PREPARATION OF ENANTIOMERIC AND RACEMIC 2,3,4,5-TETRAHYDROXYPENTYL DERIVATIVES OF ADENINE, CYTOSINE AND URACIL*

Antonín HOLÝ

Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6

Received February 3rd, 1982

1-(Adenin-9-yl)-1-deoxy-DL-ribitol (*III*), -D-arabitol (*IXa*), -L-arabitol (*XIVa*), -D,L-xylitol (*XXIVa*), 1-(cytosin-L-yl)-1-deoxy-D-arabitol (*IXb*), -L-arabitol (*XIVb*), 1-(uracil-1-yl)-1-deoxy--D-arabitol (*IXc*), -L-arabitol (*XIVc*) and -DL-xylitol (*XXIVb*) were prepared by reaction of 1-O-*p*-toluenesulfonyl-2,3:4,5-di-O-isopropylidenealditols *Ib*, *VIIb*, *XIIb* and *XXIIb* with sodium salts of adenine, N^4-benzoylcytosine or 4-methoxy-2-pyrimidone followed by removal of the protecting groups. Condensation of the mentioned sodium salts with methyl 5-O-*p*-toluenesulfonyl-2,3-O-isopropylidene-β-D-ribofuranoside (*IV*) with subsequent acid hydrolysis and reduction with sodium borohydride afforded 1-(adenin-9-yl)-1-deoxy-L-ribitol (*VIa*) and 1-cytosin--1-yl)-1-deoxy-L-ribitol (*VIb*). 1-(Adenin-9-yl)-1-deoxy-D-lyxitol (*XVII*), -L-lyxitol (*XVIII*) and -2-O-methyl-D-lyxitol (*XXI*) were prepared analogously. Acid hydrolysis of 5-(adenin-9-yl)-5-deoxy-4-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose (*XXVa*), followed by reduction with sodium borohydride and catalytic hydrogenation, gave 1-(adenin-9-yl)-1-deoxy-L-xylitol (*XXVIb*).

In previous communications of this series we described an unexpectedly strong inhibitory effect of some aliphatic adenosine analogues on S-adenosyl-L-homocysteine hydrolase[1,2] which can be correlated with the antiviral activity of these compounds[3–5]. Within the framework of detailed investigations of structure-activity relationships these effects were studied on a series of structurally modified hydroxylated 9-alkyladenine derivatives[6], particularly substituted isomeric di- and trihydroxybutyl derivatives[7,8]. This communication concerns general methods of preparation of the next higher homologues, the isomeric 2,3,4,5-tetrahydroxypentyl derivatives of nucleobases, *i.e.* compounds formally derived by replacement of one of the primary hydroxyls in the alditol by a heterocyclic base.** Although adenine derivatives are the most interesting in the above-mentioned context, the study was extended also to uracil

* Part VI in the series Studies on S-Adenosyl-L-homocysteine Hydrolase; Part V: This Journal *47*, 1392 (1982).

** For a better understanding, we use for the mentioned compounds the nomenclature derived from aldopentoses, in which the heterocyclic base is attached to the carbon of the original aldehyde function.

and cytosine compounds. As far as molecular size and number of primary and secondary hydroxyls are concerned, tetrahydroxyalkyl derivatives of nucleobases resemble natural nucleosides: some of the related compounds, such as 1-alkoxy (alkylthio)--1-deoxy-1-purin-9-yl-alditols, exhibit also interesting biological effects[9].

The method based on building the heterocyclic ring from the corresponding sugar amine[10] is not suitable for the present purpose. Therefore, we used two independent and general methods: *a*) condensation of reactive alditol derivatives with the heterocyclic base, and *b*) condensation of a reactive aldofuranose derivative with the heterocyclic base, followed by reduction of the aldehyde function of the intermediate. The first method cannot be used for preparation of enantiomeric compounds from meso-alditols. As reactive derivatives we used invariably *p*-toluenesulfonates of primary hydroxyl groups in alditols or aldofuranoses; because of extraordinarily facile intramolecular cyclization of these compounds the protection of other hydroxyl functions in the alditol was necessary. The *p*-toluenesulfonyl derivatives reacted in dimethylformamide directly with sodium salt of adenine whereas for the preparation of cytosine derivatives sodium salt of N^4-benzoylcytosine was employed. (It is worth notice that preparation of N^4-benzoylcytosine from cytosine and benzoyl cyanide[11] is better than fusion of cytosine with an excess of benzoic anhydride.) For preparation of the uracil derivatives it is advantageous to exclude the reaction at the N^3 position using salt of 4-methoxy-2-pyrimidone[12] and the subsequent transformation of the intermediate into the uracil derivative by acid hydrolysis or dealkylation.

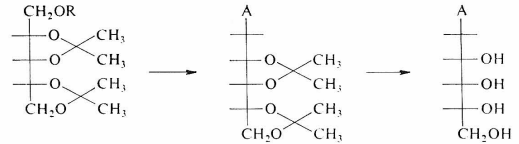
The mentioned reaction types are represented by preparation of the ribitol derivatives. DL-Ribitol was transformed by reaction with acetone into the 2,3:4,5-di-O-isopropylidene derivative *Ia* and further into the *p*-toluenesulfonyl derivative *Ib*; this was condensed with sodium salt of adenine to give the blocked derivative which on acid hydrolysis afforded 1-(adenin-9-yl)-1-deoxy-DL-ribitol (*III*). Hydrolysis with dilute sulfuric acid at room temperature proved to be the method of choice and was used throughout this work; sulfuric acid was easily removed with barium hydroxide and the product was not contaminated with N- and O-acyl derivatives arising when the hydrolysis was performed with acetic or formic acid. The L-ribitol derivatives *VI* were obtained from methyl 5-O-*p*-toluenesulfonyl-2,3-O-isopropylidene-β-D-ribofuranoside[13] (*IV*) whose condensation with sodium salt of the corresponding heterocyclic base afforded intermediates of the type *V*. Their hydrolysis gave 5-substituted D-ribofuranoses which without isolation were reduced smoothly with sodium borohydride to give 1-substituted 1-deoxy-L-ribitols. In this way we prepared the adenine and cytosine derivatives *VIa* and *VIb*, respectively. Naturally, application of this method to preparation of substituted 1-deoxy-D-ribitols requires preparation of L-ribose or enantiomer of the compound *IV*.

Both the enantiomeric derivatives of 1-deoxyarabitol can be prepared by asymmetric synthesis according to the first variant: as described[14], arabitols react directly

with acetone to give distillable 2,3:4,5-di-O-isopropylidene derivatives *VIIa* and *XIIa* which were transformed into crystalline 1-O-*p*-toluenesulfonyl derivatives *VIIb* and *XIIb*; these compounds on condensation with sodium salts of nucleobases, followed by acid hydrolysis, afforded both series of enantiomeric 1-deoxyarabitols *IX* and *XIV*, derived from adenine, uracil and cytosine. In order to check the purity of the compound *IXa*, its independent synthesis from 3,4-O-isopropylidene-D-mannitol (*Xa*) (ref.[15]) was carried out: tritylation of *Xa* afforded the monotrityl derivative *Xb* which on reaction with sodium periodate and subsequent reduction with sodium borohydride gave 5-O-trityl-2,3-O-isopropylidene-D-arabitol (*XIa*) as the sole reaction product; reaction of its mono-*p*-toluenesulfonyl derivative *XIb* with sodium salt of adenine, followed by acid hydrolysis, afforded the compound *IXa*, identical in all respects with material prepared directly from compound *VIIb*. Also its diisopropylidene derivative was identical with the compound *VIIIa*, prepared by the above-mentioned procedure. This proved indirectly also the stereochemical purity of the compound[14] *VIIa*.

The second synthetic variant was preferable for stereospecific synthesis of enantiomeric 1-deoxy-1-lyxitols *XVII* and *XVIII*. It started also from L- or D-arabinose derivatives but in this case the reactive *p*-toluenesulfonyl group (and hence also the heterocyclic base) was introduced into the position 5 whereas when starting from the compounds *VIIa* and *XIIa*, the position of the base corresponded to the original aldehyde function, *i.e.* $C_{(1)}$. 1,2-O-Isopropylidene-5-O-*p*-toluenesulfonyl-β-D-arabinofuranose (*XVa*) and its enantiomer *XVIa* (ref.[5]) were transformed by the described procedure[5,15] into the respective 5-(adenin-9-yl)-5-deoxy derivatives *XVb* and *XVIb* which on hydrolysis, followed by reduction of the free 5-substituted arabinoses with sodium borohydride, afforded pure 1-(adenin-9-yl)-1-deoxy-D-lyxitol (*XVII*) and its enantiomer *XVIII*. An analogous procedure was used in the preparation of the 3-O-methyl-D-lyxitol derivative *XXI* from the *p*-toluenesulfonate *XVa* by methylation to the O-methyl derivative *XIXa* (ref.[16]), and subsequent condensation with adenine to the compound *XIXb*, acid hydrolysis and reduction with sodium borohydride.

