NOTICE OF ENTITLEMENT

We, THE UNITED STATES OF AMERICA, REPRESENTED BY THE SECRETARY, UNITED STATES DEPARTMENT OF COMMERCE, Washington, DC 20231, United States of America, state the following in connection with Australian Patent Application No. 67426/90:

1. The persons nominated for the grant of the patent has entitlement from the actual inventors by assignment.

2. The nominated person is the assignee of the applicants of the basic application listed in the Declaration under Article 8 of the PCT.

3. The basic application is the first application made in a Convention country in respect of the invention, and a request has been made under Section 96 of the Patents Act 1990 to disregard the following application:

   USSN 06/925,620

4. The actual inventors are Kenner Cralle RICE and Amy Hauck NEWMAN.

DATED: 18 August, 1993

By PHILLIPS ORMONDE & FITZPATRICK
Patent Attorneys for the Applicant

To: The Commissioner of Patents

Our Ref: IRN 285419
TOTAL SYNTHESIS OF NORTHEBAINE, NORMORPHINE, NOROXYMORPHONE ENANTIOMERS AND DERIVATIVES VIA N-NOR INTERMEDIATES

1. A method of producing an intermediate for the production of opiate narcotics, agonist-antagonist drugs, and stereoisomers thereof, comprising the steps of:

(a) refluxing nordihydrocodeinone with an organic acid and trialkylorthoformate in a short chain alcohol ROH, where R is C1-C4 alkyl under an inert atmosphere to yield an alcoholic mixture of dialkyl ketal (I):

(I)

and a delta-6-enol ether (II):

(II)
(b) completely converting the dialkyl ketal (I) in said mixture to the delta-6-enol ether (II);
(c) reacting the delta-6-enol ether (II) from step (b) with an organic acid and a halogenating agent to yield a hydrohalide salt of a 7-halo-dialkyl ketal (III):

where X = halo.

13. Hydrobromide salt of optically active crystalline (+)7-bromodialkyl ketal of nordihydrocodeinone (III) and salts thereof.
TOTAL SYNTHESIS OF NORTHEBAINE, NORMORPHINE, NOROXYMORPHONE ENANTIOMERS AND DERIVATIVES VIA N-NOR INTERMEDIATES

Families of antagonist-agonists and opiate narcotics are produced from norhydrocodeinone. In a preferred embodiment, norhydrocodeinone is refluxed with sulfosalicylic dimethylketal and delta-6-enol ether derivatives and is then converted entirely to the ether by the addition of dry tetrahydrofuran simultaneously with the removal of the thus produced ether. The ether is then reacted with methanesulfonic acid and N-bromoacetamide to form the hydrobromide salt of the 7-bromodimethylketal derivative. From this derivative, a variety of products can be derived, including the novel further intermediate 14 hydroxy-dihydrocodeinone. The present invention enables derivation using a starting material which, unlike the starting materials of prior art processes, is available in the natural (-) or synthetic (+) form. Thus, the method of the present invention provides the only known route for the synthesis of (+) forms of various derivatives and intermediates, such as (+)-7-bromo-dimethylketal norhydrocodeinone.
TOTAL SYNTHESIS OF NORTHEBAINE,
NORMORPHINE, NOROXYMORPHONE ENANTIOMERS
AND DERIVATIVES VIA N-NOR INTERMEDIATES

Field of the Invention

The present invention relates to a total synthesis proceeding from nordihydrocodeinone (4) as in the post scheme, and a key aspect is that a facile method has now been developed, utilizing said nordihydrocodeinone intermediates throughout, for conversion of 4 to northebaine (12), noroxymorphone (19), norcodeine (39), normorphine (42) and derivatives. Since both (+)- and (-)-nordihydrocodeinone are equally available by the earlier Rice patents, the present disclosure is applicable and pertains to synthesis of compounds of both the natural (-)- and unnatural (+)-stereochemical series.

Background

Previous Rice patents, US 4,368,326 and 4,521,601, disclose the total synthesis of either enantiomer of nordihydrocodeinone (4) and the subsequent conversion of this compound to the N-methyl derivative, dihydrocodeinone (5), which is a useful intermediate in this context for synthesis of codeine (6), morphine (7) and thebaine (8); (see Chart 1, illustrated with the natural stereo-chemistry). The latter three compounds are the only raw materials obtained from opium which are of value in the production of narcotics, narcotic antagonists and the agonist-antagonist drugs. In the standard manufacturing process of the narcotic antagonists, naloxone (20), naltrexone (21), nalmefene (22), and the agonist-antagonist nalbuphine (26), (-)-thebaine [(-)-8] is obtained by extraction from opium and utilized as starting material. (-)-Codeine has also been advanced as a possible starting material for these compounds. Since both natural thebaine and codeine have a methyl substituent on the nitrogen, removal of the methyl group and replacement with a cycloalkylmethyl or allyl group and other structural alterations are necessary in order to obtain the desired pharmacological profile in the final products. For example, in the synthesis of the narcotic antagonists,
natural thebaine is sequentially oxidized to 14-hydroxycodeinone, reduced to 14-hydroxydihydrocodeinone, O-demethylated to oxymorphone. The methyl group is then removed by the following sequence: acetylation to the 3,14-diacetoxy derivative, reaction with cyanogen bromide or a chloroformate ester, and hydrolyzed to noroxymorphone which is finally alkylated with the appropriate allyl halide.

A major disadvantage of the commercial process is the multistep removal of N-methyl group involving the acylation reaction, reaction with cyanogen bromide or phosgene-derived chloroformate (which are toxic and otherwise dangerous reagents), and the hydrolysis step. The hydrolysis of the N-cyano employed in the standard process requires prolonged heating with a large excess of 25% sulfuric acid that results in partial destruction of the desired noroxymorphone.

