with water. Evaporation of the ether solutions gave 114 mg. and 179 mg., respectively, of an amorphous light brown powder which would not crystallize from methanol. Acidification of the basic extracts in both cases, yielded reddish tar.

Acknowledgment.—We wish to thank W. D. Ollis of the University of Bristol and Gideon Fraenkel of this department for enlightening discussions.

New Syntheses of Nucleosides.[1a] The Syntheses of Glycopyranosides of Purines, Pyrimidine, and Benzimidazole

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Syntheses of nucleosides of chloropurines, 6-benzamidopurine, theophylline, N^6-benzoylcytosine, and benzimidazole are presented. The method developed involved the direct condensation of the heterocyclic imino compounds such as free acylaminopurine, chloropurines, theophylline, N^6-benzoylcytosine, and benzimidazole with acylglycosyl halides in nitromethane containing hydrogen halide acceptors to give the corresponding crystalline, acylated nucleosides.

The reaction described in this paper provides a new synthesis for purine nucleosides and analogous compounds, particularly for the glycosidation of heterocyclic compounds having an imino group, *e.g.*, purines, pyrimidines, and benzimidazoles.

Several methods have been reported previously for the syntheses of purine nucleosides. In the first of these Fischer and Helferich[2] condensed silver 2,8-dichloroadenine or theophylline with 2,3,4,6-tetra-O-acetylglucopyranosyl bromide to give 2,8-dichloro-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)adenine or 7-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)theophylline.

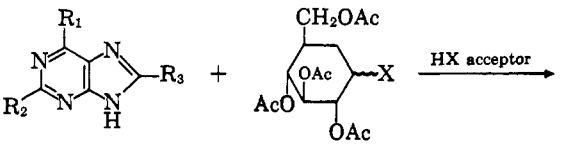
Davoll, Lythgoe, and Todd[3] observed that tri-O-acetylpentafuranosyl chlorides, due to their increased stability, gave higher yields of nucleosides than the corresponding furanosyl bromides. Another major improvement was the introduction of the use of chloromercuri derivatives of purines, rather than silver purines by Davoll and Lowy.[4] The third major improvement was the introduction of O-benzoyl blocking groups, rather than O-acetyl for the sugar moiety by Kissman, Pidacks, and Baker.[5]

Sato, Shimadate, and Ishido[6] proposed a method for the synthesis of purine nucleosides by melting a mixture of 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose with purines in the presence of *p*-toluenesulfonic acid or zinc chloride *in vacuo*.

Robins and co-workers[7] have also reported the condensation of certain 2,3-dihydro-4H-pyrans with 6-substituted purines in the presence of a catalytic amount of acid to give the corresponding 6-substituted 9-(tetrahydro-2-pyranyl)purines.

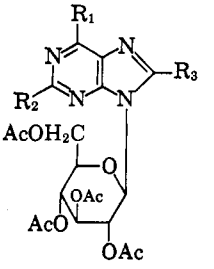
Schramm, Grötsch, and Pollmann[8] observed that the condensation of adenine with D-ribose in the presence of polyphosphate ester gave adenosine. A riboside of uric acid was synthesized from tetrakistriethylsilyluric acid and tri-O-benzoylribosyl bromide in the presence of silver perchlorate by Birkofer, Ritter, and Kühlthau.[9] Spongoadenosine was prepared by the condensation of 2,3,5-tri-O-benzyl-D-arabinofuranosyl chloride with N-benzoyladenine,[10] but Coxon and Fletcher[11] observed that the condensation of 2,3,4,6-tetra-O-acetyl-α-D-glucopyranosyl bromide with mercuric cyanide in nitromethane gave 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl cyanide.

Our method of synthesis allows us to eliminate the step for formation of the metal salt of purine or benzimidazole, the preparation of heavy metal salts being generally quite difficult. This reaction assured us an improved yield 20–40% higher than the conventional processes.[2,4,6,12]



Ia, $R_1 = R_2 = R_3 = Cl$
b, $R_1 = R_2 = Cl$; $R_3 = H$
c, $R_1 = R_3 = Cl$; $R_2 = H$
d, $R_1 = Cl$; $R_2 = R_3 = H$

II, Ac = $-\overset{\overset{O}{\|}}{C}CH_3$;
X = Cl or Br



IIIa, $R_1 = R_2 = R_3 = Cl$
b, $R_1 = R_2 = Cl$; $R_3 = H$
c, $R_1 = R_3 = Cl$; $R_2 = H$
d, $R_1 = Cl$; $R_2 = R_3 = H$

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(2) E. Fischer and B. Helferich, *Ber.*, **47**, 210 (1914).

