Synthesis of (5′*R*)-[$^2H_1$]Adenosine

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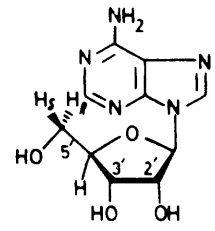
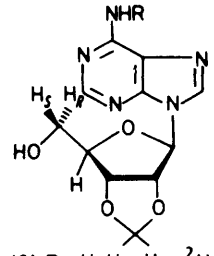
Summary The synthesis of (5′*R*)-[$^2H_1$]adenosine from 5′-[$^2H_2$]-2′,3′-*O*-isopropylideneadenosine is described.

THE nucleoside adenosine (**1**) plays a crucial role in a wide variety of important biochemical transformations, some of the most interesting of which are those in which an apparent nucleophilic substitution takes place at C-5′ of the adenosine skeleton. Reactions of this type occur in conjunction with biological transmethylations[1,2] and in the formation of the coenzyme B_{12}.[1] It is of interest to determine

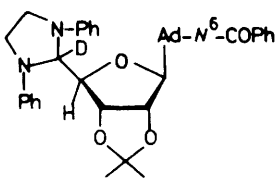
whether these enzymatic substitution reactions proceed with inversion or retention of configuration at C-5′ of (**1**). Since C-5′ is a prochiral centre, this question can only be settled by the use of adenosine which is chirally labelled at C-5′. We report a simple method for the synthesis of (5′*R*)-[$^2H_1$]adenosine (**2**).



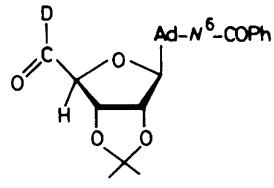
(1); $H_5 = H_R = {}^1H$
(2); $H_5 = {}^1H$, $H_R = {}^2H$



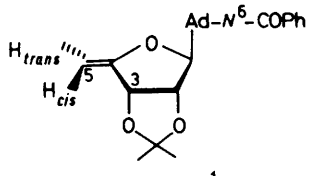
(3) R = H, $H_5 = H_R = {}^2H$
(4) R = PhCO, $H_5 = H_R = {}^2H$
(5) R = PhCO, $H_5 = {}^1H$, $H_R = {}^2H$



(6)



(7)



(8) $H_{cis} = H_{trans} = {}^1H$
(9) $H_{cis} = {}^2H$, $H_{trans} = {}^1H$

[5′-$^2H_2$]-2′,3′-*O*-Isopropylideneadenosine (**3**)[3] was converted into the benzoyl compound (**4**) (45%) by treatment with benzoyl chloride in pyridine followed by mild base hydrolysis.[4]† Oxidation of (**4**) with Me_2SO, dicyclohexylcarbodiimide, and dichloroacetic acid followed by trapping of the aldehyde with *NN*′-diphenylethylenediamine[5] gave (**6**) (56%). Removal of the aldehyde protecting group from (**6**) and conversion of the resulting aldehyde hydrate into the free aldehyde[5] gave (**7**) (72%). The deuteriated aldehyde was reduced (26%) with the adduct[6] prepared from (−)-α-pinene (*ca.* 75% optical purity) and 9-borabicyclo[3.3.1]nonane (9-BBN). The n.m.r. spectrum‡ of the resulting [5′-$^2H_1$]-N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine (**5**) indicated that the reduction had proceeded with a high degree of asymmetric induction. The n.m.r. spectrum of the corresponding unlabelled compound exhibits a double doublet for each of the C-5′ hydrogens: δ 3·73 [dd, 1H, J_{gem} 12·5, J(4′,5′a) 2·5 Hz, 5′-H_a] and 3·97 [dd, J_{gem} 12·5, J(4′,5′b) 2 Hz, 5′-H_b]. The labelled adenosine derivative (**5**) exhibited a doublet for each of the C-5′ hydrogens and the intensity of the upfield proton was much diminished: δ 3·77 [d, 0·2H J(4′,5′a) 2·5 Hz, 5′-H_a] and 3·91 [d, 0·8H, J(4′,5′a) 2 Hz, 5′-H_b]. It therefore appears that the optical purity at C-5′ of the reduction product (**5**) is *ca.* 60%.

The adduct of 9-BBN and (+)-α-pinene has been found to reduce [*formyl*-$^2H_1$]benzaldehyde to yield (*S*)-[$^2H_1$]benzyl alcohol.[6] Therefore, it was expected that the (−)-α-pinene–9-BBN adduct would reduce the deuteriated adenosine aldehyde (**7**) to yield the (*R*)-alcohol. However, the presence of asymmetric centres in (**7**) introduces an element of uncertainty into this prediction and so additional evidence is required to support this configurational assignment, which was obtained as follows. Treatment of N^6-benzoyl-2′,3′-*O*-isopropylideneadenosine [unlabelled (**5**)] with methanesulphonyl chloride in pyridine followed by potassium t-butoxide yields[4] (**8**) (45%). The n.m.r. spectrum of (**8**) shows a doublet for one of the vinyl hydrogens at C-5 and a quartet for the other C-5 hydrogen atom: δ 4·53 [d, 1H, J_{gem} 2·5 Hz, 5-H_a] and 4·67 [q, 1H, J_{gem} 2·5, J(3′,5′b) 1 Hz, 5-H_b]. Since *trans* allylic coupling constants are generally larger than *cis* allylic coupling constants,[7] the C-5 hydrogen atom (5-H_b) which appears as a quartet can be assigned to the vinyl hydrogen which is *trans* to the C-3 hydrogen. Conversion of (**5**) into (**9**) and analysis of the n.m.r. spectrum of the latter compound showed a singlet for one vinyl hydrogen and a doublet for the other; furthermore, the intensity of the *upfield* proton was much diminished: δ 4·57 [s, 0·15H, H_{cis}] and 4·66 [d, 0·85H, J(3,5b) 1 Hz, H_{trans}]. Therefore, the deuterium in (**9**) is *cis* to C-3. Since the formation of the deuteriated olefin (**9**) from the methane sulphonate almost certainly occurs *via* an *E*2 elimination process, it follows that the deuteriated adenosine derivative (**5**) has the *R* configuration at C-5′. Removal of the protecting groups from (**5**) by sequential treatment with methanolic ammonia and 90% trifluoroacetic acid[4] yields (**2**) (75%).

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† Apart from differences attributable to the presence of a deuterium label, all the labelled compounds reported here exhibited physical and chemical properties identical to those recorded in the literature for the corresponding unlabelled substances.

‡ All n.m.r. spectra were taken in $CDCl_3$ at 90 MHz.

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