Journal of Labelled Compounds and Radiopharmaceuticals
J. Labelled Cpd. Radiopharm. **XLI**, 811-821 (1998)

Protection of the Allylic Alcohol Double Bond from Catalytic Reduction in the Preparation of [1-^{3}H]Morphine and [1-^{3}H]Codeine

Herbert H. Seltzman*, Michael J. Roche, Christopher P. Laudeman, Christopher D. Wyrick, and F. Ivy Carroll

Organic and Medicinal Chemistry, Research Triangle Institute, Research Triangle Park, NC 27709-2194, USA

SUMMARY

The t-butyldimethylsilylation of the allylic alcohol of 1-iodomorphine and 1-iodocodeine protects the double bond of these molecules from catalytic reduction while allowing the reduction of the aryl iodide. This selectivity has been applied to the preparation of tritiated morphine and codeine without complicating over reduction to the dihydromorphine and dihydrocodeine.

Key Words: olefin protection, allyl silyl ether, selectivity, catalytic tritiation, morphine, codeine

INTRODUCTION

The selective catalytic reduction of one functionality in the presence of another is a frequently encountered problem in the preparation of tritium labeled compounds. In the tritium labeling of morphine and codeine by the catalytic reduction of the corresponding 1-iodo compounds, some selectivity in the reduction of the aryl iodide in the presence of the olefin was reported by the use of a poisoned catalyst.[1] When examined in our laboratories, over reduction was observed affording amounts of dihydrocodeine and dihydromorphine that depended on the degree to which the reduction was allowed to proceed.[2] While the aryl iodide reduced faster than the double bond of the allylic alcohol, difficulties in the separation of the over reduced compounds and/or starting iodide from the desired morphine and codeine prompted an alternative approach. The approach of conducting the reduction on the silyl ethers of the two morphinans gave excellent selectivity suggesting that silylation of the allylic alcohol of these compounds protected the double bond from reduction.

CCC 0362–4803/98/090811–11$17.50

Received 17 February 1998
Revised 8 April 1998
Accepted 13 April 1998

RESULTS AND DISCUSSION

1-Iodocodeine (**1b**) and 1-iodomorphine (**1a**) were prepared as reported.[3] Silylation of 1-iodomorphine with either BDCS (t-butyldimethylsilyl chloride, imidazole, DMF) or MTBSTFA (N-(t-butyldimethylsilyl)-N-methyltrifluoroacetamide) tended to give the mono-silylated derivative **1d** unless rigorously anhydrous conditions and freshly prepared BDCS were employed, in which case disilylation was obtained affording **1c**. Exposure of **1c** to deuterium gas in the presence of heterogenious catalysts demonstrated both a resistance to reduction of both the aryl iodide and the olefin as well as a very high selectivity with that catalyst that promoted reduction. Thus, no reduction of the disilyl iodomorphine **1c** was observed with 5 % $Pd/CaCO_3$ (10% w/w catalyst / substrate, Et_2O, Et_3N, 25 °C, $^2H_2$, 2 h) in contrast to the mixed reduction of both the iodide and the olefin on unsilylated iodomorphine **1a** with this catalyst. Neither was reduction observed with 5% $Pd/BaSO_4$ (23% w/w). Even the usually effective 10% Pd/C (10% w/w) gave only modest amounts of reduction (7% in 2 h, 25 °C, < 1 atm $^2H_2$). When 41% w/w of 10% Pd/C (ether, Et_3N, 25 °C, < 1 atm $^2H_2$) was employed, smooth and selective reduction was observed affording disilyl morphine **2c** (90% and 10% starting iodide) within 3 h with no over reduction to the corresponding disilyl dihydromorphine **3c**. The deuterium content of the resulting disilyl morphine **2c**, as determined by MS, was 26% d_0, 71% d_1, 3% d_2. ^1H NMR indicated the deuterium incorporation to be at the 1-position in the aryl ring by the dimunition of that resonance.

