Carbohydrate Research, 62 (1978) 73–81

AMINODEOXYNUCLEOSIDES: SYNTHESIS AND CONFORMATIONAL STUDIES OF 7-(4-AMINO-4-DEOXY-α-D-TALOPYRANOSYL)THEOPHYLLINE AND 7-(6-AMINO-6-DEOXY-α-D-MANNOPYRANOSYL)THEOPHYLLINE, AND PREPARATION OF NUCLEOSIDE–AMINO ACID DERIVATIVES

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(Received March 14th, 1977; accepted for publication May 31st, 1977)

ABSTRACT

The synthesis of new aminodeoxy and amino acid nucleosides of talose and mannose is described. The unusual conformation of these hexosylpurines revealed by n.m.r. spectroscopy is reported, as well as the unexpected results of some substitution reactions.

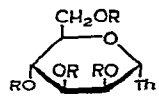
INTRODUCTION

In recent years, considerable emphasis has been placed on the biological importance of nucleoside analogues as therapeutic agents[1]. The discovery of the antitumour and antibiotic activity of amino and branched-chain aminodeoxynucleosides has enhanced interest in their synthesis[2,3].

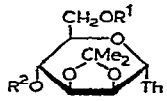
We have reported the synthesis of oxonucleosides that have shown antitumour activity[4]. Some of these new nucleosides are derivatives of theophylline. In an approach to the synthesis of aminodeoxynucleosides possessing a keto group in the sugar moiety, we now describe the synthesis of some 4′- and 6′-aminodeoxynucleosides obtained by reduction of azido intermediates. These compounds are analogues of gougerotin[5] and amicetin[6]. From the amino derivatives, some nucleoside-peptides were prepared.

RESULTS AND DISCUSSION

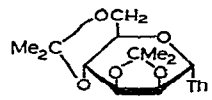
The starting material was 7-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)theophylline (**1**), which is obtainable by reaction of penta-*O*-acetyl-β-D-mannopyranose with silylated theophylline, using the Vorbrüggen method[7], in better yields (70%) than by the fusion procedure[8] (40%). The β isomer could not be isolated. The n.m.r. spectrum of **1** is in agreement with the $^1C_4$ conformation, as previously shown by Onodera *et al.*[8]. Deacetylation of **1** with methanolic ammonia gave **2** in good yield. On the basis of n.m.r. data, Onodera *et al.*[9] concluded that **2** existed preponderantly



1 R = Ac
2 R = H



3 $R^1 = R^2 = H$
5 R^1 = Bz, R^2 = H
6 R^1 = Bz, R^2 = Ms



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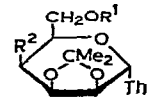


7 R^1 = Bz, $R^2 = N_3$
8 R^1 = H, $R^2 = NH_2$
9 R^1 = H, R^2 = NHTyrCbz

in the $^1C_4$ conformation in methyl sulphoxide-d_6 and pyridine-d_5, and in a rapid conformational equilibrium $^1C_4 \rightleftharpoons {}^4C_1$ in D_2O at room temperature.

Attempts to block HO-6′ of **2** by benzoylation, tritylation, or mesylation in pyridine were unsuccessful, probably because of the axial position of HO-3′ and HO-6′ in the $^1C_4$ conformation. Hence, it was necessary to block HO-2′ and HO-3′ before reacting HO-6′.

Acetonation of **2** usually afforded the di-*O*-isopropylidene derivative. Fortunately, the rate of acetalation of HO-2′ and HO-3′ was higher than that of HO-4′ and HO-6′. By using a very small quantity of acid, it was possible to stop the reaction when a maximum of 2′,3′-*O*-isopropylidene derivative had been formed, and the mono-*O*-isopropylidene compound **3** could then be obtained in pure form by crystallisation. Column chromatography of the mother liquor yielded the di-*O*-isopropylidene derivative **4** and an additional crop of **3**.

