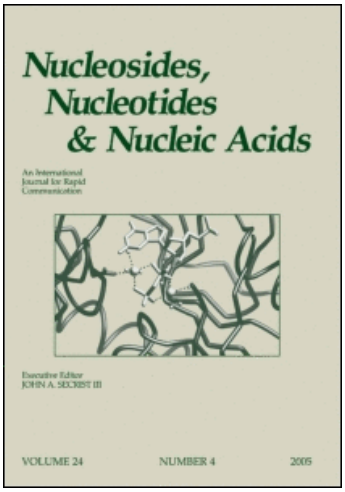

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SYNTHESIS OF 8-SUBSTITUTED THEOPHYLLINE ß-D-RIBOFURANOSIDES

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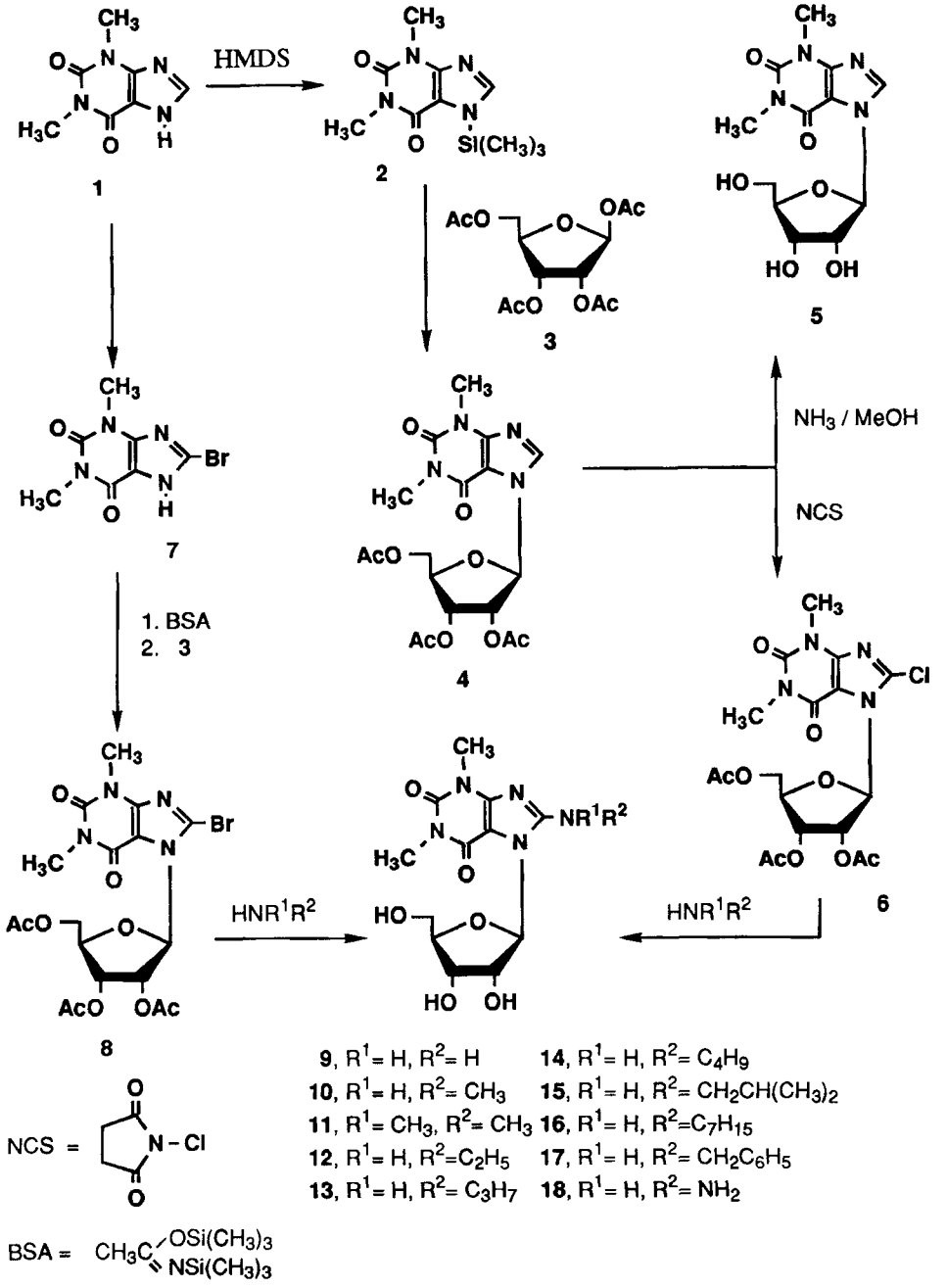
Abstract. Methods for the synthesis of 8-chloro- and 8-bromotheophylline D-riboside triacetates by the chlorination of 7-(2,3,5-tri-O-acetyl-β-D-ribofuranosyl)-theophylline with N-chlorosuccinimide or by the glycosylation of 8-bromotheophylline with 1,2,3,5-tetra-O-acetyl-ß-D-ribofuranose were found. Nucleophilic displacement of the halogen gave 8-amino-, 8-alkylamino-, 8-benzylamino-, and 8-hydrazinotheophylline ß-D-ribofuranosides.

