silica gel (0.2–0.5 mm), and thin-layer chromatograms (TLC) were run on Brinkmann silica gel G plates with a UV indicator and developed in an ethyl acetate–benzene mixture (1:1). Spots were made visible by UV light, iodine vapor, or spraying with a 50% aqueous *p*-toluenesulfonic acid solution and heating at 120 °C. Varian HA-100 and A-60 spectrometers were employed to record proton magnetic resonance spectra (^{1}H NMR), and the chemical shifts are relative to tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Beckman IR-9 spectrometer, and ultraviolet (UV) spectra were recorded on a Cary Model 14M spectrophotometer.

(20) AK4 is a 5% palladium on carbon catalyst prepared at F. Hoffmann-La Roche & Co., AG, Basle, Switz.

Formamidinesulfinic Acid Reduction of Dihydrocodeinone Derivatives

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Treatment of dihydrocodeinone (**1f**) with formamidinesulfinic acid afforded mixtures of dihydrothebainone (**3a**) and dihydroisothebainol (**4a**) under both homogeneous and heterogeneous conditions. Similar treatment of 14-hydroxydihydrocodeinone (**1g**) and 3-*O*-methylnatrexone (**1h**) gave predominantly the desired 6β-alcohols (**2g** and **2h**) under heterogeneous conditions. Under homogeneous conditions, **1g** and **1h** yielded mixtures of the 6β-alcohols and the dihydrothebainone derivatives **3b** and **3c**. Deuterium oxide studies established that ketone enolization was involved in the formamidinesulfinic acid reductions.

The reduction of dihydromorphinones **1a–e** to the corresponding 6β-alcohols **2a–e** using formamidinesulfinic acid was first reported by Chatterjie and co-workers.[1,2] Since the stereoselectivity of the new procedure was opposite to that of hydride reductions, its preparative potential was obvious.

In contrast, formamidinesulfinic acid reductions of dihydrocodeinone derivatives were less straightforward. Chatterjie and co-workers[2] reported the reduction of dihydrocodeinone (**1f**) to dihydroisocodeine (**2f**) in 63% yield. Due to the limited solubility of **1f** in the reaction medium,[3] ethanol was added as a cosolvent (homogeneous conditions)[4] in this experiment. However, our attempts to duplicate this reaction yielded dihydrothebainone (**3a**) as the major product.[5] In addition, Cone[6] reported the reduction of 14-hydroxydihydrocodeinone (**1g**) to 6β-alcohol **2g** with formamidinesulfinic acid in the absence of ethanol (heterogeneous conditions).[7]

As we had a need for the dihydroisocodeine compounds, we investigated the formamidinesulfinic acid reduction of dihydrocodeinones **1f–h** under various reaction conditions. During the course of our investigation, we discovered that use of deuterium oxide in the reaction mixture led to the polydeuterated 6β-alcohols.

Results and Discussion

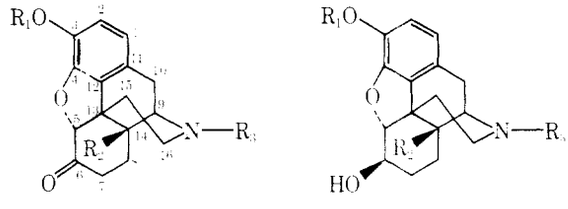
Compounds **1f–h** were treated with formamidinesulfinic acid under both homogeneous[4] and heterogeneous[6b] conditions. In addition, dihydrocodeinone (**1f**) was subjected to four additional experiments in attempts to prepare dihydroisocodeine (**2f**) directly. The results are summarized in Table I.

A comparison of the homogeneous and heterogeneous reactions showed that use of the organic cosolvent facilitated opening of the 4,5α-ether bridge. Moreover, the additional experiments on **1f** further demonstrated that bridge opening did not involve ethoxide formation (condition D) or the reaction temperature (condition E). The subsequent reduction of dihydrothebainone (**3a**) to dihydroisothebainol (**4a**)[8] could be forced to completion by use of a longer reaction time and excess reagent (condition F).

