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FUSION REACTIONS, INVOLVING ACTIVATING AGENTS, OF SOME PURINE DERIVATIVES WITH 1,3,4,6-TETRA-*O*-ACETYL-2-ACYLAMIDO-2-DEOXY-β-D-GLUCOPYRANOSES

NOBUO NAKAZAKI, TATSUMICHI TAKEDA, TERUO YOSHINO, MASAO SEKIYA, AND YOSHIHARU ISHIDO

Department of Chemistry, Faculty of Science, Tokyo Institute of Technology, O-okayama, Meguro-ku, Tokyo 152 (Japan)

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ABSTRACT

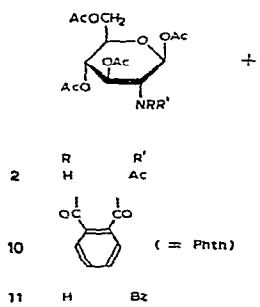
Fusion of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose, 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose, and 1,3,4,6-tetra-*O*-acetyl-2-benzamido-2-deoxy-β-D-glucopyranose with 2,6-dichloropurine, theophylline, and 6-benzylaminopurine in activating agents afforded the corresponding aminonucleosides in good yields. The simultaneous formation of a positional isomer was confirmed in three examples in the reactions with 2,6-dichloropurine and 6-benzylaminopurine. On the basis of these results, the potential effect of 2-acylamido functional groups on the reaction is discussed.

INTRODUCTION

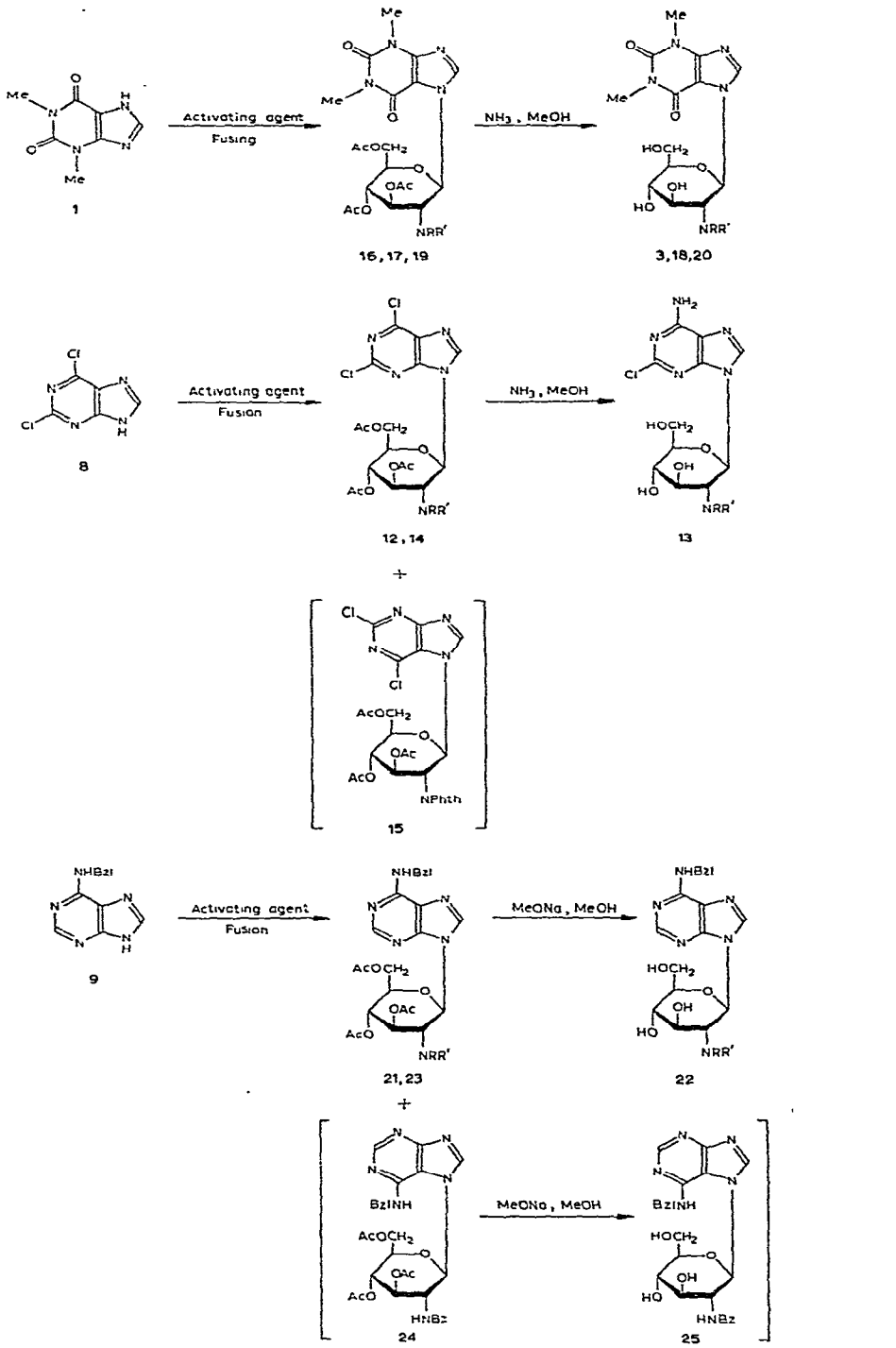
No aminonucleoside synthesis through the fusion method has been reported other than a reaction that involves an oxazoline sugar derivative as the source of the amino sugar moiety[1]. Our previous papers have demonstrated the usefulness of some activating agents in the fusion reaction[2] and their application for the synthesis of adenosine derivatives[3]. The present investigation deals with the reaction of some purine derivatives with 1,3,4,6-tetra-*O*-acetyl-2-acylamido-2-deoxy-β-D-glucopyranose in the presence of typical activating agents, as a general route for the preparation of aminonucleosides.

