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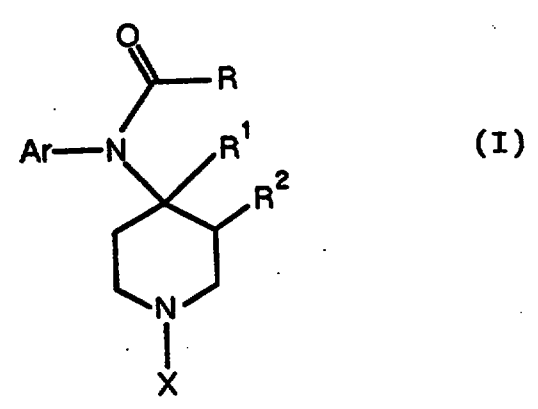
N-Phenyl-N-(4-Piperidinyl)amides Useful as Analgesics

This invention relates to N-phenyl-N-(4-piperidinyl) amides having analgesic activity, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

A number of patents disclose certain N-phenyl-N-(4-piperidinyl) amides having analgesic activity such as for example U.S. Patent No's. 3,164,600; 3,998,834; 4,179,569; 4,584,303 and 4,167,574.

We have now found a novel group of N-phenyl-N-(4-piperidinyl)amides having potent analgesic activity. The compounds differ structurally from the prior art compounds by the particular N substituent on the piperidine ring, i.e. the "X" function indicated in the hereafter formula (I) compounds. In general they also differ by their relatively short durations of analgesic action, ranging from the ultra short to medium range and their non-hepatic means of inactivation.

Thus the present invention provides a compound of formula (I):



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wherein:

X is a member selected from the group consisting of:
alkoxy-carbonyl-lower alkyl (preferred),
5 lower alkyl-carbonyloxy-lower alkyl,
alkenyloxy-carbonyl-lower alkyl, and
(C₁₋₂)alkoxy-(C₁₋₂)alkoxy-carbonyl-lower alkyl.

Ar is a member selected from the group consisting of
10 phenyl (preferred) and mono-, di- and tri-substituted
phenyl, preferably mono-substituted in the 2-position,
wherein each substituent is independently selected from
the group consisting of halo, lower alkyl, lower alkoxy
and trifluoromethyl;

15 R is a member selected from the group consisting of lower
alkyl, preferably ethyl, and lower alkoxy-lower alkyl,
preferably methoxymethyl;

20 R¹ is a member selected from the group consisting of
hydrogen, lower alkoxy-carbonyl, preferably
methoxycarbonyl, and methoxymethyl; and

R² is a member selected from the group consisting of
25 hydrogen and methyl;

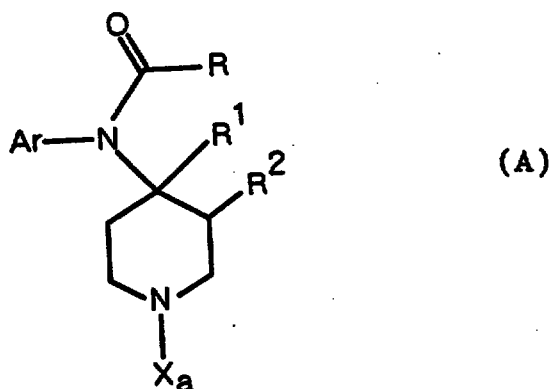
and the optically active and cis-trans isomers thereof, and
the acid addition salts, preferably the pharmaceutically
acceptable acid addition salts, of said compounds and
30 isomers.

An additional aspect of the subject invention
relates to certain novel acidic intermediates which are
useful in the synthesis of certain formula (I) compounds.
Said intermediates are represented by formula (A) wherein X_a

35



is a carboxy-lower alkyl substituent on the ring nitrogen, replacing the aforementioned X-substituent in formula (I):



As used in the foregoing definitions the term "lower" is meant to modify the so-indicated group by indicating from 1 to 4 carbon atoms; the terms "alkyl", "alkoxy" and "alkenyl" are each meant to respectively include straight and branch chained hydrocarbons, e.g. of about 1 to 10 carbons and include the group of hydrocarbons of 1 to 4 carbons; and the term "halo" is generic to halogens of atomic weight less than 127, i.e., fluoro (preferred), chloro, bromo and iodo. The term pharmaceutically acceptable acid addition salts includes all physiologically acceptable acid addition salts.

When the group Ar is a mono, di or trisubstituted phenyl group examples of suitable substituents include chlorine, fluorine, methyl, ethyl, methoxy and trifluoromethyl. When Ar is a disubstituted phenyl group the substituents are preferably in the 2,4 positions e.g. 2,4-difluoro. When Ar is a monosubstituted phenyl group the substituent is preferably at the 4 position or more particularly the 2 position.

A preferred class of compounds of formula (I) are those wherein the group Ar represents a phenyl group or 2-substituted phenyl group, more particularly when Ar represents a phenyl or 2-fluorophenyl group.

When the group R is lower alkyl this may be for example a methyl, ethyl, propyl or butyl group. A preferred class



of compounds of formula (I) are those wherein R represents a methyl, ethyl or methoxymethyl group and more particularly an ethyl group.

Preferred meanings for the group R^1 include hydrogen
5 and methoxycarbonyl more particularly methoxycarbonyl.

For the group X each member contains a lower-alkyl moiety through which it is attached to the nitrogen of the piperidine ring. Suitable lower alkyl moieties include C_{1-4} alkylene chain optionally substituted by a methyl group,
10 for example, methylene, ethylene, propylene, butylene, 1-methylethylene or 2-methylethylene chain.

When X is the group alkoxycarbonyl-lower-alkyl, examples of suitable alkoxy groups include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, secbutoxy,
15 tertbutoxy, pentyloxy, 2-methylbutoxy, isopentyloxy, neopentyloxy, hexyloxy, heptyloxy and octyloxy. Preferred alkoxy groups include methoxy, ethoxy, propoxy, butoxy, isobutoxy, pentyloxy, 2-methylbutoxy, isopentyloxy, hexyloxy, heptyloxy and octyloxy. The lower alkyl moiety of
20 the alkoxycarbonyl loweralkyl group is preferably a C_{2-4} alkylene chain optionally substituted by a methyl group such as an ethylene, 1-methylethylene, 2-methylethylene, propylene or butylene chain, more particularly an ethylene chain.

25 When X is a lower alkylcarbonyloxy-loweralkyl group examples of suitable groups include acetyloxymethyl and acetyloxyethyl groups.

When X is an alkenyloxycarbonyl-loweralkyl group examples of suitable alkenyloxy groups include vinyloxy,
30 allyloxy and butenyloxy. The lower alkyl moiety of the group is preferably ethylene.

When X is the group C_{1-2} alkoxy- C_{1-2} alkoxy-carbonyl-lower alkyl examples of the moiety C_{1-2} alkoxy- C_{1-2} alkoxy include methoxymethoxy, ethoxymethoxy, methoxyethoxy and
35 ethoxyethoxy. The lower alkyl moiety of the group preferably represents an ethylene chain.



A preferred group of compounds of formula (I) are those in which the group R represents a methyl, ethyl or methoxymethyl group; R¹ represents a hydrogen or methoxycarbonyl group; and Ar represents a phenyl or monosubstituted phenyl group, more particularly a phenyl or 2-fluorophenyl group. Within this preferred group of compounds a particular preferred subgroup are those wherein the group X is an alkoxycarbonyl-lower alkyl group, more especially an alkoxycarbonylethyl group; and the optically active and cis-trans isomers thereof and physiologically acceptable salts thereof.

The formula (I) compounds of the invention provide potent analgesia with a duration of action ranging from ultra-short to medium. Such activity is characterized by rapid onset and a half-life generally ranging from about 5 to about 40 minutes in experimental rats. In contrast, the well-known narcotic analgesic, N-(1-phenethyl-4-piperidyl) propionanilide, generically known as fentanyl, and its congeners, sufentanil and alfentanil, have durations of action of 60, 80 and 55 minutes in rats, respectively, and terminal half-lives in humans of about 1.5 to 7 (16 for geriatric patients), 2.5 and 1.2 to 3 hours, respectively (Mather, L.E., Clinical Pharmacokinetics, 1983, 8:422-446). The marked potency and very short duration of analgesia provided by the ultra-short acting compounds of this invention are highly desirable in circumstances where severe pain has to be eliminated over a short period of time, e.g., anesthesiology. With the current preponderance of short surgical procedures and the growing trend towards outpatient surgery, there exists an urgent need for a powerful but short acting analgesic as stated by Dr. Paul A.J. Janssen in Janssen: Opioids in Anesthesia. (Estafanous, F.G., ed.) Butterworth, Boston. (1984). The compounds of the invention can be used together with a pharmaceutically acceptable carrier to provide pharmaceutical compositions and can be



administered to mammals such as man in amounts sufficient to provide analgesic effects.

When X is alkoxy-carbonyl-lower alkyl, e.g. lower alkoxy-carbonyl-lower alkyl, compounds wherein the carbon of the alkoxy directly attached to the oxygen of the alkoxy is a methylene or methyl group, i.e. wherein it is substituted by no more than 1 alkyl group, are generally shorter acting. Further, the lower alkyl of the alkoxy-carbonyl-lower alkyl is, in particular, ethyl of the formula $-\text{CH}_2\text{CH}_2-$.

The formula (I) compounds may be converted to the therapeutically active acid addition salt form by treatment with an appropriate acid, such as, for example, an inorganic acid, such as hydrohalic acid, e.g., hydrochloric, hydrobromic, and the like, and sulfuric acid, nitric acid, phosphoric acid and the like; or an organic acid, such as, for example, acetic, propanoic, hydroxyacetic, α -hydroxypropanoic, 2-oxopropanoic, ethanedioic, propanedioic, butanedioic, (Z)-2-butenedioic, (E)-2-butenedioic, 2-hydroxybutanedioic, 2,3-dihydroxybutanedioic, 2-hydroxy-1,2,3-propanetricarboxylic, benzoic, 3-phenyl-2-propenoic, α -hydroxy-benzeneacetic, methanesulfonic, ethanesulfonic, benzenesulfonic, 4-methylbenzenesulfonic, cyclohexanesulfamic, α -hydroxybenzoic, 4-amino-2-hydroxybenzoic and the like acids. Conversely, the salt form can be converted by treatment with alkali into the free base form. In addition, the salt forms may be useful in the preparation of other salt forms, for example, as intermediates for conversion into the preferred pharmaceutically acceptable salt derivatives. Furthermore, the particular salt may exist as a solvate, e.g., a hydrate or a hemihydrate.

Several of the compounds of formula (I) have one or more asymmetric carbon atoms in their structure and consequently they may exist in the form of different optical isomeric forms or mixtures e.g., racemates, of such forms. When R^2 in formula (I) represents a methyl group there are



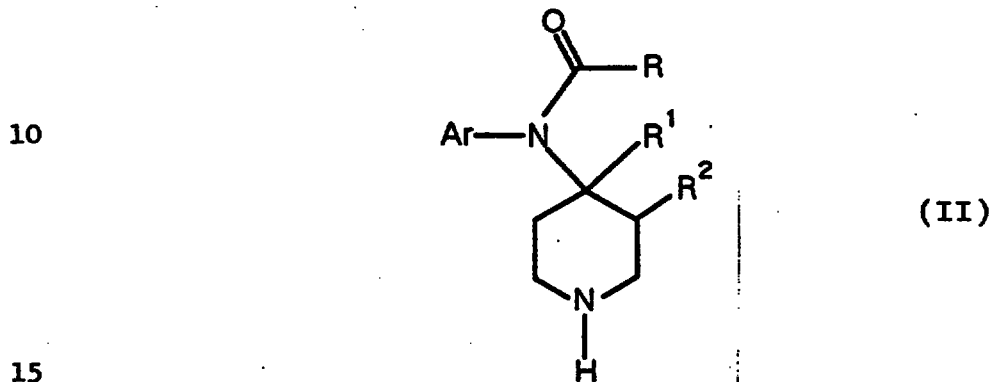
two asymmetric carbon atoms in the piperidine ring. Additional asymmetric carbon atoms may also be present in the X-substituent, for example, when X is $-\text{CH}(\text{CH}_3)\text{CH}_2\text{COOCH}_3$, $-\text{CH}_2\text{CH}(\text{CH}_3)\text{COOCH}_3$ and $-\text{CH}_2\text{COOCH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_3$. Enantiomeric forms and mixtures of such forms may be obtained separately by the application of methods of resolution known to those skilled in the art such as, for example, salt formation with an optically active acid followed by selective crystallization or chiral derivatization and in turn followed by selective crystallization or silica gel chromatography.

When R^2 is a methyl group, the relative position of said methyl group and of the substituents in the 4-position of the piperidine ring with respect to the plane of the piperidine ring may be cis or trans, according to the rules of nomenclature described in "Naming and Indexing of Chemical Substances for C.A. during the Ninth Collective Period (1972-1976) p. 861." Compounds of formula (I) having the cis- or trans-configuration, essentially free of the other, may be obtained, for example, by starting their preparation from pure cis- or trans-isomers of the appropriate precursors. When, for example, an intermediate of formula (XI) in which R^2 stands for methyl is subjected to a selective crystallization, cis- and trans-isomers are obtained separately and the thus-obtained forms are conveniently used in the further synthesis of compounds of formula (I) having the corresponding configuration. Alternatively, substantially pure forms of the cis- and trans-isomer of compounds of formula (I) may be obtained, substantially free of the other isomer, by separating a mixture of such appropriate precursor forms (e.g., see Formula XXI hereinafter) by silica gel chromatography.

Cis- and trans-forms may in turn be further resolved into their optical enantiomers, each essentially free of its optical counterpart, by the application of art-known methodologies such as noted previously.

All racemic and isomeric forms of the compounds of formula (I), including diastereomeric mixtures, pure diastereomers and enantiomers, and mixtures thereof, are intended to be within the scope of this invention.

5 The compounds of formula (I) may generally be prepared by introducing the X substituent on to the piperidine ring nitrogen of an intermediate of the formula (II):



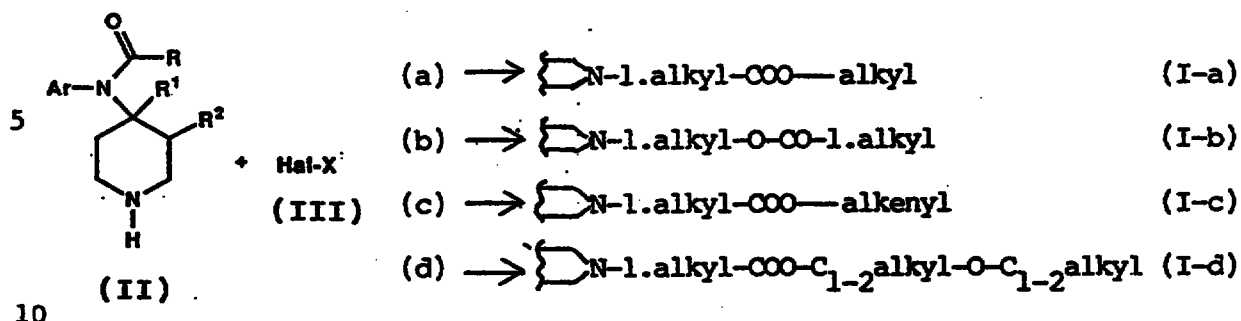
wherein Ar, R, R¹ and R² are as previously defined, by the application of conventional methodologies known in the art. Depending on the nature of the X substituent, the following
20 methods may be utilized therefor.

The compounds of formula (II) are known compounds which are obtainable by art recognized procedures. In addition, the compounds of formula (II) in which R² is methyl and R¹ is hydrogen have been prepared (see examples hereinafter)
25 from 1-methoxy-carbonyl-3-methyl-4-[1-oxopropylaryl-amino]-piperidines, which are in turn prepared from 3-methoxy-carbonyl 4-piperidinone hydrochloride using the procedure described by W.F.M. VanBerer et al., J. Med. Chem. 1974, 17, 1047 and T.R. Burke, Jr., et al., J. Med. Chem. 1986, 29,
30 1087.

