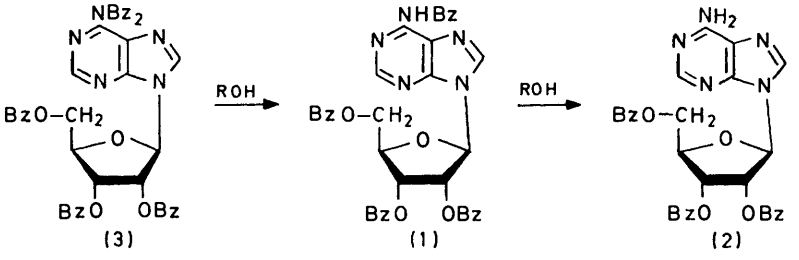
Partial Protection of Carbohydrate Derivatives. Part 1. Specific *N*-Debenzoylation of Fully Benzoylated Adenosine and Cytidine with Phenols and Alcohols; Active *N*-Benzoyl Groups

By **Yoshiharu Ishido,* Nobuo Nakazaki,** and **Nobuo Sakairi,** Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152, Japan

Specific *N*-debenzoylation of N^6.2',3',5'-tetrabenzoyladenosine (1). N^6.N^6.2',3',5'-pentabenzoyladenosine (3). and N^4.2',3',5'-tetrabenzoylcytidine (4) was achieved by treatment with nitrophenols. phenol. *p*-methoxyphenol. and a series of alcohols to give the corresponding nucleoside benzoates with free amino-groups in high yields: the reaction can also be regarded as a benzoylation of hydroxy-compounds by nucleoside *N*-benzoyl groups. On the basis of these results. the order of activity of these nucleoside benzoates was found to be (3) > (1) > (4). *N*-Benzoylation of 2',3',5'-tri-*O*-benzoyladenosine (2) with 2.4-dinitrophenyl benzoate (5) and of cytidine (6) with the pentabenzoyladenosine (3) gave the tetrabenzoyladenosine (1) and *N*-benzoylcytidine (7). respectively. in high yields.

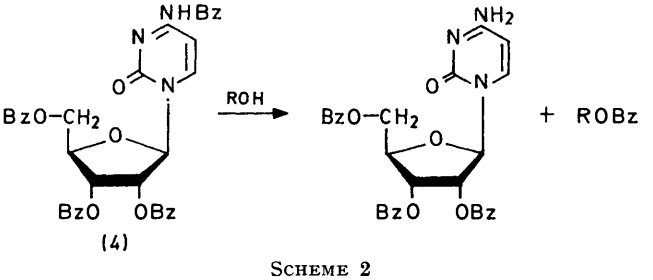
THE fusion reactions of N^6-benzoyladenine derivatives with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose in nitrophenols have been shown to involve an interesting transbenzoylation from the benzamido-groups of the resulting nucleosides to the hydroxy-groups of nitrophenols;[1] *e.g.* the reaction in *m*-nitrophenol gave predominantly 2',3',5'-tri-*O*-benzoyladenosine (2) and, in similar yield, *m*-nitrophenyl benzoate, together with a small amount of N^6,2',3',5'-tetrabenzoyladenosine (1); on the other hand, the reaction in 2,4-dinitrophenol gave no 2,4-dinitrophenyl benzoate (5) but predominantly the tetrabenzoyladenosine (1) together with a small amount of tribenzoate (2).



SCHEME 1

We now report a new specific *N*-debenzoylation of fully benzoylated nucleosides bearing aromatic amino-groups [*i.e.* compounds (1), (3), and (4)] with a series of phenols and alcohols; the reaction can also be regarded as a benzoylation of the hydroxy-compounds by the nucleoside benzoates.