In order to explore if the protection of the olefin against reduction was due to the proximal allylic silyl ether or a more general effect of the disilyl compound (such as altered binding on the catalyst as influenced by the phenolic silyl ether), reduction of each of the iodomorphines mono-silylated on the phenolic (C-3) or the alcohol (C-6) hydroxyls was undertaken. The 3-silyl ether **1d** was prepared by treating morphine with 9 equivalents BDCS reagent, in which no reaction occurred at ambient temperature, followed by one equivalent of t-butyldimethylsilyl chloride to get a mixture of **1d** and **1c** which were chromatographically separated. The 6-silyl ether **1e** was obtained from reaction of morphine with MTBSTFA and work up that included higher temperatures during evaporation of solvents which appears to induce rearrangement of the initially formed 3-silyl ether to the 6-silyl ether. Assignment of the mono-silylated position was made from the ^1H NMR shifts of the protons proximal to the silylation sites (i.e., H-2 and

H-5 for C-3 and C-6 silylations respectively). Thus, the H-2 resonance shifts upfield from that of the unsilylated **1a** by 0.1 ppm in the disilylated **1c** and in the mono-silylated **1d** but is essentially unchanged in the mono-silylated **1e**. This supports the assignment of **1d** as the C-3 mono-silyl compound. Similar observations of the H-5 resonances assigns **1e** as the C-6 mono-silyl compound.

The reduction of the allylic silyl ether **1e** and the phenolic silyl ether **1d** derivatives were conducted as for **1c**. The reaction mixture composition was determined by gas chromatographic analysis (gc) of aliquots that were subjected to cleavage of the t-butyldimethylsilyl blocking group from the mono-silyl compounds, which do not elute on gc, and subsequent exhaustive trimethylsilylation and comparison to standards. After 1 h reduction of **1e** there was 93% morphine (**2e**), 5% dihydromorphine (**3e**) and 1% unreduced iodomorphine (**1e**) silyl ethers. After only 0.5 h reduction of **1d**, analysis showed 60% morphine (**2d**), 39% dihydromorphine (**3d**) and 0% unreduced iodomorphine (**1d**) silyl ethers.

Extended reduction time on disilylated iodomorphine **1c** leads to the formation of disilylated dihydromorphine **3c** but at a slower rate than the reductive deiodination of **1c**. Over reduction to **3c** initiates after, or in the final stages of, the conversion of **1c** to **2c**.

The deuterium reduction of silylated 1-iodocodeine **1f** similarly gave high selectivity when the above conditions were employed. Thus, complete consumption of **1f** at 1 h afforded silyl codeine (**2f**) as the sole product (gc). After an additional 1.5 h, silyl dihydrocodeine (**3f**) was observed to the extent of 6% which increased to 51% after a total of 17.5 h.

Tritium reduction of the disilylated morphine **1c** was conducted as for the above deuterium reduction (~3 Ci $^3H_2$, Et_3N, 40% w/w of 10% Pd/C, ether, 3 h) to afford a 3:1 mixture of **2c** and **1c** with a trace of **3c** (gc). Desilylation and chromatographic purification afforded 286 mCi of **2a** with a measured specific activity of 25 Ci/mmol. A second preparation with excess of **1c** versus 2 Ci of tritium gas produced **2c** and **1c** in a 1.2:1 ratio with 3% of **3c** present (gc). This yielded 332 mCi (46%) of **2a** with a specific activity of 21 Ci/mmol.

The high vapor pressure of diethyl ether at ambient temperature (440 mm Hg at 20 °C) limited the amount of tritium that could be accommodated with a given head space and pressure (< 1 atm). This, combined with the slower reduction of the silyl

ethers in diethyl ether prompted a change of solvents in an effort process more substrate, drive the reaction to completion and to accelerate the reduction. The change to absolute ethanol from diethyl ether markedly accelerated the reduction so much so that dropping the amount of 10% Pd/C catalyst from 40% w/w to 10% w/w was required to provide adequate time to monitor the reaction versus time without the reaction progressing to over reduction (of the double bond). Gc analysis of the reduction of **1c** demonstrated it was 94% consumed at 78 min with no over reduction (to **3c**). At 113 min the reaction was stopped and gc analysis showed complete consumption of **1c** and a 97:3 ratio of **2c**:**3c**. No **3c** was observed until **1c** was completely consumed.

Tritium reduction of silylated iodocodeine (**1f**) in diethyl ether for 3 h gave complete reduction affording **2f** containing approximately 3% of **3f** (TLC-radioscan). The over reduced product **3f** can be accounted for from the extended reduction time; a result which is consistent with the deuterium reduction at 2.5 h above.

