Synthesis of 2′,3′-Dideoxy-3-isoadenosine:† A New Structural Analogue of the Anti-HIV Active Compound, 2′,3′-Dideoxyadenosine

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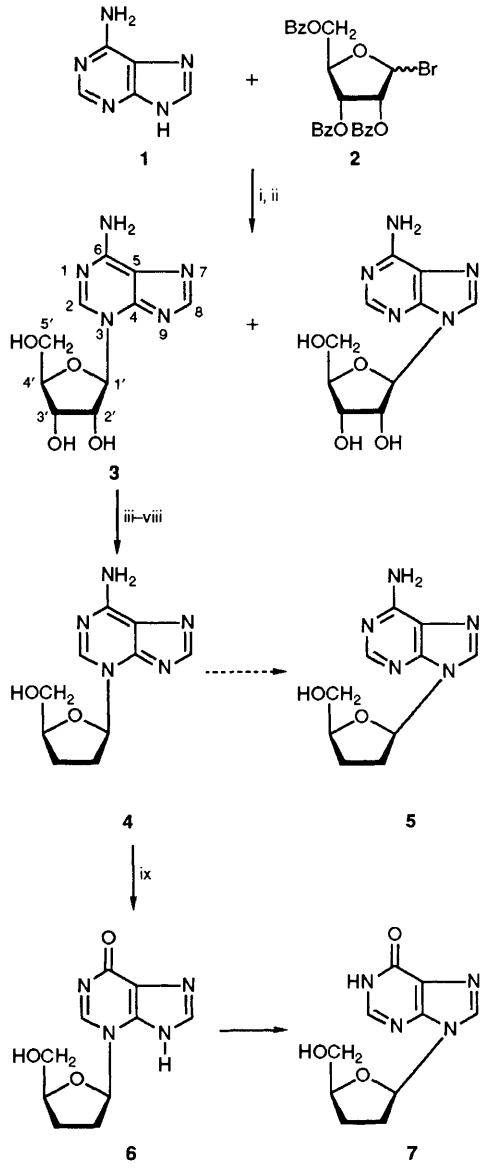
2′,3′-Dideoxy-3-isoadenosine, a unique structural isomer of the anti-HIV compound, 2′,3′-dideoxyadenosine, has been synthesized and biologically evaluated.

The synthetic nucleoside, 2′,3′-dideoxyadenosine (ddA),[1] in its biologically active triphosphate form, is known to be a chain terminator of the viral DNA of HIV and is a potent inhibitor of HIV reverse transcriptase, a critical enzyme in the replication of this virus.[1–3] Although a number of analogues of dideoxyadenosine have been synthesized (see for example, refs. 4–9), little is known about regioisomeric structures of this compound that involve modification in the position of attachment of the glycosidic bond to the base moiety. We report on the synthesis and biological investigation of 2′,3′-dideoxy-3-isoadenosine, a unique dideoxynucleoside.

The starting compound for the synthesis was 3-ribofuranosyladenine **3**, which was prepared in two steps, first by

† 3-Isoadenosine = 3-β-D-ribofuranosyladenosine.



Scheme 1 *Reagents and conditions*: i, MeCN, 50 °C; ii, tetrahydrofuran (THF), MeOH, NH_3, 0 °C; iii, Bu^tMe_2SiCl, 4-dimethylaminopyridine (DMAP), Et_3N, dimethylformamide (DMF), CH_2Cl_2; iv, Im_2CS, DMF, 25 °C; v, Bu_3SnH, AIBN, toluene, 110 °C; vi, Im_2CS, DMAP, DMF, 25 °C; vii, Bu_3SnH, AIBN, toluene, 110 °C; viii, Et_4NF, MeCN; ix, Adenosine deaminase (ADA), pH 7.4 (Bz = PhCO; Im_2CS = 1,1′-Thiocarbonyldiimidazole

coupling of 1-bromo-2,3,5-tribenzoyl-D-ribofuranose with adenine (21% yield of the separated 3-isomer), and then deprotection with methanolic ammonia (72%).[10] Selective 5′-silylation of **3**, followed by deoxygenation *via* the cyclic thionocarbonate with tributyltin hydride and azoisobutyronitrile (AIBN), provided the 2′-deoxy compound as the major product.[6,11,12] Deoxygenation of the 3′-hydroxy group *via* its imidazolide[6] and deprotection of the 5′-silyl group gave the novel target dideoxynucleoside **4** (5% overall yield from **3**). The structure of **4** was established by UV data, by fast-atom bombardment high-resolution mass spectrometry ($C_{10}H_{13}N_5O_2$), and by high-field ^1H and ^{13}C NMR data.‡

2′,3′-Dideoxy-3-isoadenosine **4** is stable at ambient temperatures (or slightly above) in organic solvents, perhaps because its conversion to the thermodynamically more stable ddA **5**, if concerted, would require a forbidden 1,3-sigmatropic shift. However, it slowly isomerizes to ddA (λ_{max} 259 nm) in aqueous solutions at room temperature. Compound **4** (270 nm) is a substrate for mammalian adenosine deaminase but it is relatively slowly deaminated by this enzyme (<10% of the activity of adenosine) to give the corresponding dideoxyisoinosine (**6**, 261 nm). Dideoxyisoinosine **6** is also unstable at room temperature in aqueous solutions and slowly rearranges to ddI (**7**, 249 nm). This rearrangement is accompanied by a small amount of glycosidic bond cleavage to give hypoxanthine. The isomerization and cleavage reactions were followed by monitoring the appearance and increase in the UV absorption at 249 nm due to the production of ddI and hypoxanthine. The latter compound was separated from ddI by reversed-phase HPLC on a Waters C_{18} analytical column and both were spectrally identified.

2′,3′-Dideoxy-3-isoadenosine **4**, although a relatively close structural analogue of ddA, showed only low activity against HIV-1 and HIV-2 replication in MT-4 cells (E.D.$_{50}$ 264 and 321 μmol dm^{-3}, respectively). Under the same experimental conditions ddA showed E.D.$_{50}$ values of 4.1 and 6.0 μmol dm^{-3}, respectively, against HIV-1 and HIV-2. Compound **4** was not cytostatic at 500 μmol dm^{-3} in MT-4 cells. It is unclear whether the activity of 3-isoddA (although low) arises from its conversion to the triphosphate or through its deamination to isoddI followed by isomerization to ddI and subsequent conversion of the latter to the bioactive ddATP *via* the AMPS synthetase/lyase pathways. Further studies on other isomeric dideoxynucleosides are currently in progress.

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‡ Data for 2′,3′-dideoxy-3-isoadenosine: m.p. 154–156 °C; ^{13}C NMR (CD_3SOCD_3) δ 24.3, 32.0, 62.0, 82.5, 89.9, 120.3, 140.9, 147.7, 151.9 and 155.1; ^1H NMR (CD_3SOCD_3) δ 2.06 (m, 2H), 2.44 (m, 2H), 3.57–3.74 (m, 2H), 4.24 (m, 1H), 5.74 (m, 1H), 6.30 (m, 1H), 7.75 (s, 1H), 7.95 (br s, 2H) and 8.66 (s, 1H); UV (H_2O) λ_{max}/nm 270 (ε 12000) and 210 (ε 18500); FAB HRMS calcd. for $C_{10}H_{13}N_5O_2$ 236.1148 (M^+ + H), found *m/z* 236.1139.