RESULTS AND DISCUSSION

Initially, the fusion of equimolar quantities of theophylline (**1**) and 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (**2**) was attempted in the presence of a catalytic amount of concentrated sulfuric acid for 30 sec at 190–195°. Conventional deacetylation with methanolic ammonia afforded 7-(2-acetamido-2-deoxy-β-D-glucopyranosyl)theophylline (**3**) in 46% yield. The structure of **3** was assigned on the basis of its u.v. ($\lambda_{max}^{H_2O}$ 274 nm) and n.m.r. ($\delta_{H-1'}$, 6.30 p.p.m. and $J_{1',2'}$, 10 Hz) spectra. However, this reaction required the drastic conditions described on account



	R	R'
2	H	Ac
10		(= Phth)
11	H	Bz



of the high melting point of **2**, and was inevitably accompanied by extensive coloration, despite the short reaction-period; this made the isolation and purification of **3** difficult and the approach was thus abandoned.

Consequently, further investigation on the reaction in the presence of activating agents was undertaken in order to develop a practicable method for aminonucleoside synthesis.

In view of our previous results[2,3], such agents as *p*-nitrophenol (**4**), 2,4-dinitrophenol (**5**), *p*-toluenesulfonamide (**6**), and *o*-nitrobenzoic acid (**7**); purine derivatives such as 2,6-dichloropurine (**8**), **1**, and 6-benzylaminopurine (**9**); and fully acylated sugars such as **2**, 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (**10**), and 1,3,4,6-tetra-*O*-acetyl-2-benzamido-2-deoxy-β-D-glucopyranose (**11**), were chosen for the present investigation. A set of reactants from the foregoing three categories was subjected to the procedure already described[2,3]; each of the fully acylated sugars was added to a homogeneous, pre-fused mixture of the purines with an excess of each of the activating agents, and the resulting mixtures were stirred at atmospheric pressure for a period of time established for each example.

The reactions of **8** with **2** and with **10** were attempted in view of the excellent co-fusibility of **8** with ordinary acetylated sugars[4]. Diminished pressure was employed to minimize the reaction period, because longer times gave undesirable coloration, probably through decomposition of the resulting aminonucleosides. The conditions used and the results thus obtained are summarized in Table I. The reaction of **8** with **2** afforded the best results when conducted in **4**, giving 9-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-2,6-dichloropurine (**12**); reactions conducted in **5**, **6**, and **7** were inferior (Table I). Glycosylation was confirmed to occur at the 9-position of **8**, based on the u.v. spectrum of the product, which was superposable

TABLE I

CONDENSATION OF 2-ACETAMIDO-1,3,4,6-TETRA-*O*-ACETYL-2-DEOXY-β-D-GLUCOPYRANOSE (**2**) AND 1,3,4,6-TETRA-*O*-ACETYL-2-DEOXY-2-PHTHALIMIDO-β-D-GLUCOPYRANOSE (**10**) WITH 2,6-DICHLOROPURINE[a] (**8**)

Fully acylated sugars	*Activating agents*	*Reaction conditions*			*Products*	*Yield (%)*
		8/agents	*Temp. (degrees)*	*Period (min)*		
2	*p*-Nitrophenol (**4**)	1	130–135	3	**12**	72
	2,4-Dinitrophenol (**5**)	1	145–150	3	**12**	46
	p-Toluenesulfonamide (**6**)	1	130–135	3	**12**	48
	o-Nitrobenzoic acid (**7**)	1	130–135	3	**12**	46
10	**4**	7	130–135	15	**14**	67
	5	6.5	140–145	40	**14, 15**	61, 8
	6	3	130–135	80	**14**	43
	7	3	140–145	60		

[a]These reactions were performed under diminished pressure with 1.1 molar equivalents of **8** to the fully acylated sugars.

on that of the corresponding 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl derivative[4]. The anomeric configuration of **12** was deduced as β from its specific rotation ($[\alpha]_D^{22}$ −44°) and from n.m.r.-spectral data ($\delta_{H-1'}$ 6.15 and $J_{1',2'}$ 10 Hz). In order to confirm this assignment, compound **12** was further converted into 9-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-6-amino-2-chloropurine (**13**), obtained in 76% yield by treating **12** with methanolic ammonia at 40° in a sealed tube. U.v.-spectral comparison of **13** with 2-chloroadenosine[5] supported the assignment. The reaction of **8** with **10** was successfully induced by fusing the reactants in **4**, **5**, and **6**, respectively; however, use of **7** brought about a marked coloration, probably through decomposition of the product, which could not be isolated. U.v. (λ_{max} 274 nm) and n.m.r. ($\delta_{H-1'}$ 6.75 p.p.m. and $J_{1',2'}$ 9.5 Hz) spectral data established the product to be 9-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)-2,6-dichloropurine (**14**).

