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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.

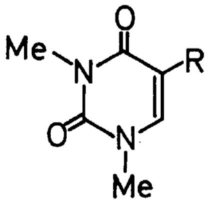
Table 1 shows that 1b hardly reacted with carbon radicals under conditions described, while it is known that thymine itself is more reactive with hydroxyl radical than other nucleic acid bases.$^{7)}$ Furthermore, it is interesting that the reaction of caffeine with carbon radicals gave 8-substituted 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)]

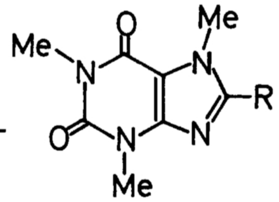
| Substrates | RCOOH<br>R | Conversion<br>% | Product<br>: Isolated Yield (%)[b)] |
|---|---|---|---|
| 1a | t-Bu | 41 | 1c: 6 |
| 1a | MeCO | 39 | |
| 1b | t-Bu | 16 | |
| 1b | MeCO | 11 | |
| 2a | t-Bu | 32 | 2c: 27 |
| 2a | MeCO | 27 | 2d: 46 |
| 2a | EtCO | 20 | 2e: 46 |
| 2a | PrCO | 14 | 2f: 52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

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.



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



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

References

1) S. Nishimoto, H. Ide, K. Nakamichi, N. Otsuki, and T. Kagiya, Chem. Lett., **1983**, 1441; T. Kagiya, R. Kimura, C, Komuro, K. Sakano, and S. Nishimoto, ibid., **1983**, 1471; M. N. Schuchmann and C. von Sonntag, J. Chem. Soc., Perkin Trans. 2, **1983**, 1525; D. K. Hazra and S. Steenken, J. Am. Chem. Soc., **105**, 4380 (1983) and references therein.

2) Y. Kawazoe, M. Maeda, and K. Nushi, Chem. Pharm. Bull., **20**, 1341 (1972); M. Maeda, K. Nushi, and Y. Kawazoe, Tetrahedron, **30**, 2677 (1974).

3) M. Ikehara, W. Limn, and T. Fukui, Chem. Pharm. Bull., **25**, 2702 (1977).

4) D. Elad, I. Rosenthal, and H. Steinmaus, J. Chem. Soc., Chem. Commun., **1969**, 305; J. Salomon and D. Elad, Photochem. Photobiol., **19**, 21 (1974); M. F. Zady and J. L. Wong, "Nucleic Acid Chemistry," ed by L. B. Townsend and R. S. Tipson, John Wiley & Sons, New York (1978), pp. 29-31.

5) For the reaction machanism, see J. M. Anderson and J. K. Kochi, J. Am. Chem. Soc., **92**, 1651 (1970).

6) All new compounds were fully characterized by $^1H$-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($CDCl_3$) $\delta$1.28(s, 9H), 3.30(s, 3H), 3.35(s, 3H), 6.95(s, 1H), MS m/e 196($M^+$), 182, 181, 153, 124. 2c: mp 176-177 °C, IR(Nujol) 1710, 1660 $cm^{-1}$, NMR($CDCl_3$) $\delta$1.46(s, 9H), 3.33(s, 3H), 3.50(s, 3H), 4.06(s, 3H), MS m/e 250($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($CDCl_3$) $\delta$1.00(t, 3H, J=7 Hz), 1.76(sext. 2H, J=7 Hz), 3.11(t, 2H, J=7 Hz), 3.40(s, 3H), 3.58(s, 3H), 4.31(s, 3H), MS m/e 264($M^+$), 249, 236, 221, 208, 194. 2g: mp 176-177 °C, IR(Nujol) 1710, 1690, 1665, 1600 $cm^{-1}$, NMR($CDCl_3$) $\delta$3.44(3, 3H), 3.60(s, 3H), 4.35(s, 3H), 7.45-7.6(m, 3H), 8.2-8.44(m, 2H), MS m/e 298($M^+$), 297, 269.

7) P. A. Cerutti, "Photochemistry and Photobiology of Nucleic Acid Bases," ed by S. Y. Wang, Acad. Press, New York (1976), Vol.II, pp. 375-401.

8) K. Rothwell, Nature, **252**, 69 (1974).

9) H. Yoshikura, Nature, **252**, 71 (1974).

10) J. A. Nathanson, Science, **226**, 184 (1984).

11) G. Ehrhart and I. Hennig, Arch. Pharm., **289**, 453 (1956).

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