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AZABICYCLO AND AZACYCLO OXIME AND AMINE CHOLINERGIC AGENTS AND METHODS OF TREATMENT

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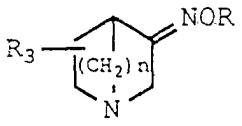
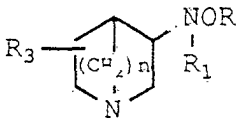
(57) Claim

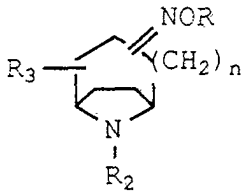
1. A compound of the following Formulas I, II, III, or IV, or a Z or E form thereof or a pharmaceutically acceptable salt thereof:



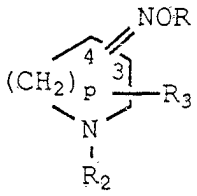
I



II



III



IV

wherein n is one or two;

wherein p is zero or one to four;

wherein each of R_1 and R_2 is hydrogen or straight or branched lower alkyl having from 1 to 4 carbon atoms;

.../2

wherein R_3 is hydrogen, a straight or branched lower alkyl group having from 1 to 6 carbon atoms, hydroxy, a straight or branched lower alkoxy group having from 1 to 4 carbon atoms, acyloxy group wherein the acyl moiety has from 2 to 5 carbon atoms, or the group $-(CH_2)_q-NR_8R_9$ wherein q is zero or 1 to 4 and each of R_8 and R_9 is the same or different and is hydrogen or a straight or branched lower alkyl group having from 1 to 4 carbon atoms; or

cycloalkyl having from 3 to 6 carbon atoms;

wherein R is hydrogen:

or the group:

$$-Y-Z$$

wherein Y is a bond or a straight or branched hydrocarbon chain having from 1 to 20 carbon atoms and optionally contains from 1 to 4 double and/or triple bonds; and Z is hydrogen;

a cycloalkyl group having from 3 to 6 carbon atoms;

an aromatic group selected from phenyl, 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl wherein the aromatic group is unsubstituted or is substituted with 1 or 2 substituents selected from chlorine, bromine, fluorine, trifluoromethyl, nitro, amino, amino substituted with 1 or 2 straight or branched lower alkyl groups having from 1 to 4 carbon atoms, or straight or branched alkoxy having from 1 to 4 carbon atoms;

$-NR_4R_5$ wherein R_4 and R_5 are the same or different and are hydrogen or straight or branched alkyl having from 1 to 4 carbon atoms;

$-\overset{O}{\overset{\|}{C}}NR_4R_5$ wherein R_4 and R_5 have the meanings defined above;

.../3

$-\overset{O}{\overset{\|}{C}}R_6$ wherein R_6 is a straight or branched alkyl group having from 1 to 6 carbon atoms;

-CN;

$-CO_2R_7$ wherein R_7 is hydrogen, a straight or branched lower alkyl having from 1 to 6 carbon atoms and is straight or branched, or benzyl; or

$-XR_{10}$ where in X is oxygen or sulfur and R_{10} is a straight or branched hydrocarbon chain having from 1 to 6 carbon atoms and which optionally contains 1 or 2 double or triple bonds;

with the proviso that the following compounds are excluded: (a) compounds of Formula I wherein n is two, and R is hydrogen, or the group Y-Z wherein Y is a bond and Z is $-C(=O)NR_4R_5$ or $-C(=O)R_6$; and

(b) compounds of Formulas III and IV wherein R is hydrogen.

16. A pharmaceutical composition useful for alleviating pain in a mammal comprising an analgesically effective amount of a compound of any one of Claims 1 to 15 together with a pharmaceutically acceptable carrier.

17. A pharmaceutical composition useful for the treatment of the symptoms of cognitive decline in a patient in need thereof which comprises administering an effective amount of a compound of any one of Claims 1 to 15 together with a pharmaceutically acceptable carrier.

COMMONWEALTH OF AUSTRALIA 630542

FORM 10

PATENTS ACT 1952

COMPLETE SPECIFICATION

FOR OFFICE USE:

Class Int.Class

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Lodged:

Complete Specification Lodged:
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Priority:

Related Art:

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Complete Specification for the Invention entitled:

"AZABICYCLO AND AZACYCLO OXIME AND AMINE CHOLINERGIC AGENTS AND METHODS OF TREATMENT"

The following statement is a full description of this invention, including the best method of performing it known to us:-

AZABICYCLO AND AZACYCLO OXIME AND AMINE CHOLINERGIC AGENTS AND METHODS OF TREATMENT

FIELD OF INVENTION

The present invention is a class of oximes and amines which are muscarinic agonists, rendering them useful as pharmaceutical agents. More specifically, the compounds are azabicyclic and azacyclic oximes and amines.

RELATIONSHIP TO OTHER APPLICATIONS

This application is a continuation-in-part of copending application Serial Number 07/591,647, filed October 2, 1990, which is a continuation-in-part of copending application Serial Number 07/488,916, filed March 6, 1990.

BACKGROUND

Disorders of cognition are generally characterized by symptoms of forgetfulness, confusion, memory loss, attentional deficits, and/or, in some cases, affective disturbances. These symptoms may arise as a result of the general aging process and/or from organic brain disease, cerebrovascular disease, head injury, or developmental or genetic defects.

The general decrease in cognitive function which accompanies the aging process is well accepted. The same phenomenon has been observed and documented in many lower mammals, including those routinely employed in pharmacological testing programs for screening and

predicting usefulness for particular drugs in higher animals, including humans.

Although disorders of cognition often accompany the general aging process, presenile and senile primary degenerative dementia are the most common accepted causes of mental deterioration in the elderly. It has been estimated that at least ten percent of persons over 60 years of age will eventually suffer severe mental deterioration. A much larger number will experience cognitive decline of sufficient severity to impede their activities.

Many of the symptoms of cognitive disorders, especially impaired memory, are associated with decreased acetylcholine synthesis and the impairment of cholinoreceptive neurons. In the hippocampus and cerebral cortex of patients suffering from primary degenerative dementia, for example, the level of the enzyme choline acetyltransferase (CAT) can be reduced by as much as 90%. (See Davies, et al, The Lancet, 1976 (Vol. 2):1403; Perry, et al, J. Neurol. Sci., 34:247-265 (1977); and White, et al, The Lancet, 1977 (Vol. 1):668-670).

Since CAT catalyzes the synthesis of acetylcholine from its precursors choline and acetyl coenzyme A, the loss of CAT reflects the loss of cholinergic, or acetylcholine-releasing, nerve endings in the hippocampus and cerebral cortex. There is abundant evidence that cholinergic terminals in the hippocampus are critically important for memory formation.

The cholinergic hypothesis suggests that drugs which restore acetylcholine levels or which mimic the action of acetylcholine (i.e., are cholinomimetic) are effective in correcting this deficit in neurotransmitter chemical and provide treatment of the

memory impairment symptom of cerebral insufficiency. Considerable biochemical, pharmacological, and electrophysiological evidence supports the hypothesis that deficits in the cholinergic system underlie geriatric cognitive dysfunction. (See C. Peterson and G. E. Gibson, Neurobiol. Aging, 4:25-30 (1983)). Aged humans and nonhuman primates with decreased cognition show improved memory when they are treated, for example, with acetylcholinesterase inhibitors such as physostigmine. These agents increase the available supply of synaptic acetylcholine by inhibiting its hydrolysis.

Aminopyridines such as 3,4-diaminopyridine ameliorate age-related cognitive deficits by increasing the release of acetylcholine from presynaptic nerve terminals, thus increasing synaptic acetylcholine. (See H. P. Davis, et al, Exp. Aging Res., 9:211-214 (1983)).

It has been known for some time that the natural alkaloid, muscarine, has the ability to act relatively selectively at autonomic effector cells to produce qualitatively the same effects as acetylcholine. Two related alkaloids, pilocarpine and arecoline (the methyl ester of 1,2,5,6-tetrahydro-1-methyl-3-pyridinecarboxylic acid), have the same principal sites of action as muscarine and acetylcholine and are thus classified as having "muscarinic" action. Although these naturally occurring alkaloids are of great value as pharmacological tools, present clinical use is largely restricted to the use of pilocarpine as miotic agent.

Recently it has been demonstrated that arecoline is effectively in ameliorating some of the symptoms of cognitive disorders in patients clinically diagnosed as having presenile primary degenerative dementia.

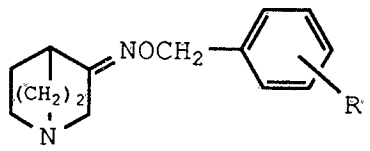
Significant improvement was observed in a test of picture recognition after administration of arecoline to patients in a double-blind study. (See Christie, et al, Brit. J. Psychiatry, 138:46-50 (1981)).

INFORMATION DISCLOSURE STATEMENT

Certain 3- or 4-ketoximes of 1-(lower alkyl)-1,2,5,6-tetrahydropyridines in which the oxygen is unsubstituted are disclosed in United States Patent 3,004,979, having utility as parasympathomimetic agents acting on nonstriated muscle.

