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Note

A convenient procedure for the synthesis of theophylline nucleosides

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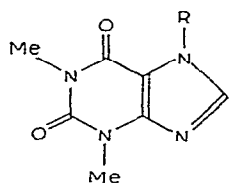
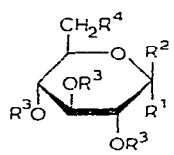
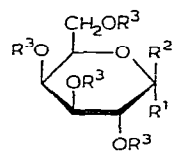
The base theophylline (1,3-dimethylxanthine, **1**) has been used frequently as a model purine for nucleoside synthesis because of its availability and the fact that only one of the nitrogen atoms (N-7) is reactive[1,2]. Furthermore, unlike other purines, there are no additional groups that need protecting prior to the coupling reactions. The 9-glycosyltheophyllines are only obtained by indirect means[2]. The use of chloromercuripurines for the synthesis of nucleosides has been reported to give improved yields for adenine and guanine nucleosides[3], but has not been applied systematically to the synthesis of theophylline nucleosides, although Onodera and Yajima[4] have briefly reported on it, without experimental details. These authors were probably not dealing with chloromercuritheophylline, as reaction of theophylline with mercuric chloride in aqueous alkali affords bis(theophyllin-7-yl)mercury (**2**) rather than the



1 R = H
2 R = ½Hg



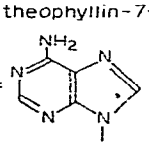
	R^1	R^2	R^3	R^4
3	Br	H	Ac	OAc
4	H	T[a]	Ac	OAc
5	H	T[a]	H	OH
6	Br	H	Ac	I
7	H	T[a]	Ac	I
8	H	T[a]	H	I
9	H	Ad(NAc)[b]	Ac	I
10	H	Ad[b]	H	I



	R^1	R^2	R^3
11	Br	H	Ac
12	H	T	Ac
13	H	T	H

[a] T = theophyllin-7-yl (see 1)

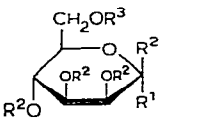
[b] Ad =



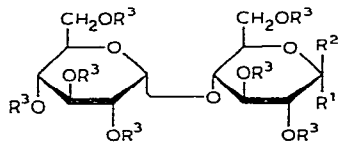
*Dedicated to Dr. Louis Long, Jr., in honour of his 70th birthday.

chloromercuri derivative. The salt has been known for some time[5] but its structure has only been established recently[1]. We have investigated the use of **2** for the improved synthesis of theophylline nucleosides.

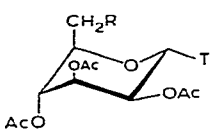
Acetylated α-glycosyl bromides **3**, **6**, **11**, **14**, **17**, and **21** were prepared from the appropriate acetylated sugar[6] by reaction with hydrogen bromide in acetic acid. The only new glycosyl bromide synthesised was 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-mannopyranosyl bromide (**17**), which was prepared in 46% yield from methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-mannopyranoside (**20**) by acetolysis followed by treatment of the crude mixture of acetates with hydrogen bromide in acetic acid. The n.m.r. spectrum of **17** indicated that it had the expected α-configuration and that it existed in the $^4C_1$(D) conformation (Table I). Reaction of each of the glycosyl halides under anhydrous conditions with bis(theophylline)mercury (**2**) afforded the corresponding acetylated nucleosides in yields mostly in the range 70–85% (see Table II). Only the maltosyl and the 6′-deoxy-6′-iodo-mannosyl nucleosides, **22** and **18**, respectively, are new derivatives.



