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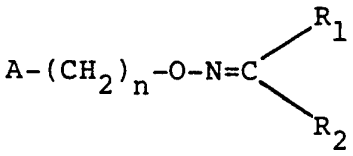

(I)

(57) Abstract

Pharmacologically active azacyclic and azabicyclic alkyliden hydroxylamines as cholinergic agents, useful in the treatment of neurological and mental diseases of formula (I), wherein A, n, R_1 and R_2 have the meanings specified in the description, a process for their preparation and pharmaceutical compositions containing them, are disclosed.

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AZACYCLIC AND AZABICYCLIC HYDROXYLAMINES AS MUSCARINIC RECEPTOR AGONISTS

The present invention relates to a class of pharmacologically active azacyclic and azabicyclic alkyliden hydroxylamines, to the process for their production, to the pharmaceutical compositions containing them. The new compounds stimulate cortical cholinergic neurotransmission and therefore they are useful in the treatment of neurological and mental diseases whose clinical manifestations are due to impaired cholinergic transmission.

Cognitive disorders are characterized by symptoms of forgetfulness, confusion, memory loss and affective disturbance. They may arise as a consequence of the normal aging process or, under pathological conditions, from an organic brain disease. The etiology and the pathogenesis of those mental diseases are still unknown. Several neurotransmitter systems (acetylcholine, noradrenaline, dopamine, serotonin, GABA, etc.), which are involved in the communication across the synapses from one cell to the other in brain areas associated with the cognitive functions, become impaired, but the evidence of the central role of the cholinergic system is overwhelming [Coyle, J.J. et al., Science, 219, 1184 (1983); Briley M. et al., Pharmacopsych. 23, 75 (1990)]. Diseases ascribed to a cholinergic deficiency include presenile and senile dementia (also known as Alzheimer's disease) Huntington's chorea, tardive dyskinesia, hyperkinesia, mania and Tourette syndrome. Many of the symptoms of these disorders are associated with the observed decrease of acetylcholine synthesis

and the impairment or the loss of cholinergic neurons just in specific brain areas such as cerebral cortex and hippocampus [Davies et al., The Lancet 2, 1403 (1976); Perry et al., J. Neurol. Sci. 32, 247 (1977)].

According to this "cholinergic hypothesis", different strategies have been attempted to restore acetylcholine levels or to mimic the action of the natural transmitter itself in the treatment of the above described diseases [Kuman V. et al., Int. J. Clin. Pharmacol. 29, 23 (1991)]. Acetylcholinesterase inhibitors such as physostigmine or tacrine, which increase the available amount of acetylcholine in the synaptic cleft by blocking the inactivating enzyme, have been proposed [Drachnan D.A. et al., Arch. Neurol. 37, 674 (1980); Summers W.K. et al., New Engl. J. Med. 315, 1241 (1986)]. Also compounds which promote acetylcholine synthesis or its release from the containing vesicles have been tested [Etienne P. "Treatment of Alzheimer's disease with lecithin" in Alzheimer's disease, Reisberg B. Editor, Free Press New York, 1983; Davis H. P. et al., Exp. Aging Res. 9, 211 (1983)]. However, the most straightforward way of improving CNS functions linked to a cholinergic pathway, appears to be the direct stimulation of the cholinergic muscarinic receptors themselves. These receptors may became lost or damaged in the presence of those diseases, but there is an increasing evidence that in patients suffering from dementia there is a differential loss of muscarinic receptor sites: the pronounced decrease of presynaptic cholinergic terminals in cerebral cortex and hippocampus is not accompanied by significant changes or losses of the post-

synaptic muscarinic receptor [Quirion R., J. of Neuroch. 1914 (1988); Caulfield M.P. et al., The Lancet, 1277 (1982)].

The use of drugs activating the central muscarinic sites has been so far limited or disappointing, owing to unfavourable circumstances. Most of the known muscarinic agonists possess quaternary ammonium groups (for instance carbachol) and therefore are expected not to cross the blood brain barrier following peripheral administration. Arecoline, aceclidine and RS86, possessing a tertiary amine group, can penetrate the brain. However, the onset of side effects (miosis, lacrimation, motility disturbances and cardiac effects) coming from the activation of peripheral muscarinic receptors, has been observed; moreover the former two compounds have a very limited duration of action owing to the presence of an easily hydrolyzable ester group [Davidson M. et al., Current Research in Alzheimer Therapy, Giacobini E. and Becker R. Editors; Taylor-Francis, New York 333 (1988)].

The recent discovery of at least five structurally distinct subtypes of muscarinic receptors [Bonner J.J. et al., Science 237, 527 (1987); Bonner J.J. et al., Neurochem. 1, 403 (1988] and the classification into three subtypes (M_1, M_2 and M_3) according to functional tests (Birdsall N.N. et al. "Nomenclature for muscarinic receptor subtypes" in Subtypes of Muscarinic Receptors IV; Levine R.R. Editor, Trends Pharmac. Sci. VII), has renewed the interest for the cholinomimetic approach.

Accordingly, the target of recent research in the

cholinomimetic field is the selective activation of the M_1 muscarinic receptor subtype which is postsynaptically placed in the cholinergic neurones and, as said before, is still present in the damaged cerebral areas.