The use of **4** and **5** afforded satisfactory yields of **14**, although the reactions needed considerably longer for their completion than those with **2**. Interestingly, the corresponding 7-isomer (**15**, λ_{max} 281 nm[6], $\delta_{H-1'}$ 7.08 and $J_{1',2'}$ 10 Hz) was formed concomitantly; the yield of **15** in the reaction in **5** was 8%, in contrast to that of **14** (60%). For the reaction in **6**, only a trace of **15** was formed (t.l.c.). In 9:1 benzene–acetone, t.l.c. analysis of the fusion of **15** (R_F 0.32) with an excess of **5** at 140–145° showed it to be progressively isomerized to **14** (R_F 0.39).

Subsequently, the reactions of **1** with **2**, **10**, and **11** were investigated; compound **11** was examined as compound **10** proved (in contrast to **2**) unexpectedly non-

TABLE II

CONDENSATION OF **2**, **10**, AND 1,3,4,6-TETRA-*O*-ACETYL-2-BENZAMIDO-2-DEOXY-β-D-GLUCOPYRANOSE (**11**) WITH THEOPHYLLINE[a] (**1**)

Fully acylated sugars	*Activating agents*	*Reaction conditions*			*Products*	*Yield (%)*
		1/agents	*Temp. (degrees)*	*Period (min)*		
2	**4**	5	130–135	180		
	5	5.4	140–145	30	**16**	30
	6	6.5	130–135	60	**16**	67
	7	6.5	145–150	60	**3**	59
10	**4**	5.8	140–145	360	**17**	13
	5	2.2	140–145	180	**17**	3
	6	2.4	140–145	180		
	7	2.4	140–145	50		
11	**4**	5.8	130–135	15	**19**	43
	5	6.6	140–145	15	**19**	49
	6	4.6	140–145	30	**19**	79
	7	4.8	140–145	10	**19**	21

[a]These reactions were performed with 1.1 molar equivalents of **1** to the fully acylated sugars.

susceptible to the reaction. The results are summarized in Table II. In the reaction with **2**, compound **4** showed no activating effect on **1** different from **5**, **6**, and **7**, which afforded 7-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)theophylline (**16**) in 30%, 67%, and 59% (of deacetylated product, **3**) yields, respectively. Such a difference in the activating effect of these agents is of interest because **4** exerts a strong effect on **1** in the reaction with 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose[2] (in contrast to this reaction involving **4**), and because of a tentative assumption on the activating mechanism[2] in connection with a delicate intermolecular interaction through polarization bonding, originally proposed by Wallwork[7a] to explain the bonding structure of intermolecular compounds; this concept has been extended to explain the crystal structures of the molecular compounds of *p*-chlorosalicylic acid with caffeine[7a] and with theobromine[7c].

The structure of **16** was assigned by the u.v. and n.m.r. spectroscopy. The reactions with **10** were unsatisfactory as activation of **1** by the agents used was not enough to induce condensation with **11**; compounds **4** and **5** afforded 7-(3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl)theophylline (**17**) in only 13% and 3% yields, respectively. Deacetylation of **17** with methanolic ammonia gave 7-[2-(*o*-carbamoylbenzamido)-2-deoxy-β-D-glucopyranosyl]theophylline (**18**) in 84% yield. The structures of **17** and **18** were determined by u.v. and n.m.r. spectroscopy.

Confronted with such low reactivity of **10**, corresponding reactions with **11** were thus attempted; the reaction in **6** gave the best (70%) yield of 7-(3,4,6-tri-*O*-acetyl-2-benzamido-2-deoxy-β-D-glucopyranosyl)theophylline (**19**). Methanolic ammonia converted **19** into 7-(2-benzamido-2-deoxy-β-D-glucopyranosyl)theophylline (**20**) in 80% yield. The structures of **19** and **20** were determined by u.v. and n.m.r. spectroscopy.

In the reaction of compound **9**, the sugar derivative **10** was found not susceptible to reaction with **9**, as in the previous case, whereas **2** and **11** afforded 9-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-6-benzylaminopurine (**21**) and 9-(3,4,6-tri-*O*-acetyl-2-benzamido-2-deoxy-β-D-glucopyranosyl)-6-benzylaminopurine (**23**), respectively, in the yields shown in Table III. On deacetylation with methanolic sodium methoxide solution at room temperature, **21** afforded a quantitative yield of 9-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-6-benzylaminopurine (**22**), whose structure was assigned by u.v. and n.m.r. spectroscopy. As with the reaction of **8**, it is noteworthy to observe the concomitant formation of **23** and its 7-isomer (**24**) in 21 and 16% yields, respectively, for the reactions in **5**. The structures of the products were determined by u.v. and n.m.r. spectroscopy, but the site of glycosylation for compound **24** could not be determined directly in terms of the sign of $\Delta\lambda_{min}$[8], (as proposed as an empirical rule for such structural assignment), because its value was zero. The assignment was, however, made from the value of +1 observed for 7-(2-benzamido-2-deoxy-β-D-glucopyranosyl)-6-benzylaminopurine (**25**, derived from **24** in 88% yield by deacetylation with methanolic sodium methoxide solution), which proved that the nucleoside was glycosylated at 7-position; glycosylation was thus confirmed to have occurred at the 9-position, giving **23**. In addition, the isomer **24**

was formed in only trace amount (t.l.c.) in the reaction with **2**; this result may be attributable to the longer reaction-period used (see Table III[3]).

