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Note

Direct fluorination at positions 3′ 4′, and 6′ of β-D-glucopyranosyltheophylline

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Considerable effort has been expended in the synthesis of deoxyfluoro sugars[1–6] as a result of interest in such analogs for use as hexokinase inhibitors[7], as carriers of ^{18}F in positron emission tomography[8] (PET), and as possible anticancer agents[9]. Also, fluorinated pentofuranose nucleosides have been investigated for the treatment of infections by *Herpes simplex*[10] (HSV) and human immunodeficiency[11] (HIV) viruses.

Little has been reported on fluorinated hexopyranose nucleosides[12] and, to our knowledge, the use of diethylaminosulfur trifluoride[14] (DAST) has not been reported hitherto for their synthesis.

We now decribe the synthesis of 3′-, 4′-, and 6′-fluoro derivatives of β-D-glucopyranosyltheophylline.

DAST can effect[2,13,14] the replacement of OH by F at primary, secondary, and tertiary positions (the last two with inversion of configuration) in high yields.

7-(2,3,4-Tri-*O*-benzoyl-6-deoxy-6-fluoro-β-D-glucopyranosyl)theophylline (**3**) was prepared in dry diglyme[3] at 60° from the tribenzoate **2**. The key precursor of 7-(2,4,6-tri-*O*-benzoyl-3-deoxy-3-fluoro-β-D-allopyranosyl)theophylline (**13**) was 7-(4,6-*O*-isopropylidene-β-D-glucopyranosyl)theophylline (**5**), which reacted with DAST in CH_2Cl_2 containing 4-dimethylaminopyridine to afford 7-(3-deoxy-3-fluoro-4,6-*O*-isopropylidene-β-D-allopyranosyl)theophylline (**11**). 7-(2,3,6-Tri-*O*-benzoyl-4-deoxy-4-fluoro-β-D-galactopyranosyl)theophylline (**9**) was obtained by the same procedure from 7-(2,3,6-tri-*O*-benzoyl-β-D-glucopyranosyl)theophylline (**8**). If the 4-dimethylaminopyridine was omitted, then 7-(2,3,6-tri-*O*-benzoyl-4-deoxy-β-D-*erythro*-hex-4-enopyranosyl)theophylline was obtained instead of **9**. Attempts to fluorinate 7-(3,4,6-tri-*O*-benzoyl-β-D-glucopyranosyl)theophylline were unsuccessful even in hot diglyme[15], probably because of steric hindrance in the formation of the reaction intermediate.

Debenzoylation (Zemplén) of **3** and **9** gave **4** and **10**, respectively, and deacetalation of **11** gave **12**.

All the compounds synthesised were characterised by their proton-coupled ^{19}F- and proton-decoupled ^{13}C-n.m.r. spectra. The n.m.r. data given in Tables I–III

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TABLE I

^{1}H-N.M.R. DATA (δ IN P.P.M., J IN Hz)

Compound	*H-1'*	*H-2'*	*H-3'*	*H-4'*	*H-5'*	*H-6'a*	*H-6'b*	$J_{1',2'}$	$J_{2',3'}$	$J_{3',4'}$	$J_{4',5'}$	$J_{5',6'a}$	$J_{5',6'b}$	$J_{6'a,6'b}$
2[a]	6.48	6.17	6.04	5.74	3.80	4.10	3.91	9.3	9.5	9.5	9.1	3.5	2.8	10.0
3[a]	6.56	6.06	6.12	5.77	4.33	4.71	4.55	8.8	9.4	9.7	9.3	2.5	2.7	7.3
4[b]	5.83	4.10	3.71	—	3.82	4.74	4.74	9.1	9.0	10.0	8.6	—	—	—
8[a]	6.21	5.98	5.68	4.32	←3.85–4.05→			9.3	9.5	9.4	9.1	—	—	—
9[a]	6.55	6.18	5.65	5.29	4.63	4.52	4.43	9.2	9.5	2.2	0	4.0	—	6.3
10[b]	5.85	4.44	3.99	4.99	4.10	←3.95–3.88→		8.2	8.2	0	0	2.3	7.4	—
5[a]	5.78	4.08	3.79	3.92	←3.85–3.69→			5.2	7.0	5.4	10.7	—	—	—
11[a]	5.92	4.20	5.08	4.00	4.00	←3.89–3.78→		9.2	1.8	0.5	—	—	—	—
12[b]	6.05	4.49	5.20	4.00	←4.14–3.78→			9.4	0.5	0	—	—	—	—
13[a]	5.64	4.80	5.50	4.80	4.49	3.92	3.53	6.9	0.5	0.5	9.2	3.8	—	12.1

[a]In $CDCl_3$ (internal Me_4Si). [b]In D_2O [internal 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt].