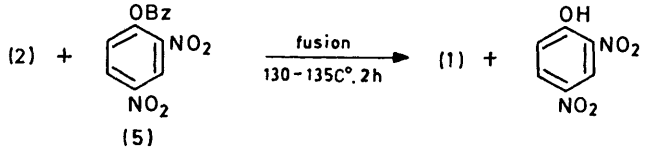
Conditions and results of reactions of the adenosine derivatives (1) and (3) are summarized in Table 1. The reaction of the tetrabenzoyl derivative (1) with *o*-nitrophenol did not occur, but the pentabenzoyladenosine (3) afforded the tetrabenzoyl compound (1) together with *o*-nitrophenyl benzoate, almost quantitatively. However, compounds (1) and (3) showed similar behaviour in reactions with *m*- and *p*-nitrophenol, although the former gave higher yields of the tribenzoate (2) and the corresponding phenyl benzoates. Prolonged reactions with *p*-nitrophenol were not studied because of rapid discolouration of the mixtures. The difficulty observed in *N*-debenzoylation of tetrabenzoyladenosine (1) with *o*-nitrophenol, in contrast with that of pentabenzoyladenosine (3), is likely to arise from the *ortho* effect of the



SCHEME 2

[1] N. Nakazaki, M. Sekiya, T. Yoshino, and Y. Ishido, *Bull. Chem. Soc. Japan*, 1973, **46**, 3858.

nitro-group. In the reaction with 2,4-dinitrophenol, the tetrabenzoyl derivative (1) was recovered quantitatively, and the pentabenzoyl compound (3) gave tetrabenzoyladenosine (1) as well as 2,4-dinitrophenyl benzoate (5) in almost quantitative yield. Thus the *N*-benzoyl



SCHEME 3

groups of compounds (1) and (3) are active enough to benzoylate such hydroxy-compounds as nitrophenols, was observed (see Table 1). The reaction in methanol resulted in quantitative recovery of the pentabenzoyladenosine (3), (even though no solubility problem was encountered), in contrast to the reactions in ethanol, propanol, and butanol. An interesting steric effect was exhibited by the reactions with diols. Little difference was observed in the yields of (2) when the reactions were conducted for 5 h, but differences were apparent when they were discontinued after 1.5 h.

Similar attempts to *N*-debenzoylate of N^2,2',3',5'-tetrabenzoylguanosine resulted in its quantitative recovery, consistent with the chemical stability of its N^2-acyl substituents.[2]

N-Debenzoylation reactions of the tetrabenzoylcytidine (4) are summarized in Table 2. Compound (4) was

TABLE 1

Specific *N*-debenzoylation of N^6,2',3',5'-tetrabenzoyladenosine (1) and N^6,N^6,2',3',5'-pentabenzoyladenodine (3) by hydroxy-compounds

			Yields (%)		
Adenosine	ROH	Reaction time (h)	(1)	(2)	Benzoate
(1)	*o*-Nitrophenol	0.8	100		
(3)	*o*-Nitrophenol	1	95		85
(1)	*m*-Nitrophenol	0.8	9	76	80
(3)	*m*-Nitrophenol	1	29	69	73
(1)	*p*-Nitrophenol	0.1	60	19	31
(3)	*p*-Nitrophenol	0.5	47	38	58
(3)	2,4-Dinitrophenol	1.5	93		92
(3)	Phenol	1.5		95	94
(3)	Phenol	5 (100—105 °C) [a]	10	90	
(3)	Phenol	48 (55 °C) [a]	<1	>99	
(3)	Phenol	7 days (room temp.) [a]	4	96	
(3)	*p*-Methoxyphenol	48 (55 °C) [a]	<1	>99	
(3)	*p*-Methoxyphenol	7 days (room temp.) [a]	9	91	
(3)	2-Methoxyethanol	24 (124 °C)		90	
(3)	Butanol	48 (117—118 °C) [a]		100	
(3)	Propanol	48 (97—98 °C) [a]	3	97	
(3)	Ethanol	48 (78.5 °C) [a]	35	46	
(3)	Methanol	48 (64.7 °C) [a]	Quantitative recovery of (3)		
(3)	Ethane-1,2-diol	1.5 [a]	10	90	
(3)	Ethane-1,2-diol	5 [a]		100	
(3)	Propane-1,2-diol	1.5 [a]	40	60	
(3)	Propane-1,2-diol	5 [a]		100	
(3)	Butane-2,3-diol	1.5 [a]	43	30	
(3)	Butane-2,3-diol	5 [a]	5	95	

All reactions, unless otherwise noted, were performed at 130—135 °C; yields are of isolated products.
[a] Reactions performed by use of 0.1 mmol of (3); yields from l.l.c. analysis.

and the activity order of the benzoates in benzoylation is (3) > (5) > (1) > benzoates of *o*-, *m*-, and *p*-nitrophenol.

