Tetrahedron Letters No. 8, pp 663 - 666, 1974. Pergamon Press. Printed in Great Britain.

MESOIONIC PURINONE ANALOGS VI. MESOIONIC 1,3-DIALKYLHYPOXANTHINES

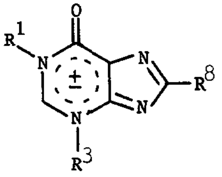
Robert A. Coburn* and Richard A. Carapellotti

Department of Medicinal Chemistry, School of Pharmacy, State University of New York at Buffalo

Buffalo, New York 14214

(Received in USA 7 September 1973; received in UK for publication 17 January 1974)

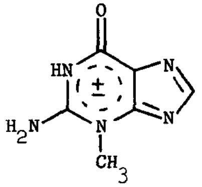
A large class of unusual bicyclic mesoionic structures, termed mesoionic purinone analogs due to their isoconjugate relationship to the purinones: xanthine, hypoxanthine, and purin-2-one, have been formulated and classified based upon known five- and six-membered ring monocyclic mesoionic compounds.[1,2] The synthesis and study of several examples of mesoionic xanthine analogs has supported quantum chemical predictions concerning facets of the ground state properties and anticipated chemistry of these analogs.[3-5] The compounds described in this report, mesoionic 1,3-dialkylhypoxanthines (1), are the first reported examples of the Class II mesoionic hypoxanthine analogs[2] and serve as spectroscopic models for the 1H,3H tautomer (2) of 3-methylguanine assigned by Townsend and Robins.[6] More recently, Pullman[7] has questioned this assignment in favor of the covalent 3H,7H tautomer on the basis of calculated total energies and the anticipated spectral properties of 2.



1 a $R^1 = R^3 = PhCH_2$, $R^8 = H$

b $R^1 = R^3 = CH_3$, $R^8 = Ph$

c $R^1 = R^3 = C_2H_5$, $R^8 = Ph$



2

Compounds 1a and 1b can be prepared from the previously reported 1,3-dibenzylhypoxanthinium bromide[8] (3) and 1,3-dimethyl-8-phenylhypoxanthinium iodide[9] (4), respectively, by treatment of a suspension of the salt in dry acetonitrile with an excess of strong base ion-exchange resin (Baker ANGA-542) at room temperature. 1,3-Diethyl-8-phenylhypoxanthinium iodide (**5**) was prepared from 8-phenylhypoxanthine by treatment with ethyl iodide in a manner identical to that reported for the synthesis of **4**.[9] Compound **1c** may be obtained from **5**, as above, or by treatment of an aqueous solution of **5** with 5% sodium bicarbonate solution (to pH 7) which results in the precipitation of **1c**. Although **1b** may be obtained by the latter procedure, **1a** undergoes slow conversion at *ca.* pH 7 to the ring-opened product, *N*-benzyl-5(4)-(*N*-benzylformamido)imidazole-4(5)-carboxamide, mp 118-121°. This product was spectroscopically identical to that previously obtained directly from the salt **3** by treatment with aqueous ammonia.[8] Treatment of **1a-c** with the appropriate acid regenerates the corresponding salt.

Table I. Properties of Mesoionic 1,3-Dialkylhypoxanthines

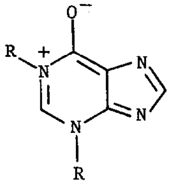
Compound[a]	mp	$\nu_{C=O}^{KBr}$	δ H-2	λ_{max}, nm	
	°C	cm^{-1}	ppm[b]	EtOH[c] (Log ε)	S_1(calcd.)
1a	212-214	1700	9.88, 7.70[d]	303 (3.73)	303 (3.58)
1b	303-305 dec	1690	9.36	319 (4.14)	317 (4.14)
1c	282-283 dec	1690	9.33	318 (4.08)	317 (4.14)

(a) Satisfactory C, H, and N elemental analyses were obtained for each compound. (b) Taken in DMSO-d_6 relative to TMS. (c) Solvent shifts in acetonitrile: +6,+6,+7 nm, respectively. (d) H-8

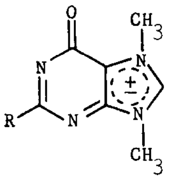
These mesoionic compounds, **1a-c**, are obtained as white crystals, easily recrystallized from acetonitrile, and stable to heat and light in air, whereas their precursor salts darken fairly rapidly upon exposure to air. Table I summarizes some of the properties of these compounds, including their longest wavelength ultraviolet absorption maxima. The assignment of pmr signals in **1a** follows from the expected electron deficiency at the 2-position and from the fact that in the salt **3** only the lowest field signal (δ 10.5 ppm) reflects slow exchange in D_2O, as has been observed in **4**,[9] possibly by an elimination mechanism.[10]

The pseudocarbonyl stretching frequency of **1b** and **1c** (Table I) occurs very close to the 1695 cm^{-1} band reported for a covalent model structure, 1-methyl-8-phenylhypoxanthine.[9] Although the latter value may have been slightly lowered by hydrogen-bonding, not possible in **1a-c**, these results substantiate quantum chemically based predictions concerning similarities between pseudocarbonyl groups of mesoionic *vs.* covalent structures of this type.[2]

Representations such as 6 for these compounds would be misleading in this regard.



