

Prins reaction under manganese dioxide control: the synthesis of 6-oxa-2-azabicyclo[3.2.1]octan-4-ones from tetrahydropyridines and formaldehyde

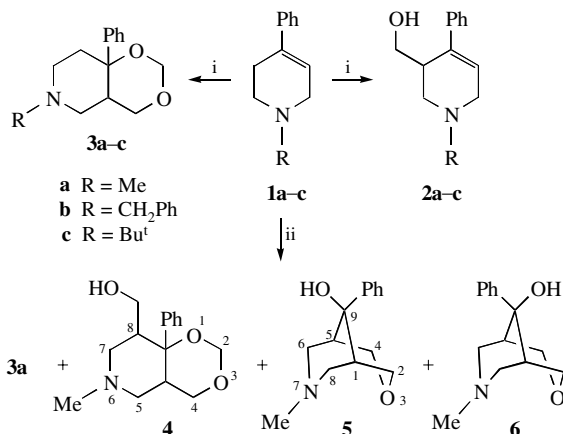
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The course of the acid-catalysed Prins reaction of tetrahydropyridines **1** with formaldehyde, leading to derivatives of piperidinodioxane **4** and 3-oxa-7-azabicyclononanes **5** and **6**, is dramatically changed in the presence of manganese dioxide to give new products, 6-oxa-2-azabicyclo[3.2.1]octan-4-ones **7** and **8**.

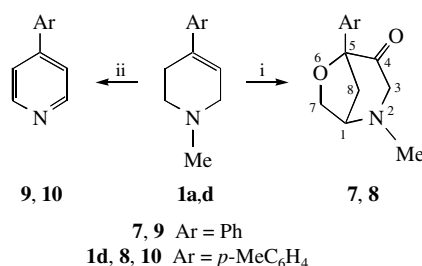
The previous studies of acid-catalysed condensation of 4-aryl-substituted tetrahydropyridines (THPs) **1** with an excess of formaldehyde and sulfuric acid have shown that this Prins reaction gave 3-hydroxymethyl THPs **2**¹ or, in the case of a tenfold molar excess of formaldehyde, corresponding piperidinodioxanes **3**² (Scheme 1). In repeating an analogous reaction of THP **1a** with a fourfold excess of formaldehyde, we separated not only known 1,3-dioxane **3a** but also three new products: 8-hydroxymethyl derivative of piperidinodioxane **4** and 3-oxa-7-azabicyclo[3.3.1]nonanes **5** and **6**, the last two being isomers by the position of 9-hydroxyl in respect to the ring nitrogen atom (*cis* N/9-OH and *trans* N/9-OH, respectively). The X-ray



Scheme 1 Reagents and conditions: i, CH₂O, H⁺; ii, **1a**:CH₂O = 1:4, boiling in aqueous H₂SO₄, 7 h, then 20 °C, 18 h.

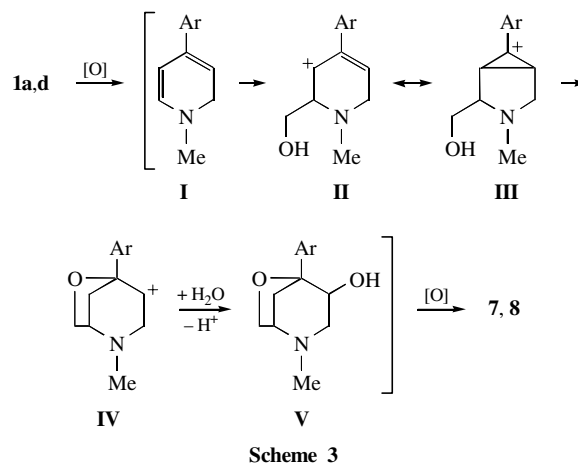
diffraction data suggest that piperidine and tetrahydropyran rings in the crystalline form of *cis*-isomer **5** (Figure 1 shows the general view and numeration of atoms in a molecule of **5**) exhibit a chair conformation; the hydroxyl group of one molecule forms an intermolecular hydrogen bond with the nitrogen atom of another molecule. In solution, the piperidine ring of the same isomer (¹H NMR spectra in CDCl₃) has a boat conformation fixed by an intramolecular hydrogen bond.

