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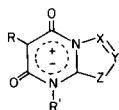
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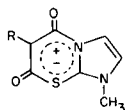
Several derivatives of mesoionic imidazo[1,2-*a*]pyrimidine-5,7-dione and 1,2,4-triazolo[1,5-*a*]pyrimidine-5,7-dione, two new examples of mesoionic xanthine ring systems, were prepared and characterized. These compounds were conveniently prepared by the condensation of bis-(2,4,6-trichlorophenyl) malonates with the appropriately substituted alkylaminoimidazole or 1,2,4-triazole.

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Thirty-six possible non-classical, *i.e.*, mesoionic, heterocyclic rings systems have been formulated that are both isoelectronic and isosteric with xanthine (1,2). These heterocycles have been designated as class II mesoionic xanthine analogs; we have previously synthesized four such ring systems, **1-4**, in order to investigate their chemical and biological properties (1-3). A positional isomer of **1**, structure **5**, has also been prepared (2).



- 1 X = Y = CH, Z = S
2 X = N, Y = CH, Z = S
3 X = CH, Y = N, Z = S
4 X = N, Y = CH, Z = O



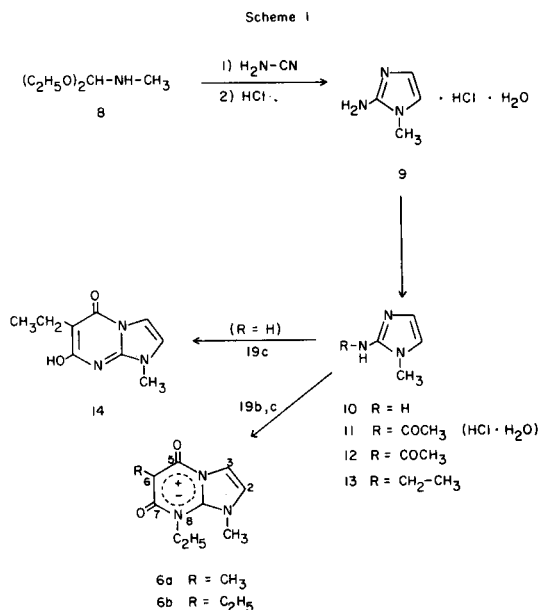
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Recently, we have found that derivatives of **1** and **2** possess activity, similar to that of theophylline, as inhibitors of adenosine-3',5'-monophosphate (cyclic AMP) phosphodiesterase (PDE) (4). Thus, it was of interest to explore the activity of mesoionic xanthine analogs which bear a greater structural similarity to theophylline, *i.e.*, examples of **1** and **2** where the sulfur atom has been replaced by an *N*-methyl group. We now wish to report the synthesis of two new members of the class II mesoionic xanthine series, namely, mesoionic imidazo[1,2-*a*]pyrimidine-5,7-diones, **6**, and mesoionic 1,2,4-triazolo[1,5-*a*]pyrimidine-5,7-diones, **7**.

Although 2-aminoimidazole was initially reported in 1919 (5), its 1-methyl derivative was not prepared for almost another forty years (6). 2-Amino-1-methylimidazole acetate has been prepared by the direct lithiation of 1-methylimidazole followed by treatment with phenyl azide in acetic acid (7). The method of Lawson (6), however, was found to be more convenient; aminoacetaldehyde diethylacetal was heated with cyanamide which, after warming with concentrated hydrochloric acid, afforded 2-amino-1-methylimidazole hydrochloride

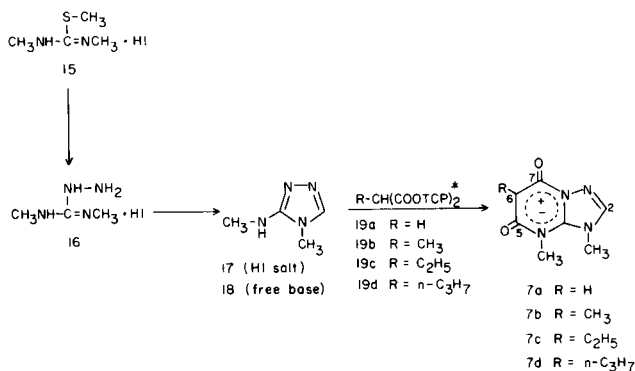
monohydrate (**9**). The free base **10** was prepared by treating the salt **9** with 3*N* sodium hydroxide; the white crystalline product darkened within several hours, however, and resulted in a dark red oil in less than twelve hours. Compound **9** was acetylated to give **11**. Again, the free base **12**, could be generated by treatment with dilute aqueous base. Lithium aluminum hydride reduction of **12** afforded the desired *N*-ethyl compound **13** in 80% yield. Like the unsubstituted amine, **13** darkened rapidly upon standing. Condensation of bis(2,4,6-trichlorophenyl) malonates with **13** gave the desired mesoionic compounds **6a** and **6b** while condensation with 2-amino-1-methylimidazole (**10**) gave the non-mesoionic compound **14**.

