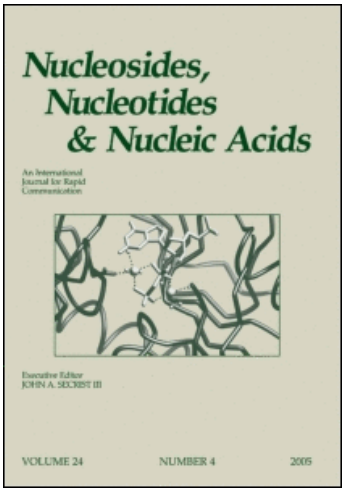

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A Direct and Efficient Synthesis of 5'-Deoxy-2', 3'-

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A DIRECT AND EFFICIENT SYNTHESIS OF 5'-DEOXY-2', 3'-O-(1-METHYLETHYLIDENE)INOSINE AN INTERMEDIATE IN THE SYNTHESIS OF N^6-CYCLOPENTYL-5'-DEOXYADENOSINE

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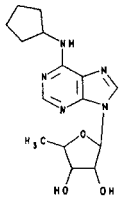
Abstract. A direct and efficient synthesis of 5'-deoxy-2',3'-O-isopropylideneinosine, 7, from readily available inosine is described. An example of a potentially general synthesis of N^6-substituted-5'-deoxyadenosines from 7 is also described.

N^6-substituted adenosines are attracting interest due to their neuroleptic, analgesic, antilipolitic, antihyperliaemic, antiinflammatory, antithrombotic, antiembolic and cardiovascular activity.[1] As a result, we developed a direct, efficient synthesis capable of multigram to kilogram scale production, of one of these compounds, N^6-cyclopentyl-5'-deoxyadenosine, (1). The process will be described herein.

Another route to 5'-deoxyadenosines and specifically 1 has been described,[2] but, this synthesis via S-arylthioinosine derivatives, while useful, suffers from the problem of 5'-cycloadenosine formation.

Several routes known to give 5'-deoxyadenosine, (2), have been explored as routes to N^6-substituted-5'-deoxyadenosines. Investigation of the direct reductive dechlorination of 5'-haloadenosines[3] and the direct desulfurization of 5'-thioalkyl-adenosines[4] as a route to N^6-substituted-5'-deoxyadenosines was



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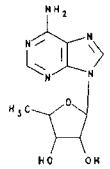

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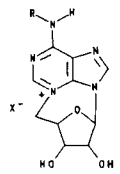

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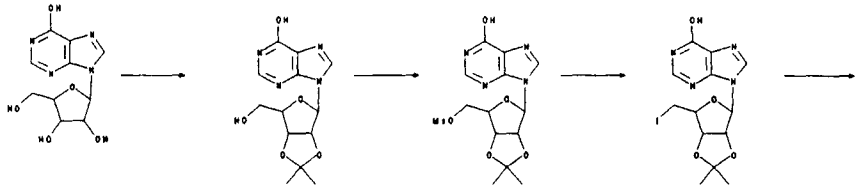
not successful.[5] The reductive dechlorination method was hampered by the tendency of the N^6-substituted-5'-haloadenosines to form the N3, 5'-cycloadenosines, 3, but this method suggested to us the possibility of using the more stable 5'-haloinosines as precursors to the desired product. Reduction of these compounds followed by elaboration at C6 should give the desired N^6-substituted-5'-deoxyadenosine.

The key intermediate in the process was the previously unreported 5'-deoxy-2', 3'-O-(1-methylethylidene)inosine, (7). By analogy to the prior work on the reduction of 5'-halo nucleosides it should be possible to prepare the deoxy inosine 7 from the known 5'-deoxy-5'-iodo-2',3'-O-(1-methylethylidene)inosine, (6),[6] by reductive hydrogenolysis.

While the reported synthesis of the iodo inosine 6, by the reaction of methyltriphenoxyphosphonium iodide (MTPI) with 2', 3'-O-(1-methylethylidene)inosine, (4), gives the 5'-iodo product in high yields, the expense and instability of MTPI would preclude its use for large scale synthesis.[6] We have found that catalytic hydrogenolysis of the iodo inosine 6 prepared by the MTPI procedure is very sluggish, possibly due to phosphorus containing impurities acting as catalyst poisons.



