Condensation Reactions of Adenine Derivatives with 1-*O*-Acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in Nitrophenols

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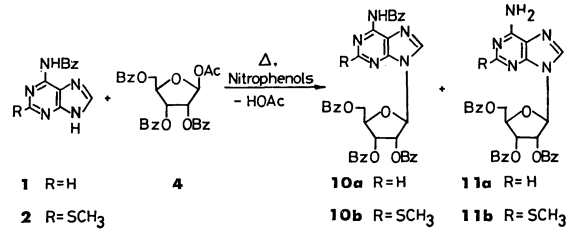
Intermolecular interaction between nitrophenols, such as *m*-, *p*-nitrophenol, 2,4-dinitrophenol, and picric acid, and adenine derivatives, such as $N_{(6)}$-benzoyladenine, $N_{(6)}$-benzoyl-2-methylthioadenine, and $N_{(6)}$-benzyladenine, was verified by the formation of the corresponding molecular compounds. On the basis of these results, condensation reactions of these adenine derivatives with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose were carried out in nitrophenols, which were used as the activating agents. They were proved to afford the corresponding nucleosides in good yields. In addition, a novel glycosyl rearrangement reaction was first observed in the case of the reaction of $N_{(6)}$-benzyladenine with the ribofuranosyl acylate.

In a previous paper[1] we described a new procedure for the synthesis of purine nucleosides involving the condensation reaction of a fully-acetylated sugar with a purine in the presence of activating agents. As an extension of this reaction, the authors now wish to report the reactions of some adenine derivatives, such as $N_{(6)}$-benzoyladenine(**1**), $N_{(6)}$-benzoyl-2-methylthioadenine(**2**), and $N_{(6)}$-benzyladenine(**3**), with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose(**4**) in nitrophenols as the activating agent, and a novel glycosyl migration reaction which was confirmed in the reaction of **3** with **4**.

Results and Discussion

The previous investigation[1] led us to assumptions that a purine may be activated by an activating agent through polarization bonding[2] and that the activated degree of a purine may be delicately varied in terms of both the mutual positions and the properties of each functional group on the aromatic nuclei of the agents and the purine nuclei. In attempts at the reactions of these adenine derivatives with **4**, a series of nitrophenols were used as potential activating agents because of their properties of forming the corresponding molecular compounds with the adenines. Such properties are conceivably intimately related to some species of intermolecular interaction such as polarization bonding; the purine counterparts may potentially be activated by forming them. In the same manner as had been described for the preparation of the molecular compound of theophylline with *p*-nitrophenol,[1] the adenines (1 mmol) were treated with an excess amount of *o*-(**5**), *m*-(**6**), *p*-nitrophenol(**7**), 2,4-dinitrophenol(**8**), or picric acid(**9**) to afford the corresponding molecular compounds, summarized in Table 1. As may be seen from the table, almost all of the molecular compounds are composed of the equimolar counterpart except those obtained from **2** and **8**, and from **3** and **7**, in the ratios of 2 : 1 and 1 : 2 respectively. The precipitated crystalline product in the cases of **1** with **9** and of **2** with **6**, however, showed broad melting points and analytically proved to have no definite integral ratio in their counterpart composition. At any rate, such differences in the ratios may provide quite an interesting problem relevant to the structures of these molecular compounds and the activation mechanism of their purine counterparts; it can thus be deduced that some intermolecular interaction such as polarization bonding[2] may play an important role in forming these compounds. Although no interpretation with respect to such phenomenon has yet been furnished, the problem is exceedingly complicated because of the following facts: 1) **5** was proved not to form a molecular compound with theophylline and showed no activating effect on it.[1] 2) *p*-Toluenesulfonamide activates theophylline to condense with an acetylated sugar, although it forms no molecular compound with it,[1] *etc.*

On the basis of the above evidence, the condensation reactions of **1**, **2**, and **3** with **4** were attempted in these potential activating agents under the conditions described in Table 2, in which the results thus obtained are summarized. In each case, a purine derivative was previously fused together homogeneously with the potential agent, and an equimolar amount of **4** was then added to the prefused mixture. The mixture was allowed to react under the corresponding conditions with continuous stirring under atmospheric pressure. After the removal of the agent, each resultant mixture was subjected to chromatography on a silica gel column by the use of a solvent system of cyclohexane–chloroform (1 : 1 v/v).



Scheme 1.

In a series of reactions of **1** with **4**, $N_{(6)}$-benzoyl-9-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine(**10a**) and 9-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**11a**) were produced, together with the corresponding nitrophenyl benzoates.[3] The failure to isolate the corresponding benzoate in the case of **8** may be ascribed to its stronger acidity(pK_a 4.11); thus, the

1) M. Sekiya, T. Yoshino, H. Tanaka, and Y. Ishido, This Bulletin, **46**, 556 (1973).

2) S. C. Wall work, *J. Chem. Soc.*, **1961**, 494.

3) Such transacylation reactions are now under investigation in our laboratory, and the detailed results will be published elsewhere.