In the course of our investigations of modified nucleosides our interest was focused on the development of methods for the synthesis of different 8-substituted purine nucleosides[1,2]. Recently we have reported on the synthesis of 8-substituted theophylline α–L-arabinofuranosides[3]. Now we have extended our studies in the series of ß-D-ribofuranosides.

Trimethylsilyltheophylline **2**, obtained from theophylline **1** in the reaction with hexamethyldisilazane, was condensed with 1,2,3,5-tetra-O-acetyl-ß-D-ribofuranose (**3**) by Vorbrüggen's procedure[4] in the presence of trimethylsilyl triflate as catalyst and 1,2-dichloroethane as solvent (50°C, 1h) (Scheme) to give the protected theophylline riboside **4**, which was isolated in 91 % yield. Removal of acetyl groups with methanolic ammonia afforded 7-(ß-D-ribofuranosyl)theophylline (**5**) (80 % yield) identical in all aspects with that reported previously[4,5].

Our attempts to introduce bromine at C-8 in the reaction of **4** with N-bromosuccinimide in 1,2 -dichloroethane or **5** with bromine-water failed. These results coincide with those we observed for the corresponding α-L-arabinofurano-



9, R^1= H, R^2= H
10, R^1= H, R^2= CH_3
11, R^1= CH_3, R^2= CH_3
12, R^1= H, R^2= C_2H_5
13, R^1= H, R^2= C_3H_7
14, R^1= H, R^2= C_4H_9
15, R^1= H, R^2= $CH_2CH(CH_3)_2$
16, R^1= H, R^2= C_7H_{15}
17, R^1= H, R^2= $CH_2C_6H_5$
18, R^1= H, R^2= NH_2

SCHEME

syl derivatives[3]. In contrast to the bromination, chlorination of **4** with N-chlorosuccinimide in 1,2-dichloroethane (room temperature, 12 h) allowed us to obtain, after flash chromatography, the desired 8-chlorotheophylline ribonucleoside triacetate **6** (84 % yield).

Furthermore we tried to obtain 8-bromotheophylline riboside by the condensation method starting from 8-bromotheophylline[6] (**7**). After silylation of **7** with N,O-bis(trimethylsilyl)acetamide (BSA) in 1,2-dichloroethane, coupling with **3** (60°C, 2 h) according to Wright's procedure[7], gave 8-bromo-7-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)theophylline (**8**) (75 % yield) after conventional work-up and chromatographical purification on silica gel. The UV spectrum of **8** [λ_{max} 281 nm (EtOH)] was about the same as that of 7-alkyl-8-bromotheophyllines[8]. The NMR spectrum of the 8-bromotheophylline nucleoside **8** was quite similar to that we obtained for 8-chlorotheophylline nucleoside **6**, thus confirming its *ß-D-ribo* - configuration.

