ANALOGS OF PURINE NUCLEOSIDES AND PURINE MONO- AND POLYNUCLEOTIDES

IV.* ACYLATION OF 6-SUBSTITUTED 9-(α,ω-DIHYDROXY-2-ALKYL)PURINES

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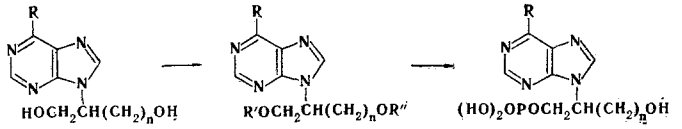
Selective protection of the amino and one of the hydroxyl groups of 6-substituted 9-(α,ω-dihydroxy-2-alkyl)purines was realized. A convenient method for the preparation of monophosphates was developed.

The phosphorylation of 6-substituted 9-(α,ω-dihydroxy-2-alkyl)purines with various phosphorylating agents under certain conditions leads to mixtures of mono-, cyclo-, and α,ω-diphosphates, which can be separated by means of ion-exchange resins [2]. This operation is laborious and inconvenient in a preparative respect, in connection with which we are presently attempting to achieve the specific synthesis of monophosphates of 6-substituted 9-(α,ω-dihydroxy-2-alkyl)purines. With this end in mind, we also investigated the possibility of protection of one of the two hydroxyl groups of the dihydroxyalkyl chain.

In addition, in connection with the fact that undesired reactions may occur at the exocyclic amino group of adenine derivatives during the formation of the polynucleotide chain [3], it became necessary to develop methods for the protection of this group and to obtain, respectively, protected monomers for subsequent polymerization to analogs of oligo- and polynucleotides. Purines with protected amino groups were obtained either by replacement of the chlorine atom in 6-chloro-9-(dihydroxy-2-alkyl)purines (I, II) by groupings that already include a protective group or by selective O-deacylation of N- and O-acylated derivatives of purines I and II.

In the course of an investigation of the first pathway, for example, reaction of I and II with benzylamine, we obtained 6-benzylamino-9-(1,3-dihydroxy-2-propyl)- (III) and 6-benzylamino-9-(1,4-dihydroxy-2-butyl)purine (IV). We were able to remove the benzyl group by means of sodium in liquid ammonia at −30°C.

6-Benzamido derivatives VIII were synthesized by benzoylation of 6-amino-9-(1,3-dihydroxy-2-propyl)- (V) and 6-amino-9-(1,4-dihydroxy-2-butyl)purine (VI) with benzoyl chloride and subsequent O-debenzoylation. In addition, a product of benzoylation at the NH_2 and OH groups (IX) was isolated (Table 1).



I, II, V, VI, XIV, XV — III, IV, VII–XIII, XVI–XXXIII — XXXIV–XXXVII

*See [1] for communication III.

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TABLE 1. 9-(Dihydroxylalkyl)purine Derivatives

