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N→N Alkyl and Glycosyl Migrations of Purines and Pyrimidines. IV.[1] *trans*-Glycosylation from Pyrimidines to Purines.[2] (A Novel Synthetic Method of Purine Nucleosides and Nucleotides)

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Application of $N^3 \rightarrow N^9(N^7)$ migration reaction of purine derivatives led to a novel synthetic procedure of purine nucleosides and nucleotides. Direct transfer of ribosyl moieties of acylated pyrimidine nucleosides, nucleotides and trimethylsilylated nucleotides to purine bases was successfully carried out in the pressence of catalyst. Adenosine, N^6,N^6-dimethyladenosine, inosine, guanosine, 7-D-ribofuranosylguanine, 7-D-ribofuranosyl theophylline, adenosine 5′-phosphate, 7-D-ribofuranosyl theophylline 5′-phosphate and other glycosyl derivatives were obtained by transglycosylation reaction.

Preparation of purine nucleosides and nucleotides by this transglycosylation reaction must be a valuable method for utilization of useless pyrimidine nucleotides which are produced during degradation of RNA together with useful purine nucleotides as seasoning.

The glycosyl migration from N-3 to N-9 (N-7)[1,4] of purine is namely the migration from the nitrogen in pyrimidine moiety to that in imidazole. This migration, intermolecular in nature, was supposed to occur between nitrogens of the separate pyrimidine and imidazole rings. Naturally occurring pyrimidine nucleosides and nucleotides are mostly cytosine and uracil glycosides, the former resemble to the 3-glycoside of isoguanine or guanine and the latter the 3-glycoside of xanthine merely in formula with respect to the pyrimidine moiety. However, glycosyl linkages in these pyrimidine glycosides have been described as being more stable than those of 9-glycosyl purines,[5] contrary to the rather labile 3-glycosyl bond of purines[1,4] under acid conditions. In order to undergo facile cleavage of the glycosyl linkage,[1,4,6,7] the pyrimidine nucleosides were acylated at the basic and the glycosyl moieties. Other modifications such as halogenation or nitration at the N-5 position, hydrogenation of the 5—6 double bond, *etc.* were considered to be effective in facilitating cleavages of glycosyl bonds but acylation seemed to be the best with respect to simplicity in treatment and high yields of the modified pyrimidine nucleosides. The acylated pyrimidine nucleosides and nucleotides were subsequently heated with purine bases in the presence of acid catalysts to effect the transfer of the glycosyl groups from pyrimidines to purines. This direct transfer of the sugar moiety will be valuable in the utilization of pyrimidine nucleotide by-products from the degradation of ribonucleic acid which accompany the purine nucleotides. It may also be possible to exchange the pyrimidine moiety of nucleoside antibiotics such as gougerotin with other bases by such a transglycosylation reaction.

Transglycosylation of Cytidine to Purines

Treatment of cytidine with acetic anhydride and pyridine afforded a quantitative amount of 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-N^4-acetylcytosine (I).[8] When I was heated with

1) Part III: M. Miyaki and B. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **18**, 1446 (1970).
2) A part of this work was presented as preliminary communication; B. Shimizu and M. Miyaki, *Tetrahedron Letters*, **1968**, 855.
3) Location: *2–58, 1–chome, Hiromachi, Shinagawa–ku, Tokyo.*
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5) A.M. Michelson, *The Chemistry of Nucleosides and Nucleotides*, **1963**, 26.
6) H.G. Khorana, A.F. Turner and J.P. Vizsolyi, *J. Am. Chem. Soc.*, **83**, 686 (1961).
7) Y. Mizuno and T. Sasaki, *J. Am. Chem. Soc.*, **88**, 863 (1966).
8) J. Beranek and J. Pitha, *Collection Czech. Chem. Commun*, **29**, 625 (1964).

N^6-benzoyladenine (IIa) and mercuric bromide at 150° for 20 hr in a mixture of xylene and DMA, the ribosyl group of I migrated to IIa to yield 9-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-N^6-benzoyladenine which was purified by chromatography on silica gel. Deacetylation of the product by sodium methoxide followed by chromatography on Dowex 1 (OH) gave 9-β-D-ribofuranosyladenine (IIIa-α) (39% yield based on cytidine) and 9-α-D-ribofuranosyladenine (IIIa-β) (6%). The ribosyl moiety was transferable also to adenine (IIb), N^6,N^6-dimethyladenine (IIc), hypoxanthine (IId), N^2-acetylguanine (IIe), theophylline (IIf), benzimidazole (IIg) and 5,6-dimethylbenzimidazole (IIh) to give the corresponding purine and imidazole ribosides as shown in Table I. All nucleosides obtained were identified by comparison with authentic samples or with reported values of melting points, ultraviolet (UV) and nuclear magnetic resonance (NMR) spectra, optical rotation and other physical properties.[9-16] Various acids were found to be effective for this transribosylation reaction and the yield of the purine riboside varied depending on the catalyst (Table II).

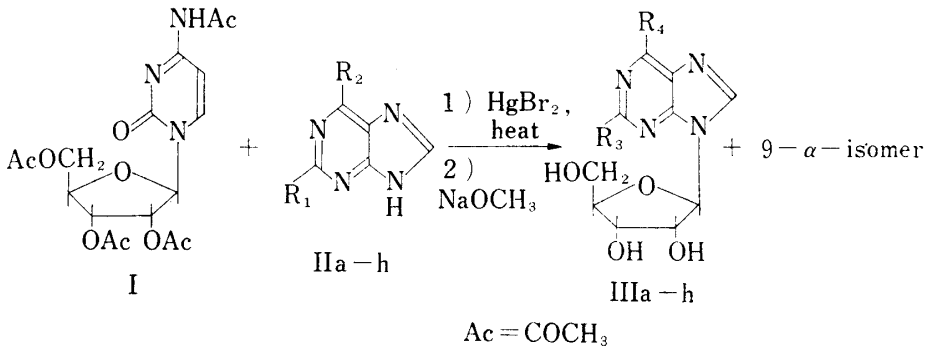

Chart 1

TABLE I. Yields of Purine Nucleosides in Transribosylation of Tetraacetylcytidine(I) to Purine Bases

Acceptor	Resulting nucleoside	Yield (%) β	Yield (%) α
N^6-Benzoyladenine (IIa)	adenosine (IIIa)	39	6
Adenine (IIb)	adenosine (IIIa)	41	3
N^6,N^6-Dimethyladenine (IIc)	N^6,N^6-dimethyladenosine (IIIb)	44	+
Hypoxanthine (IId)	inosine (IIIc)	10	
N^2-Acetylguanine (IIe)	guanosine (IIId)	21	
	7-D-ribofuranosylguanine (IIIe)	20	
Theophylline (IIf)	7-D-ribofuranosyltheophylline (IIIf)	37	2
Benzimidazole (IIg)	1-D-ribofuranosylbenzimidazole (IIIg)	20	
5,6-Dimethylbenzimidazole	1-D-ribofuranosyl-5,6-dimethylbenzimidazole	39	

