INTRAMOLECULAR CYCLIZATION OF PURINE NUCLEOSIDES BY N-HALOGENOSUCCINIMIDES/ACETIC ACID. A MECHANISTIC ASPECT ON THE C(8)-HALOGENATION OF PURINE NUCLEOSIDES

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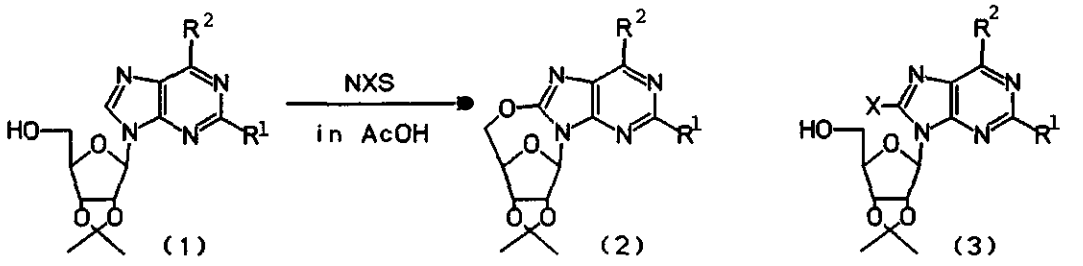
Abstract — Upon treatment with N-halogenosuccinimides in acetic acid, 2',3'-O-isopropylidene purine nucleosides (1) undergo an intramolecular cyclization leading to the corresponding 5'-O,8-cyclopurine nucleosides (2), which strongly suggests that the initial attack of a halogenium ion occurs at the N(7)-position rather than the C(8)-position in the purine ring under the conditions employed.

It is well known that treatment of purine nucleosides with a variety of halogenating agents such as halogen molecules, N-haloamides, and N-haloimides in various solvents results in the exclusive formation of the corresponding 8-halogenopurine nucleosides. [1] The mode of the C(8)-halogenation significantly depends upon the nature of the solvent and halogenating agents employed and the reaction has been generally considered to occur by the direct attack of a halogenium ion or a halogen radical at the C(8)-position in the purine ring. To the best of our knowledge, there has been no substantial examples suggesting the initial occurrence of N(7)-halogenation in the reaction of the purine nucleosides with the halogenating agents.



(1)

a) R^1=H, R^2=NH_2
b) R^1=H, R^2=NHCOPh
c) R^1=NHCOPh, R^2=OH
d) R^1=NH_2, R^2=OH

(2)

a) R^1=H, R^2=NH_2
b) R^1=H, R^2=NHCOPh
c) R^1=NHCOPh, R^2=OH
d) R^1=NH_2, R^2=OH

(3)

a) R^1=H, R^2=NH_2, X=Br
b) R^1=NHCOPh, R^2=OH, X=Br
c) R^1=NH_2, R^2=OH, X=I

Scheme 1

We now describe here an intramolecular cyclization of 2',3'-O-isopropylidene purine nucleosides (1) [2] induced by a combination of N-halogenosuccinimides (NXS) and acetic acid [3] leading to the corresponding 5'-O,8-cyclopurine nucleosides (2). [4] The reaction proceeds in preference to the C(8)-halogenation, except in the case of 2',3'-O-isopropylideneguanosine (**1d**), under the conditions employed and could be reasonably explained by considering the occurrence of the N(7)-halogenation in the initial stage of the reaction. Thus, the present result provides a chemical evidence supporting that the halogenium ion initially attacks the N(7)-position rather than the C(8)-position in the purine ring under the conditions employed.

A mixture of 2',3'-O-isopropylideneadenosine (**1a**) [25 mM] and N-iodosuccinimide (NIS) [75 mM] in acetic acid was stirred at ambient temperature for 1 day. The solvent was removed and the residue was chromatographed over silica gel by using chloroform-methanol as eluent to give 5'-O,8-cyclo-2',3'-O-isopropylideneadenosine (**2a**) in 89% yield based on (**1a**) consumed. No other products were detected by TLC analysis of the reaction mixture. The structure of (**2a**) was confirmed by spectroscopic comparison with the authentic sample prepared by base-catalyzed cyclization of 8-bromo-2',3'-O-isopropylideneadenosine (**3a**). [5]

The employment of N-bromosuccinimide (NBS) or N-chlorosuccinimide (NCS) in place of NIS in this reaction also allowed the conversion of (**1a**) into (**2a**) without any side-reactions. Analogous intramolecular cyclization was observed in the reaction of N^6-benzoyl-2',3'-O-isopropylideneadenosine (**1b**), N^2-benzoyl-2',3'-O-isopropylideneguanosine (**1c**), and (**1d**) with NXS in acetic acid. The results of these reactions are summarized in Table 1.

