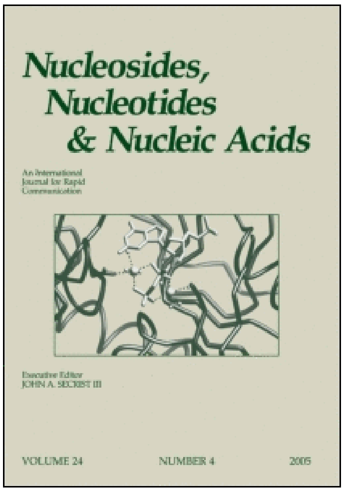

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Mesoionic Nucleosides 3: Studies on Mesoionic Imidazo [2,1-b]-1/3-thiazine Derivatives

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To cite this Article Glennon, Richard A. and Tejani, Shanaz M.(1984) 'Mesoionic Nucleosides 3: Studies on Mesoionic Imidazo [2,1-b]-1/3-thiazine Derivatives', Nucleosides, Nucleotides and Nucleic Acids, 3: 4, 389 — 399

To link to this Article: DOI: 10.1080/07328318408081277

URL: http://dx.doi.org/10.1080/07328318408081277

NUCLEOSIDES & NUCLEOTIDES, 3(4), 389-399 (1984)

MESOIONIC NUCLEOSIDES 3: STUDIES ON MESOIONIC IMIDAZO[2,1-b]-1,3-THIAZINE DERIVATIVES[1]

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ABSTRACT

Anhydro 1-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-5-hydroxy-7-oxoimidazo[2,1-b]-1,3-thiazinium hydroxide, a mesoionic imidazothiazine nucleoside, was prepared by the condensation of the appropriately acetylated ribofuranosyl imidazoline-2-thione with carbon suboxide. Although stable at or below 0°C, the product rapidly underwent ring-opening at room temperature to afford the precursor nucleoside. A possible scheme for this ring-opening reaction is proposed based on the results of a model study employing anhydro 1-methyl-5-hydroxy-7-oxoimidazo[2,1-b]-1,3-thiazinium hydroxide.

During the past few decades, a considerable effort has been directed toward the synthesis of modified nucleosides as potential chemotherapeutic agents. Mesoionic nucleosides constitute a novel class of modified nucleosides and we have recently reported the synthesis of several such compounds, e.g. the mesoionic thiazolopyrimidines 1[2]. We now wish to report the results of our attempts to prepare an isomer of 1, i.e. the imidazo[2,1-b]-thiazine nucleoside 2.

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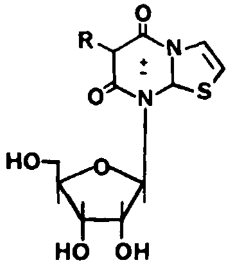

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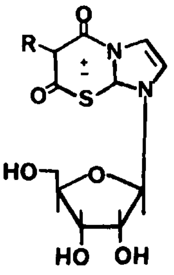

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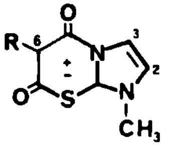
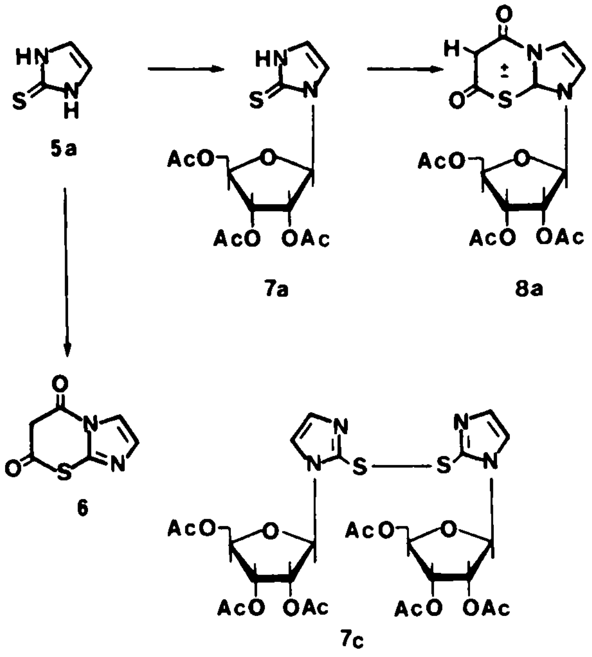


3a R= H
3b CH$_2$CH$_3$
3c CH$_2$C$_6$H$_5$
3d C$_6$H$_5$

Although a single example of a mesoionic imidazothiazine, anhydro 1-methyl-5-hydroxy-7-oxoimidazo[2,1-b]thiazinium hydroxide (3 a), is known,[3,4] its chemistry and properties have not been investigated. Thus, our approach was to explore several possible routes that might be useful for the synthesis of this ring system. This would then be followed by the preparation of derivatives of 2.

