PHOSPHONYLMETHOXYALKYL AND PHOSPHONYLALKYL DERIVATIVES OF ADENINE*

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Dedicated to the memory of Dr Karel Bláha.

Analogues of the antivirals (2*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)adenine (*Ia*) and 9-(2-phosphonylmethoxyethyl)adenine (*Ib*), modified in the alkyl chain, are described. The phosphonylmethoxyalkyl derivatives were prepared by condensation of sodium alkoxides of hydroxyalkyladenines (or their N-protected derivatives) with dimethyl *p*-toluenesulfonyloxymethanephosphonate (*II*) followed by alkaline hydrolysis and reactions with halotrimethylsilane, or by reaction of vicinal dihydroxyalkyl derivatives with chloromethanephosphonyl dichloride (*XIV*) and subsequent cyclization of the intermediates *XV* in aqueous alkali. In the second case the pure regioisomers were also obtained from substituted dihydroxy derivatives with one free hydroxyl group. The following compounds were prepared in this way: 3-O-methyl ether *IIIc* and 3-O-octyl ether *IVc*, 9-(3-phosphonylmethoxypropyl)- (*Vc*), 9-(4-phosphonylmethoxybutyl)- (*Vf*), 9-(5-phosphonylmethoxypentyl)- (*Vi*), 9-(2-phosphonylmethoxypropyl)- (*VIc*), 9-(1-phosphonylmethoxy-3-hydroxy-2-propyl)- (*XIIc*), 9-(2-methoxy-3-phosphonylmethoxypropyl)- (*XIIIc*), *erythro*-9-(2-phosphonylmethoxy-3,4-dihydroxybutyl)- (*VIIc*) and *threo*-9-(4-phosphonylmethoxy-2,3-dihydroxybutyl)adenine (*IXc*) and its enantiomer (*Xc*). 9-(2-Phosphonylmethoxy-3,3-dihydroxypropyl)adenine (*VIII*) was obtained by oxidation of *VIIc* with sodium periodate, 9-(2-phosphonylmethoxyethoxymethyl)adenine (*XIc*) by reaction of *II* with sodium salt of 9-(2-hydroxyethoxymethyl)adenine (*XIa*). 9-(1,2-Dihydroxy-2-methyl-3-propyl)adenine 1- and 2-phosphonylmethyl ether (*XVIb*), 9-(3,4-dihydroxybutyl)adenine 3- and 4-phosphonylmethyl ether (*XVIIb*) and 9-(2,3-dihydroxybutyl)adenine 2- and 3-phosphonylmethyl ether (*XVIIIb*) were prepared by reaction with chloromethanephosphonyl dichloride (*XIV*) followed by alkaline treatment. Analogous reaction was also employed in the preparation of regioisomerically pure 1-phosphonylmethyl ethers of 9-(1,2-dihydroxy-3-butyl)adenine (*XXIV*), 9-(1,2-dihydroxy-2-methyl-3-propyl)adenine (*XVIb*) and 9-(1,2-dihydroxy-3-nonyl)-adenine (*XXV*). Alkylation of adenine with diethyl chloromethoxymethanephosphonate (*XXVII*) followed by hydrolysis afforded 9-(phosphonylmethoxymethyl)adenine (*XXVIIIb*).
9-(Phosphonylmethyl)adenine (*XLI*) was obtained by condensation of adenine with compound *II*. Conversion of 9-(ω-hydroxyalkyl)adenines into the ω-halogenoalkyl derivatives followed by reaction with trialkyl phosphite and cleavage was used in the preparation of 9-(2-phosphonylethyl)-adenine (*XXXIVa*), 9-(4-phosphonylbutyl)adenine (*XXXIVb*) and 9-(2-phosphonylethoxymethyl)-adenine (*XXXIX*). 9-(2-Phosphonyl-2-hydroxyethyl)adenine (*Lc*) and 9-(3-phosphonyl-3-hydroxy-

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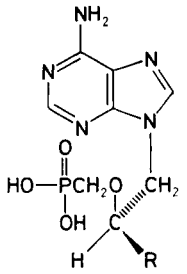
propyl)adenine (*Lb*) were synthesized by treatment of ω-(adenin-9-yl)alkanals with dialkyl phosphite and subsequent cleavage with halogenotrimethylsilane; the same procedure converted 9-(2-oxopropyl)adenine (*XLVIIIa*) into 9-(2-phosphonyl-2-hydroxypropyl)adenine (*La*).

In our previous communications of this series we described syntheses of two novel active antivirals belonging to acyclic nucleotide analogues: (*S*)-9-(3-hydroxy-2--phosphonylmethoxypropyl)adenine[1] (*Ia*; HPMPA) and 9-(2-phosphonylmethoxyethyl)adenine[2] (*Ib*; PMEA), as well as some of their metabolites and prodrugs[3]. Both the mentioned preparations exhibit a specific effect on DNA-viruses, have a suitable therapeutic index and – because they do not depend on phosphorylation with nucleoside kinase – they are also effective against TK^- mutants (e.g. herpes viruses) lacking viral thymidine kinase, which are resistent to the majority of nucleoside antivirals[4,5].



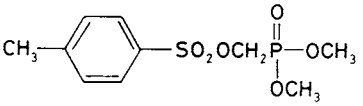
Ia, R = CH_2OH(S)
Ib, R = H

Structure–activity studies of the antiviral effect in the series of acyclic nucleotide analogues are aimed at the following three principal structural parameters: i) character of the heterocyclic base, ii) character of the aliphatic chain, and iii) the presence, character and bonding of the phosphonyl group. This paper describes synthetic methods leading to analogs of compounds *I* (in the adenine series) with varying character of the aliphatic chain and bond of the phosphonyl group to this chain, i.e. to isomers, isosters, carba-analogs and homologs of compounds *I*, as well as other derivatives with similar structural parameters. According to the character of the bond, these compounds can be divided into two main types: phosphonylmethoxyalkyl and phosphonylalkyl derivatives of adenine (or other heterocyclic bases).

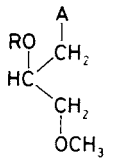
Phosphonylmethyl Ethers of Acyclic Adenosine Derivatives

This group of compounds includes analogs with preserved basic structural elements of compounds *I*, particularly their phosphonylmethyl ether functionality. The first

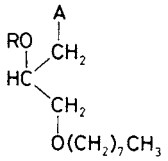
subgroup comprises compounds derived from HPMPA (*Ia*) by modification of the hydroxymethyl group in the position C-2 of the side chain. Formally, one can assume that spatial arrangement of these derivatives is analogous to that of compound *Ia*. To this subgroup belong O-alkyl ethers *IIIc*, *IVc*, deoxy derivative *VIc*, 3-hydroxymethyl derivative *VIIc* and 3-hydroxy derivative *VIII* (hydrate of the substituted aldehyde derivative).



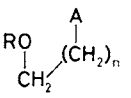
II



III



IV



Va, R = H ; n = 2

Vb, R = $CH_2P(=O)(OH)OCH_3$; n = 2

Vc, R = $CH_2P(=O)(OH)OH$; n = 2

Vd, R = H ; n = 3

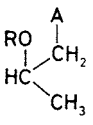
Ve, R = $CH_2P(=O)(OH)OCH_3$; n = 3

Vf, R = $CH_2P(=O)(OH)OH$; n = 3

Vg, R = H ; n = 4

Vh, R = $CH_2P(=O)(OH)OCH_3$; n = 4

Vi, R = $CH_2P(=O)(OH)OH$; n = 4



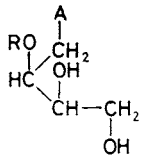
VI

In formulae *III*, *IV*, *VI*: *a*, R = H *b*, R = $CH_2P(=O)(OH)OCH_3$

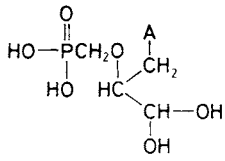
c, R = $CH_2P(=O)(OH)OH$

A = adenin-9-yl residue

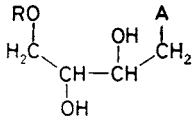
The preparation of such compounds was analogous to that[1,2] of the phosphonylmethyl ethers *I* and consisted in alkylation of sodium salt of the starting 9-(hydroxyalkyl)adenines *IIIa*, *IVa* or *VIa* (generated by in situ reaction with sodium hydride in dimethylformamide) with the phosphorus synthon *II*. The starting compounds *IIIa* and *VIa* were obtained using previously described procedures[6,7]. The hitherto undescribed octyl ether *IVa* was prepared by alkylation of adenine with 1-octyloxy-2,3-epoxypropane[8] in the presence of potassium carbonate. Mass spectrum of the



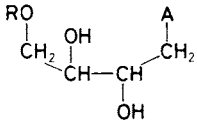
VII



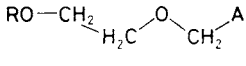
VIII



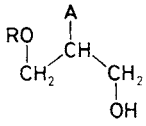
IX



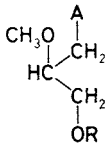
X



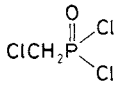
XI



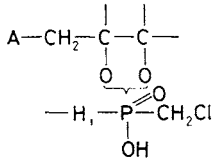
XII



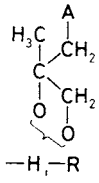
XIII



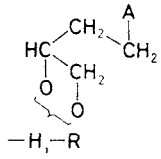
XIV



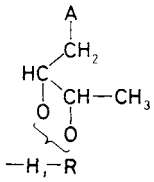
XV



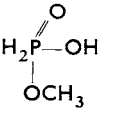
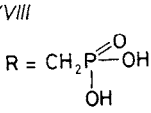
XVI



XVII



XVIII

In formulae *VII*, *IX*–*XIII*, *XV*–*XVIII*: *a*, R = H *b*, R =  *c*, R = 

A = adenin-9-yl residue

product exhibited the expected fragmentation pattern. All the three compounds mentioned so far were prepared as racemates. Since all contain only one hydroxyl group, they could be (after protection of the adenine amino group with a dimethylaminomethylene or benzoyl group under usual conditions[9]) directly alkylated with compound *II*. However, in the case of derivative *VIIc* the condensation had to be regioselective and the synthesis started from 3,4-O-isopropylidene derivative of (2*S*,3*R*)-9-(2,3,4-trihydroxybutyl)adenine (*VIIa*), prepared in connection with other investigations[10]. After the condensation and standard processing (vide infra), the 1,3-dioxolane group was removed in an acid medium. In all cases mentioned, the condensation with compound *II* was carried out with a 2–3 fold excess of sodium hydride. Since the reaction mixtures were (after evaporation of the solvent) decomposed with aqueous methanol, the resulting alkaline medium removed the protecting group on the adenine amino group and simultaneously hydrolyzed one of the phosphonate ester groups. After deionization, the second ester group in the crude intermediate was cleaved by reaction with bromo- or iodotrimethylsilane. Compounds *IIIc*, *IVc* and *VIc* (and after acid hydrolysis also *VIIc*) were purified by ionex chromatography in acetic acid and isolated as the free acids. The aldehyde *VIII* was prepared by degradation of the diol *VIIc* with sodium periodate in water and isolated in the same manner as the above-mentioned phosphonylmethyl ethers. The theoretically possible cyclic hemiacetal structure of this compound is excluded by the observed electrophoretic mobility in neutral medium, which corresponds to dissociation to the second degree, possible only in the acyclic form.

