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Stereoselective Deuteration of a Bridgehead Polycyclic 2-Nitro Alcohol through a Retro-Henry Reaction

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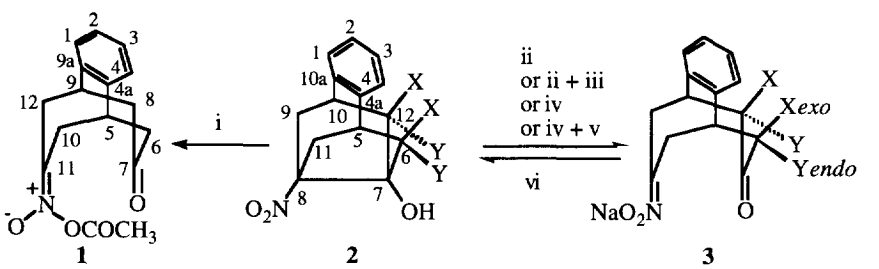
Abstract: Reaction of nitro alcohol **2a** with the stoichiometric amount of NaOH in water or D_2O gave ketonitronate **3a** or **3c**, respectively. In CD_3OD or CH_3OH solution at room temperature, **3a** and **3c** gave cleanly the dideuterated derivatives **3b** and **3d**, respectively. Treatment of **3a-d** with acetic acid gave the corresponding polycyclic nitro alcohols **2a-d**.

In connection with the synthesis of lipophilic rigid acetylcholine-like compounds derived from bridgehead polycyclic 2-amino alcohols[1], we attempted the acetylation of nitro alcohol **2a**. However, treatment of **2a** with acetyl chloride in the presence of pyridine gave in good yield the unstable nitronic acetic anhydride **1**, the product of acetylation of an intermediate *aci*-nitro ketone derived from **2a** through a retro-Henry reaction. This result prompted us to study the base-catalyzed ring opening of **2a** and the behaviour of the expected keto nitronate.



1 **2** **3**

a, X = Y = H; **b**, X = D, Y = H; **c**, X = Y = D; **d**, X = H, Y = D
i) CH_3COCl / pyridine / $CHCl_3$; ii) NaOH / H_2O; iii) CD_3OD; iv) NaOH / D_2O; v) CH_3OH; vi) HOAc

Scheme. Stereoselective deuteration of nitro alcohol **2a**

Reaction of **2a** with 1 equiv of NaOH in water under reflux for 30 min afforded quantitatively keto nitronate **3a** (Scheme) whose ^{13}C-NMR spectrum clearly showed its C_S-symmetry and the signals corresponding to the nitronate (δ = 114.4) and ketone carbon atoms (δ = 208.8). In the ^1H-NMR spectrum ([D_6]DMSO) a pair of β-nitronate protons appeared highly deshielded (δ = 3.68) as compared with their *geminal* counterparts (δ = 1.89). This kind of downfield shift is known for β-nitronate protons which lie in the plane of the nitronate group[2]. However, the α-ketone protons showed similar chemical shift. The ^1H-NMR spectrum of **3a** in [D_4]methanol, showed clearly defined signals for all of the aliphatic protons, suggesting a *twin*

chair conformation for the bicyclo[3.3.2]dec-9-ene subunit[3], the *endo*-β-nitronate and *endo*-α-ketone protons showing *vicinal* couplings (J = 6.6 and 6.3 Hz, respectively) with the bridgehead ones. The spectrum of **3a** in [D_4]methanol was time-dependent, experiencing several gradual changes, that were interpreted as a stereoselective H-D exchange of the *exo*-α-ketone protons, giving completely dideuterated keto nitronate **3b** after 16 h. The salient features of the ^{1}H-NMR spectrum of **3b** were: a) the absence of the signal corresponding to the *exo*-α-ketone protons at δ = 2.13, b) the absence of the *geminal* coupling in the signal of the *endo*-α-ketone protons, which appeared as a doublet (δ = 2.69, J = 5.7 Hz) and c) the signal of the bridgehead protons that remained as a triplet. In the ^{13}C-NMR spectrum of **3b**, the α-ketone carbon atoms, C6(8), appeared as a triplet, δ = 49.1, $^1J_{C,D}$ = 20.0 Hz. The observed stereoselectivity could be explained on the basis of stereoelectronic effects: a) preferential abstraction of the *exo*-α-ketone protons for which the C-H bonds are nearly parallel to the carbonyl π orbital in the *twin chair* conformation[3], and b) preferential *exo*-deuteration which implies perpendicular approach of the deuterium to the enolate π orbitals[4].

