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Note

Nitroalkane condensation with 2-deoxy-D-*erythro*-pentose: a route to chiral 6,8-dioxabicyclo[3.2.1]octanes

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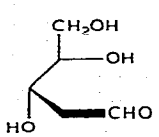
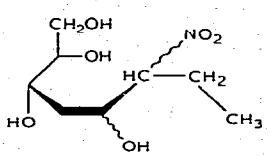
The utilization of carbohydrates as precursors to chiral pheromones[1] has led us to investigate the synthesis of chiral 6,8-dioxabicyclo[3.2.1]octanes by a variety of chain-extension procedures. We now report the preparation of the chiral 5-ethyl-6,8-dioxabicyclo[3.2.1]octane ring-system by condensation of 2-deoxy-D-*erythro*-pentose (**1**) with 1-nitropropane, followed by hydrolysis of the resulting, *aci*-nitro salt.

Preparation of the substituted, bicyclo system is hampered by the difficulty with which the nitroaldol reaction proceeds as the chain length is increased[2]. Elimination and intramolecular, Michael addition of the nitroalkane **2**, to generate epimeric nitro anhydro sugars (**3**), becomes a major pathway under mildly alkaline conditions. This reaction has been clearly documented with nitromethane derivatives[3] and various other electron-withdrawing groups[4]. Here, we indicate how these readily equilibrated isomers may be converted into a mixture of keto anhydrides (**4**).



1



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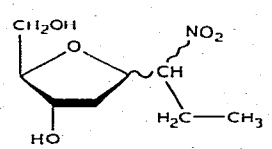

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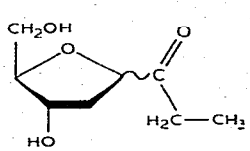

4

The condition that proved to be more conducive to the ultimate formation of the 6,8-dioxabicyclo ring-system was a system that employed an excess of aqueous base, forming the *aci* salt. These salts are much less susceptible to elimination, and are ideally suited for the Nef reaction[2]. Concentrated hydrochloric acid was employed in the hydrolysis, as it resulted in less decomposition than did sulfuric acid. The action of the acid not only provided the hydrolytic force for the Nef reaction but favored cyclization to the acetals (**5** and **7**). Uncyclized material was removed through periodate degradation, and fractionation by column chromatography gave the two diols in 11% (**5**) and 1% (**7**) yield. The diols were characterized as their crystalline 2,4-diacetates (**6** and **8**), and **7** was converted into its 2,4-bis-*p*-toluenesulfonate (**9**).

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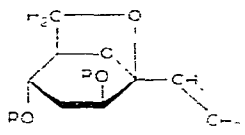
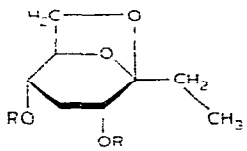


5 R = H
6 R = Ac



7 R = H
8 R = Ac
9 R = $SO_2C_6H_4Me$-*p*

EXPERIMENTAL

General methods. — Evaporations were conducted in a Büchi rotary evaporator at bath temperatures not exceeding 50°. Melting points were determined on a Fisher–Johns apparatus and are uncorrected. Optical rotations were measured with a Perkin–Elmer Model P22 spectropolarimeter. Silica gel G (E. Merck, type 60) was used for t.l.c. Detection was accomplished by spraying with 10% sulfuric acid and heating. Microanalyses were performed by Mr. M. K. Yang. Infrared spectra were recorded with a Perkin–Elmer 457 grating spectrophotometer. ^{1}H-N.m.r. spectra were recorded with a Varian A-56/60A or XL-100 instrument. All chemical-shift values are given in p.p.m. downfield from Me_4Si (δ = 0); coupling constants (J) are given in Hz. Mass spectra were recorded by Mr. G. Owen with a Hitachi–Perkin–Elmer RMU-6E spectrometer, using an ionization potential of 80 eV.

