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Note

Synthesis of N-bridgehead heterocycles from saccharide benzimidazoles

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Abstract—Treatment of D-*arabino*-tetritol-1-yl-benzimidazole with *p*-toluenesulfonyl chloride (1 mol equiv) in pyridine, afforded the N-bridgehead heterocycles, 2*R*,3*R*,4*S*-trihydroxy-1:2:3:4-tetrahydropyridino[1,2-*a*]benzimidazole. The structure of the latter compound was determined by acylation, ^{1}H, and ^{13}C NMR spectroscopy and mass spectrometry.

Keywords: D-*arabino*-Benzimidazole; N-Bridgehead heterocycles; 1:3-Diazaline

We have been interested in the synthesis of C-nucleoside analogs from saccharide heterocycles by acid-catalyzed[1–7] dehydrative cyclization of their polyhydroxyalkyl chains and in basic medium by treatment with *p*-toluenesulfonyl chloride in pyridine solution.[8,9] The dehydrative cyclization of a tetrahydroxytetryl heterocycle's side chain in acid medium[1,3–6] is stereospecific, affording glycofuronosyl C-nucleoside anomers having a trans arrangement of the base moiety and the 2′-OH group, and a cis configuration of the 1′-OH and 2′-OH groups in the cyclized product. On the other hand, the cyclization of a pentahydroxypentyl side chain[2–5,7] in acid medium is not so stereospecific, with the formation of anomeric pairs of glycofuronosyl and glycopyranosyl C-nucleoside analogs with and without inversion at C-1′. The cyclization of a tetrahydroxytetryl side chain in the basic medium is stereospecific with the formation of the primary *p*-toluenesulfonyl intermediate, as a kinetic product, which undergoes S_N2 attack by 1′-OH to get the glycofuranosyl analog without inversion[8,9] at C-1′. In this work, the dehydrative cyclization in basic medium was extended to D-*arabino*-tetritol-1-yl-benzimidazole (**1**), which afforded a polycyclic product **3** by nucleophilic attack of the benzimidazole nitrogen instead of the saccharide oxygen. The structures of the dehydrative cyclization products were determined by NMR spectroscopy and mass spectrometry.

Treatment of D-*arabino*-tetritol-1-yl-benzimidazole (**1**) with 1 mol equiv of *p*-toluenesulfonyl chloride in pyridine solution did not give 2-*C*-(α-D-*erythro*pentofuranosyl)benzimidazole (**2**) by 1′,4′-dehydrative cyclization of the polyhydroxyalkyl chain such as tetrahydroxytetryl 2-phenyl-2*H*-1,2,3-triazole. Compound **2** has been obtained from **1** by dehydrative cyclization in an acid medium,[6] but in a basic medium, the dehydrative cyclization takes place between the primary carbon atom of the polyhydroxyalkyl chain and the 1-NH group of the benzimidazole ring, giving an N-bridgehead heterocycle of the 1:3-diazaline type,[10] namely, 2*R*,3*R*,4*S*-trihydroxy-1:2:3:4-tetrahydropyridino[1,2-*a*]benzimidazole (**3**). The reaction in basic medium takes place with the formation of the primary tosyl intermediate as a kinetic product. The primary tosyl group, which is a good leaving group, instead of undergoing S_N2 attack by the 1′-hydroxyl group of the tetrahydroxytetryl side chain to give C-nucleoside **2**, is attacked faster by the more nucleophilic 1-nitrogen atom of the benzimidazole moiety giving the N-bridgehead heterocycle **3**.

The ^{1}H NMR spectrum of **3** did not show the downfield NH signal corresponding to the furanosyl C-nucleoside analog **2**. Instead, it showed three exchangeable

