SYNTHESIS OF RACEMIC AND OPTICALLY ACTIVE *erythro*- AND *threo*-9-(2,3,4-TRIHYDROXYBUTYL)ADENINES AND RELATED COMPOUNDS*

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Reduction of diethyl 2,3-O-isopropylidene-DL-tartrate (*II*) with lithium aluminium hydride afforded 2,2-dimethyl-1,3-dioxolane-*threo*-4,5-dimethanol (*III*) which was transformed to the monotosyl derivative *VI*. Reaction of this compound with sodium salt of adenine, followed by acidic deblocking, gave 9-(DL)-*threo*-(2,3,4-trihydroxybutyl)adenine (*IX*). Analogously, 9-(DL)--*erythro*-(2,3,4-trihydroxybutyl)adenine (*XVII*) was prepared from diethyl *meso*-tartrate (*XI*) *via* the diol *XIII* and the tosyl derivative *XV*. 1,3-O-Benzylidene-D-threitol (D-*XVIII*) was converted successively into the 4-O-tosyl derivative *XIX* and the 2-O-benzoyl-4-O-tosyl derivative *XX*. Reaction of the compound *XX* with sodium salt of adenine, followed by removal of the protecting groups in the intermediate *XXI*, afforded 9-(D)-*threo*-(2,3,4-trihydroxybutyl)adenine (D-*XXII*); analogously, 1,3-O-benzylidene-L-threitol (L-*XVIII*) was transformed into the 9-(L)-*threo*-derivative L-*XXII*. The D-*threo*-derivative D-*XXII* was prepared also from 5-O-tosyl-3-O-benzoyl--1,2-O-isopropylidene-α-D-xylofuranoside (*XXIII*) or from 3-O-benzyl derivative *XXIX* by condensation with sodium salt of adenine, followed by acidic hydrolysis, degradation of the 1,2-diol grouping by sodium periodate and sodium borohydride, and methanolysis or hydrogenolysis. An analogous procedure was used for preparation of 1-(D)-*threo*-(2,3,4-trihydroxybutyl)uracil (D-*XXVII*). Methyl 2,3-O-isopropylidene-5-benzoyl-6-tosyl-D-mannofuranoside (*XXXVI*) was transformed to the 5-(adenin-9-yl) derivative *XXXVII* which after hydrolysis of the dioxolane ring, followed by cleavage of the *cis*-diol with sodium periodate, reduction with sodium borohydride and methanolysis, afforded 9-(D)-*erythro* (2,3,4-trihydroxybutyl)adenine (D-*XL*). The L-enantiomer (L-*XL*) was obtained from 5-O-(adenin-9-yl)-3-O-benzoyl-1,2-O-isopropylidene-β-L-arabinofuranoside (*XXXIIIb*) by acidic cleavage, degradation of the intermediate *XXXIV* with periodate and methanolysis.

The finding of the antiviral activity of 9-(*S*)-2,3-(dihydroxypropyl)adenine stimulated systematic study of the so-called aliphatic nucleoside analogues[1,2]. Within the framework of this investigation, there have been hitherto prepared mono- and disubstituted hydroxyalkyl and aminoalkyl derivatives, modified in the heterocyclic base as well as in the side chain[3-6]. In the course of further studies the attention was drawn to 2,3,4-trihydroxybutyl derivatives in which the situation is complicated

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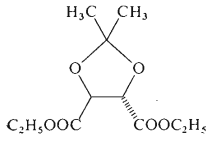
by the presence of two asymmetric carbon atoms in the side chain. These compounds are very interesting since they belong to biologically active compounds, although the kind of their activity is different: eritadenine (*I*) which can be derived by oxidation of the primary alcoholic group in one of the four adenine derivatives exhibits hypocholesterolemic activity[7,8]. The present communication describes synthesis of the six possible isomeric compounds (two racemates and four optically active compounds) derived from adenine as the carrier of the biological activity. The synthetic methods used were extended also to uracil derivatives.

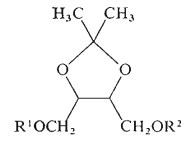
The racemic DL-*threo*-derivative *IX* was prepared starting from ethyl DL-tartrate: its reaction with dimethoxypropane afforded *threo*-2,2-dimethyl-4,6-bis(ethoxycarbonyl)-1,3-dioxolane (*II*) which was reduced with lithium aluminium hydride to give *threo*-2,2-dimethyl-1,3-dioxolane-4,6-dimethanol (*III*). Reaction of this compound with benzoyl cyanide in acetonitrile[9] led to a mixture of monobenzoyl and dibenzoyl derivative (*IV* and *V*, respectively). Tosylation of the compound *IV* afforded the expected tosyl derivative *VI* which was heated with the sodium salt of adenine. The obtained 2',3'-O-isopropylidene derivative *VII* was subjected to methanolysis in order to remove the 4'-benzoyl group and the arising intermediate *VIII* was finally hydrolysed with acetic acid to the compound *IX*. In addition to the elemental analysis, the structure of the intermediates was proved also by ^{1}H-NMR spectroscopy; the UV spectrum of the final product *IX* shows that this compound is 9-substituted adenine derivative.

Analogous synthetic procedure was chosen also for the preparation of the racemic *erythro*-derivative *XVII*: diethyl maleate (*X*) was converted to diethyl *meso*-tartrate (*XI*) which on reaction with 2,2-dimethoxypropane afforded the substituted 1,3-dioxolane *XII*. (In the case of DL-tartaric, as well as *meso*-tartaric, acid the formation of 1,3-dioxolane from the ethyl esters is extraordinarily difficult, and the yields are low. A somewhat better procedure consists in using ethyl orthoformate and acetone; nevertheless, the yields are lower than with other derivatives of *cis*-diols.) The compound *XII* was reduced with lithium aluminium hydride to the DL-erythritol derivative *XIII* which could be purified *via* the well crystallisable 1,4-dibenzoyl derivative *XIV*. The pure *XIII*, liberated from *XIV* by methanolysis, was tosylated to the tosyl derivative *XV* which was condensed with sodium salt of adenine to give the 2',3'-O-isopropylidene derivative *XVI*. Acidic hydrolysis of the dioxolane ring led to the *erythro*-derivative *XVII* with properties similar to the compound *IX* and with a UV spectrum corresponding to N^9-alkyladenines.

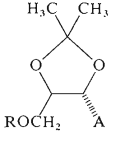
The common feature of all the synthetic approaches for the preparation of optically active *erythro*- and *threo*-2,3,4-trihydroxybutyl derivatives of nucleobases consists in the use of sugar derivatives as starting compounds for two general approaches: either the preparation of specifically blocked erythritol or threitol derivatives, bearing a tosyl group in the position 1, followed by condensation of these compounds with sodium salt of adenine, or the synthesis of specifically blocked pento- or hexo-



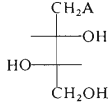
II



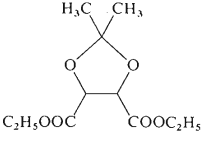
III, $R^1 = R^2 = H$
IV, $R^1 = Bz$, $R^2 = H$
V, $R^1 = R^2 = Bz$
VI, $R^1 = Bz$, $R^2 = Ts$



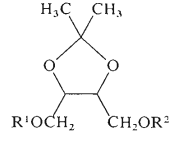
VII, R = Bz
VIII, R = H



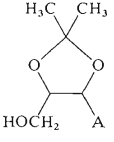
IX (DL)



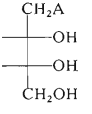
XII



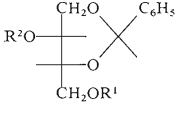
XIII, $R^1 = R^2 = H$
XIV, $R^1 = R^2 = Bz$
XV, $R^1 = H$, $R^2 = Ts$



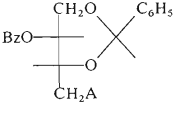
XVI



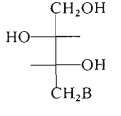
XVII (DL)



XVIII, $R^1 = R^2 = H$
XIX, $R^1 = Ts$, $R^2 = H$
XX, $R^1 = Ts$, $R^2 = Bz$



XXI



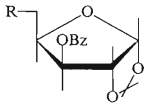
XXII, B = adenin-9-yl
XXVII, B = uracil-1-yl (D or L)

furanose derivatives with tosyl group in the position 5 or 6, their condensation with the heterocycle and subsequent partial deblocking and degradation of the sugar residue to a 2,3,4-trihydroxybutyl derivative of the heterocycle. Both these approaches were used successfully in this work.

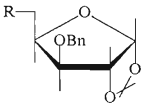
The first approach, used in the preparation of both the enantiomeric *threo*-derivatives, starts from D- or L-arabinose: reduction with sodium borohydride afforded both arabitols which on reaction with benzaldehyde were converted to the 1,3-O--benzylidene derivatives[10]. These were degraded with sodium periodate and the arising threoses[11] were reduced with sodium borohydride to give both enantiomeric 1,3-O--benzylidenethreitols (*XVIII*). The primary hydroxy group in these compounds was tosylated and the obtained tosyl derivatives *XIX* were benzoylated at the unsubstituted 2-hydroxy group. The thus-prepared compounds *XX* were then condensed with sodium salt of adenine. The reaction mixture afforded the completely blocked derivatives *XXI* whose structure was confirmed by analysis and ^{1}H-NMR spectra. The 2-benzoyl group was removed by methanolysis and the 1,3-benzylidene group by acidic hydrolysis. After deionisation, the enantiomeric 9-(D-*threo*-2,3,4-trihydroxybutyl)adenine (D-*XXII*) and 9-(L-*threo*-2,3,4-trihydroxybutyl)adenine (L-*XXII*) were obtained in analytically and chromatographically pure state.