The trend is clear; the allylic silyl ether is responsible for the major part of the protection of the double bond. The unsilylated **1a**, the phenol methylated **1b** (codeine), and the phenolic mono silyl ether **1d** all gave substantial levels of over reduced morphinans (i.e., **3a,b,d**) while the allylic silyl ethers (**1c,e,f**) gave little or no over reduction. Additional silylation (or methylation) of the phenolic hydroxyl of compounds silylated at the allylic alcohol further suppressed the modest amount of over reduction (5%) seen in **1e**. It was also observed that the silylation of the 6-hydroxyl retarded the reduction of the iodomorphines **1c** and **1e** to the point that they required a greater amount of catalyst (40% in ether vs. a more typical 10% w/w) to complete the reduction in a few hours.

The results of the present study offer a number of benefits. First, it provides an improved method for obtaining tritiated morphine and codeine, which are of current interest in studies of drug abuse, without complicating over reduction. Second, it demonstrates silylation of allylic alcohols as an approach to protecting a double bond from catalytic reduction that may have wider application to other allylic alcohol containing compounds where retaining the olefin in the final radioligand is required. Third, it presents the idea that simple derivatization of structures should be considered as a complementary approach to catalyst modification for the general problem of selectivity in catalytic reduction.

EXPERIMENTAL

Tritium and deuterium reductions were conducted on an IN/US Trisorber at an initial pressure of slightly less than one atmosphere. Mass spectra were obtained on a Model 5989A Hewlett Packard mass spectrometer with a direct insertion probe. The HPLC was a Waters system equipped with a U6K injector, a Model 510 pump, a Model 484 tuneable uv detector, and an IN/US Model 386-40 β-RAM radioactivity monitor. The gc was a Hewlett Packard Model 5890 with a J & W Scientific megabore capillary column, DB-1, 15 m, operated at a column temperature of 275 °C with FID detection. TLC-radioscan were obtained on a Berthold Tracemaster Linear Analyzer. TLC employed Whatman silica gel F 254, 250 μm, eluted with $CHCl_3$:MeOH:conc. NH_4OH, 9:1:0.1.

1-Iodomorphine-3,6-Bis-t-Butyldimethylsilyl Ether, (1c)

Anhydrous1-iodomorphine (345 mg, 0.84 mmol) (dried by vacuum azeotropic distillation from anhydrous CH_3CN three times and high vacuum drying) under a dry nitrogen atmosphere was cooled to 0 °C and treated with 8.4 mL of freshly prepared DMF solution of t-butyldimethylsilyl chloride (1 M), and imidazole (2 M). The solution was stirred over night at ambient temperature, then cooled to 0 °C and quenched by dropwise addition of dilute aqueous NH_4OH to pH 10. The resulting suspension was extracted with $CHCl_3$ (3 x 30 mL) and the combined extracts dried over Na_2SO_4. The volatiles were evaporated in vacuo and the solid residue was triturated with water with sonication until a fine suspension was obtained. Filtration, washing with water and drying in vacuum yielded 496 mg (92%). MS : 639 (M^+), 73 (base). ^1H NMR (250 MHz, $CDCl_3$) d 7.02 (s, 1 H, H-2), 5.61 (d, 1 H, J=9.7 Hz, H-7), 5.22 (dm, 1 H, J=9.7 Hz, H-8), 4.65 (d, 1 H, J=5.7 Hz, H-5), 4.21 (m, 1 H, H-6), 3.34 (m, 1 H, H-9), 2.79 (d, 1 H, J=18.8 Hz, H-10e), 2.63-2.52 (m, 2 H, H-14, H-16e), 2.44 (s, 3 H, NCH_3), 2.19 (td, 1 H, J=12.1, 3.7 Hz, H-16a), 2.07 (dd, 1 H, J=18.8, 6.4 Hz, H-10a), 1.97 (dd, 1 H, J=12.1, 5.1 Hz, H-15a), 1.81 (br d, 1 H, J=12.9 Hz, H-15e), 0.96 (s, 9 H, 3-t-butyl), 0.92 (s, 9 H, 6-t-butyl), 0.21 (s, 3 H, CH_3Si), 0.15 (s, 3 H, CH_3Si), 0.12 (s, 3 H, CH_3Si), 0.09 (s, 3 H, CH_3Si).

