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A Novel Method for the Synthesis of Purine Nucleosides using Friedel-Crafts Catalysts

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9-β-D-Ribofuranosyladenine was synthesized by condensation of N^6-octanoyladenine (I) with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (II) or 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (III) in *sym*-dichloroethane or chlorobenzene in the presence of Friedel-Crafts catalysts followed by hydrolysis of the acyl groups. By this procedure the formation of the corresponding anomer was not observed. Similarly, 9-β-D-ribopyranosyladenine was synthesized from I and 1,2,3,4-tetra-O-acetyl-β-D-ribopyranose, and 9-β-D-ribofuranosylguanine in high yield from N^2-palmitoylguanine and III.

To date several methods for the synthesis of purine nucleosides have been reported.[2] Among them, the fusion method is superior to the others, in that the method does not require the process of preparing heavy metal salts of purines or halogenosugars. However, the yields by this method widely varied depending upon the kind of purines and the reaction conditions; in fact, the method was not suitable for synthesizing adenosine or guanosine from N^6-acyladenine or N^2-acylguanine respectively, because the yield of the nucleoside was poor[3] and the formation of their isomers was inevitable.[4]

Lemieux and Shyluk[5] have reported the synthesis of methyl and phenyl glucosides by the reaction of 1,2,3,4,6-penta-O-acetyl-β-D-glucose with methanol or phenol in benzene or chloroform in the presence of stannic chloride. We tried to apply this procedure to synthesis of purine nucleosides.

N^6-Acetyl- and N^6-benzoyl-adenine, which are generally used as starting materials for the synthesis of adenine nucleosides, are practically insoluble both in chloroform and in benzene. In order to avoid this disadvantage adenine was heated in pyridine with *n*-octanoic anhydride to obtain N^6-octanoyladenine (I), which was soluble in most organic solvents. The reaction of I with 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (II) (1 eq) in chloroform or in benzene in the presence of stannic chloride, followed by deacylation with sodium methoxide, afforded an ultraviolet absorbing substance corresponding to adenosine as determined by paper electrophoresis. The yield of adenosine by this procedure was not high with the above two solvents. However, it was raised to 53% by the use of *sym*-dichloroethane as solvent (Table I). Ion exchange chromatography of the reaction mixture on Dowex-1 (Cl^-) gave adenine nucleoside fraction, whose nuclear magnetic resonance (NMR) spectrum showed the presence of only adenosine and the absence of other possible isomers. Adenosine was isolated from the fraction as colorless needles. Investigation of the time-yield profile of the reaction revealed that the yield became almost constant after 3 hours (Fig. 1). The use of aluminium chloride, ferric chloride or titanium chloride in place of stannic chloride resulted in somewhat lower yields. In all these experiments the adenosine obtained was exclusively of β-configuration as evidenced by the NMR spectrum. Adenosine was also produced,

1) Location: *Juso-Nishino-cho, Higashiyodogawa-ku, Osaka.*
2) Y. Mizuno, *Protein Nucleic Acid Enzyme* (Tokyo), **10**, 878 (1965).
3) Y. Ishido, A. Hosono, S. Isome, A. Maruyama, and T. Sato, *Bull. Chem. Soc. Japan*, **37**, 1389 (1964).
4) K. Imai, A. Nohara, and M. Honjo, *Chem. Pharm. Bull.* (Tokyo), **14**, 1377 (1966).
5) R.U. Lemieux and W.P. Shyluk, *Canad. J. Chem.*, **31**, 528 (1953).

though in lower yields, when zinc chloride, boron trifluoride–ether complex or phosphorus pentachloride was used (Table II).

Table I. Effect of Solvent on the Yield of Adenosine
Reaction Condition, Reflux 2 hr

No.	N^6–Octanoyladenine mg (mmole)	1–O–Acetyl–2,3,5–tri–O–benzoyl–β–D–ribofuranose mg (mmole)	$SnCl_4$ mg (mmole)	Solvent ml	Yield[a] %
1	26.1(0.1)	50.5(0.1)	26(0.1)	Chloroform, 2	Trace
2	26.1(0.1)	50.5(0.1)	26(0.1)	Benzene, 2	22
3	104.4(0.4)	202 (0.4)	52(0.2)	*sym*–Dichloroethane, 10	31
4	104.4(0.4)	202 (0.4)	104(0.4)	*sym*–Dichloroethane, 10	53

a) Determined by paper electrophoresis.