Table 1. Attempted syntheses of molecular compounds of adenines with nitrophenols[a]

Adenine derivatives	Nitrophenols	Ratios of counterparts (Adenines: Nitrophenols)	Molecular compounds: Mp (°C)	Calcd (%) C	Calcd (%) H	Calcd (%) N	Found (%) C	Found (%) H	Found (%) N
$N_{(6)}$-Benzoyladenine(**1**)	*m*-Nitrophenol(**6**)	1 : 1	116—119	57.14	3.73	22.21	56.86	3.73	21.96
	p-Nitrophenol(**7**)	1 : 1	196—197	57.14	3.73	22.21	56.70	3.96	22.34
	2, 4-Dinitrophenol(**8**)	1 : 1	167—168	51.05	3.12	23.15	50.68	2.88	23.27
	Picric acid(**9**)[b]	—	—	—	—	—	—	—	—
$N_{(6)}$-Benzoyl-2-methylthioadenine(**2**)	**6**[b]	—	—	—	—	—	—	—	—
	7	1 : 1	172—173	53.76	3.80	19.81	54.02	3.59	19.83
	8	2 : 1	195—200	51.10	3.45	22.25	51.02	3.43	22.24
	9	1 : 1	207—208	44.30	2.72	21.76	44.34	2.65	21.78
$N_{(6)}$-Benzyladenine(**3**)	**6**	1 : 1	135(169—175)[c]	59.33	4.43	23.07	59.09	4.40	22.71
	7	1 : 2	153—156	57.25	4.17	19.48	57.59	3.94	20.02
	8	1 : 1	190—193	52.81	3.69	23.95	53.05	3.46	24.23
	9	1 : 1	223—224.5	47.58	3.10	24.66	47.36	3.11	24.61

a) All the syntheses were carried out by the use of the adenines (1 mmol) and nitrophenols (3 mmol), respectively, in chloroform (30—40 ml) under reflux. b) Crystalline products in these cases showed broad melting point, and no definite integral ratio analytically in their counterparts. c) Dimorphism was observed in this case.

Table 2. Condensation reactions of adenine derivatives (**1**, **2**, and **3**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranose (**4**) in the presence of nitrophenols[a]

Adenine derivatives	Nitrophenols	Reaction conditions: Temp, °C	Reaction conditions: Period, hr	Products (Yields, %): Nitrophenyl[b] benzoates	Products (Yields, %): Nucleosides
1	**6**	130—135	1.5	81.5	**10a** (3.1), **11a** (50.5)
1	**7**	130—135	3	12.6	**10a** (2.1), **11a** (20), [**12**(46)]
1	**8**	140—145	1.5	—	**10a** (32.5), **11a** (3.5)
2	**6**	130—135	3	78.5	**10b** (3.7), **11b** (45.5)
2	**7**	130—135	3	9.5	**10b** (8.2), **11b** (7.3), [**12**(43)]
2	**8**	140—145	3	—	**10b** (45.5), **11b** (9.8)
3	**8**	140—145	1.5	—	**13c** (85[c])

a) All the reactions were carried out by the use of adenines (13 mmol) and **4** (10 mmol) in the presence of nitrophenols (50 mmol, except in the case of **3**; 65 mmol). b) These yields were calculated with reference to **1** or **2**. c) This yield stands for that of debenzoylated nucleoside by treating **13a** with methanolic sodium methoxide solution.

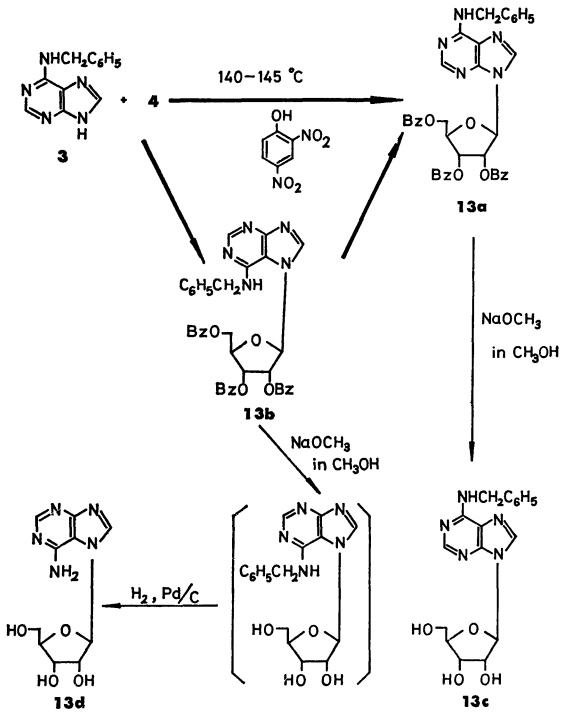
Table 3. NMR spectral data of $N_{(6)}$-benzyl-9-(**14a**) and -7-(2',3',5'-tri-*O*-acetyl-*β*-D-ribofuranosyl)adenine(**14b**)

