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SYNTHESES OF SOME PURINE NUCLEOSIDES BY THE FUSION METHOD, BY THE CONDENSATION OF ACETYLATED CHLORIDES, AND FROM 1-ACETATES IN THE PRESENCE OF TITANIUM TETRACHLORIDE: A COMPARISON

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ABSTRACT

9-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-6-benzamidopurine (**9**) and 6-benzamido-9-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)purine (**11**) have been prepared by three synthetic routes: (*a*) the fusion procedure, (*b*) direct condensation of 6-benzamido(chloromercuri)purine with the acetylated chloride, or (*c*) with the chloride formed *in situ* from the 1-acetate in the presence of titanium tetrachloride. The results obtained are briefly discussed; the direct condensation of the mercuri salt with chlorides proved to be the most convenient.

Whereas, in the condensation with acetylated chlorides, only products having the β-D anomeric configuration were isolated, the chloride protected with non-participating groups (benzyl) afforded both anomers. The removal of the benzyl groups should be preceded by hydrolytic cleavage of the benzamido group. A simple procedure for fractionation, on small columns of silica gel, of reaction mixtures obtained in the fusion reactions is described.

INTRODUCTION

In continuation of our research[1,2] on the reactivity of unsaturated amino sugars, a need arose for a reliable and simple method that would lead to the preparation of nucleosides having a carbohydrate moiety containing a 2-acetamido group at the vinyl position. Two of the methods most frequently used in the chemical synthesis of nucleosides are the mercuri salt method and the fusion method[3]. Although the fusion reaction of Sato *et al.*[4] is in some cases considered to be more favorable than the mercuri procedure of Davoll and Lowy[5], a general preference has not been evinced for either of these two methods.

Because, in the series of the unsaturated amino sugars, the corresponding halides are not accessible, the mercuri salt method is not applicable. However, there is a possibility of the formation of the glycosyl halide *in situ* from the 1-acetate in the presence of titanium tetrachloride[6–8], and, due to the availability[9] of such a

derivative in the unsaturated amino sugar series, this has now been investigated. In order to test the feasibility of this approach, the same reaction was, for purposes of comparison, conducted with saturated, polyacetylated 2-acetamido and 2-*O*-acetyl sugars. In addition, the saturated nucleosides were also prepared *via* condensation of the halide with a 6-(acylamido)(chloromercuri)purine and/or through the fusion of the 1-acetates with purines. These results are presented in this paper. A partial report[10] on the preparation of unsaturated nucleosides by the fusion procedure has already been published.

RESULTS AND DISCUSSION

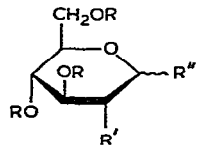
The fusion reactions of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose (**1**) and 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**2**) with theophylline and 6-benzamido- and 6-acetamido-purine will be described first. The reactions were performed in the presence of *p*-toluenesulfonic acid as the catalyst; in some cases, a larger amount of *p*-nitrophenol, as an activating agent[11], was added.

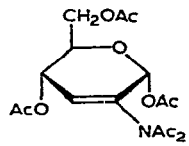
Although Ishido *et al.*[12] had stated that, in a similar fusion reaction (of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose with theophylline), *p*-nitrophenol showed no activating effect, the reaction performed in our laboratory with **1** and theophylline in the presence of a mixture of the acid catalyst and the activating agent gave good results. 7-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)theophylline (**8**) was formed in this reaction, and it was isolated in crystalline form in 45% yield. The fusion reaction carried out in the absence of the activating agent afforded a lower yield. The β-D anomeric configuration of **8** was assigned on the basis of its specific rotation ($[\alpha]_D$ −2.2°), the chemical shift, and the magnitude of splitting of the anomeric proton (H-1 at τ 3.80, $J_{1,2}$ 10.0 Hz). The ultraviolet absorption spectrum indicated 7-substitution[13].

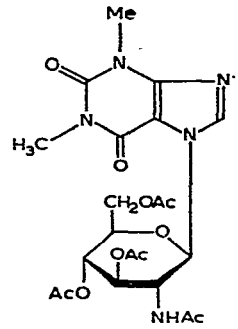
Compound **8** was also obtained when 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-α-D-glucopyranose (**3**), was used as the sugar component, indicating that one *N*-acetyl group had been selectively removed during the fusion.

