Compounds of formula (I), wherein: R₁ is H, OH, -OCH₃, -CH₂OH, -NH₂, -NHCH₃, -NHCH₂CH₃, -N(CH₃)₂, -N(CH₂CH₃)₂, formulas (II), (III), halogen, or formula (IV), wherein R₂ is H, -CH₃, or formula (V), wherein R₃ is phenyl, benzyl, or 1-4 carbon alkyl; R₄ is H, -CH₃, -CH₂OH, -CH₂CN, -CH₂-S-CH₃, -CH₂-S-CN, or formula (VI), wherein R₅ is H, 1-4 carbon alkyl, alkenyl, or alkynyl, or aralkyl having a 1-4 carbon alkylene moiety, propargyl, 2-thienylethyl or 3-thienylethyl, provided that when R₄ is H or -CH₃, R₅ is propargyl, 2-thienylethyl or 3-thienylethyl; A is -CH₂- or -CH₂CH₂-, their preparation, pharmaceutical compositions containing them and their use as dopamine agonists.
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NOVEL DOPAMINE AGONISTS

BACKGROUND OF THE INVENTION

This invention relates to new substituted hexahydronaphthoxazines, pharmaceutical preparations containing such compounds as an active ingredient, and methods for using those compounds as pharmaceutical agents. More particularly, the invention relates to compounds having dopamine receptor agonist activity for therapeutic use in treating certain diseases of the central nervous system in mammals.

Compounds having dopaminergic activity have been the subject of extensive study in recent years, and a relatively large number of such compounds is known. The utility of L-DOPA in the symptomatic treatment of Parkinson's disease is well established and L-DOPA is in widespread clinical use. However, only a relatively small number of the other recognized dopaminergic agents have ever been marketed. One of the major exceptions is Bromocriptine. Another promising compound has been Pergolide. However, most of the other compounds have not been commercialized because of a lack of pharmacological specificity; i.e., they have major and undesirable side effects.


The N-propyl-9-oxaergoline compound has been shown to be an extremely potent direct acting dopaminergic agonist, comparing favorably with pergolide.
N-PROPYL-9-OXAERGOLINE (RU 29717)

RU 29717 is an indolic compound, as are all the ergolines. The indole ring, without which the compound is inactive, is a significant limitation on the number and type of derivatives of the compound that may be prepared. Moreover, in addition to its potent dopaminergic properties, RU 29717 has adrenergic and serotonergic activity as well, giving the compound a relatively broad pharmacological profile. Its activity as an emetic is a significant problem.

The present invention is directed to a class of non-indolic dopamine receptor agonists. Surprisingly, these compounds are highly active dopaminergic agents, exhibiting dopaminergic properties comparable to RU 29717. At the same time, they are easily synthesized and have a structural flexibility which makes various phenols, catechols, and resorcinols readily available to replace the indole pharmacophore. Moreover, it is believed these compounds exhibit a much narrower pharmacological profile than RU 29717 and related compounds with the concomitant result of significantly fewer side effects and more specific action in pharmaceutical use.
SUMMARY OF THE INVENTION

The compounds of the invention have the formula:

\[
\begin{align*}
\text{wherein: } R_1 & \text{ is } \text{H, OH, } -\text{OCH}_3, -\text{CH}_2\text{OH, } -\text{NH}_2, -\text{NHCH}_3, \\
& \quad -\text{NHCH}_2\text{CH}_3, -\text{N(\text{CH}_3)}_2, -\text{N(\text{CH}_2\text{CH}_3)}_2, \\
\text{R}_2 & \text{ is } \text{H, -CH}_3, \text{ or } -\text{C-R}_3; \text{ R}_3 \text{ is phenyl, benzyl, or 1-4 carbon alkyl; R}_4 \text{ is } \text{H, -CH}_3, -\text{CH}_2\text{OH, -CH}_2\text{-CN, -CH}_2\text{-S-CH}_3, \\
& \quad -\text{CH}_2\text{-S-CN, or} \\
\text{R}_5 & \text{ is } \text{H, 1-4 carbon alkyl, alkenyl, or alkynyl, or aralkyl having a 1-4 carbon alkylene moiety, propargyl, 2-thienylethyl or 3-thienylethyl, provided that when R}_4 \text{ is } \text{H or } -\text{CH}_3, \text{ R}_5 \text{ is propargyl, 2-thienylethyl or 3-thienylethyl; A is } -\text{CH}_2\text{- or } -\text{CH}_2\text{CH}_2.}
\end{align*}
\]

It will be understood that, for example, when A is \(-\text{CH}_2\text{-}, \text{ R}_1 \text{ and OR}_2 \text{ may be on any of numbered carbons 7, 8, 9, and 10. (The numbering scheme is based on A=CH}_2\text{-). When R}_1 \text{ is H, no carbon need be specified. R}_1 \text{ and OR}_2 \text{ are}
\]
substituted for hydrogens on the ring and do not destroy its aromatic character.