Protons	Chemical shift[a]: **14a**	Chemical shift[a]: **14b**
CH_3-CO-O-	2.10 and 2.16 (9H)	2.14 (narrow d, 9H)
H-5'a, -5'b, and -4'	4.44 (m, 3H)	4.50 (m, 3H)
C_6H_5-CH_2-N-	4.82 (d, J_{CH_2-NH}=6Hz, 2H)[b]	4.97 (broad s, 2H)
H-3'	5.73 (m)	5.75 (m)
H-2'	5.98 (t, $J_{2',3'}$=5.1Hz)	5.98 (q, $J_{2',3'}$=5.5Hz)
H-1'	6.12 (d, $J_{1',2'}$=5.1Hz)	6.36 (d, $J_{1',2'}$=4.0Hz)
C_6H_5-CH_2-NH-	6.92 (t)[c]	—
C_6H_5-CH_2-	7.27 (s, 5H)	7.18 (s, 5H)
H-2 or H-8	7.86 (s, 1H)	7.84 (s, 1H)[d]
H-8 or H-2	8.45 (s, 1H)	8.21 (s, 1H)

a) These data were recorded in δ value, and determined in $CDCl_3$—TMS. b) The doublet was collapsed into a singlet on addition of deuterium oxide. c) The broad triplet was vanished by the addition of deuterium oxide. d) The signal was observed as an exceedingly broadened singlet comparing with that of **14a**.

predominant formation of **10a** in this case fully agrees with this fact. Moreover, **5** was found to be ineffective for the reaction, and **9**, inadequate, since a remarkable coloration, which may arise from the possible decomposition of the starting materials or products, was inevitably present even when we reduced the reaction period. These agents in this case can thus be ranked in effectiveness as **6**, **8**, **7**, and **5** on the basis of the total yields of the nucleosides, **10a** and **11a**, shown in Table 2, although the reaction temperature in the case of **8** must be about 10 °C higher than those in the other cases in order to make the reaction system homogeneous. It is of interest to compare the acidity of these agents, *e.g.*, **6**(pK_a 8.40) or **8**(pK_a 4.11), with that of *p*-toluenesulfonic acid(pK_a < 1.0), which has previously been used as the catalyst for the fusion method, or with that of acetic acid(pK_a 4.76), which has been shown to be ineffective as a catalyst.[4] The debenzoylation of **10a** and **11a** was carried out by treating it with a methanolic sodium methoxide solution at room temperature, thus affording $N_{(6)}$-benzoyladenosine and adenosine in 35% and 84% yields respectively. The UV spectral data of the former were substantially consistent with those of the $N_{(6)}$-benzoyl-2-deoxyadenosine phosphate derivatives.[5] Interestingly, moreover, *p*-nitrophenyl 2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside (**12**) (46% yield) was obtained concomitantly in the reaction in **7**, unlike those in **6** or **8**; the small formation of the corresponding phenyl glycosides can be noticed by tlc in the latter two cases, although no reason for it has yet been given. This fact is also of interest for its contrast with the autocatalytic fusion reaction of fully-acetylated sugars with **6** and **7** respectively, in which scarcely no such difference in their reactivity is observed.[6]

In a series of reactions of **2** with **4**, the concomitant formation of $N_{(6)}$-benzoyl-2-methylthio-9-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine(**10b**) and 2-methylthio-9-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine (**11b**) was similarly observed; The tendencies of the relative yields of **10b**, **11b**, and the corresponding nitrophenyl benzoates[3] were, as may be seen in Table 2, similar to those observed in the reaction of **1** with **4**. The effectiveness of the agents, however, varied in this case, they can be ranked as **8**, **6**, **7**, and **5** on the basis of the total yields of the nucleosides, **10b** and **11b**. Unlike the case of **10a**, the selective de-*O*-benzoylation of **10b** could not be attained because of the instability of the $N_{(6)}$-benzoyl group of **10b**: however, the complete debenzoylation of **10b** and **11b** was successfully carried out by treating them with a methanolic sodium methoxide solution to give 2-methylthioadenosine in 87% and 60% yields respectively. The reaction in **7** afforded **12** in a 43% yield, much as in the preceding series of reactions.



Scheme 2.

In a series of reactions of **3** with **4**, on the other hand, **5**, **6**, and **7** exhibited no activating effect on **3**; only **8** was found to be effective for the reaction. Moreover, **9** was concluded to be inadequate for the reaction, since it brought about a remarkable coloration such as has been mentioned, although it promotes the reaction. The condensation reaction in **8**, followed by the removal of **8** and debenzoylation, afforded $N_{(6)}$-benzyladenosine(**13c**) in an 85% yield under the conditions shown in Table 2. On following this reaction by the tlc technique with the passage of time, we also detected a glycosyl migration reaction of 7-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)-$N_{(6)}$-benzyladenine (**13b**) to the corresponding 9-ribosyl isomer(**13a**). The outline of such a glycosyl migration can easily be detected, as is demonstrated in Fig. 1. The faster-moving spot (R_f 0.84) and the slower-moving one (R_f 0.70) were found to correspond to **13a** and **13b** respectively. After the removal of **8** from the resultant reaction mixture (reaction period: 90 min), the mixture was chromatographed on a silica gel column, and then concentrated *in vacuo* to afford a sirup of **13a** (43% yield) as the first fraction and **13b** (9% yield) as the second one. The usual debenzoylation of **13a** with a methanolic sodium methoxide solution gave **13c** in an 84% yield. **13b** was, on the other hand, easily crystallized on trituration with a small amount of acetone, and a portion of the crystals was converted into 7-β-D-ribofuranosyladenine(**13d**) by debenzoylation and by subsequent debenzylation with hydrogen on palladized charcoal. The UV spectral properties of this product were consistent with those reported by Montgomery and Thomas.[7] The anomeric configuration of **13b** was deduced to be β from its

4) A. Hosono, K. Fujii, T. Tada, H. Tanaka, Y. Ohgo, Y. Ishido, and T. Sato, This Bulletin, **46**, 2814 (1973).