3-Methylamino-4-methyl-1,2,4-triazole hydroiodide was prepared according to the method of Kroger, *et al.*, (8). Cyclization of the aminoguanidine **16** proceeded in low yield; attempts to effect ring closure by refluxing **16** with triethylorthoformate were, however, unsuccessful. The



free base **18** was generated by treatment of an aqueous solution of **17** with potassium carbonate. Unlike the methylamino imidazole **10**, compound **18** was stable for an indefinite period of time. The mesoionic compounds **7a-7d** were prepared by condensation of **18** with the appropriate bis (2,4,6-trichlorophenyl) malonate.

Scheme 11



(* TCP = 2, 4, 6 - trichlorophenyl)

The spectral properties of both mesoionic ring systems are quite similar and, in addition, are similar to the spectral properties of **1** and **2**. The most dramatic difference in properties, in comparing **1** and **2** with **6** and **7** is that the latter possess considerable water solubility and are only slightly soluble in solvents such as chloroform or acetone. Out of necessity, proton magnetic resonance (nmr) data were obtained using deuterium oxide as solvent. Under these conditions, it was observed that the 2-position proton of **7** undergoes a slow deuterium oxide exchange; there is a complete disappearance of the 2-position proton signal within 48 hours.

Barlin and Batterham (9) have reported that protonation of imidazoles and 1,2,4-triazoles results in a downfield shift of C-H signals in the nmr spectra. They have attributed this shift to stabilization of the resulting cation via an amidinium-type resonance. This effect is clearly observed when the spectra of the free bases **10** and **18** are compared with the spectra of their salts **9** and **17**, respectively. This downfield shift is also quite pronounced for the ring C-H signals of the mesoionic compounds **6** and **7**. Therefore, in addition to achieving stability by extended conjugation, the mesoionic compounds **6** and **7** might also be expected to derive some stability from amidinium-type resonance.

In contrast to the mesoionic compounds **6**, the non-mesoionic analog **14** was insoluble in water and insoluble in most organic solvents. In addition to a broad carbonyl stretching band in the 1650 cm^{-1} region, the infrared spectrum of **14** displays a broad hydroxyl band in the 3000 cm^{-1} region suggesting that the dioxo compound exists in equilibrium with an enol tautomer. The nmr spectrum of

14 reveals a small but broad deuterium oxide-exchangeable signal at δ 4.30 which integrates for less than one proton. The behavior of this compound is quite reminiscent of that which we have recently reported for analogs of the non-mesoionic derivatives of **1** (10).

Mesoionic xanthine analogs **6a**, **6b**, and **7a-d** were assayed for ability to inhibit bovine heart cyclic AMP phosphodiesterase in the manner previously reported (4). None of these compounds showed interesting activity in this screen; a comparison of $I_{50}'s$ revealed that the most potent derivative, **7d** was six fold less potent than the standard inhibitor, theophylline.

EXPERIMENTAL

Proton magnetic resonance (nmr) spectra were obtained on a Hitachi Perkin-Elmer R-14 high resolution spectrometer; chemical shifts are reported relative to TMS when the solvent is deuterated dimethyl sulfoxide or deuterated chloroform, and relative to DSS when solvent is deuterium oxide. Infrared spectra were recorded on a Perkin-Elmer 283 spectrophotometer. Melting points were determined on a Thomas Hoover melting points apparatus and are uncorrected. Mass spectra were obtained using a Finnigan 4000-series GC/MS data system. Elemental analyses were performed by Atlantic Microlab, Atlanta, GA.

