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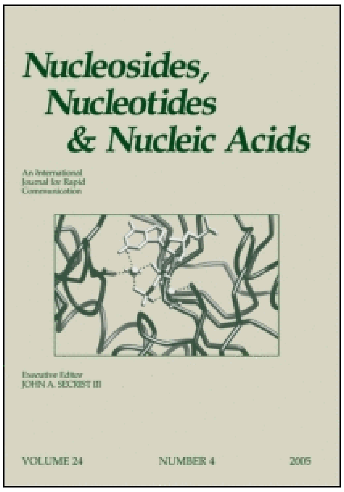

Nucleosides, Nucleotides and Nucleic Acids

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Synthesis of Mesoionic Xanthine Nucleosides

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NUCLEOSIDES & NUCLEOTIDES, 2(2), 127-146 (1983)

SYNTHESIS OF MESOIONIC XANTHINE NUCLEOSIDES

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ABSTRACT

The preparation of (anhydro-8-D-ribofuranosyl)-, (anhydro-8-D-glucopyranosyl)-, and (anhydro-8-α-D-2-deoxyribofuranosyl)-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide is described. These nucleoside analogs are the first examples of Class II mesoionic nucleosides.

In a recent communication[2] we reported the preparation of a novel class of nucleosides. These nucleosides contain 6-H-, or 6-ethyl-thiazolo[3,2-a]pyrimidine-5,7-dione as the aglycon, and they are the first examples of Class II mesoionic xanthine nucleosides.

Two major classes of mesoionic purinones have been formulated and systematically examined from a quantum chemical standpoint[3,4]. These mesoionic purinones may be envisioned as being derived from a five-membered mesoionic ring system (Class I)[3] or from a six-membered mesoionic ring system (Class II)[4]. 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[5].

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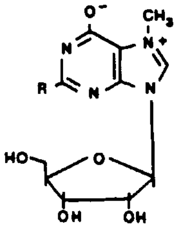
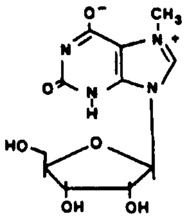
One Class II mesoionic xanthine ring system which has been fairly well characterized is the thiazolo[3,2-a]pyrimidine 4[6,7], thus this base was chosen for our initial studies. Mesoionic nucleosides, such as those described herein, may be considered as modified pyrimidine nucleosides, and are of potential interest because of their structural similarity and isoteric relationship with chemotherapeutically useful



1: R = NH_2

3: R = H



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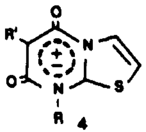

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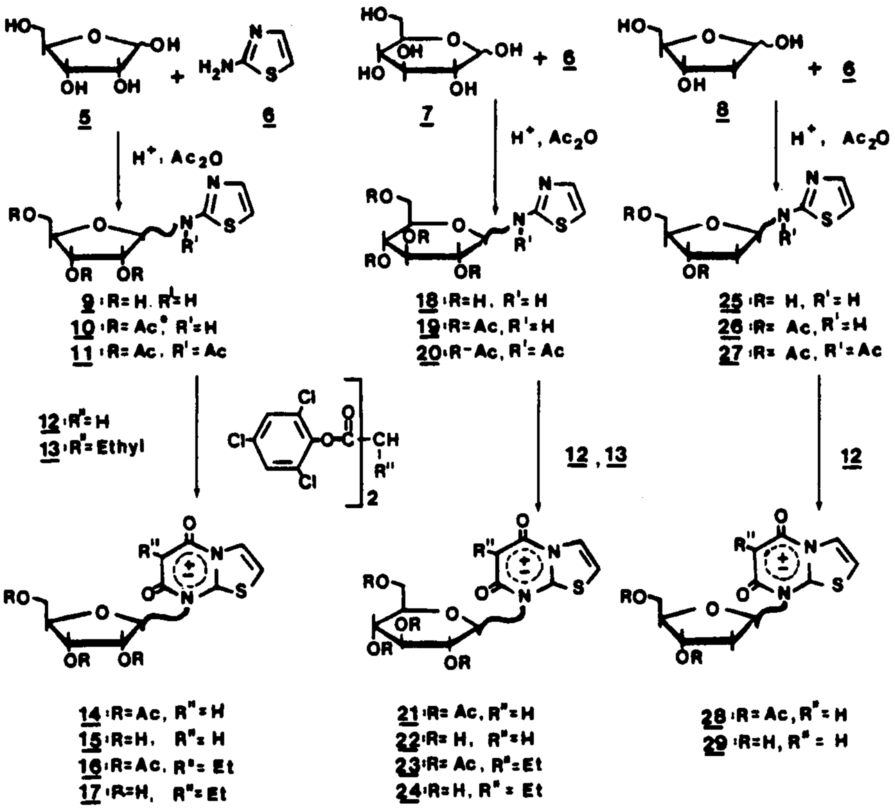
"non-mesoionic" nucleosides. Furthermore, at least one example of a Class I mesoionic nucleoside, i.e. 1, has been isolated and identified as being a naturally occurring component of ribonucleic acids from various sources[8,9]. This present study was not necessarily intended to prepare biologically active nucleosides. Rather it was of interest to explore general pathways that allow for the preparation of mesoionic nucleosides, as well as to investigate their chemical and spectral properties.

The preparation of ribose, glucose and deoxyribose derivatives of mesoionic thiazolo[3,2-a]pyrimidine-5,7-diones was accomplished by following a reaction sequence as shown in Scheme I, which consisted of the following four steps: formation of the N-glycoside by a condensation reaction, protection of the sugar hydroxyl groups by acetylation, formation of the mesoionic thiazolo[3,2-a]pyrimidine base by fusion with a malonate ester, and deprotection of the sugar portion of the nucleoside to obtain the free nucleoside. The individual synthetic steps were extensively studied using ribose (5) to ultimately obtain the mesoionic ribosides 15 and 17. The procedures that proved to be successful in the preparation of the ribosides were applied, and where necessary modified, to obtain the glucosides 22 and 24, and the 2-deoxyriboside 29.