TABLE III

CONDENSATION OF **2** AND **11** WITH 6-BENZYLAMINOPURINE[a] (**9**)

Fully acylated sugars	*Activating agents*	*Reaction conditions*			*Products*	*Yield (%)*
		9/agents	*Temp. (degrees)*	*Period (min)*		
2	**4**	5	130–135	180		
	5	5	140–145	30	**21**	26
	6	5	155–160	120[b]	**21**	38
	7	2	130–135	50[b]	**21**	58
11	**4**	5	130–135	60		
	5	7.6	140–145	15	**23, 24**	21, 16
	6	5.8	140–145	15	**23**	14
	7	5	140–145	15	**23**	15

[a]These reactions were performed with 1.1 molar equivalents of **9** to the fully acylated sugars. [b]The reactions were carried out under diminished pressure.

In conclusion, it has been shown that activating agents are useful in aminonucleoside synthesis and facilitate more-effective condensation in comparison with simple equimolar reaction of purines with such fully acylated sugars as **2**. Comparison of the reaction periods and the yields of the aminonucleosides (Tables I–III) showed the reactivity of the three sugar derivatives with purines to be in the order **11** > **2** ⩾ **10**. No rational explanation for this order can be given merely on the basis of differences in the anchimeric participation of the 2-acylamido groups on C-1, as **11** is more reactive than **2** and **10** is far less reactive than **2**. The behavior of **10** in this reaction may possibly the explained as a reflection of steric hindrance by the bulky phthalimido group to the approach of purines to 1-*O*-acetyl group[9]; this may well correspond to the reaction mechanism proposed by Hosono *et al.*[10] involving initial induction through interaction of the 1-*O*-acetyl group with the acidic proton of activated purines. Alternatively, the order may be explained in terms of the difference in the inductive effect of the 2-acylamido groups on C-1 and steric hindrance by the phthalimido group. In addition, the probable utility of **10** as demonstrated herein in combination with activating agents, is of interest in view of the inapplicability[9] of the corresponding glycosyl chloride in aminonucleoside synthesis.

EXPERIMENTAL

General methods. — Melting points are uncorrected. Solutions were evaporated *in vacuo*. T.l.c. was performed on Wakogel B-5F. U.v. spectra were recorded, unless otherwise noted, with a Hitachi EPS-3T spectrometer in 95% aqueous ethanol, and

n.m.r. spectra were recorded with a Varian T-60 spectrometer in chloroform-*d* or deuterium oxide with tetramethylsilane or sodium 4,4-dimethyl-4-silapentane-1-sulfonate as the internal standards.

7-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)theophylline (**3**). — An equimolar mixture of theophylline (**1**, 1.8 g, 10 mmol) and 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose[11] (**2**, 3.9 g, 10 mmol) in a round-bottomed flask (100 ml) together with a catalytic amount (15 mg) of concentrated sulfuric acid (introduced with a capillary tube) was fused *in vacuo* for 30 sec at 190–195° in an oil-bath. The resulting, dark mixture was dissolved in chloroform (80 ml), mixed with methanolic ammonia (~10 ml; prepared by saturating methanol at 0° with ammonia gas), and the mixture was then evaporated to a hard syrup. The syrup was dissolved in 1:1 methanol–methanolic ammonia (80 ml) and kept overnight at room temperature in a tightly stoppered flask. After cooling in an ice–water bath, the solution was evaporated to a syrup that was dissolved in warm ethanol (20 ml), and the solution was kept overnight at room temperature. After cooling, the resulting crystals were filtered off and recrystallized from ethanol (activated charcoal) to yield 7-(2-acetamido-2-deoxy-β-D-glucopyranosyl)theophylline (**3**, 1.7 g, 46%); m.p. 237–238°, $[\alpha]_D^{19}$ +3° (*c* 1.0, water); λ_{max}^{EtOH} 275 nm (ε 7900).

Anal. Calc. for $C_{15}H_{21}N_5O_7$: C, 46.99; H, 5.52; N, 18.27. Found: C, 46.97; H, 5.59; N, 18.28.

9-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-2,6-dichloropurine (**12**). — To a homogeneously pre-fused mixture of 2,6-dichloropurine[12] (**8**, 1.9 g, 10 mmol) and *p*-nitrophenol (**4**, 1.4 g, 10 mmol) at 130–135°, was added **2** (3.9 g; 10 mmol) and the resulting mixture, after rapid stirring, was immediately connected to a water pump and allowed to react for 3 min. After cooling, the mixture was dissolved in chloroform (200 ml), and the solution washed successively with 0.5M aqueous sodium hydroxide and water. The dried (calcium chloride) organic layer was concentrated to a hard syrup, that was crystallized and recrystallized from ethanol to give compound **12**, (3.8 g, 72%); m.p. 188–194° (dec), $[\alpha]_D^{22}$ −44° (*c* 1.0, chloroform); λ_{max}^{EtOH} 274 (ε 13,000) and 253 nm (8300), λ_{min}^{EtOH} 257.5 (ε7800) and 233.5 nm (4800); n.m.r.: δ 8.32 (1-proton singlet, H-8), 8.18 (1-proton doublet, $J_{NH,2'}$ 9.0 Hz, N-*H*), 6.15 (1-proton doublet, $J_{1',2'}$ 10 Hz, H-1'), 2.02, 2.00, 1.98 (3-proton singlets, OAc), and 1.55 (3-proton singlet, NAc).

Anal. Calc. for $C_{19}H_{21}Cl_2N_5O_8$: C, 44.03; H, 4.08; N, 13.51. Found: C, 43.95; H, 4.34; N, 13.70.