On the other hand, reaction of **2a** with NaOH in D_2O under reflux for 30 min, gave keto nitronate **3c**, in which complete deuteration of the α-ketone positions had taken place. This was clearly seen in the ^{1}H-NMR spectrum in which the signals corresponding to both α-ketone protons had disappeared. Moreover, the signal of the bridgehead protons had become a doublet. In the ^{13}C-NMR spectrum of **3c**, the α-ketone carbon atoms appeared as a pseudoquintuplet, δ = 46.7, $^1J_{C,D}$ = 18.9 Hz. A keto nitronate stereoselectively dideuterated at the *endo,endo*-α-ketone positions, **3d**, was obtained by dissolving **3c** in methanol and concentrating the solution to dryness after 16 h at room temp. In the ^{1}H-NMR spectrum of **3d**, the signal of the *exo*-α-ketone protons appeared as a singlet due to the absence of *geminal* and *vicinal* couplings, while the signal of the bridgehead protons remained as a doublet. In the ^{13}C-NMR spectrum of **3d**, the α-ketone carbon atoms appeared as a triplet, δ = 47.6, $^1J_{C,D}$ = 20.9 Hz.

Acidification of methanolic or aqueous solutions of **3a-d** with cold glacial acetic acid afforded in good yields the tetracyclic nitro alcohols **2a-d**, respectively. Neither the *aci*-nitro ketones derived from **3a-d** nor the tautomeric nitro ketones were observed, probably because of the easy intramolecular Henry reaction to give the corresponding nitro alcohols.

Thus, the stereoselective α,α- and β,β-dideuteration and the selective tetradeuteration of nitro alcohol **2a** has been achieved through the intermediate keto nitronate **3a** resulting from a retro-Henry reaction of the starting nitro alcohol. The key of these transformations is the completely stereoselective kinetically controlled H-D or D-H exchange of the *exo*-α-ketone hydrogen or deuterium atoms in keto nitronates **3a** and **3c**.

Experimental

Melting points were determined on a Gallenkamp melting-point apparatus, model MFB 595010M. IR spectra were recorded on a FT/IR Perkin-Elmer spectrometer, model 1600. NMR spectra were taken on Varian Gemini 300 and VXR 500 spectrometers. The chemical shifts are given in ppm (δ scale) relative to internal TMS. COSY ^{1}H/^{1}H and ^{1}H/^{13}C experiments were performed using standard procedures. Coupling constants are expressed in Hertz. The assignments given in the NMR spectra are based on DEPT, ^{1}H/^{1}H, and ^{1}H/^{13}C COSY experiments. In the ^{13}C-NMR spectra of **2b-d,** only the values of the C6(12) atoms are given since the other signals coincide with those of **2a**[1a]. The *endo*/*exo* notations for the ketonitronates **3**, considered as benzo-derivatives of a bicyclo[3.3.2]decane, have been retained in the nitro alcohols **2**. The IR spectra of **2b-d** are not given since they did not show significant differences with that of **2a**[1a]. Microanalyses were carried out at the Microanalysis Service of the Centro de Investigación y Desarrollo, CID, Barcelona, Spain.

