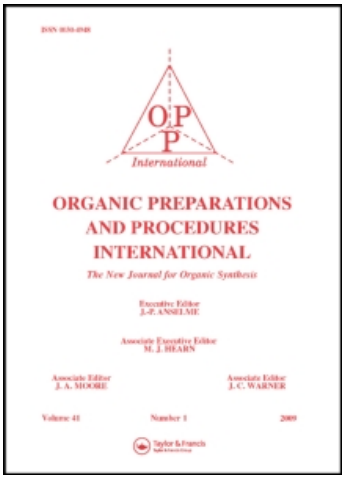

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Tai-Shun Lin[a]; Robert E. Harmon[a]
[a] Department of Chemistry, Western Michigan University, Kalamazoo, Michigan

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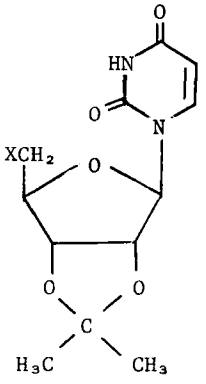
SYNTHESIS OF NITRONUCLEOSIDES[1]

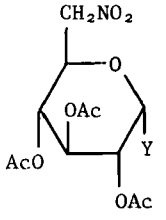
Tai-Shun Lin and Robert E. Harmon*

Department of Chemistry, Western Michigan University
Kalamazoo, Michigan 49001

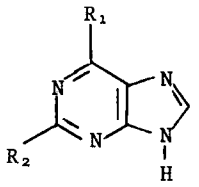
Nitronucleosides are the key intermediates for the syntheses of certain aminonucleosides. Vince and coworkers[2] have recently reported that diastereomeric carbocyclic puromycin analogs act as two distinct types of inhibitors, namely, peptidyl transferase substrates and peptidyl transferase inhibitors in protein biosynthesis. Several methods have been used to synthesize 3'-amino-3'-deoxy-hexopyranosyl nucleosides. The condensation of nitromethane with sugar dialdehydes has been used with much success.[3-5] Baer and coworkers have recently reported a L-ribo-nitronucleoside synthesis[6] which involves the conversion of 6-benzamido-9-(6'-deoxy-6'-nitro-β-D-glucopyranosyl)purine into 6-benzamido-9-(3'-deoxy-3'-nitro-α-L-ribofuranosyl)purine via an intramolecular rearrangement.



Ia X = NO_2
Ib X = OH
Ic X = I

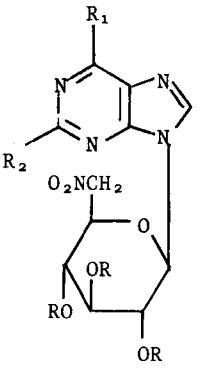


IIa Y = OCH_3
IIb Y = OAc
IIc Y = Br



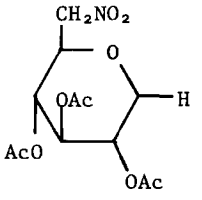
IIIa $R_1 = N(CH_3)_2$; $R_2 = CH_3S$

IIIb $R_1 = NHC\phi$; $R_2 = H$



IVa $R_1 = N(CH_3)_2$; $R_2 = SCH_3$

IVb $R_1 = NHC-\phi$; $R_2 = H$



V

As key starting compound for the synthesis of L-3'-deoxy-3'-amino-nucleosides, a nucleoside bearing a nitro group at the C-6' position of the sugar moiety is required. As part of our initial approach we attempted the preparation of Ia. Treatment of Ib with methyltriphen-oxyphosphonium iodide[7] in anhydrous N,N-dimethylformamide at room temperature for 3 hr afforded Ic[8] in 88% yield. However, all attempts to effect the conversion of the iodo nucleoside Ic to the corresponding nitro derivative Ia were unsuccessful. For instance, treatment of Ic with sodium nitrite and phloroglucinol at room temperature in DMSO-DMF (4:1) gave only unidentifiable dark decomposition products. Conducting the reaction at 0° under nitrogen atmosphere also failed to give Ia. Because of the previously mentioned unsuccessful results, a new approach was taken which involved constructing the nitrosugar moiety first and then condensing it with purine bases to give the desired nitronucleosides.

