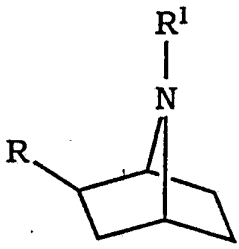




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<p>(51) International Patent Classification ⁵ : C07D 487/08, A61K 31/44 A61K 31/40 // (C07D 487/08 C07D 209:00, 209:00)</p>	A1	<p>(11) International Publication Number: WO 93/18037 (43) International Publication Date: 16 September 1993 (16.09.93)</p>
<p>(21) International Application Number: PCT/US93/01936 (22) International Filing Date: 2 March 1993 (02.03.93) (30) Priority data: 845,042 3 March 1992 (03.03.92) US (71) Applicant: THE UNITED STATES OF AMERICA, represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES [US/US]; National Institutes of Health, Box OTT, Bethesda, MD 20892-9902 (US). (72) Inventors: DALY, John, W. ; 3410 19th Street N.W., Apartment 103, Washington, DC 20012 (US). SPANDE, Thomas, F. ; 5801 Wyngate Drive, Bethesda, MD 20817 (US). GARRAFFO, Hugo, Martin ; 4 Monroe Street, #1106, Rockville, MD 20850 (US).</p>		<p>(74) Agents: KILYK, John, Jr. et al.; Leydig, Voit & Mayer, Ltd., Two Prudential Plaza, Suite 4900, Chicago, IL 60601-6780 (US). (81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i></p>
<p>(54) Title: EPIBATIDINE AND DERIVATIVES, COMPOSITIONS AND METHODS OF TREATING PAIN</p> <div style="text-align: center; margin: 20px 0;">  <p>(I)</p> </div> <p>(57) Abstract</p> <p>The present invention is directed to compounds, compositions and methods of treating pain, and derivatives that have potent analgetic activity. The compounds have formula (I) wherein R¹ is selected from H, lower alkyl, C₃-C₉ cycloalkyl, acyl, and C₃-C₉ cycloalkylalkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, or C₃-C₈ cycloalkenyl or C₃-C₈ cycloalkynyl; and wherein R is selected from cycloalkyl, aryl, heteroaryls (selected from the group consisting of pyridyl, thienyl, furanyl, imidazolyl, pyrazinyl, and pyrimidyl) or phenoxy and wherein said R groups can be substituted with hydroxyl, C₁-C₆ lower alkyl, C₂-C₆ alkenyl, C₁-C₆ lower alkoxy, halo, C₁-C₆ haloalkyl, amino, C₁-C₆ alkylamino and C₂-C₁₀ dialkylamino, and sulfonamido or a pharmaceutically acceptable salt thereof.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NL	Netherlands
BE	Belgium	GN	Guinea	NO	Norway
BF	Burkina Faso	GR	Greece	NZ	New Zealand
BG	Bulgaria	HU	Hungary	PL	Poland
BJ	Benin	IE	Ireland	PT	Portugal
BR	Brazil	IT	Italy	RO	Romania
CA	Canada	JP	Japan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SK	Slovak Republic
CI	Côte d'Ivoire	LI	Liechtenstein	SN	Senegal
CM	Cameroon	LK	Sri Lanka	SU	Soviet Union
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	MC	Monaco	TG	Togo
DE	Germany	MG	Madagascar	UA	Ukraine
DK	Denmark	ML	Mali	US	United States of America
ES	Spain	MN	Mongolia	VN	Viet Nam
FI	Finland				

EPIBATIDINE AND DERIVATIVES, COMPOSITIONS AND
METHODS OF TREATING PAIN

FIELD OF THE INVENTION

The present invention is directed to epibatidine and its derivatives, compositions and methods of treating pain.

5

BACKGROUND OF THE INVENTION

The control of pain is at present primarily through the use of opioid-like analgetics, such as morphine, fentanyl, pentazocine, etc., or through non-steroidal antiinflammatories. There are limitations to the usefulness of such agents, and other classes of analgetics for the control and amelioration of pain are needed. A trace alkaloid epibatidine from skins of a neotropical frog is two-hundred fold more potent than morphine administered subcutaneously to mice in a standard analgetic test. In addition the analgesia elicited by epibatidine is not antagonized by the opioid antagonist naloxone, indicating that the analgesia is not due to actions of epibatidine at opioid receptors. In support of this conclusion is the very low affinity of epibatidine for dihydromorphine binding sites in rodent brain membranes. Epibatidine at higher doses causes a marked Straub-tail response, as does morphine, an effect linked to activation of dopamine pathways in the spinal cord. However, the Straub-tail response to epibatidine, unlike the Straub tail response to morphine, is not blocked by the opioid-antagonist naloxone.