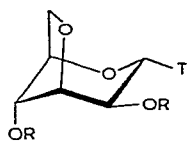
	R^1	R^2	R^3
14	Br	Ac	Ac
15	T	Ac	Ac
16	T	H	H
17	Br	Ac	I
18	T	Ac	I
19	T	H	I
20	OMe	Ac	I



	R^1	R^2	R^3
21	Br	H	Ac
22	H	T	Ac
23	H	T	H



24 R = OAc
25 R = I



26 R = H
27 R = Ac

The ^{1}H n.m.r. spectra of the theophylline nucleosides indicated the 1′,2′-*trans* configuration throughout (Table I), showing that the Tipson–Baker *trans* rule[7] is operative in this synthesis. The spectra of the *O*-acetylated theophylline nucleosides were largely first-order and the *gluco*-, *galacto*-, 6′-deoxy-6′-iodo-*gluco*-isomers (**4**, **12**, and **7**, respectively) had the expected $^4C_1$(D) all-equatorial conformation, as indicated by the values of $J_{1',2'}$ (*ca.* 9 Hz), $J_{2',3'}$ (*ca.* 9 Hz), and $J_{3',4'}$ (*ca.* 9 Hz for *gluco* and *ca.* 3.5 Hz for *galacto*). On the other hand, the *manno*- and 6′-deoxy-6′-iodo-*manno*-nucleosides (**15** and **18** respectively) were shown quite clearly to adopt the alternative $^1C_4$(D) conformation having the theophylline substituent equatorially

disposed, in accord with the work of Onodera and his co-workers[8] who reported that 7-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)theophylline (**15**) exists in the alternative chair-conformation **24**. The large coupling $J_{1',2'}$ (8.5 Hz) compares with a value of 1–2 Hz that is normally observed for α-mannopyranosides in the $^4C_1$(D) conformation[8], showing that there can be little, if any, contribution from the latter form. The assignments made from the n.m.r. spectra of **15** and **18** differ only in one respect from those made by Onodera *et al.*; decoupling experiments showed that the H-3′ and H-4′ resonances, which both gave a narrow triplets (*J* values ~4 Hz), had been assigned in reverse order.

There are two possible explanations for the anomalous behaviour of the mannosyl theophyllines. Firstly, models of the nucleoside **15** indicate that, when the theophylline moiety is axial, there is a great deal of steric clash between H-8 and H-5′ and H-3′ in the most favoured conformation in which the six-membered ring of the purine nucleus is held away from the pyranose ring. As a result, there might be expected a tendency for this group to occupy an equatorial position. Furthermore, N-7 of the theophylline nucleus is rather electropositive because of resonance in the imidazole ring[9]; this would give rise to the reverse anomeric-effect favouring equatorial substituents at the anomeric centre[10]. Lemieux[11], and Finch and Nagpurkar[12], have reported that some *O*-acetylated *N*-(α-glycopyranosyl)imidazoles exist as mixtures of the two chair conformations through operation of the reverse anomeric-effect, although with *N*-glycosylimidazoles the steric factor would be less pronounced. For **15** and **18** it seems probable that the adoption of the $^1C_4$(D) conformation results from a combination of both steric and electronic factors. From these results and those of Finch and Nagpurkar[12] it seems probable that most α-linked pyranosyl purine nucleosides exist to some extent in the $^1C_4$(D) conformation.

O-Deacetylation of the acetylated nucleosides (except for the 6′-deoxy-6′-iodo-*manno* isomer **18**) was accomplished in high yields by the use of methanolic ammonia. The overall yield of the parent nucleoside could often be improved by directly *O*-deacetylating the crude reaction product from the coupling reaction. The u.v. spectra of each of the *O*-deacetylated nucleosides showed λ_{max} near 273 nm, similar to that of caffeine (1,3,7-trimethylxanthine) and demonstrating that they were all 7-substituted theophyllines. The alternative 9-substituted theophyllines give absorptions close to 239 and 267 nm (pH 5) as does isocaffeine (1,3,9-trimethylxanthine)[13].

Attempted *O*-deacetylation of the 6′-deoxy-6′-iodo-mannopyranosyl nucleoside **18** led to the 3′,6′-anhydride **26** as the only isolable product. This ease of 3′,6′-anhydride formation is evidently due to the original 6′-deoxy-6′-iodo nucleoside's being held in the $^1C_4$(D) conformation in the ground state. The 3′,6′-anhydride was characterised by conversion into the diacetate **27**, which gave an essentially first-order n.m.r. spectrum in complete accord with its structure (see Table I).