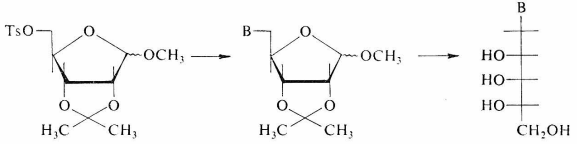
The preparation of 1-deoxyxylitol derivatives is analogous to that of ribitol derivatives: DL-xylitol was transformed into the 2,3:4,5-di-O-isopropylidene derivative *XXIIa* and its 1-O-*p*-toluenesulfonate *XXIIb*. Reaction of the latter with sodium salt of the corresponding base and subsequent acid hydrolysis afforded 1-(adenin-9-yl)-1-deoxy-DL-xylitol (*XXIVa*) and the analogous racemic uracil derivative *XXIVb*. Synthesis of the optically active derivatives started inevitably from a D-xylofuranose derivative. 5-(Adenin-9-yl)-5-deoxy-3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose (*XXVa*), accessible from 1,2:5,6-di-O-isopropylidene-α-D-glucofuranose (ref.[8]), afforded on acid hydrolysis and reduction with sodium borohydride the 3-O-benzyl derivative *XXVIa*. This intermediate was catalytically reduced to 1-(adenin-9-yl)-1-deoxy-L-xylitol (*XXVIb*), identical in all (except chiroptical) properties



Ia, R = H
Ib, R = Ts

II

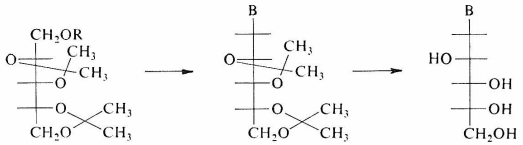
III



IV

Va, B = A
Vb, B = C

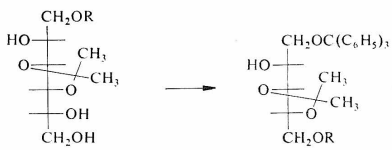
VIa, B = A
VIb, B = C



VIIa, R = H
VIIb R = Ts

VIIIa, B = A
VIIIb, B = C
VIIIc, B = U

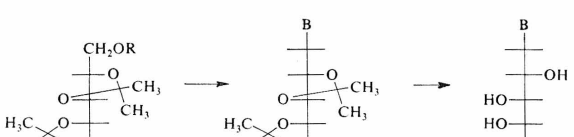
IXa, B = A
IXb, B = C
IXc, B = U



Xa, R = H
Xb, R = C(C$_6$H$_5$)$_3$

XIa, R = H
XIb, R = Ts

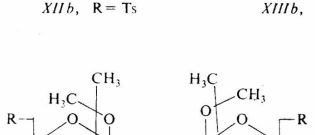
with the racemate *XXIVa*. This also confirmed the stereospecific course of the conversion of DL-xylitol into the diisopropylidene derivative *XXIIa* according to the published[14] procedure. Similarly, it would be possible to convert L-xylose into the enantiomeric 1-deoxy-D-xylitol derivative.



XIIa, R = H
XIIb, R = Ts

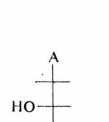
XIIIa, B = A
XIIIb, B = C

XIVa, B = A
XIVb, B = C
XIVc, B = U

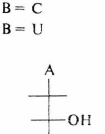


XVa, R = OTs
XVb, R = A

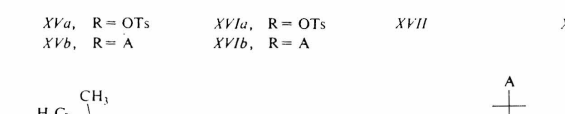
XVIa, R = OTs
XVIb, R = A



XVII



XVIII

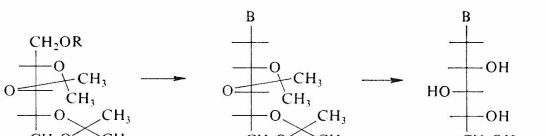


XIXa, R = OTs
XIXb, R = A

XX

XXI

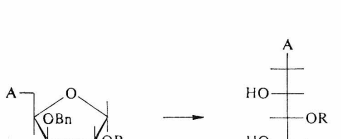
In addition to the mentioned four configurationally isomeric groups of 1-substituted aldopentitols of the *ribo*-, *arabo*-, *lyxo*- and *xylo*-configuration, we prepared also *erythro*-9-(3,4,5-trihydroxypentyl)adenine *XXX* from 2-deoxy-D-ribitol (*XXVIIa*). Reaction of the compound *XXVIIa* with benzoyl chloride afforded the 1,5-di-O-benzoyl derivative *XXVIIb* which on reaction with acetone and debenzoylation was transformed into the 1,3-dioxolane derivative *XXVIIIa*. Its tosylation gave compound *XXVIIIb* which was benzoylated with benzoyl cyanide to give the derivative *XXVIIIc*. Condensation with adenine afforded compound *XXIX* whose acid hydrolysis led to the desired compound *XXX*. The formation of *XXX* as the homogeneous product confirms at the same time that the tosylation proceeds only at the sterically more accessible of the two hydroxyalkyl groups in the 4,5-disubstituted 1,3-dioxolane *XXVIIIa*.



XXIIa, R = H
XXIIb, R = Ts

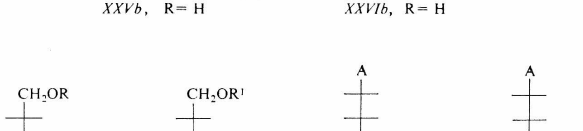
XXIIIa, B = A
XXIIIb, B = U

XXIVa, B = A
XXIVb, B = U



XXVa, R,R = $(CH_3)_2C$
XXVb, R = H

XXVIa, R = Bn
XXVIb, R = H



XXVIIa, R = H
XXVIIb, R = Bz

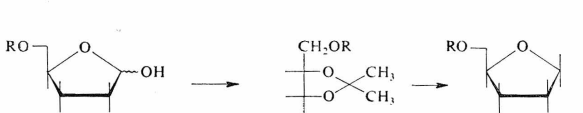
XXVIIIa, R^1 = R^2 = H
XXVIIIb, R^1 = Ts, R^2 = H
XXVIIIc, R^1 = Ts, R^2 = Bz

XXIX

XXX

In the attempts to find an easier access to substituted D-ribitol derivatives by utilizing the original aldehyde group of D-ribose for substitutions with the heterocyclic base we observed an anomalous reaction course. Tritylation of 2,3-O-isopropylidene-D-ribofuranose (*XXXIa*) (ref.[17]) afforded the compound *XXXIb* which was reduced with sodium borohydride to the expected D-ribitol derivative *XXXIIa*. Its tosylation in pyridine resulted in sterically preferred intramolecular cyclization leading to 5-O-trityl-2,3-O-isopropylidene-1,4-anhydro-D-ribitol (*XXXIIIa*). This product was formed (instead of the expected isomer of *XIa*) even under very mild conditions. Acid hydrolysis of this compound, followed by reaction with acetone, gave 2,3-O-isopropylidene-1,4-anhydro-D-ribitol (*XXXIIIb*) which was transformed

into the *p*-toluenesulfonate *XXXIIIc*. The 5-(adenin-9-yl) derivative *XXXIVa*, obtained from this compound, was hydrolyzed to give 5-(adenin-9-yl)-5-deoxy--1,4-anhydro-D-ribitol (*XXXIVb*) which was of interest because some other adenine derivatives of hexose anhydroalditols are known to possess biological activity[18].



XXXIa, R = H
XXXIb, R = C(C$_6$H$_5$)$_3$

XXXIIa, R = H
XXXIIb, R = Ts

XXXIIIa, R = C(C$_6$H$_5$)$_3$
XXXIIIb, R = H
XXXIIIc, R = Ts

XXXIVa, R, R = (CH$_3$)$_2$C
XXXIVb, R = H

In formulae *I*—*XXXIV*, A = adenin-9-yl, C = cytosin-1-yl, U = uracil-1-yl, Ts = *p*-toluenesulfonyl, Bz = benzoyl, Bn = benzyl residue.