10

15

20

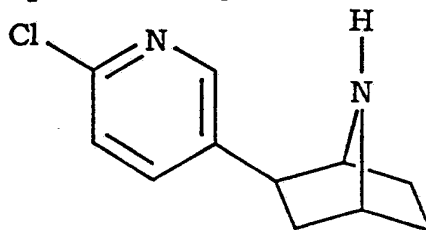
25

SUMMARY OF THE INVENTION

The present invention is directed to a purified and isolated compound having the formula:

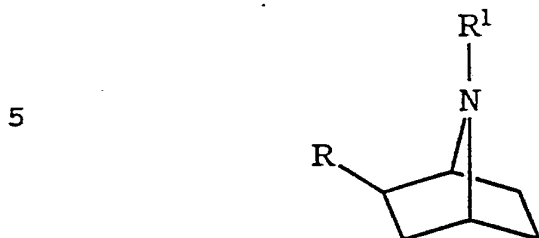
30

35



or a pharmaceutically acceptable salt thereof.

The present invention is also directed to a compound having the formula:



wherein R¹ is selected from H, lower alkyl, C₃-C₉,
10 cycloalkyl, acyl, and C₃-C₉ cycloalkylalkyl, haloalkyl,
alkenyl, alkynyl, hydroxyalkyl, or C₃-C₈ cycloalkenyl or C₃-
C₈ cycloalkynyl; and wherein R is selected from cycloalkyl,
aryl, heteroaryls (selected from the group consisting of
15 pyridyl, thienyl, furanyl, imidazolyl, pyrazinyl, and
pyrimidyl) or phenoxy and wherein said R groups can be
substituted with hydroxyl, C₁-C₆ lower alkyl, C₂-C₆ alkenyl,
C₁-C₆ lower alkoxy, halo, C₁-C₆ haloalkyl, amino, C₁-C₆
alkylamino and C₂-C₁₀ dialkylamino, and sulfonamido or a
20 pharmaceutically acceptable salt thereof with the proviso
that R is not 6-chloro-3-pyridyl and R¹ is not H.

The present invention is also directed to analgetic
compositions which comprise an effective amount of the
above compounds, and a pharmaceutically acceptable carrier
and a method for treating analgesia which comprises
25 administering to a host in need thereof a analgetic
effective amount of the compounds described above.

Typical alkenyl and alkynyl groups may have one
unsaturated bond, such as an allyl group, or may have a
plurality of unsaturated bonds, with such plurality of
30 bonds either adjacent, such as allene-type structures, or
in conjugation, or separated by several saturated carbons.

The term "pharmaceutically-acceptable salts" embraces
commonly used alkali metal salts and addition salts of free
acids or free bases. Since the compounds contain basic
35 nitrogen atoms, such salts are typically acid addition
salts, or quaternary ammonium salts with one or more C₁-C₆
alkyl or cycloalkyl groups.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Where the term "alkyl" is used, either alone or within other terms, such as "haloalkyl" and "hydroxyalkyl", the term "alkyl" embraces linear or branched radicals having
5 one to about twenty carbon atoms or, preferably, one to about ten carbon atoms.

By lower alkyl, straight or branched, is meant structured monovalent radicals having from 1 to 6 carbon atoms. Examples of lower alkyl include, but are not
10 limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tertiary-butyl, n-pentyl, iso-pentyl, methylbutyl, dimethylbutyl, neopentyl and n-hexyl.

By cycloalkyl is meant radicals originating from cycloalkanes having from 3 to 8 carbon atoms. Examples of
15 cycloalkyls, include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. The cycloalkyl groups can be further substituted with a halogen atom such as bromine, fluorine or chlorine.

By cycloalkylalkyl is meant radicals originating from
20 an alkane of 1 to 6 carbon atoms and which are further substituted by cycloalkyls having 3 to 8 carbon atoms. Examples of cycloalkylalkyl include, but are not limited to, cyclopropylmethyl, cyclobutylmethyl, 1-cyclopentylethyl, cyclohexylmethyl, 2-cyclohexylethyl and
25 3-cyclohexylpropyl.

