SYNTHESIS OF SOME 2,3-DIHYDROXYPROPYL DERIVATIVES OF PURINE BASES

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Reaction of 1-O-*p*-toluenesulfonyl-2,3-O-isopropylidene-*sn*-glycerol (*I*) with sodium salt of adenine afforded *II* which on acid hydrolysis gave 9-(*RS*)-(2,3-dihydroxypropyl)adenine (*III*). This compound was converted into the triacetyl derivative *IV* which was brominated to the 8-bromo derivative *VIII*. Methanolysis of *VIII* led to 9-(*RS*)-(2,3-dihydroxypropyl)-8-bromoadenine (*IX*) whereas its acetolysis followed by alkaline hydrolysis afforded a mixture of 9-(*RS*)-(2,3-dihydroxypropyl)-8-hydroxyadenine (*X*) and 9-(*RS*)-(2,3-dihydroxypropyl)-8-acetoxyadenine (*XI*). The 8-thioadenine derivative *XIII* was prepared by reaction of *VIII* with thiourea and methanolysis of the formed triacetate *XII*. 9-(*RS*)-(2,3-Dihydroxypropyl)-8-aminoadenine (*XIV*) was obtained by reaction of *VIII* with methanolic ammonia. Methylation of *III* with methyl iodide and subsequent alkaline treatment afforded the 6-methylaminopurine derivative *XV*. Deamination of *III* with nitrous acid followed by acetylation gave the diacetyl derivative *XVII* which on reaction with dimethylchloromethyleneammonium chloride was transformed to 2′,3′-di-O-acetyl-9-(*RS*)-(2,3-dihydroxypropyl)-6-chloropurine (*XVIII*). This was heated with dimethylamine to give the 6-dimethylaminopurine derivative *XIX*; the 6-mercaptopurine derivative *XXI* was obtained by reaction of *XVII* with phosphorus pentasulfide and methanolysis. Heating 2,2-dimethyl-4-chloromethyl-1,3-dioxolane (*XXII*) with 2,6-diaminopurine or 2-methylthioadenine in the presence of potassium carbonate and subsequent acidic hydrolysis of the intermediates led to 2,3-dihydroxypropyl derivatives of 2,6-diaminopurine or 2-methylthioadenine (*XXIV* and *XXV*, respectively). Compound *I* was condensed with the sodium salt of 2-acetylguanine to a mixture of 7- and 9-isopropylidene derivatives *XXVIII* and *XXXI* which on methanolysis and acidic hydrolysis yielded 9-(*RS*)-(2,3-dihydroxypropyl)guanine (*XXX*) and its 7-isomer *XXXIII*.

The recent observation that 9-(*S*)-(2,3-dihydroxypropyl)adenine ((*S*)-*III*) exhibits an antiviral activity, is not cytotoxic and enhances significantly the antiviral action of 9-(β-D-arabinofuranosyl)adenine and 6-azauridine[1,2], gave an impulse for the synthesis of other 2,3-dihydroxypropyl derivatives of purine bases with the aim to determine the structure-activity relationship of this type of compounds. Since it was found[1] that only the (*S*)-enantiomer of the compound *III* is biologically active whereas the (*R*)-enantiomer has no virostatic effect and that also the activity of the racemic derivative (*RS*)-*III* is comparable with that of the pure (*S*)-enantiomer, most of the compounds described in this paper were prepared as the better accessible racemates.

The first group of compounds was prepared starting from 9-(*RS*)-(2,3-dihydroxypropyl)adenine (*III*) (unless stated otherwise, the names refer to racemates); in this study there is described a larger-scale preparation of this compound using a modification of the previously published[3] method based on reaction of 1-O-*p*-toluenesulfonyl-2,3-O-isopropylidene-*sn*-glycerol (*I*) (ref.[3]) with sodium salt of adenine. prepared *in situ*. After crystallisation of the 2,3-O-isopropylidene derivative *II*, the mother liquor was subjected to acid hydrolysis and the whole mixture was freed of *p*-toluenesulfonic acid by means of a cation-exchanger in H^+-form. During this procedure the insoluble 3-isomer *VI*, which separated on the column, was isolated in the pure state and characterised by its UV spectrum, typical for 3-alkyladenines. Only small amount of this isomer is formed in the reaction, contrary to the reaction of adenine with 1-chloro-2,3-dihydroxypropane which affords a substantial amount of the 3-isomer in the mixture with *III* (ref.[4]).

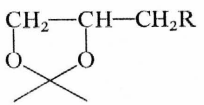
After deionisation, the remaining compound *III* was freed from the contaminating adenine by acetylation to the acetyl derivative *IV* with acetic anhydride in the presence of 4-dimethylaminopyridine[5]. As evidenced by UV and ^{1}H-NMR spectra, the compound *IV* is N^6,2′,3′-triacetyl derivative. An identical compound was prepared from the pure compound *III* by acetylation under the same conditions. From (*S*)-*III* we prepared in the same way the (*S*)-enantiomer of *IV*. Analogous reaction of *III* with propionic anhydride in the presence of 4-dimethylaminopyridine afforded the N^6,2′,3′-tripropionyl derivative *V*.

The (*R*)-enantiomer of the compound *III* was obtained previously[3] by degradation of 5-(adenin-9-yl)-5-deoxy-1-O-methyl-β-D-ribofuranoside and its synthesis was mentioned without experimental details also in the paper of other authors[6]; the present study describes the preparation of (*R*)-*III* from 2(*S*),3-O-isopropylidene-1-O-*p*-toluenesulfonylglycerol ((*S*)-*I*), prepared by a four-step synthesis from 2(*R*),3-O-isopropylideneglycerol. Also the compound (*R*)-*III* was transformed to the triacetyl derivative (*R*)-*IV* which had the same chromatographic and spectral properties as its (*S*)-enantiomer of the racemate *IV*.

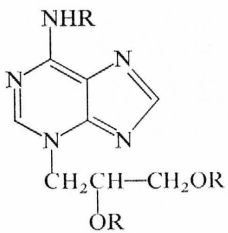
The triacetyl derivative *IV* was brominated with N-bromosuccinimide[7] to the 8-bromo derivative *VIII* which was isolated by chromatography on silica gel. The reaction proceeds very slowly but, preparatively, it is more advantageous than the direct bromination of compound *III* in an aqueous buffer, described for adenine nucleosides[8]. Methanolysis of compound *VIII* afforded free 9-(*RS*)-(2,3-dihydroxypropyl)-8-bromoadenine (*IX*). Compound *VIII* was then transformed by exchange reactions of the halogen atom in the position 8 to the 8-hydroxy derivative *X*; reaction of compound *VIII* with acetic anhydride in the presence of sodium acetate[9] proceeds *via* 8-acetoxy derivative *XI* which is deacetylated relatively sluggishly. The structure of compounds *X* and *XI* was confirmed by their typical UV spectra.