In an extension of the work, it was found that 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranosyl bromide[14] underwent condensation with 6-acetamido-9-chloromercuripurine[3] to give 6-acetamido-9-(2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-β-D-

TABLE I

^{1}H N.M.R. PARAMETERS: FIRST-ORDLR CHEMICAL SHIFTS (τ VALUES) AND COUPLING CONSTANTS (Hz) AT 100 MHz[a]

Compound	4[b]	6[c]	7[c]	9[d]	12[b]	15[c]	17[c]	18[c]	20[c,e]	27[c]
H-1′	3.33 d	3.40 d	3.78 d	3.45 d	3.21 d	3.56 d	3.70 d	3.46 d	5.29 d	3.49 d
H-2′	3.63 t	5.19 dd	4.40 t	3.84 t	3.63 t	4.08 dd	4.60 dd	4.18 dd	4.78 m	4.50 dd
H-3′	4.01 t	4.46 t	4.58 t	4.08 t	4.07 dd	4.51 t	4.29 dd	4.50 t	4.69 dd	5.47 dd
H-4′	4.34 cm	4.98 t	4.86 t	4.56 t	4.02 s	4.96 dd	4.74 t	4.68 t	4.92 t	4.89 dd
H-5′		6.00 cm	6.28 ddd	5.82 ddd	5.20 t		6.04 ddd	5.76 td	6.21 td	5.32 t
H-6′a	5.3–5.5 cm	6.64 dd	6.64 dd	6.40 dd	5.5 cm	5.1–5.8 cm	6.64 dd	6.27 dd	6.69 cm	5.58 d
H-6′b		6.84 dd	6.83 dd	6.61 dd			6.82 dd	6.44 dd	6.85 dd	5.85 dd
H-2	—			1.22 s	—					
H-8	1.44 s		2.12 s	1.24 s	1.32 s	2.14 s		2.10 s		2.12 s
OAc	7.95 s	7.92 s	7.92 s	7.96 s	7.92 s	7.80	7.84 s	7.78 s	7.87 s	7.76 s
	7.98 s	7.94 s	7.99 s	8.00 s	7.98 s	7.81 s	7.92 s	7.81 s	7.95 s	8.01 s
	8.00 s	7.98 s	8.12 s	8.32 s	8.09(2) s	7.95 s	8.01 s	8.06 s	8.03 s	
	8.10 s					8.08 s				
N–CH_3	6.54 s		6.42 s		6.55 s	6.42 s		6.39 s		6.42 s
	6.59 s		6.59 s		6.59 s	6.60 s		6.57 s		6.60 s
$J_{1',2'}$	9.5	4.0	9.0	8.5	9.0	8.5	1.5	8.5	1.7	8.5
$J_{2',3'}$	9.0	10.0	9.0	9.0	9.0	3.5	3.5	3.5	3.0	1.0
$J_{3',4'}$	9.0	9.5	9.0	9.0	3.5	4.0	10.0	4.0	9.5	6.0
$J_{4',5'}$		9.5	9.0	9.0	<1.5	2.5	10.0	3.0	9.5	3.0
$J_{5',6'a}$		3.0	3.0	3.5			3.0	~7	~3	0
$J_{5',6'b}$		5.5	6.0	6.0			6.0	~3.5	~8	~3
$J_{6'a,6'b}$		11.0	11.5	11.0			11.0	~10	~11	11.0

[a]In examples that are not nucleosides, the primed numbers should be read as non-primed. [b]In pyridine-d_5. [c]In chloroform-d. [d]In pyridine-d_5 at 60°; the *N*-acetyl group resonated at τ 7.36 and the N-H proton at τ −1.1. [e]Methoxyl singlet resonance at τ 6.54.