By acyl is meant an organic radical derived from an organic acid by the removal of the hydroxyl group, i.e., a radical having the formula $R^2C(O)-$, wherein R^2 is a lower C_1 - C_6 alkyl, C_3 - C_7 cycloalkyl, a phenyl, a benzyl or phenethyl
30 group. Examples of acyl groups, include, but are not limited to, formyl, acetyl, propionyl and butyryl.

By arylacyl is meant an acyl group as described above wherein R^2 is an aromatic radical, i.e., phenyl and naphthyl. The aromatic radical can be further substituted
35 by C_1 - C_6 lower alkyl, halogen, lower haloalkyl, lower mono- and di-alkylamino and sulfonamido groups.

By lower haloalkyl is meant a C₁-C₆ alkyl radical which is substituted with one or more, same or different, halogen atoms selected from the group consisting of bromine, chlorine and fluorine and preferred are mono- or di-halo substituted C₁-C₆ alkyl. Examples of lower haloalkyl include, but are not limited to, dibromomethyl, dichloromethyl, bromochloromethyl and trifluoromethyl.

The term "hydroxyalkyl" embraces linear or branched alkyl groups having one to about ten carbon atoms, any one of which may be substituted with one or more hydroxyl groups. The terms "alkenyl" and "alkynyl" embraces linear or branched radicals having two to about twenty carbon atoms, preferably two to about ten carbon atoms, and containing at least one carbon-carbon double- or triple-bond.

By C₂-C₆ alkenyl is meant a univalent linear or branched aliphatic radical having at least one double-bond or a plurality of bonds either adjacent, such as allene-type structures, or in conjugation or separated by several saturated carbons. Examples of alkenyl groups include, but are not limited to, ethenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1-pentenyl, 2-pentenyl, 3-pentenyl, 1-hexenyl, 2-hexenyl and 3-hexenyl.

By C₂-C₆ alkynyl is meant a univalent linear or branched radical having at least 1 triple-bond. Examples of C₂-C₆ alkynyl groups include, but are not limited to, ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne, 1-pentyne, 2-pentyne, 3-pentyne, 1-hexynyl, 2-hexynyl and 3-hexynyl.

The terms "cycloalkenyl" and "cycloalkynyl" embrace cyclic radicals having three to about ten ring carbon atoms including, at least one double- or triple-bond involving, respectively, adjacent ring carbons. The term "alkoxyl" embraces linear or branched oxy-containing radicals each having alkyl portions of one to about ten carbon atoms, such as a methoxyl group. The "alkoxyl" or "alkoxyalkyl" radicals may be further substituted with one or more

halogen atoms, such as fluorine, chlorine or bromine, to provide haloalkoxyl or haloalkoxyalkyl groups. The term "heteroaryl" embraces aromatic ring systems containing one, two or three hetero atoms selected from oxygen, nitrogen and sulfur in a ring system having five, six or seven ring members. Examples of heteroaryl groups include, but are not limited to, thienyl, furanyl, pyridinyl, thiazolyl, pyrimidyl and isoxazolyl.

Pharmaceutically acceptable salts useful in the present invention include compounds capable of forming a salt, for example, at the nitrogen atom on the ring and which are bio-compatible and are well known to those skilled in the art. Examples of pharmaceutically acceptable salts include, but are not limited to, oxalates, citrates, tartrates, hydrochloride salts and the like, since the compounds contain basic nitrogen atoms, such salts can be acid addition salts or quaternary ammonium salts with 1 or more C₁-C₆ alkyl or cycloalkyl groups.

The compounds and compositions of the present invention are useful in treating pain.

By pain is meant acute and chronic pain, due to illness, trauma or associated with inflammation or postoperative recovery.

All percentages are by weight unless otherwise stated.

Example 1

Isolation of Epibatidine. Skins from 750 *Epipedobates tricolor* from southwestern Ecuador were minced and extracted by trituration three times with methanol (total volume 1.5 L). After concentration of the methanol extract in vacuo to 500 mL and dilution with an equal volume of water, alkaloids were extracted three times into equal volumes of chloroform. The chloroform-soluble alkaloids were then extracted four times into one-half volumes of 0.1 N HCl. The combined 0.1 N HCl solutions were adjusted to pH 9 with 1 N aqueous ammonia, followed by extraction of alkaloids three times into equal volumes of chloroform.

