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The preparation of the first examples of class II mesoionic bispurinones is described. Arylaminothiazole **3** is cyclized by condensation with bis(2,4,6-trichlorophenyl) methylmalonate to yield *anhydro*-3,3'-bis(6-methyl-8-aryl-5-hydroxy-7-oxothiazolo[3,2-*a*]pyrimidinium hydroxide).

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We have previously reported [1-5] the preparation of a number of mesoionic xanthenes and related compounds **1** and **2** for use in chemical, spectral and structure-activity studies. Two major classes of mesoionic purinones have been formulated and examined from a quantum chemical standpoint [6,7]. Those mesoionic purinones which may be envisioned as being derived from a five-membered mesoionic ring system have been termed class I mesoionic purinones [6] while those derived from a six-membered mesoionic ring system have been termed class II mesoionic purinones [7].

Although several class II mesoionic purinones have been previously prepared [3,4] to date, the synthesis of a class II mesoionic bispurinone has not been described. In this communication, we wish to report our preliminary results on the synthesis of the first such xanthine ring system.

Some mesoionic purinone analogs have demonstrated bacteriostatic activities and antifungal properties [8,9].

Several derivatives of **1** and **2** have recently been found to exhibit activity as inhibitors of adenosine-3',5'-monophosphate (cyclic AMP) phosphodiesterase (PDE) [3,10] similar to that of structurally related theophylline. This prompted us to explore the preparation of a series of mesoionic bispurinones **5** in order to investigate their chemical and spectral characteristics.

Compounds **5** were conveniently prepared by the thermal (160°) condensation of an arylaminothiazole **3** [11] with 2 equivalents of previously reported bis(2,4,6-trichlorophenyl) methylmalonate **4** [12] in a manner identical to that described for the synthesis of **1** [1]. Two new bithiazoles and four new mesoionic bispurinones were prepared as shown (Figure 1). The currently accepted nomenclature for mesoionic bispurinones of type **5a-d** is *anhydro*-3,3'-bis(6-methyl-8-aryl-5-hydroxy-7-oxothiazolo[3,2-*a*]pyrimidinium hydroxide). Reaction yields and some physical data for the compounds prepared are summarized in Table 1.

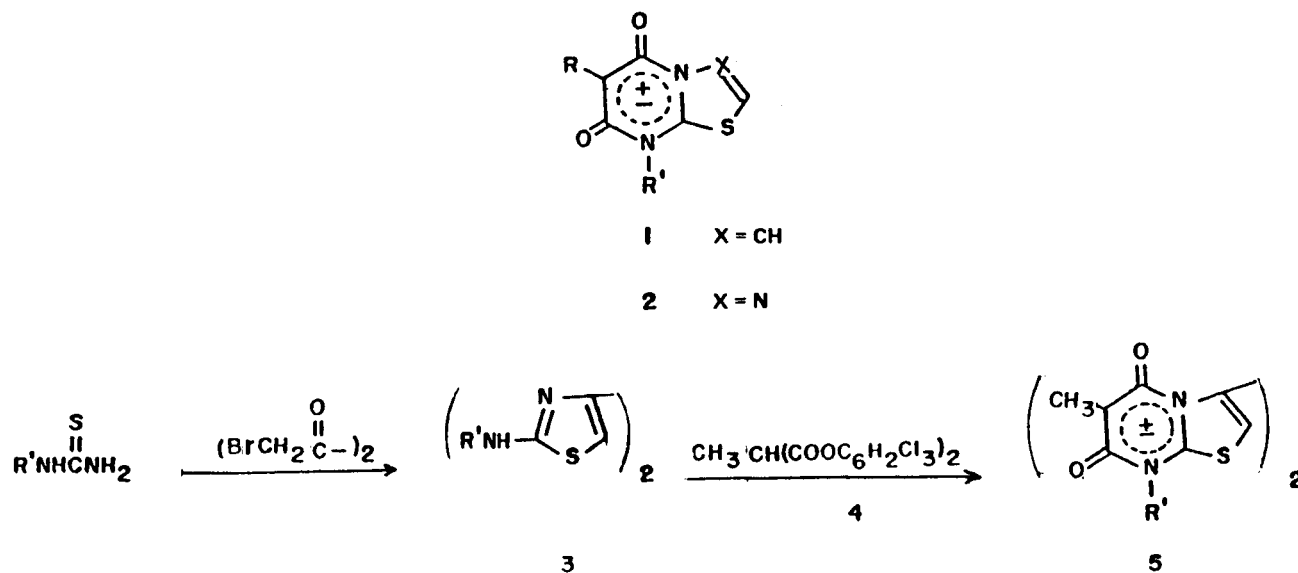


FIGURE 1.