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10) H.M. Kissmann, C. Pidacks and B.R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).
11) L.B. Townsend, R.K. Robins, R. Leoppky and N.J. Leonard, *J. Am. Chem. Soc.*, **86**, 5320 (1964).
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13) R.S. Wright, G.M. Terner and H.G. Khorana, *J. Am. Chem. Soc.*, **80**, 2004 (1958); L. Pichat, P. Dutay and Y. Lamore, *Compt. Rend.*, **259**, 2453 (1964); K. Onodera, S. Hirano and F. Matsuda, *Carbohyd. Res.*, **4**, 263 (1967).
14) T. Sato and R. Ishido, *Nippon Kagaku Zasshi*, **81**, 1440 (1960).
15) T. Kanazawa, H. Tamura and T. Sato, *Nippon Kagaku Zasshi* **79**, 393 (1958).
16) J. Davoll and G.B. Brown, *J. Am. Chem. Soc.*, **73**, 5781 (1951).

Table II. Yields of 7-(2,3,5-Tri-O-acetyl-D-ribofuranosyl)-theophylline in Transribosylation of I

Catalyst	Yield (%)	Catalyst	Yield (%)
$HgBr_2$	74	HCl	30
$SbCl_3$	50	$PbCl_2$	25
p-Toluenesulphonic acid	50	$AlCl_3$	16
HBr	40	$FeCl_3$	15

Variation in the yields of α and β-anomers depending on transribosylation conditions was as follows: the ratio of β-adenosine to α-adenosine in the transribosylation carried out at 150° in only DMA was almost the same as that in a mixture of xylene and DMA. The ratio in the reaction catalyzed by Dowex 50 (H^+) which was used to simplify the post-treatment of the reaction mixture, was 78:22. When cytidine was treated with adenine and mercuric bromide in fused benzoic anhydride, transribosylation occurred to give 9-(2,3,5-tri-O-benzoyl-D-ribofuranosyl)-N^6-benzoyladenine which was converted to β- and α-adenosine (β:α=70:30). The formation of a considerable amount of α-anomer in this reaction appeared to be similar to the result of certain condensation reactions such as "fusing"[17] and "silyl"[18] methods. These results are summarized in Table III. Differences in the yield of α-adenosine between N-3→N-9 ribosyl migration[19] (β:α=98.5:1.5) and pyrimidine purine transribosylation, both catalyzed by mercuric bromide in solvents, seemed to be mainly a reflection of the variation in reaction temperature and time. The ribosyl migration was carried out at 90—130° for 0.1—2 hr; however, the transribosylation was at 150° for 20—40 hr. Also the difference in participation of 2′-O-acetyl group should be considered, *i.e.*, 2′-O-benzoyl in the migration reaction and 2′-O-acetyl in the transribosylation.

Table III. Yields of α- and β-Adenosines under Various Conditions

Ribosyl donor	Acceptor	Catalyst	Solvent	Adenosine	
				β:α	Yield
Tetraacetylcytidine (I)	N^6-benzoyladenine (IIa)	$HgBr_2$	X+DMA	87:13	45
Tetraacetylcytidine (I)	N^6-benzoylabenine (IIa)	$HgBr_2$	DMA	84:16	17
Tetraacetylcytidine (I)	N^6-benzoylabenine (IIa)	Dowex 50(H)	X+DMA	78:22	12
Cytidine	adenine (IIb)	$HgBr_2$	$(C_6H_5CO)_2O$	71:29	8

X=xylene

Transribosylation of Uridine to Purines

Although the N-3 position of uridine was not acetylated under the same conditions as cytidine, it was benzoylated when 2′,3′,5′-tri-O-acetyluridine (IV)[20] was heated with benzoyl chloride in pyridine. The structure of the N-3- benzoylated compound was characterized in infrared (IR) spectrum by comparison with that of IV and of 3-benzoyluracil.[21] 1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-3-benzoyluracil (V) was heated with purine base in the presence of the catalyst (Chart 2, procedure a). The acyl group was effective in the transfer of the ribosyl group from uridine, however, it was extremely labile to the acid catalyst and easily cleaved from N-3 resulting in the recovery of considerable amounts of IV. When IV

17) Y. Ishido and T. Sato, *Bull. Chem. Soc. Japan*, **34**, 347 (1961).
18) T. Nishimura, B. Shimizu and I. Iwai, *Chem. Pharm. Bull.* (Tokyo), **12**, 1471 (1964).
19) M. Miyaki and B. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **18**, 732 (1970).
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21) A. Novacek, D. Hesoun and J. Gut, *Collection Czech. Chem. Commun.*, **30**, 1890 (1965).

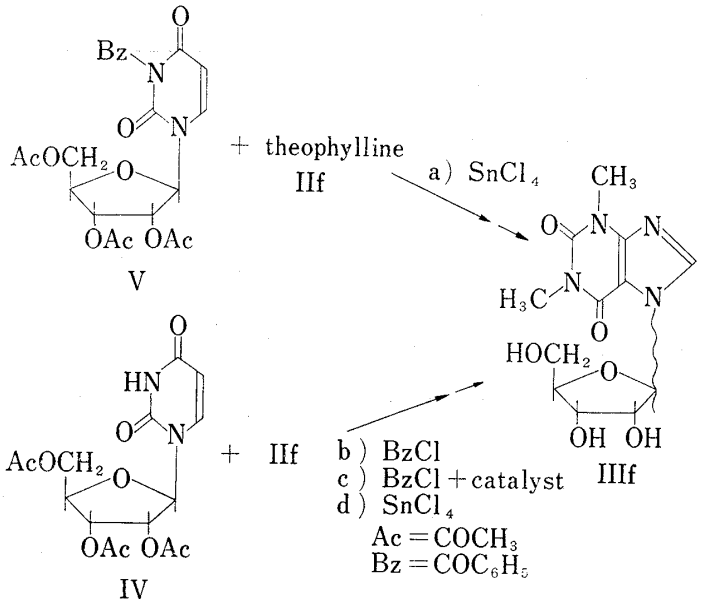


Chart 2

was heated with a purine base in the presence of benzoyl chloride (procedure b), initial N-3 benzoylation to form hydrogen chloride and subsequent cleavage of C–N glycosyl bond by hydrogen chloride afforded the purine riboside. Addition of the catalyst such as mercuric bromide to this reaction mixture resulted in the formation of a larger amount of the purine riboside (procedure c). The ribosyl moiety showed little tendency to migrate from IV itself (d). Various Lewis acids were examined for their effectivity on the transribosylation under acid conditions (Table IV).