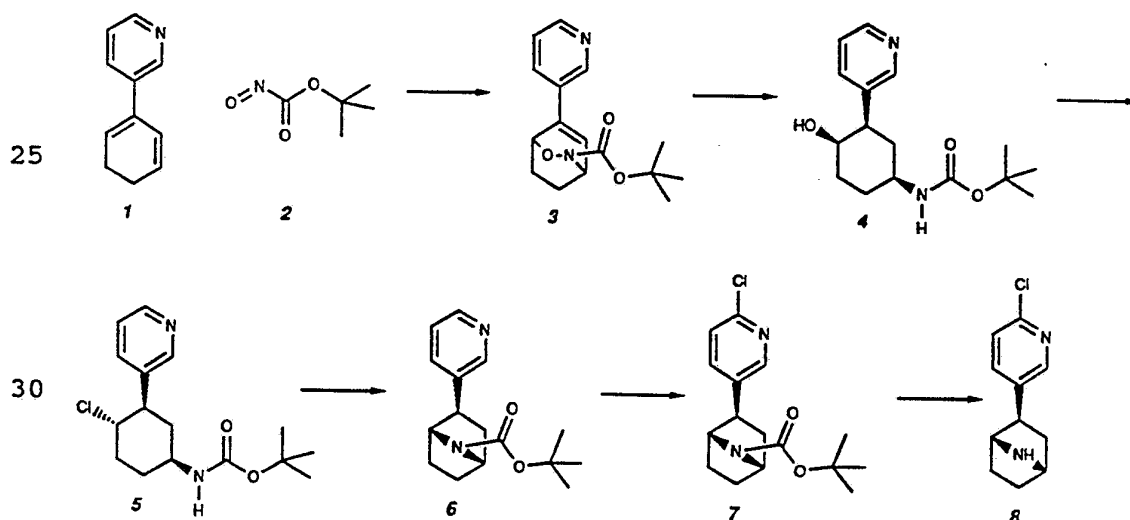
The combined chloroform solutions were dried over sodium sulfate and concentrated *in vacuo* to dryness to yield 80 mg of crude alkaloids. Sixty milligrams of crude alkaloids from *Epipedobates tricolor* were dissolved in 0.5 mL of chloroform and applied to a prepacked silica gel 60 column (Merck 1.0 x 24 cm) and eluted with 500 mL of chloroform-methanol-aqueous 6 N ammonia (800:10:0.1) and then with 1 L of chloroform-methanol-aqueous ammonia (1000:100:0.2). Five-milliliter fractions were collected. Fractions 108-111 contained the bulk of the alkaloid epibatidine that elicited the Straub-tail reaction in mice. The estimated recovery of Straub-tail equivalents from the column was about 40%. Fraction 108 in methanol was concentrated to 0.4 mL and further purified by HPLC on Partisil PXS 10/25 PAC with a solvent of acetonitrile-0.01 M (NH₄)₂CO₃ at 4 mL/min. Fractions of 0.5 mL were extracted with chloroform, the chloroform was dried over Na₂SO₄ and evaporated. Fraction 4 contained almost exclusively epibatidine based upon thin-layer and gas chromatographic analysis and was used for biological testing. Fraction 3 contained substantial amounts of epibatidine, along with other alkaloids.

Example 2

Preparation of N-Acetylepibatidine. A solution of epibatidine (~300 µg) in 1 ml of CH₃OH was evaporated and treated with 2 drops of acetic anhydride for 2 hrs. at room temperature, then saturated NaHCO₃ was added and the aqueous solution extracted with several one drop portions of EtOAc. The EtOAc layer was extracted with three 200 µl portions of 0.1 N HCl to remove any contaminating amines, dried and evaporated to dryness with a nitrogen stream. The resulting N-acetylepibatidine was homogeneous by gas chromatographic analysis and was obtained in near quantitative yield.

