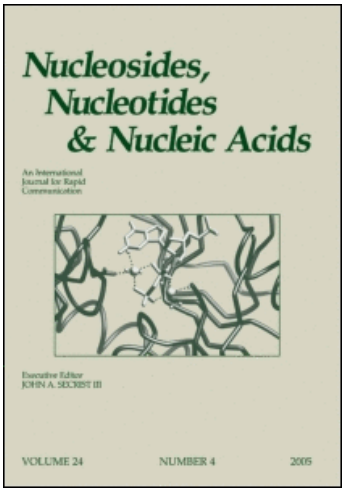

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New Approach to the Synthesis of 2',3'-dideoxyadenosine and 2',3'-Dideoxyinosine

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NEW APPROACH TO THE SYNTHESIS OF 2',3',-DIDEOXYADENOSINE AND 2',3'-DIDEOXYINOSINE

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ABSTRACT: A new approach to the synthesis of 2',3'-dideoxyadenosine and 2',3'-dideoxyinosine based on deoxygenation of 2',3'-di-*O*-mesylnucleosides was developed.

The latest successes in HIV chemotherapy stimulate the search of the routes for the effective synthesis of compounds with anti-HIV activities, such as 2',3'-dideoxynucleosides (ddN), among them 2',3'-dideoxyinosine (ddI) (**1**). ddI is the second preparation allowed for the scale use after azidothymidine and is much less toxic as compared with azidothymidine.[1] The known methods for ddN synthesis based on radical deoxygenation of various thiocarbonyl derivatives as a rule are multistage, use expensive and toxic reagents, and include complicated procedures of isolation and purification (chromatography on silica gel).[2,3]

Methods based on β-elimination of corresponding *cis*- and *trans*-2',3'-haloacetates, primarily bromoacetates, and subsequent catalytic hydrogenation of the resulting 2',3'-didehydro-2',3'-dideoxynucleosides (d4N) seem to offer more promise, both two-step methods with d4N isolation[4-7] and so-called "one-pot" methods[8-11] being developed.

The main disadvantages of these methods are the moderate yields at the stage of acetyl halide synthesis (especially in the case of ribosyl purines because of the low

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Dedicated to the spirit and memory of Prof. Tsujiaki Hata, for his inspiration and pioneering nucleoside research.

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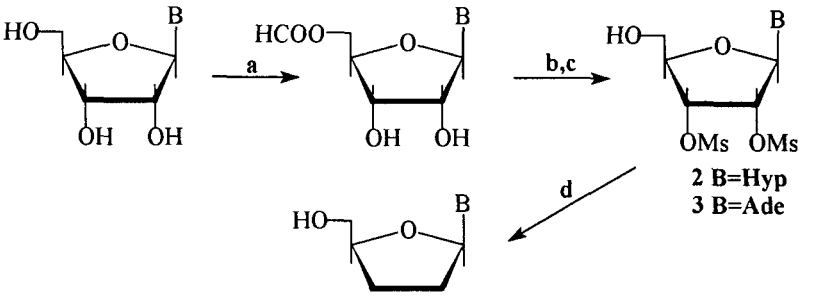
regioselectivity) and side reactions at the steps of elimination—hydrogenation (deacetylation and dehydrohalogenation), which complicate the isolation of the target products. However, the recent communication,[12] which reports the marked increase of the yields of products at all stages by accurate matching the reaction conditions, should be mentioned. Though even in this case the authors failed to escape chromatographic purification.

Introducing the sulfonyl group, which is a better leaving group than the acyl function, gives contradictory results. On the one hand, *cis*- and *trans*-2',3'-halosulfonates result in d4N[13, 14] or directly in ddN (in the case of simultaneous hydrogenation) in the presence of bases.[10] On the other hand, readily available *cis*-2',3'-disulfonates are converted into enolsulfonates[15, 16] under the basic conditions and into 2'-ketonucleosides under more rigid conditions.[17, 18]

Nevertheless, we attempted to reexamined the deoxygenation of the nucleoside's *cis*-2',3'-di-*O*-mesylates, namely 2',3'-di-*O*-mesylinosine (**2**) and 2',3'-di-*O*-mesyladenosine (**3**) (Scheme).