Compound	R	R′[a]	R″[a]	n	mp, °C	R_f (system)[b]	Empirical formula	Found, %			Calculated, %			UV spectrum, λ_{max}, nm	Yield, %
								C	H	N	C	H	N		
III	$NHCH_2C_6H_5$	H	H	1	156—157	0,86 (*II*)	$C_{15}H_{17}N_5O_2$	60,0	5,8	22,1	60,1	5,7	23,4	280	50
IV	$NHCH_2C_6H_5$	H	H	2	124—126	0,89 (*II*)	$C_{16}H_{19}N_5O_2$	61,3	6,1	22,4	61,4	6,1	22,5	270	50
VII	$NHCOC_6H_5$	H	H	1	198—199	0,80 (*II*)	$C_{15}H_{15}N_5O_3$	57,3	4,9	21,7	57,5	4,5	22,3	290	30
VIII	$NHCOC_6H_5$	H	H	2	199—201	0,83 (*II*)	$C_{16}H_{17}N_5O_3$	58,9	5,2	20,8	58,7	5,2	21,4	290	40
IX	$NHCOC_6H_5$	COC_6H_5	COC_6H_5	1	172—173	0,86 (*II*)	$C_{29}H_{22}N_5O_5$	67,1	4,4	13,4	66,9	4,2	13,4	278	50
X	NH_2	$COCH_3$	$COCH_3$	1	156—157	0,92 (*I*)	$C_{12}H_{18}N_5O_4$	48,9	4,9	23,6	49,1	5,1	23,9	262	80
XI	NH_2	$COCH_3$	$COCH_3$	2	164—166	0,82 (*I*)	$C_{13}H_{17}N_5O_4$	51,1	5,6	22,8	50,8	5,6	22,8	262	97
XII	$NHCOCH_3$	H	H	1	206—208	0,87 (*I*)	$C_{10}H_{13}N_5O_3$	48,0	5,3	27,5	47,8	5,2	27,9	275	65
XIII	$NHCOCH_3$	H	H	2	217—219	0,85 (*I*)	$C_{11}H_{15}N_5O_3$	49,9	5,6	26,1	49,7	5,7	26,4	275	89
XVI	OH	$COCH_3$	$COCH_3$	1	153—154	0,87 (*I*)	$C_{12}H_{14}N_4O_5$	48,7	4,7	18,6	49,0	4,8	19,0	252	75
XVII	OH	$COCH_3$	$COCH_3$	2	150—151	0,85 (*I*)	$C_{18}H_{16}N_4O_5$	50,8	5,25	18,0	50,6	5,2	18,2	252	64
XVIII	OH	$C_7H_7SO_2$	$C_7H_7SO_2$	1	221—222	0,86 (*II*)	$C_{22}H_{22}N_4O_7S_2$	49,9	4,5	10,2	49,5	4,2	10,5	252	20
XIX	NH_2	$C_7H_7SO_2$	$C_7H_7SO_2$	1	192—195	0,83 (*II*)	$C_{22}H_{23}N_5O_6S_2$	50,9	4,45	13,5	51,0	4,4	13,5	262	40
XX	$NHCOC_6H_5$	$C_7H_7SO_2$	$C_7H_7SO_2$	1	177—179	0,93 (*II*)	$C_{29}H_{27}N_5O_7S_2 \cdot 2H_2O$	53,1	4,55	10,5	52,9	4,75	10,65	278	26
XXI	OH	$C_7H_7SO_2$	$C_7H_7SO_2$	2	122—125	0,83 (*II*)	$C_{23}H_{24}N_4O_7S_2 \cdot H_2O$	50,1	5,0	10,4	50,5	4,8	10,1	252	20
XXII	OH	H	$COC_{10}H_{15}$	1	243—245	0,79 (*I*)	$C_{19}H_{29}N_4O_4$	61,2	6,5	14,2	61,3	6,5	15,0	250	21
XXIII	OH	$COC_{10}H_{15}$	$COC_{10}H_{15}$	1	273—275	0,90 (*I*)	$C_{30}H_{38}N_4O_5$	67,0	7,1	10,2	67,4	7,2	10,5	250	15
XXIV	NH_2	$COC_{10}H_{15}$	$COC_{10}H_{15}$	1	233—236	0,90 (*I*)	$C_{30}H_{39}N_5O_4$	67,4	7,5	13,1	67,5	7,4	13,1	262	15
XXV	NH_2	$COC_{10}H_{15}$	$COC_{10}H_{15}$	2	234—236	0,90 (*I*)	$C_{31}H_{41}N_5O_4$	12,7	66,8	7,8	12,8	67,9	7,6	262	81
XXVI	OH	$COC_{10}H_{15}$	$COC_{10}H_{15}$	2	256—259	0,90 (*I*)	$C_{31}H_{40}N_4O_5 \cdot C_2H_6O$	67,5	7,5	9,9	66,6	7,8	9,4	250	38
XXVII	NH_2	H	$C(C_6H_5)_3$	1	229—231	0,89 (*II*)	$C_{27}H_{25}N_5O_2$	71,2	5,5	15,3	71,8	5,6	15,5	260	65
XXVIII	NH_2	H	$C(C_6H_5)_3$	2	212—215	0,91 (*II*)	$C_{28}H_{27}N_5O_2$	71,9	6,1	14,6	72,2	5,9	15,0	252	70
XXIX	$NHCOC_6H_5$	H	$C(C_6H_5)_3$	1	197—198	0,95 (*II*)	$C_{34}H_{29}N_5O_3$	72,8	5,3	12,4	73,5	5,3	12,6	278	74
XXX	$NHCOC_6H_5$	H	$C(C_6H_5)_3$	2	131—133	0,95 (*II*)	$C_{35}H_{31}N_5O_3$	73,5	5,6	12,3	73,8	5,5	12,3	278	66
XXXI	OH	H	$C(C_6H_5)_3$	1	256—258	0,92 (*II*)	$C_{27}H_{24}N_4O_3$	71,8	5,4	12,3	71,7	5,35	12,4	252	69
XXXII	OH	H	$C(C_6H_5)_3$	2	249—251	0,88 (*II*)	$C_{28}H_{26}N_4O_3$	71,7	5,5	11,8	72,1	5,6	12,0	252	81
XXXIII	OH	$C(C_6H_5)_3$	$C(C_6H_5)_3$	1	268—270	0,94 (*II*)	$C_{46}H_{38}N_4O_3$	79,5	5,6	8,1	79,5	5,5	8,1	254	2