Anhydro-(1,6-Dimethyl-8-ethyl-5-hydroxy-7-oxoimidazo[1,2-*a*]pyrimidinium Hydroxide) (**6a**).

An intimate mixture of **13** (0.25 g., 2 mmoles) and bis(2,4,6-trichlorophenyl) methylmalonate (**19b**) (12) (0.95 g., 2 mmoles) was heated neat at 160° , under an atmosphere of nitrogen, until a clear melt resulted (3 minutes). When cool, the resultant gum was triturated with anhydrous ether to afford a crude solid product. Recrystallization from an ethanol-petroleum ether mixture gave 215 mg. (52%) of **6a** as small white crystals, m.p. $276\text{-}277^\circ$; ir (nujol): 1630 and 1680 (C=O) cm^{-1} ; nmr (deuterium oxide): δ 1.40 (t, 3H- CH_2CH_3), 1.85 (s, 3H, C- CH_3), 4.10 (s, 3H, N- CH_3), 4.40 (q, 2H, $-\text{CH}_2-$), 7.35 (d, 2H, imidazole protons); ms: *m/e* (relative intensity) 207 (53), 178 (45), 124 (40), 83 (100).

Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{N}_3\text{O}_2$: C, 57.96; H, 6.32; N, 20.28. Found: C, 57.70; H, 6.39; N, 20.15.

The following mesoionic compounds, **6b** and **7a-7d**, were all prepared in the same manner as **6a**, using the appropriate amine and malonate ester. The malonate esters **19a-c** were prepared by the method of Kappe and Lube (12).

Anhydro-(1-Methyl-6,8-diethyl-5-hydroxy-7-oxoimidazo[1,2-*a*]pyrimidinium Hydroxide) (**6b**).

Compound **6b** was obtained in 42% yield after recrystallization from ethanol, m.p. $250\text{-}251^\circ$; ir (nujol): 1645 and 1680 (C=O) cm^{-1} ; nmr (deuterium oxide): δ 1.08 (t, 3H, CH_3 of C-ethyl), 1.48 (t, 3H, CH_3 of N-ethyl), 2.38 (q, 2H, CH_2 of C-ethyl), 4.15 (s, 3H, N- CH_3), 4.40 (q, 2H, CH_2 of N-ethyl), 7.45 (d, 2H, imidazole protons); ms: *m/e* (relative intensity) 221 (29), 206 (100), 178 (87), 97 (50).

Anal. Calcd. for $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.65; H, 6.86; N, 18.94.

Anhydro-(3,4-Dimethyl-5-hydroxy-7-oxo-1,2,4-triazolo[1,5-*a*]pyridinium Hydroxide) (**7a**).

Compound **7a** was obtained as small yellow crystals in 70% yield after recrystallization from ethanol-ether, m.p. 220° dec.; ir (potassium bromide): 1660 , br band, (C=O) cm^{-1} ; ms: *m/e* (relative intensity) 180 (13), 112 (100).

Anal. Calcd. for $\text{C}_7\text{H}_8\text{N}_4\text{O}_2$: C, 46.66; H, 4.48; N, 31.10. Found: C, 46.47; H, 4.53; N, 30.96.

Anhydro-(3,4,6-Trimethyl-5-hydroxy-7-oxo-1,2,4-triazolo[1,5-*a*]pyrimidinium Hydroxide) (**7b**).

Compound **7b** was obtained as small white crystals in 62% yield after recrystallization from methanol, m.p. 291-292° dec.; ir (nujol): 1640 and 1680 (C=O) cm⁻¹; nmr (deuterium oxide): δ 1.80 (s, 3H, C-CH₃), 3.85 (s, 3H), 4.20 (s, 3H, N₃-CH₃; based on analogy to **6a** and **6b**), 8.60 (s, 1H, triazole proton); ms: m/e (relative intensity) 194 (43), 139 (41), 83 (100).

Anal. Calcd. for C₈H₁₀N₄O₂: C, 49.48; H, 5.19; N, 28.85. Found: C, 49.46; H, 5.21; N, 28.85.

Anhydro-(3,4-Dimethyl-6-ethyl-5-hydroxy-7-oxo-1,2,4-triazolo[1,5-*a*]pyrimidinium Hydroxide) (**7c**).

