium salt of adenine to give the 3',4'-O--isopropylidene derivative *X*. Acidic hydrolysis of this compound led to 9-(*S*)-(3,4--dihydroxybutyl)adenine (*XI*). Analogous condensation of the compound *IX* with sodium salt of uracil followed by hydrolysis with acetic acid gave 1-(*S*)-(3,4-dihydroxybutyl)uracil (*XII*). The reaction afforded also the 3-isomer of the compound[2] *XII* which, however, was not isolated.

It is worth mentioning that attempts to prepare the 3,4-dihydroxybutyl derivatives of uracil or thymine by the Hilbert–Johnson reaction of the corresponding 2,4-dimethoxypyrimidine with 4-(2-chloroethyl)-2,2-dimethyl-1,3-dioxolane[2] (*XIII*) were unsuccessful: reflux of both components in acetonitrile did not bring about the reaction, whereas the addition of anhydrous sodium iodide to the reaction mixture resulted in quantitative formation of 4-methoxy-2-pyrimidinone (*XIVa*) or 4-methoxy--5-methyl-2-pyrimidinone (*XIVb*). Acid hydrolysis of the compounds *XIVa* and *XIVb* afforded 1-methyluracil and 1-methylthymine, respectively.

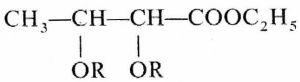
The isomeric 9-(DL)-*erythro*-(2,3-dihydroxybutyl)adenine (*XXI*) was prepared from ethyl *trans*-crotonate (*XV*) by the following reaction sequence: *cis*-hydroxylation in the presence of osmium tetroxide afforded smoothly ethyl DL-*erythro*-α,β-dihydroxybutyrate (*XVI*) (*cf.* the reported[9,10] sluggishness of this reaction). The free hydroxy groups were protected with the tetrahydropyranyl group and the obtained derivative *XVII* was reduced with lithium aluminium hydride to the partially protected *erythro*-DL-butane-1,2,3-triol *XVIII*. This compound afforded the *p*-toluenesulfonyl derivative *XIX* which was condensed with sodium salt of adenine in dimethylformamide. After removal of the protecting groups by acidic hydrolysis, the crude product was acetylated and the $N^6,O^{2',3'}$-triacetyl derivative *XX* isolated. Its structure was proved, in addition to analysis, also by the ^{1}H-NMR spectrum which displayed all the expected characteristic signals and simultaneously confirmed the stereochemical homogeneity of the product (although the value $J_{H,H} = 4{\cdot}0$ Hz cannot be unequivocally ascribed to the *erythro*-isomer because of lack of model compounds, this configuration follows from the stereochemical course of the reactions employed). Methanolysis of the acetyl derivative *XX* finally afforded the pure 2,3-dihydroxybutyl derivative *XXI*.

The homologous (*RS*)-3,5-dihydroxypent-1-yl derivatives *XXVIII* were prepared starting from diethyl acetonedicarboxylate. Catalytic hydrogenation over Raney nickel gave diethyl β-hydroxyglutarate the reaction of which with dihydropyran afforded its tetrahydropyranyl derivative *XXII*. This compound was reduced with lithium aluminium hydride to 3-tetrahydropyranyloxypentane-1,5-diol (*XXIII*) which on removal of the protecting group by acidic hydrolysis, followed by peracetylation, afforded 1,3,5-tri-O-acetylpentane-1,3,5-triol (*XXIV*). The free triol *XXV*, obtained

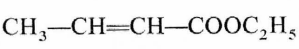
by methanolysis of *XXIV*, was treated with *p*-toluenesulfonyl chloride in pyridine to give a mixture of 1-O-*p*-toluenesulfonyl (*XXVI*) and 1,5-di-O-*p*-toluenesulfonyl (*XXVII*) derivatives, separated by chromatography on silica gel. The monotosylate *XXVI* on reaction with sodium salt of adenine afforded 9-(*RS*)-(3,5-dihydroxypentyl)-adenine (*XXVIIIa*), on reaction with sodium salt of uracil 1-(*RS*)-(3,5-dihydroxypentyl)uracil (*XVIIIb*) (the 3-isomer of this compound arose in the reaction only in minor quantity and was not obtained preparatively).



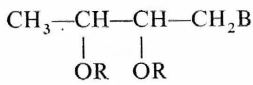
VIII, R^1, $R^1 = (CH_3)_2C$, $R^2 = OH$
IX, R^1, $R^1 = (CH_3)_2C$, R^2 = *p*-toluenesulfonyloxy
X, R^1; $R^1 = (CH_3)_2C$, R^2 = adenin-9-yl
XI, R^1 = H, R^2 = adenin-9-yl
XII, R^1 = H, R^2 = uracil-1-yl
XIII, R^1, $R^1 = (CH_3)_2C$, R^2 = Cl



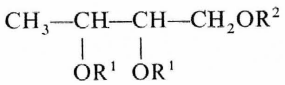
XVI, R = H
XVII, R = tetrahydropyran-2-yl



XV



XX, R = acetyl, B = N^6-acetyladenin-9-yl
XXI, R = H, B = adenin-9-yl



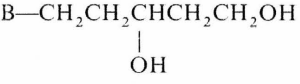
XVIII, R^1 = tetrahydropyran-2-yl, R^2 = H
XIX, R^1 = tetrahydropyran-2-yl, R^2 = *p*-toluenesulfonyl

XXII R = tetrahydropyran-2-yl

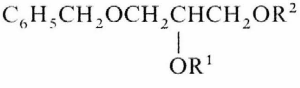
One of our previous communications[11] described a simple preparation of 9-(*RS*)-(3-methoxy-2-hydroxypropyl)adenine by reaction of adenine with 3-O-methyl-*sn*-glycerol 1,2-cyclic carbonate. Since, in contrast to adenosine, 9-(*RS*)-(2,3-dihydroxypropyl)adenine is not methylated with diazomethane, the preparation of the isomeric 2-methoxy and 2,3-dimethoxy derivatives requires a more complicated synthetic route. Both these derivatives were prepared from the same starting compound, 1-O-benzyl-*sn*-glycerol (*XXIX*). This compound on tritylation afforded the derivative *XXX* which was methylated with methyl iodide in the presence of sodium hydride and detritylated with acetic acid. The thus-obtained 1-O-benzyl-2-O-methyl-*sn*-glycerol

(*XXXI*) was transformed to the 3-O-*p*-toluenesulfonyl derivative (*XXXII*) which reacted with adenine to give the compound *XXXIII*. This was debenzylated by hydrogenolysis to 9-(*RS*)-(3-hydroxy-2-methoxypropyl)adenine (*XXXIV*). On the other hand, the direct methylation of 1-O-benzyl-*sn*-glycerol with methyl iodide followed by hydrogenolysis led to *sn*-glycerol 1,2-dimethyl ether (*XXXV*) which was transformed to the *p*-toluenesulfonyl derivative *XXXVI* and further to 9-(*RS*)-2,3-(dimethoxypropyl)adenine (*XXXVII*).

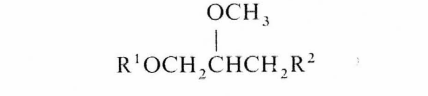
XXIII, R^1 = tetrahydropyran-2-yl, R^2 = H
XXIV, $R^1 = R^2$ = acetyl
XXV, $R^1 = R^2$ = H
XXVI, R^1 = H, R^2 = H, *p*-toluenesulfonyl
XXVII, R^1 = H, R^2 = *p*-toluenesulfonyl



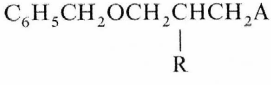
XXVIIIa, B = adenin-9-yl
XXVIIIb, B = uracil-1-yl



XXIX, $R^1 = R^2$ = H
XXX, R^1 = H, R^2 = trityl
XXXI, $R^1 = CH_3$, R^2 = H
XXXII, $R^1 = CH_3$, R^2 = *p*-toluenesulfonyl



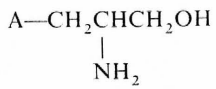
XXXIII, R^1 = benzyl, R^2 = adenin-9-yl
XXXIV, R^1 = H, R^2 = adenin-9-yl
XXXV, $R^1 = CH_3$, R^2 = OH
XXXVI, $R^1 = CH_3$, R^2 = *p*-toluenesulfonyloxy
XXXVII, $R^1 = CH_3$, R^2 = adenin-9-yl



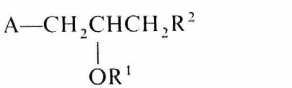
XXXVIII, R = OH
XXXIX, R = *p*-toluenesulfonyloxy
XL, R = N_3
XLII, R = NH_2
XLIII, R = benzoyloxy
A = adenin-9-yl

9-(*RS*)-(2-Amino-3-hydroxypropyl)adenine (*XLI*) was obtained from the already described[11] 3-O-benzyl derivative *XXXVIII*. This was converted into the 2-O-*p*-toluenesulfonyl-3-O-benzyl derivative *XXXIX* which on heating with sodium azide in dimethyl sulfoxide afforded the 2-azido derivative *XL*. Hydrogenation of this compound over palladium in acetic acid led, in addition to the reduction of the azido group, also to hydrogenolysis of the benzyl ether, affording thus directly the free amino alcohol *XLI*. Small amount of the benzyl derivative *XLII* was also isolated.