Summary

The instant invention is a process in which nordihydrocodeinone (4), an early intermediate in the total synthesis of codeine, morphine and thebaine, Chart 1, is converted through intermediate without substituents on nitrogen to a number of versatile N-nor intermediates. Accordingly the present invention provides a method of producing an intermediate for the production of opiate narcotics, agonist-antagonist drugs, and stereoisomers thereof, comprising the steps of:

(a) refluxing nordihydrocodeinone with an organic acid and trialkylorthoformate in a short chain alcohol ROH, where R is C1-C4 alkyl under an inert atmosphere to yield an alcoholic mixture of dialkyl ketal (I):

(I)
and a delta-6-enol ether (II):

\[
\text{(II)}
\]

(b) completely converting the dialkyl ketal (I) in said mixture to the delta-6-enol ether (II);

(c) reacting the delta-6-enol ether (II) from step (b) with an organic acid and a halogenating agent to yield a hydrohalide salt of a 7-halo-dialkyl ketal (III):

\[
\text{(III)}
\]

wherein X-halo.

In a preferred aspect of the invention step (b) is performed by continuously adding a dry aprotic solvent to said mixture and removing said alcoholic solvent, and alcohol formed during said conversion, by distillation.

These compounds can serve as precursors for a number of important drugs (with the natural opiate stereochemistry) currently used in the practice of medicine. The process thus eliminates the need for thebaine for the total synthesis of these drugs. Since nordihydrocodeinone is directly available by the total synthesis as either the (+)- or (-)-enantiomer, optional access is provided to either the natural or unnatural opiate series. Since the N-nor intermediates can be N-alkylated at any stage to afford a desired N-substituted product, the process is much more versatile than the classical route, and substantially shorter because the N-demethylation sequence is eliminated.

For total synthesis, the instant invention thus differs from the prior art by not utilizing thebaine, that
is, it is unnecessary to introduce the methyl group (4--
>5, Chart 1) and then remove it after further transforma-
tion of thebaine. This results in a shorter and more
economical process by eliminating a substantial number of
steps and requirements for labor and raw materials.
Furthermore, each step in the process gives very high
yields and each isolated intermediate is obtained pure, or
very nearly so, by simple crystallization and washing.

Detailed Description of Embodiments

A description of the preferred process follows
(Chart 2-7). Anhydrous nordihydrocodeinone (4) as either
enantiomer is treated with a mixture of trialkyl ortho-
formate, corresponding short chain alkyl alcohol, such as
methanol and 5-sulfosalicylic acid, methane sulfonic acid
or other organic acid to give a mixture of the ketal (9)
and enol ether (10) Tetrahydrofuran is added and distilled
to completely convert the mixture to enol ether (10) which
can be isolated in 90% yield. Conversion can also be
accomplished by addition of a strong base, such as potas-
sium t-butoxide, or other organic base. Treatment of the
enol ether (10) in a short chain alcohol such as methanol
with halogenating reagent, preferably a brominating
reagent such as N-bromoacetamide and organic acid such as
methanesulfonic acid 5-sulfosalicylic, give 88% yield of
crystalline bromoketal (11) as the hydrobromide. Treat-
ment of compound (11) with a strong organic base, such as
potassium t-butoxide in dimethylsulfoxide or sodium
hydride, sodium amide in aprotic organic solvent then
gives northebaine (12) in 97% yield. Oxidation of northe-
baine (12) with performic acid formed in situ afforded
pure 14-hydroxynorcodeinone (13) in 90% yield after
crystallization from any short chain alcohol, such as
methanol or other suitable purification technique.
Catalytic hydrogenation of compound (13) (generally with
palladium) smoothly affords crude nearly pure noroxycodone
(18) in quantitative yield. Addition of formaldehyde in
this hydrogenation provides the clinically used agonist
percodan (17). O-Demethylation of percodan (17) by
standard procedures gives numorphan (16) also used clinically as a potent narcotic agonist. Brief treatment (O-demethylation) of compound (18) with BBr₃ or other standard O-demethylation procedure then gives noroxymorphone (19). Percodan (17) and numorphan (16) are also available by N-methylation of compounds (18) and (19), respectively, using standard methods.

Noroxymorphone (19) is a centrally important precursor for naloxone (20), naltrexone (21) nalmefene (22), all valuable narcotic antagonists in the natural stereochemical series (Chart 3). N-alkylation of compound (19) with allyl or cyclopropylethyl bromide by standard methods gives naloxone and naltrexone, respectively. These compounds can also be obtained (Chart 3) by alkylation of noroxycodone (18) to compounds (23) and (24), followed by O-demethylation with BBr₃ or other suitable reagent. Reaction of naltrexone (21) with methylene triphenylphosphorane according to standard protocol then gives nalmefene (22). Stereoselective reduction of 14-hydroxynorcodeinone (13) generally with any stereoselective reduction agent, preferably an alkali borohydride such as sodium borohydride, gives 14-hydroxynorcodeine (14) to the exclusion of the isocodeine derivatives (Chart 2). Catalytic hydrogenation of compound (14), typically with palladium, provides a quantitative yield of 14-hydroxynor-dihydrocodeine (15).

As shown in Chart 4, N-cyclobutyl-methylation of (15) to (25) followed by O-demethylation of (25) gives nalbuphine (26, Nubaine), a clinically useful agonist-antagonist drug. Alternately, O-demethylation of (15) to 14-hydroxydihyronormorphine (27) followed by N-cyclobutylation gives nalbuphine.

