An Efficient Synthesis of *trans*-Hexahydrochroman-7-one

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The title compound is obtained in good yield from 4-(2-carboxyethyl)resorcinol (**1**) by a simplified synthesis.

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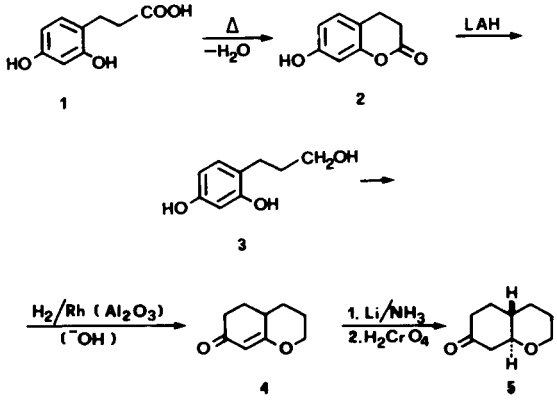
In the framework of research carried out in our laboratory on enamines from bicyclic ketones (1), we required the use of *trans*-hexahydrochroman-7-one (**5**), analogous to *trans*-decalin-2-one but having an oxygen atom in place of the more hindered methylene group (2). Many hexahydrochroman-7-one derivatives have been isolated from natural sources (3a-c) or obtained as byproducts (4) or intermediates in the course of the syntheses of natural products (5a,b). A convenient method for the preparation of the unsubstituted ketoethers, however, has hitherto not been described. The simplest route to the *trans* isomer **5** was the lithium ammonia reduction of the parent 4a,5,6,7-tetrahydrochroman-7-one (**4**), procedure which is known to lead to *trans* ring fusion (6). Compound **4** was reported (7) to form by Birch reduction of 7-methoxychroman or by hydrogenation of 4-(3-hydroxypropyl)resorcinol. In both cases, however, it was obtained in a mixture with other products (yields not reported) by repeated chromatographic separations from a complex of crude mixtures.

In the present communication we report the preparation in quantitative yield of the α,β-unsaturated ketoether **4** through a simplified reaction sequence, and the subsequent reduction to the title compound, as outlined below.

Scheme



An 8.4 g (0.051 moles) sample of **2**, obtained in quantitative yield from **1** according to the reported procedure (8), was dissolved in 240 ml of anhydrous ether. The solution was added dropwise and with constant stirring to a suspension of 5.4 g (0.142 moles) of lithium aluminum hydride (LAH) in 200 ml of the same solvent. The mixture was heated under gentle refluxing for 36 hours. After cooling, 20% sulfuric acid was cautiously added until acidity (*p*H 3-4). The organic layer was separated and the aqueous solution was extracted with ether. The extracts were combined and dried. Removal of the solvent gave a crude product from which 7 g (82%) of pure **3**, mp 91-92° (lit (7) 94-95°) was separated through rapid column chromatography (9), using toluene-anhydrous ethanol 9:1 as eluant. A 7 g (0.041 moles) sample of **3** was dissolved in 10 ml of 25% aqueous sodium hydroxide, and to this solution 0.5 g of 5% rhodium on activated alumina was added. The heterogeneous mixture was hydrogenated in a Parr apparatus at 50 psi for 5 days. The catalyst was filtered and washed with 50 ml of water. The combined filtrates were acidified with 25% sulfuric acid and extracted with 250 ml of ether-ethyl acetate 1:1. Evaporation of the solvent gave a residue which, by vacuum distillation, furnished 5.8 g (92%) of **4**, bp 120-123°/1.5 mm Hg, which crystallized on short standing at 5°, mp 55-56° (lit (7) 57-58°); ir (neat): 1650 (C=O), 1605 cm^{-1} (C=C); nmr (deuteriochloroform): δ 3.75-4.55 (broad, CH_2—O, 2H), 5.5 (s, CH=C, 1H).

A 7.5 g (0.049 moles) sample of **4** was dissolved in a mixture of 60 ml of anhydrous ether and 45 ml of *t*-butyl alcohol. The resultant solution was added within 15 minutes to a stirred solution of 2 g (0.20 g-atom) of lithium in 500 ml of liquid ammonia. After a further 30 minutes, ammonium chloride was slowly added to discharge the blue colour and ammonia was allowed to evaporate. The residue was dissolved in 75 ml of water and extracted with ether. Removal of the solvent left 6.5 g of a crude product that was dissolved in 50 ml of acetone. To the solution, cooled to 0°, Jones reagent was slowly added until an orange colour persisted for 1-2 minutes. Most of the acetone was removed under reduced pressure at 20°, the residue was diluted with water and thoroughly extracted with ether. The extracts were dried, the solvent was removed under reduced pressure, and the residue was distilled giving 5.7 g (75%) of **5** as a colourless oil, bp 91-93°/2.5 mm Hg; ir (neat): 1720 (C=O), 1090 cm^{-1} (C—O—C); nmr (deuteriochloroform): δ 5.8-6.2 (broad, CH—O, 1H), 6.3-7.18 (broad, CH_2—O, 2H).

Anal. Calcd. for $C_9H_{14}O_2$: C, 70.1; H, 9.15. Found: C, 70.12; H, 9.18.

2,4-Dinitrophenylhydrazone was obtained as yellow plates, mp 146-148° (from ethanol).

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