*Ac = $COCH_3$

SCHEME I. Synthetic Pathways for the Preparation of Mesoionic Xanthine Nucleosides.

The riboside 9 was prepared by a modification of the procedure of Helferich and Kosche[10] in which ribose (5) was heated with 2-aminothiazole (6) in 1% methanolic HCl while permitting slow evaporation of the solvent. Riboside 9 was obtained as an anomeric mixture, with the two anomers having practically identical R_f-values. Attempts to crystallize the chromatographically purified anomeric mixture from water or methanol did not produce crystalline products. In order to obtain 9 as a solid, it was necessary to remove all traces of water by azeotropic distillation with benzene. Riboside 9 was utilized in the subsequent acetylation reaction without further purification.

The protection of the hydroxyl groups in 9 was accomplished by acetylation with acetic anhydride in the presence of triethylamine. Thin-layer chromatography revealed the presence of several products. It was possible to separate the reaction mixture by repeated column chromatography to obtain pure tetraacetylated riboside 11 and another fraction containing three components.

When the fraction containing three components was concentrated under reduced pressure N-acetyl-2-aminothiazole crystallized from the solution. After removal of N-acetyl-2-aminothiazole by filtration, an anomeric mixture of the O-acetylated ribose 10 crystallized from solution. Crystalline 10 was employed in the reaction with the malonate esters 12 and 13 to give mesoionic nucleosides 14 and 16.

The IR-spectrum of 11 shows amide carbonyl absorption at 1710 cm^{-1} in addition to ester carbonyl absorption at 1750 cm^{-1}, and ^{13}C NMR data indicate the presence of four different carbonyl carbons in the range 167-172 ppm. The N-acetylation of 9 to yield a tetraacetylated derivative could occur at either the exocyclic nitrogen or on the ring nitrogen. It is known that acylation of 2-aminothiazole derivatives under acidic conditions can lead to ring nitrogen acylation, while under basic conditions acylation of the exocyclic nitrogen usually takes place[11]. A comparison of the UV spectra of riboside 9 and peracetylated riboside 11 shows that both compounds absorb at 255 nm, indicating intact aromatic character for the thiazole ring, therefore the peracetylated product is correctly represented by structure 11.

Attempts were made to selectively hydrolize the amide bond in 11 using the method reported by Goody and Walker[12], to obtain the tri-O-acetyl riboside 10. However, the reaction conditions led to the formation of several partially deprotected ribosides, together with glycosidic bond cleavage to yield 2-aminothiazole and acetylated ribose.

Acetylation of 9 in the presence of N,N-dimethyl-4-aminopyridine[13] led to the formation of riboside 11 as the major product, while acid-catalyzed acetylation[14] resulted in cleavage of the glycosidic bond.

Since the yield of riboside 10 did not exceed 40%, an attempt was made to prepare 10 by coupling of a protected ribose with 2-aminothiazole (6). Using the method of Prisbe, Verheyden and Moffat[15] an unsuccessful attempt was made to prepare the protected riboside 10 by reacting 1-O-acetyl-3,2,5-tri-O-benzoyl-D-ribofuranose with 6 in the presence of mercuric cyanide and stannic chloride. A small amount of a salt-like precipitate could be isolated which on the basis of its ^{1}H NMR spectrum (two doublets at δ6.6 and 7.2) is believed to be a coordination complex of mercury with the sulfur of the thiazole ring. Thiazole derivatives are known to readily form coordination complexes with mercury[16] and other transition metals[17].

The fusion of malonate ester 12 with riboside 10 at 160°C produced an anomeric mixture of 14. Thin-layer chromatography indicated the presence of both the α- and β-anomers. Trituration of the cooled reaction mixture with anhydrous ether resulted in crystallization of both anomers of 14. The crude crystalline mass was subjected to column chromatography on silica gel; elution with ethyl acetate removed unreacted malonate ester 12. The elution of the α-anomer, followed by elution of the β-anomer was accomplished by using 1:1 ethyl acetate-methanol as the mobile phase. Upon evaporation of the solvent, the two anomers were obtained as solids and could be crystallized from 2-propanol.

The structural assignments of the two anomers of 14 were based on the characteristic appearances of the anomeric proton signals in their ^{1}H NMR-spectra. The anomeric proton of the α-anomer appears as a doublet at δ6.7 (J=10 Hz), while the anomeric proton of the β-anomer shows as a singlet at δ6.3. This pattern is in agreement with published data used in structural assignments for ribose nucleosides[18,19]. The thiazole protons of the mesoionic heterobase experience a typical shift of 1 ppm downfield as compared to the proton of the thiazole ring in riboside 10. This shift was observed by Coburn and Glennon[6] for other derivatives of mesoionic thiazolo[3,2-a]pyrimidine-5,7-diones and is supportive evidence for the presence of mesoionic ring system.

In addition to the ester carbonyl bands, the infrared spectrum of 14 shows carbonyl bands at 1650 cm^{-1} and 1700 cm^{-1}, and these positions agree with the carbonyl absorption bands that were observed for mesoionic 8-alkyl-thiazolo[3,2-a]pyrimidine-5,7-diones[6,7]. The tentative assignments of carbonyl groups at C-5 and C-7 in riboside 14, as well as in all the following mesoionic ring systems, is based on a comparison with similar non-mesoionic ring systems. IR studies by Glennon, Bass and Schubert[20] have shown that the carbonyl stretching bands of thiazolo-pyrimidines absorbs at 1630-1640 cm^{-1} for the 7-carbonyl group, while the 5-carbonyl group absorbs at 1680-1690 cm^{-1}. These data are also consistent with the infrared spectra of mono-oxothiazolo[3,2-a] pyrimidinones and related benz-fused analogues[21-23].