The separation procedure applied in this instance is of particular interest. The crude reaction mixture (4–6 g) was mixed with silica gel (2 g), dried, and applied on the top of a small column of silica gel (10–15 g). The components were successively eluted by changing the eluant; *e.g.*, *p*-nitrophenol was eluted with ether, unreacted **1** with chloroform, and, finally, the product (**8**) with 9:1 ether–methanol. This procedure proved to be very convenient for large amounts; it has wide applicability for the fractionation of the mixtures obtained in the fusion reactions, because the components of such mixtures usually show differing solubility in a particular solvent. Therefore, the separation is successful, and the dark color normally accompanying the fusion products is retained on the silica gel.

The reaction of **1** with 6-benzamidopurine in the presence of *p*-toluenesulfonic acid afforded 9-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-6-benzamidopurine (**9**) in ~10% yield. Deacetylation of **9** with sodium methoxide gave







1 R = Ac , R′ = NHAc , R″ = OAc (α)
2 R = Ac , R′ = OAc , R″ = OAc (β)
3 R = Ac , R′ = NAc_2 , R″ = OAc (α)
4 R = Ac , R′ = NHAc , R″ = Cl (α)
5 R = Ac , R′ = OAc , R″ = Cl (α)
6 R = CH_2Ph , R′ = OCH_2Ph , R″ = Cl

7

8

9-(2-acetamido-2-deoxy-β-D-glucopyranosyl)adenine (**10**). The structure of this compound was established by comparison with the product prepared by Wolfrom and Wurmb[14] by a different route. The anomeric configuration of **9** was thus confirmed.

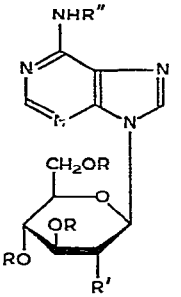
Fusion of **2** with 6-benzamidopurine in the presence of the same catalyst led to the isolation of 6-benzamido-9-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)purine (**11**) in 32% yield. This compound had previously[15] been prepared in a similar way, but in the presence of ethyl polyphosphate as the catalyst. Because of the remarkable differences between the physical constants of our sample and the literature data (see Experimental), compound **11** was fully characterized. The assignment of the β-D anomeric configuration to **11** was made on the basis of its negative specific rotation and the n.m.r.-spectral data. The fusion reactions of 6-benzamidopurine with either **1** or **2** in the presence of the activating agent failed to give the corresponding products in better yields.

From the fusion reaction of **2** with 6-acetamidopurine in the presence of mixed catalysts, 81% of unreacted base was recovered, and the expected product, 6-acetamido-9-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)purine (**12**), was obtained in only very low yield. The major product was found to be 9-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)adenine (**13**) which, according to the t.l.c. evidence, was formed in the course of the fusion. Extremely low reactivity of 6-acetamidopurine was shown in the reaction with **1**, where the product was formed only in traces, and 93% of the base was recovered.

In the alternative method, the halides **4**, **5**, and **6** were used for the condensation with 6-benzamido(chloromercuri)purine. Glycosyl halides have found numerous applications[14,16–21] in the synthesis of amino nucleosides, but due to rather modest yields in these syntheses, many synthetic pathways for introduction of the amino group into the carbohydrate moiety have also been elaborated[22].

Treatment of the chloride **4** with 6-benzamido(chloromercuri)purine in refluxing xylene[23], under the general conditions of Davoll and Lowy[5], led to the isolation of compound **9** in good yield. Condensation of the chloride **5** with the same base afforded the β-D-nucleoside **11** in 47% yield. The isolation of **11** was especially simple: it crystallized from the xylene solution in a mixture with mercuric chloride (from which it could be readily separated). The samples of **9** and **11**, thus obtained, proved to be indistinguishable from those prepared by the fusion method.

We then turned our attention to the condensation with the benzyl-protected chloride **6**. Under identical conditions, this reaction afforded two products, which were separated by column chromatography on silica gel. Thus, 6-benzamido-9-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)purine (**14**) and the α-D anomer (**14**-α) were each obtained in ~30% yield. The assignment of configuration was based on their n.m.r.-spectral data and optical rotations: crystalline **14** (H-1 at τ 4.29, $J_{1,2}$ 8.7 Hz; $[\alpha]_D$ −13.9°); syrupy **14**-α, which analyzed as a monohydrate (H-1 at τ 3.62, $J_{1,2}$ 3.0 Hz; $[\alpha]_D$ +55.5°).