We choose the formyl group for selective protection of the hydroxyl function at 5'-position. Recently we have worked out a simple method for its introduction by treating ribonucleosides with formic acid.[19] As the formyl group is rather labile, the subsequent mesylation was performed by the routine procedure without isolation of 5'-*O*-formylnucleosides.

2',3'-Di-*O*-mesylinosine (**2**) was isolated by reversed phase chromatography after mild basic hydrolysis of the mesylation product. Hydrogenolysis of **2** at heating in aqueous ethanol in the presence of 10% Pd/C and potassium bicarbonate resulted in 2',3'-dideoxyinosine. Neither 2'- nor 3'-deoxy compounds was detected in the reaction mixture. The only by-product was the hypoxantine. We believe that this is due to partial depurination of intermediate 2',3'-didehydro-2',3'-dideoxyinosine. Lability of d4N especially in polar solvents and at heating has been already mentioned.[2] However, the reaction took place only at 60 °C and higher. We succeeded in marked suppression of depurination using the less polar solvent - isopropanol. It should be mentioned that steadily reproducible results were obtained only after we had performed the reaction in the presence of the marked amount of anion-exchange resin. This can be explained by fixation



a: HCOOH; **b**: MsCl, Py; **c**: NH_3 aq; **d**: H_2/Pd, $KHCO_3$.

SCHEME

of mesylate generated, which is a catalyst poison. Hereinafter, hydrogenolysis was performed in the presence of palladium black, as it can be easily separated from anion-exchange resin by flotation. The yield of **1** was 48%.

The mechanism of the reaction needs further investigation. The discrepancy between our data and the results reported previously[15-18] is likely connected with the participation of palladium in the first stage of the process, namely elimination. The similar speculations were made by the authors of the research on the hydrogenolysis of *cis*-bromomesylates.[10]

Synthesis of 2',3'-dideoxyadenosine (**4**) was performed in the similar way. 5'-*O*-Formyl-2',3'-di-*O*-mesyladenosine was precipitated with water from acetonitrile and then was hydrolyzed under mild basic conditions. Dimesyl derivative **3** was hydrogenated without preliminary purification as described for **2** to give product **4** with 59% yield.

The structure of intermediates and products was confirmed by NMR spectroscopy and comparison with the reference compounds.

This is good reason to believe that this synthetic method is useful for purine ribonucleosides.

EXPERIMENTAL

Melting points are uncorrected. Homogeneity of compounds obtained and the progress of the reactions were controlled by TLC on Silica gel 60 F_{254} (Merck) plates in

chloroform-methanol 9 : 1 developing system. NMR spectra were recorded on a Bruker WM-500 (500 MHz) spectrometer in DMSO-d_6. Chemical shifts (δ, ppm) relative to TMS and coupling constants (J, Hz) are given. HPLC was performed on a Waters 501 instrument using Ultrasphere ODS 5 um column (25 × 0.4 cm); elution with 10% aqueous acetonitrile (unless otherwise specified), flow rate 1 mL/min.

2',3'-Di-*O*-mesylinosine (2). Inosine (200 g, 0.8 mol) was added portionwise to 1.5 L of formic acid (analytical grade, 99%) at vigorous stirring. The resulting light-yellow solution was kept at 20-25 °C for 24 h (HPLC monitoring). After completion of the reaction the acid was removed *in vacuo* (40-45 °C). The residue (viscous syrup) was triturated with acetonitrile (1 L). The crystallized mass was filtered and washed with acetonitrile (4 × 0.3 L) until formic acid odor disappeared. The residue was air-dried (12-16 h) and then dried *in vacuo* over alkaline and P_2O_5 to constant weight to give the mixture (184.8 g) containing 70% of 5'-*O*-formylinosine (HPLC data).[20] The mixture obtained (50 g) was suspended in anhydrous pyridine (1.5 L). Triethylamine (60 mL) and then mesyl chloride (35 mL) were added dropwise during ~1 h at vigorous stirring and cooling to –2 °C (ice—$CaCl_2$), so that the reaction temperature did not exceed 5 °C. The reaction was monitored by TLC. After 1.5 and 2 h mesyl chloride (10 and 20 mL, respectively) was added. The reaction mixture was kept at 0-3 °C for 30 min and then evaporated. The residue (dark viscous syrup) was dissolved in a mixture of water (1 L) and ethyl acetate (1 L). The organic layer was separated, and the water layer was additionally extracted with ethyl acetate (3 × 0.5 L). The combined extract was evaporated. The residue was dissolved in water (130 mL) at heating, and saturated aqueous ammonia (15 mL) was added to pH 8-9. The mixture was kept for 16-20 h at room temperature and then was evaporated and coevaporated with water until ammonia was completely removed. The resulting concentrated water solution was put on the column with 600 mL of sorbent (Spheron 1000, 0.025 mm, Chemapol) and eluted with water. Fractions containing product **2** were concentrated. The precipitate obtained was filtered and air-dried to yield 36 g of 2',3'-di-*O*-mesylinosine. M.p. 153-154 °C. RT 24 min. ^{1}H NMR: 3.25 (s, 3H, SO_2CH_3), 3.38 (s, 3H, SO_2CH_3), 3.72 (dd, 1H, $J_{5'a,4'}$ = 3.5, $J_{5'a,5'b}$ = 12.5, H-5'a), 3.82 (dd, 1H, $J_{5'b,4'}$ = 3.7, $J_{5'b,5'a}$ = 12.5, H-5'b), 4.41 (dt, 1H, $J_{4',5'a}$ =