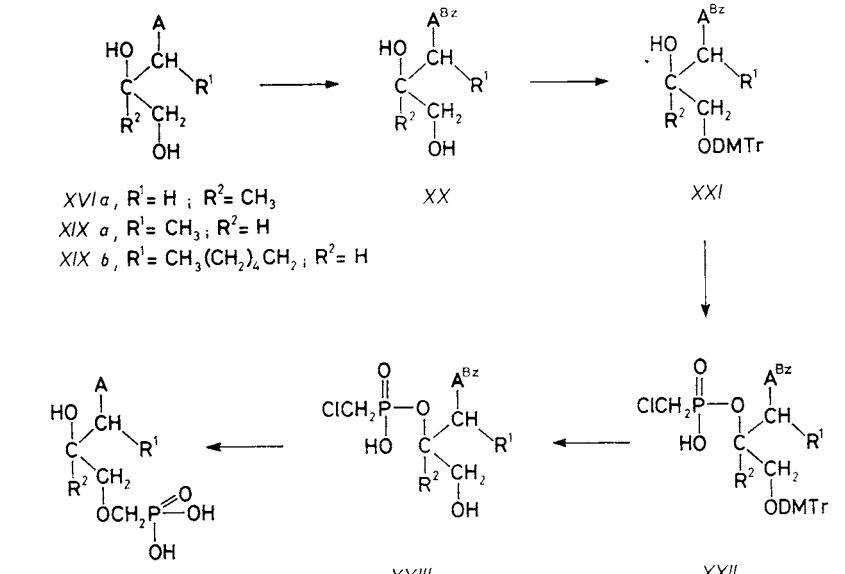
The second subgroup of analogs of compounds *I* encompasses compounds derived from 9-(2-phosphonylmethoxyethyl)adenine (*Ib*; PMEA). Its simplest members, homologues of *Ib* with a linear chain in position ω (i.e. phosphonylmethyl ethers *Vc*, *Vf* and *Vi*), were prepared from the corresponding 9-(ω-hydroxyalkyl)adenines *Va*, *Vd* and *Vg*. 9-(3-Hydroxypropyl)adenine (*Va*) had been described already previously[7], the 4-hydroxybutyl (*Vd*) and 5-hydroxypentyl (*Vg*) derivatives were obtained from adenine and the corresponding ω-acetoxyalkyl chloride in the presence of potassium carbonate. The isolated intermediates, 9-(ω-acetoxyalkyl)adenines, characterized by ^{1}H NMR and mass spectra, were readily methanolyzed to give 9-(ω-hydroxyalkyl)-adenines *Va*, *Vd* and *Vg*. Sodium salts of their N-dimethylaminomethylene or N--benzoyl derivatives were condensed with the synthon *II* in the presence of excess sodium hydride[11], worked up in an alkaline medium and treated with halogenotrimethylsilane (vide supra) to give free phosphonic acids *Vc*, *Vf* and *Vi* which were isolated by chromatography on an anion-exchanger.

9-(2-Phosphonylmethoxyethoxymethyl)adenine (*XIc*), also belonging to this group, was prepared by the same reaction sequence from the acyclovir analog, 9-(2-hydroxyethoxymethyl)adenine[12] (*XIa*). Finally, compound *XIIc*, that may be regarded both a 1-hydroxymethyl derivative of *Ib* and a regioisomer of *Ia*, in the racemic form was prepared from 9-(1,3-dihydroxy-2-propyl)adenine (*XIIa*). Although

the compound *XIIa* is already known[7], we describe another preparation based on reaction of 5-(*p*-toluenesulfonyloxy)-1,3-dioxane with sodium salt of adenine followed by hydrolysis of the formed 5-(adenin-9-yl)-1,3-dioxane in a strongly acid medium[13]. After protection of the adenine amino group (vide supra), the product reacted in the presence of excess sodium hydride with the synthon *II*, the protecting groups on the amino and phosphonic acid functionalities were removed by standard procedures (vide supra) and the compound *XIIc* was isolated by chromatography on an ion-exchanger.

The two enantiomeric *threo*-9-(4-phosphonylmethoxy-2,3-dihydroxybutyl)adenines (*IXc*, *Xc*) were prepared starting from 2,3-O-isopropylidene derivatives of *IXa* and *Xa*, described previously[10]. Condensation of N-protected derivatives of these compounds with the synthon *II*, followed by acid and alkaline hydrolysis, afforded the desired products *IXc* and *Xc*.

Further types of phosphonylmethyl ethers were prepared from compounds containing the 1,2-diol grouping. In these cases we used another synthesis of phos-

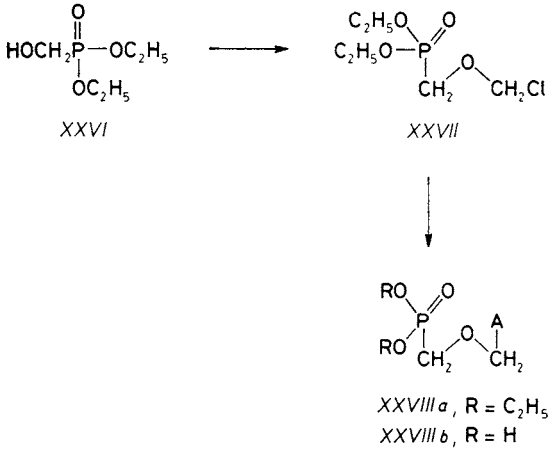


In formulae *XX*–*XXIII* *a*, $R^1 = H$; $R^2 = CH_3$ *b*, $R^1 = CH_3$; $R^2 = H$ *c*, $R^1 = CH_3(CH_2)_4CH_2$; $R^2 = H$; A = adenin-9-yl; A^{Bz} = N^6-benzoyl-adenin-9-yl; DMTr = dimethoxytrityl residue

SCHEME 1

phonylmethyl ethers consisting in intramolecular cyclization of chloromethanephosphonyl esters of these diols (*XV*) in aqueous alkali[14]. The esters *XV* were readily obtained by reaction of the corresponding N-protected 1,2-diols with chloromethanephosphonyl dichloride (*XIV*) in pyridine or with a reagent prepared by reaction of the dichloride *XIV* with an equimolecular amount of water in pyridine[1]. After ammonolysis, the obtained isomers of compounds *XV* were separated by chromatography on ion-exchanger or by HPLC and then converted quantitatively into the isomeric 3-hydroxy-substituted phosphonylmethyl ethers by treatment with aqueous alkali. In this manner we prepared the isomeric ethers *XVIc* from 9-(1,2-dihydroxy--2-methyl-3-propyl)adenine[15] (*XVIa*), the isomeric phosphonates *XVIIc* from (*S*)-9-(3,4-dihydroxybutyl)adenine (*XVIIa*) and the isomers *XVIIIc* from (2*S*,3*S*)-9--(2,3-dihydroxybutyl)adenine (*XVIIIa*).

The preparation of the single isomer of a phosphonylmethyl ether by the chloromethanephosphonate (*XV*) route requires a multiple-stage strategy. Such case is illustrated by the synthesis of 1-O-phosphonylmethyl derivative *XVIc* from 9-(1,2--dihydroxy-2-methyl-3-propyl)adenine (*XVIa*) as well as the preparation of 9-(1--phosphonylmethoxy-2-hydroxy-3-alkyl)adenines *XXIV* and *XXV* (Scheme 1): the starting diols[15] *XVIa* and *XIX* were first transformed into the N-benzoyl derivatives *XX* by reaction with chlorotrimethylsilane and benzoyl chloride in pyridine[16]. Reaction of compounds *XX* with bis(*p*-methoxyphenyl)phenylmethyl chloride led to derivatives *XXI* with trityl group on the primary hydroxyl which were readily esterified using the above-mentioned reagents derived from the dichloride *XIV*. The labile dimethoxytrityl group in compounds *XXII* was easily removed by acid cleavage



SCHEME 2

and the hydroxy compound *XXIII* underwent an intramolecular O-alkylation followed by hydrolysis to give the final products *XVIc*, *XXIV* and *XXV* with the phosphonylmethyl ether functionality bonded to the primary hydroxyl (Scheme 1).

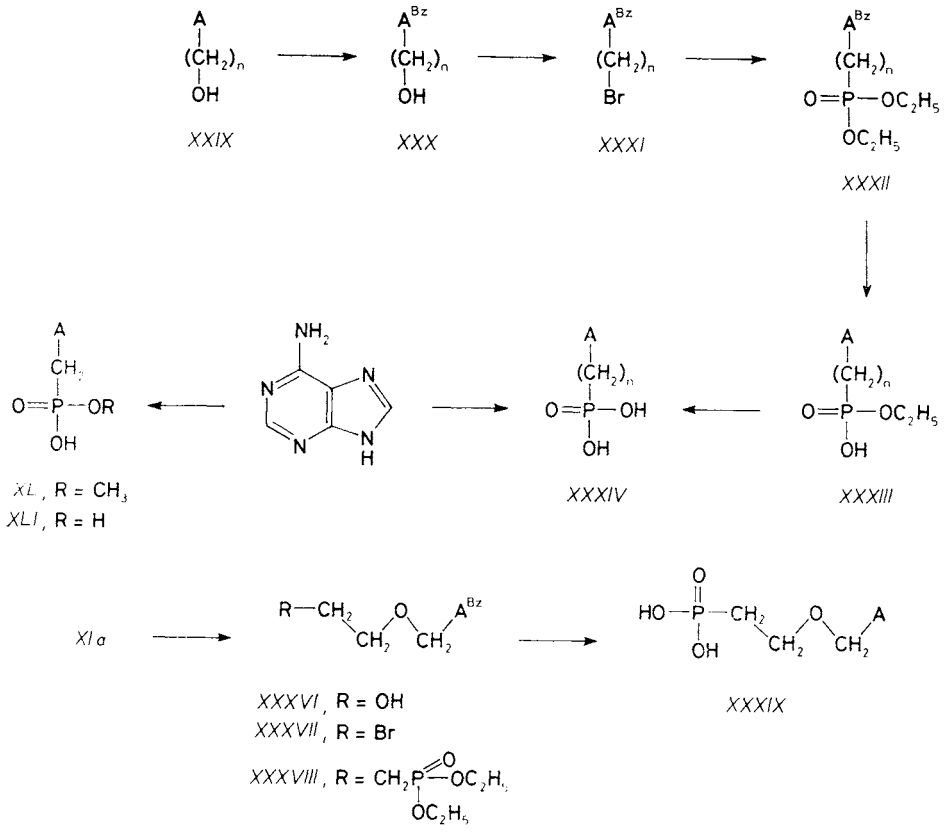
The last of the prepared phosphonylmethyl ether derivatives is 9-(phosphonylmethoxymethyl)adenine *XXVIIIb* which represents a "shortened" analog of compound *Ib*. Diethyl chloromethoxymethanephosphonate (*XXVII*), required for the synthesis, was prepared from diethyl hydroxymethanephosphonate[17] (*XXVI*) by chloromethylation with paraformaldehyde and hydrogen chloride. Compound *XXVII* was reacted with sodium salt of adenine to give the neutral ester *XXVIIIa* which on treatment with bromotrimethylsilane and subsequent hydrolysis was converted into the phosphonic acid *XXVIIIb* (Scheme 2).