The potent narcotic agonist Foxy which is useful in pharmacological studies can also be obtained (Chart 5) from (-)-(14) by hydrogenation in the presence of formaldehyde to (28), previously converted to Foxy (29). Hydrogenation of (14) to (15) followed by N-methylation of (15) gives (28) the same intermediate to Foxy. The potent
narcotic antagonist cyclofoxy (30), when labeled with \[^{18}\text{F}]\), was recently shown to be a highly useful agent for labeling opiate receptors in the living brain by positron emission tomography. This compound is easily available from (15) by N-cyclopropylation to (31) which is O-demethylated to the corresponding 6 \(\alpha\)-naltrexol 32 and treated as previously described by prior art. Alternately, conversion of (27) to the N-cyclopropylmethyl derivative affords the same intermediate naltrexol. Previously, the naltrexol was prepared by borohydride reduction of naltrexone and required chromatographic fractionation to remove the corresponding 6-B-isomer.

An additional utility of the instant invention is that it renders \(N\)-alkynorthebaines including thebaine (8) readily available by total synthesis in either the natural or unnatural series by simple alkylation or reductive alkylation of the appropriate enantiomer of northebaine (12) as shown in Chart 6. For example, treatment of northebaine with cyclopropylmethylbromide gives cyclopropylmethylnorthebaine (33), an intermediate useful for synthesis of buprenorphine (34), a state of the art agonist antagonist drug which is effective by sublingual administration. The potent antagonist diprenorphine (35) can also be prepared from \(N\)-cyclopropylmethylnorthebaine by prior art procedures which were demonstrated only in the natural stereochemical series.

It is thus clear that the instant invention is an extremely practical thebaine-free total synthesis of all clinically used 14-hydroxymorphinans and other \((\text{\textendash})\)-thebaine derivatives, such as (34) and (35), as well as other important compounds derived from opium. The process is shorter and more flexible than total synthesis through thebaine and is also applicable to synthesis of the unnatural opiate series (not available from opium derivatives), some members of which are potent antitussives.

**Applicability of the Process for Utilization of Natural Thiamine for Semisynthetic Production of Drugs**

As discussed above, the instant invention elimi-
nates requirements for thebaine for the production of medically useful drugs by total synthesis. The process is, however, applicable to synthesis of drugs from opium derived starting material via semisynthetic northebaine since northebaine is an intermediate in the invention and existing methodology developed by others permits facile, high-yielding synthesis of (−)-northebaine from natural thebaine.

The instant invention can also be used to prepare codeine (6), morphine (7), and related compounds via norcodeine (39) and normorphine (42) in both the natural and unnatural opiate series. In this sequence (Chart 7), the norbromoketal (11) is treated with a strong base, for example an organic base such as potassium t-butoxide, or sodium hydroxide or sodium amide, in an ether or hydrocarbon solvent such as tetrahydrofuran to give norcodeinone ketal (37). Hydrolysis to norcodeinone (38), followed by reduction, e.g., with sodium borohydride or other alkali butoxide, gives norcodeine (39). O-demethylation of norcodeine with BBr₃, e.g., then gives normorphine (42). N-methylation of (39) and (42) provides codeine (6) and morphine (7), respectively, as either the natural or unnatural isomers, depending upon the absolute configuration of (11). Codeine can also be obtained from norcodeinone (38) by treatment with formaldehyde and sodium borohydride or cyanoborohydride. Codeine can also be obtained by reductive alkylation of norcodeine with formaldehyde and borohydride.

As an example of the utility of (39) and (42), nalorphine 3-O-methyl ether (40) and nalorphine (41, Nalline) can be obtained by alkylation with allyl bromide under standard conditions. Treatment of 40 with BBr₃ also gives nalorphine (41), a clinically used narcotic antagonist.

EXAMPLES

Melting points were determined on a Thomas-Hoover melting point apparatus and are corrected. Elemental analyses were performed by Atlantic Microlabs, Atlanta,
Georgia. IR spectra were determined on a Beckman IR 4230 spectrophotometer; mass spectra (chemical ionization, \( \text{NH}_3 \)) were obtained on a Finnegan 1015 spectrometer (\( \text{NH}_3\text{-CI} \)) and \( \text{H}_2\text{NMR} \) were obtained on Varian XL 300 or Varian 220 NMR spectrometers. Optical rotations were measured with a Perkin-Elmer Model 241 polarimeter. Silica gel GF plates (Analtech, Newark, Del.) were employed for thin layer chromatography (TLC) and a Hewlett Packard 5880A gas chromatograph with a 6-ft methyl silicone column was used for capillary gas chromatography (GC). Acidification of non-aqueous solutions in some cases was monitored by application of an aliquot to moist pH indicator sticks (E. Merck). TLC and GC were used to compare all enantiomeric compounds throughout the synthesis and as criteria for purity. All synthesized products had Rf values and retention times which were identical with those of their authentic (\(+\))-enantiomers. All other spectral data obtained on each (\(+\))-enantiomer were identical to that of authentic (\(-\))-enantiomers with the exception of opposite optical rotation.

**Applicability of the Instant Invention to the Natural or Unnatural Opiate Series**

The following examples beginning with (\(+\))nordihydrocodeinone [(\(+\))-4] illustrate the instant invention in the unnatural (\(+\))-opiate series but in no way imply limitation to the (\(+\))-series. For synthesis of the (\(-\))-compounds with the natural opiate absolute configuration of the carbon nitrogen skeleton, it is merely necessary to employ (\(-\))-nordihydrocodeinone [(\(-\))-4] in an exact replication of the process. In this manner, the (\(-\))-enantiomers described above are obtained which are identical in every respect with authentic samples prepared by classical routes from opium. Obviously, (\(-\))-northebaine prepared by N-demethylation of natural (\(-\))-thebaine could be utilized instead of the identical substance prepared by total synthesis.
Example 1

(+)-8,14-Dihydronorthebaine, [(+)-10]