[a]The formula fragments $C_7H_7SO_2$ and $COC_{10}H_{15}$ represent the tosyl and adamantylcarbonyl groupings.
[b]See the Experimental section.

The exhaustive benzoylation of V and VI at both the amino and hydroxyl groups occurs under relatively mild conditions – at room temperature in 2-3 h. Only the corresponding derivatives involving the hydroxyl groups – diacetates X and XI – were obtained under similar conditions in the acetylation of V and VI with acetic anhydride. Acetylation of the amino group occurs at higher temperatures. 6-Acetamido derivatives XII and XIII were obtained after O-deacylation.

This method for the introduction of protection for the amino group is the most promising one. The synthesis is easy to carry out, and the reaction products are stable and easily crystallized substances and are obtained in quite good yields. The benzoyl grouping can be removed in order to regenerate the free amino group with ammonium hydroxide at room temperature in a few days, whereas the acetyl group can be removed in 10 min.

The reaction of 6-hydroxy-9-(1,3-dihydroxy-2-propyl)- (XIV) and 6-hydroxy-9-(1,4-dihydroxy-2-butyl)purine (XV) with acetic anhydride in pyridine gives diacetyl derivatives of 1',3'-diacetate XVI and 1',4'-diacetate XVII.

A considerable bathochromic shift of the absorption maximum to the long-wave region is observed in the UV spectra of III, IV, VII-IX, XII, and XIII, which have a protected exocyclic amino group, whereas the maximum at 262-263 nm characteristic for 9-substituted adenines with a free amino group [4] is retained for X and XI.

6-Substituted 9-(α,ω-dihydroxy-2-alkyl)purines contain two primary hydroxyl groups, which undergo acylation with identical probabilities, but the introduction of a bulky acyl residue at the terminal hydroxyl groups could lead to selective synthesis of monofunctional compounds. With this end in mind, we investigated the reaction of dihydroxyalkyl derivatives of purine with p-toluenesulfonyl chloride, chlorocarbonyladamantane, and triphenylchloromethane. Reaction with toluenesulfonyl chloride in pyridine at room temperature gives 1',3'- and 1',4'-ditosyl derivatives XVIII (R=OH, n=1), XIX (R=NH_2, n=1), XX (R=$NHCOC_6H_5$, n=1), and XXI (R=OH, n=2).

