The Formation of 6,8-Dihydroxypurine by the Oxidation of 7-Aminooxazolo[5,4-*d*]pyrimidine with Hydrogen Peroxide-Acetic Acid[1]

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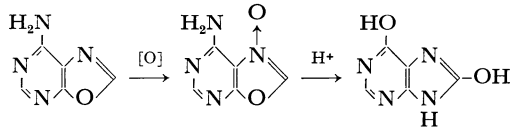
The direct oxidation of adenine with peracetic acid has been known to afford the 1-oxide,[2,3] while hypoxanthine is not convertible to the *N*-oxide by this method.[3,4] 7-Aminooxazolo[5,4-*d*]pyrimidine (I) can be considered as a compound having a structure intermediate between adenine and hypoxanthine; accordingly, its behavior when treated with a peracid is of interest. As an analogous compound, 7-aminothiazolo[5,4-*d*]pyrimidine has been reported to be oxidized to the *N*-oxide of the adenine type.[5]

We have found that the oxidation of 7-aminooxazolo[5,4-*d*]pyrimidine (I) with hydrogen peroxide and acetic acid afforded an unexpected product, 6,8-dihydroxypurine (III). Thus, one gram of I[6] was treated with 3.7 m*l* of a 30% aqueous solution of hydrogen peroxide and 10 m*l* of acetic acid at room temperature. After 2.5 days, light yellow precipitates (0.5 g, 48%) of a single compound were obtained. Recrystallization from water yielded colorless crystals, mp >340°C, which were identical with authentic 6,8-dihydroxypurine.[7]

As has been described in a previous paper,[8] 7-aminooxazolopyrimidines are easily converted into hypoxanthine. However, there is no possibility of the formation of III *via* hypoxanthine since hypoxanthine is inert under the conditions used here. Moreover, the oxidation of the pyrimidine moiety of I would not lead to such a product. Thus, the initial step of the oxidation probably occurs at the 1-*N* position of I,[9] giving 7-aminooxazolopyrimidine 1-oxide (II) as an intermediate. The conversion of II into III can be explained by analogy with the well-known rearrangement of aldonitrons into isomeric amides under acidic conditions:[10,11]



I II III

The difference in behavior towards oxidation between 7-aminooxazolo[5,4-*d*]pyrimidine and adenine or 7-aminothiazolo[5,4-*d*]pyrimidine may be attributed to the difference in the charge density on the ring-nitrogen atom, which is attacked preferentially by the electrophilic centre of the peracid. The present results may indicate that the electron-deficient character of the pyrimidine ring and the electron-excess character of the oxazole ring seem to be partly retained in the oxazolopyrimidine molecule,[12] while a more extensive donation of electrons from the five-membered ring to the pyrimidine ring takes place in purines[13] and even in thiazolopyrimidines. These factors account for the preferential oxidation on the oxazole ring in the oxazolopyrimidine.

1) Study on Oxazolopyrimidines. III.

2) M. A. Stevens, D. I. Magrath, H. W. Smith and G. H. Brown, *J. Amer. Chem. Soc.*, **80**, 2755 (1958).

3) M. A. Stevens and G. B. Brown, *ibid.*, **80**, 2759 (1958).

4) H. Kawashima, T. Meguro and I. Kumashiro, This Bulletin, **39**, 633 (1966).

5) G. B. Brown, G. Levin, S. Murphy, A. Sele, H.C. Reilley, G. S. Tarnowski, F. A. Schmid, M. N. Teller and C. C. Stock, *J. Med. Chem.*, **8**, 190 (1965).

6) Y. Ohtsuka, This Bulletin, **43**, 187 (1970).

7) R. K. Robins, *J. Amer. Chem. Soc.*, **80**, 6671 (1958).

8) Y. Ohtsuka, This Bulletin, **43**, 954 (1970).

9) Although the oxidation of azole compounds generally affords ring-opening products, the oxidation of 4-methylthiazole with hydrogen peroxide in acetic acid is known to yield the *N*-oxide [E. Ochiai and E. Hayashi, *Yakugaku Zasshi*, **67**, 34 (1947)].

10) W. Rundel, "Methoden der Organischen Chemie," ed. by E. Müller, Vol. 10/4, Georg Thieme Verlag, Stuttgart (1968), p. 428.

11) For example, pyridine *N*-oxide has been reported to afford 2-hydroxypyridine when treated with acetic anhydride [M. Katada, *Yakugaku Zasshi*, **67**, 51 (1947)]. An analogous rearrangement of pteridine derivatives [W. Hutzenlaub, G. B. Berlin and W. Pfleiderer, *Angew. Chem.*, **81**, 624 (1969)] or quinoxaline derivatives [Y. Ahmad, M S Habib, A Mohammady, B. Bakhtiari and S. A. Shamsi, *J. Org. Chem.*, **33**, 201 (1968)] seem to involve an acylation process, but we have no evidence for the involvement of acylation in the present reaction.

12) This was also suggested by the study of the spectroscopic properties of substituted 7-aminooxazolopyrimidines (see Ref. 6).

13) R. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," John Wiley and Sons, New York (1967), p. 355.