A solution of 22.8 g 5-sulfosalicylic acid (90 mmol) in 8 mL MeOH was added to 38 g trimethyl orthoformate (352 mmol) in 8 mL MeOH and allowed to stir at reflux for 5 min, under an atmosphere of argon. A solution of 22.8 g (64 mmol) of anhydrous (+)-nordihydrocodeinone [(+)-4] in 30 mL MeOH was added dropwise at a constant rate to the refluxing reaction mixture via addition funnel over 1 h. If the addition is too rapid the insoluble salt of the starting material will crystallize and the reaction will not go to completion because of the low solubility of this salt. The addition funnel was rinsed with 10 mL dry THF and the reaction mixture stirred at reflux for 30 min at which time GC analysis of the basic fraction showed complete loss of starting material and a mixture of 90% ketal and 10% 8,14-dihydrothebaine. The condenser was replaced with a fractional distillation apparatus and 30 mL MeOH was removed by distillation. The reaction mixture became cloudy, as crystals (5-sulfosalicylic acid salt of 10) separated. Dry THF was added at the rate of distillation via addition funnel; after distillation of 300 mL THF, GC (RT = 4.90, 220°C) and TLC analysis showed reaction was complete. The reaction mixture was poured, under an atmosphere of argon, into 150 mL of vigorously stirred 10% NaOH, at 0°C, and allowed to stir for 5 min; the reaction flask was washed with 30 mL THF. Removal of the residual THF in vacuo, followed by extraction with 1 x 100 mL and 2 x 50 mL CHCl₃ then washing the combined organic extract with 1 x 50 mL H₂O and removal of volatiles in vacuo resulted in a brown syrup. Crystallization from EtOAc afforded 17.09 g (90%) of (+)-10; mp 148.5-150.5°C (mp lit 152--152.5°C) which was homogeneous and identical to the (-)-enantiomer by TLC and homogenous by TLC and GC analysis (220°C). Anal. calc. for C₁₈H₂₁NO₃: C, 72.26; H, 7.02; N, 4.64. Found: C, 72.16; H, 7.12; N, 4.64. \([\alpha]_D^{28} + 217.6 \text{ (c, } 1.27, \text{ CHCl}_3)\).
Example 2

(+)-7-Bromonordihydrocodeinone Dimethyl Ketal Hydrobromide, [(+)-11].HBr

A solution of 27.0 g (+)-10 (90 mmol) in 400 mL MeOH was mechanically stirred at 0°C under an atmosphere of argon. A solution of 9.45 mL methanesulfonic acid (126 mmol) in 75 mL MeOH was added and the reaction mixture was allowed to stir at 0°C for 10 min N-bromoacetamide (NB; 11.2 g, 81 mmol) was slowly added portionwise to the reaction mixture. After stirring for 20 min, 1.0 g NBA (6.3 mmol) was added followed by 20 min stirring and an additional 250 mg NBA (1.8 mmol). After 10 min additional stirring, the reaction was complete by GC and TLC analysis. Saturation with NH₃ gas to pH 9.5 followed by removal of MeOH, in vacuo, resulted in a yellow syrup. The mixture was treated with 200 mL of 20% NH₄OH and extracted with 3 x 100 mL of CHCl₃. The organic phase was washed with 100 mL 20% NH₄OH/H₂O and evaporated to a syrup. Distillation of toluene followed by isoctane, and drying in high vacuum gave 37.55 g of off-white foam that was 95% pure by GC analysis. This material was dissolved in 40 mL hot MeOH and acidified with freshly prepared HBr/MeOH. Cooling to 0°C gave 38.1 g of white crystalline (+)-11.HBr (88%), mp 232°C. Anal. calc. for C₁₉H₂₄NO₄.HBr: C, 46.47; H, 4.09; N, 2.58. Found: C, 46.30; H, 5.18; N, 2.80. [α]D° + 116.0 (c, 1.06, CHCl₃).

Example 3

(+)-Northebaine, [(+)-12]

To a mixture of potassium t-butoxide (9.0 g, 83.2 mmol) and 40 mL DMSO at 0°C, was added 5.0 g of (+)-11 base (10.4 mmol) and allowed to stir at room temperature. The orange reaction mixture was gently warmed to 45°C and after 30 min, GC analysis showed complete loss of starting material. After 2 h, 2.25 g potassium t-butoxide was added (20.8 mmol) and the reaction was completed in 15 min. The reaction mixture was cooled to 0°C, quenched with 100 mL H₂O and extracted with 3 x 100 mL CHCl₃. The
organic phase was washed with 50 mL H₂O and evaporated to a yellow syrup. Addition and evaporation of MeOH gave crystalline product: 2.87 g (97%), mp 157-158°C, lit. Bartels-Keith, J. Chem. Soc. (C), 1966, 617-624, mp for (-)-12, mp 157-159°C. Anal. Calc. for C₁₈H₁₉NO₃: C, 72.74; H, 6.39; N, 4.71. Found: C, 72.60; H, 6.48; N, 4.65. [α]D²⁸ + 235.2 (C, 1.08, CHCl₃).

**Example 4**

(+)-14-Hydroxynorcodeinone, [(+)-13] (+)-

Northebaine [(+)-12] (14.8 g, 50 mmol) was added to a solution of 6.5 mL 88% formic acid and 26 mL 0.7% sulfuric acid, followed by addition of 7.2 mL 30% H₂O₂. The resulting heterogeneous reaction mixture became homogeneous and golden brown and was allowed to stir at room temperature for 48 h. Neutralization with 120 mL 10% Na₂CO₃ (pH 9.5) gave crystalline material that was filtered and washed with 50 mL H₂O and 100 mL MeOH to give 12.1 g (81%) cream-colored crystalline product. The aqueous filtrate was saturated with NaCl, extracted with 4 x 100 mL CHCl₃/MeOH (9:1). Evaporation of the extracts in vacuo and crystallization in MeOH resulted in 1.3 g (9%) crystalline product. Recrystallization of the combined material gave 13.4 ag (90%) product which was homogeneous by TLC; mp 209-210°C. Anal. calc. for C₁₇H₁₇NO₄·3/4 H₂O: C, 65.29; H, 5.92; N, 4.47. Found: C, 65.12; H, 6.02; N, 4.45. [α]D³⁵ + 171.73 (10.4, CHCl₃).

