Notes

[Chem. Pharm. Bull. 22(12)2979—2981(1974)] CDC 547.854.4.04

Heterocycles Related to Nucleotides. VII.[1] Reactions of Dimethyluracil and Dimethylthymine with Benzoyl Peroxide[2]

Masato Aiura and Yuichi Kanaoka

Faculty of Pharmaceutical Sciences, Hokkaido University[3]

(Received March 7, 1974)

While radical reactions of heterocyclic compounds have been studied for some time,[4] relatively little is known about the reactions of radical species with heteroaromatics compared with those of numerous ionic reactants in the chemistry of aromatics. In order to make a brief survey and a general estimate of the reactivities of heteroaromatics toward radical reagents, we have selected benzoyl peroxide **1** as a typical reagent in the course of our synthetic studies in the heterocyclic series.[2,5,6] For example, systems containing electron-rich five-membered heteroaromatics such as pyrroles[2,6b] and indoles[5,6] reacted with **1** under mild conditions to give their benzoyloxy derivatives in good yields.

Homolytic reactions in the nucleic acid chemistry seemed particularly interesting to us, but are as yet nearly unknown. Although examples of chemical carcinogeneses caused by homolytic reagents have appeared[7] and the interesting relevant C-methylation has recently been reported by Kawazoe, *et al.*,[8] homolytic chemical modification of these biopolymers are rarely found in a flood of literature in this field. In this paper we describe exploratory experiments on the reactions of benzoyl peroxide **1** with dimethyluracil **2a** and dimethylthymine **2b** as a preliminary study on the homolytic reactions of nucleotides.

1,3-Dimethyluracil **2a** was reacted with equimolar amount of **1** in refluxing acetonitrile for 12 hr. After preparative thin-layer chromatography (TLC) 1,3-dimethyl-5-phenyluracil **3** (mp 144—145° (lit.,[9] mp 147—148°); *m/e* 216 (M^+)); 8% (The corrected yield was 20% based on unrecovered **2a**) was isolated in addition to the recovered **2a** (63%). 1,3-Dimethylthymine **2b** was similarly reacted, for 24 hr in this case, to give 5-benzoyloxymethyl-1,3-dimethyluracil **4** (mp 143—144°, 25% (the corrected yield as above, 53%)). This structure was established by spectral data and elemental analysis. The nuclear magnetic resonance (NMR) spectrum showed singlet peaks at δ 3.36, 3.41 and 5.34, in an intensity ratio of 3:3:2, which are attributed to the two N-methyl groups and the newly formed methylene group, respectively.

1) Part VI: E. Sato and Y. Kanaoka, *Chem. Pharm. Bull.* (Tokyo), **22**, 799 (1974).
2) Reactions of Heteroaromatics and Aromatics with Benzoyl Peroxide. III. Part II: M. Aiura and Y. Kanaoka, *Heterocycles*, **1**, 237 (1973).
3) Location: *Kita 12, Nishi 6, Sapporo, 060, Japan.*
4) R.O.C. Norman and G.K. Radda, "Advances in Heterocyclic Chemistry," Vol. 2, ed. by A.R. Katritzky, Academic Press, New York, 1963, p. 131.
5) Y. Kanaoka, M. Aiura and S. Hariya, *J. Org. Chem.*, **36**, 458 (1971).
6) *a*) Y. Kanaoka, and M. Aiura, Absts. of Papers, The 3rd International Congress of Heterocyclic Chemisty, Sendai, 1971, p. 457; *b*) M. Aiura and Y. Kanaoka, Absts. of Papers, Symposium of the Heterocyclic Chemistry, Nagoya, 1973, p. 127.
7) *a*) Y. Kawazoe, and M. Araki, *Chem. Pharm. Bull.* (Tokyo), **19**, 1278 (1971); *b*) H. Hoshino, G. Chihara, and F. Fukuoka, *GANN*, **61**, 121 (1970); *c*) F. Minisci, R. Glli, V. Malatesta and T. Coronna, *Tetrahedron*, **26**, 4053 (1970).
8) Y. Kawazoe, M. Maeda and K. Nushi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1341 (1972).
9) J.H. Burckhalter and H.C. Scarborough, *J. Am. Pharm. Assoc.*, **44**, 545 (1955).