The introduction of the aforementioned X groups on to the ring nitrogen of (II) may conveniently be carried out by the alkylation reaction of (II) with an appropriate halide of formula (III) wherein "Hal" is bromo (preferred), chloro
35 or iodo and X represents the aforementioned groups as shown in Scheme I:



Scheme I



Formulae (Ia)-(Id) and other formulae utilize the convention of partial structures to denote the remainder of the formula as in formula (I) hereinabove.

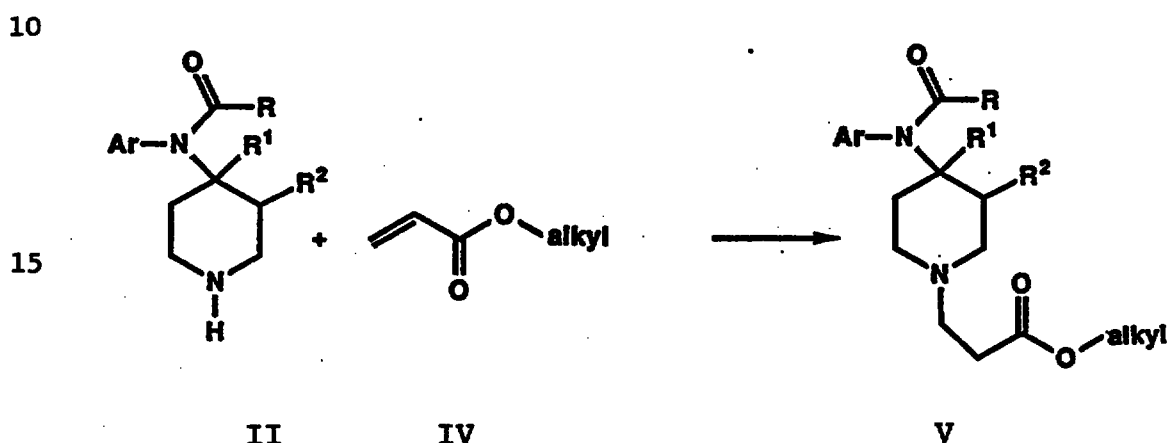
The alkylation reaction of (II) with (III) is conveniently conducted in an inert organic solvent such as, for example, acetonitrile (preferred), an aromatic hydrocarbon, e.g., benzene, methylbenzene, dimethylbenzene and the like; a lower alkanol, e.g., methanol, ethanol, 1-butanol and the like; a ketone, e.g., 4-methyl-2-pentanone and the like; an ether, e.g., 1,4-dioxane, tetrahydrofuran (THF), 1,1-oxybisethane and the like; N,N-dimethylformamide (DMF); nitrobenzene; and the like. The addition of an appropriate base such as, for example, an alkali metal carbonate or bicarbonate, preferably potassium carbonate, may be utilized to neutralize the acid that is liberated during the course of the reaction. In some circumstances, the addition of an iodide salt, preferably an alkali metal iodide such as sodium iodide, is appropriate. Ambient temperatures (22-25°C) are generally sufficient, although somewhat higher temperatures may be employed to enhance the rate of the reaction.

When X is alkoxy-carbonyl-ethyl, wherein the ethyl may be substituted with 1 or 2 C₁₋₂ alkyl groups for a total of 2-4 carbons, an alternative method of introducing this group on to the ring nitrogen of (II) to yield (V) is by way of a



conjugate addition reaction between (II) and an α,β -unsaturated carbonyl reactant of formula (IV) in an inert organic solvent such as, for example, acetonitrile, a lower alkanol, e.g., methanol, ethanol and the like, an ether, e.g., diethyl ether, dioxane and the like; and an aromatic hydrocarbon, e.g., benzene, toluene and the like as shown, for example, in Scheme II.

Scheme II

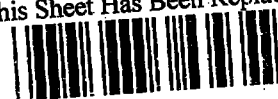


20 When X is alkoxy-carbonyl-loweralkyl in (I-a) or alkenyloxy-carbonyl-loweralkyl in (I-c), an alternative method of introducing said X-substituent onto the piperidine nitrogen is by esterification of the corresponding acidic formula (A) compounds, i.e., formula (I) wherein X is

25 carboxy-loweralkyl such as (VI), using the appropriate alkyl or alkenyl N,N-diisopropyl-pseudourea in an organic solvent, for example, chloroform, at ambient to reflux temperatures. The acids of formula (A), e.g. where X_a is a carboxyethyl thus defining (VI), are believed to be novel intermediates,

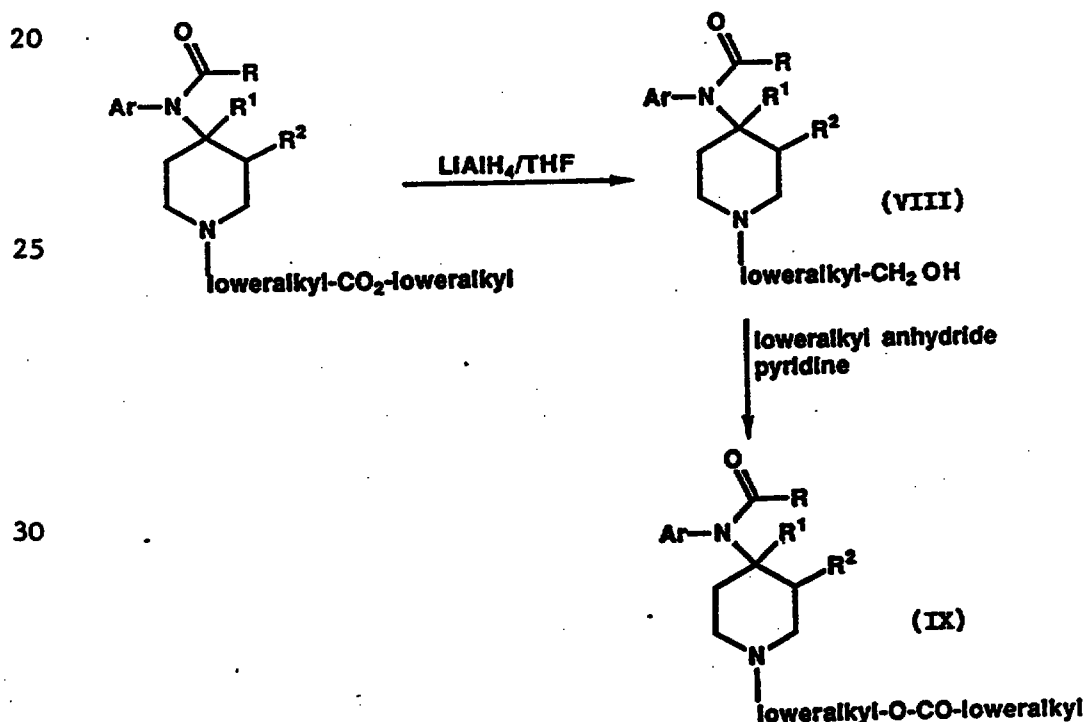
30 may be obtained by reacting (II) with an appropriate t-butyl ester of formula (III) or tertiary butyl acrylate (Michael Reaction) followed by reacting the thus-obtained product, e.g. (VII), with excess trifluoroacetic acid at 0°C to

35 ambient temperatures according to the following Scheme III:



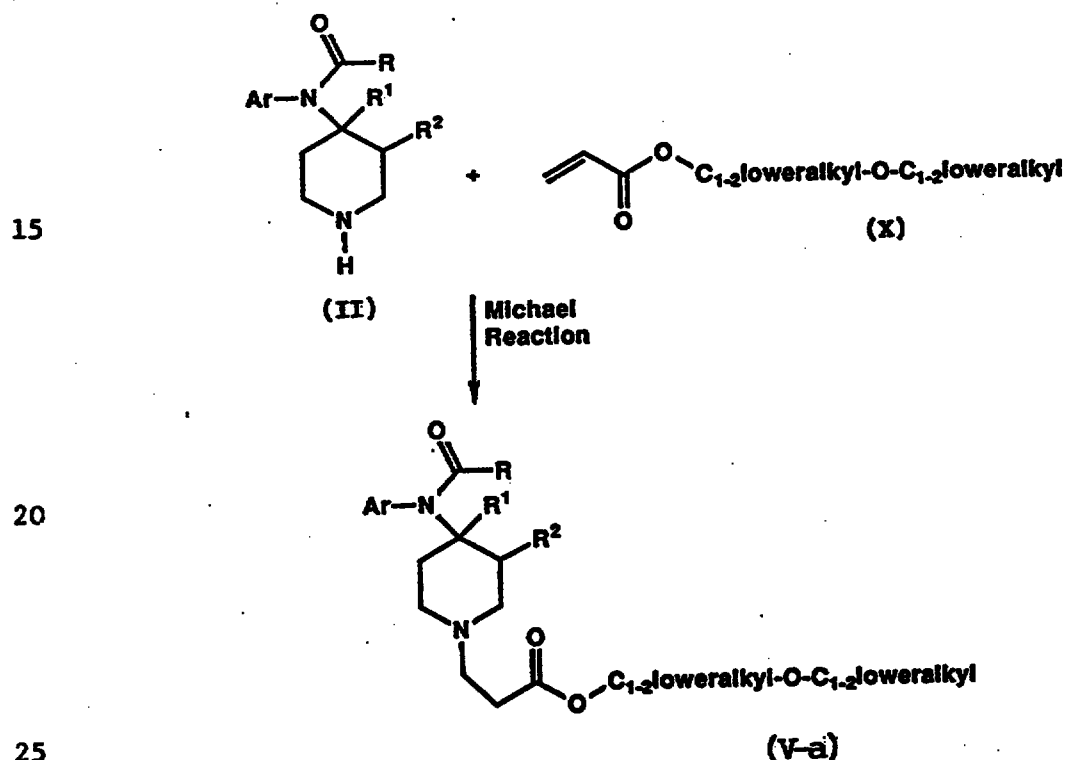
In both Scheme III and IV, when R^3 is alkenyl, the double bond is not directly attached to the oxygen of the OR^3 . In addition, the $CH_2=CH-COOH$ starting material may be substituted by $R^4R^5C=CR^6COOH$ wherein R^4 , R^5 and R^6 are as defined above. An alternative method of preparing the formula (I) compounds wherein X is loweralkyl-carbonyloxy-loweralkyl and R^1 is hydrogen or methoxymethyl is by reduction of the corresponding ester (I-a) to the corresponding alcohol (VIII), for example, by conventional lithium aluminum hydride reduction in ether solution, preferably THF, at ambient temperatures. The thus-obtained alcohol (VIII) is then transformed into the reverse ester (IX) by reaction with an appropriate loweralkyl anhydride, for example, acetic acid anhydride, propionic acid anhydride, and the like, in an organic solvent such as pyridine. This is shown in the following Scheme V wherein X is in formula (I-a) is loweralkyl- CO_2 -loweralkyl:

Scheme V



When X is C₁₋₂alkoxy-C₁₋₂alkoxy-carbonyl-ethyl, wherein the ethyl may be substituted with 1 or 2 C₁₋₂ alkyl groups for a total of 2-4 carbons, the introduction of this group on to the ring nitrogen of (II) may conveniently be carried out by the reaction of (II) with an α,β -unsaturated carbonyl reactant of formula (X) according to standard Michael Reaction conditions and solvents, acetonitrile being preferred, to yield the corresponding N-substituted product (V-a) as shown in Scheme VI:

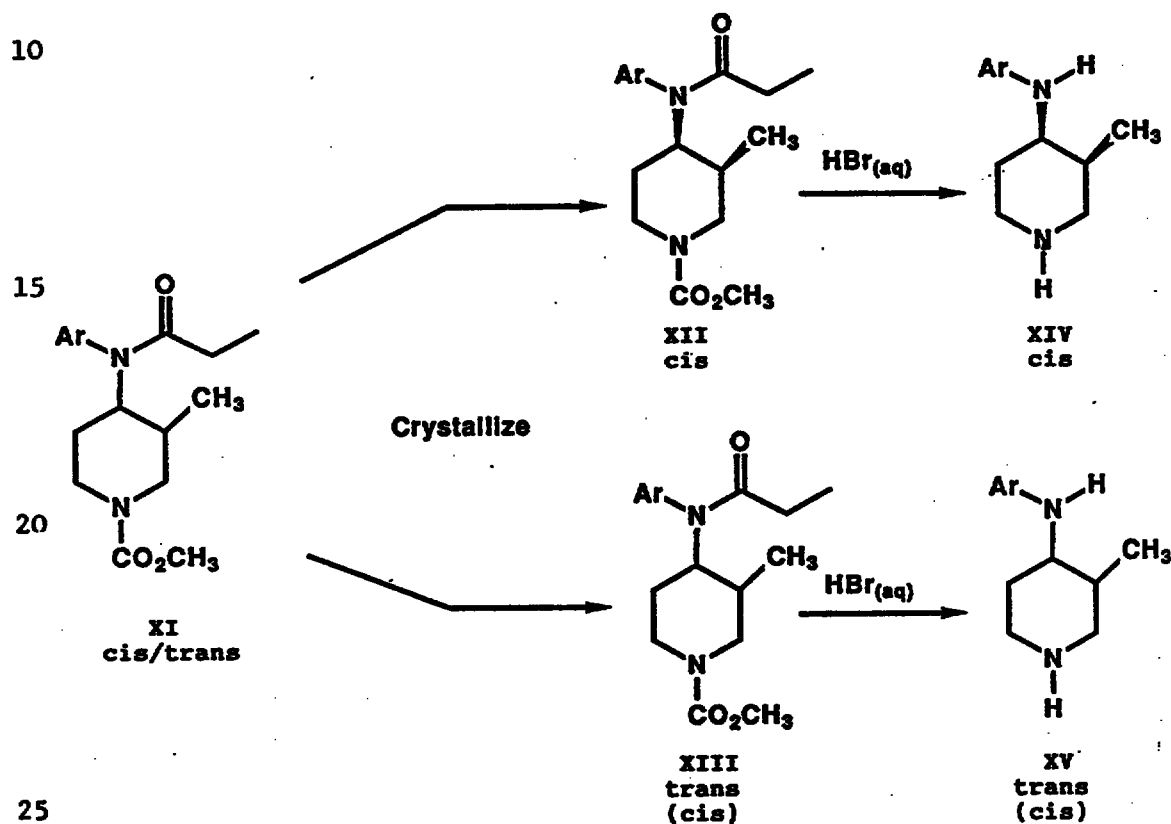
10 Scheme VI



The compounds of formula (X) having a C₁₋₂alkoxy-methoxy-carbonyl-ethyl function are obtained by the reaction of acrylic acid with an appropriate dialkoxyalkane such as dimethoxymethane and diethoxymethane in the presence of phosphorous pentoxide. The acrylic acid may be substituted by other acids of the formula R⁴R⁵C=CR⁶COOH to yield other products within the invention. The compounds of formula (X) having a C₁₋₂alkoxy-ethoxy-carbonyl-loweralkyl function are available from commercial suppliers.

As noted previously, the formula (I) compounds are capable of existence in diastereomeric and enantiomeric forms. The following schematic descriptions exemplify particular synthetic paths for preparing such diastereomers and enantiomers as pure materials starting with appropriate precursors.

Scheme VII



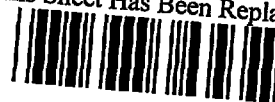
As depicted in Scheme VII, the cis/trans mixture (XI) is conveniently used as the starting material. Standard crystallization procedures using organic solvents such as ethyl acetate, ether/hexane and the like, affords separation of the corresponding pure cis isomer (XII) in crystalline form and the corresponding trans isomer (XIII) in the mother liquor with some residual cis isomer. The pure cis isomer (XII), essentially free of the corresponding trans isomer,



and the predominantly trans isomer (XIII) are each converted to the corresponding 3-methyl-4-arylaminopiperidines of respective formulas (XIV) and (XV) by treatment with a concentrated hydrohalic acid (hydrobromic acid preferred) at
5 reflux temperature. Subsequently, the resultant pure crystalline cis isomer (XIV) may then be recovered and utilized in the further synthetic pathways depicted in Scheme VIII to obtain the formula (I) final products in the corresponding cis form.