1-Iodomorphine-6-t-Butyldimethylsilyl Ether, (1e)

1-Iodomorphine (99.5 mg, 0.24 mmol) in 2 mL dry DMF and 5 mL dry CH_2Cl_2 (solvents filtered through basic Al_2O_3) was treated with MTBSTFA (0.12 mL, 0.5 mmol) and stirred for

0.5 h under nitrogen. After each 0.5 h, monitoring the conversion to products of R_f intermediate between 1-iodomorphine and the corresponding bis-silyl compound by TLC (SiO_2, $CHCl_3$:MeOH:c NH_4OH; 9:1:0.1, UV) prompted a further addition of MTBSTFA (0.06 mL, 0.25 mmol) until the opaque reaction mixture started to become clear and production of the bis-silyl iodomorphine was significant versus the middle R_f products (1.75 mmol of MTBSTFA). The reaction was quenched with MeOH (2 mL) and evaporated under aspirator vacuum at ambient temperature and then under high vacuum at 40 °C affording 110 mg. Chromatography on silica gel (10 g) eluting with 2% Et_3N in ethyl acetate yielded 10 mg of the title mono-silyl ether preceded by the disilyl ether and followed by the 3-mono-silyl ether and finally the unsilylated starting 1-iodomorphine (from a 1:1 MeOH:EtOAc 1% Et_3N flush). ^1H NMR (250 MHz, $CDCl_3$) δ 7.10 (s, 1 H, H-2), 5.62 (br d, 1 H, J=9.9 Hz, H-7), 5.24 (d, 1 H, J=9.6 Hz, H-8), 4.70 (d, 1 H, J=6.0 Hz, H-5), 4.24 (m,. 1 H, H-6), 3.44 (m, 1 H, H-9), 2.79 (d, 1 H, J=18.9 Hz, H-10e), 2.63 (m, 2 H, H-14, H-16e), 2.46 (s, 3 H, NCH_3), 2.34 ("dt", 1 H, H-16a), 1.99 (d, 1 H, J=6.5 Hz, H-10a), 2.06-1.97 (m, 1 H, H-15a), 1.69 (br d, 1 H, J=12.9 Hz. H-15e), 0.93 (s, 9 H, t-butyl), 0.14 (s, 3 H, CH_3-Si), 0.12 (s, 3 H, CH_3Si).

1-Iodomorphine-3-t-Butyldimethylsilyl Ether, (1d)

1-Iodomorphine (89 mg, 0.22 mmol) in 2.5 mL dry DMF (filtered through basic Al_2O_3) was treated with BDCS (0.43 mL, 0.22 mmol) and stirred under nitrogen at ambient temperature. The reaction was monitored by TLC (SiO_2, $CHCl_3$:MeOH:c NH_4OH; 9:1:0.1, UV) after each 0.5 h for the conversion to products of R_f intermediate between 1-iodomorphine and the corresponding bis-silyl compound and treated with a further addition of BDCS (0.43 mL, 0.22 mmol) when no reaction was observed. After 3.87 mL (1.98 mmol) of BDCS was added and no reaction was evident, t-butyldimethylsilyl chloride (40 mg, 0.27 mmol) was added where upon the starting 1-iodomorphine was consumed and the title compound and the corresponding bis silyl ether was present (TLC). The reaction was quenched with MeOH (2 mL), diluted with aqueous $NaHCO_3$ and extracted with Et_2O (3 x 150 mL). Insolubles from the partitioning were isolated by filtration and decantation, dissolved in CH_2Cl_2 and added to the combined Et_2O layers. The combined organic phases were dried over Na_2SO_4 and evaporated in vacuo to give 130 mg of an oil with crystals. Chromatography of the material on silica gel (7 g) eluting with 1 % Et_3N / EtOAc yielded 19 mg of the title compound. ^1H NMR (250 MHz, $CDCl_3$)

δ 7.04 (s, 1 H, H-2), 5.68 (d, 1 H, J=10.0 Hz, H-7), 5.28 (d, 1 H, J=10.2 Hz, H-8), 4.85 (d, 1 H, J=5.9 Hz, H-5), 4.17 (m, 1 H, H-6), 3.38 (m, 1 H, H-9), 2.79 (d, 1 H, J=18.8 Hz, H-10_e), 2.70-2.50 (m, 2 H, H-14, H-16e), 2.44 (s, 3 H, NCH_3), 2.33 ("dt", 1 H, H-16a), 2.10 (d, 1 H, J=6.0 Hz, H-10a), 2.01 (m, 1 H, H-15a), 1.83 (br d, 1 H, J=12.4 Hz, H-15e), 0.98 (s, 9 H, t-butyl), 0.20 (s, 3 H, CH_3Si), 0.17 (s, 3 H, CH_3Si).