The reactions that involved an equimolar amount of 2,4-dinitrophenol (**5**), *p*-toluenesulfonamide (**6**), and *o*-nitrobenzoic acid (**7**) in place of **4**, under the conditions shown in Table I, afforded **12** in 46, 48, and 46% yields, respectively. The washing procedures for removal of the activating agents and resulting acetic acid were performed with 0.5M aqueous sodium hydroxide for **6**, and aqueous saturated sodium hydrogen carbonate for **5** and **7**.

9-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-6-amino-2-chloropurine (**13**). — The foregoing product (**12**, 2.4 g, 4.6 mmol) was sealed in a glass tube containing

methanolic ammonia (200 ml), and the tube was heated in a water bath for 2 h at 40°. After chilling the tube to 0°, it was opened carefully and the contents were then evaporated. Dissolution of the resulting syrup in a small amount of water by warming, followed by decolorization with activated charcoal and recrystallization from water, gave compound **13**, (1.3 g, 76%); m.p. 169–171° (dec); $[\alpha]_D^{22}$ +12° (*c* 1.0, H_2O); $\lambda_{max}^{pH\ 7(H_2O)}$ 265 nm (ε 19,500), $\lambda_{min}^{pH\ 7(H_2O)}$ 230 nm (ε 6400), and $\lambda_{max}^{pH\ 1(H_2O)}$ 264.5 nm (ε 18,200), $\lambda_{min}^{pH\ 1(H_2O)}$ 233 nm (ε 4300).

Anal. Calc. for $C_{13}H_{17}ClN_6O_5$: C, 41.90; H, 4.56; N, 24.87. Found: C, 41.76; H, 4.61; N, 24.93.

*9-(3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl)-2,6-dichloropurine* (**14**) *and its 7-isomer* (**15**). — To a homogeneously pre-fused mixture of **8** (488 mg, 2.6 mmol) and **5** (2.4 g, 13 mmol) at 140–145°, was added 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose (**10**, 954 mg, 2 mmol) and the resulting mixture was treated as for compound **12**, with reaction for 40 min. A solution of the product in chloroform (200 ml) was successively washed with aqueous alkali and with water. The dried (calcium chloride) organic layer was evaporated to a hard syrup, which was then subjected to column chromatography on silica gel with 1:1 chloroform–cyclohexane. The first fraction eluted was compound **5**, followed by compound **14**, (747 mg, 61% as a pale yellow, hard syrup); $[\alpha]_D^{22}$ +39° (*c* 1.0, chloroform); $\lambda_{max}^{0.5M\ HCl\ (95\%\ EtOH)}$ 274 nm (ε 10,400), $\lambda_{min}^{0.5M\ HCl}$ 258 nm (ε 10,200), λ_{max} 274 nm (ε 10,200), λ_{min} 257.5 nm (ε 6900), and $\lambda_{max}^{0.5M\ NaOH\ (95\%\ EtOH)}$ 254 nm[13] (ε 14,500), $\lambda_{min}^{0.5M\ NaOH}$ 240 nm (ε 13,500) (in good agreement with those reported[13] for 2-chloroinosine); n.m.r.: δ 8.32 (1-proton singlet, H-8), 7.72 (4-proton multiplet, phthaloyl), 6.75 (1-proton doublet, $J_{1',2'}$ 9.0 Hz, H-1'), 2.07 (6-proton singlet, OAc), and 1.81 (3-proton singlet, OAc).

Anal. Calc. for $C_{25}H_{21}Cl_2N_5O_9$: C, 49.51; H, 3.49; N, 11.54. Found: C, 49.28; H, 3.34; N, 11.38.

Continued elution of the column with 4:1 chloroform–cyclohexane afforded the corresponding 7-isomer (**15**, 96 mg, 8% as a pale yellow, hard syrup) as the third fraction; u.v.-spectral data of the corresponding spot on t.l.c.: λ_{max}^{EtOH} 281 nm and λ_{min}^{EtOH} 260 nm; n.m.r.: δ 8.50 (1-proton singlet slightly broadened, H-8), 7.77 (4-proton multiplet, phthaloyl), 7.08 (1-proton doublet, $J_{1',2'}$ 10 Hz, H-1'), 2.10 (6-proton singlet, OAc), and 1.90 (3-proton singlet, OAc).

In the reactions involving **4** and **6** as an activating agent, the syrupy **14** (814 mg, 67%, and 519 mg, 43%, respectively) was the sole product obtained.

Thin-layer chromatographic examination of the fusion of **15** *in* **5**. — The 7-isomer (**15**, 31 mg) was fused with **5** (250 mg) *in vacuo* for 45 min at 140–145°, and then the resulting mixture was treated as already described. The product was chromatographed on a thin layer of silica gel with 9:1 benzene–acetone to give a new spot (R_F 0.39) corresponding to **14**, which exceeded the area of that of **15** (R_F 0.32); these spots were readily detected with an S. L. Light (253.7 nm; Tokyo Machinery Co., Ltd).

*7-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)theophylline* (**16**). — Under the conditions summarized in Table II, **1** (1.20 g, 6.5 mmol) and **2** (1.95 g,

5 mmol) were allowed to react in **5** (5 g, 27 mmol), and the resulting mixture was chromatographed on a column of silica gel after the removal as before of unchanged **1** and acetic acid.