The 6-ethyl-substituted mesoionic riboside 16 was prepared by following the procedures used for riboside 14 but using malonate ester 13 instead of 12. The separation of the α- and β-anomers was accomplished by column chromatography as described for 14. The ^{1}H NMR-spectra of the two anomers of 16 essentially are very similar to the anomers of riboside 14, except for the additional signals at δ2.5 and δ1.1, caused by the ethyl substituent at the 6-position of the heterobase. The anomers of 14 and 16 were formed in approximately equal amounts and their R_f-values showed about the same relative separation. ^{1}H NMR data in the riboside series are summarized in Table I.

Mesoionic xanthines are susceptible to nucleophilic ring-opening[6,24] particularly in the presence of methoxide ion. Therefore, the deprotection of nucleoside 14 and 16 was carried out in anhydrous methanol containing a catalytic amount of dimethylamine. The α-anomer of 14 also was deprotected with methanolic ammonia instead of dimethylamine, however, it appears that the use of dimethylamine for deprotection gives results that are more reproducible.

Upon concentration of the methanolic solutions, deprotected nucleosides 15 and 17 crystallized. The ^{1}H NMR spectra of the deprotected nucleosides basically agree with the spectra of the corresponding acetyl compounds, except that the anomeric proton signals are shifted upfield by 0.3-0.5 ppm, and the methyl signals of the acetyl groups are absent. The splitting pattern of the anomeric protons essentially remains the same as the one observed for their protected analogues, indicating that deprotection did not result in isomerization or racemization.

The proton signal of H-6 in 15 appears as a singlet at δ4.7. This assignment is in accord with previous results which report a singlet at δ4.5-5.5 for the 6-proton of mesoionic 8-alkyl-thiazolo[3,2-a]pyrimidine-5,7-diones[6]. The infrared spectrum of 15 and 17 show absorption bands for the mesoionic carbonyl groups at 1630 cm^{-1} and 1690 cm^{-1}, and the absence of ester carbonyl bands at 1750-1760 cm^{-1}, as well as the strong O-H stretching modes at 3200-3600 cm^{-1} confirmed that complete deprotection had taken place.

Panagopoulos, et al.[25] reported the preparation of glucosyl-aminothiazole (18) by heating 2-aminothiazole (6) and glucose (7) in methanol.

However, the method previously described for the preparation of riboside 9 produced a better yield of 18. The physico-chemical behavior of glucoside 18 was very similar to that of riboside 9; however although glucoside 18 has been reported as a crystalline substance with melting point 166-168°C[25], we were unable to obtain such a product. Therefore, 18 was acetylated without further purification to yield 19 and 20. Glucoside 18 was reacted with acetic anhydride in the presence of triethylamine at 20°C. After six hours, thin-layer chromatography of the reaction mixture showed the presence of two major products with R_f-values 0.72 and 0.55. Analogous to the acetylation products of riboside 9, it is believed that the product with R_f-value of 0.72 is the peracetylated glucoside 20. However, isolation of this material was not pursued.

Glucoside 19 was isolated by repeated column chromatography and could be obtained in 10% yield as an anomeric mixture. During column separation it was estimated that a substantial amount of glucoside 19 was present in fractions which mainly contained glucoside 20. It was possible to fuse a dry mixture of 19 containing about 30% of 20 with malonate ester 12 to yield the mesoionic glucoside 21. Unchanged 20 present in the reaction mixture after fusion could be removed by chromatographic means.

Product 19 is reported to have a melting point of 153-157°C[25], however, we obtained glucoside 19 as an amorphous substance with melting range 145-150°C. This material was employed without further characterization to prepare mesoionic nucleosides 21 and 23.

Heating the malonate esters 12 and 13 with the glycoside 19 for five minutes gave the best yield of mesoionic product. Thin-layer chromatography of the crude reaction mixture indicated the presence of the two anomers, together with a significant amount of an unidentified decomposition product. The two anomers were separated by column chromatography. The β-anomers of glucoside 21 and 23 were formed 3:1 over the respective α-anomer. The R_f values of the β-anomers were higher than the ones of the α-anomers, and during column separation, the β-anomer was eluted first. The α- or β- assignments of the obtained anomers is based on the anomeric proton signals, which appear as a singlet at δ6.7 for the α-anomers, and as a doublet at δ6.5 (J = 10 Hz) for the β-anomers. This configurational assignment compares well with published values for glucosides[26], and with nucleosides which have an acetylated pyranosyl portion[27]. The deprotection of glucosides 21 and 23 was accomplished in an identical manner to that used for the deprotection of ribosides 14 and 16. ^{1}H NMR data for compounds in the glucose series are summarized in Table I.

Deoxyriboside 25 was prepared by reaction of 2-aminothiazole (6) with deoxyribose (8) in 0.8% methanolic HCl. Concentration of the solution (during reaction) to half its volume, yielded 25 in crystalline form. The ^{1}H NMR spectrum of the deoxyriboside 25 shows the anomeric proton as a doublet of doublets at δ5.0 (J = 3.5, 7.5 Hz). This pattern is typical for α-deoxynucleosides[28], and 25 was tentatively identified by ^{1}H NMR to be the α-anomer. The β-anomer, if present, could not be isolated, however, it is possible that the α-anomer crystallized from an equilibrium mixture of α- and β-anomers. Acetylation of crystalline deoxyriboside 25α, resulted in the formation of one major product, 26α, as indicated by a single spot on its thin-layer chromatogram. By closely monitoring the acetylation reaction with TLC, it was possible to terminate the acetylation reaction before any significant amount of N-acetylated product, 27, had formed. There was still a substantial amount of monoacetylated deoxyriboside present, but after purifying the reaction mixture by column chromatography, 26α was obtained as a highly viscous liquid which did not crystallize upon standing at room temperature for several days. After standing, TLC showed the appearance of two additional products, indicating that 26 was unstable.

When the methanol mother liquor from the reaction of deoxyribose with 2-aminothiazole was evaporated a highly viscous residue was obtained. Acetylation of this residue resulted in the formation of two major products with almost identical R_f values, believed to be a mixture of the α- and β-anomers of 26. However, we were unable to isolate the pure α- and β-anomers from this mixture.

