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

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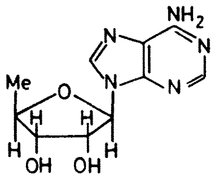
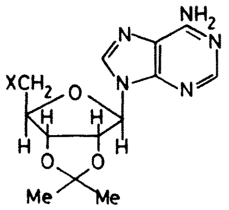
*Summary* Anaerobic irradiation of 2′,3′-*O*-isopropylidene-8-phenylthio-5′-deoxyadenosine in the presence of t-butyl hydroperoxide causes rapid conversion into the 5′,8-cycloadenosine, formed by reaction of the C(8)-radical with the neighbouring 5′-methyl group, this provides an *in vitro* analogy for 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]

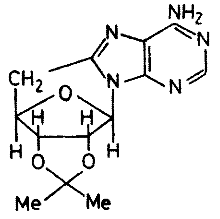


(1)

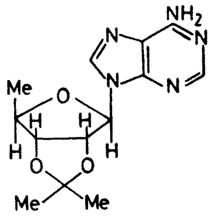


(2)

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.

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