Adamantolylation of XIV gives both mono- (XXII) and 1',3'-diacylation (XXIII) products. Primarily diadamantolyl derivatives XXIV (R=NH_2, R'=R''=$COC_{10}H_{15}$, n=1), XXV (R=NH_2, R'=R''=$COC_{10}H_{15}$, n=2), and XXVI (R=OH, R'=R''=$COC_{10}H_{15}$, n=2) are isolated from the reaction of V, VI, and XV with chlorocarbonyladamantane, although chromatographic monitoring of the solutions during the reaction also confirmed the presence of small amounts of monoacyl derivatives.

The most successful reaction proved to be that of 9-(dihydroxy-2-alkyl)purine with triphenylchloromethane in pyridine at room temperature, as a result of which primarily monotrityl esters were obtained. Under severe conditions, small amounts of the α,ω-ditrityl derivative are also formed, but they can be separated by crystallization of the chief reaction product. Selective tritylation at one hydroxyl group makes it possible to synthesize biochemically interesting monosubstituted derivatives of 9-(α,ω-dihydroxy-2-alkyl)purines as well as compounds with two different substituents.

The monophosphates of dihydroxyalkylpurines V, VI, XIV, and XV were obtained by phosphorylation of monotrityl derivatives XXVII-XXXII with β-cyanoethyl phosphate in anhydrous pyridine in the presence of dicyclohexylcarbodiimide and subsequent removal of the protective groups – trityl and β-cyanoethyl.

The structures of the synthesized compounds were proved by the PMR spectra (Table 2). The signal of the protons of the CH_2O group attached to the free ring of the alkyl chain was identified on the basis of their spin–spin coupling with the hydroxyl proton, which occurs in the monosubstituted compounds, and also by comparison with the chemical shift of 1',3'-disubstituted derivatives X, XVIII, XIX, XXIII, XXIV, and XXXIII. Acylation with acetic anhydride, p-toluenesulfonic acid, or chlorocarbonyladamantane always leads to a characteristic weak-field shift of 0.5-0.6 ppm of the signal of the OCH_2 protons. On the other hand, the introduction of a trityl group shifts the latter to strong field by 0.4-0.5 ppm.

EXPERIMENTAL

The UV spectra were obtained with a Specord UV-vis spectrophotometer. The PMR spectra of $CDCl_3$ and d_6-DMSO solutions were recorded with a Perkin–Elmer R-12A spectrometer (60 MHz) with tetramethylsilane as the internal standard. Whatmann-1 paper and the following systems were used for the chromatography: I 1 M CH_3COONH_4–ethanol (1:1) and II butyl alcohol–acetic acid–water (100:4:30); the chromatograms were developed in UV light with a UPM apparatus.

TABLE 2. Parameters of the PMR Spectra of 9-(Dihydroxylalkyl)-purine Derivatives[a]