7-α-D-Ribofuranosyltheophylline (IIIf-α) was isolated for the first time from this transribosylation reaction. Deacylation of the reaction products followed by chromatography on Dowex 1 (OH) gave α- and β-anomers of 7-D-ribofuranosyltheophylline (IIIf).

Table IV. Yields of 7-(2,3,5-Tri-O-acetyl-D-ribofuranosyl)theophylline in Transribosylation of Triacetyluridine (IV) (Method C)

Catalyst	Solvent	Bath temp. °C	hr	Yield (%)
Hg_2Cl_2	X+NO_2B (1:1)	170	20	25
Hg_2I_2	X+NO_2B (1:1)	170	4	64
$HgCl_2$	X+NO_2B (1:1)	170	20	8
$HgBr_2$	X+NO_2B (3:2)	170	4	61
$HgBr_2$	NO_2B	120—125	5	46
HgI_2	X+NO_2B (1:1)	170	4	43
$SnCl_4$	X+NO_2B (3:2)	130—140	2.5	50
$SnCl_4$	diCl B	130	4	46
$SnBr_4$	X+NO_2B (3:2)	130—140	2.5	45
$PbBr_2$	X+NO_2B (3:2)	130—140	2.5	20
$SbCl_3$	X+NO_2B (3:2)	130—140	2.5	46
$SbCl_5$	X+NO_2B (3:2)	130—140	2.5	40
$FeCl_3$	X+NO_2B (3:2)	130—140	2.5	20
$CoCl_2$	X+NO_2B (3:2)	130—140	2.5	10
$NiCl_2$	X+NO_2B (3:2)	130—140	2.5	10
NH_2SO_3H	X+NO_2B (3:2)	130—140	2.5	10

X=xylene, NO_2B=nitrobenzene, diClB=dichlorobenzene

Transphosphoribosylation of 5′-CMP to Purines

Diphenylphosphoribosyl transfer from 1-(2,3-di-O-benzoyl-5-diphenylphosphoryl-β-D-ribofuranosyl)-N^4-acetylcytosine (VI-β)[22] to N^6-benzoyladenine (IIa) or theophylline (IIf) also occurred under the same conditions as in the case of ribosyl transfer from the cytidine derivative. On the other hand, 1-(2,3-di-O-benzoyl-5-diphenylphosphoryl-α-D-ribofuranosyl)-N^4-

22) M. Asai, M. Miyaki and B. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **15**, 1856 (1967).

acetylcytosine (VI-α)[23] could not be used as the phosphoribosyl donor under these conditions, and the transdiphenylphosphoribosylation from VI-α required benzoyl chloride besides the catalyst. Such stability of the α-glycosyl bond to acidic cleavage as compared with the β-glycosyl linkage has also been observed in O→N glycosyl migration reactions.[24,25]

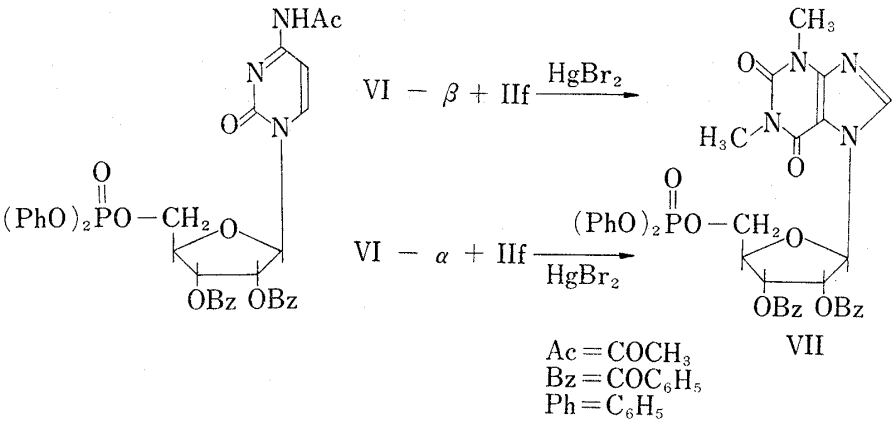


Chart 3

To utilize the naturally occurring 5′-CMP as the phosphoribosyl donor in the transphosphoribosylation reaction, it was desirable that the phosphoribosyl moiety be protected by a group which could easily be removed after the transfer reaction. 5′-CMP was acylated with acetic anhydride in pyridine to yield pyridinium 2′,3′-di-O-acetyl-N^4-acetylcytidine-5′-phos-