An alternative method was used for the preparation of D-*threo*-derivatives. The starting compound was 1,2 : 3,5-diisopropylidene-D-xylofuranose[12]; this was selectively deblocked to 1,2-O-isopropylidene derivative which on tosylation in the position 5, followed by benzoylation in the position 3 afforded 5-O-tosyl-3-O-benzoyl--1,2-O-isopropylidene-D-xylofuranose (*XXIII*). This compound was condensed with sodium salt of adenine to the derivative *XXIV* whose structure was confirmed by ^{1}H-NMR spectrum. Removal of the 1,2-O-isopropylidene group with formic acid, followed by degradation with sodium periodate, reduction with sodium borohydride and finally by alkaline hydrolysis, gave as the sole product the D-*threo*-derivative D-*XXII* which exhibited the same properties as the compound prepared by the above--mentioned method. Similarly as with sodium salt of adenine, the compound *XXIII* reacts also with the sodium salt of uracil; in this case there were isolated from the reaction mixture both the isomeric protected derivatives substituted in the position N^1 (*XXV*) as well as N^3 (*XXVI*) of the uracil ring and their structure was proved by ^{1}H-NMR spectra. The 1-isomer *XXV* was treated analogously as the adenine derivative *XXIV*, affording thus 1-(D-*threo*-2,3,4-trihydroxybutyl)uracil (D-*XXVII*). The UV spectra of the compounds *XXII* and *XXVII* also confirm the anticipated 9-alkyladenine and 1-alkyluracil structures.

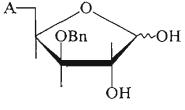
The last-mentioned method is suitable for the preparation of the D-*threo* derivative, since the starting xylose is well accessible. Similar limitation concerns also another method, starting from the analogous 3-O-benzyl derivative *XL*. This compound was easily obtained from 1,2 : 4,6-di-O-isopropylidene-D-glucofuranose[13] by reaction of its sodium salt with benzyl chloride, partial deblocking of the *cis*-diol



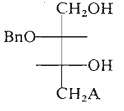
XXIII, R = OTs
XXIV, R = adenin-9-yl
XXV, R = uracil-1-yl
XXVI, R = uracil-3-yl



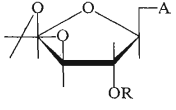
XXVIII, R = OH
XXIX, R = OTs
XXX, R = adenin-9-yl



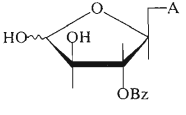
XXXI



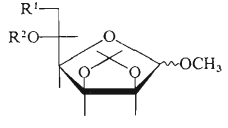
XXXII



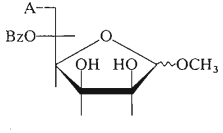
XXXIIIa, R = H
XXXIIIb, R = Bz



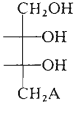
XXXIV



XXXV, R^1 = OTs, R^2 = H
XXXVI, R^1 = OTs, R^2 = Bz
XXXVII, R^1 = adenin-9-yl, R^2 = Bz
XXXVIII, R^1 = adenin-9-yl, R^2 = H



XXXIX



XL (D or L)

In formulae *II*–*XL*, A represents adenin-9-yl, Bz benzoyl, Ts *p*-toluenesulfonyl and Bn benzyl residue.

in the positions 5,6, degradation of this grouping with periodate and reduction with sodium borohydride. The thus-obtained 1,2-O-isopropylidene-3-O-benzyl-D-xylofuranose (*XXVIII*) was tosylated to give the 5-O-tosyl derivative *XXIX* which was converted by reaction with sodium salt of adenine to the completely blocked derivative *XXX* the structure of which was confirmed by ^{1}H-NMR spectrum. Hydrolysis with 50% formic acid led to the free furanose *XXXI* whose degradation with sodium periodate and sodium borohydride afforded the 3-O-benzyl derivative *XXXII*. Catalytic hydrogenation of this compound led finally to the D-*threo*-derivative *XXII*. This method, using benzyl instead of benzoyl group for protection of the 3-hydroxyl group, has certain advantages: first of all the facile preparation from D-glucose and stability of the protecting group during the synthesis; its disadvantage is the necessary hydrogenolysis in the last step and low solubility of the intermediates *XXXI* and *XXXII* which makes their purification difficult.

The optically active *erythro*-derivatives can be in principle prepared by both methods used for the synthesis of the *threo*-isomers; nevertheless, the approach, starting with the degradation of sugar derivatives of heterocyclic bases appears to be simpler; this is illustrated by two syntheses. The L-*erythro*-derivative *XL* was prepared from 5-(adenin-9-yl)-5-deoxy-L-arabinofuranose (*XXXIIIa*), described in the previous communication[6], by degradation with sodium periodate, followed by reduction with sodium borohydride, methanolysis and deionisation. The compound *XXXIIIa* was prepared previously by reduction of alkyl ester of eritadenine with sodium borohydride[8,14].

The D-*erythro* derivative *XL* was prepared previously by building up the purine ring in 2,4-O-ethylidene-D-erythritylamine[15]. Its present synthesis started from methyl 2,3-O-isopropylidene-α-D-mannofuranoside[16] which was first converted to the 6-O-tosyl derivative *XXXV* and then to the 6-O-tosyl-5-O-benzoyl derivative *XXXVI*. Protection of the 5-hydroxyl group in the vicinity of the reaction center in the reaction with sodium salt of adenine proved to be more advantageous: it increases the yield, makes the isolation simpler and eliminates the possible participation of the 5-hydroxyl in the reaction of the 6-tosyl group. The reaction mixture afforded the completely blocked adenine derivative *XXXVII* whose structure was confirmed both by ^{1}H-NMR spectrum and methanolysis to the compound *XXXVIII*, identical with the product isolated from the reaction of adenine with the compound *XXXV*. Treatment of the compound *XXXVII* with 90% formic acid at room temperature hydrolysed selectively the 2,3-dioxolane ring, the liberated *cis*-diol in the obtained product *XXXIX* was cleaved with sodium periodate and the formed dialdehyde was reduced with sodium borohydride. Alkaline methanolysis removed the benzoyl group and the residue bonded to the 3-hydroxyl group was then cleaved off in an acidic medium. The absolute configuration of the obtained product *XL* corresponded to that of the $C_{(4)}$—$C_{(5)}$ segment in D-mannose and was thus D-*erythro*-.

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 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 1M acetic acid (20 V/cm, 1 h). The chromatography on silica gel was performed on Silufol UV_{254} plates in the solvent systems S3, chloroform, S4, chloroform–ethanol (95 : 5), S5, chloroform–ethanol (9 : 1), S6, chloroform–ethanol (85 : 15), S7, chloroform–ethanol (4 : 1), S8, chloroform–methanol (3 : 2), S9, benzene–ether (7 : 3), S10, chloroform–tetrachloromethane (1 : 1). 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) or on a column (200 g) of silica gel according to Pitra (30—60 mesh; elution rate 2—3 ml/min, fraction 10 min). Chromatography on Dowex 1 X 2 (OH^-) according to Dekker was carried out on a 60 × 3 cm column under the same conditions. Deionisation was performed on a 100 ml column of Dowex 50X8 (H^+); an aqueous solution of the mixture was applied at pH 3 (hydrochloric acid), the column was washed with water until the absorption and conductivity dropped and the product was then eluted with dilute (1 : 10) ammonia. The elution was followed by 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 were taken on a Varian 100 instrument in deuteriochloroform or hexadeuteriodimethyl sulfoxide with hexamethyldisiloxane as internal standard (the chemical shifts are given in ppm, interaction constants in Hz).

DL-*threo*-2,2-Dimethyl-4,5-bis(ethoxycarbonyl)-1,3-dioxolane (*II*)

A mixture of diethyl DL-tartrate[17] (40·4 g; 0·196 mol), acetone (50 ml), 2,2-dimethoxypropane (100 ml) and 6M hydrogen chloride in dimethylformamide (1·5 ml) was set aside at room temperature for two days, made alkaline with triethylamine and taken down *in vacuo*. The residue was dissolved in ether (250 ml), washed with water (3 × 50 ml), dried over magnesium sulfate, filtered and the ether evaporated *in vacuo*. Distillation of the residue *in vacuo* afforded 26·5 g (55%) of the compound *II*, b.p. 118—120°C/0·2 Torr (reported[18] b.p. 136—140°C/10 Torr). For $C_{11}H_{18}O_6$ (246·3) calculated: 53·65% C, 7·37% H; found: 53·48% C, 7·21% H. ^{1}H-NMR spectrum ($CDCl_3$): 1·47 (s, 6 H) isopropylidene; 1·30 (t, 6 H) 2 × CH_3 (ethyl); 4·26 + 4·28 (2 × q, 2 × 2 H, J = 7·0) 2 × CH_2 (ethyl); 4·75 (s, 2 H) 2 × CH.