Refluxing the 8-bromo derivative *IX* with ethanolic solution of thiourea[10] afforded N^6,2′,3′-triacetyl-9-(*RS*)-(2,3-dihydroxypropyl)-8-thioadenine (*XII*) which on methanolysis gave the diol *XIII*. Also this compound has UV spectrum similar to that of 8-thioadenosine[10].

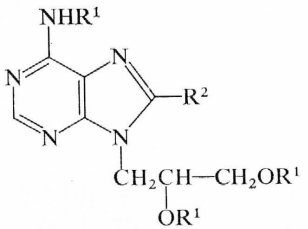
The preparation of the 8-aminoadenine derivative *XIV* is more difficult. Its synthesis from the compound[11] *XI via* the 8-azido derivative is preparatively not advantageous; the direct reaction of compound *IX* with methanolic ammonia proved to be better. The obtained derivative *XIV* was isolated by chromatography on cellulose.



I, R = *p*-toluenesulfonyloxy
II, R = adenin-9-yl
XXII, R = Cl



VI, R = H
VII, R = $COCH_3$



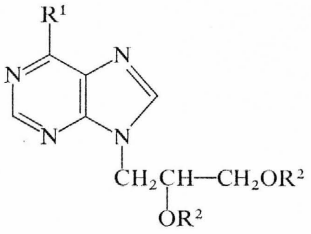
III, $R^1 = R^2 = H$
IV, $R^1 = COCH_3$; $R^2 = H$
V, $R^1 = COCH_2CH_3$; $R^2 = H$
VIII, $R^1 = COCH_3$; $R^2 = Br$
IX, $R^1 = H$; $R^2 = Br$
X, $R^1 = H$; $R^2 = OH$
XI, $R^1 = H$; $R^2 = OCOCH_3$
XII, $R^1 = COCH_3$; $R^2 = SH$
XIII, $R^1 = H$; $R^2 = SH$
XIV, $R^1 = H$; $R^2 = NH_2$

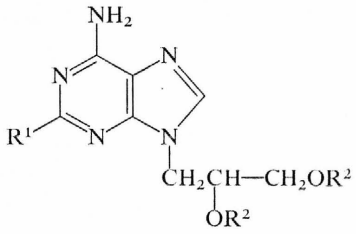
9-(*RS*)-(2,3-Dihydroxypropyl) derivatives of 6-substituted purine bases were prepared from the hypoxanthine derivative *XVII*. This 2′,3′-di-O-acetyl derivative can be prepared by deamination of the free compound *III* with nitrous acid and acetylation of the resulting crude mixture, rather than by deamination of the triacetyl derivative *IV*. Reaction of the diacetyl derivative *XVII* with dimethylchloromethyleneammonium chloride[12] afforded the 6-chloropurine derivative *XVIII* which reacted with dimethylamine in methanol with simultaneous methanolysis of the acetal groups to give directly the free 6-dimethylaminopurine derivative *XIX*. Direct thiation of the compound *XVII* with phosphorus pentasulfide in pyridine afforded 9-(*RS*)-(2,3-diacetoxypropyl)-6-mercaptopurine (*XX*) which was then deacetylated to 9-(*RS*)-(2,3-dihydroxypropyl)-6-mercaptopurine (*XXI*).

The 6-methylaminopurine derivative *XV* could be obtained analogously as the compound *XIX*, however, for its synthesis there was chosen an alternative methyla-

tion of compound *III* with methyl iodide followed by the Dimroth rearrangement of $N_{(1)}$ methyl group in an alkaline medium[13].

The two 2-substituted adenine derivatives included in this study were prepared by another route leading to 2,3-dihydroxypropyl derivatives of heterocyclic bases. Preparation of these compounds by reaction of bases with 1-chloro-2,3-dihydroxypropane has already been described previously; however, the preparative method of choice is reaction with the isopropylidene derivative of this reagent, *i.e.* with 4-(2-chloroethyl)-2,2-dimethyl-1,3-dioxolane (*XXII*). This derivative is easily accessible by reaction of 1-chloro-2,3-dihydroxypropane with 2,2-dimethoxypropane. Compound *XXII* reacted with 2,6-diaminopurine in dimethylformamide in the presence of potassium carbonate to give the isopropylidene derivative *XXIII* which on acidic hydrolysis was transformed into the free 2,6-diaminopurine derivative *XXIV*. 9-(*RS*)-(2,3-Dihydroxypropyl)-2-methylthioadenine (*XXVI*) was prepared analogously from 2-methylthio-6-aminopurine *via* the compound *XXV*.

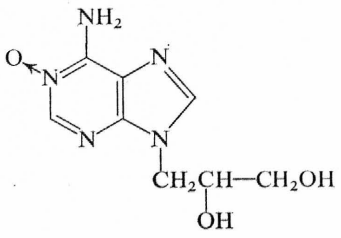




XV, $R^1 = NHCH_3$; $R^2 = H$
XVI, $R^1 = OH$; $R^2 = H$
XVII, $R^1 = OH$; $R^2 = COCH_3$
XVIII, $R^1 = Cl$; $R^2 = COCH_3$
XIX, $R^1 = N(CH_3)_2$; $R^2 = H$
XX, $R^1 = SH$; $R^2 = COCH_3$
XXI, $R^1 = SH$; $R^2 = H$

XXIII, $R^1 = NH_2$; R^2, $R^2 = (CH_3)_2C$
XXIV, $R^1 = NH_2$; $R^2 = H$

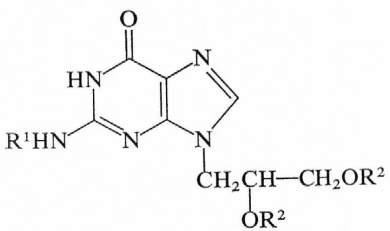
XXV, $R^1 = SCH_3$; R^2, $R^2 = (CH_3)_2C$
XXVI, $R^1 = SCH_3$; $R^2 = H$

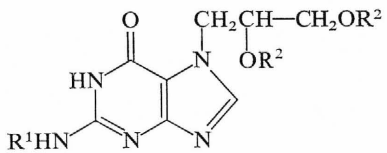


XXVII

Oxidation of the 2′,3′-O-isopropylidene derivative *II* with hydrogen peroxide in acetic acid[14], accompanied by simultaneous removal of the isopropylidene group, afforded directly chromatographically homogeneous *XXVII* (*i.e.* the N-oxide of *III*) which showed a typical UV-absorption in the short-wave region.