The compounds of the invention exhibit strong dopamine receptor agonist activity when administered to mammals. Preferably \( R_1 \) is H, OH, or OC-R_3; \( R_2 \) is H or -C-R_3; \( R_3 \) is methyl, ethyl, t-butyl, or phenyl; \( R_4 \) is H, -CH_2-S-CN, or CH_2-S-CH_3; \( R_5 \) is methyl, ethyl, propyl allyl, propargyl, cyclopropyl, phenylethyl, 2-thienylethyl or 3-thienylethyl; and \( A \) is -CH_2-. More preferably, \( R_5 \) is ethyl, propyl, phenylethyl, 2-thienylethyl, or 3-thienylethyl and \( R_1 \) is H and \( R_2 \) is H. Particularly preferred \( R_4 \) substituents in the above formula are -CH_2-S-CN and -CH_2-S-CH_3. Particularly preferred compounds of this invention are N-2-thienylethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine or a salt thereof and N-3-thienylethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine or a salt thereof.

This invention also embraces a process for the preparation of a compound of formula I which comprises reacting an appropriate precursor compound with a reducing agent when \( R_5 \) is H or reacting a compound of the formula:

\[
\begin{align*}
&\text{R}_1 &\text{R}_2 &\text{O} \\
&\text{R}_3 &\text{O} &\text{R}_4 \\
&\text{NH} &\text{NH} &\text{NH}
\end{align*}
\]

with an appropriate compound bearing a \( R_5 \) substituent, where \( R_5 \) is as defined above. Preferably the process comprises reacting a compound of the formula:
with a compound of the formula $R_5 COCl$ or $R_5 CN_2 COOH$ or $R_5 X$, where $X$ is halogen and $R_1$, $R_2$, and $R_5$ are as defined above.

The compounds of the invention are thus useful, as demonstrated by standard animal tests, for the treatment of disorders of the central nervous system, especially those related to the dopaminergic systems, because they invoke a strong dopaminergic response in such tests.

The compounds of the invention may contain up to 3 asymmetric carbon atoms. The therapeutic properties of the compounds may to a greater or lesser degree be ascribed to any of the stereoisomers. Thus, the pure enantiomers of the cis and trans forms, as well as mixtures thereof, are within the scope of this invention.

In another embodiment of this invention, there are provided pharmaceutical compositions comprising the foregoing compounds in combination with an inert pharmaceutical carrier.

This invention also encompasses a method for inducing a dopaminergic response by administering the foregoing compounds to a patient.

In still another embodiment of the present invention, there are provided pharmaceutical compositions in dosage form containing a clinically effective amount of one of the foregoing dopaminergic compounds.

This invention also embraces the use of compounds of Formula I above in the manufacture of a medicament, particularly a dopaminergic medicament and also the use of
these compounds as dopamine agonists, particularly for the treatment of Parkinson's disease.

The compounds of this invention may be prepared by the general method outlined below.

**General synthetic method**

Most of the 5, 6, 7, and/or 8-methoxy-1-tetralones are known. See, e.g., Autrey & Scullard, J. Am. Chem. Soc. 90, 4924 (1968); Thomas & Nathan, J. Am. Chem. Soc. 70, 331 (1948); Thrift, J. Chem. Soc. C, 288 (1967). The appropriate methoxy 1-tetralone (Compound 1) is reacted with n-butyl nitrite and potassium ethoxide to yield the 2-hydroxyimino-1-tetralone (Compound 2). The latter is reduced over palladium-barium sulfate to give the 2-amino-1-tetralone (Compound 3).

Reduction with sodium borohydride leads to the trans 2-amino-1-tetralol (Compound 4). Treatment of Compound 4 with chloroacetyl chloride or a suitably substituted derivative yields the chloroacetamide (Compound 5). (The size of the heterocyclic ring may be increased by substituting chloropropionyl chloride for chloroacetyl chloride.)
Reaction of (Compound 5) with sodium hydride or sodium hydroxide leads to ring closure to the lactam (Compound 6). Reduction of this lactam with lithium aluminum hydride gives the amine (Compound 7) in which A is $-\text{CH}_2-$. 

Alkylation with R*I or R*Br yields the tertiary amine (Compound 8). This can also be achieved by acylation of Compound 7 with an alkane carboxylic acid chloride followed by reduction with lithium aluminum hydride. ($R_5'$ is $R_5$ less one methylene unit.) A third alternative is to directly alkylate Compound 7 with a NaBH₄-carboxylic acid complex. On treatment with boron tribromide the methoxy group ($-\text{OCH}_3$) of Compound 8 is converted to a phenol ($-\text{OH}$).
to yield Compound 9. (The numbering of the carbons corresponds to A = -CH₂-.)

Prodrug esters of these compounds are prepared by reacting the phenols, resorcinols, or catechols with the desired corresponding acid chloride (Horn et al., J. Med. Chem. 25, 993; (1982)).

Details of this synthesis, together with modifications and variations specifically tailored for particular compounds, are set out more fully in the specific Examples which follow.

The preferred substituents for R₁ are H, OH, and -OGR₃. Preferred substituents for R₂ are H, CH₃, and -CR₃. R₃ is preferably methyl, ethyl, t-butyl, or phenyl. It is further preferred that R₄ be H, CH₂-S-CN, or CH₂SCH₃. Preferred substituents for R₅ are methyl, ethyl, propyl, allyl, propargyl, cyclopropyl, phenylethyl, and 2- and 3-thienylethyl.