Selective hydrolysis of **4** in 80% acetic acid at room temperature gave **3**; thus, contrary to the general rule, hydrolysis of the 4′,6′-acetal occurred prior to that of the 2′,3′-acetal. N.m.r. data showed that the introduction of a dioxolane ring at positions 2′,3′ caused distortion of the molecule, and the observed coupling constants were not compatible with a $^1C_4$ or $^4C_1$ conformation. By application of the Coxon formula[10], the dihedral angles corresponding to the observed coupling constants

TABLE I

CONFORMATIONAL DATA

Compound	**3**	**4**	**6**	**7**	**10**	**11**	**17**
Conformation presumed	$^4S_2$	$^4S_2$	$^2S_4$	$^4S_0$	$^4S_2$	$^4S_2$	$^4S_2$
$\phi_{1',2'}$ (th.)[b]	169	169	49	153	169	169	169
$\phi_{1',2'}$ (calc.)[c]	155	160	45	150	155	150	155
$\phi_{2',3'}$ (th.)	33	33	33	33	33	33	33
$\phi_{2',3'}$ (calc)	25	25	30	25	30	30	30
$\phi_{3',4'}$ (th.)	153	153	87	49	153	153	153
$\phi_{3',4'}$ (calc.)	155	155	80	40	145	145	145
$\phi_{4',5'}$ (th.)	169	169	49	33	169	169	169
$\phi_{4',5'}$ (calc.)	170	160	30	35	180	160	145

[a]Spectrum in acetone-d_6, *N*,*N*-dimethylformamide, methyl sulphoxide, or hexamethylphosphoric triamide. [b]Dihedral angle value for idealized skew form. [c]Dihedral angle value calculated from coupling constant observed by application of Coxon's formula.

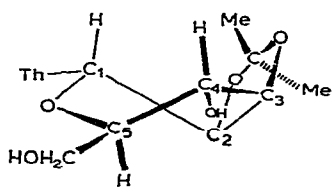
TABLE II

^{1}H-N.M.R. PARAMETERS[a]

Compound	*Solvent*	*H-1′*	*H-2′*	*H-3′*	*H-4′*	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$
1	$CDCl_3$	6.50 d[b]	5.95 q	5.03 q	5.52 t	8.7	3.3	3.7	3.7
2	D_2O	6.18 d	4.54 q	4.08 q		6.2	3.5	5.0	
3	Me_2SO-d_6	5.98 d	4.80 t	4.33 t		7.0	7.0	7.0	
3	Pyridine-d_5	5.80 d	4.63 t	4.30 t	3.80 q	7.0	7.0	7.0	9.0
4	$CDCl_3$	6.0 d	5 26 t	4.80 t	4.40 q	8.0	7.0	7.0	8.0
6	Acetone-d_6	6.33 d	4.60 q	4.30 d	4.87 d	4.0	6.0	0	6.0
6	$CDCl_3$	6 30 d	5.16 t	4.90 q	5.33 q	6.0	6.0	2.0	6.0
7	$CDCl_3$	5.90 d	5.0 t	←4.83–4.30→		7.0	7.0	5.0[c]	5.0[c]
10	Acetone-d_6	6.50 d	4 86 t	4.35 t	4.15 q	7.6	6.0	6.0	10.0
11	Acetone-d_6	5.70 d	4.43 t	4.12 t	4.87 q	6.5	6.0	6.0	8.0
17	Acetone-d_6	5.66 d	4.56 t	4.06 t	4.62 t	7.0	6.0	6.0	6.0

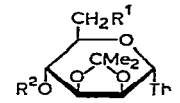
[a]First-order chemical shifts (δ values) and coupling constants (Hz) at 60 MHz. [b]Key: d, doublet; t, triplet; q, quartet. [c]Coupling constants obtained by addition of 15 mg of euroshift-F.

were calculated and compared to the ϕ values obtained for ideal skew-forms of pyranoid rings. It was concluded that **3** had a conformation very close to $^4S_2$ (Table I), in which the heterocyclic residue and HO-6′ are in equatorial positions. The dioxolane ring was locked in a $^3T_2$ conformation, which directed the *endo*-methyl group of the isopropylidene residue towards C-1 and O-5, the least congested zone in the molecule[11].