The ethyl substituted derivative 3b was prepared by the fusion of 1-methylimidazoline-2-thione (4) with bis 2,4,6-trichlorophenyl ethylmalonate at 160°C for 10 min. The white, crystalline 3b was obtained in 20% yield. Attempts to prepare 3a in a similar manner, using bis 2,4,6-trichlorophenyl malonate, failed. The use of various ($100-180^\circ$C) fusion temperatures or longer periods (up to 120 minutes) of heating resulted either in apparent decomposition or, at the lower fusion temperatures, isolation of 1-methylimidazoline-2-thione. Kappe and Gosler[5] have prepared mesoionic pyrimidothiazines using benzyl malonyl dichloride to effect cyclization. Consequently, 1-methylimidazoline-2-thione was allowed to react with benzyl malonyl dichloride at 20°C for 20 min to afford 3c. Again, attempts to prepare 3a in a similar manner, using malonyl dichloride, were unsuccessful. Although two methods were now at hand to prepare 6-alkyl derivatives of 3, neither method was useful for the synthesis of the desired 3a. We repeated our original synthesis of 3a using carbon suboxide; thus, carbon suboxide was bubbled into a benzene solution of 4 at room



Scheme I. Synthesis of nucleoside 8a, and the non-mesoionic imidazothiazine 6.

temperature to afford 3a in 88% yield.

For comparative purposes, 7-hydroxy-(5H)-imidazo[2,1-b]-1,3-thiazine-5-one (6), a related, non-mesoionic counterpart of 3a, was prepared by reaction of imidazoline-2-thione (5a) with carbon suboxide (Scheme I). Both 3a and 6 are white crystalline solids. Both compounds appear to be unstable to heat; repeated recrystallization served only to lower their respective melting points. The ^{1}H NMR spectra of 3a and 6, obtained in deuterated dimethyl sulfoxide, were quite similar. The C_2H and C_3H signals of 3a appeared as doublets at δ 7.75 and 8.0, while the corresponding doublets in the spectrum of 6 were at δ 7.9 and 8.2. The C_6H proton signal of 3a appeared at δ 4.80 as a singlet integrating for one proton; a corresponding singlet, again integrating for a single proton, was observed at δ 4.95 in the spectrum of 6. The IR (KBr) spectrum of 3a displayed pseudocarbonyl stretching bands at 1630 and 1685 cm^{-1}, while the carbonyl absorption for 6 appeared at 1620 and 1680 cm^{-1}. In addition, the spectrum of a well-dried sample of 6 revealed a broad band in the 2500-3200 cm^{-1} region which did not appear in the spectrum of 3a. The NMR spectrum of 6 also possessed a broad D_2O-exchangable signal at δ 11.75. Because the carbonyl band of various imidazo[2,1-b]-1,3-thiazine-5-ones and related compounds appears at between 1675-1700 cm^{-1}, and thiolactones normally absorb in the 1625 region,[6-8] the IR spectra of 3a and 6 are not unusual. However, both the infrared and ^{1}H NMR spectra of compound 6 suggest that the dioxo tautomer of 6 may exist in equilibrium with a hydroxy-oxo tautomer. We have previously reported similar results with a structurally related thiazolo[3,2-a]pyrimidine-5,7-dione.[9]

While this work was in progress, Coburn et al[10] reported the synthesis of 3b and 3c using the malonate condensation method (fusion at 125°C for 25 minutes), whereas Potts et al[11] prepared 3d by condensation of 1-methylimidazoline-2-thione with chlorocarbonyl phenylketene. In addition, Coburn et al[10] found that 3b and 3c were stable to light and air, and displayed no spectroscopic evidence of decomposition when exposed to 1N HCl for 24 h.

