

This article was downloaded by:

On: 26 January 2011

Access details: *Access Details: Free Access*

Publisher *Taylor & Francis*

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Nucleosides, Nucleotides and Nucleic Acids

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597286>

Synthesis of Derivatives of 3-Methylxanthine 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

To cite this Article Ozola, Vita , Maurinsh, Yuris and Lidaka, M.(1998) 'Synthesis of Derivatives of 3-Methylxanthine and 1-Methyl-3-Isobutylxanthine 7- β -D-Ribofuranosides', *Nucleosides, Nucleotides and Nucleic Acids*, 17: 9, 1983 — 1986

To link to this Article: DOI: 10.1080/07328319808004737

URL: <http://dx.doi.org/10.1080/07328319808004737>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

SYNTHESIS OF DERIVATIVES OF 3-METHYLYXANTHINE AND 1-METHYL-3-ISOBUTYLYXANTHINE 7- β -D-RIBOFURANOSIDES

Vita Ozola*, Yuris Maurinsh, Margeris Lidaka

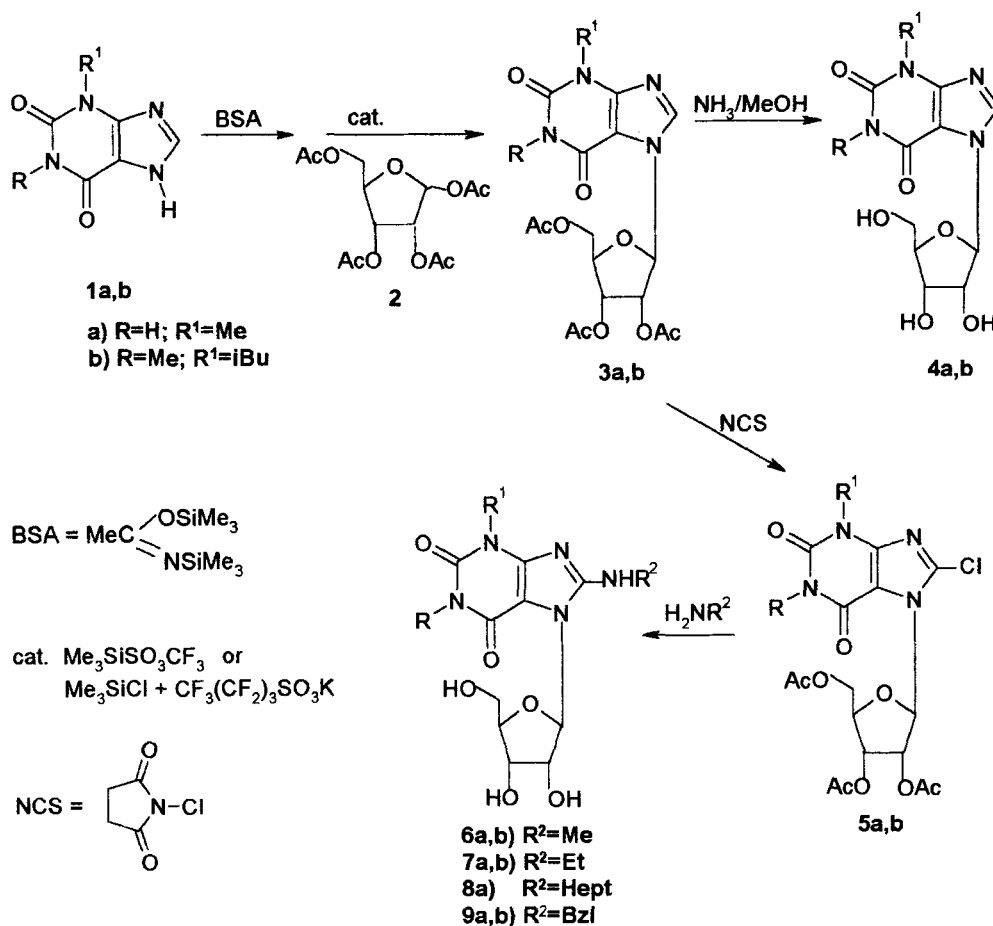
Latvian Institute of Organic Synthesis, Aizkraukles St. 21, Riga LV 1006 LATVIA

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.