Freshly prepared 26α was fused with malonate ester 12 to yield mesoionic 2-deoxyriboside 28 which was purified by column chromatography. The ^{1}H NMR spectrum of crystalline 28 shows the anomeric proton signal as a doublet of doublets at δ6.35 (J = 4, 7.8 Hz). This pattern is characteristic of the α-configuration of 2-deoxyribosides, as shown by comparison with published data[29]. The IR spectrum of 28α also has the typical carbonyl absorption band of the mesoionic base at 1650 cm^{-1} and 1700 cm^{-1}. The β-anomer of 28 did not crystallize from the methanolic

TABLE I. ^{1}H NMR Chemical Shift Values in δ and Coupling Constants (J) in Hz of Ribosides, Glucosides and 2-Deoxyribosides

Compound	thiazole-H	6-H	-CH$_2$- (J)	CH$_3$- (J)	1'-H (J)	2'-; 3'-; 4'-; 5'-; 6'-H (not specified)	acetyl CH$_3$-
10 ^{c}	7.2, 6.6 d (3.5)	-	-	-	6.3 br	5.6 t (4); 5.2 d (4); 4.0 m; 3.7 m	2.2; 2.1; 2.0 s
11 ^{c}	7.6, 7.2 d (3.5)	-	-	-	6.2 d (6)	5.6 t (3.5); 5.3 d (3); 4.1 m; 3.9 m	2.2; 2.05; 2.0 s
14α ^{c}	8.2, 7.2 d (5)	5.0 s	-	-	6.7 d (10)	5.8 t (2); 5.7 d (3); 5.5 d (2); 4.1 t (4)	2.2; 2.1; 2.0 s
14β ^{c}	8.1, 7.0 d (5)	5.0 s	-	-	6.3 s	5.6 m; 5.2 d (5); 4.15 dd (10)	2.1; 2.0; 1.9 s
15α ^{d}	8.15, 7.6 d (4.3)	4.7 s	-	-	6.3 d (9.2)	5.1 d (6); 4.8 t (3); 4.2-3.6 m's	-
15β ^{d}	8.0, 7.4 d (4.6)	4.7 s	-	-	6.0 s	5.1 t (4); 4.2-3.7 m's	-
16α ^{c}	8.2, 7.0 d (5)	-	2.5 q (5.5)	1.1 t (7)	6.8 d (10)	5.7 t (2); 5.5 d (3); 5.4 d (3); 4.0 m	2.2; 2.0; 1.9 s
16β ^{c}	8.2, 7.0 d (5)	-	2.5 q (5.5)	1.1 t (7)	6.4 s	5.7 t (2); 5.5 d (3); 5.4 d (3); 4.0 m	2.2; 2.0; 1.9 s
17α ^{d}	8.1, 7.5 d (5)	-	2.3 q (5)	1.0 t (7)	6.35 d (9)	5.0 d (3); 4.8-2.5 m's	-
17β ^{d}	8.15, 7.4 d (5)	-	2.2 q (5)	1.1 t (7)	6.0 s	5.2 m; 4.1-2.5 m's	-
21α ^{c}	8.2, 7.0 d (4.4)	5.1 s	-	-	6.7 s	5.2 s; 5.05 m; 4.3 m	2.2; 2.1; 1.9 s
21β ^{c}	8.2, 7.1 d (4.4)	5.0 s	-	-	6.5 d (10)	5.2 m; 5.15 m; 4.2 m	-
22α ^{d}	8.1; 7.4 d (5)	4.7 s	-	-	6.5 d (2)	5.4 t (4); 4.6-3.2 m's	2.15; 2.1; 2.0; 1.95 s
22β ^{d}	8.15, 7.5 d (5)	4.65 s	-	-	6.0 d (9.2)	5.35 m; 4.6-3.0 m's	-
23β ^{c}	8.2; 7.0 d (4.3)	-	2.5 q (5)	1.0 t (7)	6.6 dd (7)	5.4 dd (3); 5.1 m; 4.4-4.0 m's	1.95; 1.9; 1.85; 1.8 s
24β ^{d}	8.15, 7.5 d (5)	-	2.3 q (5)	1.0 t (7)	6.1 d (9.1)	5.2 m; 4.6 t (3); 4.0-3.4 m's	-
25α ^{d}	7.1, 6.75 d (5)	-	-	-	5.0 q (3.5, 7.5)	4.95 d (5); 4.5 d (4); 3.5 m; 2.55 m	-
28α ^{c}	8.2, 7.15 d (4.9)	5.0 s	-	-	6.35 dd (4, 7.8)	5.2 m; 4.3 d (2), 3.8 d (1.5)	2.2; 2.0 s
29α ^{d}	8.1, 7.5 d (5)	4.65 s	-	-	6.1 dd (3, 7)	4.8 m; 3.9-3.6 m's	-

c = CDCl$_3$; d = DMSO $_{d-6}$

mother liquor upon standing at room temperature for four weeks, however, the ^{1}H NMR spectrum of the residual from evaporation of the mother liquor indicates the presence of the β-anomer in the appearance of overlapping anomeric signals at δ6.3-6.6.

Deprotection of 28α was accomplished with methanolic dimethylamine, and deprotected nucleoside 29α crystallized upon trituration of the concentrated methanolic solution with ether.

Proton magnetic resonance shift values and coupling constants (J) of ribosides, glucosides, and 2-deoxyribosides are summarized in Table I. No specific assignments for sugar protons 2' to 5' (6') were attempted due to several overlapping signals, making any assignment questionable.

The deprotected mesoionic nucleosides are readily soluble in water, they can be recrystallized from low-molecular weight alcohols, and they do not appear to hydrolyze readily. The possibility of preparing mesoionic nucleosides has been demonstrated, and the way is now open for the design and synthesis of potentially useful mesoionic nucleosides.