The last, hitherto undescribed, analogue of natural nucleosides in the 2,3-dihydroxypropyl series is the guanine derivative. Since the reaction of guanine itself with the compound *I* was not satisfactory, the reaction was carried out with N^2-acetylguanine which is more soluble in dimethylformamide. Sodium salt of N^2-acetylguanine, prepared *in situ* by reaction with sodium hydride, reacted with compound *I* to give two derivatives (*XXVIII* and *XXXI*) which were separated by chromatography on silica gel. Methanolysis of the products *XXVIII* and *XXXI* afforded the respective compounds *XXIX* and *XXXII* which displayed typical UV spectra. According to the spectral evidence it was possible to ascribe the 9-substituted guanine structures to compounds *XXVIII* and *XXIX*, whereas the compounds *XXXI* and *XXXII* are 7-alkylguanine derivatives. Removal of the protecting isopropylidene groups by treatment with acetic acid resulted in 9-(*RS*)-(2,3-dihydroxypropyl)guanine (*XXX*) and its 7-isomer *XXXIII*. In spite of variation of reaction conditions it was not possible to increase the yield; the 7-and 9-isomers are formed in approximately equimolar amounts, similarly to alkylations of guanine under analogous conditions[15].





XXVIII, $R^1 = COCH_3$; R^2, $R^2 = (CH_3)_2C$

XXIX, $R^1 = H$; R^2, $R^2 = (CH_3)_2C$

XXX, $R^1 = R^2 = H$

XXXI, $R^1 = COCH_3$; R^2, $R^2 = (CH_3)_2C$

XXXII, $R^1 = H$; R^2, $R^2 = (CH_3)_2C$

XXXIII, $R^1 = R^2 = H$

All the prepared compounds were tested for antibacterial activity toward *Escherichia coli* (synthetic glucose-containing medium); none of them exhibited any significant inhibitory effect in concentrations up to 1 mg/ml of medium. The antiviral activity of these compounds will be described elsewhere.

EXPERIMENTAL

Melting points were determined on a Kofler block and are, as well as the boiling points, uncorrected. Unless stated otherwise, the solutions were taken down at 40°C/15 Torr and the compounds were dried at 0·1 Torr over phosphorus pentoxide.

Paper chromatography was carried out on a paper Whatman No 1 using the following systems: S1, 2-propanol–conc. ammonia–water (7 : 1 : 2) and S2, 1-butanol–acetic acid–water (5 : 2 : 3). Thin-layer chromatography was performed on Silufol UV_{254} plates in the solvent systems S3, chloroform–ethanol (9 : 1), S4, chloroform–ethanol (4 : 1), S5, chloroform–methanol (7 : 3), S6, chloroform–methanol (3 : 2). Preparative chromatography was carried out on loose layers (40 × 16 × 0·3 cm) of fluorescent-indicator-containing silica gel (produced by Service Laboratories of this Institute) or on columns of the Pitra silica gel (200 g; 30—60 mesh) in chloroform (90 ml/h). Chromatography on cellulose was performed on a column (80 × 3 cm) of microcrystalline cellulose (Macherey-Nagel) in 70% aqueous 2-propanol (30 ml/h). Solutions were deionised on a Dowex 50 X 8 (H^+) column (100 ml, unless stated otherwise), which was then washed with water (3 ml/min) until the UV-absorption and conductivity of the eluate dropped, and then with dilute (1 : 10) ammonia. The UV-absorption of the eluate was followed continuously on a Uvicord (LKB, Sweden) instrument.

UV spectra of aqueous solutions were taken on a Specord (Zeiss, Jena, GDR) spectrometer and are given in Table I. ^{1}H-NMR spectra were measured in deuteriochloroform on a Varian 100 instrument using hexamethyldisiloxane as internal standard (chemical shifts expressed in ppm, coupling constants in Hz).

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

Sodium hydride (10·2 g; 0·42 mol) was added to a suspension of adenine (54 g; 0·4 mol) in dimethylformamide (800 ml; distilled from phosphorus pentoxide) and the mixture was stirred under exclusion of moisture at 60°C for 1 h. Compound *I* (143 g; 0·5 mol) was added in one portion and the stirring was continued for 15 h (total) at 100°C. The mixture was taken down at 70°C/0·1 Torr and the residue crystallised (charcoal) from methanol (1 l), affording 44·7 g (45%) of compound *II*, which was chromatographically homogeneous (S3) and identical with an authentic sample[3]. This product was refluxed with 80% acetic acid (400 ml) for 2 h and taken down *in vacuo*. The residue was coevaporated with water (4 × 50 ml), ethanol (3 × 50 ml), and crystallised from 90% ethanol (refrigerator), ether being added until the solution became turbid. The separated product was filtered, washed with ethanol, ether, and dried *in vacuo*; yield 31·7 g (85%) of *III*, m.p. 207—208°C; identical with authentic material[3] (chromatography in S1, S2 and S5).

3-(*RS*)-(2,3-Dihydroxypropyl)adenine (*VI*)

The mother liquor after crystallisation of *II* from methanol (see preparation of *III*) was evaporated *in vacuo* and the residue extracted with boiling chloroform (500 ml). The hot suspension was filtered and washed with hot chloroform until the precipitate was free of *II*. The filtrate was evaporated *in vacuo*, the residue refluxed with 80% acetic acid (250 ml) for 2 h, the mixture taken down *in vacuo* and the residue codistilled with water (2 × 50 ml). The residue was taken up in water (200 ml), acidified with hydrochloric acid (pH 3) and the solution applied to a Dowex 50 X 8 (H^+) column (300 ml) and deionised. After elution with ammonia the UV absorbing eluate was used for the preparation of the compound *IV*. The Dowex resin was then transferred from the column to a sintered glass filter and washed with boiling water (8 × 250 ml). The filtrate

was taken down *in vacuo* and the residue crystallised from water, affording 5·6 g (6·7%, referred to the starting adenine) of *VI* which did not melt below 260°C. For the monohydrate: $C_8H_{13}N_5O_3$ (227·2) calculated: 42·29% C, 5·77% H, 30·83% N; found: 42·59% C, 5·55% H, 30·83% N. R_F 0·43 (S1), 0·47 (S2); *III* 0·49 (S1), 0·50 (S2).