The first fraction eluted by chloroform was unchanged **2** (500 mg, 26%), and the second fraction eluted by 2% methanolic chloroform gave **16** (1.52 g, 61% as a hard glass); $[\alpha]_D^{22}$ +12° (*c* 1.0, chloroform); λ_{max}^{EtOH} 275 nm (ε 4700); n.m.r.: δ 8.20 (1-proton singlet, H-8), 6.30 (1-proton doublet, $J_{1',2'}$ 10 Hz, H-1'), 3.58, 3.38 (3-proton singlets, N-CH_3), 2.07 (6-proton singlet, OAc), and 1.75 (3-proton singlet, NAc).

Anal. Calc. for $C_{21}H_{27}N_5O_{10}$: C, 50.50; H, 3.43; N, 14.03. Found: C, 50.21; H, 3.58; N, 14.35.

The reaction performed in **6** (5.5 g, 32.5 mmol), used in place of **5**, followed by the same isolative procedure gave syrupy **16** (1.68 g, 67%). In the reaction performed in **7** (5.4 g, 32.5 mmol) the resulting mixture was treated with methanolic ammonia, after removal of **7** and acetic acid as before, on account of the unexpected coloration. Similar treatment to that described in the first experiment then gave **3** (1.13 g, 59%), identical with the known product.

*7-(3,4,6-Tri-O-acetyl-2-deoxy-2-phthalimido-β-*D*-glucopyranosyl)theophylline* (**17**). — Under the conditions summarized in Table II, **1** (1.20 g, 6.5 mmol) and **10** (2.40 g, 5 mmol) were allowed to react in **4** (4 g, 29 mmol), and the resulting mixture was dissolved in chloroform (100 ml). The solution was treated as previously described. Column chromatography as before gave unchanged **10** (1.6 g, 68%) as the first fraction, and a syrup as the second fraction which, after crystallization and recrystallization from ethanol, gave **17** (0.39 g, 13%); m.p. 240–241°, $[\alpha]_D^{22}$ +7° (*c* 1.0, chloroform); λ_{max}^{EtOH} 274 nm (ε 3900) and λ_{min}^{EtOH} 254 nm (ε 5900); n.m.r.: δ 7.82 (1-proton singlet, H-8), 7.7 (4-proton multiplet, phthaloyl), 7.00 (1-proton doublet, $J_{1',2'}$ 9.0 Hz, H-1'), 3.57, 3.40 (3-proton singlets, NCH_3), 2.07, 2.03, and 1.86 (3-proton singlets, OAc).

Anal. Calc. for $C_{27}H_{27}N_5O_{11}$: C, 54.28; H, 4.52; N, 11.72. Found: C, 54.19; H, 4.58; N, 11.77.

The reaction conducted in **5** (2 g, 11 mmol), in place of **4**, followed by similar treatment and subsequent column chromatography, afforded unchanged **10** (2.0 g, 84%) and **17** (76 mg, 3%). Attempted reactions in **6** and **7** afforded no product, and compound **10** was almost quantitatively recovered.

*7-[2-(*o*-Carbamoylbenzamido)-2-deoxy-β-*D*-glucopyranosyl]theophylline* (**18**). — The foregoing product (**17**, 192 mg, 0.32 mmol) was dissolved in methanolic ammonia (20 ml), and the resulting solution was refrigerated overnight in a tightly stoppered flask. After chilling the flask in an ice–water bath, the solution was evaporated to a hard syrup, which was dissolved by heating in a small volume of abs. methanol. Crystallization gave **18** (127 mg, 84%); m.p. 218–220°, $[\alpha]_D^{22}$ −10° (*c* 0.7, water); $\lambda_{max}^{H_2O}$ 274 nm (ε 9200) and $\lambda_{min}^{H_2O}$ 251.5 nm (ε 5100).

Anal. Calc. for $C_{21}H_{24}N_6O_8 \cdot H_2O$: C, 50.69; H, 5.06; N, 16.89. Found: C, 51.10; H, 4.99; N, 16.75.

7-(3,4,6-Tri-O-acetyl-2-benzamido-2-deoxy-β-D-glucopyranosyl)theophylline (**19**). — To a homogeneously prefused mixture of **1** (1.20 g, 6.5 mmol) and **4** (4 g, 29 mmol), was added **11** (2.3 g, 5 mmol), and the resulting mixture was stirred for 15 min at 130–135°. The cooled mixture was dissolved in chloroform (200 ml), and the solution was washed successively with 0.5M aqueous sodium hydroxide and with water. After drying (anhydrous calcium chloride) the organic layer was evaporated to a hard syrup that was then subjected to chromatography on a column of Wakogel C-300 (40 g). Elution with chloroform gave unchanged **11** (1.1 g, 48%), and elution with 99:1 chloroform–acetone gave syrupy **19**, which crystallized from ethanol; yield 1.2 g (43%); m.p. 262–262.5°, $[\alpha]_D^{22}$ −35° (*c* 1.0, chloroform); λ_{max}^{EtOH} 275 nm (ε 8400) and λ_{min}^{EtOH} 250.5 nm (ε 3900); n.m.r.: δ 8.14 (1-proton singlet, H-8), 7.7–7.0 (5-proton multiplet, N-COC$_6H_5$), 6.24 (1-proton doublet, $J_{1',2'}$ 10 Hz, H-1'), 3.50, 3.10 (3-proton singlet, N-CH_3), 2.06, 2.05, and 1.92 (3-proton singlets, OAc).

Anal. Calc. for $C_{26}H_{29}N_5O_{10}$: C, 54.64; H, 5.11; N, 12.25. Found: C, 54.52; H, 5.07; N, 12.15.