(3) J. Davoll, B. Lythgoe, and A. R. Todd, *J. Chem. Soc.*, 967 (1948).

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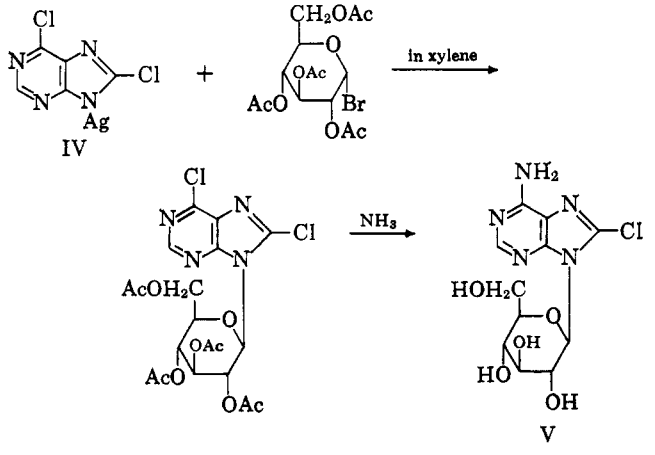
The condensation of a purine with acylglycosyl halide in a solvent medium containing a hydrogen halide acceptor gave purine nucleosides in a good yield.

The condensation of 2,6,8-trichloropurine[13] (Ia) with acetobromoglucose (II) was attempted in solvents containing various metal salts. Thus, when 2,6,8-trichloropurine was condensed with tetra-O-acetylglucosyl bromide[14] in nitromethane containing mercuric cyanide at room temperature, 2,6,8-trichloro-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)purine (IIIa) was obtained in a few per cent yield; however, in boiling nitromethane this nucleoside was obtained in 61% yield. Oxides and weak acid salts of metals were used as the acceptors for hydrogen halide in this reaction, and it was found that particularly suitable hydrogen halide acceptors are those which are reactive with hydrogen halide without formation of water. Nitromethane, *n*-heptane, and acetonitrile were also used in this condensation; nitromethane was found to be most satisfactory for the purine nucleoside synthesis.

2,6-Dichloro-9-β-D-ribofuranosylpurine,[15] the key intermediate for the synthesis of some 2,6-disubstituted in purine ribosides, was previously prepared by the condensation of bis(2,6-dichloropurinyl)mercury with tri-O-benzoylribofuranosyl chloride. We synthesized 2,6-dichloro-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)purine (IIIb) from 2,6-dichloropurine[16] (Ib) and acetobromoglucose (II) in boiling nitromethane containing mercuric cyanide. This crystalline nucleoside was obtained in yield of 79%.

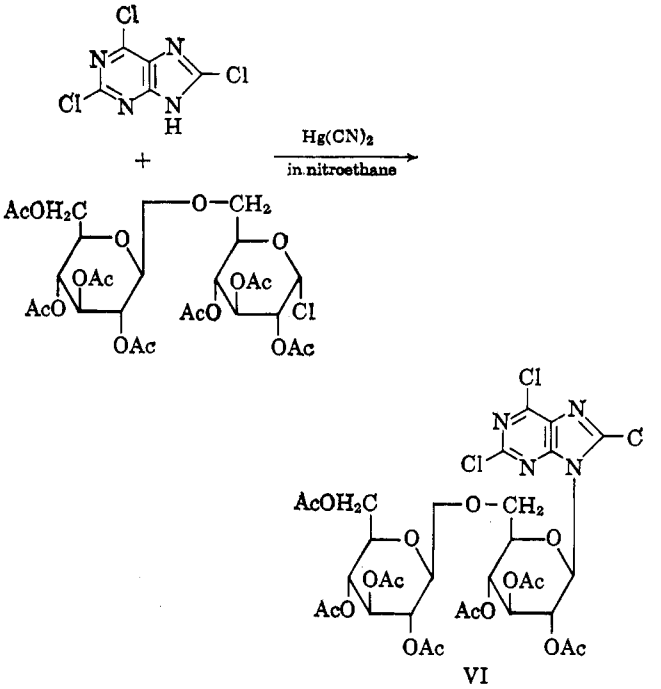
The synthesis of 6,8-dichloropurine nucleoside was not reported in the literature. This compound is one of the most important key intermediates for the preparation of 6,8-disubstituted purine nucleosides and was synthesized in order to improve the preparation of purine nucleoside. Since the chloromercuri 6,8-dichloropurine was soluble in water and its silver salt (IV) was insoluble, silver salt and 2,3,4,6-tetra-O-acetylglucopyranosyl bromide were mixed in boiling xylene to give 6,8-dichloro-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)purine (IIIc) in 23% yield.