6



7 a R = H

b R = NH_2

Compounds 1a-c differ from other reported examples of mesoionic hypoxanthine analogs, such as 7a[11] and 7b[12] in that the five-membered ring is electron rich rather than electron deficient. Evidence for this is the occurance of the H-8 resonance of 1a above the range (δ 7.83-7.93 ppm) associated with the H-8 resonance of the mono anions of the mono-methyl hypoxanthines.[13] The pK_a of 3 has been estimated to be ca. 5.2 via potentiometric titration. The mesoionic isomer 1a is, therefore, a substantially stronger base than covalent mono- and dimethylhypoxanthines (basic pK_a 2.1-2.6).[13]

Since the observed longest wavelength electronic absorption appears at considerably shorter wavelength than that anticipated from the earlier prediction[7] of a 514 nm band for 2, 1a was employed as a spectroscopic model in a variable electronegativity PPP-πSCF-CI calculation of the longest wavelength $\pi \rightarrow \pi^*$ singlet transition (S_1) for 2. The assignment of the 303 nm band to this transition is not inconsistent with the anticipated low energy of this transition, observed intensity, and solvent shift[14] ($\Delta\lambda = 6$ nm in acetonitrile). A description of this semi-empirical calculation and the parameterization employed has been given.[2] The constant in the Wolfsberg-Helmholz approximation of resonance integrals was adjusted to a value of 0.625 in order to reproduce the electronic spectrum of 1a. A triangular set of singly excited configurations (10 configurations) was employed.

The calculated S_1 transition for 1b and 1c agrees closely with that observed (Table I). Introduction of a 2-amino group in 1a is predicted to result in a substantial hypsochromic shift to 263 nm for S_1. The longest wavelength absorption maximum observed in the spectrum of 3-methylguanine[14] (in ethanol) occurs at 268 nm. From this one must conclude that in ethanol solution the existance of the mesoionic tautomer 2 of 3-methylguanine cannot be excluded on the basis of ultraviolet spectroscopic data, even though evidence has now been obtained that the 3*H*,7*H* tautomer is preferred in the solid state.[15]

Acknowledgment: The authors are grateful to the SUNY/Buffalo Computing Center for their donation of computing services of a CDC 6400 computer.

References:

1) R.A. Coburn, *J. Heterocycl. Chem.*, **8**, 881 (1971).
2) R.A. Coburn, R.A. Carapellotti, and R.A. Glennon, *J. Heterocycl. Chem.*,**10**, 479 (1973).
3) R.A. Coburn and R.A. Glennon, *J. Heterocycl. Chem.*, **10**, 486 (1973).
4) R.A. Coburn and R.A. Glennon, *J. Pharm. Sci.*, **62**, In Press.
5) R.A. Coburn and B. Bhooshan, *J. Org. Chem.*, **38**, 3868 (1973).
6) L.B. Townsend and R.K. Robins, *J. Amer. Chem. Soc.*, **84**, 3008 (1962).
7) B. Pullman in "The Jerusalem Symp. on Quant. Chem. and Biochem. II." E. Bergmann and B. Pullman, Ed., Academic Press, Inc., N.Y. , 1970, pp 292-307.
8) J.A. Montgomery, K. Hewson, S.J. Clayton, and H.J. Thomas, *J. Org. Chem.*, **31**, 2202 (1966).
9) Z. Neiman, *J. Chem. Soc.* (*C*), 91, 1970.
10) R.A. Coburn, J.M. Landesberg, D.S. Kemp, and R.A. Olofson, *Tetrahedron*, **26**, 685 (1970).
11) J.W. Jones and R.K. Robins, *J. Amer. Chem. Soc.*, **84**, 1914 (1962).
12) H. Brederick, G. Christmann, and W. Koser, *Chem. Ber.*, **93**, 1206 (1960).
13) D. Lichtenberg, F. Bergmann, and Z. Neiman, *Isr. J. Chem.*, **10**, 805 (1972).
14) We thank Dr. Leroy B. Townsend for an authentic sample of 3-methylguanine.
15) D.J. Abraham, private communication.