Phosphonylalkyl Derivatives of Heterocyclic Bases

This group of compounds comprises analogs of compounds *I*, containing, instead of the phosphonylmethyl ether functionality, a phosphonyl group bonded directly to the carbon chain. These derivatives can be thus regarded as carba-analogs of the above-described compounds. They were synthesized using the following two approaches: *a*) alkylation of the corresponding heterocyclic base with an organophosphorus synthon (suitably substituted alkanephosphonic acid), *b*) introduction of the phosphonic acid moiety by additional modification of a substituted alkyl derivative of this base. Both methods are outlined in Scheme 3.

Reaction of sodium salt of adenine with dimethyl *p*-toluenesulfonyloxymethanephosphonate (*II*), followed by hydrolysis via the monomethyl ester *XL*, afforded the simplest derivative of this group, 9-(phosphonylmethyl)adenine (*XLI*). Similarly we prepared the homolog, 9-(2-phosphonylethyl)adenine (*XXXIVa*) by direct reaction of adenine with disodium 2-chloroethanephosphonate[17] (*XXXV*); the low yield of this reaction was due to using the salt instead of the diester of compound *XXXV* as well as to the easy elimination of hydrogen chloride from the synthon *XXXV* leading under the reaction conditions to vinylphosphonic acid. The same product *XXXIVa* was obtained by the second route, i.e. by the Arbuzov reaction, from the corresponding protected 9-(2-bromoethyl)adenine *XXXIa* which in turn was obtained from 9-(2-hydroxyethyl)adenine[7] (*XXIXa*) by N-benzoylation and treatment of the obtained N-benzoyl derivative *XXXa* with triphenylphosphine and tetrabromomethane. Heating the bromoethyl derivative *XXXIa* with triethyl phosphite followed by alkaline hydrolysis afforded the monoethyl ester *XXXIIIa* from which we finally obtained 9-(2-phosphonylethyl)adenine (*XXXIVa*), identical with the product prepared in different way (vide supra). Using the analogous reaction sequence, 9-(4-phosphonylbutyl)adenine (*XXXIVb*) and its monoethyl ester *XXXIIIb* were obtained from 9-(4-hydroxybutyl)adenine (*XXIXb*) via the N^6-benzoyl derivative *XXXb*, 4-bromobutyl derivative *XXXIb* and 9-(4-diethoxyphos-

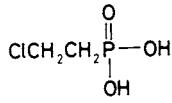
phonylbutyl)-N^6-benzoyladenine (*XXXIIb*). The 2-oxa analog of compound *XXXIVb*, 9-(2-phosphonylethoxymethyl)adenine (*XXXIX*), formally an isomer of *Ib* or a homolog of *XXVIIIb*, was synthesized analogously from 9-(2-hydroxyethoxymethyl)adenine (*XIa*) via the N^6-benzoyl derivative *XXXVI* and 2-bromoethoxymethyl derivative *XXXVII* (Scheme 3).



In formulae *XXIX*–*XXXIV*: *a*, n = 2 *b*, n = 4 ; A = adenin-9-yl ;
A^{Bz} = N^6-benzoyladenin-9-yl residue

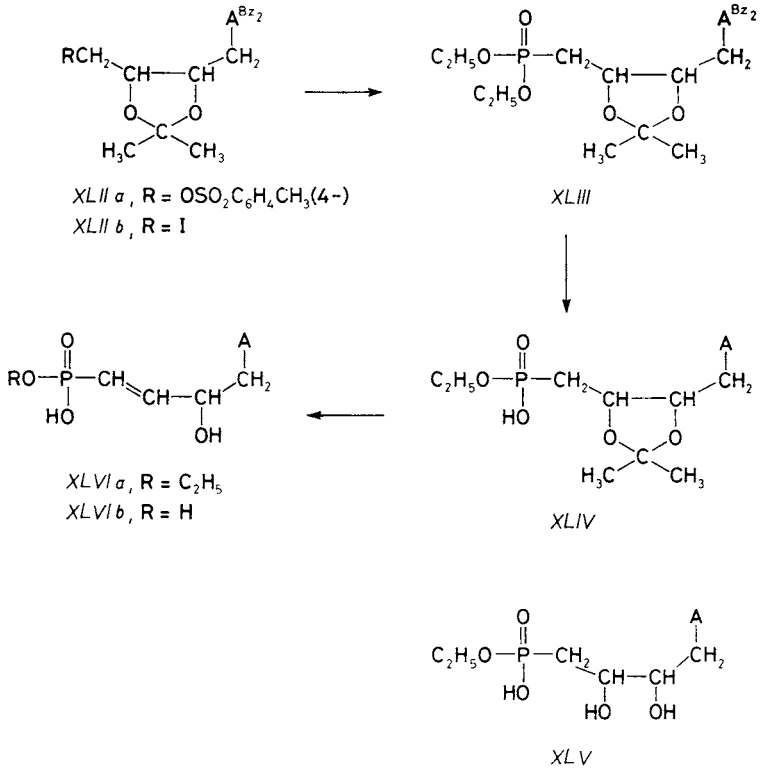
SCHEME 3

Similarly as in the phosphonylmethyl ether series, the preparation of phosphonylalkyl adenine derivatives, hydroxyl-functionalized in the alkyl chain, required a specific protection of the starting polyhydroxyalkyl compounds: the 2′,3′-O-isopropyli-



XXXV

dene derivative of compound *IXa* (ref.[10]) or *Xa* was converted into the 4'-O-*p*-toluenesulfonyl derivative *XLIIa* which on subsequent reaction with sodium iodide in the presence of 15-crown-5 furnished the corresponding iodoalkyladenine derivative *XLIIb*. This compound was treated with triethyl phosphite and the obtained diethyl ester *XLIII* was alkali-hydrolyzed to give the monoester *XLIV*. However, acid hydrolysis of the protecting isopropylidene functionality led solely to the unsaturated derivative *XLVIa* instead of the expected *XLV*. Reaction of bromotri-



XLII a, R = $OSO_2C_6H_4CH_3(4-)$
XLII b, R = I

XLIII

XLIV

XLVI a, R = C_2H_5
XLVI b, R = H

XLV

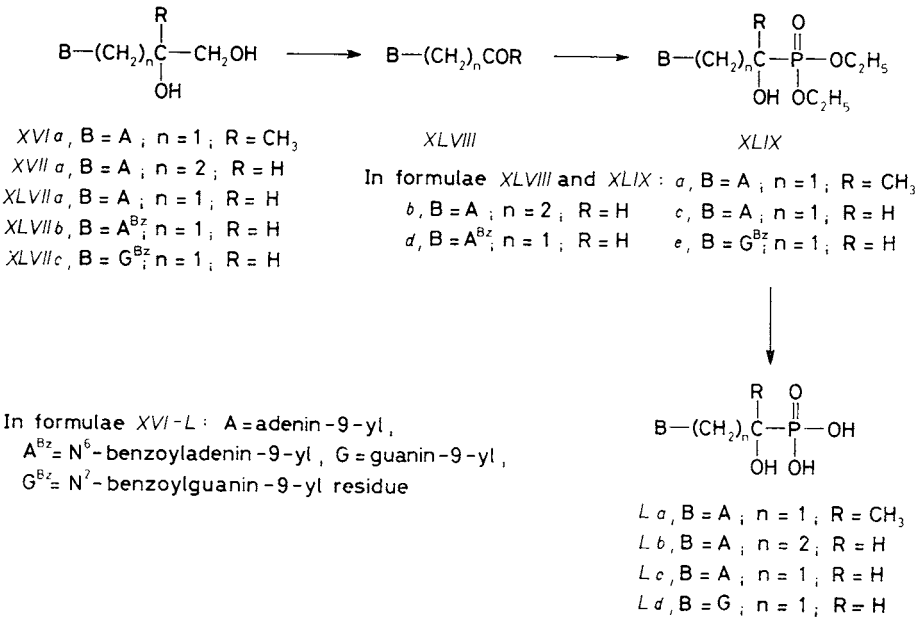
In formulae *XLII*–*XLVI* : A = adenin-9-yl ; A^{Bz_2} = N^1,N^6-dibenzoyl-adenin-9-yl residue

SCHEME 4

methylsilane with the ester *XLVIa* gave 9-(4-phosphonyl-2-hydroxy-3-buten-1-yl)-adenine (*XLVIb*), shown by NMR spectroscopy to be pure *trans*-isomer (Scheme 4).

