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Study on Oxazolopyrimidines. II. Conversion of 7-Aminooxazolo-[5,4-*d*]pyrimidines into Hypoxanthine Derivatives

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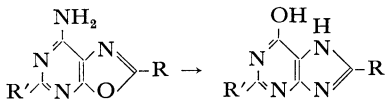
Several 7-aminooxazolo[5,4-*d*]pyrimidines have been synthesized from oxazole derivatives.[1] During the examination of the chemical behavior of these compounds, a new transformation of 7-aminooxazolopyrimidines into hypoxanthine derivatives was found.

Hitchings *et al.*[2] have converted some oxazolopyrimidines into purine derivatives by heating with alcoholic ammonia at 160°C for a long period. These conditions are similar to those of the well-known conversion of oxazoles into imidazoles.[3,4] In these cases, severe conditions are required for the substitution of oxygen atom by imino group. On the other hand, Ishidate and Yuki[5] found that 7-mercaptooxazolopyrimidine derivative was converted into 7-hydroxythiazolopyrimidine derivative under such mild conditions as by boiling with dilute acid for 20 min or by heating the crystals at 270—300°C.

The conversion of 7-aminooxazolopyrimidines into hypoxanthines proceeds under mild conditions. Thus, the treatment of the oxazolopyrimidines with aqueous 4N sodium hydroxide solution at room temperature followed by warming at 60—80°C, was found to be the most appropriate for the transformation.



(Ia—e) (IIa—e)

a: R=R′=H
b: R=H, R′=CH_3
c: R=CH_3, R′=H
d: R=R′=CH_3
e: R=H, R′=OC_2H_5

By this treatment, 2- and/or 5-substituted 7-aminooxazolopyrimidines can be converted into the corresponding hypoxanthines. The yields of the hypoxanthines were 60 to 80% but more careful workup seemed to improve them. The structures of the products, IIa—d, were confirmed by comparison with authentic samples. The structure of IIe was confirmed by acid hydrolysis to afford xanthine.

All the hypoxanthines examined here are easily soluble in aqueous alkaline solution, while oxazolopyrimidines have sparing solubilities in the solvent. Therefore, it was thought that completion of the initial step of the reaction could be estimated from the time required for complete dissolution of the starting materials.

Table 1. The time of complete dissolution of several 7-aminooxazolopyrimidine (45°C aq 4N NaOH solution)

Compound	Time (hr)
Ia	0.2
Ib	2.5
Ic	2.7
Id	7.5
Ie	5.0

The results in Table 1 show that when R and R′ are substituted by CH_3 or OEt, a longer time is needed for dissolution of the starting materials. This would mean the initial attack by alkali is retarded by these substituents.

The reaction proceeds through oxazole ring rupture by attack of OH^- followed by imidazole ring formation. This reaction provides a new route to hypoxanthine derivatives under mild conditions. The scope and applications of the reaction are under investigation.

Experimental

The IR, NMR and mass spectra were recorded with Perkin-Elmer 337, Varian HA-100 and Hitachi RMU-6E spectrometer respectively. The synthesis of the starting material has been described in the previous paper.[1]

Conversion of 7-Aminooxazolopyrimidines into Hypoxanthine Derivatives. General method: 7-Aminooxazolo[5,4-*d*]pyrimidine (1 g) and aqueous 4N sodium hydroxide solution (10 ml) were stirred at room temperature for 30 min. Then the mixture was warmed at 60—80°C for 30 min, and after cooling, the reaction

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3) K. Hoffmann, "Imidazole and Its Derivatives," Part I, Interscience Pub., New York (1953), pp, 43—44.
4) G. Theilig, *Chem. Ber.*, **86**, 96 (1953).
5) M. Ishidate and H. Yuki, *Chem. Pharm. Bull.* (Tokyo), **8**, 137 (1960).

mixture was acidified with conc. HCl. The resultant precipitates were filtered, and the products, about 60—80% yields, were recrystallized from water. These were identified by the comparisons of their IR, NMR and mass spectra with authentic samples (IIa: commercial product, IIb and IId,[6] and IIc[7]; prepared by known procedures). 2-Ethoxyhypoxanthine (IIe); colorless needles, mp >330°C. Found: C, 46.69; H, 4.49; N, 31.14%. Calcd for $C_7H_8N_4O_2$: C, 46.66; H, 4.48; N, 31.10%. NMR in DMSO-d_6 (δ-values): 7.90 (C_8-proton), 1.33, 4.35 (OEt).

7-Aminooxazolopyrimidine, Ia, was most easily converted into hypoxanthine, IIa; heating of Ia at the melting point, solids which were confirmed to be hypoxanthine deposited while other oxazolopyrimidines gave only degraded products. Moreover, on refluxing with acetic anhydride for 2 hr, Ia afforded IIa (60%). With more dilute alkali or at higher initial temperature, 7-aminooxazolopyrimidines were decomposed to acid soluble materials, which by the IR spectra are probably aminohydroxypyrimidine derivatives although they have not been confirmed.

Acid Hydrolysis of 2-Ethoxyhypoxanthine. 2-Ethoxyhypoxanthine (1 g) and 4N hydrochloric acid (20 m*l*) were heated under reflux for 4 hr. After neutralization of the reaction mixture with alkali, 0.7 g of product was obtained. The IR and NMR spectra of the product were identical with those of authentic xanthine.

Determination of the Time of Complete Dissolution. 7-Aminooxazolopyrimidines (2 mg) were suspended in aqueous 4N NaOH solution (1 m*l*) and the mixtures were stirred in the temperature-controlled bath. The time of complete dissolution was measured two or three times in each samples, and the mean deviation of those data were about ±20%.

6) F. Craveri and G. Zoni, *Boll. Chim. Farm.*, **97**, 393 (1958).

7) F. Bergmann and M. Tamari, *J. Chem. Soc.*, **1961**, 4468.