[1-^{3}H]Morphine, (2a)

1-Iodomorphine bis(t-butyldimethylsilyl) ether (**1c**) (35 mg, 0.055 mmol) dissolved in anhydrous Et_2O was treated with 10% Pd/C (14 mg) to remove potential catalyst poisons, filtered through Celite followed by an ether wash, and evaporated in vacuo. The residue was redissolved in anhydrous Et_2O (0.5 mL) and transferred to an oven-dried tritiation flask containing fresh 10% Pd/C (14 mg) and followed by Et_3N (0.1 mL, 0.72 mmol). The mixture was stirred at ambient temperature under an atmosphere of tritium (2 Ci, 0.034 mmol) for 3 h consuming a calculated 2.1 Ci of tritium. The suspension was filtered through Celite and the exchangeable tritium was removed by dilution in EtOH (2 mL) and removal of the volatiles in vacuum (3x) affording 739 mCi of activity. TLC-radioscan (SiO_2, $CHCl_3$:MeOH:conc. NH_4OH, 9:1:0.1) showed a single radioactive peak with R_f identical to that of unlabeled **2c**. Gc (275 °C) showed a mixture of product (**2c**) and excess starting material (**1c**) in the ratio of 1.2:1 with only 3% of **3c** relative to **2c**. The material was stored in absolute ethanol (25 mL) and stored at -70 °C.

The ethanol was removed by rotary vacuum evaporation followed by azeotropic evaporation (3x) with toluene. The residue (0.5 mL) was dissolved in anhydrous THF (3.5 mL) and treated with 1M n-Bu_4F in THF (0.4 mL, 0.4 mmol) and stirred for 2 h under N_2 when TLC-radioscan showed the desilylation to be complete. Work up involved acidification with acetic acid to pH 4 and evaporation of the volatiles with a nitrogen stream. Storage in 25 mL of methanol at -70 °C was followed by concentration to 1 mL which was loaded onto a Waters reversed-phase C-18 μBondapak column (25 mm x 10 cm, 10 μ, 125Å) equipped with a Guard-Pak and eluted with 5% MeOH/ 95% [H_2O:HOAc:Et_3N, 850:25:19, pH 4] to afford 332 mCi (46 %) of 98% radiochemically pure (HPLC) tritium labeled **2a** which was diluted to 100 mL with MeOH. The specific activity was determined to be 21.4 Ci/mmol by liquid scintillation counting and UV quantitation at 286 nm (ε = 1490 L/mole cm) in the above solvent mixture.

1-Iodocodeine t-Butyldimethylsilyl Ether, (1f)

A solution of 1-iodocodeine [3] (**1a**) (300 mg, 0.70 mmol) in 5 mL dry CH_2Cl_2 and 1 mL dry DMF was treated with MTBSTFA (1.5 mL, 6.1 mmol) at room temperature under nitrogen overnight. The volatiles were removed by rotary evaporation followed by high vacuum drying. The residue was chromatographed on silica gel (16 g) eluting with 1.5% Et_3N in EtOAc to afford 129 mg (34%) of 98% pure **1f.** ^1H NMR (250 MHz, $CDCl_3$) δ 7.05 (s, 1 H, H-2), 5.66 (d, 1 H, J=9.8 Hz, H-7), 5.25 (d, 1 H, J=9.8 Hz, H-8), 4.70 (dd, 1 H, J=6.2, 1.2 Hz, H-5), 4.26 (m, 1 H, H-6), 3.84 (s, 3 H, O-CH_3), 3.39 (m, 1 H, H-9), 2.79 (d, 1 H, J=18.7 Hz, H-10e), 2.64-2.54 (m, 2 H, H-14, H-16e), 2.45 (s, 3 H, N-CH_3), 2.32 (dt, 1 H, J-3.7, 12.1 Hz, H-16a), 2.10 (d, 1 H, J=6.3 Hz, H-10a), 2.08-1.94 (m, 1 H, H-15a), 1.85 (br d, 1 H, H-15e), 0.92 (s, 9 H, t-butyl), 0.13 (s, 6 H, CH_3Si), 0.12 (s, 6 H, CH_3Si).

