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A RAPID, NEARLY QUANTITATIVE CONVERSION OF CODEINE TO HYDROCODONE

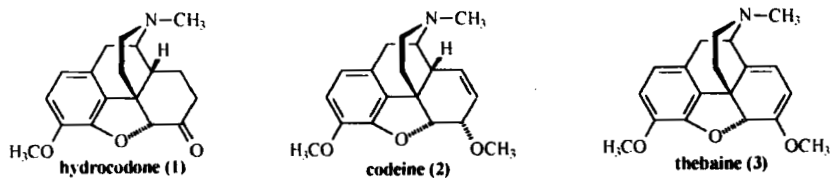
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Abstract: A very rapid, two-step, virtually quantitative synthesis of hydrocodone from codeine, via the intermediacy of dihydrocodeine, has been developed.

In the course of a project involving the synthesis of potentially very specific opiate antagonists, we recently required multi-gram quantities of hydrocodone (**1**, see Figure) as the free base. This material is commercially

Figure



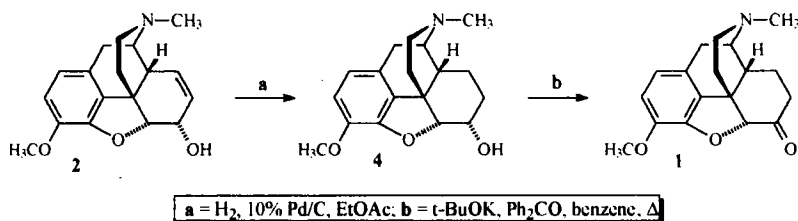
available only as the bitartrate salt, and the price is prohibitively expensive for a synthetic starting material (*ca.* \$450/g¹), especially considering that the tartaric

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acid would immediately be removed in the planned sequence.

Consultation of the literature revealed several syntheses of hydrocodone, usually beginning with either codeine (2) or thebaine (3). The most promising of these appeared to be a method published by Rapoport *et al.* in 1950,² which entailed the catalytic hydrogenation of codeine in dilute acetic acid followed by an Oppenauer oxidation that, although rather operationally complex and possibly dangerous, provided a reported 83% yield of the desired product. Using this sequence as a starting point, we expended considerable effort toward the development of an inexpensive, scaleable, high-yield process, and we now report a very facile, operationally straightforward sequence that provides pure

Scheme



hydrocodone in *nearly quantitative overall yield from codeine*, which can be obtained for about \$17/g.³ The procedure, which is depicted below, has run smoothly on scales greater than 10 grams and the overall conversion, which requires no discrete purification steps, can be completed in a single day.

In our hands, the catalytic hydrogenation of codeine in dilute acetic acid to dihydrocodeine (4), as called for in the original paper, gave material that was rather gummy and not suitable for carrying on to the oxidation step. After

considerable experimentation, we determined that ethyl acetate constituted an ideal solvent. Hydrogenation of codeine at room temperature in a Parr apparatus at 35psi of hydrogen for two to three hours afforded a quantitative yield of pure, snowy-white dihydrocodeine, the melting point of which was higher than any reported value.²

Considerable time was invested in optimization of the oxidation step, including the examination of a variety of oxidation methods (PCC, hypochlorite/TEMPO, DMSO-based oxidants, etc.) that were unavailable fifty years ago. However, the notorious acid-lability of the morphinan skeleton precluded the utilization of any of the alternative methods tested, as in each case only a complex mixture of polar material was recovered. Therefore, we focused our attention on streamlining or refining the reported Oppenauer method in an attempt to maximize the yield, shorten the operation, and render the transformation less dangerous. In Rapoport's paper, potassium *t*-butoxide was prepared from potassium and *t*-butyl alcohol, after which time the excess alcohol was removed via co-distillation with benzene, which served as the reaction solvent. We utilized instead a commercially available 1M solution of potassium *t*-butoxide in tetrahydrofuran,⁵ which worked very well as long as the tetrahydrofuran was removed prior to the addition of the oxidation reagents. Reactions in which the small amount of THF was left in the reaction mixture failed to provide any oxidized material, returning mostly impure starting material. Also, the attempted substitution of toluene for benzene (due to its notorious carcinogenicity) proved unsatisfactory, regardless of whether the reaction was

carried out at 80 °C (the boiling point of benzene) or at reflux (110 °C). In all experiments, only unreacted starting material was recovered.