EXPERIMENTAL SECTION

Infrared spectra were obtained on a Perkin-Elmer 283 spectrophotometer as KBr disks. Proton magnetic resonance spectra (^{1}H NMR) and carbon-13 magnetic resonance spectra (^{13}C NMR) were recorded on a JEOL FX 90 Q Fourier Transform Spectrometer. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were measured using a Finnigan 4000 GC-MS data system; UV spectra were determined with a Beckman Acta M VII spectrophotometer, results are expressed λ_{max} in nanometers (ε). Optical rotation was measured on a Perkin-Elmer 141 polarimeter.

All melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia; the C,H,N analyses of all the protected and deprotected mesoionic nucleosides agrees with the calculated value within ±0.4%, except compounds 22 (0.5% C). Mass spectrometric analysis of the prepared nucleosides indicate the correct molecular weights. Deoxyriboside 25α did not display a molecular ion peak but the fragmentation pattern agreed with the assigned structure.

Column chromatographic separations were performed on activated silica gel, mesh size 60 - 200, Davison Chemical Corp., Baltimore, Maryland, with columns of length 55 cm, inner diameter 2 cm, containing 55 g silica gel, or length 110 cm, inner diameter 2 cm, containing 100 g silica gel. Thin-layer chromatography was performed on thin-layer chromatography plates, precoated with silica gel GHLF, thickness 250 microns, Analtech, Newark, Delaware. Solvents for chromatographic separations were of reagent grade. The visualization of products in thin-layer chromatograms was accomplished by UV absorbance, followed by charring with 40% H_2SO_4.

The 2-aminothiazole was purified by sublimation prior to use; all other starting materials were used without further purification.

2-(D-Ribofuranosylamino)thiazole (9)

D-ribose (5) (7.50 g, 0.05 mol) and 2-aminothiazole (6) (5.50 g, 0.555 mol) were dissolved in methanol (10 mL) which contained conc. HCl (0.25 mL). Warming on a steam bath for 5 minutes afforded a clear, amber solution. Heating was continued until most of the methanol had evaporated. The highly viscous residue was dissolved in water (50 mL), and the aqueous phase was extracted with four 20 mL portions of ethyl acetate to remove unreacted 6 from the reaction mixture. The aqueous solution was concentrated under reduced pressure, and the resulting syrup was dried by azeotropic distillation with benzene. Evaporation of benzene left 9 as a foamy yellow solid, yield 10.6 g (91%), melting range, 110-135°C, R_f 0.58 (methanol); UV max (MeOH): 255 nm (ε 8200).

This material was acylated without further purification.

2-(D-Glucopyranosylamino)thiazole (18)

D-glucose (7) (18.00 g, 0.1 mol) and 2-aminothiazole (6) (10.00 g, 0.1 mol) were heated in refluxing methanol (30 mL) which contained conc. HCl (0.4 mL). After six hours, the reaction mixture was cooled, and unreacted glucose (0.50 g) was collected by filtration. The filtrate was concentrated to half its volume, and purified by column chromatography (110 cm column, 100 g silica gel), first with 9:1 ethyl acetate/methanol as eluent, then with 1:1 ethyl acetate/methanol. The fraction containing 18 was evaporated to dryness to afford semi-crystalline 18 19.80 g (76.5%); R_f 0.55 (methanol); lit. mp^{25} 166-168°C.

Semi-crystalline 18 was acetylated without further purification.

2-(D-2-Deoxyribofuranosylamino)thiazole (25)

D-2-deoxyribose 8 (4.00 g, 0.03 mol) and 2-aminothiazole (6) (3.00 g, 0.03 mol) were heated in methanol (6 mL) containing conc. HCl (0.1 mL). The solvent was evaporated with heating until the solution was concentrated to half its volume. Upon standing at 0°C for several hours, compound 25 crystallized as fine needles. The precipitate was collected by filtration; the filtrate was concentrated by evaporation, and additional product was obtained. The combined precipitate was recrystallized from 2:1 methanol/2-propanol to give 3.45 g (53%) of 25. mp 167-168°C. R_f 0.53 (methanol); MS m/e (relative intensity) 216 (M^+, 21), 99 (100).

Anal Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found: C, 44.30; H, 5.62; N, 12.88.

2-(2',3',5'-Tri-O-acetyl-D-ribofuranosylamino)thiazole (10) and 2-(N^2-Acetyl-2',3',5'-tri-O-acetyl-D-ribofuranosylamino)thiazole (11)

2-(D-ribofuranosylamino)thiazole (9) (10.00 g, 0.043 mol) was stirred initially at 10°C in a mixture of triethylamine (50 mL, 0.35 mol) and acetic anhydride (50 mL, 0.35 mol) until a clear solution was obtained (2 hours). The temperature was kept at 15-18°C until TLC monitoring (ethyl acetate) indicated the disappearance of starting material. The reaction mixture was diluted with chloroform (50 mL), washed twice with water (100 mL), then with 5% sodium bicarbonate solution (50 mL). The organic phase was dried ($MgSO_4$), and the solvent was removed under reduced pressure. TLC (ethyl acetate) showed the presence of 10, R_f 0.68 (ethyl acetate), and 11, R_f 0.77 (ethyl acetate).

Quantitative separation of 10 and 11 was achieved by repeated column separation (column 110 cm, 100 g silica gel, flow rate 10 ml/hour) with ethyl acetate as eluent. After evaporating the solvent under reduced pressure, semi-crystalline 10 and 11 were obtained.

Compound 11 was recrystallized from 2-propanol to yield 4.20 g (24%) of an anomeric mixture, mp 135°C. IR 1710 cm^{-1} (amide C=O), 1750 cm^{-1} (ester C=O); ^{13}C NMR ($CDCl_3$) ppm 172 (1 C=O), 169 (1 C=O), 168 (1 C=O), 167 (1 C=O), 156 (1 C=N), 140 (1 thiazole C), 122 (1 thiazole C), 78 (1 ribose C), 68 (1 ribose C), 66 (1 ribose C), 65 (1 ribose C), 64 (1 ribose C), 23 (1 methyl C), 20 (1 methyl C), 19.5 (2 methyl C). MS m/e (relative intensity) 400 (M^+, 1), 259 (100); UV max (MeOH): 255 nm (ϵ 5500).

