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SYNTHESIS OF DEHYDRO-1,3-DIMETHYLURIC ACID

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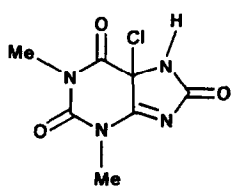
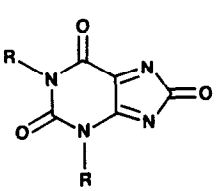
Summary-Pyrolytic dehydrochlorination of 5-chloro-1,3-dimethyl-isouric acid (1) gave dehydro-1,3-dimethyluric acid (2b) as the first example of a quinonoid redox state in uric acid series.

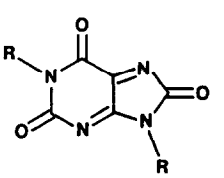
The elevation to an oxidation state above that of urate, a focal point of the redox chemistry of purines, continues to evade universally acceptable interpretation of its unique and often complex chemical reactivity. All discussions of chemical and biological mechanisms which involve the uric acid system[1-3] have suffered from the fact that quinonoid dehydro-uric acids are unknown as a class of compounds. There are two possible tautomeric structures for the parent dehydro-uric acid, depending on the location of the hydrogen atom on the acylamidine function, namely the ortho-quinonoid (2a) and para-quinonoid (3a) arrays, which are reminiscent of alloxazine/isoalloxazine isomers. The putative dehydro-uric acid undergoes nucleophilic additions with such facility that all attempts at its isolation or direct detection have failed.[4]



1



2



3 a: R=H; b: R=Me

As the probability of successfully obtaining 2 or 3 under accessible reaction and work-up conditions in solution was from all indications negligible, it was decided to attempt an alternative approach involving pyrolytic elimination as the key step. Chlorination of theophylline following Biltz's procedure produced 5-chloro-1,3-dimethyl-isouric acid (1).[5] A portion of finely powdered 1 (46mg, 0.2mmol) was heated in a vacuum sublimator[6] at 195-200°(10^{-3}Torr). The first white sublimate was discarded.[7] The remainder of the sublimate collected on a hot surface (120°, heating tape) as glistening yellow needles (21-30mg, 45-65%); m.p. 195-196°. The yellow substance **2b** decolourizes rapidly in air and must be kept under strictly anhydrous conditions. It shows no presence of chlorine (Beilstein's test, alcoholic silver nitrate) and gives a murexide reaction. MS, m/e(rel intensity) 195(5.2), 194(49.0, M^+), 167(8.8), 166 (100.0, M^+-CO), 142(5.0, m*), 138(3.5), 137(42.2), 110(4.8), 109(56.3), 65(1.5), 64(4.5), 56(2.0). UV, λ_{max} (logε) 237(4.25), 290(3.89), 366(3.45) nm. IR: 1772, 1700, 1696, 1666(C=O), 1605, 1592 (C=N), 1466, 1420, 1369, 1290, 1236, 1122, 1087, 925, 826, 797, 784, 773, 738, 464, 412, 398 cm^{-1}. ^{1}H-NMR, δ 3.54(s,3H), 3.39(s,3H). ^{13}C-NMR, δ 175.8(s), 165.3(s), 162.9(s), 157.2(s), 150.5

(s), 32.6(q), 29.3(q).[8] The fact that the quinonoid product **2b** could be reduced back to 1,3-dimethyluric acid proved that no further skeletal alterations could have resulted from pyrolysis.[9]

In conclusion, it can be stated that a route to a dehydro-uric acid derivative has been demonstrated which makes these quinonoid systems available for further study. Extension of the above dehydrochlorination method to a para-quinonoid array, such as that in **3b**, is in progress.

Acknowledgement – We thank the Research Council of Croatia for support of this work.

References and Notes

[1] Semiquinonoid (radical) intermediates were detected in chemical and enzymic oxidations of uric acid: K.R.Maples and R.P.Mason, *J.Biol.Chem.* **263**, 1709 (1988). During the recent years evidence has accumulated to show that urate acts as a primary biological antioxidant which replaces some of the functions of ascorbate: *cf.* K.J.A.Davies, A.Sevanian, S.F.Muakkassah-Kelly, and P.Hochstein, *Biochem.J.* **235**, 747 (1986).

[2] Dehydro-uric acid has been suggested as a transient intermediate in uricolytic pathway to allantoin: M.Poje and L.Sokolić-Maravić, *Tetrahedron* **42**, 747 (1986); *Ibid.* **44**, 6723 (1988).

[3] A range of alloxan-like compounds derived from uric acid exerted a strong cytotoxic effect upon the β-cells of rat pancreatic islets of Langerhans; the active compounds may be regarded as isosteres of dehydro-uric acids **2a**/**3a** or their hydrated equivalents, thus suggesting a plausible hypothesis for the aetiology of diabetes mellitus: *cf.* S.J.H.Ashcroft, D.E.Harrison, M.Poje, and B.Ročić, *Br.J.Pharm.* **89**, 469 (1986).

[4] Reduction peak observed on cyclic voltametry of uric acid has been proposed to be due to electrochemical reduction of an incipient quinonoid intermediate; in solution it was rapidly hydrated and the reaction was found to be first order, having a rate constant of $32{,}5\,s^{-1}$. at pH 8; J.L.Owens, H.A.Marsh, and G.Dryhurst, *J.Electroanal.Chem.* **91**, 231 (1978); M.Z. Wrona, J.L.Owens, and G.Dryhurst, *Ibid.* **105**, 295 (1979).

[5] H.Biltz, *Liebigs Annln Chem.* **413**, 159 (1916).

[6] A simple and effective assembly consists of a pyrolytic tube connected to removable cylinders (50x12mm) by means of ground glass joints.

[7] Identification of the colourless sublimate as **1** is suggestive of the reversibility of the pyrolytic dehydrochlorination reaction.

[8] Measurement of the spectra is complicated unless special precautions are taken to use hydrate-free **2b** and rigorously exclude moisture. M.ps. were determined using a Kofler apparatus and are uncorrected. Microanalyses were within ±0.4%. Mass spectrum was determined on a Varian MAT CH-7 instrument. UV spectrum was recorded on a Hitachi 200 spectrophotometer for a MeCN soln. IR spectra were determined on a Perkin-Elmer 783 spectrometer for KBr disks. NMR spectra were obtained on a JEOL FX-100 spectrometer for acetone-d_6 solns. Chemical shifts are given in δ units (ppm) relative to internal TMS.

[9] Powdered **2b** (58mg, 0.3mmol) was added over a period of 15 min to a stirred soln of $LiAlH_4$ (3mg) in THF (10ml). After initial reaction, the mixture was heated under reflux for 3 h. Cautious addition of water (0.1ml) in THF (2ml) gave a gelatinous mass which was diluted with ether to facilitate stirring. The solvent was removed and 10% H_2SO_4 (5ml) added to the residue. The product was collected and recrystallized from water to give colourless needles (38mg, 65%), m.p. 408-410° dec, identical in all respects with 1,3-dimethyluric acid.

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