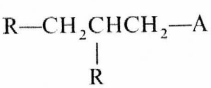
The isomeric 3-amino-2-hydroxypropyl derivative *XLVIII* was obtained by a more complicated route. The 3-benzyloxy derivative *XXXVIII* was benzoylated with benzoyl cyanide to give the compound *XLIII* whose rapid hydrogenolysis over palladium afforded the monobenzoyl derivative *XLIV* (the chosen reaction conditions minimise the possibility of the benzoyl group migration). This intermediate was treated with *p*-toluenesulfonyl chloride to give the derivative *XLV* which was transformed by substitution reaction with sodium azide to the 3-azido derivative *XLVI*. Since this compound contains a vicinal benzoyl group and its hydrogenation could thus lead to formation of phenyloxazoline derivative, the benzoyl protecting group in *XLVI* was first removed by methanolysis and the obtained 3-azido-2-hydroxypropyl derivative *XLVII* was subjected to hydrogenation.



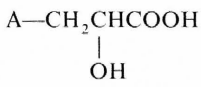
XLI, A = adenin-9-yl



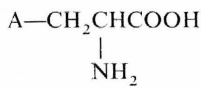
XLIV, R^1 = benzoyl, R^2 = OH
XLV, R^1 = benzoyl, R^2 = *p*-toluenesulfonyloxy
XLVI, R^1 = benzoyl, R^2 = N_3
XLVII, R^1 = H, R^2 = N_3
XLVIII, R^1 = H, R^2 = NH_2
A = adenin-9-yl



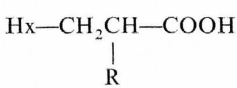
XLIX, R = OH
L, R = *p*-toluenesulfonyloxy
LI, R = N_3
LII, R = NH_2
A = adenin-9-yl



(*S*) *LIV*
(*R*) *LVI*



LVII

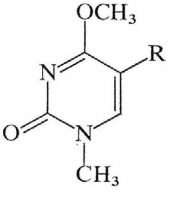


LVIII, R = OH
LIX, R = Cl
Hx = hypoxanthin-9-yl

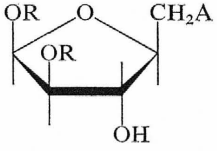
Treatment of 9-(*RS*)-(2,3-dihydroxypropyl)adenine (*XLIX*) with *p*-toluenesulfonyl chloride in pyridine afforded the 2′,3′-di-O-*p*-toluenesulfonyl derivative *L* as the principal product (even with an equimolar amount of the reagent). Reaction of *L*

with sodium azide in dimethyl sulfoxide gave the 2,3-diazidopropyl derivative *LI* which was catalytically hydrogenated in acetic acid to 9-(*RS*)-(2,3-diaminopropyl)-adenine (*LII*). The amino derivatives *XLI*, *XLVIII* and *LII* show UV spectra typical for 9-alkyladenines, differ chromatographically and electrophoretically (in acid medium) from the compound *XLIII* and from each other, and give positive ninhydrin reaction.

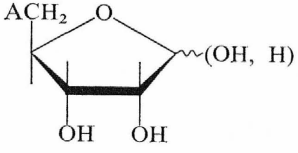
In connection with studies of possible metabolism of the compound *XLIII*, there were prepared also its oxidation products, *i.e.* 3-(adenin-9-yl)lactic acids. These compounds were prepared by two-step oxidation of 5-(adenin-9-yl)-5-deoxyaldofuranoses *LIII* and *LV*, first with sodium periodate which oxidises the 1,2-diol grouping, and then with sodium periodate in the presence of ruthenium catalyst which converts the intermediate aldehydic derivative to the carboxylic acid. The L-*arabino* derivative *LIIIb*, prepared analogously as described for the D-enantiomer[12] (*i.e.* by reaction of 5-O-*p*-toluenesulfonyl-1,2-O-isopropylidene-L-arabinofuranose with sodium salt of adenine, followed by acid deblocking), afforded the (*S*)-derivative *LIV*; the D-*ribo* derivative *LV* (ref.[2,12]) gave the (*R*)-enantiomer *LVI*. Both the compounds *LIV* and *LVI* are homogeneous on paper electrophoresis and have identical electrophoretic mobilities; also their UV spectra, typical for 9-alkyladenines, are identical. All this confirms the anticipated structure of these compounds.



XIVa, R = H
XIVb, R = CH_3



LIIIa, R, R = $(CH_3)_2C$
LIIIb, R = H
A = adenin-9-yl



LV
A = adenin-9-yl

Closely related to both these compounds is the hypoxanthine derivative which could be the possible product of *in vivo* deamination and oxidation of the compounds *LIV* or *LVI*. The racemate of this compound, *LVIII*, was prepared by action of nitrous acid on 3-(adenin-9-yl)-DL-alanine[13] (*LVII*). The reaction proceeded slowly and afforded two products, separable by chromatography on ion-exchange resin. As expected, the desired 3-(*RS*)-(hypoxanthin-9-yl)lactic acid (*LVIII*) was accompanied by (DL)-2-chloro-3-(hypoxanthin-9-yl)propionic acid (*LIX*). Both products were characterised by their UV spectra, typical for 9-alkylhypoxanthines.

All the described compounds were tested for antibacterial activity towards *Escherichia coli* (on a glucose-containing synthetic medium). None of them were inhibitory in concentrations up to 1000 μg per ml. Results of the antiviral screening will be published elsewhere.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Unless stated otherwise, the solutions were taken down at 40°C/15 Torr and the compounds dried at 0·1 Torr over phosphorus pentoxide. The paper chromatography was performed by the descending technique, on paper Whatman No 1 in the solvent systems S1, 2-propanol–conc. aqueous ammonia–water (7 : 1 : 2) or S2, 1-butanol–acetic acid–water (5 : 2 : 3). Paper electrophoresis was carried out on paper Whatman No 3MM in 0·1M triethylammonium hydrogen carbonate (E1) or 1M acetic acid (E2). The chromatography on silica gel was performed on Silufol UV_{254} plates in the solvent systems S3, ethanol–chloroform (5 . 95), S4, ethanol–chloroform (1 : 9), S5, ethanol–chloroform (1 : 4), S6, methanol–chloroform (3 : 7), S7, methanol–chloroform (2 : 3). Preparative chromatography was performed on loose layers (40 × 16 × 0·3 cm) of silica gel, containing a fluorescent indicator (prepared by the Service Laboratories of this Institute). Column chromatography: on cellulose: microcrystalline cellulose Macherey–Nagel (80 × 2 cm) in 70% aqueous 2-propanol (elution rate 0·4 ml/min); on silica gel: 200 g of silica gel according to Pitra (30—60 mesh); on DEAE cellulose: 80 × 4 cm column of Cellex in the hydrogen carbonate form (elution rate 3 ml/min, linear gradient 2 l water and 0·2M triethylammonium hydrogen carbonate pH 7·5); on Dowex 1 X 8 in OH^- form according to Dekker: 50 × 3 cm column of the ion exchange resin in water (3 ml/min); on Dowex 50 X 8 in H^+ form: column of 100 ml of the resin (unless otherwise stated) (2 ml/min). The elution with aqueous and aqueous–ethanolic solutions was followed on a Uvicord (LKB) instrument. The UV spectra were measured in aqueous solutions on a Specord (Zeiss, Jena, G.D.R.) spectrometer, ^{1}H-NMR spectra on a Varian 100 instrument in deuteriochloroform or hexadeuteriodimethyl sulfoxide with hexamethyldisiloxane as internal standard; the chemical shifts are given in ppm and the coupling constants in Hz.

3-(Adenin-9-yl)propionic Acid (*I*) and 3-(Adenin-3-yl)propionic Acid (*IV*)

A mixture of adenine (8·1 g; 60 mmol), 50% pyridine (320 ml) and methyl acrylate (40 ml) was refluxed for 6 h, taken down, dissolved in water (200 ml) and extracted with ether (3 × 50 ml). The aqueous phase was filtered with charcoal and applied to a DEAE-cellulose column. The neutral absorbing components were removed by elution with water and the product was obtained by gradient elution with buffer. The product fraction (0·10—0·12M) was taken down, the residue coevaporated with ethanol and heated to the boil with ethanol (50 ml). Acetone (200 ml) was added to this hot suspension, the separated product filtered, washed with acetone, ether, and dried. This material was dissolved in 30% pyridine and applied to a column of Dowex 50 X 8 (100 ml) in the pyridinium form, eluted with 30% pyridine (500 ml), the elutate taken down and the residue coevaporated with water (3 × 50 ml). Crystallisation from water yielded 1·5 g (11·2%) of the compound *I* (as monohydrate), m.p. 265°C. For $C_8H_{11}N_5O_3$ (225·2) calculated: 42·66% C, 4·98% H, 31·10% N; found: 42·50% C, 4·62% H, 31·56% N. UV spectrum (pH 7, 12): λ_{max} 262 nm. R_F 0·39 in S1, E_{Up} 0·48 (E1).

The mother liquors from the crystallisation of the compound *I* were taken down, the residue dissolved in methanol (20 ml), and the product precipitated with ether (200 ml); yield 2·8 g (22·5%) of the 3-isomer *IV*, m.p. 175—176°C. For $C_8H_9N_5O_2$ (207·2) calculated: 46·37% C, 4·38% H, 33·81% N; found: 46·72% C, 4·65% H, 33·89% N. UV spectrum (pH 7, 12): λ_{max} 276 nm. R_F 0·19 in S1, E_{Up} 0·48 (E1).

Methyl 3-(Adenin-9-yl)propionate (*II*)

An ethereal solution of diazomethane was added portionwise at 0°C to a stirred suspension of monohydrate of the compound *I* (1·0 g; 4·45 mmol) in methanol (50 ml) till the reaction

was complete (thin-layer chromatography in S4). The solution formed was stirred for 1 h at room temperature, taken down and the residue dissolved in a minimum volume of hot methanol, ether being added until the solution was turbid. After standing in a refrigerator, the separated crystals were filtered, washed with ether and dried *in vacuo*, yielding 0·90 g (91·5%) of the product, melting at 182—183°C. For $C_9H_{11}N_5O_2$ (221·2) calculated: 48·89% C, 5·01% H, 31·67% N; found: 49·28% C, 5·34% H, 31·75% N. UV-spectrum (pH 2, 7): λ_{max} 261 nm. R_F 0·72 in S1, 0·32 in S4, E_{Up} −0·25 (E1).

