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Oxidation of Uracil Derivatives and Pyrimidine Nucleosides by Dimethyldioxirane: A New and Mild Synthesis of 5,6-Oxiranyl-5,6-dihydro and 5,6-Dihydroxy-5,6-dihydro-derivatives.

Paolo Lupattelli[a], Raffaele Saladino[b]* and Enrico Mincione[b]*.

a C.N.R. Centro di Studio delle Sostanze Naturali, Università di Roma "La Sapienza", p.le Aldo Moro 5, 00185 Roma. b Dipartimento AgrochimicoAgrobiologico, Università degli Studi di Viterbo "La Tuscia, via San Camillo de Lellis, 01100 Viterbo.

Abstract: The oxidation of title substrates with dimethyldioxirane afforded 5,6-oxiranyl-5,6-dihydro and cis- /trans-5,6-disubstituted-5,6-dihydro-derivatives.

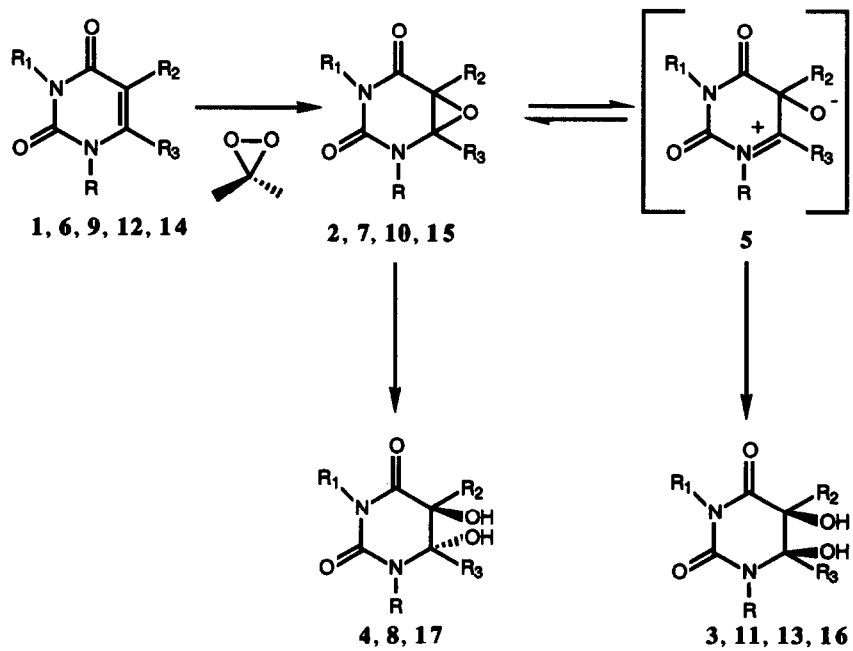
Because of possible biological implications, the oxidation of nucleic acids and their components has been extensively studied[1]. It was noted[2] that in most cases the primary products of nucleic acid components are not well known because of the complexity of product mixtures and the tendency of initial products to undergo further reactions. Moreover, due to the low reactivity of these substrates, towards electrophilic epoxidizing agents, no epoxidation takes place even with a prolonged reaction time and side reactions lead to undesidered products take place, as in the case of the oxidation of 1,3-dimethyl derivatives of pyrimidine bases with m-chloroperbenzoic acid[3].

A powerful and selective oxidant for this purpose, which performs under strictly neutral conditions, is dimethyldioxirane[4]. The oxidations performed with dimethyldioxirane often have the advantages of simple procedure, mild reaction conditions, ease of product isolation even in the case of sensitive epoxides of enol ethers[5], siliyl enol ethers[6] and α,β-unsaturated ketones, acids, esters and lactones[7]. In this communication we report that uracil derivatives and pyrimidine nucleosides may be conveniently converted into their 5,6-oxiranyl-5,6-dihydro- and 5,6-dihydroxy-5,6-dihydro-derivatives in good yield using dimethyldioxirane as oxidizing agent.