In addition to the usual criteria, the purity of all the prepared substituted 1-deoxyaldopentitols was checked also by ^{1}H NMR spectra and UV absorption spectra which were consistent with behaviour of 9-alkyladenines, 1-alkylcytosines or uracils. The stereochemical homogeneity was checked further by electrophoresis and HPLC. Paper electrophoresis in an alkaline borate buffer[7] separated some groups of compounds; the mobility of all the studied adenine derivatives was higher than, or comparable with that of adenosine: this is in accord with the easier formation of borate complexes. The electrophoretic mobility increases in the order *lyxo* < *ribo* ~ ~ *xylo* < *arabo*. Even better for separation of stereoisomers and checking their homogeneity proved to be HPLC which allowed to separate all the four configurational groups of compounds. For adenine derivatives the elution times increased in the order *xylo* < *arabo* < *lyxo* < *ribo* (Table I).

All the derivatives were tested for antibacterial activity against *Escherichia coli* B (synthetic medium with glucose). Neither of them showed any growth inhibition at concentrations up to 1 mg/ml ($3{\cdot}7 \cdot 10^{-3}$M). The antiviral activity of these compounds and their inhibition of S-adenosyl-L-homocysteine hydrolase will be the subject of another communication in this series.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Unless stated otherwise, the solutions were taken down at 40°C/2 kPa and the compounds dried at room temperature and 13 Pa over phosphorus pentoxide. Paper chromatography was performed on a Whatman No 1 paper (descendent arrangement) in the system S1 2-propanol–conc. aqueous ammonia–water (7 : 1 : 2); thin-layer chromatography was carried out on Silufol UV 254 plates (Kavalier, Czechoslovakia) in the systems S2 chloroform, S3 chloroform–ethanol (95 : 5), S4 chloroform–ethanol (9 : 1), S5 chloroform–methanol (9 : 1), S6 chloroform–methanol (4 : 1), S7 benzene–ethyl acetate (95 : 5), S8 benzene–ethyl acetate (4 : 1). Spots were detected in UV light or in the case of sugars by carbonization. Paper electrophoresis was carried out on a Whatman No 1 paper

TABLE I
1-(Adenin-9-yl) and 1-(Pyrimidin-1-yl)-1-deoxyaldopentitols

Formula	Configuration	R_F [a]	E_{Urd} [b]	τ [c], min	$[\alpha]_D^{20}$ [d]	Ultraviolet spectra	
						λ_{max}, nm	ε_{max}
III	DL-*ribo*	0·48	0·58	13·6	—	262	12 500
VIa	L-ribo	0·48	0·58	13·6	+28·4°	262	13 400
VIb	L-*ribo*	0·42	0·80	—	+143·1°	286	11 400
IXa	D-*arabo*	0·39	0·71	10·0	+ 32·0°	262	13 500
IXb	D-*arabo*	0·44	0·83	—	+ 79·8°	285	11 800
IXc	D-*arabo*	0·44	0·80	—	+ 69·6°	264	10 500
XIVa	L-*arabo*	0·39	0·71	10·0	− 32·6°	262	13 000
XIVb	L-*arabo*	0·44	0·80	—	− 77·2°	286	11 200
XIVc	L-*arabo*	0·44	0·83	—	− 72·0°	264	10 500
XVII	D-*lyxo*	0·36	0·55	12·2	+ 19·2°	262	13 000
XVIII	L-*lyxo*	0·36	0·55	12·2	− 18·2°	262	12 800
XXI	D-*lyxo*	0·60	0·44	—	—	262	13 000
XXIVa	DL-*xylo*	0·52	0·60	9·6	—	262	14 000
XXIVb	DL-*xylo*	0·50	0·82	—	—	261	10 500
XXVIb	L-*xylo*	0·52	0·60	9·6	+ 24·7°	262	13 500
XXX	D-*ribo*	0·54	—	—	—	261	13 800
XXXIVb	D-*ribo*	0·48	0·60	—	+ 53·2°	262	14 200

[a] in S1; [b] electrophoretic mobility in E1 referred to uridine; [c] elution time in HPLC; [d] in 1M-HCl.

in 0·05M sodium tetraborate (system E1) at 20 V/cm (1 h). Preparative chromatography on silica gel was performed on a column (particle size 30—40 μ; 200 g; Service Laboratory of this Institute) or on loose layers (50 × 15 × 0·3 cm) of silica gel, containing a fluorescence indicator (the same provenience). Solutions of the adenine and cytosine derivatives were deionized on a column of Dowex 50X8 (H^+-form; usually 100 ml) by elution with water till the UV absorption and conductivity dropped. The products were then eluted with 2·5% aqueous ammonia with continuous monitoring the UV absorption. The UV spectra were measured in aqueous solutions on a Specord UV-VIS (Carl Zeiss, Jena) spectrometer, the ^1H NMR spectra on a Varian 100 instrument in deuteriochloroform or in hexadeuteriodimethyl sulfoxide (chemical shifts in ppm, coupling constants in Hz). High performance liquid chromatography was carried out on Separon SI C18 (10 μ; column 250 × 4 mm), elution (1 ml/min) with 0·01M ammonium dihydrogen phosphate, containing 5% (vol.) of methanol; detection at 260 nm. The reaction mixtures after hydrolysis with sulfuric acid were neutralized to pH 7·00 ± 0·05 with a saturated barium hydroxide solution (pH measured with a digital pH-meter from Developmental Workshops of Czechoslovak Academy of Sciences, Prague), the mixture was incubated at 60°C for 1 h and filtered through Celite.

N^4-Benzoylcytosine

A mixture of cytosine (5·6 g; 50·5 mmol), benzoyl cyanide (7·2 g; 55 mmol), acetonitrile (100 ml) and triethylamine (2 ml) was stirred overnight at room temperature under exclusion of moisture. The separated product was collected on filter, washed with acetonitrile and ether and dried *in vacuo*; yield 8·3 g (76·5%) of chromatographically (S3) homogeneous N^4-benzoylcytosine, identical with an authentic sample.

1,2:3,4-Di-O-isopropylidene-DL-ribitol (*Ia*)

A solution of sodium borohydride (15 g) in ice-cold water (100 ml) was added dropwise to a pre-cooled and stirred solution of D-ribose (60 g; 0·4 mol) in water (400 ml), the temperature being kept below +10°C. The mixture was stirred in ice for 3 h, at room temperature for 1 h and the excess hydride was destroyed by addition of Dowex 50X8 (H^+). The mixture (pH 6) was taken down and the residue codistilled with methanol (3 × 100 ml) and toluene (2 × 200 ml). The residue was mixed with anhydrous potassium acetate (16·5 g) and acetic anhydride (500 ml) and warmed till an exothermic reaction began. After the reaction had ceased, the mixture was refluxed (calcium chloride protecting tube) for 90 min and taken down *in vacuo*. The residue was codistilled with toluene (3 × 100 ml), dissolved in chloroform (500 ml), the solution washed with water (4 × 100 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*. The residue was dried at 70°C/13 Pa for 1 h, dissolved in methanol (500 ml) and treated with a 1M sodium methoxide solution until the alkaline reaction persisted (moist pH-indicator paper). The mixture was set aside at room temperature overnight, acidified by addition of Dowex 50 X8 (H^+-form), filtered and the filtrate taken down *in vacuo*. Crystallization from ethanol afforded 44·9 g (74%) of DL-ribitol.

This product (40 g; 0·263 mol) was stirred with a mixture of acetone (150 ml), 2,2-dimethoxypropane (100 ml) and *p*-toluenesulfonic acid hydrate (3·5 g) until it dissolved, the solution was set aside at room temperature overnight, made alkaline with triethylamine and taken down *in vacuo*. The residue was dissolved in ethyl acetate (200 ml), the solution washed with water (2 × 25 ml), dried over magnesium sulfate, filtered, the solid washed with ethyl acetate and the combined filtrates taken down *in vacuo*. Distillation of the residue gave 52·0 g (85%) of *Ia*, b.p. 99—102°C/13 Pa.

1-O-*p*-Toluenesulfonyl-2,3:4,5-di-O-isopropylidene-DL-ribitol (*Ib*)

p-Toluenesulfonyl chloride (63 g; 0·33 mol) was added in one portion to a solution of the compound *Ia* (69 g; 0·3 mol) in pyridine (300 ml), cooled with ice. After stirring for 1 h at 0°C and standing for 3 days at room temperature, methanol (50 ml) was added and the mixture was taken down *in vacuo*. The residue was dissolved in ethyl acetate (400 ml), washed with water (3 × 100 ml), dried over magnesium sulfate and taken down *in vacuo*. The residue was codistilled with toluene (3 × 100 ml) and crystallized from ethanol (100 ml) by addition of light petroleum (700 ml) under stirring and cooling with ice. Yield 71·5 g (62%) of chromatographically pure (R_F 0·26 in S2) compound *Ib*, m.p. 44–46°C. For $C_{18}H_{26}O_7S$ (386·4) calculated: 55·93% C, 6·78% H, 8·30% S; found: 56·51% C, 6·60% H, 8·69% S.

