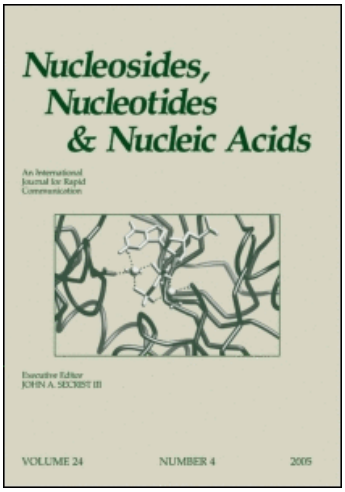

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Synthesis of 2',3'-Dideoxyinosine

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SYNTHESIS OF 2',3'-DIDEOXYINOSINE

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Abstract. The synthesis of 2',3'-dideoxyinosine (ddI, **1**) from 2'-deoxyinosine and 2',3'-dideoxyadenosine (ddA, **2**) is described. Chemically, selective benzoylation of the 5' hydroxyl group of 2'-deoxyinosine is followed by deoxygenation at the 3' position via the thioimidazolide **4**. De-protection of the resulting 5'-O-benzoyl-2',3'-dideoxyinosine **5** gave 2',3'-dideoxyinosine **1**. Enzymatically, deamination of ddA **2** with adenosine deaminase also yielded ddI.

The advent of AIDS and the resulting need to develop strategies for the chemotherapy of this disease has focused attention on dideoxynucleosides.[2] Recently, Mitsuya and Broder reported the inhibition of infectivity and cytopathic effect of the AIDS virus by 2',3'-dideoxynucleosides,[3] indicating their potential for use as antiviral agents against HIV, the virus known to be responsible for AIDS.

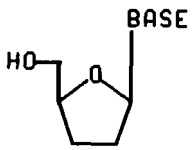
Surprisingly, these compounds have received little recent synthetic attention.[4] The syntheses of ddA (2',3'-dideoxyadenosine) and ddG (2',3'-dideoxyguanosine)[5] as well as the dideoxypyrimidine nucleosides ddT (2',3'-dideoxythymidine) and ddC (2',3'-dideoxycytidine) (from the corresponding 2',3'-didehydro-dideoxy-pyrimidinenucleosides) have been reported.[6] Although Moffatt and co-workers[7] described the synthesis of 2',3'-didehydro-2',3'-dideoxyinosine from chromous acetate reduction of the precursor haloacetate nucleoside, the synthesis of 2',3'-dideoxyinosine has not

been reported. This may be due, in part, to instability that has been associated with dideoxynucleosides.[8] For example, Ueda reported that attempted deoxygenation of an inosine analogue through tin hydride reduction of the thioimidazolide led to extensive hydrolysis to hypoxanthine during workup.[9]

Described herein is a procedure for the synthesis of 2',3'-dideoxyinosine (ddI) 1 by direct 5'-O- benzoylation[10] of 2'-deoxyinosine, followed by deoxygenation at 3' position and benzoyl group removal. The synthesis of 1 was accomplished in moderate yield generally without chromatographic purification of intermediates . In addition, an enzymatic procedure relying on the deamination of ddA 2 by adenosine deaminase to give ddI 1 is also reported.

2'-Deoxyinosine was suspended in pyridine, and treated dropwise with a pyridine solution of benzoyl chloride. The progress of the reaction was monitored by TLC. The volatiles were removed, and the crude benzoate triturated first with ethyl acetate, and then with hot water to give the 5'-O-benzoate 2 as a granular solid. After drying, the crude benzoate 3 was dissolved in dry DMF and treated with 1,1'-thiocarbonyldiimidazole, and the mixture was heated at 80°C for 1 hour. The crude imidazolide 4 was isolated simply by trituration with ethyl acetate, and 4 was deoxygenated by suspension in hot 1,4-dioxane and exposure to bis-(tributyltin)oxide and polymethylhydrosiloxane/ AIBN.[5] Crude 5 could be separated from the debris in the tin reduction by partitioning between methanol and hexane, and purified by column chromatography. De-benzoylation of 5 with methanolic ammonia gave ddI 1. The identity of 1 was verified by spectroscopic comparison with an authentic sample,[11] and by elemental analysis (see experimental section).