2′,3′,N^6-Triacetyl-9-(*RS*)-(2,3-dihydroxypropyl)adenine (*IV*)

a) *From compound* III: A suspension of *III* (10·45 g; 50 mmol) and 4-dimethylaminopyridine (1·1 g) in acetic anhydride (100 ml) was stirred until homogeneous and then set aside at room temperature. The mixture was taken down at 40°C/0·1 Torr, the residue coevaporated with toluene (50 ml), dissolved in chloroform (100 ml) and washed with water (20 ml). The chloroform layer was dried over magnesium sulfate, filtered and taken down *in vacuo*. The residue was dissolved in hot ethanol (100 ml) and light petroleum was added to the hot solution to incipient

TABLE I

Ultraviolet Absorption Spectra (in aqueous solutions)

Formula	pH 2			pH 7			pH 12		
	λ_{max} nm	ε_{max} (10^3)	λ_{min} nm	λ_{max} nm	ε_{max} (10^3)	λ_{min} nm	λ_{max} nm	ε_{max} (10^3)	λ_{min} nm
III	259	13·0	—	261	11·5	—	261	11·8	—
VI	276	14·0	—	275	13·5	—	274	13·8	—
IX	264	20·0	233	—	—	—	266	19·4	234
X	289	15·5	253	286	13·6	255	295	15·0	247
XI	279	12·7	238	276	15·0	238	273	12·7	238
XIII	243	19·5	260	238	26·7	253	241	20·9	260
	308	32·0		304	37·3		306	33·0	
XV	264	14·7	234	268	13·8	232	268	13·8	232
XVI	250	10·6	223	250	10·8	223	252	12·0	224
XIX	270	15·7	235	278	16·0	237	278	16·3	237
XXI	322	25·8	256	322	27·5	256	310	23·6	262
XXIV	252	9·7	268	255	8·4	263	255	8·4	263
	290	10·0		280	9·7		280	10·4	
XXVI	270	17·8	242	—	—	—	233	26·6	250
							277	17·6	
XXVII	220	12·5		224	12·0		—	—	—
	254	10·7	227	254	10·6	227	254	10·6	227
	278	6·7		278	6·7		278	6·7	
XXXIII	251	9·0	230	151	9·0	230	282	6·7	258

turbidity. Standing overnight in a refrigerator afforded 13·3 g (80%) of chromatographically (S3) pure crystalline product, m.p. 139—140°C. For $C_{14}H_{17}N_5O_5$ (335·3) calculated: 50·14% C, 5·11% H, 20·39% N; found: 50·43% C, 5·00% H, 20·89% N. R_F 0·40 (S3).

The (*S*)-enantiomer of *IV*, m.p. 106—107°C (ethanol) was prepared analogously from (*S*)-*III* in 79·5% yield. Found: 50·67% C, 5·38% H, 20·93% N. R_F 0·40 (S3). The (*R*)-enantiomer of *IV*, m.p. 102—104°C, was obtained from (*R*)-*III* (10 mmol) in the same manner as the racemic compound; yield 79%. Found: 49·67% C, 5·39% H, 20·23% N. R_F 0·40 (S3).

b) *From mother liquors after crystallisation of* III. The ammonia eluate after deionisation of the mother liquor from *III* on the Dowex 50 X 8 (H^+) column was taken down, the residue coevaporated with ethanol (3 × 100 ml), toluene (2 × 50 ml) and shaken with acetic anhydride (200 ml) and 4-dimethylaminopyridine (1·4 g) at room temperature overnight. The mixture was evaporated at 40°C/0·1 Torr, codistilled with toluene (50 ml), the residue taken up in chloroform (500 ml) and washed with water (50 ml). The chloroform layer was dried, filtered, and concentrated *in vacuo* to about 100 ml. Chromatography of the residue on a silica gel column (chloroform) afforded chromatographically pure *IV*; yield 9·6 g (28·7 mmol, 7·2% referred to the starting adenine).

N^6,2′,3′-Tripropionyl-9-(S)-(2,3-dihydroxypropyl)adenine (*V*)

A mixture of the compound (*S*)-*III* (ref.[3]) (0·7 g; 3·35 mmol), propionic anhydride (10 ml) and 4-dimethylaminopyridine (0·25 g) was stirred for 15 min till dissolution, set aside overnight at room temperature and evaporated at 40°C/0·1 Torr. The residue was chromatographed on two layers of loose silica gel (see above) in the system S3. Bands of the products were eluted with methanol (300 ml) and the solvent evaporated. Crystallisation of the residue from ethanol (light petroleum added to turbidity) afforded 0·80 g (63·3%) of material melting at 118—119°C. For $C_{17}H_{23}N_5O_5$ (377·4) calculated: 54·09% C, 6·15% H, 18·56% N; found: 54·34% C, 6·18% H, 18·50% N. R_F 0·70 (S3).

N^6,2′,3′-Triacetyl-3-(*RS*)-(2,3-dihydroxypropyl)adenine (*VII*)

A mixture of the compound *VI* (1·0 g, 4·8 mmol), 4-dimethylaminopyridine (0·3 g) and acetic anhydride (25 ml) was treated analogously as described for *V* to afford 1·30 g (81%) of *VII*, m.p. 106—108°C. For $C_{14}H_{17}N_5O_5$ (335.3) calculated: 50·14% C, 5·11% H, 20·89% N; found: 50 01% C, 5·09% H, 20·16% N. R_F 0·17 (S3). ^{1}H-NMR spectrum: 1·96 + 2·08 + 2·48 (3 s, 3 × 3 H) acetyl; 4·21 dd ($J_{CH_2,CH}$ = 4·5) + 4·46 dd ($J_{CH_2,CH}$ = 4·0, J_{gem} = 12·5) (2 H) CH_2; 4·69 dd + 4·98 (2 dd, 2 H, $J_{CH_2,CH}$ = 6·5 and 3·5, J_{gem} = 11·5) CH_2; 8·23 s + 8·64 s (2 × 1 H) $H_2 + H_8$.