This nucleoside was obtained in 36% yield by the direct condensation of 6,8-dichloropyrine[17] (Ic) with acetobromoglucose (II) in boiling nitromethane containing mercuric cyanide. Since the Cl-6 atom is much more reactive than the Cl-8 atoms in the free purine, it is logical to assume that the chlorine atoms of the corresponding glucose would show a similar difference in reactivity. According to this idea,[17] 8-chloroadenine nucleoside (V) was synthesized by the reaction of acetylated 6,8-dichloropurine nucleoside with alcoholic ammonia at 100° in high yield.

In a model experiment of 6-chloropurine nucleoside[18] 6-chloropurine[19] (Id) was heated in nitromethane containing mercuric cyanide with acetobromoglucose (II) to give the crystalline product of 6-chloro-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)purine[20] (IIId) in good yield.

We synthesized 2,6,8-trichloro-9-(hepta-O-acetyl-β-D-gentiobiosyl)purine (VI) as model experiment for the preparation of nucleoside containing a disaccharide which was first prepared by Wolfrom, McWain, and Thompson.[21]



The crystalline product was directly obtained by the condensation of 2,6,8-trichloropurine (Ia) with hepta-O-acetylgentiobiosyl chloride[22] in the boiling nitroethane containing mercuric cyanide, though the same nucleoside was not obtained by the procedure of Fischer and Helferich.[2]

Similarly, the condensation of 6-benzamidopurine[23] (VII) with acetobromoglucose (II) in the boiling nitromethane containing mercuric cyanide gave crystalline 6-benzamido-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)purine (VIII) in a good yield.

Theophylline nucleoside was first prepared from the silver theophylline and acetobromoglucose in boiling xylene by Fischer and Helferich.[2] 7-β-Ribofuranosyl-

