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New synthesis of (±)2,3-dimethoxyhexahydroberbine

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The total synthesis of (±)2,3-dimethoxyhexahydroberbine **7** from the key compound *trans*-hexahydroisochroman-3-one **5** has been reported.

The key compound *trans*-hexahydroisochroman-3-one **5** has been generated by Baeyer-Villiger oxidation[1-4] of **4**. It was prepared in high yield by the pyrolysis of *trans*-1,2-cyclohexanediacetic acid **3**, obtained by the nitric acid oxidation of *trans*-bicyclo[4.4.0]decan-3-one **2**. Compound **2** in turn was synthesised by the chromic acid oxidation of *trans*-bicyclo[4.4.0]decan-2-ol **1**.

trans-Hexahydroisochroman-3-one **5** on treatment with 3,4-dimethoxyphenylethylamine in refluxing alcohol afforded the amide **6**. The latter on Bischler-Napieralski cyclisation using phosphorus oxychloride followed by reduction of the resultant imine with sodium borohydride in methanol resulted in (±)2,3-dimethoxyhexahydroberbine **7** (Chart I) in 50% yield. This work constitutes the first report on the synthesis of (±)2,3-dimethoxyhexahydroberbine. The structure of the compound was established from a detailed study of its spectral data.

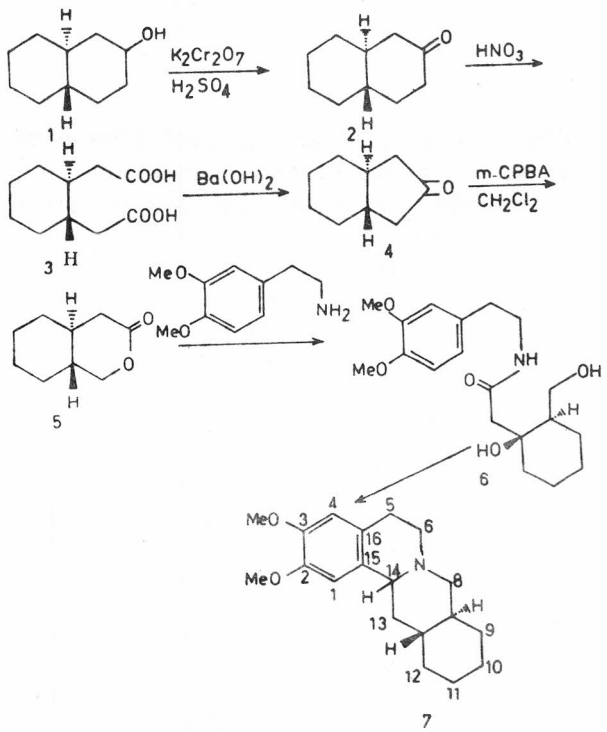

Chart I

Experimental Section

General. Melting points were recorded in an electrically heated metal-bath and are uncorrected. IR spectra were measured in KBr phase using a Perkin-Elmer 782 spectrophotometer. 300 MHz ^1H and 75.5 MHz ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker WH-300 spectrometer and mass spectra on an AEIMS 3074 mass spectrograph.

Analytical samples were routinely dried *in vacuo* over P_2O_5 for 24 hr. Anhydrous sodium sulphate was used to dry the organic solvents. Petrol refers to pet. ether of b.p. 60°-80°.

Preparation of *trans*-bicyclo[4.4.0]decan-3-one (2). Chromic acid solution was added dropwise to *trans*-2-decalol **1** (25 g, 162.20 mmoles) in 100 mL of ether. The reaction mixture was allowed to stand for 6 hr, diluted with water (100 mL) and extracted with ether (3×150 mL). The organic layer was washed with 2% sodium bicarbonate solution (2×100 mL), water (3×50 mL) and dried. Removal of the solvent under reduced pressure afforded *trans*-bicyclo[4.4.0]decan-3-one **2** in 95% yield, b.p. 116°/14 mm of Hg (Found: C, 78.9; H, 10.5. $C_{10}H_{16}O$ requires C, 78.9; H, 10.5%); IR : 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) : δ1.17-1.80 (12H, m), 2.14-2.20 (4H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$) : 209.9, 44.1 38.0, 37.4, 33.7, 27.6, 27.5, 27.2, 22.6 and 21.7 ppm; MS:m/z 152 (M^+).

Preparation of *trans*-cyclohexan-1,2-diacetic acid 3. Concentrated nitric acid (150 mL) was heated to boil. *trans*-2-Decalone **2** was added to it dropwise and the reaction mixture heated for 5-10 min and then kept overnight at 25°C. The fine crystalline compound which precipitated was filtered and washed with ice-cold water. The mother liquor was extracted with ether, washed with saturated sodium bicarbonate solution (30 mL), acidified with concentrated hydrochloric acid and extracted with dichloromethane (3 × 30 mL). The solvent on evaporation afforded *trans*-cyclohexan-1,2-diacetic acid **3** in 50% yield, m.p. 154° (Found: C, 59.9; H, 8.9. $C_{10}H_{16}O_4$ requires C, 60.0; H, 8.0%); IR : 1705, 1695 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) : δ 1.40-2.49 (10H, m), 2.50 (4H, d, J=8.0Hz); ^{13}C NMR (75.5 MHz, DMSO-d_6): 174.3, 38.9, 35.3, 28.6, 23.0 ppm; MS: m/z 200 ($M^{+\cdot}$).