1-(Adenin-9-yl)-1-deoxy-2,3:4,5-di-O-isopropylidene-DL-ribitol (*II*)

A mixture of adenine (2·70 g; 20 mmol), dimethylformamide (100 ml) and sodium hydride (0·48 g, 20 mmol) was stirred at 60°C for 1 h (calcium chloride tube). After addition of the compound *Ib* (7·8 g; 22 mmol), the mixture was stirred at 100°C for 12 h and taken down at 50°C/13 Pa. The residue was extracted with hot chloroform (500 ml total), the extract filtered through Celite and the filtrate evaporated *in vacuo*. The residue was chromatographed on a column of silica gel. After washing the column with chloroform, the product (R_F 0·66 in S6) was eluted with chloroform–methanol (95 : 5), the eluate was taken down and the product crystallized from ethyl acetate (light petroleum added), affording 4·8 g (68·7%) of compound *II*, m.p. 224–225°C. For $C_{16}H_{23}N_5O_4$ (349·4) calculated: 55·00% C, 6·64% H, 20·05% N; found: 54·93% C, 6·57%H, 19·85% N.

1-(Adenin-9-yl)-1-deoxy-DL-ribitol (*III*)

A solution of the compound *II* (3·5 g; 10 mmol) in 0·25M sulfuric acid (100 ml) was kept at 37°C for 24 h, diluted with water (200 ml), neutralized with barium hydroxide solution, and filtered. The filtrate was taken down *in vacuo* and the residue crystallized from 70% aqueous ethanol (with addition of ether), yielding 2·3 g (85%) of compound *III*, m.p. 203–205°C. Mass spectrum: M^+ 269. For $C_{10}H_{15}N_5O_4$ (269·3) calculated: 44·60% C, 5·62% H, 26·01% N; found: 43·82% C, 5·66% H, 25·76% N.

1-(Adenin-9-yl)-1-deoxy-L-ribitol (*VIa*)

A solution of compound *Va* (ref.[5]; 6·4 g; 20 mmol) and concentrated sulfuric acid (1·2 ml) in water (120 ml) was heated to 75°C till the reaction (followed in S5) was complete, cooled, diluted with water (200 ml) and neutralized with barium hydroxide. The filtrate was concentrated *in vacuo* to 250 ml, cooled with ice and a solution of sodium borohydride (1·5 g) in ice-cold water (20 ml) was added dropwise. After stirring for 1 h at 0°C and standing overnight, the mixture was adjusted to pH 6 by addition of Dowex 50X8 (H^+ form), made alkaline with triethylamine, filtered, the filtrate concentrated to about 100 ml and de-ionized on a column (300 ml) of the same ion exchange resin. After washing with water, the resin was suspended in water and the mixture made alkaline with concentrated ammonia, stirred for 1 h, filtered and washed with boiling water (1 litre). The filtrate was taken down *in vacuo* and crystallized from 50% ethanol, affording 4·7 g (87%) of compound *VIa*, m.p. 212–123°C. For $C_{10}H_{15}N_5O_4$ (269·3) calculated: 44·60% C, 5·61% H, 26·02% N; found: 44·56% C, 5·56% H, 25·73% N.

1-(Cytosin-1-yl)-1-deoxy-L-ribitol (*VIb*)

Sodium hydride (0·50 g of 50% dispersion in mineral oil) was added to a solution of N^4-benzoylcytosine (2·15 g; 10 mmol) in dimethylformamide (30 ml). After stirring at 60°C for 1 h, the compound *IV* (ref.[13]; 3·6 g; 10 mmol) was added, the mixture stirred at 100°C for 15 h under exclusion of moisture, taken down at 60°C/13 Pa and the residue set aside with 0·1M methanolic sodium methoxide (100 ml) at room temperature overnight. The mixture was neutralized by addition of Dowex 50X8 (H^+ form), made alkaline with triethylamine, filtered and the filtrate taken down *in vacuo*. The residue was extracted with boiling chloroform (3 × 100 ml), filtered through Celite, the filtrate taken down and the residue chromatographed on a silica gel column. Elution with chloroform–ethanol (9 : 1) gave 2·0 g (67·4%) of the compound *Vb*, R_F 0·50 (S6), which was heated in 0·25M sulfuric acid (50 ml) to 70°C till the reaction was complete (S6). The mixture was neutralized with barium hydroxide, filtered and the filtrate concentrated *in vacuo* to 50 ml. A solution of sodium borohydride (1·0 g) in ice-cold water (20 ml) was added under cooling with ice and the mixture allowed to stand overnight. After acidification with Dowex 50X8 (H^+ form), the suspension was poured on a column of the same ion exchange resin (100 ml). The column was washed with water until the UV absorption disappeared and the product was eluted with 2·5% aqueous ammonia. The UV-absorbing eluate was taken down *in vacuo* and the residue was crystallized from 90% aqueous ethanol, yielding 1·5 g (91% based on *Vb*) of the compound *VIb*, m.p. 118°C. For $C_9H_{15}N_3O_5$ (245·2) calculated: 44·07% C, 6·16% H, 17·13% N; found: 44·37% C, 6·34% H, 16·76% N.

2,3:4,5-Di-O-isopropylidene-D-arabitol (*VIIa*) (ref.[14])

A solution of sodium borohydride (25 g) in ice-cold water (70 ml) was added dropwise to a stirred solution of D-arabinose (100 g; 0·67 mol) in water (600 ml) under cooling with ice, the temperature being kept below 15°C. After stirring for 2 h at 0°C the mixture was set aside overnight, adjusted to pH 6 with Dowex 50X8 (H^+ form) and worked up as described for DL-ribitol (see *Ia*). Crystallization from ethanol afforded 66·1 g (65·2%) of D-arabitol. This product was stirred overnight with a mixture of acetone (1 litre), anhydrous cupric sulfate (140 g) and concentrated sulfuric acid (5 ml), filtered, made alkaline with triethylamine and taken down *in vacuo*. The residue was taken up in ethyl acetate (600 ml), washed with water (3 × 100 ml), dried over magnesium sulfate and taken down. Distillation of the residue gave 78·8 g (78%) of the product, boiling at 120°C/13 Pa.

1-O-*p*-Toluenesulfonyl-2,3:4,5-di-O-isopropylidene-D-arabitol (*VIIb*)

A solution of *p*-toluenesulfonyl chloride (47·6 g; 0·25 mol) in pyridine (120 ml) was added dropwise to a stirred and ice-cooled solution of the compound *VIIa* (46·4 g; 0·2 mol) in pyridine (120 ml), the mixture was stirred for 2 h in ice, allowed to stand overnight and mixed with ethanol (10 ml). After 30 min the mixture was taken down *in vacuo*, the residue dissolved in ethyl acetate (500 ml), the solution washed with water (100 ml), dilute (1 : 10) sulfuric acid (100 ml portions; to acid reaction), saturated sodium hydrogen carbonate solution (100 ml portions; to alkaline reaction), and water (2 × 100 ml), dried over magnesium sulfate and filtered. The filtrate was taken down and the residue stirred at 0°C with light petroleum (500 ml). The product which crystallized was collected on a filter, washed with light petroleum and dried *in vacuo*, affording 47·9 g (72%) of compound *VIIb*, m.p. 79—80°C, $[\alpha]_D^{20}$ +14·0° (*c* 0·5, chloroform). For $C_{18}H_{26}O_7S$ (386·4) calculated: 55·93% C, 6·78% H, 8·30% S; found: 56·47% C, 7·05% H, 8·51% S.

1-(Adenin-9-yl)-1-deoxy-2,3:4,5-di-O-isopropylidene-D-arabitol (*VIIIa*)

Sodium hydride (1·5 g) was added to a mixture of adenine (8·1 g; 60 mmol) and dimethylformamide (150 ml). After stirring at 60°C for 1 h the compound *VIIa* (23·2 g; 60 mmol) was added and stirring (with exclusion of moisture) was continued for 15 h, this time at 100°C. The mixture was taken down at 60°C/2 kPa, the residue codistilled with toluene (2 × 100 ml), extracted with hot chloroform (5 × 100 ml), the extract filtered through Celite and taken down *in vacuo*. Crystallization of the residue from ethanol (150 ml) gave 11·7 g (56%) of compound *VIIIa*, m.p. 249–250°C, $[\alpha]_D^{20}$ +24·6° (*c* 0·5, 1M-HCl); R_F 0·41 (S4). For $C_{16}H_{23}N_5O_4$ (349·4). calculated: 55·00% C, 6·64% H, 20·05% N; found: 54·68% C, 6·45% H, 19·45% N.