As a continuation of our work on the new oxidative reactions of dihydropyridines initiated by manganese compounds,^{3–5} we report the reaction of THPs **1a,d** with an excess of formaldehyde in the presence of manganese dioxide with an emphasis on the modification of the Prins method to prepare an oxidatively new heterocyclic system (Scheme 2, conditions i). A conventional chromatographic procedure gave product **7** in an isolated yield of 31% (from THP **1a**) and a product **8** in 35% yield (from **1d**). The structures of these compounds were different from those of compounds obtained by the Prins reaction previously^{1,2,6} or in this work (Scheme 1, conditions ii). Compounds **7** and **8** showed spectroscopic data consistent with the structure of 6-oxa-2-azabicyclo[3.2.1]octan-4-ones, indicating an unexpected addition of formaldehyde at the α-position of a THP heterocycle and unusual oxidation of the latter into a β-piperidone fragment.



Scheme 2 Reagents and conditions: i, **1**:CH₂O:MnO₂:H₂SO₄ = 1:3:5:6, boiling in an aqueous solution, 7 h; ii, **1**:MnO₂ = 1:10, boiling in toluene, 3 h.

The key step in the mechanism of the formation of bicyclo-octanes **7, 8** may be the oxidative dehydrogenation of the initial THPs to form intermediate 1,2-dihydropyridines. It is clear that analogous dihydropyridines should be formed as intermediates in other experiments (Scheme 2, conditions ii), which demonstrated the readiness of THPs **1a,d** to transformation into pyridines **9, 10** on boiling in toluene in the presence of MnO₂. The data thus obtained allow us to propose the following sequence for the synthesis of bicyclooctanones **7, 8** (Scheme 3).



Scheme 3

Dihydropyridines **I** formed at the initial oxidative step are then selectively attacked by protonated formaldehyde at the α-position (C-6) to give carbocations **II** stabilised by species **III**. The intramolecular cycloaddition yields bicyclic cation **IV**, which leads to final products **7** and **8** via hydroxylation followed by the oxidative dehydrogenation of intermediate alcohol **V**. The transformation of secondary alcohols into ketones under the action of MnO₂ is well documented.⁷ The ¹H and ¹³C NMR spectral data together with the Dreiding modelling and molecular mechanic calculations of conformer energies are consistent with a distorted (flatted) boat conformation of a piperidine ring *cis*-1,3-diaxially condensed with a tetrahydrofuranic ring, which has a rigid envelope conformation.

Thus, the series of conversions demonstrates a new useful method for an effective control of the Prins reaction by man-

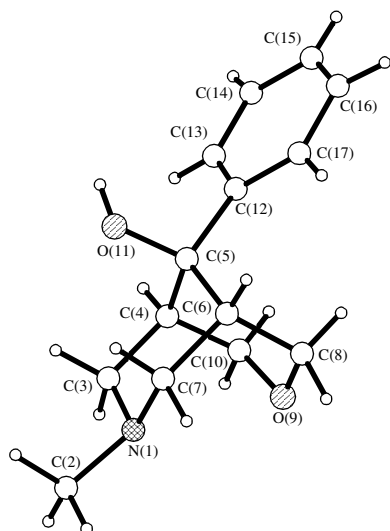


Figure 1 General view and numeration of atoms in a molecule of **5** (X-ray diffraction data).

ganese dioxide, which dramatically changes the course of condensation of tetrahydropyridines with formaldehyde leading to a new group of 6-oxa-2-azabicyclo[3.2.1]octan-4-ones.

The structures of compounds **3a** and **4–10** were confirmed spectroscopically.[†]

[†] NMR spectra were recorded at 300 MHz (¹H) and 75.5 MHz (¹³C), standard TMS, CDCl₃. Compounds **3a** and **4–10** gave satisfactory elemental analyses.