The synthesis of the mesoionic nucleosides required the preparation of 1-(2',3',5'-tri-0-acetyl-β-D-ribofuranosyl) imidazoline-2-thione (7a) and its 4,5-dihydro derivative 7b. Imidazoline-2-thione (5a) was fused with 1,2,3,5-tetra-0-acetyl-β-D-ribofuranose in the presence of freshly sublimed iodine, according to the procedure of Gosselin et al,[12] to afford a mixture of products. GC/Mass spectral analysis of the crude product revealed a mixture of nucleosides including what is presumably 7c (m/e = 714). The desired product, 7a, was isolated by column chromatography; although 7a was reported to be an oil,[12] we found this product to be a low-melting solid. Compound 7b was prepared from imidazolidine-2-thione (5b) in a manner similar to that used for the synthesis of 7a. All attempts to cyclize either

7a or 7b to the mesoionic nucleosides 8a and 8b, using either the malonate condensation method or the malonyl dichloride method, were, as anticipated, unsuccessful. Reaction of 7b with carbon suboxide also failed to yield a product. Bubbling carbon suboxide through a benzene solution of 7a, at room temperature, gave an immediate yellow precipitate. However, the presence of only one substance, 7a, could be identified by thin-layer chromatography. When the carbon suboxide condensation was performed at 0°C, a fluffy, white precipitate (crude product, mp 140-141°C) was obtained (Scheme I); all attempts to purify this compound by recrystallization or column chromatography were unsuccessful and resulted in the isolation of 7a as the only product. ^{1}H NMR and IR spectra were obtained on freshly prepared samples of 8a (Table 1). The ^{1}H NMR ($CDCl_3$) spectrum revealed the characteristic downfield shift of the imidazole proton signals, and the presence of the C_6H singlet. The IR (KBr) spectrum of 8a showed a strong pseudocarbonyl absorption at 1630 cm^{-1} (with a shoulder at 1680 cm^{-1}) in addition to the acetate band at 1750 cm^{-1}. However, ^{1}H NMR and IR spectra of a 24-h old sample of 8a were essentially identical to those obtained for 7a. Further investigation of 8a revealed that while it was stable for several months at -10°C (with exclusion of moisture), at room temperature 8a undergoes on apparent ring-opening reaction within a matter of several hours to afford 7a. This is supported by thin layer chromatography as well as by the above-mentioned spectral studies.

This unusual behavior prompted us to investigate the stability of 3a. 6-Alkyl derivatives of mesoionic thiazolopyrimidines (e.g. 1, R=alkyl) are known to be more resistant to hydrolysis than their corresponding 6-unsubstituted derivatives (although the latter are stable in solution at room temperature). And, although Coburn et al[10] have described the stability of 3b and 3c to hydrolytic conditions, neither they nor Potts et al[11] prepared any derivatives of 3 unsubstituted at the 6-position. Thin-layer chromatographic (tlc) analysis of a freshly prepared sample of 3a revealed homogeneity. However,

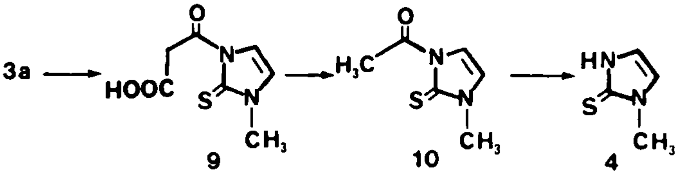
TABLE 1. Pertinent Spectral Data for Compounds 7a, 7b and 8a.

	^{1}H NMR (CDCl$_3$)					IR (KBr)	
	C_4H/C_5H	H_1'	CH_3	NH	C_6H	Ester C=O	Amide C=O
7a[a]	6.94/6.78	6.48(d)	2.08(s)	11.62(br)	-	-	-
7a	6.95(d)/6.80(d)	6.50(d)	2.10(s)	11.60(br)	-	1750	-
7b	3.75(t)[b]/1.25	6.50(d)	2.15(s)	11.20(br)	-	1740	-
8a	7.70(d)/7.50(d)	6.65(d)	2.20(s)	-	5.35(s)	1750	1630,1680(sh)

[a] Data from Gosselin et al.[12] [b] Superimposed over a broad multiplet.

similar analysis of a 3-week old solid sample of 3a revealed the presence of 3a, 4 and a third, unidentified material; two weeks later, this same sample contained only 4. A freshly prepared sample of 3a was dissolved in aqueous methanol, and the chromatographic pattern observed after 1 h of standing was identical to that of the 3-week old solid sample; complete conversion of 3a to 4 was noted after a total of 12 h. The product 4, was recovered and identified by mixture melting point determination using an authentic sample of 4. Similar behavior was seen for compound 6; however, this was not studied in detail.