5) R. K. Ralph and H. G. Khorana, *J. Amer. Chem. Soc.*, **83**, 2926 (1961); Y. Lapidot and H. G. Khorana, *ibid*, **86**, 3857 (1963).

6) Unpublished data, H. Tanaka, M. Sekiya, K. Iwabuchi, M. Sato, K. Fujii, Y. Ishido, and T. Sato; The results will published elsewhere.

7) E. M. Montgomery and H. J. Thomas, *J. Amer. Chem. Soc.*, **85**, 2672 (1963).

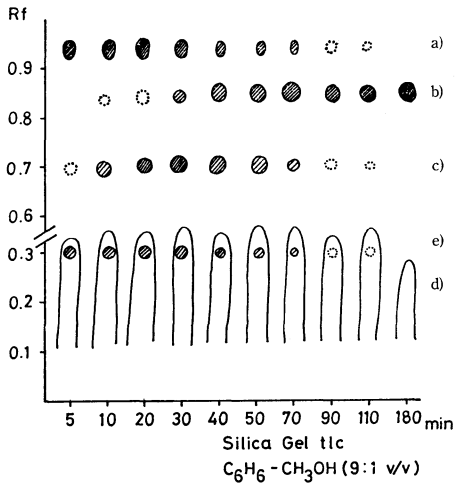


Fig. 1. The outline of the condensation reaction of $N_{(6)}$-benzyladenine(**3**) with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose(**4**) in the presence of 2,4-dinitrophenol(**8**) observed in tlc; a: **4**, b: **13a**, c: **13b**, d: **8**, and e: **3**.

specific rotational value ($[\alpha]_D^{30}$ −65°). Subsequently, the above-observed glycosyl migration reaction of **13b** into **13a** was confirmed by fusing the sirup of **13b** in an excess amount of **8** at 140—145 °C with stirring and by following its process thin-layer chromatographically as has been described above. A novel glycosyl migration reaction was thus first observed in the fusion reaction of a fully-acylated sugar with a purine; it is of interest in contrast with the $N_{(3\text{ or }7)} \rightarrow N_{(9)}$ alkyl and glycosyl migration, which had been observed in the condensation reaction of adenine derivatives with alkyl or blocked glycosyl halides.[8]

In order to elucidate the possibility of the concomitant formation of the corresponding α-anomers in these reactions, a condensation reaction of 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose with **3** in **8** was attempted, since the confirmation of the α-anomer formation may possibly be unattainable by nmr spectroscopy because of the benzyl aromatic proton signals, which are observed between δ 7.2—8.1.

The reaction was unexpectedly accompanied by a considerable coloration; however, the same treatment of the resultant mixture as has been described for the reaction of **3** with **4** afforded the sirups of $N_{(6)}$-benzyl-9-(**14a**)(20% yield) and -7-(2′,3′,5′-tri-*O*-acetyl-β-D-ribofuranosyl)adenine(**14b**)(9% yield). The NMR data of these products are summarized in Table 3; an examination of their anomeric proton region by means of the signal-to-noise enhancement (120 times) proved them to be composed of the β-nucleosides exclusively. Thus, these condensation reactions involving **4** were concluded to give the corresponding nucleosides with the anomeric configuration of β, although a more detailed investigation would be required to elucidate the mechanism of the glycosyl migration reaction.[9] **14a** was derived into **13c** by deacetylation with a methanolic sodium methoxide solution in a 93% yield; its structure was thus confirmed. The deacetylated product from **14b** was identified with that obtained from **13b** by thin-layer and paper chromatography and by studying the UV spectra.

In view of these results, the assumptions with respect to the activation mechanism of the purine counterparts,[1] described at the beginning of this article, can be said to be supported.

8) M. Miyaki, Doctoral Thesis, Hokkaido Univ., 1968; B. Shimizu and M. Miyaki, *Chem. Pharm. Bull.* (Tokyo), **18**, 570 (1970); M. Miyaki and B. Shimizu, *Agr. Biol. Chem.*, **33**, 119 (1969).

9) This work is now in progress in our laboratory.

Experimental

All the melting points are uncorrected. The IR absorption spectra were taken with a Hitachi EPI-2S apparatus. The UV absorption spectra were measured on a Hitachi EPS-3T apparatus in purified ethanol or distilled water. The NMR spectra were determined with a Varian T-60 apparatus in deuteriochloroform, using tetramethylsilane as the internal standard. The plates for tlc examination were prepared with Wakogel B-5F, and the solvent system of 9 : 1 v/v benzene–methanol was used for the development. Paper chromatography was carried out using Toyo-Roshi No. 50 filter paper, while solvent system of 86 : 14 v/v *n*-butanol–distilled water was used for the development. The confirmation of each spot was done with a UV lamp (S. L. Light, Tokyo Machinery Co., Ltd.; 2537 and 3650 Å) or by spraying a diluted aqueous sulfuric acid solution on the tlc plates and then heating them.

