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A REINVESTIGATION OF ALLOXAN-LIKE COMPOUNDS DERIVED FROM URIC ACID[1]

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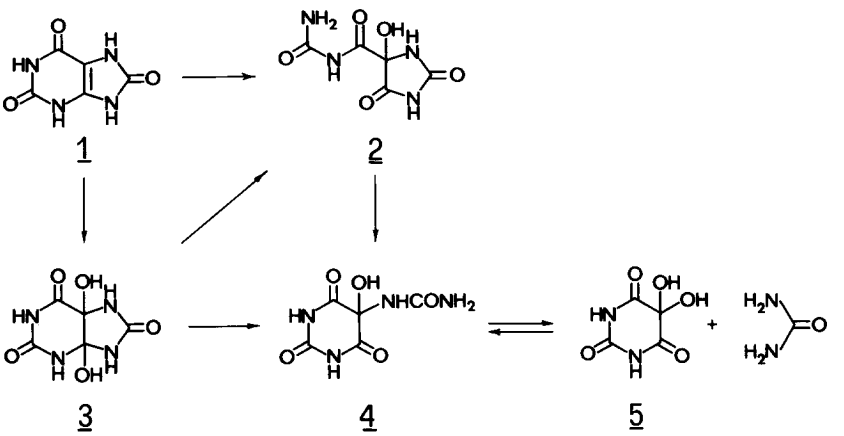
Summary: The structures of two isomeric intermediates in the oxidative conversion of uric acid (1) to alloxan (5) are revised and the compounds shown to be uric acid glycol (3) and 5-hydroxy-pseudouric acid (4), respectively.

Recently we showed that Biltz's formula 3[2] for the oxidation product of uric acid (1) with bromine was inconsistent with spectral and degradative evidence and assigned the correct structure 2 by *X*-ray structure analysis[1]. An extension of the foregoing revision indicated a possible alternative formulation of isomeric alloxan-like compounds. In view of the interest in the β-cytotoxic compounds derived from 1[3], the structure of these products has been reinvestigated.



The chlorination of 1 in acetic acid in the presence of an equimolar amount of water and subsequent work-up, according to Biltz's procedure[4], afforded a product $C_5H_6N_4O_5$, m.p. 210° dec. Its IR spectrum, however, failed to show the absorptions characteristic of a primary amide, as expected for the originally assigned structure 4, but was consistent with the bicyclic structure 3: νmax (KBr) 3465(OH), 3350,3200,3120(NH),1735,1720,1705(CO) cm^{-1}; UV spectrum[5] λmax (H_2O) 199(ε 15520), sh 220(ε 6900), 250(ε 2590) nm. The extensive thermal dehydration eliminates the molecular ion from the mass spectrum[6] of 3 giving rise to a M-18 peak at m/e 184. The structure 3 is also consistent with facile acid hydrolysis to alloxan (5) and urea. Under appropriate conditions, however, the cleavage of the five-membered ring in 3 occurred affording the isomeric intermediate 4.

Compound 3 was dissolved in a minimal amount of water at 70° and evaporation under reduced pressure yielded crystalline 4 (38%), m.p. 133-4° dec., which analyses for $C_5H_6N_4O_5 \cdot H_2O$. Removal of water of hydration by heating with an excess of acetic anhydride gave anhydrous 4 (90%) as fine yellow needles, $C_5H_6N_4O_5$, m.p. 185-6° dec. IR (KBr), νmax 3480,3440(NH_2), 3460(OH),3360,3250,3140(NH), 1760,1725 (CO), 1650,1630($CONH_2$) cm^{-1}; UV spectrum[5] λmax (H_2O) 199(ε 17120), sh220(ε 8080) nm. The mass spectrum[7] gave supporting evidence for the structure 4. Besides the thermal dehydration and subsequent fragmentation similar to that in 3, two complemental peaks were observed at m/e 142 and 60, corresponding to McLafferty--rearrangement ions 5 and urea.

The reaction of 5 with urea which has been described previously[8], yielded a product identical in all respects with 4. The ease of formation of the addition product may be due to stabilization by internal hydrogen bonding in outcome 4 which is absent from the parent *gem*-diol 5[9]. On being heated, or in aqueous solution, an equilibrium 4 ⇄ 5 + urea is likely to be set up, and the ready disproportionation into original components is consistent with reactions reported earlier[8]. All attempts to achieve the re-cyclisation 4 → 3 remained unsuccessful. A bromine-catalysed rearrangement, however, takes place in aqueous solutions of 3 and 4 to give the third constitutional isomer 2 (50-60%) which no longer possesses an alloxan-like structure[1].

The results provide a basis for further studies relating to *in vivo* degradation of 1 and we hope to report the ongoing work in this area in due course[10].

REFERENCES AND NOTES

1. Oxidation of Uric Acid. II. For part I, see M. Poje, E. F. Paulus, and B. Ročić, *J. Org. Chem.*, in press.
2. H. Biltz and M. Heyn, *Chem. Ber.* 45, 1677 (1912); *ibid.* 47, 459 (1914).
3. M. Poje and B. Ročić, *Experientia*, in press.
4. H. Biltz and M. Heyn, *Ann. Chem.* 413, 7 (1916). Dimethyl ether of 3 prepared by chlorination of 1 in methanol had νmax(KBr) 3320,3200,3090,1750,1715 cm^{-1}.
5. It is noteworthy that UV spectra of 3 and 4 show considerable resemblance to the spectra of primary oxidation products of 1-methyluric acid obtained by the action of horse radish peroxidase. K. G. Paul and Y. Avi-Dor, *Acta Chem. Scand.* 8, 637 (1954).
6. MS (200°), m/e (rel intensity) 184(4),156(1),141(12),129(9),114(15),113(17), 98(6),86(17),85(4),70(15),69(4),60(10),55(12),54(5),44(55),43(100),42(46); metastable peaks m/e 108.1,90.6 |184 → 141 → 113|; 68.1 |141 → 98|.
7. MS m/e (rel intensity) 184(2),156(1),142(7),141(1),129(1),114(4),113(5),86 (7),71(4),70(6),69(3),60(15),55(3),54(2),44(100),43(54),42(15); metastable peaks m/e 17.9 |202 → 60|; 90.6 |141 → 113|; 64.9 |114 → 86|.
8. R. Behrend and R. Zieger, *Ann. Chem.* 410, 337 (1915). We employed a slightly modified procedure: on admixing saturated solutions of 5 and 2 mol.equiv. of urea at 50°, heat is evolved, and crystalline 4 separated in a 60% yield.
9. An analoguous behaviour is observed in the α-halogenated aldehydes which also form stable *gem*-diols: H.E.Zaugg and W.B.Martin, *Org. Reactions* 14, 52 (1965).

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