Table 1. Reactions of 2',3'-O-Isopropylidenepurine Nucleosides (1) with NXS in Acetic Acid [a]

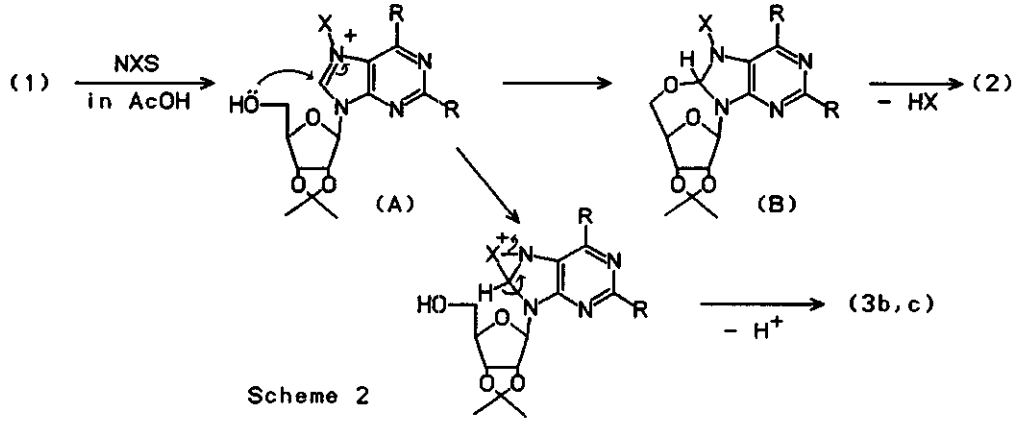
Entry No.	Purine Nucleoside	NXS	Conversion Yield (%) [b]	Products (2) (%) [c]	(3) (%) [c]
1	(**1a**)	NIS	27	(**2a**) (89)	-
2	(**1a**)	NBS	21	(**2a**) (95)	-
3	(**1a**)	NCS	22	(**2a**) (91)	-
4	(**1b**)	NIS	78	(**2b**) (96) [d]	-
5	(**1b**)	NBS	38	(**2b**) (97)	-
6	(**1c**)	NIS	46	(**2c**) (78) [e]	-
7	(**1c**)	NBS	94	(**2c**) (95)	(**3b**) (trace)
8	(**1d**)	NIS	80	(**2d**) (18) [f]	(**3c**) (60)

a) Reaction conditions: a mixture of (**1**) [25 mM] and NXS [75 mM] in acetic acid was stirred at ambient temperature for 1 day. b) The value was estimated by TLC densitometry. c) Isolated yield based on (**1**) consumed. d) Ref. 4b. e) Ref. 4a. f) M. Ikehara and K. Muneyama, Chem. Pharm. Bull., 1970, **18**, 1196.

The Table indicates that the presence of the N-benzoyl group in the purine nucleosides facilitates the 5'-O,8-cyclization (see Entry 4-7) and the reactions of (**1c**) with NBS and (**1d**) with NIS give the corresponding 8-halogenoguanosine derivatives (**3b**) [2], mp 235°C [6] and **3c**, mp 255°C, along with the 5'-O,8-cyclized products (see Entry 7 and 8).

When the reaction of (**1a**) with NBS was carried out in dry acetonitrile or N,N-dimethylformamide, the 8-bromoadenosine (**3a**) was obtained in high yield without the formation of the 5'-O,8-cycloadenosine (**2a**). No conversion of (**3a**) into (**2a**) was observed in further treatment of (**3a**) with NBS in acetic acid. These facts clearly indicate that the 5'-O,8-cyclization of (**1**) is markedly affected by the solvent employed and the 8-halogenopurine nucleosides (cf. **3**) is not an intermediate for the formation of (**2**) in the reaction of (**1**) with NXS in acetic acid.

Taking the above facts and the chemical behavior of NXS in acetic acid [7] into consideration, we propose a possible reaction sequence for the present reaction as outlined in Scheme 2. The reaction is initiated by the attack of a halogenium ion at the imidazole ring-nitrogen [N(7)] [8] to generate a purinyl cation (**A**). The subsequent intramolecular capture of the transient cationic species (**A**) by the 5'-hydroxy group on the 2',3'-O-isopropylidene protected ribofuranosyl ring [9] could give an intermediate (**B**) which is drived to the final product (**2**) as a result of elimination of hydrogen halide.



Scheme 2

The prominent substituent effect of the benzoyl group on the present 5'-O,8-cyclization accommodates our previous observations on the comparative increase in the nucleophilicity of the imidazole ring-nitrogen [N(7)] against the pyrimidine ring-nitrogen which arises from the introduction of the N^6-benzoyl group into adenosines, [10] supporting the occurrence of the N(7)-halogenation in the initial stage of the present reaction.