4,7-Anhydro-1,2,3,5-tetradeoxy-3-nitro-D-erythro-*octane-6,8-diols* (**3**). — Sodium (175 mg, 15 mmol) was added to a solution of 1-nitropropane (8.9 g, 100 mmol) in methanol (25 mL); a vigorous reaction was observed, and the solution turned pale yellow. This solution was added to a solution of 2-deoxy-D-*erythro*-pentose (**1**) (1 g, 7.45 mmol) in methanol (25 mL), and the progress of the reaction was monitored by t.l.c. (1:4 ethanol–ether), which indicated formation of transient compounds (R_F 0.28, 0.31, 0.35, and 0.38). With the disappearance of these transient compounds, a set of stable compounds (R_F 0.46, 0.49, 0.56, and 0.59) was formed, as indicated by t.l.c. After 24 h, no starting-material was present, and the mixture was processed. Sodium ions were removed by means of Dowex 50 (H^+) cation-exchange resin, and the solution was evaporated to a syrup (1 g; 62%). The compounds corresponding to the four t.l.c. spots (R_F 0.46, 0.49, 0.56, and 0.59) could be neither oxidized with sodium periodate nor separated on silica gel; λ_{max}^{MeOH} 274 (ε 52.5); ν_{max}^{neat} 3350 (s) (OH), 2900 (s) (CH), 1500 (s), and 1370 (s) cm^{-1} (NO_2); n.m.r. data (D_2O): δ 0.92 (t, 3 H, H-1, ^3J 7), 1.6–2.2 (m, 4 H, H-2,5), 3.4–3.7 (m, 3 H, H-6,8), 3.8–4.1 (m, 1 H, H-7), 4.3–4.6 (m, 1 H, H-3); m.s. (110°): *m/z* 174 (M — HNO, 10.4), 158 (M — HNO_2, 20.9), 143 (24.7), 117 (M — $C_3H_6NO_2$, 34.9), 90 (27.9), 85 (100), 81 (21.8), 73 (38), 71 (77), 57 (37.2), 55 (52.3), 45 (27.8), 43 (53.3), and 41 (55.6).

Anal. Calc. for $C_8H_{15}NO_5$: C, 46.83; H, 7.31; N, 6.83. Found: C, 46.53; H, 7.53; N, 6.55.

4,7-Anhydro-1,2,5-trideoxy-3-oxo-D-erythro-*octane-6,8-diols* (**4**). — A solution

of 4,7-anhydro-nitro sugars (**3**) (3 g, 13.4 mmol) in 5% aqueous sodium hydroxide solution (30 mL) was treated dropwise with 3M sulfuric acid (36 mL) at −10°, with efficient stirring. A transient, blue color was observed during addition of the acid. The mixture was stirred for 1 h, diluted with water (150 mL), and kept overnight. Barium carbonate was added to neutralize the acid, and the suspension was filtered. The filtrate was de-ionized by successively passing it through columns of Dowex-50 (H^+) and Dowex-3 (OH^-) ion-exchange resins, and evaporated to a syrup which was chromatographed on silica gel, with ether, to yield the 4,7-anhydro sugars (**4**; 1.25 g, 50%); R_F 0.21 and 0.24 in 1:10 toluene–ether; ν_{max}^{neat} 3600 (s) (br. OH), 2940 (s) (CH), and 1715 (s) cm^{-1} (CO); n.m.r. data ($CDCl_3$): δ 1.06 (t, 3 H, H-1, ^3J 7), 1.9–2.4 (m, 2 H, H-5), 2.4–2.8 (q, 2 H, H-2, ^3J 7), and 3.5–4.8 (m, 7 H); m.s. (90°): *m/z* 156 (M − H_2O, 14), 117 (M − C_2H_5CO, 100), 99 (117 − H_2O, 45.7), 86 (39.6), 73 (65.7), 71 (41.1), 69 (24.2), 57 (C_2H_5CO, 68.1), 45 (65.5), 43 (57.7), and 41 (27).

Anal. Calc. for $C_8H_{14}O_4$: C, 55.17; H, 8.05. Found: C, 55.01; H, 8.25.