9-(3-Hydroxypropyl)adenine (*III*)

Sodium borohydride (total 2·0 g) was added in the course of 2 h at 0°C to a stirred solution of the compound *II* (0·80 g; 3·6 mmol) in methanol (50 ml). The mixture was then stirred for 1 h at room temperature, taken down *in vacuo*, the residue dissolved in water (50 ml), adjusted to pH 3 by addition of hydrochloric acid and applied to a column of Dowex 50 X 8 in the H^+ form. The column was eluted with water until the UV absorption and acidity disappeared and then with dilute (1 : 10) aqueous ammonia. The UV-absorbing fraction of the product was taken down, the residue coevaporated with ethanol and crystallised from methanol (charcoal), ether being added until the solution was turbid. Crystallisation in a refrigerator afforded 0·50 g (72%) of the compound *III*, m.p. 215—216°C. For $C_8H_{11}N_5O$ (193·2) calculated: 49·72% C, 5·74% H, 36·25% N; found: 49·67% C, 5·48% H, 36·22% N. UV spectrum (pH 2): λ_{max} 261 nm, ε_{max} 13 500. R_F 0·70 (S1).

1-(2-Carboxyethyl)cytosine (*V*)

A mixture of cytosine (1·0 g; 9 mmol), methyl acrylate (5 ml) and 50% pyridine (40 ml) was refluxed for 16 h and taken down *in vacuo*. Water (50 ml) was added, the mixture extracted with ether (2 × 25 ml), the aqueous layer taken down, the residue boiled with 2·5% lithium hydroxide (20 ml) and set aside for 4 h. After neutralisation of the mixture with Dowex 50 X 8 (H^+-form), ammonia was added (pH 10), the suspension filtered, washed with water and the filtrate concentrated and applied to a column of Amberlite IR 4B in the acetate form (100 ml). The column was washed with water till the UV absorption dropped and then with 1M acetic acid. The UV-absorbing acidic eluate was evaporated *in vacuo*, the residue coevaporated with water (4 × 50 ml) and crystallised from water (100 ml), yielding 0·60 g (36·5%) of the compound *V* which did not melt below 260°C. For $C_7H_9N_3O_3$ (183·2) calculated: 45·89% C, 4·95% H, 22·94% N; found: 45·35% C, 5·17% H, 22·73% N. UV-spectrum (pH 2): λ_{max} 278 nm (ε_{max} 13000). R_F 0·40 (S1), E_{Up} 0·60 (E1).

9-Bis(ethoxycarbonyl)methyladenine (*VI*)

Sodium hydride (0·50 g; 20 mmol) was added to a stirred solution of adenine (2·70 g; 20 mmol) in dimethylformamide (50 ml). After stirring for 30 min, a solution of ethyl bromomalonate (5·5 g; 23 mmol) in dimethylformamide (20 ml) was added. The mixture was stirred for 3 days at room temperature, taken down at 40°C/0·1 Torr, the residue heated to the boil with ethanol (70 ml), filtered through Celite and the filtrate cooled in a refrigerator. The crystalline product was filtered, washed with ethanol and ether, and dried, affording 4·0 g (68%) of the compound *VI*, m.p. 164°C. For $C_{12}H_{15}N_5O_4$ (293·3) calculated: 49·14% C, 5·16%, 23·88% N; found: 48·91% C, 5·34% H, 23·82% N.

N^6,1,3-Triacetyl-2-(adenin-9-yl)propane-1,3-diol (*VIIa*)

Sodium borohydride (10·0 g) was added portionwise in the course of 1 h to a stirred and ice-cooled solution of the compound *VI* (5·0 g; 17 mmol) in methanol (120 ml). The mixture was stirred for another hour at room temperature, acidified with acetic acid and taken to dryness *in vacuo*. The residue was dissolved in water (100 ml), acidified (pH 4) with hydrochloric acid and applied to a column of Dowex 50 X 8 (H^+) (300 ml). The column was washed with water until the UV-absorption and conductivity dropped. The product was then eluted with dilute (1 : 10) ammonia, the UV-absorbing eluate taken down and the residue dried over phosphorus pentoxide in vacuo. Acetic anhydride (50 ml) and 4-dimethylaminopyridine (0·5 g) were added, the mixture was stirred overnight at room temperature, taken down at 0·1 Torr (40—50°C), coevaporated with toluene, the residue taken up in chloroform (100 ml) and the extract washed with water (20 ml). The chloroform layer was dried over magnesium sulfate, taken down and the residue chromatographed on two loose layers of silica gel in the system S3. The product band was eluted with methanol, the solvent evaporated and the residue crystallised from ethanol (light petroleum added until the solution was turbid), affording 3·60 g (72·3%) of the compound *VIIa*, melting at 140—141°C. For $C_{14}H_{17}N_5O_5$ (335·3) calculated: 50·14% C, 5·11% H, 20·89% N; found: 50·63% C, 5·43% H, 20·59% N. R_F 0·65 in S4.

2-(Adenin-9-yl)propane-1,3-diol (*VIIb*)

The compound *VIIa* (2·40 g; 8·2 mmol) was dissolved under stirring in 30% methanolic ammonia (50 ml) and the solution set aside in a stoppered flask at room temperature overnight. Evaporation of the solvent *in vacuo* followed by crystallisation from ethanol (ether added until the solution was turbid) in a refrigerator overnight gave 1·20 g (70%) of chromatographically pure *VIIb*, m.p. 193—195°C. For $C_8H_{11}N_5O_2$ (209·2) calculated: 45·92% C, 5·30% H, 33·48% N; found: 46·06% C, 5·55% H, 32·98% N. UV spectrum (pH 2): λ_{max} 261 nm. R_F 0·59 in S1, 0·42 in S6.

1,2-O-Isopropylidene-(S)-1,2,4-butanetriol (*VIII*)

A mixture of L-malic acid (40 g; 0·29 mol), ethanol (160 ml) and 25% ethanolic hydrogen chloride (7 ml) was refluxed for 4 h, made alkaline with triethylamine (pH 8) and taken down *in vacuo*. Ether (250 ml) was added to the residue, the solution washed with water (2 . 50 ml), dried over magnesium sulfate, filtered, taken down and the residue distilled *in vacuo* to give 34·7 g (63%) of diethyl L-malate, b.p. 140°C/20 Torr (reported[14] b.p. 131—132°C/12 Torr). This product was stirred with 2,3-dihydropyran (40 ml) and 6M hydrogen chloride in dimethylformamide (2 ml) at room temperature overnight. Silver oxide (20 g) was added, the mixture stirred for 1 h, filtered, washed with ether (50 ml) and the filtrate distilled *in vacuo*, yielding 48·7 g (97%) of diethyl tetrahydropyranyl-L-malate, b.p. 120—130°C/0·2 Torr (reported[8] b.p. 119°C/0·4 Torr). A solution of this product in ether (50 ml) was added dropwise under stirring and cooling with ice to a suspension of lithium aluminium hydride (20 g) in ether (500 ml). The mixture was refluxed for 3 h, cooled with ice and decomposed by successive addition of ethyl acetate (70 ml), water (20 ml) and 4M sodium hydroxide (20 ml). The inorganic material was filtered off, washed with ether (500 ml) and hot chloroform (200 ml), the combined filtrates were dried over magnesium sulfate, filtered and taken down *in vacuo*. Fractionation of the residue *in vacuo* afforded 15·67 g (46%) of 2-O-tetrahydropyranyl-(*S*)-butane-1,2,4-triol, b.p. 160—165°C/0·16 Torr; $[\alpha]_D^{20}$ −12·0° (*c* 2·1, acetone) (reported[8] b.p. 115—123°C/0·2 Torr).

This product was stirred with methanol (100 ml) and *p*-toluenesulfonic acid hydrate (0·5 g) for 1 h at room temperature, the mixture neutralised with 1M sodium methoxide and taken down

in vacuo. The residue was allowed to stand with acetone (20 ml), 2,2-dimethoxypropane (40 ml) and *p*-toluenesulfonic acid monohydrate (0·5 g) at room temperature overnight. The mixture was again neutralised with 1M sodium methoxide, taken down *in vacuo*, the residue mixed with ether (100 ml), filtered, the material on the filter washed with ether, the filtrate evaporated and distilled *in vacuo* to give 12·1 g (64%) of the compound *VIII*, b.p. 100°C/0·2 Torr. For $C_7H_{14}O_3$ (146·2) calculated: 57·51% C, 9·65% H; found: 58·00% C, 9·63% H.

4-O-*p*-Toluenesulfonyl-1,2-O-isopropylidene-(*S*)-butane-1,2,4-triol (*IX*)

p-Toluenesulfonyl chloride (11·5 g; 60 mmol) was added at −10°C to a solution of the compound *VIII* (12 g; 52 mmol) in pyridine (100 ml). The mixture was set aside at −10°C for 30 min and then at 0°C for 2 days. Methanol (5 ml) was added, the mixture taken down *in vacuo*, the residue diluted with chloroform (200 ml), washed successively (50 ml portion each) with water, saturated sodium hydrogen carbonate solution (3 ×) and again with water, dried over magnesium sulfate, filtered and taken down *in vacuo* (finally at 70°C/0·1 Torr). The obtained product *IX* (10·8 g; 54%) was used in further condensations.