11-Acetyloximino-6,7,8,9-tetrahydro-5,9-propano-5H-benzocyclohepten-7-one N-oxide (1). To a solution of **2a** (300 mg, 1.22 mmol) and pyridine (0.2 ml, 2.48 mmol) in anhydrous $CHCl_3$ (8 ml), a solution of acetyl chloride (0.25 ml, 2.11 mmol) in anhydrous $CHCl_3$ (1 ml) was added dropwise under argon. The reaction mixture was heated under reflux for 24 h, concentrated in vacuo and the resulting residue was extracted with benzene (4 x 15 ml). The combined organic extracts were evaporated at reduced pressure, to give a crude product

consisting of a mixture of **1** and **2a**, in an approximate ratio 2:1. Treatment of this crude product under the same reaction conditions gave almost pure **1**, as an unstable oil. IR ($CHCl_3$) ν: 1760, 1722 and 1668 (C=O), 1545 (C=N) and 1374 (N=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ: 2.17 (m, 1 H), 2.21 (s, 3 H), 2.5-2.7 (complex abs., 3 H), 2.86 (ddd, J = 16.6 Hz, J' = 4.5 Hz, J" = 1.8 Hz, 1 H), 2.96 (ddd, J = 16.6 Hz, J' = 4.5 Hz, J" = 1.8 Hz, 1 H), 3.08 (ddd, J = 14.0 Hz, J' = 6.0 Hz, J" = 2.0 Hz, 1 H), 3.33 (m, 1 H), 3.42 (m, 1 H), 3.76 (ddd, J = 14.0 Hz, J' = 6.0 Hz, J" = 2.0 Hz, 1 H), 7.28 (m, 4 H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 19.4 (CH_3), 32.4 (CH_2) and 38.9 (CH_2) (C10 and C12), 37.9 (CH) and 39.5 (CH) (C5 and C9), 47.9 (CH_2) and 48.2 (CH_2) (C6 and C8), 127.7 (CH), 127.8 (CH), 127.9 (CH) and 128.4 (CH) (C1, C2, C3 and C4), 142.7 (C) and 142.9 (C) (C4a and C9a), 164.6 (C, C11), 168.5 (C, COO), 208.5 (C, C7).

11-*aci*-Nitro-6,7,8,9-tetrahydro-5,9-propano-5H-benzocyclohepten-7-one sodium salt (3a). To a suspension of **2a** (1.50 g, 6.12 mmol) in water (30 ml), NaOH (244 mg, 6.10 mmol) was added. The reaction mixture was heated under reflux for 30 min and filtered, and the filtrate was concentrated *in vacuo* to give **3a** (1.57 g, 96% yield), mp 149 °C (dec). IR (KBr) ν: 1698 (C=O), 1543 (C=N), 1165, 1154, 1082 cm^{-1}. ^{1}H-NMR ([D_6]DMSO, 300 MHz) δ: 1.89 [d, J = 13.5 Hz, 10(12)-H*exo*], 2.49 [br. s, 6(8)-H*endo* and 6(8)-H*exo*], 3.28 [m, 5(9)-H], 3.68 [dd, J = 13.5 Hz, J' = 5.5 Hz, 10(12)-H*endo*], 7.13-7.25 (m, ar-H). ^{1}H-NMR ([D_4]methanol, 300 MHz) δ: 2.06 [d, J = 12.6 Hz, 10(12)-H*exo*], 2.13 [d, J = 13.5 Hz, 6(8)-H*exo*], 2.59 [dd, J = 13.5 Hz, J' = 6.3 Hz, 6(8)-H*endo*], 3.48 [pseudotriplet, J = 6.3 Hz, 5(9)-H], 3.62 [dd, J = 12.6 Hz, J' = 6.6 Hz, 10(12)-H*endo*], 7.20-7.30 (m, ar-H). ^{13}C-NMR ([D_6]DMSO, 75.5 MHz) δ: 34.3 [CH_2, C10(12)], 44.6 [CH, C5(9)], 47.6 [CH_2, C6(8)], 114.4 (C, C11), 126.9 (CH) and 128.6 (CH) (ar-CH), 145.4 (C, ar-C), 208.8 (C, C7). Anal. Calcd. for $C_{14}H_{14}NO_3Na \cdot 2/3\ H_2O$: C, 60.27; H, 5.53; N, 5.02. Found: C, 60.31; H, 5.55; N, 4.95.