Alternatively, ddA 2, prepared from N6,5'O-dibenzoyl-2'-deoxyadenosine[10] using the above procedure,[5] was dissolved in water and treated with 1% by weight adenosine deaminase. Recrystallization from methanol yielded ddI 1, identical to the material prepared as described above.

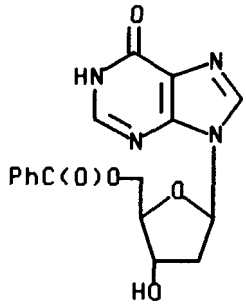


1 : BASE =

hypoxanthine : ddI

2 : BASE =

adenine : ddA



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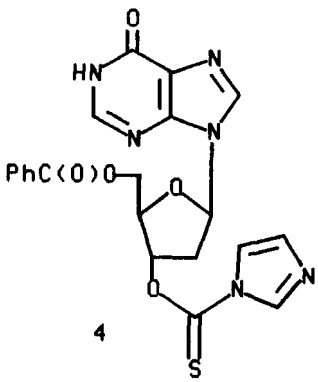

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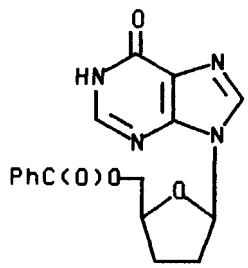

5

EXPERIMENTAL

5'-O-Benzoyl-2'-deoxyinosine 3: 2'-deoxyinosine (1.00g, 0.0039mol) was dried by co-evaporation with 4 successive volumes of pyridine and suspended in dry pyridine (100mL). To this suspension was added benzoyl chloride (0.50mL, 0.0043mol) dissolved in pyridine (10mL). After the reaction was complete (12h), pyridine was removed under reduced pressure, and the residue was triturated with ethyl acetate and then with hot water to yield 0.60g (43%) of **3** as a granular solid. Chromatography over silica gel eluting with

20% ethanol in ethyl acetate yielded an analytical sample as rhomboid crystals: mp. 165-167°C (softens), 184-186°C (softens), and 205°C(melts sharply); ^{1}H NMR (360MHz, DMSO-d_6) δ 12.36(brs, 1H, NH), 8.25(s, 1H, C-8H), 8.01(d, J=3Hz, 1H, C-2H), 7.90(d, J=6Hz, 2H, ArH), 7.65(t, J=6Hz, 1H, ArH), 7.50(t, J=6Hz, 2H, ArH), 6.34(t, J=5.5Hz, 1H, 1'-H), 5.54(d, J=3.5Hz, 1H, 3'-H), 4.58(m, complex, 1H, 4'-H), 4.51(dd, J=6, 9Hz, 1H, 2'-H), 4.39(dd, J=6, 9Hz, 1H, 2'-H), 4.12(q, J=6Hz, 1H, OH), 2.81(m, 5 lines, 1H, 5'-H), 2.38(m, complex, 1H, 5'-H). Analysis ($C_{17}H_{16}N_4O_5$) C, H, N.

Thioimidazolide 4: 5'-O-benzoyl-2'-deoxyinosine (**3**, 0.70 g, 0.002 M) dissolved in dry dimethylformamide (20mL) was treated in one portion with 1,1'-thiocarbonyldiimidazole (0.45 g, 0.0022M), and the resulting light yellow mixture was heated at 80°C (oil bath) for 1 h. TLC analysis of the mixture (10% methanol in methylene chloride) revealed the absence of the starting material. The solvent was removed under reduced pressure, and the residue triturated with ethyl acetate and dried under vacuum to give 0.89 g (93%) of thioimidazolide **4** as an off-white solid: mp. 220°C(sharp); ^{1}H NMR (DMSO-d_6) δ 12.4(brs, 1H, NH), 8.6(d, J=1Hz, 1H, C-2H), 8.26(s, 1H, C-8H), 8.0(m, complex, 4H, ArH overlapping imidazole-H), 7.7(t, J=3Hz, 1H, ArH), 7.6(t, J=3Hz, 2H, ArH), 7.09(d, J=2Hz, 1H, imidazole-H), 6.53(dd, J=6Hz, 1H, 1'-H), 6.2(d, J=3Hz, 1H, 3'-H), 4.8(m, 6 lines, 1H, 4'-H), 4.67(dd, B part, ABq, J=3, 10Hz, 1H, 2'-H), 4.56(dd, A part, ABq, J=6, 10Hz, 1H, 2'-H), 3.34(m, 5 lines, 1H, 5'-H), 2.95(qd, J=1.5, 5Hz, 1H, 5'-H). Analysis ($C_{21}H_{18}N_6O_5S$) C, H, N.