Compound	Chemical shifts, δ, ppm								
	1′-H	2′-H	3′-H	4′-H	2-H	8-H	NH	OH	protons of the other groups
VI	3,78	4,64	2,05	3,32	7,92	7,92	7,0	3,6	
X	4,50	4,9	4,50	—	7,86	8,30	5,99	—	1,96 ($COCH_3$)
XI	4,44	4,8	2,40	3,98	7,88	8,28	6,08	—	1,96, 1,94 ($COCH_3$)
XIII	3,81	4,72	2,10	3,36	8,52	8,32	10,3	3,6	2.30 ($COCH_3$)
XIV	3,86	4,55	3,86	—	8,05	8,05	13,0	4,8	—
XV	3,82	4,68	2,08	3,35	7,90	7,90	13,0	3,5	—
XVII	4,50	4,9	2,45	4,05	7,94	8,38	13,0	—	1,99, 1,96 ($COCH_3$)
XVIII	4,41	4,96	4,41	—	7,47	7,77	12,5	—	2,37, 7,13, 7,36 ($CH_3C_6H_4$)
XIX	4,45	5,0	4,45	—	7,66	7,85	6,9	—	2,36 (CH_3), 7,10, 7,38 ($CH_3C_6H_4$)
XXII	4,40	4,7	3,86	—	7,96	8,04	12,0	5,0	1,86, 1,61 ($C_{10}H_{15}$)
XXIII	4,43	5,0	4,43	—	7,94	8,06	12,0	—	1,85, 1,63 ($C_{10}H_{15}$)
XXIV	4,49	5,0	4,49	—	8,08	8,12	7,0	—	1,88, 1,64 ($C_{10}H_{15}$)
XXVI	4,37	4,8	2,40	3,92	7,97	8,12	12,2	—	1,88, 1,63 ($C_{10}H_{15}$)
XXVII	3,40	4,7	3,90	—	8,03	8,03	7,0	3,5	7,15 (C_6H_5)
XXVIII	3,70	4,8	2,3	2,90	7,95	8,08	7,0	4,9	7,18 (C_6H_5)
XXIX	3,40	4,8	3,70	—	8,58	8,41	10,5	5,1	7,14, 7.5—8,0 (C_6H_5)
XXX	3,80	4,9	2,4	2,94	8,58	8,29	10.5	5,0	7,17, 7.5—8,0 (C_6H_5)
XXXI	3,43	4,7	3,88	—	7,91	8,02	12,0	3,5	7,20 (C_6H_5)
XXXII	3,70	4,8	2,2	2,90	7,88	7,88	13,1	4,9	7,18 (C_6H_5)
XXXIII	3,50	4,9	3,50	—	7,81	7,86	11,5	—	7,17 (C_6H_5)

[a]The spectra of X, XI, and XVII were obtained from $CDCl_3$ solutions, whereas the spectra of the remaining compounds were obtained from d_6-DMSO solutions.

6-Benzamido-9-(1,3-dihydroxy-2-propyl)purine (VII). A 3.3-ml (0.028 mole) sample of benzoyl chloride was added to a suspension of 1.23 g (0.005 mole) of V in 30 ml of dry pyridine, and the mixture was stirred at room temperature for 3 h, after which it was poured into 90 ml of water. The aqueous mixture was stirred for 15 min and extracted with chloroform (three 40-ml portions). The extract was evaporated to dryness, and the residue was dissolved in 25 ml of ethanol and 20 ml of pyridine. The solution was cooled (to no higher than 5°), 25 ml of 2 N NaOH in 25 ml of ethanol was added, and the mixture was stirred; the entire debenzoylation operation took no more than 5 min. Dowex 50 (pyridinium form) (60 ml) was added, and the solution (pH 7) was filtered rapidly. The filtrate was evaporated to 30-40 ml and cooled. Purine VII was removed by filtration and crystallized from water. The yield was 1.2 g.

6-Benzamido-9-(1,4-dihydroxy-2-butyl)purine (VIII). The reaction was carried out as in the preparation of VII starting with 1.12 g (0.05 mole) of amine VI and 3.3 ml (0.028 mole) of benzoyl chloride in 30 ml of pyridine. In order to isolate the reaction product, the solution (with pH 7) was evaporated to dryness, 100 ml of water was added to the oily residue, and the mixture was extracted with ether (two 30-ml portions). The aqueous extract was evaporated to 10-15 ml, and benzoyl derivative VIII precipitated. The yield was 0.9 g.

6-Benzamido-9-(1,3-dibenzoxy-2-propyl)purine (IX). A 3.3-ml (0.028 mole) sample of benzoyl chloride in 10 ml of pyridine was added slowly to a solution of 0.98 g (0.004 mole) of the hydrochloride of V in 50 ml of dry pyridine, and the mixture was held at room temperature for 2 h. It was then poured into 200 ml of water, and the benzoylation product was extracted with chloroform (three 50-ml portions). The solvent was evaporated, and IX was crystallized from aqueous ethanol.