We then attempted to carry out the *N*-debenzoylation of compound (3) with hydroxy-compounds with larger pK_a values, such as phenol, *p*-methoxyphenol, and a series of alcohols. The reactions proceeded smoothly and advantageously, without discolouration, even under milder conditions, to give the tribenzoate (2) in high yield and the corresponding aryl and alkyl benzoates in yields corresponding well to those of (2), as exemplified by the reaction with phenol. Almost all the yields in Table 1 were determined by liquid–liquid chromatography, and those of the corresponding aryl and alkyl benzoates were not estimated because of the larger errors which arose from contamination of the earlier peaks in the chromatograms. In the reactions with primary alcohols an apparent temperature dependence active enough to be *N*-debenzoylated by *m*- and *p*-nitrophenol, phenol, and 2-methoxyethanol, but not by

TABLE 2

Specific *N*-debenzoylation of N^4,2',3',5'-tetrabenzoylcytidine (4) by hydroxy compounds

	Temp.	Period	Yield (%)	
ROH	(°C)	(h)	(2)	Benzoate
m-Nitrophenol	130—135	1	83	87
p-Nitrophenol	130—135	1.5	76	72
Phenol	130—135	1.5	90	89
2-Methoxyethanol	124	24	76	33

All reactions were performed by use of 1 mmol of (4); yields are of isolated products.

o-nitrophenol and 2,4-dinitrophenol. All the reactions proceeded without the undesirable discolouration

[2] M. Smith, G. I. Drumond, and H. G. Khorana, *J. Amer. Chem. Soc.*, 1961, **83**, 698.

observed in those of the adenosine derivatives (1) and (3) with the nitrophenols. This reflects the greater stability of the glycosidic bond of (4) in comparison with (1) and (3). Phenol was found in this case to be a useful *N*-debenzoylating reagent. The extremely low yield of 2-methoxyethyl benzoate is likely to arise from its loss during distillation *in vacuo*. These results indicated that tetrabenzoylcytidine (4) was as active as tetrabenzoyladenosine (1), in being *N*-debenzoylated by *m*- and *p*-nitrophenol, but not by *o*-nitro- and 2,4-dinitro-phenol. We compared their activities kinetically by following the reactions with phenol by liquid–liquid chromatography. The conditions and the rate constants obtained are summarized in Table 3. The

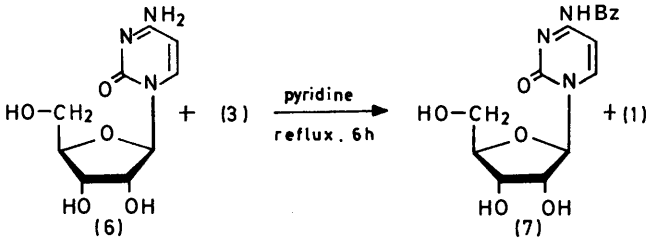
TABLE 3

Rate constants for the reactions of N^6,2′,3′,5′-tetrabenzoyladenosine (1) and N^4,2′,3′,5′-tetrabenzoylcytidine (4) with phenol

	$10^6k/s^{-1}$	
T/°C	(1)	(4)
58	10	5.8
70	33	
80	100	68

constants were obtained on a first-order basis, as for ordinary solvolyses; the adenosine (1) was thus concluded to be 1.5—1.6 times as active as the cytidine (4). Compound (4) could thus be ranked between (1) and the mononitrophenyl benzoates in the activity order described previously.

On the basis of this activity order, specific *N*-benzoylation reactions of the tribenzoate (2) with 2,4-dinitrophenyl benzoate (5) and of cytidine (6) with pentabenzoyladenosine (3) were performed. Fusion of the tribenzoate (2) with 1.4 mol. equiv. of the ester (5) gave tetrabenzoyladenosine (1) in 90% yield, and treatment of cytidine (6) with an equimolar amount of pentabenzoyladenosine (3) in pyridine under reflux similarly gave N^4-benzoylcytidine (7) in 73% yield. No



SCHEME 4

products other than (1) or (7) were detected; the *N*-benzoylations were thus seen to proceed with high regiospecificity, like the *N*-debenzoylations.