DL-*threo*-2,2-Dimethyl-1,3-dioxolane-4,5-dimethanol (*III*)

A solution of the compound *II* (26·5 g; 0·107 mol) in ether (100 ml) was added to a stirred suspension of lithium aluminium hydride (5·3 g) in ether (80 ml) without cooling at such a rate that the mixture boiled (about 30 min). It was then refluxed for 3 h under stirring (calcium chloride tube), cooled with ice and decomposed by addition of ethyl acetate (20 ml), water (20 ml) and 4M sodium hydroxide (10 ml), again with stirring. The solids were filtered off, washed with hot chloroform (500 ml) and extracted with ether in a Soxhlet extractor for 2 days. The ethereal extract was combined with the first filtrate, dried over magnesium sulfate and taken down *in vacuo*. Distillation of the residue afforded 9·6 g (61·5%) of the compound *III*, b.p. 160°C/0·2 Torr (reported[18] b.p. 106—108°C/0·4 Torr).

DL-*threo*-2,2-Dimethyl-4-benzoyloxymethyl-5-hydroxymethyl-1,3-dioxolane (*IV*) and DL-*threo*-2,2-Dimethyl-4,5-bis(benzoyloxymethyl)-1,3-dioxolane (*V*)

A solution of benzoyl cyanide (5·9 g; 45 mmol) in acetonitrile (50 ml) was added dropwise during 1 h to a stirred solution of the compound *III* (6·0 g; 41·3 mmol) and triethylamine (0·5 ml) in acetonitrile (200 ml). The mixture was set aside overnight at room temperature, ethanol (5 ml) was added and the solvent evaporated *in vacuo*. Chromatography on a silica gel column (eluant chloroform) afforded the product fractions, R_F 0·77 (S3) which on crystallisation from ethanol gave the compound *V* (1·7 g, 11·4%), m.p. 83—84°C. For $C_{21}H_{22}O_6$ (370·4) calculated: 68·09% C, 5·99% H; found: 68·14% C, 6·34% H. ^{1}H-NMR spectrum ($CDCl_3$): 1·47 (s, 6 H) isopropylidene, 4·20—4·65 (m, 6 H) CH + CH_2; 7·25—7·70 (m, 6 H) + 7·95—8·20 (m, 4 H) aromatic protons. Fractions, containing a compound of R_F 0·30 (S3) produced an amorphous foam (5·9 g, 53·6%) of the compound *IV* which was used in the further reaction.

DL-*threo*-2,2-Dimethyl-4-benzoyloxymethyl-5-*p*-toluer esulfonyloxymethyl-1,3-dioxolane (*VI*)

p-Toluenesulfonyl chloride (5·0 g; 26 mmol) was added under cooling (0°C) to the compound *IV* (5·7 g; 23·7 mmol) in pyridine (50 ml) and the mixture was stirred at 0°C till it became homogeneous. After 2 days at 0°C methanol (10 ml) was added, the mixture was taken down *in vacuo*, the residue diluted with ethyl acetate (150 ml), washed with water, saturated sodium hydrogen carbonate and again water (50 ml each), dried over magnesium sulfate, filtered and the filtrate taken down *in vacuo*. The residue was crystallised from cyclohexane (50 ml), the crystals washed with cyclohexane and dried *in vacuo* yielding 8·7 g (91%) of the compound *VI*, m.p. 84—85°C; For $C_{21}H_{24}O_7S$ (420·5) calculated: 59·98% C, 5·75% H, 7·62% S; found: 60·01% C, 5·78% H, 8·00% S.

9-(DL-*threo*-2,3-O-Isopr opylidene-4-O-benzoyl-2,3,4-trihydroxybutyl)adenine (*VII*)

Sodium hydride (0·40 g; 16·7 mmol) was added to a suspension of adenine (2·03 g; 15 mmol) in dimethylformamide (40 ml). After stirring for 1 h under exclusion of moisture, the compound *VI* (4·03 g; 10 mmol) was added and the mixture was heated to 100°C for 6 h with stirring and exclusion of moisture. After cooling, the insoluble material was filtered and washed with dimethylformamide (20 ml), the filtrate was taken down at 40°C/0·1 Torr and the residue extracted with boiling chloroform. The extract was filtered through Celite which was then washed with hot chloroform (200 ml) and the filtrate was taken down *in vacuo*. Crystallisation of the residue from ethanol afforded 2·75 g (75%) of the compound *VII*, m.p. 144—145°C. R_F 0·50 (S5). For $C_{19}H_{21}$. N_5O_3 (367·4) calculated: 62·11% C, 5·76% H, 19·07% N; found: 60·01% C, 6·01% H, 19·49%N . ^{1}H-NMR spectrum ($CDCl_3$): 1·32 + 1·42 (2 s, 2 × 3 H) isopropylidene; 3·97 (m, 1 H) $H_{2'}$; 4·40 (m, 1 H) $H_{3'}$; 4·54 (t, 4 H, J = 3·5) $H_{1'}$ + $H_{4'}$; 5·95 (br, 2 H) NH_2; 7·97 (s, 1 H) H_2; 8·28 (s, 1 H) H_8.

9-(DL-*threo*-2,3-O-Isopropylidene-2,3,4-trihydroxybutyl)adenine (*VIII*)

A suspension of the compound *VII* (1·5 g; 4·1 mmol) in 0·2M methanolic sodium methoxide (25 ml) was heated till it dissolved and was set aside at room temperature overnight. The mixture was neutralised with Dowex 50X8 (H^+), treated with triethylamine (2 ml), filtered, the material on the filter washed with methanol (100 ml) and the filtrate taken down *in vacuo*. The residue was crystallised from ethanol (5 ml), light petroleum being added until the solution became turbid, yielding 0·85 g (74%) of the compound *VIII*, m.p. 158—159°C. R_F 0·25 (S5). For $C_{12}H_{17}N_5O_3$

(279·3) calculated: 51·60% C, 6·14% H, 25·08% N; found: 51·46% C, 6·26% H, 24·81% N. ^{1}H-NMR spectrum ($CDCl_3$): 1·25 + 1·39 (2 s, 2 × 3 H) isopropylidene; 3·55—3·90 (m, 3 H) H_3, + 2 H_4,; 4·27 (m, 1 H) H_2,; 4·49 (t, 2 H, J = 4·0) 2 H_1,; 6·67 (br, 2 H) NH_2; 7·98 (s, 1 H) H_2; 8·30 (s, 1 H) H_8.

9-(DL-*threo*-2,3,4-Trihydroxybutyl)adenine (*IX*)

A solution of the compound *VIII* (0·6 g; 2·15 mmol) in 80% acetic acid (50 ml) was refluxed for 1 h, evaporated, the residue coevaporated with water (3 × 20 ml) and crystallised from 80% ethanol, affording 0·4 g (72%) of the compound *IX*, m.p. 214—216°C (monohydrate). For $C_9H_{15}N_5O_4$ (257·3) calculated: 42·01% C, 5·88% H, 27·23% N; found: 42·14% C, 5·84% H, 27·65% N. R_F 0·38 (S1).

Diethyl *meso*-Tartrate (*X*)

A mixture of maleic acid (250 g; 2·15 mol), 99% ethanol (700 ml) and 25% ethanolic hydrogen chloride (50 ml) was refluxed for 8 h, neutralised with triethylamine and taken down *in vacuo*. The residue was diluted with ether (1 l), washed with water (2 × 300 ml), dried over magnesium sulfate, filtered and the filtrate evaporated *in vacuo*. The residue was distilled to give 212 g (57·5%) of diethyl maleate (*X*), b.p. 120—123°C/20 Torr. For $C_8H_{12}O_4$ (172·2) calculated: 55·80% C, 7·03% H; found: 55·71% C, 6·93% H.

A mixture of *X* (172 g; 1 mol), potassium chloride (150 g) and osmium tetroxide (0·94 g) in 50% ethanol (1 l) was heated to 50°C for 4 h with stirring. Potassium chlorate (100 g) was added and the stirring was continued for 8 h at 50°C (according to thin-layer chromatography in S3 the reaction was quantitative). The mixture was cooled down, evaporated *in vacuo* to a half of the original volume, saturated with sodium chloride, filtered and the filtrate extracted with ether (7 × 200 ml). The ethereal extract was dried over magnesium sulfate, filtered and the filtrate was taken down *in vacuo*. Distillation of the residue afforded 160·5 g of the product which was purified by fractionation *in vacuo*, yielding 110·5 g (53·7%) of the compound *XI*, b.p. 162 to 163°C/15 Torr (reported[17] b.p. 156·5°C/15 Torr) which crystallised on cooling (reported[17] m.p. 58°C).

DL-*erythro*-2,2-Dimethyl-4,5-bis(ethoxycarbonyl)-1,3-dioxolane (*XII*)

A mixture of the compound *XI* (110 g; 0·535 mol), acetone (100 ml), 2,2-dimethoxypropane (150 ml) and 6M hydrogen chloride in dimethylformamide (5 ml) was set aside at room temperature for 7 days, stirred with sodium hydrogen carbonate (50 g) until the reaction was neutral (1 h), filtered and the filtrate taken down *in vacuo*. The residue was distilled and fractionated *in vacuo* to yield 72 g (55%) of the compound *XII*, b.p. 140—142°C/15 Torr (reported[18] b.p. 136—140°C/10 Torr). For $C_{11}H_{18}O_6$ (246·2) calculated: 53·65% C, 7·35% H; found: 52·98% C, 7·38% H. ^{1}H-NMR spectrum ($CDCl_3$): 1·40 + 1·63 (2 s, 2 × 3 H) isopropylidene; 1·27 (t, 6 H) CH_3; 4·20 (q, 4 H, J = 7·0) CH_2; 4·82 (s, 2 H) O—CH.