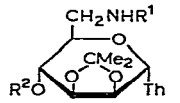


3

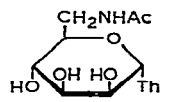
Selective benzoylation of the primary hydroxyl group was then performed at low temperature with pyridine and one equivalent of benzoyl chloride, and then mesylation of HO-4′ with mesyl chloride was effected. Introduction of the mesyl group tips the molecule towards the $^2S_4$ conformation in such solvents as acetone-d_6, hexamethylphosphoric triamide, or *N*,*N*-dimethylformamide. This conformation is not very stable, because of the $^2T_3$ conformation of the dioxolane ring and of the axial positions of the mesyl, benzoyl, and heterocyclic groups. The unusual axial position of purine bases in nucleosides has been reported by Onodera *et al.*[9] for 7-α-L-rhamnosyltheophylline and 9-α-D-mannopyranosyladenine hydrochloride, and by Herscovici and Antonakis[12] for 7-(6-deoxy-α-L-*lyxo*-hexopyranosyl-4-ulose)theophylline. For **6**, this conformation can be explained by a repulsion between the electronegative mesyl group and O-3′ and O-6′. This repulsion was emphasized in $CDCl_3$ where a variation of the coupling constants occurred, indicating a decrease of $\phi_{1',2'}$ and $\phi_{3',4'}$ (Table II).



10 R^1 = OMs, R^2 = Bz
11 R^1 = N_3 R^2 = Bz
12 R^1 = N_3, R^2 = H
13 R^1 = OMs, R^2 = Ac
14 R^1 = N_3, R^2 = Ac



15 R^1 = R^2 = H
17 R^1 = R^2 = Ac
18 R^1 = TyrCbz, R^2 = H
19 R^1 = Ac, R^2 = H



16

Th = Theophyllin-7-yl
TyrCbz = *N*-Benzyloxycarbonyl-L-tyrosinyl

Although the mesyl group was axial and the attack of azide ion was from the equatorial direction, the replacement of MsO-4′ in **6** by an azide group was very difficult to accomplish, probably because of steric effects due to BzO-6′ and the 2′,3′-*O*-isopropylidene group. This substitution could be effected by heating strongly in hexamethylphosphoric triamide with sodium azide, but only in poor yield (50% after chromatography). Assignments of the various protons in the n.m.r. spectrum were in agreement with a $^4S_0$ conformation for the resulting *talo* compound **7**, with the theophylline residue equatorial and the azide group axial.

Removal of the benzoyl group from **7** by sodium methoxide, followed by hydrogenation of the product in the presence of Adams' catalyst, afforded semi-crystalline 7-(4-amino-4-deoxy-2,3-*O*-isopropylidene-α-D-talopyranosyl)theophylline (**8**). Reaction of **8** with a mixture of *N*-benzyloxycarbonyl-L-tyrosine, dicyclohexyl-carbodi-imide, and *N*-hydroxysuccinimide[13] was very slow (24 h) because of steric factors, and 7-{6-[(*N*-benzyloxycarbonyl-L-tyrosinyl)amino]-6-deoxy-2,3-*O*-isopropylidene-α-D-talopyranosyl}theophylline (**9**) was formed in very poor yield and could not be purified.

In an alternative approach, **3** was treated with one equivalent of mesyl chloride at low temperature followed by benzoylation of HO-4′. The resulting 7-(4-*O*-benzoyl-2,3-*O*-isopropylidene-6-*O*-mesyl-α-D-mannopyranosyl)theophylline (**10**) reacted readily with sodium azide in *N*,*N*-dimethylformamide to give the 6′-azide **11** in good yield. Both **10** and **11** have a conformation very close to $^4S_2$, in which the 4′ and 6′ substituents are equatorial, but saponification of benzoyl groups was unexpectedly difficult; a boiling M solution of sodium hydroxide in acetone was required. Under such drastic conditions, **12** was rather unstable and could be obtained only in poor yield. Hence, HO-4′ was blocked by an acetyl group which could be easily removed by M sodium methoxide at room temperature.

Catalytic hydrogenation of 7-(6-azido-6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranosyl)theophylline (**12**) over Adams' catalyst gave the 6′-amino-6′-deoxy derivative **15** as a syrup. Treatment of **15** with acetic anhydride in methanol also hydrolysed the isopropylidene group to give **16**. Acetylation of the amino group of **15** without cleavage of acetal was effected at low temperature with one equivalent of acetic anhydride in pyridine, and **19** could be isolated as a syrup. It is interesting to note that the n.m.r. analysis of the di-*N*,*O*-acetyl derivative **17** showed a decrease

of the dihedral angles $\phi_{1',2'}$ and $\phi_{4',5'}$ consistent with the ideal $^4S_2$ conformation (Table I).

