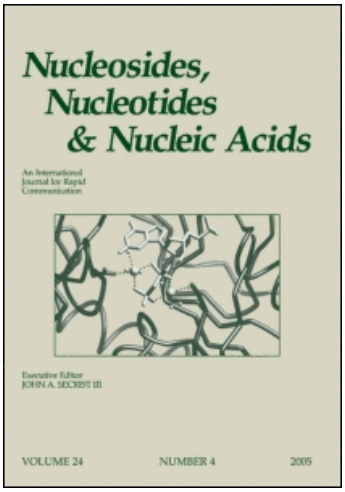

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Nucleosides, I Ribosylation of 8-Substituted Theophylline Derivatives

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NUCLEOSIDES, I
RIBOSYLATION OF 8-SUBSTITUTED THEOPHYLLINE DERIVATIVES

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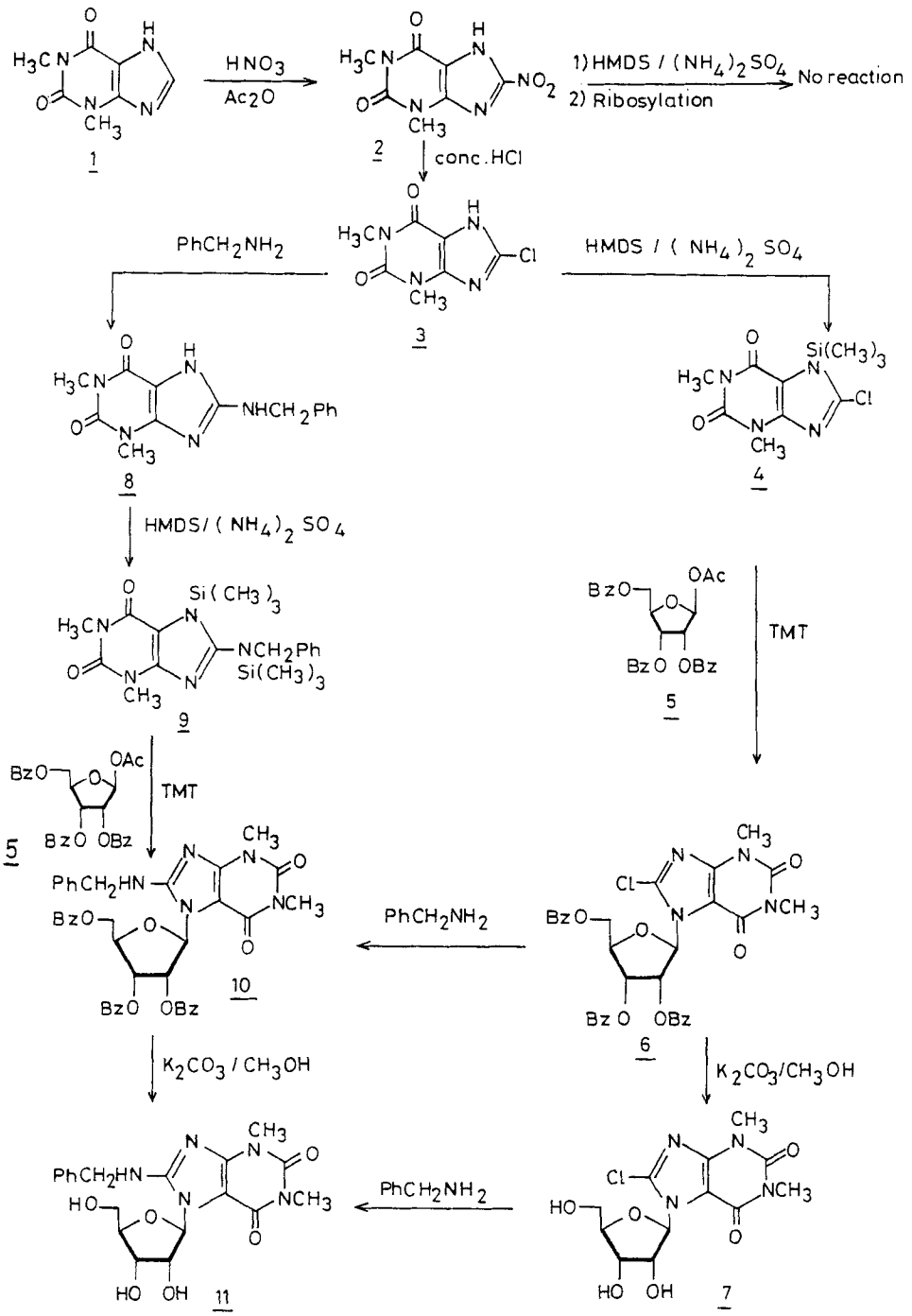
Abstract. The attempted ribosylation reaction of 8-nitrotheophylline (2) with 1-O-acetyl-2,3,5-tri-O-benzoyl-D-ribofuranose (5) failed to give any nucleoside product, whereas the reaction of 8-chlorotheophylline (3) with 5 afforded the 8-chloro-7-(2,3,5-tri-O-benzoyl)β-D-ribofuranosyltheophylline (6) in good yield. The product 6 reacted with benzylamine producing the 8-benzylamino-7-(2,3,5-tri-O-benzoyl)β-D-ribofuranosyltheophylline (10), which could also be synthesised by ribosylation of 8-benzylaminotheophylline (8) with 5. Debenzoylation of 6 and 10 gave the corresponding 7-β-D-ribofuranosyltheophylline nucleosides (7) and (11), respectively. Compound 7 could be converted into 11 by reaction with benzylamine. The newly synthesised compounds have been characterised by elemental analysis, ^{1}H-NMR and UV spectra.

