HYDROLYTIC RING CLEAVAGE OF THIADIAZOLO[3,2-a]PYRIMIDINONES

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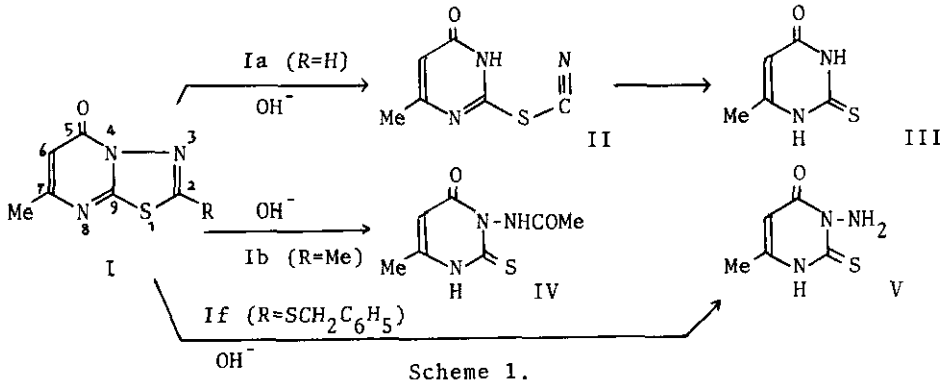
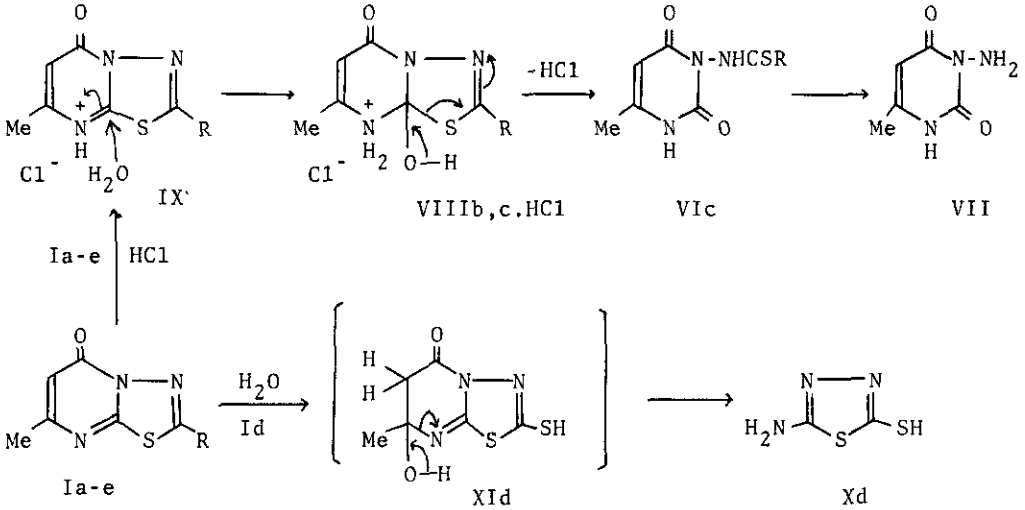
Abstract ——— The alkali and acid hydrolysis of 2-substituted 7-methyl-5H-thiadiazolo[3,2-a]pyrimidin-5-ones gave 3-amino-6-methyluracil, 3-amino-6-methyl-2-thiouracil and 2-amino-1,3,4-thiadiazole derivatives according to the kind of substituents. While, the treatment of 7-methyl-5H-thiadiazolopyrimidin-5-one with methanolic hydrochloric acid gave 6-methyl-2-thiouracil.

