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Chemical synthesis of novel taurine-containing uridine derivatives

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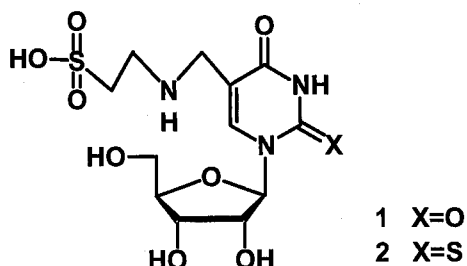
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ABSTRACT

Recently, novel taurine-containing uridine derivatives were discovered in mammalian mitochondrial tRNAs, and these modified ribonucleosides existed at the first position of the anti-codon. This paper describes the chemical synthesis of these novel uridine derivatives, 5-taurinomethyluridine ($\tau\text{m}^5\text{U}$) and 5-taurinomethyl-2-thiouridine ($\tau\text{m}^5\text{s}^2\text{U}$). These taurine-containing uridine derivatives were synthesized in the good yields by the reaction of the corresponding 5-hydroxymethyluridine derivatives with taurine under basic conditions.

INTRODUCTION

Many post-transcriptionally modified ribonucleosides have been found in biologically important RNAs such as tRNA, rRNA, and mRNA.¹ It is considered that these modified ribonucleosides have specific functions, which are difficult to realize by normal RNAs consist of only four unmodified nucleosides. Recently 5-taurinomethyluridine ($\tau\text{m}^5\text{U}$, **1**) and 5-taurinomethyl-2-thiouridine ($\tau\text{m}^5\text{s}^2\text{U}$, **2**) were discovered in mammalian mitochondrial tRNAs.² $\tau\text{m}^5\text{U}$ was existed in tRNAs for Leu and Trp, and $\tau\text{m}^5\text{s}^2\text{U}$ did in tRNAs for Lys, Gln, and Glu. These two novel uridine derivatives locate at the first position of the anti-codon (wobble position).



It is well known that the mammalian mitochondrial decoding system consists of only 22 tRNAs, which is the minimum set capable of decoding all the sense codon

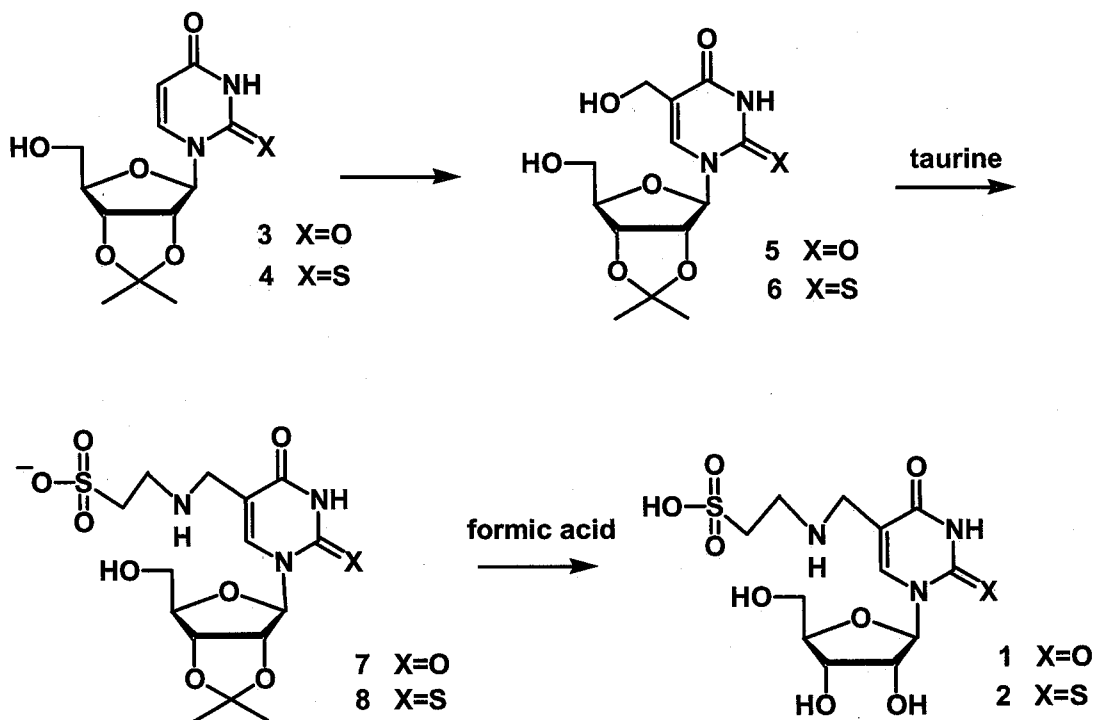
throughout all living organisms and organelles.³ Therefore, these two modified ribonucleosides are expected to have specific functions in interaction and recognition of codon-anticodon base pairing. In addition, the lack of the taurine-containing uridines causes mitochondrial human diseases.⁴ In order to elucidate detailed functions of these novel modified uridine derivatives, their chemical synthesis and structural characterization are of great importance. In this paper we report the first time efficient synthesis of $\tau\text{m}^5\text{U}$ and $\tau\text{m}^5\text{s}^2\text{U}$.