9-(*S*)-(3,4-O-Isopropylidene-3,4-dihydroxybutyl)adenine (*X*)

A mixture of adenine (2·03 g; 15 mmol), dimethylformamide (50 ml) and sodium hydride (0·40 g; 16·5 mmol) was stirred for 10 min under exclusion of moisture. A solution of the compound *IX* (5·37 g; 14 mmol) in dimethylformamide (20 ml) was added and the stirred mixture was heated to 100°C for 7 h, again under exclusion of moisture. The mixture was taken down at 40°C/0·1 Torr, the residue dissolved in chloroform (50 ml) and the solution filtered through Celite which was then washed with chloroform (50 ml). The filtrate was chromatographed on a silica gel column and, the product eluted with a chloroform–ethanol (96 : 5) mixture (30 ml fractions). The product-containing fractions were combined, evaporated and the obtained compound *X* crystallised from ethanol, m.p. 150°C; yield 1·9 g (51·5%). For $C_{12}H_{17}N_5O_2$ (263·3) calculated: 54·73% C, 6·51% H, 26·60% N; found: 55·08% C, 6·72% H, 26·84% N, $[\alpha]_D^{20}$ −9·8° (*c* 0·5, dimethylformamide). R_F 0·50 in S3.

9-(*S*)-(3,4-Dihydroxybutyl)adenine (*XI*)

A solution of the compound *X* (1·0 g; 3·8 mmol) in 80% acetic acid (25 ml) was refluxed for 1 h, taken down *in vacuo*, the residue coevaporated with water (4 . 20 ml) and ethanol (3 . 20 ml) and crystallised from 90% ethanol, affording 0·50 g (59%) of the compound *XI*, m.p. 226–227°C; $[\alpha]_D^{20}$ −25·9° (*c* 0·48, 0·1M-HCl). For $C_9H_{13}N_5O_2$ (223·2) calculated: 48·42% C, 5·87% H, 31·48% N; found: 48·18% C, 6·24% H, 29·93% N. R_F 0·53 in S1. ^{1}H-NMR spectrum ([$^2H_6$]-dimethyl sulfoxide): 1·55–2·17 (m, 2 H) $H_{2'}$; 3·10–3·50 (m, 3 H) $H_{3'} + H_{4'}$; 4·20 (t, 2 H, J = = 7·5) H_1; 7·02 (br s, 2 H) NH_2; 8·01 (s, 1 H) H_2; 8·09 (s, 1 H) H_8.

1-(*S*)-(3,4-Dihydroxybutyl)uracil (*XII*)

Sodium hydride (0·40 g; 16·7 mmol) was added to a stirred suspension of uracil (1·68 g; 15 mmol) in dimethylformamide (25 ml), and the mixture was stirred for 30 min under exclusion of moisture. A solution of the compound *IX* (5·37 g; 14 mmol) in dimethylformamide (10 ml) was added, the mixture stirred for 8 h at 100°C, taken down at 40°C/0·1 Torr, the residue extracted with boiling chloroform (100 ml), filtered, and the material on the filter washed with hot chloroform (2 . 50 ml). The filtrate was concentrated *in vacuo* to about 50 ml and applied to a silica gel

column. Elution with chloroform afforded the isopropylidene derivative of compound *XII* (R_F 0·55 in S4) which was dried *in vacuo* (1·65 g) and refluxed with 80% acetic acid (20 ml) for 1 h. After evaporation *in vacuo* the residue was coevaporated with water (3 . 20 ml) and ethanol (3 . 20 ml) and crystallised from ethanol (ether added till the solution was turbid, yielding 1·0 g (35·7%) of the compound *XII*, m.p. 126–127°C; $[\alpha]_D^{20}$ −39·4° (*c* 0·5; 0·1N-HCl). For $C_8H_{12}.N_2O_4$ (200·2) calculated: 47·99% C, 6·04% H, 14·00% N; found: 48·01% C, 6·28% H, 13·88% N. UV spectrum (pH 2, 12): λ_{max} 262 nm. R_F 0·55 in S1, 0·27 in S4. ^{1}H-NMR spectrum ([$^2H_6$]dimethyl sulfoxide): 3·20–3·40 (m, 2 H) $H_{2'}$; 3·45 (m, 1 H) $H_{3'}$; 3·60–3·90 (m, 2 H) $H_{4'}$; 4·30 to 4·50 (m, 2 H) $H_{1'}$; 5·45 (d, 1 H, $J_{5,6}$ = 8·0, $J_{5,NH}$ = 1·0) H_5; 7·45 (d, 1 H) H_6; 10·0 (br s, 1 H)NH.

Reaction of 4-(2-Chloroethyl)-2,2-dimethyl-1,3-dioxolane (*XIII*) with 2,4-Dimethoxypyrimidine

A mixture of the compound *XIII* (see ref.[2]) (4·13 g; 25 mmol), 2,4-dimethoxypyrimidine (2·8 g; 20 mmol) and acetonitrile (25 ml) was refluxed for 6 h under exclusion of moisture. Chromatography (S4) showed that no reaction took place. After addition of anhydrous sodium iodide (3·3 g; 20 mmol) and reflux for 20 h the reaction was shown (S4) to be quantitative. The mixture was evaporated *in vacuo*, the residue taken up in boiling chloroform (100 ml), filtered, the material on the filter washed with chloroform and the filtrate concentrated *in vacuo*. Chromatography of the residue on a silica gel column and crystallisation from ethyl acetate (light petroleum being added until the solution was turbid) afforded 1·90 g (68·0%) of the product *XIVa*, m.p. 153 to 155°C (reported[15] m.p. 149–150°C). UV spectrum (pH 2, 7, 12); λ_{max} 275 nm (ε_{max} 5300); R_F 0·30 in S4.

Refluxing the compound *XIVa* (0·7 g; 5 mmol) with 3·5% HCl (20 ml) for 3 h, followed by neutralisation with ammonia and crystallisation of the residue from water gave 0·40 g (63·6%) of 1-methyluracil, m.p. 233–234°C (reported[15] m.p. 233°C). UV spectrum (pH 2, 7): λ_{max} 266 nm (ε_{max} 13 700); pH 12: λ_{max} 264 nm (ε_{max} 9850), R_F 0·30 in S4. For $C_5H_6N_2O_2$ (126·1) calculated: 47·61% C, 4·80% H, 22·21% N; found: 47·61% C, 4·98% H, 21·77% N.

Reaction of 4-(2-Chloroethyl)-2,2-dimethyl-1,3-dioxolane (*XIII*) with 1,4-Dimethoxy-5-methylpyridine

This reaction was performed in the same manner as described for the compound *XIVa*, the reaction time being 6 h without sodium iodide and 16 h after its addition. The work-up procedure was the same as described for *XIVa* and afforded 2·05 g (66·5%) of the compound *XIVb*, m.p. 140–141°C (reported[16] m.p. 144°C). UV spectrum (pH 2, 7, 12): λ_{max} 280 nm (ε_{max} 5300). R_F 0·58 in S4. For $C_7H_{10}N_2O_2$ (154·2) calculated: 54·33% C, 5·54% H, 18·17% N; found: 54·63% C, 6·70% H, 17·83% N. Refluxing the compound *XIVb* (1·0 g; 6·5 mmol) with 3·5% HCl (20 ml) for 3 h, followed by neutralisation with ammonia and crystallisation from water, gave 0·75 g (82·5%) of 1-methylthymine (did not melt below 270°C; reported[17] m.p. 280–291°C). For $C_6H_8.N_2O_2$ (140·1) calculated: 51·42% C, 5·75% H, 19·99% N; found: 51·46% C, 5·96% H, 20·06% N. UV spectrum (pH 2, 7): λ_{max} 272 nm (ε_{max} 14 700), pH 12: λ_{max} 270 nm (ε_{max} 11 000). R_F 0·45 in S4.

N^6,O^2,O^3-Triacetyl-9-(DL)-erythro-(2,3-dihydroxybutyl)adenine (*XX*)

A mixture of crotonic acid (100 g; 1·16 mol), anhydrous ethanol (200 ml) and sulfuric acid (10 g) was refluxed (calcium chloride protection tube) for 5 h, cooled, neutralised with triethylamine (pH 8), diluted with ether (1 l), washed with saturated sodium hydrogen carbonate solu-

tion and with water (200 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*. Distillation *in vacuo* afforded 96 g (72·5%) of ethyl crotonate, b.p. 56—58°C/20 Torr. A mixture of this compound (0·842 mol), 50% ethanol (850 ml), potassium chlorate (170 g) and osmium tetroxide (0·98 g) was stirred at 50°C for 7 h (according to thin-layer chromatography in S3, the reaction was complete after 3 h), filtered through Celite and the ethanol evaporated *in vacuo*. The remaining aqueous solution was extracted with ether (4 . 100 ml), the extract dried over magnesium sulfate and taken down. The residue was fractionated *in vacuo*, yielding 77·3 g (62·2%) of the compound *XVI*, b.p. 112—118°C/14 Torr (reported[9] b.p. 113°C/10 Torr for the *erythro*-isomer). This product was stirred with 2,3-dihydropyran (75 ml) and 6M hydrogen chloride in dimethylformamide (10 ml) at room temperature overnight. Silver oxide (20 g) was added, the mixture was stirred for 1 h, filtered, the residue washed with ether and the filtrate fractionated *in vacuo*, affording 59 g (36%) of the compound *XVII*, b.p. 140—142°C/20 Torr. A solution of this product (0·187 mol) in ether (100 ml) was added dropwise to a cooled and stirred suspension of lithium aluminium hydride (29 g) in ether (600 ml). The mixture was then refluxed under stirring for 3 h, cooled with ice and decomposed by successive dropwise addition of ethyl acetate (100 ml), water (30 ml) and 4M sodium hydroxide (30 ml). The precipitate was filtered, washed with ether (200 ml), and chloroform (300 ml), the filtrate dried over magnesium sulfate, taken down and fractionated *in vacuo*, yielding 25·6 g (50%) of the compound *XVIII*, b.p. 150 to 160°C/0·1 Torr.