To obtain deacetylated 8-chloro- or 8-bromotheophylline ß-D-ribofuranosides we tried to apply the methods employed for the synthesis of 8-chloro-7-(α-L-arabinofuranosyl)theophylline[3]. However, the reaction of **6** or **8** with triethylamine in 50 % aqueous ethanol at room temperature did not proceed, presumably due to low solubility of the starting material. Increasing the temperature resulted in a mixture of decomposition products. In addition, the direct chlorination of 7-(ß-D-ribofuranosyl)theophylline upon treatment with N-chlorosuccinimide in 1,2 -dichloroethane or acetonitrile also did not allow us to obtain the target compound 8-chloro-7-(ß-D-ribofuranosyl)theophylline. Although chromatographic evaluation (TLC) of the reaction mixtures showed the formation of small amounts of the desired reaction product, we assume this 8-chlorotheophylline riboside underwent complete decomposition during our attempts to isolate it by chromatographic means.

Contrary to the unsuccessful trials to obtain deacetylated 8-chloro- or 8-bromotheophylline ß-D-ribofuranosides, simultaneous deacetylation and displacement of bromine or chlorine with an amino group was achieved both by treating **6** and **8** with methanolic ammonia (60°C, 3h). During the course of reaction no other nucleoside was observed. Pure 8-amino-7-(ß-D-ribofuranosyl)theophylline (**9**) was obtained after chromatography on silica gel, followed by chromatography on Silasorb C_{18} and recrystallization from ethanol (29 % and 20 % yield, respectively).

TABLE. ^{1}H NMR Spectroscopy Data for Theophylline β-D-Ribofuranosides

Compound	Chemical shifts, δ (ppm)					Other protons
	H-1'	H-2'	H-3'	H-4'	H-5',5''	
4	6.29d ($J_{1',2'}$ = 5.4 Hz)	5.69dd	5.43m	4.08—4.47m		8.39s (1H,H-8), 3.41s (3H,CH_3), 3.21s (3H,CH_3), 2.05s (3H,OAc), 1.99s (6H,2×OAc)
5	6.08d ($J_{1',2'}$ = 3.8 Hz)	4.26t	4.06t	3.85m	3.58m	8.42s (1H,H-8), 5.40d (1H,2'-OH), 5.08d (1H,3'-OH), 5.01t (1H,5'-OH), 3.38s (3H,CH_3), 3.17s (3H, CH_3)
6	6.18d ($J_{1',2'}$ = 4.8 Hz)	5.37—5.72m		4.00—4.41m		3.34s (3H,CH_3), 3.19s (3H,CH_3), 2.05s (3H,OAc), 2.00s (3H,OAc), 1.94s (3H,OAc)
8	6.11d ($J_{1',2'}$ = 4.6 Hz)	5.38—5.74m		4.00—4.40m		3.34s (3H,CH_3), 3.18s (3H,CH_3), 2.04s (3H,OAc), 2.00s (3H,OAc), 1.94s (3H,OAc)
9	6.04d ($J_{1',2'}$ = 7.2 Hz)	4.30m	3.96m	3.83m	3.53m	7.09bs (2H,NH_2), 5.45t (1H,5'-OH), 5.04d, 4.96d (2H,2'-OH,3'-OH), 3.26s (3H,CH_3), 3.09s (3H,CH_3)
10	6.17d ($J_{1',2'}$ = 7.2 Hz)	4.35m	4.05m	3.92m	3.66m	7.30bs (1H,NH), 5.72t (1H,5'-OH), 5.12d, 5.06d (2H,2'-OH,3'-OH), 3.39s (3H,CH_3), 3.19s (3H, CH_3), 2.89d (3H, CH_3)
11	5.43d ($J_{1',2'}$ = 7.2 Hz)	4.64m	3.96m	3.77m	3.55m	5.11d, 5.00d (2H,2'-OH,3'-OH), 4.64m (5'-OH), 3.35s (3H, CH_3), 3.15s (3H,CH_3), 2.96s (6H,2CH_3)
12	6.12d ($J_{1',2'}$ = 7.0 Hz)	4.28m	3.96m	3.82m	3.55m	7.22t (1H,NH), 5.64bs (1H,5'-OH), 5.05bs (2H,2'-OH,3'-OH), 3.28s (3H, CH_3), 3.23m (2H,CH_2), 3.11s (3H,CH_3), 1.10t (3H,CH_3)
13	6.26d ($J_{1',2'}$ = 7.2 Hz)	4.37m	4.06m	3.91m	3.63m	7.37t (1H,NH), 5.75t (1H,5'-OH), 5.17d, 5.10d (2H,2'-OH,3'-OH), 3.34s (3H,CH_3), 3.28m (2H,CH_2), 3.17s (3H,CH_3),1.54m (2H,CH_2), 0.86t (3H,CH_3)
14	6.13d ($J_{1',2'}$ = 7.2 Hz)	4.30m	3.97m	3.85m	3.57m	7.20t (1H,NH), 5.65t (1H,5'-OH), 5.06d, 5.01d (2H,2'-OH,3'-OH), 3.29s (3H,CH_3), 3.25m (2H,CH_2), 3.12s (3H,CH_3), 1.08–1.57m (4H,2CH_2), 0.84t (3H, CH_3)

