Reductive Cleavage of the O–C(8) Bond in 5′-*O*,8-Cycloadenosines. Intramolecular Protection of the 8-Position and the 5′-Hydroxy Group in Adenosines

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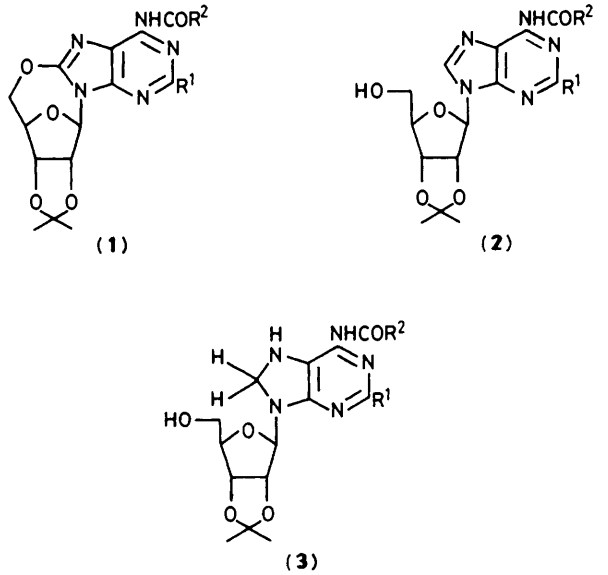
Upon treatment with $NaBH_3CN$ in acetic acid at ambient temperature, N^6-acyl-5′-*O*,8-cycloadenosines (**1**) with or without carbon functional groups on the 2-position undergo exclusively a reductive O–C(8) bond cleavage to give the corresponding N^6-acyladenosines (**2**).

5′-*O*,8-Cycloadenosines [*e.g.* (**1**)], prepared with ease by the oxidation of adenosines,[1] are labile in acidic or basic medium, undergoing exclusive C(5′)–O bond cleavage to give the corresponding 8-hydroxyadenosines.[1a–c] To the best of our knowledge, however, the reductive cleavage of the O–C(8) bond is unprecedented.

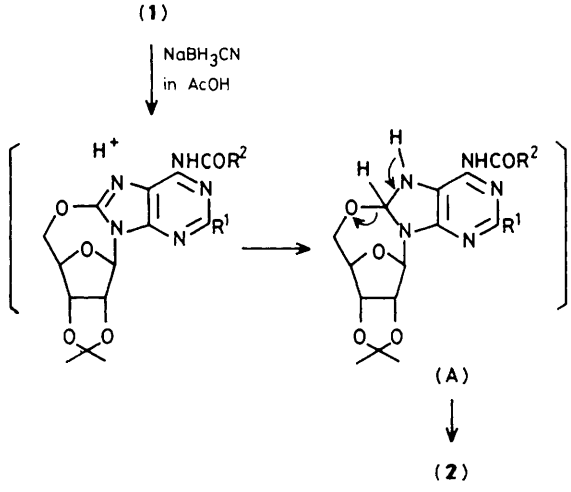
We report here the reductive O–C(8) bond cleavage of N^6-acyl-5′-*O*,8-cycloadenosines (**1**) leading to the corresponding N^6-acyladenosines (**2**). This conversion was achieved by taking advantage of the prominent substituent effect of the N^6-acyl group, causing an increase in the nucleophilicity of the imidazole ring nitrogen [N(7)],[2] and the appropriate reducing capacity of sodium cyanoborohydride ($NaBH_3CN$) under acidic conditions.[3]



a; R^1 = H, R^2 = Ph
b; R^1 = H, R^2 = Me
c; R^1 = $CONH_2$, R^2 = Ph
d; R^1 = Me, R^2 = Ph

Scheme 1

A mixture of N^6-benzoyl-5′-*O*,8-cyclo-2′,3′-*O*-isopropylideneadenosine (**1a**)[1e] (1.0 mmol) and $NaBH_3CN$ (3.0 mmol) in acetic acid was stirred at ambient temperature for 1 day. The solvent was removed and the residue was chromatographed over silica gel to provide N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine (**2a**) in 84% yield, together with a small amount of N^6-benzoyl-7,8-dihydro-2′,3′-*O*-isopropylideneadenosine (**3a**), m.p. 93 °C.† No other products were detected by t.l.c. The structure of (**2a**) was confirmed by spectroscopic comparison with an authentic sample.[1e] Treatment of (**2a**) with $NaBH_3CN$ in acetic acid led to the slow formation of (**3a**), which reverted smoothly to (**2a**) on



Scheme 2

† Satisfactory analytical and spectroscopic data were obtained for all new compounds described.

Table 1. Reduction of N^6-acyl-5′-*O*,8-cyclo-2′,3′-*O*-isopropylideneadenosines (**1**) with $NaBH_3CN$ in acetic acid.[a]

Starting material [m.p. (°C)]	Conv. (%)[b]	Product [m.p. (°C)]	Yield (%)[c]
(**1a**)[d]	66	(**2a**)[d]	84
(**1b**) [119]	55	(**2b**) [194]	62
(**1c**) [215]	52	(**2c**) [186]	62
(**1d**)[e]	60	(**2d**)[e]	64[e]

[a] Reaction conditions: (**1**) (1.0 mmol), $NaBH_3CN$ (3.0 mmol), acetic acid (10 ml), at ambient temperature, for 1 day. In every case, the corresponding N^6-acyl-5′-*O*,8-cyclo-7,8-dihydroadenosine (**3**) was detected as a minor product. [b] Estimated by t.l.c. densitometry. [c] Isolated yield based on (**1**) consumed. [d] Ref. 1e. [e] Compound (**1d**) and (**2d**) were contaminated by a small amount of 2-unsubstituted compound, (**1a**) or (**2a**), respectively. The yield of (**2d**) was estimated by n.m.r. spectrometry.

oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in dry acetonitrile.‡

Analogous reductive cleavage of the O–C(8) bond was observed in the reactions of the N^6-acetyl-5′-*O*,8-cycloadenosine derivative (**1b**) and the 2-substituted N^6-benzoyl-5′-*O*,8-cycloadenosine derivatives (**1c** and **1d**) with $NaBH_3CN$ in acetic acid (Table 1).