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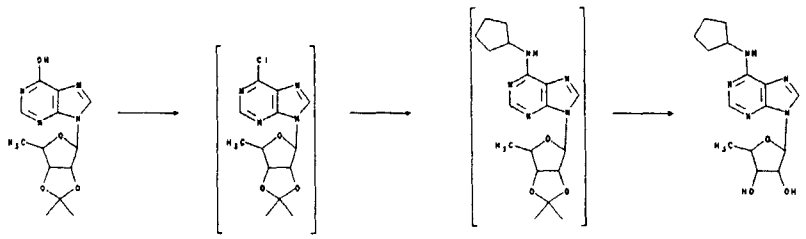

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Several syntheses of 5'- substituted nucleosides have used the nucleophilic displacement of 5'- mesylates or 5'- tosylates to synthesize a wide variety of 5'- substituted nucleosides.[7] In fact, the somewhat troublesome to prepare, 2', 3'-O- (1-methylethylidene)-5'-O-p-toluenesulfonylinosine[8] has been converted to the iodo intermediate 6 by refluxing with sodium iodide in acetone by Hampton and coworkers.[9]
Interestingly, we have found that 2', 3'-O-(1-methylethylidene)-5'-O-(methanesulfonyl)inosine (5),[10] by treatment with sodium iodide in refluxing acetone, is converted to the iodo inosine 6 in 62% yield. It is also noteworthy that the mesylate 5 has been found to be stable for three years as a crystalline solid at room temperature and should be a very useful substrate for other nucleophilic displacement reactions at C5'. Attempted reduction of the mesylate to give the deoxy inosine 7 directly was unsuccessful using $LiBEt_3H$ and $NaBH_4$/DMSO.[11] Catalytic reduction of the iodide 6 gave the key intermediate 7 in good yield.

Treatment of 2',3'-O-(1-methylethylidene)inosine,(4), with methanesulfonylchloride for ninety minutes at room temperature, instead of overnight as reported previously,[11] gave a 79% yield of 2',3'-O-(1-methylethylidene)-5'-O-(methanesulfonyl)inosine, (5). Reaction of 5 with sodium iodide in refluxing acetone followed by crystallization from acetone/water gave the iodo compound 6 in 62% yield. The material obtained by this nucleophilic displacement procedure displayed identical physical and spectroscopic properties to that obtained previously by Moffatt.[6] The reduction of 6 using 10% palladium on carbon as catalyst in methanol in the presence of triethylamine was complete in two hours to give 5'-deoxy-2',3'-O-(1-methylethylidene)inosine, (7), in 73% yield. [2,12] The parent nucleoside, 5'-deoxyinosine, has been of some recent interest, so, the synthesis of 7 reported here and which has been successfully utilized on a multi-kilogram scale, constitutes a much improved formal synthesis of this interesting compound.[13]

The required intermediate 7 in hand, the conversion to a N^6-cyclopentyl-5'-deoxyadenosine was accomplished in a three step procedure. Chlorination of 7 with phosphorus oxychloride/dimethylformamide in methylene chloride gave crude 6-chloro-9-(5'-deoxy-2',3'-O-(1-methylethylidene)-α-D-ribofuranosyl) purine, (8), as a yellow oil. The oil was dissolved in ethyl alcohol and treated with a mixture of triethylamine and cyclopentylamine to give crude N^6-cyclopentyl-5'-deoxy-2',3'-O-(1-methylethylidene)adenosine, (9), as a red oil that resisted

attempted crystallization. The crude protected adenosine 9 was deprotected to give 1 using 50% aqueous formic acid and recrystallized from water. Higher concentrations of formic acid and higher temperatures (greater than 30°C) result in cleavage of the sugar moiety.

EXPERIMENTAL

Reagents and Instrumentation

All solvents were purchased from commercial sources and used as received. The following reagents were purchased and used as received p-toluenesulfonic acid monohydrate (Sloss Industries), inosine (U. S. Biochemical), triethylorthoformate (Huls), methanesulfonyl chloride (Lancaster), sodium iodide (Mallinckrodt), triethylamine (BASF), 10% palladium on carbon catalyst (Engelhard), phosphorus oxychloride (Occidental Chem.), sodium carbonate (Rhone-Poulenc), sodium sulfate anhydrous (Saskatchewan Minerals), and cyclopentylamine (Lancaster).