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(14) R. U. Lemieux, *Methods Carbohydrate Chem.*, **2**, 221 (1963).
(15) H. J. Schaeffer and H. J. Thomas, *J. Am. Chem. Soc.*, **80**, 3738 (1958).
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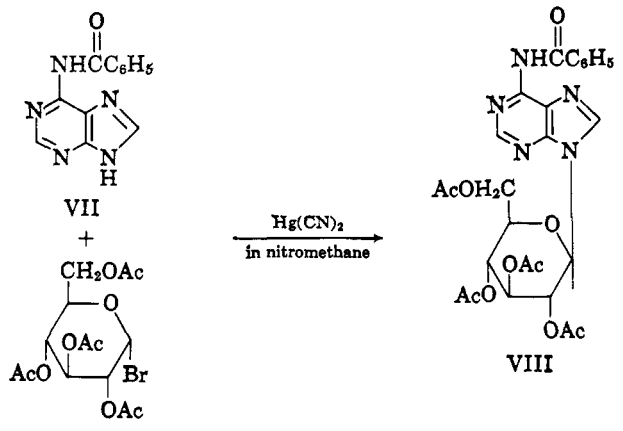
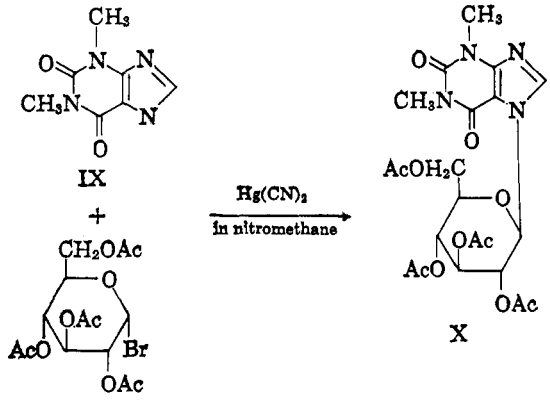
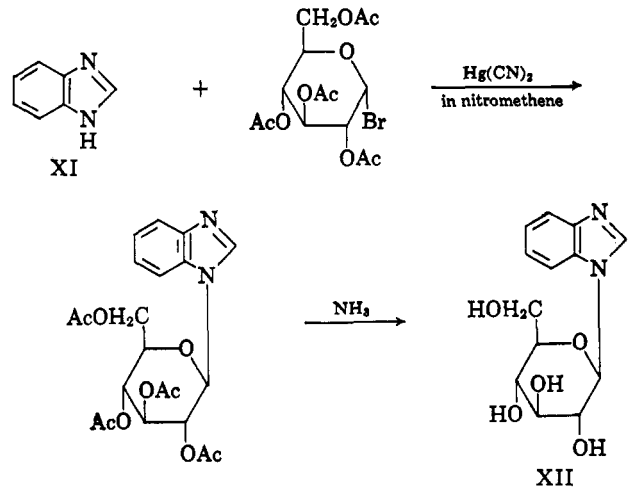


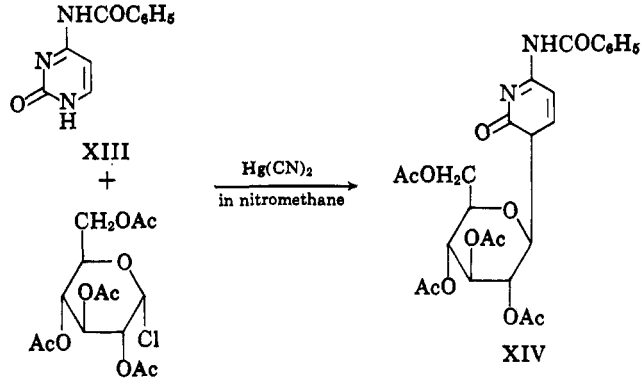
theophylline[6] was prepared by melting a mixture of theophylline and tetra-O-acetylribofuranose in the presence of *p*-toluenesulfonic acid *in vacuo* and followed by deacetylation with methanolic ammonia. We found that 7-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)theophylline[2,24] (X) was obtained by the condensation of theophylline (IX) with acetobromoglucose in good yield. Under similar condition the condensation of theophylline with 2,3,4-tri-O-acetylribopyranosyl chloride[25] gave 7-β-D-ribopyranosyltheophylline.



One of the analogous compounds 1-D-ribofuranosyl-5,6-dimethylbenzimidzole[26] has been discovered to evince a vitamin B_{12} like response in rats. 1-Glycosylbenzimidazoles were obtained by the condensation of chloromercuribenzimidazole with acylated halogenosugar in boiling xylene and followed by deacetylation with methanolic ammonia.[27] Under similar conditions benzimidazole (XI) was condensed with acetobromoglucose to give the powdered acetylated nucleoside, which when deacetylated with methanolic ammonia gave 1-β-glucopyranosylbenzimidazole (XII)[27] in good yield.

Similarly, when N^6-benzoylcytosine[28] (XIII) was treated with 2,3,4,6-tetra-O-acetylglucopyranosyl chloride in boiling nitromethane containing mercuric cyanide, 1-(tetra-O-acetyl-β-D-glucopyranosyl)-4-benzamido-2(1H)pyrimidone (XIV) was obtained in good yield.[29]





Experimental

2,6,8-Trichloro-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl-purine (IIIa).—A mixture of 3.7 g. of II (X = Cl), 2.5 g. of mercuric cyanide, and 5 g. of anhydrous calcium sulfate (Drierite) was added to a solution of 2.2 g. of Ia in 100 ml. of nitromethane dried by azeotropic distillation. The mixture was refluxed and stirred for 3 hr. excluding moisture. The reaction mixture was filtered hot and the filter cake was washed with 10 ml. of hot nitromethane. The filtrate was combined with washings and the combined solution was evaporated to dryness *in vacuo*. The residue was obtained as white crystals from ethanol. Recrystallization from ethanol gave 3.7 g. of IIIa (68%), m.p. 168°, undepressed by admixture with an authentic sample.

