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OXIDATIVE PHOTOCYCLIZATION OF *N*^{6}-BENZOYLADENOSINE DERIVATIVES. FACILE FORMATION OF THE QUINAZOLINOPURINE RING SYSTEM

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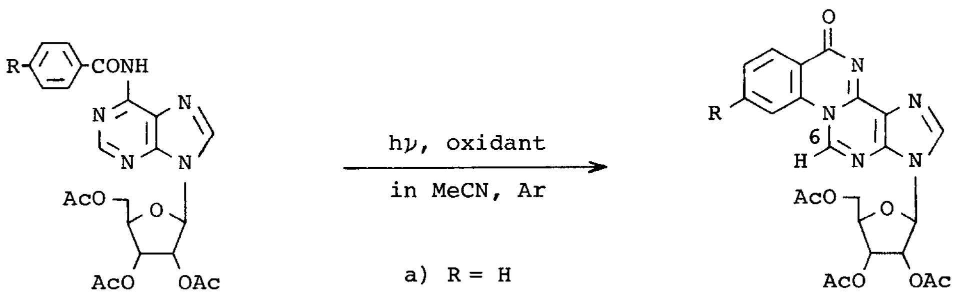
Abstract: Irradiation of 2',3',5'-tri-*O*-acetyl-*N*^{6}-benzoyl adenosine derivatives **1** in the presence of an oxidant resulted in a novel type of the oxidative photocyclization leading to 8-(2',3',5'-tri-*O*-acetyl-β-*D*-ribofuranosyl)quinazolino[2,1-*i*]purin-12-one derivatives **2**.

Oxidative and nonoxidative photocyclizations of enamides have been extensively investigated because of their wide variety of applicability to the synthesis of azaheterocycles containing naturally occurring alkaloids.[1-4] These types of the photoreactions can be regarded primarily as the photo-induced electrocyclic reaction of the 3-azahexatriene system $(-\overset{|}{C}=\overset{|}{C}-\underset{+}{\overset{H}{N}}=\overset{O^-}{C}-\overset{|}{C}=\overset{|}{C}-)$ to the cycloazahexadiene or cycloazahexatriene system involving the C-C bond formation. To our best knowledge, however, the oxidative photocyclization of the 1,3-diazahexatriene system $(-N=\overset{|}{C}-\underset{+}{\overset{H}{N}}=\overset{O^-}{C}-\overset{|}{C}=\overset{|}{C}-)$ involving the C-N bond formation has been unprecedented.[5]

In this paper we wish to report an intriguing photocyclization of 2',3',5'-tri-*O*-acetyl-*N*^{6}-benzoyladenosine derivatives **1** to novel quinazolino-[2,1-*i*]purine nucleosides **2** in high yields in the presence of an oxidant. The initial stage of the present reaction could be explained in terms of the C-N bond formation induced photochemically in the 1,3-diazahexatriene system which originates from the benzoyl-amidine moiety of **1**. The present results also provide a new method for the molecular manipulation of adenosines.



1

a) R = H
b) R = Me
c) R = Cl
d) R = CO_2Me

2

Scheme I

A mixture of 2',3',5'-tri-O-acetyl-N^6-benzoyladenosine (**1a**) [0.5mM] and pyrimido[5,4-g]pteridine N-oxide **3**[6,7] [1mM] in dry acetonitrile was irradiated with a 400W high pressure mercury arc lamp through a Pyrex filter at room temperature under argon for 3h. After removal of the solvent, the residue was chromatographed over silica gel as quickly as possible[8] to isolate 8-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)quinazolino[2,1-i]purin-12-one **2a** in 60% yield, together with pyrimido[5,4-g]pteridine **4** (95%) and unchanged **1a** (35%). The photocyclization of **1a** leading to **2a** was also accomplished by the employment of tetracyanoethylene (TCNE), p-dinitrobenzene (DNB), or iodine in the place of **3**. The photocyclization of **1a** was not observed in the absence of an oxidant. Thermal cyclization of **1a** to **2a** did not occur even under the oxidative conditions.

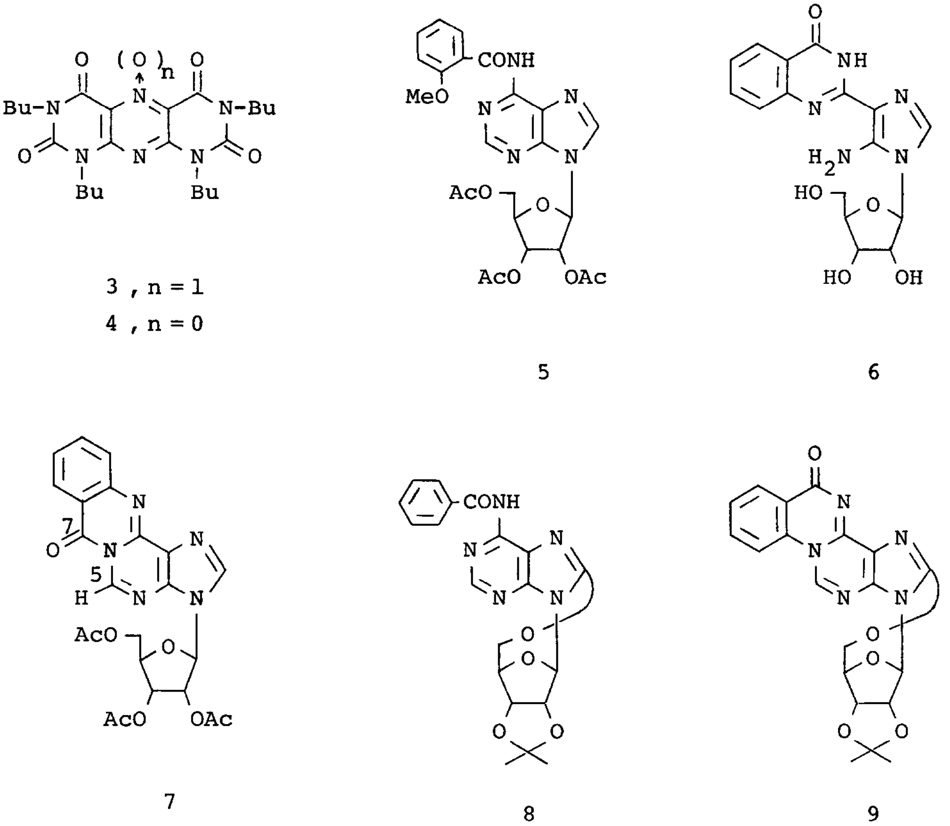
Analogous irradiation of N^6-(p-substituted)benzoyladenosines **1b-d** gave the corresponding quinazolino[2,1-i]purines **2b-d**. All results of the photocyclization of **1a-d** are summerized in Table I.