TABLE (Continued)

Compound	Chemical shifts, δ (ppm) H-1'	H-2'	H-3'	H-4'	H-5',5''	Other protons
15	6.16d ($J_{1',2'}$ = 7.0 Hz)	4.31m	4.00m	3.88m	3.58m	7.24t (1H,NH), 5.65t (1H,5'-OH), 5.04m (2H,2'-OH,3'-OH), 3.28s (3H,CH_3), 3.11s (3H,CH_3) 3.05m (2H,CH_2), 1.85m (1H,CH) 0.88d (6H,2CH_3)
16	6.19d ($J_{1',2'}$ = 7.0 Hz)	4.31m	4.02m	3.90m	3.62m	7.24t (1H,NH), 5.65t (1H,5'-OH), 5.06m (2H,2'-OH,3'-OH), 3.35s (3H, CH_3), 3.29m (2H,CH_2), 3.17s (3H,CH_3), 1.10—1.70m (10H,5CH_2), 0.87m (3H, CH_3)
17	6.14d ($J_{1',2'}$ = 7.2 Hz)	4.32m	4.04m	3.90m	3.60m	7.96t (1H,NH), 7.32m (5H,C_6H_5), 5.72t (1H,5'-OH), 5.10d, 5.02d (2H,2'-OH,3'-OH), 4.50d (2H,CH_2), 3.35s (3H,CH_3), 3.18s (3H,CH_3)
18	6.11d ($J_{1',2'}$ = 7.2 Hz)	4.24dd ($J_{2',3'}$ = 5.5 Hz)	4.00m	3.85m	3.58m	8.12bs (1H,NH), 5.65bs (1H,5'-OH), 5.04m (2H,2'-OH,3'-OH), 4.40bs (2H,NH_2), 3.34s (3H,CH_3), 3.15s (3H,CH_3)

The UV spectrum of **9** (λ_{max} 290 nm, H_2O) coincided with that we obtained for 8-amino-7-(α-L-arabinofuranosyl)theophylline[3] and was close to the value reported for 7-alkyl-8-aminotheophyllines (λ_{max} 292 nm, (EtOH).[9] The structure of **9** was confirmed also by ^{1}H NMR, where the deuterium exchangeable signal at 7.02 ppm assigned to the amino group was observed (Table) as well as by the FAB mass spectra [m/e 327 (M^+)].

It should be mentioned that during the reaction of **6** or **8** with methanolic ammonia traces of many by-products were detected (TLC) which could not be isolated in a pure state due to their instability. This was in sharp contrast to the reaction of 8-chloro-7-(2,3,5-tri-O-acetyl-α-L-arabinofuranosyl)theophylline with methanolic ammonia where two reaction products could be isolated: the main compound - 8-amino-7-(α-L-arabinofuranosyl)theophylline in 54 % yield, and a

minor one - 8-chloro-7-(α-L-arabinofuranosyl)theophylline, amount of which largely depended on the conditions of the reaction.

From these observations we have to assume that the 8-chloro-7-(ß-D-ribofuranosyl)theophylline formed from **6** during methanolic ammonia treatment is much more instable, contrary to its α-L-arabinofuranosyl counterpart, even during the isolation procedure.