DL-*erythro*-2,2-Dimethyl-4,5-bis(benzoyloxymethyl)-1,3-dioxolane (*XIV*)

A solution of the compound *XII* (72 g; 0·292 mol) in ether (200 ml) was added over 30 min to a stirred and ice-cooled suspension of lithium aluminium hydride (17 g; 0·445 mol) in ether (350 ml). The mixture was refluxed (calcium chloride tube) for 2 h under stirring, cooled down with ice and decomposed by successive dropwise addition of ethyl acetate (120 ml), water (55 ml)

and 4M sodium hydroxide (55 ml). The suspension was filtered, the solids washed with acetone (4 × 200 ml) and ether (300 ml), the filtrate was dried over magnesium sulfate and the solvent evaporated. The residue (compound *XIII*; 49 g) was mixed with pyridine (160 ml) and benzoyl chloride (58 ml, 70·2 g; 0·5 mol) and set aside overnight under exclusion of moisture. Ethanol (20 ml) was added, the mixture was evaporated *in vacuo*, the residue diluted with ethyl acetate (1 l), washed with water (3 × 200 ml), the organic layer dried over magnesium sulfate, filtered and taken down *in vacuo*. Crystallisation of the residue from ethanol afforded 80·5 g (72%) of the compound *XIV*, m.p. 113—114°C. For $C_{21}H_{22}O_6$ (370·4) calculated: 68·09% C, 5·99% H; found: 67·81% C, 5·66% H. ^{1}H-NMR spectrum ($CDCl_3$): 1·42 + 1·47 (2 s, 2 × 3 H) isopropylidene; 4·25—4·70 (m, 6 H) CH + CH_2; 7·25—7·70 (m, 6 H) + 7·95—8·15 (m, 4 H) aromatic protons.

DL-*erythro*-2,2-Dimethyl-4-*p*-toluenesulfonyloxymethyl-5-hydroxymethyl-1,3-dioxolane (*XV*)

A suspension of the compound *XIV* (48·1 g; 0·13 mol) in 0·1M methanolic sodium methoxide (200 ml) was heated till dissolution and then set aside at room temperature overnight. After neutralisation with Dowex 50 X 8 (H^+) the mixture was filtered, the filtrate taken down *in vacuo*, the residue coevaporated with pyridine (3 × 100 ml) and dissolved in pyridine (100 ml). *p*-Toluenesulfonyl chloride (25 g; 0·13 mol) was added at −60°C and the mixture was allowed to warm to 0°C during 2 h. The solution was set aside at 0°C overnight under exclusion of moisture. Ethanol (50 ml) was added, the mixture was taken down, the residue diluted with ethyl acetate (300 ml) and washed with water (3 × 50 ml). The organic phase was dried over magnesium sulfate, filtered, the material on the filter washed with ethyl acetate and the filtrate taken down *in vacuo*, finally at 40°C/0·1 Torr. The residue was stirred with light petroleum at 0°C until it crystallised, the product was filtered, washed with ice-cold light petroleum and dried *in vacuo*, affording 21·3 g (52%) of the compound *XV*, m.p. 104—105°C. R_F 0·33 (S3). For $C_{14}H_{20}O_6S$ (316·4) calculated: 53·15% C, 6·37% H, 10·13% S; found: 52·71% C, 5·66% H, 10·54% S.

9-(DL-*erythro*-2,3,4-Trihydroxybutyl)adenine (*XVII*)

Sodium hydride (0·50 g; 22 mmol) was added to a suspension of adenine (2·7 g; 20 mmol) in dimethylformamide (40 ml), and the mixture was stirred for 1 h at room temperature. Compound *XV* (3·15 g; 10 mmol) was added, the mixture was stirred under exclusion of moisture at 100°C for 12 h, filtered through Celite and the filtrate taken down at 40°C/0·1 Torr. The residue was refluxed with 80% acetic acid (100 ml) for 90 min, the solvent evaporated and the residue coevaporated with water (3 × 20 ml) and then deionised on a column of Dowex 50 X 8. The ammonia eluate was taken down and the residue chromatographed on a column of Dowex 1 X 2 (OH^-). The product-containing fractions (R_F 0·60 in S1) were combined, taken down and the residue coevaporated with ethanol, dissolved in methanol (20 ml) and precipitated with ether (200 ml). After filtration and washing with ether the product was dried *in vacuo*. Yield 0·54 g (21%) of the compound *XVII*, homogeneous according to thin-layer chromatography (R_F 0·60 in S1, 0·50 in S2). For the monohydrate $C_9H_{15}N_5O_4$ (257·3) calculated: 42·01% C, 5·88% H, 27·23% H; found: 42·72% C, 6·06% H, 26·89% N.

1,3-O-Benzylidene-D-threitol (D-*XVIII*)

A mixture of 1,3-O-benzylidene-D-arabinitol (50 g; 0·208 mol; prepared according to ref.[10], m.p. 152°C), water (1·5 l; temperature 30°C) and a solution of sodium periodate (48 g) in water

(500 ml) was stirred without cooling for 1 h. A 1M solution of barium acetate (150 ml) was added and the mixture was filtered through celite. The filtrate was taken to dryness with barium carbonate (5 g), the residue coevaporated with ethanol (3 × 100 ml), extracted with boiling ethanol (300 ml), filtered through celite which was then washed with boiling ethanol (100 ml), and the filtrate was evaporated. The residue was dissolved in hot water (200 ml) and set aside in a refrigerator overnight. 1,3-O-Benzylidene-D-threose which crystallised (38·0 g; 84%) was collected and added in the course of 10 min to a cooled (ice) solution of sodium borohydride (8·5 g) in water (50 ml) and ethanol (200 ml). After stirring at 0°C for 20 min and at temperature for 2 h, the excess hydride was decomposed by several drops of acetic acid, the mixture was concentrated *in vacuo* and water (300 ml) was added to the residue. The mixture was acidified with hydrochloric acid (pH 5) and extracted with ethyl acetate (4 × 100 ml). The extract was washed with saturated solution of sodium hydrogen carbonate (2 × 100 ml) and water (100 ml), dried over magnesium sulfate, filtered and taken down. The residue was crystallised from ethyl acetate (with addition of light petroleum until the solution was turbid), yielding 10·0 g (23%) of the compound D-*XVIII*, m.p. 146—147°C. R_F 0·27 (S5), 0·23 (S4). For $C_{11}H_{14}O_4$ (210·2) calculated: 62·85% C, 6·71% H; found: 62·74% C, 6·81% H.

1,3-O-*Benzylidene*-L-*threitol* (L-*XVIII*) was prepared analogously in 27% yield; m.p. 139 to 141°C. Found: 62·97% C, 6·68% H; R_F 0·27 (S5), 0·23 (S4).

4-O-*p*-Toluenesulfonyl-1,3-O-benzylidene-D-threitol (D-*XIX*)

p-Toluenesulfonyl chloride (7·0 g; 36·7 mmol) was added at 0°C to a solution of the compound *D-XVIII* (5·0 g; 23·8 mmol) in pyridine (40 ml) and the mixture set aside at room temperature overnight. After addition of ethanol (3 ml), the mixture was allowed to stand at room temperature for 2 h and taken down. Chloroform (100 ml) was added to the residue, the solution washed with water (2 . 50 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*. The residue was coevaporated with toluene (2× 25 ml) and crystallised from ethanol (50 ml) with addition of light petroleum until the solution was turbid; yield 6·2 g (71·5%) of the compound D-*XIX*, m.p. 102—104°C. For $C_{18}H_{20}O_6S$ (364·3) calculated: 59·34% C, 5·51% H, 8·80% S; found: 59·53% C, 5·56% H, 9·06% S. R_F 0·45 (S4).

4-O-p-*Toluenesulfonyl*-1,3-O-*benzylidene*-L-*threitol* (L-XIX): was prepared similarly in 72·5% yield from the compound L-*XVIII* (8·8 g; 24 mmol). M.p. 99—100°C. Found: 58·98% C, 5·54% H, 8·84% S. R_F 0·45 (S4).

2-O-Benzoyl-4-O-*p*-toluenesulfonyl-1,3-O-benzylidene-D-threitol (D-*XX*)

Benzoyl chloride (2·8 g; 20 mmol) was added dropwise during 10 min to a stirred and cooled (0°C) solution of the compound D-*XIX* (5·5 g; 15 mmol) in pyridine (40 ml) and the mixture was set aside at room temperature overnight. Ethanol (5 ml) was added, the solvents evaporated *in vacuo*, the residue mixed with chloroform (100 ml), the mixture washed with water (3× 25 ml), dried over magnesium sulfate, filtered, taken to dryness and the residue coevaporated (3× 25 ml) with toluene. Chromatography on a silica gel column in a chloroform–tetrachloromethane (1 : 1) mixture afforded 4·0 g (57%) of D-*XX* in the form of a foam; R_F 0·78 (S3). For $C_{25}H_{24}O_7S$ (468·5) calculated: 64·08% C, 5·16% H, 6·84% S; found: 64·47% C, 4·99% H, 6·58% S.