The *N*-debenzoylation may be induced by nucleophilic attack of the hydroxylic oxygen atom on the carbonyl carbon atom of the *N*-benzoyl group, by analogy with normal solvolytic reactions. The present *N*-debenzoylation is of interest in comparison with that of fully benzoylated 2′-deoxyribonucleosides such as N^6,N^6,3′,5′-tetrabenzoyl-2′-deoxyadenosine by hydrazine hydrate in 1 : 4 glacial acetic acid–pyridine, giving 3′,5′-di-*O*-benzoyl-2′-deoxyadenosine.[3]

EXPERIMENTAL

U.v. spectra were recorded with a Hitachi EPS-3T spectrometer for solutions in ethanol. T.l.c. was performed on Wakogel B-5F, and column chromatography on Wakogel C-300. Liquid–liquid chromatography (l.l.c.) was performed with a Varian LC-8520 apparatus [column of Micro-Pak SI-10 (25 cm × 2 mm); mobile phase hexane (solvent A) and 20% isopropyl alcohol in dichloromethane (solvent B); solvent composition 20—40% B with a slope of 2% min^{-1}; flow rate 50 ml h^{-1}; detection by u.v. at 260 nm (Variscan apparatus)].

N-Debenzoylation of N^6,2′,3′,5′-*Tetrabenzoyladenosine* (1) *with* o-, m-, *and* p-*Nitrophenol.*—Compound (1) was obtained by the reaction of phenols with N^6,N^6,2′,3′,5′-pentabenzoyladenosine (3) (see later).

(a) *Reaction with* m-*nitrophenol.* A mixture of compound (1) (1 370 mg, 2 mmol) and *m*-nitrophenol (1 390 mg, 10 mmol) was heated at 130—135 °C for 50 min with stirring. The resulting mixture was dissolved in chloroform (100 ml) and the solution was successively washed with aqueous 0.5M-sodium hydroxide and water to remove unchanged *m*-nitrophenol. The organic layer was dried ($CaCl_2$) and evaporated to a syrup, which was subjected to chromatographic separation on a column (2.5 cm diam., packed with 15 g of silica gel). Chloroform eluted *m*-nitrophenyl benzoate (390 mg, 80%) [m.p. 83 °C (lit.,[4] 96 °C)], which was crystallized from ethanol and recrystallized from light petroleum ether, followed by starting material (1) as a glass (120 mg, 9% recovery), respectively. Chloroform–methanol (98 : 2) then eluted 2′,3′,5′-*tri*-O-*benzoyladenosine* (2) (glass) (880 mg 76%), $[\alpha]_D^{22}$ −71° (*c* 1.0 in $CHCl_3$); $\lambda_{max.}$ (EtOH) 258 (ε 20 500) and 231 nm (47 100), $\lambda_{min.}$ (EtOH) 252 nm (ε 19 900) [*cf.*[3] data for 3′,5′-di-*O*-benzoyl-2′-deoxyadenosine: $\lambda_{max.}$ (50% aq. EtOH) 259 nm (ε 14 000] (Found: C, 62.4; H, 4.25; N, 11.85. $C_{31}H_{25}N_5O_7$ requires C, 62.25; H, 4.35; N, 12.1%).

(b) *Reaction with* p-*nitrophenol.* A mixture of compound (1) (2 mmol) and *p*-nitrophenol (10 mmol) was treated as above (10 min) to give *p*-nitrophenyl benzoate [190 mg, 30%; m.p. 141—142 °C (lit.,[5] 142.5 °C)] and compounds (1) (850 mg, 62% recovery) and (2) (220 mg, 19%).