**Example 5**

(+)-Noroxycodone [(+)-18]

Catalytic hydrogenation of (-)-13 (4.5 g, 15 mmol) in 90 mL 10% glacial acetic acid (w/w) and 500 mg 5% Pd/BaSO₄ was followed by filtration over celite and washing the filter pad with 100 mL glacial acetic acid and 100 mL 10% glacial acetic acid. Neutralization of the filtrate with NH₄ OH to pH 9.5 and extraction with 3 x 50 mL CHCl₃ and 3 x 50 mL CHCl₃/MeOH 9:1 followed by removal of volatiles, in vacuo, resulted in a white powder 4.5 g (100% crude) that was 98.8% pure by GC analysis. Purifi-
cation by preparation of the HI salt, in MeOH followed by recrystallization with MeOH/ether gave the HI salt of (+)-18 which was homogeneous TLC. Anal. calc. for C<sub>17</sub>H<sub>19</sub>NO<sub>4</sub> HI: C, 47.58; H, 4.66; N, 3.26. Found: C, 47.55; H, 4.74; N, 3.23. [α]<sup>25</sup> + 100.4 (C, 0.55, MeOH).

Example 6

(+)-Noroxymorphone [(+)-19]

O-Demethylation of (+)-18 was performed, dissolving 150 mg of (+)-18 (0.5 mmol) in 1.5 mL CHCl<sub>3</sub> and adding the solution to a stirring mixture of BBr<sub>3</sub> (0.3 mL, 30 mmol) in 1.5 mL CHCl<sub>3</sub> at 0°C. The pale yellow heterogeneous reaction mixture was allowed to stir at 0°C for 20 min and at room temperature for 40 min. The reaction was quenched by pouring onto 4 g ice/2 ml NH<sub>4</sub> OH (pH 9.5) and was allowed to stir at 0°C for 30 min. The white crystalline material was filtered, washed with 10 mL cold H<sub>2</sub>O and 10 mL cold CHCl<sub>3</sub>, and dried in a vacuum oven over night. The crystalline (+)-19, 80 mg (60% yield), was homogeneous and identical to authentic (-)-noroxymorphone by TLC, mp d >260°C, mp (-)-noroxymorphone d >260°C, MS (CI) M+1 288, (HCl salt) The HCl salt of (+)-19 was formed in MeOH and gave (+)-19-HCl which was homogeneous by TLC, mp >260°C. [α]<sup>22</sup> + 126.95 (C, 0.82, MeOH).

Example 7

(+)-Naloxone-3-0-methyl Ether.HCl [(+)-23.HCl]

A mixture of 2.1 g of (+)-18 (7 mmol), 21 mL dry DMF and 4.9 g anhydrous K<sub>2</sub>CO<sub>3</sub> (35 mmol) was allowed to stir at 0°C. Allyl bromide (0.7 mL, 8 mmol) was added and the heterogeneous reaction mixture was allowed to stir at 0°C for 10 min and room temperature for 1.5 h. The inorganic material was removed by suction filtration and washed repeatedly with a total of 50 mL CHCl<sub>3</sub>. The filtrate was then washed with 3 x 10 ml 10% Na<sub>2</sub>CO<sub>3</sub> and 1 x 10 mL H<sub>2</sub>O; evaporated in vacuo to a clear syrup, then dried on a vacuum pump at 50°C, resulting in 2.2 g white foam (92% crude). The crude product was dissolved in a minimum volume of hot 2-proparol and acidified in pH <2 with HCl/2
propanol. Crystallization and recrystallization in 2 propanol gave 2.8 g of (+)-23.HCl (86%) mp 248-250°C. Anal. calc. for C_{20}H_{22}NO_4.HCl.1/2 H_2O: C, 62.12; H, 6.21; N, 3.62. Found: C, 62.34; H, 6.49; N, 3.62. [α]_D^{2} + 176.11 (C, 0.95, MeOH).

Example 8
(+)-Naloxone [(+)-20]
Conversion of 680 mg of (+)-23.HCl (1.8 mmol) to the free base was performed in the usual manner. The dry, foamy free base was dissolved in 5 mL CHCl_3 and added dropwise to a stirring solution of 1.0 mL BBr_3 (10.7 mmol) in 5 mL CHCl_3 at 0°C. The addition funnel was washed with 2 ml CHCl_3 and the reaction mixture was allowed to stir at 0°C for 40 min then room temperature for 20 min. The reaction was quenched by pouring onto 15 g ice/4 mL NH_4 OH (pH 9) and allowed to vigorously stir at 0°C for 30 min. The organic layer was removed and the aqueous layer extracted with 4 x 10 mL CHCl_3. The organic fractions were combined and washed with 2 x 10 mL brine and 2 x 10 mL H_2O. Volatiles were removed in vacuo to give 450 mL white solid (80% crude). The crude product crystallized and was recrystallized in hot EtOAc to give 300 mg crystalline (+)-20 (60%), mp 167-168°C. The free base was converted to the hydrochloride salt by dissolving in a minimum volume of 2 propanol and accordingly to pH 2 with HCl/2-propanol. Recrystallization in absolute ethanol gave (+)-20:HCl as white crystals, mp 206-210°C, lit. Merck Index, 10th ed., 1983 or (-)-20:HC 1, mp 200-205°C. Anal. Calc. C_{19}H_{21}NO_4:HCl:2H_2O: C, 57.10; H, 6.51; N, 3.50. Found: C, 57.07; H, 6.37; N, 3.37. [ A ]_D^{2} + 148.6 (0.97, MeOH).