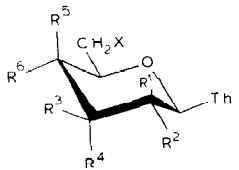

TABLE Ia

	R_1	R_2	R_3	R_4	R_5	R_6	X
1	H	OBz	OBz	H	H	OBz	OTr
2	H	OBz	OBz	H	H	OBz	OH
3	H	OBz	OBz	H	H	OBz	F
4	H	OH	OH	H	H	OH	F
5	H	OH	OH	H	H	O-CMe_2-O	
6	H	OBz	OBz	H	H	O-CMe_2-O	
7	H	OBz	OBz	H	H	OH	OH
8	H	OBz	OBz	H	H	OH	OBz
9	H	OBz	OBz	H	F	H	OBz
10	H	OH	OH	H	F	H	OBz
11	H	OH	H	F	H	O-CMe_2-O	
12	H	OH	H	F	H	OH	OH
13	H	OBz	H	F	H	OBz	OBz

TABLE II

^{19}F-N.M.R. DATA (δ IN P.P.M., J IN Hz)

Compound	*F*	$J_{F\text{-}6',H\text{-}6'}$	$J_{F\text{-}6',H\text{-}5'}$	$J_{F\text{-}4',H\text{-}4'}$	$J_{F\text{-}4',H\text{-}3'}$	$J_{F\text{-}4',H\text{-}5'}$	$J_{F\text{-}3',H\text{-}3'}$	$J_{F\text{-}3',H\text{-}4'}$	$J_{F\text{-}3',H\text{-}2'}$
3[a]	−56.3	46.6	21.2						
4[b]	−56.2	47.3	25.4						
9[a]	−48.2			52.1	25.6	25.6			
10[b]	−46.8			51.4	30.9	30.9			
11[a]	−50.6						54.0	27.0	27.0
12[b]	−48.2						53.6	28.9	28.9
13[a]	−48.1						53.7	28.9	28.9

[a]In $CDCl_3$ (internal C_6F_6). [b]In D_2O (external C_6F_6).

establish the location of the fluorine substituents and the configuration of the products.

The ^{13}C-signals (Table III) were assigned by comparing the spectra with those of the parent compounds. Replacement of OH by F causes a downfield shift of the resonance of the attached carbon by 15–20 p.p.m., upfield shifts of the signals of the adjacent carbons by 2–5 p.p.m., and $^1J_{F,C}$ values of 180–200 Hz (Table III). Thus, the locations of the fluorine substituents were shown to be at position 6 in **3** and **4**, at position 4 in **9** and **10**, and at position 3 in **11–13**.

For **9–13**, the $^1J_{F,C}$ values (Table III) are in accordance with the results of Wray[16] (175.9–183.1 Hz), but those for **3** and **4** (177.5 and 169.5) are higher than the previous values (~167.5)[16]. The $J_{F\text{-}6,C\text{-}5}$ value of 18.5 Hz for **3** and **4** is identical to that for 6-deoxy-6-fluoro-β-D-glucopyranose[16]. This author recorded $^2J_{F,C}$ values of ~17.5 when the oxygen function on the coupled carbon was *gauche* to the coupled fluorine, but smaller values were found for **9** and **11–13** (Table III).

