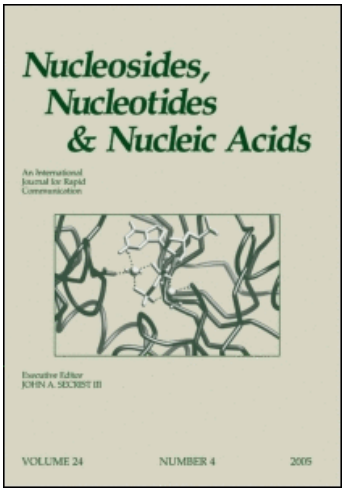

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Intramolecular Transformations Related to the Structures of Allyl Derivatives of Hypoxanthine and Uracil

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To cite this Article Škari, V. , Škarić-Mlakar, M. , Jokić, M. and Škarić, D.(1987) 'Intramolecular Transformations Related to the Structures of Allyl Derivatives of Hypoxanthine and Uracil', Nucleosides, Nucleotides and Nucleic Acids, 6: 1, 371 — 372
To link to this Article: DOI: 10.1080/07328318708056224
URL: http://dx.doi.org/10.1080/07328318708056224

NUCLEOSIDES & NUCLEOTIDES, 6(1&2), 371-372 (1987)

INTRAMOLECULAR TRANSFORMATIONS RELATED TO THE STRUCTURES OF ALLYL DERIVATIVES OF HYPOXANTHINE AND URACIL

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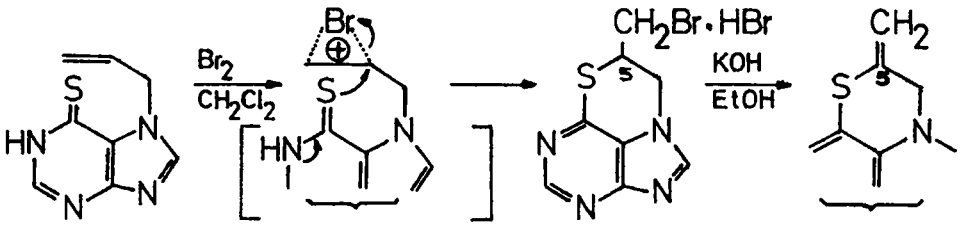
Abstract. The allylation of hypoxanthine and methylation of 1-allyl-4-thiouracil has been investigated. New synthetic routes to [1,4]-thiazino[4,3,2 gh]purine derivatives from 7-allyl-6-thiohypoxanthine and 8-azaxanthine nucleoside analogs from uracil were also described.

Allyl derivatives and suitably alkylated and halogenated nucleic bases have been found to inhibit the replication of a number of DNA and RNA viruses[1,2]. The present report deals with the allylation ambiguities on hypoxanthine and the methylation effects on 1-allyl-4-thiouracil.

The allylation of hypoxanthine by silyl method afforded 3,7-diallyl-(1, R_F ca. 0.76, 41%), 7-allyl-(2, R_F ca. 0.47, 21%) and 3-allyl-(3, R_F ca. 0.39, 16%) hypoxanthine, spectroscopically identified by the IR, UV, MS and NMR data and the elemental analysis.

In the addition to the previously reported synthesis of 2,3-dihydro-2-methylene-7H-thiazolo[3,2-a]pyrimidin-7-one[3], the intramolecular cyclisation of 7-allyl-6-thiohypoxanthine (4), in a reaction with bromine in methylene chloride, gave the hitherto unknown 5-bromomethyl-4,5-dihydro[1,4]thiazino[4,3,2 gh]purine hydrobromide (5), almost in quantitative yield. This structure was confirmed by being converted into 5-methylene derivative (6), in the reaction with ethanolic KOH.



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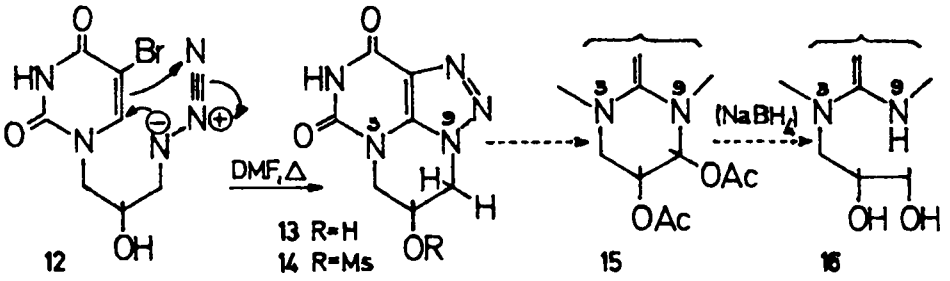
The methylation of 1-allyl-4-thiouracil with diazomethane afforded, in order of their chromatographic mobilities, 1-allyl-3-methyl-4-thiouracil (7, 35%), 1-allyl-4-methylthiouracil (8, 63%) and 1-allyl-2-methoxy-4-thiouracil (9, 2%). From the methylation, however, with methyl iodide under basic conditions, only 4-methylthio-isomer (8) was isolated.

In contrast to uracil and its 2-thio-analog, which on allylation by silyl method afforded only 1-allyl derivatives, 4-thiouracil underwent to an unexpected reaction to give 4-allylthiouracil (10) and, after prolongated allylation, 1-allyl-4-allylthiouracil (11).

The intramolecular 1,3-dipolar cyclisation to the 5,6-double bond of 1-(3-azido-2-hydroxypropyl)-5-bromouracil (12), followed by a dehydrobromination, afforded 9,3`-cyclo-3(2`-hydroxypropyl)-8-azaxanthine (13). The mesylation of 13, followed by a regioselective elimination



of the thus obtained mesyl derivative (14) gave intermediary prop-2`--enyl derivative. The latter was then cis-hydroxylated and acetylated to give the cis-glycol system (15). From these results it can be deduced a novel synthesis of the 8-azaxanthine analogs. Thus, the reduction of (15) under the basic conditions (with $NaBH_4$), yielded 1-(2,3-hydroxypropyl)-8-azaxanthine.

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