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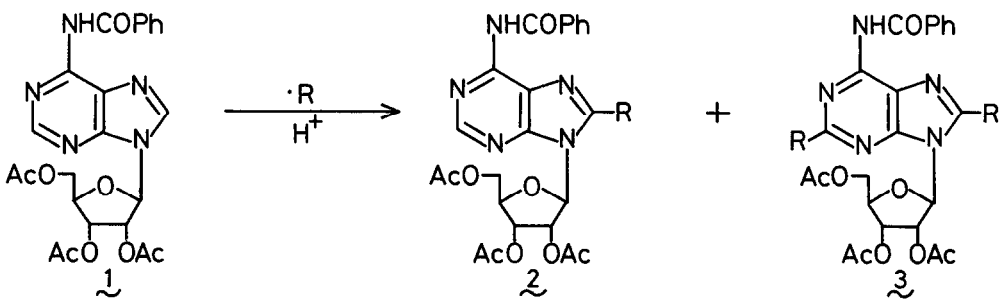
FACILE HOMOLYTIC SUBSTITUTION OF N(6)-BENZOYLADENOSINES

Yoshifumi Maki*, Keiji Kameyama, Magoichi Sako, and Kosaku Hirota
Gifu College of Pharmacy, 6-1, Mitahora-higashi 5 chome, Gifu, 502, Japan

Summary : Contrary to adenosine, N(6)-benzoyl-2',3',5'-tri-O-acetyladenosine 1 undergoes smoothly homolytic methylation, hydroxymethylation, acetylation, and carbamoylation in the acidic medium at the C(8)-position and subsequently at the C(2)-position.

Our previous works have demonstrated that N(6)-acyl groups in 9-substituted adenines alter the preferential site of protonation and alkylation from N(1) to N(7), and accelerate markedly the C(8)-hydrogen exchange.[1,2] These observations are promissingly applicable to efficient chemical modifications of 9-substituted adenines.

We report here that N(6)-benzoyl-2',3',5'-tri-O-acetyladenosine 1 undergoes with ease homolytic methylation, hydroxymethylation, acetylation, and carbamoylation in the acidic medium at the C(8)-position, which subsequently occur at the C(2)-position. The present results provide a new method for the direct introduction of the C-substituents at the C(8)-position and at both the C(8)- and C(2)-position of adenosine.[3]



Scheme 1

Methyl, hydroxymethyl, acetyl, and carbamoyl radicals were generated by reaction systems which have been extensively studied by Minisci and co-worker.[4] The reaction of the N(6)-benzoyladenosine 1 with these radicals was carried out in an acidic solution(50%-acetic acid–5N-sulfuric acid) at 10°C for 1hr. 8-Substituted adenosine 2 and 2,8-disubstituted adenosine 3 thus produced were isolated by silica gel chromatography, although the homolytic hydroxymethylation and acetylation under the conditions employed resulted in the preferential formation of 8-hydroxymethyladenosine 2b and 2,8-diacetyladenosine 3c, respectively (see Table)

Table Homolytic Methylation, Hydroxymethylation, Acetylation, and Carbamoylation of N(6)-Benzoyl-2',3',5'-tri-O-acetyladenosine 1

	Reaction systems	Generated radicals	Products[a] (yield % and mp°C)	
b	t-BuOOH, $FeSO_4 \cdot 7H_2O$	·Me	2a(50%, oil)	3a(35%, oil)
c	$(NH_4)_2S_2O_8$, $FeSO_4 \cdot 7H_2O$, MeOH	$\cdot CH_2OH$	2b(40%, 142°)	3b(trace)[e]
d	$(NH_4)_2S_2O_8$, $FeSO_4 \cdot 7H_2O$, MeCHO	·COMe	2c(trace)[e]	3c(85%, oil)
d	$(NH_4)_2S_2O_8$, $FeSO_4 \cdot 7H_2O$, $HCONH_2$	$\cdot CONH_2$	2d(20%, 187°)	3d(65%, 148°)

a All products gave satisfactory spectral data and microanalytical results consistent with their structures. 8-Methyl and 8-carbamoyladenosines, 2a and 2d, were deprotected to convert into the known adenosine derivatives. In all reactions the starting material 1 was recovered to some extent.

b To a solution of 1 (2 m mol) in 50% acetic acid(50 ml) was added 5N-sulfuric acid(6 ml). t-Butylhydroperoxide(20 m mol) and ferrous sulfate(30 m mol) in water(25 ml) were separately and simultaneously added to the acidic solution.

c To the acidic solution of 1 prepared in a similar manner to the case of methylation was added methanol(10 ml). Ammonium peroxodisulfate(20 m mol) and ferrous sulfate(30 m mol) in water(25 ml) were further added to the solution.