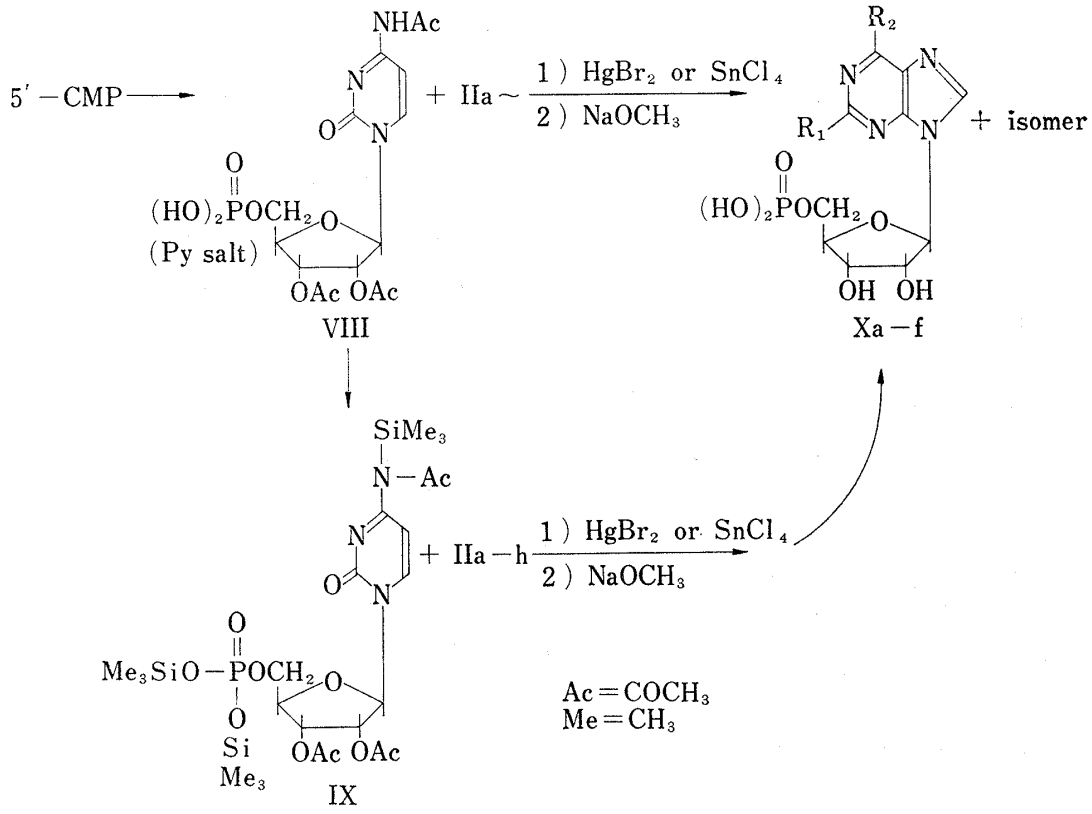


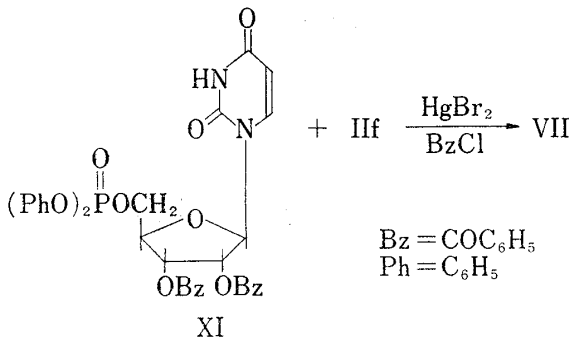
Chart 4

23) B. Shimizu, A. Saito, T. Nishimura and M. Miyaki, *Chem. Pharm. Bull.* (Tokyo), **15**, 2011 (1967).
24) G. Wagner and H. Pischel, *Arch. Pharm.*, **295**, 373 (1962).
25) H. Pischel and G. Wagner, *Arch. Pharm.*, **300**, 737 (1967).

phate (VIII). The phosphoribosyl group was transfered to N^6-benzoyladenine (IIa) to give 5′-AMP (17% yield). Protection of phosphoryl moiety by trimethylsilyl group was found to be effective in the transfer reaction as follows: triacetyl-5′-CMP (VIII) was easily trimethylsilylated at the phosphate moiety by treatment with trimethylsilyl chloride and triethylamine. When 1-(2,3-di-O-acety-5-bistrimethylsilylphosphoryl-β-D-ribofuranosyl)-N^4-acetyltrimethylsilylcytosine (IX) was heated at 110° for 10 hr with IIa and mercuric bromide in a solvent the silylphosphoribosyl group was transfered to IIa to form the corresponding adenine nucleotide which was converted to 5′-AMP (50% yield based on 5′-CMP) by treatment with sodium methoxide. The phosphoribosyl moieties were transferable also to theophylline (IIf), N^2-acetylguanine (IIe) and hypoxanthine (IId) to afford the corresponding purine nucleotides as shown in Table V.

Table V. Yields of Purine Nucleotides in Transphosphoribosylation of Acetyl-CMP (VIII) or Silylacetyl-CMP (IX) to Purine Bases

Donor	Acceptor	Resulting nucleotide	Yield (%)
VIII	IIa	5′-AMP (Xa)	17
VIII	IIf	7-D-Ribofuranosyltheophylline 5′-phosphate (Xb)	14
IX	IIa	5′-AMP (Xa)	45.5
IX	IIe	7-D-Ribofuranosylguanine 5′-phosphate (Xc)	17
IX	IIe	5′-GMP (Xd)	9
IX	silyl-IId	7-D-Ribofuranosylhypoxanthine 5′-phosphate	21
IX	silyl-IId	5′-IMP (Xf)	24



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Transphosphoribosylation of 5′-UMP to Purine

Diphenylphosphoribosyl transfer from 1-(2,3-di-O-benzoyl-5-diphenylphosphoryl-β-D-ribofuranosyl)uracil (X)[26] to theophylline (IIf) was observed when X and IIf were heated in the presence of $HgBr_2$ and benzoyl chloride to give the theophylline ribotide (VII) (Chart 5).

Experimental[27]

Acetylation of Cytidine——A mixture of cytidine (1.216 g), acetic anhydride (20 ml) and pyridine (20 ml) was stirred at 15—20° for 4 hr and evaporated to dryness *in vacuo*. The residue was codistilled with anhydrous xylene to give 1-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl-N^4-acetylcytosine (I) (2.00 g, 97.5%), amorph. UV λ_{max}^{EtOH} mμ (ε): 250 (15300), 299 (6300); $\lambda_{max}^{H^+\text{-}EtOH}$: 250 (12650) and 297 (6800). *Anal.* Calcd. for $C_{17}H_{21}O_9N_3$: C, 49.63; H, 5.15; N, 10.22. Found: C, 49.88; H, 5.40; N, 9.99.

Transribosylation of 1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl-N^4-acetylcytosine (I) to N^6-Benzoyladenine (IIa)——A mixture of I (882 mg), IIa (956 mg), $HgBr_2$ (720 mg), xylene (4 ml) and DMA (1.5 ml) was heated at 150° for 20 hr and was evaporated to dryness *in vacuo*. The residue was extracted with $CHCl_3$ and the $CHCl_3$ solution was washed successively with 30% KI and H_2O, and then dried. The extract was chromatographed on silica gel (20 g). The fraction eluted with $CHCl_3$–MeOH (99:1) on evaporation of the solvent gave 9-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-N^6-benzoyladenine (770 mg). This compound (325 mg)

26) B. Shimizu, M. Asai and T. Nishimura, *Chem. Pharm. Bull.* (Tokyo), **15**, 1843 (1967).

27) NMR spectra were measured on a Varian A60 Spectrometer. Thin-layer chromatography (TLC) was carried out on Avicel with the following solvent systems: A: BuOH–H_2O (86:14), B:0.01M NH_4HCO_3, C:butyric acid–H_2O–NH_3 (66:34:0.1), D: iso-PrOH–H_2O–HCl (70:10:20), E: 0.02M ammonium tartarate, F: MeOH–HCl–H_2O (70:20:10), G: iso-BuOH–AcOH–H_2O (50:20:30), H: sat. $(NH_4)_2SO_4$–1M AcONa–iso-PrOH (80:18:2).

was deacetylated with 0.1N NaOMe/MeOH (30 ml) and the product was chromatographed on Dowex 1 (OH^-, column 20 ml). A small amount of cytidine was recovered from the first fraction eluted with H_2O–MeOH (80:20). The second fraction gave α-adenosine (IIa-α) (14 mg, 6% yield based on I), mp 219—220°. UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 257; pH 7, 259; pH 13, 259.5. *Anal.* Calcd. for $C_{10}H_{13}O_4N_5$: C, 44.94; H, 4.90; N, 26.21. Found: C, 44.85; H, 5.18; N, 26.15; *Rf* (TLC): A, 0.27. The third fraction on evaporation of the solvent and recrystallization from H_2O gave β-adenosine (IIIa-β) (90 mg, 39%), mp 233.5—235°. UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 257.5; pH 7, 260; pH 13, 260. *Anal.* Calcd. for $C_{10}H_{13}O_4N_5 \cdot H_2O$: C, 42.10; H, 5.27; N, 24.54. Found: C, 41.81; H, 5.53; N, 24.29. *Rf* (TLC): A, 0.33. Unchanged I (130 mg) was eluted from the silica gel column after acetylated adenosine.