Preparations of Molecular Compounds of $N_{(6)}$*-Benzoyladenine (**1**),* $N_{(6)}$*-Benzoyl-2-methylthioadenine(**2**), and* $N_{(6)}$*-Benzyladenine(**3**) with the Nitrophenols.* The method of preparation is exemplified by that of compound of **1** with picric acid(**9**): **1**(239 mg, 1 mmol) and **9**(687 mg, 3 mmol) were dissolved in chloroform(30—40 ml) under reflux, and the resultant solution was allowed to cool at room temperature for crystallization. After cooling overnight, the precipitated crystals were filtered by suction and dried over phosphorus pentoxide *in vacuo* at 110°C to give a molecular compound of **1** with **9**. The other molecular compounds were prepared in the same manner; all the results thus obtained are the summarized in Table 1.

The Condensation Reactions of $N_{(6)}$*-benzoyladenine(**1**) with 1-O-Acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (**4**) in the Presence of* m-*(**6**),* p-*Nitrophenol (**7**), or 2,4-Dinitrophenol (**8**).* *a)* The reaction with **6** : **1** (3.1 g, 13 mmol) and **6**(6.9 g, 50 mmol) were heated at 130—135 °C to fuse them homogeneously under stirring, and then **4**(5.0 g, 10 mmol)[10] was added to the prefused mixture. After the addition the mixture was stirred for 1.5 hr at that temperature under atmospheric pressure. The resultant mixture was dissolved in chloroform(300 ml), and the solution was successively washed with a 0.5 M aqueous sodium hydroxide solution to remove the co-produced acetic acid, unchanged **1**, and **6**, and with water, and then dried over anhydrous calcium chloride. After the desiccant had been removed by filtration, the organic layer was concentrated *in vacuo* to a pale brown glassy sirup. The resultant sirup was chromatographed on a silica gel column, packed with a ten-fold weight of Mallincrodt silicic acid(72 g) relative to the sirup, by the use of a solvent system of cyclohexane–chloroform(1 : 1 v/v) for the elution. *m*-Nitrophenyl benzoate (2.6 g, 81.5% yield;[11] recrystalized from ethanol, mp 92 °C[12]) was obtained as the first fraction, while glassy sirups of $N_{(6)}$-benzoyl-9-(2′,3′,5′-tri-*O*-benzoyl-β-D-birofuranosyl)adenine(**10a**) (0.12 g, 3.1% yield) and 9-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine(**11a**) (2.9 g, 50.5% yield) were obtained as the second and third fractions.

10) E. F. Recondo and H. Rinderknecht, *Helv. Chim. Acta*, **42**, 1171 (1959).

b) The reaction with **7**: To the prefused mixture prepared from **1**(13 mmol) and **7**(6.9 g, 50 mmol) at 130—135 °C, we added **4**(10 mmol); the resultant mixture was stirred at that temperature under atmospheric pressure for 3 hr. After it had been cooled at room temperature, the resultant mixture was dissolved in chloroform(300 ml); the solution was then treated and chromatographed in the way described in the previous experiment. A mixture of *p*-nitrophenyl benzoate (0.4 g, 12.6% yield,[11] mp 140 °C[13]) and *p*-nitrophenyl 2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranoside [mp 124—125 °C, $[\alpha]_D^{20}$ −45° (*c* 1.0, $CHCl_3$). Found: C, 65.59; H, 4.22; N, 2.36%. Calcd for $C_{32}H_{25}O_{10}N$: C, 65.88; H, 4.32; N, 2.40%], which was easily fractionated by recrystallization from ethanol, was obtained as the first fraction. Glassy sirups of **10a** (0.15 g, 2.1% yield) and **11a** (1.2 g, 20% yield) were successively obtained as the second and third fractions respectively.

c) The reaction with **8**: To the prefused mixture prepared from **1** (13 mmol) and **8** (12 g, 65 mmol) at 140—145 °C, we added **4** (10 mmol); the resultant mixture was stirred at that temperature under atmospheric pressure for 3 hr. After cooling, the mixture was dissolved in chloroform (300 ml); the resultant solution was successively washed with an aqueous sodium bicarbonate solution and with water, and then dried over anhydrous calcium chloride. After the removal of the desiccant by filtration, the organic layer was concentrated *in vacuo* to a hard sirup. The residual sirup was subjected to chromatography as described in the previous experiments. Glassy sirups of **10a** (3.4 g, 59% yield) and **11a** (0.7 g, 12% yield) were obtained as the second and third fractions respectively. Prior to these fractions, the unchanged **4** (1.5 g) was recovered in a crystalline state. R_f values of **10a** and **11a** in tlc: 0.47 and 0.32 respectively.

*Structural Determination of **10a** and **11a** by Debenzoylation.*

a) **10a**: The glassy sirup of **10a** (679 mg, 1 mmol) was dissolved in absolute methanol (4 ml), and then a 1 M methanolic sodium methoxide solution (1 ml) was added to this solution. After the addition, the solution was stirred at room temperature for 1 hr and the solvent was evaporated to dryness. The residue was then dissolved in water (50 ml), the aqueous solution was washed with diethyl ether (50 ml × 2), and the aqueous layer was further treated with Amberlite IR-120B(NH_4 form)(1.5 equivalents to sodium ion), by batch. After the removal of the resin by filtration, the filtrate was concentrated *in vacuo* to about 1/4 volume of the original and the precipitated crystals were gathered by suctional filtration. The crystals were dissolved in a possibly smaller volume of water by warming, followed by decoloration with active charcoal, and then allowed to cool in a refrigerator. $N_{(6)}$-benzoyladenosine (139 mg, 35.4% yield) was obtained as fine needles. Mp 134—135 °C. $[\alpha]_D^{20}$ −30° (*c* 0.5, DMF). Found: C, 52.24; H, 4.97; N, 17.73%. Calcd for $C_{17}H_{17}O_5N_5 \cdot H_2O$: C, 52.44; H, 4.92; N, 17.99%. $\lambda_{max}^{pH\,1}$ 292 nm(*ε* 23900), $\lambda_{min}^{pH\,1}$ 263 nm(*ε* 9300); $\lambda_{max}^{pH\,7}$ 281 nm (*ε* 23200), $\lambda_{min}^{pH\,7}$ 245 nm(*ε* 11100); $\lambda_{max}^{pH\,12}$ 303 nm(*ε* 25200), and $\lambda_{min}^{pH\,12}$ 250 nm(*ε* 14300).[5] NMR(DMSO-d_6, DSS): *δ* 6.10 (H-1′ d, $J_{1',2}$ =5.0 Hz).