Baker, *et al.*[6-8] carried out the chlorination of 1–O–acetyl–2,5–di–O–benzoyl–3–acetamido–3–deoxy–D–ribofuranose with titanium chloride, and they used the resulting chlorosugar–titanium chloride complex, without isolation, for coupling with chloromercuri–2–methylmercapto–6–dimethylaminopurine or chloromercuri–N^6–benzoyladenine to give the corresponding nucleoside. As compared with Baker's procedure, the present technique eliminates the step of preparing chloromercuri derivatives of purines. Yamaoka, *et al.*[9] have developed a new method involving the direct condensation of heterocyclic imino compounds with acylglycosyl halides in the presence of hydrogen halide acceptors. Our method requires neither the step for halogenation of acylsugars nor the use of hydrogen halide acceptors.

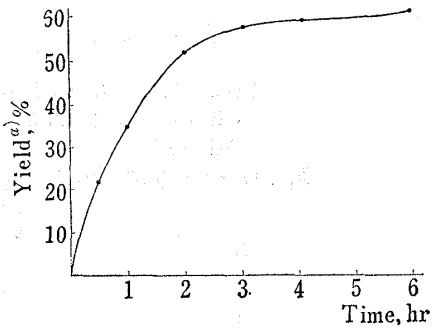


Fig. 1. Effect of Reaction Time on the Yield of Adenosine.
Reaction Mixture: N^6–Octanoyl adenine, 130.6 mg (0.5 mmole); 1–O–Acetyl–2,3,5–tri–O–benzoyl–β–D–ribofuranose, 252 mg (0.5 mmole); $SnCl_4$, 130 mg (0.5 mmole); *sym*–Dichloroethane, 12 ml
a) See Table I

Condensation of I with 1,2,3,5–tetra–O–acetyl–β–D–ribofuranose (III), which is more economical than II, in the presence of stannic chloride in *sym*–dichloroethane followed by deacylation furnished adenosine. The maximum yield was obtained when 1.25 mole each of I and stannic chloride per 1 mole of III was used (Table III). It should be pointed out that the yield of adenosine was greatly affected by a choice of Friedel–Crafts catalyst and solvent (Table IV), *i.e.*, stannic chloride resulted in better yields with a low boiling solvent such as *sym*–dichloroethane or carbon disulfide (No. 22>27, 26>32), whereas aluminium chloride was more satisfactory with a high boiling solvent such as chlorobenzene, *sym*–tetrachloroethane or xylene (No. 23<28, 24<30, 25<31), the maximum yield being 66%.

Condensation of 1,2,3,4–tetra–O–acetyl–β–D–ribopyranose with I in the presence of aluminium chloride in chlorobenzene gave, after deacylation and ion-exchange chromatography on Dowex–1 (Cl^-), 9–β–D–ribopyranosyladenine.[10]

Our attempts at the synthesis of guanosine from N^2–acetylguanine was unsuccessful on account of insufficient solubility of N^2–acetylguanine in the solvent. Therefore, N^2–octanoyl– (IV) and N^2–palmitoyl–guanine (V) were synthesized, which were moderately

6) B.R. Baker, R.E. Schaub, J.P. Joseph, and J.W. Williams, *J. Am. Chem. Soc.*, **77**, 12 (1955).
7) B.R. Baker and R.E. Schaub, *J Am Chem. Soc*, **77**, 2396 (1955).
8) B.R. Baker, R.E. Schaub, and H.M. Kissman, *J. Am. Chem. Soc.*, **77**, 5911 (1955).
9) N. Yamaoka, K. Aso, and K. Matsuda, *J. Org. Chem.*, **30**, 149 (1965).
10) M. Viscontini and S. Huwyler, *Helv. Chim. Acta*, **43**, 782 (1960).

