

The Stereoselective Reduction of Tropinone to Tropine

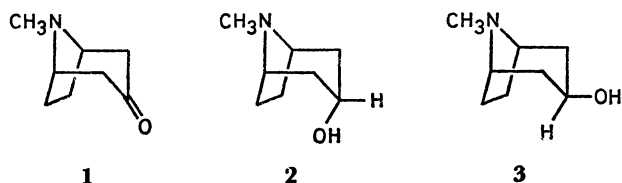
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Synopsis. The reduction of tropinone with diisobutylaluminum hydride in tetrahydrofuran at -78°C leads to tropine selectively.

The stereochemistry of the reduction of tropinone (**1**) has been extensively studied.¹⁾ The kinetically-controlled reduction with lithium aluminum hydride, sodium borohydride, or potassium borohydride afforded a mixture of tropine (**2**) and ψ -tropine (**3**), with a ratio between 28 : 72 and 55 : 44.^{2,3)} Although an increased proportion of **2** was obtained by the use of Meerwein-Pondorf-Verley reduction (the highest **2** : **3** ratio was 71 : 29), a prolonged reaction gave a mixture in which the unnatural isomer, **3**, was favored.²⁾ The **2** : **3** stereoisomeric composition after equilibrium had been reached was 11 : 88. The treatment of the ketone, **1**, or the α alcohol, **2**, with sodium metal in alcoholic solvents also led thermodynamically to the more stable β epimer, **3**. The treatment of **1** with zinc-hydriodic acid gave a mixture of **2**, **3**, and an over-reduction product, tropane, the ratio of **2** and **3** being 5 : 2.⁴⁾ The conversion of **1** to **2** with high stereoselectivity has thus been achieved only by catalytic reduction.⁵⁾ During the course of the development of a new tropane alkaloid synthesis^{6,7)} which requires a method for the chemical reduction of tropinone derivatives to the corresponding α alcohols, we have found that the use of diisobutylaluminum hydride in tetrahydrofuran solvent is suitable for this purpose. The present procedure was both highly efficient and selective; the tropine (**2**) thus obtained from **1** in a 95% yield was contaminated with only 3% of the epimer, **3**.



Experimental

Reduction of Tropinone (1). A solution of 1.0 g (7.0 mmol) of tropinone (**1**) (97% pure, Aldrich) in 45 ml of dry tetrahydrofuran was flushed with argon and cooled at -78°C . Into the magnetically-stirred solution was then added 3.6 g (25 mmol) of diisobutylaluminum hydride (Alpha Inorganics) over a period of 20 min. The mixture was stirred at the same temperature for 17 hr and then quenched by adding 3 ml of water carefully over a 20-min period. The

resulting voluminous gel was treated with 50 ml of ethyl acetate and filtered. The filter cake was washed with 100 ml of ethyl acetate. The combined organic solutions were concentrated *in vacuo* to give 1.2 g of a crude viscous oil, which consisted mainly of tropine (**2**) and ψ -tropine (**3**) (97 : 3 ratio, 95% combined yield). The isomeric ratio was determined by a comparison of the characteristic NMR signals due to the NCH_3 groups. The bulb-to-bulb distillation of the oil at $100\text{--}110^{\circ}\text{C}/0.1\text{ mmHg}$ (bath temperature) gave 0.869 g (89%) of a 97 : 3 mixture of **2** and **3** as a crystalline solid; mp $61\text{--}63^{\circ}\text{C}$. A pure sample of **2** was obtained readily by recrystallization from benzene; mp and mmp $62\text{--}63^{\circ}\text{C}$ (lit.⁸⁾ $63\text{--}64^{\circ}\text{C}$). IR (CHCl_3) 3600 and 3400 cm^{-1} (OH); NMR (CDCl_3 , 100 MHz) δ 1.66 (br d, $J=13.5\text{ Hz}$, 2H, equatorial protons at C(2) and C(4)), 1.9–2.3 (m, 7H, C(6) H_2 , C(7) H_2 , axial protons at C(2) and C(4), and OH), 2.28 (s, 3H, NCH_3), 3.25 (m, 2H, NCH), and 4.05 (br t, $J=5.1\text{ Hz}$, 1H, CHOH). The chromatography of the mother liquor of recrystallization on a column packed with neutral alumina (Merck, activity II–III) gave pure samples of **2** (1 : 20 methanol–ethyl acetate as the eluent) and **3** (1 : 10 methanol–ethyl acetate). The identity of the latter was established by a comparison of its physical properties with those of an authentic sample. Mp and mmp $106\text{--}108^{\circ}\text{C}$ (from *n*-hexane–benzene) (lit.⁹⁾ 108°C ; IR (CCl_4) 3600 and 3400 cm^{-1} (OH); NMR (CDCl_3 , 100 MHz) δ 1.5–1.9 (m, 6H, C(6) H_2 , C(7) H_2 , and equatorial protons at C(2) and C(4)), 1.9–2.2 (m, 2H, axial protons at C(2) and C(4)), 2.34 (s, 3H, NCH_3), 3.10 (br s, 1H, OH), 3.20 (m, 2H, NCH), and 3.88 (m, 1H, CHOH).

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