Treatment of methyl 6-deoxy-6-iodo-2,3,4-tri-O-acetyl-α-D-glucopyranoside[9] with sodium nitrite and phloroglucinol in DMSO-DMF (4:1) at 15-20° for 3 days afforded IIa[10] which was converted to the tetra-O-acetyl derivative IIb in 70% yield using Ac_2O-AcOH (1:1) mixture in the presence of concd sulfuric acid.[11] Compound IIb was then transformed into IIc in 65% yield by treating IIb with aluminium bromide using bromoform as solvent.[12] The conventional hydrogen bromide in glacial acetic acid bromination process did not succeed in this instance. The bromosugar IIc was then condensed with IIIa which was prepared in an eight step synthesis according to the procedure reported by B.R. Baker and coworkers[13]; and with IIIb[14,15] in the presence of mercuric cyanide and anhydrous calcium sulfate, in refluxing nitromethane[16] to yield IVa and IVb in yields of 25% and 42% respectively. The nitronucleoside IVa was also prepared in 30% yield by coupling the bromide IIc with chloromercuric salt of IIIa in refluxing nitromethane. The tlc of the reaction mixtures revealed the presence of unreacted purines IIIa and IIIb and an unidentified compound, possibly a decomposition product of nitro bromosugar IIc. It was found that 3 hr refluxing time was the optium condition for the reactions. Prolonged heating caused decomposition of the nitronucleosides leading to decreased yields. The β-D configuration of nitronucleosides IVa and IVb were established by their rotations which are levorotatory and by a rather large coupling constant observed in the nmr signal assigned to H-1'.

The attempt to couple the nitroglucopyranosyl bromide IIc with 6-dimethylaminopurine[17] in the presence of mercuric cyanide and anhydrous calcium sulfate using nitromethane as solvent was unsuccessful. Instead of the desired nitro nucleoside, an unsaturated nitro sugar derivative

V and black tar were obtained. Mass spectrum and elemental analyses data of compound V were in accord with the assigned structure.

The acetyl groups in IVa were removed using the procedure by cautious treatment of IVa with sodium methoxide in chloroform at 0° to give IVc in 86% yield.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover Unimelt apparatus and are uncorrected. A Beckman IR-8 spectrophotometer was used to determine the ir spectra. The uv spectra were obtained on a Cary-14 spectrophotometer. The nmr spectra were run on Varian A-60 and/or Varian XL-100 spectrometers using Me_4Si as internal standard. The mass spectra were recorded on ATLAS CH4 or LKB 9000 instruments. Optical rotations were measured with a Perkin Elmer 141 polarimeter. The tlc was performed on Eastman precoated 6061 silica gel plates using the following solvent systems (v/v): (a) chloroform; (b) chloroform-ethanol (4:1). The tlc plates were observed under uv light and/or developed with iodine. The elemental analyses were carried out by Midwest Microlab, Inc., Indianapolis, Indiana.

2,3,4,-Tri-O-acetyl-6-deoxy-6-nitro-α-D-glucopyranosyl Bromide (IIc). - Anhydrous aluminum bromide (1.6 g, 0.006 mol) was added to a solution of IIb[6] (1.9 g, 0.0056 mol) in 50 ml of bromoform. The mixture was heated to 80° (oil bath) with stirring for 24 hrs. and filtered through celite to remove the insoluble material. The bromoform solution was washed with ice-cold water (2 x 50 ml), dried (Na_2SO_4), and evaporated to dryness *in vacuo*. The residue was then dissolved in 100 ml of chloroform, clarified with Norit and the solvent was evaporated to dryness under reduced pressure. The residue was crystallized from acetone to give 1.3 g (65%) of the product, mp 210-212° (dec); $[\alpha]_D^{26}$ +173.4° (C, 1, DMF); ir (Nujol), 1740 (C=O), 1550 (NO_2), 1220 with shoulder at 1250 cm^{-1} (C-O); nmr ($CDCl_3$), δ 6.56 (d, 1, $J_{1,2}$ = 4Hz, H_1), 2.10-2.06 (3 s, 9, C_2, C_3 and C_4 OAc), mass spectrum M^+ (m/e)397=$C_{12}H_{16}BrNO_9$.