For **3a**: yield 15%, mp 60–62 °C (lit.,² **3a**·HCl, mp 320 °C). ¹H NMR, δ: 1.8 (m, 2H, 8-CH₂), 2.37 (s, 3H, Me), 2.5–3.2 (m, 5H, 5-CH₂ and 7-CH₂ and 4-H_a), 3.6 (d, 1H, 4-CH₂, ²J 11.5 Hz), 3.8 (dd, 1H, 4-CH₂, ²J 11.5 Hz, ³J 2.5 Hz), 4.77 and 4.83 (2d, 1H each, 2-CH₂, ²J 6.5 Hz), 7.3 (m, 5H, Ph). MS (EI, 70 eV), *m/z* (%): 233 (7) [M⁺], 174 (38), 128 (5), 105 (11), 77 (12), 57 (13), 44 (100).

For **4**: yield 6%, mp 88–90 °C. ¹H NMR, δ: 1.57 (br. s, 1H, 8-H), 2.34 (s, 3H, Me), 2.83–3.05 (m, 6H, 5-CH₂ and 7-CH₂ and CH₂OH), 3.53 (d, 1H, 4-CH₂, ²J 11.6 Hz), 3.61 (dd, 1H, 4-CH₂, ²J 11.6 Hz, ³J 2.6 Hz), 3.9 (dd, 1H, 4-H_a, ³J 11.7 Hz, ⁴J 2.0 Hz), 4.75 and 4.83 (2d, 1H each, ²J 6.1 Hz), 7.28–7.5 (m, 5H, Ph). ¹³C NMR, δ: 35.1 (8-C), 46.1 (Me), 47.1 (4a-C), 55.2 (5-C), 57.2 (7-C), 65.8 (COH), 66.2 (4-C), 77.7 (C_{quat}-O), 89.4 (2-C), 126.5, 127.5, 128.4, 129.3 and 140.7 (6C, Ph); MS, *m/z*: 263 [M⁺]. IR (KBr, ν/cm⁻¹): 3310 (OH). Found (%): C, 68.21; H, 8.16; N, 5.28. Calc. for C₁₅H₂₁NO₃ (%): C, 68.44; H, 7.99; N, 5.32.

For **5**: yield 14%, mp 176 °C. ¹H NMR, δ: 2.38 (s, 3H, Me), 2.68 (m, 2H, 1-H and 5-H), 2.84 (dd, 2H, 6-H and 8-H, ²J 11.1 Hz, ³J 2.5 Hz), 3.25 (dd, 2H, 6-H and 8-H, ²J 11.1 Hz, ³J 7.3 Hz), 3.64 (d, 2H, 2-H and 4-H, ²J 11.4 Hz), 3.75 (d, 2H, 2-H and 4-H, ²J 11.4 Hz), 7.3–7.5 (m, 5H, Ph). ¹³C NMR, δ: 37.9 (1-C and 5-C), 45.1 (Me), 55.9 (6-C and 8-C), 69.8 (2-C and 4-C), 71.8 (9-C), 126.1, 127.8, 128.9 and 141.6 (6C, Ph). MS, *m/z* (%): 233 (100) [M⁺], 232 (38), 216 (27), 190 (20), 184 (8), 170 (10), 133 (34), 128 (35), 105 (38), 91 (15), 77 (16). IR (KBr, ν/cm⁻¹): 3220 and 3410 (br. OH). Found (%): C, 71.92; H, 8.27; N, 5.85. Calc. for C₁₄H₁₉NO₂ (%): C, 72.10; H, 8.27; N, 6.01.

For **6**: yield 7%, mp 180 °C. ¹H NMR, δ: 2.12 (s, 3H, Me), 2.37 (m, 2H, 1-H and 5-H), 2.42 (d, 2H, 6-H and 8-H, ²J 11.4 Hz), 3.0 (d, 2H, 6-H and 8-H, ²J 11.4 Hz), 4.02 (dd, 2H, 2-H and 4-H, ²J 10.9 Hz, ³J 2.3 Hz), 4.54 (dd, 2H, 2-H and 4-H, ²J 10.9 Hz, ³J 2.3 Hz), 7.3–7.5 (m, 5H, Ph). ¹³C NMR, δ: 38.3 (1-C and 5-C), 46.5 (Me), 58.3 (6-C and 8-C), 67.4 (2-C and 4-C), 71.3 (9-C), 125.4, 128.0, 129.1, 142.4, (6C, Ph). MS, *m/z* (%): 233 (100) [M⁺]. IR (KBr, ν/cm⁻¹): 3200 and 3420 (br. OH). Found (%): C, 72.2; H, 8.23; N, 5.91. Calc. for C₁₄H₁₉NO₂ (%): C, 72.10; H, 8.27; N, 6.01.