In sharp contrast to the foregoing results, 5′-*O*,8-cyclo-2′,3′-*O*-isopropylideneadenosine[1a] itself was stable under the reaction conditions. When tetrahydrofuran or *N*,*N*-dimethylformamide was employed as a solvent, reduction of (**1a**) with $NaBH_3CN$ did not proceed. The use of sodium borohydride in place of $NaBH_3CN$ resulted in preferential formation of N^6-benzyl-5′-*O*,8-cyclo-2′,3′-*O*-isopropylideneadenosine, m.p. 165 °C,§ rather than (**2a**). Thus the presence of an N^6-acyl group and the employment of $NaBH_3CN$ in acetic acid as reducing agent are pre-requisites for the reductive cleavage of the O–C(8) bond of the 5′-*O*,8-cycloadenosines.

‡ The 7,8-dihydroadenosine (**3a**) was autoxidised gradually at ambient temperature to (**2a**). Analogous autoxidation of 7,8-dihydroadenine derivative has been observed; *cf.* J. L. Kelley and J. A. Linn, *J. Org. Chem.*, 1986, **51**, 5435 and references cited therein.

§ The formation of this compound could be due to further reduction of the N^6-benzoyl group in (A) followed by smooth autoxidation of the product, N^6-benzyl-5′-*O*,8-cyclo-7,8-dihydro-2′,3′-*O*-isopropylideneadenosine.

In view of the foregoing results, and of the effect of N^6-acyl groups on the reactivity of adenosines,[2] the formation of (**2**) in this reaction can be explained by a mechanism involving the formation of a transient 5′-*O*,8-cyclo-7,8-dihydroadenosine (A) (Scheme 2): preferential protonation at the N(7) in (**1**) and nucleophilic attack of hydride ion on the activated C(8) afford the intermediate (A) in a manner similar to the case of N^6-acyladenosine derivatives.[2a,f] Subsequent O–C(8) cleavage in (A) occurs under the conditions employed.

The 2-substituted 5′-*O*,8-cycloadenosines (**1c** and **d**) were prepared by the reaction of (**1a**) with methyl radical or carbamoyl radical, respectively in acidic medium, in moderate yields. The present result indicates the effective utilisation of 5′-*O*,8-cyclisation as a means of protecting the 8-position in (**2a**); homolytic substitution of (**2a**) in acidic medium occurs at the C(8) and subsequently at C(2).[2d] A combination of homolytic substitution in the N^6-acyl-5′-*O*,8-cycloadenosines under acidic conditions and reduction of the resulting 2-substituted N^6-acyl-5′-*O*,8-cycloadenosines with $NaBH_3CN$ in acetic acid represent a new method for the introduction of carbon functional groups at C(2) of adenosines.[4]

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References

1 (a) M. Ikehara and M. Kaneko, *J. Am. Chem. Soc.*, 1968, **90**, 497; (b) K. L. Nagpal and M. M. Dhar, *Tetrahedron Lett.*, 1968, 47; (c) M. Ikehara, M. Kaneko, and R. Okano, *ibid.*, 1970, **26**, 5675; (d) K. Kameyama, M. Sako, K. Hirota, and Y. Maki, *J. Chem. Soc., Chem. Commun.*, 1984, 1658; (e) M. Sako, K. Shimada, K. Hirota, and Y. Maki, *ibid.*, 1986,, 1704.

2 (a) Y. Maki, M. Suzuki, and K. Ozeki, *Tetrahedron Lett.*, 1976, 1199; (b) Y. Maki, M. Suzuki, K. Kameyama, M. Kawai, M. Suzuki, and M. Sako, *Heterocycles*, 1981, **15**, 895; (c) Y. Maki, M. Suzuki, K. Kameyama, and M. Sako, *J. Chem. Soc., Chem. Commun.*, 1981, 658; (d) Y. Maki, K. Kameyama, M. Sako, and K. Hirota, *Tetrahedron Lett.*, 1983, **24**, 799; (e) K. Kameyama, M. Sako, K. Hirota, and Y. Maki, *Synthesis*, 1983, 849; (f) Y. Maki, K. Kameyama, M. Suzuki, M. Sako, and K. Hirota, *J. Chem. Research* 1984, (*S*) 388; (*M*), 3601.

3 M. M. Kreevoy and J. E. C. Hutchins, *J. Am. Chem. Soc.*, 1969, **91**, 4329; R. F. Borch, M. D. Bernstein, and H. D. Durst, *ibid.*, 1971, **93**, 2897.

4 K. Kikugawa, H. Suehiro, and R. Yanase, *Chem. Pharm. Bull.*, 1977, **25**, 1959; A. Matsuda, M. Shinozaka, T. Miyasaka, H. Machida, and T. Abiru, *ibid.*, 1985, **33**, 1766 and references cited therein.