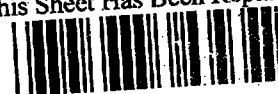
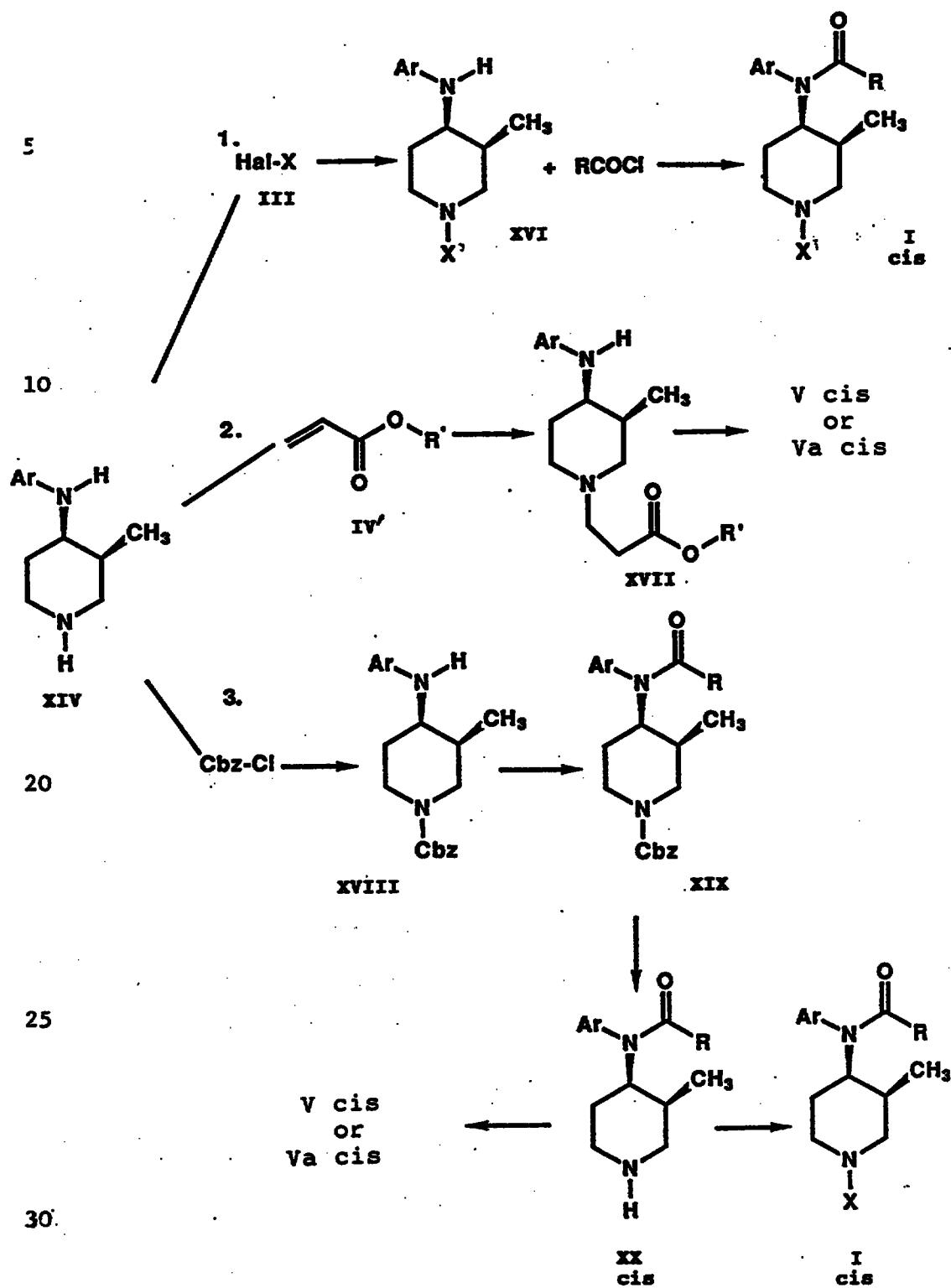
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Scheme VIII



As shown in pathway 1 of Scheme VIII, the cis precursor (XIV) is subjected to the previously described alkylation reaction with a formula (III) halide to yield the corresponding N-substituted compounds of formula (XVI).

5 Acylation of the arylamino group in (XVI) with an appropriate acid chloride (RCOCl in which R is as previously defined) provides the respective formula (I) compounds in cis form. The acylation reaction is conveniently carried out utilizing an appropriate 4-dialkylaminopyridine as an
10 acylation catalyst and a polar aprotic solvent such as acetonitrile (preferred), dimethyl formamide, hexamethyl phosphoramide and the like at temperatures ranging from 40° to 85°C. Other formula (I) compounds where R¹ and R²=H can be produced by using the respective (XVI) compounds.

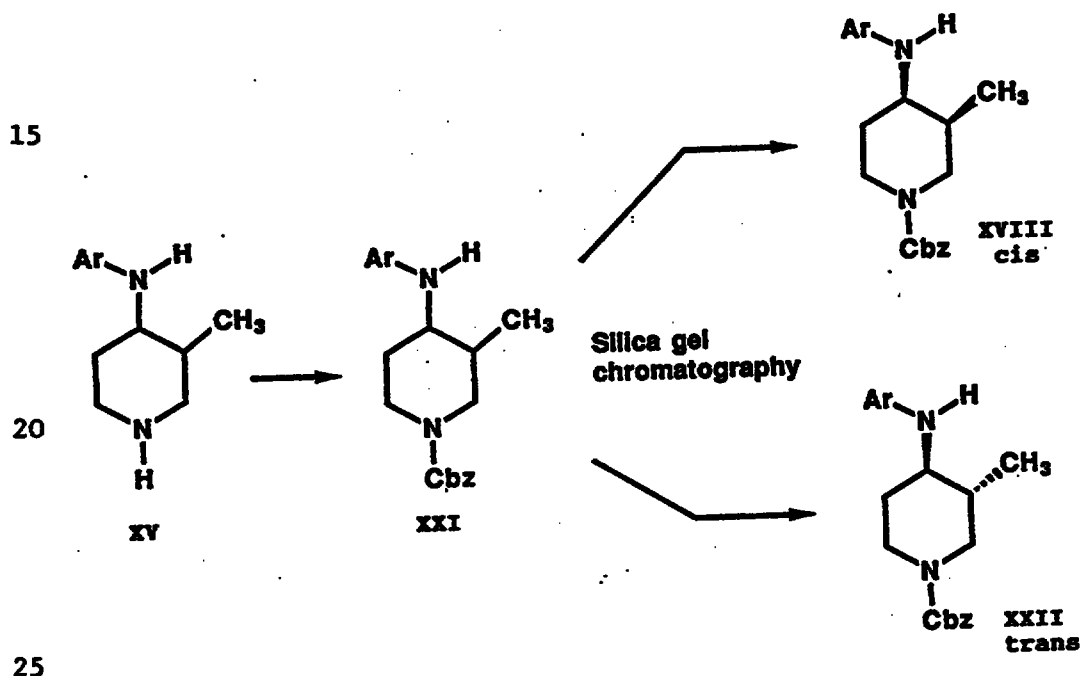
15 Pathway 2 of Scheme VIII depicts the alternative route for introducing an alkoxy-carbonyl-ethyl or C₁₋₂alkoxy-C₁₋₂alkoxy-carbonyl-ethyl substituent on to the ring nitrogen of (XIV) by the previously described conjugate addition (Michael addition) reaction with an α,β-unsaturated
20 carbonyl reactant of formula (IV') to yield the corresponding cis form of (XVII) which is then acylated with RCOCl as previously described to yield cis product forms of (V) or (V-a). The symbol R' in Scheme VIII represents alkyl, C₁₋₂alkoxy-C₁₋₂alkyl or alkenyl. By analogy to
25 previous schemes, the acrylic ester of formula (IV') may be substituted by R⁴R⁵C=CR⁶COOR' or alkyl.

Alternative routes for synthesizing cis-(I), cis-(V) and cis-(V-a) are depicted in pathway 2 of Scheme VIII. Reaction of the cis precursor (XIV) with benzylchloroformate (Cbz-Cl) using Schotten-Baumann conditions, two phases
30 consisting of water and an ether, e.g., diethyl ether, tetrahydrofuran, dioxane and the like, in the presence of an appropriate base, e.g., sodium carbonate or bicarbonate, alkali metal (sodium preferred) hydroxide and the like, to scavenge the released acid during the reaction, at about
35 0-35°C, provides the ring substituted compounds of formula (XVIII), wherein Cbz = benzyloxycarbonyl. Similar acylation



of the arylamino group in (XVIII) with RCOCl provides the corresponding amides (XIX). Conventional hydrogenolysis of the benzylcarbamate function of (XIX), for example, with hydrogen at 1-3 atmospheres of pressure in the presence of a catalyst (such as Pd-C) in a mixture of an organic alkanol (such as methanol and ethanol) and acetic acid at ambient temperature provides the cis precursor (XX) wherein the ring nitrogen is unsubstituted. The cis precursor (XX) is then converted to the cis final products of formulas (I), (V) or (V-a) by the respective alkylation and Michael additional methodologies previously described using (XX) as the (II) compound.

Scheme IX



As indicated in Scheme VII, the trans derivatives (XIII) and (XV) contain some residual corresponding cis isomer. However, final products of formula (I) in pure trans form may be obtained from the trans(cis) derivative (XV) by the purification methodology depicted in Scheme IX. The trans(cis) derivative (XV) is converted to the corresponding trans(cis) N-benzyloxycarbonyl derivative (XXI) under Schotten-Baumann conditions as previously



described. The trans(cis) isomers of (XXI) are separable by flash silica gel chromatography (for example, see W. C. Still et al, J. Org. Chem., 1978, 43, 2923) to yield cis (XVIII) and trans (XXII) isomers, each substantially free
5 from the respective corresponding isomeric form. The thus-obtained trans isomers may then be converted to the respective trans form of final products (I) by application of the methodologies heretofore described for the corresponding cis compounds (e.g. pathway 3 of Scheme VIII).

10 A methodology for synthesizing the corresponding optically isomeric (+) and (-) forms of the pure cis and trans isomers is depicted in Scheme X. For illustration purposes, the racemic cis isomers of formula (XIV) are shown as the starting material, although the corresponding racemic trans isomers can similarly be utilized.

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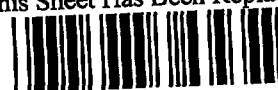
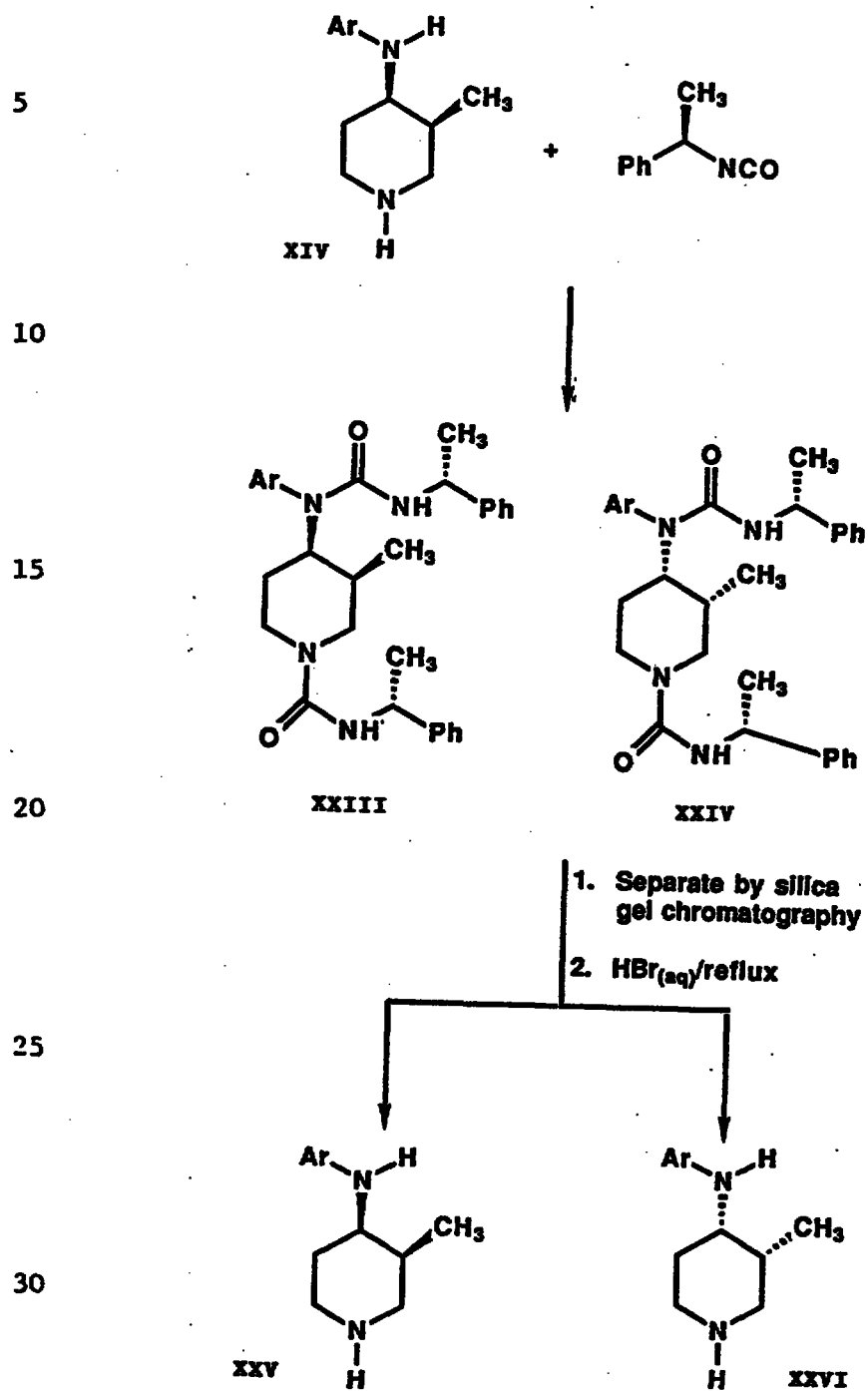
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Scheme X



Reaction of racemic cis (XIV) with R- α -methylbenzyl isocyanate at elevated temperatures (about 100-150°C) in the presence of an appropriate 4-dialkylaminopyridine catalyst generates the racemic mixture of diastereomeric compounds (XXIII) and (XXIV) which are separable by flash silica gel chromatography. Each of the separated diastereomers are then converted to the respective enantiomeric piperidines (XXV) and (XXVI) by treatment with refluxing hydrobromic acid which, in turn, may then be used as the starting precursor for preparing the corresponding form of the formula (I) compounds in accordance with the previously described methodologies in Scheme VIII.

The compounds of formula (I) and the isomeric forms and pharmaceutically acceptable acid addition salts thereof are useful analgesics, as demonstrated, for example, in experimental animals. Typical of the in vitro and in vivo testing procedures for analgesic activity are the guinea pig ileum assay and the rat tail withdrawal assay, respectively.