In the case of the dihydromorphinones, the 14-hydroxyl group was evidently nonessential for ketone reduction.[2,9] However, the results with the dihydrocodeinones indicated that the 14-hydroxyl group was necessary to obtain ketone reduction rather than 4,5α-ether bridge opening. For example, some 14-hydroxydihydroisocodeine (**2g**) and 3-*O*-methyl-6β-naltrexol (**2h**) were isolated even under the homogeneous conditions, while no dihydroisocodeine (**2f**) was ever obtained from **1f**. Further study is needed to elucidate the effect of the 14-hydroxyl group.

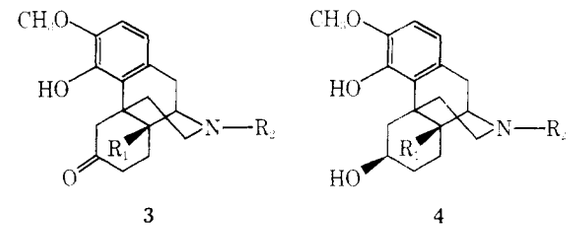
Dihydrocodeinone (**1f**) was also subjected to the heterogeneous reaction conditions with three further variations: (1) omission of the formamidinesulfinic acid, (2) use of sulfur dioxide in place of formamidinesulfinic acid, and (3) use of hydrochloric acid in place of sodium hydroxide. In each case the starting material was recovered unchanged in 98–100% yield. Attempts to reduce naltrexone (**1a**)[1] using variations (1) or (2) above also gave no reduction. These data indicated that both the formamidinesulfinic acid and the sodium hydroxide were necessary for reaction to occur.

Chart I



1 2

a, R_1 = H; R_2 = OH; R_3 = CH_2-c-C_3H_5
b, R_1 = H; R_2 = OH; R_3 = $CH_2CH{=}CH_2$
c, R_1 = H; R_2 = OH; R_3 = CH_2-c-C_4H_7
d, R_1 = H; R_2 = OH; R_3 = CH_3
e, R_1 = R_2 = H; R_3 = CH_3
f, R_1 = R_3 = CH_3; R_2 = H
g, R_1 = R_3 = CH_3; R_2 = OH
h, R_1 = CH_3; R_2 = OH; R_3 = CH_2-c-C_3H_5



3 4

a, R_1 = H; R_2 = CH_3
b, R_1 = OH; R_2 = CH_3
c, R_1 = OH; R_2 = CH_2-c-C_3H_5

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Table I. Formamidinesulfinic Acid Reduction of Dihydrocodeinone Derivatives

Ketone	Registry no.	Conditions[a]	Products (yield)[b]
1f	125-29-1	A	**3a** (69%) and **4a** (10%)
		B	**3a** (33%) and **4a** (36.5%)[c]
		C	**3a** (77.5%)
		D	**3a** (89%)
		E	Mixture of **1f** and **3a** (100%)[d]
		F	**4a** (54%)
1g	76-42-6	A	**2g** (32%) and **3b** (25%)[e]
		B	**2g** (101%)[f]
1h	16617-07-5	A	**2h** (44%) and **3c** (44%)
		B	**2h** (81.5%) and **3c** (16.5%)[g]

[a] Conditions: A, homogeneous (see text); B, heterogeneous (see text); C, same as B except that reaction was run at room temperature; D, same as A except that *p*-dioxane was used in place of ethanol; E, same as A except that reaction was run overnight at room temperature; F, same as A except for increased reaction time and use of excess reagent. [b] Except where indicated, yields are for chromatographed or crystallized samples. [c] One run under these conditions yielded exclusively **4a** (30%). [d] The experiment was stopped when **3a** was observed as the only product being formed. [e] One run under these conditions also yielded **4b** (15.5%). Compound **4b** was not observed in other runs. [f] The product was contaminated with a trace of **3b**. [g] The product was contaminated with **2h**. Compound **3c** was not purified.

It has been suggested that enolization of the ketone is necessary for the formamidinesulfinic acid reduction to occur.[10] Consequently, we repeated the heterogeneous reaction on dihydrocodeinone (**1f**) using deuterium oxide as the solvent, and we obtained dihydrothebainone-5,7,7-d_3 (**3a**) and dihydroisothebainol-5,5,6α,7,7-d_5 (**4a**). In like manner, 6β-naltrexol-5β,6α,7,7-d_4 (**2a**) was prepared from naltrexone (**1a**) and dihydroisomorphine-5β,6α,7,7-d_4 (**2e**) from dihydromorphinone-5β,7-d_2 (**1e**). The deuterated compounds were analyzed by mass spectrometry and NMR (^{1}H and ^{13}C).

