Synthesis of (5'R)-[²H₁]Adenosine

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Summary The synthesis of (5'R)-[²H₁]adenosine from 5'-[²H₂]-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
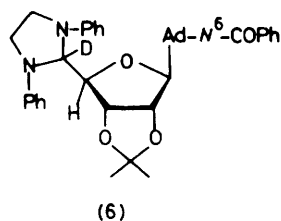
whether these enzymatic substitution reactions proceed with inversion or retention of configuration at C-5' of (1). Since C-5' is a prochiral centre, this question can only be settled by the use of adenosine which is chirally labelled at C-5'. We report a simple method for the synthesis of (5'R)-[2H1]adenosine (2).
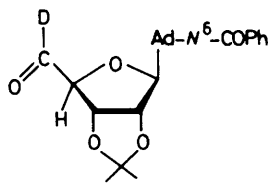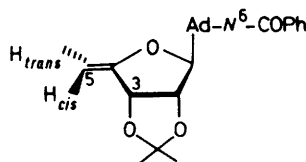

(1); $H_S = H_R = {}^1H$
(2); $H_S = {}^1H, H_R = {}^2H$
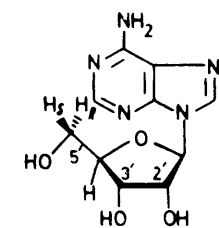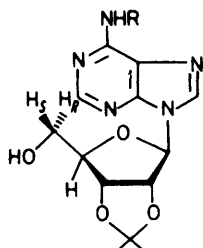
(3) R = H, $H_S = H_R = {}^2H$
(4) R = PhCO, $H_S = H_R = {}^2H$
(5) R = PhCO, $H_S = {}^1H, H_R = {}^2H$

(6)

(7)

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

[5'-²H₂]-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 Me₂SO, 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'-²H₁]-N⁶-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-²H₁]benzaldehyde to yield (S)-[²H₁]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 N⁶-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 E2 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%).

† 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 CDCl₃ at 90 MHz.

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