Table I Oxidative photochemical cyclization of 2',3',5'-tri-O-acetyl-N^6-benzoyladenosines **1**

Starting material	Oxidant	Irradiation time (h)	Product	M.P.(dec.) (°C)	Yield (%)*
1a	**3**	3	**2a**	193	60
1a	TCNE	9	**2a**		95
1a	DNB	4	**2a**		95
1a	I_2	5	**2a**		78
1b	**3**	3	**2b**	123	63
1b	DNB	3	**2b**		95
1c	DNB	3	**2c**	167	95
1d	DNB	4	**2d**	127	85

*Isolated yield

The structures of the products **2**[9] were confirmed on the basis of the following facts : 1) Irradiation of N^6-(o-methoxybenzoyl)adenosine derivative **5** in dry acetonitrile in the absence of an oxidant under argon for 2h caused the nonoxidative photocyclization accompanied by elimination of methanol to give **2a** independently in 56% yield.[10] 2) Treatment of **2a** with 0.1N NaOH/MeOH gave 4-amino-5-(4(3H)-quinazolinon-2-yl)-3-β-D-ribofuranosylimidazole **6**. 3) The quinazolino[2,1-i]purine derivative **2a** caused with ease the Dimroth-type rearrangement to give an isomeric quinazolino[2,3-i]purine derivative **7** upon treatment with methanol containing a catalytic amount of hydrochloric acid. The P.M.R. spectrum of **2a** showed a signal at δ 9.22 ascribed to a ring proton (C_6-H), whereas a ring proton signal (C_5-H) of **7** appeared at δ 9.54. This down-field shift of the ring proton (C_5-H) in the P.M.R. spectrum of **7** can be rationalized in terms of the anisotropic effect of the neighboring C_7-carbonyl group. The UV spectrum of **7** showed its absorption bands in the longer wavelength comparing with those of **2a**. (UV λ_{max}^{MeCN} nm for **7**: 395, 376, 360, 332, 315, 289, 277, 252, 238. UV λ_{max}^{MeCN} nm for **2a**: 306, 304, 279, 264, 253, 245, 238). The reaction of **7** with 0.1N NaOH/MeOH resulted in the formation of the ring opening product **6**, which is identical with the product obtained from **2a** in every respect.



3 , n = 1
4 , n = 0

5

6

7

8

9

Scheme II

In contrast to the above results, when 5'-O-nonprotected-N^6-benzoyladenosine derivative, e.g. N^6-benzoyl-2',3'-O-isopropylideneadenosine, was irradiated in the presence of **3**, TCNE, or DNB in a similar manner to the case of **1**, a different type of photocyclization initially occurred to give the corresponding 5'-O,8-cycloadenosine derivative **8**.[11] Further irradiation of **8** in the presence of an oxidant led to the formation of the corresponding quinazolino[2,1-*i*]purine cyclonucleoside **9** in high yield.

Thus the 5'-O-protection in the ribofuranosyl moiety of N^6-benzoyladenosines is requisite for the photochemical preparation of the quinazolino-[2,1-*i*]purine nucleosides **2**.

In the case of N^2-benzoyl-2',3',5'-tri-O-acetylguanosine, analogous photocyclization was not observed.

We are now investigating the scope and limitation of this type of the photocyclization.

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7 We have recently reported that the *N*-oxide **3** behaves as an electron acceptor and transfers efficiently its oxygen atom to the substrates without any side reactions under irradiation of UV-visible light. M. Sako, K. Shimada, K. Hirota, and Y. Maki, *Tetrahedron Lett.*, **1985**, *26*, 6493; *idem.*, *ibid.*, **1986**, *27*, 3877; idem., *J. Am. Chem. Soc.*, **1986**, in press.

8 The product **2a** undergoes the Dimroth-type rearrangement to the isomeric quinazolino[2,3-*i*]purine system **7** by contact with silica gel for a long period.

9 All new compounds described herein gave satisfactory microanalytical results and spectral data consistent with their structures.

10 Benzanilides with an *o*-methoxy group on the benzoyl ring undergo the nonoxidative photocyclization to give phenanthridones accompanied by elimination of methanol, which was widely applied to the regioselective photocyclization of enamides. (cf. Y. Kanaoka and K. Itoh, *Chem. Commun.*, **1973**, 647; I. Ninomiya, T. Kiguchi, and T. Naito, *ibid.*, **1974**, 81 ; I. Ninomiya, T. Kiguchi, O. Yamamoto, and T. Naito, *J. Chem. Soc., Perkin I*, **1979**, 1723; I. Ninomiya and T. Naito, in " The Alkaloids ", ed. by A. Brossi, Vol. XXII, Chapter 4, Academic Press, New York, **1983**.)

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