The reactions performed in **5** (6 g, 33 mmol), **6** (4 g, 23 mmol), and **7** (4 g, 24 mmol) under the conditions summarized in Table II gave unchanged **11** (520 mg, 25%; 120 mg, 5%; and 122 mg, 5%; respectively) and **19** (1.4 g, 48%; 2.1 g, 74%; and 590 mg, 21%; respectively).

7-(2-Benzamido-2-deoxy-β-D-glucopyranosyl)theophylline (**20**). — The foregoing product (**19**, 1.900 g, 3.3 mmol) was dissolved in methanolic ammonia (20 ml), and the solution was refrigerated overnight in a tightly stoppered flask. After chilling it in an ice–water bath, the solution was evaporated to a hard syrup that crystallized from abs. methanol to yield **20** (1.149 g, 60%); m.p. 229–230°, $[\alpha]_D^{22}$ +18° (*c* 1.0, water); $\lambda_{max}^{H_2O}$ 274.5 nm (ε 8200) and $\lambda_{min}^{H_2O}$ 254 nm (ε 5100).

Anal. Calc. for $C_{20}H_{23}N_5O_7$: C, 53.93; H, 5.20; N, 15.72. Found: C, 53.59; H, 5.20; N, 15.46.

9-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-6-benzylaminopurine (**21**). — Under the conditions summarized in Table III, **2** (3.9 g, 10 mmol) and **9** (2.5 g, 11 mmol) were allowed to react in **4** (9 g, 50 mmol), and the resulting mixture was treated as already described. Crystallization of the resulting syrup from ethanol afforded **21** (1.4 g, 26%); m.p. 154°, $[\alpha]_D^{22}$ −35° (*c* 1.0, chloroform); λ_{max}^{EtOH} 266.5 nm (ε 26100) and λ_{min}^{EtOH} 233 nm (ε 3700); n.m.r.: δ 8.40 (1-proton singlet, H-2 or 8), 8.28 (1-proton singlet, H-8 or 2), 7.32 (5-proton singlet, CH_2–C_6H_5), 5.97 (1-proton doublet, $J_{1',2'}$ 10 Hz, H-1'), 2.05 (6-proton singlet, OAc), 2.00 (3-proton singlet, OAc), and 1.61 (3-proton singlet, NAc).

Anal. Calc. for $C_{26}H_{30}N_6O_8$: C, 56.31; H, 5.45; N, 15.16. Found: C, 55.81; H, 5.69; N, 15.16.

The reactions performed in **6** (8.5 g, 50 mmol) and **7** (3.4 g, 20 mmol) *in vacuo* under the conditions summarized in Table III yielded **21** (2.1 g, 38%; and 3.2 g, 58%; respectively).

9-(2-Acetamido-2-deoxy-β-D-glucopyranosyl)-6-benzylaminopurine (**22**). — Deacetylation of **21** (1.11 g, 2 mmol) with M methanolic sodium methoxide solution

(1 ml) in abs. methanol (10 ml) for 1 h at room temperature resulted in the precipitation of crystals of **22**, which were filtered off and washed with a small volume of abs. methanol to afford **22** (890 mg, 99%); m.p. 152°, $[\alpha]_D^{22}$ +6° (*c* 1.0, $HCONMe_2$); λ_{max} 265.5 nm (ε 19,800) and λ_{min} 239 nm (ε 3700).

Anal. Calc. for $C_{20}H_{24}N_6O_5 \cdot H_2O$: C, 53.80; H, 5.87; N, 18.83. Found: C, 53.53; H, 6.10; N, 18.42.

9-(3,4,6-tri-O-acetyl-2-benzamido-2-deoxy-β-D-glucopyranosyl)-6-benzylaminopurine (**23**) *and its 7-isomer* (**24**). — To a homogeneously pre-fused mixture of **9** (1.5 g, 6.5 mmol) and **5** (7 g, 38 mmol), was added **11** (2.3 g, 5 mmol), and the resulting mixture was allowed to react for 15 min at 140–145°. The cooled mixture was dissolved in chloroform (200 ml), and the solution was successively washed with saturated aqueous sodium hydrogen carbonate and with water. After drying the solution (calcium chloride), it was evaporated to a hard syrup, which was then chromatographed on a column of Wakogel C-300 (40 g). Elution with chloroform gave unchanged **11** (390 mg, 17%), and elution with 99:1 chloroform–acetone afforded a syrup that crystallized quantitatively from ethanol to give **23** (648 mg, 21%); m.p. 224–225°, $[\alpha]_D^{22}$ −79° (*c* 1.0, chloroform); $\lambda_{max}^{0.5M\ HCl\ (95\%\ EtOH)}$ 265 nm (ε 22,900) and $\lambda_{min}^{0.5M\ HCl}$ 246 nm (ε 15000), λ_{max} 266 nm (ε 22,900) and λ_{min} 246 nm (ε 15,000), $\lambda_{max}^{0.5M\ NaOH\ (95\%EtOH)}$ 265 nm (ε 23,200) and $\lambda^{0.5M\ NaOH}$ 243 nm (ε 15,800); n.m.r.: δ 8.45 (1-proton singlet, H-2 or 8), 8.25 (1-proton singlet, H-8 or 2), 7.26 (5-proton singlet, CH_2–C_6H_5), 6.13 (1-proton doublet, $J_{1',2'}$ 10 Hz, H-1'), 2.00 (6-proton singlet, OAc), and 1.90 (3-proton singlet, OAc).