Anal. Calcd for $C_{12}H_{16}BrNO_9$: C, 36.20; H, 4.05; Br, 20.07; N, 3.52. Found: C, 36.11; H, 4.12; Br, 20.75; N, 3.49.

2-Methylmercapto-6-dimethylamino-9-(2',3',4'-tri-O-acetyl-6'-deoxy-6'-nitro-β-D-glucopyranosyl)purine (IVa). - A suspension of 2-methylmercapto-6-dimethylamino purine IIIa[13] (1.65 g, 7.53 m mol) in nitromethane (150 ml) was dried azeotropically by distilling 50 ml of the solvent. A mixture of the bromide IIc (3.00 g, 7.53 m mol), mercuric cyanide (1.90 g, 7.53 m mol) and anhydrous calcium sulfate (1.20 g, 8.82 m mol) was added and the reaction mixture was then heated to reflux (oil bath temp. 110-115°) with vigorous stirring for 3 hr. with exclusion of moisture. The hot mixture was filtered through celite. The filtrate was evaporated to dryness under reduced pressure. The residue as well as the filter cake were extracted by stirring each with 100 ml of chloroform for 20 min. The combined extracts were washed successively with 30% aqueous potassium iodide solution (2 x 100 ml) and water (2 x 100 ml) and then dried over anhydrous sodium sulfate. The chloroform solution (clarified with Norit) was then evaporated to dryness in vacuo to afford a glassy syrup (2.60 g) which was crystallized twice from ethanol to yield 0.99 g (25%) of IVa as white fine needles, mp 208-210° (dec). A third recrystallization from ethanol gave analytically pure sample, mp 211-212° (dec); $[\alpha]_D^{25}$ -3.0° (C, 1, $CHCl_3$); tlc, R_f = 0.6($CHCl_3$); ir (film), ν_{max} 1750 (C=O), 1590 (C=C, C=N), 1560 (NO_2), 1230 cm^{-1} (C-O); uv (EtOH), λ_{max} 274 nm (ε 18,182), λ_{max} 236 nm (ε 25,573); nmr ($CDCl_3$), δ 7.74 (s, 1, H-8), 5.93 (d, 1, H-1', with $J_{1',2'}$ = 8.5 Hz), 3.46 [s, 6, $N(CH_3)_2$], 2.57 (s, 3, SCH_3), 2.10, 2.04, 1.80, (3 s, 9, 3 acetyl); mass spectrum (70 eV), M^+ (m/e) 526 = $C_{20}H_{26}N_6O_9S$.

Anal. Calcd for $C_{20}H_{26}N_6O_9S$: C, 45.62; H, 4.98; N, 15.96; S, 6.09. Found: C, 45.43; H, 4.93; N, 15.91; S, 6.30.

Compound IVa was also synthesized in 30% yield (0.68 g) by condensing the bromosugar IIc (1.75 g, 4.39 m mol) with the chloromercuric

salt of IIIa (2.00 g, 4.39 m mol) in the presence of Celite (3.00 g) in refluxing nitromethane (120 ml) according to the procedures described previously.