Certain particularly preferred compounds include N-n-propyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b] [1,4]oxazine, N-ethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b] [1,4]oxazine, N-phenylethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b] [1,4]oxazine, N-2-thienylethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-
[1, 2-b] [1,4]oxazine, and prodrug esters (i.e., $R_1=\text{OC-R}_3$
and/or $R_2=\text{C-R}_3$) and pharmaceutically-acceptable salts
thereof.

The substituents $R_1$ and $R_2$ are defined as including a
large category of compounds, including various esters.
The most pharmaceutically active form of the compounds of
the invention is the hydroxy form. It will be understood,
however, that the ester compounds (and to some extent the
ether compounds) are prodrugs which are hydrolyzed in vivo
by esterases to produce the active hydroxy form. For this
reason, such hydrolyzable prodrug esters are deemed to be
equivalents of the hydroxy compounds for purposes of this
invention.

Accordingly, a wide range of ester and ether
substituted compounds fall within the scope of the
invention. Appropriate substituents may be selected by
those of ordinary skill in the art on the basis of
pharmaceutical considerations, such as palatability, and
pharmacokinetic considerations, such as rapidity of
hydrolysis to the active hydroxy form. Particularly
preferred prodrug esters are the pivalates and benzoates.

Pharmaceutical Formulation

The esters and acid addition salts of the compounds of
the general formula are prepared in the conventional
manner. As acid addition salts, the salts derived from a
therapeutically acceptable acid such as hydrochloric acid,
acetic acid, propionic acid and, more particularly, from a
di- or poly- basic acid such as phosphoric acid, succinic
acid, maleic acid, fumaric acid, citric acid, glutaric
acid, citraconic acid, glutarconic acid, tartaric acid,
malic acid, and ascorbic acid can be used.

A preferred embodiment of this invention is a method
of treatment which comprises the administration of a
therapeutically effective amount of the compounds of the
above formula. In general the daily dose can be from 0.01 mg/kg to 10 mg/kg per day and preferably from 0.2 mg/kg to 4 mg/kg per day, bearing in mind, of course, that in selecting the appropriate dosage in any specific case, consideration must be given to the patient's weight, general health, metabolism, age and other factors which influence response to the drug.

In another embodiment of this invention there are provided pharmaceutical compositions in dosage unit form which comprise from about 1 mg to about 150 mg of a compound of the above formula, and preferably from about 5 mg to about 100 mg.

The pharmaceutical composition may be in any form suitable for oral use, such as tablets, aqueous or oily suspensions, dispersible powders or granules emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide a pharmaceutically elegant and palatable preparation. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets. These excipients may be inert diluents, for example calcium carbonate, sodium carbonate, lactose, calcium phosphate; granulating and disintegrating agents, such as corn starch, or alginic acid; binding agents, for example starch, gelatine or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period.
Formulations for oral use may also be presented as hard gelatine capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatine capsules wherein the active ingredient is mixed with an oil medium, for example arachis oil, liquid paraffin or olive oil.

The present invention also comprehends aqueous suspensions containing the active compound in admixture with suitable pharmacologically-acceptable excipients. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol, for example polyoxyethylene sorbitol monooleate, or condensation product of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan monooleate. The said aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl-p-hydroxy benzoate, one or more coloring agents, one and more flavoring agents, and one and more sweetening agents, such as sucrose, saccharin, aspartame, mannitol, sorbitol, or sodium or calcium cyclamate.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent, and one or
more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavoring, and coloring agents, may also be present.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative, and flavoring and coloring agents.

The pharmaceutical compositions may also be in the form of a sterile injectable preparation, for example as a sterile injectable aqueous suspension. This suspension may be formulated as is conventional using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butandiol.

The pharmaceutical compositions may be tableted or otherwise formulated so that for every 100 parts by weight of the composition there are present between 5 and 95 parts by weight of the active ingredient and preferably between 25 and 85 parts by weight of the active ingredient. The dosage unit form for humans will generally contain between about 1 mg and about 100 mg of the active ingredient of the formula stated above.

From the foregoing formulation discussion it is apparent that the compositions of this invention can be administered orally or parenterally. The term parenteral as used herein includes subcutaneous injection, intravenous, intramuscular, or intrasternal injection or infusion techniques.

The following Examples illustrate the present invention. Parenthetical reference will be made to the corresponding compounds of the general synthesis, together
with reference to the identity and position of the R groups.

Example 1 illustrates the synthesis of a compound of the invention where R₂ is methyl and R₅ is propyl.

**EXAMPLE 1**

Preparation of N-n-propyl-9-methoxy 2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4]oxazine.

The known compound 2-hydroximino-7-methoxy-1-tetralone (Compound 2, R₁ = H, R₂ = Me on C7) was prepared according to the method of Chiemprasert et al., 1965 Liebig's Ann. Chem. 685, 141-148. The yield was 50%. 9.9 g of this compound was dissolved in a mixture of 250 ml of methanol and 40 ml of 2 N HCl. 1.5 g of Pd-BaSO₄ was added and the mixture was reduced in a Parr apparatus at room temperature under a hydrogen pressure of 0.9 atmospheres until the theoretical amount of hydrogen had been absorbed. The mixture was then filtered and the solvents were removed under reduced pressure. The resulting crude product was recrystallized from methanol-ether to yield a HCl salt [8.5 g, 77% yield, m.p. 234-235°] of the known amino ketone (Compound 3, R₁ = H, R₂ = Me on C7). This compound has been previously prepared by another method.

