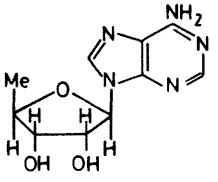
Intramolecular Free-radical Functionalisation of the Methyl Group of 5′-Deoxyadenosine

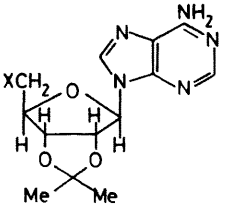
By DAVID GANI, ALAN W JOHNSON,* and MICHAEL F LAPPERT
(*School of Molecular Sciences, University of Sussex Falmer, Brighton, Sussex* BN1 9QJ)

Summary Anaerobic irradiation of 2′,3′-*O*-isopropylidene-8-phenylthio-5′-deoxyadenosine in the presence of t-butyl hydroperoxide causes rapid conversion into the 5′,8-cycloadenosine, formed by reaction of the C(8)-radical with the neighbouring 5′-methyl group, this provides an *in vitro* analogy for the functionalisation of this methyl group involved in many of the coenzyme B_{12}-controlled rearrangement reactions

5′-DEOXYADENOSINE (**1**) has been shown[1] to be an intermediate in some coenzyme B_{12}-catalysed rearrangement reactions, and its formation is ascribed to the abstraction of hydrogen from the substrate by the 5′-deoxyadenosyl radical, itself formed by homolytic fission of the cobalt–carbon bond of the coenzyme. After rearrangement of the substrate radical, the product radical then re-abstracts hydrogen from (**1**) to form the product and the 5′-deoxyadenosyl radical which then continues the catalytic cycle. Several attempts have been made to functionalise (**1**) in model systems but with only limited success. Thus Schrauzer *et al.*[2] claim to have produced coenzyme B_{12} in 'detectable' amounts by reaction of (**1**) with aqueous VCl_3 and B_{12r} (Co^{II} form) in the presence of oxygen, but experimental details are not available. No functionalisation of the methyl group was observed when (**1**) was incubated with enzyme-bound formylmethylcobalamin in the presence of ammonia.[3]

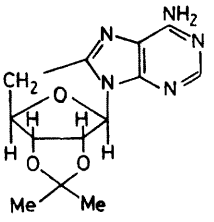


(1)

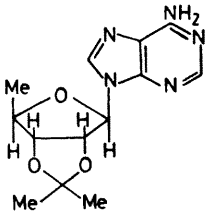


(2)

It seemed that the methyl group of (**1**) could be functionalised best by an intramolecular free-radical reaction, and in view of the facile cyclisation of 5′-adenosyl radicals [derived from photolyses either of the B_{12} coenzyme[4] or of 2′,3′-*O*-isopropylidene-5′-phenylthio-5′-deoxyadenosine (**2**, X = SPh)[5]] to 5′,8-cycloadenosines (*e.g.* **3**), it was decided to create a radical centre at the 8-position of (**1**) (a similar strategy to that adopted by Matsuda, *et al.*[5a] for the case of adenosine cyclisation), which should then be ideally situated for interaction with the methyl group. 2′,3′-*O*-Isopropylidene-5′-deoxyadenosine (**2**, X = H) was synthesised by an improved method (*cf.*, ref. 1) from 2′,3′-*O*-isopropylideneadenosine (**2**, X = OH), *via* the 5′-chloro- (**2**, X = Cl) and 5′-phenylthio- (**2**, X = SPh) derivatives. Desulphurisation (100 °C for 90 min) with Raney nickel then gave the required 5′-deoxy-derivative (**2**, X = H; 50%). Spectra, including mass spectra, of all the compounds described herein are in agreement with the structures shown.



(3)



(4)

For the creation of the C(8)-radical, compound (**4**) was brominated to the 8-bromo-derivative and then treated with sodium benzenethiolate in methanol to give the 8-phenylthio-derivative (60%). A smaller quantity (30%) of 8-methoxy-5′-deoxyadenosine was formed in the reaction and was separated off.

Irradiation of 2′,3′-*O*-isopropylidene-8-phenylthio-5′-deoxyadenosine under anaerobic conditions in acetonitrile solution in the presence of t-butyl hydroperoxide gave a high yield (75%, after chromatographic purification) of the 5′,8-cyclonucleoside (**3**), identical in all respects with the product derived from the irradiation of the coenzyme.[4a] The results of these experiments therefore provide an *in vitro* parallel for the enzymic radical induced functionalisation of the methyl group of 5′-deoxyadenosine.

We are indebted to the S.R.C. for financial support.

(*Received*, 22*nd September* 1980; *Com.* 1031.)

[1] O. W. Wagner, H. A. Lee, P. A. Frey, and R. H. Abeles, *J. Biol. Chem.*, 1966, **241**, 1751; B. M. Babior and J. S. Krouwer, *Crit Rev. Biochem.*, 1979, **6**, 35.
[2] G. N. Schrauzer, J. H. Grate, M. Hashimoto, and A. Maihub, 'Vitamin B_{12},' de Gruyter, Berlin, 1979, p. 511.
[3] J. S. Krouwer and B. M. Babior, *J. Biol. Chem.*, 1977, **252**, 2004.
[4] (a) A. W. Johnson and N. Shaw, *J. Chem. Soc.*, 1962, 4608; (b) K. N. Joblin, A. W. Johnson, M. F. Lappert, and B. K. Nicholson, *J. Chem. Soc., Chem. Commun.*, 1975, 441.
[5] (a) A. Matsuda, M. Tezuka, and T. Ueda, *Tetrahedron*, 1978, **34**, 2449; (b) A. Matsuda, K. Muneyama, T. Nishida, T. Sato, and T. Ueda, *Nucleic Acids Res.*, 1976, **3**, 3349.