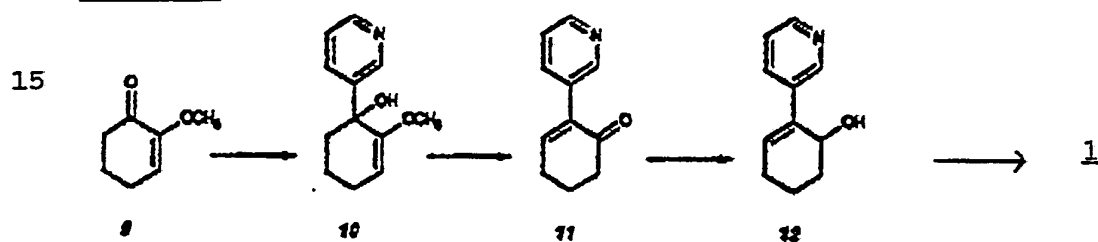
Example 3

Synthesis of (±) Epibatidine (8). The synthesis of epibatidine is shown in Scheme 1. 3-Pyridyl-2-cyclohexa-1,3-diene (1) prepared from cyclohexane-1,2-dione by the steps of Scheme 2 is reacted with tertiary butylnitrosoformate (2) in methylene chloride to provide the Diels-Alder Adduct 3. Reagent 2 is generated *in situ* from tertiary-butylloxycarbonylhydroxylamine and tetraethylammonium periodate. Adduct 3 (one of the two regioisomers is shown; both produce the same cyclized product 6) is hydrogenated with a 5% palladium-on-charcoal catalyst in methanol to the amino alcohol derivative 4. The amino alcohol 4 is then treated with thionyl chloride in pyridine to give the chloro amide 5 which is cyclized with base-treatment to give 6. Free radical chlorination of 6 (carbon tetrachloride, UV light source) provides 7, which on deblocking with trifluoroacetic acid in methylene chloride gives (±) epibatidine (8).

20 Scheme 1

As shown in Scheme 2, cyclohexane-1,2-dione is converted to 2-methoxy-cyclohex-2-enone (9) with trimethyl orthoformate and acid, and reacted with the Grignard derivative from 3-bromopyridine, 3-pyridylmagnesium bromide, in tetrahydrofuran to produce 10, which is dehydrated with phosphorous oxychloride in pyridine and hydrolyzed with dilute aqueous hydrochloric acid to give 11. Compound 11 is reduced with sodium borohydride in methanol containing cerium chloride to the allylic alcohol 12, which is dehydrated with phosphorous oxychloride in pyridine at 0°C to give 1.

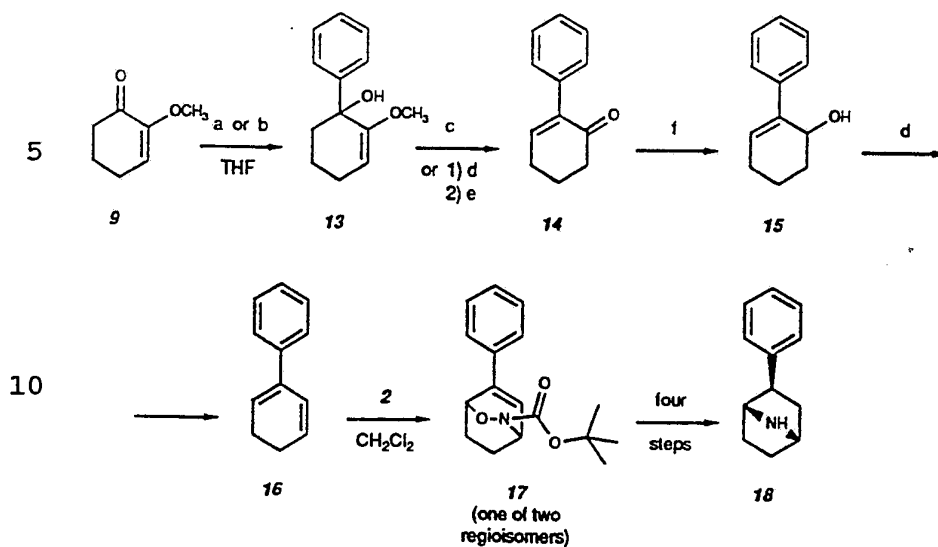
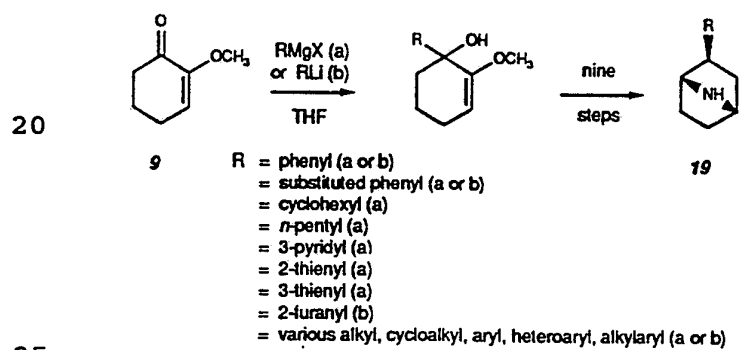
Scheme 2