Treatment of **15** with *N*-benzyloxycarbonyl-L-tyrosine afforded crystalline 7-{6-[(*N*-benzyloxycarbonyl-L-tyrosinyl)amino]-6-deoxy-2,3-*O*-isopropylidene-α-D-mannopyranosyl}theophylline (**18**).

A preliminary study of the oxidation of **8** and **19** did not give satisfactory results. The difficulty in oxidising these structures must be due to their unusual conformations. The results of a systematic study of the oxidation of these aminonucleosides and of biological tests will be published elsewhere.

EXPERIMENTAL

All melting points are uncorrected. U.v. spectra were recorded on a Varian 635 spectrometer and the n.m.r. spectra were determined on a Varian T-60 (60 MHz). T.l.c. was performed on silica gel (Schleicher and Schüll type S 254) with chloroform–methanol (9:1). Column chromatography was performed on Merck Silica Gel G (type 60).

7-α-D-Mannopyranosyltheophylline (**2**) *and its tetra-acetate* **1**. — Exclusion of moisture is necessary throughout. To a suspension of theophylline (235 mg, 1.3 mmol) in hexamethyldisilazane (0.4 ml) and dichloroethane (2.4 ml), chlorotrimethylsilane (10 μl) was added. The mixture was boiled under reflux with stirring until dissolution occurred (30–60 min). The solvents were then removed *in vacuo* and the residual, powdery, silylated theophylline, together with penta-*O*-acetyl-β-D-mannopyranose (1 mmol), was dissolved in acetonitrile (6 ml, dried over molecular sieves 3 Å) and $SnCl_4$ (11.7 μl, 0.1 equiv.). The mixture was stirred at 80° until the reaction was complete (~3 h), and was then concentrated. Chloroform was added, and the resulting solution was washed with saturated, aqueous sodium hydrogen carbonate and then water to pH 7, dried (Na_2SO_4), and concentrated. Crystallization of the residue from ethanol gave **1** (70%), m.p. 170–172°; lit.[8] m.p. 136°.

A solution of **1** (510 mg, 1 mmol) in saturated methanolic ammonia (150 ml) was stored for 2 h at room temperature and then concentrated, and the residue was recrystallised from ethanol to give **2** (95%), m.p. 193–194°; lit.[8] m.p. 199–200°.

7-(2,3-O-Isopropylidene-α-D-mannopyranosyl)theophylline (**3**). — (*a*) To a suspension of **2** (340 mg, 1 mmol) in dry acetone, acetic acid (1.5 ml) and conc. H_2SO_4 (0.17 ml, 3.2×10^{-2} mmol) were added. The mixture was stirred at room temperature until dissolution occurred, and then the reaction was monitored by t.l.c. until **2** could not be detected. The mixture was neutralised with M NaOH, filtered, and concentrated. A solution of the residue in chloroform was washed with water, dried, and concentrated, and the syrupy residue was crystallised from ethyl acetate to give **3**, m.p. 179–180°, $[\alpha]_D^{20}$ +62.5° (*c* 0.1, methanol), R_F 0.34 (chloroform–methanol, 9:1).

Anal. Calc. for $C_{16}H_{22}N_4O_7$: C, 49.91; H, 6.01; N, 14.49. Found: C, 49.83; H, 5.72; N, 14.26.

The mother liquor was concentrated, and the residue was eluted from silica

gel with ethyl acetate to give, first, 7-(2,3:4,6-di-*O*-isopropylidene-α-D-mannopyranosyl)theophylline (**4**, 60%), m.p. 214–216° (from methanol), $[\alpha]_D^{20}$ +5° (*c* 0.1, methanol), R_F 0.52 (chloroform–methanol, 9:1).

Anal. Calc. for $C_{19}H_{26}N_4O_7$: C, 54.03; H, 6.16; N, 13.27. Found: C, 54.06; H, 6.15; N, 13.47.