In the ^{1}H- and ^{19}F-n.m.r. spectra (Tables I and II, respectively), $^2J_{F,H}$ was 46.6–47.3 for **3** and **4**, 51.4–52.1 for **9** and **10**, and 53.6–54.0 for **11–13**. These values agree with other data[2,17] on deoxyfluorosugars. The $J_{F\text{-}6,H\text{-}5}$ values of 21.2–25.4 for **3** and **4** accord with other observations[3] and indicate the preponderance of the rotamer with F-6 antiperiplanar to H-5. The values of $^3J_{F,H}$ for vicinal *trans*-diaxial nuclei in pyranose structures are generally[18] in the range of 21–30 Hz. The observed $^3J_{F,H}$ values 25.6–30.9 for **9–13** confirm the vicinal *trans*-diaxial H/F relationships. Therefore, the fluorine substituent is axial and the compounds have the $^4C_1$(D) conformation, which shows that replacement of OH by F does not affect the conformation[6].

EXPERIMENTAL

General methods. — Melting points are uncorrected. T.l.c. was performed on Silica Gel 60-F_{254} (Merck) and flash chromatography on Silica Gel 60 (240–400

TABLE III

^{13}C-N.M.R. DATA (δ IN P.P.M., J IN Hz)

Compound	*C-1'*	*C-2'*	*C-3'*	*C-4'*	*C-5'*	*C-6'*	$J_{F\text{-}6',C\text{-}6'}$	$J_{F\text{-}6',C\text{-}5'}$	$J_{F\text{-}6',C\text{-}4'}$	$J_{F\text{-}4',C\text{-}4'}$	$J_{F\text{-}4',C\text{-}5'}$	$J_{F\text{-}4',C\text{-}3'}$	$J_{F\text{-}3',C\text{-}3'}$	$J_{F\text{-}3',C\text{-}2'}$	$J_{F\text{-}3',C\text{-}4'}$	$J_{F\text{-}3',C\text{-}1'}$
2[a]	82.7	71.3	72.8	68.7	77.4	60.9										
3[a]	82.5	71.9	73.8	68.3	75.8	81.0	177.5	18.5	5.4							
4[b]	80.0	71.8	76.1	70.7	74.5	80.2	169.5	18.5								
8[a]	83.2	71.1	79.2	66.6	—	61.7										
9[a]	82.3	68.9	72.0	86.3	74.3	61.9				186.7	17.6	16.0				
10[b]	84.1	71.7	72.9	82.9	75.4	62.4				183.5	13.9	14.8				
5[a]	85.7	72.9	74.6	75.0	62.0	70.8										
11[a]	84.3	69.9	90.1	70.7	61.9	66.9							181.2	14.8	14.8	3.7
12[b]	85.3	68.0	95.8	71.3	78.7	63.3							175.4	14.8	14.8	
13[a]	80.7	69.7	87.8	67.2	72.2	62.4							177.6	9.1	14.8	7.4

[a]In $CDCl_3$ (internal Me_4Si). [b]In D_2O [internal 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt].

mesh, Merck). N.m.r. spectra were recorded at room temperature with a Bruker 300 MSL spectrometer.

7-(2,3,4-Tri-O-benzoyl-β-D-glucopyranosyl)theophylline (**2**). — A solution of β-D-glucopyranosyltheophylline[19] (2 g) and trityl chloride (1.7 g) in anhydrous pyridine (100 mL) was boiled under reflux overnight. Benzoyl chloride (2.2 mL) was then added and, after 2 h, the mixture was cooled, diluted with dichloromethane, washed twice with ice–water, and concentrated. Crystallisation of the residue from ethanol gave 7-(2,3,4-*O*-benzoyl-6-trityl-β-D-glucopyranosyl)theophylline (**1**; 4 g, 77%), m.p. 227–228°, $[\alpha]_D^{20}$ −22° (*c* 0.1, methanol).

Anal. Calc. for $C_{53}H_{44}N_4O_9$: C, 72.27; H, 5.00; N, 6.36. Found: C, 72.76; H, 4.96; N, 6.47.

A solution of **1** (5.6 g, 6 mmol) in 3:2 HCOOH–ether[20] (20 mL) was kept at room temperature for 30 min, then diluted with ether (150 mL), washed successively with brine and with saturated aq. sodium hydrogencarbonate, dried, and concentrated. Flash chromatography (EtOAc–hexane, 7:3) of the syrupy residue gave **2** (3.3 g, 80%), m.p. 146–147° (from methanol), $[\alpha]_D^{20}$ −5° (*c* 0.1, methanol).

Anal. Calc. for $C_{34}H_{30}N_4O_{10}\cdot H_2O$: C, 60.71; H, 4.76; N, 8.33. Found: C, 60.62; H, 4.89; N, 8.17.