In the further course of this work we examined the reaction of **6** with various amines. Facile displacement of the chlorine with alkylamines proceeded smoothly with simultaneous deacetylation. After purification, the corresponding amino-substituted 8-aminotheophylline-ß-D-ribofuranosides **10-17** were obtained in moderate to good yields.The reactions of 8-bromo derivative **8** with amines gave the same results.

The treatment of **6** with 99 % aqueous hydrazine in ethanol (1:2, v/v) (60°C, 1h) gave 8-hydrazino-7-(ß-D-ribofuranosyl)theophylline (**18**) in 74 % yield.The prolonged boiling of **6** in the 99 % hydrazine solution without addition of ethanol leads to the decomposition of the starting material and did not allow us to obtain **9**. A similar result has been reported for the synthesis of 8-amino-guanosine[10] and 8-aminoxanthosine[11] from their 8-bromo derivatives.

The presence of a hydrazino group in **18** was confirmed by the ^{1}H-NMR spectra where deuterium exchangeable resonance signals for a hydrazino group were detected at 8.12 ppm (NH) and 4.40 ppm (NH_2). The FAB mass spectral data [m/e 343 (M^++1)] and elemental analysis also supported this structure.

It can be noted that introduction of a substituent at C-8 of theophylline ß-D-ribofuranoside increases the coupling constant $J_{1',2'}$ from 3.8 Hz for **5** (Table) to 7.0 - 7.2 Hz for **9 - 18**. We have observed previously such $J_{1',2'}$ values for 9-(ß-D-ribofuranosyl)uric acid[1] (7.5 Hz), 7-(ß-D-ribofuranosyl)uric acid[1] (8.0 Hz), as well as for N,N'-(bis-adenosin-8-yl)diaminoalkanes[2] (7.3 - 7.5 Hz), and for 8-(α-hydroxyisopropyl)-adenosine[12] $J_{1',2'}$ = 7.1 Hz, indicating that a C-8 substituent influences the sugar conformation to a large extent.

EXPERIMENTAL

UV spectra were recorded on a Specord UV-VIS (Carl Zeiss). ^{1}H-NMR spectra were obtained on a Bruker WH-90 with tetramethylsilane as internal

standard. Fast-atom bombardment (FAB) mass spectra were recorded on a KRATOS MS-50. Melting points were determined using Boethius hot-stage microscope and are uncorrected. Thin layer chromatography (TLC) was carried out on silica gel Silufol UV-254 (Kavalier) using the following solvent systems (v/v):

A) chloroform-methanol, 4:1;

B) chloroform-methanol, 9:1;

C) chloroform-ethyl acetate, 1:1.

Column chromatography was performed on silica gel L 100/160 (Chemapol) and Silasorb C_{18} (30 μm) (Chemapol).

7-(2,3,5-Tri-O-acetyl-ß-D-ribofuranosyl)theophylline (4).

A suspension of theophylline **1** (5.0 g; 27.7 mmol) and ammonium sulphate (20 mg) in hexamethyldisilazane (50 ml) was refluxed for 1 h. The reaction mixture was evaporated to dryness *in vacuo* and coevaporated twice with 20 ml xylene. The residue was dissolved in 1,2-dichloroethane, and 1,2,3,5-tetra-O-acetyl-ß-D-ribofuranose (**3**) (8.82 g: 27.7 mmol) and trimethylsilyl triflate (5.96 ml; 33.3 mmol) were added. The solution was heated at 50°C for 1 h, then poured with vigorous stirring into $NaHCO_3$ (20 g) suspension in chloroform (300 ml). The mixture was stirred for 1 h and the precipitate was filtered off and washed with chloroform (3x50 ml). The pooled filtrates were washed with saturated aq. $NaHCO_3$ (2x100 ml) and water (2x100 ml). After drying over anhydrous Na_2SO_4, the solvent was evaporated *in vacuo* and the resulting oil crystallized from ethanol/hexane to yield 11.1 g (91 %) of **4**; m.p. 99-100°C; R_f 0.60 (system B); UV spectrum: λ_{max} (EtOH) 274 nm (ε 9700).