Table II. Effect of Catalyst on the Yield of Adenosine
N^6-Octanolyladenine, 104.4 mg (0.4 mmole); 1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose, 202 mg (0.4 mmole); Solvent, 10 ml; Reaction Condition, Reflux 2 hr

No.	Catalyst, mg (mmole)	Solvent	Yield[a] (%)
5	$AlCl_3$, 26.7(0.2)	*sym*-Dichloroethane	21
6	$AlCl_3$, 53.4(0.4)	*sym*-Dichloroethane	40
7	$FeCl_3$, 64.9(0.4)	*sym*-Dichloroethane	40
8	$TiCl_4$, 75.9(0.4)	*sym*-Dichloroethane	31
9	$ZnCl_2$, 54.6(0.4)	*sym*-Dichloroethane	7
10	47% BF_3·Ether complex, 57.6(0.4)	*sym*-Dichloroethane	20
11	PCl_5, 20.8(0.1)	*sym*-Dichloroethane	0
12	PCl_5, 83.3(0.4)	*sym*-Dichloroethane	Trace
13	PCl_5, 20.8(0.1)	*sym*-Tetrachloroethane	16
14	PCl_5, 30 (0.144)	*sym*-Tetrachloroethane	18
15	PCl_5, 83.3(0.4)	*sym*-Tetrachloroethane	0

a) See Table I.

Table III. Effect of the Molar Ratios of N^6-Octanoyladenine (I) and Stannic Chloride to 1,2,3,5-Tetra-O-acetyl-β-D-ribofuranose (III) on the Yield of Adenosine.
III, 127.2 mg (0.4 mmole); *sym*-Dichloroetnane, 10 ml; Reaction Condition, Reflux 2 hr

No.	Molar ratio I/III	Molar ratio $SnCl_4$/III	Yield[a] (%)
16	0.5	1.0	11
17	1.0	1.0	55
18	1.0	1.5	4
19	1.0	2.0	11
20	1.25	1.25	62
21	2.0	1.0	24

a) Based on III. See Table I.

Table IV. Effect of Catalyst and Solvent on the Yield of Adenosine
1,2,3,5-Tetra-O-acetyl-β-D-ribofuranose, 127.2 mg (0.4 mmole); Solvent, 10 ml; Reaction Condition, Reflux 2 hr

No.	N^6-Octanoyladenine mg (mmole)	Catalyst mg (mmole)	Solvent	Yield[a] (%)
22	130.6(0.5)	$SnCl_4$, 130 (0.5)	*sym*-Dichloroethane	62
23	130.6(0.5)	$SnCl_4$, 130 (0.5)	Chlorobenzene	40
24	104.4(0.4)	$SnCl_4$, 104 (0.4)	*sym*-Tetrachloroethane	24
25	104.4(0.4)	$SnCl_4$, 104 (0.4)	Xylene	26
26	104.4(0.4)	$SnCl_4$, 104 (0.4)	Carbon disulfide	42
27	130.6(0.5)	$AlCl_3$, 66.7(0.5)	*sym*-Dichloroethane	52
28	130.6(0.5)	$AlCl_3$, 66.7(0.5)	Chlorobenzene	66
29	104.4(0.4)	$AlCl_3$, 53.4(0.4)	Chlorobenzene	59
30	104.4(0.4)	$AlCl_3$, 53.4(0.4)	*sym*-Tetrachloroethane	30
31	104.4(0.4)	$AlCl_3$, 53.4(0.4)	Xylene	48
32	104.4(0.4)	$AlCl_3$, 53.4(0.4)	Carbon disulfide	0
33	104.4(0.4)	$AlCl_3$, 53.4(0.4)	Dimethylformamide	8
34	104.4(0.4)	$AlCl_3$, 53.4(0.4)	Dimethylsulfoxide	0
35	104.4(0.4)	$FeCl_3$, 64.9(0.4)	*sym*-Tetrachloroethane	15
36	104.4(0.4)	$FeCl_3$, 32.5(0.2)	*sym*-Tetrachloroethane	24
37	104.4(0.4)	$FeCl_3$, 30 (0.185)	Dioxane	17
38	104.4(0.4)	BF_3·Ether,[b] 57.6(0.4)	Benzene	23
39	104.4(0.4)	BF_3·Ether,[b] 57.6(0.4)	Carbon disulfide	16

a) See Table I. b) See Table II.