1-(Adenin-9-yl)-1-deoxy-D-arabitol (*IXa*)

a) A solution of the compound *VIIIa* (12·9 g; 37 mmol) in 0·25M-H_2SO_4 (250 ml) was kept at 60°C till the reaction was complete (S4; 4 h), diluted with water (200 ml), neutralized with barium hydroxide, filtered through Celite and taken down. The residue was crystallized from 50% aqueous ethanol, affording 9·85 g (99%) of compound *IXa*, m.p. 225–227°C. For $C_{10}.H_{15}N_5O_4$ (269·3) calculated: 44·60% C, 5·61% H, 26·01% N; found: 44·74% C, 5·44% H, 25·53% N.

b) The compound *Xa* (ref.[15]; 45·4 g; 0·204 mol) was added to an ice-cooled and stirred solution of trityl chloride (69·6 g; 0·25 mol) in pyridine (300 ml) and the stirring was continued till all the material dissolved. After standing overnight the mixture was poured into water (2 l), extracted with chloroform (3 × 200 ml), the extract washed with water (3 × 100 ml) and taken down. The residue was codistilled with toluene (3 × 200 ml) and applied on a column of silica gel (600 g). The column was washed with chloroform (3 l) and the product eluted with chloroform–ethanol (95 : 5); yield 59·5 g (63%) of oily *Xb*; R_F 0·34 (S3). A solution of this product in acetone (700 ml) was cooled with ice, sodium periodate (28 g; 0·13 mol) in water (300 ml) was added and the mixture was stirred without cooling for 1 h (after this time the reaction ended (S3)). The mixture was filtered and the solid washed with acetone which was removed from the filtrate by evaporation *in vacuo*. The remaining aqueous portion was extracted with chloroform (5 × 100 ml), the extract washed with water (100 ml), dried and taken down *in vacuo*. The residue was dissolved in ethanol (300 ml), cooled with ice, treated with sodium borohydride and stirred at 0°C for 1 h (quantitative reaction according to S3). The mixture was decomposed with acetic acid (pH 7), made alkaline with triethylamine (pH 9) and taken down *in vacuo*. The residue was taken up in chloroform (500 ml), the solution washed with water (3 × 100 ml), dried over magnesium sulfate, filtered, taken down *in vacuo* and the residue dried at 13 Pa, yielding 54 g (97%) of compound *XIa* as a glassy substance, R_F 0·30 (S3). This product (54 g; 125 mmol) was dissolved in pyridine (300 ml), cooled with ice and a solution of *p*-toluenesulfonyl chloride (27 g; 0·142 mol) in pyridine (100 ml) was added dropwise with stirring in the course of 30 min. After stirring for 5 h at 0°C and standing for 2 days at room temperature, the solution was poured on ice (1 kg), extracted with chloroform (2 × 400 ml), the extract washed with water (2 × 100 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*. The residue was dried at 13 Pa, yielding 70·5 g (96·5%) of the chromatographically homogeneous (R_F 0·20 in S2) amorphous *XIb*.

A solution of *XIb* (70·5 g; 0·12 mol) in dimethylformamide (100 ml) was added dropwise to a stirred suspension of adenine (13·5 g; 0·1 mol) in dimethylformamide (200 ml) which had been stirred with sodium hydride (2·4 g; 0·1 mol) for 1 h at 60°C under exclusion of moisture. The stirred mixture was heated to 100°C for 15 h, taken down at 50°C/13 Pa, the residue was codistilled with toluene (200 ml) and extracted with hot chloroform (5 × 100 ml). The extract was filtered through Celite, the filtrate evaporated, the residue dissolved in ethyl acetate (100 ml)

and filtered through a column of neutral alumina (200 g). Elution with ethyl acetate and evaporation of solvent gave material of R_F 0·53 (S4) which was boiled for 2 h with 80% acetic acid (400 ml). The solution was cooled, taken down *in vacuo* and coevaporated with water (300 ml). The residue was mixed with water (200 ml), filtered and the solid washed with water (500 ml). The filtrate was shaken with ether (3 × 100 ml), the aqueous phase taken down and the residue coevaporated with water (3 × 100 ml). Crystallization from ethanol afforded 8·9 g (33% based on adenine) of compound *IXa*, identical (S1, E1, HPLC) with product prepared according to the procedure *a*).

1-(Cytosin-1-yl)-1-deoxy-2,3:4,5-di-O-isopropylidene-D-arabitol (*VIIIb*)

Sodium hydride (20 mmol) was added to a solution of N^4-benzoylcytosine (4·3 g; 20 mmol) in dimethylformamide (50 ml). After stirring for 1 h at 60°C, the compound *VIIb* (8 g; 20·7 mmol) was added. The mixture was stirred at 100°C for 15 h under exclusion of moisture, taken down at 50°C/13 Pa and the residue mixed with 0·1M sodium methoxide (100 ml) and set aside overnight. The mixture was neutralized with Dowex 50X8 (H^+ form), made alkaline with triethylamine, filtered and the solvent evaporated. The residue was extracted with boiling chloroform (3 × × 100 ml), the extract filtered through Celite, the filtrate taken to dryness *in vacuo* and the residue chromatographed on two layers of silica gel in the system S5. The product bands (R_F 0·21 in S5) were eluted with methanol (500 ml), the eluate taken down and the product crystallized from ethanol (light petroleum added), affording 3·1 g (61%) of compound *VIIIb*, m.p. 238 to 240°C, $[\alpha]_D^{20}$ −41·4° (*c* 0·5, dimethylformamide). For $C_{15}H_{23}N_3O_5$ (325·4) calculated: 55·37% C, 7·12% H, 12·92% N; found: 55·24% C, 6·98% H, 13·14% N.

1-(Cytosin-1-yl)-1-deoxy-D-arabitol (*IXb*)

A solution of compound *VIIIb* (2·35 g; 7·2 mmol) in 0·25M-H_2SO_4 (25 ml) was set aside overnight at room temperature, diluted with water (50 ml), neutralized with barium hydroxide, filtered and the filtrate taken down. Crystallization of the residue from 80% ethanol (with ether added) gave 1·65 g (93%) of the product *IXb*, m.p. 198°C. For $C_{15}H_{15}N_3O_5$ (245·2) calculated: 44·07% C, 6·16% H, 17·14% N; found 43·97% C, 6·02% H, 16·80% N.

1-(Uracil-1-yl)-1-deoxy-D-arabitol (*IXc*)

Sodium hydride (0·72 g; 30 mmol) was added to a solution of 4-methoxy-2-pyrimidone[12] (3·80 g; 30 mmol) in dimethylformamide (90 ml). After stirring for 30 min at 60°C with exclusion of moisture, the compound *VIIb* (11·8 g; 30 mmol) was added. The mixture was heated to 100°C for 15 h, taken down at 50°C/13 Pa and the residue was dissolved in 0·25M-H_2SO_4 (70 ml). The solution was kept at 60°C for 5 h, neutralized with barium hydroxide, filtered and the filtrate taken down. The residue was coevaporated with ethanol (3 × 100 ml), dried *in vacuo*, stirred with a mixture of acetic anhydride (150 ml) and 4-dimethylaminopyridine (0·5 g) overnight and taken down at 50°C/13 Pa. After codistillation with toluene (3 × 50 ml). the residue was dissolved in chloroform (100 ml), the solution filtered through Celite and chromatographed on a column of silica gel (150 g). The product (R_F 0·50 in S4) was eluted with a mixture of ethanol and chloroform (5 : 95). The residue after evaporation (peracetate of compound *IXc*) was set aside with 0·1M sodium methoxide (100 ml) overnight, the mixture neutralized with Dowex 50X8 (H^+ form), filtered, taken down *in vacuo* and the residue crystallized from water, yielding 3·35 g (45%) of compound *IXc*, m.p. 227—229°C. For $C_9H_{14}N_2O_6$ (246·2) calculated: 43·90% C, 5·73% H, 11·38% N; found: 44·27% C, 5·78% H, 11·56% N.

2,3:4,5-Di-O-isopropylidene-L-arabitol (*XIIa*)

The title compound, b.p. 118—120°C/13 Pa, was prepared in 85% yield from L-arabinose (100 g) in the same way as described for the compound *VIIa*.

1-O-*p*-Toluenesulfonyl-2,3:4,5-di-O-isopropylidene-L-arabitol (*XIIb*)

This compound was synthesized in 65% yield from *XIIa* by the procedure described for *VIIb*; m.p. 78—79°C (light petroleum), $[\alpha]_D^{20}$ −10·8° (*c* 0·5, dimethylformamide). For $C_{18}H_{26}O_7S$ (386·4) calculated: 55·93% C, 6·78% H, 8·30% S; found: 56·47% C, 7·10% H, 8·58% S.