1-O-*p*-Toluenesulfonyl-2(*S*),3-O-isopropylideneglycerol ((*S*)-*I*) (*cf.*[6])

2(*R*),3-O-Isopropylideneglycerol (33 g; 0·25 mol; redistilled, b.p. 89—90°C/20 Torr; cf.[3]) was added dropwise to a stirred suspension of sodium hydride (6·25 g; 0·26 mol) in toluene (150 ml) during 30 min. After stirring for 20 min at room temperature benzyl chloride (38 g; 0·3 mol) in toluene (50 ml) was added in one portion. The mixture was stirred under reflux (calcium chloride protective tube) for 6 h, filtered through Celite which was then washed with toluene (100 ml), and the filtrate was evaporated *in vacuo*. The residue was refluxed with 20% acetic acid (200 ml) for 2 h, the mixture taken down *in vacuo* and the residue coevaporated with ethanol (2 × 50 ml) and distilled, affording 39·1 g (85·7%) of 1-O-benzyl-2(*S*)-glycerol, b.p. 148—152°/0·2 Torr.

A solution of this compound (0·214 mol) in pyridine (50 ml) was added dropwise under cooling with ice to a stirred mixture of *p*-toluenesulfonyl chloride (57 g; 0·3 mol) and pyridine (250 ml). The mixture was stirred for 1 h at 0°C, set aside in a stoppered flask at room temperature overnight, methanol (20 ml) was then added and the whole evaporated *in vacuo*. The residue was dissolved in ethyl acetate (500 ml) and water (100 ml), the organic layer washed with water (4 × 100 ml), dried over magnesium sulfate, filtered, taken down *in vacuo* and dried at 40°C/0·1 Torr, affording 61·4 g (61%) of 1-O-benzyl-2(*S*)-3-O-*p*-toluenesulfonylglycerol. This compound (0·183 mol) was hydrogenated under atmospheric pressure over 5% palladium on charcoal (3·5 g) in dioxane (500 ml) containing conc. hydrochloric acid (1 ml). After the hydrogen consumption had ceased (4·5 l), the mixture was filtered through Celite which was then washed with dioxane and the filtrate taken down *in vacuo*. The residue was mixed with acetone (150 ml) and 2,2-dimethoxypropane (100 ml) and acidified with 6M hydrogen chloride solution in dimethylformamide. The mixture was allowed to stand for 2 days at room temperature, neutralised with triethylamine and evaporated *in vacuo*. The residue was dissolved in ethyl acetate (500 ml), washed with water (3 × 100 ml), dried over magnesium sulfate, filtered and taken down *in vacuo*, finally at 70°C/0·1 Torr. The thus-obtained chromatographically pure product (46·1 g; 88%) was used in further experiments without purification.

9-(*R*)-(2,3-Dihydroxypropyl)adenine (*R-III*)

The reaction was carried out analogously as described for the preparation of the racemic derivative *III* from adenine (50 mmol), affording 5·45 g (44%) of (*R*)-*II*, m.p. 214—215°C. For $C_{11}H_{15}N_5O_2$ (249·3) calculated: 52·99% C, 6·06% H, 28·09% N; found: 53·02% C, 6·39H G, 29·45% N.

This product (5·0 g; 20 mmol) was refluxed with 80% acetic acid (50 ml) for 1 h, the acid was distilled off, the residue coevaporated with water (3 × 20 ml), ethanol (3 × 20 ml), and crystallised from ethanol, affording 2·6 g (62·2%) of (*R*)-*III*, m.p. 206°C. This product was identical with an authentic material prepared according to ref.[3] and with the racemic derivative (systems S1,S2 and S5).

N^6,2′,3′-Triacetyl-9-(*RS*)-(2,3-dihydroxypropyl)-8-bromoadenine (*VIII*)

A mixture of *IV* (7·3 g; 21·7 mmol), N-bromosuccinimide (8·9 g; 50 mol) and 1,2-dichloroethane (150 ml) was refluxed for 40 h (calcium chloride protective tube) and the reaction was followed by thin-layer chromatography (S3). The mixture was diluted with chloroform (100 ml), washed with saturated aqueous sodium bisulfite solution (2 × 50 ml) and water, dried over magnesium sulfate, filtered and taken down *in vacuo*. The residue was chromatographed on a silica gel column with chloroform as eluant. The product-containing fractions were combined, taken down and the residue crystallised from boiling ethyl acetate (light petroleum added to incipient turbidity), affording 5·85 g (65%) of *VIII*, m.p. 128—130°C. For $C_{14}H_{16}BrN_5O_5$ (414·3) calculated: 40·59% C, 3·89% H, 19·30% Br, 16·91% N; found: 40·50% C, 4·22% H, 18·82% Br, 16·70% N. R_F 0·66 (S3).

9-(*RS*)-(2,3-Dihydroxypropyl)-8-bromoadenine (*IX*)

A solution of *VIII* (1·1 g; 2·4 mmol) in methanol (25 ml) was mixed with 1M sodium methoxide in methanol (1 ml) and set aside overnight. The mixture was neutralised with acetic acid, the separated crystals *IX* (0·50 g; 72·3%) were collected on filter, washed with ethanol and ether and dried *in vacuo*; yield 0·50 g (72·3%) of *IX*; the product did not melt below 260°C. R_F 0·62 (S1), 0·67 (S2). For $C_8H_{10}BrN_5O_2$ (288·2) calculated: 33·34% C, 3·50% H, 27·75% Br, 24·31% N; found: 33·69% C, 4·07% H, 27·49% Br, 24·12% N.

9-(*RS*)-(2,3-Dihydroxypropyl)-8-hydroxyadenine (*X*)
and 9-(*RS*)-(2,3-Dihydroxypropyl)-8-acetoxyadenine (*XI*)

A mixture of the compound *VIII* (1·1 g; 2·41 mmol), fused sodium acetate (1·2 g; 15 mmol) and acetic anhydride (40 ml) was refluxed for 3 h and taken down at 40°C/0·1 Torr. The residue was dissolved in methanol (50 ml), made alkaline with 1M methanolic sodium methoxide and allowed to stand at room temperature overnight. The mixture was neutralised with acetic acid, taken down and the residue deionised by passing through a Dowex 50X8 column. The ammonia UV-absorbing eluate was taken down and crystallised (charcoal) from methanol (ether added to incipient turbidity), affording 0·28 g (43·5%) of compound *XI*, m.p. 243—244°C. For $C_{10}H_{13}N_5O_4$ (267·3) calculated: 44·94% C, 4·90% H, 26·21% N; found: 44·36% C, 4·90% H, 25·72% N. R_F 0·61 (S1), 0·70 (S2).