3.5, $J_{4',5'b}$ = 3.7, $J_{4',3'}$ = 3.5, H-4'), 5.55 (dd, 1H, $J_{3',4'}$ = 3.5, $J_{3',2'}$ = 5, H-3'), 5.83 (t, 1H, $J_{2',3'}$ = 5, $J_{2',1'}$ = 6, H-2'), 6.28 (d, 1H, $J_{1',2'}$ = 6, H-1'), 8.1 (s, 1H, H-8), 8.35 (s, 1H, H-2).

2',3'-Dideoxyinosine (1). Compound **2** (30 g, 0.073 mol), palladium black (1.5 g), Dowex 1×8 (100-200 mesh, HCO_3^-) anion-exchange resin (350 mL), isopropanol (720 mL), and potassium bicarbonate (3.6 g) solution in 80 mL of water were loaded in 2 L autoclave and hydrogenated for 1.5 h at 70 °C and 25-30 atm.[21] The hot mixture was filtered, and the resin was washed with water (2-3 L). The combined filtrate was evaporated. The solid residue was dissolved in ethanol at heating, and warm solution was filtered through silica gel layer. Silica gel was then washed with ethanol, and the combined neutral and colorless filtrates were concentrated. 2',3'-Dideoxyinosine was slowly crystallized from the solution at room temperature. Crystallization was completed at cooling (0-5 °C) to give 5 g of pure **1**. The mother liquor was evaporated, and the residue (6 g) was chromatographed on DEAE Cellulose 23 (Whatman) (elution with water) to give additional 3 g of **1**. Common yield of **1** was 48%. M.p. 180-182 °C (lit.[12] m.p. 160-163 °C, lit.[2] m.p. softens at 184-186 °C, but does not melt up to 300 °C)[22]. λ_{max} 250 nm (H_2O). R_f 0.2. RT 5.4 min. ^{1}H NMR: 2.02 (m, 2H, H-2'a,2'b), 2.35 (m, 1H, H-3'a), 2.46 (m, 1H, H-3'b), 3.53 (dt, 1H, $J_{5'a,4'} = J_{5'a,OH}$ = 5, $J_{5'a,5'b}$ = 12, H-5'a), 3.64 (ddd, 1H, $J_{5'b,4'} = J_{5'b,OH}$ = 6, $J_{5'b,5'a}$ = 12, H-5'b), 4.12 (tt, 1H, $J_{4',5'a} = J_{4',5'b}$ = 5, $J_{4',3'a} = J_{4',3'b}$ = 7.5, H-4'), 4.97 (t, 1H, $J_{OH,5'a} = J_{OH,5'b}$ = 6, -OH), 6.28 (dd, 1H, $J_{1',2'a}$ = 3.25, $J_{1',2'b}$ = 7, H-1'), 7.98 (s, 1H, H-8), 8.24 (s, 1H, H-2), 12.2 (br s, 1H, NH). Anal. Calcd. for $C_{10}H_{12}N_4O_3$: C 50.84; H 5.12; N 23.72. Found: C 50.64; H 5.13; N 23.69.