Thiadiazolo[3,2-a]pyrimidine derivatives were synthesized by two routes starting from 3-amino-2-thiouracils[1] and 2-amino-1,3,4-thiadiazoles[2], and some of them were noted the selective herbicidal activity[2], but the chemical properties including the stability were little known. Previously, the authors described the alkaline hydrolysis of thiadiazolo[3,2-a]pyrimidines to form 2-thiocyanato-pyrimidine derivatives as a result of N-N bond cleavage[3]. Subsequently, Okabe, et al.[4] reported that 7-methyl-5H-thiadiazolo[3,2-a]pyrimidin-5-one (Ia) was hydrolyzed with alkali to 6-methyl-2-thiouracil (III) via 2-thiocyanato derivative (II), while the 2-methyl and 2-benzylthio derivatives of Ia (Ib and If) were converted to 3-acetamido- (IV) and 3-amino-6-methyl-2-thiouracil (V) by C_2-S



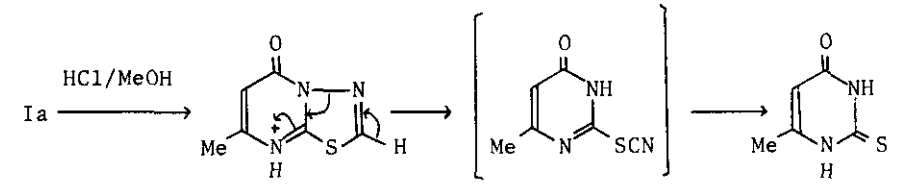
Scheme 1.

bond cleavage, respectively. Now, the authors found that the acid-catalyzed hydrolysis of I afforded 3-amino- and 3-substituted amino-6-methyluracils (VI and VII) by C_9-S bond cleavage together with other products, and further revealed that the alkaline hydrolysis of I gave V and/or VII according to the kind of substituents. When a solution of Ib (200 mg) in 5% HCl (2 ml) was refluxed for 2 hr, VIIIb.HCl (R=Me) was obtained in 63% yield. VIIIb.HCl; mp 260° (dec), UV $\lambda_{max}^{H_2O}$ 211, 253, 326 nm: NMR (DMSO-d_6) δ2.26 (9-OH), 2.68 (7-Me), 2.91 (2-Me), 7.45 (ring C-H): IR (KBr) 2640, 1592 cm^{-1} (N^+H_2). On prolonged reflux with HCl, VIIIb was converted to VII, which was identical with the authentic sample[5]. On similar treatment, Ic (R=SMe) afforded the mixture of 3-(methyldithiocarbamido)-6-methyluracil (VIc, 61%) and VIIIc.HCl (13%). VIc[6]; mp 230° (dec), UV $\lambda_{max}^{H_2O}$ 248, 273 nm (pH 1). VIIIc.HCl; mp 192° (dec); UV $\lambda_{max}^{H_2O}$ 256, 332 nm: IR (KBr) 2590, 1593 cm^{-1} (N^+H_2). Both VIc and VIIIc.HCl were converted to VII by further treatment with HCl, indicating that the reaction course to VII from I involves the successive formations of the HCl salt of I (IX) and VIII. IX was obtained by the treatment of I with HCl at room temperature. The reaction of Ia (R=H) and Ie ($R=NH_2$) with 5% HCl gave VII in 53 and 61 % yields, respectively, and that of Id (R=SH) produced the thiadiazole compound (Xd) in 24% yield along with the formation of VII in 64% yield. Xd, mp 245°, was identical with the authentic sample[7]. Although the decomposition of pyrimidine moiety in I was unexpected, the formation of Xd would involve the intermediacy of hydrate compound (XId).