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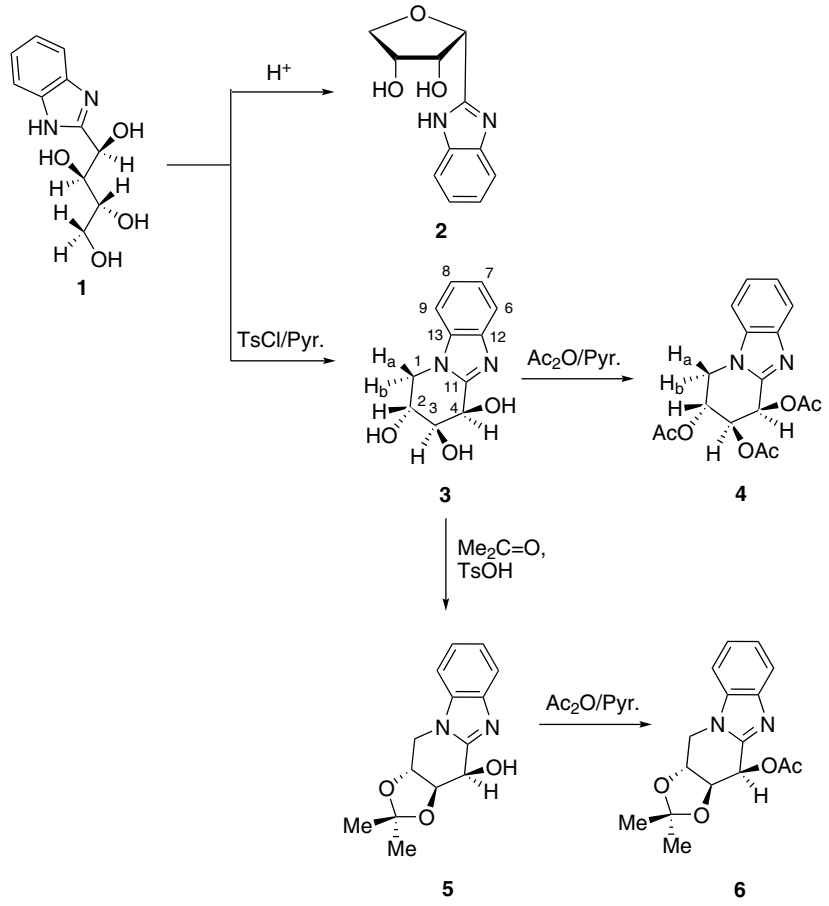
hydroxyl signals at δ 5.93 (1H) and 5.37 (2H). Acetylation of **3** gave the tri-*O*-acetyl derivative **4** having three singlets at δ 2.106 (3H), 2.108 (3H), and 2.20 (3H) corresponding to three *O*-acetyl groups. No downfield *N*-acetyl signal was observed. In addition, the N-bridgehead structure **3** was unequivocally ascertained from its ^{13}C NMR spectrum that showed the (CH_2–N) signal at δ 44.4 shifted upfield from the corresponding furanosyl (CH_2–O–) signal, which usually appears[11] at δ 72.3 for a 1,4-anhydroerythritol.

Acetonation of **3** afforded the mono-*O*-isopropylidene derivative **5**. Its ^{1}H NMR spectrum showed the two methyl signals of the 2,2-dimethyldioxolane ring at δ (3H) corresponding to the *O*-acetyl group, which was shifted downfield from the two methyl signals of the 2,2-dimethyldioxolane ring (δ 1.01 and 1.33, $\Delta\delta$ 0.32). However, its ^{13}C NMR spectrum showed the acetyl CH_3 signal at δ 20.6, shifted upfield from the isopropylidine methyl signals (δ 23.9 and 26.1). The CH_2–N signal was shown at δ 44.7. The position of acetonation was determined by comparing the ^{1}H NMR spectrum of **5** and **6**. Compound **6** showed downfield shift (−0.82 ppm) of H-4 compared to that for compound **5**, due to α-acetylation at this position. The isopropylidene formation took place between the two cis adjacent 2-OH and 3-OH groups.



1.34 and 0.97 having $\Delta\delta$ value 0.37. This $\Delta\delta$ value is too large for β-furanosyl nucleoside isopropylidene groups ($\geqslant$0.18) or α-furanosyl analogs[12,13] ($\leqslant$0.10), excluding the formation of a glycofuranosyl isopropylidene structure. The observed value is in accord with the formation of the N-bridged piperidino isopropylidene structure **3**, where the nucleoside $\Delta\delta$ criterion cannot be applied. These results are in accord with the formation of the N-bridgehead structure **3**, rather than the furanosyl C-nucleoside analog **2**. Acetylation of **5** gave the mono-*O*-acetyl-mono-*O*-isopropylidene derivative **6**. Its ^{1}H NMR spectrum showed a singlet at δ 2.08

The electron-impact mass spectrum for compound **3** showed a molecular ion at *m*/*z* 220, and a base peak was shown at *m*/*z* 191 corresponding to the fragment (M−CHO). The fragmentation pattern of compound **3** was different from that of C-nucleosides, which are characterized[14] by the formation of the ion BCHOH as the base peak. In addition, the peaks of the base BH_2, BH, and B, which are faint for C-nucleosides, were more abundant for this N-bridgehead analog **3**. Fragments corresponding to the sequential loss of HCN molecules from the benzimidazole base moiety were shown at *m*/*z* 92, 91, 90, 65, 64, and 63 (see Section 1).

