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A NEW SYNTHESIS OF 2',3'-DIDEOXYINOSINE

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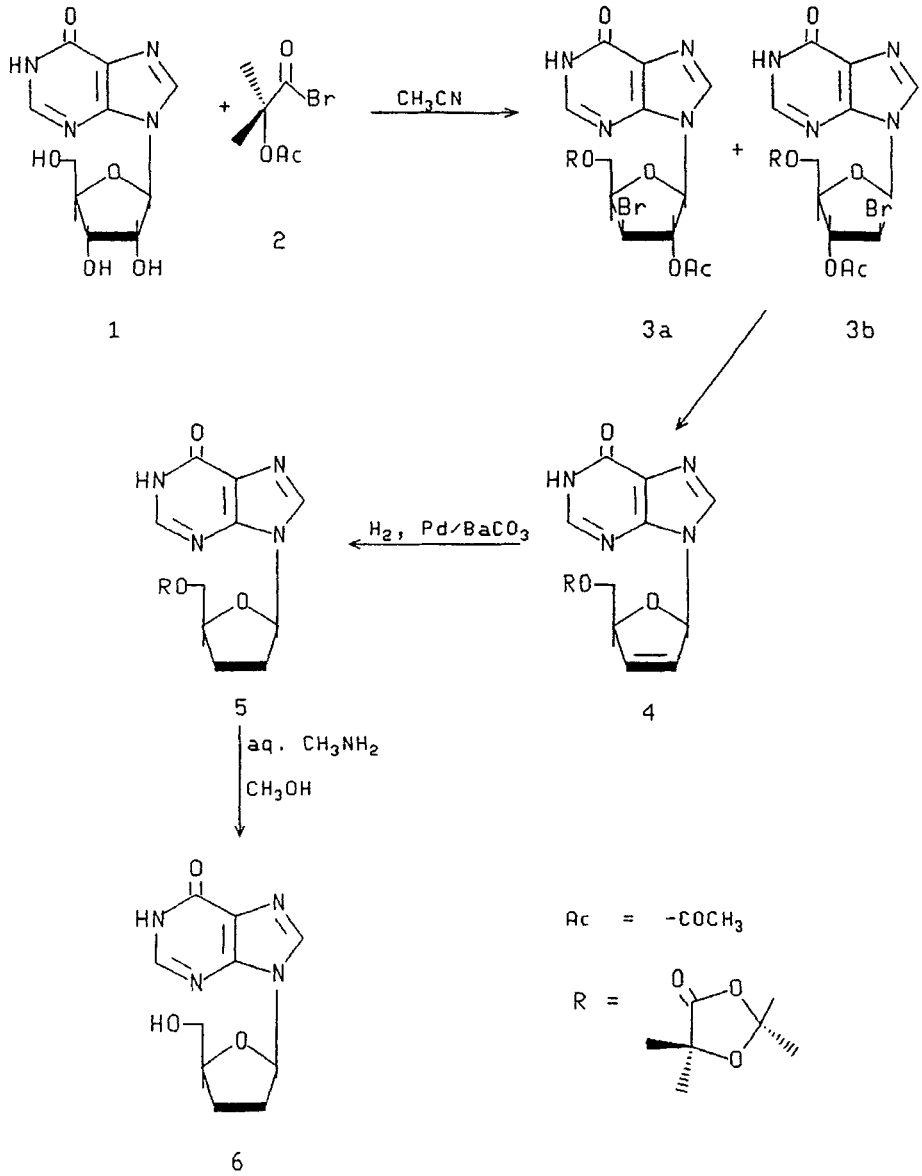
ABSTRACT: The title compound is prepared in excellent yield in four steps starting from inosine(1).

Several 2',3'-dideoxynucleosides have recently been shown to have clinical anti-retroviral activity against human immunodeficiency virus(HIV), the causative agent of acquired immune deficiency syndrome(AIDS)[3,4]. Very recently, the Food and Drug Administration of the U.S.A. has approved the use of 2',3'-dideoxyinosine (**6**, DDI, Videx, Didanosine) in the U.S. and Canada for adults and children with advanced HIV infection, who are intolerant to, or whose health has significantly deteriorated on 3'-azido-2',3'-dideoxythymidine(AZT), the only other drug approved for AIDS therapy.

Although several elegant syntheses of DDI have been reported in the literature[5], most of these start either from adenosine or from the expensive 2'-deoxyinosine barring few exceptions[6]. In this communication, we describe a short and elegant synthesis of **6** starting from inosine(**1**) employing readily available raw materials.

Reaction of **1** with three equivalents of 2-acetoxyisobutyryl bromide (**2**) at 5-10^0 C gave, after extractive work-up, a mixture of two isomeric bromoacetates(**3a** and **3b**)



1 2 3a 3b 4 5 6

as a white foam. The nature of the 5'-O-protecting group in this mixture was determined exclusively to be dioxolane by proton NMR and IR spectra. It is worth mentioning that if the reaction of **1** with **2** were carried out at room temperature as was the case with adenosine[7], substantial decomposition occurs with the resulting bromoacetates having their 5'-O position protected as a mixture of 2-acetoxyisobutyrate and dioxolane. Treatment of the bromoacetates **3a** and **3b** with Zn/Cu couple in THF at room temperature resulted in the formation of the protected olefin (**4**) in good yield(53% overall from **1**). Hydrogenation of the olefin (**4**) in a mixture of methanol/2-methoxyethanol employing Pd/$BaCO_3$(5% Pd) as the catalyst afforded the 5'-O-protected DDI(**5**), which without isolation, was deprotected with aqueous methylamine in methanol to give DDI in 96% yield.