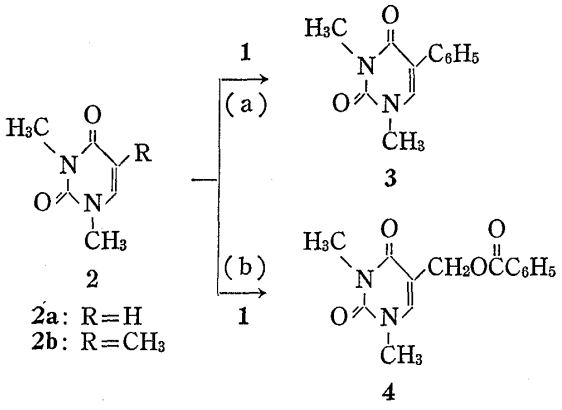

Chart 1

Thermolysis of **1** is known to yield two benzoyloxy radical **5**, some of which, by loss of carbon dioxide, yield phenyl radicals **6** which participate in the arylation of aromatic substrates, usually by way of σ-complex **8** with radical character, to give phenyl products **10**. Alternatively, benzoyloxy radicals **5** also react with aromatic substrates to give esters **9** by way of a related σ-complex **7**, which loses a hydrogen atom in the presence of appropriate hydrogen acceptors to form benzoyloxy products **9** (Chart 2).[10a,11a] In homolytic substitution of aromatics with **1**, usually phenylation to **10** is a major reaction accompanied by benzoyloxylation to form **9** as a side reaction. Benzoyloxylation increases with the reactivity of the aromatic substrates toward homolytic attack.[10b] Such dual behaviors of **1**, phenylation and benzoyloxylation, were now typically demonstrated in these results with **2a** and **2b** (Chart 1).

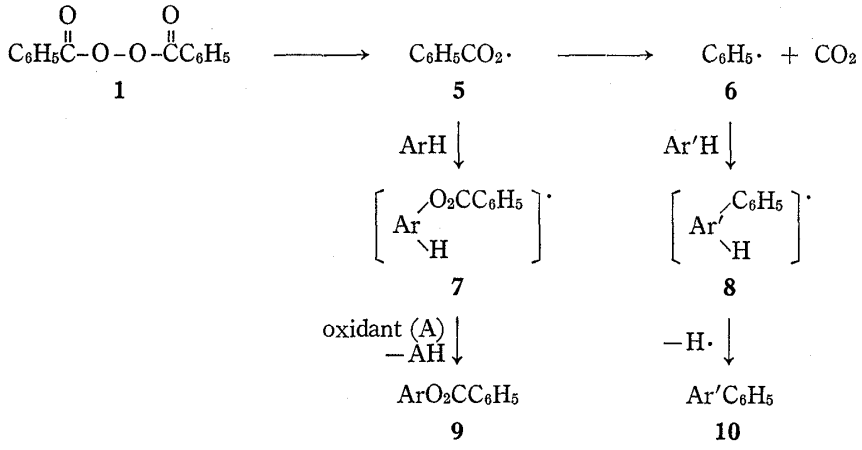

Chart 2

Reactions at the 5,6-double bond of the pyrimidine nucleotides have drawn considerable attention since, for example, template-activity, photolesions and photodimerization, ability to be incorporated into t-ribonucleic acid (tRNA) and deoxyribonucleic acid (DNA), and therefore potential cytotoxic activity, are intimately associated with the 5,6-unsaturation and substitution.[12,13] Homolytic reactivities of the 5,6-positions have been argued particularly in relation to radio- and photochemistry of the pyrimidine nucleotides.[14] Free valence value, a simple parameter which is assumed to be pertinent to homolytic reactivity,[10c,15] is highest at the 5-carbon of the uracil molecule: 5-, 0.526; 6-, 0.434.[16] The above result that **3** is a sole product from **2a** is in agreement with this theoretical prediction. By contrast,

10) *a*) G.H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, London, 1960, p. 34; *b*) *Idem, ibid.*, p. 116; *c*) *Idem, ibid.*, p. 14.
11) *a*) W.A. Pryor, "Free Radicals," McGraw-Hill, New York, 1966, p. 253; *b*) *Idem, ibid.*, p. 91.
12) B.R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," J. Wiley, New York, 1967.
13) A. Goldin, H.B. Wood Jr., and R.E. Engle, *Cancer Chemother. Rep.*, **1**, 1 (1968).
14) *a*) J.G. Bun, "Advances in Photochemistry," Vol. 6, ed. by W.A. Noyes, Jr., G.S. Hammond and J.N. Pitts Jr., Interscience Publishers, New York, 1968. p. 193; *b*) B. Pullman and A. Pullman, "Progress in Nucleic Acid Research and Moleculaer Biology," Vol. 9, ed. by J.N. Davidson and W.E. Cohen, Academic Press, New York, 1969, p. 328; *c*) A.J. Lomant and J.R. Fresco, *ibid.*, Vol., **12**, 1972, p. 1.
15) A. Streitwieser, Jr., "Molecular Orbital Theory", J. Wiley, New York, 1961, p. 329, 339.
16) B. Pullman and A. Pullman, "Quantum Biochemistry," Interscience Publishers, New York, 1963, p. 279.