The deuterium results established that enolization of the 6-keto compounds occurred under the reaction conditions[11] and that the 6α proton probably came from the solvent. Thus, in the present case, the ease with which enolization takes place may account for the ease with which the observed reactions take place. Moreover, the observed stereoselectivity of the reduction may be due to the fact that it is the enol being reduced. In addition, since back-exchange cannot occur once the reduction has taken place, the use of deuterium oxide in formamidinesulfinic acid reductions provides a convenient procedure for preparing the polydeuterated 6β-alcohols. Such compounds are potentially useful in metabolism studies.

The synthesis of compounds **2g** and **2h** demonstrated that 14-hydroxydihydrocodeinones could be reduced directly to the corresponding 6β-alcohols under the appropriate reaction conditions. Moreover, since compound **2f** could be readily obtained by methylation of dihydroisomorphine (**2e**), the reduction procedure was also applicable to the synthesis of dihydroisocodeine derivatives lacking a 14-hydroxyl group. For both **2g** and **2f** the new procedure was preferable to the previously reported synthesis.[12,13]

Our observations further demonstrate that formamidinesulfinic acid is a potentially valuable reagent in organic synthesis. It is also clear that its reactions are influenced by a number of variables. Further investigations are necessary to elucidate the full nature and magnitude of those variables.

Experimental Section

Infrared (IR) spectra were recorded on a Perkin-Elmer 467 spectrophotometer. Proton magnetic resonance (^{1}H-NMR) spectra were obtained on a Varian HA-100 spectrometer. All chemical shifts are reported in δ values relative to a tetramethylsilane standard. Carbon magnetic resonance (^{13}C-NMR) spectra were determined at 25.03 MHz on a JEOL JNM-PS-100 FT NMR spectrometer interfaced with a Nicolet 1085 20K computer system. Mass spectra were run on an AEI MS-902 mass spectrometer. Analyses were performed by Integral Microanalytical Laboratories, Inc., Raleigh, N.C.

Formamidinesulfinic Acid Reductions Using Homogeneous Conditions.[4] A. General Procedure. A solution of NaOH (0.95 g, 0.024 mol) and formamidinesulfinic acid (0.60 g, 0.0056 mol) in H_2O (60 mL) was added to a solution of the ketone (0.50 g, 0.0017 to 0.0014 mol) in EtOH (120 mL). The resultant mixture was stirred under nitrogen at 80–85 °C for 1 h. It was then cooled to room temperature and the EtOH was removed in vacuo. If a solid precipitated at this point, it was collected and washed with H_2O. The aqueous solution (or filtrate) was then acidified with concentrated HCl and rebasified with concentrated NH_4OH. The aqueous phase was next extracted with $CHCl_3$ (3×), and the combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated. If necessary, product mixtures were subsequently chromatographed on silica gel plates (1 mm) to obtain the pure compounds.

B. Dihydrocodeinone (1f). Chromatography afforded 0.35 g (69%) of dihydrothebainone (**3a**) and 0.05 g (10%) of dihydroisothebainol (**4a**). Compound **3a** was obtained as a white foam: IR (CH_2Cl_2) 1715 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.38 (s, 3 H), 3.78 (s, 3 H), 4.25 (d, 1 H, one 5-**H**, J = 14 Hz), 6.60 ppm (ABq, 2 H). Except for the aromatic carbon signals, the ^{13}C-NMR spectrum of **3a** was similar to that reported for the corresponding 4-desoxy compound.[14] Crystallization of the foam from acetone/hexane (1:1) yielded clear, off-white needles, mp 148–150 °C (lit.[15] 144–146 °C; lit.[16] 138–148 °C). Anal. Calcd for $C_{18}H_{23}NO_3 \cdot H_2O$: C, 67.68; H, 7.89; N, 4.38. Found: C, 67.45; H, 7.64; N, 4.18.