glucopyranosyl)purine (**9**), albeit in rather poor yield (21%). Deacetylation at *N* and *O* with ammonia gave 9-(6-deoxy-6-iodo-β-D-glucopyranosyl)adenine (**10**). The acetylated adenine was characterised by its n.m.r. spectrum, which showed that it possessed a β-configuration ($J_{1',2'}$ 8.5 Hz), and by its u.v. spectrum which showed an absorption at $\lambda_{max}^{H_2O}$ 258 nm (pH 13 and 7) with a slight hypsochromic shift to 256 nm at pH 1, a feature characteristic of 9-substituted adenines[15].

TABLE II

PHYSICAL CONSTANTS AND YIELDS OF 7-(β-D-GLYCOPYRANOSYL)THEOPHYLLINES

Derivative	*Yield* (%)	*m.p., degrees*	$[\alpha]_D$, *degrees*	$\lambda_{max}^{H_2O}$ (nm)	ε_{max}
Tetra-*O*-acetyl-*gluco*[17] (**4**)	81	146–148	−17 ($CHCl_3$)		
gluco[17] (**5**)	83	272–277	−45 (H_2O)	275	8,500
Tetra-*O*-acetyl-*galacto*[18] (**12**)	85	135–140	+5 ($CHCl_3$)		
galacto[18] (**13**)	74	240–247	+21 (H_2O)	275	8,600
Tetra-*O*-acetyl-*manno*[8] (**15**)	66	174–176	+30($CHCl_3$)		
manno[8] (**16**)	78	200–202	+93 (H_2O)	275	7,700
Tri-*O*-acetyl-6′-deoxy-6′-iodo-*gluco*[19,20] (**7**)	65	125–140	−10 ($CHCl_3$)		
6′-Deoxy-6′-iodo-*gluco*, monohydrate[a] (**8**)	92	125–145	−17 (H_2O)	275	9,000

[a] *O*-Deacetylation was conducted with methanolic sodium methoxide.

EXPERIMENTAL

General methods. — Melting points were determined on a Kofler microscope hot-stage and are uncorrected. Optical rotations were determined on a Perkin–Elmer Model 141 automatic polarimeter with 1-dm microcells. U.v. spectra were recorded on a Pye Unicam SP. 800 spectrophotometer, with 1-cm silica cells. All concentrations were carried out under diminished pressure on a rotary evaporator. T.l.c. was performed on microscope slides covered with 0.2 mm of Kieselgel G (Merck). Detection was effected by spraying the eluted plates with 5% ethanolic sulphuric acid followed by heating for 1–2 min at 200° Preparative t.l.c. was carried out on 20-cm square plates covered with 0.5 mm of Kieselgel G (Merck) and the separated components were detected by iodine vapour. The required bands were scraped off, the iodine allowed to evaporate, and the products extracted with boiling chloroform.

Bis(theophyllin-7-yl)mercury[5] (**2**). — Theophylline (**1**) hydrate (50.0 g) was dissolved in hot water (1.5 litres) and sodium hydroxide (10.2 g, 1 mol) was added. To the vigorously stirred solution was added a hot solution of mercuric chloride (35.3 g, 0.5 mol) in ethanol (100 ml), causing an immediate white precipitate. The suspension was cooled, and the product was filtered off and washed with distilled water until the filtrate was neutral. After partially drying by suction, the product was

stored over phosphoric oxide *in vacuo* to give a quantitative yield of **2**, m.p. >347° (Found: C, 29.8; H, 2.5; N, 19.7. $C_{14}H_{14}HgN_8O_4$ calc: C, 30.1; H, 2.5; N, 20.1%).

