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THE SYNTHESIS OF THEBAINE-1-^{3}H

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SUMMARY

A synthesis of thebaine is described where the C-1 position is labelled with tritium to specific activity of 16 Ci/mmole. From codeine (2), 1-iodocodeine (3) was prepared and converted to 1-iodothebaine (7) in 3 steps. The subsequent key reaction was the selective hydrogenolysis of the carbon-iodine bond in 7 in the presence of the dienic-enol ether system. Using 10% Pd/C as catalyst, the desired reaction occurs in about 80% yield.

Key Words: Thebaine-^{3}H, 1-iodothebaine, selective hydrogenolysis

INTRODUCTION

Certain opiates have been found to exist in mammalian tissue[1] and these could conceivably be linked via the intermediacy of thebaine. To probe for the possible existence of a specific thebaine receptor, radioactively labelled thebaine at reasonably high specific activity was required. Tritium, with its maximum enrichment of 30 Ci/mA, would attain the required specific activity and its substitution for hydrogen would not cause configurational or electronic distortions in the thebaine molecule. An attractive pathway to tritium-labelled thebaine is tritium hydrogenolysis of suitably halogenated thebaine. However, a precursor of this type has not been reported in the literature and we were unsuccessful in attempts at direct halogenation.

RESULTS AND DISCUSSION

We previously reported[2] the iodination of codeine (2) with iodine monochloride to afford 1-iodocodeine (3, Scheme 1). This undergoes oxidation with pyridinium chlorochromate (PCC) to provide 1-iodocodeinone (4) in reasonable yield.

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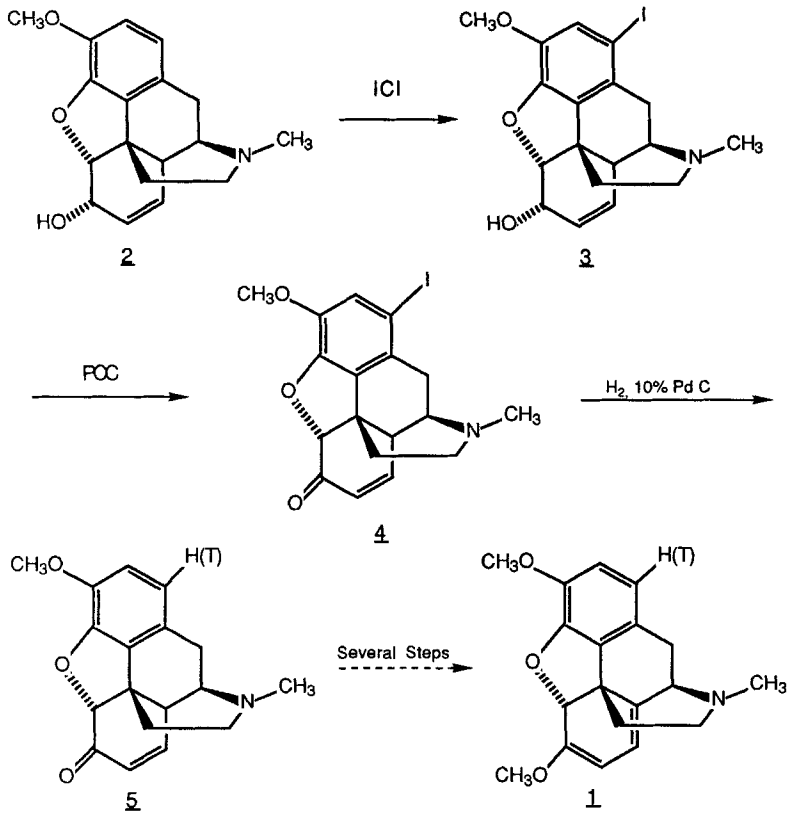
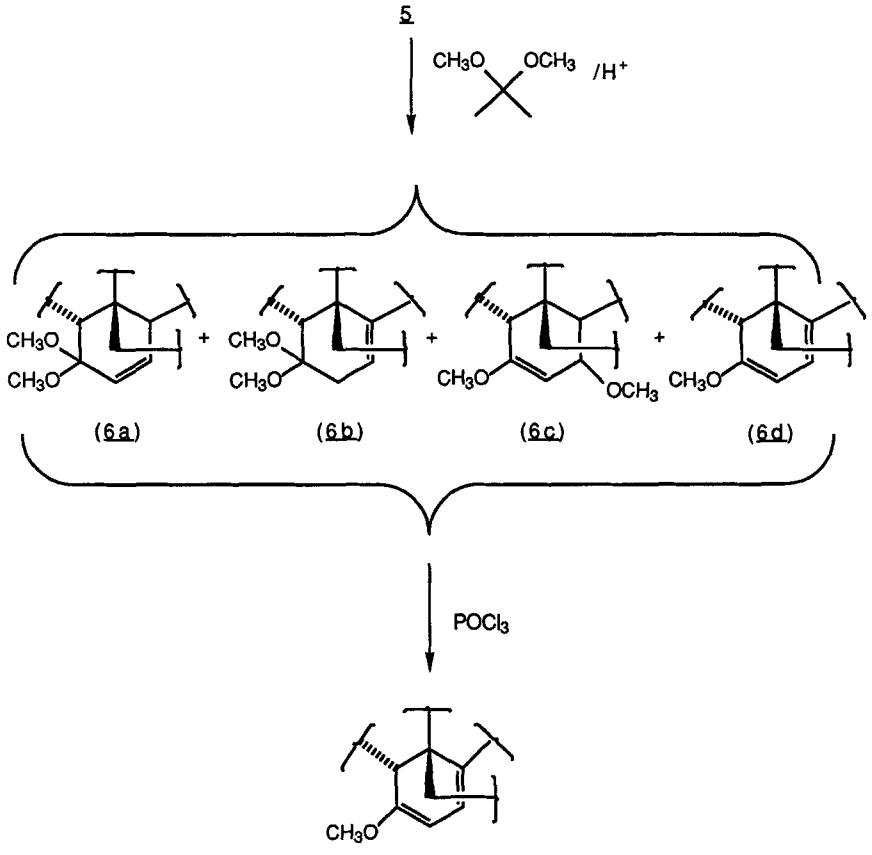
Scheme 1 Proposed Synthesis of Thebaine-1-^{3}H