[*exo*-6,*exo*-8-$^2H_2$]-11-*aci*-Nitro-6,7,8,9-tetrahydro-5,9-propano-5H-benzocyclohepten-7-one sodium salt (3b). A solution of **3a** (100 mg, 0.37 mmol) in [D_4]methanol (1.5 ml) was kept at room temp. for 16 h, to give a solution of essentially pure **3b**. ^{1}H-NMR ([D_4]methanol, 300 MHz) δ: 2.12 [d, J = 12.9 Hz, 10(12)-H*exo*], 2.69 [br. d, J = 5.7 Hz, 6(8)-H*endo*], 3.47 [t, J = 5.7 Hz, 5(9)-H], 3.60 [dd, J = 12.9 Hz, J' = 5.7 Hz, 10(12)-H*endo*], 7.27 (m, ar-H). ^{13}C-NMR ([D_4]methanol, 75.5 MHz) δ: 37.4 [CH_2, C10(12)], 44.9 [CH, C5(9)], 49.1 [CDH, t, J = 20.0 Hz, C6(8)], 120.5 (C, C11), 128.4 (CH) and 129.8 (CH) (ar-CH), 145.6 (C, ar-C), 198.0 (C, C7).

[6,6,8,8-$^2H_4$]-11-*aci*-Nitro-6,7,8,9-tetrahydro-5,9-propano-5H-benzocyclohepten-7-one sodium salt (3c). The same procedure described above for **3a**, except for the use of D_2O instead of water was followed. From **2a** (150 mg, 0.61 mmol), **3c** (152 mg, 92% yield) was obtained. ^{1}H-NMR ([D_4]methanol, 300 MHz) δ: 2.10 [d, J = 13.0 Hz, 10(12)-H*exo*], 3.47 [d, J = 6.1 Hz, 5(9)-H], 3.67 [dd, J = 13.0 Hz, J' = 6.1 Hz, 10(12)-H*endo*], 7.28 (m, ar-H). ^{13}C-NMR (D_2O, 75.5 MHz) δ: 33.5 [CH_2, C10(12)], 41.2 [CH, C5(9)], 46.7 [CD_2, pseudoquintuplet, J = 18.9 Hz, C6(8)], 125.5 (C, C11), 127.4 (CH) and 128.4 (CH) (ar-CH), 143.9 (C, ar-C), 215.8 (C, C7).

[*endo*-6,*endo*-8-$^2H_2$]-11-*aci*-Nitro-6,7,8,9-tetrahydro-5,9-propano-5H-benzocyclohepten-7-one sodium salt (3d). A solution of **3c** (44 mg, 0.16 mmol) in methanol (3 ml) was kept at room temp. for 16 h, to give a solution of essentially pure **3d**. ^{1}H-NMR ([D_4]methanol, 300 MHz) δ: 2.09 [d, J = 13.5 Hz, 10(12)-H*exo*], 2.20 [s, 6(8)-H*exo*], 3.47 [d, J = 6.2 Hz, 5(9)-H], 3.65 [dd, J = 13.5 Hz, J' = 6.2 Hz, 10(12)-H*endo*], 7.28 (m, ar-H). ^{13}C-NMR ([D_6]DMSO, 75.5 MHz) δ: 34.7 [CH_2, C10(12)], 44.6 [CH, C5(9)], 47.6 [CDH, t, J = 20.9 Hz, C6(8)], 127.0 (CH) and 128.7 (CH) (ar-CH), 145.3 (C, ar-C), the quaternary carbon atoms C7 and C11 were not detected.

[6α,12α-$^2H_2$]-8-Nitro-5,6,7,8,9,10-hexahydro-5,8:7,10-dimethanobenzocycloocten-7-ol (2b). The above solution of **3b** was treated with cold glacial acetic acid until pH ≈ 6-7. The resulting suspension was diluted with water (2-3 ml) and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were dried with anhydrous