General procedure for the preparation of acetylated glycosyl bromides. — Fully acetylated sugars[6] were treated with 50% (*w/v*) hydrogen bromide in acetic acid (3 ml for each g of substrate) with the addition of dichloromethane to aid solution, if necessary. The solutions were then kept for *ca.* 1 h at 0° followed by work-up as described for 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-mannopyranosyl bromide (**17**) (see following experiment). With the exception of the 6-iodo-*manno*- **17**, 6-iodo-*gluco*[14] **6**, and the *gluco*-isomer **3**, the glycosyl bromides were isolated as syrups that were used directly for nucleoside synthesis.

2,3,4-Tri-O-acetyl-6-deoxy-6-iodo-α-D-mannopyranosyl bromide (**17**). — *A.* Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-mannopyranoside[16] (**20**) (30 g) was dissolved in a 4% solution of sulphuric acid in acetic anhydride (150 ml) and the solution was stored overnight at 0°. The reaction mixture was then poured into ice–water (1 litre), and the precipitated syrup was washed by decantation and dissolved in dichloromethane (300 ml). The solution was shaken with aqueous sodium hydrogen carbonate, and water, and dried ($MgSO_4$). Evaporation gave a syrup (25 g) that was dissolved in a minimum of dichloromethane and treated with 50% *w/v* hydrogen bromide in acetic acid (75 ml).

The reaction mixture was kept for 1.5 h at 0° and then poured into ice-cold dichloromethane (*ca.* 500 ml), which was then washed with ice–water (3 × 400 ml) and saturated aqueous sodium hydrogen carbonate to remove all of the acid present. After a final wash with ice–water (400 ml) the solution was dried ($MgSO_4$), concentrated to about 400 ml, and poured cautiously into gently boiling isopropyl alcohol (1.4 litres) with stirring. On cooling, needles of the product separated, which were filtered off, washed with cold isopropyl alcohol and dried, giving 15.5 g (46%) of the bromide. Recrystallisation from diisopropyl ether gave needles, m.p. 136–137° (softening from 122°), $[\alpha]_D$ +110° (*c* 1.0, chloroform). (Found: C, 30.1; H, 3.3. $C_{12}H_{16}BrIO_7$ calc.: C, 30.1; H, 3.4%.)

General procedure for the preparation of theophylline nucleosides by condensation of acetylated glycosyl bromides with bis(theophyllin-7-yl)mercury. — Finely powdered bis(theophyllin-7-yl)mercury (**2**, 0.5 mole) was suspended in sodium-dried xylene and the solvent was partially distilled off to remove traces of water azeotropically. When the boiling temperature of the mixture had risen to 137°, the residual suspension was allowed to cool (below 50°). The acetylated glycosyl bromide, either as a solid or as a xylene solution, was then added and the vigorously stirred mixture was refluxed for 5–10 min, during which time the suspension cleared to give a pale-yellow solution. T.l.c. examination at this stage usually indicated that the reaction was complete. The hot, clear xylene solution was then poured cautiously into vigorously stirred light petroleum (60–80°) (*ca.* 3 litres), which precipitated the product. The crude product was filtered off, washed with light petroleum, and then partitioned between dichloromethane (*ca.* 400 ml) and 20% aqueous potassium iodide (*ca.* 100 ml). The organic phase was shaken with a further portion of potassium iodide solution to

remove the last traces of mercuric salts, washed with water (2 × 100 ml), dried ($MgSO_4$), and evaporated to give the crude, acetylated nucleoside. The crude product was then crystallised from ethanol or methanol or *O*-deacetylated directly to afford the free nucleoside. For the latter, the crude product was suspended in methanol and the cooled (0°) suspension saturated with ammonia. The ammoniacal solution was stored at 0° overnight and then evaporated to dryness. Trituration of the residue with ethanol or acetone, which dissolved the acetamide, afforded the free nucleoside. One or two recrystallisations (from methanol, aqueous ethanol, or water) generally gave the analytically pure nucleoside.