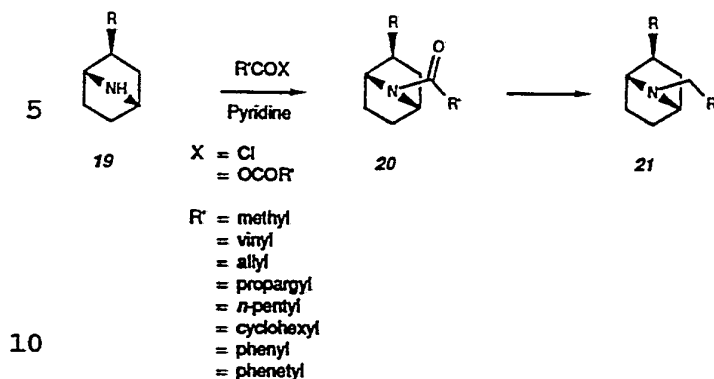
When phenylmagnesium bromide (a) or phenyllithium (b) is used in place of 3-pyridylmagnesium bromide, the phenylcarbinol enol ether 13 arises (Scheme 3). This is refluxed with acetic anhydride (c) or dehydrated with phosphorous oxychloride and pyridine (d) and hydrolyzed with aqueous hydrochloric acid (e) to give 2-phenyl-2-cyclohexenone (14). Reduction of 14 with sodium borohydride and cerium chloride in methanol (f) provides the allylic alcohol 15 which is dehydrated (d) to 2-phenyl-1,3-cyclohexadiene 16. Reaction of 16 with tertiary butyl nitrosoformate (2) as in Scheme 1, provides the Diels-Alder cycloadduct 17, which can be converted in four steps to (\pm) exo-2-phenyl-7-azabicyclo[2.2.1]heptane (18), the phenyl analog of epibatidine.

25

30

Scheme 3**15 Scheme 4**

If instead of a) or b) above, 2- or 3-thienylmagnesium bromide or 2-lithiofuran is used, the analogous exo 2-(2-thienyl)-, 2-(3-thienyl)-, or 2-(2-furanyl)-7-azabicyclo-
 30 [2.2.1]heptanes (19) are produced (See Scheme 4).

Scheme 5

The exo 2-alkyl, 2-cycloalkyl or 2-aryl-substituted 7-azabicyclo[2.2.1]heptanes (19) can be N-acylated to amides (20) with a variety of acyl chlorides or acid anhydrides (see Scheme 5) as described for the conversion of epibatidine to N-acetyl epibatidine (see Example 2 above). These in turn can be reduced to N-alkyl, N-cycloalkyl-20 methylene, or N-arylmethylene-2-substituted 7-azabicyclo [2.2.1]heptanes (21) using lithium aluminum hydride in tetrahydrofuran.

BIOLOGICAL DATA

25 The assay of analgetic activity of epibatidine and comparison with morphine was conducted by a standard procedure [Eddy N.B. and Leimbach, D., J. Pharmacol. Exp. Therap. 107, 385-393, 1953]. NIH mice were dropped onto a hot plate maintained at 55°C and the reaction time was 30 determined. The criterion for a reaction was kicking the hind leg, attempting to jump out, or shaking a foot and turning and licking it. Reaction time for each mouse was determined at least twice before and 5, 10, 20, 30, 45 and 60 min after administration of compound. An analgetic 35 effect was significant if the reaction times over the 60 min assay exceeded the values calculated based on preinjection time by 300 sec. A range of concentrations of

a compound was used to determine the ED₅₀, i.e., the dose at which 50% of the mice would show a significant analgetic effect.

Analgetic activity also was apparent for epibatidine in the Nilsen assay [Nilsen, P.L., Acta Pharmacol. Toxicol. 18, 10-22, 1961].

Table 1. Comparison of Activity of Morphine and Epibatidine as Analgetics.

	ED ₅₀ Dose for Hot Plate Analgesia	Effect of Naloxone (5 mg/kg sc)
Morphine	1 mg/kg sc	Blockade of Analgesia
Epibatidine	0.005 mg/kg sc	No effect

The Straub-tail reaction was assayed by a standard procedure [Aceto, M.D., et.al., Brit. J. Pharmacol. 36, 225-239, 1969]. Briefly the degree of Straub-tail reaction was observed after subcutaneous (sc) injection of doses of morphine and epibatidine and the dose required for a greater than 45° arch of tail was determined. A dose of 10 mg/kg of morphine was required, while a dose of 20 µg/kg of epibatidine elicited a comparable Straub-tail reaction. Naloxone at 5 mg/kg administered 20 min prior to either morphine or epibatidine prevented the Straub-tail reaction to 10 mg/kg morphine, but only slightly reduced the Straub-tail reaction to 20 µg/kg epibatidine.