Example 9
(+)-Naltrexone-3-0-methyl Ether.HCl.1 Isopropanol [(+)-24]
A heterogeneous solution of 5.57 g of (+)-18 (18.5 mmol), 50 mL dry DMF and 13.0 g anhydrous K_2CO_3 (92.5 mmol) was allowed to stir at 0°C. Bromomethylcyclopropane (2.2 mL, 22 mmol) was added and the heterogeneous reaction
mixture was allowed to stir at 0°C for 10 min, then for 24 h at room temperature. The inorganic material was removed by suction filtration and washed with 200 mL CHCl₃. The filtrate was washed with 3 x 100 mL 10% aqueous Na₂CO₃ and 100 mL H₂O and the volatiles were removed in vacuo. Distillation of toluene and drying at 50°C in high vacuum gave a white foamy product, 5.9 g (90% crude). The free base was converted into the hydrochloride salt by dissolving in a minimum volume of hot 2-propanol and acidifying to pH 2 with HCl/2-propanol. Crystallization and recrystallization gave 7.0 g (84%) of (+)-24-HCl.1 isopropanol white crystalline salt: mp 235-238°C. Anal. Calc. C₂₁H₂₅NO₄·HCl·3/₂ H₂O: C, 60.23; H, 6.93; N, 3.34. Found: C, 60.41; H, 6.89; N, 3.34.

**Example 10**

(+)-Naltrexone [(+)-21]

Conversion of 2.35 g (+)-24-HCl isopropanol into the free base was performed by extraction from 10% aqueous Na₂CO₃ into CHCl₃ to give 2.1 g of white foamy free base which was dissolved in 18 mL CHCl₃ (dried over 3A molecular sieves) and added dropwise to a stirring solution of 3.5 mL BBr₃ (freshly distilled over Hg) and 18 mL CHCl₃ at 0°C. The addition funnel was washed with 7 mL CHCl₃ and the reaction was allowed to stir for 20 min at 0°C and 45 min at room temperature. The reaction mixture was quenched on 53 g ice/18 mL NH₄OH (pH 9.5) and after washing the reaction flask with aqueous NH₄OH/CHCl₃, it was allowed to stir for 30 min at 0°C. The aqueous mixture was extracted with 4 x 30 mL CHCl₃ and the organic phase was washed with 2 x 30 mL H₂O and 2 x 50 mL brine, dried (Na₂SO₄) and the volatiles were removed in vacuo resulting in 1.8 g white foam (88% crude). Crystallization and recrystallization in EtOAc gave 1.15 g of (+)-21 white crystals (57%); mp 155°C. Anal. calc for: C₂₈H₂₃NO₄.1/4 EtOAc: C, 69.44; H, 6.88; N, 3.85. Found: C, 69.42; H, 6.88; N, 4.00.[α]₂⁰ + 194.51 ;(C, 0.82, MeOH).
Example 11

(+)-Nalmefene.HCl [(+)-22.HCl]

This compound can be prepared from (+)-naltrrexone [(+)-21] as described by Hahn, et al, J. Med. Chem., 1975, Vol. 18, pp 259-262, for the (-)-isomer. The (+)-compound showed mp 186-187°C, (-)-nalmefene, mp 187-189°C (GC analysis showed 100% purity, RT = 7.42, 220°C). The hydrochloride salt was prepared in 2-propanol with HCl/2-propanol (pH 2), and crystallized and recrystallized in 2 propanol to give (+)-nalmefene.HCl mp 199-200°C, lit. Hahn, et al, J. Med. Chem., 1975, Vol. 18, pp 259-262, mp for (-)-nalmefene.HCl 197-198°C. Anal. calc. for C_{21}H_{25}NO_{3}.HCl.1/2 H_{2}O: C, 65.47; H, 7.41; N, 3.45. Found: C, 65.52; H, 7.07; N, 3.63. [c]^{20}_{D} = 1.43.7 (C, 1.05, MeOH), corrected for anhydrous + 147.2 [α]_{D}^{22} (authentic (-)-145.4 (C, 1.04, MeOH).

Example 12

(+)-Norcodeinone Dimethyl Ketal [(+)-37]

Conversion of 2.5 g of (+)-11 to the free base (2.13 g foam, 4.26 mmol) was done with 20% NH₄ OH and ether extraction followed by drying. To a solution of the free base in 42 mL dry THF, 1.15 g potassium t-butoxide (8.5 mmol) was added and the reaction mixture was allowed to stir at room temperature, under an atmosphere of argon for 24 h. GC analysis showed the reaction was complete (RT = 5.17, 220°C); the THF was removed in vacuo and 15 ml H₂O was added. The (+)-37 was isolated as a white feathery dihydrate (as seen in NMR analysis) 1.60 g (100%) mp 113-114°C, lit., Bartels-Keith, J. Chem. Soc. (C), 1966, 617-624, for (+)-37, mp 113-114°C. Anal. calc. for C_{19}H_{23}NO_{4}.3/4 H₂O: C, 66.58; H, 7.14; N, 4.08. Found: C, 66.49; H, 7.23; N, 4.00 δ^{28} + 215.9 (C, 1.09, CHCl₃).