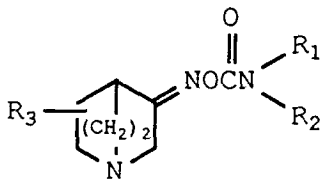
U.S. 4,710,508 describes O-substituted 1-(1,2,3,6-tetrahydro-1-methyl-3-pyridinyl)ketone oximes and O-substituted 1-(1,2,3,6-tetrahydro-4-pyridinyl)ketone oximes which are useful as analgesic agents or agents for the treatment of the symptoms of cerebral insufficiency characterized by decreased central acetylcholine production.

Dissertation Abstracts Int. B 1984, 45(7), 2120; CA102:113440 m describes oxime-O-ethers of the following formula as having anticholinergic properties:



wherein R is F, Cl, Br, NO_2, OCH_3, CF_3, or CH_3. Particularly relevant are pages 128-136, 166, 167, 198-203.

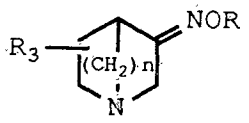
French 2,086,292 describes 3-quinuclidinone oxime carbamates of the following formula having insecticidal and acaricidal activity.



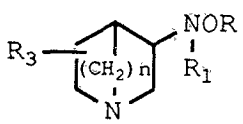
wherein R_3 is alkyl, alkenyl, alkylidene, halogen, cyano, haloalkyl, haloalkenyl, alkoxy, etc; R_1 and R_2 are hydrogen, lower alkyl, acyl which may be substituted, lower alkenyl, or the group $R-O-CH_2-$ wherein R is methyl, ethyl, isopropyl; propyl-1,2-diene, allyl, 1-methyl-2-propenyl; phenyl or benzyl.

SUMMARY OF THE INVENTION

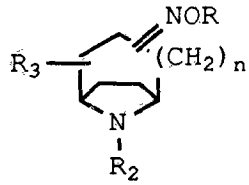
The present invention is directed to compounds of the following general Formulas I, II, III, and IV and pharmaceutically acceptable salts thereof.



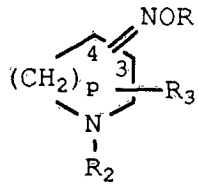
I



II



III



IV

wherein n is one or two; wherein p is zero or one to four, wherein each of R_1 and R_2 is hydrogen or straight or branched lower alkyl having from 1 to 4 carbon atoms; wherein R_3 is hydrogen, a straight or branched lower alkyl group having from 1 to 6 carbon atoms, or cycloalkyl having from 3 to 6 carbon atoms, hydroxy, a straight or branched lower alkoxy group having from 1 to 4 carbon atoms, an acyloxy group wherein the acyl moiety has from 2 to 5 carbon atoms or the group $-(CH_2)_qNR_8R_9$ wherein q is zero or one to four and each of R_8 and R_9 is the same or different and is hydrogen or a straight or branched lower alkyl group having from 1 to 4 carbon atoms; wherein R is hydrogen or the group:

$$-Y-Z$$

wherein Y is a bond or a straight or branched hydrocarbon chain having from 1 to 20 carbon atoms and optionally contains from 1 to 4 double and/or triple bonds; and Z is hydrogen;

a cycloalkyl group having from 3 to 6 carbon atoms;

an aromatic group selected from phenyl, 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl wherein the aromatic group is unsubstituted or is substituted with 1 or 2 substituents selected from chlorine, bromine, fluorine, trifluoromethyl, nitro, amino, amino substituted with 1 or 2 straight or branched lower alkyl groups having from 1 to 4 carbon atoms, or straight or branched alkoxy having from 1 to 4 carbon atoms;

$-NR_4R_5$ wherein R_4 and R_5 are the same or different and are hydrogen or straight or branched alkyl having from 1 to 4 carbon atoms;

$-\overset{O}{\overset{\|}{C}}NR_4R_5$ wherein R_4 and R_5 have the meanings defined above;

$-\overset{O}{\overset{\|}{C}}R_6$ wherein R_6 is a straight or branched alkyl group having from 1 to 6 carbon atoms;

$-CN$;

$-CO_2R_7$ wherein R_7 is hydrogen, a straight or branched lower alkyl having from 1 to 6 carbon atoms and is straight or branched, or benzyl; or

$-XR_{10}$ wherein X is oxygen or sulfur and R_{10} is a straight or branched hydrocarbon chain having from 1 to 6 carbon atoms and which optionally contains 1 or 2 double or triple bonds;

with the proviso that the following compounds are excluded: (a) compounds of Formula I wherein n is two, and R is hydrogen, or the group Y-Z wherein Y is a bond and Z is $-C(=O)NR_4R_5$ or $-C(=O)R_6$; and (b) compounds of Formulas III and IV wherein R is hydrogen.

Pharmaceutical compositions comprising compounds of Formulas I, II, III, or IV are also included in the present invention as well as methods of using the compounds as analgesics and in the treatment of cognitive decline.

DETAILED DESCRIPTION OF THE INVENTION

In the compounds depicted by general Formulas I, II, III, and IV the various substituents are further described as follows. Illustrative examples of straight or branched lower alkyl having from 1 to 4 carbon atoms or from 1 to 6 carbon atoms included methyl, ethyl, n-propyl, isopropyl, n-butyl, tert-butyl, n-pentyl, n-hexyl.

Illustrative of lower alkoxy groups having from 1 to 4 carbon atoms are methoxy, ethoxy, and n-propoxy.

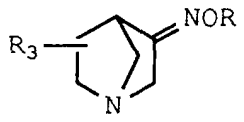
Illustrative examples of a saturated straight or branched hydrocarbon chain having from 1 to 8 carbon atoms include n-octyl, n-heptyl, and all the illustrative examples of straight or branched lower alkyl groups having from 1 to 6 carbon atoms set forth above.

Illustrative examples of straight or branched unsaturated hydrocarbon chains which contain from 1 to 3 unsaturations which are double or triple bonds are ethenyl, 2,4-pentadienyl, 1,4-pentadienyl, 2,4-pentadiynyl, 1,4-pentadiynyl, (E&Z) 2-penten-4-ynyl, 2-pentyn-4-enyl, 2-propenyl, 3-butenyl, 1-methyl-2-propenyl, 2-pentenyl, 2-ethyl-3-butenyl, 4-hexenyl, ethynyl, 2-propynyl, 1-methyl-2-propynyl, 1-ethyl-2-propynyl, 1-methyl-3-butynyl, 3-butynyl, or 4-pentynyl. Illustrative examples of cycloalkyl groups having from 3 to 6 carbon atoms are cyclopropyl, cyclobutyl, and cyclohexyl.

Pharmaceutically acceptable acid addition salts of the compounds of Formulas I, II, III, and IV are illustratively hydrochloric, sulfuric, phosphoric, acetic, benzoic, citric, malonic, salicylic, malic, fumaric, oxalic, succinic, tartaric, lactic, gluconic, ascorbic, maleic, aspartic, benzenesulfonic, methane and ethanesulfonic, hydroxymethane- and hydroxyethanesulfonic. (See, for example, "Pharmaceutical Salts," J. Pharm. Sci. 66(1):1-19 (1977).

Preferred compounds of the present invention are those of Formulas I and III with the compounds of Formula I being more preferred. The most preferred compounds of this invention are those of Formula I

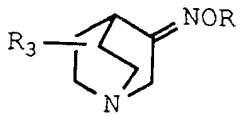
wherein n is one, i.e., compounds of the following Formula V:



V

In general, Formula V R and R_3 have the same meanings as set forth above for Formulas I, II, III, and IV. Compounds of Formula V wherein R_3 is hydrogen and R is other than hydrogen or Y-Z wherein Z is NR_4R_5 are more preferred.

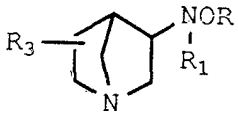
Compounds of Formula I wherein n is two may be depicted as set forth below in Formula VI:



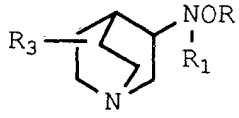
VI

wherein R and R_3 have the meanings defined above.

Compounds of Formula II wherein n is one may be depicted as set forth below in Formula VII and wherein n is two may be depicted as set forth below in Formula VIII:



VII



VIII

In Formulas VII and VIII the substituent groups represented by R_3, R, and R_1 have the meanings defined hereinabove in Formulas I, II, III, and IV.

In the compounds of Formulas III and IV the =NOR group is attached to either the 2-, 3-, or 4-position

(Formula III) or the 3- or 4-position (Formula IV) of the ring.

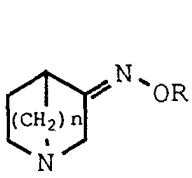
In addition to the novel compounds of the present invention as represented by Formulas I through VIII above, the present invention provides novel pharmaceutical preparations.