Some 8-substituted purines are known as chemotherapeutic agents and are currently in use for the treatment of leukemias via the cytodestruction of the neoplastic cells.[1]

8-Substituted guanosines, such as 8-dimethylamino, 8-methylamino, 8-amino and 8-hydroxy derivatives, have the potential to terminate leukemic cell proliferation through conversion to end-stage differentiated cells.[1]

It was therefore of interest to study the ribosylation reaction of some 8-substituted theophyllines leading to the corresponding theophylline ribonucleosides, for use as inducers of the differentiation of the Friend erythroleukemia.

The starting material, 8-nitrotheophylline (2) was prepared by nitration of Theophylline (1) with nitric acid in acetic acid anhydride.[2,5]



Scheme (1)

The ribosylation of 8-nitrotheophylline (2) with 1-O-acetyl-2,3,5-tri-O-benzoyl-ß-D-ribofuranose (5) was investigated using the silyl method with trimethylsilyl trifluoromethanesulfonate (TMT) as a catalyst.[3] First 8-nitrotheophylline (2) and hexamethyldisilazane (HMDS) were heated at reflux in the presence of a catalytic amount of ammonium sulfate. After prolonged heating the reaction mixture did not become homogeneous and also after stirring with 5 in the presence of TMT in 1,2-dichloroethane, only starting materials were obtained and no nucleoside product was isolated.

The 8-nitrotheophylline (2) was then converted into the 8-chloroderivative (3) by heating in conc. hydrochloric acid.[4,5]

The ribosylation of 3 was carried out as described for 2 by refluxing in HMDS with a catalytic amount of ammonium sulfate followed by stirring with 5 and TMT in 1,2-dichloroethane; 8-chloro-7-(2,3,5-tri-O-benzoyl-ß-D-ribofuranosyl)theophylline (6) was isolated (Scheme 1) in 72% yield.