The other preparation of 2,6,8-trichloro-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)purine by the condensation of 2,6,8-trichloropurine with 2,3,4,6-tetra-O-acetylglucopyranosyl halide in inert solvents containing various hydrogen halide acceptor is shown in Table I.

Silver 6,8-Dichloropurine (IV).—To a solution of 4.8 g. of 6,8-dichloropurine in 50 ml. of aqueous ethanol was added 50 ml. of dilute aqueous ammonia solution containing 4.4 g. of silver nitrate. The white product was collected by filtration, washed with cold water, ethanol, and finally with ether, and dried *in vacuo* over phosphorous pentaoxide, yielding 7.2 g. (96%).

6,8-Dichloro-9-(2,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-purine (IIIc) A.—The crystalline product of 9.5 g. of II (X = Br) was added to a azeotropically dried suspension of 7.2 g. of IV and 5 g. of Celite in 300 ml. of xylene. The mixture was refluxed and stirred for 2 hr. excluding moisture and filtered hot; the filter cake was washed with hot chloroform (three 70-ml. portions). The filtrate was evaporated *in vacuo;* the residue was extracted with chloroform (200 ml.); and the extract was combined with the washings. The combined solutions were washed with 30% aqueous potassium iodide (two 25-ml. portions) and

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(27) (a) J. Davoll and G. B. Brown, *ibid.*, **73**, 5781 (1951). (b) A. J. Cleaver, A. B. Foster, and W. G. Overend, *J. Chem. Soc.*, 409 (1959). (c) British Patent 690,119; *Chem. Abstr.*, **48**, 6471a (1954). (d) A. W. Johnson, G. W. Miller, J. A. Mills, and A. R. Todd, *J. Chem. Soc.*, 3061 (1953).
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TABLE I

II		Ia, g.	HX acceptor (g.)	Solvent (ml.)	Drierite, g.	Refluxed time, hr.	IIIa, g.	Yield, %
X	g.							
Br	6.2	3.3	Ag_2O (4.0)	CH_3NO_2 (100)	5	1	2.2	27
Br	6.2	3.3	Ag_2O (4.0)	CH_3NO_2 (100)	...	1	1.1	14
Br	6.2	3.3	$Hg(CN)_2$ (4.0)	CH_3NO_2 (100)	5	2	5.0	61
Br	6.2	3.3	$Hg(CN)_2$ (4.0)	n-C_7H_{16} (110)	5	2	0.2	2
Br	2.1	1.1	$Hg(CN)_2$ (1.2)	CH_3CN (60)	3	4	1.4	51
Cl	1.9	1.2	$Zn(CN)_2$ (0.6)	CH_3NO_2 (80)	3	4	0.8	27
Br	4.1	2.3	AgCN (1.5)	CH_3NO_2 (100)	...	1	2.5	44
Br	2.1	1.1	KCN (0.6)	CH_3NO_2 (80)	3	3	1.3	48

water (two 25-ml. portions), then dried over anhydrous sodium sulfate, and filtered. The filtrate was evaporated to dryness *in vacuo*. Crystallization of the residue from ethanol gave fine needles: yield 2.5 g. (20%); m.p. 236°; $[\alpha]^{10}D$ −37° (*c* 1, chloroform); ν (KBr) 1750 (C=O ester), 1590, and 1570 $cm.^{-1}$ (C=C and C=N).

Anal. Calcd. for $C_{19}H_{20}Cl_2N_4O_9$: C, 43.91; H, 3.85; N, 10.79. Found: C, 44.04; H, 4.01; N, 10.77.

B.—A mixture of 1.7 g. of II (X = Br), 2 g. of mercuric cyanide, and 4 g. of anhydrous calcium sulfate (Drierite) was added to a solution of 0.8 g. of Ic in100 ml. of nitromethane dried by azeotropic distillation. The mixture was refluxed and stirred for 2 hr. excluding moisture. The product was isolated exactly as described for the corresponding IIIa. The residue was obtained as white crystals from ethanol. Recrystallization from ethanol gave 0.8 g. (36%) of IIIc, m.p. 236°.