RESULTS AND DISCUSSION

2',3'-*O*-Isopropylidenuridine (**3**) has been reported to be converted to the corresponding 5-(dialkylamino)methyl derivatives by a Mannich-type reaction with formaldehyde and a dialkylamine in an aqueous solution.⁵ At first, we examined reaction of 2',3'-*O*-isopropylidenuridine, taurine, and formaldehyde in the presence of triethylamine in water. Upon heating of the reaction mixture at 95 °C for 24 h, about a half amount of the starting material was converted to a highly polar product. The product was isolated by reverse-phase column chromatography to give the desired 5-taurinomethyluridine derivative (**7**) in about 20% yield. A prolonged reaction time resulted in the formation of a complex mixture. When the reaction was carried out in the presence of a large excess amount of Et₃N, 5-hydroxymethyluridine derivative (**5**) was formed as a major product in the early stage of the reaction. The compound **5** was gradually converted to **7**. The above fact would indicate that the readily accessible compound **5**⁶ can be used as a starting material for the synthesis of **7**.

Thus compound **5** was allowed to react with taurine in the presence of NaOH in water at 95 °C. The reaction was completed after 7 days, and the product **7** was obtained in good yield. Treatment of compound **7** with aqueous formic acid gave $\tau\text{m}^5\text{U}$ (**1**) in quantitative yield.

Next, the synthesis of 2-thiouridine derivative **8** was carried out under similar conditions; 5-hydroxymethyl-2-thiouridine (**6**) was allowed to react with taurine in the presence of NaOH in



water at 95 °C. The reaction was completed within 7 days. However, the analysis of the purified product by ^1H NMR spectroscopy indicated the complete loss of the sulfur atom at the 2-position of the uracil ring. The attack of hydroxide ion might cause the substitution of the sulfur atom to the oxygen atom. In order to avoid this reaction, anhydrous basic conditions should be employed. Finally, sodium hydride was found to be effective. Thus, the reaction of 5-hydroxymethyl-2-thiouridine (6) with taurine in the presence of NaH in dry pyridine at 95 °C gave 5-taurinomethyl-2-thiouridine derivative (8) in good yield after 7 days. In this case, about 10% of desulfurization was observed by a reverse-phase HPLC analysis. The above reaction conditions using anhydrous NaH were successfully applied to the synthesis of compound 7.

Chemical and physicochemical properties of tm^5U and $\text{tm}^5\text{s}^2\text{U}$ were also investigated by UV, CD, ^{13}C NMR, and ^1H NMR.

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