Compound 6 was treated with benzylamine in ethanol at reflux for one hour to give the corresponding 8-benzylaminonucleoside (10) in good yield. The product 10 could also be obtained by ribosylation of 8-benzylaminotheophylline (8)[6], which was prepared by heating a mixture of 8-chlorotheophylline (3) in benzylamine. Debenzoylation of 6 and 10 under moderately basic conditions, using a catalytic amount of potassium carbonate in methanol at room temperature, afforded the free nucleosides 7 and 11 in 80% and 85% yields, respectively.

Nucleoside 7 can be converted into the 8-benzylaminotheophylline nucleoside (11) in good yield by heating with benzylamine in ethanol at reflux.

The structural assignments for the newly synthesised theophylline nucleosides were based on their reaction with benzylamine and on UV and ^{1}H-NMR spectroscopy (Table 1 & 2).

It has previously been shown repeatedly that theophylline is glycosylated by a variety of methods at $N_{(7)}$ only.[7-11]

A comparison of the UV absorption data of the synthesised Nucleosides 6, 7, 10 and 11 with those of the N_7-methyltheophylline derivatives (caffeine and 8-benzylamino-3-benzyl-1,7-dimethylxanthine)[5,12] (Table 1) lends support to their structure assignment. Other fine structural features can be depicted

Table 1. UV- Absorption spectra of the synthesised nucleosides and some theophylline derivatives in MeOH

Compound No.	λmax.(nm)	log ε
6	225, 278	4.50, 3.95
7	228, 275	3.70, 3.90
10	220, 291	4.30, 4.00
11	222, 293	3.90, 3.96
Caffeine[12]	272	4.02
8-Benzyl-amino-3-benzyl-1,7-dimethyl-xanthine[5]	222, 296	4.37, 4.33

from the ^{1}H-NMR spectra (Table 2). As expected,[10,11] the ribosylation in the presence of TMT resulted exclusively in the formation of ß-anomer as indicated by an upfield chemical shift of 1'-H. However this result is in agreement with earlier findings[7-9], proving that in an anomeric pair the chemical shift of the anomeric 1'-H of the α-D-riboside tends to appear at lower field compared to that of the corresponding ß-form. Furthermore, the coupling constants of the α-D-ribosides are mostly larger than in the ß-series.[7-9]

EXPERIMENTAL

UV Spectra were recorded on a Perkin Elmer spectrophotometer Lambda 5; ^{1}H-NMR spectra were recorded on a Bruker AC-250 and WM-250 spectrometer with tetramethylsilane as an internal standard and on a δ-scale in ppm. Thin layer chromatography was performed on silica gel sheets F 1550 LS 254 of Schleicher & Schüll, column chromatography on Merck silica gel 60 (particale size 0.063-0.20 mm). Drying of the substances was achieved in vacuum desiccator at room temperature and at a slightly elevated temperature. Melting points are not corrected.

Table 2. ^{1}H-NMR Spectra of 8-substituted theophylline nucleosides in DMSO*-d_6 or $CDCl_3$(values in ppm).

Compd. No.	N_1-CH_3 ; N_3-CH_3 ; C_8-CH_2 , C_8-NH ; & aromatic protons	sugar protons								
		1'-H (1H)	$J_{1',2'}$ (Hz)	2'-H (1H)	3'-H (1H)	4'-H (1H)	5'-H (1H) & 5''-H (1H)	2'-OH	3'-OH	5'-OH
6	3.36(s,3H); 3.55(s,3H); ——— ——— 7.18-8.80 (m,15H,3ArH)	6.37 (d)	3.60	6.15 (pt)	6.15 (pt)	4.75 (bs)	4.70 (dd) 4.89 (dd)			
7*	3.40(s,3H); 3.60(s,3H); ——— ——— ———	5.17 (d)	4.00	4.30 (dd)	4.00 (dd)	3.89 (dd)	3.60 (m)	6.10 (d)	5.48 (d)	5.00 (t)
10	3.39(s,3H); 3.60(s,3H); 4.00(d,2H); 8.85(m,1H); 7.00-8.10 (m,20H,4ArH)	7.00 (d)	4.55	6.50 (pt)	6.30 (dd)	4.80 (bs)	4.70 (m)			
11*	3.35(s,3H); 3.58(s,3H); 4.50(d,2H); 9.00(m,1H); 7.50-8.20 (m,5H,ArH)	5.30 (d)	5.10	4.50 (dd)	4.20 (dd)	3.90 (dd)	3.71 (m)	6.50 (d)	5.50 (d)	5.10 (t)