The present invention provides pharmaceutical compositions useful as analgesic agents comprising an analgesically effective amount of a compound as defined above in combination with a pharmaceutically acceptable carrier. In another aspect, the present invention provides a method of alleviating pain in a mammal comprising administering to a mammal in need of such treatment an analgesically effective amount of a compound as defined above in combination with a pharmaceutically acceptable carrier.

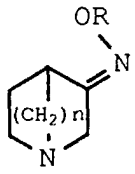
In another aspect, the present invention provides pharmaceutical compositions for treating the symptoms of senile cognitive decline comprising a cholinergically effective amount of a compound as defined above in combination with a pharmaceutically acceptable carrier. In yet another aspect, the present invention provides a method of treating the symptoms of senile cognitive decline in the elderly characterized by decreased cerebral acetylcholine production or release comprising administering to a patient in need of such treatment of cholinergically effective amount of a compound as defined above in combination with a pharmaceutically acceptable carrier.

The compounds of the present invention may exist in either of two Z and E isomeric forms. The present invention includes goth forms of the compounds as well as mixtures of the Z and E forms. Illustratively Formulas IX and X depict the Z and E forms of the

compounds of Formula I. Moreover, in those compounds in which there is a double bond in a carbon chain, both the Z and E forms of the olefins are included in the present invention.

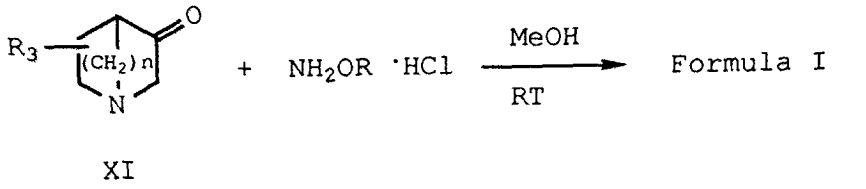


Z form
IX

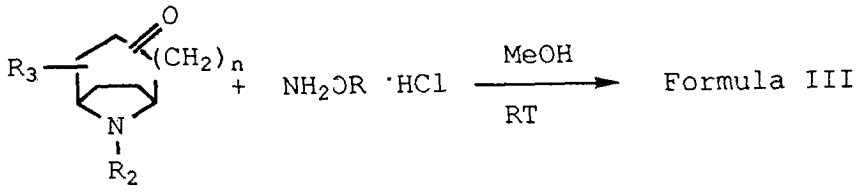


E form
X

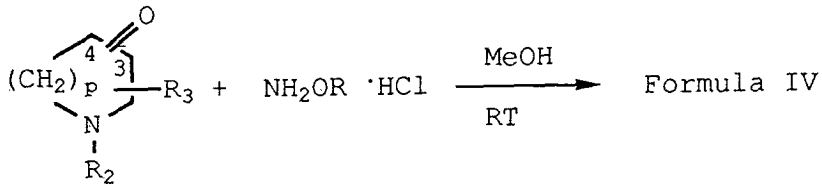
The compounds of Formulas I, III, and IV are prepared by reacting a ketone of the following Formulas XI, XII, and XIII with an amine of the formula $NH_2OR \cdot HCl$ wherein R and R_3 have the meanings defined in Formulas I, II, III, and IV as depicted below:



XI



XII



XIII

In each of the above depicted reactions, typically methanol is used as the solvent and the reaction is carried out at room temperature.

The compounds of Formula II are prepared by reducing Formula I compounds by procedures well known in the art, for example, by treatment with sodium cyanoborohydride under controlled pH conditions. Therefore, not only are the compounds of Formula I pharmaceutically useful they are also useful as starting material to make pharmaceutically useful compounds. Similarly, the compounds of Formula I wherein R is hydrogen may be used to prepare compounds of Formula I wherein R is the group $-C(=O)R_6$.

The salts are prepared by contacting the free base form of the compounds of this invention with a

sufficient amount of the desired acid to produce the salt in the conventional manner. The free base forms may be regenerated, if desired, by treating the salt form with a base. For example, dilute aqueous solutions of such bases as sodium hydroxide, potassium carbonate, ammonia, and sodium bicarbonate maybe utilized for this purpose.

The free base forms of the compounds of this invention differ somewhat from their respective salt forms in such physical properties as melting point and solubility in polar solvents, but the salts are otherwise equivalent to their respective free acid or base forms for the purposes of the invention.

The starting materials represented by Formulas XI, XII, and XIII are known in the art or can be prepared by procedures generally known in the art. See, for example, J. Saunders, et al, J. Chem. Soc., Chem. Comm. 1988, 1618 and R. J. Snow and L. J. Street, Tet. Lett. 1989, 30, 5795. Also, the amines represented by NH_2OR are commercially available or may be prepared by procedures generally known in the art.

EXAMPLE 1

1-Azabicyclo[2.2.1]hept-3-one oxime hydrochloride

1-Azabicyclo[2.2.1]hept-3-one was prepared by the procedure described in J. Chem. Soc., Chem. Comm. 1988, 1618.

1-Azabicyclo[2.2.1]hept-3-one (2 g, 18 mmol) and hydroxylamine hydrochloride (1.25 g, 18 mmol) was dissolved in 10 mL MeOH and stirred at room temperature for 18 hours. The reaction mixture was concentrated in vacuo. The crystalline residue was recrystallized from ethanol to afford 2.04 g (70%) of the title product, m.p. 211°C.

$C_6H_{11}ClN_2O$: Calc.: C, 44.31; H, 6.82; N, 17.23.

Found: C, 44.25; H, 6.64; N, 17.18.

Mass Spec.: m/e 126.1 (M+ for free base)

^{1}H NMR: δ ($CDCl_3$) 0.87 (1H, m), 1.31-1.46 (1H, m), 2.39-2.57 (5H, m), 3.01-3.21 (2H, m), 10.15 (1H, s), 10.58-10.82 (1H, br s). ^{13}C NMR δ ($CDCl_3$) 25.2, 40, 50.5, 54.5, 58.5, 153.5

EXAMPLE 2

1-Azabicyclo[2.2.1]hept-3-one, O-ethyloxime hydrochloride

1-Azabicyclo[2.2.1]hept-3-one (2 g, 18 mmol) was dissolved in 25 mL of methanol. Ethoxyamine hydrochloride (1.76 g, 18 mmol) was added and the reaction was stirred at room temperature for 18 hours. The reaction was concentrated in vacuo to afford a yellow solid. The residue was dissolved in water, basified with saturated aqueous potassium carbonate, and extracted with dichloromethane (3 x 150 mL). The combined extracts were dried over anhydrous sodium sulfate and concentrated in vacuo to afford a clear, yellow liquid. The liquid was dissolved in diethyl ether and filtered through Celite. The filtrate was treated with ethereal hydrogen chloride to yield 2.5 g (75%) of the title product, m.p. 158-160°C.

$C_8H_{15}ClN_2O$: Calc.: C, 50.39; H, 7.93; N, 14.69.

Found: C, 49.96; H, 7.76; N, 14.56.

Mass Spec.: m/e 154.1 (M+ for free base)

^{1}H NMR: δ ($CDCl_3$) 1.20-1.28 (3H, t), 1.97-2.05 (1H, m), 240-253 (1H, m), 3.29-3.42 (2H, m), 3.52-3.62 (2H, m), 3.83-3.95 (2H, m), 4.06-4.14 (2H, q), 4.20-4.27 (1H, m). ^{13}C NMR: δ ($CDCl_3$) 14.4, 26.1, 40, 51.7, 55.8, 59.6, 70.3, 153.1.

EXAMPLE 3

1-Azabicyclo[2.2.1]hept-3-one, O-methyloxime hydrochloride

1-Azabicyclo[2.2.1]hept-3-one (1.9 g, 17.1 mmol) was dissolved in 10 mL of methanol. Methoxyamine hydrochloride (1.4 g, 17.1 mmol) was added and the reaction was stirred at room temperature for 18 hours. The reaction was concentrated in vacuo to afford a white solid. Recrystallization of the residue from ethanol-diisopropyl ether afforded 2.27 g (75%) of the title product as a mixture of syn and anti isomers, m.p. 210-211°C.

$C_7H_{13}ClN_2O$: Calc.: C, 47.59; H, 7.42; N, 15.86.
Found: C, 47.46; H, 7.54; N, 15.84

Mass Spec.: m/e 140.1 (M+ for free base).

^1H NMR: δ ($CDCl_3$) 1.99 (1H, m), 2.36-2.52 (1H, m), 3.37-3.65 (4H, m), 3.86, 3.88 (3H, 2s) (3H, s), 3.89-4.00 (2H, m), 4.21-4.29 (1H, m). ^{13}C NMR: δ ($CDCl_3$) 25, 26, 37.2, 40, 51.5, 51.7, 55.7, 56.5, 59.0, 59.6, 62.3, 153, 153.5.

The above procedure was utilized for the synthesis of the products listed in Table 1.