Thioesters are more susceptible than amides to hydrolytic conditions;[13] thus, if ring-opening occurs, it might be expected to occur preferentially at C_7-S bond. This is consistent with the relative stability of imidazo[2,1-b]-1,3-thiazine-5-ones.[7] Ring-opening of 3a, to afford 4, might be expected to proceed as shown in Scheme II. The known hydrolytic susceptibility of N-acylimidazoles[14] makes this an attractive possibility. Compound 10, prepared by acetylation of 1-methylimidazoline-1-thione, was found to co-chromatograph (in four different solvent systems) with the unidentified material observed upon hydrolysis of 3a. Furthermore, 10 underwent hydrolysis to 4 after standing for several h in methanol at room temperature. It is likely that



Scheme II. Possible route of decomposition of the mesoionic imidazothiazine 3a.

the mesoionic nucleoside 8a undergoes a similar sort of ring-opening reaction to afford 7a. Future attempts to prepare such nucleosides will be directed toward the synthesis of 6-alkyl substituted derivatives.

EXPERIMENTAL SECTION

Infrared spectra (IR) were obtained on a Perkin-Elmer 257 spectrophotometer using KBr disks, and proton magnetic resonance (^{1}H NMR) spectra were recorded on a Perkin-Elmer R-24 spectrometer using tetramethylsilane as an internal standard. Mass spectra (70 eV) were obtained on a Finnigan 4000 Series GC/MS; a Beckman Model 25 spectrophotometer was used for recording ultraviolet (UV) spectra. All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were performed by Atlantic Microlab, Atlanta, GA. Column chromatographic separations were performed using glass columns and activated silica gel (mesh size 60-200) from Davison Chemical Corporation, Baltimore, MD. Thin-layer chromatographic analyses used pre-coated silica gel GHLF (250 micron thickness) glass plates (Analtech; Newark, Delaware); visualization was accomplished by ultraviolet absorbance followed by charring with 40% sulfuric acid.

Imidazoline-2-thione (5a) was prepared according to the procedure of Markwald,[15] whereas carbon suboxide[16-18] was prepared by the dropwise addition of dibromomalonyl dichloride[16] to a stirred mixture of zinc turnings and anhydrous ether at room temperature.

Anhydro 1-Methyl-5-hydroxy-7-oxoimidazo[2,1-b]-1,3-thiazinium Hydroxide (3a).

Carbon suboxide was generated and bubbled into a solution of 1-methylimidazoline-2-thione (4) (0.1 g, 0.8 mmol) in anhydrous benzene (10 mL), at room temperature, for a period of approximately 15 min. The white precipitate that formed was collected by filtration and was washed well with portions of anhydrous ether to afford 0.13 g (88%) of 3a, mp 188-189°C (lit.[3] mp 188-189°C); attempted recrystallizations resulted in lowered melting points. IR 1630 and 1680 cm^{-1} (C=O); ^1H NMR ($DMSO-d_6$): 8.0 (d, 1, arom H), 7.75 (d, 1, arom H), 4.80 (s, 1, C_6H), 3.65 (s, 3, CH_3); MS m/e 182 (M^+).

Anhydro 1-Methyl-6-ethyl-5-hydroxy-7-oxoimidazo[2,1-b]-1,3-thiazinium Hydroxide (3b)

Bis-(2,4,6-trichlorophenyl) ethylmalonate (0.43 g, 0.87 mmol) and 4 (0.1 g, 0.87 mmol) were heated neat at 160°C (oil bath temperature), under a slow stream of nitrogen, until a clear melt resulted (10 min). When cool, the residue was triturated with anhydrous ether (10 mL) until crystallization occurred. The crude product was collected by filtration and was recrystallized from ethyl acetate to yield 0.18 g (20%) of 3b as white crystals, mp 194-196°C (lit.[10] mp 194-195°C).

Anhydro 1-Methyl-6-benzyl-5-hydroxy-7-oxoimidazo[2,1-b]-1,3-thiazinium Hydroxide (3c)

Benzylmalonyl dichloride (0.25 g, 1.0 mmol) was added dropwise to a stirred suspension of 4 (0.1 g, 1.0 mmol) in chloroform (1.5 mL) at 20°C, under a nitrogen atmosphere. The reaction mixture was stirred for 20 min and the resultant white precipitate was collected by filtration. Recrystallization of the crude product from methanol afforded 0.06 g (22%) of 3c as white needles, mp 184-186°C (lit.[10] mp 185-186°C).