Table I
Physical Properties of Bithiazoles **3a-d** and Mesoionic Bispirinones **5a-d**

Compound	R'	Yield %	Mp (°C)	Recrystallization Solvent [c]	ν N-H cm^{-1} [d]	ν C=O cm^{-1}	δ CH ₃ ppm [e]	δ (Thiazole-H and Aryl-H) ppm	MS m/e (%)	Formula	Analyses (%) Calcd./ (Found)
											C H N
3a	C ₆ H ₅	90	241-242 [a]	TP	3500	-	-	7.0-7.8 (12H, m)		C ₁₁ H ₁₄ N ₄ S ₂	- - -
3b	<i>p</i> -ClC ₆ H ₄	95	170-171	TP	3500	-	-	7.2-7.8 (10H, m)		C ₁₁ H ₁₁ Cl ₁ N ₄ S ₂	51.55 2.88 13.36 (51.39) (2.91) (13.31)
3c	<i>p</i> -CH ₃ C ₆ H ₄	80	238-240 [b]	TP	3500	-	2.3 (6H, s)	7.0-7.7 (10H, m)		C ₁₀ H ₁₀ N ₄ S ₂	- - -
3d	<i>p</i> -CH ₃ OC ₆ H ₄	88	258-260	TP	3500	-	3.8 (6H, s)	6.9-7.7 (10H, m)		C ₁₀ H ₁₁ N ₄ O ₂ S ₂	58.17 4.41 13.64 (58.46) (4.46) (13.60)
5a	C ₆ H ₅	95	356-358	TFA-E	-	1630	2.2 (6H, s)	7.2-7.8 (12H, m)	514 (M ⁺ , 3), 351 (25) 350 (48), 175 (15), 119 (100)	C ₂₂ H ₁₈ N ₄ O ₂ S ₂ ·H ₂ O	58.60 3.79 10.50 (58.65) (3.74) (10.43)
5b	<i>p</i> -ClC ₆ H ₄	70	345-346	TFA-E	-	1630	2.2 (6H, s)	7.4-7.8 (10H, m)	582 (M ⁺ , 5), 169 (10), 153 (100), 125 (25)	C ₂₂ H ₁₆ N ₄ O ₂ S ₂ Cl ₁ ·H ₂ O	51.91 3.01 9.30 (51.70) (2.80) (9.40)
5c	<i>p</i> -CH ₃ C ₆ H ₄	85	317-318	TFA-E	-	1650	2.2 (6H, s)	7.2-7.8 (10H, m)	542 (M ⁺ , 10) 189 (25), 149 (15), 134 (100), 118 (25), 104 (30)	C ₂₂ H ₂₂ N ₄ O ₂ S ₂ ·½H ₂ O	60.96 4.17 10.09 (60.55) (4.17) (10.09)
5d	<i>p</i> -CH ₃ OC ₆ H ₄	75	352-353	TFA-E	-	1670	2.2 (6H, s)	7.4-7.8 (10H, m)	574 (M ⁺ , 2), 205 (10), 150 (80), 149 (100), 134 (25), 106 (20)	C ₂₂ H ₂₂ N ₄ O ₂ S ₂	58.52 3.85 9.75 (58.55) (3.92) (9.73)

[a] Lit [11] mp 241-242°. [b] Lit [11] mp 238°. [c] Recrystallization Solvents: Tetrahydrofuran-Petroleum ether (TP), trifluoroacetic acid-ether (TFA-E). [d] Infrared spectra were recorded as potassium bromide disks. [e] ¹H nmr data of **3a-d**, **5a-d** were taken in DMSO-d₆ and TFA-d respectively relative to TMS; N-H protons are not included.

The 6-methyl-8-aryl derivatives of **5** were chosen for our initial studies because the products **5a-d** were obtained in the highest yields and purity. Attempts to prepare the 6,8-dimethyl and 6-unsubstituted derivatives of the bispurinones **5** did not give satisfactory results in preliminary experiments. Chromatographic purification was unsuccessful in separating the resulting complex mixtures from which any characterized substance was not isolated.