1-(Adenin-9-yl)-1-deoxy-2,3:4,5-di-O-isopropylidene-L-arabitol (*XIIIa*)

Prepared from the *p*-toluenesulfonyl derivative *XIIb* as described for the compound *VIIIa*; yield 68% (based on adenine). M.p. 249—252°C (ethanol). For $C_{16}H_{23}N_5O_4$ (349·4) calculated: 55·00% C, 6·64% H, 20·05% N; found: 54·87% C, 6·78% H, 20·15% N. ^{1}H NMR spectrum ($CDCl_3$): 1·31 (s, 3 H) + 1·36 (s, 6 H) + 1·47 (s, 3 H) $(CH_3)_2C$; 3·40—4·70 (m, 7 H) O—CH: 5·94 (br, 2 H) NH_2; 7·97 (s, 1 H) H_8; 8·36 (s, 1 H) H_2.

1-(Adenin-9-yl)-1-deoxy-L-arabitol (*XIVa*)

This compound was prepared in 87% yield from compound *XIIIa* as described for *IXa* (method *a*); m.p. 225—226°C (50% aqueous ethanol). For $C_{10}H_{15}N_5O_4$ (269·3) calculated: 44·60% C, 5·61% H, 26·01% N; found: 45·04% C, 5·78% H, 25·97% N. ^{1}H NMR spectrum (hexadeuteriodimethyl sulfoxide): 3·40—3·60 (m) CH; 4·0—4·80 (m) O—CH; 6·97 (br) NH_2; 7·98 (s) H_8; 8·09 (s) H_2.

1-(Cytosin-1-yl)-1-deoxy-2,3:4,5-di-O-isopropylidene-L-arabitol (*XIIIb*)

Prepared in 59% yield from compound *XIIb* as described for preparation of *VIIIb*, m.p. 158°C, R_F 0·21 (S5); $[\alpha]_D^{20}$ +42·6° (*c* 0·5, dimethylformamide). For $C_{15}H_{23}N_3O_5$ (325·4) calculated: 55·37% C, 7·12% H, 12·92% N; found: 54·48% C, 7·88% H, 13·11% N.

1-(Cytosin-1-yl)-1-deoxy-L-arabitol (*XIVb*)

Prepared in 96% yield from compound *XIIIb* by the procedure described for compound *IXb*; m.p. 183—195°C (80% aqueous ethanol). For $C_9H_{15}N_3O_5$ (245·2) calculated: 44·07% C, 6·16% H, 17·14% N; found: 44·12% C, 6·09% H, 16·95% N.

1-(Uracil-1-yl)-1-deoxy-L-arabitol (*XIVc*)

Prepared in 37% yield from compound *XIIb* as described for the preparation of *IXc*; m.p. 228 to 229°C (water). Identical (HPLC, S1, E1) with *IXc*. For $C_9H_{14}N_2O_6$ (246·2) calculated: 43·90% C, 5·73% H, 11·38% N; found: 43·97% C, 5·72% H, 11·45% N.

1-(Adenin-9-yl)-1-deoxy-D-lyxitol (*XVII*)

A mixture of the compound *XVa* (ref.[5]; 1·3 g; 4 mmol), sodium salt of adenine (0·80 g; 5·2 mmol) and dimethylformamide (10 ml) was heated to 100°C for 15 h, taken down *in vacuo*, the residue coevaporated with toluene, extracted with hot chloroform (100 ml) the extract filtered through Celite and taken down. Crystallization of the residue from ethanol afforded 0·92 g

(75%) of compound *XVb*, identical with the product obtained according to ref.[5]. A solution of this compound in 0·25M - H_2SO_4 (25 ml) was kept at 37°C overnight, neutralized with barium hydroxide, filtered through Celite and the filtrate concentrated *in vacuo* to about 70 ml. A solution of sodium borohydride (0·76 g) in water (20 ml) was added dropwise under cooling with ice. The mixture was allowed to stand in ice for 1 h and at room temperature overnight, acidified to pH 6 with Dowex 50X8 (H^+ form) and the suspension was poured on a column of the same ion exchange resin (100 ml). After washing with water the product was eluted with 2·5% ammonia, the ammonia eluate taken down *in vacuo* and the residue crystallized from 70% aqueous ethanol (with addition of ether); yield 0·45 g (55·7% based on compound *XVb*), m.p. 216—218°C; homogeneous according to S1, E1 and HPLC. For $C_{10}H_{15}N_5O_4$ (269·3) calculated: 44·60% 5·61% H, 26·01% N; found: 44·93% C, 6·00% H, 25·75% N.

1-(Adenin-9-yl)-1-deoxy-L-lyxitol (*XVIII*)

Prepared from 20 mmol of the compound *XVIb* (ref.[5]) as described for the compound *XVII*. The yield of *XVIII* was 2·70 g (56·4%), m.p. 222—223°C (methanol–ether). The product was homogeneous (S1, E1 and HPLC) and identical with *XVII*. For $C_{10}H_{15}N_5O_4$ (269·3) calculated: 44·60% C, 5·61% H, 26·01% N; found: 45·00% C, 5·54% H, 26·34% N.

5-(Adenin-9-yl)-5-deoxy-3-O-methyl-1,2-O-isopropylidene-D-arabinofuranose (*XIXb*)

Compound[16] *XIXa* (40 g; 0·125 mol) was added to a mixture of adenine (17·6 g; 0·13 mol), dimethylformamide (300 ml) and sodium hydride (3·1 g; 0·13 mol) which had been stirred at 60°C for 1 h. The mixture was heated to 100°C for 15 h and taken down *in vacuo*. The residue was co-distilled with toluene (2 × 300 ml), extracted with boiling chloroform (3 × 200 ml), the extract filtered and taken down. Chromatography on a column of silica gel (200 g) in chloroform–methanol (95 : 5), followed by crystallization from methanol, afforded 9·0 g (22·6%) of the chromatographically pure (R_F 0·40 in S5) product *XIXb*; m.p. 238—239°C, $[\alpha]_D^{20}$ —18·8° (*c* 0·5, dimethylformamide). For $C_{14}H_{19}N_5O_4$ (321·3) calculated: 52·32% C, 5·96% H, 21·80% N; found: 52·24% C, 5·75% H, 21·56% N.

1-(Adenin-9-yl)-1-deoxy-3-O-methyl-D-lyxitol (*XXI*)

A solution of compound *XIXb* (1·6 g; 5 mmol) in 0·25M-H_2SO_4 (25 ml) was warmed to 37°C for 18 h and neutralized with barium hydroxide. The crude compound *XX* was reduced with sodium borohydride and worked up in the same manner as described for compound *XVII*. Crystallization from ethanol (ether added) afforded 0·20 g (14%) of chromatographically pure (E1, S1) compound *XXI*, m.p. 225°C. Mass spectrum: M^+ 283, 268 (M—CH_3), 252 (M—CH_2OH), 234 (252 — H_2O), 178 (Ade + CH_2CHOH), 148 (Ade — CH_2), 136 (BH_2), 135 (BH).

1,2:3,4-Di-O-isopropylidene-DL-xylitol (*XXIIa*)

Prepared from DL-xylitol in 72% yield by the procedure described for compound *VIIa*. B.p. 140°C/25 Pa.

1-O-*p*-Toluenesulfonyl-2,3:4,5-di-O-isopropylidene-DL-xylitol (*XXIIb*)

This compound was prepared in 45·5% yield from compound *XXIIa* as described for compound *VIIb*; m.p. 103°C. For $C_{18}H_{26}O_7S$ (386·4) calculated: 56·93% C, 6·78% H, 8·30% S; found: 56·12% C, 6·24% H, 8·14% S.

1-(Adenin-9-yl)-1-deoxy-2,3:4,5-di-O-isopropylidene-DL-xylitol (*XXIIIa*)

A mixture of compound *XXIIb* (11·8 g; 30 mmol) and a solution of sodium salt of adenine, prepared from adenine (30 mmol) in dimethylformamide (90 ml) by the above-described procedure, was heated to 100°C for 15 h. Further work-up procedure was the same as described for compound *VIIIa*. Crystallization from ethanol afforded 6·1 g (58·3% based on adenine) of compound *XXIIIa*, m.p. 202–203°C; R_F 0·27 (S4). For $C_{16}H_{23}N_5O_4$ (349·4) calculated: 55·00% C, 6·64% H, 20·05% N; found: 54·62% C, 6·55% H, 19·77% N.

1-(Adenin-9-yl)-1-deoxy-DL-xylitol (*XXIVa*)

A solution of compound *XXIIIa* (4 g; 11·5 mmol) in 0·25M-H_2SO_4 (70 ml) was heated to 70°C for 3 h, neutralized with barium hydroxide, filtered and the solid washed with hot water. The combined filtrates were taken down *in vacuo* and the compound *XXIVa* (2·95 g; 95%) was obtained by crystallization from water; m.p. 215°C. It was homogeneous according to S1, E1 and HPLC. For $C_{10}H_{17}N_5O_5$ (287·3) (monohydrate) calculated: 41·80% C, 5·96% H, 23·38% N; found: 41·72% C, 5·86% H, 24·42% N.