soluble in the solvent under heating. The reaction of IV and V with III in chlorobenzene in the presence of aluminium chloride and subsequent removal of the protecting group afforded an ultraviolet absorbing spot corresponding to guanosine in the yield of 36 and 66%, respectively, as determined by paper electrophoresis (Table V). In the latter case the reaction mixture was purified by ion-exchange chromatography on Dowex-1 (Cl^-) to isolate guanosine in 59% yield. From the mother liquor was obtained a small quantity of an ultraviolet absorbing substance,[11] which was insufficient for further investigation.

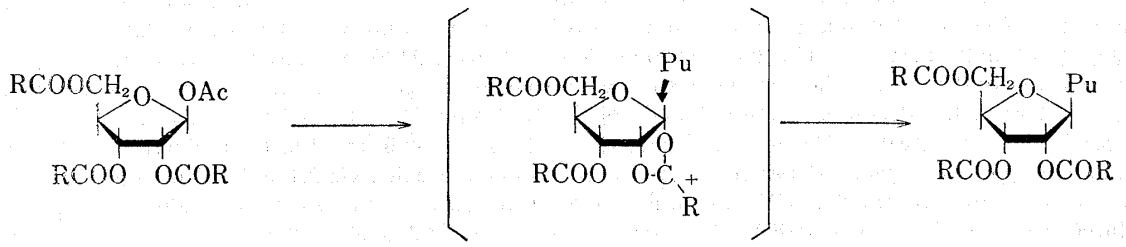
Table V. Condensation of N^2-Acylguanine and 1,2,3,5-Tetra-O-acetyl-β-D-ribofuranose (III)

No.	N^2-Acylguanine (mg) (mmole)	III (mg) (mmole)	Catalyst (mg) (mmole)	Solvent (ml)	Reflux time (hr)	Yield[a] (%)
1	N^2-Acetylguanine 96.5 (0.5)	127.2 (0.4)	$SnCl_4$ 130 (0.5)	*sym*-Dichloroethane 10	7	0
2	N^2-Acetylguanine 96.5 (0.5)	127.2 (0.4)	$AlCl_3$ 66.7 (0.5)	*sym*-Dichloroethane 10	7	3
3	N^2-Octanoylguanine 27.7 (0.1)	31.8 (0.1)	$AlCl_3$ 13.3 (0.1)	Chlorobenzene 2	2	36
4	N^2-Palmitoylguanine 38.9 (0.1)	31.8 (0.1)	$AlCl_3$ 13.3 (0.1)	*sym*-Dichloroethane 2	2	10
5	N^2-Palimtoylguanine 38.9 (0.1)	31.8 (0.1)	$AlCl_3$ 13.3 (0.1)	Chlorobenzene 2	2	66

a) See Table I.

There has been reported a fusion method, in which the synthesis of guanosine from N^2-acetylguanine has been described. The method, however, gave a mixture of 9-α-, 9-β-, 7-α- and 7-β-isomers.[4] On the other hand, the chloromercuri method furnished 7-β- and 9-β-isomers each of glucopyranosyl-[12] and 3'-deoxy-D-ribofuranosylguanine[13] in low yields. We have succeeded for the first time in synthesizing guanosine from guanine *via* N^2-palmitoylguanine in high yield.

The mechanism of the reaction of pentaacetyl-β-D-glucopyranose with methanol or phenol in the presence of stannic chloride has been explained on the basis of a cyclic carbonium ion intermediate, which is prone to nucleophilic attack by methanol or phenol to give the β-glucoside. The stereospecific nature of our method for the synthesis of nulecosides would probably be explicable on the basis of a similar mechanism as summarized in Chart 1.



II : R=phenyl

III : R=methyl

Pu : Purine Base

Chart 1

11) The UV spectrum of this substance was identical with those of 7-methylguanine (J.M. Gulland and L.F. Story, *J. Chem. Soc.*, **1938**, 692).