Phosphonylalkyl derivatives with hydroxyl in α-position to the phosphonate group were prepared relatively easily by reaction of diethyl phosphite with oxoalkyl derivatives in the presence of a base, e.g. triethylamine[18]. This reaction was successfully used in preparation of the corresponding adenine and guanine derivatives. The required 9-oxoalkyl compounds *XLVIII* were obtained by oxidation of vicinal 9-(dihydroxyalkyl) derivatives *XVIa*, *XVIIa* and *XLVII* with sodium periodate. Thus, 9-(2,3-dihydroxypropyl)adenine (*XLVIIa*) and its N-benzoyl derivative *XLVIIb* afforded the respective adenin-9-ylethanals *XLVIIIc* and *XLVIIId* (see ref.[19]), reaction of 9-(3,4-dihydroxybutyl)adenine[7] (*XVIIa*) gave 3-(adenin-9-yl)propanal *XLVIIIb*, and 9-(1,2-dihydroxy-2-methyl-3-propyl)adenine (*XVIa*) was converted into 9-(2-oxopropyl)adenine (*XLVIIIa*). The guanine derivative *XLVIIIe* was obtained analogously as compound *XLVIIId* by oxidation of 9-(2,3-dihydroxypropyl)-N^2-benzoylguanine (*XLVIIc*). The prepared oxo compounds were isolated in the pure state after deionization and have been shown by NMR spectroscopy to form stable hydrates.

The reaction with diethyl phosphite took place both with aldehyde (*XLVIIIb* to *XLVIIIe*) and keto (*XLVIIIa*) derivatives. The corresponding diesters *XLIX*, isolated by chromatography, were treated with a halogenotrimethylsilane to give 9-(ω-phosphonyl-ω-hydroxyalkyl) derivatives of adenine (*La*–*Lc*) and guanine (*Ld*).



SCHEME 5

Alkaline hydrolysis of compound *XLIXc* led to ethyl ester of acid *Lc* (compound *LI*); obviously, the α-hydroxyphosphonate grouping in compounds *XLIX* is stable towards alkaline hydrolysis (except cleavage of the ester bond) (Scheme 5).

All the obtained derivatives of phosphonic acids were purified to HPLC homogeneity. In most cases they were isolated as the free acids with correct analytical data. Also their electrophoretic mobilities in a weakly alkaline medium did not differ markedly from those of compounds *I* and their ultraviolet spectra showed parameters of 9-substituted derivatives of the corresponding heterocyclic base.

The NMR spectra of the studied compounds exhibit singlets of H-2 and H-8 protons in the base at δ 8·00–8·40 and δ 8·40–8·75, respectively (for the N-benzoyl derivatives). Of the side-chain protons, the signals of H-1′ appear at the lowest field. The spectra of phosphonylmethoxyalkyl derivatives (Tables I and II) show that the

TABLE I

Proton NMR parameters of acyclic nucleosides and their N^6-benzoyl derivatives (in hexadeuterodimethyl sulfoxide)

Compound	Chemical shifts (δ)						*J* (Hz)			Further parameters
	H-2	H-8	H-1′	H-2′	H-3′	OH	1′,2′	2′,3′	H, OH	
Va[a]	8·46	8·72	4·35	2·02	3·44	4·64	7·2	6·0	5·3	
Vd[a]	8·49	8·73	4·30	1·92	1·42	4·44	7·0	[b]	5·2	3·44 t, 2 H, H–H′ $J(3',4') = 6·5$
XXa	8·34	8·72	4·37 4·17	—	3·29	4·97 4·87	—	—	5·4	0·97 s 3 H, CH_3 $J(1',1') = 14·2$
XXb	8·48	8·71	4·94	3·86	3·37	4·77 5·25	5·5	6·2	5·7 5·5	1·54 d, 3 H, CH_3 $J(1', CH_3) = 7·0$
XXc	8·50	8·71	4·78	3·90	3·35	4·71 5·29	5·0	6·0	5·5 5·5	
XXXIa	8·53	8·75	4·72	4·03	—	—	6·0	—	—	
XXXIb	8·51	8·74	4·33	2·01	1·80	—	6·8	[b]	—	3·58 t, 2 H, H–H′ $J(3',4') = 6·5$
XXXVI	8·63	8·78	5·71	—	3·54	4·68	—	[b]	5·0	
XLVIIIb	8·09	8·14	4·18	2·02	4·52	6·13	7·2	5·8	7·3	
XLVIIIc	8·05	8·16	4·06	5·10	—	6·23	5·5	—	6·1	
XLVIIId	8·37	8·71	4·23	5·19	—	6·30	6·0	—	6·2	
XLVIIIe	—	7·93	4·03	5·11	—	6·28	5·0	—	6·2	

[a] N^6-Benzoyl derivative; [b] unresolved multiplet, the value of *J* cannot be estimated.

TABLE II

Proton NMR parameters of phosphonylmethoxyalkyl derivatives (in D_2O)

Compound	Chemical shifts (δ)						J (Hz)			Further parameters
	H-2	H-8	H-1′	H-2′	H-3′	*	1′,2′	2′,3′	P, H	
IIIc	8·16	8·26	4·47	3·94	3·56	3·61	5·0	3·9	9·6	J(P—CH_A, H_B) = = 12·2[b,c]
IVc	8·14	8·28	4·44	3·96	3·61 3·44	3·65	4·7	3·0 4·0	[a]	[b]
Vb	8·12	8·14	4·30	2·21	3·55	3·62	7·0	6·0	8·4	
Vc	8·15	8·16	4·31	2·12	3·54	3·47	7·0	6·0	8·9	
Vf	8·14	8·18	4·23	1·92	1·57	3·54	7·0	[a]	8·4	3·58 t, 2 H, H–H′ J(3′,4′) = 6·5
Vi	8·09	8·15	4·18	1·85	1·30	3·56	7·0	[a]	8·2	1·59 m, 2 H, H–H′ 3·55 t, 2 H, H–H5′
VIb	8·40	8·42	4·49 4·30	4·00	1·22	3·73 3·49	3·5 7·4	6·5	8·8 9·3	J(P—CH_A, H_B) = = 13·5[b]
VIc	8·13	8·26	4·36 4·23	3·97	1·09	3·55 3·43	4·0 5·2	6·4	9·3 9·3	J(P—CH_A, H_B) = = 12·4[b]
VIIc	8·17	8·20	4·56	3·74	3·55	3·51	3·5	6·8	8·8	3·79 and 3·69 dd, 2 H, H–H′, J(3′,4′) = 5·3; 3·5 J(4′,4′) = 12·0
VIII	8·44	8·44	4·57	3·82	5·08	3·78	3·5 7·5	4·5	9·6	[b]
IXb	8·37	8·42	4·54 4·43	4·14	3·91	3·75	4·8 8·0	3·5	8·6	3·74 d, 2 H, H–H′ [b] J(3′,4′) = 6·0
IXc	8·12	8·15	4·34	4·12	3·90	3·56	5·2	[a]	8·6	3·72 d, 2 H, H–H′ J(3′,4′) = 6·0
XIc	8·22	8·28	5·68	—	3·72	3·46	—	—	8·4	
XIIc	8·18	8·39	4·85	4·09	—	3·53	[a]	—	8·4	4·09 m, 2 H, 1′-CH_2
XIIIb	8·35	8·43	4·60 4·47	3·94	3·76 3·61	3·71	4·7 6·5	4·3 4·3	8·0	3·38 s, 3 H, OCH_3 [b,c]
XIIIc	8·14	8·18	4·47 4·36	3·88	3·72 3·51	3·50	4·8 7·0	3·8 4·5	8·7	3·30 s, 3 H, OCH_3 [b,c]
XVIc	8·16	8·16	4·40	—	3·55	3·55	—	—	[a]	[b] 1·06 s, 3 H, CH_3
XXIV	8·44	8·48	4·96	4·21	3·71 3·54	3·65	5·0	4·6 6·4	8·8	1·67 d, 3 H, 1′-CH_3 J(1′, CH_3) = 7·0
XXV	8·26	8·29	4·60	4·25	3·56 3·43	3·45	6·8	2·5 7·0	8·7	[c]
XXVIIIa	8·19	8·29	5·61	—	—	3·95	—	—	9·2	
XXVIIIb	8·12	8·23	5·64	—	—	3·66	—	—	9·6	

* P—CH_AH_B; [a] unresolved multiplet, the value of J cannot be estimated; [b] J(1′,1′) = 14·5 to 15·0 Hz; [c] J(3′,3′) = 11·0 Hz.

P—CH_2O methylene protons are mostly equivalent (δ 3·45–3·75). The observed splitting due to the hydrogen-phosphorus coupling is characterized by the ^2J(P, CH) coupling constants amounting to 8·2–9·6 Hz. Some of the studied derivatives contain a methyl or ethyl group bonded to the phosphorus atom. The methyl esters exhibit doublets at δ 3·40–3·60 (^3J(P, OCH) = 10·2–10·4 Hz). The methylene protons in the ethyl esters are equivalent and their signals appear as doublets of quartets at δ 3·65–4·00 with coupling constants ^3J(P, OCH) = 7·8–8·9 and ^3J(H, H) = 7·1 Hz. The methyl protons give rise to triplets at δ 1·0–1·18, ^3J(H, H) = = 7·1 Hz, split by long-range coupling with phosphorus atom, ^4J(P, OCCH) = = 0·5 Hz.

Proton NMR spectra of phosphonyl derivatives in which the phosphonic acid moiety is directly bonded to the carbon chain (Tables III and IV) display a characteristic geminal coupling constant ^2J(P, CH) = 17–18 Hz and a vicinal coupling

TABLE III

Proton NMR parameters of phosphonylalkyl derivatives of adenine (in D_2O)

Compound	Chemical shifts (δ)						J (Hz)			Further parameters
	H-2	H-8	H-1′	H-2′	H-3′	H-H′	1′,2′	2′,3′	P, H	
XXXIIa[b]	8·51	8·75	4·48	2·52	—	—	7·3	—	—	J(1′, P) = 13·4 J(2′, P) = 17·8
XXXIIb	8·52	8·75	4·31	1·96	1·46	1·79	6·8	[a]	[a]	J(4′, P) = 17·6
XXXIIIa	8·11	8·16	4·39	2·20	—	—	7·3	—	—	J(1′, P) = 14·0 J(2′, P) = 16·9
XXXIIIb	8·11	8·16	4·21	1·93	1·40–1·65		7·0	[a]	[a]	
XXXIVa	8·08	8·10	4·38	1·76	—	—	[a]	—	—	J(2′. P) = 17·6
XXXIVb	8·08	8·08	4·15	1·86	1·30–1·60		7·3	[a]	[a]	
XXXVIII	8·54	8·72	5·74	—	3·78	2·21	—	—	7·0	J(4′, P) = 18·0
XXXIX	8·17	8·26	5·62	—	3·80	1·78	—	—	8·5	J(4′. P) = 17·8
XL	8·32	8·41	4·53	—	—	—	—	—	—	J(1′, P) = 11·5
XLI	8·20	8·30	4·16	—	—	—	—	—	—	J(1′, P) = 12·7
XLVIa	8·09	8·12	4·30	4·67	6·41	5·67	5·8 5·8	5·4	17·2	J(3′, P) = 20·3[c] J(4′, P) = 18·1
XLVIb	8·08	8·12	4·36 4·16	4·55	6·24	6·01	4·2 8·5	5·7	17·8	J(3′, P) = 17·8[c] J(4′, P) = 14·5

[a] Unresolved multiplet, the value of J cannot be estimated; [b] in hexadeuterodimethyl sulfoxide; [c] J(2′,4′) = 1·4 Hz.

constant ^3J(P, CCH) = 13–14 Hz for the CH—CH—P grouping. The introduction of α-hydroxyl to the phosphorus atom in compound *LI* results in decrease of the coupling constant ^2J(P, CH) to 10 Hz and ^3J(P, CCH) to 4 Hz in accord with the known electronegative substituent effect.