1. Experimental

1.1. General methods

Melting points were determined with a Fisher–Johns melting point apparatus and are uncorrected. Evaporations were performed under diminished pressure below 60 °C. Thin-layer chromatography (TLC) was carried out on silica gel (Kieselgel G, E. Merck) with solvent A, 5:2 CH_2Cl_2–EtOH, solvent B, 3:1 EtOAc–*n*-hexane, and solvent C, 1:4 EtOAc–*n*-hexane. Spots were detected under ultraviolet light at 245 nm. ^{1}H NMR spectra were recorded with a Jeol EX 400-MHz or a Bruker 500-MHz spectrometer using tetramethylsilane as the internal standard. ^{13}C NMR spectra were recorded with a Jeol EX 400 at 100.4 MHz or a Bruker 500 at 125.8 MHz instrument. Assignment of peaks were verified by 2D, ^{1}H–^{13}C, COSY, and DEPT experiments. An asterisk (*) indicates carbons that may be interchangeable or uncertain. Mass spectra were recorded with an AEI MS 902 spectrometer. High-resolution mass spectra were recorded with a VG 70-250 spectrometer. Combustion analyses were carried out at the Chemistry Department, Faculty of Science, Cairo University, Cairo, Egypt.

1.2. 2*R*,3*R*,4*S*-Trihydroxy-1:2:3:4-tetrahydropyridino-[1,2-*a*]benzimidazole (3)

2-(D-*arabino*-Tetritol-1-yl)benzimidazole[15] (1 g, 4.3 mmol) in dry pyridine (50 mL) was treated portionwise with *p*-toluenesulfonyl chloride (0.882 g, 4.7 mmol, 1.1 equiv), at room temperature with stirring. The mixture was stirred at room temperature for 48 h. A few drops of water were added to decompose excess *p*-toluenesulfonyl chloride, the solution was evaporated to a syrup, and the remaining pyridine was removed by spin coevaporation with toluene (3 × 20 mL). The residual syrup was applied to a column (2.5 × 45 cm) of Silica Gel 60 and eluted with solvent A. Fractions were collected, and evaporated to dryness. Compound **3** was obtained as a precipitate that was recrystallized from dilute MeOH as colorless needles (yield 0.220 g, 24%), mp 190–192 °C, R_f 0.65 (solvent A); ^{1}H NMR (400 MHz; Me_2SO-d_6): δ 3.86 (dd, 1H, $J_{1b,2}$ 8.3, $J_{1a,1b}$ 11.2 Hz, H-1b), 3.94 (m, 1H, H-3), 4.23 dd (1H, $J_{1a,2}$ 5.4 Hz, H-1a), 4.38 (m, 1H, H-2), 4.68 (dd, 1H, $J_{3,4}$ 4.9 Hz, H-4), 5.37 (m, 2H, 2-OH, 3-OH), 5.93 (d, 1H, 4-OH), 7.17–7.49 (m, 2H, H-7, H-8), 7.53 (d, 1H, H-9), 7.57 (d, 1H, H-6); after addition of CD_3CO_2D the three OH signals disappeared δ 3.87 (dd, 1H, $J_{1b,2}$ 8.3 Hz, $J_{1a,b}$ 11.7 Hz, H-1b), 3.93 (m, 1H, J 1.5 Hz, H-3), 4.23 (dd, 1H, $J_{1,2}$ 5.4 Hz, H-1a), 4.37 (m, 1H, H-2), 4.69 (d, 1H, $J_{3,4}$ 4.9 Hz, H-4); ^{13}C NMR (Me_2SO-d_6, 125.8 MHz), δ 44.4 (C-1), 64.3 (C-2), 66.8 (C-4), 72.3 (C-3), 110.1 (C-9), 118.7 (C-6), 121.7 (C-7), 121.9 (C-8), 134.1 (C-12), 143.1 (C-13), 152.2 (C-11); EIMS (selected ions): *m*/*z* 221 (9, M+1), 220 (64, M), 202 (2, M−H_2O), 192 (12, M−CO), 191 (100, M−CHO), 185 (13, MH−2H_2O), 184 (8, M−2H_2O), 173 (17), 160 (9, BCHCHOH, where B = benzimidazole moiety), 159 (4, BCHCHO), 157 (6), 156 (6), 148 (17, BCH_2OH), 147 (30, BCHOH), 146 (6, BCHO), 133 (7), 132 (66, BCH_3), 131 (63, BCH_2), 119 (19, BH_2), 118 (19, BH), 104 (12, PhCNH), 92 (BH_2−HCN), 91 (6, BH−HCN), 90 (3, B−HCN), 77 (12, Ph), 65 (5, BH_2−2HCN), 63 (1, B−2HCN). HREIMS of the molecular ion peak: calcd for $C_{11}H_{12}N_2O_3$, *m*/*z* 220.0848; found, *m*/*z* 220.0847. Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.18; H, 5.38; N, 12.82.