Specific N-*Debenzoylation of Pentabenzoyladenosine* (3) *with Phenols and Alcohols.*—(a) *With* 2,4-*dinitrophenol.* Similar treatment of a mixture of compound (3) [6] (788 mg, 1 mmol) and 2,4-dinitrophenol (368 mg, 2 mmol) (removed by washing with aqueous sodium hydrogen carbonate after the reaction) afforded 2,4-dinitrophenyl benzoate (5) (265 mg, 92%) [m.p. 132—133 °C (lit.,[7] 132—135 °C)] and N^6,2′,3′,5′-*tetrabenzoyladenosine* (1) (620 mg, 93%) (glass), $[\alpha]_D^{22}$ −94° (*c* 1.0 in $CHCl_3$) {lit.,[8] $[\alpha]_D^{15}$ −90° (*c* 0.37 in $CHCl_3$)}; $\lambda_{max.}$

[3] R. L. Letsinger, P. S. Miller, and G. W. Grams, *Tetrahedron Letters*, 1968, 2621; this procedure has recently been extended to the regioselective 2′-*O*-deacylation of fully acylated ribonucleosides (Y. Ishido, N. Nakazaki, and N. Sakairi, *J.C.S. Chem. Comm.*, 1976, 832).

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[5] G. Neumann, *Ber.*, 1886, **19**, 2018.

[6] H. R. Bentley, K. G. Cunningham, and F. S. Spring, *J. Chem. Soc.*, 1951, 2301.

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[8] M. Miyaki and B. Shimizu, *Chem. and Pharm. Bull* (*Japan*), 1970, **18**, 732.

(EtOH) 279 (ε 22 400) and 230 nm (49 200), $\lambda_{min.}$ (EtOH) 259 nm (ε 21 600) (Found: C, 66.55; H, 4.3; N, 10.15. $C_{38}H_{29}N_5O_8$ requires C, 66.75; H, 4.3; N, 10.25%) (chloroform as eluant).

(b) *With* o-*nitrophenol*. Similar treatment of the mixture from the reaction of compound (3) (2 mmol) with *o*-nitrophenol (10 mmol) gave *o*-nitrophenyl benzoate [410 mg, 85%; m.p. 57—58 °C] and tetrabenzoyladenosine (1) (1 290 mg, 95%).

(c) *With* m-*nitrophenol*. The reaction of compound (3) (2 mmol) with *m*-nitrophenol (10 mmol) afforded *m*-nitrophenyl benzoate (710 mg, 73%) and compounds (1) (370 mg, 29%) and (2) (800 mg, 69%).

(d) *With* p-*nitrophenol*. The reaction of compound (3) (2 mmol) with *p*-nitrophenol (10 mmol) gave *p*-nitrophenyl benzoate (560 mg, 58%) and compounds (1) (640 mg, 47%) and (2) (440 mg, 38%).

(e) *With phenol*. The reaction of compound (3) (790 mg, 1 mmol) with phenol (470 mg, 5 mmol) gave phenyl benzoate (370 mg, 94%) [m.p. 70—71 °C (lit.,[10] 70.5—71.5 °C)] and compound (2) (550 mg, 95%).

(f) *With* 2-*methoxyethanol*. Compound (3) (790 mg, 1 mmol) was treated in 2-methoxyethanol (b.p. 124 °C; 30 ml) for 24 h under reflux. The methoxyethanol was then evaporated off and the residue chromatographed to give 2-methoxyethyl benzoate [260 mg, 72%; b.p. 46—50 °C at 1.05 mmHg (lit.,[11] b.p. 254—256 °C)] (Found: C, 66.5; H, 6.85. Calc. for $C_{10}H_{12}O_3$: C, 66.65; H, 6.7%) and compound (2) (520 mg, 90%).

Estimation of the Products by High Performance Liquid Chromatography.—Compound (3) (0.1 mmol) was treated with a phenol (5 mmol), diol (5 ml), or alcohol (2 ml) under the conditions given in Table 1. Each mixture was then dissolved in chloroform (10 ml), and the solution was analysed on the Varian LC-8520 apparatus. The yields of compounds (1) and (2) were estimated from peak areas corresponding to retention times *ca.* 2 and 12 min, respectively. A small amount of chloroform was added to each room temperature reaction mixture to homogenize it.