During a repeat of this experiment using 0.20 g of dihydroisocodeine (**2f**), the mixture was heated for 23.5 h with more reducing agent (one-half original amount) being added after 18.5 h. After cooling, the reaction mixture was stirred overnight at room temperature. Subsequent work-up and chromatography afforded 0.11 g (54%) of **4a** as an off-white foam: IR (CH_2Cl_2) no carbonyl; ^{1}H-NMR ($CDCl_3$) δ 2.34 (s, 3 H), 3.3–3.9 (m, 3 H, two 5-**H** and 6α-**H**), 3.79 (s, 3 H), 6.62 ppm (ABq, 2 H). The ^{13}C-NMR spectrum of **4a** was also similar to that reported for the corresponding 4-desoxy compound.[14] In particular the resonances at δ 25.66 (C-8), 35.41 (C-7), 45.46 (C-5), and 67.79 ppm (C-6) were helpful in determining the stereochemistry of the alcohol. Crystallization of the foam was unsuccessful. Anal. Calcd for $C_{18}H_{25}NO_3$: 303.1834. Found: 303.1831.

C. 14-Hydroxydihydrocodeinone (1g). The reaction yielded 0.16 g (32%) of 14-hydroxydihydroisocodeine (**2g**) and 0.13 g (25%) of 14-hydroxydihydrothebainone (**3b**). Compound **2g** was identical to the product from the heterogeneous reduction. Compound **3b** was obtained as a tan foam: IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.36 (s, 3 H), 3.80 (s, 3 H), 3.95 (d, 1 H, one 5-**H**, J = 14 Hz), 6.62 ppm (ABq, 2 H). Except for the effects of the 14-hydroxyl group,[17] the ^{13}C-NMR spectrum of **3b** was identical to that of **3a**. Crystallization of the foam was unsuccessful. Anal. Calcd for $C_{18}H_{23}NO_4$: 317.1627. Found: 317.1630.

From a repeat reaction was isolated 0.08 g (15.5%) of 14-hydroxydihydroisothebainol (**4b**) as an off-white foam. Compound **4b** was identified by its IR and NMR (^{1}H and ^{13}C) spectra.

D. 3-*O*-Methylnaltrexone (1h).[18] From the reduction of **1h** was obtained 0.22 g (44%) of 3-*O*-methyl-6β-naltrexol (**2h**) as a white solid which precipitated after the removal of EtOH. The white solid was identical to material prepared using the heterogeneous conditions. Subsequent work-up of the filtrate provided 0.22 g (44%) of *N*-cyclopropylmethyl-14-hydroxy-*N*-nordihydrothebainone (**3c**) as a viscous oil: IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.80 (s, 3 H), 3.93 (d, 1 H, one 5-**H**, J = 14 Hz), 6.60 (ABq, 2 H). Except for the effects of the *N*-cyclopropylmethyl group,[17] the ^{13}C-NMR spectrum of **3c** was identical to that of **3b**. Anal. Calcd for $C_{21}H_{27}NO_4$: 357.1940. Found: 357.1943.

Formamidinesulfinic Acid Reductions Using Heterogeneous Conditions.[6b] A. General Procedure. The ketone (0.50 g, 0.0017 to 0.0014 mol) was suspended in H_2O (50 mL), and 0.32 M NaOH (0.64 g in 50 mL) was added until the suspension was basic. Formamidinesulfinic acid (0.73 g, 0.0068 mol) was dissolved in the remaining NaOH solution and subsequently added to the suspension of ketone. The resultant mixture was stirred under nitrogen at 50–55 °C until the starting material had been consumed (17 to 30 h). The mixture was then cooled to room temperature and was worked up in the same manner as the aqueous phases obtained from the homogeneous reactions.

B. Dihydrocodeinone (1f). Chromatography of the product mixture afforded 0.165 g (33%) of **3a** and 0.185 g (36.5%) of **4a**. A reaction time of 90 h was required to obtain exclusively **4a**.

C. 14-Hydroxydihydrocodeinone (1g). The reduction afforded 0.51 g (101%) of **2g** as a white foam. The IR and ^{1}H-NMR spectra of the product were identical to those of a reference sample supplied by Dr. Cone. Careful TLC analysis showed that the crude product was contaminated with a trace amount of **3b**. Crystallization of the foam from acetone/water (1:1) gave white needles, mp 167–168 °C (lit.[19] 166–167 °C).