Structural assignments were based on spectral and elemental analyses [13]. The proton nuclear magnetic resonance (^1H nmr) and the infrared (ir) spectral properties of the bispurinones had many features in common with those of the bicyclic analogs. For example, the pseudocarbonyl stretching frequencies of **5a-d** (Table 1) occur in the carbonyl stretching region $1690\text{-}1630\text{ cm}^{-1}$ reported [3,4] for the bicyclic compounds **1** and **2**.

The relative insolubility of compounds **5a-d** in most organic solvents made purification difficult and marked a dramatic contrast from the bicyclic analogs **1** and **2** many of which are soluble in solvents such as acetone, acetonitrile, chloroform and ethanol. Out of necessity, the ^1H nmr data of **5a-d** were obtained using deuteriotrifluoroacetic acid (TFA-d) as a solvent while a mixture of TFA and petroleum ether was used as the recrystallization solvent.

The mesoionic bispurinones **5** were found to be higher melting than the bicyclic counterparts. A common characteristic of the mesoionic thiazolo[3,2-*a*]pyrimidine-5,7-diones **1** is the occurrence of two absorption maxima at 245 and 275 nm in their ultraviolet (uv) spectra [1,4]. In contrast, the bispurinones display 3-band absorbances at 204, 250 and 290 nm. This may indicate an appreciable electronic interaction between the two adjacent purinone nuclei in compound **5**. In addition, **5** is expected to exhibit resonance stabilization by extended conjugation. This is confirmed by the observed bathochromic shift. Similar bathochromic shift was observed in the uv spectrum of 3,3'-dibenzyl-4,4'-bissydnone when compared to that of isolated sydnone ring [14].

Studies on the biological activities of the mesoionic bispurinones described in this paper and other related compounds are in progress and will be reported elsewhere.

EXPERIMENTAL

General.

Melting points were obtained with a Thomas-Hoover apparatus and are uncorrected. The starting materials 1,4-dibromo-2,3-butanedione, *N*-phenylthiourea, *N*-(4-methoxyphenyl)thiourea [15a], *N*-(4-chlorophenyl)thiourea [15b] and *N*-(4-Tolyl)thiourea [15c] were obtained from either commercially available sources or made by standard literature procedures. Reagent grade solvents were used in all reactions and column chromatographic separations. The solvents were freshly distilled before use. Thin-layer chromatography (tlc) was performed on tlc plates precoated with silica gel 13181 (Eastman Kodak Co, Rochester, New York). The visualization of products in thin-layer chromatograms was accomplished by uv absorbance or iodine.

Infrared spectra (ir) were recorded as potassium bromide disks on a

Perkin-Elmer 283 spectrophotometer and an AEI MS-9 mass spectrometer was used for mass spectra. Proton magnetic resonance spectra (^1H nmr) were obtained with either a Varian T-60 or a JEOL FX90QII spectrometer. The concentration of the samples was approximately 35 mg/0.5 ml of dimethyl- d_6 sulfoxide (DMSO- d_6) or deuteriotrifluoroacetic acid as specified. All ^1H nmr spectra were obtained using 5 mm spinning tubes and signals were referenced to internal tetramethylsilane (TMS).

The ^1H nmr signals are designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad singlet. Ultraviolet spectra (uv) were recorded on a Beckman Acta MVII spectrophotometer using either spectrograde or purified solvents. Results are expressed as max in nanometers (nm).

Elemental analyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia.

Anhydro-3,3'-bis(6-methyl-8-aryl-5-hydroxy-7-oxothiazolo[3,2-*a*]pyrimidinium Hydroxide). General Procedure.

An intimate mixture of bis(2,4,6-trichlorophenyl) methylmalonate **4** (2.5 mmoles) and appropriate bithiazole **3** (1.2 mmoles) was heated neat at 160° , under a slow stream of nitrogen, until a clear melt resulted (10 minutes). When cool, the resultant gum was triturated with anhydrous diethyl ether and the solid product was collected by filtration. Recrystallization from trifluoroacetic acid-ether gave the desired compound **5**.

2,2'-*N,N'*-Diaryl-4,4'-bithiazole **3a-d**. General Procedure.

To a solution of 1,4-dibromo-2,3-butanedione (13 mmoles) in ethanol (250 ml) was added the appropriate arylthiourea [15] (26 mmoles) with stirring. The reaction mixture became a clear solution in about 15 minutes and was allowed to stir overnight at room temperature. The precipitated product was filtered off and recrystallized from tetrahydrofuran-petroleum ether. Melting points for compounds **3a** and **3c** were consistent with those reported [11] (Table 1).

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