In the derivative *XLVI* the phosphonic acid moiety is located in immediate vicinity of *trans*-disubstituted double bond. Whereas the geminal constants ^2J(P, CH-9) are similar to those of the above-discussed compounds (14–18 Hz), the vicinal coupling constant ^3J(P, CCH) is markedly higher (18–20 Hz) as the result of the fixed zero dihedral angle.

The presented study opens methodical approaches to many types of acyclic nucleotide analogs. Its further extension to syntheses of compounds with modified heterocyclic bases, as well as the results of structure–activity studies of the described derivatives, will be the subject of a further communication.

EXPERIMENTAL

Unless stated otherwise, the solvents were evaporated at 40°C/2 kPa and the compounds dried over phosphorus pentoxide at 13 Pa. The melting points were determined on a Kofler block and are uncorrected. Thin-layer chromatography on silica gel (Silufol UV 254, Kavalier, Votice, Czechoslovakia) was performed in the systems chloroform–methanol (v/v): S1 95 : 5, S2 9 : 1, S3 17 : 3, S4 4 : 1; chloroform–ethanol: S5 4 : 1. Column chromatography was carried out on silica gel (30–60 μm; product of Service Laboratories of this Institute). Paper electrophoresis (20 V/cm, 1 h) was done on a Whatman No 3MM paper in 0·05M-triethylammonium hydrogen

TABLE IV

Proton NMR parameters of α-hydroxyphosphonylalkyl derivatives (in D_2O)

Compound	Chemical shifts (δ)				*J* (Hz)	Further parameters	
	H-2	H-8	H-1′	H-2′	1′,2′		
XLIXc[b]	8·07	8·17	4·25–4·47		[a]		
XLIXd[b]	8·40	8·73	4·42–4·60[a]		[a]		
XLIXe	—	8·00	4·20–4·40		[a]		
La	—	7·84	3·90–4·48		[a]		
Lb	8·11	8·13	4·45	—	—	1·10 d, 3 H, HH_3	J(P, H) = 13·9
Lc	8·10	8·12	4·58	3·93	1·5	J(1′, P) = 4·3	J(2′, P) = 9·8
Ld	8·02	8·05	4·33	2·28 2·11	7·0	3·61 dq, 1 H, H-3′ J(2′,3′) = 10·0 a 13·0	J(3′, P) = 19·0
LI	8·11	8·14	4·10–4·54		4·0		

[a] Unresolved multiplet, the value of *J* cannot be estimated; [b] in hexadeuterodimethyl sulfoxide.

carbonate pH 7·5 (S6) and the electrophoretic mobilities (E_{Up}) are referred to uridine 3′-phosphate. Purity of the compounds was checked by HPLC in S6 with a gradient of methanol on a 250 × 4 mm column of Separon SGX C18 (5 μm). UV spectra were measured in aqueous solutions on a Specord UV/VIS instrument (Zeiss, Jena), NMR spectra on a Varian XL-200 spectrometer (see Tables I—IV) with tetramethylsilane as internal standard; chemical shifts δ are given in ppm, coupling constants J in Hz. Mass spectra were measured on an AEI 902 spectrometer (ion source temperature 120°C, electron energy 70 eV, direct inlet). The elemental compositions were determined at the resolution 10 000. Chromatography on DEAE-Sephadex A 25 (hydrogen carbonate form) was carried out with a linear gradient (0—0·3 mol l^{-1}) of the buffer S6 (total volume 20 times greater than the column volume), elution rate 3 ml/min, continuous detection with Uvicord (LKB, Uppsala, Sweden) at 254 nm. The UV-absorbing fractions were combined, evaporated in vacuo and the excess buffer was removed by codistillation with methanol in vacuo. Chromatography on Dowex 1X2 (acetate form) was done with a linear gradient (0—1 mol l^{-1}) of acetic acid (total volume equal to 20 column volumes) under conditions similar to those above. After evaporation in vacuo, the excess acetic acid was removed by codistillation with water. Chromatography on octadecylsilica gel (30—60 μm; prepared in the Service Laboratories of this Institute) was performed on 200 ml columns in the system S6 with increasing methanol content. Desalting was effected on a column of Dowex 50X8 (H^+ form; 10 ml of Dowex/mmol compound) by elution with water or aqueous methanol (1 : 1) until the UV absorption and conductivity of the eluate dropped to the original values. The product was then eluted with 2·5% aqueous ammonia and the eluate was taken down and processed further. The compounds were converted into their sodium and lithium salts on columns of Dowex 50X8 (Na^+ or Li^+ form) (10 ml of Dowex/mmol) compound). The salts were eluted with water, the UV-absorbing eluate was taken down in vacuo, the residue was codistilled with ethanol and the salt was precipitated with ether from methanol solution.

(*RS*)-9-(2-Hydroxy-3-octyloxypropyl)adenine (*IVa*)

A mixture of adenine (6·75 g; 50 mmol), potassium carbonate (10·00 g; 72·3 mmol), 1-octyloxy-2,3-epoxypropane[8] (10·00 g; 54 mmol) and dimethylformamide (120 ml) was stirred (reflux condenser, calcium chloride protective tube) at 140°C for 5 h. The hot mixture was filtered, the salts were washed with dimethylformamide (50 ml) and the filtrate was taken down. The residue was codistilled with toluene (3 × 50 ml), extracted with boiling chloroform (500 ml total) and the extract was washed with water (3 × 100 ml). The aqueous phase was extracted with chloroform (2 × 50 ml) and the combined chloroform extracts were dried over magnesium sulfate. After evaporation, the residue was chromatographed on a column of silica gel (300 ml) in chloroform. The product (R_F 0·60 in S4) was eluted with chloroform–methanol (98 : 2) and the solvents were evaporated in vacuo. The residue was dissolved in hot ethanol, mixed with the same volume of ether and then light petroleum was added to turbidity. The product, which crystallized on standing in a refrigerator, was collected on filter, washed with light petroleum and dried in vacuo, m.p. 141—142°C; yield 9·0 g. For $C_{16}H_{27}N_5O_2$ (321·4) calculated: 59·78% C, 8·47% H, 21·79% N; found: 59·78% C, 8·34% H, 21·63% N. Mass spectrum, *m/z*: 321 (M^+), 208 (M — C_8H_{17}),190 (208 — H_2O), 178 (base peak B + CH_2CHOH), 148 (B + CH_2), 136 (BH_2), 135 (BH).

9-(4-Hydroxybutyl)adenine (*Vd*)

4-Acetoxybutyl bromide (b.p. 92°C/2 kPa; 35·3 g; 0·18 mol) was added dropwise to a stirred suspension of adenine (13·5 g; 0·1 mol) and potassium carbonate (29 g; 0·21 mol) in dimethylformamide (150 ml). The mixture was stirred under reflux condenser (calcium chloride tube)

at 140°C for 16 h and then filtered while hot. The filtrate was taken down in vacuo, the residue was codistilled with toluene (2 × 50 ml) and extracted with boiling chloroform (3 × 250 ml). After evaporation of the solvent, the residue was chromatographed on a column of silica gel (300 g) in chloroform and the product fraction (R_F 0·25 in S2) was crystallized from ethanol–ether (1 : 2) (with light petroleum added to turbidity), affording 9·2 g (33%) of 9-(4-acetoxybutyl)adenine, m.p. 169°C. For $C_{11}H_{15}N_5O_2$ (249·3) calculated: 53·00% C, 6·07% H, 28·10% N; found: 53·32% C, 6·14% H, 28·12% N. ^{1}H NMR (hexadeuterodimethyl sulfoxide): 8·14 s, 8·15 s (2 H, H-2, H-8); 7·20 br s (2 H, NH_2); 4·17 t (2 H, 1′-CH_2, J = 7·0); 4·00 t (2 H, 4′-CH_2, J = 6·5), 1·98 s (3 H, CH_3CO), 1·85 m (2 H, 2′-CH_2), 1·53 m (2 H, 3′-CH_2).

To a solution of this compound (8·0 g; 32 mmol) in hot methanol (90 ml) was added methanolic solution of 1M-sodium methoxide (10 ml) and the mixture was set aside for 30 min. The crystalline product *Vd* was collected, washed successively with ethanol and ether and dried in vacuo; m.p. 199°C; yield 6·15 g (93%). For $C_9H_{13}N_5O$ (207·2) calculated: 52·15% C, 6·32% H, 33·80% N; found: 51·96% C, 6·44% H, 33·65% N. Mass spectrum, *m/z*: 277 (M^+), 190 (M − OH), 177, 176 (M − CH_2OH), 163, 149, 135 (BH). ^{1}H NMR (hexadeuterodimethyl sulfoxide): 8·14 s (2 H, H-2 + H-8; 7·18 bs (2 H, NH_2); 4·45 t (1 H, J = 5·2, OH); 4·15 t (2 H, 1′-CH_2, J = 7·1); 3·40 dt (2 H, 4′-CH_2, J = 6·4); 1·84 (2 H, 2′-CH_2); 1·37 m (2 H, 3′-CH_2).