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For **7**: yield 31%, colourless oil (purified by chromatography on a silica gel column; eluent, acetone; *R_f* 0.7). ¹H NMR, δ: 2.51 (s, 3H, Me), 3.0 (t, 1H, 8-H_a, ²J ≈ ³J 12.6 Hz), 3.16 (br. d, 1H, 8-H_e, ²J 12.6 Hz), 3.73 (t, 1H, 7-H_a, ²J 10.7 Hz), 4.0 (m, 1H, 1-H_e), 4.12 (d, 1H, 3-H_a, ²J 9.5 Hz), 4.23 (br. d, 1H, 7-H_e, ²J ≈ ³J 10.7 Hz), 4.42 (br. d, 1H, 3-H_e, ²J 9.5 Hz), 7.3–7.5 (m, 5H, Ph). MS, *m/z* (%): 217 (16) [M⁺], 202 (43), 187 (15), 131 (12), 105 (100), 77 (37). IR (paraffin oil, ν/cm⁻¹): 1680 (C=O), 3360 (br. OH). Found (%): C, 71.7; H, 7.03; N, 6.52. Calc. for C₁₃H₁₅NO₂ (%): C, 71.89; H, 6.91; N, 6.45.

For **8**: yield 35%, colourless oil (purified by chromatography on a silica gel column; eluent, acetone; *R_f* 0.7). ¹H NMR, δ: 2.39 (s, 3H, Me), 2.51 (s, 3H, Me), 2.98 (t, 1H, 8-H_a, ²J ≈ ³J 12.9 Hz), 3.16 (br. d, 1H, 8-H_e, ²J 12.9 Hz), 3.76 (t, 1H, 7-H_a, ²J 10.9 Hz), 4.07 (m, 1H, 1-H_e), 4.10 (d, 1H, 3-H_a, ²J 9.4 Hz), 4.20 (br. d, 1H, 7-H_e, ²J 10.9 Hz), 4.40 (br. d, 1H, 3-H_e, ²J ≈ ³J 9.4 Hz), 7.27 and 7.86 (AA'BB' system, 4H, Ar, ³J 7.2 Hz, ⁴J 1.1 Hz). ¹³C NMR, δ: 22.6 (CMe), 40.3 (1-C), 40.8 (NMe), 55.8 (8-C), 70.2 (7-C), 86.7 (3-C), 129.7 (5-C), 129.3, 130.5, 144.3, 145.4 (C_{arom}), 200.0 (C=C). MS, *m/z* (%): 231 (7) [M⁺], 216 (36), 203 (6), 188 (28), 172 (34), 160 (38), 145 (12), 119 (100), 91 (45). IR (paraffin oil, ν/cm⁻¹): 1675 (C=O), 3350 (br. OH). Found (%): C, 73.01; H, 7.49; N, 5.90. Calc. for C₁₄H₁₇NO₂ (%): C, 72.72; H, 7.36; N, 6.06.

For **9**: yield 45%, mp 76–78 °C (lit.,⁸ mp 76–78 °C). ¹H NMR and mass spectra are identical to those given in ref. 3.

For **10**: yield 42%, mp 43–45 °C. ¹H NMR, δ: 2.4 (s, 3H, Me), 7.25 and 7.5 (AA'BB' system, 4H, Ar, ³J 7.1 Hz, ⁴J 1.1 Hz), 7.61 and 8.63 (AA'XX' system, 4H, Py, ³J 5.4 Hz, ⁴J 2.0 Hz). MS, *m/z* (%): 169 (100) [M⁺], 168 (43), 155 (95), 91 (20). Found (%): C, 84.98; H, 6.67; N, 8.01. Calc. for C₁₂H₁₁N (%): C, 85.21; H, 6.51; N, 8.28.