Alkylxanthines 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 A₁, A_{2a} and A₃ receptors¹.

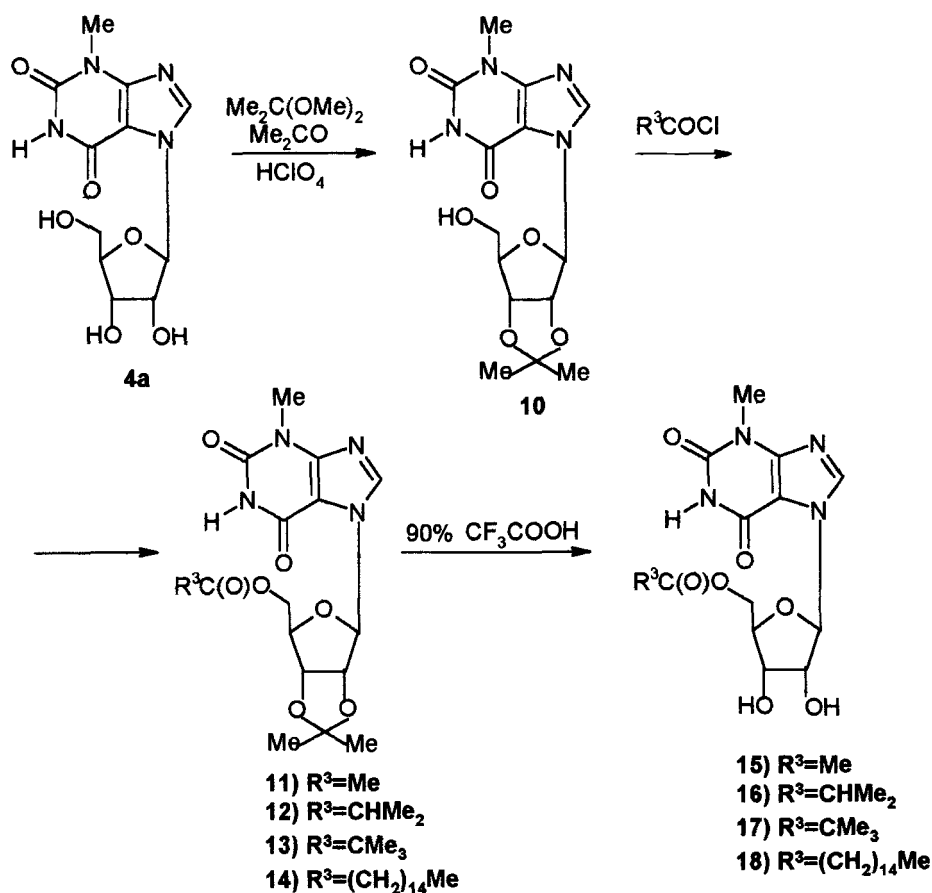
Synthesis of the C-8 derivatives of theophylline nucleosides has been a subject of our studies in previous years^{2,3}. Now we have extended our studies on the synthesis of various derivatives of alkylxanthine nucleosides.

According to Vorbrüggen's procedure⁴, 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 immunosuppressants for the treatment of atopic dermatitis⁵. 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-dimethoxypropane 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.

REFERENCES

1. Kim, H.O.; Ji, X.-D.; Melman, N.; Olah, M.E.; Stiles, G.L.; Jacobson, K.A. *J.Med.Chem.*, **1994**, *37*, 4020-4030.
2. Ozola, V.; Ramzaeva, N.; Maurinsh, Yu.; Lidaks, M. *Nucleosides & Nucleotides*, **1993**, *12*, 479-486.
3. Ozola, V.; Ramzaeva, N.; Maurinsh, Yu.; Lidaks, M. *Nucleosides & Nucleotides*, **1993**, *12*, 827-839.
4. Vorbrüggen, H.; Krolikiewicz, K.; Bennua, B. *Chem. Ber.*, **1981**, *114*, 1234-1255.
5. H.Iwabuchi et al, Jpn. Kokai Tokkyo Koho JP 07,109,290 [95,109,290], 25 Apr **1995**.
6. Sharma, M.; Wikiel, H.; Hromchak, R.; Bloch,A.; Bobek, M. *Nucleosides & Nucleotides*, **1993**, *12*, 295-304.