9 R = Ac, R' = NHAc, R'' = COPh
10 R = H, R' = NHAc, R'' = H
11 R = Ac, R' = OAc, R'' = COPh
12 R = Ac, R' = OAc, R'' = Ac
13 R = Ac, R' = OAc, R'' = H
14 R = CH_2Ph, R' = OCH_2Ph, R'' = COPh
15 R = CH_2Ph, R' = OCH_2Ph, R'' = H
16 R = H, R' = OH, R'' = H

It is important to note that the *N*-benzoyl group should be removed prior to catalytic hydrogenolysis of the benzyl groups. In an attempted debenzylation of **14**-α, a series of products was formed as a result of partial removal of the *N*-benzoyl as well as the benzyl groups. Treatment of **14** with sodium methoxide yielded 9-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)adenine (**15**), which was also characterized as the picrate. Catalytic hydrogenolysis of **15** readily afforded 9-β-D-glucopyranosyladenine (**16**).

It is well known[24] that glycosyl halides that have suitable nonparticipating groups, such as benzyl, react with nucleophiles with inversion of the configuration at C-1. The fact that the condensation with the chloride **6** resulted in the formation of the *trans*- and the *cis*-nucleosides (**14** and **14**-α) in approximately the same yield

suggests that the sample of compound **6** used was not anomerically pure. Although these samples of **6** were found to be more dextrorotatory than hitherto noted[25,26], and their n.m.r. spectra showed a narrow doublet at τ 3.95 ($J_{1,2}$ 3.2 Hz), the tentative existence of the axially oriented H-1 for the β anomer could easily have been obscured by unresolved signals of the methylene groups in the region τ 4.8–5.5. Our results are in agreement with the finding of Goodman *et al.*[27] that condensation of 2,3,4-tri-*O*-benzyl-D-arabinopyranosyl chloride with 6-(benzamido)(chloromercuri)purine afforded both anomers, in the ratio 1:1.

The ultraviolet spectral data for compounds **9–16** support the assignment of N-9 as the site of glycosylation[28].

In conclusion it should be noted that, in the scope of our investigation, the mercuri salt method proved to be superior to the fusion method; the products were obtained in better yields, were of higher purity, and were readily separable.

The formation of the glycosyl chlorides *in situ* was next studied. The method explored[6–8] uses the sugar in the form of its 1-acetate; this is treated with titanium tetrachloride to give the chloride, which then reacts with the mercuri salt of a purine base to give the nucleoside. Thus, treatment of **1** and **2** with 6-(benzamido)(chloromercuri)purine gave nucleosides **9** and **11**, respectively; the yields were somewhat lower than in the direct condensation described earlier in this paper. It should be noted that, in this two-step reaction, the formation of the corresponding chloride **4** (or **5**) is a fast process.

With this background, an attempt at application to 1,4,6-tri-*O*-acetyl-2-(*N*-acetylacetamido)-2,3-dideoxy-α-D-*erythro*-hex-2-enopyranose[9] (**7**), a stable, unsaturated amino sugar derivative, was made. However, under identical reaction-conditions, compound **7** decomposed and formation of the nucleoside did not occur. As this proved not to be a method of choice for the preparation of nucleosides containing unsaturated amino sugars, we turned to a consideration of the fusion procedure[10].

EXPERIMENTAL

General methods. — T.l.c. was conducted on plates (5 × 10 cm) of silica gel F 254 (E. Merck) in the following solvent systems: *A*, 9:1 ether–methanol; *B*, 5:1 ether–methanol; *C*, 10:1 chloroform–methanol; *D*, 1:2 ether–petroleum ether; *E*, 80:5:15:1 acetonitrile–acetone–water–acetic acid; and *F*, 25:1 ether–methanol, all ratios being v/v. The components were detected under u.v. light, or by spraying with 10% sulfuric acid and heating. Column chromatography was performed on silica gel (E. Merck; 0.05–0.20-mm particle size) with the solvent system specified.