See Chiemprasert et al., 1965.

This amino ketone was reduced to the known trans-2-amino-7-methoxy-1-tetralol (Compound 4, R₁ = H, R₂ = Me on C7) with sodium borohydride according to the method of Chiemprasert et al., 1965. The yield was 78%.

To 3.4 g of this amino alcohol dissolved in 180 ml chloroform, a solution of 4.3 g of sodium hydroxide in 35 ml water was added. 3.38 g of chloracetylchloride was then added dropwise. This mixture was stirred for 2 hr. at room temperature. The reaction mixture was then poured into 200 ml of water. The separated aqueous layer was extracted with dichloromethane (3 x 50 ml) and then
combined with the chloroform layer. The organic extracts were washed with water (2 x 50 ml) and then dried over anhydrous magnesium sulfate. Removal of the organic solvents under reduced pressure yielded 3.1 g (78%) of the chloroacetamide (Compound 5, R₁ = H, R₂ = Me on C7, R₄ = H). Recrystallization from ethyl acetate produced white crystals m.p. 166-167°C.

700 mg of the chloroacetamide (Compound 5) was dissolved in 125 ml of dimethoxyethane (DME) and added dropwise to 400 mg of sodium hydride (55% in oil) in 25 ml DME. The reaction mixture was stirred for 2.5 hr at room temperature. It was then poured into 200 ml of water and extracted with dichloromethane (3 x 25 ml). The organic layer was separated, shaken with water, dried over magnesium sulfate and then evaporated to dryness. Recrystallization from acetone-hexane gave the lactam (Compound 6, R₁ = H, R₂ = Me on C9, R₄ = H) as a white solid, 480 mg (79%) m.p. 218-221°C.

The lactam (Compound 6) (470 mg) was dissolved in 50 ml of tetrahydrofuran (THF) and 380 mg LiAlH₄ was added. The mixture was refluxed for 3 hr. under a nitrogen atmosphere. The excess LiAlH₄ was destroyed by careful addition of 0.4 ml water followed by 0.4 ml 4N sodium hydroxide solution and a further 1.2 ml water. The mixture was filtered and the solid washed with ether. The organic filtrate was dried over magnesium sulfate. Removal of the solvent gave an oil. This was dissolved in dry ether and ether-HCl was added dropwise to produce the amine (Compound 7, R₂ = Me on C9, R₄ = H, A = -CH₂-) as a white solid, 480 mg (93%) m.p. 235-237°C.

450 mg of this amine, 800 mg of potassium carbonate, and 1.7 g of n-propyl iodide were dissolved in 50 ml of DMF. The solution was stirred for 2 hr at 55°C and then poured into 200 ml of water and extracted with ether (4 x 50 ml). The organic layer was separated and washed with a saturated solution of sodium chloride (3 x 10 ml) and once
with a 10% ammonium chloride solution (10 ml). The ether layer was then dried and evaporated to dryness to yield an oil which was converted to a HCl salt of the amine (Compound 8, R₁ = H, R₂ = Me on C9, R₄ = H, R₅=n-propyl, A = -CH₂-); 346 mg (66%); m.p. 214-217°C.

Example 2 illustrates the conversion of the methoxy compound into the active hydroxy compound.

**EXAMPLE 2**

**Preparation of N-n-propyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4]oxazine.**

500 mg of Compound 8 from Example 1 were dissolved in 35 ml of CH₂Cl₂ and the temperature of the solution was lowered to -60°C with a dry ice/acetone bath. 2 ml of 1 mol. solution of BBr₃ in CH₂Cl₂ was then added and the reaction mixture was stirred for 2 hr. at a temperature between -30 and -40°C. The temperature was then allowed to rise and the mixture was stirred for a further 20 hr. at room temperature. The reaction mixture was then poured into water (100 ml) made alkaline by the addition of dilute sodium bicarbonate solution and then extracted with ether (5 x 50 ml). The combined ether extracts were washed with saturated saline (3 x 10 ml) and dried over MgSO₄. Removal of the ether under reduced pressure yielded a semi-solid white product. Conversion to a HCl salt gave 450 mg of crude product. Recrystallization from ethanol yielded 310 mg (65%) of pure product, Compound 9, (R₁ = H, R₂ = OH on C9, R₄ = H, R₅ = n-propyl, A = -CH₂-), m.p. 244-247°C. The structures of all new compounds were established with the help of I.R. and N.M.R. spectroscopy, mass spectrometry and elemental analysis.

Example 3 illustrates the preparation of the 8,9-dimethoxy compound in which R₁ is OCH₃ on C8 and R₂ is CH₃ on C9.
EXAMPLE 3

Preparation of N-n-propyl-8,9-dimethoxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4]oxazine.

The known compound 2-hydroxyimino-6,7-dimethoxy-1-tetralone is prepared according to the method of Thrift, J. Chem Soc. C, 288 (1967). (Compound 2, R_1=OMe on C6, R_2=Me on C7.) The synthesis then proceeds according to Example 1 to form Compound 8, N-n-propyl-8,9-dimethoxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2b][1,4]oxazine.

