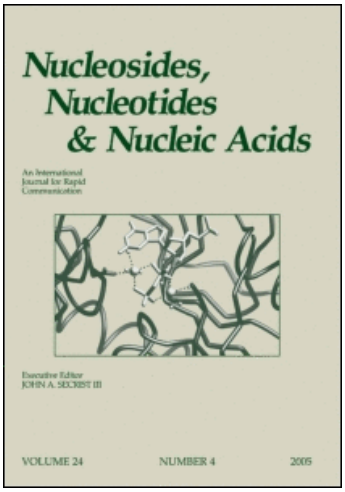

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Synthesis of Derivatives of 3-Methylxantheve and 1-Methyl-3-Isobutylxanthine 7-β-D-Ribofuranosides

Vita Ozola[a]; Yuris Maurinsh[a]; M. Lidaka[a]
[a] Latvian Institute of Organic Synthesis, Riga, LV, LATVIA

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SYNTHESIS OF DERIVATIVES OF 3-METHYLXANTHINE AND 1-METHYL-3-ISOBUTYLXANTHINE 7-β-D-RIBOFURANOSIDES

Vita Ozola*, Yuris Maurinsh, Margeris Lidaka

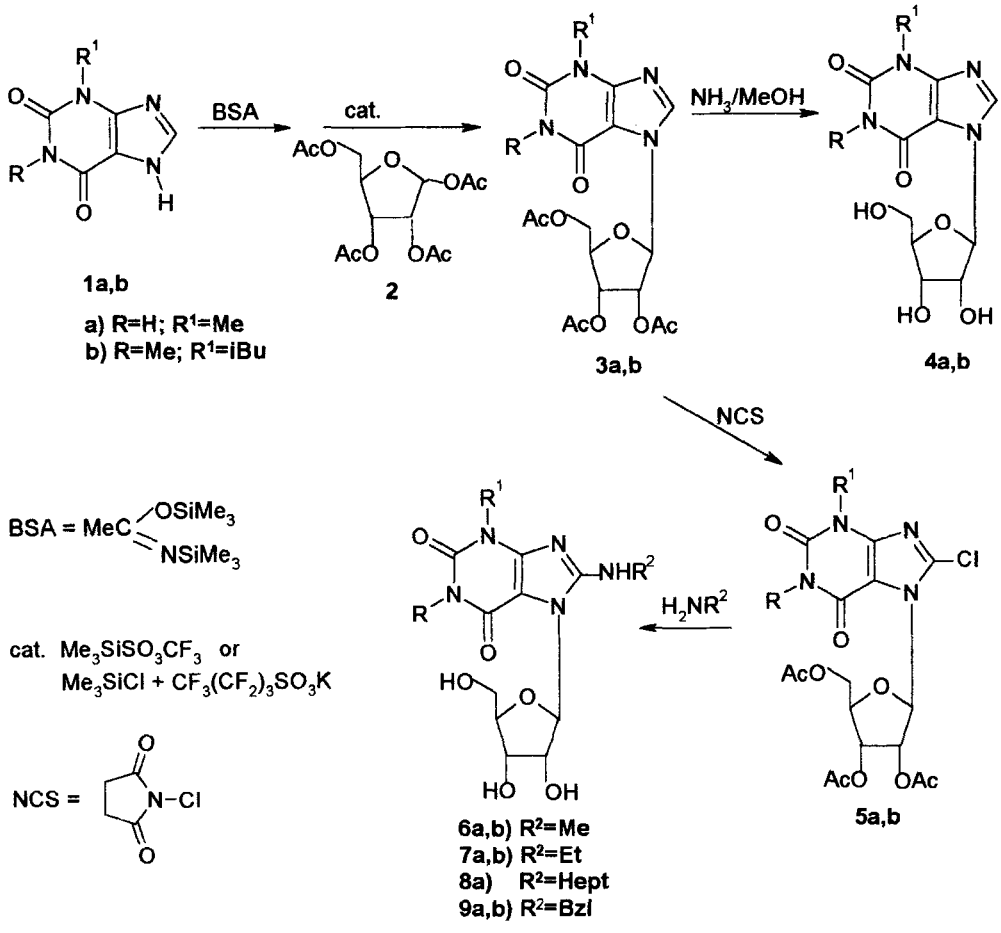
Latvian Institute of Organic Synthesis, Aizkraukles St. 21, Riga LV 1006 LATVIA

Abstract. Methods of synthesis of 7-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-8-chloro-3-methylxanthine (**5a**) and 1-methyl-3-isobutylxanthine (**5b**) were reported. Further nucleophilic displacement of chlorine has provided the corresponding 8-alkylamino and 8-benzylamino derivatives (**6a,b-9a,b**). Several 5'-acyl analogues of 3-methylxanthine-7-β-D-ribofuranoside (**15-18**) were synthesized using 7-(2',3'-di-O-isopropylidene-β-D-ribofuranosyl)-3-methylxanthine (**10**) as intermediate.

Akylxanthines and their C-8 substituted derivatives represent a major class of adenosine receptors antagonists. Modification of xanthine 7-ribosides with various alkyl substituents at 1- and 3-positions, as well as with uronamide group at the 5'-position was reported and the synthesized compounds were tested on adenosine A_1, A_{2a} and A_3 receptors[1].