7-(2,3,4-Tri-O-benzoyl-6-deoxy-6-fluoro-β-D-glucopyranosyl)theophylline (**3**). — DAST (0.585 mL, 6 mmol) was added dropwise to a stirred solution of **2** (980 mg, 1.5 mmol) in dry diglyme (6 mL) at −20°. The temperature was raised slowly to 60° and maintained for 1 h. The mixture was poured into ice, the precipitate was collected, and a solution in CH_2Cl_2 was washed once with M $NaHCO_3$ and twice with water, then concentrated. Flash chromatography (dichloromethane–ethyl acetate, 4:1) of the resulting oil gave **3** (615 mg, 68%), m.p. 179–180° (from MeOH), $[\alpha]_D^{20}$ −4° (*c* 0.1, methanol).

Anal. Calc. for $C_{34}H_{29}FN_4O_9\cdot 0.5CH_3OH$: C, 61.62; H, 4.58; F, 2.83; N, 8.32. Found: C, 61.68; H, 4.47; F, 2.80; N, 8.30.

7-(6-Deoxy-6-fluoro-β-D-glucopyranosyl)theophylline (**4**). — To a solution of **3** (665 mg, 1 mmol) in anhydrous methanol (10 mL) was added methanolic M sodium methoxide (1 mL). The mixture was stirred for 2 h at room temperature, neutralised with Amberlite IR-120 (H^+) resin, and concentrated. Recrystallisation of the residue from methanol gave **4** (310 mg, 90%), m.p. 218–220°, $[\alpha]_D^{20}$ −12° (*c* 0.12, methanol).

Anal. Calc. for $C_{13}H_{17}FN_4O_6\cdot CH_3OH$: C, 44.68; H, 5.58; F, 5.05; N, 14.89. Found: C, 44.89; H, 5.53; F. 4.92; N, 15.0.

7-(4,6-O-Isopropylidene-β-D-glucopyranosyl)theophylline (**5**). — A mixture of 7-β-D-glucoyranosyltheophylline[19] (1.8 g), 2,2-dimethoxypropane (5 mL), and dry *p*-toluenesulfonic acid (15 mg) in dry *N,N*-dimethylformamide (15 mL) was stirred at room temperature for 20 h. M $NaHCO_3$ (1 mL) was added and the mixture concentrated under vacuum. A solution of the residue in dichloromethane was filtered and concentrated, and the residue was crystallised from ethanol to give **5** (1.39 g, 70%), m.p. 208–210°, $[\alpha]_D^{20}$ −33° (*c* 0.13, methanol).

Anal. Calc. for $C_{16}H_{22}N_4O_7$: C, 50.26; H, 5.76; N, 14.66. Found: C, 50.06; H, 5.80; N, 14.65.

7-(2,3-Di-O-benzoyl-β-D-glucopyranosyl)theophylline (**7**). — Conventional treatment of **5** with pyridine and benzoyl chloride and crystallisation of the product from ethanol gave 7-(2,3-di-*O*-benzoyl-4,6-*O*-isopropylidene-β-D-glucopyranosyl)-theophylline (**6**, 90%), m.p. 136–139°, $[\alpha]_D^{20}$ −33° (*c* 0.13, methanol).

Amberlite IR-120 (H^+) resin was added to a methanolic solution of **6**, which was boiled under reflux for 1 h, then filtered, and concentrated. The syrupy residue was crystallised from ethanol to give **7** (90%), m.p. 225–226°, $[\alpha]_D^{20}$ −12° (*c* 0.1, methanol).

Anal. Calc. for $C_{27}H_{26}N_4O_8 \cdot H_2O$: C, 57.04; H, 4.93; N, 9.86. Found: C, 57.23; H, 4.81; N, 10.08.

7-(2,3,6-Tri-O-benzoyl-β-D-glucopyranosyl)theophylline (**8**). — To a stirred solution of **7** (500 mg, 1 mmol) in pyridine (50 mL) at −30° was added, dropwise, 1 equiv. (0.116 mL) of benzoyl chloride. The mixture was stored at 0° for 72 h and then worked-up in the usual manner. Flash chromatography (ethyl acetate–hexane, 70:30) of the product gave **8** (460 mg, 70%), m.p. 226° (from EtOH), $[\alpha]_D^{20}$ −12° (*c* 0.13, methanol).