6-Amino-9-(1,3-diacetoxy-2-propyl)purine (X). A suspension of 0.17 g (0.84 mmole) of V in 5 ml of pyridine and 0.56 g (8 mmole) of acetic anhydride was stirred at room temperature for 1.5 h until the solid had dissolved completely. The mixture was then evaporated to dryness, the residue was treated with chloroform (three 20-ml portions), and the chloroform solution was filtered. The chloroform was evaporated, and diacetate X was crystallized from chloroform–carbon tetrachloride to give 0.23 g of product.

6-Amino-9-(1,4-diacetoxy-2-butyl)purine (XI). This compound was obtained as in the preceding experiment from 0.9 g (0.004 mole) of VI and 1.9 ml (0.02 mole) of acetic anhydride in 20 ml of pyridine. The yield was 1.2 g.

6-Acetamido-9-(1,3-dihydroxy-2-propyl)purine (XII). A 0.2-g (0.8 mmole) sample of V and 0.75 ml (0.007 mole) of acetic anhydride were stirred in 15 ml of dry pyridine at 100° for 2 h, after which the sol-

vent was removed by distillation. The residue was dissolved in 5 ml of aqueous ethanol, and the solution was cooled to 0°. After 5 min, a mixture of 5 ml of ethanol and 15 ml of 0.2 N NaOH was added, and the mixture was allowed to stand for 5 min. The solution was then neutralized with Dowex-50 resin in the pyridinium form to pH 7, after which it was allowed to stand for 3-5 min. It was then filtered rapidly, and the filtrate was evaporated. The oily residue was crystallized from absolute ethanol. The yield was 0.13 g.

6-Acetamido-9-(1,4-dihydroxy-2-butyl)purine (XIII). This compound was obtained as in the preceding experiment from 0.45 g of amine VI, 2 ml (0.02 mole) of acetic anhydride, and 15 ml of pyridine. The yield was 0.47 g.

6-Hydroxy-9-(1,3-diacetoxy-2-propyl)purine (XVI). A 0.51-g (0.01 mole) sample of acetic anhydride was added to a suspension of 0.21 g (0.001 mole) of hydroxypurine XIV in 10 ml of pyridine, and the mixture was stirred for 2.5 h. It was then poured into 25 ml of water, and the aqueous mixture was extracted with chloroform (three 40-ml portions). The chloroform solution was evaporated to dryness with the addition of two 10-ml portions of toluene, and the residue was crystallized from chloroform–carbon tetrachloride (1 : 2). The yield was 0.21 g.

6-Hydroxy-9-(1,4-diacetoxy-2-butyl)purine (XVII). A 1.9-ml (0.02 mole) sample of acetic anhydride was added to a suspension of 0.9 g (0.004 mole) of XV in 20 ml of pyridine, and the reaction was then carried out as in the preparation of diacetate XVI. Diacetate XVII was crystallized from ethanol–ether. The yield was 0.8 g.

6-Amino-9-(1,3-ditosyloxy-2-propyl)purine (XIX). A solution of 1.23 g (0.005 mole) of the hydrochloride in V in 60 ml of anhydrous pyridine was cooled to 0°, and 1.9 g (0.01 mole) of p-toluenesulfonyl chloride was added. The mixture was shaken until the solids had dissolved, and the solution was maintained at room temperature. Water (10 ml) and 100 ml of an ice-saturated solution of sodium bicarbonate were added. The aqueous pyridinium solution was extracted with cold chloroform (three 100-ml portions), and the extract was washed with a saturated cold solution of $NaHSO_4$ (two 200-ml portions) and water (two 100-ml portions) at 0°. The aqueous pyridinium solution was evaporated, and the oily residue was dissolved in the minimum amount of chloroform. The tosylation product was precipitated with petroleum ether. This operation was repeated several times until the tosylate of XIX had crystallized completely. The yield was 0.8 g.

Compounds XVIII, XX, and XXI were similarly obtained.