1-(Uracil-1-yl)-1-deoxy-DL-xylitol (*XXIVb*)

Prepared from compound *XXIIb* (30 mmol) and sodium salt of 4-methoxy-2-pyrimidone (30 mmol) in dimethylformamide (90 ml) by the procedure described for compound *IXc*. Crystallization of the deacetylation product from 80% ethanol (ether added) afforded 3·7 g (50%) of compound *XXIVb*, m.p. 162–163°; homogeneous according to E1, S1 and HPLC. For $C_9H_{14}N_2O_6$ (246·2) calculated: 43·90% C, 5·73% H, 11·38% N; found: 44·20% C, 5·64% H, 11·38% N.

1-(Adenin-9-yl)-1-deoxy-3-O-benzyl-L-xylitol (*XXVIa*)

A solution of compound[8] *XXVa* (15·9 g; 40 mmol) in 80% formic acid (500 ml) was set aside overnight at room temperature and taken down. The residue was codistilled with water (3 × × 100 ml), dissolved in water (100 ml) and made slightly alkaline with ammonia. The separated product was collected on filter, washed with water, ethanol and ether and dried *in vacuo*, yielding 12·5 g (87·5%) of the chromatographically homogeneous (R_F 0·45 in S6) compound *XXVb*. A solution of this product (35 mmol) in ethanol (300 ml) was cooled with ice and sodium borohydride (5 g) was added in portions with stirring. The stirring was continued for 5 h in ice and overnight at room temperature. The mixture was neutralized with acetic acid, filtered, the solid washed with ethanol and the filtrate taken down. A methanolic solution of the residue was applied on a column of silica gel (100 g). Washing with chloroform–methanol (95 : 5) removed impurities and elution with chloroform–methanol (9 : 1) afforded the product *XXVIa* (R_F 0·30 in S6) which was purified by precipitation from ethanol with ether. Yield 7·1 g (63·5%, based on *XXVa*); m.p. 98–99°C, $[\alpha]_D^{20}$ −4·2° (*c* 0·5, 1M-HCl). For $C_{17}H_{21}N_5O_4$ (359·4) calculated: 56·81% C, 5·89% H, 19·49% N; found: 57·03% C, 5·70% H, 19·45% N.

1-(Adenin-9-yl)-1-deoxy-L-xylitol (*XXVIb*)

Compound *XXVIa* (20 mmol) in methanol (400 ml) was hydrogenated in the presence of concentrated hydrochloric acid (2 ml) over 10% Pd/C (4·0 g) under atmospheric pressure. After the hydrogen uptake had ceased (30 min), the mixture was filtered through Celite which was then washed with methanol and aqueous ammonia (200 ml). The filtrate was taken down

in vacuo, the residue dissolved in water (50 ml) acidified with Dowex 50X8 (H^+ form) and the suspension applied on the same kind of resin (100 ml). After washing with water the ion exchange resin was suspended in water (200 ml), made alkaline with ammonia, filtered and washed with boiling water (500 ml). The filtrate was taken down and crystallized from 80% ethanol, yielding 4·2 g (78%) of compound *XXVIb*, m.p. 191—192°C, homogeneous according to S1, E1 and HPLC. For $C_{10}H_{15}N_5O_4$ (269·3) calculated: 44·60% C, 5·61% H, 26·01% N; found: 43·88% C, 5·59% H, 25·67% N.

1,5-Di-O-benzoyl-2-deoxy-D-erythropentitol (*XXVIIb*)

Sodium borohydride (1·5 g) was added during 1 h to a stirred ice-cooled solution of 2-deoxy--D-ribose (5 g; 37·3 mmol) in methanol (150 ml). After stirring for 3 h in ice, the mixture was acidified with Dowex 50X8 (H^+ form), filtered, the solid washed with methanol and the filtrate taken down. The residue was codistilled with methanol (3 × 50 ml) and pyridine (2 × 50 ml) and taken up in pyridine (50 ml). Benzoyl chloride (9 ml; 75·5 mmol) was added dropwise to the ice-cooled solution which was then stirred for 2 h at 0°C. After standing overnight at 0°C, the mixture was mixed with water (10 ml), after 30 min taken down, the residue was dissolved in ethyl acetate (200 ml) and the solution washed with water (3 × 50 ml). After evaporation of solvent and codistillation with toluene (2 × 50 ml) the residue was dissolved in a sufficient volume of ethyl acetate. Light petroleum was added to the stirred hot solution until it was persistently turbid. The product which crystallized in a refrigerator was collected on filter, washed with a mixture of light petroleum and ethyl acetate (2 : 1) and dried. Yield 6·3 g (49%) of *XXVIIb*, m.p. 93—94°C; $[\alpha]_D^{20}$ —10·1° (*c* 0·5, chloroform); R_F 0·13 (S2). For $C_{19}H_{20}O_6$ (344·4) calculated: 66·27% C, 5·85% H; found: 66·55% C, 6·06% H.

1-(Adenin-9-yl)-1,2-dideoxy-D-erythropentitol (*XXX*)

A mixture of the compound *XXVIIb* (6·0 g; 17·4 mmol), acetone (50 ml), ethyl orthoformate (10 ml) and *p*-toluenesulfonic acid hydrate (0·4 g) was stirred until homogeneous and then set aside in a stoppered flask. After 4 h the reaction was complete (S2). Sodium hydrogen carbonate (4 g) was added, the mixture was stirred for 2 h, filtered, the solid washed with acetone (200 ml) and the filtrate taken down *in vacuo*, finally at 50°C/13 Pa. The residue (R_F 0·62 in S2) was set aside with 0·1M sodium methoxide (100 ml) overnight, the solution neutralized with Dowex 50X8 (H^+ form), filtered, the solid washed with methanol and the filtrate taken down *in vacuo*.

This residue (compound *XXVIIIa*) was dissolved in chloroform (50 ml), the solution mixed with triethylamine (3·5 ml; 25 mmol) cooled to 0°C and a solution of *p*-toluenesulfonyl chloride (3·8 g; 20 mmol) in chloroform (25 ml) was added dropwise. After stirring for 1 h at 0°C and standing overnight, the mixture was washed successively (25 ml) with water, saturated sodium hydrogen carbonate solution and twice with water, dried over magnesium sulfate, filtered and taken down. Chromatography of the residue on a column of silica gel (100 g) in chloroform afforded as the principal product compound *XXVIIIb* (R_F 0·30 in S2) as a yellowish oil (2·7 g, 47% based on *XXVIIIa*). This material (8·2 mmol) was taken up in acetonitrile (20 ml) and treated with benzoyl cyanide (1·3 g; 10 mmol) and triethylamine (0·5 ml). After 30 min the mixture was taken down and the residue chromatographed on two layers of silica gel in the system S2. The bands of the product *XXVIIIc* (R_F 0·35, S2) were eluted with ethyl acetate (500 ml), the eluate evaporated and the residue dried *in vacuo*, yielding 2·9 g (78·7% based on compound *XXVIIIb*) of a yellowish foam.

Compound *XXVIIIc* (2·9 g; 6·45 mmol) was added to a solution of sodium salt of adenine (prepared by the above-described procedure from 10 mmol of adenine in 40 ml of dimethyl-

formamide). After heating to 100°C for 15 h under exclusion of moisture, the mixture was taken down *in vacuo* and the residue set aside with 0·1M sodium methoxide (50 ml) overnight. The mixture was neutralized with Dowex 50X8 (H^+ form), filtered, the resin washed with methanol and the filtrate taken down *in vacuo*. The residue was chromatographed on two plates of silica gel in the system S4, the product bands eluted with methanol (500 ml) and the solvent evaporated. Crystallization of the residue from ethanol (light petroleum added) afforded 0·72 g (38%) of compound *XXIX*, m.p. 164–165°C, $[\alpha]_D^{20}$ +32·2° (*c* 0·5, dimethylformamide); R_F 0·40 (S6). For $C_{13}H_{19}N_5O_3$ (293·3) calculated: 53·22% C, 6·53% H, 23·88% N; found: 53·54% C, 6·60% H, 23·79% N.

A solution of this compound (0·3 g) in 0·25M-H_2SO_4 (20 ml) was set aside at room temperature overnight, neutralized with barium hydroxide, filtered and taken down *in vacuo*. Crystallization of the residue from methanol (with addition of ether) yielded 0·20 g (77%) of compound *XXX*, m.p. 185°C. For $C_{10}H_{15}N_5O_3$ (253·3) calculated: 47·42% C, 5·97% H, 27·66% N; found 47·27% C, 5·91% H, 27·50% N.