This product (12·8 g; 46·5 mmol), dissolved in pyridine (20 ml), was added dropwise to an ice-cooled mixture of *p*-toluenesulfonyl chloride (19 g; 0·1 mol) and pyridine (50 ml). After standing overnight at room temperature, the mixture was treated with ethanol (20 ml), taken down and partitioned between ethyl acetate (200 ml) and water (50 ml), the organic layer washed with water (2 × 50 ml), dried over magnesium sulfate, filtered, the filtrate taken down *in vacuo*, the residue coevaporated with toluene (3 . 50 ml) and dried at 70°C/0·1 Torr. The remaining oily compound *XIX* (17·5 g; 40 mmol) was used in the next step without further purification.

A mixture of adenine (6·75 g; 50 mmol), sodium hydride (1·2 g; 50 mmol) and dimethylformamide (100 ml) was stirred for 1 h under exclusion of moisture. A solution of the compound *XIX* (40 mmol) in dimethylformamide (50 ml) was added dropwise and the mixture stirred at 100°C for 14 h. After removal of the solvent at 40°C/0·1 Torr the mixture was extracted with hot chloroform (200 ml), the mixture filtered, the solid on the filter washed with hot chloroform (500 ml) until it did not contain any product (according to thin-layer chromatography in S5) and the filtrate taken down *in vacuo*. The residue was refluxed with 80% acetic acid (200 ml) and the mixture taken down *in vacuo*. Water (200 ml) was added, the mixture extracted with ether (2 . 50 ml), the aqueous layer evaporated, the residue taken up in water (50 ml) and the solution (pH 3) applied to a column of Dowex 50 X 8 (H^+). The column was washed with water until the absorption of the eluate disappeared and its conductivity dropped, and then with ammonia (1 : 10). The UV-absorbing eluate was taken down, dried at 0·1 Torr overnight and stirred with acetic anhydride (50 ml) and 4-dimethylaminopyridine (0·5 g) for 20 h. The mixture was filtered through Celite which was then washed with acetic anhydride (20 ml) and the filtrate was taken down at 40°C/0·1 Torr. The residue was dissolved in chloroform (100 ml), washed with water (20 ml) and the organic layer dried and evaporated. The residue was chromatographed on silica gel (*vide supra*) with chloroform as eluant. The fraction of R_F 0·48 (S4) after evaporation and crystallisation from ethanol (with addition of light petroleum till the solution was turbid) afforded 4·0 g (30%) of the compound *XX*, m.p. 154—155°C. For $C_{15}H_{19}N_5O_5$ (349·3) calculated: 51·57% C, 5·48% H, 20·05% N; found: 51·27% C, 5·61% H, 21·04% N. ^{1}H-NMR spectrum (deuteriochloroform): 1·27 (d, 3 H) 4-CH_3; 2·00 + 2·07 (2 s, 2 × 3 H) O-acetyl; 2·61 (s, 3 H) N-acetyl; 4·33 (dd, 1 H, J_{gem} = 14·5, $J_{CH_3,H}$ = 8·0) and 4·57 (dd, 1 H, J_{gem} = 14·5, $J_{H,H}$ = 4·0)

1′-CH_2; 5·11 (m, 1 H, J_{H,CH_3} = 6·5, $J_{H,H}$ = 4·0) 3′-CH; 5·38 (m, 1 H, $J_{H,H}$ = 4·0, J_{H,CH_3} = 8·0 and 4·0) 2′-CH_2; 8·20 + 8·67 (2 s, 2 × 1 H) H_2 + H_8.

9-(DL)-*erythro*-(2,3-Dihydroxybutyl)adenine (*XXI*)

A suspension of the compound *XX* (3·85 g; 11·5 mmol) in 30% methanolic ammonia (150 ml) was stirred in a stoppered flask at room temperature overnight, taken down *in vacuo* and the residue crystallised from ethanol (ether added to incipient turbidity), yielding 1·6 g (62·5%) of the compound *XXI*, m.p. 229–230°C. For $C_9H_{13}N_5O_2$ (223·2) calculated: 48·42% C, 5·87% H, 31·38% N; found: 49·02% C, 6·25% H, 31·76% N. R_F 0·54 in S1, 0·52 in S6. UV spectrum (pH 2): λ_{max} 260 nm (ε_{max} 13 500).

Ethyl 3-Tetrahydropyranyloxyglutarate (*XXII*)

Diethyl acetonedicarboxylate (60 g, 0·3 mol) in ethanol (300 ml) was hydrogenated over Raney nickel (20 g) at 150 atm and 80°C for 16 h, the mixture was filtered through Celite which was then washed with ethanol. The filtrate was taken down *in vacuo*, finally at 30°C/0·1 Torr, the residue stirred with a mixture of 2,3-dihydropyran (50 ml) and 6M hydrogen chloride in dimethylformamide (5 ml) at room temperature overnight. Silver oxide (20 g) was added, the mixture stirred for 1 h, filtered, washed with ether (50 ml), the filtrate taken down and the residue fractionated *in vacuo*, affording 74 g (85·5%) of the compound *XXII*, b.p. 175–176°C/12 Torr. For $C_{14}H_{24}O_6$ (288·4) calculated: 58·31% C, 8·39% H; found: 58·82% C, 8·22% H.

1,3,5-Triacetoxypentane (*XXIV*)

A solution of the compound *XXII* (74 g; 0·256 mol) in ether (100 ml) was added dropwise under stirring and cooling with ice to a slurry of lithium aluminium hydride (29 g) in ether (600 ml). The mixture was refluxed with stirring for 3 h, cooled with ice and decomposed by the successive addition of ethyl acetate (100 ml), water (30 ml) and 4M sodium hydroxide (30 ml). The solid hydroxides were filtered off (Celite), washed with ether (500 ml) and then with chloroform (200 ml), the filtrate was dried, taken down *in vacuo* and the residue refluxed with 80% acetic acid (300 ml) for 2 h. After evaporation of the solvent the residue was coevaporated with toluene (3 × 100 ml) and pyridine (100 ml), dissolved in pyridine (100 ml) and treated with acetic anhydride (100 ml). The mixture was set aside at room temperature for 3 days, taken down *in vacuo* and the residue dissolved in chloroform (200 ml). The solution was washed with water (3 . 50 ml), dried over magnesium sulfate, filtered, taken down *in vacuo* and the residue distilled to give 43·8 g (69·5%) of the compound *XXIV*, b.p. 130–136°C/0·15 Torr. For $C_{10}H_{18}O_6$ (234·2) calculated: 51·27% C, 7·74% H; found: 50·84% C, 7·56% H.

1-O-*p*-Toluenesulfonyl-(*RS*)-pentane-1,3,5-triol (*XXVI*) and
1,5-di-O-*p*-Toluenesulfonyl-(*RS*)-pentane-1,3,5-triol (*XXVII*)

A solution of the compound *XXIV* (21·9 g; 89 mmol) in 0·005M methanolic sodium methoxide (100 ml) was set aside at room temperature overnight, neutralised with Dowex 50 X 8 (H^+), filtered and the filtrate taken down *in vacuo*. The residue (compound *XXV*) was dried at 40°C : 0·1 Torr. A solution of this residue (*XXV*) in pyridine (100 ml) was cooled to −40°C, *p*-toluenesulfonyl chloride (19·0 g; 0·1 mol) was added and the stirred mixture was allowed to warm to room temperature. After two days at 0°C ethanol (10 ml) and water (10 ml) were added, the mixture was taken down *in vacuo*, partitioned between ethyl acetate (300 ml) and water (100 ml),

the organic phase washed with water (2 . 50 ml), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*. The residue was chromatographed on a silica gel column in chloroform, the separation being monitored by thin-layer chromatography in S3. The fraction of R_F 0·27 (S3) was evaporated and dried at 0·1 Torr, leaving 8·8 g (23%) of the di-*p*-toluenesulfonyl derivative *XXVII*; from the fraction R_F 0·07 (S3) the mono-*p*-toluenesulfonate *XXVI* was obtained (5·8 g; 23·5%). The compound *XXVI* was used in further experiments without purification.

9-(*RS*)-(3,5-Dihydroxypentyl)adenine (*XXVIIIa*)

Sodium hydride (0·30 g; 12·5 mmol) was added to a suspension of adenine (1·62 g; 12 mmol) in dimethylformamide (20 ml). After stirring at room temperature for 45 min a solution of the compound *XXVI* (2·9 g; 10·5 mmol) in dimethylformamide (10 ml) was added. The mixture was heated to 110°C for 20 h under exclusion of moisture, taken down at 40°C/0·1 Torr, the residue taken up in water (50 ml), acidified with hydrochloric acid (pH 3) and applied to a column of Dowex 60 X 8 (H^+). The column was washed with water until all the UV-absorbing material was eluted and the eluate was no more acidic. Elution with dilute (1 : 10) ammonia afforded UV-absorbing fraction which was taken down *in vacuo* and the residue was chromatographed on a column of Dowex 1 X 8 (OH^- form) according to Dekker. The fraction of R_F 0·15 (in S5) was free of adenine and after evaporation of the solvent *in vacuo* the residue was crystallised from ethanol (the same volume of ether being added) yielding 1·0 g (40·0%) of the compound *XXVIIIa*, m.p. 177—179°C. For $C_{10}H_{15}N_5O_2$ (237·3) calculated: 50·62% C, 6·37% H, 29·52% N; found: 50·29% C, 6·53% H, 28·71% N. R_F 0·57 in S1, 0·15 in S5. UV spectrum (pH 2): λ_{max} 260 nm (ε_{max} 13 500).