The formation of the C(8)-halogenated guanosines (**3b,c**) along with 5'-O,8-cycloguanosines (**2c,d**) under the present conditions may be explained in the terms of the concurrent migration of halogens in the initially formed intermediate (**A**) as depicted in Scheme 2. In fact, the halogenation of 5-

O-protected guanosine, e.g., 5'-O-acetyl-2',3'-O-isopropylideneguanosines, under the analogous conditions resulted in the exclusive formation of the corresponding C(8)-halogenated guanosines.

REFERENCES AND NOTES

1. M. Ikehara and S. Uesugi, Chem. Pharm. Bull., 1969, **17**, 348 and references cited therein; L. Goodman, in " Basic Principles in Nucleic Acid Chemistry ", Vol. 1, ed. by P. O. P. Ts'O, Academic Press, New York, 1974, p 146.
2. The predominant tautomer of the guanosine derivatives (**1c**), (**1d**), (**3b**), and (**3c**) or 5'-O,8-cycloguanosine derivatives (**2c**) and (**2d**) is the keto form at the C(6)-position. For convenience in drawing, the enol form is shown in the structures in Scheme 1.
3. Analogous intramolecular cyclization of nucleosides induced by NXS has been already observed in the reactions of 2',3'-O-isopropylidenetubercidin with NBS in a mixed solvent (acetone-methylene chloride) and 5-amino-1-(2,3-O-isopropylidene-β-D-ribofuranosyl)imidazole-4-carboxylate with NCS under alkaline conditions. The mechanisms proposed for these reactions, however, are different from that for the present 5'-O,8-cyclization. cf. K. Anzai and M. Matsui, Bull. Chem. Soc. Jpn., 1974, **47**, 417; G. Mackenzie, G. Shaw, and H. A. Wilson, Nucleosides and Nucleotides, 1984, **3**, 339.
4. Recently, we have demonstated facile syntheses of the 5'-O,8-cyclopurine nucleosides (**2**) starting from the corresponding purine nucleosides (**1**) which involves the intramolecular oxidative cyclization induced by lead tetraacetate or irradiation with UV-visible light in the presence of an electron acceptor. a) K. Kameyama, M. Sako, K. Hirota, and Y. Maki, J. Chem. Soc., Chem. Commun., 1984, 1658. b) M. Sako, K. Shimada, K. Hirota, and Y. Maki, ibid., 1986, 1704.
5. K. L. Nagpal and M. M. Dhar, Tetrahedron Lett., 1968, 47; M. Ikehara and M. Kaneko, J. Am. Chem. Soc., 1968, **90**, 497; M. Ikehara, M. Kaneko, and R. Okano, Tetrahedron, 1970, **26**, 5675.
6. The new products (**3b**) and (**3c**) gave satisfactory microanalytical and spectroscopic data consistent with their structures.
7. The NXS-carboxylic acids system is used as the source of a halogenium ion. cf. H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Inc., Menlo Park, California, 1972, p 432; M. Adinolfi, M. Parrilli, G. Barone, G. Laonigro, and L. Mangoni, Tetrahedron Lett., 1976, **40**, 3661; P. E. Sonnet, J. Org. Chem., 1980, **45**, 154.
8. Analogous initial step has been proposed in C(2)-bromination of imidazoles by bromine and oxygenation of pyridines using acetyl hypofluorite. cf. J. A. Joule and G. F. Smith, "Heterocyclic Chemistry", van Nostrand Reinhold, London, 1972, p 308 ; S. Rozen, D. Hebel, and D. Zamir, J. Am. Chem. Soc., 1987, **109**, 3789.
9. It has been documented that 2',3'-O-isopropylidene protection of purine and pyrimidine nucleosides facilitates the interaction between the 5'-hydroxy group and the aglycon under certain conditions. cf. D. V. Santi and C. F. Brewer, J. Am. Chem. Soc., 1968, **90**, 6236; Idem., Biochem., 1973, **13**, 2416; D. J. Cushly, S. R. Lipsky, and J. J. Fox, Tetrahedron Lett., 1968, 5393; B. A. Otter, E. A. Falco, and J. J. Fox, J. Org. Chem., 1969, **34**, 1390; K. Anzai and J. Uzawa, ibid., 1984, **49**, 5076; Ref. 4a and 4b.
10. Y. Maki, K. Kameyama, M. Suzuki, M. Sako, and K. Hirota, J. Chem. Research, 1984, (S) 388; (M) 3601 and references cited therein.

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