12) Z.A. Shabarova, Z.P. Polyakova, and M.A. Prokofev, *Zh. Obshch. Khim.*, **29**, 215 (1959); *Chem. Abstr.*, **53**, 21998 (1959).

13) S.R. Jenkins, F.W. Holly, and E. Walton, *J. Org. Chem.*, **30**, 2851 (1965).

Experimental[14]

N^6-Octanoyladenine (I)——To a suspension of adenine (4.46 g, 33 mmoles) in pyridine (60 ml) was added *n*-octanoic anhydride (21.8 g, 80 mmoles) and the mixture was refluxed for 2 hr. Pyridine was removed *in vacuo* from the reaction mixture and EtOH (140 ml) was added to the residue. The mixture was refluxed for 2 hr and cooled. The resulting crystals were recrystallized from EtOH (150 ml) to give colorless leaflets (7.2 g, 84% yield). mp 188°. *Anal.* Calcd. for $C_{13}H_{19}ON_5$: C, 59.77; H, 7.24; N, 26.71. Found: C, 60.05; H, 7.54; N, 27.00. UV mμ: λ_{max}^{EtOH} 271, λ_{min}^{EtOH} 239. IR ν_{max}^{KBr} cm^{-1}: 1690 (carbonyl).

General Method of Condensation——A mixture of an acyl-adenine or -guanine and 1,2,3,5-tetra-O-acyl-β-D-ribofuranose was refluxed in an appropriate solvent in the presence of a Friedel-Crafts catalyst. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in 2.3% NaOMe in MeOH (2 ml per 0.1 mmole of 1,2,3,5-tetra-O-acyl-β-D-ribofuranose) and refluxed for 1 hr. The solution was evaporated to dryness *in vacuo*. The residue was taken up in H_2O and neutralized with AcOH. The resulting precipitate was centrifuged off and an aliquot of the supernatant was subjected to paper elelctrophoresis (0.05 M borax, pH 9.2). An UV-absorbing spot corresponding to adenosine or guanosine was eluted from the filter paper with 0.1 N NH_4OH and the amount of the nucleoside was determined spectrophotometrically at 260 mμ.

Adenosine (9-β-D-Ribofuranosyladenine)——A mixture of I (130.6 mg, 0.5 mmole), 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (III) (127.2 mg, 0.4 mmole) and $AlCl_3$ (66.7 mg, 0.5 mmole) was refluxed in chlorobenzene (10 ml) for 2 hr (Table IV, No. 28). The reaction mixture was deacylated as described above and desalted with activated charcoal. The pH of the solution was adjusted to 11 with NH_4OH and the solution applied to a column (5 ml) of Dowex-1 (Cl^-). The column was eluted with 0.01 M NH_4Cl-NH_4OH (pH 10.5) and the eluate (200 ml, TOD_{260}[15] 3810) was again desalted with activated charcoal and evaporated to dryness *in vacuo*. The residue was recrystallized from H_2O to give colorless needles (64 mg, 60% yield). mp 229—230° (decomp.). *Anal.* Cacld. for $C_{10}H_{13}O_4N_5$: C, 44.94; H, 4.90; N, 26.21. Found: C, 45.17; H, 5.19; N, 26.41. UV mμ: $\lambda_{max}^{pH\,2}$ 257, $\lambda_{min}^{pH\,2}$ 230, $\lambda_{max}^{pH\,6}$ 260, $\lambda_{min}^{pH\,6}$ 227. $[\alpha]_D^{24}$ −60.7° (c=1.0, H_2O). NMR τ: $H_{1'}$ 4.15 (doublet, $J_{1'2'}$=6.0 cps). Adenosine was similarly isolated from the reaction mixture; Table I (No. 4), Table II (Nos. 6, 7, 8), Table III (No. 17) and Table IV (No. 27).