Anal. calcd. for $C_{18}H_{22}N_4O_9$: C, 49.32;H, 5.06; N, 12.78.

Found: C, 49.36; H 4.97; N, 12.88.

7-(ß-D-Ribofuranosyl)theophylline (5).

Compound **4** (10 g; 22.8 mmol) was dissolved in a saturated solution of ammonia in methanol (100 ml), and the reaction mixture was kept at room temperature for 12 h. The solvent was removed *in vacuo* and the residue was recrystallized from water to yield 5.7 g (80 %) of **5**; m.p. 190-191°C (Ref.[4] 191-193°C; ref.[5] 193°C); R_f 0.26 (A); UV spectra: λ_{max} (0.1 N HCl) 274 nm (ε 8600),

λ max (H_2O) 274 nm (ε 9300), λ max (0.1 N NaOH) 274 nm (ε 8500).

Anal. calcd. for $C_{12}H_{16}N_4O_6$: C, 46.15; H, 5.16; N, 17.94.
Found: C, 46.34; H, 5.23; N, 18.00.

8-Chloro-7-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)theophylline (6). - To a solution of compound **4** (1.65 g; 3.76 mmol) in 1,2-dichloroethane (10 ml) was added N-chlorosuccinimide (0.75 g; 7.5 mmol). After stirring at room temperature for 12 h, precipitated succinimide was filtered off, the filtrate evaporated *in vacuo* and the residue chromatographed on silica gel column. The column was eluted with chloroform-ethylacetate (1:1, v/v) to obtain 1.5 g (84 %) of compound **6**; m.p. 138-140°C; R_f 0.27 (C); UV spectrum: λ max (EtOH) 280 nm (ε 10800).

Anal. calcd. for $C_{18}H_{21}ClN_4O_9$: C, 45.72; H, 4.48; N, 11.85.
Found: C, 46.05; H, 4.47; N, 11.54.

8-Bromo-7-(2,3,5-tri-O-acetyl-ß-D-ribofuranosyl)theophylline (8). - To a suspension of 8-bromotheophylline[6] (**7**) (1.28 g; 5 mmol) in 1,2-dichloroethane (30 ml) was added N,O-bis(trimethylsilyl)acetamide (1.6 ml; 7.8 mmol). The reaction mixture was boiled with reflux for 30 min. After cooling to room temperature, **3** (1.59 g; 5 mmol) and trimethylsilyl triflate (1.09 ml; 6.1 mmol) were added, and the reaction mixture was heated at 60°C for 2 h. Conventional work-up and chromatographic purification on silica gel column with chloroform as eluent yielded 1.94 g (75 %) of **8** as a foam; R_f 0.67 (B); UV spectrum: λ max (EtOH) 281 nm (ε 9200).

Anal. calcd. for $C_{18}H_{21}BrN_4O_9$: C, 41.80; H, 4.09; N, 10.83.
Found: C, 41.74; H 4.02; N, 10.77.

8-Amino-7-(ß-D-ribofuranosyl)theophylline (9).

Compound **6** (1.0 g; 2.11 mmol) was dissolved in a saturated solution of ammonia in methanol and heated in a sealed tube at 60°C for 3 h. After cooling to room temperature, the solvent was evaporated and the residue adsorbed on silica gel and dried *in vacuo*. The silica gel mass was put on the top of a silica gel column (50 cm^3), which was eluted with an ethanol gradient in chloroform (99:1 to 3:1, 200 ml each). The fractions containing **9** were pooled and

evaporated. The residue was chromatographed on a column with Silasorb C_{18} (50 cm^3) with H_2O - CH_3CN (95:5, v/v, 150 ml). The appropriate fractions were evaporated and crystallized from ethanol to yield 0.2 g (29 %) of **9**; m.p. 223-224°C; R_f 0.22 (A); UV spectra: λ max (0.1 N HCl) 289 nm (ε 11500), λ max (H_2O) 290 nm (ε 15100), λ max (0.1 N NaOH) 292 nm (ε 15900); FAB MS: m/e 327 (M^+).