1.3. 2*R*,3*R*,4*S*-Tri-*O*-acetyl-1:2:3:4-tetrahydropyridino-[1,2-*a*]benzimidazole (4)

Compound **3** (10 mg, 0.038 mmol) in pyridine (2 mL) was treated with Ac_2O (2 mL) and kept at room temperature for 24 h. The mixture was evaporated until dry, and traces of pyridine were removed by spin coevaporation with toluene. The dry residue was chromatographed on a short column (1 × 10 cm) of Silica Gel 60, eluted with solvent B, giving a colorless syrup (yield 17 mg): R_f 0.42, (solvent B); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.106 (s, 3H, OAc), 2.108 (s, 3H, OAc), 2.20 (s, 3H, OAc), 4.29 (dd, 1H, $J_{1a,2}$ 5.1 Hz, $J_{1a,1b}$, 12.7 Hz, H-1a), 4.43 (dd, 1H, $J_{1b,2}$ 4.2 Hz, H-1b), 5.59 (dd, 1H, $J_{3,4}$ 2.3 Hz, $J_{2,3}$ 7.1 Hz, H-3), 5.82 (m, 1H, H-2), 6.40 (d, 1H, $J_{3,4}$ 7.1 Hz, H-4), 7.33 (m, 3H, H-7, H-8, H-9), 7.82 (m, 1H, H-6); ^{13}C NMR (125.8 Hz, $CDCl_3$): δ 20.7, 20.8, 21.0 (three *O*-acetyl CH_3) 44.5 (C-1), 64.8 (C-4), 66.2 (C-2), 69.3 (C-3), 110.0 (C-6), 119.2 (C-9), 124.9 (C-7, C-8), 133.0 (C-12), 143.0 (*C-13), 146.2 (C-11), 169.7, 169.8 and 169.8 (three OAc carbonyl groups); EIMS (selected ions): *m*/*z*: 347 (2, M+1), 346 (12, M), 304 (4, M−CH_2CO), 303 (20, M−Ac), 287 (4, M−OAc), 286 (1, M−AcOH), 244 (12, M−AcOH−CH_2CO), 202 (4, M−AcOH−2Ac), 201 (25, M−AcOH−2Ac−H), 186 (M−2OAc−CH_2CO), 185 (100, M−AcOH−OAc−CH_2CO), 184 (8, M−AcOH−OAc−Ac), 147 (5, BCHOH), 131 (4, BCH_2), 119 (3, BH_2) 118 (3, BH), 117 (1, B), 91 (7, PhN), 69 (8), and 43 (55, CH_3CO). HREIMS of the molecular ion peak: calcd for $C_{17}H_{18}N_2O_6$: *m*/*z* 346.1165; found, *m*/*z* 346.1165.

1.4. 4-Hydroxy-2,3-*O*-isopropylidene-1:2:3:4-tetrahydropyridino[1,2-*a*]benzimidazole (5)

Compound **3** (100 mg, 0.375 mmol) in dry acetone (50 mL) was treated with *p*-toluenesulfonic acid (150 mg, 0.80 mmol), and the mixture was stirred for 72 h. TLC indicated the formation of a more mobile