9-(*RS*)-(3,5-Dihydroxypentyl)uracil (*XXVIIIb*)

Sodium hydride (0·30 g; 12·5 mmol) was added to a suspension of uracil (1·35 g; 12 mmol) in dimethylformamide (20 ml). After stirring for 30 min (calcium chloride protective tube) a solution of the compound *XXVI* (2·9 g; 10·5 mmol) in dimethylformamide (10 ml) was added. The mixture was heated to 100°C for 15 h, taken down at 40°C/0·1 Torr and the residue crystallised from 80% ethanol. The separated uracil was filtered off and the filtrate applied to a column of Dowex 1 X 2 (acetate form) (150 ml). Elution with water afforded a UV-absorbing fraction which was taken down *in vacuo*, applied to a column of Dowex 50 X 8 (H^+) (100 ml) and again eluted with water. The UV-absorbing eluate was taken down and chromatographed on a loose layer of silica gel (S5). The product band (R_F 0·33 in S5, uracil R_F 0·55) was eluted with methanol (500 ml), the eluate taken down *in vacuo* and the residue chromatographed on a column of cellulose in 70% 2-propanol. The product-containing fraction (R_F 0·60 in S1, 0·33 in S5) was taken down and the residue crystallised from ethanol to give 0·55 g of the compound *XXVIIIb*, m.p. 115 to 116°C. For $C_9H_{14}N_2O_4$ (214·2) calculated: 50·46% C, 6·59% H, 13·08% N; found: 50·92% C, 6·36% H, 12·63% N. UV spectrum (pH 2): λ_{max} 262 nm (ε_{max} 9 600).

1-O-Benzyl-2-O-methyl-*sn*-glycerol (*XXXI*)

A solution of 1-O-benzyl-*sn*-glycerol[11] (*XXIX*) (0·2 mol) and trityl chloride (70 g; 0·25 mol) in pyridine (200 ml) was set aside at room temperature for 2 days, diluted with ethyl acetate (500 ml), washed with water (5 . 100 ml), dried over magnesium sulfate, filtered and the filtrate taken down *in vacuo*, finally at 70°C/0·1 Torr. The obtained crude product *XXX* was dissolved in dimethylformamide (50 ml) and added dropwise to a stirred suspension of sodium hydride (6 g; 0·25 mol) in dimethylformamide (200 ml). After 30 min of stirring, methyl iodide (40 ml) was added through the reflux condenser and the mixture was stirred at room temperature for 6 h

in a flask equipped with a reflux condenser fitted with a calcium chloride protecting tube. After standing overnight, the mixture was filtered through Celite and the filtrate taken down at 60°C/15 Torr. The residue was refluxed with 80% acetic acid (250 ml) for 2 h, cooled with ice, filtered and the filtrate taken to dryness *in vacuo*. The residue was codistilled with toluene (2 . 100 ml) and fractionated *in vacuo*, affording 20·1 g (52%) of the product *XXXI*, b.p. 124—128°C/0·005 Torr.

1-O-Benzyl-2-O-methyl-3-O-*p*-toluenesulfonyl-*sn*-glycerol (*XXXII*)

p-Toluenesulfonyl chloride (20·0 g; 0·105 mol) was added in portions to a pre-cooled (ice) solution of the compound *XXXI* (20·0 g; 0·1 mol) in pyridine (70 ml). After standing for 24 h at room temperature ethanol (20 ml) was added, the solvent evaporated *in vacuo*, the residue dissolved in ethyl acetate (200 ml), the solution washed with water (5 . 50 ml), dried over magnesium sulfate and filtered. The filtrate was evaporated *in vacuo* and the residue chromatographed on a silica gel column (chloroform). The product fractions (R_F 0·25 in S3) were taken down and the residue dried *in vacuo*, leaving 30·6 g (84%) of the oily compound *XXXII*.

9-(*RS*)-(3-Benzyloxy-2-methoxypropyl)adenine (*XXXIII*)

Sodium hydride (0·60 g; 25 mmol) was added to a suspension of adenine (3·77 g; 25 mmol) in dimethylformamide (40 ml). After stirring at 60°C for 30 min under exclusion of moisture a mixture of the compound *XXXII* (12·2 g; 35 mmol) and dimethylformamide (10 ml) was added dropwise. The resulting mixture was stirred at 100°C for 16 h, taken down at 40°C/0·1 Torr, the residue coevaporated with toluene (50 ml) and extracted with hot chloroform (100 ml). The extract was filtered through Celite, which was then washed with hot chloroform (200 ml), the filtrate was taken down *in vacuo* and the residue chromatographed on a silica gel column. The product was eluted with a chloroform–ethanol (95 : 5) mixture and after evaporation of the solvents crystallised from ethyl acetate (light petroleum being added till the solution was turbid), affording 3·44 g (44%) of the compound *XXXIII*, m.p. 111—112°C. For $C_{16}H_{19}N_5O_2$ (313·4) calculated: 61·32% C, 6·11% H, 22·35% N; found: 61·85% C, 6·18% H, 21·90% N. R_F 0·50 in S5. UV spectrum (pH 2, 12): λ_{max} 262 nm (ε_{max} 12000).

9-(*RS*)-(2-Hydroxy-2-methoxypropyl)adenine (*XXXIV*)

To a solution of the compound *XXXIII* (1·25 g; 4 mmol) in methanol (100 ml) there were added conc. hydrochloric acid (0·5 ml), 20% solution of palladium chloride (0·5 ml) and 5% Pd/C (0·9 g), and the suspension was hydrogenated at room temperature and atmospheric pressure. After the consumption of hydrogen (120% of theory) had ceased, the mixture was filtered through Celite, basified with triethylamine, the filtrate taken to dryness *in vacuo*, the residue dissolved in water (20 ml), acidified (pH 3) with hydrochloric acid and deionised on a column of Dowex 50 X 8. The product-containing ammonia eluate was taken down and the residue crystallised from ethanol to give 0·65 g (73%) of the compound *XXXIV*, m.p. 174—175°C. For $C_9H_{13}N_5O_2$ (223·2) calculated: 48·42% C, 5·78% H, 31·38% N; found: 48·80% C, 5·65% H, 30·97% N. R_F 0·64 (S1), 0·68 (S2) (identical with the 3′-isomer, see ref.[11]). UV spectrum (pH 2, 12): λ_{max} 262 nm, ε_{max} 12900.

9-(*RS*)-(2,3-Dimethoxypropyl)adenine (*XXXVII*)

1-O-Benzyl-*sn*-glycerol[11] (*XXIX*) (0·2 mol) was added dropwise to a stirred solution of sodium hydride (0·4 mol) in toluene (250 ml) and after 1 h at room temperature methyl iodide (60 ml)

was added through the reflux condenser. The mixture was stirred at 100°C for 20 h, filtered through Celite, which was then washed with toluene (100 ml) and the filtrate taken down *in vacuo*. Fractionation of the residue *in vacuo* afforded 19·0 g (45·7%) of 1-O-benzyl-2,3-di-O-methyl--*sn*-glycerol, b.p. 138—140°/15 Torr. This product was mixed with methanol (100 ml) and conc. hydrochloric acid (0·5 ml) and hydrogenated over 5% Pd/C (1·5 g) at room temperature and atmospheric pressure until the hydrogen consumption ceased (3 days). The suspension was filtered through Celite which was then washed with methanol (100 ml), the filtrate made alkaline with triethylamine and evaporated *in vacuo*. The residue was fractionated *in vacuo* to give 9·6 g (80 mmol; 88·7%) of 2,3-di-O-methyl-*sn*-glycerol (*XXXV*), b.p. 125—130°C/15 Torr.

p-Toluenesulfonyl chloride (15·3 g; 80 mmol) was added under cooling with ice to a solution of the compound *XXXV* (9·6 g; 80 mmol) in pyridine (70 ml), the mixture was set aside at room temperature for 2 days and evaporated *in vacuo*. The residue was diluted with water (100 ml), extracted with chloroform (4 . 50 ml), the extract dried over magnesium sulfate, filtered and taken down *in vacuo*. Chromatography of the residue on a silica gel column in chloroform yielded 12·1 g (44 mmol; 55%) of the *p*-toluenesulfonyl derivative *XXXVI* (R_F 0·27 in S3).

A suspension of adenine (3·37 g; 25 mmol) and sodium hydride (0·60 g; 25 mmol) in dimethylformamide (40 ml) was stirred at 60°C for 1 h, a solution of the compound *XXXVI* (12·1 g; 44 mmol) in dimethylformamide (20 ml) was added and the mixture stirred at 100°C for 16 h under exclusion of moisture. The mixture was taken down at 40°C/0·1 Torr, the residue extracted with boiling chloroform (100 ml), filtered through Celite which was then washed with hot chloroform (2 . 50 ml), the filtrate evaporated *in vacuo* and the residue chromatographed on a silica gel column in chloroform. The product was eluted with a chloroform–ethanol (95 : 5) mixture, the pertinent fractions combined, evaporated *in vacuo* and the residue crystallised from ethanol (light petroleum added until the solution was turbid), affording 3·60 g (60·8%) of the compound *XXXVII*, m.p. 184—185°C. For $C_{10}H_{15}N_5O_2$ (237·3) calculated: 50·62% C, 6·37% H; 29·52% N; found: 50·91% C, 6·36% H, 28·95% N. R_F 0·70 (S1), 0·30 (S4), 0·62 (S5). UV spectrum (pH 2, 7, 12): λ_{max} 262 nm, ε_{max} 13 500.