s=singlet; bs=broad singlet; d=doublet; dd=doublet of doublet; pt=pseudo triplet; q=quadruplet; m=multiplet.

8-Chloro-7-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-theophylline (6).

A mixture of 8-chlorotheophylline[4,5] (2.20g, 10 mmol) and dry hexamethyldisilazane (200 ml) was heated under reflux for 24 h with a catalytic amount of ammonium sulfate. After the solution cooled, it was evaporated to dryness under anhydrous

condition to give the silylated derivative (4), which was dissolved in 100 ml of dry 1,2-dichloroethane. To this was added a solution of 1-O-acetyl-2,3-5-tri-O-benzoyl-β-D-ribofuranose (5) (4.80g, 9.80 mmol) dissolved in dry 1,2-dichloroethane (100 ml), and the mixture was treated with trimethylsilyl trifluoromethanesulfonate (2.00 ml, 10mmol) as catalyst. After the solution had been stirred for 10 h at room temperature, it was evaporated and the residue was partitioned between $CHCl_3$ and aqueous sodium bicarbonate. The organic layer was dried (Na_2SO_4), filtered and evaporated to give after addition of diethylether a yellowish solid (6.0g). Separation of the pure product was achieved after applying the product twice to silica gel column (33x4 cm) chromatography with chloroform as solvent. On evaporation of the main fraction, 6 was obtained as a colorless solid (4.75g, 72%) and yielded on recrystallisation from ethanol, colorless crystals of m.p. 178-180°C.

Anal. Calc. for $C_{33}H_{27}ClN_4O_9$ (660.6):
C, 60.25; H,4.20; N,8.48; Cl,5.37 ; Found: C,60.10; H,3.90; N,8.22; Cl,5.40.

8-Chloro-7-β-D-ribofuranosyltheophylline (7).

Compound 6 (0.66g, 1.0 mmol) in abs. MeOH (100 ml) and potassium carbonate (0.4g) were stirred for 5 h at room temperature. Evaporation of solvent under vacuum gave a colorless solid, which was dissolved in hot water and neutralised with AcOH to pH 4-5. The precipitate was filtered off and afforded on recrystallisation from MeOH, compound 7 as colorless crystals (0.28g, 80%), m.p. 205-206°C.

Anal. Calc. for $C_{12}H_{15}ClN_4O_6$ (346.6): C,41.62; H,4.34; N, 16.18; Cl,10.26 ; Found: C,41.31; H,4.40; N,15.88; Cl,10.25.

8-Benzylamino-7-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)-theophylline (10).

Method A: Ribosylation of 8

A mixture of 8-benzylaminotheophylline (8)[6] (1.0g, 3.5 mmol) and a trace amount of ammonium sulfate was heated in anhydrous hexamethyldisilazane (100 ml) under reflux for 15 h. After the solution cooled, it was evaporated under dry condition to dryness to give the silylated theophylline (9). To

a solution of this residue in anhydrous 1,2-dichloroethane (100 ml) was added a solution of 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose (5) (1.7g, 3.37 mmol) in anhydrous 1,2-dichloroethane (10 ml) followed by dropwise addition of the catalyst trimethylsilyl trifluoromethanesulfonate (0.7 ml, 3.5 mmol). After the mixture had been stirred for 6 h at room temperature, $CHCl_3$ (100 ml) was added and the mixture was partitioned with a cold solution of sodium bicarbonate. The organic extract was dried (Na_2SO_4), filtered and evaporated to a solid residue (2.0g). Recrystallisation from EtOH/$CHCl_3$ gave the pure colorless nucleoside (10) (1.6g, 61%, m.p. 213-215°C).