Anal. Calcd. for $C_{19}H_{20}Cl_2N_4O_9$: N, 10.79. Found: N, 10.77

8-Chloro-9-β-D-glucopyranosyladenine (V).—The crystalline product of 0.8 g. of IIIc was added to 15 ml. of ethanol saturated with ammonia at 0°. The solution was heated in a steel tube at 100° for 2 hr. The solution was evaporated to dryness *in vacuo* and the crystallization of the residue from water gave 0.4 g. (78%) of V: m.p. 220° dec.; $[\alpha]^{10}D$ +34° (*c* 1, 0.1 *N* HCl); ν (KBr) 3500–3200 (OH and NH), 1650 (NH), 1600, and 1575 $cm.^{-1}$ (C=C and C=N).

Anal. Calcd. for $C_{11}H_{14}ClN_5O_5$: C, 39.83; H, 4.25; N, 21.11. Found: C, 40.03; H, 4.49; N, 21.00.

In the paper chromatography [*n*-butyl alcohol saturated with water, water saturated with ammonium sulfate–isopropyl alcohol–water (79:2:19)], this nucleoside gave a single spot, and the hydrolysate gave the spot of 8-chloroadenine.

2,6-Dichloro-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)purine (IIIb).—A mixture of 6.2 g. of II (X = Br), 4.5 g. of mercuric cyanide, and 5 g. of anhydrous calcium sulfate (Drierite) was added to a solution of 2.8 g. of Ib in 100 ml. of nitromethane dried by azeotropic distillation. The mixture was refluxed and stirred for 2.5 hr. excluding moisture. The product was isolated exactly as described for the corresponding IIIa. Recrystallization from ethanol gave 6 g. (79%) of IIIb, m.p. 162°, $[\alpha]^{10}D$ −84° (*c* 0.5, chloroform).

Anal. Calcd. for $C_{19}H_{20}Cl_2N_4O_9$: N, 10.79. Found: N, 10.94.

6-Chloro-9-(2′,3′,4′6′-tetra-O-acetyl-β-D-glucopyranosyl)purine (IIId).—A mixture of 8.2 g. of II (X = Br), 3 g. of mercuric cyanide, and 5 g. of anhydrous calcium sulfate (Drierite) was added to a solution of 2.9 g. of Id in 100 ml. of nitromethane dried by azeotropic distillation. The mixture was refluxed and stirred for 2.5 hr. excluding moisture. The reaction mixture was filtered hot and the filter cake was washed with 20 ml. of hot nitromethane. The filtrate was combined with the washings and the combined solutions were evaporated to dryness *in vacuo*. The residue was extracted with chloroform. The extract was washed with 30% aqueous potassium iodide and with water, dried over sodium sulfate, and evaporated to sirup. The sirup was crystallized from ethanol. Recrystallization from ethanol gave 5.2 g. (55%) of IIId, m.p. 168°.

Anal. Calcd. for $C_{19}H_{21}ClN_4O_9$: N, 11.55. Found: N, 11.57.

2,6,8-Trichloro-9-(hepta-O-acetyl-β-D-gentiobiosyl)purine (VI).—A mixture of 3 g. of hepta-O-acetylgentiobiosyl chloride, 1.2 g. of mercuric cyanide, and 3 g. of anhydrous calcium sulfate (Drierite) was added to a solution of 1 g. of Ia in 50 ml. of nitroethane dried by azeotropic distillation. The mixture was refluxed and stirred for 3 hr. excluding moisture. The product was isolated exactly as described for the corresponding IIIa. Recrystallization from ethanol gave 1.6 g. (45%) of VI, m.p. 157°, $[\alpha]^{10}D$ −27° (*c* 1, chloroform).

Anal. Calcd. for $C_{31}H_{35}Cl_3N_4O_{17}$: N, 6.66. Found: N, 6.47.