Example 4 illustrates the preparation of the 8,9-dihydroxy compound from the compound of Example 3.

EXAMPLE 4

Preparation of N-n-propyl-8,9-dihydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4]oxazine.

The compound of Example 3 is converted into the 8,9-dihydroxy compound (Compound 9, R_1=OH on C8, R_2=H on C9, R_4=H, R_5=n-propyl and A = -CH_2-) in accordance with Example 2.

Example 5 demonstrates how any desired prodrug ester may be prepared from the corresponding hydroxy compound.

EXAMPLE 5

Preparation of a prodrug ester

The benzoate of the compound of Example 2 is prepared by reacting the hydroxy Compound 9 with benzoyl chloride. See Horn et al., J. Med. Chem. 25, 993 (1982).

Examples 6-10 illustrate the method by which substituent R_5 is selected by reacting Compound 7 with the appropriate hydrocarbon halide or acid.
EXAMPLE 6

Synthesis of N-ethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine.

The synthesis proceeds in accordance with Examples 1 and 2, with the exception that Compound 7 is reacted with ethylidodide instead of n-propylidodide.

EXAMPLE 7

Synthesis of N-propargyl-9-methoxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine.

The synthesis proceeds in accordance with Example 1, with the exception that Compound 7 is reacted with propargyl bromide instead of n-propylidodide.

EXAMPLE 8

Synthesis of N-phenylethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine

The synthesis proceeds in accordance with Example 1 with the exception that Compound 7 is reacted with phenylacetic acid and NaBH₄ instead of n-propylidodide, as follows:

NaBH₄ is added portionwise to a stirred solution of phenylacetic acid. The amine (Compound 7, R₂ = Me on C9, R₄ = H, A = -CH₂-) is added, and the mixture is refluxed and then treated with NaOH. The organic layer is dried with Na₂SO₄, and the solvent is evaporated. The residue is then converted to the HCl amine (Compound 8, R₁ = H, R₂ = Me on C9, R₄ = H, R₅ = phenylethyl, and A = -CH₂-). See Hacksell et al., J. Med. Chem. 22, 1469 (1979). The synthesis then proceeds in accordance with Example 2 to yield the desired compound.

EXAMPLE 9

Synthesis of N-2-thienylethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine

The synthesis proceeds in accordance with Example 8 with the exception that Compound 7 is reacted with 2-thienylacetic acid instead of phenylacetic acid.
EXAMPLE 10

Synthesis of N-3-thienylethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine

The synthesis proceeds in accordance with Example 8 with the exception that Compound 7 is reacted with 3-thienylacetic acid instead of phenylacetic acid.

Example 11 illustrates the manner in which R₄ substituents are placed on carbon 2.

EXAMPLE 11

Preparation of N-n-propyl-2-methyl-9-methoxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine.

The synthesis proceeds according to Example 1, except that Compound 4 is reacted with β-chloropropionyl chloride instead of chloroacetylchloride.

Examples 12 - 14 demonstrate another method for introducing R₄ substituents on carbon 2.

EXAMPLE 12

Preparation of 2-cyanomethyl-9-methoxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine.

The synthesis of Example 1 proceeds through preparation of Compound 4 (R₂=Me on C7). Compound 4 is then reacted with an excess of epichlorohydrin and distilled under reduced pressure to yield Compound 10.
Compound 10 is dissolved in 98% H₂SO₄ and heated to 150°C for 30 minutes to effect ring closure by dehydration. The resulting solution is cooled, added to ice and NaOH, and extracted with toluene. Concentration and recrystallization yields the 2-chloromethyl Compound 11 (R₄ = CH₂Cl). Treatment with potassium cyanide produces the desired compound. (Compound 12, R₁ = H, R₂=CH₃ on C9, R₄=CH₂CN, R₅=H.) If necessary, an alkali metal iodide in stoichiometric amounts may be used to accelerate the reaction and improve the yield.

\[
\begin{align*}
\text{H₂SO₄} & \xrightarrow{\Delta} \text{Cl} \\
\text{KCN} & \rightarrow \\
\end{align*}
\]

**EXAMPLE 13**

Preparation of 2-(Methylthio)methyl-9-methoxy-2,3,4a, 5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4]oxazine.

The synthesis proceeds according to Example 12, except Compound 11 is reacted with sodium thiomethoxide instead of potassium cyanide to form the desired 2-(methylthio)methyl compound (R₁ = H, R₂=CH₃ on C9, R₄=CH₂SCH₃, R₅=H).
EXAMPLE 14
Preparation of 2-hydroxymethyl-9-methoxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine.

Compound 11 is added to a solution of 10% molar excess of water in formamide and the resulting mixture is heated under reflux for 3 hours. The resulting solution is cooled and another 10% molar excess of water is added. The solution is further refluxed for 2 hours, cooled to room temperature and diluted with water. The resulting solution is made strongly basic (pH 12) with aqueous sodium hydroxide solution and the basic solution is extracted with an organic solvent, dried over MgSO₄ and concentrated to give the hydroxymethyl compound. The pure compound is obtained by recrystallization. (R₁=H, R₂=CH₃ on C₉, R₄=CH₂OH, R₅=H)

The manner in which an R₅ substituent may be added to Compound 12 for increased dopaminergic activity is demonstrated in Example 15.