The mother liquors from crystallisation of *XI* were chromatographed on a column of cellulose (S1). Fractions, containing the main component, on crystallisation from ethanol afforded chromatographically pure *X* (0·18 g; 33·2%), m.p. 223—224°C. For $C_8H_{11}N_5O_3$ (225·3) calculated: 42·66% C, 4·92% H, 31·10% N; found: 42·56% C, 4·91% H, 30·54% N. R_F 0·50 (S1), 0·61 (S2(.

N^6,2′,3′-Triacetyl-9-(*RS*)-(2,3-dihydroxypropyl)-8-thioadenine (*XII*)

A solution of *VIII* (1·1 g; 2·41 mmol) and thiourea (1·0 g; 13·1 mmol) in 99% ethanol (50 ml) was refluxed for 15 h, evaporated *in vacuo* and the residue purified by chromatography on two layers of loose silica gel (S3). The product bands were eluted with methanol (300 ml), the eluate taken down and the residue crystallised from ethanol with addition of light petroleum to incipient turbidity. Yield 0·60 g (67·8%) of *XII*, m.p. 150—151°C. For $C_{14}H_{17}N_5O_5S$ (367·4) calculated 45·77% C, 4·66% H, 19·06% N, 8·72% S; found: 45·94% C, 4·76% H, 18·58% N, 8·62% S. R_F 0·54 (S3).

9-(*RS*)-(2,3-Dihydroxypropyl)-8-thioadenine (*XIII*)

A solution of the compound *XII* (0·50 g; 1·36 mmol) in 0·2M methanolic sodium methoxide (25 ml) was left aside at room temperature overnight, neutralised with Dowex 50 X 8 (H^+) filtered and the filtrate taken down *in vacuo*. Dissolution of the residue in methanol (10 ml) and precipitation with ether (200 ml) afforded 0·30 g (80%) of chromatographically pure *XIII*, m.p. 198°C (decomposition). For $C_8H_{11}N_5O_2S$ (241·3) calculated: 39·82% C, 4·60% H, 29·03% N, 13·29% S; found: 40·15% C, 4·26% H, 30·82% N, 13·65% S. R_F 0·46 (S1), 0·65 (S2).

9-(*RS*)-(2,3-Dihydroxypropyl)-8-aminoadenine (*XIV*)

A mixture of the compound *VIII* (3·0 g; 7·25 mmol) and 30% methanolic ammonia (80 ml) was heated in an autoclave to 120°C for 24 h, evaporated *in vacuo* and the residue chromatographed on a column of cellulose using 70% 2-propanol as eluant. Fractions containing the compound *XIV* (according to S1) were combined and taken down *in vacuo*, the residue coevaporated with ethanol, dissolved in methanol (20 ml) and precipitated with ether (200 ml), affording 0·80 g (49·3%) of *XIV* which did not melt below 260°C. For $C_8H_{13}N_6O_2$ (225·2) calculated: 42·66% C, 5·82% H, 37·32% N; found: 42·89% C, 5·96% H, 36·70% N. R_F 0·46 (S1).

9-(*RS*)-(2,3-Dihydroxypropyl)-N^6-methyladenine (*XV*)

A mixture of the compound *II* (2·5 g; 10 mmol), dimethylformamide (20 ml) and methyl iodide (6·0 ml; 96·5 mmol) was stirred in a stoppered bottle for 3 days at room temperature, then diluted with acetone (200 ml), the separated material collected, washed with acetone, ether and dried *in vacuo*. This product was refluxed with 0·25M sodium hydroxide (50 ml) for 2 h, neutralised with Dowex 50 X 8 (H^+), taken down *in vacuo* and the residue chromatographed on two layers of loose silica gel (S3). The product bands were eluted with methanol (500 ml), the solvent evaporated and the residue refluxed with 80% acetic acid (20 ml) for 2 h. Evaporation *in vacuo*, coevaporation with water (3 × 50 ml) and ethanol (30 ml), and crystallisation from ethanol (with addition of ether to turbidity) afforded 1·20 g (54%) of chromatographically pure *XV*, m.p. 155—156°C. For $C_9H_{13}N_5O_2$ (223·2) calculated: 48·41% C, 5·87% H, 31·38% N; found: 48·70% C, 5·95% H, 30·94% N. R_F 0·70 (S1), 0·50 (S5). (III: R_F 0·24 in S5).

2′,3′-Di-O-acetyl-9-(*RS*)-(2,3-dihydroxypropyl)hypoxanthine (*XVII*)

A mixture of the compound *III* (5·2 g; 25 mmol), sodium nitrite (6·9 g; 0·1 mol), water (100 ml) and conc. hydrochloric acid (10 ml) was allowed to stand in a stoppered flask at room temperature for 16 h, when, according to thin-layer chromatography (S5), the reaction was complete (*III*, R_F 0·30, *XVI*, R_F 0·15). The mixture was neutralised with ammonia, evaporated and the residue coevaporated with pyridine (3 × 50 ml). Pyridine (50 ml) and acetic anhydride (50 ml) were added, the mixture stirred at room temperature overnight, and taken down at 50°C/0·1 Torr. Chloroform (200 ml) was added, the mixture filtered through Celite which was then washed with chloroform (200 ml), the filtrate was concentrated *in vacuo* and applied to a silica gel column. Elution with chloroform afforded chromatographically homogeneous compound *XVII* which was crystallised from ethanol (addition of light petroleum); yield 5·55 g (74%), m.p. 160—162°C. For $C_{12}H_{14}N_4O_5$ (294·3) calculated: 48·97% C, 4·79% H, 19·04% N; found: 48·32% C, 5·19% H, 19·47% N. R_F 0·21 (S3).