Hydrogenolysis to codeinone (5) occurs quite smoothly. Since thebaine has been prepared from codeinone dimethyl ketal (6a) on reaction with phosphorus oxychloride, we attempted direct conversion of codeinone, as the potential label carrier, to codeinone dimethyl ketal. In the reported[3] conversion, dehydrobromination of 7-bromodihydrocodeinone dimethyl ketal was regarded as the successful method to obtain 6a, since the reaction of trimethylorthoformate on codeinone led only to 8-methoxy-Δ^6-dihydrothebaine (6c, Scheme 2). We attempted the direct conversion by treating codeinone (5) with 2,2-dimethoxypropane and a catalytic amount of acid. As shown in Scheme 2, a mixture of 4 products were obtained as judged by TLC analysis and were postulated to have structures 6a-6d. In principle, these products should produce the same intermediate when treated with phosphorus oxychloride and then proceed to thebaine (1) and indeed this was the case and in reasonable yield.

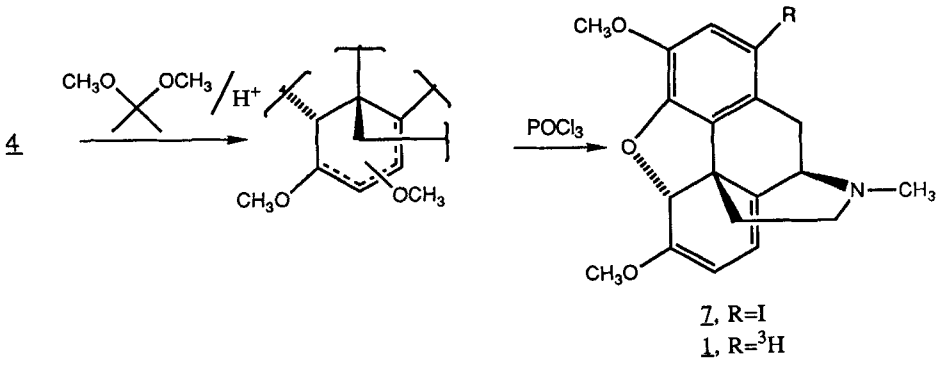
Tritium labelling could, therefore, be effected by the sequence from 1-iodocodeinone to codeinone-^{3}H to the tritium labelled ether mixture (6a-6d) and then to thebaine-^{3}H. A radiochemically more efficient approach, however, utilizes tritium labelling of 1-iodothebaine which eliminates two steps using labelled intermediates. Accordingly, 1-iodocodeinone was subjected to the same sequence of reactions as codeinone and showed the same chemical behavior to provide 1-iodothebaine (7) as seen in Scheme 3. Under the

Scheme 2.



conditions of the tritium hydrogenolysis, no significant reduction of the diene system in ring C occurred and thebaine-1-^{3}H (1) having a specific activity of 16 Ci/mmole and radiochemical purity greater than 97% was obtained.

Scheme 3. Preparation of Thebaine-1-^{3}H



7, R=I
1, R=^{3}H

EXPERIMENTAL

General. Radioactivity was measured by the liquid scintillation technique using a Beckman Model LS7500. All solvents were distilled prior to use. Tetrahydrofuran was distilled from benzophenone ketyl. Radiochemical purity was determined on thin layer chromatograms with an LB2832 Berthold TLC Linear Analyzer System. Tritium gas was purchased from New England Nuclear, Dupont.

Nuclear magnetic resonance spectra (NMR) were determined in $CDCl_3$ and were recorded at 200 MHz. Infrared (IR) spectra were determined in $CDCl_3$. Chemical shifts are expressed in parts per million (ppm) relative to tetramethylsilane (s=singlet, d=doublet, t=triplet, m=multiplet). Mass spectra (MS) were determined with a direct inlet system with ionization energy of 70 eV. Thin layer plates (TLC, silica-gel G) were purchased from Merck (Darmstadt); spots were visible under short wavelength UV light.

1-Iodocodeinone (4): A 250 mL round-bottomed flask equipped with a magnetic bar was charged with 1.16 g (2.71 mmole) of 1-iodocodeine[2] (3) in 100 mL of methylene chloride. A 1.37 g (6.37 mmole) sample of pyridinium chlorochromate was added and the resulting mixture was stirred at room temperature overnight. The reaction was quenched with 1 mL of isopropanol and after stirring for 1 h it was washed with 50 mL of 1N aqueous sodium hydroxide solution, the washings being extracted with 25 mL of methylene chloride. The combined organic extract was washed with 25 mL of brine and the brine wash re-extracted with 25 mL of methylene chloride. The combined organic extract was dried over anhydrous magnesium sulfate, filtered and concentrated to give 853 mg of brown gum. This brown gum was taken up in 5 mL of methylene chloride, 5 mL of ethanol and 20 mL of hexane. An impurity which precipitated out was filtered and discarded. The filtrate was concentrated, taken up in 20 mL of toluene, decolorized with charcoal, filtered and reconcentrated to give a light brown gum. This light brown gum was taken up in 2 mL of toluene and slowly added to 20 mL of hexane during which the desired product crystallized out (455 mg, light tan solid). A second crop of 125 mg isolated from the mother liquor, after concentration, was added to the first crop and used for the next reaction. IR ($CHCl_3$) 1678 (ketone). NMR($CDCl_3$) δ 1.84 (m,1H); 2.08 (m,2H); 2.21 (m,1H); 2.46 (s,3H,NCH_3); 2.61 (m,1H); 2.90 (d,1H); 3.17 (br s,1H); 3.47 (br s,1H); 3.84 (s,3H,-OCH_3); 4.70 (s,1H,-OCH<); 6.10, 6.63 (dd,dd,1H,1H,-CH=CH-); 7.10 (s,1H,aromatic). m/z 423 (calcd. for $C_{18}H_{18}NIO_3$, 423). Anal. Calcd. for $C_{18}H_{18}NIO_3$: C, 51.08; H, 4.29. Found: C, 50.83; H, 4.22.