9-(5-Hydroxypentyl)adenine (*Vg*)

A mixture of adenine (10·1 g; 75 mmol), sodium hydride (1·8 g; 75 mmol) and dimethylformamide (170 ml) was stirred under exclusion of moisture at 80°C for 1 h. 5-Acetoxypentyl bromide (16·4 g; 78·5 mmol) was added and the stirring at 80°C under exclusion of moisture was continued for further 20 h. After evaporation in vacuo, the residue was codistilled with toluene (2 × 50 ml) and extracted with boiling chloroform (1 000 ml). The extract was filtered, the chloroform evaporated and the residue crystallized from methanol (50 ml). The separated product was filtered, washed with ethanol, ether and dried in vacuo, affording 7·5 g of 9-(5-acetoxypentyl)-adenine, m.p. 154°C, R_F 0·50 (S3). Chromatography of the mother liquor on silica gel gave further 2·8 g of the same product (total yield 52%). For $C_{12}H_{17}N_5O_2$ (263·3) calculated: 54·73% C, 6·51% H, 26·60% N; found: 55·06% C, 6·43% H, 26·70% N. ^{1}H NMR (hexadeuterodimethyl sulfoxide): 8·14 s (2 H, H-2 + H-8); 7·22 brs (NH_2); 4·13 t (2 H, 1′-CH_2, J = 7·0); 3·9 t (2 H, 3′-CH_2, J = 6·6); 1·96 s (3 H, CH_3CO); 1·82 br pen (2 H, 2′-CH_2); 1·08 br pent (2 H, 4′-CH_2).

A solution of the obtained compound (7· 0 g; 28· mmol) in 0·05M-methanolic sodium methoxide (100 ml) was briefly boiled and allowed to stand in a refrigerator overnight. The crystalline product was collected, washed with ethanol and ether and dried, affording 5·2 g (23·5 mmol, 82·5%) of *Vg*, m.p. 203–204°C. For $C_{10}H_{15}N_5O$ (221·3) calculated: 54·28% C, 6·83% H, 31·66% N; found: 54·32% C, 7·02% H, 31·78% N. Mass spectrum, *m/z*: 221 (M^+), 204 (M − OH), 190 (M − C_2OH), 163 (B + C_2H_5), 148 (B + CH_2), 135 (BH).

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

Adenine (27 g; 0·2 mol) was added to a suspension of sodium hydride (4·8 g; 0·2 mol) in dimethylformamide (600 ml) and the mixture was stirred at 100°C for 1 h under exclusion of moisture. 5-*p*-Toluenesulfonyloxy-1,3-dioxane (51·6 g; 0·2 mol) was added and the mixture was stirred at 140°C for 16 h under reflux condenser (calcium chloride tube). After evaporation in vacuo and codistillation with toluene (2 × 200 ml), the residue was extracted with boiling chloroform (3 × 500 ml), filtered and the solvent was evaporated in vacuo. Chromatography on silica gel (300 g) in chloroform–methanol (95 : 5) afforded 10·1 g (23%) of 5-(adenin-9-yl)-

-1,3-dioxane, m.p. 219–220°C. For $C_9H_{11}N_5O_2$ (221·2) calculated: 48·86% C, 5·01% H, 31·66% N; found: 49·02% C, 5·14% H, 31·94% N. Mass spectrum, *m/z*: 221 (M^+), 192(M – CHO), 176, 162, 148 (B + CH_2); 135 (BH).

A solution of the above-obtained compound (10·0 g; 45 mmol) in 2M-HCl (400 ml) was refluxed for 8 h. After evaporation in vacuo, the residue was codistilled with water (3 × 50 ml), dissolved in water (50 ml) and chromatographed on a column of Dowex 50X8 (H^+ form; 300 ml). The column was washed with water until the UV absorption and acid reaction of the eluate dropped and then the product was eluted with dilute (1 : 10) aqueous ammonia. The UV-absorbing ammonia eluate was taken down in vacuo and the residue in water was filtered through a column (90 ml) of octadecylsilica gel. The UV-absorbing eluate was taken down in vacuo and the residue was crystallized from ethanol (with ether added to turbidity), affording 5·7 g (59%) of *XIIa*, m.p. 177°C. For $C_8H_{11}N_5O_2$ (209·2) calculated: 45·92% C, 5·30% H, 33·48% N; found: 46·06% C, 5·28% H, 33·65% N. Mass spectrum, *m/z*: 209 (M^+), 192 (M – OH), 179 (M – CH_2O), 178 (M – CH_2OH), 169 (179 – OH), 161 (M – CH_2O – H_2O), 149 (B + CH_3), 135 (BH). ^{1}H NMR (hexadeuterodimethyl sulfoxide): 8·12 s (H-8); 8·10 s (H-2); 7·18 brs (2H, NH_2); 5·06 br (2 H, OH); 4·52 br pent (1 H, N—CH, J = 5·9); 3·83 dd (4 H, OCH_2).

N^6-Dimethylaminomethylene derivatives of compounds IIIa, IVa, Vg, VIa, VIIa (*3',4'-O-isopropylidene derivative*), IXa (*2',3'-O-isopropylidene derivative*), Xa (*2',3'-O-isopropylidene derivative*), XIIa, XIIIa *and* XVIa–XVIIIa were prepared by reaction of dimethylformamide dimethylacetal with the corresponding nucleosides[6,7,10,15,20,21] in dimethylformamide according to the described method[9]. The thus-obtained compounds were used further without any purification.

N^6-Benzoyl derivatives XXa–XXc, XXXa, XXXb, XXXVI, XLVIIb, XLVIIc *and the N^6-benzoyl derivative of* Va were obtained from 5 mmol of *XVIa*, *XIXa* (ref.[19]), *XIXb* (ref.[19]), *XXIXa*, *XXIXb*, *XIa*, *XLVIIa*, 9-(2,3-dihydroxypropyl)guanine[22] or *Va* by successive treatment with chlorotrimethylsilane and benzoyl chloride in pyridine as described in ref.[16]. The compounds were isolated by chromatography on silica gel in methanol–chloroform. Yields, % (R_F in S1): *XXa* 86 (0·47), *XXb* 48 (0·48), *XXc* 37 (0·68), *XXXa* 80 (0·45), *XXXb* 74 (0·55), *XXXVI* 60 (0·43), *XLVIIb* 84 (0·40), *XLVIIc* 65 (0·38) and N^6-benzoyl derivative of *Va* 82 (0·50).

O-Dimethoxytrityl derivatives XXI were prepared from compounds *XX* by treatment with chlorodi(4-methoxyphenyl)phenylmethane (1·2 equivalents) in pyridine (10 ml/mmol) at room temperature for 16 h. After dilution with the same amount of saturated sodium hydrogen carbonate solution, the reaction mixture was extracted with chloroform, the organic layer washed with water and the solvent evaporated in vacuo together with some toluene. The dimethoxytrityl derivatives were chromatographed on silica gel in chloroform–benzene (1 : 1), containing 0·1% of triethylamine. The product fractions were evaporated and the obtained material was used directly in further reactions. Yields, % (R_F in S1): *XXIa* 40 (0·70), *XXIb* 95 (0·70), *XXIc* 85 (0·45 in chloroform).

Removal of Ester Groups in the Phosphonate Derivatives (General Procedure)

A) Iodotrimethylsilane (5–7 equivalents) was added at 0°C to a solution of the monoester (free acid or triethylammonium salt) or the diester in dimethylformamide (10 ml/mmol). After standing at room temperature for 16 h, the homogeneous solution was diluted with 2M-triethylammonium hydrogen carbonate (pH 7·5), briefly boiled and set aside for 20 min. After evaporation, the residue was deionized on Dowex 50 (H^+ form). The free phosphonates were finally purified on Dowex 1X2 (acetate form) or on DEAE-Sephadex A25.

B) The ester functionality was cleaved with bromotrimethylsilane in acetonitrile under conditions described under *A*. After standing at room temperature, the solution was taken down, the residue was twice codistilled with acetonitrile, dissolved in 10% triethylamine in 50% aqueous acetonitrile and allowed to stand at room temperature for 1 h. After evaporation, the further processing was the same as described in procedure *A*.

Preparation of Esters of 9-Phosphonylmethoxyalkyladenines by Reaction with Dimethyl 4-Toluenesulfonyloxymethanephosphonate (*II*)

Sodium hydride (2 mol. equivalents) was added under vigorous stirring to a solution of N^6-dimethylaminomethylene derivative of *III*, *IVa*, *Vg*, *VIa*, *VIIa* (3',4'-O-isopropylidene derivative), *IXa* (2',3'-O-isopropylidene derivative), *Xa* (2',3'-O-isopropylidene derivative), *XIIa*, *XIIIa*, benzoyl derivative *XXXb*, *XXXVI*, or N^6-benzoyl derivative of *Va* in dimethylformamide (10 ml/mmol). After vigorous stirring for 20—40 min, compound *II* (1 equivalent) was added. The mixture was stirred at room temperature for 48—72 h, diluted with the same volume of 2M-NaOH and the homogeneous solution was heated to 50°C for 5 h. The solution was neutralized with Dowex 50 (H^+ form) and the suspension was poured on a column of the same resin (10 ml/mmol). The column was washed with water (50% aqueous methanol in case of N-benzoyl derivatives to speed up the elution of benzoic acid) to disappearance of UV absorption and the crude monomethyl esters *IIIb*—*VIb* and *XIb*—*XIIIb* were eluted with 5% aqueous ammonia (in case of *IVb* and *Vh* with ammonia in 50% aqueous methanol). Prior to deionization, the isopropylidene derivatives of compounds *VIIb*, *IXb* and *Xb* were deblocked by treatment with 0·1M-H_2SO_4 (20 ml/mmol) at room temperature for 16 h.

This method was used for preparation of monomethyl esters *Vb*, *VIb*, *IXb*, *Xb* and *XIIIb* which were then purified on Dowex 1X2 (acetate form) and isolated as the free acids. Yields: *Vb* 31%, *VIb* 23%, *IXb* 60%, *Xb* 55% and *XIIIb* 43%. The esters *IIIb*, *IVb*, *Ve*, *Vh*, *VIIb*, *XIb* and *XIIb*, also prepared in this manner, were used further without purification.

Preparation of 9-Phosphonylmethoxyalkyladenines from Monoalkyl Esters

A) The ester functionality in monoesters *IIIb*—*VIb* and *XIb*—*XIIIb* was split with iodo- or bromotrimethylsilane according to the above-described general method.

B) Monoesters *VIIb*, *IXb* and *Xb* were first heated to 90°C with 1M-LiOH (20 ml/mmol) for 10 h and the formed free phosphonates *VIIc*, *IXc* and *Xc* were deionized on Dowex 50 (H^+ form).

C) Phosphonates *IIIc*, *Vc*, *Vf*, *VIc*, *VIIc*, *IXc*—*XIIc*, prepared as described under *A*) and *B*), were purified on Dowex 1X2 (acetate form) and isolated as the free acids in the following yields: *IIIc* 51%, *Vc* 80%, *Vf* 30%, *VIc* 88%, *VIIc* 48%, *IXc* 87%, *Xc* 82%, *XIc* 23%, *XIIc* 9% and *XIIIc* 85%. The phosphonates *IVc* and *Vi*, prepared from esters *IVb* and *Vh*, were chromatographed on a column of octadecylsilica gel and converted into the sodium salts on a column of Dowex 50 (Na^+ form) in 50% aqueous methanol. Yields 27% of *IVc* and 8% of *Vi*.