Once the solution of potassium *t*-butoxide in benzene was prepared, it was cooled slightly and a solution of codeine and benzophenone in benzene was added in one portion, causing a sudden but mild exotherm and the precipitation of a small amount of white material. The resulting mixture was refluxed for a short time under dry nitrogen, whereupon a standard extraction sequence provided pure hydrocodone in nearly quantitative (99%) yield.

Experimental Section

All reactions were carried out under dry nitrogen, unless otherwise specified. Glassware was routinely oven-dried at 120 °C for a minimum of 4 h and was then assembled under a nitrogen stream. Anhydrous solvents were obtained by distillation, immediately prior to use, from sodium benzophenone ketyl (tetrahydrofuran, diethyl ether), barium oxide (diisopropylamine, dimethylformamide), or sodium (benzene, toluene). ¹H NMR spectra were recorded at 60 or 360 MHz. Thin layer chromatographic analyses were carried out on Analtech silica gel G (250 μm) plates using the specified solvent as eluent; visualization was effected by either ultraviolet light or by charring with phosphomolybdic acid. Codeine sulfate was obtained from Research Biochemicals International, Natick, MA or Sigma Chemical Co., St. Louis, MO; it was converted to the free base before use.

Dihydrocodeine (4). In a Parr hydrogenator jar, codeine (2.0g, 6.7mmol) and 10 percent palladium-on-carbon catalyst (200mg) were combined in ethyl acetate

(75mL). This mixture was hydrogenated at room temperature at 37 psi for 2 hours. During this time, the hydrogen pressure decreased to 34 psi within 30 min., was increased back to 37 psi, and thereafter remained constant for the duration of the reaction. The mixture was filtered through Celite, the filter cake was washed with two 10mL portions of ethyl acetate, and the resulting solution was stripped of solvent using a rotary evaporator followed by high vacuum. The product foamed considerably upon initial application of high vacuum, so care was taken not to lose any product. Leaving the product on high vacuum overnight afforded a white, crunchy, crystalline solid (2.0g (99.3 %) mp 113-4 °C [lit.² 112-3 °C]).

Dihydrocodeinone (Hydrocodone, 1). A 100 mL round bottom flask was weighed and equipped with a Vigreux column and distillation head along with benzene (20mL). Using a syringe, potassium *tert*-butoxide (5mL of a 1.0M solution in tetrahydrofuran, 5mmol) was added to the reaction flask and the resulting yellow mixture was distilled under a dry nitrogen atmosphere. Fresh benzene was added periodically until the head temperature reached 80 °C and remained constant. When about 20 mL of benzene had been distilled, the apparatus was allowed to cool and the reaction flask was set up for reflux. In a 25 mL round bottom flask was prepared a solution of dihydrocodeine (500mg, 1.66mmol), benzophenone (3g, 16.5mmol), and benzene (15 mL), which was added in a single portion via syringe to the reaction flask, accompanied by a slight exotherm. The reaction was flushed with nitrogen and then was gently refluxed for 2.5 hours. During the reflux, the formation of a greenish-brown precipitate

was observed. The reaction mixture turned a deep green color by the end of the reaction time and contained large quantities of a white solid.

At this time, the reaction flask was cooled in an ice bath and hydrochloric acid (15 mL of a 3M solution, 45mmol) was added to the flask. The resulting mixture was transferred to a separatory funnel and the layers were separated. The organic (benzene) layer was extracted twice with hydrochloric acid (15 mL of a 3M solution, 45mmol). The first aqueous layer and the combined aqueous extracts from the two organic layer extractions were then combined and extracted twice with 15 mL of diethyl ether. The ether layers were discarded.

The aqueous layers were then basified with 20 percent aqueous sodium hydroxide solution, causing the separation of a white clumpy precipitate. This mixture was extracted three times with 100 mL of ethyl acetate. The combined organic extracts were dried with magnesium sulfate, stripped of solvent on a rotary evaporator, and then placed on high vacuum to remove residual traces of solvent. This protocol afforded 492mg (99%) of a snowy-white solid, mp 195-6 °C (lit.² 194-5 °C).

Acknowledgments

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