Transribosylation of I to Adenine (IIc)——A mixture of I (411 mg), IIb (270 mg), $HgBr_2$ (360 mg), xylene (3 ml) and nitrobenzene (2 ml) was heated at 150° for 15 hr with stirring and evaporated to dryness. The residue was extracted with $CHCl_3$, the $CHCl_3$ solution was treated with 30% KI as described above and the solvent was evaporated. After being deacetylated with sat. NH_3/MeOH at 0° for 15 hr, the products were chromatographed on Dowex 1 (OH). The first fraction eluted with H_2O–MeOH (70:30) gave cytidine (30 mg, 12%), the second fraction gave α-adenosine (IIIa-α), mp 220—221° (67 mg, 2.6%) and the third fraction gave β-adenosine (IIIa-β), mp 233° (110 mg, 41%). These compounds were identical in all respects to the authentic samples.

Transribosylation of I to N^6,N^6-Dimethyladenine (IIc)——A mixture of I (822 mg), IIc (490 mg), $HgBr_2$ (720 mg), xylene (5 ml) and DMA (1.5 ml) was heated at 150—160° for 24 hr and then evaporated to dryness. The $CHCl_3$ extract of the residue was treated as described above and chromatographed on silica gel (20 g). The fraction eluted with $CHCl_3$ gave 9-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-N^6,N^6-dimethyladenine (600 mg), amorph. UV λ_{max}^{EtOH}: 274 mμ, $\lambda_{max}^{HCl/EtOH}$: 268 mμ. Deacetylation of this compound (255 mg) with 0.05N NaOMe/MeOH gave 9-β-D-ribofuranosyl-N^6,N^6-dimethyladenine (IIIb-β) (110 mg, 44% yield based on I), mp 183—184° (lit.[10] mp 183—184°). UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 268.5; pH 7, 275; pH 13, 275. *Anal.* Calcd. for $C_{12}H_{17}O_4N_5$: C, 48.80; H, 5.80; N, 23.72. Found: C, 48.58; H, 5.94; N, 24.03.

Transribosylation of I to Hypoxanthine (IId)——A mixture of I (882 mg), IId (400 mg), $HgBr_2$ (720 mg), xylene (5 ml) and DMA (1.7 ml) was heated at 150° for 15 hr with stirring and the reaction mixture was treated as described above. Chromatography of the products gave 9-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-hypoxanthine (96 mg, 12%), mp 238°, UV λ_{max}^{EtOH}: 245, 252, 270 (sh) mμ, which was converted to 9-D-ribofuranosyl hypoxanthine (IIIc) (54 mg, 10% yield based on I). UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 249 (11500); pH 7, 249 (11500); pH 13, 254 (12200). *Anal.* Calcd. for $C_{10}H_{12}O_5N_4 \cdot 2H_2O$; N, 18.41. Found: N, 18.18. *Rf* (TLC): B. 0.78; C, 0.51; D, 0.15; these values were identical with those of inosine.

Transribosylation of I to N^2-Acetylguanine (IIe)——A mixture of I (822 mg), IIe (700 mg), $HgBr_2$ (720 mg), xylene (5 ml) and DMA (1.5 ml) was heated at 150° for 40 hr with stirring. The reaction mixture was treated as described above and the products were chromatographed on alumina column (15 g). The fraction eluted with acetone on evaporation of the solvent afforded 7-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-N^2-acetylguanine (250 mg) which was deacetylated with 0.1N NaOMe/MeOH to give 7-D-ribofuranosylguanine (IIIe) (112 mg, 20% yield based on I), mp 255° (decomp.). UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 249.5 (8860) and 273 (sh); pH 7, 285.5 (6760); pH 13, 281.5 (6080). *Anal.* Calcd. for $C_{10}H_{13}O_5N_5 \cdot H_2O$: C, 39.90; H, 5.01; N, 23.30. Found: C, 40.04; H, 4.92; N, 23.12. *Rf* (TLC): B, 0.67; C, 0.53; D, 0.93; E, 0.42. These values were identical with those of the authentic sample. The fraction eluted with acetone–MeOH (99:1) afforded 9-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-N^2-acetylguanine (220 mg) which was deacetylated to give 9-D-ribofuranosylguanine (137 mg, 21%), mp 260° (decomp.). UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 254.5 (12400) and 278.5 (sh); pH 7, 251.0 (13400) and 271 (sh); pH 13, 257 (sh) and 265 (11300). *Anal.* Calcd. for $C_{10}H_{13}O_5N_5$: C, 42.40; H, 4.63; N, 24.73. Found: C, 42.66; H, 4.78; N, 24.56. *Rf* (TLC): B, 0.71; C, 0.50; D, 0.165; E, 0.51, these value were identical with those of guanosine.

Transribosylation of I to Theophylline (IIf)——A mixture of I (822 mg), IIf (720 mg), $HgBr_2$ (720 mg), xylene (5 ml) and DMA (1 ml) was heated at 150—160° for 40 hr and the reaction mixture was treated as described above. The products were chromatographed on a silica gel column. The fraction eluted with $CHCl_3$ on evaporation of the solvent gave an anomeric mixture of 7-(2,3,5-tri-O-acetyl-D-ribofuranosyl)theophyllines, amorphous (650 mg, UV λ_{max}^{EtOH} 230 (sh) and 276 mμ), which was deacetylated and then chromatographed on Dowex 1 (OH). The α- and β-anomers were eluted separately with H_2O–MeOH (70:30). The first fraction on evaporation of the solvent and recrystallization from H_2O gave 7-α-D-ribofuranosyltheophylline (IIIf-α) (12 mg, 2% yield based on I), mp 196—198°, UV λ_{max}^{pH7}: 274.5 mμ, which was identified with the authentic sample described later by mixed melting point. The second fraction gave 7-β-D-ribofuranosyltheophylline (IIIf-β) (123 mg, 37%), mp 194—195°. UV $\lambda_{max}^{H_2O}$ mμ: pH 1, 274.5; pH 7, 275; pH 13, 274.5. *Anal.* Calcd. for $C_{12}H_{16}O_6N_4$: C, 46.15; H, 5.16; N, 17.94; Found: C, 45.85; H, 5.20; N, 17.94. These values were identical with those of authentic sample.[14]

Transribosylation of I to Benzimidazole (IIg)——A mixture of I (822 mg), IIg (300 mg), $HgBr_2$ (720 mg), xylene (5 ml) and DMA (0.8 ml) was heated at 150° for 40 hr, and the reaction mixture was treated by the usual manner. The $CHCl_3$–extract of the product was chromatographed on silica gel. The fraction eluted with $CHCl_3$ afforded 1-(2,3,5-tri-O-acetyl-D-ribofuranosyl)benzimidazole (210 mg), amorph. UV λ_{max}^{PHI}:

254, 262 and 275 mμ. Deacetylation of the compound with 0.05N NaOMe/MeOH and purification by chromatography on Dowex 1 (OH) gave 1-D-ribofuranosylbenzimidazole (103 mg, 20% yield), mp 110°. UV $\lambda_{max}^{H_2O}$ mμ (ε); pH 1, 254 (5100), 262 (5400), 268 (6400) and 275 (5500); pH 7, 245 (7300), 246 (3500), 272.5 (4000) and 279.5 (3700); pH 13, 246 (6800), 264 (3600), 272.5 (3800) and 279.5 (3500): these values were similar to those reported.[16] *Anal.* Calcd. for $C_{12}H_{14}O_4N_2 \cdot \frac{1}{4} H_2O$: C, 56.58; H, 5.70; N, 11.00. Found: C, 56.72; H, 5.91; N, 10.70. NMR: $H_{1'}=5.92$ ppm ($J_{1'-2'}=6$ cps) from TMS in DMSO-d_6.

Transribosylation of I to 5,6-Dimethylbenzimidazole (IIh)——A mixture of I (822 mg), IIh (320 mg), $HgBr_2$ (720 mg), xylene (5 ml) and DMA (0.8 ml) was heated at 150° for 40 hr and then the reaction mixture was treated by usual manner and chromatographed on silica gel. The fraction eluted with $CHCl_3$ on evaporation of the solvent afforded 1-(2,3,5-tri-O-acetyl-D-ribofuranosyl)-5,6-dimethylbenzimidazole (430 mg), amorphous, UV λ_{max}^{pH1}: 278 and 286.5 mμ. This derivative was deacetylated with sat. NH_3/MeOH to give 1-β-D-ribofuranosyl-5,6-dimethylbenzimidazole (IIIh) (217 mg, 39%), mp 183—185°. UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 278 (7510) and 286 (6950); pH 7, 249.5 (6680), 280 (4510) and 288 (4360); pH 13, 250 (6630), 280 (4440) and 288 (4320); these values were similar to those described.[16] *Anal.* Calcd. for $C_{14}H_{18}O_4N_2 \cdot \frac{1}{2}H_2O$: C, 58.65; H, 6.62; N, 9.76. Found: C, 58.92; H, 6.41; N, 9.60. NMR: $H_{1'}=5.82$ ppm ($J_{1'-2'}=6$ cps) from TMS in DMSO-d_6.

Transribosylation of I to IIa catalyzed by Dowex 50 (H)——A mixture of I (411 mg,) IIa (478 mg), dried Dowex 50 (H^+) (500 mg), xylene (4 ml) and DMA (1.5 ml) was heated at 130—150° for 23 hr with stirring. The resin was filtered off and washed with C_6H_6. The filtrate and the washing were combined and evaporated to dryness. The residue was deacylated with 0.15N NaOMe/MeOH (15 ml) and the products were chromatographed on Dowex 1 (OH). Cytidine (85 mg, 35%) was recovered from the first fraction eluted with H_2O–MeOH (70:30), and α-adenosine (IIIa-α) (7 mg, 2.6%) and β-adenosine (IIIa-β) (25 mg, 9.3%) were obtained from the subsequent fractions respectively.

Transribosylation of Cytidine to Adenine (IIb) in Benzoic Anhydride——A mixture of cytidine (243 mg), adenine (135 mg), $HgBr_2$ (360 mg) and benzoic anhydride (2.26 g) was fused at 150° for 2 hr and the reaction mixture was extracted with C_6H_6. The extract was adsorbed to a silica gel column (6 g), the column was washed with C_6H_6 and the product was eluted with $CHCl_3$–MeOH (99:1—97:3). The fraction which exhibit the UV absorption maxima at 230 and 279 mμ (A230/279=2.2) was evaporated to dryness. Debenzoylation and chromatography on Dowex-1 (OH) of the residue gave α-adenosine (IIIa-α) ($OD_{260}=180$, 2.4%) and β-adenosine (IIIa) ($OD_{260}=432$, 5.8%).

1-(2,3,5-Tri-O-acetyl-β-D-ribofuranosyl)-3-benzoyluracil (V)——Uridine (2.44 g) was stirred in a mixture of acetic anhydride (40 ml) and pyridine (4 ml) at room temperature for 3 hr and the reaction mixture was evaporated to dryness *in vacuo*. Crystallization of the residue from EtOH afforded 2′,3′,5′-tri-O-acetyluridine (IV) (3.5 g, 92% yield), mp 130°. UV λ_{max}^{EtOH}: 258 mμ (ε 9900). *Anal.* Calcd. for $C_{15}H_{18}O_9N_2$: C, 48.65; H, 4.90; N, 7.57. Found: C, 48.81; H, 4.91; N, 7.77. IV (1.67 g) was heated with benzoyl chloride (3.06 g) in pyridine (50 ml) under reflux for 80 min and excess of benzoyl chloride and pyridine were evaporated. The $CHCl_3$–extract of the residue was chromatographed on silica gel (20 g) and the fraction eluted with $CHCl_3$ on evaporation of the solvent gave V (1.535 g, 72% yield), amorph. UV λ_{max}^{EtOH}: 252.5 mμ (ε 20200). IR ν_{max}^{KBr} cm^{-1}: 1677, 1713 and 1745 (C=O). *Anal.* Calcd. for $C_{22}H_{22}O_{10}N_2$: C, 55.69; H, 4.67; N, 5.91. Found: C, 55.77; H, 4.70; N, 5.84.

Transribosylation of V or IV to Theophylline (IIf)——a) A mixture of V (237 mg), IIf (180 mg), $SnCl_4$ (0.058 ml), xylene (1.2 ml) and nitrobenzene (1.2 ml) was heated at 130° for **30** min with stirring. The reaction mixture was evaporated to dryness and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried concentrated and chromatographed on silica gel (9 g). Deacetylation and chromatography on Dowex 1 (OH) of the fraction eluted with $CHCl_3$ gave 7-α-D-ribofuranosyltheophylline (IIIf-α) ($OD_{274.5}=40$, 0.9%) and 7-β-D-ribofuranosyltheophylline (IIIf-β $OD_{274.5}=347$, 7.9%). IV was recovered from the fraction eluted with $CHCl_3$–MeOH (99:1) (110 mg, 59%.)