5'-O-Benzoyl-2',3'-dideoxyinosine 5: Thioimidazolide **4** (0.60 g, 0.0012M) suspended in 1,4-dioxane (20mL) was treated with bis-(tributyltin)oxide (1mL), polymethylhydrosiloxane (1mL) and AIBN (50mg).[5] The resulting suspension was de-gassed with nitrogen for 10 minutes, then heated at reflux for 1/2 h (oil bath), at which time the mixture was homogeneous.

The mixture was then cooled, the volatiles removed under reduced pressure, and the residue partitioned between hexane and methanol. The combined methanol layers were concentrated under reduced pressure and purified by chromatography over silica gel eluting with 10% methanol in methylene chloride to yield 380 mg (93%) of **5** as a white solid: mp. 125°C with softening at 97°C; re-solidifies above 130°C with no further melting;[12] ^{1}H NMR(DMSO-d_6) δ 12.33(brs, 1H, NH), 8.23(s, 1H, C-8H), 8.00(d, J=3Hz, 1H, C-2H), 7.87(d, J=5Hz, 2H, ArH), 7.65(t, J=5Hz, 1H, ArH), 7.49(t, J=5Hz, 2H, ArH), 6.24(t, J=4Hz, 1H, 1'-H), 4.44(two overlapping m, complex, 3H, 4'-H and 2'-H's), 2.52(m, overlapping m, 2H, 3'-H's), 2.19(q, J=6Hz, 2H, 5'-H's). Analysis ($C_{17}H_{16}N_4O_4$) C, H, N.

2',3'-Dideoxyinosine 1: A solution of **5** (0.250 g, 0.734 mM) in methanol (10mL) was treated with anhydrous methanol saturated with anhydrous ammonia at 0°C. The solution was then heated at 60°C for 48 h when TLC revealed the absence of the starting benzoate. The solution was cooled, and the volatiles were removed under reduced pressure. The residue was triturated with methylene chloride and then with acetone to yield 0.156 g (90%) of ddI **1** as a white solid: mp.160-163°C which was chromatographically and spectroscopically identical to an authentic sample;[11] ^{1}H NMR(D_2O) δ 8.3(s, 1H, C-2H), 8.1(s, 1H, C-8H), 6.3(q, J=3Hz, 1H, 1'-H), 4.78 (brs, 1H, OH), 4.31(m, complex, 1H, 4'-H), 3.76(B part, ABq, J=2.5, 10Hz, 1H, 2'-H), 3.61(A part, ABq, J=4.5, 10Hz, 1H, 2'-H), 2.54(m, complex, 2H, 3'-H's), 2.17 (m, complex, 1H, 5'-H), 2.01(m, complex, 1H, 5'-H).

Analysis ($C_{10}H_{12}N_4O_3$) C, H, N.

Enzymatic Degradation of ddA to ddI:
2',3'-Dideoxyadenosine[5] (ddA, **2**, 1.00g, 0.0049 M) in water (50 mL) was treated with 1% by weight (10mg) adenosine deaminase (Sigma, type 2, 0.9 units/mg) at room temperature.

The reaction was monitored by HPLC and was complete in 1 h. The solution was then concentrated under reduced pressure, and the residue recrystallized from methanol to give 0.85 g (85%) of ddI **1**, spectroscopically identical to an authentic sample.[11]

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12. This melting point behavior is consistent with that of other dideoxynucleoside derivatives noted by previous authors: see reference 6.

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