TABLE 1
(Page 1 of 4)

Hydroxylamine·HCl	Product	Example No.
$NH_2OCH_2C{\equiv}CH$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2-propynyl)oxime hydrochloride, m.p. 203°C (dec)	4
NH_2OCH_2Ph	1-Azabicyclo[2.2.1]-heptan-3-one, O-(phenylmethyl)oxime hydrochloride, m.p. 173-174°C	5
$NH_2OCH_2CH_2CH_3$	1-Azabicyclo[2.2.1]-heptan-3-one, O-propyloxime hydrochloride, m.p. 165-166°C	6
$NH_2OCH(CH_3)_2$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(1-methylethyl)oxime hydrochloride, m.p. 188-189°C	7
$NH_2OCH_2CH{=}CH_2$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2-propenyl)oxime oxalate, m.p. 126-127°C	8
$NH_2OCH_2CH_2NH_2$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2-aminoethyl)oxime hydrochloride, m.p. 232-234°C	9
NH_2OCH_2 	1-Azabicyclo[2.2.1]-heptan-3-one, O-(cyclopropylmethyl)-oxime hydrochloride, m.p. 165-167°C	10
$NH_2OCH_2CH_2OCH_3$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2-methoxyethyl)oxime hydrochloride, m.p. 176-178°C	11

TABLE 1
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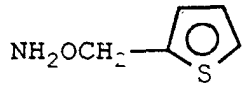
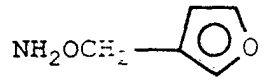
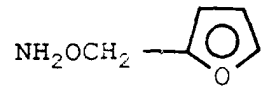
Hydroxylamine·HCl	Product	Example No.
NH_2OPh	1-Azabicyclo[2.2.1]-heptan-3-one, O-phenyloxime, hydrochloride, m.p. 130-131°C	12
	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2-thienylmethyl)oxime hydrochloride, m.p. 188-191°C	13
	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2-furylmethyl)oxime oxalate, m.p. 116-117°C	14
	1-Azabicyclo[2.2.1]-heptan-3-one, O-(3-furylmethyl)oxime hydrochloride, m.p. 120-122°C	15
$NH_2OCH(CH_3)CH=CH$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(1-methyl-2-propenyl)oxime oxalate, m.p. 120-122°C	16
$NH_2OCH_2CH_2CH=CH_2$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(3-butenyl)oxime oxalate, m.p. 96-98°C	17
$NH_2OC(CH_3)_3$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(tert-butyl)oxime hydrochloride, m.p. 231-232°C	18
$NH_2OCH_2-C\equiv C-CH_3$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2-butynyl)oxime oxalate, m.p. 68-70°C	19
$NH_2OCH_2CH_2-C\equiv CH$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(3-butynyl)oxime oxalate, m.p. 177-178°C	20

TABLE 1
(Page 3 of 4)

Hydroxylamine·HCl	Product	Example No.
$NH_2OCH(CH_3)C{\equiv}CH$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(1-methyl-2-propynyl)oxime oxalate, m.p. 108-111°C	21
$NH_2OCH_2CH{=}CH{-}C{\equiv}CH$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(E-2-penten-4-ynyl)oxime hydrochloride, m.p. 130-134°C	22
$NH_2OCH_2CH{=}CH{-}C{\equiv}CH$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(Z-2-penten-4-ynyl)oxime hydrochloride	23
$NH_2OCH_2C{\equiv}C{-}CH{=}CH_2$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2-pentyn-4-enyl)oxime hydrochloride	24
$NH_2OCH_2C{\equiv}C{-}C{\equiv}CH$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2,4-pentadiynyl)oxime hydrochloride	25
$NH_2O{-}CH(C{\equiv}CH)_2$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(1-ethynylpropynyl)-oxime hydrochloride	26
$H_2NOCH_2C{\equiv}N$	[[(1-Azabicyclo[2.2.1]-hept-3-ylidene)amino]-oxy]acetonitrile hydrochloride, m.p. 202-203°C	27
$H_2NOCH_2CH{=}CH{-}CH{=}CH_2$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2,4-pentadienyl)oxime hydrochloride, m.p. 150-154°C	28
$H_2NOCH_2CH{=}CH{-}CH{=}CHCH_3$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2,4-hexadienyl)oxime hydrochloride, m.p. 179-180°C	29

TABLE 1
(Page 4 of 4)

Hydroxylamine·HCl	Product	Example No.
$H_2NOCH_2CH=CHCH_3$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(Z-2-butenyl)oxime oxalate, m.p. 135-140°C	30
$H_2NOCH_2CH=CHCH_3$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(E-2-butenyl)oxime hydrochloride, m.p. 154-156°C	31
$H_2NOCH_2C\equiv CCH_2C\equiv CH$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2,5-hexadiynyl)oxime oxalate, m.p. 144-146°C	32
$H_2NOCH_2CH=CH-C\equiv CH$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(2-penten-4-ynyl)oxime oxalate, m.p. 130-134°C	33
$H_2NOCH_2C\equiv C-CH_2OCH_3$	1-Azabicyclo[2.2.1]-heptan-3-one, O-(4-methoxy-2-butynyl)oxime hydrochloride, m.p. 193-195°C	34
$H_2NOCH_2CO_2CH_3$	[[(1-Azabicyclo[2.2.1] heptan-3-ylidene) amino]oxy] acetic acid methyl ester hydrochloride, m.p. 174-175°C	35
$H_2NOCH_2C\equiv CCH_2CH_3$	1-Azabicyclo[2.2.1] heptan-3-one, O-(2-pentynyl)oxime hydrochloride, m.p. 147-149°C	36

EXAMPLE 37

1-Azabicyclo[2.2.2]octan-3-one, O-methyloxime

A mixture of the ketoamine·HCl (5.56 g, 0.03 mole), 3-quinuclidinone (2.51 g, 0.03 mole), and potassium carbonate (11.0 g, 0.08 mole) in methanol (250 mL) was allowed to reflux for 2 hours. After removing the methanol under reduced pressure, the solution was suspended in water and extracted with ethyl ether (3 x 125 mL), dried over $MgSO_4$, filtered, and concentrated to give a mixture of syn and anti isomers. The oxalate salt was formed from the oil, m.p. 125-28°C.

NMR: δ ($CDCl_3$) 9.01 (br s, 2H), 4.03 (s, 1H), 3.89 (s, 1H), 3.80, 3.79 (two s, 3H), 3.27-3.12 (br m, 5H), 2.10-1.79 (br m, 4H). $_{13}C$ NMR: δ 164.7, 155.1, 154.6, 61.4, 59.4, 50.7, 50.1, 45.6, 45.5, 26.7, 22.5, 22.1, 21.4, 21.2 IR (cm^{-1}) 2361, 1748, 1693, 1652, 1463, 1403, 1320, 1221, 1103, 1048, 861, 832, 785, 721, 670.

Mass Spec.: 154, 137, 123, 108, 97, 82, 67, 55.

C, H, N $C_8H_{14}N_2O \cdot 1.25C_2H_2O_4$

Calc.: C, 47.28; H, 6.23; N, 10.50.

Found: C, 47.57; H, 6.32; N, 10.27.

EXAMPLE 38

(E)- and (Z)- 1-Azabicyclo[2.2.2]octan-3-one, O-(2-propynyl)oxime

3-Quinuclidinone (1.5 g, 12 mmol) and 2-propynyl-hydroxylamine hydrochloride (1.29 g, 12 mmol) were dissolved in 20 mL of methanol and stirred at room temperature for 16 hours. The reaction was evaporated in vacuo to afford a dark brown semi-solid. The crude semi-solid was basified with aqueous K_2CO_3 and extracted with chloroform. The chloroform extract was evaporated to give the crude oxime as a mixture of the

E- and Z-isomers. Separation of the isomers by chromatography (silica gel; dichloromethane-acetone-methanol (150:10:5), gave isomer A, 1.0 g (m.p. 81-83°C) and isomer B, 0.42 g (m.p. 100-101°C), respectively.

Isomer A:

$C_{10}H_{14}N_2O$: Calc.: C, 67.39; H, 7.92; N, 15.72.
Found: C, 67.26; H, 7.94; N, 15.59.

Mass Spec.: m/e 178

^1H NMR: δ ($CDCl_3$) 1.7-1.85 (4H, m); 2.40-2.55 (1H, m), 2.58-2.65 (1H, m), 2.75-3.05 (4H, m), 3.63 (@H, s), 4.62 (2H, s). $_{13}C$ NMR: δ ($CDCl_3$) 26.3, 28.6, 47.2, 52.3, 60.9, 74.2, 81.0, 166.0.

Isomer B:

$C_{10}H_{14}N_2O$: Calc.: C, 67.39; H, 7.92; N, 15.72.
Found: C, 66.95; H, 8.02; N, 15.59.

Mass Spec.: m/e 178

^1H NMR: δ ($CDCl_3$) 1.6-1.8 (4H, m), 2.45-2.50 (1H, m), 2.78-3.0 (4H, m), 3.35-3.44 (1H, m), 3.45 (2H, s), 4.6 (2H, s). $_{13}C$ NMR: δ ($CDCl_3$) 23.5, 24.8, 47.2, 53.6, 60.8, 70.1, 81.0, 165.0.