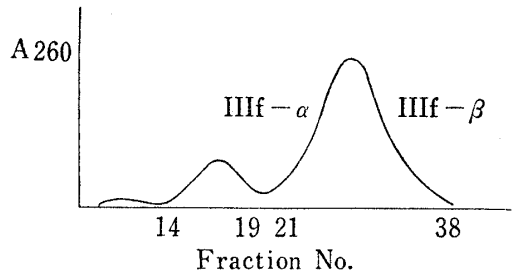
b) A mixture of IV (333 mg), benzoyl chloride (510 mg), IIf (324 mg), xylene (3 ml) and nitrobenzene (2 ml) was heated at 150° for 70 hr with stirring and the reaction mixture was evaporated to dryness. The $CHCl_3$ extract of the residue was washed with $NaHCO_3$ solution and H_2O, dried and chromatographed on silica gel. The fraction eluted with $CHCl_3$ was deacetylated by NaOMe and separated using Dowex 1 (OH) column (60 ml). The former fraction eluted with H_2O–MeOH (80:20) gave IIIf-α ($OD_{274.5}=62$, 0.8%) and the latter fraction afforded III-β ($OD_{274.5}=358$, 4.5%).

c) A mixture of IV (333 mg), benzoyl chloride (381 mg), IIf (324 mg), $HgBr_2$ (650 mg), xylene (3 ml) and nitrobenzene (2 ml) was heated at 170° for 4 hr and evaporated to dryness *in vacuo*. The $CHCl_3$ extract of the residue was washed with 30% KI and H_2O, dried and chromatographed on silica gel. The fraction exhibited UV absorption maximum at 274.5 mμ was deacetylated by NaOMe and purified by Dowex 1 (OH) column chromatography. IIIf-α and IIIf-β were obtained in 8% (22 mg) and 24% (75 mg) yield, respectively.

Properties of 7-α-D-Ribofuranosyltheophylline (IIIf-α)——One of the products of transribosylation of I, IV or V to IIf was characterized to be the α-anomer by comparison of the following properties with those of the β-anomer.

	IIIf-α	IIIf-β
mp (°C)	196—198	192—194
UV λ_{max}^{pH7} mμ (ε)	274.5(8760)	274.5(8770)
$H_{1'}$ from dioxane in D_2O (cps)	−166	−140
$J_{1'-2'}$ (cps)	4.5	3.5
$M_{288}^{20°}$ (H_2O) (°)	−4400	+1740

Dowex 1(OH) chromatogram (H_2O–MeOH (70:30) of anomeric mixture of IIIf



Transphosphoribosylation of 1-(2,3-Di-O-benzoyl-5-diphenylphosphoryl-β-D-ribofuranosyl)-N⁴-acetylcytosine (VI-β) to IIa——A mixture of VI-β (362 mg), IIa (195 mg), $HgBr_2$ (270 mg), acetonitrile (0.25 ml) and nitrobenzene (1 ml) was heated at 110° for 3 hr with stirring. The reaction mixture was evaporated and the residue was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with 30% KI, then with H_2O, and dried over $MgSO_4$. Removal of $CHCl_3$ afforded a sirup which was chromatographed on silica gel (12 g). Elution with $CHCl_3$ gave 9-(2,3-di-O-benzoyl-5-diphenylphosphoryl-β-D-ribofuranosyl)-N⁶-benzoyladenine (109 mg, 27%), its α-anomer (7 mg, 1.7%) and unreacted VI-β (145 mg, 40%). These compounds were identical with the authentic samples in their *Rf* values of TLC and UV and IR spectra, respectively.

Transphosphoribosylation of VI-β to IIf——A mixture of VI-β (200 mg), IIf (75 mg) $HgBr_2$ (100 mg), acetonitrile (0.25 ml) and nitrobenzene (1 ml) was heated at 150° for 20 hr with stirring. The reaction mixture was treated as described above and chromatographed on silica gel (12 g). The fraction eluted with C_6H_6–$CHCl_3$ (50:50) on recrystallization from EtOH gave 7-(2,3-di-O-benzoyl-5-diphenylphosphoryl-D-ribofuranosyl)theophylline (VII) (42 mg, 20%), mp 154—156°. UV λ_{max}^{EtOH} mμ (ε): 229.5 (32400) and 275 (10200). *Anal.* Calcd. for $C_{38}H_{32}O_{11}N_4P$: C, 60.71; H, 4.61; N, 7.31. Found: C, 60.64; H, 4.39; N, 7.45. IR spectrum of this compound was identical with that of the authentic sample.[22]

Transphosphoribosylation of 1-(2,3-Di-O-benzoyl-5-diphenylphosphoryl-α-D-ribofuranosyl)-N⁴-acetylcytosine (VI-α) to IIf——A mixture of VI-α (100 mg), IIf (50 mg), benzoyl chloride (52 mg), $HgBr_2$ (50 mg), xylene (0.5 ml) and nitrobenzene (0.5 ml) was heated at 120—125° for 10 hr with stirring. Treatment of the reaction mixture as described above gave VII (20 mg, 19%), mp 156°. UV λ_{max}^{EtOH}: 231 and 276 mμ. IR spectrum of this compound was identical with that of the authentic sample.[22]

Pyridinium 2′,3′-Di-O-acetyl-N⁴-acetylcytidine-5′-phosphate (VIII)——To a stirring mixture of 5′-CMP (6.46 g) and pyridine (100 ml) was added dropwise acetic anhydride (100 ml) and stirring was continued over night at room temperature. The reaction mixture was evaporated *in vacuo* to leave a syrup which was treated with CH_3CN (20 ml) and then ether (100 ml). The precipitates were dissolved in DMF and the solvent was evaporated *in vacuo* to give VIII (10.7 g, 100%), amorph. UV λ_{max}^{EtOH}: 251 and 301 mμ. $\lambda_{max}^{HCl/EtOH}$: 251 and 309 mμ. *Anal.* Calcd. for $C_{15}H_{20}O_{11}N_3P \cdot C_5H_5N$: C, 45.45; H, 4.73; N, 10.61. Found: C, 45.18; H, 4.56; N, 10.35.

Transphosphoribosylation of VIII to IIa——A mixture of VIII (528 mg), IIa (480 mg), acetic anhydride (0.3 ml), $SnCl_4$ (860 mg), acetonitrile (1 ml) and nitrobenzene (2 ml) was heated at 115—120° for 3 hr with stirring. After being cooled, the reaction mixture was diluted with MeOH (10 ml). To this solution was added ether to afford precipitates which were extracted with MeOH. The MeOH solution was neutralized with 1N NH_3/EtOH and evaporated to dryness. The residue was heated in 0.27N NaOMe/MeOH (55 ml) under reflux for 70 min and then the solvent was removed. The residue was dissolved in H_2O (10 ml) and pH was adjusted to 5.5 by addition of Dowex 50 (H). After removal of the resin by filtration, the filtrate was concentrated *in vacuo* to 5—10 ml and chromatographed on Dowex 1 (Cl form, 47 ml). Elution with 0.003N HCl containing 0.003M LiCl gave the two fractions, A and B. Evaporation of the fraction A left a small amount of 5′-CMP. Fraction B was neutralized with 1N LiOH and evaporated to dryness *in vacuo*. Removal of LiCl by washing with EtOH and acetone gave dilithium salt of 5′-AMP (Xa) (17% yield based on 5′-CMP) which was identical with the authentic sample of 5′-AMP in UV spectra and *Rf* values of TLC solvent F.G. and H). NMR (ppm): 8.37, 7.91 (H_2 or H_8 of the β-anomer), 8.22, 7.91 (H_2 or H_8 of the α-anomer), 6.26 ($H_{1'}$ of the β-anomer, $J_{1'-2'}$=5 cps), 5.91 ($H_{1'}$ of the α-anomer, $J_{1'-2'}$=5 cps) from DSS in D_2O 5′-AMP thus obtained was incubated with alkaline phosphatase in 0.2M glycine buffer (pH 8.5) at 37° for 3 hr

and the hydrolyzate was chromatographed on Dowex 1 (OH). Elution with H_2O–MeOH (60:40) gave α- and β-adenosine separately. The ratio of the amounts of α- and β-anomers was 1:4.5. Each of these compounds was identical in all respects with the authentic sample.

