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NUCLEOSIDES OF BRANCHED-CHAIN NITROMETHYL, CYANOMETHYL, AND AMINOMETHYL SUGARS

Alex Rosenthal, M. Sprinzl, and Donald A. Baker

Department of Chemistry, The University of British Columbia,
Vancouver 8, B.C., Canada

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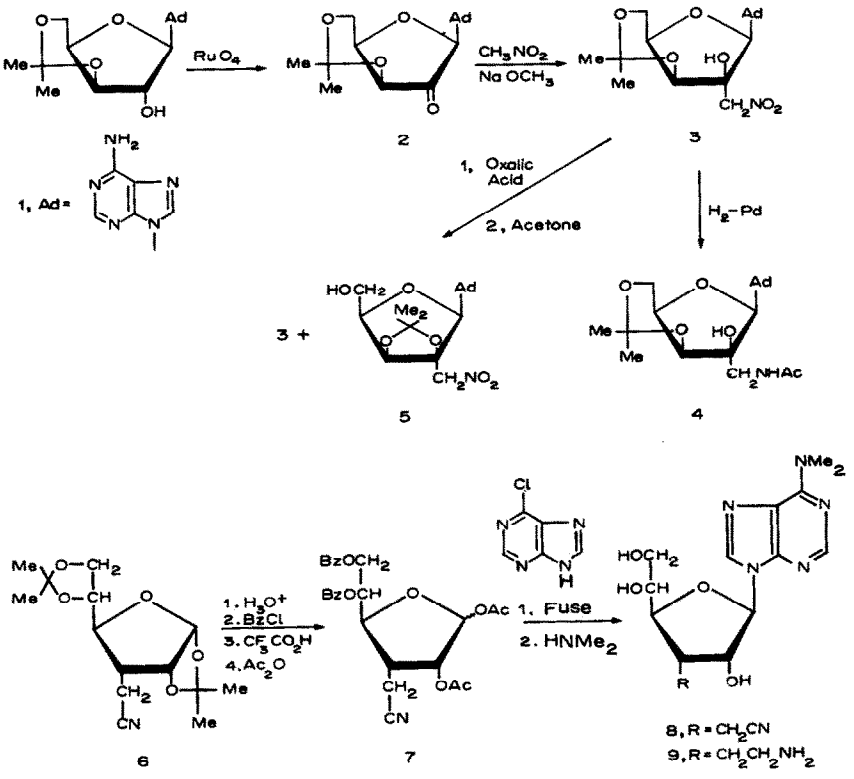
The natural occurrence of nucleoside antibiotics (1) containing deoxy amino sugars as moieties has created interest in their synthesis. Although there is no mention in the literature of nucleosides of amino sugars containing an hydroxyl and aminoalkyl group on the same carbon there are several reports describing the synthesis of branched-chain nitro sugars and branched-chain aminoalkyl sugars *via* the addition of nitromethane to ketoses (2). In this communication we wish to present, as described below, novel approaches to the synthesis of both of the aforementioned types of nucleosides.

Oxidation of 9-(3',5'-*O*-isopropylidene-β-D-xylofuranosyl)adenine (1) (3) with ruthenium tetroxide (4) in a mixture of carbon tetrachloride, aqueous sodium hydrogen carbonate, and 5% aqueous sodium metaperiodate (stoichiometric amount must be added dropwise) gave 9-(3',5'-*O*-isopropylidene-2'-keto-β-D-xylofuranosyl)adenine (2) as the hydrate in 74% yield, m.p. 165-166°, $[\alpha]_D^{22}$ +4° (c 2, methanol), $\lambda_{max}^{CH_3OH}$ 260 mμ (ε 16,800). The keto nucleoside hydrate (0.57 g) was dehydrated by distillation under reduced pressure (three times) of a mixture of toluene-methanol (20:1) from it. To pure 2 was then added a mixture of 4 ml of nitromethane, 2 ml of anhydrous methanol, and 1 ml of 1 N sodium methoxide in methanol, and the reactants were left at room temperature for 12 hrs, then neutralized with an equivalent amount of Dowex 50 (H^+) resin. After removal of the resin the solvent was evaporated under reduced pressure leaving a residue (0.41 g) which was crystallized from methanol to give pure nucleoside (3) in 67% yield, m.p. 130-131°, $[\alpha]_D^{22}$ -28° (c 2, methanol), c.d. $[\theta]_{max}^{CH_3OH}$ 277 mμ +4140, $\lambda_{max}^{CH_3OH}$ 260 mμ (ε 10,720). Deacetonation of (3) with 0.1 N aqueous oxalic acid at room temperature for 1 hr gave 9-(2'-*C*-nitromethyl-β-D-lyxofuranosyl)adenine in 75% yield, m.p. 102-105° (with decomposition), $[\alpha]_D^{22}$ -34° (c 2, methanol), $\lambda_{max}^{H_2O}$ 261 mμ (ε 13,060).