9-(*RS*)-(3-Benzyloxy-2-*p*-toluenesulfonyloxypropyl)adenine (*XXXIX*)

p-Toluenesulfonyl chloride (5·7 g; 30 mmol) was added to an ice-cooled solution of 9-(*RS*)--(3-benzyloxy-2-hydroxypropyl)adenine[11] (*XXXVIII*) (7·5 g; 25 mmol) in pyridine (50 ml) and the mixture set aside at room temperature for 3 days. Ethanol (20 ml) was added, followed after 1 h with ethyl acetate (300 ml), and the mixture was washed with water (3 . 100 ml). After drying over magnesium sulfate, filtration and evaporation of the solvent *in vacuo*, the residue was chromatographed on a column of silica gel. The product was eluted with an ethanol–chloroform mixture (5 : 95) and crystallised from ethyl acetate (light petroleum added till the solution was turbid) to yield 2·60 g (23%) of the compound *XXXIX*, m.p. 188—189°C. For $C_{22}H_{23}N_5O_4S$ (453·5) calculated: 58·26% C, 5·11% H, 15·45% N; 7·07% S; found: 57·83% C, 5·45% H, 15·31% N, 7·36% S. R_F 0·63 in S5. Further elution afforded (on crystallisation from ethyl acetate with addition of light petroleum) 3·1 g (41·4%) of the starting *XXXVIII*.

9-(*RS*)-(3-Benzyloxy-2-azidopropyl)adenine (*XL*)

A mixture of the compound *XXXIX* (2·3 g; 5 mmol) and sodium azide (1·3 g) in dimethyl sulfoxide (25 ml) was stirred at 100°C for 8 h under exclusion of moisture, evaporated at 80°C/0·1 Torr, the residue treated with boiling chloroform (50 ml) and filtered through Celite which was then washed with hot chloroform (100 ml). The filtrate was taken down *in vacuo* and the residue crystallised from ethanol (light petroleum added) to give 1·3 g (80%) of the compound *XL*, m.p.

131—132°C. For $C_{15}H_{16}N_8O$ (324·4) calculated: 55·54% C, 4·97% H, 34·55% N; found: 55·63% C, 4·68% H, 34·01% N. R_F 0·55 in S5.

9-(*RS*)-(3-Hydroxy-2-aminopropyl)adenine (*XLI*)

A mixture of acetic acid (120 ml), 20% palladium chloride (1 ml) and 5% palladium on charcoal (Merck) was hydrogenated under normal pressure for 1 h, then compound *XL* (1·1 g; 3·4 mmol) was added and the mixture stirred under normal pressure for 3 h. After this time the reaction was complete (thin-layer chromatography in S6). The mixture was filtered through Celite which was then washed with acetic acid (50 ml), the filtrate evaporated *in vacuo*, the residue codistilled with water (4 . 20 ml), made alkaline with ammonia, taken down and chromatographed on a loose layer of silica gel (S6). The product band (R_F 0·08 in S6) was eluted with methanol (500 ml) and the eluate taken down. Crystallisation from ethanol (with addition of ether till the solution was turbid) afforded 0·30 g (42·4%) of the compound *XLI*, m.p. 220—223°C. For $C_8H_{12}N_6O$ (208·2) calculated: 46·14% C, 5·81% H, 40·37% N; found: 46·66% C, 5·56% H, 40·03% N. UV spectrum (pH 2, 7, 12):λ_{max} 261 nm (ε_{max} 13 500). R_F *XLI*: 0·47 in S1, 0·42 in S2; *XLII*: 0·81 in S1, 0·73 in S2, both compounds are ninhydrin-positive. E_{Ade} = 1·32 (E2) (*XLIX*, E_{Ade} = 0·75 in E2). Analogous work-up procedure afforded further the compound *XLII* (0·25 g; 23·5%), m.p. 145°C. R_F 0·40 in S6. For $C_{15}H_{18}N_6O$ (298·4) calculated: 60·38% C, 6·08% H, 28·17% N; found: 60·66% C, 5·80% H, 28·08% N.

9-(*RS*)-(3-Benzyloxy-2-benzoyloxypropyl)adenine (*XLIII*)

Triethylamine (3 ml) was added to a suspension of the compound *XXXVIII* (9·0 g; 30 mmol) and benzoyl cyanide (5·1 g; 39 mmol) in acetonitrile (100 ml). The mixture was stirred for 1 h at room temperature, taken down *in vacuo* and the residue chromatographed on a silica gel column. The product fraction was taken down and crystallised from ethyl acetate to give 10·0 g (83%) of the compound *XLIII*, m.p. 89—90°C. For $C_{22}H_{21}N_5O_3$ (403·4) calculated: 65·49% C, 5·25% H, 17·36% N; found: 65·56% C, 5·57% H, 17·30% N. R_F 0·62 (S4).

9-(*RS*)-(3-Hydroxy-2-benzoyloxypropyl)adenine (*XLIV*)

A solution of the compound *XLIII* (8·4 g; 20·8 mmol) in methanol (400 ml) was mixed with conc. hydrochloric acid (3 ml), 20% palladium chloride solution (1 ml) and 5% palladium on charcoal (1·5 g) and hydrogenated at 0·1 atm overpressure. After the hydrogen uptake had ceased (20 min), the mixture was neutralised with methanolic ammonia and filtered through Celite which was washed with methanol (100 ml). The filtrate was taken down *in vacuo*, the residue dissolved in chloroform (200 ml), the solution washed with water (2 . 50 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*. Crystallisation of the residue from ethyl acetate (600 ml) afforded 5·3 g (81·5%) of the compound *XLIV*, m.p. 127—128° C. For $C_{15}H_{15}N_5O_3$ (313·3) calculated: 57·50% C, 4·83% H, 22·36% N; found: 57·68% C, 4·97% H, 22·34% N. R_F 0·31 (S4).

9-(*RS*)-(3-*p*-Toluenesulfonyloxy-2-benzoyloxypropyl)adenine (*XLV*)

p-Toluenesulfonyl chloride (3·25 g; 17 mmol) was added to a pre-cooled (0°C) solution of the compound *XLIV* (4·7 g; 15 mmol) in pyridine (50 ml) and the mixture was set aside at room temperature overnight. After addition of ethanol (10 ml) the mixture was allowed to stand for 30 min, taken down *in vacuo*, and the residue homogenised in ethyl acetate (200 ml) and water

(50 ml). The ethyl acetate layer was washed with water (2 . 50 ml), dried over magnesium sulfate, filtered and the filtrate was taken down *in vacuo*. Crystallisation of the residue from ethanol afforded 5·40 g (77·6%) of the compound *XLV*, m.p. 153–154°C. For $C_{22}H_{21}N_5O_5S$ (467·5) calculated: 56·52% C, 4·53% H, 14·98% N, 6·86% S; found: 56·48% C, 4·38% H, 15·22% N, 7·01% S. R_F 0·46 (S4).

9-(*RS*)-(3-Azido-2-benzoyloxypropyl)adenine (*XLVI*)

A solution of the compound *XLV* (5·0 g; 10·7 mmol) and sodium azide (3·0 g; 46 mmol) in dimethyl sulfoxide (50 ml) was heated to 100°C for 14 h. After evaporation at 60°C/0·1 Torr the residue was extracted with boiling chloroform (4 . 50 ml), filtered, the filtrate crystallised from ethyl acetate (light petroleum added till the solution was turbid) to give 3·0 g (83%) of the compound *XLVI*, m.p. 203–204°C. For $C_{15}H_{14}N_8O_2$ (338·3) calculated: 53·25% C, 4·17% H, 33·13% N; found: 53·80% C, 4·09% H, 32·97% N. R_F 0·46 (S4).

9-(*RS*)-(3-Azido-2-hydroxypropyl)adenine (*XLVII*)

A suspension of the compound *XLVI* (2·9 g; 8·6 mmol) in 0·04M methanolic sodium methoxide (50 ml) was stirred at room temperature overnight, filtered, washed with ethanol and ether and dried *in vacuo*, leaving 1·65 g (82%) of the chromatographically homogeneous compound *XLVII*, m.p. 201–202°C. For $C_8H_{10}N_8O$ (234·2) calculated: 41·02% C, 4·30% H, 47·85% N; found: 41·15% C, 4·47% H, 48·12% N. R_F 0·69 (S1), 0·72 (S2), 0·50 (S5).

9-(*RS*)-(3-Amino-2-hydroxypropyl)adenine (*XLVIII*)

The compound *XLVII* (1·55 g; 6·6 mmol) in 80% acetic acid (100 ml) was hydrogenated over 5% Pd/C (1 g) under 0·1 atm. overpressure. The reaction was complete in 1 h and the mixture was then filtered through Celite which was washed with acetic acid (50 ml) and the filtrate was taken down *in vacuo*. Crystallisation of the residue from water gave 1·35 g (98%) of the compound *XLVIII*, m.p. 184–185°C. For $C_8H_{12}N_6O$ (208·2) calculated: 46·14% C, 5·81% H, 40·37% N; found: 46·20% C, 5·83% H, 41·00% N. R_F 0·42 (S1), 0·45 (S2), 0·15 (S5).

9-(*RS*)-(2,3-Di-*p*-toluenesulfonyloxypropyl)adenine (*L*)

A mixture of 9-(*RS*)-(2,3-dihydroxypropyl)adenine[2] (*XLIX*) (4·2 g; 20 mmol) and *p*-toluenesulfonyl chloride (9·5 g; 50 mmol) in pyridine (50 ml) was set aside at room temperature for 2 days with intermittant stirring. Ethanol (10 ml) was added, the mixture evaporated, taken up in ethyl acetate (200 ml), washed with water (3 . 50 ml), dried over magnesium sulfate, filtered, the filtrate taken down *in vacuo* and the residue codistilled with toluene (3 . 50 ml). The product *L* (5·9 g; 57%) crystallised from ethanol (ether being added until the solution was turbid) in a refrigerator; m.p. 144–145°C; R_F 0·27 in S4. For $C_{22}H_{23}N_5O_6S_2$ (517·6) calculated: 51·05% C, 4·48% H, 13·54% N, 12·39% S; found: 50·46% C, 5·31% H, 14·06% N, 12·50% S.