Transphosphoribosylation of VIII to IIf——A mixture of VIII (528 mg), IIf (360 mg), acetic anhydride (2.5 ml), $HgBr_2$ (540 mg), DMF (0.5 ml) and nitrobenzene (2 ml) was heated at 120° for 12 hr with stirring. After treating the reaction mixture as described above, the resulting crude theophylline nucleotide was purified by chromatography on Dowex 1 (Cl). The fraction eluted with 0.01N HCl containing 0.01M LiCl on neutralization, evaporation and treatment with EtOH and acetone afforded lithium salt of 7-β-D-ribofuranosyltheophylline-5′-phosphate (Xb) (14% yield). UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 274 (9050); pH 7, 274 (9030); pH 13, 274 (9030). NMR: $H_{1'}$=6.05 ppm ($J_{1'-2'}$=4.5 cps), H_8=8.32 ppm from DSS in D_2O. The ratio of the total phosphorous to ribosyltheophylline was 0.996.

1-(2,3-Di-O-acetyl-5-bistrimethylsilylphosphoryl-β-D-ribofuranosyl-N^4-acetyltrimethylsilylcytosine (IX)——To a stirring mixture of VIII (4.8 g), trimethylsilyl chloride (3.6 g) in anhydrous benzene (30 ml) was added dropwise triethylamine (3.5 g) with exclusion of moisture at room temperature. Triethylamine hydrochloride and unreacted VIII were filtered off and the filtrate was evaporated to dryness *in vacuo*. The syrupy residue (IX) (UV $\lambda_{max}^{dioxane}$: 252 and 305 mμ) was used as the phosphoribosyl donor in the transphosphoribosylation reaction without further purification.

Transphosphoribosylation of IX to IIa——A mixture of IX (653 mg), IIa (480 mg), $HgBr_2$ (540 mg), CH_3CN (0.5 ml) and nitrobenzene (2 ml) was heated at 110° for 40 hr with stirring. After being detrimethylsilylated by addition of EtOH, the reaction mixture was treated as described in the case of transphosphoribosylation of VIII. The crude product was deacetylated and chromatographed on Dowex 1 (Cl) to give an anomeric mixture of dilithium salt of 5′-AMP (Xa) (45.5% yield based on 5′-CMP). The ratio of amounts of α to β-isomer was found to be 1:3 by dephosphorylation of the mixture and separation of the resulting α- and β-adenosines.

Transphosphoribosylation of IX to IIe——A mixture of IX (653 mg), IIe (400 mg), $HgBr_2$ (540 mg), CH_3CN (0.5 ml) and nitrobenzene (2 ml) was heated at 110° for 5 hr with stirring. The reaction mixture was treated as described above and the products were applied on Dowex 1 (Cl) column and eluted with 0.01N HCl containing 0.01M LiCl. Each fraction was neutralized with LiOH and evaporated to dryness and the residue was washed with EtOH and acetone. The first fraction gave 7-D-ribofuranosylguanine 5′-phosphate (Xc) (17%). UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 249.5 (9040) and 272 (sh); pH 7, 285.5 (8760); pH 13, 281.5 (6300). NMR: $H_{1'}$=6.22 ppm ($J_{1'-2'}$=3.5 cps), H_8=8.15 ppm from DSS in D_2O. Ratio of total phosphorous to 7-D-ribofuranosylguanine: 0.98. The second fraction gave 9-D-ribofuranosylguanine 5′-phosphate (Xd) (9%): UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 255 (1200) and 278 (sh); pH 7, 251.5 (13400) and 270 (sh); pH 13, 264 (11500). NMR: $H_{1'}$=5.69 ppm ($J_{1'-2'}$=5.0 cps), H_8=7.92 ppm from DSS in D_2O. Ratio of phosphorous to guanosine: 0.996.

Transphosphoribosylation of IX to Bistrimethylsilylhypoxanthine——A mixture of IX (653 mg), bistrimethylsilylhypoxanthine (560 mg), $HgBr_2$ (540 mg) and xylene (3 ml) was heated at 110° for 5 hr. Treatment of the reaction mixture as described above gave dilithium salt of 7-D-ribofuranosylhypoxanthine 5′-phosphate (Xe) (21% yield) and 9-D-ribofuranosylhypoxanthine 5′-phosphate (Xf) (24%). Xe: UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 251 (9200); pH 7, 256 (8470); pH 13, 263 (8920). NMR: $H_{1'}$=6.19 ppm ($J_{1'-2'}$=4.5 cps), H_2 or H_8=8.06 or 8.71 ppm from DSS in D_2O. $R_{5'-IMP}$ (TLC): F, 1.0; G, 1.0; H, 0.89. Ratio of total phosphorous to 7-D-ribofuranosylhypoxanthine: 1.02. Xf: UV $\lambda_{max}^{H_2O}$ mμ (ε): pH 1, 249 (11400); pH 7, 248.5 (12100); pH 13, 253 (12800). NMR: $H_{1'}$=5.93 ppm ($J_{1'-2'}$=5 cps), H_2 or H_8=8.02 or 8.36 ppm. This compound was identical with an authentic sample of 5′-IMP in its *Rf* value of TLC. Ratio of total phosphorous to inosine: 1.003.

Transphosphoribosylation of 1-(2,3-Di-O-benzoyl-5-diphenylphosphoryl-β-D-ribofuranosyl)uracil (XI) to IIf——A mixture of XI (342 mg), IIf (180 mg), benzoyl chloride (0.2 ml), $HgBr_2$ (360 mg), xylene (0.5 ml) and nitrobenzene (1.5 ml) was heated at 140° for 2 hr. Treating the reaction mixture as described in case of transphosphoribosylation of VI gave VII (202 mg, 54%), mp 154—156° (λ_{max}^{EtOH}: 231 and 275 mμ), and the unchanged XI (99 mg, 29%) was recovered.

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