That this nucleoside had the *lyxo*- rather than the C-2'-epimeric *xylo*-configuration was demonstrated by its conversion, using acetone, 2,2-dimethoxypropane and di-*p*-nitrophenyl hydrogen phosphate (3) into a mixture of two acetonides, namely 3 and the 2',3'-*O*-isopropylidene derivative



(5), m.p. 192-193°, $[\alpha]_D^{22}$ -48° (c 2, methyl sulfoxide), $\lambda_{max}^{H_2O}$ 260 mμ (ε 14,600). Compounds (3) and (5) were separated by preparative t.l.c. on silica gel using ethyl acetate-methanol (9:1) as developer. Interestingly, the positive circular dichroism (c.d.) maxima exhibited by (3) is in accord with the lyxo-configuration (5).

Reduction of 3 in methanol-water-acetic acid (5:5:1) over 10% palladium on charcoal at room temperature for 3 hrs. followed by N-acetylation of the aminomethyl group and subsequent t.l.c. separation of the products on silica gel using ethyl acetate-ethanol (4:1) as developer gave in 62% yield, 9-(2'-C-acetamidomethyl-3',5'-O-isopropylidene-β-D-lyxofuranosyl)adenine (4), m.p. 144-146°, $[\alpha]_D^{22}$ -16° (c 1, methanol), λ_{max}^{water} 262 mμ (ε 8,400).

In the second procedure the branched-chain cyanomethyl sugar was condensed with a purine to give a structural analogue of puromycin. This condensation of 1,2:5,6-di-O-isopropylidene-α-D-ribo-hexofuranos-3-ulose with diethyl cyanomethylphosphonate in the presence of sodium hydride

followed by hydrogenation over 10% palladium on charcoal according to a procedure already published (6) afforded the branched-chain cyanomethyl sugar (6), m.p. 109°, $[\alpha]_D^{22}$ +91° (c 2, chloroform) in over 80% yield. Selective hydrolysis of the latter followed by benzoylation, hydrolysis of the 1,2-O-isopropylidene group and finally acetylation using previously published procedures (7) yielded the branched-chain cyanomethyl sugar (7), m.p. 104°, $[\alpha]_D$ +0° (c 2, chloroform), in an overall yield of 30% based on (6). Fusion of the latter with 6-chloropurine at 150° for about 30 minutes under vacuum with a trace of chloroacetic acid (or without) (8) gave solid (glass) 6-chloro-9-(2'-O-acetyl-5',6'-di'-O-benzoyl-3'-deoxy-3'-C-cyanomethyl-β-D-allofuranosyl)-purine in 66% yield, $[\alpha]_D^{22}$-2° (c 1, chloroform), ν2200 (C≡N), τ^{CDCl_3} 1.73 and 1.37 (H-2, H-8), 8.2 (Ac). Treatment of the latter with methanol-water-dimethylamine (25%) for 1 day, gave 6-dimethylamino-9-(3'-deoxy-3'-C-cyanomethyl-β-D-allofuranosyl)purine (with $2CH_3OH$) (8) in 60% yield, recrystallized from methanol, m.p. 104-105°, $[\alpha]_D^{22}$-61° (c 1, methanol), $\lambda_{max}^{CH_3OH}$ 275 mμ (ε =18,000); τ^{DMSO-d_6} 1.60, 1.70 (H-2, H-8), 4.03 (d, $J_{1',2'}$ = 3 Hz, H-1').

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