7-Hydroxy-(5H)-imidazo[2,1-b]-1,3-thiazine-5-one (6)

Carbon suboxide was slowly bubbled into a solution of 5a (0.1 g, 1 mmol) in acetonitrile (30 mL) for a period of approximately 30 min. At this time, the cream-colored solid was collected by filtration and washed with anhydrous ether to afford 0.12 g (71%) of crude 6, mp 170-175°C (d). Recrystallization was precluded by the thermal instability of 6. The crude product was suspended in acetonitrile (50 mL) and was stirred for 12 h; the product was again collected and washed well with anhydrous ether to yield a fine, white solid, mp 174-175°C (d). IR 1620 and 1680 cm^{-1} (C=O); ^1H NMR (DMSO-d_6): 8.2 (d, 1, arom H), 7.9 (d, 1, arom H), 4.95 (s, 1, C_6H).

Anal Calc for $C_6H_4N_2O_2S\cdot\frac{1}{4}H_2O$: C, 41.79, H, 2.48; N, 16.24. Found: C, 41.74; H, 2.59; N, 16.19.

1-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)imidazoline-2-thione (7a)

Compound 7a was prepared via the method of Gosselin et al;[12] however, column chromatography (see conditions described for 7b) of the crude product afforded an off-white solid product after evaporation of solvent and vacuum drying, mp 50-55°C. This product slowly absorbed moisture upon standing to yield an oil that was homogeneous and identical by thin-layer chromatography to the solid product. UV and MS data for 7a were consistent with that reported by Gosselin et al,[12] and portions of the ^1H NMR data are reproduced in Table 1 for comparison with that for 8a.

1-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-imidazolidine-2-thione (7b)

Compound 7b was prepared in essentially the same manner reported by Gosselin et al[12] for the synthesis of 7a. A dry, finely powdered mixture of imidazolidine-2-thione (5b; 1.0 g, 9.8 mmol), 1,2,3,5-tetra-O-acetyl-β-D-ribofuranose (3.3 g, 9.8 mmol) and twice-sublimed iodine (0.05 g) was fused for 20 min at 180°C in a pear-shaped flask under reduced pressure (55 mm Hg; water aspirator). Separation of the desired 7b was achieved by column chromatography (column 50 x 7 cm, 40 g silica gel) by first eluting with chlorform, and then with a 9:1 chlorform/acetone mixture. The fractions containing the desired compound were pooled and evaporated to dryness to afford a homogeneous oil. Continuous drying under high vacuum and reduced pressure resulted in 300 mg (8%) of a hygroscopic solid; MS, m/e 360 (M^+). See Table 1 for spectral data.

Anal Calc for $C_{14}H_{20}N_2O_7S$: C, 46.70; H, 5.60; N, 7.78. Found: C, 46.56; H, 5.70; N, 7.85.

Anhydro 1-(2',3',5'-Tri-O-acetyl-β-D-ribofuranosyl)-5-hydroxy-7-oxoimidazo[2,1-b]-1,3-thiazinium hydroxide (8a)

Carbon suboxide was bubbled into a solution of 7a (0.1 g, 0.27 mmol) in benzene (10 mL) at 0°C for a period of approximately 40 minutes. The white fluffy precipitate was collected by filtration, and was quickly washed with several 10-mL portions of cold (0°C) anhydrous ether to afford 0.08 g (66%) of 8a, mp 140-141°C. The product was stable for several months at -10°C, but rapidly decomposed at room temperature. See Table 1 for spectral data.

1-Acetyl-3-methylimidazoline-2-thione (10)

Acetic anhydride (1.0 g, 10 mmol) was added to a solution of 1-methylimidazoline-2-thione (4) (1.1 g, 10 mmol) in triethylamine (10 mL); the reaction mixture was heated at reflux for 2 h, and the solvent was then removed under reduced pressure. The resultant mass was dried under high vacuum for 12 h to afford a solid material. Purification of the compound was achieved by column chromatography (column 25 x 4 cm, 6 g silica gel) by first eluting with benzene, and then by a 1:1 benzene/ethyl acetate mixture to afford 0.4 g (25%) of 10 as a white solid, mp 70-72°C (lit[19] mp 72-74°C).

ACKNOWLEDGEMENT

This work was supported in part by a seed grant from the American Cancer Society and by an A. H. Robins Graduate Fellowship for SMT.

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Received February 1, 1984