Specific rotations were measured at 20–24°. I.r. spectra were recorded with a Perkin–Elmer 137 Infracord instrument. The n.m.r. spectra were recorded at 60 MHz with a Varian A-60-*A* spectrometer, for solutions in the solvents specified, with tetramethylsilane as the internal standard. U.v.-spectral data were obtained

with a Perkin–Elmer double-beam spectrophotometer (Model 124) for solutions in methanol.

7-(2-Acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)theophylline (**8**). — A mixture of theophylline (900 mg, 5 mmol), *p*-nitrophenol (2.1 g, 15 mmol), and *p*-toluenesulfonic acid (50 mg) was heated in an oil bath at 130°. To this melt was added 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose[29] (**1**) (1.95 g, 5 mmol), the mixture was stirred, and heating was continued for 4 h at the same temperature, the progress of the reaction being monitored by t.l.c. with solvent *A*. The light-colored melt was then cooled to room temperature and dissolved in chloroform (150 ml). The solution was successively washed with saturated aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and evaporated *in vacuo* to dryness. The foamy residue was dissolved in chloroform (1 ml), the solution mixed with silica gel (2 g), and the mixture dried overnight at room temperature, and then applied to a column of silica gel (15 g) prepacked in ether; the column was successively eluted: first, with ether (50 ml) to remove *p*-nitrophenol; then, with chloroform (40 ml), which eluted unchanged **1** (36%); and finally, with solvent *A* to give fractions containing homogeneous material. From these fractions, the title product **8** was obtained in crystalline form (1.16 g, 45%); it was recrystallized from ethanol, m.p. 193–194°, $[\alpha]_D$ −2.2° (*c* 1.0, chloroform) {lit.[12] hard glass, $[\alpha]_D$ +12° (chloroform)}; λ_{max}^{MeOH} 212 and 275 nm (ε_{mM} 19.6 and 8.7); ν_{max}^{KBr} 3550 (NH), 1760 (OAc), 1720 (C=O), 1610 (C=C), 1670 and 1550 (Amide I and II), and 1240 cm^{-1} (OAc); n.m.r. data (in $CDCl_3$): τ 1.89 (s, H-8), 3.13 (broad d, NH), 3.80 (d, $J_{1,2}$ 10.0 Hz, H-1), 6.41 and 6.62 (2 NCH_3), 7.94 (9 H) and 8.23 (OAc and NAc).

Anal. Calc. for $C_{21}H_{27}N_5O_{10}$: C, 49.51; H, 5.34; N, 13.75. Found: C, 49.25; H, 5.58; N, 13.86.

In an analogous reaction with 1,3,4,6-tetra-*O*-acetyl-2-(*N*-acetylacetamido)-2-deoxy-α-D-glucopyranose[30] (**3**) as the sugar component, compound **8** was obtained in 40% yield.

Fusion of **1** *with 6-benzamidopurine.* — A mixture of equimolar amounts of **1** and 6-benzamidopurine[31] was stirred and fused in the presence of *p*-toluenesulfonic acid (20 mg/mmol) for 4 h at 155–160° (bath temperature). The dark melt was dissolved in chloroform; the solution was mixed with silica gel, dried, and processed further as described for the preparation of **8**. The column of silica gel was prepacked in chloroform; for elution, chloroform was first used (recovered **1**, 40–50%), and then solvent *B*, which eluted the product contaminated with 6-benzamidopurine. This mixture was washed with solvent *B*, to give homogeneous product in 8–14% yield. The i.r. spectrum, mixed m.p., and chromatographic behavior identified it as *9-(2-acetamido-3,4,6-tri-O-acetyl-2-deoxy-β-D-glucopyranosyl)-6-benzamidopurine* (**9**), more fully described later in this paper.

A solution of **9** (0.5 g) in methanol (75 ml) containing 0.1M sodium methoxide (40 ml) was boiled under reflux for 1 h. Evaporation of the solvent afforded a crude residue from which, after two recrystallizations from ethanol, pure *9-(2-acetamido-2-deoxy-β-D-glucopyranosyl)adenine* (**10**) was obtained: m.p. 231–233°, $[\alpha]_D$ −8.4°

(*c* 0.79, 7:3 methanol–water {lit.[14] m.p. 236–237°, $[\alpha]_D$ −11° (same solvent)}; λ_{max}^{MeOH} 211 and 259 nm (ε_{mM} 20.0 and 17.9); n.m.r. data (in Me_2SO-d_6: τ 1.85 and 1.88 (singlets, H-2 and H-8), 2.16 (broad d, removed by D_2O exchange, NH), 2.86 (broad s, 2 H, removed by D_2O exchange, NH_2), 4.42 (d, $J_{1,2}$ 10.0 Hz, H-1), and 8.47 (NAc).