A. Guinea Pig Ileum Assay (in vitro):

Compounds are tested for opioid activity in the isolated guinea pig ileum using the method of Kosterlitz, H.W. and Watt, A.J., Br. J. Pharmacol. 33:266-276 (1968) with modifications found in James, M.K. and Leighton, H.J., J. Pharmacol. Exp. Ther. 240:138-144 (1987). The terminal ileum is removed from male Hartley guinea pigs after sacrifice by cervical dislocation. The isolated ileum is washed and placed in Krebs-Henseleit buffer oxygenated with 95% O₂ and 5% CO₂ mixture and maintained at 37°C. The washed ileum is cut into segments (2.0-2.5 cm) and mounted on platinum ring electrodes. The ileal segments are then placed in 10 ml temperature-controlled tissue baths containing oxygenated Krebs-Henseleit buffer. The tissues are connected to force-displacement transducers and stretched to a resting tension of 1.0 gram. The composition

of Krebs-Henseleit buffer is as follows (millimolar): NaCl, 118.1; KCl, 4.15; CaCl₂, 2.5; MgSO₄, 1.2; KH₂PO₄, 1.23; NaHCO₃, 25.5 and glucose, 11.1.

The ileal segments are stimulated at 0.1 Hertz, 0.5
5 milliseconds duration at a supramaximal voltage to induce
contractions. Opioid activity in the test compounds is
manifested as inhibition of electrically evoked
contractions. A non-cumulative concentration-effect curve
for each test compound is performed to assess the ability of
10 the compound to inhibit contraction in the guinea pig ileum.
After the concentration-effect curve is completed, naloxone
is added to the tissue baths to determine if the
compound-induced inhibition of contraction is reversed.
Antagonism of the inhibition by naloxone confirms that the
15 inhibitory effects of the compounds are mediated through
opioid receptors. Assay results are expressed as EC₅₀
values (a measure of potency), defined as the concentration
producing fifty percent of the maximal response, and is
expressed in molar units (moles of compound/liter).

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B. Rat Tail Withdrawal Assay (in vivo).

The analgesic efficacy of test compounds are evaluated
in a rat tail withdrawal reflex model modified from D'Amour,
F.E. and Smith, D.L., J. Pharmacol. Exp. Ther. 72:74-79
25 (1941). Male Sprague-Dawley rats are anesthetized and
implanted with femoral vein cannulae and allowed to recover
overnight. After recovery, the test compounds are
administered intravenously through the cannula and effects
on tail withdrawal latency are measured. Tail withdrawal
30 latency is measured as the time to tail movement by the rat
after exposure of the tail to a radiant heat source. The
heat source is calibrated to produce a temperature of 62°C
after 15 seconds. Tail withdrawal latency in the absence of
drugs is six to eight seconds. Test compounds demonstrating
35 analgesic activity prolong tail withdrawal latency beyond
that seen in the absence of drugs. A maximal latency



cut-off of fifteen seconds is imposed to prevent tissue damage. The assay is verified with known opioids as standards. Results of these studies are expressed as ED₅₀ values, calculated as the dose producing a tail withdrawal latency equal to half the difference between the maximum
5 latency (15 seconds) and the baseline latency (six to eight seconds). ED₅₀ values are expressed as milligrams of compound/kilogram of body weight. Duration of action is defined as the time (in minutes) necessary for the tail
10 withdrawal response to return to baseline values after being elevated in response to drug administration. Duration of action is measured at the lowest dose producing a fifteen second (maximum) tail withdrawal latency.

15 In Table I, test results obtained from the aforementioned A. guinea pig ileum assay and B. rat tail withdrawal assay are listed for the indicated compounds of formula (I). Said results are not given for the purpose of limiting the invention to said compounds but to exemplify
20 the analgesic activity of all compounds within the scope of formula (I). For comparison purposes, test results obtained for three well known 4-anilidopiperidine analgesics, fentanyl, sufentanil and alfentanil, are also listed.

25

30

35



TABLE I

<u>Compound of Example</u>	<u>Assay A</u>	<u>Assay B</u>	<u>Assay B</u>
	<u>EC₅₀ (molar)</u>	<u>ED₅₀ (mg/kg)</u>	<u>Duration of Action (min)</u>
2 - maleate	1.66 $\pm$ 0.59x10 ⁻⁶	3.2	10-15
3 - maleate	3.60 $\pm$ 0.30x10 ⁻⁶	3.4	10
6 - HCl	2.62 $\pm$ 0.62x10 ⁻⁶	4.7	5-10
7 - oxalate	3.71 $\pm$ 0.20x10 ⁻⁷	13.4	5-10
8 - oxalate	1.03 $\pm$ 1.00x10 ⁻⁵	-	-
10 - oxalate	3.55 $\pm$ 0.23x10 ⁻⁹	0.0044	15
12 - oxalate	1.02 $\pm$ 0.63x10 ⁻⁸	0.8	30
14 - oxalate	6.89 $\pm$ 1.61x10 ⁻⁹	1.4	15
15 - oxalate	5.11 $\pm$ 0.24x10 ⁻⁷	<0.03	10
16 - oxalate	6.72 $\pm$ 2.10x10 ⁻⁸	0.016	25
17 - oxalate	3.47 $\pm$ 0.53x10 ⁻⁷	0.028	15
18 - oxalate	2.13 $\pm$ 0.30x10 ⁻⁶	>3.0	-
19 - oxalate	1.18 $\pm$ 0.20x10 ⁻⁷	>3.0	-
20 - oxalate	4.95 $\pm$ 0.09x10 ⁻⁶	1.4	25
21 - oxalate	2.18 $\pm$ 0.18x10 ⁻⁶	1.4	15
22 - HCl	1.98 $\pm$ 0.21x10 ⁻⁸	<0.03	30
23 - oxalate	7.51 $\pm$ 0.81x10 ⁻⁸	0.51	10
24 - oxalate	1.64 $\pm$ 0.10x10 ⁻⁸	>3.0	-

(TABLE I continued next page)



TABLE I Continued

25 - oxalate	$1.47 \pm 0.09 \times 10^{-7}$	0.052	5
27 - HCl	$9.29 \pm 6.36 \times 10^{-9}$	<0.003	10
29 - oxalate	$2.23 \pm 1.00 \times 10^{-8}$	0.14	10
34 - HCl	$6.63 \pm 1.96 \times 10^{-8}$	0.0052	10
35 - oxalate	$1.22 \pm 0.09 \times 10^{-8}$	0.26	20
36 - oxalate	$6.87 \pm 0.83 \times 10^{-9}$	-	-

fentanyl	$1.76 \pm 0.36 \times 10^{-9}$	0.0046	60
sufentanil	$7.43 \pm 1.53 \times 10^{-9}$	0.0013	80
alfentanil	$2.01 \pm 0.12 \times 10^{-8}$	0.0045	55

The results in Table I illustrate that the subject compounds have opioid activity as demonstrated by naloxone-reversible inhibition of electrically evoked contraction in the guinea pig ileum. The most preferred compounds are those potent analgesics which also have unexpectedly short durations of action, as compared to known compounds of the 4-anilidopiperidine series (fentanyl, sufentanil and alfentanil). Among the most preferred compounds are:

1. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester (Example 10);
2. 5-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]pentanoic acid, methyl ester (Example 12);
3. 2-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]ethyl acetate (Example 16);



4. 3-[4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]-
propanoic acid, methyl ester (Example 17);

5. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-
5 piperidine]propanoic acid, vinyl ester (Example 15B);

and the pharmaceutically acceptable isomers and salts
thereof. A particular group of compounds of the invention
are the alkyl esters of 3-[4-methoxycarbonyl-4-[(1-oxopropyl)-
10 phenylamino]-1-piperidine]propanoic acid and their
pharmaceutically acceptable salts.

The aforementioned properties of the most preferred
compounds are extremely beneficial in that they allow more
control over the level of analgesia in a surgical setting or
15 other situation where precise control of opioid levels are
necessary or desirable. These properties would also allow
for more rapid recovery after the conclusion of a surgical
procedure or after the use of these compounds in other
circumstances.

20 In addition, to their analgesic activity, the compounds
(I) of this invention may be subject to extensive metabolism
in blood as well as potential metabolism in the liver, as
has been typically observed with the most preferred
compounds. In contrast, fentanyl and alfentanil are
25 reported to be primarily metabolized in the liver in humans,
for example, see McClain, D.A. and Hug, Jr., C.C., Clin.
Pharm. Ther. 28:106-114 (1980), and Schuttler, J. and
Stoeckel, H., Anesthesist 31:10-14 (1982). Rapid
30 elimination or biotransformation to inactive or less active
products would minimize accumulation with prolonged or
repeated administration. This property has been cited as
one of the properties of an "ideal" intravenous analgesic or
anesthetic (White, P.F., Anesthesia and Analgesia 68:
35 161-171 (1989)). In addition, rapid degradation of an
opioid analgesic to inactive or less active products in the
blood, as occurs with the neuromuscular blocker,



succinylcholine, would allow more predictable correlation of dose with duration of pharmacologic effect (Stanski, D.R. and Hug, C.C., Jr. Anesthesiology 57: 435-438 (1982)).

This non-hepatic means of inactivation may be demonstrated with one of the most preferred compounds, 3-[4-methoxycarbonyl-4-[(1-oxo-propyl)phenylamino]-1-piperidine]propanoic acid, methyl ester, as the hydrochloride salt (Test Compound), which is found to be rapidly degraded in rat and human blood in vitro whereas fentanyl, sufentanil and alfentanil are found to degrade at a much slower rate.

The relative assay using rat blood is performed as follows. One hundred microliters of fresh heparinized rat blood is placed in eighteen 15-ml plastic centrifuge tubes. The tubes are then placed in a temperature-controlled water bath at 37°C for 2 minutes. At that time, 2 ug (at a concentration of 1 ug/ml in water) of the Test Compound (12 tubes), fentanyl (2 tubes), sufentanil (2 tubes) and alfentanil (2 tubes) are added to each tube. Two tubes containing the Test Compound are removed at the following times: 0.5, 1.0, 2.0, 5.0, 10.0 and 20.0 minutes. Two tubes each containing the fentanyl, sufentanil and alfentanil are removed after 60 minutes. Immediately after removal from the water bath, 500 ng of an internal standard is added (4-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]butanoic acid, methyl ester oxalic acid salt (Example 11) at 0.1 ug/ml in water), the solution briefly mixed, and 900 ul of a saturated solution of sodium carbonate is added. After addition of the sodium carbonate solution, the tube contents are mixed and 10 ml of n-hexane is added.

The aqueous phase is mixed with the n-hexane phase for 10 minutes and centrifuged at 2000 x g for 10 minutes. The n-hexane layers are removed, placed in clean tubes and evaporated to dryness under a stream of dry nitrogen. To the residue from the evaporation, 100 ul of ethyl acetate is added, mixed and the solution analyzed by gas-liquid



chromatography. 1 Microliter aliquots of the ethyl acetate solution are injected into a gas chromatograph fitted with a 0.32 mm (internal diameter) x 15 m column coated with DB5 (brand name of J&W Scientific, Rancho Cordoba, CA for a 5% diphenylpolysiloxane and 95% dimethylpolysiloxane mixture) to a film thickness of 0.25 μ . The injector port is held at 280°C. The detector is a nitrogen phosphorous detector held at 270°C, and the carrier gas is helium at a flow rate of 2 ml/minute. The column is held at 45°C for one minute after injection; then heated to 270°C at a rate of 25°C/minute, and held at 270°C for seven minutes. Under these conditions, the internal standard has a retention time of 11.6 minutes. The Test Compound, fentanyl, sufentanil and alfentanil have retention times of 11.0, 12.1, 12.8 and 14.3 minutes, respectively.

In this study, it has been found that more than 90% of the Test Compound disappeared after incubation for 30 seconds, whereas 65%, 85% and 75% of the added sufentanil, alfentanil and fentanyl are still present at the end of a one hour incubation period. These results demonstrate that the Test Compound is rapidly degraded in rat blood in vitro in contrast to the three comparative compounds, which degrade at a very slow rate. As a consequence of these findings, the analgesic compounds of this invention may be subject to extensive metabolism in blood as well as potential hepatic metabolism. This property is viewed as advantageous because it offers an alternative means of inactivating the analgesic compound and thereby could produce a predictable pharmacokinetic profile.

Beyond 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester this non-hepatic means of inactivation may be demonstrated with the related ethyl, propyl, butyl, isopropyl, isobutyl and sec-butyl esters. These compounds (test compounds below in Table II) have been found to be rapidly degraded in human blood when compared to their degradation in phosphate buffer.

The relative assay using human blood is performed as follows. Twenty ml of fresh, heparinized human blood is placed in a temperature-controlled water bath at 37°C for 10 minutes. At that time, 400 µl of 2 mg/ml solution of the
5 test compound is added to the blood to give a blood concentration of 40µg/ml of the test compound. Solutions of the test compounds are prepared just before the assay was started. Two 500 µl of blood are withdrawn at various timepoints for measurement of the test compound and the
10 propanoic acid formed by ester hydrolysis. A trial run was performed with each test compound and thereafter timepoints were set for sampling over two to three half-lives. Chemical hydrolysis is measured by incubating the test compounds in phosphate buffer (0.1 M, pH=7.4) instead of
15 blood. Duplicate samples are taken at 1, 30, 60, 120, 180, 240 and 300 minutes.

Acetonitrile (700 µl) is added to the samples removed from the incubation mixture along with 50 µl of a solution of the internal standard (4-[4-methoxycarbonyl-4-[(1-oxopropyl)-
20 phenylamino]-1-piperidine]butanoic acid, methyl ester, 0.12 mg/ml in acetonitrile). Samples are mixed and immediately centrifuged at 30,000 x g for 10 minutes. The supernatant is removed and cooled to 8°C. Twenty microliters of the supernatant is injected into the high performance liquid
25 chromatograph (HPLC) for analysis.

The HPLC analysis is performed using a 5µ Spherisorb CN column (250 x 4.6 mm)(Keystone Scientific, Inc., State College, PA) with a flow rate of 2 ml/min. The mobile phase for the assay is 0.1 M phosphate buffer (pH=2.0) and
30 acetonitrile in a gradient elution. Acetonitrile is increased from 10-11% at 0 to 5 minutes to 16% by 10 minutes. Acetonitrile is maintained at 16% through the remainder of the elution (16 minutes inclusive). These conditions provide for resolution of the propanoic acid
35 formed by ester hydrolysis, the internal standard and all of the test compounds except the ethyl ester. Retention times



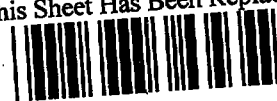
are (in minutes): propanoic acid 5.1; methyl ester 7.5; internal standard 8.6; ethyl ester 9.0; isopropyl ester 11.1; propyl ester 11.8; sec-butyl ester 13.9; iso-butyl ester 14.4.; and butyl ester 14.9.

5 Slowing the flow rate to 1 ml/minute allows the resolution of the ethyl ester from the internal standard. At this flow rate the retention times are 10.1 minutes for the propanoic acid, 15.1 minutes for the internal standard and 15.8 minutes for the ethyl ester. Elution of these
10 substances is detected by monitoring ultraviolet absorption at a wavelength of 220 nm.

Data from the HPLC assay is analyzed by a simple pseudo-first order kinetic model for disappearance of the test compounds. Pseudo-first order rate constants were
15 calculated for each test compound from these data along with the apparent half-lives in minutes ($t_{1/2}$). These results are shown in Table II below for the various esters of 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propionic acid. Where k_{Bu} is the pseudo-first order
20 rate constant for degradation of the test compounds in phosphate buffer and k_{Bl} is the similar constant for degradation in blood.