6-Hydroxy-9-(1-adamantylcarbonyloxy-3-hydroxy-2-propyl)purine (XXII). A 0.32-g (0.0015 mole) sample of purine XIV was added to a solution of 0.89 g (0.0045 mole) of adamantoyl chloride in 20 ml of pyridine, and the solution was refluxed for 5 h. It was then cooled, 5 ml of water was added, and the mixture was stirred for 30 min. It was then evaporated to 5 ml, and the residue was dissolved in chloroform. The chloroform solution was extracted with water. The chloroform solution was evaporated, and the crystalline residue was washed with ether and crystallized from absolute ethanol. The yield was 0.12 g.

6-Amino-9-(1,3-diadamantylcarbonyloxy-2-propyl)purine (XXIV). A 0.31-g (0.0012 mole) sample of V was added with stirring to a solution of 0.89 g (0.0045 mole) of adamantoyl chloride in 15 ml of pyridine, after which the mixture was refluxed for 10 h. Water (5 ml) was then added, and the mixture was allowed to stand at room temperature for 2 h. The resulting precipitate was removed by filtration, washed with water, and crystallized from absolute ethanol. The yield was 0.77 g.

Compounds XXIII, XXV, and XXVI were similarly obtained.

6-Hydroxy-9-(1-trityloxy-3-hydroxy-2-propyl)purine (XXXI). A suspension of 1.9 g (0.009 mole) of XIV and 3.9 g (0.014 mole) of triphenylchloromethane in 50 ml of pyridine was stirred at room temperature for 8 h, after which it was allowed to stand overnight. The pyridine was evaporated to dryness, 20 ml of ethanol was added to the residue, and the mixture was poured into 500 ml of water. The resulting precipitate was removed by filtration, washed with water, vacuum dried over P_2O_5, and treated with hot heptane (three 20-ml portions). The solvent was evaporated, and the residue was crystallized from acetone. The yield was 2.84 g.

6-Hydroxy-9-(1,3-dirityloxy-2-propyl)purine (XXXIII). A suspension of 1.0 g (0.0048 mole) of XIV and 2.05 g (0.0074 mole) of triphenylchloromethane in 30 ml of pyridine was refluxed for 2 h, after which the pyridine was evaporated to dryness, and 20 ml of methanol was added to the residue. The resulting precipitate was removed by filtration, washed with water, and vacuum dried over P_2O_5. The reaction product was crystallized from absolute ethanol.

Compounds XXVII-XXX and XXXII were similarly obtained.

6-Hydroxy-9-(1,3-dihydroxy-2-propyl)purine Monophosphate (XXXVI). A 5-ml sample of anhydrous pyridine was added to 15 ml of a standard solution of the pyridinium salt of β-cyanoethyl phosphate, and the mixture was evaporated to dryness at 30°. This operation was repeated three times. A 1-g (0.0022 mole) sample of XXXI in 10 ml of pyridine was then added to the residue, the mixture was vacuum evaporated to dryness, and the residue was dissolved in 110 ml of anhydrous pyridine. A solution of 2.71 g (0.0132 mole) of dicyclohexylcarbodiimide in 10 ml of anhydrous pyridine was added, and the mixture was held at room temperature for 3 days. Water (4 ml) was added to the reaction mixture, and the aqueous mixture was allowed to stand for 1 h. The solvent was evaporated to dryness, the operation was repeated twice, 50 ml of 80% acetic acid was added, and the mixture was heated on a boiling-water bath for 15 min. The mixture was evaporated to dryness with the addition of two 20-ml portions of water. A total of 150 ml of 0.5 N LiOH solution was added, and the mixture was heated on a boiling-water bath for 1 h. The resulting precipitate was removed by filtration, and the filtrate was passed through a Dowex-50 ion-exchange resin in the H^+ form, and the column was eluted with water. The eluate was vacuum evaporated to 10 ml, and 80 ml of ethanol was added. The solution was cooled, and the resulting precipitate was removed by filtration to give 0.32 g (48%) of a product with mp 204-206° and R_f 0.45.

Compounds XXXIV, XXXV, and XXXVII [2] were similarly obtained.

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