(*b*) A solution of **4** (300 mg) in 80% acetic acid (25 ml) was stirred at room temperature until reaction was complete. The mixture was concentrated, and a solution of the syrupy residue in chloroform was washed with water to remove **2** formed during hydrolysis, dried, and concentrated. Crystallisation of the residue from methanol gave **3** (80%), m.p. 179–180°.

7-(6-O-Benzoyl-2,3-O-isopropylidene-α-D-mannopyranosyl)theophylline (**5**). — To a stirred solution of **3** (382 mg, 1 mmol) in anhydrous pyridine (10 ml) at −30°, benzoyl chloride (0.12 ml, 1 mmol) was added. The solution was stored at −15° overnight and then at room temperature for 2 h. Chloroform was added and the solution was washed thrice with water, dried, and concentrated. The syrupy residue crystallised on the addition of methanol to give **5** (390 mg, 80%), m.p. 197–198°, $[\alpha]_D^{20}$ +41° (*c* 0.07, methanol), λ_{max}^{MeOH} 274 nm (ε 9300).

Anal. Calc. for $C_{23}H_{26}N_4O_8$: C, 56.79; H, 5.35; N, 11.52. Found: C, 56.74; H, 5.44; N, 11.42.

7-(6-O-Benzoyl-2,3-O-isopropylidene-4-O-mesyl-α-D-mannopyranosyl)theophylline (**6**). — To a solution of **5** (486 mg, 1 mmol) in anhydrous pyridine (10 ml), mesyl chloride (0.1 ml, 1.4 mmol) was added and the mixture was stored at room temperature for 2 h. Chloroform was then added and the solution was washed several times with water, dried, and concentrated. The syrupy residue was crystallised from a small quantity of methanol to give **6** (530 mg, 94%), m.p. 111–112°, $[\alpha]_D^{20}$ +48° (*c* 0.57, methanol), R_F 0.82 (chloroform–methanol, 95:5), λ_{max}^{MeOH} 274 nm (ε 9200), ν_{max}^{KBr} 1720 (C=O) and 1175 cm^{-1} (SO_2).

Anal. Calc. for $C_{24}H_{28}N_4O_{10}S \cdot 0.5H_2O$: C, 50.26; H, 5.06; N, 9.77. Found: C, 50.17; H, 5.08; N, 10.37.

7-(4-Azido-6-O-benzoyl-4-deoxy-2,3-O-isopropylidene-α-D-talopyranosyl)theophylline (**7**). — A mixture of **6** (560 mg), anhydrous hexamethylphosphoric triamide (5 ml), and sodium azide (0.5 g) was stirred at 170° for 2 h, and then cooled. The nucleoside was precipitated by the addition of ice and collected, and a solution in chloroform was washed several times with water, dried, and concentrated. Crystallisation of the residue from methanol gave **7** (230 mg, 45%), m.p. 174°, $[\alpha]_D^{20}$ +54.5° (*c* 0.07, methanol), R_F 0.94 (chloroform–methanol, 95:5), λ_{max}^{MeOH} 274 nm (ε 8500); ν_{max}^{KBr} 2130 (-N=N^+=N), 1730 (C=O, benzoyl), and 720 cm^{-1} (phenyl).

Anal. Calc. for $C_{23}H_{25}N_7O_7$: C, 54.01; H, 4.89; N, 19.18. Found: C, 53.74; H, 4.94; N, 19.35.

7-(4-Amino-4-deoxy-2,3-O-isopropylidene-α-D-talopyranosyl)theophylline (**8**). — To a solution of **7** (255 mg, 0.5 mmol) in methanol (5 ml) and chloroform (2 ml), methanolic 2M sodium methoxide (1 ml) was added, and the mixture was kept at room temperature overnight. After concentration and addition of methanol, the

mixture was neutralised with M H_2SO_4 and concentrated. A solution of the oily residue in chloroform was washed twice with water, dried, and concentrated to give a colourless oil, a solution of which in methanol (20 ml) was hydrogenated in the presence of Adams' catalyst (50 mg) at atmospheric pressure and room temperature for 3 h. The mixture was then filtered and concentrated, and the residue was eluted from silica gel with chloroform–methanol (9:1). The appropriate fractions were combined, concentrated, and treated with methanol to give **8** in semi-crystalline form, m.p. 93–95°, $[\alpha]_D^{20}$ +75° (*c* 0.09, methanol), R_F 0.2 (chloroform–methanol, 9:1), λ_{max}^{MeOH} 272.5 nm (ε 7800).