Na_2SO_4 and concentrated *in vacuo* to give nitro alcohol **2b** (69 mg, 74% overall yield from **2a**), mp 164-166 °C (sublimed at 110 °C / 0.3 torr). GLC/MS (70 eV) m/z (%): 247 (12) $[M]^{\cdot+}$, 230 (1) $[M - OH]^+$, 201 (10) $[M - NO_2]^+$, 184 (9) $[M - NO_2 - OH]^{\cdot+}$, 183 (15), 182 (10), 171 (11), 169 (10), 167 (10), 159 (12), 158 (12), 157 (28), 156 (100), 155 (29), 154 (14), 143 (13), 142 (21), 141 (27), 132 (10), 131 (28), 130 (40), 129 (36), 128 (21), 117 (11), 116 (30), 115 (29), 77 (10). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.04 [d, J = 12.0 Hz, 9(11)-Hα], 2.36 [d, J = 6.5 Hz, 6(12)-Hβ], 2.42-2.54 (broad, OH), 3.30-3.35 [m, 9(11)-Hβ], 3.37 [t, J = 6.5 Hz, 5(10)-H], 7.15 (s, ar-H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 48.5 [CDH, t, J = 20.9 Hz, C6(12)]. Anal. Calcd. for $C_{14}H_{13}D_2NO_3$: C, 68.00; H + D, 6.13; N, 5.66. Found: C, 68.01; H + D, 6.18; N, 5.57.

[6,6,12,12-$^2H_4$]-8-Nitro-5,6,7,8,9,10-hexahydro-5,8:7,10-dimethanobenzocycloocten-7-ol (2c): It was prepared in 86% yield from the solution of **3c** in D_2O, in a similar way to that described for **2b**, mp 165-167 °C (sublimed at 110 °C / 0.3 torr). GLC/MS (70 eV) m/z (%): 249 (12) $[M]^{\cdot+}$, 232 (1) $[M - OH]^+$, 203 (13) $[M - NO_2]^+$, 187 (11), 186 (6) $[M - NO_2 - OH]^{\cdot+}$, 185 (13), 184 (14), 170 (15), 169 (12), 168 (11), 160 (12), 159 (12), 158 (25), 157 (100), 156 (55), 155 (14), 154 (10), 144 (13), 143 (18), 142 (14), 141 (26), 133 (18), 132 (32), 131 (32), 130 (31), 129 (22), 128 (13), 118 (12), 117 (22), 116 (25), 115 (16). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 1.50-1.70 (broad, OH), 2.04 [d, J = 12.0 Hz, 9(11)-Hα], 3.30-3.34 [m, 9(11)-Hβ], 3.36 [d, J = 6.5 Hz, 5(10)-H], 7.15 (br. s, ar-H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 48.0 [CD_2, pseudoquintuplet, J = 19.7 Hz, C6(12)]. Anal. Calcd. for $C_{14}H_{11}D_4NO_3$: C, 67.45; H + D, 6.08; N, 5.62. Found: C, 67.41; H + D, 6.08; N, 5.53.

[6β,12β-$^2H_2$]-8-Nitro-5,6,7,8,9,10-hexahydro-5,8:7,10-dimethanobenzocycloocten-7-ol (2d). It was prepared in 76% yield from the solution of **3d** in methanol, in a similar way to that described for **2b**, mp 162-164 °C (sublimed at 140 °C / 1 torr). GLC/MS (70 eV) m/z (%): 247 (5) $[M]^{\cdot+}$, 201 (12) $[M - NO_2]^+$, 184 (6) $[M - NO_2 - OH]^+$, 183 (15), 182 (11), 171 (10), 170 (14), 169 (13), 168 (10), 158 (18), 157 (45), 156 (100), 155 (58), 154 (16), 153 (10), 143 (15), 142 (22), 141 (32), 132 (16), 131 (34), 130 (48), 129 (41), 128 (22), 117 (15), 116 (32), 115 (28), 92 (10), 77 (11). ^{1}H-NMR ($CDCl_3$, 500 MHz) δ: 2.04 [dd, J = 12.0 Hz, J' = 2.0 Hz, 9(11)-Hα], 2.09 [d, J = 2.0 Hz, 6(12)-Hα], 2.48 (broad, OH), 3.30-3.35 [m, 9(11)-Hβ], 3.37 [d, J = 6.5 Hz, 5(10)-H], 7.15 (s, ar-H). ^{13}C-NMR ($CDCl_3$, 75.5 MHz) δ: 48.4 [CDH, t, J = 19.5 Hz, C6(12)]. Anal. Calcd. for $C_{14}H_{13}D_2NO_3$: C, 68.00; H + D, 6.13; N, 5.66. Found: C, 68.07; H + D, 6.13; N, 5.50.

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