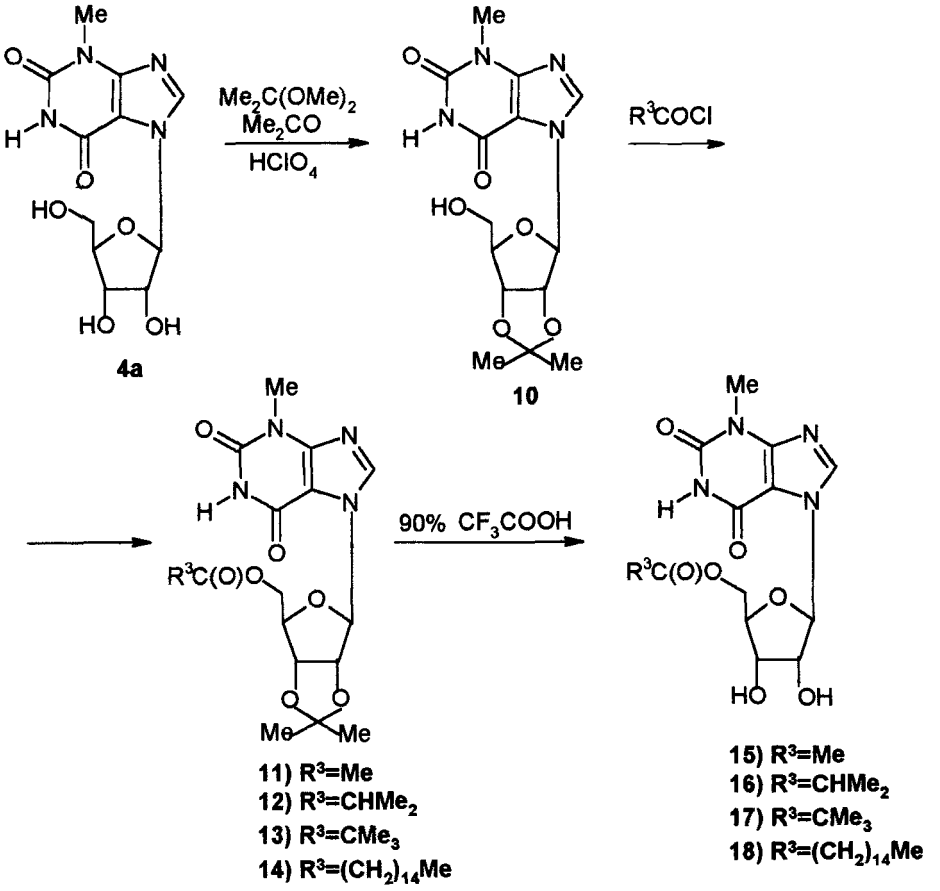
Synthesis of the C-8 derivatives of theophylline nucleosides has been a subject of our studies in previous years[2,3]. Now we have extended our studies on the synthesis of various derivatives of alkylxanthine nucleosides.

According to Vorbrüggen's procedure[4], after silylation of 3-methylxanthine **1a** and 1-methyl-3-isobutylxanthine **1b** with N,O-bis(trimethylsilyl)-acetamide (BSA) in 1,2-dichloroethane (**Scheme 1**), the corresponding trimethylsilyl derivatives were glycosylated with 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose **2** in the presence of trimethylsilyl triflate or potassium nonafluorobutane sulfonate with trimethylsilyl chloride as catalyst and 1,2-dichloroethane as solvent (60°C, 2h). After



SCHEME 1

chromatographic purification we obtained the protected nucleosides **3a** (91% yield) and **3b** (75% yield). Deacetylation of **3a,b** with methanolic ammonia produced xanthine 7-ribosides **4a** and **4b**. For the synthesis of alkylxanthine ribofuranosides bearing alkylamino group at C-8 of purine ring, alkylxanthine (3-methylxanthine or 1-methyl-3-isobutylxanthine) β-D-ribofuranosides **3a** and **3b** were first converted to the corresponding 8-chloroderivatives **5a** (84% yield) and **5b** (71% yield) by the chlorination with N-chlorosuccinimide. Nucleophilic displacement of halogen atom gave 8-methylamino- , 8-ethylamino-, 8-heptylamino-, 8-benzylaminoderivatives of 3-



SCHEME 2

methylxanthine-β-D-ribofuranoside **6a-9a** and 1-methyl-3-isobutylxanthine-β-D-ribofuranoside **6b,7b, 9b** in moderate to good yields.

Higher fatty acid esters of inosine and 2'-deoxyinosine has been found to be useful immunosuppresants for the treatment of atopic dermatitis[5]. This prompted us to synthesize 3-methylxanthine 7-riboside analogues modified at the ribose 5'-position.

In order to synthesize 5'-acyl modified xanthine nucleosides (**Scheme 2**), the 2'- and 3'-hydroxyl groups of 7-(β-D-ribofuranosyl)-3-methylxanthine **4a** were selectively protected by isopropylidenation with acetone and 2,2-dimetoxypropane using

perchloric acid as a catalyst, a method previously reported by M.Sharma et al.[6]. In the reaction of protected nucleoside **10** with acid chlorides (acetyl, isobutyryl, pivaloyl, palmitoyl) and subsequent acid hydrolysis (90% trifluoroacetic acid, 0.5h) of isopropylidene group a series of 5'-acylderivatives of 7-(β-D-ribofuranosyl)-3-methylxanthine **15-18** were obtained.

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