Fusion of **2** *with 6-benzamidopurine.* — A mixture of **2** (1.95 g, 5 mmol), 6-benzamidopurine (1.2 g, 5 mmol), and *p*-toluenesulfonic acid (100 mg) was stirred and fused for 4 h at 160°, the progress of the reaction being monitored by t.l.c. in solvent *A*. The melt was dissolved in chloroform (10 ml), the solution mixed with silica gel (3 g), and the mixture dried, and applied to a column of silica gel (10 g) prepacked in ether. Elution with ether (150 ml) afforded unreacted **2** (56%), and further elution with chloroform gave *6-benzamido-9-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)purine* (**11**) in the form of a stable foam (905 mg, 32%). It was crystallized from ethanol: m.p. 167–168°, $[\alpha]_D$ −33.4° (*c* 0.91, chloroform) {lit.[15] m.p. 234°, $[\alpha]_D$ −25° (chloroform)}; λ_{max}^{MeOH} 210 and 278 nm (ε_{mM} 25.4 and 21.2); ν_{max}^{KBr} 3400 (NH), 1750 (OAc), 1700 and 1580 (Amide I and II), 1600 (C=C), and 1230 cm^{-1} (OAc); n.m.r. data (in $CDCl_3$): τ 1.26 and 1.72 (singlets, H-2,8), 1.9–2.5 (aromatic protons), 3.94 (d, $J_{1,2}$ 9.5 Hz, H-1), 7.95, 7.98, 7.99, and 8.25 (OAc).

Anal. Calc. for $C_{26}H_{27}N_5O_{10}$: C, 54.83; H, 4.78; N, 12.30. Found: C, 54.81; H, 4.86; N, 12.55.

Fusion of **2** *with 6-acetamidopurine.* — A mixture of 6-acetamidopurine[5,32] (1.77 g, 10 mmol), *p*-nitrophenol (2.1 g, 15 mmol), and *p*-toluenesulfonic acid (50 mg) was heated in an oil bath at 130°. 1,2,3,4,6-Penta-*O*-acetyl-β-D-glucopyranose (**2**) (1.88 g, 5 mmol) was then added, and the melt was stirred, and heated at the same temperature. After 1 h, the formation of two products was revealed by t.l.c. in solvent *A*. The reaction was terminated after 5 h, although the presence of the starting sugar was still detectable. To the cooled mixture was added chloroform (120 ml), and the undissolved part was removed by filtration (1.43 g, 81%); its i.r. spectrum identified it as 6-acetamidopurine. The filtrate was successively washed with saturated, aqueous sodium hydrogencarbonate and water, dried (Na_2SO_4), and concentrated *in vacuo* to ~5 ml. It was then mixed with silica gel (2 g), dried overnight at room temperature, and applied to a column of silica gel (90 g) prepacked in solvent *A*. The column was eluted with the same solvent, 8-ml fractions of eluate being collected.

Fractions 10–20 afforded unchanged **2** (1.41 g, 75%). Fractions 33–55 contained a mixture of two products (507 mg); this was rechromatographed on silica gel with solvent *C*, to give, first, *6-acetamido-9-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)purine* (**12**): 87 mg, 3%. After crystallization from ethanol, it had m.p. 223–224° and $[\alpha]_D$ −37.5° (*c* 0.75, chloroform) (lit.[5] m.p. 227°); λ_{max}^{MeOH} 214 and 272 nm (ε_{mM} 22.5 and 18.9); ν_{max}^{KBr} 3570 (NH), 1760 (OAc), 1620 (C=C), 1720 and 1590 (Amide I and II), and 1230 cm^{-1} (OAc); n.m.r. data (in $CDCl_3$): τ 0.89 (broad s, NH), 1.30 and 1.75 (singlets, H-2,8), 4.0–4.7 (unresolved, ring protons, 4 H), 5.7–6.0 (H-5,6,6'), 7.38 (NAc), 7.93, 7.96, 7.98, and 8.24 (OAc).