The oxidation of 1,3-dimethyluracil **1** with dimethyldioxirane[8] performed in CH_2Cl_2 at 25 °C afforded a mixture of three easily chromatographically separable products, 1,3-dimethyl-5,6-oxiranyl-5,6-dihydrouracil **2** (10%)[9], cis-1,3-dimethyl-5,6-dihydroxy-5,6-dihydrouracil **3** (50%)[10] and trans-1,3-dimethyl-5,6-dihydroxy-5,6-dihydrouracil **4** (25 %)[10] [Scheme]. The isolation of the epoxide **2** is very interesting because this compound was postulated to be the initial product in the oxidation of 1,3-dimethylpyrimidine derivatives with peracids[3] and in the

α-diketone sensitized photooxidation of pyrimidine bases[11], but to the best of our knowledge this is the first example of isolation and characterization of this epoxide. The formation of diols **3** and **4** may result from the ring opening of epoxide **2** performed by the water present in the dioxirane acetone solution. In fact, when the reaction was performed in presence of Na_2SO_4 as drying agent the yield of epoxide **2** increased (50 %)[12]. Moreover, when the reaction was carried out in presence of water (5 ml) only diols **3** (65%) and **4** (30%) were obtained. The formation of the cis diol **3** is inconsistent with the S_N2 ring opening mechanism through which the diol **4**, having the trans configuration should result. In accord with the previously reported hypothesis[11] it is resonable to suggest that the reaction proceeds, in part, via an α-stabilized nitrogen cationic intermediate **5**, in which a positive charge is localized on the N(1) position of the uracil ring. Bond formation of C-6 with water would now be expected to proceed with energetically favorable cisoid[13] (gauche) stereochemistry to yield the cis-diol[14].

SCHEME



1, 2, 3, 4 : R=R_1=CH_3, R_2=R_3=H. **6, 7, 8** : R=R_1=R_2=CH_3, R_3=H. **9, 10, 11**: R=R_1=R_3=CH_3, R_2=H. **12, 13**: R=Sugar, R_1=R_2=R_3=H. **14, 15, 16, 17**: R=Sugar, R_1=R_3=H, R_2=CH_3.

The oxidation of 1,3,5-trimethyluracil **6** (1,3-dimethylthymine) with dimethyldioxirane in CH_2Cl_2 at 25 °C afforded only two products; the 5,6-epoxide **7** (30 %)[15] and the trans-diol **8** (57%)[16]. Instead, the oxidation of 1,3,6-trimethyluracil **9**, under the previously described conditions, yielded the 5,6-epoxide **10** (37%)[17]

and the cis-diol **11** (53%)[18], while only a trace of trans-diol was recovered [Scheme]. On the basis of these data the presence of a methyl group on the 5,6-double bond increased the stability of 5,6-epoxide **7** and **10** which may be isolated in appreciable amount even in absence of drying agents. Moreover, the position of the methyl substituent is very important for the stereochemistry of the oxiranyl ring opening. In fact, in the case of epoxide **10** the nucleophilic attack on C-6[19] via S_N2 mechanism is prevented by the steric hindrance of the methyl group. Thus the epoxide is stable enough to be the main product, the cis-diol being the only isolated ring opening product. On the other hand, epoxide **7**, which lacks of C-6 substituent, is easily opened to give the trans-diol, providing better method than others previously reported procedures [1d,2a,20].

The oxidation of 2',3',5'-tri-O-acetyluridine **12**[21] with dimethyldioxirane in CH_2Cl_2 at 25 °C afforded exclusively cis diols **13** (70%)[18], while no epoxide was recovered even in the presence of Na_2SO_4 in the reaction mixture. Probably, in this case, the sugar moiety may aid the oxiranyl ring opening[22]. The oxidation of 5'-O-trityl thymidine **14**[23] with dimethyldioxirane in similar reaction conditions afforded 5,6-epoxide **15** (10%)[24], cis-diol **16** (33%) and trans-diol **17** (12%) [Scheme]. In this case we did not detect any trace of oxidation of the C_3'-OH group of the sugar moiety, in spite of general reactivity of alcohols with dimethyldioxirane[4]. It is interesting to note that in the case of pyrimidine nucleosides, as previously shown for uracil derivatives, the presence of substituents on 5,6-double bond stabilized the epoxide to permit the formation of trans-diols. Work is in progress in our laboratories to find a general synthesis of C-6 substituted uracil derivatives *via* nucleophilic ring-opening of the isolated 5,6-oxiranyl-5,6-dihydro-derivatives.