2-O-Benzoyl-4-O-*p*-toluenesulfonyl-1,3-O-benzylidene-L-threitol (L-*XX*): was prepared analogously to the compound *D-XX*. Yield 49% of chromatographically (R_F 0·78 in S3) homogeneous foam. Found: 63·92% C, 5·02% H, 6·22% S.

9-(D-*threo*-3-O-Benzoyl-2,4-O-benzylidene-2,3,4-trihydroxybutyl)adenine (D-*XXI*)

Sodium salt of adenine (0·6 g; 3·8 mmol) was added to a solution of the compound D-*XX* (1·4 g; 3 mmol) in dimethylformamide (10 ml). The mixture was heated with stirring to 100°C for 14 h under exclusion of moisture and taken down at 40°C/0·1 Torr. The residue was taken up in chloroform (100 ml), the solution washed with water (40 ml), dried over magnesium sulfate, filtered, the solvent evaporated *in vacuo* and the residue chromatographed on a loose layer of silica gel in the system S3. The product band was eluted with methanol (300 ml), the eluate taken down and the residue dried *in vacuo*, leaving 0·50 g (38·5%) of the compound D-*XXI*. For $C_{23}H_{21}N_5O_4$ (431·5) calculated: 64·01% C, 4·90% H, 16·23% N; found: 63·69% C, 4·89% H, 16·65% N. R_F 0·27 (S3). ^{1}H-NMR spectrum ($CDCl_3$): 4·21 (br s, 1 H) + 4·44 (d, 2 H, $J = 10$) + 4·61 (d, 2 H, $J = 5$) 2 $H_{1'}$ + $H_{2'}$ + 2 $H_{4'}$; 5·56 (m, 1 H) $H_{3'}$; 5·72 (s, 1 H) phenyl-CH (one single diastereoisomer); 6·88 (br, 2 H) NH_2; 7·20–8·05 (12 H, m) arom. protons + H_2 + H_8.

9-(L-threo-3-O-*Benzoyl*-2,4-O-*benzylidene*-2,3,4-*trihydroxybutyl*)*adenine* (L-XXI): was prepared analogously as the compound D-*XXI* in 46% yield. Foam, R_F 0·27 in S3. Found: 64·08% C, 5·12% H, 16·04% N. Its ^{1}H-NMR spectrum was identical with that of the compound D-*XXI* (one single diastereoisomer).

TABLE I

Circular Dichroism Spectra in 0·1N-Hydrochloric Acid of Adenine 9-(2,3,4-Trihydroxybutyl) Derivatives[a]

Wavelengths in nm, molar ellipticities in parentheses.

Formula	Configuration	λ_I	λ_{II}	$\lambda_{\Theta=0}$
D-*XXII*	D-*threo*	249 (−1 100)	210 (+4 200)	231
L-*XXII*	L-*threo*	250 (+1 500)	204 (−4 100)	231
D-*XL*	D-*erythro*	253 (−1 100)	212 (+2 400)	231
L-*XL*	L-*erythro*	254 (+1 300)	210 (−2 500)	235

[a] 9-((*S*)-2,3-Dihydroxypropyl)adenine: λ_I 259 nm (+500), λ_{II} 212 nm (−2 200), $\lambda_{\Theta=0}$ 236.

3-O-Benzoyl-5-O-*p*-toluenesulfonyl-1,2-O-isopropylidene-α-D-xylofuranose (*XXIII*)

Dry Dowex 50 X 8 (H^+) (50 ml) was added to a solution of 1,2 : 3,5-di-O-isopropylidene-α--D-xylofuranose[12] (56 g; 0·244 mol) in 50% methanol (300 ml) and the suspension was stirred at room temperature for 2·5 h. According to thin-layer chromatography in S4 (detection with iodine vapours) the reaction was complete. The mixture was filtered, the solid washed with methanol (100 ml) the filtrate taken down *in vacuo* and the residue coevaporated with pyridine

(5× 50 ml). The residue was dissolved in pyridine (200 ml) and *p*-toluenesulfonyl chloride (57 g; 0·3 mol) was added under cooling with ice. The mixture was set aside at room temperature overnight, taken down *in vacuo*, diluted with chloroform (500 ml), washed with water, saturated sodium hydrogen carbonate solution and again with water (100 ml each), dried over magnesium sulfate, filtered and taken down. The crystalline residue was suspended in pyridine (200 ml) and benzoyl chloride (35 ml; 42·1 g; 0·4 mol) was added dropwise under cooling with ice. The mixture was stirred for 1 h with ice-cooling, set aside at room temperature for 2 days and taken down *in vacuo*. The residue was diluted with chloroform (500 ml), washed with saturated sodium hydrogen carbonate solution (3× 100 ml) and water (100 ml), dried over magnesium sulfate, taken down and the residue coevaporated with toluene, finally at 50°C/0·1 Torr, leaving a chromatographically homogeneous glass (R_F 0·10 in S3); yield 79 g (75%). A 0·92M solution of this product (*XXIII*) in dimethylformamide was used in further reactions.

5-(Adenin-9-yl)-5-deoxy-3-O-benzoyl-1,2-O-isopropylidene-D-xylofuranose (*XXIV*)

A mixture of the compound *XXIII* (30 mmol) and sodium salt of adenine (30·5 mmol) in dimethylformamide (50 ml) was stirred at 100°C for 16 h under exclusion of moisture, filtered and the solids washed with dimethylformamide (20 ml). The filtrate was taken down at 40°C/0·1 Torr, the residue extracted with chloroform (100 ml), the extract filtered through celite which was then washed with chloroform (50 ml), the filtrate evaporated *in vacuo* and the residue chromatographed on a column of silica gel in chloroform. The product was eluted with a chloroform–ethanol (95 : 5) mixture, the pertinent fractions were combined, taken down and the residue dried *in vacuo*, yielding 5·8 g (47%) of a foam of the compound *XXIV*, R_F 0·24 (S4), 0·60 (S5). For $C_{20}H_{21}N_5O_5$ (411·4) calculated: 58·38% C, 5·15% H, 17·03% N; found: 58·17% C, 4·87% H, 17·41% N. ^{1}H-NMR spectrum ($CDCl_3$): 1·32 + 1·49 (2 s, 2 × 3 H) isopropylidene; 4·37 (dd, 1 H, $J_{5'',4'} = 8·0$, $J_{gem} = 14·5$) $H_{5''}$; 4·64 (dd, 1 H, $J_{5',4'} = 3·0$, $J_{gem} = 14·5$) $H_{5'}$; 4·70 (d, 1 H, $J_{2',1'} = 4·0$, $J_{2',3'} < 0·5$) $H_{2'}$; 4·80 (m, 1 H) $H_{4'}$; 5·59 (d, 1 H, $J_{3',2'} < 0·5$, $J_{3',4'} = 3·0$) $H_{3'}$; 5·95 (br, 2 H) NH_2; 7·96 (s, 1 H) H_2; 8·26 (s, 1 H) H_8; 7·30–7·65 (3 H, m) + 7·90–8·05 (m, 2 H) aromatic protons.

5-(Uracil-1-yl)- and 5-(Uracil-3-yl)-5-deoxy-3-O-benzoyl-1,2-O-isopropylidene-D-xylofuranose (*XXV* and *XXVI*)

Sodium hydride (0·6 g; 25 mmol) was added to a suspension of uracil (2·8 g; 25 mmol) in dimethylformamide (50 ml) and after stirring for 30 min a 0·92M solution (27 ml; 25 mmol) of the compound *XXIII* in dimethylformamide was added. The mixture was heated to 100°C for 24 h with stirring, taken down at 40°C/0·1 Torr, extracted with hot chloroform (200 ml) and filtered through celite which was then washed with chloroform (50 ml). The filtrate was concentrated *in vacuo* and chromatographed on a silica gel column in tetrachloromethane. The column was gradient-eluted with tetrachloromethane with increasing amount of chloroform, finally with pure chloroform. Fractions with R_F 0·15 (S3) afforded 3·0 g (31%) of the compound *XXVI* in the form of a foam. For $C_{19}H_{20}N_2O_7$ (388·4) calculated: 58·76% C, 5·19% H, 7·21% N; found: 59·27% C, 5·39% H, 7·67% N. R_F 0·15 (S3), 0·85 (S4).

Fractions of R_F 0·10 (S3) gave 2·36 g (24·3%) of the compound *XXV* as a foam; R_F 0·10 (S3), 0·50 (S4). Found: 59·13% C, 5·14% H, 7·36% N. ^{1}H-NMR spectrum ($CDCl_3$): 1·31 + 1·50 (2 s, 2 × 3 H) isopropylidene; 3·72 (dd, 1 H, $J_{5'',4'} = 8·0$, $J_{gem} = 14·5$) $H_{5''}$; 4·34 (dd, 1 H, $J_{5',4'} = 3·0$, $J_{gem} = 14·5$) $H_{5'}$; 4·60 (m, 1 H, $J_{3',2'} < 1·0$) $H_{4'}$; 4·79 (d, 1 H, $J_{2',1'} = 3·5$, $J_{2',3'} < 1·0$) $H_{2'}$; 5·56 (d, 1 H, $J_{5,NH} = 1·5$, $J_{5,6} = 8·0$) H_5; 5·43 (d, 1 H, $J_{3',2'} = 1·0$, $J_{3',4'} = 3·0$) $H_{3'}$; 6·01 (d, 1 H, $J_{1',2'} = 3·5$) $H_{1'}$; 7·40 (d, 1 H, $J_{6,5} = 8·0$) H_6; 11·08 (br, 1 H) NH.