TABLE II

25	<u>Ester</u>	k_{Bu}	<u>Buffer</u>	k_{bl}	<u>Blood</u>
			$t_{1/2}$		$t_{1/2}$
	methyl	$7.4 \pm 0.6 \times 10^{-3}$	94	$2.0 \pm 0.1 \times 10^{-2}$	36.5
30	ethyl	$4.6 \pm 0.2 \times 10^{-3}$	150	$1.8 \pm 0.7 \times 10^{-2}$	38.5
	propyl	$3.0 \pm 0.5 \times 10^{-3}$	231	$2.5 \pm 0.3 \times 10^{-2}$	27.7
	butyl	$3.0 \pm 0.5 \times 10^{-3}$	231	$8.5 \pm 0.6 \times 10^{-2}$	8.2
	isopropyl	$1.3 \pm 0.5 \times 10^{-3}$	533	$1.0 \pm 0.1 \times 10^{-2}$	69.3
	isobutyl	$4.0 \pm 0.6 \times 10^{-3}$	173	$9.0 \pm 2.0 \times 10^{-2}$	7.7
35	secbutyl	$2.0 \pm 0.2 \times 10^{-3}$	346	$9.0 \pm 1.0 \times 10^{-3}$	77.0



In this study, it was found that the test compounds were rapidly degraded in blood as compared to buffer. The test compounds were found to be rapidly degraded in human blood in vitro in contrast to the marketed compounds, fentanyl, sufentanil and alfentanil, which have been found to be primarily metabolized in the liver in vivo see D.A. McClain et al, Clin. Pharm. Ther. 28:106-114 (1982). As demonstrated in this study, the analgesic compounds of this invention may be subject to extensive metabolism in blood as well as potential hepatic metabolism. This property is viewed as advantageous because the compounds of this invention would not depend on redistribution for the termination of their effects and thereby would likely have a more consistent and predictable pharmacokinetic and pharmacodynamic profile.

In view of their analgesic activity, the subject compounds may be formulated into various pharmaceutical forms for administration purposes. To prepare the pharmaceutical compositions of this invention, an effective analgesic amount of the particular compound, in base or acid-addition salt form, as the active ingredient is combined in intimate admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirable in unitary dosage form suitable, for example, for administration orally, transdermally, rectally or parenterally. For example, in preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid pharmaceutical carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. For parenteral compositions,



the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included. Injectable solutions, for example may be prepared in which the carrier comprises
5 isotonic saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. Acid addition salts of (I), due to their increased water
10 solubility over the corresponding base form, are obviously more suitable in the preparation of aqueous compositions.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage.
15 Dosage unit form, as used herein, refers to physically discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated in product the desired therapeutic effect in association with the required pharmaceutical carrier.
20 Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonsfuls and the like, and segregated multiples thereof.

In view of the analgesic activity of the subject
25 compounds, it is evident that the present invention provides a method of preventing or combatting pain, that is, providing analgesia, in warm-blooded mammals, including humans, by the systemic administration of an effective analgesic amount of a compound of formula (I) or a
30 pharmaceutically acceptable isomer or acid addition salt thereof in admixture with a pharmaceutical carrier. Although the amount of active ingredient to be administered may vary within rather wide limits, depending on the particular circumstances of the case, doses of from about
35 0.001 to about 10 mg/kg, and preferably from about 0.01 to about 1.0 mg/kg, administered once, repeatedly or



continuously (e.g., i.v. drip), are generally found effective. The preferred route of administration is parenteral, particularly by the intravenous route.

The following examples are intended to illustrate, and not to limit the scope of the present invention.

Example 1

4-[(1-Oxopropyl)phenylamino]-1-piperidineacetic acid, methyl ester

A mixture of 4-[(1-oxopropyl)phenylamino]-piperidine (500mg, 2.15mmol), prepared according to the procedure of P.A.J. Janssen et al, U.S. Patent 3,164,600, methyl bromoacetate (0.25ml, 2.58mmol), and potassium carbonate (594mg, 4.3mmol), in acetonitrile (2.5 ml) is stirred at room temperature for five hours. The reaction mixture is diluted with 1:1 water and ethyl acetate (20 ml total). The phases are separated and the aqueous phase extracted with ethyl acetate (2x) and the combined organics washed with brine, dried over sodium sulfate and then concentrated. The residue is chromatographed on silica gel (95/5 CHCl₃/MeOH) to give 4-[(1-oxopropyl)phenylamino]-1-piperidineacetic acid, methyl ester, as an oil: 348mg, 53% yield. An equimolar amount of maleic acid in ether is added to a solution of the free base in ethyl acetate to give the maleate salt as a white solid; maleate salt: m.p. 130-133°C.

Elemental Analysis for C₂₁H₂₈N₂O₇:

	C%	H%	N%
Found:	59.7	6.8	6.6
Calculated:	60.0	6.7	6.7

Example 2

3-[4-[(1-Oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester

To a solution of 4-[(1-oxopropyl)phenylamino]-piperidine (1.0gm, 4.31mmol) in acetonitrile (10ml) is added



methyl acrylate (776 μ l, 8.62mmol) at room temperature. The solution is stirred at 50°C for 2 hours, cooled to room temperature and concentrated to an oily residue. The residue is chromatographed on silica gel (EtOAc) to yield
5 3-[4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester as an oil: 1.34gm, 98%. The maleate salt, which is made as described in Example 1 and recrystallized from ethyl acetate, is a white solid; maleate salt: m.p. 118-120°C.

10 Elemental Analysis for $C_{22}H_{28}N_2O_7$:

	C%	H%	N%
Found:	60.8	7.0	6.7
Calculated:	60.8	7.0	6.5

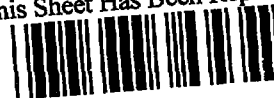
15 Example 3

4-[4-[(1-Oxopropyl)phenylamino]-1-piperidine]butanoic acid, methyl ester

A mixture of 4-[(1-oxopropyl)phenylamino]-piperidine (250mg, 1.08mmol), methyl 4-bromobutanoate (224mg, 1.23mmol), prepared according to the procedure of G. A. Olah
20 et al, Synthesis 1982, 963, sodium iodide (81mg, 0.54 mmol), and potassium carbonate (298mg, 2.15mmol), in acetonitrile (1.1ml) is stirred at room temperature for five hours. The mixture is diluted with water and ethyl acetate
25 and worked up in an analogous manner of Example 1. The residue is chromatographed on silica gel (EtOAc) to give 4-[4-[(1-oxopropyl)phenylamino]-1-piperidine]butanoic acid, methyl ester as an oil: 223mg, 62%. The maleate salt is made as described in Example 1; maleate salt: m.p. 101.5-103.5°C.

30 Elemental Analysis for $C_{23}H_{32}N_2O_7$:

	C%	H%	N%
Found:	61.3	7.0	6.2
Calculated:	61.6	7.2	6.3



Example 4

5-[4-[1-Oxopropyl]phenylamino]-1-piperidine]pentanoic acid, methyl ester

A mixture of 4-[(1-oxopropyl)phenylamino]-piperidine (300mg, 1.29mmol), methyl-5-bromopentanoate (290mg, 1.49mmol), prepared according to the procedure of G. A. Olah et al, Synthesis 1982, 963) sodium iodide (97mg, 0.65 mmol), and potassium carbonate (357mg, 2.58mmol), in acetonitrile (1.3ml) is stirred at room temperature for five hours. The crude residue is isolated according to the procedure of Example 1. The residue is chromatographed on silica gel (95/5 EtOAc/MeOH) to give 5-[4-[1-oxopropyl]phenylamino]-1-piperidine]pentanoic acid, methyl ester, as a white solid: 239 mg; 53%; m.p. 64-66°C. The maleate salt is made as described in Example 1; maleate salt: m.p. 105-106°C.

Elemental Analysis for $C_{24}H_{34}N_2O_7$:

	C%	H%	N%
Found:	62.3	7.4	6.0
Calculated:	62.3	7.4	6.1

20

Example 5

3-[4-[1-Oxopropyl]phenylamino]-1-piperidine]propanoic acid, trifluoroacetate

A solution of 4-[(1-oxopropyl)phenylamino]-piperidine (500mg, 2.15mmol) and t-butyl acrylate (0.37ml, 2.58mmol), in acetonitrile (2.5ml) is stirred at room temperature for 24 hours. The solution is concentrated and the residue is chromatographed on silica gel (EtOAc) to give 4-[2-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, t-butyl ester as an oil: 605mg, 78%. To the ester (309mg, 0.857mmol) is added trifluoroacetic acid (4ml). The homogeneous reaction mixture is stirred at room temperature for one hour and then concentrated to an oil which is triturated with ether to give a white solid, 3-[4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, trifluoroacetate: 316mg, 88%; m.p. 187-189°C.



Elemental Analysis for $C_{19}H_{25}N_2O_5F_3$:

	C%	H%	N%
Found:	54.6	6.0	6.7
Calculated:	54.5	6.0	6.7

5

Example 6

A. Methoxymethyl acrylate

In a separatory funnel is added acrylic acid (2ml, 29.17 mmol), dimethoxymethane (2ml), phosphorous pentoxide (0.5g) and ether (20ml). The mixture is vigorously shaken for five minutes and then an additional aliquot of phosphorous pentoxide is added (0.5g) and the procedure repeated three times. The solids are separated from the liquid and the ether solution washed with saturated $NaHCO_3$ solution (3x), then dried over anhydrous Na_2SO_4 and the ether distilled from the product to yield methoxymethyl acrylate as a light yellow oil: 450mg, 13%.

B. 3-[4-[(1-Oxopropyl)phenylamino]-1-piperidine]propanoic acid, methoxymethyl ester

A solution of 4-[(1-oxopropyl)phenylamino]-piperidine (150mg, 0.65mmol) and methoxymethyl acrylate (182mg, 1.57mmol), in acetonitrile (0.8ml) is stirred at room temperature for eleven hours. The solution is evaporated and the residue chromatographed on silica gel (EtOAc) to give 3-[4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methoxymethyl ester as an oil: 138mg, 25%. Gaseous hydrochloric acid is passed through a solution of the free base dissolved in ethyl acetate/ether (1/4 ratio) to give the hydrochloride salt as a white solid; HCl salt: m.p. 128-131°C.

Elemental Analysis for $C_{19}H_{29}N_2O_4Cl$:

	C%	H%	N%
Found:	59.0	7.6	7.4
Calculated:	59.3	7.6	7.3

35



Example 7

2-[4-[(1-Oxopropyl)phenylamino]-1-piperidine]ethyl acetate

To a solution of 4-[(1-oxopropyl)phenylamino]-1-piperidineacetic acid, methyl ester (250mg, 0.82mmol) in tetrahydrofuran (10ml) at -78°C is added lithium aluminum hydride (250mg, 6.57mmol) in portions. The suspension is stirred at -78°C for one hour and then quenched with 2N sodium hydroxide (10ml). Magnesium sulfate is added to the resulting suspension until it becomes granular. The suspension is then filtered and the filtrate concentrated to a residue. The residue is chromatographed on silica gel (9/1 $\text{CHCl}_3/\text{CH}_3\text{OH}$) to yield 2-[4-[(1-oxopropyl)phenylamino]-1-piperidine]ethanol as an oil: 155mg, 68%.

A solution of 2-[4-[(1-oxopropyl)phenylamino]-1-piperidine]ethanol (256mg, 0.957mmol), acetic anhydride (0.72ml, 7.63mmol), and 4-dimethylaminopyridine (50mg, 0.41mmol) in pyridine (5ml) is stirred at 25°C for two hours. The solution is concentrated to an oil which is chromatographed on silica gel (EtOAc) to give 2-[4-[(1-oxopropyl)phenylamino]-1-piperidine]ethyl acetate as an oil: 243mg, 82%. An equimolar amount of oxalic acid is added to a solution of the free base in ethyl acetate. The precipitated salt is recrystallized by adding methanol and heating until the solid goes back into solution. Upon cooling the salt precipitates as a white solid; oxalate salt: m.p. $153-155^{\circ}\text{C}$. Elemental Analysis for $\text{C}_{20}\text{H}_{28}\text{N}_2\text{O}_7$:

	C%	H%	N%
Found:	58.7	6.9	6.8
Calculated:	58.8	6.9	6.9

Example 8

3-[4-Methoxymethyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]-propanoic acid, methyl ester

A solution of 4-methoxymethyl-4-[(1-oxopropyl)phenylamino]piperidine (300mg, 1.0mmol), prepared by the procedure



of P.G.H. Van Daele et al, *Arzneim.-Forsch. Drug. Res.* 1976, 26, 1521, methyl acrylate (325 μ l, 3.61mmol) and methanol (20ml) is stirred at 60°C for 2 hours. The reaction solution is cooled to room temperature and concentrated to an oily residue. The residue is chromatographed on silica gel (9/1 CHCl₃/MeOH) to yield 3-[4-methoxy-methyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester as an oil: 250mg, 64%. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 180-182°C.

Elemental Analysis for C₂₂H₃₂N₂O₈:

	C%	H%	N%
Found:	58.2	7.2	6.1
Calculated:	58.4	7.1	6.2

15

Example 9

4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine-acetic acid, methyl ester

A mixture of 4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]piperidine (200mg, 0.68mmol), prepared according to the procedure of P.G.H. Van Daele et al, *Arzneim.-Forsch. Drug Res.* 1976, 26, 1521, methyl bromoacetate (200 μ l, 2.11mmol), and potassium carbonate (200mg, 5.3mmol), in acetonitrile (1.1ml) is stirred at room temperature for 2 hours. The reaction mixture is concentrated and chromatographed on silica gel (95/5 CHCl₃/MeOH) to yield 4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine-acetic acid, methyl ester as an oil: 142mg, 57%. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 130-135°C.

Elemental Analysis for C₂₁H₂₈N₂O₉:

	C%	H%	N%
Found:	55.3	6.1	6.1
Calculated:	55.8	6.2	6.2

35

Example 10

3-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester

To a solution of 4-methoxycarbonyl-4-[(1-oxopropyl)-phenylamino]-piperidine (200mg, 0.68mmol) in acetonitrile (1.1ml) is added methyl acrylate (124μl, 1.36mmol) at room temperature. The solution is stirred at 50°C for 2 hours, cooled to room temperature, and concentrated to an oily residue. The residue is chromatographed on silica gel (EtOAc) to give 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester as an oil: 253mg, 97%. The oxalate salt, which is made as described in Example 7 is recrystallized from methanol and 2-butanone; m.p. 170-172°C. The HCl salt can be made by dissolving the free base oil in methanol, adding HCl gas, adding ether to complete crystallization and filtration, m.p. 212-214°C.

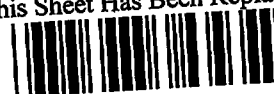
Elemental Analysis for $C_{22}H_{30}N_2O_9$:

	C%	H%	N%
Found:	56.5	6.5	6.0
Calculated:	56.7	6.4	6.0

Example 11

4-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]-butanoic acid, methyl ester

A mixture of 4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-piperidine (150mg, 0.517mmol), methyl 4-bromobutanoate (187mg, 1mmol), potassium carbonate (39.3mg, 1mmol), sodium iodide (155mg, 1.0mmol) and acetonitrile (1ml) is stirred at 50°C for 2 hours. The mixture is cooled to room temperature, diluted with ethyl acetate (1ml) and filtered. The filtrate is concentrated to an oily residue which is chromatographed on silica gel (9/1 $CHCl_3$ /MeOH) to yield 4-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]butanoic acid, methyl ester as an oil: 177 mg, 88%. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 153-155°C.



Elemental Analysis for $C_{23}H_{32}N_2O_9$:

	C%	H%	N%
Found:	57.1	6.6	5.8
Calculated:	57.5	6.7	5.8

5

Example 12

5-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]pentanoic acid, methyl ester

A mixture of 4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
10 amino]piperidine (150mg, 0.517mmol) methyl 5-bromopentanoate
(200mg, 1mmol), potassium carbonate (40mg, 1mmol), sodium
iodide (1.55mg, 1mmol) and acetonitrile (1.0ml) is stirred
at 52°C for 22.5 hours and then at 25°C for 12 hours. The
reaction mixture is diluted with ethyl acetate (1ml) and
15 filtered. The filtrate is concentrated to an oily residue
which is chromatographed on silica gel (90/9/1 $CHCl_3$ /MeOH/
triethylamine) to yield 5-[4-methoxy-carbonyl-4-[(1-oxo-
propyl)phenylamino]-1-piperidine]pentanoic acid, methyl
ester as an oil: 184mg, 88%. The oxalate salt is made as
20 described in Example 7; oxalate salt: m.p. 164-166°C.