Anal. Calc. for $C_{21}H_{25}N_5O_{10}$: C, 49.72; H, 4.97; N, 13.81. Found; C, 49.49; H, 5.04; N, 13.62.

From further fractions, a mixture was obtained (41 mg), and then the homogeneous second product, *9-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)adenine* (**13**): 306 mg, 13%. Crystallized from ethanol, m.p. 205–207°, $[\alpha]_D$ −22.6° (*c* 0.67, chloroform); λ_{max}^{MeOH} 210 and 258 nm (ε_{mM} 28.9 and 18.0); ν_{max}^{KBr} 3550 (NH), 1770 (OAc), 1650 (NH_2), 1600 (C=C), and 1230 cm^{-1} (OAc); n.m.r. data (in $CDCl_3$): τ 1.55 and 1.85 (singlets, H-2,8), 3.45 (broad s, 2 H, removed by D_2O exchange, NH_2), 3.9–4.7 (unresolved, ring protons, 4 H), 5.7–6.0 (H-5,6,6'), 7.95 (6 H), 7.98, and 8.25 (OAc).

Anal. Calc. for $C_{19}H_{23}N_5O_9$: C, 49.03; H, 4.98; N, 15.05. Found: C, 49.26; H, 5.25; N, 15.00.

*9-(2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-6-benzamidopurine* (**9**). — (*a*) *From 2-acetamido-3,4,6-tri-*O*-acetyl-α-*D*-glucopyranosyl chloride*[33,34] (**4**). A mixture of 6-benzamido(chloromercuri)purine[23] (2.6 g, 5.5 mmol), Celite (2.6 g), and cadmium carbonate (1.04 g) was suspended in anhydrous xylene (200 ml), and the liquid slowly distilled until the distillate was clear (~50 ml). To the residual suspension was added a solution of **4** (2.0 g, 5.5 mmol) in chloroform (10 ml), and the mixture was refluxed for 1.5 h, when t.l.c. in solvent *B* showed the absence of the chloride. Inorganic material was removed by filtration of the hot reaction-mixture, and the filtrate was evaporated *in vacuo* to dryness. The precipitate was washed with hot methanol (30 ml), and these washings were used to dissolve the crude residue. This solution was concentrated to ~5 ml, mixed with silica gel (3 g), and the mixture dried overnight at room temperature, and then applied to a column of silica gel (10 g) prepacked in chloroform. The column was eluted first with chloroform (250 ml), to remove a mixture of by-products (1.16 g), and then with solvent *B* (150 ml) to isolate the title product **9**, which partially crystallized in the eluate. After removal of the crystals (293 mg, m.p. 227–228°), the eluate was evaporated to dryness (827 mg), and the residue crystallized from methanol to give a second crop of **9** (127 mg, m.p. 212–213°, total yield 39%). For analysis, it was recrystallized from methanol: m.p. 238–239°. The substance is not appreciably soluble in any solvent tested without heating. It showed λ_{max}^{MeOH} 211 and 281 nm (ε_{mM} 25.4 and 23.6); ν_{max}^{KBr} 3400 (NH), 1750 (OAc), 1650 (C=C), 1680 and 1560 (Amide I and II), 1600 and 1500 (aromatic protons), and 1230 cm^{-1} (OAc).

Anal. Calc. for $C_{26}H_{28}N_6O_9$: C, 54.93; H, 4.96; N, 14.78. Found: C, 54.71; H, 5.11; N, 14.66.

(*b*) *From* **1** *with titanium tetrachloride.* A mixture of 6-benzamido(chloromercuri)purine, Celite, and cadmium carbonate in anhydrous xylene, containing **1**, was treated as described in (*a*). To the residual suspension was added titanium tetrachloride dissolved in xylene; the reaction was conducted and then the mixture was processed as already described. The product isolated (30% yield) was identified as **9**.

*6-Benzamido-9-(2,3,4,6-tetra-*O*-acetyl-β-*D*-glucopyranosyl)purine* (**11**). — (*a*)

From 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl chloride[35] (**5**). The reaction conditions were analogous to those described for the preparation of **9**. After refluxing for 24 h, inorganic material was removed by filtration; on cooling the filtrate, crystalline material was precipitated. It was filtered off, dissolved in chloroform, and the solution washed with a 30% solution of potassium iodide. The chloroform solution, containing chromatographically pure **11**, was evaporated *in vacuo*, to give a stable foam which crystallized from ethanol (47% yield). The m.p., $[\alpha]_D$, and chromatographic behavior were indistinguishable from those of a sample of **11** prepared by the fusion procedure.