Incidentally, a tlc examination of the above filtrate of recrystallization proved in to consist almost entirely of $N_{(6)}$-benzoyladenosine[R_f 0.55; developed with benzene-methanol (7 : 3 v/v)]; adenosine (R_f 0.32; developed with the same solvent) could be detected merely as a pale spot on the tlc.

b) **11a**: The glassy sirup of **11a** (575 mg, 1 mmol) was dissolved in absolute methanol(4 ml); the solution was mixed with a 1 M methanolic sodium methoxide solution (1 ml), and it was stirred at room temperature for 1 hr. The precipitated crystals were gathered by suctional filtration, washed with the absolute methanol (about 3 ml), and dried over phosphorus pentoxide at 110 °C *in vacuo* to give adenosine (224 mg, 84% yield) as fine needles. Mp 226.5—227 °C (natural product: mp 234—235 °C). $[\alpha]_D^{20}$ −61° (*c* 1.0, H_2O) [natural product: $[\alpha]_D$ −61.7° (H_2O)]. Found: C, 44.70; H, 4.91; N, 26.10%. Calcd for $C_{10}H_{13}O_4N_5$: C, 44.90; H, 4.90; N, 26.03%. UV: $\lambda_{max}^{pH\,1}$ 257 nm(*ε* 15600), $\lambda_{min}^{pH\,1}$ 230 nm(*ε* 6800); $\lambda_{max}^{pH\,7}$ 258.5 nm(*ε* 15600), $\lambda_{min}^{pH\,7}$ 226.5 nm (*ε* 3000); and $\lambda_{max}^{pH\,12}$ 260 nm(*ε* 15700) [natural product: $\lambda_{max}^{pH\,2}$ 257 nm(*ε* 14600), $\lambda_{min}^{pH\,2}$ 230 nm(*ε* 3500); $\lambda_{max}^{pH\,11}$ 260 nm (*ε* 14900), and $\lambda_{min}^{pH\,11}$ 227 nm(*ε* 2250)].

*The Condensation Reactions of $N_{(6)}$-Benzoyl-2-methylthioadenine (**2**) with **4** in the Presence of **6**, **7**, or **8**.*

a) The Reaction with **6**: To a prefused mixture of **2** (3.7 g, 13 mmol) and **6** (10 g, 72 mmol) at 130—135 °C, we added **4** (5.0 g, 10 mmol) and the resultant mixture was stirred at that temperature for 3 hr. The mixture was then treated in the way described in the reactions of **1** with **4** to afford *m*-nitrophenyl benzoate [2.5 g, 78.5%;[11] mp 92 °C (lit,[12] mp 95 °C)], and the glassy sirups of $N_{(6)}$-benzoyl-2-methylthio-9-(2′,3′,5′-tri-*O*-benzoyl-*β*-D-ribofuranosyl)adenine(**10b**) (0.3 g, 3.7% yield) and 2-methylthio-9-(2′,3′,5′-tri-*O*-benzoyl-*β*-D-ribofuranosyl)adenine(**11b**) (2.8 g, 45.5% yield) as the first, second, and third fractions respectively. R_f values of **10b** and **11b** in tlc: 0.57 and 0.41 respectively.

b) The Reaction with **7**: The reaction was carried out by the use of **7** (10 g, 72 mmol) in place of **6** in the above reaction, and the resultant mixture was treated in the way described in *a*. The first fraction of the column chromatography afforded, after fractional recrystallization from ethanol, *p*-nitrophenyl benzoate (0.3 g, 9.5% yield) and *p*-nitrophenyl 2,3,5-tri-*O*-benzoyl-*β*-D-ribofuranoside (**12**)(2.5 g, 43% yield). Successively, the glassy sirups of **10b** (0.6 g, 8.2% yield) and **11b** (0.5 g, 7.3% yield) were afforded in turn.

c) The Reaction with **8**: To a prefused mixture of **2** (3.7 g, 13 mmol) and **8** (12 g, 65 mmol) at 140—145 °C, we added **4** (5.0 g, 10 mmol), after which the resultant mixture was stirred for 3 hr under atmospheric pressure. The resultant reaction mixture was treated in the way described in the reaction of **1** with **4** in the presence of **8**. By column chromatography, the glassy sirups of **10b** (3.3 g, 45.5% yield) and **11b** (0.6 g, 9.8% yield) were obtained as the second and third fractions, in addition to the first fraction, which was the unchanged **4**(1.8 g).