Compound **7c** was prepared in 80% yield after recrystallization from absolute ethanol, m.p. 290-292° dec.; ir (potassium bromide): 1630 and 1670 (C=O) cm⁻¹; nmr (deuterium oxide): δ 0.95 (t, 3H, ethyl CH₃), 2.35 (q, 2H, CH₂), 3.85 (s, 3H), 4.20 (s, 3H, N₃-CH₃), 8.60 (s, 1H, triazole proton); ms: m/e (relative intensity) 208 (43), 194 (28), 125 (100), 100 (56), 97 (86).

Anal. Calcd. for C₉H₁₂N₄O₂: C, 51.91; H, 5.81; N, 26.91. Found: C, 51.80; H, 5.81; N, 26.89.

Anhydro-(3,4-Dimethyl-6-*n*-propyl-5-hydroxy-7-oxo-1,2,4-triazolo[1,5-*a*]pyrimidinium Hydroxide) (**7d**).

Compound **7d** was prepared in 34% yield after recrystallization from isopropyl alcohol, m.p. 260-263° dec.; ir (potassium bromide): 1650, br band, (C=O) cm⁻¹; nmr (deuterium oxide): δ 0.90 (t, 3H, propyl-CH₃), 1.2-1.7 (m, 2H, CH₂-CH₂), 2.35 (t, 2H, C-CH₂), 3.85 (s, 3H), 4.20 (s, 3H, N₃-CH₃), 8.55 (s, 1H, triazole proton); ms: m/e (relative intensity) 222 (35), 125 (100), 111 (28), 83 (43).

Anal. Calcd. for C₁₀H₁₄N₄O₂: C, 54.04; H, 6.35; N, 25.21. Found: C, 54.00; H, 6.38; N, 25.21.

2-Amino-1-methylimidazole (**10**).

2-Amino-1-methylimidazole hydrochloride monohydrate (**9**) was prepared according to the method by Lawson, m.p. 81-83° [lit. (6) m.p. 84°] after recrystallization from an ethanol/ethyl acetate mixture; nmr (DMSO-*d*₆): δ 3.55 (s, 3H, N-CH₃), 5.10 (deuterium oxide-exchangeable broad signal, 2H, NH₂), 7.05 (overlapping doublets, 2H, imidazole protons). Compound **9** (1.5 g.) was dissolved in 3*N* sodium hydroxide (4 ml.); the solution was extracted with chloroform (4 × 50 ml.) and the organic layer was dried (sodium sulfate) and evaporated to dryness to yield 0.45 g. of **10** as white crystals. The compound was very hygroscopic and liquified almost immediately; the liquid rapidly darkened and decomposed. In subsequent reactions, the product was used immediately upon isolation; nmr (DMSO-*d*₆): δ 3.30 (s, 3H, N-CH₃), 5.10 (deuterium oxide-exchangeable broad signal, 2H, NH₂), 6.50 (overlapping doublets, 2H, imidazole protons).

N-(1-Methyl-2-imidazolyl)acetamide (**12**).

The hydrochloride monohydrate of **12** was prepared according to the method of Lawson, m.p. 140-143° [lit. (6) m.p. 141°]. This product (1.94 g.) was dissolved in 3*N* sodium hydroxide (4 ml.), extracted with ethyl acetate (3 × 50 ml.) and the organic phase was evaporated to dryness after drying with sodium sulfate. The white crystalline solid was recrystallized from chloroform to give 0.6 g. of **12**, m.p. 181-182°; ir (chloroform): 1695 (C=O) cm⁻¹; nmr (DMSO-*d*₆): δ 2.05 (s, 3H, CO-CH₃), 3.46 (s, 3H, N-CH₃), 6.95 (d, 2H, imidazole protons).

2-Ethylamino-1-methylimidazole (**13**).

A solution of the amide **12** (1.53 g., 11 mmoles) in THF (35 ml.) was added dropwise to a stirred suspension of lithium aluminum hydride (0.63 g., 16.5 mmoles) in THF (35 ml.) at 0°. The mixture was refluxed for 3 hours, cooled to 0° and wet (20% water) THF was added dropwise until evolution of hydrogen stopped. The mixture was filtered. The solid residue was extracted twice with hot THF (50 ml.) and these solutions were combined with the filtrate. After drying (Na₂SO₄), the solution was

evaporated to dryness to yield one gram (80%) of a colorless oil which darkened rapidly upon standing; ir (chloroform): 3380 (NH) cm⁻¹; nmr (deuteriochloroform): δ 1.20 (t, 3H, C-CH₃), 3.30 (m, 5H, N-CH₃, N-CH₂), 3.70 (deuterium oxide-exchangeable broad signal, 1H, NH), 6.60 (overlapping doublets, 2H, imidazole protons).

