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SYNTHESIS OF MESOIONIC XANTHINE NUCLEOSIDES

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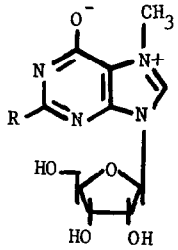
ABSTRACT: The synthesis of the first examples of Class II mesoionic xanthine nucleosides is described. Tri-O-acetylribofuranosylaminothiazole is cyclized by condensation with bis (2,4,6-trichlorophenyl) malonate and the resultant product is de-protected to yield anhydro (8-β-D-ribofuranosyl-5-hydroxy-7-oxothiazolo [3,2-a] pyrimidinium hydroxide); the glucosyl derivative is prepared in a similar manner.

Bredereck, et al[1]; methylated guanosine to obtain what they believed to be 1-methylguanosine. Jones and Robins[2] later identified the alkylation product as being 7-methylguanosine (1, only one resonance structure shown). Likewise, methylation of xanthosine and inosine were found to give the corresponding 7-methylated derivatives, 2 and 3, respectively; each of these compounds was easily hydrolyzed to its corresponding 7-methyl purine base.[2] These studies represent some of the early work with what may now be considered as a much larger class of mesoionic purinones. Two major classes of mesoionic purinones have been formulated and systematically examined from a quantum chemical standpoint.[3,4] Those mesoionic purinones which may be envisioned as being derived from a five-membered mesoionic ring system have been termed class I mesoionic purinones,[3] while those derived from a six-membered mesoionic ring system are termed class II mesoionic purinones.[4] Each of these two classes may be further divided into three subclasses: mesoionic xanthine, mesoionic hypoxanthine and mesoionic 2-purinone analogs. Thus, compounds 1 and 3 may be considered to be examples of class I mesoionic hypoxanthines while 2 is a class I mesoionic xanthine derivative.

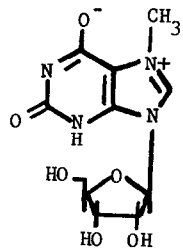
Mesoionic nucleosides may be of potential interest because of their structural similarity and isosteric relationship with chemotherapeutically useful "non-mesoionic" nucleosides. Furthermore, at least one example of a class I mesoionic nucleoside, i.e. 1, has been identified (and isolated) as being a naturally occuring component of ribonucleic acids from various sources.[5,6] Although several class II mesoionic purinone bases have been previously prepared,[7-9] to date, the synthesis of a class II mesoionic nucleoside has not been described. We report here the synthesis of the first such nucleoside.

One class II mesoionic xanthine ring system which has been fairly well characterized is the thiazolo [3,2-a] pyrimidine 4; thus, this base was chosen for our initial studies. The prime objective of this work was to determine a) whether the glycosylaminothiazoles would be stable to the conditions required for cyclization (e.g. 7 → 8) and, because the mesoionic base is known to



1 R = NH_2

3 R = H



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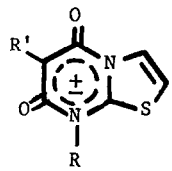

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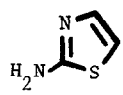

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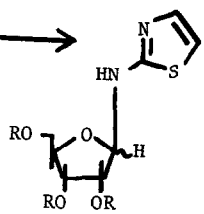
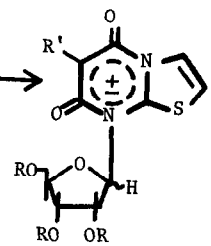


6 R = H

7 R = $COCH_3$

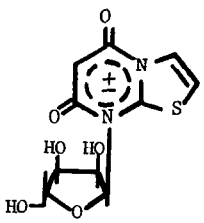


8 R = $COCH_3$, R' = H

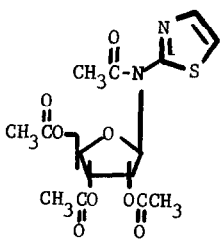
9 R = R' = H

10 R = $COCH_3$, R' = C_2H_5

11 R = H, R' = C_2H_5



9α



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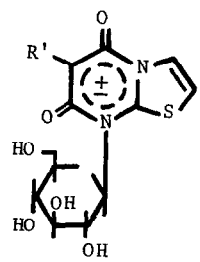

13β R' = H

14β R' = C_2H_5

be susceptible to nucleophilic attack with concommitant ring-opening,[7] b) whether the protected mesoionic nucleosides would be stable to conditions necessary for deprotection (e.g. 8 ⟶ 9).

Condensation of freshly sublimed 2-aminothiazole (5) with D-ribose in a manner similar to that reported by Panagopoulos, et al.[10] afforded 6, which could be converted to an anomeric mixture of 7 (m.p. 164-165°, from methanol, 20-80% yield) by treatment with acetic anhydride. Yields of 7 were variable due to the formation of inconsistent amounts of a side-product 12 (m.p. 135°). Compound 7 could be purified by column chromatography; however, the presence of small quantities of 12 did not interfere in the conversion of 7 to 8. Equimolar quantities of bis (2,4,6-trichlorophenyl) malonate[11] and 7 were heated neat at 160° for three minutes to afford a 1:1 anomeric mixture of 8 in 90% yield. Separation of the anomeric mixture was accomplished by column chromatography (silica gel/ethyl acetate) to give 8 β (m.p. 236-238°, from isopropanol) and 8α (m.p. 232-234°, from isopropanol). Treatment of 8 β and 8α with methanolic dimethyl amine (0.1%) at room temperature for 100 hours afforded anhydro (8-β -D-ribofuranosyl-5-hydroxy--7-oxothiazolo[3,2-a] pyrimidinium hydroxide) (9 β) (m.p. 221°d, from methanol, 97% yield) and its anomer 9α (m.p. 205-206°, from methanol, 90% yield), respectively. The NMR spectrum of 9 β reveals the anomeric proton signal as an apparent singlet at δ 6.0 while the anomeric proton signal of 9α appears as a doublet at δ 6.3 (J = 10 Hz). The ethyl derivative 11 β (m.p. 192-198° from aqueous methanol, 98% yield) was prepared in the same manner except that bis(2,4,6-trichlorophenyl) ethyl-malonate was used in place of the unsubstituted ester and methanolic ammonia (0.4%) was employed to deprotect 10 β (m.p. 243-244°, from abs. ethanol, 82% yield). The glucosyl derivatives 13 β (m.p. 258-262°, from aqueous methanol, 4% overall yield) and 14 β (m.p.-229-230°, from isopropanol, 17% overall yield) prepared in like manner. Jones and Robins[2] reported that 1-3 crystallized with one to two moles of water, were relatively unstable to heat and prone to hydrolysis. Compounds 13β and 14 β also crystallized with a mole of water which could be removed by heating (65°) in vacuo. Although detailed hydrolytic studies are yet to be performed, the mesoionic nucleosides reported herein are relatively stable toward hydrolysis, and several have been recrystallized from water.

Mass spectral, infrared, proton magnetic resonance[12] and microanalytical data are consistent with the assigned structures.[13] No attempts were made to optimize yields. Work is currently in progress on several deoxyribosyl derivatives and on other related mesoionic purinone nucleosides.

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12. Proton magnetic resonance spectra were obtained using a JEOL FX-90 Q spectrometer with $CDCl_3$ as solvent for the protected nucleosides, and DMSO-d_6 as solvent for the unprotected nucleosides.
13. This work has been reported, in part, at the 181st National American Chemical Society Meeting (MED1-35) in Atlanta, GA, March, 1981.
14. In partial fulfilment of the requirements for a Ph.D. degree in Chemistry, VCU.

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