Anal. Calc. for $C_{40}H_{35}N_5O_9$ (729.5): C,65.85; H,4.80; N,9.60; Found: C,65.50; H,5.00; N,9.37.

Method B: Reaction of 6 with benzylamine.

A mixture of 8-chloro-7-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)theophylline (6) (0.33g, 0.5 mmol) and 5 ml of benzylamine was boiled in 20 ml of abs. EtOH for 1 h. After the solution cooled, 20 ml of diethylether was added and the mixture was stirred at room temperature for 15 h. The crude product was collected by filteration and recrystallised from MeOH to give pale yellow crystals of 10 (0.25g, 69%, m.p. 212°C). The products from A and B have the same m.p. (mixture m.p. did not give depression) and they are identical according to Tlc.

8-Benzylamino-7-β-D-ribofuranosyltheophylline (11).

Method A: Debenzoylation of 10.

A solution of 10 (0.37g, 0.5 mmol) in abs. MeOH (30 ml) and potassium carbonate (0.2g) were stirred for 10 h at room temperature. MeOH was evaporated and followed by addition of H_2O and AcOH to pH 4-5 to yield a colorless precipitate. Recrystallisation from EtOH gave a compound 11 (0.18g, 85%, m.p. 230°C).

Anal. Calc. for $C_{19}H_{23}N_5O_6$ (417.4): C,54.68; H,5.52; N,16.79; Found: C,55.0; H,5.50; N,16.62.

Method B: Reaction of 7 with benzylamine.

A mixture of 8-chloro-7-β-D-ribofuranosyltheophylline (7) (0.3g, 0.87 mmol) and 1 ml of benzylamine in 20 ml of abs.

EtOH was heated at reflux for 3 h. After the solution cooled, it was evaporated to dryness and 20 ml of diethylether was added. The resulting solid was filtered and recrystallised from EtOH to give pale yellow crystals (0.23g, 65%, m.p. 228°C).

The products from A and B have the same m.p. (mixture m.p. did not give depression) and they are identical by Tlc.

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REFERENCES

1. Tai-Shun Lin, Jia-Chong Cheng, Kimiko Ishiguro and Alan C. Sartorelli, J. Med. Chem., 28, 1481-1485 (1985).
2. B. F. Dusel, H. Berman and R. J. Schater, J. Am. Pharm. Assoc. Sci. Edn., 43, 619 (1954).
3. H. Vorbrüggen and G. Höffe, Chem. Ber., 114, 1256 (1981).
4. F. Cacace, Ann. Chim. (Italy), 47, 366 (1957).
5. M. A.N. Mosselhi, Ph. D. Thesis, Konstanz University, Germany (1990).
6. F. Cacace and R. Masironi, Ann. Chim. (Italy), 47, 362 (1957).
7. R. U. Lemieux and M. Hoffer, Can. J. Chem., 39, 110 (1961).
8. M. J. Robins and R. K. Robins, J. Am. Chem. Soc., 87, 4934 (1965).
9. I. W. Southon and W. Pfleiderer, Chem. Ber., 111, 996 (1978).
10. H. Vorbrüggen, K. Krolikiewicz and B. Bennua, Chem. Ber., 114, 1234 (1981).
11. Juris A. Mauriņš, Ruta A. Paegle, Margeris J. Līdaks, Evgeny I. Kvasyuk, Pjotr V. Kuzmichkin and Igor A. Mikhailopulo, Nucleosides & Nucleotides, 5(1), 79-93 (1986).

12. W. Pfleiderer and G. Nübel, Liebigs Ann. Chem., 647, 155 (1961).

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