1-Iodothebaine (7): A 50 mL round-bottomed flask equipped with a magnetic bar and a water cooled reflux condenser was charged with 489 mg (1.14 mmole) of 1-iodocodeinone, 20 mL of benzene and 3 mL of 2,2-dimethyoxypropane. Four hundred milligrams (2.10 mmole) of p-toluenesulfonic acid monohydrate was added and the resulting mixture was stirred at room temperature overnight during which time the starting

material disappeared and four faster running spots appeared as judged by TLC (4 ethyl acetate/0.2 triethylamine/1 methanol). The reaction mixture was poured into 75 mL of chloroform which was washed with 25 mL of dilute ammonium hydroxide followed by 25 mL of brine. The organic extract was dried over anhydrous magnesium sulfate, filtered and concentrated to give 579 mg of the intermediates as a mixture of four products. This crude mixture was taken up in 25 mL of toluene, 2 mL of pyridine, and 1 mL of phosphorus oxychloride. The resulting reaction mixture was heated in a hot oil bath (90°C) for 6 hr during which all intermediates were converted to the final product (1-iodothebaine) as judged by TLC.

The reaction mixture was taken up in 50 mL of chloroform and washed with 50 mL of 2.5N aqueous sodium hydroxide solution. The organic extract was dried over anhydrous magnesium sulfate, filtered and concentrated to give a brown gum which was purified by flash chromatography over 60 g of silica gel (230-400 mesh, 9 ethyl acetate/1 methanol/0.1 triethylamine) to give 280 mg of 1-iodothebaine as an off-white foamy solid. IR ($CHCl_3$) 1668 (C=C), 1605 (aromatic). NMR ($CDCl_3$) δ 1.72 (m,1H); 2.18 (m,1H); 2.47 (s,3H,NCH_3); 2.66 (m,2H); 3.07 (d,1H); 3.29 (d,1H); 3.60, 3.83 (s,s,3H,3H,-OCH_3, -OCH_3); 3.66 (d,1H); 5.05, 5.59 (d,d,1H,1H, =CH-CH=), 5.27 (s, 1H,-OCH<); 7.06 (s,1H,aromatic). m/z 437 (Calcd. for $C_{19}H_{20}NIO_3$, 437). Anal. Calcd. for $C_{19}H_{20}NIO_3$: C, 52.19; H, 4.61; N, 3.20; I, 29.02. Found: C, 52.37; H, 4.67; N, 3.12; I, 28.77.

Thebaine-1-^{3}H (1). A 73.0 mg (0.166 mmole) portion of 1-iodothebaine was dissolved in 10 mL of purified tetrahydrofuran, 0.23 mL (0.166 mmole) of triethylamine and 20 mg of 10% palladium on carbon was added. The reaction vessel, which also contained a small magnetic stirring bar, was connected to a Toeppler system and was treated in the usual manner (freeze-thaw) under vacuum to degas the system. A 3.9 cc (10 Ci, 0.166 mmole) sample of tritium gas was introduced and the isolated system was stirred at room temperature overnight (18 h). After recovering any unreacted tritium, the system was opened and the mixture was filtered through Celite. The filtrate was concentrated to a residue which was treated two times with methanol (3 volumes each) to remove labile tritium and again concentrated to a residue. The reaction appeared to be 80% complete as judged by TLC. The crude residue was purified by flash chromatography (silica gel 230-400 mesh, 85 ethyl acetate/10 methanol/5 triethylamine) to give 41 mg of tritium-labelled thebaine (2.14 Ci, specific activity=16 Ci/mmole) of thebaine-^{3}H having a radiochemical purity of greater than 97% (Berthold), and chromatographically identical to an authentic sample of non-labelled thebaine.

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