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8. Dimethyldioxirane has been prepared from potassium peroxysulfate as a distilled 0.05 M solution in acetone using the procedure desribed by Murray: Murray, R.W.; Jeyaraman, R.

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9. 1,3-Dimethyl-5,6-oxiranyl-5,6-dihydrouracil **2**- oil, Mass spectrum m/e=156 (M+, 19%); IR ($CHCl_3$) vmax 1730 (CO) and 1650 (α,β-unsaturated ketone) cm^{-1}; ^1H-NMR ($CDCl_3$) δ ppm: 4.92 (1H, d J=3 Hz, CH), 4.30 (1H, d J=3 Hz, CH), 3.16 (3H, s, CH_3), 3.12 (3H, s, CH_3).
10. Diols **3** and **4** were identified by comparison with authentic samples prepared from **1** according to the methods reported in literature[2a].
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12. In these experimental conditions the yield of diols **3** and **4** decreased to 15% and 7% respectively.
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15. 1,3,5-Trimethyl-5,6-oxiranyl-5,6-dihydrouracil **6**-oil, Mass spectrum m/e=170 (M+, 7%); IR ($CHCl_3$) vmax 1730 (CO) and 1650 (α,β-unsaturated ketone) cm^{-1}; ^1H-NMR ($CDCl_3$) δ ppm: 4.44 (1H, s, CH), 3.08 (3H, s, CH_3), 3.00 (3H, s, CH_3), 1.37 (3H, s, CH_3).
16. Respect to the ^1H-NMR (DMSO-d_6) data reported in literature[1d], in the spectra recovered in $CDCl_3$ the methyl groups appear as distinct singlets at 3.0 and 3.15 δ.
17. 1,3,5-Trimethyl-5,6-oxiranyl-5,6-dihydrouracil **9**-oil, Mass spectrum m/e=170 (M+, 7%); IR ($CHCl_3$) vmax 1730 (CO) and 1650 (α,β-unsaturated ketone) cm^{-1}; ^1H-NMR ($CDCl_3$) δ ppm: 5.59(1H, s, CH), 3.36 (3H, s, CH_3), 3.30 (3H, s, CH_3), 2.20 (3H, s, CH_3).
18. Cis-diols were positive to metaperiodate/benzidine[2a] analysis.
19. It is known that nucleophiles attack the uracil ring in the C-6 electrophilic position: (a) Saito, I.; Ikeira, H.; Matsuura, T. *Tetrahedron Lett.* **1985**, 26, 1993-1994. (b) Fourrey, J.L.; Henry, G.; Jouin, P. *Tetrahedron Lett.* **1979**, 11, 951-954. (c) Inoue, H.; Ueda, T. *Chem. Pharm. Bull.* **1978**, 26, 2657.
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22. An example of the influence of sugar moiety on the reactivity of the C-6 position of pyrimidine nucleosides is reported by Tanaka in the regiospecific lithiation of uridine derivatives: Tanaka, H.; Hayakawa, H.; Shuji, I.; Haraguchi, K.; Miyasaka, T. *Tetrahedron* **1985**, 5, 861-866.
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24. 5'-O-Trityl-5,6-oxiranyl-5,6-dihydrothymidine **15**-oil, Mass spectrum m/e= 474 (M+, 5%); IR($CHCl_3$) vmax 1720 (CO) cm^{-1}; ^1H-NMR ($CDCl_3$) δ ppm: 7.45 (15H, m, Ph), 6.05 (2H, m, C_1'-H + C_6-H), 4.30 (1H, m, C_3'-H), 3.75 (1H, m, C_4'-H), 3.35 (2H, m, C_5'-H), 2.20 (2H, m, C_2'-H), 1.40 (3H, s, CH_3).

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