(*b*) *From* **2** *with titanium tetrachloride.* A mixture of **2**, 6-benzamido(chloromercuri)purine, Celite, and cadmium carbonate in anhydrous xylene was treated as described in preparation (*a*) of **9**. To the residual suspension was added titanium tetrachloride dissolved in xylene, and the mixture was refluxed for 5 h, the progress of the reaction being monitored in solvent *A*. Inorganic material was removed by filtration of the hot reaction mixture; t.l.c. indicated that the product had been co-precipitated. The precipitate was thoroughly washed with warm chloroform, and the chloroform extracts were combined, successively washed with a 30% solution of potassium iodide, and water, and evaporated *in vacuo*; the residue was purified on a column of silica gel in solvent *A*, to give the title product **11** in 27% yield.

2,3,4,6-Tetra-O-benzyl-D-glucopyranosyl chloride (**6**) was prepared by a modification[36] of the procedure of Baddiley *et al.*[25]. 2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranose[37] was treated with freshly distilled thionyl chloride for 3 days at 0°, and the reagent was removed by coevaporation with toluene; the thoroughly dried chloride, which was chromatographically homogeneous (solvent *D*), showed $[\alpha]_D$ +82° (*c* 0.72, chloroform) [lit.[26] +62° (chloroform)], and was used in the next reaction-step without further purification.

Condensation of 6-benzamido(chloromercuri)purine with **6**. — A mixture of 6-benzamido(chloromercuri)purine (1.34 g), Celite (1.34 g), and cadmium carbonate (0.54 g) was suspended in anhydrous xylene (55 ml), and the liquid slowly distilled until the distillate was clear (~20 ml). To the residual suspension was added a solution of crude **6** [prepared from 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose (1.0 g)] in xylene (25 ml), and the mixture was refluxed for 4 h, the progress of the reaction being monitored by t.l.c. in ether. At the end of the reaction, spots for the starting chloride and two new components were detectable. Inorganic material was removed by filtration of the hot reaction-mixture, and the filtrate was evaporated *in vacuo* to dryness. The precipitate was washed with warm chloroform (2 × 20 ml), and these washings were used to dissolve the crude residue. The chloroform solution was successively washed with 30% aqueous potassium iodide solution and water, dried (sodium sulfate), and evaporated to dryness. The residue was then chromatographed on a column of silica gel (90 g) with ether, 8-ml portions of eluate being collected.

From fractions 7–10 was recovered unreacted chloride **6** (20–30%). A few further fractions contained a minor amount of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose.

Fractions 24–25 contained homogeneous material (400 mg, 29%); this was rechromatographed on silica gel with ether, to give pure *6-benzamido-9-(2,3,4,6-tetra-O-benzyl-α-D-glucopyranosyl)purine* (**14**-α) in the form of a stable foam that failed to crystallize: $[\alpha]_D$ +55.5° (*c* 1.3, chloroform); λ_{max}^{MeOH} 210 and 280 nm (ε_{mM} 55.4 and 20.6); n.m.r. data (in $CDCl_3$): τ 1.16 and 1.60 (H-2,8), 2.6–2.7 (aromatic protons, 20 H), and 3.62 (d, $J_{1,2}$ 3.0 Hz, H-1).

Anal. Calc. for $C_{46}H_{43}N_5O_6 \cdot H_2O$: C, 70.84; H, 5.81; N, 8.98; H_2O, 2.31. Found: C, 70.67; H, 5.75; N, 9.06; H_2O, 2.15.

Fractions 46–50 contained a mixture (68 mg). Fractions 51–75 were pooled, and evaporated to give the second product as semicrystalline material: 429 mg, 30%. When recromatographed with ether, pure *6-benzamido-9-(2,3,4,6-tetra-O-benzyl-β-D-glucopyranosyl)purine* (**14**) crystallized in fractions: m.p. 120–121°, $[\alpha]_D$ −13.9° (*c* 0.94, chloroform); λ_{max}^{MeOH} 209 and 280 nm (ε_{mM} 55.0 and 21.7); n.m.r. data (in $CDCl_3$): τ 0.73 (broad s, removed by D_2O exchange, NH), 1.20 and 1.97 (H-2,8), 2.6–2.7 (aromatic protons, 20 H), and 4.29 (d, $J_{1,2}$ 8.7 Hz, H-1).

