CHEMISTRY LETTERS, pp. 2203-2204, 1991.

Oxidation of 5-Bromo- and 5-Fluoro-1,3-dimethyluracils by Peroxomono- and Peroxodisulfate Ions

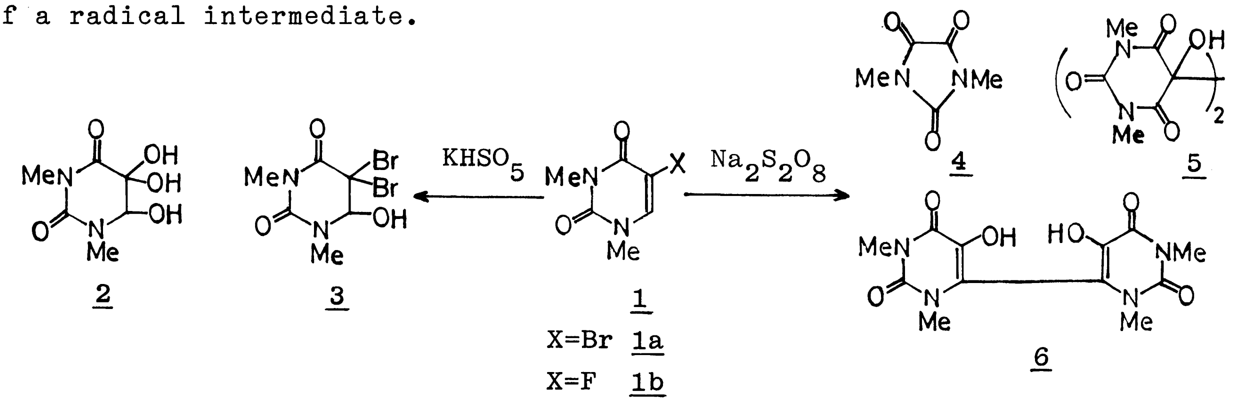
Toshio ITAHARA* and Akihiro NISHINO
Institute of Chemistry, College of Liberal Arts,
Kagoshima University, Korimoto, Kagoshima 890

Oxidation of 5-bromo-1,3-dimethyluracil by $KHSO_5$ gave 5,5-dibromo-6-hydroxy- and 5,5,6-trihydroxy-1,3-dimethyl-5,6-dihydrouracils and that of 5-fluoro-1,3-dimethyluracil by $Na_2S_2O_8$ gave a 6,6'-dimeric product.

5-Fluorouracil has been widely used in the chemotherapy of malignant neoplasms but has toxicity such as neurotoxicity.1) Hence, metabolism of 5-fluorouracil is of interest.1) Also, 5-bromouracil is a mutagenic compound and cells with DNA containing 5-bromouracil are deactivated by γ- and UV-radiation. The γ-radiation2) and photoreaction3) of 5-bromouracils have, therefore, been investigated. However, little attention has been paid to oxidation of these compounds. As a part of the investigation concerning a comparison of products on oxidation of nucleic acid bases and nucleosides between by peroxomonosulfate ion (HSO_5^-) and by peroxodisulfate ion ($S_2O_8^{2-}$),4) we studied the oxidation of 5-bromo- and 5-fluoro-1,3-dimethyluracils as model compounds.

A solution of 5-bromo-1,3-dimethyluracil (1a) (1 mmol) and $KHSO_5$ (1 mmol) in water (50 ml) was heated at 70 °C for 5 h under argon atmosphere. The reaction mixture was submitted to chromatography on ODS-silica gel.4) By elution with water, a fraction containing 5,5,6-trihydroxy-1,3-dimethyl-5,6-dihydrouracil (2) was obtained. Further elution with a mixture of water and acetonitrile led to the isolation of 1a (0.04 mmol, 4 %) and 5,5-dibromo-6-hydroxy-1,3-dimethyl-5,6-dihydrouracil (3)5) (0.33 mmol, 33 % yield). The fraction containing 2 was further separated by gel-filtration chromatography (Tosoh HW-40) with water to give 26) (32 %). Similarly treatment of 5-fluoro-1,3-dimethyluracil (1b) with $KHSO_5$ gave 2 (11 %) together with recovered 1b (59 %). On the other hand, reaction of 1a (1 mmol) with $Na_2S_2O_8$ (1 mmol) in water (50 ml) at 80 °C for 5 h under argon atmosphere gave a complex reaction mixture, which was chromatographed on silica gel with ethyl acetate to give 1,3-dimethylparabanic acid (4)7) (11

%), amalic acid (tetramethylalloxantine) (5)$^{8)}$(10 %), and recovered 1a (43 %). Under similar conditions, the reaction of 1b with $Na_2S_2O_8$ interestingly gave a 6,6'-dimeric product (6)$^{9)}$ (18 %) together with 4 (3 %), 5 (3 %), and recovered 1b (68 %). The structure of 6 resembles that of the dimeric product from γ-radiation of thymidine$^{10)}$ and the formation of 6 suggests that the oxidation by $Na_2S_2O_8$ is reasonably explained in terms of formation of a radical intermediate.



We thank Professor Kenichi Somekawa, Faculty of Engineering, Kagoshima University, for valuable support throughout the study.

References

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6) 2: Oil; ^{1}H-NMR (D_2O) δ 3.00 (Me), 3.01 (Me), 5.28 (H-6); (d_6-DMSO) δ 2.82 (Me), 2.85 (Me), 4.96 (H-6), 6.2-6.7 (broad, OH-5,5,6); ^{13}C-NMR (D_2O) δ 27.29, 28.27, 89.23, 92.13, 160.57, 176.61. The compound 2 was stable in D_2O for more than 2 days but labile in d_6-DMSO.

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9) 6: mp 290-296 °C; ^{1}H-NMR (d_6-DMSO) δ 3.15 (Me), 3.26 (Me), 9.30 (OH); (D_2O) δ 3.27 (Me), 3.39 (Me); (D_2O+NaOH, pD 13) δ 3.22 (Me), 3.37 (Me); ^{13}C-NMR (d_6-DMSO) δ 28.35, 32.47, 123.05, 130.74, 149.91, 159.91; MS, m/z (relative intensity) 310 (M^+, 16), 309 (100). Anal. Found: C, 46.39; H, 4.59; N, 17.78 %. Calcd for $C_{12}H_{14}N_4O_6$: C, 46.45; H, 4.55; N, 18.06 %.

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(Received September 12, 1991)