In conclusion, a simple and practical synthesis of DDI has been achieved starting from inosine in 51% overall yield without involving any chromatographic purification of the intermediates.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point appartatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM 390 spectrometer using tetramethylsilane as the internal standard. Elemental analyses were performed by MHW Laboratories, Phoenix, Arizona. Thin-layer chromatography was run on silica gel GF plates (Analtech, Newark, Del.), where the products were visualized by UV light as well as 10% H_2SO_4 in MeOH spray followed by heating. Evaporations were carried out under reduced pressure with bath temperature below 40^0 C. 2-Acetoxyisobutyryl bromide and Zn/Cu couple were purchased from Fairfield Research Chemicals.

2',3'-Didehydro-5'-O-(2,5,5-trimethyl-1,3-dioxolan-4-on-2-yl)-2',3'-dideoxyinosine(4). To a cold (ca 5^0 C) suspension of inosine 1(5 g, 18.6 mmol) in acetonitrile (80 mL) was added with stirring 2-acetoxyisobutyryl bromide 2 (11.7 g, 56 mmol) in one portion. After stirring the reaction mixture at 5-10^0 C for 2 h, the stirring was continued at ambient temperatures for another 45 min. The mixture was poured into 5% aqueous $NaHCO_3$ solution (200 mL) and the resulting solution was extracted with ethyl acetate (2x 150 mL). The organic layer was separated, dried ($MgSO_4$) and concentrated under reduced pressure to give 8.7 g of a white foam containing the mixture of bromoacetates 3a and 3b.

The above foam was dissolved in THF (50 mL) and to the clear solution was added Zn/Cu couple (7.5 g) followed by glacial acetic acid (0. 6 mL)[8]. The heterogeneous reaction mixture was stirred at room temperature for 45 min. The excess Zn/Cu couple was removed by filtration through Celite pad and the pad was washed with THF (20 mL). The combined filtrates were concentrated to ~ 25 mL in volume which was then poured into 10% aqueous solution of EDTA trisodium salt(50 mL). The resulting solution was extracted with ethyl acetate(2x75 mL) and the organic layer was finally washed with 5% aqueous $NaHCO_3$ solution[9]. The ethyl acetate layer was separated, dried($MgSO_4$) and concentrated under reduced pressure to provide a white foam. The foam was triturated with anhydrous ethyl ether (100 mL) to afford a white solid which was collected by filtration, washed with ether (25 mL) and air-dried to give 3.6 g (53%) of the title product 4, mp 150-153^0 C. An analytically pure sample was prepared by recrystallization from acetone/ethanol. ^1H NMR (DMSO-d_6) δ : 12.36(br s, 1H, NH), 8.15(s, 1H, H-2), 8.05(s, 1H, H-8), 6.98(m, 1H, H-1'), 6.56(br d, J=6H_Z, 1H, H-3'), 6.27(br d, J=6H_Z, 1H, H-2'), 5.10(m, 1H, H-4'), 3.74(d, J=3H_Z, H-5's), 1.67(s, 3H, CH_3) and 1.43(s, 6H, O-C(CH_3)$_2$-CO).

Anal. Calcd for $C_{16}H_{18}N_4O_6$(362.3): C, 53.03; H, 5.01; N, 15.46. Found: C, 52.77; H, 5.08; N, 15.28.

2',3'-Dideoxyinosine(6): The olefin **4**(2g, 5.52 mmol) was dissolved in a mixture of methanol (15 mL) and 2-methoxyethanol (20 mL) and then subjected to hydrogenation employing 1.5 g of $Pd/BaCO_3$(5% Pd) catalyst using a balloon filled with hydrogen gas as the source of hydrogen. After 4 h, the catalyst was removed by filtration using a Celite pad and the pad was washed with methanol(20 mL). The combined filtrates were concentrated in vacuo to a viscous gum which was redissolved in methanol (20 mL) and cooled to 5^0 C. Excess (20 mL) methylamine in water (40% by wt.) was added and the clear, colorless solution was stirred at room temperature for 16 h. Solvents were removed under reduced pressure and the residue was triturated with ethyl acetate (25 mL). The resulting white solid was collected by filtration, washed with ethyl acetate (20 mL) and air-dried to give 1.25 g (96%) of DDI. An analytically pure sample was obtained by recrystallization from methanol, mp: softens at 177-180^0 C. ^1H NMR (DMSO-d_6) δ : 12.37(br s, 1H, NH), 8.40 (s, 1H, H-2), 8.13(s, 1H, H-8), 6.27(dd, J= 3& 6 H_z, 1H, H-1'), 4.18(m, 1H, H-4'), 3.60(m, 2H, H-5's), 2.47 (m, 2H, H-2') and 2.10 (m, 2H, H-3'). UV (0.01 N KH_2PO_4) λ_{max} 248nm (ε 12,400).

Anal. Calcd for $C_{10}H_{12}N_4O_3$(236.2): C, 50.84; H, 5.12; N, 23.72; O, 20.32. Found: C, 50.60; H, 5.19; N, 23.59; O, 20.48.

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8. Addition of acetic acid is not necessary if the Zn/Cu couple is fresh.

9. The organic layer was washed more, if necessary, with 10% aqueous EDTA trisodium salt solution until it gives a clear solution with aqueous $NaHCO_3$.

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