2',3'-Di-*O*-mesyladenosine (3). Adenosine (10 g, 0.04 mol) was added to 170 mL of formic acid (analytical grade, 90%) at vigorous stirring. The resulting solution was kept for 24 h at 20-25 °C (HPLC monitoring). After completion of the reaction the acid was removed *in vacuo* (35 °C). The residue (viscous syrup) was triturated with acetonitrile (0.5 L). The crystallized mass was filtered and washed with acetonitrile (4 × 0.1 L) until formic acid odor disappeared. The precipitate was air-dried (12-16 h) and then dried *in vacuo* over alkaline and P_2O_5 to constant weight to give the mixture (8.9 g) containing 84% of 5'-*O*-formyladenosine (HPLC data). The mixture obtained (7 g) was dissolved in anhydrous pyridine (100 mL), and mesyl chloride (5 mL) was added dropwise at vigorous

stirring and cooling to –2 °C (ice—$CaCl_2$). The reaction was monitored by TLC. The reaction mixture was kept at 20-25 °C for 12 h and evaporated. The residue (viscous syrup) was dissolved in acetonitrile (10 mL), and the product was precipitated with water. The precipitate was filtered and dried to give crude 5'-O-formyl-2',3'-di-*O*-mesyladenosine (8.4 g). The compound obtained was dissolved in the mixture of methanol (200 mL) and water (1 mL), and saturated aqueous ammonia (15 mL) was added to pH 8-9. The mixture was kept for 16-20 h at room temperature. 2',3'-Di-*O*-mesyladenosine precipitated was filtered and air-dried to give 6.7 g of **3**. M.p. 163-165 °C. ^{1}H NMR: 3.17 (s, 3H, SO_2CH_3), 3.31 (s, 3H, SO_2CH_3), 3.73 (dd, 1H, H-5'a), 3.82 (dd, 1H, H-5'b), 4.41 (m, 1H, H-4'), 5.51 (dd, 1H, H-3'), 5.82 (t, 1H, H-2'), 6.25 (d, 1H, H-1'), 7.12 (br s, 2H, NH_2), 8.15 (s, 1H, H-8), 8.31 (s, 1H, H-2).

2',3'-Dideoxyadenosine (4). Compound **3** (1.37 g, 3.3 mmol), Pd/C (0.07 g, 20%, $Pd(OH)_2$ form), Dowex 1×8 (100-200 mesh, HCO_3^-) anion-exchange resin (35 mL), isopropanol (55 mL), and potassium bicarbonate (0.36 g) solution in 14 mL of water were loaded in 0.5-L two-necked flask and hydrogenated for 2.5 h at 70 °C. The hot mixture was filtered, and the resin was washed with methanol (500 mL). The combined filtrate was evaporated. The solid residue was dissolved in water, and warm solution was filtered through Dowex 1×8 (100-200 mesh, OH^-) anion-exchange resin (200 mL). Product **4** was slowly crystallized from methanol at cooling (0-5 °C) to give pure ddA (450 mg, 59%). M.p. 187-189 °C. R_f 0.38. RT 7.1 min (15% MeCN). ^{1}H NMR: 2.01 (m, 2H, H-2'a,2'b), 2.42 (m, 2H, H-3'a,3'b), 3.52 (dd, 1H, $J_{5'a,4'}$ = 4, $J_{5'a,5'b}$ = 12, H-5'a), 3.61 (dd, 1H, $J_{5'b,4'}$ = 3, $J_{5'b,5'a}$ = 12, H-5'b), 4.05 (m, 1H, H-4'), 5.05 (br s, 1H, OH), 6.21 (br t, 1H, $J_{1',2'a} = J_{1',2'b}$ = 5.5, H-1'), 7.15 (br s, 2H, NH_2), 8.15 (s, 1H, H-8), 8.30 (s, 1H, H-2). ^{13}C NMR: 155.97 (C-2), 152.41 (C-6), 148.82 (C-4), 139.11 (C-8), 84.48 (C-1'), 81.71 (C-4'), 62.90 (C-5'), 31.79 (C-3'), 25.70 (C-2').

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20. The mixture also contains starting inosine and a quantity of di-O-formil derivatives.
21. It has been observed, that an increased pressure doesn't influence the yield of ddN and in the case of the large scale preparation the high pressure is due to the technical reason.
22. The discrepancy in the melting points may be due to the different solvents used for the crystallization.