Anal Calcd for $C_{16}H_{20}N_2O_8S$: C, 47.99; H, 5.03; N, 6.99. Found: C, 47.93; H, 5.08; N, 6.95.

Crystallization from methanol gave 4.80 g (31.5%) of 10, mp 164-165°C; IR 1750 cm^{-1} (ester C=O); MS m/e (relative intensity) 358 (M^+, 4), 97 (100); UV max (MeOH): 255 nm (ε 6800).

Anal Calcd for $C_{14}H_{18}N_2O_7S$: C, 46.92; H, 5.06; N, 7.82. Found: C, 46.70; H, 5.06; N, 7.76.

2-(2',3',4',6'-Tetra-O-acetyl-D-glucopyranosylamino)thiazole (19)

Compound 18 (15.00 g, 0.057 mol) was stirred at room temperature in a mixture of triethylamine (75 mL, 0.52 mol) and acetic anhydride (75 mL, 0.8 mol) for six hours. The dark solution was poured into 5% sodium bicarbonate solution (400 mL), and the organic material was extracted twice with ethyl acetate (100 mL), washed with water (200 mL) and dried ($MgSO_4$). TLC (ethyl acetate) showed the presence of two major products, R_f 0.72 and R_f 0.65. Column separation, identical to the procedure used for the separation of compounds 10 and 11, was performed to obtain an anomeric mixture of the tetra-O-acetylated glucoside 19. Yield: 2.40 g (9.8%); mp 145-150°C; lit.[25] mp 153-157°C (R_f 0.65; ethyl acetate).

Product 19 was employed without further purification to prepare 21 and 23. The product with R_f 0.72, believed to be the peracylated glucoside 20 was not characterized because of difficulties in purification.

2-(3',5'-Di-O-acetyl-D-2-deoxyribofuranosylamino)thiazole (26)

Deoxyriboside (25) (1.70 g, 8 mmol) was stirred at room temperature in triethylamine (10 mL, 70 mmol) and acetic anhydride (10 mL, 100 mmol) until all the solid had dissolved (20 minutes). When TLC monitoring indicated the first appearance of peracylated product 27 (R_f 0.72, ethyl acetate), chloroform (40 ml) was added to the reaction mixture. The organic phase was washed with water twice (80 mL), followed by 5% sodium bicarbonate solution (50 mL). The chloroform layer was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure to yield 26 as an oily product. Crude 26 was purified by column chromatography (short column, 50 g silica gel, ethyl acetate 80 ml/hour).

Compound 26 was obtained as a yellow liquid: 1.20 g (41%). TLC determination (ethyl acetate) of product 26 showed the presence of two compounds with R_f values 0.61 and 0.58 (ethyl acetate), believed to be the α- and β-anomers. However, the product did not crystallize.

The anomeric mixture was employed for the synthesis of 28 without further purification.

Anhydro-6-ethyl-8-(2',3',5'-tri-O-acetyl-D-ribofuranosyl)-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (16)

Bis(2,4,6-trichlorophenyl)ethyl malonate[30] (13) (1.40 g, 2.9 mmol) and 2-(2',3',5'-tri-O-acetyl-D-ribofuranosylamino)thiazole (10) (1.00 g, 2.8 mmol) were heated in an oil bath at 160°C for three minutes. A slow stream of nitrogen was passed over the reaction mixture to aid in the removal of 2,4,6-trichlorophenol. After cooling, the resultant syrup was crystallized by trituration with anhydrous ether and the resultant crude product 16 was collected by filtration. TLC (ethyl acetate) indicated the presence of the α-anomer, R_f 0.22, and the β-anomer, R_f 0.10, in approximately equal amounts.

Purification and separation of the anomers was achieved by column chromatography (column 55 cm, 55 g silica gel) with ethyl acetate as eluent to remove unreacted malonate ester 13, followed by a 1:1 ethyl acetate/methanol mixture to elute 16α and 16β. The fractions containing 16α and 16β were concentrated to dryness under reduced pressure, and both residues were recrystallized from absolute ethanol.

Yield of 16α: 590 mg (45%); mp 255-256°C; IR 1620 cm^{-1} (C^7=O, s), 1690 cm^{-1} (C^5=O, m), 1760 cm^{-1} (ester C=O); MS m/e (relative intensity) 454 (M^+, 4.4), 97 (100); UV max (MeOH) 246 nm (ε 27400), 275 nm (ε 3800).

Yield of 16β: 553 mg (42%); mp 243-244°C; IR carbonyl stretches were identical to the α-anomer carbonyl stretches; the MS spectrum and the ^1H NMR ($CDCl_3$) spectrum were identical to 16α, except for the anomeric signal at δ 6.4 (1H, s, H-1').

Anal Calcd for $C_{19}H_{22}N_2O_9S$: C, 50.22; H, 4.88; N, 6.16. Found: C, 50.08; H, 4.91; N, 6.13.

Anhydro-8-(2',3',5'-tri-O-acetyl-D-ribofuranosyl)-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (14)

Bis(2,4,6-trichlorophenyl) malonate[30] (12) (2.10 g, 4.5 mmol) and 2-(2',3',5'-tri-O-acetyl-D-ribofuranosylamino)thiazole (10) (1.60 g, 4.4 mmol) were fused by following the procedure employed for the preparation of 16. Column separation with ethyl acetate afforded 820 mg (43%) of 14α, mp 232-234°C (from 2-propanol) and 900 mg (47%) 14β, mp 236-238°C (from 2-propanol); 14α: IR, 1650 cm^{-1} (C^7=O, s), 1700 cm^{-1} (C^5=O, m), 1760 cm^{-1} (ester C=O); MS m/e (relative intensity) 426 (M^+, 1), 97 (100); UV max (MeOH) 242 nm (ε 28000). IR carbonyl stretches and the mass spectrum were identical to 14β.

14β: MS m/e (relative intensity) 426 (M^+, 2), 97 (100).