9-(*RS*)-(2,3-Dihydroxypropyl)-6-dimethylaminopurine (*XIX*)

A mixture of *XVII* (5·6 g; 19 mmol) and 2M solution of dimethylchloromethyleneammonium chloride[16] in chloroform (55 ml) was refluxed (calcium chloride protective tube) for 10 h, after which time thin-layer chromatography (S3) showed quantitative conversion. After cooling, the mixture was poured on ice (250 g), the chloroform layer was washed with ice-cold water (20 ml), dried over magnesium sulfate and filtered. The material on the filter was washed with chloroform, the filtrate taken down *in vacuo* and the residue stirred with light petroleum (100 ml) at 0°C for 2 h. The crystalline *XVIII* was filtered, washed with light petroleum and dried *in vacuo*; yield 5·35 g (89%), R_F 0·60 (S3). This product (17 mmol) was heated in an autoclave with 2·2M dimethylamine in methanol (75 ml) to 100°C for 7 h, the mixture was cooled down and evaporated *in vacuo*. The residue was taken up in water (50 ml), acidified (pH 3) with hydrochloric acid and de-ionised on a Dowex 50 X 8 column (see above). The ammonia eluate was taken down, the residue codistilled with ethanol (3 . 50 ml) and crystallised from ethanol (ether added to turbidity), yielding the compound *XIX* (3·90 g; 96·5%), m.p. 131°C; R_F 0·76 (S5), 0·75 (S1), 0·72 (S2). For $C_{10}H_{15}N_5O_2$ (237·3) calculated: 60·62% C, 6·37% H, 29·52% N; found: 50·38% C, 6·65% H, 29·78% N.

2′,3′-Di-O-acetyl-9-(*RS*)-(2,3-dihydroxypropyl)-6-mercaptopurine (*XX*)

A stirred mixture of the compound *XVII* (2·94 g; 10 mmol), phosphorus pentasulfide (7·3 g; 32·9 mmol) and pyridine (100 ml) was refluxed (calcium chloride protective tube) for 5 h, cooled, concentrated *in vacuo* to half of its original volume and poured into boiling water (800 ml). The resulting neutral solution was decolorised with charcoal, filtered through Celite while hot, the material on the filter washed with boiling water (100 ml) and the orange filtrate concentrated *in vacuo* to about 100 ml. The resulting suspension was dissolved by heating and allowed to stand in a refrigerator. The separated crystals were collected, washed successively with water and ethanol and crystallised from ethanol, yielding 1·25 g (40·5%) of the compound *XX*, m.p. 248–249°C. R_F 0·56 (S3). For $C_{12}H_{14}N_4O_4S$ (310·3) calculated: 46·44% C, 4·55% H, 18·06% N, 10·33% S; found: 45·84% C, 4·66% H, 17·66% N, 10·61% S.

9-(*RS*)-(2,3-Dihydroxypropyl)-6-mercaptopurine (*XXI*)

A solution of the compound *XX* (1·1 g; 3·55 mmol) in 0·1M sodium methoxide (50 ml) was set aside overnight at room temperature, neutralised with Dowex 50 X 8 (H^+) (separation of crystals!), collected on filter, washed with water (50 ml) and the filtrate taken down *in vacuo*. The residue was coevaporated with ethanol (50 ml) and crystallised from ethanol, affording 0·70 g (87%) of the compound *XXI*, which did not melt below 260°C. For $C_8H_{10}N_4O_2S$ (226·3) calculated: 42·46% C, 4·54% H, 24·77% N, 14·17% S; found: 42·11% C, 4·74% H, 24·31% N, 14·47% S. R_F 0·40 (S1).

2,2-Dimethyl-4-(2-chloromethyl)-1,3-dioxolane (*XXII*)

A mixture of 1-chloro-2,3-dihydroxypropane (50 g; 0·45 mol), acetone (50 ml) and 2,2-dimethoxypropane (40 ml) was acidified with 6M hydrogen chloride in dimethylformamide (to moist indicator paper), allowed to stand for 2 days at room temperature and then neutralised with 1M sodium methoxide, filtered through Celite, washed with acetone, taken down *in vacuo* and the residue distilled, b.p. 146–150°C/750 Torr. Yield 63 g (93·5%) of *XXII* (d_4^{20} 1·090).

2′,3′-O-Isopropylidene-9-(*RS*)-(2,3-dihydroxypropyl)-2,6-diaminopurine (*XXIII*)

A mixture of 2,6-diaminopurine hemisulfate (2·0 g; 10 mmol), potassium carbonate (3·8 g; 30 mmol), the compound *XXII* (3·0 g; 20 mmol) and dimethylformamide (25 ml) was stirred at 100°C for 12 h under exclusion of moisture. After cooling, the mixture was filtered, the material on filter washed with dimethylformamide (10 ml), the filtrate taken down at 50°C/0·1 Torr and the residue chromatographed on two layers of loose silica gel (S3). The product bands were eluted with methanol (300 ml) and the eluates evaporated. The residue upon crystallisation from ethanol (light petroleum added to turbidity) afforded 1·62 g (61·5%) of *XIII*, m.p. 194 to 196°C. R_F 0·42 (S4) (II, 0·62 in S4). For $C_{11}H_{16}N_6O_2$ (264·3) calculated: 49·98% C, 6·11% H, 31·80% N; found: 49·75% C, 5·93% H, 31·95% N.

9-(*RS*)-(2,3-Dihydroxypropyl)-2,6-diaminopurine (*XXIV*)

A mixture of the compound *XXIII* (0·70 g; 2·65 mmol) and 80% acetic acid (30 ml) was refluxed for 2 h, taken down, coevaporated with water (3 × 20 ml) and ethanol (2 × 20 ml) and the resi-

due crystallised from methanol, yielding 0·40 g (67·7%) of *XXIV*, m.p. 261—263°C. For $C_8H_{12}N_6O_2$ (224·2) calculated: 42·85% C, 5·40% H, 37·48% N; found: 42·22% C, 5·50% H, 36·93% N. R_F 0·31 (S1), 0·59 (S2).

2′,3′-O-Isopropylidene-9-(*RS*)-(2,3-dihydroxypropyl)-2-methylthioadenine (*XXV*)

A stirred mixture of 2-methylthioadenine (1·80 g; 10 mmol), potassium carbonate (2·7 g; 20 mmol), the compound *XXII* (3 g; 20 mmol) and dimethylformamide (25 ml) was heated to 100°C for 16 h with exclusion of moisture and worked up similarly as described for the compound *XXIII*, affording 1·4 g (47·5%) of *XXV*, m.p. 180—181°C. R_F 0·66 (S2). For $C_{12}H_{17}N_5O_2S$ (295·4) calculated: 48·79% C, 5·80% H, 23·72% N, 10·85% S; found: 48·61% C, 5·85% H, 23·27% N, 10·80% S.