spot, R_f 0.44 (solvent C). The mixture was treated with satd aq $NaHCO_3$ (1 mL), and evaporated to dryness. The residue was extracted with $CHCl_3$. The organic layer was washed with water, dried over anhyd Na_2SO_4, and evaporated until dry, giving colorless needles (yield 40 mg, 41%) that were recrystallized from EtOAc–hexane mp 178–180 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97, 1.34 (2s, 6H, CMe_2, $\Delta\delta$ 0.37), 4.49 (s, 2H, H-1a, H-1b), 4.94 (m, 2H, H-2, H-3), 5.45 (d, 1H, $J_{3,4}$ 2.1 Hz, H-4), 7.28 (d, 1H, $J_{7,8}$ 7.6, Hz, H-7), 7.35 (t, 1H, H-8), 7.56 (d, 1H, $J_{8,9}$ 8.0 Hz, H-9), and 7.61 (d, 1H, $J_{6,7}$ 8.1 Hz, H-6); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 23.9, 26.1 (two CH_3, $^{13}C\Delta\delta$ 2.2), 44.2 (C-1), 63.4 (C-4), 72.5 (C-3), 76.7 (C-2), 109.4 (acetonide carbon), 110.1 (*C-6), 117.3 (*C-9), 124.0 (**C-7), 124.5 (**C-8), 133.3 (*C-12), 136.6 (*C-13), 151.4 (C-11, originally C-2 of the benzimidazole moiety), assignment verified by 2D, ^{1}H–^{13}C COSY, and DEPT experiments); EIMS (selected ions): *m*/*z* 261 (11, M+1), 260 (64, M), 245 (33, M−CH_3), 232 (12), 231 (78, M−CHO), 203 (7, MH−CH_3COCH_3), 185 (12, MH−CH_3COCH_3−H_2O), 173 (30), 158 (7), 157 (30), 147 (8, BCHOH), 146 (28, BCHO), 145 (7, BCO), 132 (15, BCH_3), 131 (12, BCH_2), 129 (11), 119 (13, BH_2), 118 (100, BH), 117 (4, B), 92 (5, BH_2−HCN), 91 (8, BH−HCN), 77 (13, Ph), 65 (6, BH_2−2HCN), 63 (B−2HCN); HREIMS of the molecular ion peak: calcd for $C_{14}H_{16}N_2O_3$: *m*/*z* 260.1161; found, *m*/*z* 260.1162. Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.19; N, 18.44. Found: C, 64.66; H, 6.24; N, 18.84.

1.5. 4-*O*-Acetyl-2,3-*O*-isopropylidene-1:2:3:4-tetrahydropyridino[1,2-*a*]benzimidazole (6)

Compound **5** (10 mg, 0.038 mmol) was acetylated with a 1:1 mixture of pyridine–Ac_2O (2 mL) for 24 h and worked up as described for **4**. It gave a colorless syrup that was chromatographed on Silica Gel 60, eluting with solvent B, giving a syrup that crystallized from dilute MeOH as colorless needles: mp 170–173 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.01, 1.33 (2s, 6H, CMe_2, $\Delta\delta$ 0.32), 2.08 (s, 3H, OAc), 4.28 (dd, 1H, $J_{1a,2}$ 2.7 Hz, $J_{1a,1b}$ 13.8 Hz, H-1a), 4.56 (dd, 1H, $J_{1b,2}$ 1.5 Hz, H-1b), 4.78 (dd, 1H, $J_{3,4}$ 2.3 Hz, $J_{2,3}$ 6.8 Hz, H-3), 4.88 (m, 1H, H-2), 6.27 (d, 1H, $J_{3,4}$ 2.0 Hz, H-4), 7.35 (m, 2H, H-7, H-8), 7.42 (d, 1H, $J_{8,9}$ 7.8 Hz, H-9), 7.87 (d, 1H, $J_{6,7}$ 7.8 Hz, H-6); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 20.6 (acetyl-CH_3), 23.9, 26.2 (CMe_2, $^{13}C\Delta\delta$ 2.3), 44.7 (C-1), 63.6 (C-4), 71.4 (C-2), 74.2 (C-3), 110.7 (acetonide carbon), 110.9 (*C-6), 117.2 (*C-9), 127.1, 127.3 (C-7, C-8), 131.4 (C-12), 144.6 (C-13), and 168.4 (CO); EIMS (selected ions): *m*/*z* 303 (7, MH), 302 (31, M), 287 (5, M−CH_3), 260 (18, M−CH_2CO), 259 (58, M−Ac), 201(7), 186 (13, M−AcO−CH_3−CH_2CO), 185 (100, M−OAc−CH_3-$COCH_3$), 173 (27, MH−OAc−Ac−$2CH_3$−CH_2CO), 168 (8), 157 (25, BCH_2CO), 156 (9), 131 (7, BCH_2), 119 (6, BH_2), 118 (28, BH), 117 (3, B), 77 (Ph), and 43 (51, CH_3CO); HREIMS of the molecular ion peak: calcd for $C_{16}H_{18}N_2O_4$: *m*/*z* 302.1266; found *m*/*z* 302.1266.

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