The affinity of morphine and epibatidine for opioid-binding sites in guinea pig brain preparations was conducted by a standard procedure [Pert, C.P. and Snyder, S., Mol. Pharmacol., 10, 868-879, 1974]. Briefly, cerebral tissue from brains of male Hartley guinea pigs was homogenized in 10 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.4) for 20 sec. in a Polytron homogenizer at 3000 rpm. After centrifugation at 18,000 G for 10 min., the pellet was reconstructed to the same volume in Tris buffer. Aliquots of the suspension (1.9 ml) were incubated with 1nM

[³H]dihydromorphine and various concentrations of morphine or epibatidine in a final volume of 2 ml for 30 min. at 25° in the dark. Samples were chilled to 0° and filtered through glass fiber filters, followed by two washes with 5 ml of ice cold Tris buffer. Radioactivity retained on the filter was determined with a liquid scintillation counter. Nonspecific binding of [³H]dihydromorphine was determined in the presence of 100 nM naloxone. Morphine had an IC₅₀ of 1.1 nM, while epibatidine was nearly inactive with an IC₅₀ of 8,800 nM.

Embraced within this invention would be pharmaceutical compositions consisting of the epibatidine-class compound in association with one or more pharmaceutically-acceptable carriers and/or diluents and/or adjuvants (collectively referred to herein as "carrier" materials) and, if desired, other active ingredients. The compounds of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in an analgetic dose effective for the treatment intended. Therapeutically effective analgetic doses of the compounds of the present invention required to prevent or arrest the progress of the medical condition will be readily ascertained by one of ordinary skill in the art. The compounds and compositions may, for example, be administered parenterally, for example, intravascularly, intraperitoneally, subcutaneously, intramuscularly; or topically.

For oral administration, the pharmaceutical compositions may be in the form, for example, of a tablet, capsule, suspension, or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. The active ingredient may also be administered by injection as a composition wherein, for example, saline or dextrose solutions or water may be used as a suitable carrier. A suitable dose can be administered, in multiple sub-doses

per day. These sub-doses may be administered in unit dosage forms.

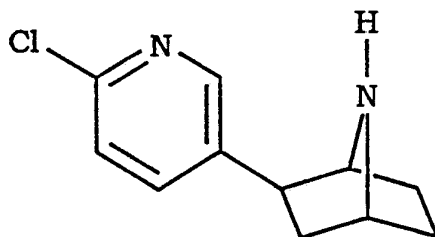
By analgetic effective amount is meant the dosage regimen for treating chronic or acute pain with the compounds and/or compositions of this invention and would be selected in accordance with a variety of factors, including the type, age, weight, sex and medical condition of the patient, the severity of the disease, the route of administration, and the particular compound employed. An analgetic effective amount would be considered between from about 0.1 to 20 $\mu\text{g}/\text{kg}$ body weight per parenteral dose. A preferred dose would be from about 1 - 6 $\mu\text{g}/\text{kg}$ body weight per parenteral dose.

For therapeutic purposes, the compounds of this invention are ordinarily combined with one or more adjuvants appropriate to the indicated route of administration. If administered per os, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets may contain a controlled-release formulation as may be provided in a dispersion of active compound in hydroxypropylmethyl cellulose. Formulations of parenteral administration may be in the form of aqueous or non-aqueous isotonic sterile injectable solutions or suspensions. These solutions and suspensions may be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The compounds may be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, or various buffers. Other adjuvants and modes of administration are well and widely known in the pharmaceutical art.

Although this invention has been described with respect to specific embodiments, the details of these embodiments are not to be construed as limitations. Various equivalents, changes and modifications may be made
5 without departing from the spirit and scope of this invention, and it is understood that such equivalent embodiments are part of this invention.

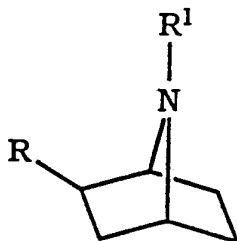
WHAT IS CLAIMED IS:

1. A purified and isolated compound having the formula:



or a pharmaceutically acceptable salt thereof.