(*1*R:*2*S:*4*S:*5*R)-*5-Ethyl-2,4-dihydroxy-6,8-dioxabicyclo[3.2.1]octane* (**5**) *and* (*1*R:*2*R:*4*R:*5*R)-*5-ethyl-2,4-dihydroxy-6,8-dioxabicyclo[3.2.1]octane* (**7**). — To a solution of 2-deoxy-D-*erythro*-pentose (**1**; 5 g, 38.5 mmol) in water (10 mL) was added 1-nitropropane (45 mL, 500 mmol), and the resulting mixture was made homogeneous by adding methanol (50 mL). Aqueous sodium hydroxide solution (100 mL, 2M) was then added dropwise, with stirring, during 1.5 h; methanol (100 mL) was added during this process in order to maintain the homogeneity. Monitoring by t.l.c. (10:1 ether–ethanol) showed the conversion of **1** (R_F 0.31) into products having R_F values of 0.42, 0.45, 0.51, and 0.53. Another portion of 2M aqueous sodium hydroxide solution (87 mL) was rapidly added to the mixture; t.l.c. indicated the presence of products only at the origin, and a trace of the starting material (**1**). The resulting solution was extracted with ether (3 × 30 mL) to remove the excess of 1-nitropropane, and the aqueous methanolic fraction was added dropwise to 12M hydrochloric acid (120 mL). During this process, the mixture turned blue and later purple. This strongly acidic solution was stirred for 15 min, made neutral with barium carbonate, the suspension filtered, and the filtrate evaporated. The residue was triturated with acetone (250 mL), the solid was filtered off, and the filtrate was evaporated to a syrup which contained components having R_F values of 0.42, 0.51, 0.62, and 0.80, as indicated by t.l.c. A solution of this crude mixture in water (50 mL) was treated with saturated, aqueous sodium periodate solution (100 mL), and kept in the dark for 24 h at pH 5.5. Monitoring by t.l.c. showed the presence of only two components, R_F 0.42 and 0.62. The solution was evaporated, and acetone (100 mL) was added to precipitate inorganic salts. The salts were removed by filtration, and the filtrate was evaporated to a syrup which was chromatographed on silica gel. Elution with 50:1 ether–ethanol gave the 2-exo-4-endo-diol **5** (750 mg, 11.6%) and the 2,4-exo-diol **7** (70 mg, 1.1%).

Compound **5** had $[\alpha]_D^{25}$ −79° (*c* 0.63, water); ν_{max}^{neat} 3400 (s) (OH) and 2950 (s) cm^{-1} (CH); n.m.r. data ($CDCl_3$): δ 0.97 (t, 3 H, H-10, ^3J 7), 1.5–2.4 (m, 6 H, H-3, 9, OH), 3.5–4.0 (m, 4 H, H-2, 4, 7), and 4.5 (m, 1 H, H-1); m.s. (70°, 15 eV):

m/z 174 (M, 0.1), 156 (M — H_2O, 0.3), 130 (M — CH_2CHOH, 12.4), 117 (M — C_2H_5CO, 4.5), 100 (M — $EtCO_2H$, 10.3), 99 (10.8), 82 (6.8), 75 (41.2), 73 (15.0), 57 (C_2H_5CO, 100), 56 (13.7), and 54 (16.0).

Anal. Calc. for $C_8H_{14}O_4$: C, 55.17; H, 8.04. Found: C, 55.45, H, 8.32.

Compound **7** had $[\alpha]_D^{25}$ −54° (*c* 0.59, water); ν_{max}^{neat} 3350 (s) (OH) and 2950 (s) cm^{-1} (CH); n.m.r. data ($CDCl_3$): δ 0.96 (t, 3 H, H-10, ^3J 7), 1.64–2.2 (m, 4 H, H-6,9), 3.3–3.9 (m, 6 H, H-2, 4, 7, OH), and 4.5–4.65 (m, 1 H, H-1); m.s. (100°, 15 eV): *m/z* 174 (M, 0.2), 156 (M — H_2O, 0.9), 130 (M — CH_2CHOH, 20.2), 117 (M — C_2H_5CO, 5.1), 100 (M — $EtCO_2H$, 24.5), 99 (14), 75 (42), 73 (11.9), 57 (C_2H_5CO, 100), 56 (16.1), and 54 (33.2); exact mass, *m/z* 174.0891 (Calc. 174.0892).

(*1*R:*2*S:*4*S:*5*R)-*2,4-Di*-O-*acetyl-5-ethyl-6,8-dioxabicyclo*[*3.2.1*]*octane* (**6**). — The 2-exo-4-endo-diol **5** (650 mg, 3.7 mmol) was acetylated with acetic anhydride (12 mL)–pyridine (12 mL) at room temperature. The reaction was monitored by t.l.c. (1:1 toluene–ether), which indicated the formation of two intermediate (mono-acetylated) products (R_F 0.15 and 0.2), and then complete conversion into a final product of R_F 0.42. The mixture was processed after 24 h by adding water (50 mL), and extracting with chloroform (3 × 30 mL). The extracts were combined, washed with water (25 mL), dried (sodium sulfate), and evaporated, and the crude product was chromatographed on silica gel. Elution with 25:1 petroleum ether–ether gave the 2-exo-4-endo-diacetate **6** (750 mg, 78%) which was recrystallized from pentane, m.p. 48°, $[\alpha]_D^{25}$ −75° (*c* 1.5, $CHCl_3$); ν_{max}^{neat} 2940 (s) (CH) and 1740 (s) cm^{-1} (OAc); n.m.r. data (100 MHz, $CDCl_3$): δ 0.93 (t, 3 H, H-10, ^3J 7), 1.5–2.4 (m, 4 H, H-3, 9), 2.07 (s, 3 H, 4-Ac), 2.14 (s, 3 H, 2-Ac), 3.86 (dd, 2 H, H-7), 4.5–4.64 (m, 1 H, H-1), 4.78–4.88 (m, 1 H, H-2), and 4.9–5.6 (q, 1 H, H-4, $^3J_{4,3a}$ 10, $^3J_{4,3e}$ 6); m.s. (90°): *m/z* 259 (M + 1, 0.5), 258 (M, 1.0), 198 (M — AcOH, 8.9), 156 (30), 130 (25.4), 129 (12.9), 128 (25.7), 127 (20.3), 115 (30.4), 99 (29.4), 82 (68.4), 81 (87.8), 57 (C_2H_5CO, 100), 54 (85), and 43 (CH_2CO, 100).