EXAMPLE 39

4-Piperidinone O-methyloxime hydrochloride

4-Piperidinone hydrochloride monohydrate (5 g, 32.5 mmol), methoxyamine hydrochloride (4.18 g, 50 mmol) and potassium carbonate (13.82 g, 100 mmol) were taken into 100 mL of ethanol and stirred at room temperature for 16 hours. The reaction mixture was filtered and the filtrate evaporated to afford a white solid. The crude solid was dissolved in water, made basic with solid potassium carbonate, and extracted with dichloromethane (3 x 100 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated in vacuo to afford a clear, colorless

liquid. It was converted to its hydrochloride salt by treating with ethereal hydrogen chloride to give 233 g, m.p. 140-141°C.

$C_6H_{12}N_2O \cdot HCl$: Calc.: C, 43.77; H, 7.96; N, 17.02.
Found: C, 43.78; H, 7.96; N, 17.08

$_1H$ NMR: δ ($CDCl_3$) 2.68-2.73 (t, 2H), 2.92-2.97 (t, 2H), 3.27-3.34 (m, 4H), 3.84 (s, 3H), 9.93 (br.s, 1H).

$_{13}$NMrR: δ ($CDCl_3$) 21.76, 28.05, 42.92, 44.29, 61.61, 150.07.

Mass Spec.: m/e 128.08 (M^+ for free base).

EXAMPLE 40

1-Methyl-4-piperidinone O-methyloxime hydrochloride

1-Methyl-4-piperidone (5 g, 44.2 mmol) and methoxyamine hydrochloride (3.69 g, 44.2 mmol) were taken into 25 mL of methanol and stirred at room temperature for 2 days. The reaction mixture was evaporated in vacuo to afford a solid residue. The residue was dissolved in water, made basic with solid potassium carbonate, and extracted with dichloromethane (3 x 100 mL). The combined extracts were dried over anhydrous sodium sulfate and evaporated to give a clear, yellow liquid that was purified on silica gel, eluting with dichloromethane-methanol (95:5) to afford 2.55 g of the desired product. Treatment with ethereal hydrogen chloride gave the hydrochloride salt, 2.99 g, m.p. 145-147°C.

$C_7H_{14}N_2O \cdot HCl$: Calc.: C, 47.06; H, 8.46; N, 15.68.
Found: C, 46.94; H, 8.41; N, 15.60.

^1H NMR: δ ($CDCl_3$) 2.53-2.58 (m, 1H), 2.69-3.20 (m, 4H), 2.87-2.89 (d, 3H), 3.36-3.49 (m, 1H), 3.55-3.76 (m, 2H), 3.84 (s, 3H), 12.90 (br.s, 1H).

$_{13}$CCC NMR: δ ($CDCl_3$) 21.97, 28.25, 43.46, 53.09, 54.36, 61.64, 149.17.

Mass spec.: m/e 142.17 (M^+) for free base).

EXAMPLE 41

Z-(±)-1-Azabicyclo[2.2.1]heptan-3-one O-2-propenyloxime oxalate and E-(±)-1-azabicyclo[2.2.1]-heptan-3-one O-z-propenyloxime oxalate

1-Azabicyclo[2.2.1]heptan-3-one (2 g, 18 mmol) and O-allylhydroxylamine hydrochloride hydrate (1.97 g, 18 mmol) were dissolved in 25 mL of methanol and stirred at room temperature for 18 hours. The reaction was evaporated in vacuo to give a viscous oil. The crude oil was dissolved in 50 mL of water, made basic with a saturated solution of potassium carbonate, and extracted with ether (3 x 100 mL). The combined extracts were dried over anhydrous sodium sulfate, and evaporated to give a clear, yellow liquid which was purified on silica gel, eluting with dichloromethane-methanol (10:1). Isomer A, the less polar isomer, was isolated and converted to the oxalate salt to give 1.365 g, m.p. 130-132°C.

$C_9H_{14}N_2O \cdot C_2H_2O_4$: Calc.: C, 51.55; H, 6.29; N, 10.93.
Found: C, 51.52; H, 6.37; N, 10.88.

^1H NMR: δ (DMSO) 12.0 (br.s, 2H), 5.86-6.02 (m, 1H), 5.17-5.31 (m, 2H), 4.5-4.52 (d, 2H), 3.85-4.06 (q, 2H), 3.16-3.42 (m, 5H), 2.14-2.27 (m, 1H), 1.70-1.75 (m, 1H).

Mass Spec.: m/e 166.1 (M^+ for free base)

Isomer B, the more polar isomer, was converted to the oxalate to give 0.829 g, m.p. 102-104°C.

$C_9H_{14}N_2O \cdot C_2H_2O_4$ Calc.: C, 51.55; H, 6.29; N, 10.93.
Found: C, 51.02; H, 6.22; N, 10.63.

^1H NMR: δ (DMSO) 11.2 (br.s, 2H), 5.88-6.04 (m, 1H), 5.17-5.33 (m, 2H), 4.50-4.55 (d, 2H), 3.73-4.00 (m,

3H), 3.11-3.42 (m, 4H), 2.08-2.21 (m, 1H), 1.62-1.66 (m, 1H).

Mass Spec.: m/e 166.1 (M^+ for free base).

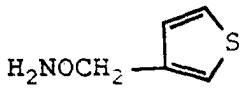
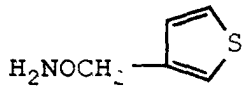
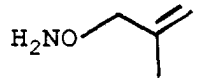
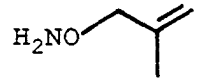
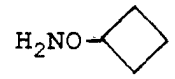
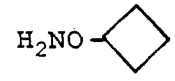
The above procedure was utilized for the synthesis of the following E and Z isomers:









Example No.	Amine·HCl	Product
42	$H_2NOCH_2C{\equiv}CH$	Z-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-2-propynyloxime hydrochloride, m.p. 199-200°C
43		Z-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-(3-thienylmethyl)oxime oxalate, m.p. 142-144°C
44		E-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-(3-thienylmethyl)oxime oxalate, m.p. 142-143°C
45		Z-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-(2-methyl-2-propenyl)-oxime oxalate; m.p. 131-133°C
46		E-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-(2-methyl-2-propenyl)-oxime oxalate, m.p. 124-226°C.
47		Z-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-cyclobutyloxime hydrochloride, m.p. 209-210°C
48		E-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-cyclobutyloxime hydrochloride, m.p. 207-208°C
49	$H_2NO(CH_2)_3C{\equiv}CH$	Z-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-4-pentynyloxime oxalate, m.p. 119-121°C
50	$H_2NO(CH_2)_3C{\equiv}CH$	E-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-4-pentynyloxime oxalate, m.p. 110-113°C

Example No.	Amine·HCl	Product
51	$H_2NO(CH_2)_2C{\equiv}CCH_3$	Z-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-3-pentynyloxime oxalate, m.p. 161-162°C
52	$H_2NO(CH_2)_2C{\equiv}C-CH_3$	E-(±)-1-azabicyclo-[2.2.1]heptan-3-one, O-3-pentynyloxime oxalate, m.p. 149-150°C
53	$H_2NOCH_2C{\equiv}CCH_2C{\equiv}CCH_3$	Z-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(2,5-heptadiynyl)oxime oxalate, m.p. 65-70°C
54	$H_2NOCH_2C{\equiv}CCH_2C{\equiv}CCH_3$	E-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(2,5-heptadiynyl)oxime oxalate, m.p. 108-110°C
55	$H_2NOCH_2C{\equiv}CCH_2CH{\equiv}CH_2$	Z-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(2-hexyn-5-enyl)oxime oxalate, m.p. 94-96°C
56	$H_2NOCH_2C{\equiv}C-Ph$	Z-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(3-phenyl-2-propynyl) oxime oxalate, m.p. 162-164°C
57	$H_2NOCH_2C{\equiv}C-Ph$	E-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(3-phenyl-2-propynyl) oxime oxalate, m.p. 83-85°C
58	$H_2NOCH_2C{\equiv}C-C(CH_3){=}CH_2$	Z-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(4-methyl-2-pentyn-4-enyl)oxime oxalate, m.p. 118-119°C
59	$H_2NOCH_2C{\equiv}CC(CH_3){=}CH_2$	E-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(4-methyl-pentyn-4-enyl)oxime oxalate, m.p. 78-83°C