Elemental Analysis for $C_{24}H_{34}N_2O_9$:

	C%	H%	N%
Found:	58.0	7.0	5.7
Calculated:	58.3	7.0	5.7

25

Example 13

3-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, trifluoroacetate

This compound is formed by following the procedure of
30 Example 5 except that an equivalent amount of 4-methoxy-
carbonyl-4-[(1-oxopropyl)phenylamino]-piperidine is
substituted for the 4-[(1-oxopropyl)phenylamino]-piperidine
used therein; m.p. 189-190°C.

35



Elemental Analysis for $C_{21}H_{27}N_2O_7F_3$:

	C%	H%	N%
Found:	53.0	5.7	5.9
Calculated:	52.9	5.7	5.9

5

Example 14

3-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]-propanoic acid, methoxymethyl ester

A solution of 4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
 10 amino]piperidine (200mg, 0.69mmol) and methoxymethyl
 acrylate (120mg, 1.03mmol) in acetonitrile (0.7ml) is
 stirred at room temperature for fifteen hours. The solution
 is diluted with 1:1 water and ethyl acetate and the aqueous
 phase extracted with ethyl acetate (2x). The combined
 15 organics are washed with brine, dried over sodium sulfate
 and concentrated. The residue is chromatographed on silica
 gel (EtOAc) to give 3-[4-methoxycarbonyl-4-[(1-oxopropyl)-
 phenylamino]-1-piperidine]propanoic acid, methoxymethyl
 ester as an oil: 160 mg, 57%. The oxalate salt is made as
 20 described in Example 7; oxalate salt: m.p. 141-143°C.

Elemental Analysis for $C_{23}H_{32}N_2O_{10}$:

	C%	H%	N%
Found:	55.4	6.5	5.5
Calculated:	55.6	6.5	5.6

25

Example 15

A. Vinyl 3-bromopropionate

This compound is prepared according to the procedure of
 R. L. Adelman, J. Org. Chem. 1949, 1057. To a solution of
 30 3-bromo-propionic acid (1.0g, 6.54mmol) in vinyl acetate
 (3.6ml) is added copper (100mg), mercuric acetate (104mg)
 and concentrated sulphuric acid (1 drop) in that order. The
 reaction is stirred at room temperature for two days. The
 heterogeneous mixture is diluted with pentane (10ml) and
 then filtered through celite to remove the solids. The
 35 filtrate is washed with water (2x), saturated sodium



bicarbonate (1x) and then brine. The organics are dried over anhydrous sodium sulfate and concentrated to an oil, vinyl 3-bromopropionate: 760mg, 65%.

5 B. 3-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, vinyl ester

A mixture of 4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]piperidine (200mg, 0.689mmol), vinyl 3-bromopropionate (185mg, 1.03mmol), and potassium carbonate (214mg, 10 1.55mmol), in acetonitrile (1ml) is stirred at room temperature for two hours. The reaction mixture is diluted with 1:1 water and ethyl acetate and extracted with ethyl acetate (2x). The combined organics are washed with brine, dried over sodium sulfate and concentrated. The residue is 15 chromatographed on silica gel (EtOAc) to yield 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]-propanoic acid, vinyl ester as a white solid: 197mg, 74%, m.p. 70-72°C. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 156-158°C.

20 Elemental Analysis for $C_{23}H_{30}N_2O_9$:

	C%	H%	N%
Found:	57.6	6.4	5.9
Calculated:	57.7	6.3	5.9

25 Example 16

2-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]-ethyl acetate

A mixture of 4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]piperidine (300mg, 1.0mmol), 2-bromoethyl acetate 30 (172mg, 1.0mmol), potassium carbonate (79mg, 2.0mmol), sodium iodide (154mg, 1.0mmol) and acetonitrile (1.0ml) is stirred at 65°C for 12 hours, cooled to room temperature, and filtered. The filtrate is concentrated to an oily residue which is chromatographed on silica gel (EtOAc) to 35 yield 2-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]ethyl acetate as a yellow oil: 300mg, 77%. The

oxalate salt is made as described in Example 7; oxalate salt: m.p. 191-193°C.

Elemental Analysis for $C_{22}H_{30}N_2O_9$:

	C%	H%	N%
5 Found:	56.6	6.5	6.0
Calculated:	56.6	6.5	6.0

Example 17

3-[4-[(1-Oxopropyl)-2-fluorophenylamino]-1-piperidine]- 10 propanoic acid, methyl ester

A mixture of 4-[(1-oxopropyl)-2-fluorophenylamino]-piperidine (200mg, 0.80mmol), methyl acrylate (0.1ml, 1.12mmol) and potassium carbonate (275mg, 2.0mmol) in methanol (2ml) is stirred at room temperature for two hours.

15 The reaction mixture is diluted with 1:1 water and ethyl acetate. After extracting the aqueous phase with ethyl acetate (2x) the combined organics are washed with brine, then dried over sodium sulfate and concentrated. The residue is chromatographed on silica gel (EtOAc) to give
20 3-[4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]-propanoic acid, methyl ester as an oil which solidifies upon standing: 176mg, 65%. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 183-184°C.

Elemental Analysis for $C_{20}H_{27}N_2O_7F$:

	C%	H%	N%
25 Found:	55.9	6.4	6.5
Calculated:	56.3	6.4	6.6

Example 18

30 3-[4-[(1-Oxopropyl)-2-fluorophenylamino]-1-piperidine]-propanoic acid, vinyl ester

By following the procedure in Example 15, except that an equivalent amount of 4-[(1-oxopropyl)-2-fluorophenyl-amino]piperidine is substituted for the 4-methoxycarbonyl-

35 4-[(1-oxopropyl)phenylamino]-piperidine used therein and the reaction mixture is stirred for sixteen hours, there is

obtained 3-[4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]propanoic acid vinyl ester as an oil: 66% yield. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 141-143°C.

5 Elemental Analysis for $C_{21}H_{27}N_2O_7F$:

	C%	H%	N%
Found:	57.6	6.2	6.4
Calculated:	57.5	6.2	6.4

10 Example 19

3-[4-[(1-Oxopropyl)-2-fluorophenylamino]-1-piperidine]-propanoic acid, 3-butenyl ester

A solution of 3-[4-[(1-oxopropyl)phenylamino]-1-piperidine]-propanoic acid, trifluoroacetate (370mg, 0.848mmol),
15 m.p. 139.5-141°C, is prepared in an analogous manner in which 3-[4-[(1-oxopropyl)-phenylamino]-1-piperidine]propanoic acid, trifluoroacetate is described in example 5, is dissolved in a 1M phosphate buffer solution (0.5M Na_2HPO_4 and 0.5M Na_2HPO_4) and stirred for ten minutes. The solution
20 is then diluted with a 3/1 mixture of chloroform/isopropanol and extracted (5x). The combined organics are dried over sodium sulfate and concentrated to the free base: 215mg, 79% yield. A solution of 3-[4-[(1-oxopropyl)-2-fluoro-phenyl-amino]-1-piperidine]propanoic acid (185mg, 0.574mmol)
25 in chloroform (5ml) is added O-3-butenyl-N,N-diisopropylpseudo urea (570mg, 2.87mmol), prepared using the procedure given in L.J. Mathias, Synthesis, 1979, 561. The solution is refluxed for 24 hours, cooled, and concentrated. The residue is chromatographed on silica gel (1/1 hexanes/EtOAc)
30 to give 3-[4-(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]propanoic acid, 3-butenyl ester as an oil: 120mg, 56%. The oxalate salt is made as described in example 7; oxalate salt: m.p. 165.5-166.5°C;

Elemental Analysis for $C_{23}H_{31}N_2O_7F$:

	C%	H%	N%
35 Found:	58.8	6.8	6.0
Calculated:	59.2	6.7	6.0



Example 20

3-[4-[(2-Methoxy-1-oxoethyl)phenylamino]-1-piperidine]-propanoic acid, methyl ester

A solution of 4-[(2-methoxy-1-oxoethyl)phenylamino]-piperidine (200mg, 0.805mmol), prepared according to the procedures of B. S. Huang et al, U.S. Patent 4,584,303, and methyl acrylate (94 μ l, 1.05mmol), in methanol (1ml) is stirred at room temperature for four hours. The reaction solution is concentrated to a residue which is chromatographed on silica gel (95/5 CHCl₃/MeOH) to give the free base, 3-[4-[(2-methoxy-1-oxoethyl)phenylamino]-1-piperidine]propanoic acid, methyl ester, as an oil: 260mg, 97%. An equimolar amount of oxalic acid in ether is added to a solution of the free base in ether. The gummy precipitate is triturated with ethyl acetate to give the oxalate salt as a white solid; oxalate salt: m.p. 188-190°C. Elemental Analysis for C₂₀H₂₈N₂O₈:

	C%	H%	N%
Found:	56.6	6.7	6.6
Calculated:	56.6	6.7	6.6

20

Example 21

3-[4-[(2-Methoxy-1-oxoethyl)-2-fluorophenylamino]-1-piperidine]propanoic acid, methyl ester

A solution of 4-[(2-methoxy-1-oxoethyl)-2-fluorophenylamino]piperidine (250mg, 0.94mmol), methyl acrylate (170 μ l, 1.88mmol) and methanol (5.0ml) is stirred at room temperature for 24 hours. The reaction solution is concentrated to an oily residue and chromatographed on silica gel (EtOAc) to yield 3-[4-[(2-methoxy-1-oxoethyl)-2-fluorophenylamino]-1-piperidine]propanoic acid, methyl ester as an oil: 202mg, 61%. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 186-188°C.

Elemental Analysis for C₂₀H₂₇N₂O₈F:

	C%	H%	N%
Found:	54.3	6.1	6.4
Calculated:	54.3	6.2	6.3

35



Example 22

[±]-Cis-3-[3-methyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester

A solution of (±)-cis-3-methyl-4-phenylaminopiperidine (750mg, 3.94mmol), prepared according to the procedure of W.F.M. Van Bever et al., J. Med. Chem. 1974, 17, 1047, methyl acrylate (710μl, 7.88mmol), and methanol (2.5ml) is stirred at room temperature for 30 minutes. The resultant solution is concentrated to an oily residue which is chromatographed on silica gel (EtOAc) to yield (±)-cis-3-(3-methyl-4-phenylamino-1-piperidine)propanoic acid, methyl ester as an oil: 787mg, 72%.

A solution of (±)-cis-3-(3-methyl-4-phenylamino-1-piperidine)-propanoic acid, methyl ester (500mg, 1.8mmol), propionyl chloride (785μl, 9.0mmol), and 4-dimethylamino-pyridine (320mg, 2.63mmol) in acetonitrile (10ml) is stirred and refluxed for 30 minutes. The resultant solution is cooled to room temperature and diluted with cold saturated sodium carbonate (25ml). The mixture is extracted with ethyl acetate (2 x 25ml) and the organic phase dried over magnesium sulfate and concentrated to an oily residue which is chromatographed on silica gel (EtOAc) to give (±)-cis-3-[3-methyl-4-[(3-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methyl ester as an oil: 392mg, 65%. The hydrochloride salt is made by dissolving the free base in toluene, saturating the solution with dry hydrogen chloride and concentrating to a solid. The solid is then recrystallized from ethyl acetate; hydrochloride salt: m.p. 180-187°C.

Elemental Analysis for $C_{19}H_{29}N_2O_3Cl$:

	C%	H%	N%
Found:	61.5	7.9	7.9
Calculated:	61.9	7.9	7.6



Example 23

[±]-Cis-3-[3-methyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methoxymethyl ester

A mixture of (±)-cis-3-methyl-4-phenylaminopiperidine (350mg, 1.8mmol), 2-bromopropanoic acid methoxymethyl ester (450mg, 2.28mmol), potassium carbonate (350mg, 2.54mmol), 4-dimethyl-aminopyridine (50mg, 0.41mmol), and acetonitrile (3ml) is stirred at room temperature for 24 hours and diluted with saturated sodium bicarbonate (20ml). The resultant mixture is extracted with ethyl acetate (2 x 20ml) and the organic phases combined, dried over magnesium sulfate, and concentrated to an oily residue which is chromatographed on silica gel (EtOAc) to give (±)-cis-3-(3-methyl-4-phenylamino-1-piperidine)propanoic acid, methoxymethyl ester as an oil: 371mg; 66%.

A solution of (±)-cis-3-(3-methyl-4-phenylamino-1-piperidine)propanoic acid, methoxymethyl ester (350mg, 1.14mmol), 4-dimethyl-aminopyridine (250mg, 2.0mmol), propionyl chloride (1.0ml, 11.5mmol), and acetonitrile (10ml) is stirred and refluxed for 30 minutes and cooled to room temperature. The reaction solution is diluted with cold saturated sodium carbonate solution (25ml) and extracted with ethyl acetate (3 x 25ml). The organic extracts are combined, dried over magnesium sulfate and concentrated to an oily residue which is chromatographed on silica gel (1/1 EtOAc/Hex) to give (±)-cis-3-[3-methyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, methoxymethyl ester as an oil: 253mg, 60%. The oxalate salt hemihydrate is made as described in Example 7; oxalate salt hemihydrate: m.p. 83-92°C.

Elemental Analysis for $C_{22}H_{32}N_2O_8 \cdot 0.5 H_2O$:

	C%	H%	N%
Found:	57.4	7.2	6.2
Calculated:	57.3	7.2	6.1



Example 24

[±]-Cis-3-[3-methyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]propanoic acid, allyl ester

A solution of (±)-cis-3-methyl-4-phenylamino piperidine (400mg, 2.1mmol), allyl acrylate (471mg, 4.2mmol), and acetonitrile (5ml) is stirred at room temperature for 4 hours and concentrated to an oily residue which is chromatographed on silica gel (EtOAc) to give (±)-cis-3-[3-methyl-4-phenylamino-1-piperidine]propanoic acid, allyl ester as an oil: 405mg; 64%.

A solution of (±)-cis-3-(3-methyl-4-phenylamino-1-piperidine)propanoic acid, allyl ester (400mg, 1.32mmol), 4-dimethylaminopyridine (250mg, 2.0mmol), propionyl chloride (1.15ml, 13.2mmol), and acetonitrile (10ml) is stirred and refluxed for 30 minutes and cooled to room temperature. The reaction solution is diluted with a solution of cold saturated sodium carbonate (25ml) and extracted with ethyl acetate (3 x 25ml). The organic extracts are combined, dried over magnesium sulfate, and concentrated to an oily residue which is chromatographed on silica gel (1/1 EtOAc/Hex) to give (±)-cis-3-[3-methyl-4-[(1-oxopropyl)-phenylamino]-1-piperidine]propanoic acid, allyl ester as an oil: 335mg; 74%. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 150-152°C.

Anal Calcd. for $C_{23}H_{32}N_2O_7$:

	C%	H%	N%
Found:	61.6	7.2	6.3
Calculated:	61.6	7.2	6.3

Example 25

[±]-Cis-2-[3-methyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]ethyl acetate

A mixture of (±)-cis-3-methyl-4-phenylaminopiperidine (300mg, 1.57mmol), bromoethyl acetate (865μl, 789mmol), 4-dimethyl-aminopyridine (100mg, 0.82mmol), potassium carbonate (250mg, 1.81mmol), and acetonitrile (4ml) is



stirred at room temperature for 6 hours. The resultant mixture is diluted with water (25ml) and extracted with ethyl acetate (3 x 25ml). The combined organic phases are dried over magnesium sulfate and concentrated to an oily residue which is chromatographed on silica gel (3/1 EtOAc/Hex) to give (±)-cis-2-(3-methyl-4-phenylamino-1-piperidine)ethyl acetate as an oil: 402mg, 92%.

A solution of (±)-cis-2-(3-methyl-4-phenylamino-1-piperidine)ethyl acetate (400mg, 1.45mmol), propionyl chloride (1.25ml, 14.5mmol), 4-dimethylaminopyridine (353mg, 2.89mmol), and acetonitrile (10ml) is stirred and refluxed for 30 minutes. The resultant solution is cooled to room temperature and diluted with a cold saturated sodium carbonate solution (3 x 25ml) and the organic phase dried over magnesium sulfate and concentrated to an oily residue which is chromatographed on silica gel (EtOAc) to give (±)-cis-2-[3-methyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]ethyl acetate as an oil: 389mg, 81%. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 148-150°C.