2,3-O-Isopropylidene-1,4-anhydro-D-ribitol (*XXXIIIb*)

Trityl chloride (64 g; 0·23 mol) was added to a solution of 2,3-O-isopropylidene-D-ribofuranose[17] (*XXXIa*) (36 g; 0·19 mol) in pyridine (80 ml). The mixture was stirred until it became homogeneous, set aside overnight, poured into water (1 litre) and decanted. The precipitate was taken up in chloroform (500 ml), the solution washed with water (2 × 100 ml), dried over magnesium sulfate and taken down. A solution of the residue (*XXXIb*; R_F 0·60 in S2, 0·62 in S8) in ethanol (500 ml) was cooled with ice and sodium borohydride (5·9g) was added portionwise under stirring in the course of 1 h. After stirring at 0°C for 2 h (the reaction was complete according to S8) the mixture was acidified with acetic acid to pH 6, taken down *in vacuo*, the residue was taken up in chloroform (500 ml) the organic layer washed with water (3 × 100 ml), dried over magnesium sulfate, filtered and the solvent evaporated. The remaining compound *XXXIIa* (R_F 0·30 in S2, 0·32 in S8) was dissolved in pyridine (300 ml) and a solution of *p*-toluenesulfonyl chloride (47·6 g; 0·25 mol) in pyridine (150 ml) was added dropwise with ice-cooling and stirring. After stirring for 2 h at 0°C and standing overnight at the same temperature, the mixture was concentrated at 30°C *in vacuo*, diluted with ethyl acetate (600 ml), washed with water (3 × 100 ml), dried and taken down *in vacuo* (50°C/13 Pa). The residue (*XXXIIb*; chromatographically homogeneous; R_F 0·80 in S2) was mixed with acetone (300 ml), methanol (80 ml) and concentrated sulfuric acid (2 ml) and set aside at room temperature till the reaction was complete (disappearance of the starting compound, R_F 0·27 in S7) (6 h). Calcium hydroxide (20 g) was added, the mixture was stirred for 1 h until neutral, filtered, the solid was washed with acetone and the filtrate taken down *in vacuo*. A solution of the residue in ether (200 ml) was washed with water (2 × × 50 ml), dried and the solvent evaporated. Distillation gave 13·5 g (40·5% based on *XXXIa*) of the compound *XXXIIIb*, b.p. 112–114°C/13 Pa; $[\alpha]_D^{20}$ +37·0° (*c* 0·5, chloroform). For $C_8H_{14}.O_4$ (174·2) calculated: 55·16% C, 8·11% H; found: 53·75% C. 7·84% H. ^{1}H NMR spectrum ($CDCl_3$): 3·68 (2 × dd, 2 H, $J_{5,4}$ = 4·34, $J_{5',4}$ = 6.10, $J_{5,5'}$ = 11·6) 2 H_5; 4·03 (d, 2 H, $J_{1,2}$ = = 3·12) 2 H_1; 4·17 (dq, 1 H, $J_{4,3}$ = 2·0, $J_{4'5}$ = 4·34, $J_{4,5'}$ = 6·10) H_4; 4·68 (dd, 1 H, $J_{3,2}$ = = 6·27, $J_{3,4}$ = 1·83) H_3; 4·87 (pent, 1 H, $J_{2,1}$ = 3·15, $J_{2,3}$ = 6·33) H_2.

5-(Adenin-9-yl)-5-deoxy-2,3-O-isopropylidene-1,4-anhydro-D-ribitol (*XXXIVa*)

A solution of compound *XXXIIIb* (13·5 g; 77·6 mmol) in pyridine (25 ml) was added dropwise during 30 min to an ice-cooled and stirred solution of *p*-toluenesulfonyl chloride (15 g; 78·7 mmol) in pyridine (50 ml). The mixture was stirred for 2 h at 0°C, allowed to stand in a refrigerator

overnight, decomposed with water (10 ml) and taken down *in vacuo*. The residue was taken up in ethyl acetate (300 ml), the solution washed with water (3 × 50 ml), dried, filtered and the solvent evaporated *in vacuo*, finally at 50°C/13 Pa, giving 22·7 g (89·3% based on *XXXIIIb*) of the chromatographically (R_F 0·35 in S2) homogeneous oily product *XXXIIIc*.

A solution of this compound (69 mmol) in dimethylformamide (50 ml) was added to a suspension of sodium salt of adenine (80 mmol) in dimethylformamide (200 ml). The mixture was heated to 100°C for 24 h under stirring and exclusion of moisture, taken down *in vacuo*, the residue was extracted with boiling chloroform (5 × 100 ml), the solution filtered through Celite, taken down and the product crystallized from methanol. Yield 11·0 g (56%) of compound *XXXIVa*, m.p. 187–188°C, $[\alpha]_D^{20}$ +91·5° (*c* 0·5, dimethylformamide), R_F 0·58 (S6). For $C_{13}H_{17}N_5O_3$ (291·3) calculated: 53·59% C, 5·88% H, 24·05 N; found: 54·06% C, 5·92% H, 24·25% N. ^{1}H NMR spectrum ($CDCl_3$): 1·23 + 1·34 (2 × s, 6 H) $(CH_3)_2C$; 3·80 (d, 1 H, $J_{1',1''} = 11·8$, $J_{1'',2'} < 1·0$) $H_{1''}$; 3·94 (dd, 1 H, $J_{1',2'} = 3·8$, $J_{1',1''} = 11·0$) $H_{1'}$; 4·10–4·35 (m, 3 H) $H_{4'}$ + + 2 $H_{5'}$; 4·65 (d, 1 H, $J_{3',2'} = 6·0$, $J_{3',4'} < 1·0$) $H_{3'}$; 4·83 (dd, 1 H, $J_{2',1'} = 3·8$, $J_{2',3'} = 6·0$) $H_{2'}$.

5-(Adenin-9-yl)-5-deoxy-1,4-anhydro-D-ribitol (*XXXIVb*)

A suspension of the compound *XXXIVa* (5·0 g; 17·6 mmol) in 0·25M-H_2SO_4 (100 ml) was stirred overnight at room temperature, the formed solution neutralized with barium hydroxide, filtered and taken down. Crystallization of the residue from 80% ethanol (with addition of ether) afforded 3·5 g (79%) of compound *XXXIVb*, m.p. 219–220°C; R_F 0·16 (S6). Mass spectrum: M^+ 251. For $C_{10}H_{13}N_5O_3$ (251·2) calculated: 47·80% C, 5·21% H, 27·88% N; found: 48·00% C, 5·28% H, 27·61% N.

The author is indebted to Dr M. Masojídková for measurement and interpretation of the NMR *spectra, Dr J. Kohoutová for measurement and interpretation of the mass spectra, Mrs Z. Ledvinová for optical rotation determinations, Dr I. Rosenberg for the HPLC analyses and Dr I. Votruba for the antibacterial tests. The excellent technical assistance of Mrs B. Nováková is acknowledged.*

REFERENCES

1. Votruba I., Holý A.: This Journal *45*, 3039 (1980).
2. Votruba I., Holý A.: This Journal *47*, 167 (1982).
3. DeClercq E., Descamps J., DeSomer P., Holý A.: Science *200*, 563 (1978).
4. DeClercq E., Holý A.: J. Med. Chem. *22*, 510 (1979).
5. Holý A., Votruba I., DeClercq E.: This Journal, *47*, 1392 (1982).
6. Holý A., Votruba I., DeClercq E.: Symposium on Ribosomes and RNA Metabolism, Smolenice 1981. Publishing House of Slovak Academy of Sciences, Bratislava 1982, p. 111.
7. Holý A.: This Journal *47*, 173 (1982).
8. Holý A.: This Journal *44*, 593 (1979).
9. Horton D., Baker D. C., Kokrady S. S.: Ann. N. Y. Acad. Sci. *255*, 131 (1975).
10. Ikehara M., Ohtsuka E.: Chem. Pharm. Bull. *11*, 1095 (1963).
11. Holý A., Souček M.: Tetrahedron Lett. *1971*, 185.
12. Holý A., Ivanova G. S.: Nucleic Acids Res. *1*, 19 (1974).
13. Leonard N. J., Carraway K. L.: J. Heterocycl. Chem. *3*, 485 (1966).
14. Nakagawa T., Tokuoka H., Shinoto K., Yoshimura J., Sato T.: Bull. Chem. Soc. Jap. *40*, 2150 (1967).

15. Wiggins L. F.: J. Chem. Soc. *1946*, 13.
16. Kawazu M., Kanno T., Yamamura S., Mizoguchi T., Saito S.: J. Org. Chem. *38*, 2887 (1973).
17. Levene P. A., Stiller E. T.: J. Biol. Chem. *102*, 187 (1933).
18. Giovanninetti G., Cavrini V., Garuti L., Roveri P., Amorosa M., Gaggi R., Defaye J.: Eur. J. Med. Chem. *15*, 23 (1980).

Translated by M. Tichý.