Anal. Calc. for $C_{12}H_{18}O_6$: C, 55.81; H, 6.97. Found: C, 55.52; H, 7.12.

(*1*R:*2*S:*4*R:*5*R)-*2,4-Di*-O-*acetyl-5-ethyl-6,8-dioxabicyclo*[*3.2.1*]*octane* (**8**). — The 2,4-exo-diol **7** (500 mg, 2.8 mmol) was acetylated, and the product processed in the same way as the 2-exo-4-endo-diol, to afford the 2,4-exo-diacetate **8** (580 mg, 80%), of R_F 0.40 (1:1 toluene–ether), which crystallized from pentane–ether; m.p. 69°, $[\alpha]_D^{25}$ −80° (*c* 1.55, $CHCl_3$); ν_{max}^{neat} 2950 (s) (CH) and 1740 (s) cm^{-1} (OAc); n.m.r. data (100 MHz, $CDCl_3$): δ 0.92 (t, 3 H, H-10, ^3J 7), 1.54–2.26 (m, 4 H, H-3, 9), 2.14 (s, 6 H, 2 Ac), 3.85 (dd, 2 H, H-7), 4.6–4.8 (m, 3 H, H-1,2,4); m.s. (90°): *m/z* 259 (M + 1, 0.5), 258 (M, 0.9), 198 (M — AcOH, 9.8), 156 (35.6), 130 (31.4), 129 (18.4), 128 (33.0), 127 (26.7), 115 (37.5), 99 (37.5), 82 (65), 81 (90.4), 75 (25), 57 (C_2H_5CO, 98), 54 (82.8), and 43 (CH_2CO, 100).

Anal. Calc. for $C_{12}H_{18}O_6$: C, 55.81; H, 6.97. Found: C, 55.61; H, 7.36.

(*1*R:*2*S:*4*R:*5*R)-*5-Ethyl-2,4-di*-O-p-*tolylsulfonyl-6,8-dioxabicyclo*[*3.2.1*]*octane* (**9**). — A solution of *p*-toluenesulfonyl chloride (9.6 g, 10.6 mmol) in pyridine (15 mL) was added to a solution of **7** (900 mg, 5.17 mmol) in pyridine (15 mL). After 24 h at room temperature, t.l.c. indicated complete conversion into the ditosylate

9 (R_F 0.60, 1:1 toluene–ether). The mixture was poured into ice–water (150 mL), and extracted with chloroform (50 mL × 3), and the extracts were combined, washed with water (50 mL), dried (sodium sulfate), and evaporated. The residue was recrystallized from ether–chloroform to give the ditosylate **9** (2.0 g, 80%); m.p. 159–160°, $[\alpha]_D^{25}$ −55° (*c* 0.24, $CHCl_3$); ν_{max}^{KBr} 2900 (br. m) (CH), 1350 (s), 1190 (s), and 1180 (s) cm^{-1} (-SO_2OR); ^{1}H-n.m.r. data ($CDCl_3$): δ 8.2 (t, 3 H, H-10, ^3J 7), 1.5–2.3 (m, 4 H, H-3,9), 2.47 (s, 6 H, 2 CH_3), 3.7–3.85 (m, 2 H, H-7), 4.3–4.5 (m, 2 H, H-2,4), 4.52–4.65 (m, 1 H, H-1), and 7.2–8.0 (m, 8 H).

Anal. Calc. for $C_{22}H_{26}O_8S_2$: C, 54.77; H, 5.39. Found: C, 54.69; H, 5.78.

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