Anal. calcd. for $C_{12}H_{17}N_5O_6$ x 0.5 H_2O: C, 42.86; H, 5.39; N, 20.82.
Found: C, 42.76; H, 5.18; N, 20.48.

8-Methylamino-7-(ß-D-ribofuranosyl)theophylline (10).

To a solution of compound **6** (1.0 g; 2.1 mmol) in ethanol (20 ml) was added 25 % methylamine water solution (10 ml). After 2 h at room temperature the reaction mixture was evaporated *in vacuo* and the residue was crystallized from ethanol/hexane to yield 0.60 g (83 %) of **10**; m.p. 240-241°C; R_f 0.37 (A); UV spectra: λ max (0.1 N HCl) 297 nm (ε 14900), λ max (H_2O) 298 nm (ε 16800), λ max (0.1 N NaOH)) 299 nm (ε 14500).

Anal. calcd. for $C_{13}H_{19}N_5O_6$ x 0.5 H_2O: C, 44.57; H, 5.75; N, 19.99.
Found: C, 44.38; H, 5.40; N, 19.89.

8-Dimethylamino-7-(ß-D-ribofuranosyl)theophylline (11).

To a solution of **6** (0.5 g; 1.06 mmol) in ethanol (2 ml) was added 33 % dimethylamine water solution (6 ml). After stirring at room temperature for 2 h, the reaction mixture was evaporated *in vacuo*. The residue was preadsorbed on silica gel and chromatographed on a silica gel column. The column was subsequently eluted with chloroform (100 ml) and chloroform-ethanol (95:5, v/v, 300 ml). The fractions containing **11** were evaporated and triturated twice with ether to obtain 0.26 g (69 %) of **11**; m.p. 152-154°C; R_f 0.56 (A); UV spectra: λ max (0.1 HCl) 302 nm (ε 17200), λ max (H_2O) 302 nm (ε 18700), λ max (0.1 N NaOH) 303 nm (ε 17200).

Anal. calcd. for $C_{14}H_{21}N_5O_6$: C, 47.32; H, 5.95; N, 19.71.
Found: C, 47.29; H, 5.86; N, 19.37.

8-Ethylamino-7-(ß-D-ribofuranosyl)theophylline (12).

Compound **6** (0.2 g; 0.42 mmol) was dissolved in 30 % ethylamine solution in methanol (3.5 ml) and heated in a sealed tube at 50°C for 2 h. The reaction mixture was cooled to room temperature and evaporated to dryness. Chromatographic purification in a procedure as described above for **11** gave 0.10 g (67 %) of **12**, which was further chromatographed on a column with Silasorb (50 cm^3) with 0.2 M CH_3COONH_4 - CH_3CN (78:22, v/v, 100 ml). The fractions containing **12** were evaporated, and the residue crystallized from water to give analytical sample of **12** (0.08 g; 54 %); m.p. 239-240°C; R_f 0.52 (A); UV spectra: λ_{max} (0.1 HCl) 298 nm (ε 18400), λ_{max} (H_2O) 299 nm (ε 20100), λ_{max} (0.1 N NaOH) 299 nm (ε 18300).

Anal. calcd. for $C_{14}H_{21}N_5O_6$ x 0.5 H_2O: C, 46.15; H, 6.09; N, 19.22.
Found: C, 46.33; H, 5.93; N, 19.15.

8-Propylamino-7-(ß-D-ribofuranosyl)theophylline (13).

To a solution of **6** (0.4 g; 0.84 mmol) in ethanol (5 ml) was added propylamine (1 ml) and the resulting mixture was stirred at room temperature for 3 h, then evaporated *in vacuo*. The residue was coevaporated several times with ethanol and crystallized from water with the addition of charcoal to give 0.19 g (60 %) of **13**; m.p. 240-241°C; R_f 0.58 (A); UV spectra: λ_{max} (0.1 N HCl) 298 nm (ε 16600), λ_{max} (H_2O) 299 nm (ε 20000), λ_{max} (0.1 N NaOH) 300 nm (ε 17800).