Anal. Calc. for $C_{16}H_{23}N_5O_6 \cdot 0.5\ CH_3OH$: C, 49.39; H, 6.53; N, 16.94. Found: C, 49.10; H, 6.25; N, 17.12.

7-(4-O-Benzoyl-2,3-O-isopropylidene-6-O-mesyl-α-D-mannopyranosyl)theophylline (**10**). — To a solution of **3** (764 mg, 2 mmol) in anhydrous pyridine (30 ml) at −30°, mesyl chloride (0.15 ml, 2 mmol) was added. The mixture was kept at −15° overnight and then allowed to attain room temperature. Benzoyl chloride (0.3 ml, 2.5 mmol) was added and, after 2 h, the mixture was diluted with chloroform (50 ml), washed three times with cold water, dried (Na_2SO_4), and concentrated. Crystallisation of the syrupy residue from methanol, gave **10** (0.7 g, 64%), m.p. 127–128°, $[\alpha]_D^{20}$ +39° (*c* 0.11, methanol), R_F 0.91 (chloroform–methanol, 9:1), λ_{max}^{MeOH} 274 nm (ε 10,900), ν_{max}^{KBr} 1720 (C=O) and 1175 cm^{-1} (SO_2).

Anal. Calc. for $C_{23}H_{28}N_4O_{10}S \cdot 0.5\ H_2O$: C, 50.26; H, 5.06; N, 9.7. Found: C, 50.24; H, 5.04; N, 9.45.

7-(6-Azido-4-O-benzoyl-6-deoxy-2,3-O-isopropylidene-α-D-mannopyranosyl)-theophylline (**11**). — A mixture of **10** (550 mg, 1 mmol), *N,N*-dimethylformamide (15 ml), and sodium azide (130 mg, 2 mmol) was heated to 120° for 30 min and then cooled. Ice was added and the crude product was collected and crystallised from methanol–water at 0° to give **11** (400 mg, 78%), m.p. 130–135°, $[\alpha]_D^{20}$ +98° (*c* 0.17, methanol), R_F 0.81 (chloroform–methanol, 9:1), λ_{max}^{MeOH} 274 nm (ε 8700), ν_{max}^{KBr} 2100 (-N=N^+=N) and 1715 cm^{-1} (C=O).

Anal. Calc. for $C_{23}H_{25}N_7O_7 \cdot H_2O$: C, 52.17; H, 5.10; N, 18.52. Found: C, 52.17; H, 5.19; N, 18.39.

7-(4-O-Acetyl-2,3-O-isopropylidene-6-O-mesyl-α-D-mannopyranosyl)theophylline (**13**). — To a solution of **3** (1.15 g) in anhydrous pyridine at −30°, mesyl chloride (0.25 ml, 3 mmol) was added. The solution was left for 2 h at −15° and then for 1 h at room temperature. Acetic anhydride (0.3 ml) was added, and the mixture was kept at 0° overnight and then allowed to attain room temperature. Chloroform (100 ml) was added, and the resulting solution was washed three times with water, dried (Na_2SO_4), and concentrated. The residue was crystallised from ether to give **13** as a semi-crystalline product, m.p. 96–101°, $[\alpha]_D^{20}$ +56° (*c* 0.12, methanol), λ_{max}^{MeOH} 274 nm (ε 8900).

Anal. Calc. for $C_{19}H_{26}N_4O_{10}S$: C, 45.41; H, 5.17; N, 11.1. Found: C, 45.53; H, 5.48; N, 10.79.

7-(4-O-Acetyl-6-azido-6-deoxy-2,3-O-isopropylidene-α-D-mannopyranosyl)theo-

phylline (**14**). — A solution of **13** (470 mg, 1 mmol) in *N,N*-dimethylformamide (15 ml) was treated with sodium azide, as described for **11**, to give **14**, m.p. 172° (from methanol), $[\alpha]_D^{20}$ +99° (*c* 0.2, methanol), R_F 0.67 (chloroform–methanol, 9:1), λ_{max}^{MeOH} 275.5 nm (ε 7000), ν_{max}^{KBr} 2100 (-N=N⁺=N) and 1770 cm^{-1} (C=O).