Anal. Calcd for $C_{17}H_{18}N_2O_9S$: C, 47.88; H, 4.25; N, 6.57. Found: C, 47.67; H, 4.30; N, 6.53.

Anhydro-6-ethyl-8-(2',3',4',6'-tetra-O-acetyl-β-D-glucopyranosyl)-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (23β)

A mixture of bis (2,4,6-trichlorophenyl)ethyl malonate (13) (500 mg, 1 mmol) and tetra-O-acetyl-glucosylaminothiazole (19) (400 mg, 0.9 mmol) was heated at 160°C for 5 minutes to yield predominantly the β-anomer of 23 (R_f 0.21; ethyl acetate), and a very small amount of the α-anomer (R_f 0.09; ethyl acetate), after trituration with anhydrous ether.

Upon purification by column chromatography with 4:1 ethyl acetate/methanol, 105 mg (23%) of the β-anomer was obtained, mp 242°C after recrystallization from 2-propanol. IR 1630 cm^{-1} (C^7=O, s), 1690 cm^{-1} (C^5=O, m), 1755 cm^{-1} (ester C=O, s), 3400-3600 cm^{-1} (O-H, m); MS m/e (relative intensity) 526 (M^+, 0.1), 57 (100).

Anal. Calcd. for $C_{22}H_{26}N_2O_{11}S \cdot H_2O$: C, 48.52; H, 5.18; N, 5.14. Found: C, 48.91; H, 4.85; N, 5.18.

Heating 23 at 65°C under vacuum for 24 hours removed the water of crystallization, mp 242°C.

Anal. Calcd. for $C_{22}H_{26}N_2O_{11}S$: C, 50.18; H, 4.97; N, 5.31. Found: C, 49.79; H, 4.77; N, 5.05.

The 23α anomer could not be isolated in sufficient quantity for characterization.

Anhydro-8-(2',3',4',6'-tetra-O-acetyl-D-glucopyranosyl)-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (21)

Malonate ester (12) (460 mg, 1 mmol) and acetylated glucosylaminothiazole (19) (400 mg, 0.9 mmol) were heated at 160°C for 5 minutes. TLC indicated the formation of the β-anomer (R_f 0.28; ethyl acetate) and the α-anomer (R_f 0.09; ethyl acetate). Column separation (4:1 ethyl acetate-methanol) afforded 21α: 40 mg (8%), mp 220°C (from ethanol) and 21β: 120 mg (24%), mp 226-227°C (from ethanol). 21α and β: IR 1650 cm^{-1}

(C^7=O, s), 1700 cm^{-1} (C^5=O, m), 1755 cm^{-1} (ester C=O, s), 3400-3600 cm^{-1} (O-H, m). Elemental analysis was performed on the hydrate of 21β. Insufficient quantity of 21α for elemental analysis.

Anal. Calcd. for $C_{20}H_{22}N_2O_{11}S \cdot H_2O$: C, 46.51; H, 4.68; N, 5.41. Found: C, 46.50; H, 4.68; N, 5.41.

Anhydro-8-(3',5'-diacetyl-D-2'-deoxyribofuranosyl)-5-hydroxy-7-oxothiazolo-[3,2-a]pyrimidinium hydroxide (28)

Crude 26 (850 mg, 3.9 mmol) and malonate ester 12 (1.85 g, 4 mmol) were heated at 160°C for 2 minutes. Upon cooling, the semi-crystalline solid formed was dissolved in chloroform (5 mL) and added to anhydrous ether (50 mL) to precipitate 28. The precipitate was collected by filtration and redissolved in chloroform (5 mL). The chloroform solution was subjected to column chromatographic separation, first with ethyl acetate to elute unreacted starting materials 12 and 26, followed by elution with 4:1 ethyl acetate/methanol to elute 28. The fraction containing 28 was concentrated to an oil, and crystals were obtained upon trituration with anhydrous ether. Crystallization from methanol gave 28: 1.05 g (73%), mp 160-168°C.

TLC indicated the presence of the α- and the β-anomer; however, the anomers could not be separated by column chromatography due to nearly identical R_f values (R_f 0.13; ethyl acetate). Upon fractional recrystallization from methanol, the 28α was obtained, yield 360 mg (25%); mp 185-7°C; IR 1650 cm^{-1} (C^7=O, s), 1700 cm^{-1} (C^5=O, m), 1750 (ester C=O, s).

Anal. Calcd. for $C_{15}H_{16}O_7N_2S \cdot H_2O$: C, 46.62; H, 4.69; N, 7.25; Found: C, 46.60; H, 4.72; N, 7.24.

The pure β-anomer of 28 was not obtained.

Anhydro-6-ethyl-8-α-D-ribofuranosyl-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (17α)

The protected riboside 16α (650 mg, 1.43 mmol) was dissolved in anhydrous methanol (50 mL), then conc. ammonia (50 μL) was added. Upon standing at room temperature for 18 hours, TLC indicated complete removal of acetyl groups (R_f 0; ethyl acetate), (R_f 0.53; methanol). The solution was concentrated under reduced pressure and 17α was obtained as white crystals from 1:1 methanol/2-propanol: 400 mg (85%), mp 185-186°C. IR 1630 cm^{-1} (C^7=O, s), 1690 cm^{-1} (C^5=O, m), 3200-3600 (O-H, s);

MS m/e (relative intensity) 328 (M^+, 23); 198 (100); UV max (MeOH): 242 nm (ε 27200), 246 nm (ε 25400).

Anal. Calcd. for $C_{13}H_{16}N_2O_6S$: C, 47.55; H, 4.91; N, 8.53. Found: C, 47.30; H, 4.98; N, 8.48.

Anhydro-6-ethyl-8-β-D-ribofuranosyl-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (17β)

The protected riboside 16β (550 mg, 1.21 mmol) was dissolved in methanol (20 mL), then dimethylamine (60 µL) was added. Upon standing at room temperature for 100 hours the acetyl groups were completely removed. The solution was concentrated under reduced pressure, and 17β was obtained as faint yellow crystals, yield 390 mg (98%), mp 194-198°C (from aqueous methanol). IR carbonyl stretches at 1630 and 1690 cm^{-1} were identical to the ones of compound 17α.