1-Methyl-6-ethyl-7-hydroxy-4,5-dihydroimidazo[1,2-*a*]pyrimidin-5-one (**14**).

An intimate mixture of **10** (0.29 g., 3 mmoles) and bis-(2,4,6-trichlorophenyl)ethylmalonate (**19c**) (12) (1.47 g., 3 mmoles) was heated neat at 160°, under a slow stream of nitrogen, for 3 minutes. When cool, the solid mass was recrystallized from a large amount of ethanol to give 0.47 g. (81%) of **14** as white crystals, m.p. 258-260°; ir (nujol): 1650 (C=O) cm⁻¹; nmr (DMSO-*d*₆): δ 1.00 (t, 3H, C-CH₃), 2.2-2.8 (m, includes DMSO), 3.60 (s, 3H, N-CH₃), 4.30 (deuterium oxide-exchangeable broad signal, ½H, -OH) 7.44 (br s, 2H, imidazole protons), ms: m/e (relative intensity) 193 (36), 178 (100), 124 (72), 110 (25).

Anal. Calcd. for C₉H₁₁N₃O₂: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.92; H, 5.76; N, 21.73.

3-Methylamino-4-methyl-1,2,4-triazole (**18**).

The hydroiodide salt of **18** was prepared by the method of Kroger, *et al.*, (8), m.p. 215-218° [lit. (8) m.p. 207-208], nmr (deuterium oxide): δ 3.10 (s, 3H), 3.65 (s, 3H), 8.40 (s, 1H, triazole proton). The HI salt (0.24 g.) was dissolved in water (0.6 ml.) to which potassium carbonate (0.07 g.) had previously dissolved. *t*-Butyl alcohol (25 ml.) was added to this mixture and all solvent was removed by evaporation under reduced pressure. The crude product was recrystallized from a hexane-ethyl acetate mixture to afford 0.09 g. of **18** as small cream-colored crystals, which soften at 60-66° and melt at 71°; nmr (deuterium oxide): δ 2.90 (s, 3H, NH-CH₃ based on spectrum of 3-methylamino-1,2,4-triazole (11), 3.40 (s, 3H, N-CH₃), 7.95 (s, 1H, triazole proton).

Bis(2,4,6-trichlorophenyl) *n*-Propylmalonate (**19d**).

A mixture of diethyl *n*-propylmalonate (20.2 g., 0.1 mole), potassium hydroxide (16.8 g., 0.3 mole) and water (25 ml.) was stirred at room temperature for 16 hours. At 0°, the mixture was acidified to pH 2 with cold 50% sulfuric acid, filtered and the filtrate was evaporated under reduced pressure to an oily residue. The residue was extracted twice with ethyl acetate (100 ml.); the organic phase was dried with sodium sulfate and evaporated to dryness to yield 10.8 g. of propylmalonic acid, m.p. 94-96°; after recrystallization from petroleum ether. A mixture of the above acid (14.5 g., 0.1 mole), 2,4,6-trichlorophenol (31.6 g., 0.16 mole) and phosphorus oxychloride (33.7 g., 0.22 mole) was heated on an oil bath (90-100°) for 6 hours. The crude reaction mixture was cooled to room temperature and was then poured onto 200 g. of ice. The aqueous phase was decanted and the residue was dissolved in ether (100 ml.). The ether solution was dried (sodium sulfate) and evaporated to dryness to afford the crude product. Recrystallization from hexane gave 41.5 g. (82%) of the desired product, m.p. 72-74°; ir (potassium bromide): 1780 (C=O) cm⁻¹; nmr (deuteriochloroform): δ 1.1 (t, 3H, CH₃), 1.3-2.55 (m, 4H, -CH₂CH₂-), 4.15 (t, 1H, CH), 7.41 (s, 4H, aromatic protons).

Anal. Calcd. for C₁₈H₁₂Cl₆O₄: C, 42.81; H, 2.40. Found: C, 42.94; H, 2.47.

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