7-[4-O-(α-D-Glucopyranosyl)-β-D-glucopyranosyl]theophylline (**23**) *and its hepta-acetate* (**22**). — A suspension of bis(theophyllin-7-yl)mercury (10.0 g) in xylene (150 ml) was treated with a xylene solution of syrupy hepta-*O*-acetyl-α-maltosyl bromide (**21**) (26 g, 2 mol, in 78 ml). The crude, syrupy product was crystallised from dichloromethane–ethanol to give a slightly impure product (12.8 g, 45%), as indicated by t.l.c. (CH_2Cl_2–EtOH, 15:1). The impurity could not be removed by recrystallisation, but p.l.c. ($CHCl_3$–Me_2CO, 5:2) gave an analytical sample, m.p. 233–237° (EtOH), $[\alpha]_D^{24}$ +58° (*c* 1, chloroform). (Found: C, 49.3; H, 5.3; N, 6.8. $C_{33}H_{42}N_4O_{19}$ calc.: C, 49.6; H, 5.3; N, 7.0%.)

^{1}H n.m.r. data at 220 MHz, τ (integration, multiplicity, assignment, coupling constant given in Hz): 1.87 (1*H*, s, H-8), 3.66 (1*H*, d, H-1′, $J_{1',2'}$ 9.0), 4.09 (1*H*, t, H-2′, $J_{2',3'}$ 9.5), 4.27 (1*H*, ot, H-3′, $J_{3',4'}$ 8.5), 4.33 (1*H*, ot, H-3″, $J_{3'',4''}$ 9.5), 4.45 (1*H*, d, H-1″, $J_{1'',2''}$ 4.0), 4.72 (1*H*, t, H-4″, $J_{4'',5''}$ 9.5), 4.88 (1*H*, q, H-2″, $J_{2'',3''}$ 10.0), 5.29 (1*H*, q, H-6′$_A$ or H-6″$_A$, $J_{5,6}$ 2.5, $J_{6_A6_B}$ 12.0), 5.55–5.75 (5*H*, c, H-4′, H-5′ or H-5″, H-6′$_A$ or H-6″$_A$, H-6′$_B$, H-6″$_B$), 5.84 (1*H*, oct, H-5′ or H-5″), 6.69 (3*H*, s, N-Me), 6.75 (3*H*, s, N-Me), 8.02 (3*H*, s, OAc), 8.07 (6*H*, os, 2 × OAc), 8.09 (3*H*, s, OAc), 8.11 (3*H*, s, OAc), 8.14 (3*H*, s, OAc), 8.27 (3*H*, s, OAc).

O-Deacetylation of the crystalline, slightly impure hepta-acetate (**22**) (5.0 g) with methanolic ammonia (50 ml) gave, after trituration of the crude, syrupy product with ethanol, the free nucleoside (3.11 g, 98%), recrystallisation of which from methanol gave fine needles of **23** as the alcoholate, m.p. 264–274°, $[\alpha]_D$ +70° (*c* 1.0, water). $\lambda_{max}^{H_2O}$ 274 nm (ε_{max} 9,800, pH 7). (Found: C, 44.4; H, 6.2; N, 10.3. $C_{19}H_{28}N_4O_{12}\cdot CH_3OH$ calc.: C, 44.8; H, 6.0; N, 10.5%.)

7-(2,3,4-Tri-O-acetyl-6-deoxy-6-iodo-α-D-mannopyranosyl)theophylline (**18**). — Bis(theophyllin-7-yl)mercury (12.0 g) and crystalline 2,3,4-tri-*O*-acetyl-6-deoxy-6-6-iodo-α-D-mannopyranosyl bromide (**17**) (20.6 g, 2.0 mol) were condensed in boiling xylene (*ca.* 150 ml) to give 21.5 g (86%) of a syrup that could not be crystallised. T.l.c. (EtOAc) indicated the presence of an impurity (*ca.* 5%) migrating slightly faster than the product. P.l.c. (double elution in ether) gave the product **18**, $[\alpha]_D$ +22° (*c* 1, chloroform), which could not be crystallised. Although the product gave a largely first-order n.m.r. spectrum in complete accord with its structure (Table I) and was chromatographically homogeneous, a satisfactory analysis could not be obtained.