9-(*RS*)-(2,3-Dihydroxypropyl)-2-methylthioadenine (*XXVI*)

A mixture of the compound *XXV* (1·20 g; 4·06 mmol) and 80% acetic acid (30 ml) was refluxed for 2 h, taken down and codistilled with water (3 × 50 ml) and ethanol (2 × 20 ml). Crystallisation of the residue from ethanol gave 0·75 g (72·5%) of *XXVI*, m.p. 194—195°C. R_F 0·69 (S1), 0·75 (S2). For $C_9H_{13}N_5O_2S$ (255·3) calculated: 42·34% C, 5·13% H, 27·44% N, 12·56% S; found: 42·29% C, 5·18% H, 27·19% N, 11·85% S.

9-(*RS*)-(2,3-Dihydroxypropyl)adenine-N-oxide (*XXVII*)

A mixture of the compound *II* (1·1 g; 4·42 mmol), acetic acid (40 ml) and 30% hydrogen peroxide (10 ml) was allowed to stand at room temperature for 6 days. The unreacted peroxide was decomposed with manganese dioxide, the mixture filtered and the filtrate taken down *in vacuo*. The residue was codistilled with water (2 × 20 ml) and crystallised twice from ethanol, yielding 0·50 g (50%) of *XXVII*; R_F 0·35 (S1), 0·47 (S2), 0·10 (S6). For $C_8H_{13}N_5O_3$ (225·2) calculated: 42·66% C, 4·92% H, 31·10% N; found: 42·65% C, 4·91% H, 30·87% N.

2′,3′-O-Isopropylidene-9-(2,3-dihydroxypropyl)-N^2-acetylguanine (*XXVIII*) and
2′,3′-O-Isopropylidene-7-(2,3-dihydroxypropyl)-N^2-acetylguanine (*XXXI*)

N^2-Acetylguanine (38·6 g; 0·2 mol) was added to a stirred suspension of sodium hydride (3·8 g; 0·2 mol) in dimethylformamide (250 ml) and stirring was continued for 1 h at 60°C with exclusion of moisture. Compound *I* (68·6 g, 0·24 mol) was then added and the mixture heated under exclusion of moisture to 100°C for 40 h under stirring. The cooled mixture was filtered and washed with 100 ml of dimethylformamide. (From the precipitate, 23·6 g (60%) of N^2-acetylguanine was recovered by crystallisation from methanol). The filtrate was taken down at 40°C/0·1 Torr, the residue refluxed with chloroform (1 liter) for 30 min, filtered and the material on the filter washed with boiling chloroform (500 ml). The filtrate was taken down *in vacuo*, and the residue chromatographed on a silica gel column, eluant chloroform–ethanol (95 : 5). Fractions, containing the compound of R_F 0·40 (S4), on evaporation and crystallisation from ethanol afforded 4·90% (8%) of *XXXI*, not melting below 260°C. For $C_{13}H_{17}N_5O_4$ (307·3) calculated: 50·80% C, 5·58% H, 22·79% N; found: 51·26% C, 6·02% H, 22·09% N. UV spectrum, pH 2: λ_{max} 263 nm (ε_{max} 16180), λ_{min} 234 nm; pH 7: λ_{max} 264 nm (ε_{max} 14200), λ_{min} 238 nm; pH 12: λ_{max} 268 nm (ε_{max} 11500), λ_{min} 245 nm.

Fractions of R_F 0·20 (S4) on crystallisation from ethanol afforded 4·70 g (7·6%) of *XXVIII*, not melting below 260°C. Calculated: see *XXXI*; found: 50·80% C, 5·82% H, 22·82% N. UV spectrum, pH 2: λ_{max} 263 nm (ε_{max} 16100), λ_{min} 228 nm; pH 7: λ_{max} 260 nm (ε_{max} 14900), λ_{min} 228 nm; pH 12: λ_{max} 263 nm (ε_{max} 11800), λ_{min} 239 nm.

2′,3′-O-Isopropylidene-9-(*RS*)-(2,3-dihydroxypropyl)guanine (*XXIX*)

A solution of the compound *XXVIII* (3·4 g; 11·1 mmol) in 0·2M sodium methoxide (250 ml) was allowed to stand overnight, neutralised with Dowex 50 X 8 (H^+), filtered, and the material on the filter washed with water (100 ml) and dilute (1 : 10) ammonia (200 ml). The filtrate was taken down and the residue crystallised from ethanol, affording the compound *XXIX* (2·65 g; 90%), m.p. 263°C. For $C_{11}H_{15}N_5O_3$ (265·3) calculated: 49·80% C, 5·70% H, 26·41% N; found: 49·93% C, 5·66% H, 26·18% N. Its UV spectrum was identical with that of *XXX*.

2′,3′-O-Isopropylidene-7-(*RS*)-(2,3-dihydroxypropyl)guanine (*XXXII*)

This compound was prepared from *XXXI* (3·9 g; 12·7 mmol) analogously as described for *XXIX*. Yield 3·2 g (92%); it did not melt below 260°C. Calculated: see *XXIX*; found: 49·77% C, 6·05% H, 26·60% N. Its UV spectrum was identical with that of *XXXIII*.

9-(*RS*)-(2,3-Dihydroxypropyl)guanine (*XXX*)

A solution of the compound *XXIX* (2·65 g; 10 mmol) in 80% acetic acid (100 ml) was refluxed for 1 h, evaporated, coevaporated with water and crystallised from 90% ethanol (ether added to turbidity). The obtained compound *XXX* (2·0 g; 77%) did not melt below 260°C. R_F 0·37 (S1). For $C_8H_{11}N_5O_3$ (225·3) calculated: 42·66% C, 4·92% H, 31·10% N; found: 41·18% C, 4·91% H, 30·50% N.

7-(*RS*)-(2,3-Dihydroxypropyl)guanine (*XXXIII*)

This compound was prepared from the compound *XXXII* (10 mmol) analogously to the 9-isomer *XXX* and was purified by crystallisation from 90% ethanol; yield 1·84 g (82%). It did not melt below 260°C. Calculated: see *XXX*; found: 42·59% C, 4·98% H, 31·45% N. R_F 0·33 (S1).

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