EXAMPLE 15
Preparation of N-n-propyl-2(methylthio)methyl-9-methoxy-2,3,4a,5,6,10b-hexahydro-4H-naphth-[1,2-b][1,4] oxazine.

The compound of Example 13 is reacted with 1-bromopropane in the presence of a base such as diisopropylethylamine to form the N-n-propyl Compound 8 (R₁ = H, R₂ = CH₃ on C₉, R₄ = CH₂-SCH₃, R₅ = n-propyl).

To the extent that appropriately substituted tetralones (Compound 1) or 2-hydroxyimino-1-tetralones (Compound 2) are not available, they may be synthesized, e.g., from a substituted 4-phenylbutanoic acid in accordance with Examples 16 and 17.
EXAMPLE 16

Synthesis of substituted tetralones

4-(p-methoxyphenyl)butanoic acid (Compound 13, R_1=H, R_2=CH_3) is treated with polyphosphoric acid (PPA) to form 7-methoxytetralone via Friedel-Crafts acylation (Compound 1, R_1=H, R_2=CH_3 on C7).

The tetralone (Compound 1) is then reacted with N-butylnitrite and potassium ethoxide to yield 2-hydroxyimino-7-methoxy-1-tetralone (Compound 2, R_2=CH_3 on C7).

EXAMPLE 17

Synthesis of disubstituted tetralones.

4-(o-dimethylamino-p-methoxyphenyl)butanoic acid is cyclized with PPA as in Example 15 to yield 5-dimethylamino-7-methoxytetralone (Compound 1, R_1=N(CH_3)_2 on C5, R_2=CH_3 on C7).

The method by which the oxazine ring is enlarged to a seven-member ring is illustrated in Example 18.

EXAMPLE 18

Enlargement of the heterocyclic ring

The synthesis proceeds according to Example 1, with the exception that Compound 4 is reacted with β-chloropropionyl chloride instead of chloroacetyl chloride. The resulting compound has a seven-member heterocyclic ring (Compound 7, A = -CH_2CH_2-).

Pharmacological activity of certain analogues

The dopaminergic activity of three analogues (A,B,C) was evaluated in comparison with the indolic structural
analogue RU 29717 (Nedelec et al., 1983, J. Med. Chem., 26, 522) in three test systems. Compounds B and C are within the scope of the present invention. Compound A, a novel compound having an unsubstituted aromatic ring, is included for comparison to demonstrate the effect of aromatic ring substituents on activity.

EXAMPLE 19

Radioligand binding assay.

The ability of the above compounds to displace the specific binding of $^{3}$H-5,6-dihydroxy-N,N-dipropyl-2-aminotetralin, a potent DA receptor agonist (Fenstra et al., Life Sci., 32, 1313 (1983)) to homogenates of rat corpus striatum was studied.

Method

The assay was performed essentially according to the method of Leysen and Gommeran J. Neurochem. 36, 701 (1981) for $^{3}$H-apomorphine binding.

Results

<table>
<thead>
<tr>
<th>Compound</th>
<th>$IC_{50}$ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RU 29717</td>
<td>3.0</td>
</tr>
<tr>
<td>A</td>
<td>110.0</td>
</tr>
<tr>
<td>B</td>
<td>80.0</td>
</tr>
<tr>
<td>C</td>
<td>2.8</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>3.2</td>
</tr>
</tbody>
</table>
-23-

The IC$_{50}$ is the concentration of drug required to inhibit the specific binding by 50%. The results are presented as the mean values of 3 independent experiments each analyzed in triplicate over the concentration range 10$^{-11}$ to 10$^{-5}$M.

Conclusion

Compound C has a similar potency to RU 29717 and apomorphine. Compound B has some activity, and the least potent is compound A.

EXAMPLE 20

Effect on dopamine metabolism

Dopamine agonists are known to produce a lowering of the striatal levels of one of the main metabolites of dopamine, homovanillic acid, HVA, (Feenstra et al., 1983 Arch. Pharmaco., 324, 108).

Method

Female Wistar rats (160-180 g) were injected with the drugs under test dissolved in saline and were then decapitated 60 min later. The HVA content of the corpus striatum was determined according to the method of Westerink and Mulder (J. Neurochem., 1981 36, 1449).

Results

<table>
<thead>
<tr>
<th>Compound-dose</th>
<th>HVA (µg/g)</th>
<th>% control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.98 ± 0.08 (5)</td>
<td>100 ± 8.2</td>
</tr>
<tr>
<td>RU 29717, 0.2 µmol/kg</td>
<td>0.50 ± 0.04 (4)**</td>
<td>51.0 ± 4.1</td>
</tr>
<tr>
<td>RU 29717, 0.4 µmol/kg</td>
<td>0.46 ± 0.02 (4)**</td>
<td>46.9 ± 2.0</td>
</tr>
<tr>
<td>A, 0.4 µmol/kg</td>
<td>0.90 ± 0.02 (4)</td>
<td>91.8 ± 2.0</td>
</tr>
<tr>
<td>B, 0.4 µmol/kg</td>
<td>0.96 ± 0.12 (4)</td>
<td>98.0 ± 12.2</td>
</tr>
<tr>
<td>C, 0.2 µmol/kg</td>
<td>0.62 ± 0.04 (4)*</td>
<td>63.3 ± 4.1</td>
</tr>
<tr>
<td>C, 0.4 µmol/kg</td>
<td>0.47 ± 0.01 (4)</td>
<td>48.0 ± 1.0</td>
</tr>
</tbody>
</table>

Values are presented as means ± S.E.M. with the number of determinations in parenthesis.

