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REACTION OF 1,3-DIMETHYLURACIL, 1,3-DIMETHYLTHYMINE, AND CAFFEINE WITH CARBON RADICALS

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Reaction of 1,3-dimethyluracil, 1,3-dimethylthymine, and caffeine with carbon radicals formed on treatment of carboxylic acids, silver nitrate, and ammonium peroxodisulfate was investigated.

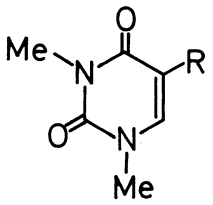
Increasing interest is being shown in reaction of nucleic acids with radical species. The reaction of nucleic acid bases with hydroxyl radical has been particularly studied as a model for the damage of nucleic acids by radiation.[1] However, little attention has been paid to reaction with carbon radicals except for some reports concerning methylation[2,3] and photoreaction[4] of purines, although some chemical carcinogens produce carbon radicals.[2] On the other hand, it is known that carbon radicals are formed upon treatment of carboxylic acids with silver nitrate and ammonium peroxodisulfate.[5] Also, previous reports show that hydroxyl radical reacts with pyrimidine bases to give addition product of the double bond at their 5- and 6-positions. These observations led us to examine treatment of 1,3-dimethyluracil (1a), 1,3-dimethylthymine (1b), and caffeine (2a) with carboxylic acids, silver nitrate, and ammonium peroxodisulfate in water.

Reaction of 1a with carboxylic acids such as pivalic acid and pyruvic acid, silver nitrate, and ammonium peroxodisulfate resulted in 39 and 41 % of conversion of 1a, respectively, but only a small amount of 8-tert-butyl-1,3-dimethyluracil (1c)[6] was isolated from the reaction product with pivalic acid. Under similar conditions, almost no reaction occurred in the case of 1b. On the other hand, the treatment of 2a with pivalic acid, pyruvic acid, 2-ketobutyric acid, 2-ketovaleric acid, and benzoylformic acid gave the corresponding 8-substituted caffeines (2c,d,e,f,g) in good yields based on 2a consumed. These results are summarized in Table 1.

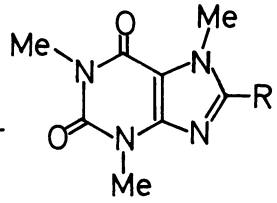
Table 1 shows that 1b hardly reacted with carbon radicals under conditions described, while it is known that thymine itself is more reactive with hydroxyl radical than other nucleic acid bases.[7] Furthermore, it is interesting that the reaction of caffeine with carbon radicals gave 8-substituted caffeines in good yields on the basis of caffeine consumed. Although some physiological and biological activities of caffeine were reported, that is, dose-related inhibition of chemical carcinogenesis in mouse skin,[8] inhibition of induction of endogenus C-type virus,[9] and inhibition of insect feeding,[10] our results suggest that caffeine may be a radical scavenger in nature.

Table 1. Reaction of 1,3-dimethyluracil, 1,3-dimethylthymine, and caffeine with carbon radicals[a)]

Substrates	RCOOH R	Conversion %	Product : Isolated Yield (%)[b)]
1a	t-Bu	41	1c: 6
1a	MeCO	39	
1b	t-Bu	16	
1b	MeCO	11	
2a	t-Bu	32	2c: 27
2a	MeCO	27	2d: 46
2a	EtCO	20	2e: 46
2a	PrCO	14	2f: 52
2a	PhCO	23	2g: 78



	R
1a	H
1b	Me
1c	t-Bu



	R
2a	H
2c	t-Bu
2d	MeCO
2e	EtCO
2f	PrCO
2g	PhCO

a) A mixture of substrate (2 mmol), RCOOH (2 mmol), $(NH_4)_2S_2O_8$ (2 mmol), $AgNO_3$ (2 mmol) and H_2O (150 ml) was refluxed under N_2 for 17 h.

b) Yield based on substrates consumed.

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6) All new compounds were fully characterized by ^{1}H-NMR, IR, and mass spectroscopy and by elemental analysis. The spectral data are as follows: 1c: mp 76-77.5 °C, IR (Nujol) 1690, 1660, 1630(broad) cm^{-1}, NMR($CDCl_3$) δ1.28(s, 9H), 3.30(s, 3H), 3.35(s, 3H), 6.95(s, 1H), MS m/e 196(M^+), 182, 181, 153, 124. 2c: mp 176-177 °C, IR(Nujol) 1710, 1660 cm^{-1}, NMR($CDCl_3$) δ1.46(s, 9H), 3.33(s, 3H), 3.50(s, 3H), 4.06(s, 3H), MS m/e 250(M^+), 235. 2d: mp 200-202 °C (lit.[11] 200 °C). 2e: mp 143-144 °C (lit.[11] 142-143 °C). 2f: mp 140-141 °C, IR(Nujol) 1710, 1690, 1670, 1600 cm^{-1}, NMR($CDCl_3$) δ1.00(t, 3H, J=7 Hz), 1.76(sext. 2H, J=7 Hz), 3.11(t, 2H, J=7 Hz), 3.40(s, 3H), 3.58(s, 3H), 4.31(s, 3H), MS m/e 264(M^+), 249, 236, 221, 208, 194. 2g: mp 176-177 °C, IR(Nujol) 1710, 1690, 1665, 1600 cm^{-1}, NMR($CDCl_3$) δ3.44(3, 3H), 3.60(s, 3H), 4.35(s, 3H), 7.45-7.6(m, 3H), 8.2-8.44(m, 2H), MS m/e 298(M^+), 297, 269.

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