Anal. Calc. for $C_{18}H_{23}N_7O_7$: C, 48.32; H, 5.14; N, 21.47. Found: C, 48.21; H, 5.18; N, 21.57.

*7-(6-Acetamido-6-deoxy-2,3-*O*-isopropylidene-α-*D*-mannopyranosyl)theophylline* (**19**) *and its 4'-acetate* (**17**). — (*a*) To a solution of **11** (510 mg, 1 mmol) in acetone (50 ml), 0.1M sodium hydroxide (10 ml) was added, and the solution was boiled under reflux for 1 h. The cooled mixture was neutralised with Amberlite IR-120 (H^+) resin and concentrated to give a syrupy product which contained the 6-azide **12** as the major component, R_F 0.52 (chloroform–methanol, 9:1). The syrup was used without further purification.

Alternatively, 2M methanolic sodium methoxide (30 ml) was added to a solution of **14** (450 mg, 1 mmol) in a small amount of chloroform, and the solution was left at room temperature for 4 h. Chloroform was added (100 ml), and the mixture was washed with cold water to pH 7, dried, and concentrated to give a syrup (**12**) which was identical with that obtained from **11**.

(*b*) A solution of **12** (430 mg, 1 mmol) in methanol (150 ml) was hydrogenated in the presence of Adams' catalyst (50 mg) for 3 h. The filtered solution was concentrated to give syrupy **15** which was used without further purification. To a solution of **15** (720 mg, 1.89 mmol) in anhydrous pyridine (40 ml) at −30°, acetic anhydride (0.178 ml, 1.89 mmol) was added, and the mixture was stored overnight at −15°. Chloroform was then added, and the solution was washed with water and concentrated to give **19** as a syrup, R_F 0.18 (chloroform–methanol, 9:1), which was used for further oxidations.

(*c*) To a solution of **15** (720 mg, 1.89 mmol) in anhydrous pyridine (30 ml), acetic anhydride (2 ml) was added, and the mixture was stored at room temperature for 2 h. Chloroform was added, the solution was washed with water and concentrated, and the residue was crystallized from methanol to give **17**, m.p. 196–198°, $[\alpha]_D^{20}$ +89° (*c* 0.03, methanol), R_F 0.41 (chloroform–methanol, 9:1), λ_{max}^{MeOH} 274.4 nm (ε 15,000); ν_{max}^{KBr} 3300 (*N*-monosubstituted amide), 1770 (C=O), and 1560 cm^{-1} (*N*-monosubstituted amide).

Anal. Calc. for $C_{20}H_{27}N_5O_8 \cdot 0.5\ CH_3OH$: C, 51.14; H, 6.03; N, 14.55. Found: C, 50.92; H, 5.71; N, 14.48.

*7-{6-[(N-Benzyloxycarbonyl-*L*-tyrosinyl)amino]-6-deoxy-2,3-*O*-isopropylidene-α-*D*-mannopyranosyl}theophylline* (**18**). — To a solution of **15** (450 mg, 1 mmol) in *N,N*-dimethylformamide (0.5 ml), *N*-benzyloxycarbonyl-L-tyrosine (315 mg, 1 mmol) and *N*-hydroxysuccinimide (115 mg, 1 mmol) were added. The mixture was stirred until dissolution occurred, and then cooled before adding dicyclohexylcarbodi-imide (206 mg, 1 mmol). The mixture was stirred at room temperature for 4 h and then filtered, and the crystals were washed with a small amount of *N,N*-dimethylformamide. The filtrate was diluted with chloroform, washed with water, dried, and

concentrated. The resulting syrup was purified by t.l.c. (ethyl acetate) and crystallised from ethanol–water to give **18**, m.p. 155–157°, $[\alpha]_D^{20}$ +23° (*c* 0.1, methanol), λ_{max}^{MeOH} 275.5 nm (ε 10,400), R_F 0.53 (chloroform–methanol, 9:1).

Anal. Calc. for $C_{32}H_{38}N_6O_{10}$: C, 57.66; H, 5.70; N, 12.6. Found: C, 58.10; H, 6.16; N, 12.0.

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