homolytic reactivity of the methyl group of thymine derivatives has been little recognized. The conversion of **2b** into **4** on reaction with **1** is remarkable since only very few examples are known of the benzoyloxylation of the methyl group attached to a benzene ring.[17] Such a functionalization at the methyl of thymine derivatives by means of **1** is even synthetically important in view of that 5-hydroxymethylpyrimidines are of interest because of their biological activity[19] as well as chemical behavior.[20]

Thus homolytic reactions of nucleotides will be interesting both in chemical modification and synthetic aspects in the nucleic acid chemistry.

Experimental[21]

1,3-Dimethyl-5-phenyluracil 3——A solution of 420 mg (3 mmole) of **2a**[22] and 726 mg (3 mmole) of **1** in 6 ml of CH_3CN was refluxed for 12 hr. The solvent was removed *in vacuo*, and the remaining mixture was extracted with 20 ml of EtOAc. The extract was washed with aq. $NaHCO_3$ to remove benzoic acid formed, and then with brine, dried (Na_2SO_4) and evaporated *in vacuo*. The residue, after preparative TLC (ether), gave **2a** (265 mg 63%) and **3** (52 mg, 8% (20%)). **3** was recrystallized from EtOAc–hexane to give colorless needles, mp 144—145° (lit.,[9] 147—148°). Mass Spectrum *m/e*: 216 (M^+). NMR ($CDCl_3$), δ: 3.38 (s, 1-CH_3, 3-CH_3), 7.10—7.60 (m, 6H).

5-Benzoyloxymethyl-1,3-dimethyluracil 4——A solution of 310 mg (2 mmole) of **2b**[23] and 484 mg (2 mmole) of **1** in 6 ml of CH_3CN was refluxed for 24 hr. The solvent was evaporated *in vacuo*, and the residue was extracted with 20 ml of EtOAc. The extract was washed with aq. $NaHCO_3$ to remove benzoic acid formed and then with brine and dried (Na_2SO_4). After the solvent was removed *in vacuo*, the resultant residue was subjected to preparative TLC (EtOAc) to give **2b** (155 mg, 50%) and **4** (121 mg, 25% (53%)). **4** was obtained as colorless prisms from EtOAc–hexane, mp 143—144°. *Anal.* Calcd. for $C_{14}H_{14}O_4N_2$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.23; H, 5.17; N, 10.13. UV λ_{max}^{EtOH} nm (log ε): 228 (4.24), 268 (4.06). Mass Spectrum *m/e*: 169 (base), 105, 96. NMR ($CDCl_3$), δ: 3.36 (s, CH_3), 3.41 (s, CH_3), 5.24 (s, CH_2), 7.20—7.60 (m, 4H), 7.90—8.15 (m, 2H).

Acknowledgement This work was supported in part by a grant from the Naito Foundation.

17) The only examples[18] are benzoyloxylation of chroman derivatives in connection with vitamin E chemistry, in which the hydroxy group *ortho* to the methyl may participate.
18) *a*) G.E. Inglet and H.A. Mattill, *J. Am. Chem. Soc.*, **77**, 6552 (1955); *b*) C.T. Goodhue and H.A. Ricley, *Biochem. Biophys. Res. Comm.*, **17**, 549 (1964).
19) T.L.V. Ulbricht, "Progress in Nucleic Acid Research and Molecular Biology," ed. by J.N. Davidson and W.E. Cohen, Vol. 4, Academic Press, New York, 1965, p. 189.
20) D.V. Santi and A.L. Pogolotti, Jr., *Tetrahedron Letters*, **1968**, 6159.
21) Melting points are uncorrected.
22) D. Davidson and O. Bandisch, *J. Am. Chem. Soc.*, **48**, 2379 (1926).
23) T.B. Johnson and S.H. Clapp, *J. Biol. Chem.*, **5**, 49.