*Structural Determination of **10b** and **11b** by Debenzoylation.*

a) **10b**: A solution of **10b** (725 mg, 1 mmol) in absolute methanol(10 ml) was, after mixing with a 1 M methanolic sodium methoxide solution (1 ml), boiled under reflux for 1 hr. After cooling, the solvent was evaporated *in vacuo* to dryness, and the residue was triturated with a small amount of water to crystallize it. The resultant crystals were gathered by suctional filtration and then washed with a small amount of chloroform. The crystals were dried over phosphorous pentoxide at 110 °C *in vacuo* to give 2-methylthioadenosine (187 mg, 58% yield) as fine needles. Mp 215—217 °C, and remelted at 223.5—224.5 °C after resolidification. On admixture with an authentic specimen (mp 222—223 °C[14]), no depression was observed. $[\alpha]_D^{20}$ −1° (*c* 1.0, 0.1 M HCl–H_2O) [$[\alpha]_D^{18}$ −2° (*c* 0.51, 0.1 M HCl–H_2O)[14]].

b) **11b**: A solution of **11b**(621 mg, 1 mmol) in absolute methanol(6 ml) was, after mixing with a 1 M methanolic sodium methoxide solution(1 ml), stirred at room temperature for 2 hr. The precipitated crystals were gathered by suctional filtration, washed with absolute methanol (3 ml), and then

11) This yield was calculated based on the $N_{(6)}$-benzoyladenine.
12) G. Neumann, *Ber.*, **19**, 2979 (1886).
13) G. Neumann, *ibid.*, **19**, 2019 (1886).

dried over phosphorus pentoxide at 110 °C *in vacuo*. 2-Methylthioadenosine (271 mg, 86.5%) was thus obtained as fine needles. Mp 215—217 °C, and remelted at 223.5—224 °C after resolidification. On admixture with an authentic specimen (mp 222—223 °C[14]), no depression was observed. $[\alpha]_D^{20}$ −2° (*c* 1.0, 0.1 M HCl–H_2O) {$[\alpha]_D^{18}$ −2° (*c* 0.51, 0.1 M HCl–H_2O)[14]}.

The Condensation Reaction of $N_{(6)}$*-Benzyladenine (**3**) with **4** in the Presence of **8***. *a*) Preparation of $N_{(6)}$-benzyladenosine(**13c**): To a homogeneously-prefused mixture of **3** (3.0 g, 13 mmol) and **8** (12 g, 65 mmol), we added **4**(5.0 g, 10 mmol), after which the resultant mixture was stirred at 140—145 °C for 3 hr under atmospheric pressure. A solution of the mixture in chloroform (300 ml), after the removal of **8** by washing with an aqueous sodium bicarbonate solution and with water, and after drying over anhydrous calcium chloride, was concentrated *in vacuo*. The residual sirup showed a considerable coloration, although its tlc proved it to be pure (R_f 0.84). It was thus subjected to purification on a short column of silica gel by elution with chloroform. The fraction corresponding to $N_{(6)}$-benzyl-9-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine(**13a**) was concentrated *in vacuo* to a hard, glassy sirup (6.3 g, 94.4% yield). The sirup was dissolved in absolute methanol (50 ml), and the resultant solution was, after having been with a 1 M methanolic sodium methoxide solution(5 ml), stirred at room temperature for 2 hr. The crystals thus precipitated were gathered by suctional filtration, washed with the absolute methanol(total 5 ml), and dried over phosphorus pentoxide 110 °C *in vacuo* to give **13c** (3.0 g, 90% yield). Mp 165—166 °C(lit,[15] mp 177—179 °C). $[\alpha]_D^{30}$ −68° (*c* 1.0, EtOH) {lit,[15] −68.6°(*c* 0.55, EtOH)}. Found: C, 57.16; H, 5.01; N, 19.92%. Calcd for $C_{17}H_{18}O_4N_5$: C, 57.13; H, 5.36; N, 19.60%. UV: $\lambda_{max}^{pH\ 1}$ 265 nm(ε 19200), $\lambda_{min}^{pH\ 1}$ 234 nm (ε 4050); $\lambda_{max}^{pH\ 7}$ 268 nm(ε 20000), $\lambda_{min}^{pH\ 7}$ 232 nm(ε 2740); $\lambda_{max}^{pH\ 12}$ 270 nm(ε 20100), and $\lambda_{min}^{pH\ 12}$ 233 nm(ε 3100) {lit,[15] λ_{max}^{acid} 266 nm (ε 20600), λ_{min}^{acid} 235 nm (ε 4140); $\lambda_{max}^{neutral}$ 268 nm(ε 20850), $\lambda_{min}^{neutral}$ 233 nm(ε 2570); λ_{max}^{base} 269 nm(ε 21300), and λ_{min}^{base} 237 nm(ε 3570)}.