Example No.	Amine·HCl	Product
60	$H_2NOCH_2C{\equiv}C(CH_2)_2CH_3$	Z-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(2-hexynyl)oxime oxalate, m.p. 109-110°C
61	$H_2NOCH_2C{\equiv}C(CH_2)_2CH_3$	E-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(2-hexynyl)oxime oxalate, m.p. 105-107°C
62	$H_2NOCH_2C{\equiv}C(CH_2)_3CH_3$	Z-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(2-heptynyl)oxime oxalate, m.p. 109-110°C
63	$H_2NOCH_2C{\equiv}C(CH_2)_3CH_3$	E-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(2-heptynyl)oxime oxalate, m.p. 100-104°C
64	$H_2NOCH_2CH_2SCH_2C{\equiv}CH$	Z-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(2-(2-propynylthio) ethyl)oxime oxalate, m.p. 101-103°C
65	$H_2NOCH_2CH_2SCH_2C{\equiv}CH$	E-(±)-1-azabicyclo [2.2.1]heptan-3-one, O-(2-(2-propynylthio) ethyl)oxime oxalate, m.p. 121-122°C

EXAMPLE 66

N-Methyl-8-Azabicyclo[3.2.1]octa-3-one methyl oxime hydrochloride

A solution of methoxyamine hydrochloride (4.18 g, 0.05 mol) in methanol was added to a rapidly stirring solution of N-methyl-8-azabicyclo[3.2.1]octa-3-one (commercially available) (6.96 g, 0.05 mol) in methanol while cooling with an ice-bath. The reaction mixture was allowed to warm up to room temperature, stirred at room temperature for 16 hours and then the solvent removed. The resulting solid residue was

partitioned between CH_2Cl_2 and conc. aqueous K_2CO_3 solution. The organic layer was dried (K_2CO_3), and concentrated to give an oil. The oil was dissolved in ether and treated with ethereal-HCl. The resulting white solid ppt was separated by filtration and recrystallized from isopropanol-isopropyl ether to give 4.88 g (45%) of oxime hydrochloride as white solid: mp turns brown at 197°C to 200°C and melts with decomposition at 217°C and 220°C; ^1H NMR (D_2O) δ 4.710 (s, 4H), 4.013-3.939 (bd 1H). 3.765 (s, 3H), 3.259-3.194 (bd, 1H), 2.745 (s, 3H), 2.476-2.232 (m, 3H), 1.909-1.722 (m, 1H); ^{13}C NMR (D_2O) δ 154.411, 66.306, 65.520, 64.257, 41.756, 38.930, 33.925, 27.461, 26.657; MS, m/e (relative intensity) 182 (0.15), 170 (8), 169 (71), 168 (64), 167 (9), 153 (2), 138 (13), 137 (97), 136 (4), 122 (7), 109 (7), 108 (11), 98 (3), 97 (16), 96 (71), 95 (12), 94 (26), 93 (3), 88 (4), 87 (72), 85 (2), 92 (100), 81 (24), 80 (7). Anal. Calcd. for $C_9H_{16}N_2O \cdot HCl$: C, 52•80; H ,8•37; N, 13•69. Found: C, 52•87; H, 8•31; N, 13•45.

EXAMPLE 67

N-Methyl-8-Azabicyclo[3.2.1]octan-3-one methyl oxime hydrochloride

The preparation of this compound is depicted in the Flow Chart set forth hereinafter and as described hereinbelow.

(a) Preparation of Ethyl 1,3,4,5-cycloheptatriene-1-carboxylate (2). Ethyl diazoacetate (43.4 g, 0.38 mol) was added slowly (syringe pump) over a period of 7 hours to a mixture of benzene (594.32 g, 7.61 mol) and tetrakis(perfluorobenzoato)

dirhodium(II) (0.84 g, 00.16 mol). After stirring at room temperature for 16 hours, the solvent was removed and the oily residue distilled in vacuo to give 50.44 g (81%) of ethyl 1,3,5-cycloheptatriene-1-carboxylate: bp 90-96°C 2.4-3.0 mm Hg); ^{1}H NMR ($CDCl_3$) δ6.6 (m, 2H), 6.2 (m, 2H), 5.3 (m, 2H), 4.2 (q, 2H OCH_2CH_3), 2.5 (t, 1H), 1.3 (t, 3H CH_2CH_3).

(b) Preparation of N-Methyl Ethyl 8-Azabicyclo [3.2.1]oct-2-ene-2-carboxylate (3). A mixture of ethyl 1,3,5-cycloheptatriene-1-carboxylate (12.72 g, 0.077 mol), methylamine (23.13 g, 0.74 mol) and NaOH (3.1 g, 0.078 mol) in MeOH (60 mL) was autoclaved at 125°C for 26 hours. The reaction mixture was filtered, and the filtrate concentrated to give an oil. The oil was dissolved in MeOH (400 mL) and saturated with HCl gas; conc. sulphuric acid (8 mL) was added and the mixture refluxed for 12 hours. The oily residue obtained after evaporation of MeOH was partitioned between aqueous conc. Na_2CO_3 and ET_2O. The ether layer was evaporated as brown oil: IR (neat) 1720 ($COOCH_3$); ^{1}H ($CDCl_3$) δ6.8 (bt, 1H), 3.7 (s, 3H OCH_3), 2.35 (s, 3H NCH_3), 3.4-2.4 (m, 3H), 2.3-1.4 (m, 6H).

(c) Preparation of N-Methyl-2-acetyl-8-azabicyclo[3.2.1]oct-2-ene (4). To a mixture of ethyl trop-2-ene-2-carboxylate (3.43 g, 0.019 mol) and Me_3SiCl (10.32 g, 0.095 mol) in THF (70 mL) cooled to -100°C,

MeLi (1.4 M, 17.07 mL, 0.0239 mol) was added dropwise. After warming up to room temperature, the reaction mixture was stirred for 16 hours. Excess Me_3SiCl and THF was evaporated off and the resulting residue was stirred with EtOH (6 mL) followed by water (6 mL). The mixture was then made acidic (6N HCl) and extracted with ether. The aqueous layer was made basic (solid K_2CO_3) and extracted with chloroform, dried (K_2CO_3) and concentrated to give 3.14 g (81%) of 2-acetyltrop-2-ene as an oil: IR (neat) 1670 ($COCH_3$); ^1H NMR ($CDCl_3$) δ6.7 (bt, 1H), 2.3 (s, NCH_3), 2.2 (s, $C(\equiv O)CH_3$).

(d) N-Methyl-2-Acetyl-8-azabicyclo[3.2.1]octane, compound (5) is obtained by catalytic reduction (H_2/RaNi) of compound (4) and is converted to N-Methyl-8-azabicyclo [3.2.1]octan-2-one, compound (7) by procedures known in the art, see J. Org. Chem. 55, 5025 (1990). In compound (6) TBDMSO stands for testing butyl dimethylsilyloxy. The ketone, compound (7) is converted to the methyloxime as generally described above in Example 66.

Similarly when N-methyl-2-acetyl-9-azabicyclo [4.2.1]nonane, which can be prepared from 2-acetyl-9-azabicyclo[4.2.1]non-2-ene which is commercially available, is substituted for N-methyl-2-acetyl-8-azabicyclo[3.2.1]octane, compound (5), N-methyl-8-azabicyclo[4.2.1]nonan-2-one methyl oxime is obtained.

The compounds of the present invention are centrally acting muscarinic agents and are thus useful as analgesic agents for the treatment of pain in mammals including man, as sleep aids, and as agents for treating the symptoms of senile dementia, Alzheimer's disease, Huntington's chorea, tardive dyskinesia, hyperkinesia, mania, or similar conditions of cerebral insufficiency characterized by decreased cerebral acetylcholine production or release.

The biological activity of compounds of the present invention was evaluated using a number of tests. The activity of compounds of this invention as central muscarinic binding site agonists and antagonists was measured. In the RQNB screening assay, which is described more fully by Mark Watson, et al, J. Pharmacol. and Exp. Ther., 237(2):411 (1986), rat cerebral cortex tissue was treated with radiolabeled quinuclidinyl benzilate, a known muscarinic binding site antagonist. The concentrations of test compound required to inhibit 50% of the binding of this muscarinic antagonist were then determined.

Similarly, in the RCMD screening assay, described more fully by T. W. Vickeroy, et al, 229(3):747 (1984), rat cerebral cortex tissue was treated with radiolabeled cis-methyldioxolane, a known muscarinic binding site agonist. The concentrations of test compounds required to inhibit 50% of the binding of this muscarinic agonist were then determined. These values are reported as IC_{50} concentrations in Table 2 and demonstrate that the compounds of the present invention possess significant muscarinic activity.

TABLE 2

Example No.	IC_5nM RCMD	IC_{50}nM RQNB
3	18.2	24558
2	12.5	
		3112
4	3.5	2967
5	133	5947
6	120	3846
7	46	2030
8	53	4775
27	116	8820
28 (Isomer A)	12.9	434
28 (Isomer B)	256	9650

In therapeutic use as agents for treating pain or for treating cerebral insufficiency, the compounds utilized in the pharmaceutical method of this invention are administered to the patient at dosage levels of from 0.07 to 700 mg per day. For a normal human adult of approximately 70 kg of body weight, this translates into a dosage of from 0.01 to 100 mg/kg of body weight per day. The specific dosages employed, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the activity of the compound being employed. The determination of optimum dosages for a particular situation is within the skill of the art.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances which may also act is diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component. In tablets, the active compound is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppositories, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted, and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture is then poured into convenient sized molds and allowed to cool and solidify.

