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Coupling of 1,3-Dimethylthymine and Adenine with Sodium Peroxodisulfate

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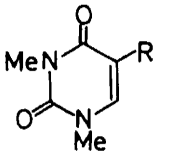
Heating of a solution of 1,3-dimethylthymine and adenine in water containing sodium peroxodisulfate at 80 °C resulted in the formation of their coupling products.

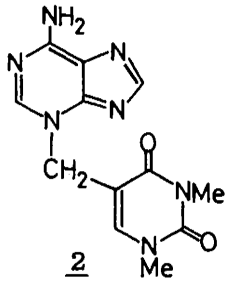
Crosslinks between DNA and biomolecules such as proteins are important as a DNA damage. Therefore, couplings between thymines and amino acids by UV-[1)] and γ-radiation[2)] have been reported. The reaction of thymine epoxides with amino acid derivatives has been also investigated.[3)] However little attention has been paid to the coupling between thymines and the other nucleobases, although the formation of thymine dimers by UV-[4)] and γ-radiation[5)] is known. In the course of an investigation of the oxidation of thymines by sodium peroxodisulfate,[6)] the reaction of 1,3-dimethylthymine (1) with $Na_2S_2O_8$ in the presence of adenine was studied.

A solution of 1 (3 mmol) and adenine (1 mmol) in water (50 ml) containing $Na_2S_2O_8$ (3 mmol) was heated at 80 °C for 4 h under nitrogen atmosphere. The reaction mixture was evaporated to give a solid mass which was extracted with chloroform. Droplet countercurrent chromatography (Tokyo Rikakikai, DCC-300-G2) was used for separation of the residue. The separation with $CHCl_3$-MeOH-H_2O (5:5:3) by the descending method led to the isolation of coupling products between 1 and adenine such as 2 (0.04 mmol) and 3 (0.04 mmol). The chloroform extract was submitted to chromatography on silica gel with low pressure pump. Two dimeric compounds of 1 such as 4[6)] (0.08 mmol) and 5: mp 282-285 °C (lit.[7)] 284-285 °C) (0.09 mmol) were obtained from the extract together with 5-hydroxymethyl-1,3-dimethyluracil (6)[6)] (0.34 mmol), 5-formyl-1,3-dimethyluracil (7)[6)] (0.11 mmol), and recovered 1 (2.01 mmol).

In order to elucidate the mechanism for the formation of 2 and 3, a treatment of 6 (1 mmol) with $NaHSO_4$ (4 mmol) in the presence of adenine (1 mmol) in water (50 ml) at 80 °C for 7 h under nitrogen atmosphere was attempted. The reaction gave 2 (0.02 mmol), 3 (0.03 mmol), 4 (0.05 mmol), 5 (0.04 mmol), and the recovered 6 (0.72 mmol). This suggests that 2, 3, 4, and 5 may be formed from 6. Benzylation of adenine with benzyl chloride is known to occur at N-3 and N-9 positions.[8] The structures of 2 and 3 were, therefore, determined by a comparison of spectral data[9] with the benzyladenines. Furthermore, the product 5 is of interest in connection with the formation of 5,6-dihydro-5-(α-thyminyl)thymine by UV-irradiation of DNA.[10]



1: R = Me
6: R = CH$_2$OH
7: R = CHO



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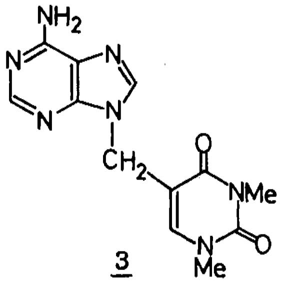

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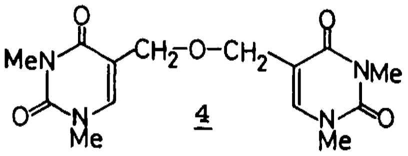

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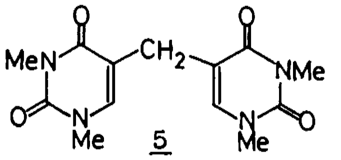

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9) 2: mp 234-237 °C; ^{1}H-NMR (d$_6$-DMSO) δ8.37 (s, 1H), 8.09 (s, 1H), 7.76 (s, 1H), 7.85 (s, 2H, NH$_2$), 5.13 (s, 2H), 3.33 (s, 3H), 3.13 (s, 3H); ^{13}C-NMR (d$_6$-DMSO) δ162.51, 154.82, 152.29, 150.97, 149.53, 145.65, 143.59, 120.36, 104.58, 46.24, 36.55, 27.32; Mass: m/e 288 (13), 287 (M$^+$, 73); λ_{max} in nm (εx10^{-3}) pH 1.0: 275.4(16.8), pH 11.4: 270.8(11.6). 3: mp 260-263 °C; ^{1}H-NMR (d$_6$-DMSO) δ8.15 (s, 1H), 8.09 (s, 1H), 7.95 (s, 1H), 7.18 (s, 2H, NH$_2$), 4.97 (s, 2H), 3.32 (s, 3H), 3.15 (s, 3H); ^{13}C-NMR (d$_6$-DMSO) δ162.37, 155.82, 152.30, 151.08, 149.35, 144.44, 140.79, 118.51, 105.98, 40.08, 36.45, 27.37; Mass: m/e 288 (15), 287 (M$^+$, 82); λ_{max} in nm (εx10^{-3}) pH 1.0: 264.8(14.8), pH 11.7: 264.2(14.5).

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