b) Chromatographic Separation of **13a** and $N_{(6)}$-Benzyl-7-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl) adenine (**13b**): The reaction described in *a* was stopped after 90 min, after which the mixture was treated in the same way as in *a*. The sirup obtained by removing **8** was chromatographed in the same way. This chromatography was successfully carried out by the use of either 9 : 1 v/v benzene–methanol or chloroform for the elution. The concentration of the fraction corresponding to the faster-moving spot (R_f 0.84) afforded a glassy sirup of **13a**(2.9 g, 43% yield), while that of the fraction corresponding to the slower-moving spot (R_f 0.70) afforded a glassy sirup of $N_{(6)}$-benzyl-7-(2′,3′,5′-tri-*O*-benzoyl-β-D-ribofuranosyl)adenine(**13b**)(0.6 g, 9% yield). The former was easily identified by deriving it into **13c** by debenzoylation. A small portion of the latter sirup was crystallized on trituration with a small amount of acetone; the crystals were, after filtration, recrystallized from ethanol and then dried over phosphorus pentoxide at 110 °C *in vacuo*. Mp 169—170 °C. $[\alpha]_D^{30}$ −65° (*c* 1.04, $CHCl_3$). Found: C, 68.16; H, 4.80; N, 10.76%. Calcd for $C_{38}H_{31}O_7N_5$: C, 68.15; H, 4.67; N, 10.46%. UV: λ_{max}^{EtOH} 300 nm(ε 9290), and $\lambda_{shoulder}^{EtOH}$ 285 nm(ε 8300) and 277 nm(ε 7300).

The latter sirup(200 mg) was dissolved in absolute methanol (4 ml), and the solution was, after having been mixed with a 1 M methanolic sodium methoxide solution(0.5 ml), stirred for 2 hr at room temperature. After the evaporation of the solvent *in vacuo* to dryness, the residue was dissolved in water(15 ml) and the solution was washed with diethyl ether (5 ml×3). The aqueous layer was, after neutralization with acetic acid, subjected to paper chromatography; the R_f value of this nucleoside was found to be 0.76 at 25 °C (*cf.* **13c**: 0.70). Subsequently, the UV spectrum of the spot was determined by extraction with ethanol, which had previously been distilled after treatment with sodium hydroxide under reflux: λ_{max}^{EtOH} 284 nm and 213 nm, and λ_{min}^{EtOH} 240 nm. Furthermore, the aqueous solution was, after acidification with acetic acid, stirred under a hydrogen atmosphere in the presence of 10%-palladized charcoal (30 mg) for 30 hr as usual. After the filtration of the catalyst, which was washed with water(5 ml×3), the filtrate and washings were combined and neutralized with a diluted aqueous sodium hydroxide solution. It was then concentrated *in vacuo* to several milliliters. The newly-appeared spot ($R_f^{25°C}$ 0.23) in the paper chromatography was extracted with pH 1, pH 7, and pH 12 water, and the UV spectrum of each extract was determined; $\lambda_{max}^{pH\ 1}$ 272 nm, $\lambda_{min}^{pH\ 1}$ 252 nm; $\lambda_{max}^{pH\ 7}$ 270 nm, $\lambda_{min}^{pH\ 7}$ 248 nm; $\lambda_{max}^{pH\ 12}$ 270 nm, and $\lambda_{min}^{pH\ 12}$ 249 nm {lit,[7] $\lambda_{max}^{0.1M\ HCl}$ 272 nm(ε 13600) and $\lambda_{max}^{0.1M\ NaOH}$ 270 nm(ε 9800); 7-β-D-ribofuranosyladenine}.

c) *The Condensation Reaction of **3** with 1,2,3,5-Tetra-O-acetyl-β-D-ribofuranose in **8***: To a homogeneously-prefused mixture of **3** (3.0 g, 13 mmol) and **8** (12 g, 65 mmol), we added 1,2,3,5-tetra-*O*-acetyl-β-D-ribofuranose (3.2 g, 10 mmol), and the resultant mixture was stirred at 140—145 °C for 1 hr; a considerable coloration was thus observed. After cooling, mixture was treated and chromatographed in the way described in *a*. 1,2,3,5-Tetra-*O*-acetyl-β-D-ribofuranose (1.6 g) was recovered as the first fraction. The glassy sirups of the acetates corresponding to **14a** (1.0 g, 21% yield) and **14b** (0.4 g, 8% yield) were obtained in turn as the second and third fractions. The NMR spectral data of these products are summarized in Table 3; in addition, no anomeric proton signals corresponding to their α-anomer could be detected on the enhancement of the signal-to-niose ratio by time-averaging (120 times). All the former sirup was subjected to deacetylation by stirring in absolute ethanol(4 ml)-1 M methanolic sodium methoxide solution(0.5 ml) at room temperature; white crystals began to precipitate within several minutes. They were, after 30 min, filtered, washed with absolute methanol(3 ml), and then dried over phosphorus pentoxide at 110 °C *in vacuo* to give **13c** (0.3 g, 84% yield). Mp 165—166 °C. No depression was observed on admixture with the authentic sample obtained in the previous experiment. Its UV spectral data were also consistent with the sample; $\lambda_{max}^{pH\ 7}$ 268 nm(ε 19000) and $\lambda_{min}^{pH\ 7}$ 231 nm(ε 2300). An attempt at the crystallization of the latter sirup resulted in failure; it was then subjected to deacetylation in the above way. After the evaporation of the solvent *in vacuo* to dryness, the residue was dissolved in water (*ca.* 5 ml), and washed with diethyl ether(5 ml×2). The UV spectrum of the resultant aqueous layer was determined, extracting the spot of the paper chromatogram (R_f 0.76); λ_{max}^{EtOH} 284 nm and 213 nm, and λ_{min}^{EtOH} 240 nm.

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