Anal. Calc. for $C_{46}H_{43}N_5O_6$: C, 72.52; H, 5.69; N, 9.19. Found: C, 72.42; H, 5.80; N, 9.15.

Catalytic hydrogenolysis of **14**-α. — A solution of **14**-α (300 mg) in methanol (15 ml) was added to a suspension of palladium chloride (300 mg) in methanol (40 ml) presaturated with hydrogen. The mixture was stirred with hydrogen overnight, until absorption of the gas had ceased. The catalyst was removed by filtration through a layer of Celite, and the filtrate was evaporated *in vacuo* to dryness (259 mg). T.l.c. in solvent *E* revealed the presence of the starting **14**-α, as well as of at least four new compounds.

The crude material thus obtained was dissolved in methanol (30 ml) containing sodium methoxide (pH 8), and the solution was boiled under reflux for 6 h, and then kept overnight at room temperature. It was made neutral with Dowex-50 X-8 (H^+) ion-exchange resin, the suspension filtered, and the filtrate evaporated to dryness. The residue was again hydrogenolyzed, and processed as just described, to yield *9-α-D-glucopyranosyladenine* (**16**-α): 185 mg, 88%. It was characterized as the picrate: m.p. 213–215° (lit.[38] m.p. 210–215°).

9-(2,3,4,6-Tetra-O-benzyl-β-D-glucopyranosyl)adenine (**15**). — A solution of **14** (350 mg) in methanol (30 ml) containing sodium methoxide (pH 8) was boiled under reflux for 1 h, cooled, treated with Dowex-50 X-8 (H^+) ion-exchange resin until neutral, the suspension filtered, and the filtrate evaporated. The residue was chromatographed on a column of silica gel (15 g) in solvent *F*, to yield the title compound **15** in the form of a white, stable foam: 161 mg, 49%; $[\alpha]_D$ +5.9° (*c* 1.15, chloroform); λ_{max}^{MeOH} 214 and 260 nm (ε_{mM} 29.3 and 15.1); n.m.r. data (in $CDCl_3$): τ 1.68 and 2.20 (singlets, H-2,8), 3.88 (broad s, 2 H, removed by D_2O exchange, NH_2), and 4.41 (d, $J_{1,2}$ 8.5 Hz, H-1).

Anal. Calc. for $C_{39}H_{39}N_5O_5 \cdot 3H_2O$: C, 65.81; H, 6.37; N, 9.84; H_2O, 7.59. Found: C, 66.02; H, 6.41; N, 9.97; H_2O, 7.04.

A sample of **15** was dissolved in ethanol and treated with an equimolar amount

of picric acid, to give the picrate, 80% yield, m.p. 125–126°; λ_{max}^{MeOH} 210 and 254 nm (ε_{mM} 54.2 and 20.2).

Anal. Calc. for $C_{45}H_{42}N_8O_{12}$: C, 60.94; H, 4.77; N, 12.64. Found: C, 60.71; H, 4.41; N, 12.46.

Catalytic hydrogenolysis of **15**. — A solution of **15** (147 mg) in methanol (10 ml) was added to a suspension of palladium chloride (70 mg) in methanol (30 ml) presaturated with hydrogen. The mixture was agitated with hydrogen overnight, until the absorption of the gas had ceased. The catalyst was removed by filtration through a layer of Celite, and the filtrate was evaporated *in vacuo* to dryness (86 mg, 78%). Crude *9-β-D-glucopyranosyladenine* (**16**), which was chromatographically homogeneous in solvent *E*, failed to crystallize (lit.[5] m.p. 238–239°), and so was characterized as the picrate: m.p. 250–251° [lit.[5] 252° (dec.)]; λ_{max}^{MeOH} 212 and 255 nm (ε_{mM} 24.5 and 17.3).

Anal. Calc. for $C_{17}H_{18}N_8O_{12}$: C, 38.79; H, 3.45; N, 21.29. Found: C, 38.65; H, 3.72; N, 21.20.

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