Anal. Calc. for $C_{34}H_{30}N_4O_{10}$: C, 62.38; H, 4.59; N, 8.56. Found: C, 62.30; H, 4.63; N, 8.56.

7-(2,3,6-Tri-O-benzoyl-4-deoxy-4-fluoro-β-D-galactopyranosyl)theophylline (**9**). — To a stirred solution of **8** (654 mg, 1 mmol) and 4-dimethylaminopyridine (244 mg, 2 mmol) in dry dichloromethane (20 mL) at −30° was added DAST (0.195 mL, 2 mmol) during 15 min under nitrogen. The mixture was then allowed to attain room temperature. After 24 h, the mixture was cooled to 0°, methanol was added, solvents were removed under vacuum, and the resulting oil was poured into ice–water. The precipitate was collected, and a solution in CH_2Cl_2 was washed with M $NaHCO_3$ and water to pH 7, dried, and concentrated. Flash chromatography (dichloromethane–ethyl acetate, 9:1) of the residue gave **9** (446 mg, 68%), m.p. 125–126° (from MeOH), $[\alpha]_D^{20}$ +25° (*c* 0.1, ethyl acetate).

Anal. Calc. for $C_{34}H_{29}FN_4O_9$: C, 62.20; H, 4.42; F, 2.90; N, 8.54. Found: C, 62.05; H, 4.38; F, 2.29; N, 8.29.

7-(4-Deoxy-4-fluoro-β-D-galactoyranosyl)theophylline (**10**). — Debenzoylation of **9**, as for **3**, gave **10** (90%), m.p. 215–216° (from MeOH), $[\alpha]_D^{20}$ +32° (*c* 0.1 methanol).

Anal. Calc. for $C_{13}H_{17}FN_4O_6 \cdot 0.5CH_3OH$: C, 45.0; H, 5.27; F, 5.27; N, 15.55. Found: C, 44.84; H, 5.22; F, 5.23; N, 15.52.

7-(3-Deoxy-3-fluoro-4,6-O-isopropylidene-β-D-allopyranosyl)theophylline (**11**). — A solution of **5** (1.53 g, 4 mmol) and 4-dimethylaminopyridine (1 g, 8 mmol) in dry CH_2Cl_2 at −20° was treated with DAST (0.8 mL, 8 mmol) as described for **9**. Column chromatography (ethyl acetate–hexane, 3:1) of the product gave **11** (740 mg, 43%), m.p. 235–236° (from EtOH), $[\alpha]_D^{20}$ −13° (*c* 0.1, ethyl acetate).

Anal. Calc. for $C_{16}H_{21}FN_4O_6 \cdot 0.5H_2O$: C, 48.85; H, 5.60; F, 4.83; N, 14.24. Found: C, 49.01; H, 5.59; F, 4.90; N, 14.21.

7-(3-Deoxy-3-fluoro-β-D-allopyranosyl)theophylline (**12**). — To a solution of **11** in methanol was added Amberlite IR-120 (H^+) resin, and the mixture was boiled under reflux for 90 min, then filtered, and concentrated to give **12** (90%), m.p. 246° (from EtOH), $[\alpha]_D^{20}$ −22° (*c* 0.1, methanol).

Anal. Calc. for $C_{13}H_{17}FN_4O_6 \cdot 0.25C_2H_5OH$: C, 45.56; H, 5.20; F, 5.34; N, 15.75. Found: C, 45.58; H, 5.13; F, 5.30; N, 15.80.

7-(2,4,6-Tri-O-benzoyl-3-deoxy-3-fluoro-β-D-allopyranosyl)theophylline (**13**). — Conventional treatment of **12** with benzoyl chloride–pyridine gave **13** (80%), m.p. 126–127° (from MeOH), $[\alpha]_D^{20}$ −35° (*c* 0.1, methanol).

Anal. Calc. for $C_{34}H_{29}FN_4O_9$: C, 62.20; H, 4.40; F, 2.90; N, 8.50. Found: C, 62.20; H, 4.34; F, 2.83; N, 8.40.

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