NMR Spectra were recorded on a Varian XL-200 and are referenced to tetramethylsilane. Melting points were obtained using a Thomas-Hoover melting point apparatus and are uncorrected. Microanalyses were obtained in the Microanalytical Laboratory Pharmaceutical Research Division, Ann Arbor MI.

2',3'-O-(1-methylethylidene)inosine. (4)

A solution of p-toluenesulfonic acid monohydrate 320g (1.68 moles) in 7.6L of acetone was treated with 410g (1.53 moles) of inosine. The resulting suspension was treated with 906g (6.11 moles) triethylorthoformate over a period of 15 minutes. Approximately 15 minutes after the addition was complete the reaction mixture became very thick and was stirred at ambient temperature for three hours. Ammonium hydroxide (11.1L of 0.17M solution) was added and the new solution was stirred for thirty minutes at ambient temperature and then cooled to 5°C and held at that temperature for 16h. The precipitated solid was filtered to yield 217g (46%) of the desired protected inosine.

A second crop was obtained by concentration of the filtrate to approximately 4L and storing the solution at 5°C for 48h. Yield 186g (40%). Total yield 403g (86%). Both crops exhibited identical spectral characteristics to those reported previously.[14] Anal. Calcd for $C_{13}H_{16}N_4O_5$: C, 50.65; H, 5.23; N, 18.17. Found: C, 50.06; H, 5.31; N, 18.04. mp > 300°C.

2',3'-O-(1-methylethylidene)-5'-O-(methanesulfonyl)inosine. (5)

A solution of 120g (.389 moles) of 4 in 2L of pyridine was treated with 67.2g (.587 moles) of methanesulfonyl chloride. Upon

complete addition the solution was stirred for 90 minutes and then quenched by the addition of 4.2L of water. The resulting mixture was extracted with methylene chloride (1 x 2.4L and 1 x 1.2L) and the combined methylene chloride extracts dried over sodium sulfate. The methylene chloride/pyridine solution of 5 was concentrated to an oil by vacuum distillation at less than 45°C. The oil was suspended in 3L of ethanol, warmed to 50°C (30 minutes) and cooled slowly to 5°C (2 hours) yielding 119.5g (79%) of the desired mesylate as a white crystalline solid. ^{1}H NMR (d^6-DMSO) 1.34 (s, 3H), 1.55 (s, 3H), 3.15 (s, 3H), 4.41 (d, J=4.1 Hz, 2H), 4.44 (br s,1H), 4.45 (m, 1H), 5.06 (m, 1H), 5.40 (m, 1H), 6.23 (d, J=1.9 Hz, 1H), 8.12 (s, 1H), 8.33 (s, 1H). Anal. Calcd for $C_{14}H_{18}N_4O_7S$: C, 43.52; H, 4.70; N, 14.49; S, 8.30. Found: C, 43.58; H, 4.62; N, 14.36; S, 8.27. m.p. 170-172°C with decomposition.

5'-deoxy-5'-iodo-2', 3'-O-(1-methylethylidene)inosine. (6)

An acetone solution (5.8L) of 5 (186g, 0.48 mole) and sodium iodide (434g, 2.89 mole) was refluxed for seven hours. The mixture was allowed to cool slowly to room temperature and stirred for 16 hours. The precipitated salts were removed by filtration, washed with 200ml of acetone and the combined acetone filtrates concentrated by vacuum distillation to a volume of 1.5-2.0L. The acetone/product solution was diluted with 3.7L of water and cooled to 5-10°C to give 124g (62%) of the desired iodide as a white crystalline solid exhibiting identical spectral characteristics to that reported previously.[6] Anal. Calcd for $C_{13}H_{15}IN_4O_4$: C, 37.33; H, 3.61; N, 13.38; I, 30.34. Found: C, 37.40; H, 3.52; N, 13.36; I, 30.06. m.p. 190-193°C with decomposition.