* p < 0.05, ** p < 0.01, Dunnett's t-test.

Conclusions

Compound C is comparable in activity to RU 29717.
EXAMPLE 21

Presynaptic DA activity in the GBL model.

The ability of a dopamine agonist to counteract the gamma-butyrolactone (GBL) induced rise in DOPA levels in the rat striatum is an indication of its activity at presynaptic dopamine receptors. (Walters and Roth, 1976 Arch. Pharmacol., 296, 5).

Method

The experiments were performed in rats according to the method of Walters and Roth (ibid). The striatal levels of DOPA were determined using the method of Westerink and Mulder (1981 J. Neurochem. 36, 1449). NSD 1015 was used as decarboxylase inhibitor.

Results

<table>
<thead>
<tr>
<th>Compound</th>
<th>DOPA (µg/g)</th>
<th>% Reversal vs. GBL group</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSD 1015</td>
<td>1.89 ± 0.09</td>
<td>(5) 100</td>
</tr>
<tr>
<td>GBL + NSD 1015</td>
<td>5.41 ± 0.46</td>
<td>(5) 0</td>
</tr>
<tr>
<td>RU 29717, 0.2 µmol/kg</td>
<td>2.30 ± 0.16</td>
<td>(4) 88.4*</td>
</tr>
<tr>
<td>A, 0.2 µmol/kg</td>
<td>5.25 ± 0.09</td>
<td>(4) 4.5</td>
</tr>
<tr>
<td>B, 0.2 µmol/kg</td>
<td>4.80 ± 0.37</td>
<td>(4) 17.3</td>
</tr>
<tr>
<td>C, 0.2 µmol/kg</td>
<td>2.08 ± 0.12</td>
<td>(4) 94.6*</td>
</tr>
</tbody>
</table>

* p < 0.01, Dunnett's t-test.

Conclusion

Compound C appears to be slightly more potent than RU 29717 in this test system.

General Conclusion

Compounds B and C both exhibit useful levels of dopamine agonist activity. Compound C appears to be as active as the known DA agonist RU 29717 in various tests which evaluate pre- and post-synaptic dopaminergic activity. Compound A, lacking an R substituent on the aromatic ring, was significantly less active.
WHAT IS CLAIMED IS:

1. A compound of the formula:

\[
\begin{align*}
\text{wherein: } R_1 \text{ is } & \text{H, OH, } -\text{OCH}_3, -\text{CH}_2\text{OH}, -\text{NH}_2, -\text{NHCH}_3, \\
& -\text{NHCH}_2\text{CH}_3, -\text{N(CH}_3)_2, -\text{N(CH}_2\text{CH}_3)_2, \\
& \text{N-OC-R}_3;
\end{align*}
\]

\[
\begin{align*}
R_2 \text{ is } & \text{H, -CH}_3, \text{ or -C-R}_3; R_3 \text{ is phenyl, benzyl, or 1-4} \\
& \text{carbon alkyl; } R_4 \text{ is } \text{H, -CH}_3, -\text{CH}_2\text{OH}, -\text{CH}_2\text{-CN, -CH}_2\text{-S-CH}_3, \\
& -\text{CH}_2\text{-S-CN, or}
\end{align*}
\]

\[
\begin{align*}
R_5 \text{ is } & \text{H, 1-4 carbon alkyl, alkenyl, or alkynyl, or aralkyl} \\
& \text{having a 1-4 carbon alkylene moiety, propargyl, 2-} \\
& \text{thienylethyl or 3-thienylethyl, provided that when } R_4 \text{ is } \text{H} \\
& \text{or -CH}_3, R_5 \text{ is propargyl, 2-thienylethyl or} \\
& 3\text{-thienylethyl; } A \text{ is } -\text{CH}_2\text{- or -CH}_2\text{CH}_2\text{- or a salt thereof.}
\end{align*}
\]

2. A compound as claimed in Claim 1, wherein R_1 is

\[
\begin{align*}
H, \text{OH, or OC-R}_3; R_2 \text{ is } & \text{H or -C-R}_3; R_3 \text{ is methyl, ethyl,} \\
& \text{t-butyl, or phenyl; } R_4 \text{ is H, -CH}_2\text{-S-CN, or CH}_2\text{-S-CH}_3; R_5
\end{align*}
\]
is methyl, ethyl, propyl allyl, propargyl, cyclopropyl, phenylethyl, 2-thienylethyl or 3-thienylethyl; and A is -CH₂-.

3. A compound as claimed in Claim 1 or 2, wherein R₅ is ethyl, propyl, phenylethyl, 2-thienylethyl, or 3-thienylethyl.

4. A compound as claimed in Claim 2, wherein R₁ is H and R₂ is H.

5. A compound as claimed in Claim 1, wherein R₄ is -CH₂-S-CN.

6. A compound as claimed in Claim 1, wherein R₄ is -CH₂-S-CH₃.

7. A compound as claimed in Claim 1, comprising N-2-thienylethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth[1,2-b](1,4) oxazine or a salt thereof.