Anal. Calc. for $C_{31}H_{32}N_6O_8$: C, 60.38; H, 5.32; N, 13.63. Found: C, 60.09; H, 5.15; N, 13.51.

Subsequent elution of the column with 99:1 chloroform methanol–afforded a syrup that crystallized quantitatively from ethanol to give the 7-isomer **24** (500 mg, 16%); m.p. 243–244°, $[\alpha]_D^{22}$ −98° (*c* 1.0, chloroform); $\lambda_{max}^{0.5M\ HCl\ (95\%\ EtOH)}$ 291 nm (ε 24,700) and $\lambda_{min}^{0.5M\ HCl}$ 254 nm (ε 8,000), λ_{max} 299 nm (ε 17,400) and λ_{min} 254 nm (5600), $\lambda_{max}^{0.5M\ NaOH\ (95\%\ EtOH)}$ 295 nm (ε 16,000) and $\lambda_{min}^{0.5M\ NaOH}$ 255 nm (ε 9,100); n.m.r.: δ 8.55 (1-proton singlet, H-2 or 8), 7.63 (1-proton singlet, considerably broadened, H-8 or 2), 7.25 (5-proton singlet, CH_2–C_6H_5), 6.41 (1-proton doublet, $J_{1',2'}$ 10 Hz, H-1'), 2.09 (6-proton singlet, OAc), and 1.93 (3-proton singlet, OAc).

Anal. Calc. for $C_{31}H_{32}N_6O_8$: C, 60.38; H, 5.32; N, 13.51. Found: C, 60.07; H, 5.09; N, 13.48.

The reactions were performed in **6** (5 g, 29 mmol) and **7** (4.2 g; 25 mmol) under the conditions summarized in Table III, after which the resulting mixtures were treated in the same way as already described. They gave unchanged **11** (1.2 g, 49%; and 495 mg, 22%; respectively) and **23** (443 mg, 14%; and 475 mg, 15%; respectively), but no **24** in either instance.

7-(2-Benzamido-2-deoxy-β-D-glucopyranosyl)-6-benzylaminopurine (**25**). — The foregoing product (**24**) (215 mg, 0.35 mmol) was dissolved in methanolic ammonia (20 ml), and the solution was refrigerated overnight in a tightly stoppered flask. After chilling the solution in an ice–water bath, it was evaporated to a hard syrup that

crystallized from methanol to give **25** (166 mg; 88%); m.p. 188–189°, $[\alpha]_D^{22}$ −111° (*c* 0.76, ethanol); $\lambda_{max}^{0.5M\ HCl\ (95\%\ EtOH)}$ 299 nm (ε 22,500) and $\lambda_{min}^{0.5M\ HCl}$ 265 nm (ε 7,800), λ_{max} 302.5 nm (ε 17,200) and λ_{min} 264 nm (ε 6,200), $\lambda_{max}^{0.5M\ NaOH\ (95\%\ EtOH)}$ 305.5 nm (ε 16,000) and $\lambda_{min}^{0.5M\ NaOH}$ 265 nm (ε 6,300).

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REFERENCES

1 M. L. WOLFROM AND M. W. WINKLEY, *J. Org. Chem.*, 31 (1966) 3711–3713.
2 M. SEKIYA, T. YOSHINO, H. TANAKA, AND Y. ISHIDO, *Bull. Chem. Soc. Japan*, 46 (1973) 556–561.
3 N. NAKAZAKI, M. SEKIYA, T. YOSHINO, AND Y. ISHIDO, *Bull. Chem. Soc. Japan*, 46 (1973) 3858–3863.
4 Y. ISHIDO, T. MATSUBA, A. HOSONO, K. FUJII, AND T. SATO, *Bull. Chem. Soc. Japan*, 40 (1967) 1007–1009.
5 Y. ISHIDO, Y. KIKUCHI, AND T. SATO, *Nippon Kagaku Zasshi*, 86 (1965) 240–243.
6 A. G. BEAMAN AND R. K. ROBINS, *J. Org. Chem.*, 28 (1963) 2310–2313.
7 (a) S. G. WALLWORK, *J. Chem. Soc.*, (1961) 494–499; (b) E. SHEFTER, *J. Pharm. Sci.*, 57 (1968) 350–351; (c) E. SHEFTER, T. E. BRENNAN, AND P. SACKMAN, *Chem. Pharm. Bull.*, 19 (1971) 746–752.
8 L. B. TOWNSEND, R. K. ROBINS. AND N. J. LEONARD, *J. Amer. Chem. Soc.*, 86 (1964) 5320–5325.
9 B. R. BAKER, J. P. JOSEPH, R. E. SHAUB, AND J. H. WILLIAMS, *J. Org. Chem.*, 19 (1954) 1786–1792.
10 A. HOSONO, K. FUJII, T. TADA, H. TANAKA, Y. OGHO, Y. ISHIDO, AND T. SATO, *Bull. Chem. Soc. Japan*, 46 (1973) 2814–2810.
11 (a) O. WESTPHAL AND H. HOLZMAN, *Ber.*, 75 (1931) 1274–1282; (b) M. BERGMANN AND L. ZERVAS, *Ber.*, 64 (1931) 975–980.
12 G. B. ELISON AND G. H. HITCHINGS, *J. Amer. Chem. Soc.*, 78 (1956) 3508–3510.
13 A. YAMAZAKI, T. SAITO, Y. YAMADA, AND I. KUMASHIRO, *Chem. Pharm. Bull.* (Tokyo), 17 (1969) 2581–2585.