3-(Adenin-9-yl)-2-phosphonylmethoxypropanal (*VIII*)

A solution of compound *VIIc* (200 mg; 0·6 mmol) and sodium periodate (214 mg; 1 mmol) in water (7·5 ml) was allowed to stand at room temperature for 10 min. The product *VIII* was chromatographed on Dowex 1X2 (acetate form) and isolated at the free acid in 55% yield.

Preparation of 9-Phosphonylmethoxyalkyladenines by Reaction with Chloromethanephosphonyl Dichloride (*XIV*)

A) A solution of the reagent, prepared by partial hydrolysis of compound *XIV* (3 equivalents) in pyridine[14], was added to dried N^6-dimethylaminomethylene derivative of *XVIa*—*XVIIIa*. After standing at room temperature for 30 min, the reaction mixture was diluted with the same volume of 2M-triethylammonium hydrogen carbonate, pH 7·5, and then taken down in vacuo. The residue was heated to 70°C with 2M-NaOH (20 ml/mmol) for 10 h and the mixture was deionized on Dowex 50 (H^+ form). The obtained compounds *XVIc*—*XVIIIc* were purified on Dowex 1X2 (acetate form) and isolated as the free acids (vide supra). The described procedure was applied to preparation of *XVIc* (63%), *XVIIc* (67%), (2*S*,3*S*)-*XVIIIc* (62%) and (*RS*)-*XVIIIc* (80%). Isomeric composition (%): *XVIc* (25·4, 74·6), *XVIIc* (72·6, 27·4), and *XVIIIc* (26·7, 73·3).

B) Dimethoxytrityl derivatives *XXIa*—*XXIc* were phosphorylated as described under *A*). After standing at room temperature for 30 min, the reaction mixture was cooled in an ice bath, diluted with the same volume of 2M-triethylammonium hydrogen carbonate pH 7·5 and allowed to stand in an ice bath for 10 min. The formed chloromethanephosphonyl esters *XXIIa*—*XXIIc* were taken up in chloroform (3 × 50 ml/mmol). The organic layer was washed with water and the solvent was evaporated with addition of toluene and a little triethylamine. The solid residue was detritylated in a mixture trifluoroacetic acid–methanol–chloroform (3 : 17 : 30; 50 ml/mmol) at room temperature for 10 min, the mixture was made alkaline with triethylamine and taken down with addition of some dioxane. To remove side products of the detritylation, the solid residue was extracted with ether–light petroleum (1 : 1) (in case of *XXIIIc*) or from the aqueous solution with ether (*XXIIIa* and *XXIIIb*).

The thus-prepared chloromethanephosphonyl esters *XXIIIa*—*XXIIIc* were heated with 2M-NaOH (20 ml/mmol) to 75°C for 10 h. The crude phosphonylmethyl ethers *XVIc* (3′-isomer) and *XXIV* were deionized on Dowex 50 (H^+ form), purified on Dowex 1X2 (acetate form) and isolated in the form of free acids. Yield 20% and 23% for *XVIc* (3′-isomer) and *XXIV*, respectively.

In case of compound *XXIIIc*, the alkaline reaction mixture was neutralized by stirring with solid Dowex 50 (pyridinium form) for 10 min. The suspension was filtered and the resin washed with 50% aqueous pyridine. The combined filtrates were taken down with triethylamine and the residue was freed of pyridine by codistillation with dioxane. Compound *XXV* was purified by chromatography on a column of octadecylsilica gel and isolated as the sodium salt; yield 16%.

9-(Diethoxyphosphonylmethoxymethyl)adenine (*XXVIIIa*) and 9-(Phosphonylmethoxymethyl)adenine (*XXVIIIb*)

Paraformaldehyde (0·35 g; 12 mmol) and finely ground anhydrous calcium chloride (4 g) were added to a solution of diethyl hydroxymethanephosphonate[17] (*XX5I*; 2 g; 12 mmol) in 1,2-dichloroethane (30 ml). The vigorously stirred mixture was saturated at 0°C with dry hydrogen chloride. After 4 h the suspension was filtered under exclusion of moisture, the solids were washed with dry benzene and the combined filtrates were taken down in vacuo. The oily residue of compound *XXVII* was twice codistilled with benzene and used in the further reaction.

Compound *XXVII* was dissolved in dimethylformamide (10 ml) and added to a stirred suspension of sodium salt of adenine (10 mmol; prepared in situ from adenine and sodium hydride) in dimethylformamide (50 ml). After standing at room temperature for 1 h, the mixture was heated to 50°C for 10 h, neutralized with acetic acid and the solvent was evaporated in vacuo. The solid residue was dissolved in ethanol, adsorbed on silica gel (25 g), codistilled with toluene

in vacuo, suspended in chloroform (200 ml) and applied onto a column of silica gel equilibrated with chloroform. The diester *XXVIIIa* was eluted with methanol–chloroform (5 : 95); yield 10% (R_F 0·45 in S5).

This product was further processed by treatment with bromotrimethylsilane (vide supra) and the compound *XXVIIIb* was isolated on Dowex 1X2 (acetate form) and converted into the sodium salt. Yield of the sodium salt 90%.

9-(2-Bromoethyl)-N^6-benzoyladenine (*XXXIa*),
9-(4-Bromobutyl)-N^6-benzoyladenine (*XXXIb*) and
9-(2-Bromoethoxymethyl)-N^6-benzoyladenine (*XXXVII*)

Tetrabromomethane followed by triphenylphosphine (1·2 equivalents each) was added to a refluxing solution of *XXXa* (5 mmol), *XXXb* (3 mmol) or *XXXVI* (15 mmol) in dioxane (30 ml/mmol), the mixture was boiled for three hours and then further amount of the two above-mentioned reagents (0·3 equivalent of each) was added. After reflux for 1 h the mixture was cooled, filtered through Celite and the solution was taken down in vacuo. The obtained products were isolated by chromatography on silica gel in chloroform–ethanol (99 : 1); yield of the compounds in % (R_F in S5): *XXXIa* 66 (0·55), *XXXIb* 87 (0·70), *XXXVII* 36 (0·50). Elemental analyses: *XXXIa*: For $C_{14}H_{12}BrN_5O$ (346·3) calculated: 48·57% C, 3·49% H, 23·08% Br, 20·23% N; found: 48·30% C, 3·47% H, 23·59% Br, 20·19% N. *XXXIb*: For $C_{16}H_{16}BrN_5O$ (374·3) calculated: 51·35% C, 4·31% H, 21·35% Br, 18·71% N; found: 51·19% C, 4·38% H, 21·65% Br, 18·76% N. *XXXVII*: For $C_{15}H_{14}BrN_5O_2$ (376·3) calculated: 47·89% C, 3·75% H, 21·24% Br, 18·62% N; found: 48·12% C, 3·80% H, 21·60% Br, 18·80% H.

9-(2-Diethoxyphosphonylethyl)-N^6-benzoyladenine (*XXXIIa*),
9-(4-Diethoxyphosphonylbutyl)-N^6-benzoyladenine (*XXXIIb*) and
9-(2-Diethoxyphosphonylethoxymethyl)-N^6-benzoyladenine (*XXXVIII*)

A solution of the bromo derivatives *XXXIa*, *XXXIb* or *XXXVII* in triethyl phosphite (10 to 20 ml/mmol) was stirred at 125°C for 20 h with exclusion of moisture. After distilling off the phosphite in vacuo the oily residue was chromatographed on silica gel in chloroform–ethanol (stepwise gradient up to 10% ethanol). Yield in % (R_F in S5): *XXXIIa* 36 (0·50) *XXXIIb* 42 (0·65) and *XXXVIII* 37 (0·45).

9-(2-Ethoxyphosphonylethyl)adenine (*XXXIIIa*) and
9-(4-Ethoxyphosphonylbutyl)adenine (*XXXIIIb*)

Diethyl ester *XXXIIa* or *XXXIIb* was stirred with 1M-NaOH (20 ml/mmol) at 40°C to dissolution (about 2 h) and the solution was set aside at this temperature for 16 h. The products were desalted on Dowex 50 (H^+ form), purified on Dowex 1X2 (acetate form) and isolated as the free acids in 90% and 86% yield for *XXXIIIa* and *XXXIIIb*, respectively.

9-(Methoxyphosphonylmethyl)adenine (*XL*)

The reagent *II* (2 mmol) was added to a solution of sodium salt of adenine (2 mmol) in dimethylformamide (20 ml). After heating to 60°C for 20 h the solution was diluted with aqueous sodium hydroxide (2 mol l^{-1}; 20 ml) and kept at 40°C for 16 h. The reaction mixture was desalted on Dowex 50 (H^+ form). The ester *XL* was obtained by chromatography on Dowex 1X2 (acetate form) in 31% yield (free acid).

2′,3′-O-Isopropylidene-*threo*-9-(4-iodo-2,3-dihydroxybutyl)-N^1,N^6-dibenzoyladenines (*XLIIb*)

4-Dimethylaminopyridine (0·1 g) was added to a solution of 2′ 3′-O-isopropylidene-threo-9-(4-*p*--toluenesulfonyloxy-2 3-dihydroxybutyl)adenine[10] (6·0 g; 14 mmol) in pyridine (50 ml). The mixture was cooled in ice and benzoyl chloride, (4 ml; 34·5 mmol) was added under stirring. After stirring at 0°C for 1 h and at room temperature for 20 h ethanol (5 ml) was added and the mixture was taken down in vacuo. The residue was codistilled with toluene (3 × 50 ml) and purified by chromatography on silica gel (200 ml) in chloroform. Crystallization of the product (R_F 0·70 in S1) from ethyl acetate–light petroleum afforded 5·8 g (64%) of (D-*threo*)-*XLIIa*, m.p. 209°C. For $C_{33}H_{31}N_5O_7S$ (641·7) calculated: 61·76% C, 4·74% H, 10·92% N, 5·00% S; found: 61·62% C, 4·74% H, 10·64% N, 4·89% S.

Analogous procedure was used in the preparation of (L-*threo*)-*XLIIa*, m.p. 211—213°C, identical in S1 with the D-*threo*-enantiomer; yield 86·5%.

