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Study on Oxazolopyrimidines. IV. The Preparation of 7-Aminooxazolo[5,4-*d*]pyrimidine 6-Oxide

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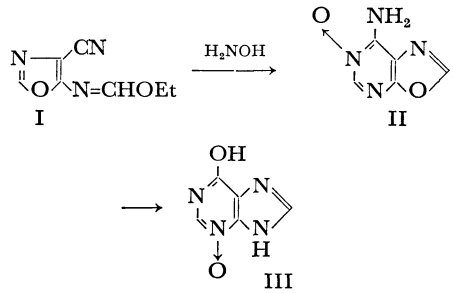
Various *N*-oxides of nitrogen-containing heteroaromatic compounds have been prepared, and several purine *N*-oxides have been shown to exhibit biological activities.[1,2] Although amino-substituted purines[3] and 7-aminothiazolo[5,4-*d*]pyrimidine[2] have been known to yield the corresponding *N*-oxides with peroxyacetic acid, the treatment of 7-aminooxazolo[5,4-*d*]pyrimidine under similar oxidizing conditions led to the formation of 6,8-dihydroxypurine.[4] Another way to *N*-oxide has recently been provided by the preparation of adenosine 1-oxides by the treatment of 5-amino-4-cyanoimidazole derivatives with ethyl orthoformate, followed by hydroxylamine.[5] A similar approach was previously used for the synthesis of hypoxanthine 1-oxide.[6]

The synthesis of 7-aminooxazolo[5,4-*d*]pyrimidine 6-oxide (II) has now been accomplished in a 61% yield by the treatment of 4-cyano-5-ethoxymethyleneaminooxazole (I)[7] with hydroxylamine. By the same treatment, 4-cyano-5-ethoxymethyleneaminoimidazole[8] gave adenine 1-oxide.

The structure of the *N*-oxide (II) was supported by the results of elementary analysis, its spectroscopic data, and its rearrangement to hypoxanthine 3-oxide (III) when stirred in an aqueous alkali for 2 days, but an attempt to obtain 7-aminooxazolopyrimidine by catalytic hydrogenation with Pt/C was unsuccessful.

The present method for the preparation of the *N*-oxide of the pyrimidine derivative by the cyclization of cyanoethoxymethyleneamino compound with



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hydroxylamine can generally be applied to a variety of systems, including a relatively unstable system such as oxazolopyrimidine.

Experimental

Preparation of 7-Aminooxazolo[5,4-*d*]pyrimidine 6-Oxide (II). 4-Cyano-5-ethoxymethyleneaminooxazole (I)[7] (1.65 g) was added to an ice-cooled solution of hydroxylamine hydrochloride (0.70 g) and sodium hydroxide (0.4 g) in water (5 m*l*). A precipitate was formed at an early stage of the reaction. When the mixture was stirred at room temperature, it gradually dissolved and then crystals deposited again. The product (0.92 g) was collected after 15 min and washed with water and ethanol. Recrystallization from water gave colorless needles, mp>300°C.

This compound gave a positive $FeCl_3$ test (violet) and a negative TTC (triphenyltetrazolium chloride) test. Its mass spectrum showed a pattern identical with that of 7-aminooxazolopyrimidine[7] except for the peak of the molecular ion, m/e=152 (14.4% in intensity relative to the peak, m/e=136). The relatively small pH-dependence of the UV spectra seems to support the oxazolopyrimidine structure (λ_{max} (mμ), logε; 231, 4.45; 256, 3.94; 300, 3.34 (pH=2.9): 230, 4.52; 259, 3.96; 301, 3.40 (pH=8.5): 226, 4.41; 259, 3.85; 289, 3.63 (pH=12.0)). This compound possessed paper chromatographic R_f values of 0.53 and 0.27 in solvents A and B[9] respectively.

Found: C, 39.45; H, 2.93; N, 36.73%. Calcd for $C_5H_4N_4O_2$: C, 39.48; H, 2.65; N, 36.84%.

Adenine 1-Oxide. 4-Cyano-5-ethoxymethyleneaminoimidazole[8] (0.22 g) was treated by the same procedure as has been described above. The product (0.10 g) was identified as adenine 1-oxide[3] from its IR spectrum

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9) Solvent A; BuOH–HOAc–H_2O (60 : 15 : 25 v/v): solvent B; *i*-PrOH–NH_4OH–H_2O (7 : 1 : 2 v/v): solvent C; 5% disodium phosphate - *i*-AmOH (3 : 2 v/v).

and R_f value.

Conversion of the Oxide II to Hypoxanthine 3-Oxide (III). The *N*-oxide (II, 0.8 g) was stirred in a 4N aqueous NaOH solution (10 *ml*) at room temperature for 2 days. After this period, the reaction mixture was acidified with acetic acid. The product was collected and purified by reprecipitation from an aqueous alkali with acetic acid. The yield was 42% (0.52 g). The structure of the compound was identified as hypoxanthine 3-oxide[10] on the basis of its UV spectra at various pH (pH=3, 8.5 and 12) and R_f values in solvents A, B, and C.[9]

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