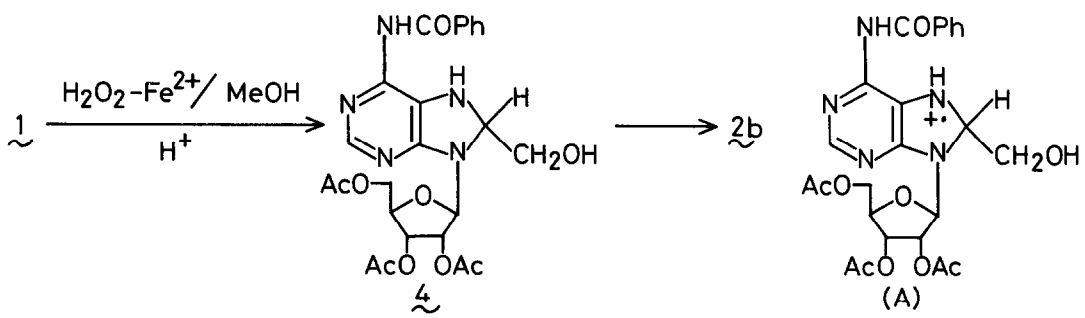
d Acetaldehyde or formamide(10 ml) in place of methanol in the hydroxymethylation was added to the acidic solution of 1. Ammonium peroxodisulfate (10 m mol) and ferrous sulfate(10 m mol) were employed for these reactions.

e 8-Acetyl and 2,8-dihydroxymethyladenosines, 2c and 3b, were not isolated in a pure state. Their formations were supported by n.m.r. spectroscopy.

Homolytic methylation of adenosine by using t-butylhydroperoxide in the presence of ferrous ions in an acidic medium has been shown to give 2- and 8-methyladenosines, and 2,8-dimethyladenosine in 5.4%, 7.2%, and 8.3% yields, respectively.[5] In the homolytic methylation of 1 under analogous conditions, however, no formation of an appreciable amount of 2-methyl derivative was observed, and the yields of 8-methyl and 2,8-dimethyl derivatives, 2a and 3a, are comparatively high (50%,35%). Change of the distribution of the methylated products, 2a and 3a, during the reaction support that 2a is the intermediate in the formation of 3a, indicating occurrence of the homolytic substitution at the C(8)-position with regioselectivity in the initial stage of the reaction.

The homolytic hydroxymethylation, acetylation, and carbamoylation of 1 also proceeded readily in comparison with these of adenosine and did not produce a detectable amount of 2-substituted derivatives.

When hydrogen peroxide was used in place of ammonium peroxodisulfate in the hydroxymethylation of 1, 7,8-dihydro-8-hydroxymethyl-N(6)-benzoyladenosine 4 was obtained in 55% yield. The 7,8-dihydroadenosine 4 was strikingly stable and showed the u.v. spectrum[λ_{max}^{MeOH}nm(ε): 282(5400), 330(9400)] characteristic of 7,8-dihydroadenosines.[6] Oxidation of 4 into 2b was achieved quantitatively by employment of 2,3-dichloro-5,6-dicyanobenzoquinone as an oxidant. C(8)-Homolytic methylation of some purines in the acidic medium[7] has been claimed to be initiated by the reaction of the N(7)-protonated species of purines with a methyl radical and proceed via an intermediacy of 7,8-dihydro-8-methylpurinyl cation radical. The formation of the 7,8-dihydro derivative 4 may be explained



Scheme 2

in terms of the one-electron reduction of a cation radical intermediate(A) presumably with a ferrous ion(Fe^{2+}), which could occur instead of hydrogen abstraction of (A) by a hydroxy radical($\cdot OH$)[8] leading to 2b.

High susceptibility of the N(6)-benzoyladenosine 1 to homolytic substitution in the acidic medium at the C(8)-position accommodates that the N(6)-benzoyl group in adenosine causes the change of the preferential protonation site [N(1)→ N(7)].[1]

Further studies on the synthetic application of the present results are now in progress.

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