A stirred mixture of (D-*threo*)-*XLIIa* (5·6 g; 8·7 mmol), sodium iodide (7·1 g), 15-crown-5 (0·3 ml) and benzene (350 ml) was refluxed for 16 h. The reaction was almost quantitative. The mixture was washed with water (3 × 50 ml), the organic phase dried over magnesium sulfate and the solvent evaporated in vacuo. The residue was chromatographed on a column of silica gel (200 ml) in chloroform. The product fraction was taken down and the residue crystallized from ethyl acetate–light petroleum, yielding 4·2 g (80·8%) of (D-*threo*)-*XLIIb*, m.p. 168°C. For $C_{26}H_{24}IN_5O_4$ (597·4) calculated: 52·72% C, 4·05% H, 21·24% I, 11·73% N; found: 52·18% C, 3·98% H, 21·05% I, 11·60% N.

Analogously was prepared (L-*threo*)-*XLIIb* (79%), m.p. 162°C, identical in S1 with the D-*threo*--enantiomer.

^{1}H NMR ($CDCl_3$): 1·24 s and 1·43 s, 6 H (isopropylidene); 3·29 dd and 3·36 dd (4′-CH_2, J(4′, 3′) = 4·8, J(4′, 4″) = −10·6, J(4″, 3′) = 6·2; 4·19 dq (2′-CH, J(2′, 3′) = 7·5); 4·45 dd and 4·61 dd (1′-CH_2, J(1′, 2′) = 3·4, J(1″, 2′) = 5·4, J(1′, 1″) = −14·6); 8·20 s, 1 H (2-H); 8·68 s, 1 H (8-H); 7·80—7·90 m and 7·25—7·50 m, 8 H (arom. protons).

9-(*Z*)-(4-Ethoxyphosphonyl-2(*S*)-hydroxy-3-buten-1-yl)adenine (*XLVIa*) and
9-(*Z*)-(4-Ethoxyphosphonyl-2(*R*)-hydroxy-3-buten-1-yl)adenine (*XLVIa*)

The iodo derivatives (D-*threo*)-*XLIIb* or (L-*threo*)-*XLIIb* were converted into diesters *XLIII* by reaction with triethyl phosphite as described for compounds *XXXII* and *XXXVIII*. After removal of triethyl phosphite by distillation in vacuo, the residue was stirred with 1M-NaOH (20 ml/mmol) at 60°C for 5 h and the homogeneous solution was neutralized with Dowex 50 (H^+ form). The suspension was made alkaline with aqueous ammonia, filtered, the ion exchanger was washed with 0·1% aqueous ammonia and the combined filtrates were taken down in vacuo. The residue was dissolved in 0·1M-H_2SO_4 and after standing at room temperature for 10 h the product was deionized on a column of Dowex 50 (H^+ form). Chromatography on Dowex 1X2 (acetate form) afforded esters *XLVIa* (free acids) in the yields of 20% and 32% (2*S*- and 2*R*-enantiomer, respectively).

9-(2-Phosphonylethyl)adenine (*XXXIVa*)

A solution of disodium 2-chloroethanephosphonate[23] (25 mmol) in dimethylformamide (50 ml) was added to a stirred suspension of sodium salt of adenine (25 mmol) in dimethylformamide (100 ml) (vide supra) under exclusion of moisture. After stirring at 100°C for 24 h, the homogeneous solution was taken down in vacuo, the residue was dissolved in water (100 ml) and the

formed suspension was filtered through Celite. The filtrate was applied onto a column of Dowex 50 (H^+ form; 200 ml) and, after washing with water to loss of conductivity, the product was eluted with dilute aqueous ammonia. The eluate was concentrated in vacuo to a small volume and the separated adenine was removed by filtration through Celite. Chromatography on DEAE--Sephadex A25, followed by chromatography on Dowex 1X2, afforded homogeneous *XXXIVa* in a yield of 5·4% (free acid).

9-(2-Phosphonylethyl)adenine (*XXXIVa*), 9-(4-Phosphonylbutyl)adenine (*XXXIVb*), 9-(2-Phosphonylethoxymethyl)adenine (*XXXIX*), 9-Phosphonylmethyladenine (*XLI*) and 9-(*Z*)-(4-Phosphonyl-2(*S*)-hydroxy-3-buten-1-yl)adenine (*XLVIb*)

The ester groups in compounds *XXXIIIa*, *XXXIIIb* and (2*S*)-*XLVIa* were cleaved with iodotrimethylsilane in dimethylformamide, in case of compound *XXXVIII* with bromotrimethylsilane in acetonitrile, according to the general procedure described above. Compound *XXXVIII* was cleaved and after processing the product was debenzoylated in concentrated aqueous ammonia (30 h at 40°C; 50 ml/mmol) to give *XXXIX*. The phosphonates *XXXIVa*, *XXXIVb*, *XXXIX*, *XLI* and *XLVIb* were purified by chromatography on Dowex 1X2 (acetate form) and isolated as the free acids in the respective yields of 90%, 92%, 79%, 65% and 90%.

9-(2-Oxopropyl)adenine (*XLVIIIa*) and 3-(Adenin-9-yl)propanal (*XLVIIIb*)

A solution of *XVIa* (3 mmol) or *XVIIa* (10 mmol) and sodium periodate (1·2 equivalents) in water (30 ml/mmol) was stirred at room temperature for 5 h (the transformation of *XVIIa* into the aldehyde *XLVIIIb* was, however, not quantitative even when excess sodium periodate and prolonged reaction time were used). The reaction mixture was concentrated in vacuo and the homogeneous solution was applied onto a column of Dowex 1X2 (acetate form). Elution with water afforded pure keto derivative *XLVIIIa*, m.p. 243—245°C; yield 82%. For $C_8H_9N_5O$ (191·2) calculated: 50·26% C, 4·74% H, 36·63% N; found: 50·02% C, 4·96% H, 36·50% N.

Compound *XLVIIIb*, prepared in this manner, was not completely pure; the crude product was used in the reaction with diethyl phosphite without further purification.

3-(Adenin-9-yl)ethanal (*XLVIIIc*)

Compound *XLVIIa* (10 mmol) was oxidized as described for *XLVIIIa*. After stirring for 5 h, the formed suspension was concentrated in vacuo to a small volume (50 ml). The separated product was collected, washed with a small amount of ice-cold water and stirred with acetone (50 ml). Ether (100 ml) was added and the suspension was filtered after 10 minutes' stirring. The solid was washed with ether and dried over phosphorus pentoxide in vacuo. Yield 90% of monohydrate of *XLVIIIc*. For $C_7H_7N_5O.H_2O$ (195·2) calculated: 43·07% C, 4·65% H, 35·88% N; found: 42·80% C, 4·90% H, 35·79% N.

2-(N^6-Benzoyladenin-9-yl)ethanal (*XLVIIId*) and 2-(N^2-Benzoylguanin-9-yl)ethanal (*XLVIIIe*)

Compounds *XLVIIb* (5 mmol) and *XLVIIc* (1·1 mmol) were oxidized with sodium periodate (1·2 equivalents) in 50% aqueous acetone (30 ml/mmol) at room temperature for 15 h and 6 h, respectively. The processing of the reaction mixture and isolation of the products were performed in the same manner as described for *XLVIIIc*. Yield of *XLVIIId* was 96%. For $C_{14}H_{11}N_5O_2.H_2O$ (299·3) calculated: 56·18% C, 4·38% H, 23·40% N; found: 55·80% C, 4·55% H, 23·10% N. Yield of *XLVIIIe* was 90%. For $C_{14}H_{11}N_5O_3.H_2O$ (315·3) calculated: 53·33% C, 4·16% H, 22·21% N; found: 53·02% C, 4·30% H, 21·91% N.

Diethoxyphosphonyl Derivatives *XLIX*

Triethylamine (0·25 ml/mmol) was added to a suspension of *XLVIIIa* (0·8 mmol), *XLVIIIb* (4·7 mmol), *XLVIIIc* (4 mmol), *XLVIIId* (4 mmol) or *XLVIIIe* (0·82 mmol) in diethyl phosphite (5 ml/mmol) and the mixture was kept at 75°C to homogeneity. After standing for 16 h at room temperature, the diethyl phosphite was distilled off in vacuo, the residue was dissolved in ethanol and precipitated with excess of ether. The solid was filtered, washed successively with ethanol–ether (1 : 9) and ether, and dried in vacuo over phosphorus pentoxide.

The crude amorphous diesters *XLIX* were chromatographed on silica gel in ethanol–chloroform (5 : 95). Yield of the product in % (R_F in S_5): *XLIXa* 75 (0·40), for $C_{12}H_{20}N_5O_4P$ (329·4) calculated: 21·27% N, 9·41% P; found: 20·98% N, 9·60% P. *XLIXb* 40 (0·42), for $C_{12}H_{20}N_5O_4P$ (329·4) calculated: 21·27% N, 9·41% P; found: 21·05% N, 9·57% P. *XLIXc* 98 (0·38), for $C_{11}H_{18}N_5O_4P$ (315·3) calculated: 22·22% N, 9·82% P; found: 22·40% N, 9·75% P. *XLIXd* 93 (0·53), for $C_{18}H_{22}N_5O_5P$ (419·5) calculated: 16·70% N, 7·39% P; found: 16·82% N, 7·58% P. *XLIXe* 84 (0·49), for $C_{18}H_{22}N_5O_6P$ (435·5) calculated: 16·09% N, 7·11% P; found: 15·98% N, 7·45% P.

9-(2-Ethoxyphosphonyl-2-hydroxyethyl)adenine (*LI*)

A solution of diester *XLIXc* (230 mg; 1 mmol) in aqueous 2M-sodium hydroxide (10 ml) was allowed to stand at room temperature for 72 h and neutralized with Dowex 50 (H^+ form). The suspension was made alkaline with aqueous ammonia and filtered. The ion exchanger was washed with 0·1% aqueous ammonia and the combined filtrates were taken down in vacuo. The product *LI* was purified on Dowex 1X2 (acetate form) and isolated as the free acid; yield 80%.

Phosphonyl Derivatives *L*

The ester groups in compounds *XLIX* were cleaved with bromotrimethylsilane according to the general method described above. In case of N-benzoyl derivatives of *Lc* and *Ld*, after evaporation of the reaction mixture the benzoyl groups were removed by treatment with concentrated aqueous ammonia (48 h, 40°C; 30 ml/mmol). The crude compounds *La*—*Lc* were purified on Dowex 1X2 (acetate form) and isolated as the free acids. Compound Ld was chromatographed on DEAE-Sephadex A25 and converted into the sodium salt using Dowex 50 (Na^+ form). Yield: *La* 78%, *Lb* 74%, *Lc* 80% (84% based on *XLIXd*) and *Ld* 70% (sodium salt).

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