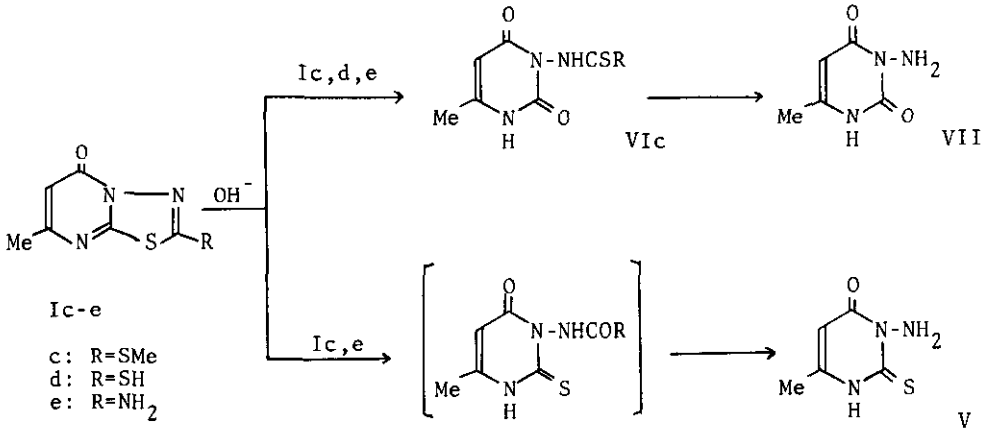
Scheme 2.

When Ic was allowed to stand with HCl-saturated MeOH at room temperature for 2 weeks, VIc was obtained by C_9-S bond cleavage. On the other hand, the similar treatment of Ia with HCl-saturated MeOH afforded the unexpected 6-methyl-2-thiouracil, III, exclusively. Since the treatment of 2-thiocyanato compound, II, with HCl-saturated MeOH gave III, it was assumed that the reaction involves the intermediacy of II accompanying the N-N bond cleavage.



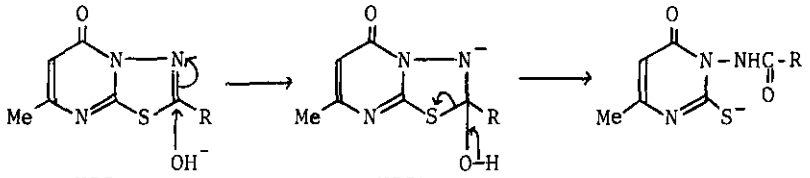
Scheme 3.

Next, the alkaline hydrolysis of I was attempted. The reaction of 2-methylthio derivative (Ic) (300 mg) with 1% NaOH (10 ml) for 10 days at room temperature gave the mixture of VIc (62%) and V (20%). The reflux of Id (R=SH) with 1% NaOH for 2 hr afforded VII, and that of Ie ($R=NH_2$) gave the mixture of V (31%) and VII (23%), which were separated by the preparative thin layer chromatography on silica gel using MeOH-$CHCl_3$ (3:17).



Scheme 4.

The initial step in C_2-S bond cleavage of Ib and If might be the attack by hydroxide ion on the C_2=N double bond as shown in Scheme 5 (XII). On the other hand, the C_2-S bond cleavage was not observed in the hydrolysis of Id. Such a formation of I-hydroxide adduct (XIII) as illustrated in Scheme 5 might not occur in Id, since the electron-withdrawing action of 2-S^- substituent would be

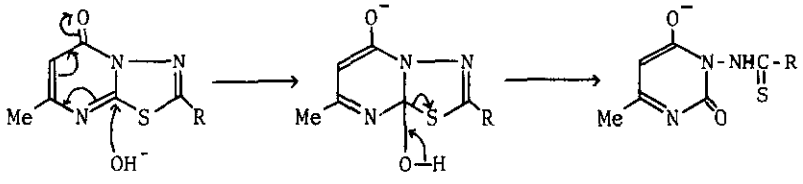


XII XIII XIV

R=Me (Ib)
R=SMe (Ic)
R=NH_2 (Ie)
R=$SCH_2C_6H_5$ (If)

Scheme 5.

unfavorable for pushing a π-electron of C_2=N double bond to the N atom in XII. As depicted in Scheme 6, the C_9-S bond cleavage in the hydrolysis of Id is presumably initiated by the attack of hydroxide ion on the C_9 atom. The weak electron-with-



XV XVI XVII

R=SMe (Ic)
R=S^- (Id)
R=NH_2 (Ie)

Scheme 6.

drawing action of 2-methylthio and 2-amino substituents in Ic and Ie would cause the attack by hydroxide ion on both C_2 and C_9 atoms.

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