Example 13

(+)-Norcodeine [(+)-6]

A solution of 1.0 g (+)-37 (3 mmol) in 15 mL 3N HCOOH (2.35 g 88% HCOOH in a total volume of 15 mL H₂O) was allowed to stir at room temperature for 20 min at
which time GC analysis showed complete loss of starting material. The reaction mixture was neutralized to pH 5.5-6.0 with portionwise addition of solid NaHCO₃ at 0°C¹. Sodium borohydride (90 mg, 3.4 mmol) was added and the reaction mixture, was allowed to stir for 20 min. To the completed reaction mixture, 6 mL 1.0 N NaOH was added and extraction with 3 x 10 mL CHCl₃ followed by removal of solvent in vacuo resulted in a white foam which crystallized in 2-propanol to give a (+)-6. 750 mg (90%) mp 178-181°C, d-authentic sample of (-)-6, mp 181-183°C. Anal. Calc. for C₁₇H₁₉NΟ₃: C, 71.60; H, 6.66; N, 4.91. Found: C, 71.45; H, 6.76; N, 4.84. [α]_D^28 + 115.23 (C, 1.09, CHCl₃).

**Example 14**
(+)-Nalorphine-0-methylether [(+)–40]

To a solution of 540 mg (+)-norcodeine [(+)–39] (1.9 mmol) in 6 mL of dry DMF, 1.33 g K₂CO₃ (9.5 mmol) and 0.19 mL allyl bromide (2.1 mmol) were added at 0°C. The reaction mixture was allowed to stir at 0°C for 10 min, then at room temperature for 50 min. Inorganic material was removed by suction filtration and washed with 10 mL CHCl₃. Volatiles were removed in vacuo from the filtrate which was then extracted with 3 x 10 mL CHCl₃ from 10 mL 10% Na₂CO₃ followed by washing of the organic phase with 10 mL H₂O and evaporation of solvent. Crystallization from ether gave 445 mg white crystalline (+)-40 (72%) that was homogeneous by TLC. mp 91–93°C, lit, J. Am. Chem. Soc., 1942, 64:869, mp for (+)-40, 93°C. Anal. Calc. for C₂₉H₂₃NΟ₃: C, 73.86; H, 7.07; N, 4.31. Found: C, 73.76; H, 7.13; N, 4.28. [α]_D^28 + 130.40 (C, 0.99, CHCl₃).

**Example 15**
(+)-Nalorphine [(+)–41]

A solution of 235 mg (+)-40 (.72 mmol) in 1.5 mL CHCl₃ was added dropwise over 1 min to a solution of 0.44

¹ Note the intermediate nocodeinone [(+)–38] can be isolated as a white foam by solvent extraction and evaporation.
mL BBr₃ (4.3 mmol freshly distilled over Hg) in 13 mL CHCl₃ at 0°C. The addition funnel was washed with 1 mL CHCl₃ and the reaction mixture was allowed to stir at 0°C for 20 min and room temperature for 20 min. The yellow heterogeneous reaction mixture was poured onto 6 g ice/3 mL NH₄ OH (pH 9.5) and allowed to stir at 0°C for 45 min. The volatiles were removed in vacuo resulting in a gummy product which was dissolved in 5 mL CHCl₃ and washed with 2 x 10 mL 10% NH₄ OH; the aqueous phase was then washed with 5 x 10 mL CHCl₃ and the combined CHCl₃ fractions were washed with 1 x 10 mL H₂O. Evaporation of solvent and distillation of toluene resulted in 300 mg crude product which crystallized in ether, to give 200 mg of (+)-41, (89%) mp 188-191°C, lit, Merck Index, 10th ed., 1983, mp for (1)-41, 208-209°C. Purification by formation of the hydrochloride salt in 2-propanol and recrystallization in MeOH gave 150 mg (45%) of pure HCl (+)-41 as the salt, mp >260, lit. Merck Index, 10th ed., 1983, mp for (-)-41·HCl d 269°C. [α]₂⁰⁺ 99.91 :(C, 1.06, MeOH).

It is understood that in the claim structure below the compounds in their preparation and use are made both in the natural (generally (-)-) and the unnatural (generally (+)-) stereochemical series.
CHART 1: KEY INTERMEDIATES IN THE TOTAL SYNTHESIS OF CODEINE, MORPHINE AND THEBAINE (APPLICABLE TO BOTH THE NATURAL AND UNNATURAL SERIES)
CHART 2: SYNTHESIS OF KEY INTERMEDIATES, PERCODAN AND NUMORPHAN FROM NORDIHYDROCODEINONE. ILLUSTRATED IN THE NATURAL STEREOREGULAR SERIES, BUT EQUALLY APPLICABLE TO THE UNNATURAL SERIES.

(-)-NORDIHYDROCODEINONE

(-)-9

(-)-10

(-)-11

(-)-14-HYDROXYDIHYDRON

(-)-14-HYDROXYNORCODEINE

(-)-14-HYDROXYNORCODEINONE

(-)-NORTHEBAINE

(-)-12

(-)-13

(-)-14

(-)-15

(-)-16

PERCONDAN

NUMORPHAN

NOROXYCODONE

(-)-17

(-)-18

(-)-NOROXYMORPHONE
CHART 3:

A: SYNTHESIS OF NALOXONE (20), NALTREXONE (21) AND NALMEFENE (22) FROM NOROXYMORPHONE (19)

B: SYNTHESIS OF NALOXONE (20), NALTREXONE (21) AND NALMEFENE (22) FROM NOROXYCODONE (18)
CHART 4: SYNTHESIS OF NALBUPHINE (NUBAINE)
CHART 5: SYNTHESIS OF FOXY AND CYCLOFOXY

(-)-14 \rightarrow \text{(Intermediate 1)} \rightarrow \text{(Intermediate 2)} \rightarrow \text{FOXY} \\
\text{(-)-29} \rightarrow \text{CYCLOFOXY} \\
\text{(-)-30} \rightarrow \text{(Intermediate 3)}
CHART 6: SYNTHESIS FROM NORTHEBAINE (12)