Anal. calcd. for $C_{15}H_{23}N_5O_6$ x 0.5 H_2O: C, 47.61; H, 6.39; N, 18.51.
Found: C, 47.98; H, 6.20; N, 18.43.

8-Butylamino-7-(ß-D-ribofuranosyl)theophylline (14).

Compound **14** was prepared in 59 % yield from **6** as described for the conversion of **6** to **13**; m.p. 223-224°C; R_f 0.54 (A); UV spectra: λ_{max} (0.1 HCl) 298 nm (ε 16900), λ_{max} (H_2O) 300 nm (ε 18100), λ_{max} (0.1 N NaOH) 301 nm (ε 17500).

Anal. calcd. for $C_{16}H_{25}N_5O_6$ x 0.5 H_2O: C, 48.97; H, 6.69; N, 17.85.
Found: C, 49.11; H, 6.43; N, 17.70.

8-Isobutylamino-7-(ß-D-ribofuranosyl)theophylline (15).

Compound **15** was prepared in 50 % yield from **6** as described for the conversion of **6** to **13**. Analytical sample was obtained after recrystallization from water; m.p. 215-217°C; R_f 0.47 (A); UV spectra: λ max (0.1 N HCl) 298 nm (ε 17400), λ max (H_2O) 300 nm (ε 19300), λ max (0.1 N NaOH) 300 nm (ε 19200).

Anal. calcd. for $C_{16}H_{25}N_5O_6$: C, 50.12; H, 6.57; N, 18.27.
Found: C, 49.75; H, 6.72; N, 18.02.

8-Heptylamino-7-(ß-D-ribofuranosyl)theophylline (16).

To a solution of **6** (0.5 g; 1.06 mmol) in ethanol (5 ml) was added heptylamine (2 ml) and the reaction mixture heated at 50°C for 2 h. The solvent was removed *in vacuo*, and the residue was crystallized from water with addition of charcoal to give 0.3 g (66 %) of **16**; m.p. 218-220°C; R_f 0.72 (A); UV spectra: λ max (0.1 N HCl) 298 nm (ε 13400), λ max (H_2O) 300 nm (ε 18200), λ max (0.1 N NaOH) 301 nm (ε 17600).

Anal. calcd. for $C_{19}H_{31}N_5O_6 \times 0.5\ H_2O$: C, 52.52; H, 7.42; N, 16.12.
Found: C, 52.49; H, 7.19; N, 15.89.

8-Benzylamino-7-(ß-D-ribofuranosyl)theophylline (17).

Compound **6** (0.5 g; 1.06 mmol) and benzylamine (10 ml) were heated at 130°C for 2 h. The reaction mixture was evaporated *in vacuo* to an oil that was dissolved in water (10 ml) and extracted with ether (3x5 ml). The water solution was evaporated and the residue was crystallized from 30 % ethanol with addition of charcoal to give 0.16 g (37 %) of **17**; m.p. 232-235°C; R_f 0.50 (A); UV spectra: λ max (0.1 N HCl) 298 nm (ε 16300), λ max (H_2O) 298 nm (ε 18600), λ max (01. N NaOH) 299 nm (ε 12700).

Anal. calcd. for $C_{19}H_{23}N_5O_6$: C, 54.67; H, 5.55; N, 16.78.
Found: C, 54.35; H, 5.50; N, 16.59.

8-Hydrazino-7-(ß-D-ribofuranosyl)theophylline (18).

A solution of **6** (0.5 g; 1.06 mmol) in a mixture of ethanol (2 ml) and 99 % hydrazine (1 ml) was heated in a sealed tube at 60°C for 1 h, and then cooled to

room temperature. The deposited crystals of **1 8** were filtered off and carefully washed with ice water to give 0.27 g (74 %) of analytically pure **1 8**; m.p. 232-233°C; R_f 0.16 (A); UV spectra: λ max (0.1 N HCl) 286 nm (ε 13000), λ max (H_2O) 295 nm (ε 15000); FAB MS: m/e 343 (M^+ +1).

Anal. calcd. for $C_{12}H_{18}N_6O_6$: C, 42.11; H, 5.30; N, 24.55.
Found: C, 42.03; H, 5.21; N, 24.73.

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