2. A compound having the formula:



wherein R¹ is selected from H, lower alkyl, C₃-C₉ cycloalkyl, acyl, and C₃-C₉ cycloalkylalkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, or C₃-C₈ cycloalkenyl or C₃-C₈ cycloalkynyl; and wherein R is selected from cycloalkyl, aryl, heteroaryls (selected from the group consisting of pyridyl, thienyl, furanyl, imidazolyl, pyrazinyl, and pyrimidyl) or phenoxy and wherein said R groups can be substituted with hydroxyl, C₁-C₆ lower alkyl, C₂-C₆ alkenyl, C₁-C₆ lower alkoxy, halo, C₁-C₆ haloalkyl, amino, C₁-C₆ alkylamino and C₂-C₁₀ dialkylamino, and sulfonamido or a

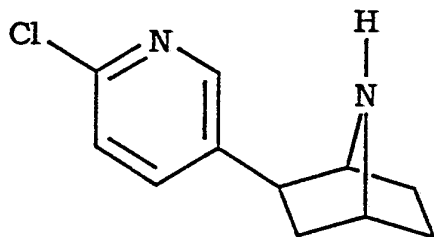
pharmaceutically acceptable salt thereof with the proviso that R is not 6-chloro-3-pyridyl and R¹ is not H.

3. The compound according to Claim 2, wherein R is 6-chloro-3-pyridyl and R¹ is CH₃C(O)- or a pharmaceutically acceptable salt thereof.

4. An analgetic composition which comprises an effective analgetic amount of a compound according to Claim 1 and a pharmaceutically acceptable carrier.

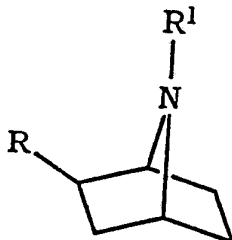
5. An analgetic composition which comprises an effective analgetic amount of a compound according to Claim 2 and a pharmaceutically acceptable carrier.

6. A method of treating pain which comprises administering to a host in need thereof, an effective amount of a compound having the formula:



or a pharmaceutically acceptable salt thereof.

7. A method of treating pain which comprises administering to a host in need thereof, an effective amount of a compound having the formula:



wherein R¹ is selected from H, lower alkyl, C₃-C₉ cycloalkyl, acyl, and C₃-C₉ cycloalkylalkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, or C₃-C₈ cycloalkenyl or C₃-C₈ cycloalkynyl; and wherein R is selected from cycloalkyl, aryl, heteroaryls (selected from the group consisting of pyridyl, thienyl, furanyl, imidazolyl, pyrazinyl, and pyrimidyl) or phenoxy and wherein said R groups can be substituted with hydroxyl, C₁-C₆ lower alkyl, C₂-C₆ alkenyl, C₁-C₆ lower alkoxy, halo, C₁-C₆ haloalkyl, amino, C₁-C₆ alkylamino and C₂-C₁₀ dialkylamino, and sulfonamido or a pharmaceutically acceptable salt thereof with the proviso that R is not 6-chloro-3-pyridyl and R¹ is not H.

INTERNATIONAL SEARCH REPORT

PCT/US 93/01936

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 C07D487/08; A61K31/44; A61K31/40; //(C07D487/08, 209:00,209:00)		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07D ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹		
Category ^o	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	WO,A,8 502 847 (SANDOZ) 4 July 1985 see claims 1,8	2,4
P,X	----- JOURNAL OF THE AMERICAN CHEMICAL SOCIETY vol. 114, no. 9, 22 April 1992, WASHINGTON, DC US pages 3475 - 3478 J.D. DALY ET AL. 'Epibatidine: A novel (chloropyridyl)azabicycloheptane with potent analgesic activity from an Ecuadoran poison frog' see complete article -----	1-5
<p>^o Special categories of cited documents : ¹⁰</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"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)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"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</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"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.</p> <p>"&" document member of the same patent family</p>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
10 JUNE 1993	21. 06. 93	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	ALFARO FAUS I.	

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 93/01936

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 6 and 7 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.:
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:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. 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 claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9301936
SA 71631

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 10/06/93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-8502847	04-07-85	AU-A- 3409089	21-09-89
		AU-B- 586414	13-07-89
		AU-A- 3707384	04-07-85
		BE-A- 901274	14-06-85
		CH-A- 666268	15-07-88
		DE-A- 3445377	04-07-85
		FR-A, B 2557110	28-06-85
		GB-A, B 2152049	31-07-85
		JP-A- 60226858	12-11-85
		LU-A- 85687	12-09-85
		NL-A- 8403823	16-07-85
		SE-A- 8406585	24-06-85
		US-A- 5001133	19-03-91