Powders and tablets preferably contain between about 5% to about 70% by weight of the active ingredient. Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier, which is thus in association with it. In a similar manner, cachets are also included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

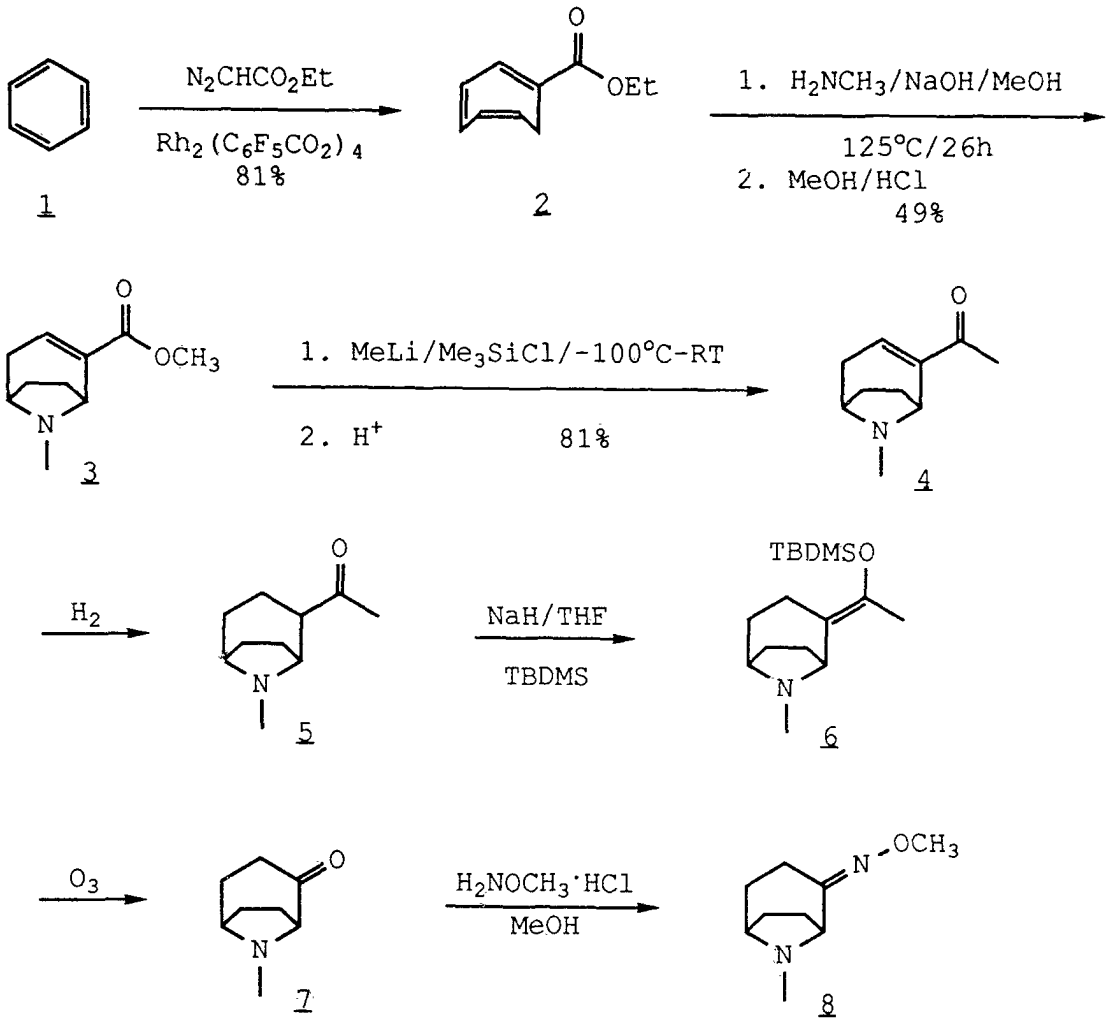
Liquid form preparations include solutions suitable for oral or parenteral administration, or suspensions, and emulsions suitable for oral administration. Sterile water solutions of the active component or sterile solutions of the active component in solvents comprising water, ethanol, or propylene glycol may be mentioned as examples of liquid preparations suitable for parenteral administration.

Sterile solutions may be prepared by dissolving the active component in the desired solvent system, and then passing the resulting solution through a membrane filter to sterilize it or, alternatively, by dissolving the sterile compound in a previously sterilized solvent under sterile conditions.

Aqueous solutions for oral administration can be prepared by dissolving the active compound in water and adding suitable flavorants, coloring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural or synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

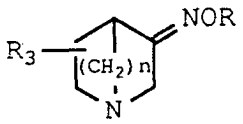
Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is divided into unit doses containing appropriate quantities of the active component. The unit dosage form can a packaged preparation, the package containing discrete quantities of the preparation, for example, packeted tablets, capsules, and powders in vials or ampoules. The unit dosage form can also be capsule, cachet, or tablet itself, or it can be the appropriate number of any of these packaged forms.

Flow Chart

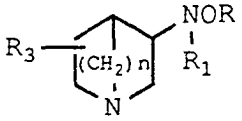

N2CHCO2Et
Rh2(C6F5CO2)4
81%
OEt
1. H2NCH3/NaOH/MeOH
125°C/26h
2. MeOH/HCl
49%
OCH3
1. MeLi/Me3SiCl/-100°C-RT
2. H+
81%
H2
NaH/THF
TBDMS
TBDMSO
O3
H2NOCH3·HCl
MeOH
OCH3
1
2
3
4
5
6
7
8

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

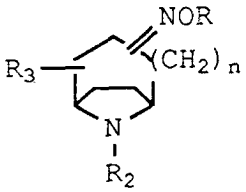
1. A compound of the following Formulas I, II, III, or IV, or a Z or E form thereof or a pharmaceutically acceptable salt thereof:



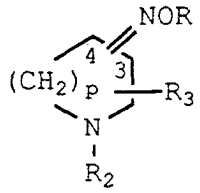
I



II



III



IV

wherein n is one or two;

wherein p is zero or one to four;

wherein each of R_1 and R_2 is hydrogen or straight or branched lower alkyl having from 1 to 4 carbon atoms;

wherein R_3 is hydrogen, a straight or branched lower alkyl group having from 1 to 6 carbon atoms, hydroxy, a straight or branched lower alkoxy group having from 1 to 4 carbon atoms, acyloxy group wherein the acyl moiety has from 2 to 5 carbon atoms, or the group $-(CH_2)_q-NR_8R_9$ wherein q is zero or 1 to 4 and each of R_8 and R_9 is the same or different and is hydrogen or a straight or branched lower alkyl group having from 1 to 4 carbon atoms; or

cycloalkyl having from 3 to 6 carbon atoms;

wherein R is hydrogen:

or the group:

-Y-Z

wherein Y is a bond or a straight or branched hydrocarbon chain having from 1 to 20 carbon atoms and optionally contains from 1 to 4 double and/or triple bonds; and Z is hydrogen;

a cycloalkyl group having from 3 to 6 carbon atoms;

an aromatic group selected from phenyl, 2- or 3-thienyl, 2- or 3-furanyl, 2- or 3-pyrrolyl wherein the aromatic group is unsubstituted or is substituted with 1 or 2 substituents selected from chlorine, bromine, fluorine, trifluoromethyl, nitro, amino, amino substituted with 1 or 2 straight or branched lower alkyl groups having from 1 to 4 carbon atoms, or straight or branched alkoxy having from 1 to 4 carbon atoms;

$-NR_4R_5$ wherein R_4 and R_5 are the same or different and are hydrogen or straight or branched alkyl having from 1 to 4 carbon atoms;

$-\overset{O}{\overset{\|}{C}}NR_4R_5$ wherein R_4 and R_5 have the meanings defined above;

$-\overset{O}{\overset{\|}{C}}R_6$ wherein R_6 is a straight or branched alkyl group having from 1 to 6 carbon atoms;

-CN;

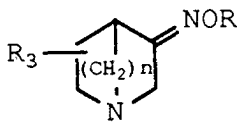
$-CO_2R_7$ wherein R_7 is hydrogen, a straight or branched lower alkyl having from 1 to 6 carbon atoms and is straight or branched, or benzyl; or

$-XR_{10}$ where in X is oxygen or sulfur and R_{10} is a straight or branched hydrocarbon chain having from 1 to 6 carbon atoms and which optionally contains 1 or 2 double or triple bonds;

with the proviso that the following compounds are excluded: (a) compounds of Formula I wherein n is two, and R is hydrogen, or the group Y-Z wherein Y is a bond and Z is $-C(=O)NR_4R_5$ or $-C(=O)R_6$; and

(b) compounds of Formulas III and IV wherein R is hydrogen.

2. A compound of Claim 1 having the formula



I

wherein n, R_3, and R have the meanings defined in Claim 1.