Attempted O-deacetylation of **18**. — The syrupy 6′-deoxy-6′-iodo nucleoside

(9.5 g) was treated with methanolic ammonia (70 ml) to give a mixture of two products as indicated by t.l.c. ($CHCl_3$–EtOH; 6:1). Trituration of the crude, syrupy mixture with ethanol afforded 2.2 g (42%) of the major component. Recrystallisation from acetone gave 7-(3,6-anhydro-α-D-mannopyranosyl)theophylline (**26**) as needles, m.p. 203–206°, $[\alpha]_D$ +75° (*c* 1, water). $\lambda_{max}^{H_2O}$ 276 nm (ε_{max} 8,100, pH 7). (Found: C, 48.2; H, 5.0; N, 17.3. $C_{13}H_{16}N_4O_6$ calc.: C, 48.1; H, 5.0; N, 17.3%.)

Acetylation of the anhydride (acetic anhydride–pyridine) afforded the diacetate **27** in 86% yield as a hemihydrate. It crystallised with difficulty from ethanol, m.p. 90–110° with transition at *ca* 85°, $[\alpha]_D$ +3° (*c* 2, chloroform). (Found: C, 48.6; H, 5.6; N, 12.6. $C_{17}H_{20}N_4O_8 \cdot \frac{1}{2}H_2O$ calc.: C, 48.9; H, 5.0; N, 13.4%.)

6-Acetamido-9-(2,3,4-tri-O-acetyl-6-deoxy-6-iodo-β-D-glucopyranosyl)purine (**9**). — 6-Acetamido-9-chloromercuripurine was prepared by a modification of the literature procedure[3]. 6-Acetamidopurine (15.1 g) was shaken with aqueous sodium hydroxide (4.5 g, 1.5 mol, in 250 ml) until solution was complete (*ca.* 3 min). To the vigorously stirred solution was added a warm ethanolic solution of mercuric chloride (24 g, 1 mol). The resulting flocculent white precipitate was filtered off and washed with water until the filtrate was neutral. After drying by suction, the product was powdered and dried over phosphoric oxide, *in vacuo*, to give 34.2 g (97.5%) of the mercurichloride.

The foregoing chloromercuripurine (15.0 g) was condensed with 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranosyl bromide (15.7 g, 0.90 mol) in a manner exactly similar to that described for theophylline nucleosides. The xylene suspension (350 ml) was refluxed for 1 h and then processed in the usual way to give the crude product (5.5 g, 29%). Crystallisation from dichloromethanol–ethanol gave the analytical product (3.9 g, 21%), m.p. 240–243° (decomp.), $[\alpha]_D$ −8° (*c* 1.0, chloroform), λ_{max}^{EtOH} 272 nm (ε_{max} 23,000). (Found: C, 39.7; H, 3.9; N, 12.2. $C_{19}H_{22}I\,N_5O_8$ calc.: C, 39.7; H, 3.9; N, 12.2%.)

9-(6-Deoxy-6-iodo-β-D-glucopyranosyl)adenine (**10**). — The 6-acetamidopurine nucleoside (**9**, 1.02 g) was treated with methanolic ammonia (25 ml) to give, after trituration with acetone, 0.58 g (77%) of the crude product. Recrystallisation from water gave needles of the hydrate which decomposed without melting above 220°, $[\alpha]_D$ −8.0° (*c* 1.0, 0.1M hydrochloric acid); $\lambda_{max}^{H_2O}$ 258 nm (ε_{max} 13,200 in 0.1M sodium hydroxide), 258 nm (ε_{max} 14,000 in water, pH 7) and 256 nm (ε_{max} 15,100 in 0.1M hydrochloric acid). (Found: C, 31.5; H, 3.9; N, 16.3. $C_{11}H_{14}I\,N_5O_4 \cdot H_2O$ calc.: C, 31.1; H, 3.8; N, 16.6%.)

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