D. 3-*O*-Methylnaltrexone (1h). When the reaction mixture was cooled, **2h** (0.41 g, 81.5%) precipitated as a white olid: mp 172–173 °C; IR ($CHCl_3$) no carbonyl; ^{1}H-NMR ($CDCl_3$) δ 3.46–3.72 (m, 1 H, 6α-**H**), 3.84 (s, 3 H), 4.47 (d, 1 H, 5β-**H**, J = 6 Hz), 6.63 ppm (ABq, 2 H). The ^{13}C-NMR of **2h** was very similar to that of 6β-naltrexol (**2a**).[17] Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.43; H, 7.84; N, 3.75.

Extraction of the filtrate afforded 0.08 g (16.5%) of a yellow foam. TLC analysis showed a major (**3c**) and a minor (**2h**) component. On repeat runs of this reaction the precipitated product was sometimes contaminated with **3c**.

Deuterium Experiments. A. Dihydrocodeinone (1f). Repetition of the heterogeneous reaction on a one-fifth scale using D_2O as the solvent afforded 58 mg of deuterated **3a** (mass spectrum: d_0, 9.6%; d_1, 26.5%; d_2, 36.3%; d_3, 21.4%; d_4, 6.2%) and 9 mg of deuterated **4a** (mass spectrum: d_0, 0.4%; d_1, 1.4%; d_2, 2.3%; d_3, 14.3%; d_4, 37.8%; d_5, 36.7%; d_6, 7.1%). In the ^{13}C-NMR spectrum of the major product the C-5 resonance was partially collapsed while the C-7 resonance was totally collapsed. Moreover, the C-6 resonance was extremely weak due to the removal of the nearby protons needed for efficient ^{13}C–^{1}H dipolar relaxation.[20] The lower deuterium content of **3a** was due in part to back-exchange during work-up and chromatography.

B. Naltrexone (1a). Reduction[1] of naltrexone (136 mg) using D_2O as the solvent afforded 128 mg of deuterated 6β-naltrexol (**2a**) (mass spectrum: d_1, 3.0%; d_2, 20.3%; d_3, 43.4%; d_4, 32.0%; d_5, 1.3%). In the ^{13}C-NMR spectrum of the product the C-5 resonance was partially collapsed while the C-6 and C-7 resonances were totally collapsed.

C. Dihydromorphinone (1e). The starting material (285 mg) was subjected to an exchange reaction using D_2O and potassium *tert*-butoxide to get 273.5 mg of deuterated **1e** (mass spectrum: d_0, 7.3%; d_1, 41.4%; d_2, 37.9%; d_3, 13.4%). A 200-mg sample of this material was subsequently reduced[2] using D_2O as the solvent. This reaction afforded 45 mg of deuterated dihydroisomorphine (**2e**) (mass spectrum: d_2, 6.3%; d_3, 34.2%; d_4, 56.4%; d_5, 3.1%). The C-5, C-6, and C-7 resonances were completely collapsed in the ^{13}C-NMR spectrum of the product.

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Registry No.—**2f,** 795-38-0; **2g,** 61949-73-3; **2h,** 65150-66-5; **3a,** 847-86-9; **3b,** 6199-38-8; **3c,** 65150,67-6; **4a,** 2447-32-7; formamidinesulfinic acid, 1758-73-2.

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(8) We have used "iso" to distinguish **4a** from the corresponding 6α isomer.
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Reactions of Magnesium Hydrides. 1. Reduction of Organic Functional Compounds by Magnesium Hydride and 2,6-Diisopropylphenoxymagnesium Hydride

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The reducing properties of magnesium hydride and tetrahydrofuran-soluble 2,6-diisopropylphenoxymagnesium hydride toward some representative organic functional compounds such as benzaldehyde, 4-*tert*-butylcyclohexanone, 1-iodo-, 1-bromo-, and 1-chlorodecanes, iodobenzene, nitrobenzene, ethyl benzoate, benzoyl chloride, 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one, octene, and phenylacetylene have been studied. For the first time it has been shown that MgH_2 (if prepared in an active form) and HMgOR compounds are very effective reducing agents in the reduction of certain organic functional groups. The fact that these hydrides reduce some functional groups at a much faster rate than others indicates their usefulness in functional group selectivity.

Introduction

Simple and complex metal hydrides of boron and aluminum have been known for over two decades for their reducing properties toward organic functional compounds.[1] Some of these hydrides have been found to be extremely reactive but have poor selectivity. For example, $LiAlH_4$ is a very powerful reducing reagent, capable of reducing most functional groups, but is of little value for selective reductions. On the other hand,

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