9-(*RS*)-(2,3-Diazidopropyl)adenine (*LI*)

A mixture of the compound *L* (5·17 g; 10 mmol), sodium azide (5·0 g; 77 mmol) and dimethyl sulfoxide (100 ml) was heated to 120°C for 14 h and then taken down at 80°C/0·1 Torr. The residue was extracted with boiling ethyl acetate, filtered, the insoluble material washed on the filter with hot ethyl acetate (100 ml) and the solvent evaporated *in vacuo*. The residue was chro-

matographed on a column of silica gel and the product was eluted with a mixture of chloroform and ethanol (95 : 5). The combined fractions were taken down and the residue crystallised from ethanol (light petroleum added), affording 1·65 g (63·6%) of the compound *LI*, m.p. 143–145°C. For $C_8H_9N_{11}$ (259·3) calculated: 37·05% C, 3·50% H, 59·44% N; found: 36·95% C, 4·08% H, 58·38% N. R_F 0·32 (S4).

9-(*RS*)-(2,3-Diaminopropyl)adenine (*LII*)

A mixture of acetic acid (120 ml), 20% solution of palladium chloride (1 ml) and 5% Pd/C (Merck; 1·8 g) was hydrogenated under normal pressure for 30 min, then the compound *XLV* (1·3 g; 5 mmol) was added and hydrogenated under stirring at normal pressure and room temperature for 3 days. The mixture was filtered through Celite which was then washed with acetic acid (50 ml), the filtrate was taken down, codistilled with water (3 . 20 ml), made alkaline with ammonia and taken down. The residue was chromatographed on two loose layers of silica gel in the solvent system S6, the product band (near the start) was eluted with methanol (500 ml) in a column, the eluate was taken down and the residue chromatographed on a column of cellulose in 70% 2-propanol. The product fractions (according to thin-layer chromatography in S1) were taken down, the product precipitated from ethanol (20 ml) by addition of ether (200 ml), collected on filter, washed with ether and dried in vacuo to give 0·50 g (48·4%) of the compound *LII*, m.p. 54–55°C. For $C_8H_{13}N_7$ (221·3) calculated: 43·42% C, 5·92% H, 50·65% N; found: 43·67% C, 6·25% H, 50·11% N. R_F 0·35 in S1. E_{Ade} = 1·61 (E2) (*XLIX*, E_{Ade} = 0·75 in E2). UV spectrum (pH 2): λ_{max} 262 nm (ε_{max} 13 800).

5-O-(Adenin-9-yl)-5-deoxy-L-arabinofuranose (*LIIIb*)

A 25% solution of hydrogen chloride in methanol (25 ml) was added to a solution of L-arabinose (50 g) in methanol (1 l) and the mixture was stirred at room temperature overnight. Pyridine (50 ml) was added to the clear solution, evaporated, the residue was coevaporated with toluene (2 . 100 ml), dissolved in pyridine (450 ml), the solution was cooled with ice and mixed with *p*-toluenesulfonyl chloride (63 g; 0·33 mol). The mixture was set aside at room temperature overnight and taken down *in vacuo*. The residue was dissolved in chloroform (500 ml), the solution washed with water (2 . 100 ml), dried over magnesium sulfate, filtered and the filtrate taken down *in vacuo*. The residue was mixed with acetone (300 ml) and conc. sulfuric acid (5 ml) and allowed to stand overnight. The mixture was neutralised with methanolic ammonia, evaporated, taken up in chloroform (300 ml), washed with water (3 . 100 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*. The residue was chromatographed on a silica gel column in chloroform and the obtained product crystallised from hot ethanol (100 ml) on gradual addition of light petroleum under stirring (total 500 ml). After 2 days in refrigerator, the crystalline 5-O-*p*-toluenesulfonyl-5-deoxy-1,2-O-isopropylidene-L-arabinofuranose (R_F 0·24 in S3) was collected on filter (suction) washed with light petroleum and dried *in vacuo*; yield 24·2 g (22·4%).

A mixture of this product (19·2 g; 59 mmol) and dry sodium salt of adenine (9·5 g) in dimethylformamide (70 ml) was stirred at 100°C for 14 h under exclusion of moisture. After removal of the solvent at 40°C/0·1 Torr, the residue was extracted with hot chloroform (500 ml) and the filtrate evaporated *in vacuo*. Crystallisation of the residue from ethanol afforded 4·8 g (28%) of the 1,2-O-isopropylidene derivative *LIIIa*, m.p. 239–240°C. For $C_{13}H_{17}N_5O_4$ (307·3) calculated: 50·81% C, 5·58% H, 22·79% N; found: 50·49% C, 5·66% H, 22·74% N. R_F 0·72 in S1, 0·68 in S2, 0·36 in S4.

A solution of the compound *LIIIa* (4·5 g; 15·6 mmol) in water (80 ml), containing 18 mmol of hydrogen chloride, was heated to 80°C for 6 h, cooled down, neutralised with Dowex 1 X 2

(OH^- form), filtered and the material on the filter washed with hot water (4 . 100 ml). The filtrate was taken down and the residue crystallised from water, yielding monohydrate of the compound *LIIIb* (2·6 g; 58%), m.p. 183°C. For $C_{10}H_{15}N_5O_5$ (285·2) calculated: 42·10% C, 5·32% H, 24·60% N; found: 42·71% C, 5·28% H, 24·70% N. R_F 0·41 in S1, 0·36 in S2; *XLIX*: R_F 0·36 in S1, 0·35 in S2.

3-(*S*)-(Adenin-9-yl)lactic Acid (*LIV*)

The compound *LIIIb* (0·71 g; 2·5 mmol) was added at 0°C to a stirred solution of sodium periodate (1·17 g; 5·5 mmol) in 70% acetone (50 ml) and the mixture was stirred at 0°C for 1 h. Sodium periodate (1·17 g; 5·5 mmol), followed by 0·5% ruthenium tetrachloride solution (0·2 ml), was added and the stirring was continued at 0°C for 1 h and then at room temperature for 30 min. The suspension was filtered, the material on the filter washed with acetone (100 ml) and the filtrate taken down *in vacuo*. The residue was allowed to stand with dilute (1 : 1) ammonia (50 ml) for 2 h, evaporated *in vacuo* and applied to a column of Dowex 50 X 8 (H^+ form). The column was eluted with water until the absorption and conductivity of the eluate dropped, and then with dilute (1 : 10) ammonia. The alkaline UV-absorbing eluate was taken down and the residue chromatographed on a column of DEAE cellulose. The product fractions (0·02—0·05M) were evaporated, the residue was coevaporated with methanol (3 . 20 ml) and applied to a column of Dowex 50 X 8 in the pyridinium form (50 ml). The column was eluted with 30% pyridine (200 ml), the eluate taken down and the residue coevaporated with ethanol (3 . 50 ml). The residue was taken up in methanol (10 ml) and precipitated with ether (200 ml), filtered, washed with ether and dried *in vacuo* to give the compound *LIV* (0·35 g; 63%) which 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: 43·56% C, 41·5% H, 32·20% N. R_F 0·38 in S1, E_{Up} 0·58. UV spectrum (pH 2): λ_{max} 262 nm (ε_{max} 14 000).

3-(*R*)-(Adenin-9-yl)lactic Acid (*LVI*)

This compound was prepared from 1·43 g (5 mmol) of 5-(adenin-9-yl)-5-deoxy-D-ribofuranose (*LV*) (ref.[2,12]) in the same manner as described for *LIV*; yield 0·64 g (57%), it did not melt below 260°C. Analysis: 43·39% C, 4·34% H, 30·98% N. Paper chromatography, electrophoresis and UV spectrum were identical with those of the compound *LIV*.

3-(*RS*)-(Hypoxanthin-9-yl)lactic Acid (*LVIII*) and
3-(*RS*)-(Hypoxanthin-9-yl)-2-chloropropionic Acid (*LIX*)

A solution of 3-(*RS*)-(adenin-9-yl)alanine[13] (*LVII*) (1·1 g; 5 mmol) and sodium nitrite (1·4 g; 20 mmol) in water (25 ml) was mixed with conc. hydrochloric acid (3 ml) and set aside under exclusion of air at room temperature for 4 days. The mixture was then applied on a column of Dowex 50 X 8 (H^+ form) and eluted with water. The first fraction contained salts, the second (UV-absorbing) one was taken down and the residue crystallised from water, affording 0·42 g (34·5%) of the compound *LIX*, m.p. 210°C. For $C_8H_7N_4O_3Cl$ (242·6) calculated: 39·60% C, 2·91% H, 23·10% N, 14·61% Cl; found: 39·09% C, 2·90% H, 22·89% N, 14·98% Cl. UV spectrum (pH 2): λ_{max} 250 nm (ε_{max} 11 800). R_F 0·48 in S1, 0·40 in S2. Evaporation of the third (UV-absorbing) fraction and crystallisation of the residue from water gave 0·40 g (33%) of the compound *LVIII*, m.p. 171°C. For the monohydrate of $C_8H_8N_4O_4$ (242·2) calculated: 39·67% C, 4·16% H, 23·14% N; found: 39·19% C, 4·08% H, 22·90% N. R_F 0·33 in S1, 0·30 in S2. UV spectrum (pH 2): λ_{max} 250 nm (ε_{max} 10 600).

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