3-O-Benzyl-5-O-*p*-toluenesulfonyl-1,2-O-isopropylidene-α-D-xylofuranose (*XXIX*)

1,2 : 5,6-Di-O-isopropylidene-α-D-glucofuranose[13] (48·4 g; 0·2 mol) was added to a slurry of sodium hydride (4·8 g; 0·2 mol) in dimethylformamide (150 ml) under exclusion of moisture and the mixture was stirred until it was homogeneous (20 min). Benzyl chloride (32 g; 0·25 mol) was added dropwise under stirring in the course of 20 min, the mixture was stirred at 110 to 120°C for 6 h (calcium chloride tube), cooled down and filtered through celite which was then washed with dimethylformamide (50 ml). The filtrate was taken down at 40°C/0·1 Torr, the residue stirred with methanol (200 ml), water (70 ml) and dry Dowex 50 X 8 (H^+) for 5 h (the reaction was quantitative according to thin-layer chromatography in S3; starting compound R_F 0·50, product R_F 0·17). The mixture was filtered, the solid on the filter washed with methanol (200 ml), and the filtrate taken down. The residue was diluted with water (200 ml), extracted with ether (2 × 100 ml), and the extract washed with water (2 × 50 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*. The residue was chromatographed on a silica gel column with chloroform as eluant, affording 43·5 g (74·5%) of 3-O-benzyl-1,2-O-isopropylidene--α-D-glucofuranose. This product (0·149 mol) was dissolved in 70% methanol (1 l) and sodium periodate (35·4 g; 165 mmol) added at 0°C. The mixture was stirred at 0°C for 30 min, filtered and sodium borohydride (15 g; 0·4 mol) was added to the filtrate. After stirring at room temperature for 2 h the excess borohydride was destroyed by addition of acetic acid, the mixture was filtered, the filtrate concentrated *in vacuo* to about 500 ml and extracted with chloroform (5 × × 100 ml). The extract was dried over magnesium sulfate, filtered and taken down *in vacuo*, finally at 50°C/0·1 Torr, yielding 36·4 g (93·5%) of 3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose (*XXVIII*).

A solution of this compound (0·139 mol) in pyridine (50 ml) was added dropwise over 30 min to *p*-toluenesulfonyl chloride (28·6 g; 0·15 mol) in pyridine (150 ml) under cooling with ice. The mixture was stirred at 0°C for 2 h, then set aside at room temperature for 2 days and taken down *in vacuo*. Ethyl acetate (300 ml) and water (100 ml) were added, the organic layer washed with water (3 × 50 ml), dried over magnesium sulfate, filtered and evaporated *in vacuo*, yielding 53·7 g (93%) of the compound *XXIX*, R_F 0·66 (S3) which was used in further experiments.

5-(Adenin-9-yl)-3-O-benzyl-1,2-O-isopropylidene-α-D-xylofuranose (*XXX*)

Sodium hydride (3·1 g; 0·13 mol) was added to a suspension of adenine (17·5 g; 0·13 mol) in dimethylformamide (150 ml) and the mixture was stirred at 60°C for 1 h under exclusion of moisture. A solution of the compound *XXIX* (53·7 g; 0·129 mol) in dimethylformamide (100 ml) was added dropwise at 60°C and the stirring was continued at 100°C for 14 h under exclusion of moisture. The mixture was evaporated at 40°C/0·1 Torr, the residue taken up in boiling chloroform (500 ml), 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 in chloroform. The product was eluted with an ethanol–chloroform (5 : 95) mixture and was obtained as chromatographically uniform foam; yield 27·9 g (54·6%). R_F 0·82 (S1), 0·35 (S4), 0·70 (S5). For $C_{20}H_{23}N_5O_4$ (397·4) calculated: 60·44% C, 5·83% H, 17·62% N; found: 60·42% C, 5·92% H, 17·76% N. ^{1}H-NMR spectrum ($CDCl_3$): 1·29 + 1·40 (2 s, 2 × 3 H) isopropylidene; 4·04 (d, 1 H, $J_{3',2'} = 0·5$, $J_{3',4'} = 3·0$) $H_{3'}$; 4·25—4·60 (m, 2 H) $2\,H_{5'}$; 4·50 + 4·75 (2 d, 2 H, $J = 12·0$) benzyl; 4·60 (m, 1 H) $H_{4'}$; 4·68 (d, 1 H, $J_{2',1'} = 3·8$) $H_{2'}$; 5·99 (d, 1 H, $J_{1',2'} = 3·8$) $H_{1'}$; 6·42 (br, 2 H) NH_2; 7·35 (m, 5 H) aromatic protons; 7·87 (s, 1 H) H_8; 8·33 (s, 1 H) H_2.

5-(Adenin-9-yl)-5-deoxy-3-O-benzyl-D-xylofuranose (*XXXI*)

A solution of the compound *XXX* (27·8 g; 70 mmol) in 50% formic acid (250 ml) was heated to 100°C for 40 min (according to thin-layer chromatography in S4, the reaction was quantitative), cooled down, evaporated *in vacuo* and the residue coevaporated with water (6 × 50 ml) in order to remove the formic acid and evaporated again with dilute (1 : 20) ammonia. Crystallisation from 90% ethanol afforded 16·2 g (65%) of the compound *XXXI*, m.p. 140—146°C. For $C_{17}H_{19}.N_5O_4$ (357·4) calculated: 57·12% C, 5·35% H, 19·60% N; found: 56·89% C, 5·44% H, 19·34% N. R_F 0·68 (S1), 0·10 (S4).

Methyl 6-O-*p*-Toluenesulfonyl-2,3-O-isopropylidene-D-mannofuranoside (*XXXV*)

A mixture of 2,3:5,6-diisopropylidene-α-D-mannofuranose[19] (25 g; 91 mmol), dimethylformamide (100 ml), methyl iodide (120 ml) and silver oxide (50 g) was stirred at room temperature overnight and filtered through celite which was then washed with chloroform (500 ml). The filtrate was taken down *in vacuo* (finally at 40°C/0·1 Torr) and the residue chromatographed on a column of silica gel in chloroform. The product fractions (R_F 0·70, S9, detection with iodine) were taken down, and the residue mixed with ethanol (100 ml) and 0·2M hydrochloric acid (100 ml) and set aside overnight. The mixture was neutralised with Dowex 1X2 (HCO_3^-), filtered, the solid material washed with methanol and the filtrate taken down *in vacuo*. The residue was taken up in benzene (100 ml) and extracted with water (3 × 25 ml). The aqueous solution was evaporated *in vacuo* and the residue coevaporated with ethanol (3 . 20 ml) and dried, yielding 19·5 g (86%) of methyl 2,3-O-isopropylidene-D-mannofuranoside, pure according to chromatography (R_F 0·15, S9). This product (78·5 mmol) was dissolved in pyridine (50 ml) and *p*-toluenesulfonyl chloride (15·0 g; 78·5 mmol) was added portionwise at 0°C. The mixture was set aside at 0°C for 2 days, treated with water (5 ml), allowed to stand at room temperature for 1 h and taken down *in vacuo*. The residue was taken up in chloroform (200 ml), the solution washed with water (3 × 50 ml), dried over magnesium sulfate, filtered and the solvent evaporated *in vacuo*, leaving the compound *XXXV* (30·2 g; 75 mmol; 96%) which was used directly in further reactions.

Methyl 5-O-Benzoyl-6-O-*p*-toluenesulfonyl-2,3-O-isopropylidene-α-D-mannofuranoside (*XXXVI*)

Benzoyl chloride (7 ml, 8·45 g; 60 mmol) was added dropwise to a cooled and stirred solution of the compound *XXXV* (20·2 g; 50 mmol) in pyridine (50 ml), and the mixture was set aside at room temperature for 2 days. After addition of ethanol (5 ml) and water (5 ml), the mixture was allowed to stand for 1 h and poured into water (1 l). The product was taken up in chloroform (3 × 200 ml), the organic layer washed with water (3 × 100 ml), dried over magnesium sulfate, filtered and the filtrate taken down *in vacuo*. The residue was crystallised from ethanol (100 ml), affording 13·5 g (53·4%) of the compound *XXXVI*, m.p. 139—142°C. For $C_{24}H_{28}O_9S$ (492·5) calculated: 58·52% C, 5·73% H, 6·51% S; found: 58·89% C, 5·68%, 6·57% S. ^{1}H-NMR spectrum ($CDCl_3$): 1·16 + 1·32 (2 s, 2 × 3 H) isopropylidene; 2·24 (s, 3 H) *p*-tolyl; 3·25 (s, 3 H) 1-methyl; 4·26 (dd, 1 H, $J_{4,3} = 3·5$, $J_{4,5} = 8·0$) H_4; 4·33 (m, 2 H) 2 H_6, 4·48 (d, 1 H, $J_{2,3} = 6·0$) H_2; 4·78 (dd, 1 H, $J_{3,2} = 6·0$, $J_{3,4} = 3·5$) H_3; 4·83 (s, 1 H, $J_{1,2}$ 0·5) H_1; 5·34 (dt, 1 H) $J_{5,4} = 8·0$, $J_{5,6} = J_{5,6'} = 3·0$) H_5; 7·0—8·0 (m, 9 H) aromatic protons.