3. A compound of Claim 2 wherein n is one.

4. A compound of Claim 3 wherein R_3 is hydrogen and R is other than hydrogen.

5. A compound of Claim 4 which is

1-Azabicyclo[2.2.1]heptan-3-one, O-ethyloxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-methyloxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-2-propynyloxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(phenylmethyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-propyloxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(1-methylethyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2-propenyl)oxime oxalate;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2-aminoethyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(cyclopropylmethyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2-methoxyethyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-phenyloxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2-thienylmethyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2-furylmethyl)oxime oxalate;

1-Azabicyclo[2.2.1]heptan-3-one, O-(3-furylmethyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(1-methyl-2-propenyl)oxime oxalate;

1-Azabicyclo[2.2.1]heptan-3-one, O-(3-butenyl)oxime oxalate;

1-Azabicyclo[2.2.1]heptan-3-one, O-(tert-butyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2-butynyl)oxime oxalate;

1-Azabicyclo[2.2.1]heptan-3-one, O-(1-methyl-2-butynyl)oxime oxalate;

1-Azabicyclo[2.2.1]heptan-3-one, O-(1-methyl-2-propynyl)oxime oxalate;

1-Azabicyclo[2.2.1]heptan-3-one, O-(E-2-penten-4-ynyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(Z-2-penten-4-ynyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2-pentyn-4-enyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2,4-pentadiynyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(1-ethynylpropynyl)oxime hydrochloride;

[1-Azabicyclo[2.2.1]heptane-3-ylidine)-amino]oxyacetonitrile hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2,4-pentadienyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2,4-hexadienyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(Z-2-butenyl)oxime oxalate;

1-Azabicyclo[2.2.1]heptan-3-one, O-(E-2-butenyl)oxime hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2,5-hexadiynyl)oxime oxalate;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2-penten-4-ynyl)oxime oxalate;

1-Azabicyclo[2.2.1]heptan-3-one, O-(4-methoxy-2-butynyl)oxime hydrochloride;

[[(1-Azabicyclo[2.2.1]heptan-3-ylidene)amino]oxy]acetic acid methylester hydrochloride;

1-Azabicyclo[2.2.1]heptan-3-one, O-(2-pentynyl)oxime hydrochloride;

Z-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-2-propenyloxime oxalate;

E-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-2-propenyloxime oxalate;

Z-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-2-propynyloxime hydrochloride;

Z-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-(3-thienylmethyl)oxime oxalate;

E-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-(3-thienylmethyl)oxime oxalate;

Z-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-(2-methyl-2-propenyl)oxime oxalate;

E-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-(2-methyl-2-propenyl)oxime oxalate;

Z-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-cyclobutyloxime hydrochloride;

E-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-cyclobutyloxime hydrochloride;

Z-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-4-pentynyloxime oxalate;

E-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-4-pentynyloxime oxalate;

Z-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-3-pentynyloxime oxalate;

E-(±)-1-Azabicyclo[2.2.1]heptan-3-one, O-3-pentynyloxime oxalate;

Z-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(2,5-heptadiynyl)oxime oxalate;

E-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(2,5-heptadiynyl)oxime oxalate;

Z-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(2-hexyn-5-enyl)oxime oxalate;

Z-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(3-phenyl-2-propynyl)oxime oxalate;

E-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(3-phenyl-2-propynyl)oxime oxalate;

Z-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(4-methyl-2-pentyn-4-enyl)oxime oxalate;

E-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(4-methylpentyn-4-enyl)oxime oxalate;

Z-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(2-hexynyl)oxime oxalate;

E-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(2-hexynyl)oxime oxalate;

Z-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(2-heptynyl)oxime oxalate;

E-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(2-heptynyl)oxime oxalate;

Z-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(2-(2-propynylthio)ethyl)oxime oxalate; and

E-(±)-1-azabicyclo[2.2.1]heptan-3-one, O-(2-2-propynylthio)ethyl)oxime oxalate.

6. A compound of Claim 2 wherein n is 2.

7. A compound of Claim 6 wherein R_3 is hydrogen and R is other than hydrogen.

8. A compound of Claim 4 which is

1-Azabicyclo[2.2.2]octan-3-one, O-ethyloxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-methyloxime,

1-Azabicyclo[2.2.2]octan-3-one, O-2-(propynyl)oxime;

1-Azabicyclo[2.2.2]octan-3-one, O-(phenylmethyl)oxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-propyloxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-(1-methylethyl)oxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-(2-propenyl)oxime oxalate;

1-Azabicyclo[2.2.2]octan-3-one, O-(2-aminoethyl)oxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-(cyclopropylmethyl)oxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-(2-methoxyethyl)oxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-phenyloxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-(2-thienylmethyl)oxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-(2-furylmethyl)oxime oxalate;

1-Azabicyclo[2.2.2]octan-3-one, O-(3-furylmethyl)oxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-(1-methyl-2-propenyl)oxime oxalate;

1-Azabicyclo[2.2.2]octan-3-one, O-(3-butenyl)oxime oxalate;

1-Azabicyclo[2.2.2]octan-3-one, O-(tert-butyl)oxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-(2-butynyl)oxime oxalate;

1-Azabicyclo[2.2.2]octan-3-one, O-(1-methyl-2-propynyl)oxime oxalate;

1-Azabicyclo[2.2.2]octan-3-one, O-(1-methyl-2-butynyl)oxime oxalate;

1-Azabicyclo[2.2.2]octan-3-one, O-(E-2-penten-4-ynyl)oxime hydrochloride;

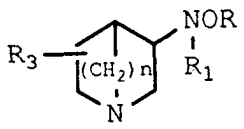
1-Azabicyclo[2.2.2]octan-3-one, O-(Z-2-penten-4-ynyl)oxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-(2-pentyn-4-enyl)oxime hydrochloride;

1-Azabicyclo[2.2.2]octan-3-one, O-(2,4-pentadiynyl)oxime hydrochloride; and

50 1-Azabicyclo[2.2.2]octan-3-one, O-(1-ethynylpropynyl)oxime hydrochloride.

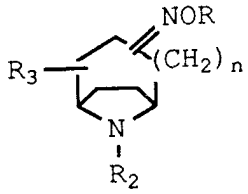
9. A compound of Claim 1 which is



II

wherein n, R_3, R_1, and R have the meanings defined in Claim 1.

10. A compound of Claim 1 having the formula:



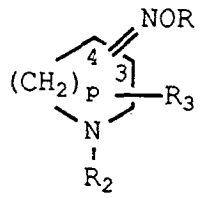
III

wherein n, R, R_2, and R_3 have the meanings defined in Claim 1.

11. A compound of Claim 10 wherein n is one.

12. A compound of Claim 11 which is N-methyl-8-azabicyclo[3.2.1]octa-3-one methyl oxime hydrochloride or N-methyl-8-azabicyclo[3.2.1] octa-2-one methyloxime hydrochloride.

13. A compound of Claim 1 having the formula:



IV

wherein p, R, R_2, and R_3 have the meanings defined in Claim 1.

14. A compound of Claim 13 wherein p is 2.

15. A compound of Claim 14 which is 4-piperidinone O-methyloxime hydrochloride; or 1-methyl-4-piperidinone O-methyloxime hydrochloride.

16. A pharmaceutical composition useful for alleviating pain in a mammal comprising an analgesically effective amount of a compound of any one of Claims 1 to 15 together with a pharmaceutically acceptable carrier.

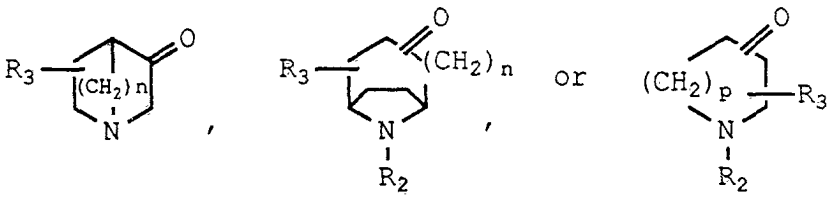
17. A pharmaceutical composition useful for the treatment of the symptoms of cognitive decline in a patient in need thereof which comprises administering an effective amount of a compound of any one of Claims 1 to 15

together with a pharmaceutically acceptable carrier.

18. A method of alleviating pain in a mammal which comprises administering to a mammal in need of such treatment a composition of Claim 16.

19. A method of treating the symptoms of cognitive decline in a patient in need thereof which comprises administering to said patient an effective amount of a composition of Claim 17.

20. A method for preparing a compound of any one of Claims 1 to 15 which comprises to obtain a compound of Formula I, III, or IV, respectively, reacting a ketone selected from the formula



with an amine hydrochloride of the formula $NH_2OR \cdot HCl$ wherein n, p, R_3, R_2, and R have the meanings defined in Claim 1 in methanol at room temperature and to obtain compounds of Formula II, reducing the compounds of Formula I.

21. A compound according to Claim 1 substantially as herein described with reference to any one of the examples.

22. A method for preparing a compound according to Claim 1 substantially as herein described with reference to any one of the examples.

DATED this 4th Day of March, 1991
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