Preparation of *trans*-bicyclo[4.3.0]nonane-8-one 4. A mixture of barium hydroxide (0.3 g, 1.75 mmoles) and cyclohexane diacetic acid (4.6 g, 23.01 mmoles) was taken in a two-necked round bottom flask. The reaction mixture was heated under nitrogen atmosphere at 250°C on a salt-bath for 2 hr. The temperature was slowly raised to 280°C. The reaction product on distillation at low pressure gave *trans*-bicyclo[4.3.0]nonane-8-one **4** in 80% yield, b.p. 90°/11 mm of Hg (Found: C, 78.1; H, 10.1. $C_9H_{14}O$ requires C, 78.3; H, 10.1%); IR: 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.11-1.23 (14H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): 219.6, 35.2, 27.1, 22.1 ppm; MS : m/z 138 ($M^{+\cdot}$).

Preparation of *trans*-hexahydroisochroman-3-one 5. *trans*-Bicyclo[4.3.0]nonan-8-one **4** (1g, 9.8 mmoles) in dry CH_2Cl_2 (10 mL) was cooled in ice. A solution of *m*-chloroperbenzoic acid (3g, 1.74 mmoles) was added to **4** and the reaction mixture allowed to stand at 25°C for 48 hr. Excess of *m*-chloroperbenzoic acid was destroyed with 10% sodium bisulphite solution and the organic layer dried. Removal of the solvent afforded *trans*-hexahydroisochroman-3-one **5** in 90% yield, m.p. 38.5° (Found: C, 70.0; H, 8.9. $C_8H_{14}O_2$ requires C, 70.1; H, 10.2%); IR: 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.91-2.60 (10H,m); ^{13}C NMR (75.5 MHz, $CDCl_3$): 170.7, 72.0, 32.4, 30.6, 32.5, 28.2, 24.2, 22.9 and 21.2 ppm; MS : m/z 154 ($M^{+\cdot}$).

Preparation of N-[2-(3,4-dimethoxyphenyl)ethyl] - (1 - hydroxy - 2 - hydroxymethyl)cyclo hexaneacetamide 6. A mixture of homoveratrylamine (0.3 g, 1.65 mmoles) and *trans*-hexahydroisochroman-3-one **5** (0.2 g, 1.3 mmoles) was refluxed for 24 hr under nitrogen atmosphere in absolute ethanol (10 mL). The residue was chromatographed over silica gel and the chloroform-methanol (95:5) eluate afforded **6** in 80% yield (Found: C, 68.1; H, 8.7; N, 4.2. $C_{19}H_{29}O_4N$ requires C, 68.0; H, 8.0; N, 4.1%); IR: 3500-3200, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.70 (1H, d, J=8.8 Hz), 6.62 (2H, s), 6.16 (1H, m), 3.74 (6H, s), 3.67 (2H, d, J=6.6 Hz), 3.64 (2H, t, J=6.9 Hz), 3.28 (2H, d, J=7.2 Hz), 3.20 (1H, s), 2.65 (2H, t), 2.25-1.10 (10H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): 173.9, 149.0, 147.7, 131.4, 119.6, 111.0, 110.4, 63.0, 54.9(2), 39.8, 34.2(2), 31.3, 29.9(2), 24.4, 23.5 and 21.7 ppm; MS: m/z 335 ($M^{+\cdot}$).

Preparation of (±)-2,3-dimethoxyhexahydroberbine 7. N-[2-(3,4-Dimethoxyphenyl)ethyl-(1 - hydroxy - 2 -hydroxymethyl)cyclohexaneactamide **6** (0.28 g, 0.47 mmoles) was refluxed with phosphorus oxychloride (5 mL) under nitrogen atmosphere for 4 hr. Excess of phosphorylchloride was evaporated under vacuum. The residue was treated with $NaBH_4$ (0.9 g, 13.1 mmoles) in methanol (10 mL). The reaction mixture was kept for 12 hr at 25°C. Excess of $NaBH_4$ was decomposed over ice-chips and the solution extracted with chloroform (2 × 50 mL). The residue was chromatographed over silica gel. The benzene-chloroform (1:1) eluated afforded (±)2,3-dimethoxyhexahydroberbine **7** in 50% yield (Found: C, 75.5; H, 8.7; N, 4.6. $C_{19}H_{27}O_2N$ requires C, 75.7, H, 9.0, N, 4.6%); IR : 1600, 1520, 1440, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.57 (1H, s), 6.51 (1H, s), 4.15 (1H, t, J=4.8 Hz), 3.79 (3H, s), 3.77 (3H, s), 2.35 (2H, t), 2.0-1.2 (12H, m); ^{13}C NMR (75.5 MHz, $CDCl_3$): 147.3(2), 132.5, 127.0, 111.6, 108.4, 63.5, 56.04(2), 52.8(2), 36.4, 35.3, 32.2, 31.8, 30.3, 28.9, 26.6(2) ppm; MS : m/z 301 ($M^{+\cdot}$).

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