Methyl 6-(Adenin-9-yl)-6-deoxy-5-O-benzoyl-1,2-O-isopropylidene-α-D-mannofuranoside (*XXXVII*)

A mixture of the compound *XXXVI* (5·0 g; 10 mmol) and sodium salt of adenine (1·9 g; 12·1 mmol) in dimethylformamide (40 ml) was stirred at 100°C for 8 h under exclusion of moisture and then taken down at 40°C/0·1 Torr. The residue was taken up in chloroform (100 ml), the solution washed with water (2 × 25 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*. The residue was chromatographed on two loose layers of silica gel in the system S4 and the product bands were eluted with methanol (300 ml). The eluant was taken down and the resulting foam dried *in vacuo*. Yield 2·8 g (61·5%) of the compound *XXXVII*, chromatographically uniform (R_F 0·38, S4). For $C_{22}H_{25}N_5O_6$ (455·5) calculated: 58·00% C, 5·53% H, 15·37% N; found: 57·78% C, 5·54% H, 15·61% N. ^{1}H-NMR; spectrum ($CDCl_3$): 1·18 + 1·40 (2 s, 2 × 3 H) isopropylidene; 3·29 (s, 3 H) 1-methyl; 3·97 (dd, 1 H, $J_{4',3'} = 3·5$, $J_{4',5'} = 8·0$) $H_{4'}$; 4·55–4·95 (m, 2 H) 2 $H_{6'}$; 4·48 (d, 1 H, $J_{2',3'} = 6·0$) $H_{2'}$; 4·70 (q, 1 H, $J_{3',2'} = 6·0$, $J_{3',4'} = 3·5$) $H_{3'}$; 4·83 (s, 1 H, $J_{1',2'} = 0·5$) $H_{1'}$; 5·58 (sept., 1 H, $J_{5',4'} = 8·0$, $J_{5',6'} = 5·0$, $J_{5',6''} = 3·0$) $H_{5'}$; 6·70 (br, 2 H) NH_2; 7·20–7·75 (3 H) + 7·70 to 7·90 (2 H) aromatic protons; 7·82 (s, 1 H) H_2; 7·95 (s, 1 H) H_8.

Methyl 6-(Adenin-9-yl)-6-deoxy-2,3-O-isopropylidene-α-D-mannofuranoside (*XXXVIII*)

a) *From the compound* XXXV: A mixture of the compound *XXXV* (10·0 g; 25 mmol) and sodium salt of adenine (3·9 g; 25 mmol) in dimethylformamide (40 ml) was heated to 100°C for 8 h with stirring and under exclusion of moisture. After evaporation at 40°C/0·1 Torr the residue was crystallised from ethanol (50 ml) and filtered. The filtrate was taken down *in vacuo* and the residue chromatographed on a silica gel column in chloroform. The product was eluted with a chloroform–ethanol (95 : 5) mixture and the fractions were combined and taken down. Crystallisation of the residue from ethanol with addition of light petroleum until the solution was turbid afforded 1·1 g (12·5%) of the compound *XXXVIII*, m.p. 186°C. R_F 0·43 (S6). For $C_{15}H_{21}N_5O_5$ (351·4) calculated: 51·27% C, 6·02% H, 19·92% N; found: 51·28% C, 5·95% H, 19·27% N. ^{1}H-NMR spectrum ($CDCl_3$): 1·23 + 1·35 (2 s, 2 × 3 H) isopropylidene, 3·16 (s, 3 H) O-methyl; 3·33 (br, 1 H) 5′-OH; 3·59 (dd, 1 H, $J_{4',3'} = 4·0$, $J_{4',5'} = 8·0$) $H_{4'}$; 4·0–4·55 (m, 3 H) $H_{5'}$ + 2 $H_{6'}$; 4·43 (d, 1 H, $J_{2',1'} = 0·5$) $J_{2',3'} = 6·0$) $H_{2'}$; 4·72 (dd, 1 H, $J_{3',2'} = 6·0$, $J_{3',4'} = 4·0$) $H_{3'}$; 4·80 (s, 1 H, $J_{1',2'} = 0·5$) $H_{1'}$; 6·90 (br, 2 H) NH_2; 7·99 (s, 1 H) H_2; 8·14 (s, 1 H) H_8.

b) *From the compound* XXXVII: A solution of the compound *XXXVII* (0·50 g; 1·1 mmol) in 0·1M methanolic sodium methoxide (10 ml) was set aside at room temperature overnight, neutralised with Dowex 50 X 8 (H^+), made alkaline (pH 10) with ammonia, filtered and the filtrate was taken down *in vacuo*. The residue was crystallised from ethanol (ether being added until the solution was turbid), yielding 0·27 g (70%) of the compound *XXXVIII*, m.p. 186°C, identical (in S6) with the authentic sample prepared according to *a*).

Methyl 6-(Adenin-9-yl)-6-deoxy-5-O-benzoyl-α-D-mannofuranoside (*XXXIX*)

A solution of the compound *XXXVII* (1·05 g; 2·3 mmol) in 90% formic acid (10 ml) was set aside at room temperature overnight, taken down *in vacuo*, the residue coevaporated successively with 50% ethanol (20 ml), ethanol, and 5% triethylamine in ethanol, and chromatographed on a loose layer of silica gel in the system S5. The product band was eluted with methanol (300 ml) the eluate evaporated and the residue crystallised from ethanol (ether added until the solution was turbid) to give 0·60 g (62·5%) of the compound *XXXIX*, m.p. 200–201°C, For $C_{19}H_{21}N_5O_6$ (415·4) calculated: 54·93% C, 5·10% H, 16·86% N; found: 55·06% C, 5·21% H, 16·82% N. R_F 0·12

(S5). ^{1}H-NMR spectrum ($CDCl_3$): 3·37 (s, 3 H) OCH_3; 3·85—4·40 (m, 3 H) $H_{2'} + H_{3'} + H_{4'}$; 4·07 (m, 1 H) $H_{2'}$; 4·69 (m, 2 H, $J_1 = 7·0$, $J_2 = 3·5$, $J_{gem} = 15·0$) 2 $H_{6'}$; 4·89 (s, 1 H, $J_{1',2'} = 2·5$) $H_{1'}$; 5·64 (m, 1 H) $H_{5'}$; 6·98 (br, 2 H) NH_2; 7·93 + 7·97 (2 s, 2 H) $H_2 + H_8$; 7·25—7·75 + + 7·70—7·85 (2 × m, 5 H) aromatic protons.

9-(D-*threo*-3-Benzyloxy-2,4-dihydroxybutyl)adenine (*XXXII*)

Sodium periodate (13 g) was added to a solution of the compound *XXXI* (16·2 g; 45 mmol) in 50% dioxane (500 ml) under cooling with ice. After stirring for 1 h at 0°C, ethylene glycol (1 ml) was added and the mixture was stirred at 0°C for further 15 min. Ethanol (200 ml) was added and the mixture filtered through celite. The filtrate was stirred with sodium borohydride (9·0 g) at room temperature for 1 h, the mixture was acidified with acetic acid (pH 6), concentrated *in vacuo*, coevaporated with pyridine (3 × 50 ml) and the residue shaken with pyridine (100 ml and acetic anhydride (100 ml) overnight. The suspension was filtered through celite, the filtrate taken down *in vacuo* and coevaporated with toluene, finally at 50°C/0·1 Torr. The residue was taken up in chloroform (300 ml), washed with water (4 × 50 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*. The residue was dissolved in chloroform and filtered through a column of silica gel (50 g) in order to remove the impurities. The column was washed with chloroform (500 ml), the filtrate evaporated, the residue taken up in methanol (100 ml), adjusted to pH 10 (moistened indicator paper) by addition of sodium methoxide and set aside at room temperature overnight. After neutralisation with Dowex 50 X 8 (H^+), the mixture was filtered, the resin washed with methanol and the filtrate taken down *in vacuo*. The residue was chromatographed on two loose layers of silica gel in the solvent system S5 and the product bands eluted with methanol (1 l) in a column. The eluate was taken down, the residue dissolved in methanol (20 ml), the product precipitated with ether (200 ml), collected on filter, washed with ether and dried *in vacuo*. Yield 7·60 g (51%) of the compound *XXXII*. R_F 0·77 (S1). For $C_{16}H_{19}N_5O_3$ (329·4) calculated: 58·34% C, 5·82% H, 21·27% N; found: 58·48% C, 6·04% H, 21·75% N. UV spectrum (pH 2, 7, 12): λ_{max} 262 nm, ε_{max} 11 500.

3-O-Benzoyl-5-(adenin-9-yl)-5-deoxy-1,2-O-isopropylidene-L-arabinofuranoside (*XXXIIIb*)

A mixture of 5-(adenin-9-yl)-5-deoxy-1,2-O-isopropylidene-L-arabinofuranose (*XXXIIIa*, see[6]) (1·60 g; 6 mmol), benzoyl cyanide (1·4 g; 10·5 mmol) acetonitrile (20 ml) and triethylamine (1 ml) was stirred for 2 h. Ether (50 ml) was added, the product filtered, washed with ether and dried *in vacuo*, yielding 1·72 g (77·5%) of the compound *XXXIIIb*, m.p. 232—233°C, R_F 0·42 (S4). For $C_{20}H_{21}N_5O_5$ (411·4) calculated: 58·38% C, 5·15% H, 17·03% N; found: 59·02% C, 5·21% H, 17·20% N.