Elemental Analysis for $C_{21}H_{30}N_2O_7$:

	C%	H%	N%
Found:	59.6	7.3	6.6
Calculated:	59.7	7.2	6.6

25

Example 26

(-)-Cis-3S-methyl-4R-[(N-1R-methylbenzylamido)phenylamino]-1-(N-1R-methylbenzylamido)piperidine and (-)-cis-3R-methyl-4S-[(N-1R-methylbenzylamido)phenylamino]-1-(N-1R-methylbenzylamido)piperidine

A solution of (±)-cis-3-methyl-4-phenylaminopiperidine (2.0gm, 10.5mmol), 4-dimethylaminopyridine (250mg, 2.0mmol), and R-(+)-α-methylbenzyl isocyanate (4.0gm, 27.2mmol) is stirred at 120° for 6 hours. The resultant solution is cooled to room temperature and chromatographed on silica gel (1/1 EtOAc/Hex) to give two diastereomers. The less polar



of the two is recrystallized from EtOAc to give (-)-cis-3S-methyl-4R-[(N-1R-methylbenzylamido)phenylamino]-1-(N-1R-methylbenzylamido)piperidine as a solid: 1.5gm; m.p. 172-173°C; $[\alpha]_D^{25} = -114.4^\circ$ (c 1.5, MeOH).

Elemental Analysis for $C_{30}H_{36}N_3O_2$:

5		C%	H%	N%
	Found:	74.4	7.5	11.6
	Calculated:	74.4	7.5	11.6

The more polar diastereomer is recrystallized from EtOAc/Hex to give (-)-cis-3R-methyl-4S-[(N-1R-methyl-benzyl-
10 amido)phenylamino]-1-(N-1R-methylbenzylamido)-piperidine as a solid: 1.8gm; m.p. 105-106°C; $[\alpha]_D^{25} = -63.6^\circ$ (c 1.8, MeOH).

Example 27

[-]-Cis-3-[3R-methyl-4S-[(1-oxopropyl)phenylamino]-1-piper-
15 idine]propanoic acid, methyl ester

A suspension of (-)-cis-3R-methyl-4S-[(N-1R-methyl-benzyl-amido)phenylamino]-1-(N-1R-methylbenzylamido)-
piperidine (1.75gm, 3.6mmol) in 48% hydrobromic acid (40ml) is stirred and refluxed for 24 hours. It is cooled and
20 concentrated to an oil which is dissolved in water (20ml) and extracted with ether (2 x 50ml). The aqueous phase is basified to pH 10.5 with 5N NaOH and extracted with ethyl acetate (2 x 25ml). The ethyl acetate extracts are combined, dried over magnesium sulfate, and concentrated to
25 give a solid which is recrystallized from EtOAc/Hex giving (+)-cis-3R-methyl-4S-phenylaminopiperidine as a solid: 610mg; 89%; m.p. 95-97°C; $[\alpha]_D^{25} = 7.5^\circ$ (c 2.5, MeOH).

A solution of (+)-cis-3R-methyl-4S-phenylamino-piperidine (500mg, 2.63mmol), methyl acrylate (473ul, 5.26mmol), and methanol (10ml) is stirred at room
30 temperature for 6 hours and concentrated to an oily residue which is chromatographed on silica gel (EtOAc) to give (+)-cis-3-(3R-methyl-4S-phenylamino-1-piperidine)propanoic acid, methyl ester as an oil: 623mg; 86%; $[\alpha]_D^{25} = +25.7^\circ$ (c 1.85, MeOH).
35



A solution of (+)-cis-3-(3R-methyl-4S-phenylamino-1-piperidine)propanoic acid, methyl ester (600mg, 2.17mmol), 4-dimethylaminopyridine (250mg, 2.05mmol), propionyl chloride (1.89ml, 21.7mmol), and acetonitrile (10ml) is stirred and refluxed for 30 minutes and cooled to room temperature. It is diluted with cold saturated sodium carbonate (50ml) and extracted with ethyl acetate (3 x 25ml). The extracts are dried over magnesium sulfate and concentrated to an oily residue which is chromatographed on silica gel (1/1 EtOAc/Hex) to give (-)-cis-3-[3R-methyl-4S-[(1-oxopropyl)-phenyl-amino]-1-piperidine]propanoic acid, methyl ester as an oil: 453mg; 63%; $[\alpha]_D^{25} = -3.2^\circ$ (c 1.5, MeOH). The hydrochloride salt is made as described in Example 22; hydrochloride salt: m.p. 151-152°C;

Elemental Analysis for $C_{19}H_{29}N_2O_3Cl$:

	C%	H%	N%
Found:	62.2	7.9	7.8
Calculated:	61.9	7.9	7.6

Example 28

Trans-3-methyl-4-[(1-oxopropyl)phenylamino]-piperidine

A mixture of cis and trans-3-methyl-4-phenylamino-piperidine (1.2g, 6.35mmol) (predominantly trans due to isolation of the pure cis isomer by crystallization), prepared according to the procedure of W.F.M. Van Berer et al., J. Med. Chem. 1974, 17, 1047 and T.R. Burke, Jr. et al., J. Med. Chem. 1986, 29, 1087, benzylchloroformate (1ml, 6.98mmol), sodium bicarbonate (1g, 11.8mmol), ether (5ml), ethyl acetate (5ml), and water (10ml) is vigorously stirred at room temperature for one hour. The organic layer is separated, washed with 2N NaOH (2 x 5ml), dried over magnesium sulfate, and concentrated to an oily residue which is chromatographed on silica gel (EtOAc) to give trans-N-benzylloxycarbonyl-3-methyl-4-phenyl-aminopiperidine as an oil: 1.82g; 91%, followed by less than 5% of cis-N-benzylloxycarbonyl-3-methyl-4-phenylaminopiperidine.



To a solution of trans-N-benzyloxycarbonyl-3-methyl-4-phenylaminopiperidine (1.5g, 4.6mmol), 4-dimethylamino-pyridine (375mg, 3.1mmol), and acetonitrile (10ml) is added propionyl chloride (3.6ml, 41mmol). The solution is stirred
5 and refluxed for 30 minutes, cooled to room temperature, and diluted with a saturated solution of sodium carbonate (30ml). The resultant mixture is extracted with ethyl acetate (2 x 30ml) and the organic phases combined, dried over magnesium sulfate, and concentrated to an oily residue
10 which is chromatographed on silica gel (1/1 EtOAc/Hex) to give trans-N-benzyloxycarbonyl-3-methyl-4-[(1-oxopropyl)-phenylamino]piperidine as an oil: 1.6g, 91%.

A mixture of trans-N-benzyloxycarbonyl-3-methyl-4-[(1-oxopropyl)phenylamino]-piperidine (1.5g, 3.94mmol), 10%
15 Pd-C (200mg), methanol (20ml), and acetic acid (20ml) is hydrogenated at 50 psi for 24 hours. The resultant suspension is filtered through a bed of Celite and the filtrate concentrated. The residue is diluted with ethyl acetate (50ml), basified to pH 11 with 2N NaOH and shaken.
20 The organic layer is separated, dried over magnesium sulfate, and concentrated to trans-3-methyl-4-[(1-oxopropyl)-phenylamino]-piperidine: 720mg; 96%.

Example 29

25 Trans-3-[3-methyl-4-[(1-oxopropyl)phenylamino]piperidine]-propanoic acid, methyl ester

A solution of trans-3-methyl-4-[(1-oxopropyl)phenylamino]-piperidine (250mg, 1mmol), methyl acrylate (182μl, 2mmol), and methanol (2ml) is stirred for 24 hours at room
30 temperature, concentrated to an oily residue, and chromatographed on silica gel (EtOAc) to give trans-3-[3-methyl-4-[(1-oxopropyl)phenylamino]-piperidine]propanoic acid, methyl ester as an oil: 300mg; 89%. The monohydrate oxalate salt is made as described in Example 7; oxalate salt
35 monohydrate: m.p. 125-130°C.



Elemental Analysis for $C_{21}H_{32}N_2O_8$:

	C%	H%	N%
Found:	57.4	7.0	6.4
Calculated:	57.3	7.3	6.4

5

Example 30

Trans-3-[3-methyl-4-[(1-oxopropyl)phenylamino]piperidine]-propanoic acid, ethoxymethyl ester

A solution of trans-3-methyl-4-[(1-oxopropyl)phenyl-
10 amino]-piperidine (300mg, 1.2mmol), ethoxymethyl acrylate (350mg, 2.4mmol), and acetonitrile (10ml) is stirred at room temperature for 24 hours, concentrated to an oily residue, and chromatographed on silica gel (EtOAc) to give trans-3-[3-methyl-4-[(1-oxopropyl)phenylamino]piperidine]propanoic
15 acid, ethoxymethyl ester as an oil: 300mg; 65%. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 115-116°C.

Example 31

20 Trans-3-[3-methyl-4-[(1-oxopropyl)phenylamino]piperidine]-propanoic acid, allyl ester

A solution of
trans-3-methyl-4-[(1-oxopropyl)phenylamino]-
piperidine (300mg, 1.2mmol), allyl acrylate (272mg, 2.4mmol)
25 is stirred at room temperature for 16 hours and concentrated to an oily residue which is chromatographed on silica gel (EtOAc) to give trans-3-[3-methyl-4-[(1-oxopropyl)phenylamino]piperidine]propanoic acid, allyl ester as an oil: 300mg; 69%.

30 The oxalate salt is made as described in Example 7: oxalate salt: m.p. 147-148°C.

Elemental Analysis for $C_{23}H_{32}N_2O_7$:

	C%	H%	N%
Found:	61.7	7.2	6.2
35 Calculated:	61.6	7.2	6.2



Example 32

Trans-2-[3-methyl-4-[(1-oxopropyl)phenylamino]piperidine]-ethyl acetate

A mixture of trans-3-methyl-4-[(1-oxopropyl)phenyl-amino]piperidine (250mg, 1mmol), 2-bromoethyl acetate (338mg, 2.0mmol), potassium carbonate (300mg, 2.2mmol), sodium iodide (50mg, 0.3mmol), and acetonitrile is stirred at room temperature for 16 hours. The resultant mixture is diluted with a saturated solution of sodium bicarbonate (25ml) and extracted with ethyl acetate (2 x 25ml). The organic extracts are combined, dried over magnesium sulfate, and concentrated to an oily residue which is chromatographed on silica gel (EtOAc) to give trans-2-[3-methyl-4-[(1-oxopropyl)phenylamino]piperidine]ethyl acetate as an oil: 300mg; 89%. The oxalate salt is made as described in Example 7; oxalate salt: m.p. 149-150°C.

Elemental Analysis for $C_{21}H_{30}N_2O_7$:

	C%	H%	N%
Found:	59.6	7.2	6.6
Calculated:	59.7	7.2	6.6

Example 33

(±)-Cis-3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-piperidine

A solution of 1-methoxycarbonyl-3-methyl-4-(2-fluorophenyl-amino)-piperidine (12.95g, 48.6mmol), prepared according to the procedure of W.F.M. Van Berer et al., J. Med. Chem. 1974, 17, 1047 and T.R. Burke, Jr. et al., J. Med. Chem. 1986, 29, 1087, except that 2-fluoroaniline was substituted for aniline, and propionic anhydride (12.5ml, 97.2mmol) is refluxed for fifteen hours. The cooled solution is diluted with ethyl acetate and washed with 2N sodium hydroxide (2x), saturated sodium bicarbonate (5x), 1M phosphoric acid (1x) and brine (1x). The organics are dried over sodium sulfate and then concentrated. The residue is dissolved in ether and hexanes and cooled to -10°C for

fifteen hours. The solid that precipitated is collected and recrystallized from ether and hexanes to give cis-1-methoxycarbonyl-3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-piperidine as a solid: 3.2g; 20%; m.p. 128-130°C. The
5 mother liquors are combined and concentrated to give a mixture of cis and trans isomers along with some other impurities.

A suspension of cis-1-methoxycarbonyl-3-methyl-4-
10 [(1-oxo-propyl)-2-fluorophenylamino]-piperidine (3.2g, 9.89mmol) in 48% aqueous HBr (20ml) is refluxed for two hours. Upon heating the mixture dissolution occurs. The solution is cooled to 0°C and 5N NaOH is added until the pH is between 11 and 12. The aqueous phase is extracted with
15 methylene chloride (5x) and the combined organics dried over sodium sulfate and concentrated to give cis-3-methyl-4-(2-fluorophenylamino)-piperidine as an oil: 2.0g; 97%.

To a rapidly stirred mixture of benzylchloroformate (0.39ml, 2.76mmol) and sodium bicarbonate (284mg, 3.6mmol)
20 in water (4ml) and ether (4ml) is added cis-3-methyl-4-(2-fluoro-phenylamino)-piperidine (500mg, 2.4mmol) as a solution in ether (2ml). The mixture is stirred for one hour at ambient temperature, the layers are separated, and the organics washed with 2N NaOH (2x) and brine (1x). The
25 organics are dried over sodium sulfate and concentrated to give cis-1-benzyloxycarbonyl-3-methyl-4-(2-fluorophenyl-amino)-piperidine as an oil: 740mg; 90%.

To a solution of cis-1-benzyloxycarbonyl-3-methyl-4-(2-fluoro-phenylamino)-piperidine (740mg, 2.16mmol) and
30 4-dimethylaminopyridine (395mg, 3.24mmol) in acetonitrile (10ml) is added propionyl chloride (0.38ml, 4.32mmol). The reaction is heated to 50°C for ten hours. The mixture is concentrated and the residue dissolved in ethyl acetate and water. The organic phase is washed with saturated sodium bicarbonate (2x), 1M phosphoric acid (1x), and brine (1x).
35 The organics are dried over sodium sulfate and concentrated



to give pure cis-1-benzyloxycarbonyl-3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-piperidine as an oil: 769mg; 89%.

A mixture of cis-1-benzyloxycarbonyl-3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-piperidine (576mg, 1.45mmol) and 10% Pd-C (100mg) in methanol (25ml) and acetic acid (5ml) is hydrogenated at 50 psi for five hours. The reaction mixture is filtered through celite and the filtrate is concentrated. The residue is diluted with ethyl acetate, basified to pH 11 with 2N NaOH and shaken. The separated organics are dried over sodium sulfate and concentrated to give cis-3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-piperidine as an oil: 333mg; 87%.

Example 34

(±)-Cis-3-[3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]propionic acid, methyl ester

A solution of (±)-cis-3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-piperidine (200mg, 0.757mmol) and methyl acrylate (0.1ml, 1.13mmol) in acetonitrile (2ml) is stirred at room temperature for twelve hours. The solution is concentrated and the residue chromatographed on silica gel (2/1 EtOAc/Hex) to yield (±)-cis-3-[3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]propanoic acid, methyl ester as an oil: 44mg, 17% yield. The hydrochloride salt is prepared by bubbling gaseous HCl through a toluene solution of the free base and concentrating to a white solid; hydrochloride salt: m.p. 177-178°C;

Elemental Analysis for $C_{19}H_{28}N_2O_3ClF$:

	C%	H%	N%
Found:	59.0	7.3	7.2
Calculated:	59.0	7.3	7.2

Example 35

(±)-Cis-3-[3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]propanoic acid, ethoxymethyl ester



A solution of (±)-cis-3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-piperidine (70mg, 0.265mmol) and ethoxymethyl acrylate (73μl, 0.265 mmol) in acetonitrile (1ml) is stirred at room temperature for eighteen hours.