5'-deoxy-2', 3'-O-(1-methylethylidene)inosine. (7)

To a mixture of 281g (0.67 mole) of 6, 3.8L of methyl alcohol and 102g (1.00 mole) of triethylamine, under a nitrogen atmosphere, was added 38g of 10% palladium on carbon (50% water wet) catalyst. The mixture was then hydrogenated under 50psi hydrogen pressure at 20-30°C until the uptake of hydrogen stopped (about two hours). The catalyst was filtered and washed with methyl alcohol (2 x 800mL). The filtrate and wash were combined and concentrated to induce crystallization. The product slurry was then cooled at 5°C for two hours to give the desired deoxy nucleoside 7 as a white crystalline solid (144g, 73%). ^{1}H NMR (d^6-DMSO) 1.27 (d, J=6.7 Hz), 1.32 (s, 3H), 1.53 (s, 3H), 2.09 (s, 1H), 4.25 (m, 1H), 4.77 (m, 1H), 5.41 (m, 1H), 6.07 (d, J=1.9 Hz, 1H), 8.11 (s, 1H), 8.29 (s, 1H). Anal. Calcd. for $C_{13}H_{16}N_4O_4$:

C, 53.42; H, 5.52; N, 19.17. Found: C, 52.74; H, 5.58; N, 19.08. m.p. 182-184°C.

N^6-cyclopentyl-5'-deoxyadenosine. (1)

To a solution of 7 (667.8g, 2.28 mole) in 12.5L methylene chloride was added dimethylformamide (253g, 3.46 mole). The resulting solution was treated with phosphorus oxychloride (880g, 5.74 mole) and the temperature rose to 35°C. The mixture was heated to reflux for 7h and then an additional 100g (0.65 mole) of $POCl_3$ was added and the mixture held at reflux for an additional 16h. The reaction was quenched in 30L of 10% aqueous Na_2CO_3 at 0°C. The layers were separated and the CH_2Cl_2 layer was washed with water (15L). The combined aqueous phases were back-extracted with 8L of fresh CH_2Cl_2 and the combined methylene chloride layers were dried over Na_2SO_4. The methylene chloride was removed by vacuum distillation to give crude 6-chloro-9-(5'-deoxy-2',3'-O-isopropylidene-α-D-ribofuranosyl)purine,(8), as a yellow-orange oil. Yield 590.5g used without further purification. ^{1}H NMR (d^6-DMSO) 1.25 (d, J=6.7 Hz, 3H), 1.30 (s, 3H), 1.52 (s, 3H), 4.30 (m, 1H), 4.81 (m, 1H), 5.51 (m, 1H), 6.22 (d, J=1.5 Hz, 1H), 8.80 (s, 1H), 8.85 (s, 1H). MS (M^+ = 310).

The oil was dissolved in 12L ethyl alcohol and treated with a mixture of triethylamine (214g, 2.1 mole) and cyclopentylamine (179g, 2.1 mole). The resulting solution was heated to reflux and held at reflux for 20h. The ethanol was removed by vacuum distillation at 60°C, the residue taken up in 25L of CH_2Cl_2 and the CH_2Cl_2/product solution was washed with water (2 x 15L) and dried over Na_2SO_4. The methylene chloride was removed by vacuum distillation at 45°C to give crude N^6-cyclopentyl-5'-deoxy-2',3'-O-isopropylidene-adenosine,(9), as a red oil. Yield 560g. ^{1}H NMR ($CDCl_3$) 1.38 (d, J = 6.6 Hz, 3H), 1.41 (s, 3H), 1.63 (s, 3H), 1.72 (m, 6H),2.10 (m, 2H), 4.40 (m, 1H), 4.65 (br s, 1H), 4.80 (m, 1H), 5.56 (m, 1H), 5.93 (m, 1H), 6.05 (d, J = 2.3 Hz, 1H), 7.87 (s, 1H), 8.42 (s, 1H).

The crude protected adenosine, 9, was dissolved in 9.6L of 50% formic acid while maintaining the temperature below 30°C. The resulting solution was stirred for 10h at 25-30°C and then methanol (2L) was added and the solution neutralized with 28% NH_4OH while maintaining the temperature below 30°C. The crude product was collected and recrystallized from 14L boiling water. The yield of fine white crystalline 1 was 152.2g (21% overall from 7). ^{1}H NMR (d^6-DMSO) 1.28 (d, J = 5.4 Hz, 3H), 1.52-1.69 (m, 6H), 1.90 (m, 2H), 3.95 (m, 2H), 4.50 (br s, 1H), 4.65 (m, 1H), 5.13 (d, J = 4.4 Hz, 1H), 5.41 (d, J = 6.0 Hz, 1H), 5.82 (d, J =

4.3 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 8.18 (s, 1H), 8.29 (s, 1H). Anal. Calcd for $C_{15}H_{21}N_5O_3$ 1.5 H_2O: C, 52.01; H, 6.98; N, 20.22. Found: C, 52.10; H,6.98; N, 20.54.

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