9-β-D-Ribopyranosyladenine——A mixture of I (261.2 mg, 1 mmole), 1,2,3,4-tetra-O-acetyl-β-D-ribopyranose (254.4 mg, 0.8 mmole) and $AlCl_3$ (133.4 mg, 1 mmole) was refluxed in chlorobenzene for 3 hr. The reaction mixture was worked up as descirbed for adenosine to give colorless needles (75 mg, 35% yield). mp 235—240° (decomp.). *Anal.* Calcd. for $C_{10}H_{13}O_4N_5 \cdot \frac{1}{2}H_2O$: C, 43.45; H, 5.07; N, 25.32. Found: C, 44.29; H, 5.38; N, 25.23. UV mμ: $\lambda_{max}^{pH\,2}$ 256, $\lambda_{min}^{pH\,2}$ 228, $\lambda_{max}^{pH\,6}$ 259, λ_{min}^{pH6} 225. $[\alpha]_D^{24}$ −30.0° (c=0.3, H_2O). [lit.[9] mp 237° (decomp.), $[\alpha]_D^{23}$ −38° (c=0.34, H_2O)] NMR τ: $H_{1'}$ 4.36 (doublet, $J_{1'2'}$=9.0 cps).

N^2-Palmitoylguanine (V)——To a suspension of guanine (604 mg, 4 mmoles) in pyridine (20 ml) was added palmitoyl chloride (3.3 g, 12 mmoles) and the mixture was refluxed for 2 hr. Pyridine was removed *in vacuo* from the reaction mixture. The residue was suspended in EtOH (200 ml) and refluxed for 1 hr. The insoluble matter was filtered while hot and washed with hot EtOH (200 ml) to give a white powder (1.4 g, 90% yield). *Aanl.* Calcd. for $C_{21}H_{35}O_2N_5$: C, 64.73; H, 9.07; N, 17.97. Found: C, 64.58; H, 9.34; N, 17.92. IR ν_{max}^{KBr} cm^{-1}: 2930 (methylene).

Guanosine (9-β-D-Ribofuranosylguanine)——A mixture of V (585 mg, 1.5 mmole), III (382 mg, 1.2 mmole) and $AlCl_3$ (200 mg, 1.5 mmole) was refluxed in chlorobenzene (40 ml) for 4 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was dissolved in 2.3% NaOMe in MeOH (30 ml) and refluxed for 1 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was taken up in H_2O (80 ml) and applied to a column (90 ml) of Dowex-1 (Cl^-). The column was eluted with 0.06 M KCl+0.04 M $Na_2B_2O_7$ to obtain 2 fractions. The 2nd fraction (3.5 liter, TOD_{260} 9400) was desalted with activated charcoal and evaporated to dryness. The residue was recrystallized from H_2O to give colorless needles (200 mg, 59% yield). mp 230—240° (decomp.). *Anal.* Calcd. for $C_{10}H_{13}O_5N_5 \cdot \frac{1}{2}H_2O$: C, 41.10; H, 4.83; N, 23.96. Found: C, 41.25; H, 5.05; N, 24.04. UV mμ: $\lambda_{max}^{pH\,2}$ 257, $\lambda_{max}^{pH\,6}$ 252. $[\alpha]_D^{25}$ −60.9° (c=1.0, 0.1 N NaOH). NMR τ: $H_{1'}$ 4.20 (doublet, $J_{1'2'}$=6.5 cps). Paper chromatography (isobutyric acid: N/2 NH_4OH 10:6, ascending method) of the mother liquor revealed 2 UV absorbing spots at *Rf* 0.51 (=guanosine) and 0.60. The latter spot was eluted from the filter paper with 1 N NH_4OH. UV mμ: $\lambda_{max}^{pH\,1.5}$ 250, $\lambda_{min}^{pH\,1.5}$ 230; $\lambda_{max}^{pH\,6}$ 283, $\lambda_{min}^{pH\,6}$ 260; $\lambda_{max}^{pH\,13}$ 282, $\lambda_{min}^{pH\,13}$ 258.

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14) All melting points were uncorrected. NMR spectra were recorded on a Varian A-60 spectrometer in NaOD using tetramethylsilane as an external standard.

15) TOD_{260}=optical density at 260 mμ × ml.