Anal. Calcd. for $C_{13}H_{16}N_2O_6S$: C, 47.55; H, 4.91; N, 8.53. Found: C, 47.88; H, 4.60; N, 8.28.

Anhydro-8-α-D-ribofuranosyl-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (15α)

Protected riboside 14α (200 mg, 0.47 mmol) was dissolved in anhydrous methanol (20 mL), then dimethylamine (20 µL) was added. The solution was stirred for 15 hours at room temperature. TLC indicated complete deprotection (R_f 0.0; ethyl acetate), (R_f 0.51; methanol). Product 15α crystallized after standing at 0°C for several hours. The white, needle-like crystals were collected by filtration to afford 132 mg (94% of 15α, mp 205-206°C (from methanol). IR 1630 cm^{-1} (C^7=O, s), 1690 cm^{-1} (C^5=O, m), 3200-3600 cm^{-1} (O-H, s); MS m/e (relative intensity) 300 (M^+, 0.2), 107 (100); UV max (MeOH) 242 nm (ε 27500), 275 nm (ε 3000); $[a]_D^{20}$ 290° (c 1.5 in MeOH).

Anal. Calcd. for $C_{11}H_{12}N_2O_6S$: C, 44.00; H, 4.03, N, 9.32. Found: C, 43.84; H, 4.07; N, 9.28.

Anhydro-8-β-D-ribofuranosyl-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (15β)

To a solution of 14β (220 mg, 0.52 mmol) in methanol (25 mL) dimethylamine (25 µL) was added, and the solution was stirred at room temperature for 30 hours. Product precipitated during deprotection and was collected by filtration to yield 110 m of 15β. From the mother liquor an additional 40 mg of product could be isolated to give a total of 150 mg (96%) of 15β, mp 221°C (from methanol). IR 1650 cm^{-1} (shoulder at 1630 cm^{-1}, C^7=O, s), 1670 cm^{-1}, 1680 cm^{-1} (split peak, C^5=O, m), 3200-3600 cm^{-1} (O-H, s); MS m/e (relative intensity) 300 (M^+, 0.8), 69 (100); UV max (MeOH): 242 nm (ε 28400), 275 nm (ε 3200); $[\alpha]_D^{20}$: -295° (c 1.5 in MeOH).

Anal. Calcd. for $C_{11}H_{12}N_2O_6S$: C, 44.00; H, 4.03; N, 9.32. Found: C, 44.10; H, 4.05; N, 9.33.

Anhydro-6-ethyl-8-β-D-glucopyranosyl-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (24β)

Protected glucoside 23β (350 mg, 0.67 mmol) was dissolved in 100:1 methanol/conc. ammonia (35 mL) and allowed to stand at room temperature for 40 hours; TLC indicated complete deprotection (R_f 0.0; ethyl acetate), (R_f 0.70; methanol). The solvent was evaporated under reduced pressure, and the white, crystalline residue was recrystallized from water to yield 85 mg (35%) 24β, mp 229-230°C. IR 1630 cm^{-1} (C^7=O, s), 1660 cm^{-1}, 1680 cm^{-1} (split peak, C^5=O, m), 3200-3600 (O-H, s); MS m/e (relative intensity) 358 (M^+, 0.5), 100 (100).

Anal. Calcd. for $C_{14}H_{18}N_2O_7S \cdot H_2O$: C, 44.67; H, 5.35; N, 7.44; Found: C, 44.70; H, 5.37; N, 7.43.

Anhydro-8-α-D-glucopyranosyl-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (22α)

Compound 21α (40 mg, 0.08 mmol) was dissolved in 50:1 absolute methanol/dimethylamine (10 mL). After standing at room temperature for 40 hours, deprotection was complete (R_f 0.0; ethyl acetate), (R_f 0.44; methanol). The solvent was evaporated under reduced pressure, and the crystalline residue was recrystallized from methanol to yield 6 mg (23%) of 22α, mp 246-248°C (from methanol). IR 1650-1660 cm^{-1} (C=O, broad), 3200-3600 (O-H, s).

Anhydro-8-β-D-glucopyranosyl-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (22β)

Protected glucoside 21β (120 mg, 0.24 mmol) was dissolved in 50:1 absolute methanol/dimethylamine (26 mL). After standing at room temperature for 18 hours the deprotected nucleoside 22β precipitated as white crystals. The product was collected by filtration to yield 65 mg (82%)

of 22β, mp 258-262°C (from methanol). IR 1650 cm^{-1} (C^7=O, broad), 1680 cm^{-1} (C^5=O, weak shoulder), 3200-3600 cm^{-1} (O-H, s); MS m/e (relative intensity), 330 (M^+, 0.5), 278 (98), 99 (100).

Anal. Calcd. for $C_{12}H_{14}N_7O_2S \cdot 1/2\ H_2O$: C, 42.50; H, 4.45; N, 8.25. Found: C, 43.00; H, 4.47; N, 7.91.

Anhydro-8-α-D-2'-deoxyribofuranosyl-5-hydroxy-7-oxothiazolo[3,2-a]pyrimidinium hydroxide (29α)

Deoxyriboside 28α (300 mg, 0.82 mmol) was dissolved in anhydrous methanol (30 mL), then dimethylamine (20 μL) was added. The solution was stirred at room temperature. After 20 hours deprotection was complete (R_f 0.0; ethyl acetate), (R_f 0.50; methanol). The solvent was evaporated under reduced pressure, and the resulting oil was triturated with anhydrous ether (10 mL) to afford crystalline 29α: 220 mg (95%), mp 167-169°C (from 2:1 methanol/ethyl acetate). IR 1630 cm^{-1} (C^7=O, split peak), 1690 cm^{-1} (C^5=O, split peak), 3200-3600 (O-H, s).

Anal. Calcd. for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.25; N, 9.85. Found: C, 46.46; H, 4.26; N, 9.82.

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