8. A compound as claimed in Claim 1, comprising N-3-thienylethyl-9-hydroxy-2,3,4a,5,6,10b-hexahydro-4H-naphth[1,2-b](1,4) oxazine or a salt thereof.

9. A compound as claimed in Claim 1, wherein R₁ is H, OH, or O-C-R₃; R₂ is H or -C-R₃; R₃ is methyl, ethyl, t-butyl, or phenyl; R₄ is H, -CH₂-S-CN, or CH₂-S-CH₃; and R₅ is 2-thienylethyl or 3-thienylethyl.

10. A pharmaceutical composition comprising a compound of the formula:

wherein: R₁ is H, OH, -OCH₃, -CH₂OH, -NH₂, -NHCH₃, -NHCH₂CH₃, -N(CH₃)₂, -N(CH₂CH₃)₂,

H, halogen, or
R₁ is H, OH, -OCH₃, -CH₂OH, -NH₂, -NHCH₃, -NHCH₂CH₃, -N(CH₃)₂, -N(CH₂CH₃)₂,

[, HNCCH₃, halogen, or...
R₂ is H, -CH₃, or -C-R₃; R₃ is phenyl, benzyl, or 1-4 carbon alkyl; R₄ is H, -CH₃, -CH₂OH, -CH₂-CN, -CH₂-S-CH₃, -CH₂-S-CN, or
\[
\text{\textbackslash N} \quad \text{\textbackslash O}
\]

R₅ is H, 1-4 carbon alkyl, alkenyl, or alkynyl, or aralkyl having a 1-4 carbon alkylene moiety, propargyl, 2-thienylethyl or 3-thienylethyl, provided that when R₄ is H or -CH₃, R₅ is propargyl, 2-thienylethyl or 3-thienylethyl; A is -CH₂- or -CH₂CH₂-; characterized in that said process comprises reacting an appropriate precursor compound with a reducing agent when R₅ is H or reacting a compound of the formula:

\[
\text{\textbackslash N} \quad \text{\textbackslash O}
\]

with an appropriate compound bearing a R₅ substituent, where R₅ is as defined above.

13. A process as claimed in Claim 12, which comprises reacting a compound of the formula:
with a compound of the formula $R_5\text{COCl}$ or $R_5\text{CH}_2\text{COOH}$ or $R_5X$, where $X$ is halogen and $R_1$, $R_2$, $R_4$, $A$ & $S$ are as defined in Claim 1.

14. A process as claimed in Claim 12, as applied to the preparation of a compound as claimed in any of Claims 2 to 9.

15. The use of a compound according to any of Claims 1-9 for the manufacture of a medicament.

16. The use of a compound according to any of Claims 1-9 for the manufacture of a dopaminergic medicament.

17. A compound as claimed in any of Claims 1 to 9 for use as a dopamine agonist.

# INTERNATIONAL SEARCH REPORT

## I. CLASSIFICATION OF SUBJECT MATTER

According to international Patent Classification (IPC) or to both National Classification and IPC:

- **INT. CL. 3**: A61K 31/535, 31/55; C07D 265/36, 267/14, 413/02
- **US. CL. 260/243.3, 244.4, 330.3, 330.7; 514/211, 230, 232, 234, 236, 237, 239
- 544/73, 101

## II. FIELDS SEARCHED

**Minimum Documentation Searched**

<table>
<thead>
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<th>Classification System</th>
<th>Classification Symbols</th>
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<td>260/243.3, 244.4, 330.3, 330.7</td>
</tr>
<tr>
<td></td>
<td>514/211, 230, 232, 234, 236, 237, 239</td>
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<tr>
<td></td>
<td>544/73, 101</td>
</tr>
</tbody>
</table>

**Documentation Searched other than Minimum Documentation**

to the extent that such documents are included in the fields searched

## CAS ONLINE

## III. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of Document, * with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No.</th>
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<tbody>
<tr>
<td>A</td>
<td>US, A, 4,420,480 Published 13 December 1984, Jones.</td>
<td>1-18</td>
</tr>
</tbody>
</table>

## IV. CERTIFICATION

- **Date of the Actual Completion of the International Search**: 17 May 1985
- **Date of Mailing of this International Search Report**: 07 JUN 1985

**International Searching Authority**: ISA/US

Form PCT/ISA/210 (second sheet) (October 1981)

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* Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance.
  - "E" earlier document but published on or after the international filing date.
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified).
  - "O" document referring to an oral disclosure, use, exhibition or other means.
  - "P" document published prior to the international filing date but later than the priority date claimed.
  - "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention.
  - "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step.
  - "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
  - "A" document member of the same patent family.
<table>
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<tr>
<th>Category</th>
<th>Citation of Document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to Claim No</th>
</tr>
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</table>
FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

(Continued From I.)

234, 236, 237, 239; 544/73,101

V. OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE

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

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

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

VI. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

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

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

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

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

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

Remark on Protest
☐ The additional search fees were accompanied by applicant’s protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/ISA/219 (supplemental sheet (2)) (October 1981)