(-)-12

(-)-33: R = \[\triangleup\]

(-)-36: R = \[\square\]

(-)-12: R = CH₃

34: R = t-Bu

(BUPRENORPHINE)

35: R = CH₃

(DIPRENORPHINE)
SCHMITT OF NORCODEINE, NORMORPHINE, NALORPHINE, CODEINE AND MORPHINE FROM 11

CHART 7

(-)-NORCODEINONE

(-)-NORCODEINE

(-)-NALORPHINE (NALLINE)

(-)-CODEINE

(-)-7
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A method of producing an intermediate for the production of opiate narcotics, agonist-antagonist drugs, and stereoisomers thereof, comprising the steps of:

(a) refluxing nordihydrocodeinone with an organic acid and trialkylorthoformate in a short chain alcohol ROH, where R is C₁-C₄ alkyl under an inert atmosphere to yield an alcoholic mixture of dialkyl ketal (I):

\[
\text{(I)}
\]

and a delta-6-enol ether (II):

\[
\text{(II)}
\]

(b) completely converting the dialkyl ketal (I) in said mixture to the delta-6-enol ether (II);

(c) reacting the delta-6-enol ether (II) from step (b) with an organic acid and a halogenating agent to yield a hydrohalide salt of a 7-halo-dialkyl ketal (III):

\[
\text{(III)}
\]

where X=halo.
2. A method according to claim 1, further comprising dehalogenating said 7-halodialkyl ketal (III) by reaction with a base in an aprotic solvent to produce northebaine.

3. A method according to any one of claims 1 or 2, performed by continuously adding a dry aprotic solvent to said mixture and removing said alcoholic solvent, and alcohol formed during said conversion, by distillation.

4. A method according to any one of claims 1 or 2, wherein step (b) is performed by addition of a base.

5. A method according to claim 4, wherein said base is potassium t-butoxide.

6. A method according to claim 4, wherein said base is organic.

7. A method according to claim 2, further comprising oxidizing said northebaine to yield 14-hydroxynorcodeinone.

8. A method according to claim 7, wherein said oxidation of northebaine to 14-hydroxynorcodeinone is accomplished by reaction with performic acid.

9. A method according to any one of claims 1 to 8, further comprising dehalogenating said 7-halodialkylether by reaction with a base in an ether or hydrocarbon solvent to yield norcodeinone ketal.

10. A method according to claim 9, wherein said solvent is tetrahydrofuran and said base is potassium t-butoxide.

11. A method according to any one of claims 9 or 10, further comprising hydrolyzing said norcodeinone ketal to norcodeinone, and reducing said norcodeinone to yield norcodeine.

12. A method according to claim 11, wherein said reducing is by reaction with an alkali butoxide.

13. Hydrobromide salt of optically active crystalline (+)7-bromodialkyl ketal of nordihydrocodeinone (III) and salts thereof.
14. A method according to claim 1 substantially as hereinbefore described with reference to the examples.
I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) 3

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): C07D 489/08
U.S. Cl.: 546/44; 546/45

II. FIELDS SEARCHED

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<td>U.S.</td>
<td>546/44; 546/45</td>
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Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Chemical Abstracts CAS ONLINE search

III. DOCUMENTS CONSIDERED TO BE RELEVANT 14

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, 16 with indication, where appropriate, of the relevant passages 17</th>
<th>Relevant to Claim No. 14</th>
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<tbody>
<tr>
<td>Y</td>
<td>U.S., A, 3,299,072 (Bartels-Keith) 17 January 1967; see entire document</td>
<td>1-13</td>
</tr>
<tr>
<td>Y</td>
<td>U.S., A, 4,141,897 (Olofson, et al.) 27 FEBRUARY 1979; see entire document</td>
<td>7-12</td>
</tr>
<tr>
<td>Y</td>
<td>U.S., A, 4,472,253 (Schwartz) 18 SEPTEMBER 1984; see entire document</td>
<td>7-12</td>
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<td>U.S., A, 4,639,520 (Kavka) 27 JANUARY 1987; see entire document</td>
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<td>Y</td>
<td>U.S., A, 4,521,601 (Rice) 4 JUNE 1985, see entire document</td>
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<td>X,Y</td>
<td>U.S., A, 4,613,668 (Rice) 23 SEPTEMBER 1986; see entire document</td>
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<td>Y</td>
<td>U.S., A, 4,368,326 (Rice) 11 JANUARY 1983; see entire document</td>
<td>7-12</td>
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<td>Y</td>
<td>FR, A 1, 2,208,902 (Merck &amp; Co.) 02 AUGUST, 1974; see abstract, pages 2-11</td>
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<td>Y</td>
<td>WO, A 1, 80/00841, (Wilson, et al.) 1 MAY 1980; see pages 1-10</td>
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<td>Y</td>
<td>WO, A 1, 81/00409 (Mal fer, et al.) 19 FEBRUARY 1981; see pages 1-8, Figures 1-2</td>
<td>7-12</td>
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</table>

* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed
  - "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
  - "X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
  - "Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
  - "A" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search 1 4 March 1991
Date of Mailing of this International Search Report 1 04 APR 1991
International Searching Authority 1 ISA/US
Signature of Authorized Officer 12 Diana G. Rivers

Form PCT/ISA/210 (second sheet) (May 1986)
### FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

| Y | EP, Al, (Wallace) 16 OCTOBER 1985 see abstract, pages 10-28 | 7-12 |

### V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. Claim numbers, because they relate to subject matter not required to be searched by this Authority, namely:

2. Claim numbers, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

### VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This International Searching Authority found multiple inventions in this international application as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claim:

3. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest
- No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (supplemental sheet (2) (May 1996)
### III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

<table>
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