3-O-Benzoyl-5-(adenin-9-yl)-5-deoxy-L-arabinofuranose (*XXXIV*)

A solution of the compound *XXXIIIb* (2·0 g; 5·4 mmol) in 90% formic acid (20 ml) was heated to 70°C for 75 min, cooled down and taken down *in vacuo*. The residue was coevaporated with ethanol (3 × 20 ml) and then with 5% ethanolic triethylamine (20 ml). Crystallisation from ethanol gave 1·4 g (78·5%) of the compound *XXXIV* (R_F 0·18 in S5) which did not melt below 260°C. For $C_{17}H_{17}N_5O_5$ (371·4) calculated: 54·98% C, 4·62% H, 18·86% N; found: 55·12% C, 4·48% H, 18·70% N.

9-(D-*threo*-2,3,4-Trihydroxybutyl)adenine (D-*XXII*)

a) *From the compound* D-XXI: A mixture of the compound D-*XXI* (0·65 g; 1·5 mmol) and 0·1M methanolic sodium methoxide (20 ml) was set aside at room temperature overnight, taken down and the residue allowed to stand with 90% formic acid (20 ml) at room temperature for 3 h. After evaporation *in vacuo*, the residue was coevaporated with water (4 × 20 ml) and deionised on a 50 ml column of Dowex 50 X 8 (H^+). The product-containing ammonia eluate was taken down, the residue was coevaporated with ethanol (2 × 20 ml) and the product precipitated from ethanol (20 ml) by addition of ether (200 ml); yield 0·27 g (75%) of the compound *D-XXII*. For $C_9H_{13}N_5O_3$ (239·2) calculated: 45·18% C, 5·48% H, 29·28% N; found: 45·03% C, 5·60% H, 29·19% N; R_F 0·15 (S7). $[\alpha]_D^{20}$ +32·0° (*c* 0·5, 2M-HCl).

b) *From the compound* XXIV: A solution of the compound *XXIV* (2·80 g; 6·8 mmol) in 90% formic acid (50 ml) was heated to 100°C till the reaction was complete (1 h). The mixture was taken down, the residue coevaporated with water (3 × 50 ml) and dissolved in ethanol (50 ml). The pH was adjusted to 8 by addition of triethylamine and the solution was taken down *in vacuo*. The residue was dissolved in a mixture of dioxane (50 ml) and water (20 ml) and after cooling with ice, sodium periodate (2·5 g) was added, the insoluble portion was filtered and washed with ethanol (20 ml). Sodium borohydride (1·5 g) was added to the filtrate and after standing at 0°C for 1 h the mixture was acidified (pH 6) with acetic acid, taken down *in vacuo* and the residue set aside overnight with 0·2M methanolic sodium methoxide (50 ml). The mixture was neutralised with Dowex 50X8 (H^+), the ion-exchange resin was filtered and washed with methanol (50 ml) and the filtrate was taken down *in vacuo*. The residue was dissolved in water (20 ml), acidified to pH 3 with hydrochloric acid and deionised under standard conditions. The ammonia eluate was taken down *in vacuo* and the residue purified by chromatography on Dowex 1X2 (OH^-) in water. The product-containing fractions were taken down and the product crystallised from 90% ethanol, yielding 1·03 g (59%) of the compound D-*XXII*, m.p. 207—209°C (monohydrate). For $C_9H_{15}N_5O_4$ (257·3) calculated: 42·01% C, 5·88% H, 27·23% N; found: 41·71% C, 5·53% H, 29·20% N. $[\alpha]_D^{20}$ +32·4° (*c* 0·5, 2M-HCl).

c) *From the compound* XXXII: A mixture of the compound *XXXII* (3·3 g; 10 mmol), methanol (200 ml), 5% Pd/C (1·5 g), 20% palladium chloride solution (1 ml), and conc. hydrochloric acid (1·5 ml) was shaken with hydrogen at room temperature and normal pressure. After the hydrogen absorption had ceased (about 300 ml), the mixture was filtered through celite which was then washed with methanol (200 ml), the filtrate was neutralised with triethylamine and taken down *in vacuo*. The residue was dissolved in water (50 ml), the solution acidified and deionised on a Dowex 50 column (*vide supra*). The ammonia eluate of the product was taken down and the residue crystallised from water to give monohydrate of the compound D-*XXII* (1·52 g; 63·7%); m.p. 206—207°C. R_F 0·47 (S1), 0·49 (S2), 0·13 (S7), E_{Ade} = 0·60. UV spectrum (pH 2, 12): λ_{max} 262 nm, ε_{max} 14 700. $[\alpha]_D^{20}$ +32·9° (*c* 0·5, 2M-HCl).

9-(L-threo-2,3,4-*Trihydroxybutyl)adenine* (L-XXII) was prepared from the compound L-*XXI* analogously to the compound D-*XXII* in 82% yield. For $C_9H_{13}N_5O_3$ (239·2) calculated: 45·18% C, 5·48% H, 29·28% N; found: 45·16% C, 5·76% H, 28·89% N. $[\alpha]_D^{20}$ −32·8° (*c* 0·5, 2M-HCl).

1-(D-*threo*-2,3,4-Trihydroxybutyl)uracil (D-*XXVII*)

A solution of the compound *XXV* (1·5 g; 3·9 mmol) in 90% formic acid (20 ml) was set aside at room temperature overnight, evaporated, the residue coevaporated with water (2 × 25 ml), ethanol and dried *in vacuo* overnight. The residue was dissolved in dioxane (30 ml) and water (10 ml) and stirred at 0°C with sodium periodate (1·5 g) for 2 h. Ethanol (200 ml) was added,

the mixture filtered through celite and the filtrate stirred at 0°C with sodium borohydride (1 g) for 1 h, acidified (pH 6) with acetic acid and taken down. The residue was coevaporated with ethanol (3 × 25 ml) and chromatographed on two loose layers of silica gel in the system S7. The product bands were eluted on a column with methanol (1 l), the eluate was taken down and the residue chromatographed on a column of cellulose in 70% 2-propanol. The product-containing fractions were combined, taken down *in vacuo* and the residue crystallised from ethanol, affording 0·43 g (51%) of the compound *XXVII*, m.p. 100—107°C, R_F 0·38 (S1). For $C_8H_{12}N_2O_5$ (216·2) calculated: 44·44% C, 5·60% H, 12·96% N; found: 44·13% C, 5·76% H, 12·65% N. UV spectrum (pH 2): λ_{max} 260 nm, ε_{max} 9 800.

9-(D-*erythro*-2,3,4-Trihydroxybutyl)adenine (D-*XL*)

Sodium periodate (0·43 g; 2 mmol) was added under cooling with ice to a solution of the compound *XXXIX* (0·23 g; 0·55 mmol) in 50% dioxane (10 ml). After 30 min, sodium borohydride (0·50 g) was added, the mixture was stirred at room temperature for 30 min, neutralised with acetic acid and taken down *in vacuo*. The residue was set aside with 0·2M methanolic sodium methoxide (20 ml) overnight, neutralised with acetic acid and taken down. The residue in water (20 ml) was acidified (pH 3) with hydrochloric acid. This solution was deionised on Dowex 50, the ammonia eluate was taken down *in vacuo*, the residue coevaporated with ethanol and crystallised from methanol (ether being added until the solution was turbid). Yield 0·12 g (85%) of the monohydrate of the compound D-*XL*, m.p. 204—206°C; R_F 0·50 (S1), E_{Ade} = 0·60. For C_9H_{15}·N_5O_4 (257·3) calculated: 42·01% C, 5·88% H, 27·23% N; found: 41·92% C, 5·41% H, 26·94% N. UV spectrum (pH 2, 12): λ_{max} 262 nm, ε_{max} 12 500.

9-(L-*erythro*-2,3,4-Trihydroxybutyl)adenine (L-*XL*)

Sodium periodate (1·3 g) was added to a solution of the compound *XXXIV* (1·4 g; 4·24 mmol) in 50% dioxane (50 ml) and the mixture was stirred at 0°C for 1 h. Ethylene glycol (0·1 ml) was added and the stirring continued for 15 min at 0°C. After addition of ethanol (50 ml) the mixture was filtered, the filtrate stirred with sodium borohydride (1 g) at room temperature for 1 h, neutralised with acetic acid and taken down *in vacuo*. The residue was coevaporated with ethanol (3 × × 25 ml) and set aside with 0·2M methanolic sodium methoxide (100 ml) at room temperature overnight. The solution was neutralised with acetic acid and taken down *in vacuo*. The residue was dissolved in water (50 ml) and the solution adjusted to pH 3 with hydrochloric acid and deionised on Dowex 50. The product-containing ammonia eluate was taken down, the residue coevaporated with ethanol (2 × 25 ml) and crystallised from methanol (ether added until the solution was turbid), yielding monohydrate of the compound L-*XL* (0·90 g; 89%), m.p. 210—212°C; Found: 42·28% C, 5·66% H, 27·42% N. UV spectrum (pH 2, 12): λ_{max} 262 nm, ε_{max} 12 400. R_F 0·50 (S1); E_{Ade} = 0·60; $[\alpha]_D^{20}$ −17·7° (*c* 0·5, 2M-HCl).

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