[1-^{3}H]Codeine, (2b)

t-Butyldimethylsilyl 1-iodocodeine (22.3 mg, 0.0413 mmole) dissolved in anhydrous Et_2O was treated with 10% Pd/C (9 mg) and filtered through Celite with an Et_2O wash. The volatiles were evaporated in vacuo and the residue was re-dissolved in anhydrous Et_2O (0.50 ml) and transferred to an oven-dried tritiation flask containing fresh 10% Pd/C (9 mg) and Et_3N (65µl, 0.46 mmole). The mixture was stirred at ambient temperature under approximately 0.8 atmosphere of T_2(g) (4Ci, 0.069 mmole) for 3 h, then filtered through a plug of Celite into a round bottomed flask. The exchangeable tritium was removed by adding EtOH and subsequent vacuum transfer onto Solusorb. The residue was dissolved volumetrically in EtOH-toluene (9:1) and the activity was determined to be 1.35 Ci by scintillation counting. TLC-radioscan (SiO_2, $CHCl_3$-MeOH-conc. NH_4OH, 9:1:0.1) showed a major radioactive peak with an R_f identical to that of unlabeled t-butyldimethylsilyl codeine and a peak with an R_f identical to the over reduced "dihydro" product in the area ratio of 9:1 (3% **3f** corrected for tritium content). The product was purified on two preparative SiO_2 plates (Whatman, 20 x 20 cm, 1000 µm, 150 A, F 254 nm) eluting with $CHCl_3$MeOH-conc.NH_4OH (9:1:0.1). The band corresponding to t-butyldimethylsilyl codeine was removed and extracted with $CHCl_3$-EtOH (1:1). A yield of 0.56 Ci was determined by scintillation counting.

An aliquot containing 279 mCi was evaporated in vacuo followed by azeotropic evaporation with toluene. Anhydrous THF (1.5 mL) was added and the solution was

transferred to an oven-dried reacti-vial (equipped with a stir bar and septum). This was treated with n-Bu_4NF (0.05 mL, 1M in THF, 0.045 mmole) and stirred for 40 min at ambient temperature under N_2. The volatiles were removed in vacuo and H_2O (10 mL) was added followed by 1N HCl to pH 2. The neutrals were removed by extraction with Et_2O and the aqueous layer was adjusted to pH 8 using aqueous bicarbonate. Further extraction with $CHCl_3$ yielded 194 mCi of desilylated product which contained < 3% silylated material by TLC-radioscan (SiO_2, $CHCl_3$-MeOH-conc.NH_4OH, 9:1:0.1). The product was purified on a SiO_2 plate (Whatman 20 x 20 cm, 250 μm, F 254) eluting with $CHCl_3$-MeOH-conc.NH_4OH (9:1:0.1). The band corresponding to codeine was removed and extracted with $CHCl_3$-EtOH (1:1). The filtered extract was concentrated in vacuo to remove the $CHCl_3$ the residue diluted with EtOH to a volume of 10 mL and counted; yield 144 mCi of the title compound: >99% pure by TLC-radioscan (SiO_2, $CHCl_3$-MeOH-conc.NH_4OH, 9:1:0.1) and HPLC (Waters RCM C-18, 10 u, 8 mm x 10 cm, 5%MeOH/ 95%[H_2O-HOAc-Et_3N, 850:25:19, pH 4], β-RAM detection). The specific activity was determined to be 21.3 Ci/mmole liquid scintillation counting and UV quantitation at 274 nm (ε = 1490 L/mole cm) in water.

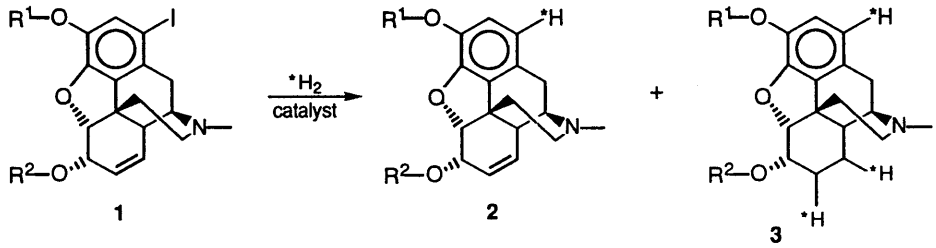
Comparative Spectra

Morphine, 2a[4]