- 5 The solution is concentrated and the residue chromatographed on silica gel (EtOAc) to give (±)-cis-3-[3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]propanoic acid, ethoxymethyl ester as an oil: 84mg, 80% yield. The oxalate salt is made by dissolving the free base in ethyl acetate
10 and adding an ethereal solution of oxalic acid. The gum that precipitates is redissolved in hot ethyl acetate and recrystallizes to give a white solid upon cooling; oxalate salt: m.p. 96-97°C;

Elemental Analysis for $C_{23}H_{33}N_2O_8F$:

15		C%	H%	N%
	Found:	56.6	6.8	6.1
	Calculated:	57.0	6.9	5.8

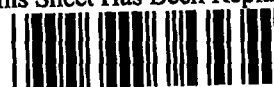
Example 36

- 20 (±)-Cis-3-[3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]propanoic acid, allyl ester

- A solution of (±)-cis-3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-piperidine (100mg, 0.378mmol) and allyl acrylate (90ml, 0.757mmol) in acetonitrile (1ml) is stirred
25 at room temperature for sixteen hours. The solvent is removed and the residue chromatographed on silica gel (1/1 EtOAc/Hex) to give (±)-cis-3-[3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]propanoic acid, allyl ester as an oil: 76mg, 53%. The oxalate salt monohydrate is made
30 by dissolving the free base in ethyl acetate and then adding an ethereal solution of oxalic acid. The white solid that precipitates is collected and washed with ether and ethyl acetate; oxalate salt monohydrate: m.p. 96-98°C;

Elemental Analysis for $C_{23}H_{33}N_2O_8F$:

35		C%	H%	N%
	Found:	57.3	6.7	5.8
	Calculated:	57.0	6.9	5.8



Example 37

(±)-Cis-2-[3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]ethyl acetate

A suspension of (±)-cis-3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-piperidine (250mg, 0.946mmol), 2-bromo-ethyl acetate (0.16ml, 1.42mmol), potassium carbonate (260mg, 1.89mmol) and a catalytic amount of sodium iodide in acetonitrile (3ml) is stirred at 45°C for ten hours. The mixture is diluted with water and ethyl acetate. The aqueous is extracted with ethyl acetate (2x) and the combined organics washed with brine (1x), then dried over sodium sulfate and concentrated. The residue is chromatographed on silica gel (EtOAc) to give (±)-cis-2-[3-methyl-4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine]ethyl acetate as an oil: 241mg, 73%. The oxalate salt hemihydrate is made as described in Example 7; oxalate salt hemihydrate: m.p. 118-127°C;

Elemental Analysis for $C_{21}H_{29}N_2O_7 \cdot 0.5H_2O$:

	C%	H%	N%
Found:	55.7	6.6	6.2
Calculated:	56.1	6.7	6.2

Example 38

A pharmaceutical composition for parenteral or intravenous analgesic administration can be prepared from the following ingredients:

<u>Ingredients</u>	<u>Amount</u>
3-[4-Methoxycarbonyl-4-[(1-(oxopropyl)-phenylamino]-1-piperidine]-propanoic acid, methyl ester, HCl salt.....	1 mg
Isotonic saline.....	1 liter

Other compounds of the invention of course can be substituted for the foregoing specific compound, utilizing a relative amount of such other compounds in the composition depending on the effective analgesic activity of the particular compound.

Example 39

The compounds of formula (I) listed in Table III are prepared by following the procedures described herein using equivalent amounts of appropriate starting materials.

TABLE III

15

	<u>X</u>	<u>R</u>	<u>R¹</u>	<u>R²</u>
	a. $-(CH_2)_2COOMe$	Et	H	H
	b. $-(CH_2)_2COOnBu$	Et	H	H
20	c. $-(CH_2)_2COOtBu$	Et	H	H
	d. $-(CH_2)_2COOMe$	Et	H	H
	e. $-(CH_2)_2COO(CH_2)_2OMe$	Et	H	H
	f. $-(CH_2)_2COO(CH_2)_2OEt$	Et	H	H
	g. $-(CH_2)_2COOCH_2OMe$	Et	H	H
25	h. $-CH(CH_3)CH_2COOMe$	Et	H	H
	i. $-CH_2CH(CH_3)COOMe$	Et	H	H
	j. $-(CH_2)_2COOMe$	Me	H	H
	k. $-(CH_2)_2COOCH_2OMe$	Et	H	H
	l. $-(CH_2)_2COOMe$	Me	MeO-CO-	H
30	m. $-(CH_2)_2COOMe$	Me	MeO-CH ₂ -	H
	n. $-(CH_2)_2COOMe$	Me	H	cis(±)-Me
	o. $-(CH_2)_2COOMe$	Et	H	cis(±)-Me

35

(TABLE III continued next page)



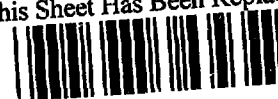
TABLE III Continued

	<u>Ar</u>	<u>salt</u>	<u>m.p. (°C)</u>
	a. 2,4-di-F-Ph	oxalate	177-178
	b. 2,4-di-F-Ph	oxalate	181-182
5	c. 2-F-Ph	oxalate	160-162
	d. 2-MeO-Ph	oxalate	139-140
	e. Ph	oxalate	164-165
	f. Ph	oxalate	140-141
	g. 2-F-Ph	oxalate	131-133
10	h. Ph	oxalate	148-149.5
	i. Ph	oxalate	146-148
	j. 2-Me-Ph	oxalate	-
	k. 2-Et-Ph	oxalate	-
	l. Ph	HCl	-
	m. Ph	HCl	-
15	n. 4-CF ₃ -Ph	oxalate	-
	o. 2-Cl-Ph	oxalate	-

Examples 40-53

20 Following the procedure of Example 10 and substituting an equivalent amount of the appropriate alkyl acrylate for the methyl acrylate of Example 10, the following compounds of formula (I) are obtained with melting points for the
25 oxalate salt being indicated below:

40. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-amino]-1-piperidine]propanoic acid, ethyl ester.....m.p. 166-167°C.



41. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, propyl
ester.....m.p. 169-170°C.
- 5 42. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, isopropyl
ester.....m.p. 176-177°C.
- 10 43. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, n-butyl
ester.....m.p. 153-154°C.
- 15 44. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, iso-butyl
ester.....m.p. 177-178°C.
- 20 45. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, sec-butyl
ester.....m.p. 160-161°C.
- 25 46. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, n-pentyl
ester.....m.p. 141-142°C.
- 30 47. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, 2-methylbutyl
ester.....m.p. 162-163°C.
- 35 48. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, isopentyl
ester.....m.p. 148-149°C.
49. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, neopentyl
ester.....m.p. 157-158°C.



50. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, hexyl
ester.....m.p. 141-142°C.
- 5 51. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, heptyl
ester.....m.p. 129-130°C.
52. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, octyl
10 ester.....m.p. 141-142°C.
53. 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenyl-
amino]-1-piperidine]propanoic acid, tert-butyl
ester.....m.p. 157-158°C.

15

In the synthesis procedure of Examples 40-53, the alkyl
acrylate starting material may be available commercially,
may be synthesized by literature procedures or may be
synthesized by the following procedure, substituting an
20 equivalent amount of the appropriate alcohol for 3-methyl
butanol:

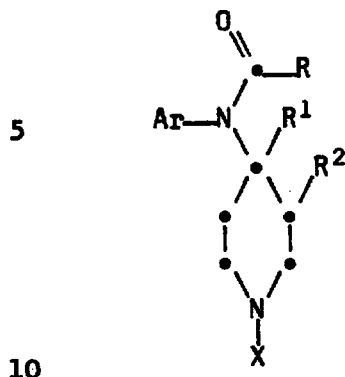
To a stirred solution of 3-methyl butanol (2.0 g, 22.6
mmol) and acryloyl chloride (2.05 g, 22.6 mmol) in
dichloromethane (5 ml) at 0°C is added dropwise
25 triethylamine (3.2 ml, 22.7 mmol). The solution is stirred
for 30 minutes at room temperature and then concentrated to
a residue. The residue is washed with hexanes (2 x 10 ml)
and the resultant combined organics are concentrated and
filtered through a plug of silica to give 3.0 g of
30 3-methylbutyl acrylate as an oil, 93% yield.

It will be understood that the embodiments described
herein are merely exemplary and that a person skilled in the
art may make many variations and modifications without
departing from the spirit and scope of the invention. All
35 such modifications and variations are intended to be
included within the scope of the invention as defined in the
appended claims.



CLAIMS

(1) A compound of formula (I)



wherein:

X is a member selected from the group consisting of:

- 15
- alkoxy-carbonyl-lower alkyl,
 - lower alkyl-carbonyloxy-lower alkyl,
 - alkenyloxy-carbonyl-lower alkyl, and
 - (C₁₋₂)alkoxy-(C₁₋₂)alkoxy-carbonyl-lower alkyl.

20

Ar is a member selected from the group consisting of phenyl, mono-, di- and tri-substituted phenyl, wherein each substituent is independently selected from the group consisting of halo, lower alkyl, lower alkoxy and trifluoromethyl;

R is a member selected from the group consisting of lower alkyl, and lower alkoxy-lower alkyl;

25

R¹ is a member selected from the group consisting of hydrogen, lower alkoxy-carbonyl, and methoxymethyl; and

R² is a member selected from the group consisting of hydrogen and methyl;

and the diastereomeric and enantiomeric isomers thereof, and the acid addition salts of said compounds and isomers.

30

(2) A compound according to Claim 1 in which Ar represents a phenyl or 2-substituted phenyl group.

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- (3) A compound according to Claims 1 or 2 wherein Ar represents a phenyl or 2-fluorophenyl group.
- (4) A compound according to any of Claims 1 to 3 wherein R represents an ethyl group.
- 5 (5) A compound according to any of Claims 1 to 4 wherein R¹ represents a hydrogen atom or a methoxycarbonyl group.
- (6) A compound according to any of Claims 1 to 5 wherein R¹ represents a methoxycarbonyl group.
- (7) A compound according to any of Claims 1 to 6 wherein X is an
- 10 alkoxy carbonyl-lower alkyl group.
- (8) A compound according to any of Claims 1 to 7 wherein X is an alkoxy carbonyl ethyl group.
- (9) A compound according to any of Claims 1 to 8 wherein said compound is an alkyl ester of 3-[4-methoxycarbonyl-4[(1-oxopropyl)phenyl-
- 15 amino]-1-piperidine]propanoic acid.
- (10) A compound of Claim 9 wherein the carbon atom of the alkyl portion of the said alkyl ester, directly attached to the oxygen is a methylene or methyl group.
- (11) A compound selected from:
- 20 5-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine]-pentanoic acid methyl ester;
- 2-[4-methoxycarbonyl-4[(1-oxopropyl)phenylamino]-1-piperidine)ethyl acetate;
- 3-[4-[(1-oxopropyl)-2-fluorophenylamino]-1-piperidine] propanoic acid,
- 25 methyl ester; or
- 3-[4-methoxycarbonyl-4-[(1-oxopropyl)phenylamino]-1-piperidine] propanoic acid vinyl ester;
- or a pharmaceutically acceptable acid addition salt thereof.
- (12) 3-[4-Methoxycarbonyl-4-[(1-oxopropyl)phenyl-amino]-1-piperidine]
- 30 propanoic acid methyl ester, and pharmaceutically acceptable acid addition salts thereof.
- (13) A compound according to any of Claims 1 to 12 or a pharmaceutically acceptable acid addition salt thereof for use in therapy.



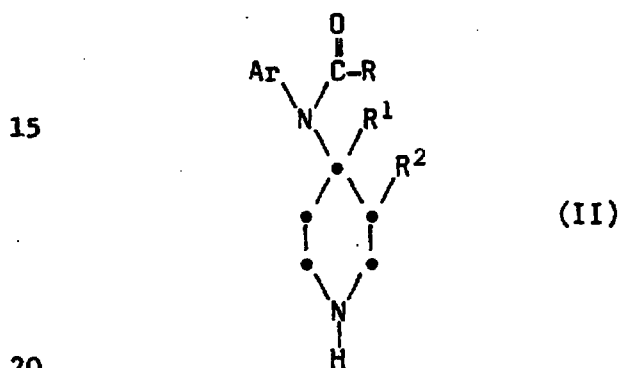


(14) The use of a compound according to any of Claims 1 to 12 or a pharmaceutically acceptable acid addition salt thereof in the manufacture of a medicament for use in the treatment of pain:

(15) A pharmaceutical composition which comprises a compound of formula (I) as defined in Claim 1 and the diastereomeric and enantiomeric isomers thereof and the pharmaceutically acceptable acid addition salts of said compounds and isomers together with a pharmaceutically acceptable carrier thereof.

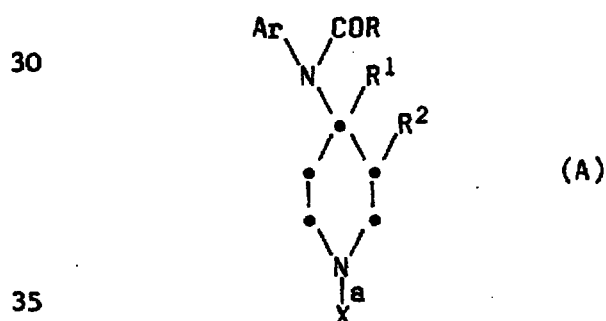
(16) A process for the preparation of a compound of formula (I) as defined in Claim 1 which comprises

(A) reacting a compound of formula (II)



in which the groups Ar, R, R¹ and R² have the meanings defined above for formula (I), with a reagent serving to introduce the group X.

(B) A process for preparing compounds of formula I wherein X is an alkoxy-carbonyl-lower alkyl group or an alkenyloxy-carbonyl-lower alkyl group which comprises esterifying a compound of formula (A)



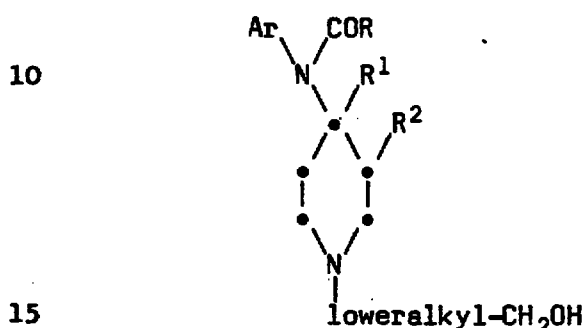
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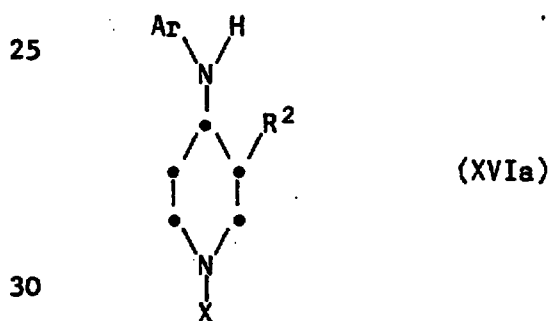
in which the groups Ar, R, R¹ and R² have the meanings defined above and X_a represents a carboxy-lower alkyl substituent.

(C) A process for the preparation of compounds of formula (I) wherein
 5 X represents a lower alkyl-carbonyloxy-lower alkyl group and R¹
 represents a hydrogen atom or a methyl group which comprises reacting
 a compound of formula (VIII)



in which the groups Ar, R and R² are as defined in formula (I) and R¹
 represents hydrogen or methoxymethyl with an appropriate lower
 alkylandhydride.

20 (D) A process for the preparation of a compound of formula (I) in
 which R¹ represents a hydrogen atom.
 which comprises reacting a compound of formula (XVIa)



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in which the groups Ar, R² and X have the meanings defined in formula (I) with a compound serving to introduce the group COR where R has the meanings defined in formula (I).

- 5 (E) Subjecting another compound of formula (I) to an interconversion reaction;
and if necessary or desired subjecting the compound from any of the steps (A) to (E) to one or two further reactions comprising:
(i) converting a compound of formula (I) or a salt thereof into a
10 pharmaceutically acceptable salt thereof.
(ii) resolution of a racemic mixture to give a specific enantiomer thereof.

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