6-Benzamido-9-(2',3',4'-tri-O-acetyl-6'-deoxy-6'-nitro-β-D-glucopyranosyl)purine (IVb)[6]. - To a solution of N-benzoyladenine[18] (1.80 g, 7.53 m mol) in 120 ml of nitromethane dried by azeotropic distillation was added a mixture of the bromosugar IIc (3.00 g, 7.53 m mol), mercuric cyanide (1.90 g, 7.53 m mol) and anhydrous calcium sulfate (1.00 g). The mixture was refluxed with stirring for 3 hrs under anhydrous condition. The product was isolated in the same manner described in the synthesis of IVa. The residue, crystallized twice from ethanol, gave 1.78 g (42%) of IVb, mp 203-203.5° (dec); $[\alpha]_D^{25}$ -26.0° (C, 1, $CHCl_3$); tlc, R_f = 0.2 ($CHCl_3$); ir (film), ν_{max} 3280 (NH), 1740 (acetyl C=O), 1680 (N-benzoyl C=O), 1590 (C=C, C=N), 1550 (NO_2), 1260-1177 cm^{-1} (C-O); uv (EtOH), λ_{max} 276 nm (ε 21,000); nmr ($CDCl_3$); δ 8.76 (s, 1H, H-2), 8.23 (s, 1H, H-8), 8.09-7.95 (m, 2H, -Ph), 7.60-7.45 (m, 3H, -Ph), 6.07 (d, 1H, H-1', with $J_{1',2'}$ = 8.7 Hz), 2.11, 2.05, 1.76, (3 s, 9 H, 3 acetyl).

Anal. Calcd for $C_{24}H_{24}N_6O_{10}$: C, 51.80; H, 4.35; N, 15.10. Found: C, 51.93; H, 4.27; N, 15.25.

2-Methylmercapto-6-dimethylamino-9-(6'-deoxy-6'-nitro-β-D-glucopyranosyl)purine (IVc). - To a magnetically-stirred solution of IVa (1.3 g, 0.00247 mol) in chloroform (20 ml) at 0°, was added dropwise a freshly prepared solution of sodium (0.3 g, 0.013 mol) in methanol (20 ml). The reaction mixture was kept at 0° with stirring for 1 hr, and then time water (20 ml) was added. The solution was then acidified to pH 5 by adding glacial acetic acid dropwise with continued cooling. Removal of most of the organic solvents under reduced pressure (bath temperature

35°) caused sudden crystallization of white crystals from the concentrated solution. The product was collected at once, washed with water, ice-cold ether, and dried in vacuo over P_2O_5 at room temperature; yield, 0.85 g (86%), mp 180-185° (dec), showing one spot on tlc [R_f 0.7, $CHCl_3$-EtOH (4:1)]. Two recrystallizations from ethanol gave the analytical sample, mp 184-185° (dec); ir (Nujol), 3250 (broad, OH), 1620 (C=C, C=N), 1550 cm^{-1} (NO_2).

Anal. Calcd for $C_{14}H_{20}N_6O_6S$: C, 41.99; H, 5.03; N, 20.98; S, 8.00. Found: C, 42.13; H, 5.16; N, 21.22; S, 8.15.

Reaction of IIc with 6-Dimethylaminopurine and Mercuric Cyanide. - To a solution of 6-dimethylaminopurine (1.23 g, 7.53 m mol) in 150 ml of nitromethane dried by azeotropic distillation, was added a mixture of the bromide IIc (3.00 g, 7.53 m mol), mercuric cyanide (2.10 g, 8.28 m mol), and anhydrous calcium sulfate (3.59 g). The mixture was refluxed for 3 hr with vigorous stirring. At the end of this time, the reaction mixture had turned dark brown. The crude product isolated using the method described in the synthesis of IIa, was crystallized 3 times from ethanol to yield white needles (0.34 g) which were identified as hydroxyl glucal derivative V: mp 231-233° (dec); mass spectrum (70 eV), M^+ (m/e) 317 = $C_{12}H_{15}NO_9$.

Anal. Calcd for $C_{12}H_{15}NO_9$: C, 45.43; H, 4.77; N, 4.42. Found: C, 44.83; H, 5.16; N, 4.17.

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