Specific N-*Debenzoylation of* N^4,2′,3′,5′-*Tetrabenzoylcytidine* (4) *with Some Hydroxy-compounds*.—(*a*) *With* m-*nitrophenol*. A mixture of compound (4) [12] (660 mg, 1 mmol) and *m*-nitrophenol (700 mg, 5 mmol) was treated at 130—135 °C for 1 h with stirring, then dissolved in chloroform (100 ml) and the solution was successively washed with aqueous 0.5M-sodium hydroxide solution and water to remove unchanged *m*-nitrophenol. The organic layer was dried ($CaCl_2$) and evaporated to a syrup, which was then chromatographed. Elution with chloroform gave *m*-nitrophenyl benzoate (210 mg, 87%) and compound (4) (70 mg, 10% recovery). Elution with 96 : 4 chloroform–methanol then gave 2′,3′,5′-*tri*-O-*benzoylcytidine* (460 mg, 83%) as a hygroscopic white powder, m.p. 183—184 °C; $[\alpha]_D^{22}$ −32° (*c* 1.0 in $CHCl_3$); $\lambda_{max.}$(EtOH) 230.5 (ε 51 600) and 265—275br,sh. nm (ε 13 900) (Found: C, 63.9; H, 4.6; N, 7.4. $C_{30}H_{25}N_3O_8$,0.5H_2O requires C, 63.7; H, 4.65; N, 7.4%).

The reaction of (4) with *p*-nitrophenol left 23% unchanged (4) but from the reaction with phenol no starting material (4) was recovered.

(b) *With* 2-*methoxyethanol*. The products are given in Table 1; 15% starting material (4) was recovered.

Rate Constants for N-*Debenzoylation of Compounds* (1) *and* (4).—A sample (1 ml) of a chloroform solution (10 ml) containing 1 mmol of compound (1) or (4) was evaporated to dryness, and the residue was mixed with phenol (5 mmol). Each mixture was treated under the conditions shown in Table 3 with continuous stirring for the scheduled period, then diluted with chloroform to 10 ml; and the resulting solution was analysed with the Varian LC-8520 apparatus. Each result was checked with respect to unchanged (1) or (4), estimated from the areas of the peaks with retention times *ca.* 2 and 5 min, respectively.

N^6-*Benzoylation of Tri*-O-*benzoyladenosine* (2) *with* 2,4-*Dinitrophenyl Benzoate* (5).—A mixture of compounds (2) (560 mg, 1 mmol) and (5) (404 mg, 1.4 mmol) was stirred at 130—135 °C for 2 h, then dissolved in chloroform (100 ml). The solution was successively washed with saturated aqueous sodium hydrogen carbonate solution and water (to remove 2,4-dinitrophenol), dried ($CaCl_2$), and evaporated to a syrup. This was then chromatographed as described previously. Elution with chloroform afforded compounds (5) (150 mg, 37% recovery) and (1) (560 mg, 83%). Subsequent elution with 98 : 2 chloroform–methanol afforded compound (2) (78 mg, 14% recovery).

N^4-*Benzoylation of Cytidine* (6) *with Pentabenzoyladenosine* (3).—A solution of compounds (3) (1.47 g, 2 mmol) and (6) (486 mg, 2 mmol) in pyridine (20 ml) was heated under reflux for 6 h, then evaporated. The residue was dissolved in water (10 ml) and the solution evaporated again; this procedure was repeated until the odour of pyridine was not detected, giving a syrup. Trituration gave crystals, and several subsequent washings with a small amount of chloroform gave *N*^{4}-benzoylcytidine (7) (640 mg, 92%). Recrystallization from ethanol gave a sample (510 mg, 73%), m.p. 218 °C (lit.,[13] 218 °C), $[\alpha]_D^{22}$ +30° (*c* 0.5 in $Me_2N{\cdot}CHO$); $\lambda_{max.}$ (EtOH) 303 (ε 7 000) and 260 nm (17 700), $\lambda_{min.}$ (EtOH) 295.5 nm (ε 6 900) [lit.,[13] $\lambda_{max.}$(MeOH) 305 and 260 nm].

Column chromatography of the combined filtrate and washings on silica gel afforded compound (1) (1.26 g, 92%).

We thank the members of the Laboratory of Organic Analysis, Tokyo Institute of Technology, for elemental analyses, and the Minsitry of Education, Japanese Government, for a Grant-in-aid for Scientific Research.

[6/1367 *Received*, 12*th July*, 1976]

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