^1H NMR (500 MHz, $CDCl_3$ w/ MeOD-d4) δ 6.62 (d, 1 H, J=8.1 Hz, H-2), 6.48 (d, 1 H, J=8.1 Hz, H-1), 5.66 (d, 1 H, J=9.9 Hz, H-7), 5.27 (dd, 1 H, J=2.2, 9.9 Hz, H-8), 4.84 (d, 1 H, J=6.4 Hz, H-5), 4.18 (m, 1 H, H-6), 3.36 (dd, 1 H, J=3.4, 6.3 Hz, H-9), 3.02 (d, 1 H, J=18.7 Hz, H-10e), 2.65 (t, 1 H, J=2.6 Hz, H-14), 2.61 (dd, 1 H, J=12.3, 4.2 Hz, H-16e), 2.44 (s, 3 H, NCH_3), 2.43 (m, 1 H, H-16a), 2.32 (dd, 1 H, J=6.4 Hz, 18.7 Hz, H_a-10), 2.06 (dt, 1 H, J=5.1, 12.6 Hz, H-15a), 1.90 (dd, 1 H, J=1.8, 12.9 Hz, H-15e).

1-Iodocodeine, 1b[3]

^1H NMR (250 MHz, $CDCl_3$) δ 7.07 (s, 1 H, H-2), 5.72, (br d, 1 H, J=9.9 Hz, H-7), 5.28 (br d, 1 H, J=10.1 Hz, H-8), 4.89 (dd, 1 H, J=6.5, 1.2 Hz, H-5), 4.17 (m, 1 H, H-6), 3.83 (s, 3 H, O-CH_3), 3.39 (m, 1 H, H-9), 2.81 (d, 1 H, J=18.8 Hz, H-10e), 2.69-2.55 (m, 2H, H-14, H-16e), 2.45 (s, 3 H, N-CH_3), 2.30(dt, 1 H, J=3.6, 12.2 Hz, H-16a), 2.11 (d, 1 H, J=6.2 Hz, H-10a), 2.04 (m, 1 H, H-15a), 1.86 (br d, 1 H, J=12.7 Hz, H-15e).



* = 2, 3

Figure 1. Reduction of Iodomorphine, Iodocodeine and their Silylated Derivatives

Table 1. Reduction Results

CMPD	R^1	R^2	Rxn hrs	% Catalyst[b]	$*H_2$/ Solvent	% Composition[a] 1	2	3
a	H	H	--	--	--	--	--	--
b	CH_3	H	3.5[c]	100	H_2/MeOH	27	49	24[d]
c	TBDMS	TBDMS	3	41	D_2/Et_2O	10	90	0
			3[e]	41	T_2/Et_2O	25	75	trace
			3[e]	41	T_2/Et_2O	46	52	2
			1.3	10	T_2/EtOH	6	94	0
			1.9	10	T_2/EtOH	0	97	3
d	TBDMS	H	0.5	40	D_2/Et_2O	0	60	30
e	H	TBDMS	1	39	D_2/Et_2O	1	93	5
f	CH_3	TBDMS	1	40	D_2/Et_2O	0	100	0
			2.5	40	D_2/Et_2O	0	94	6
			17.5	40	D_2/Et_2O	0	49	51
			3	40	T_2/Et_2O	0	97	3[f]

a By gc of per TMS derivative (see experimental section), or by TLC-radioscan or HPLC where noted
b 10% Pd/C w/w except where noted
c 5%Pd/$CaCO_3$, 100% w/w, MeOH, Et_3N; (ref. 2)
d HPLC
e Reduction with a deficiency of tritium gas
f Tlc-radioscan (see experimental section); area ratios corrected for the number of tritium atoms $\left(\text{e.g., } \frac{2}{1}:\frac{3}{3}\right)$

ACKNOWLEDGMENT

This work was supported, in part, on NIDA Contract No. N01DA-1-7311.

REFERENCES

1. Bloxsidge J.P., Elvidge J.A., Gower M., Jones J.R., Evans E.A., Kitcher J.P. and Warrell D.C. — *J. Labelled Compd. Radiopharm.* XVIII: 1141 (1981).
2. A. H. Lewin and P. Lamb — Unreported results from these laboratories,
3. Liebman A.A., Malarek D.H., Blount J.F., Nelson N.R. and Delaney C.M. — *J. Org. Chem.* 43(4): 737 (1978).
4. Neville G.A., Ekiel I. and Smith I.C.P. — *Magn. Reson. Chem.*, 25(1): 31 (1987).