6-Benzamido-9-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-purine (VIII).—A mixture of 4.1 g. of II (X = Br), 3 g. of mercuric cyanide, and 5 g. of anhydrous calcium sulfate (Drierite) was added to a solution of 2.4 g. of VII in 200 ml. of nitromethane dried by azeotropic distillation. The mixture was refluxed and stirred for 3 hr. excluding moisture. The product was isolated exactly as described for the corresponding IIId. Recrystallization from ethanol gave 4.0 g. (75%) of VIII, m.p. 171°, $[\alpha]^{10}D$ +6° (*c* 1, chloroform).

Anal. Calcd. for $C_{26}H_{27}N_5O_{10}$: N, 12.29. Found: N, 12.19.

7-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosyl)theophylline (X).—A mixture of 4.1 g. of II (X = Br), 2.7 g. of mercuric cyanide, and 5 g. of anhydrous calcium sulfate (Drierite) was added to a solution of 2.0 g. of IX (monohydrate) in 100 ml. of nitromethane dried by azeotropic distillation. The mixture was refluxed and stirred for 3 hr. excluding moisture. The product was isolated exactly as described for the corresponding IIIa. Recrystallization from ethanol gave 4.8 g. (94%) of X, m.p. 167°, undepressed by admixture with an authentic sample.

Anal. Calcd. for $C_{21}H_{26}N_4O_{11}$: N, 10.98. Found: N, 11.06.

7-β-D-Ribopyranosyltheophylline.—A mixture of 2.4 g. of 2,3,4-tri-O-acetyl-α-D-ribopyranosyl chloride, 2 g. of mercuric cyanide, and 3 g. of anhydrous calcium sulfate (Drierite) was added to a solution of 1.5 g. of IX in 100 ml. of nitromethane dried by azeotropic distillation. The mixture was refluxed and stirred for 6 hr. excluding moisture. The product was isolated exactly as described for the corresponding IIId. To 2.2 g. of amber gum was added 50 ml. of methanol saturated with ammonia at 0°. The solution was refrigerated overnight and then evaporated to dryness. The residue crystallized from aqueous methanol gave 1.35 g. (57%) of 7-β-D-ribopyranosyltheophylline, m.p. 235–236°, $[\alpha]^{10}D$ −33° (*c* 1, water).

Anal. Calcd. for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.16; N, 17.94. Found: C, 46.44; H, 4.90; N, 17.77.

1-β-D-Glucopyranosylbenzimidazole (XII).—A mixture of 7.4 g. of II (X = Cl), 2.5 g. of mercuric cyanide, and 5 g. of anhydrous calcium sulfate (Drierite) was added to a solution of 1.2 g. of XI in 100 ml. of nitromethane dried by azeotropic distillation. The mixture was refluxed and stirred for 4 hr. excluding moisture. The reaction mixture was filtered hot and the filter cake was washed with 20 ml. of hot nitromethane. The filtrate was combined with washings and the combined solutions were evaporated to dryness *in vacuo*. The residue was obtained: 5.5 g. (63%) of light yellowish powder from ethanol. To 2 g. of the powder was added 100 ml. of methanol saturated with ammonia at 0°. The solution was refrigerated overnight and then evaporated to dryness. The residue was crystallized from ethanol. Recrystallization from aqueous ethanol gave 0.8 g. of XII, m.p. 211–212°, $[\alpha]^{10}D$ −4° (*c* 1, water).

Anal. Calcd for $C_{13}H_{16}N_2O_5$: N, 10.00. Found: N, 9.90.

1-(2′,3′,4′,6′-Tetra-O-acetyl-β-D-glucopyranosyl)-4-benzamido-2(1H)-pyrimidone (XIV).—A mixture of 0.9 g. of II (X = Cl) and 0.7 g. of mercuric cyanide was added to a solution of 0.6 g. of XIII in 100 ml. of nitromethane dried by azeotropic distillation. The mixture was refluxed and stirred for 20 hr. excluding moisture. The product was isolated exactly as described for the corresponding IIId. Recrystallization from ethanol gave 0.7 g. (46%) of XIV, m.p. 260°, $[\alpha]^{25}D$ −15° (*c* 1, chloroform).

Anal. Calcd. for $C_{25}H_{27}N_3O_{11}$: N, 7.70. Found: N, 7.30.

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