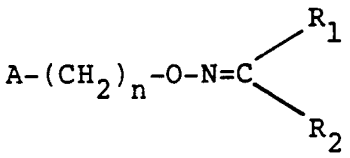
The inability to activate M_2 and M_3 subtypes is highly sought as these latter are responsible for unwanted effects resulting from peripheral cholinergic stimulation. This aspect is particularly relevant considering that a large amount of a drug penetrating into the CNS, is however present in the periphery. Moreover, the lack of agonistic activity at M_2 subtypes could be favourably accompanied by a weak antagonistic effect at the same receptor subtypes. It has been suggested that the release of acetylcholine is negatively regulated by a feed-back mechanism, mediated by the endogenous agonist acting at a presynaptic muscarinic receptor of M_2 subtype. Thus the beneficial effect coming from direct stimulation of M_1 receptors will be boosted by a increased amount of the acetylcholine released.

It has now been found, and this is the object of the present invention, a new class of compounds which possess good affinity for the muscarinic receptors and are able to stimulate the same receptors. An additional favourable feature of the these compounds, included in the present invention, is their capacity to activate differentially the M_1, M_2 and M_3 muscarinic receptor subtypes owing to a different intrinsic efficacy. As a consequence, certain of the compounds, here provided, possess a selective stimulant action at the M_1 receptor sites relative to the M_2 and M_3. In other particular compounds the selective stimulant effect at the M_1 sub-

type is even increased by an antagonistic effect at the M_2 subtype.

These new compounds can be useful in the treatment or in the prevention of disorders related to a central cholinergic deficit. In particular their use may be beneficial in the treatment of cognitive disorders, age associated memory impairment, in different forms of dementia, in Alzheimer's disease, in Huntington's chorea, in tardive dyskinesia, in hyperkinesia, in Tourrette syndrome. Moreover, as centrally acting muscarinic agents, the compounds included in the present invention can be also of use as analgesics in the treatment of pain.

According to the present invention, we provide compounds of general formula (I)



(I)

wherein:

A represents the residue of a 4-8 membered azacycloalkane, or of a 7-9 membered azabicycloalkane, optionally N- substituted by a C_{1-3} alkyl;

n represents 0 or 1;

R_1 and R_2 represent independently hydrogen; linear or branched C_{1-6} alkyl optionally substituted by alkoxy groups, alkylmercapto, CN or by halogen; C_{2-6} alkenyl; C_{2-6} alkynyl; halogen; aryl optionally substituted by halogen, C_{1-3} alkyl, C_{1-3} alkoxy; C_{6-12} aralkyl; heteroaryl; or together with the carbon atom to which they are linked, represent a 4-7 membered ring; the chain $-(CH_2)_n-O-$

$N=CR_1R_2$ being linked to carbon atoms not close to the nitrogen atom of azacycloalkane or azabicycloalkane.

Non-limitative examples of azacycloalkane reside A are 1-azacyclobut-3-yl, 1-azacyclopent-3-yl, 1-azacyclohex-3-yl, 1-azacyclohex-4-yl and 1-azacyclopent-3-yl groups, optionally N-substituted by C_{1-3} alkyl.

Non-limitative examples of azabicycloalkane residue A are 1-azabicyclo[2.2.1]-hept-3-yl, 1-azabicyclo[2.2.2]-oct-3-yl, 1-azabicyclo[3.2.1]-oct-3-yl, 1-azabicyclo[3.2.1]-oct-6-yl, 1-azabicyclo[3.3.1]-non-3-yl, and 8-azabicyclo[3.2.1]-oct-3-yl groups optionally N-substituted by C_{1-3} alkyl.

When in the compounds of formula (I) R_1 and R_2 represent a linear or branched C_{1-6} alkyl group, it may, for example, be methyl, ethyl, n-propyl, i-propyl, butyl, pentyl, hexyl, 2-methylpentyl and the like. When R_1 and R_2 represent an alkyl groups optionally containing a substituent, they may be, methoxyethyl, methylthioethyl, ethylthioethyl or cyanoethyl. The term halogen means fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine, particularly fluorine and chlorine. When R_1 and R_2 represent C_{2-6} alkenyl group, it may, for example, be allyl or 3-methyl-buten-2-yl. When R_1 and R_2 represent C_{2-6} alkynyl group, it may, for example, be propargyl. When R_1 and R_2 represent an aryl group, it may, for example, be phenyl, optionally substituted by one or more substituents selected from methyl, ethyl, methoxy, ethoxy, fluorine, chlorine or bromine. When R_1 and R_2 represent a C_{6-12} aralkyl group, it may, for example,

be benzyl. When R_1 and R_2 are heteroaryl, it may, for example, be a 5-6 membered ring containing 1-3 heteroatoms, such as furan, pyridine, piridazine, oxadiazole. When R_1 and R_2 together with the carbon atom to which they are linked represent a 4 to 7 membered ring, it may, for example, be cyclobutane or cyclopentane.

Compounds according to the present invention, which possess one or more asymmetric carbon atoms can exist as the optical active enantiomers with a defined configuration, or they can exist as a particular diastereoisomer or a diastereoisomeric mixture and also as a full racemic mixture. In addition some of the compounds of the present invention can exist as endo and exo isomers; the term endo is here referred to that possessing the hydroxylamine side chain on the opposite side of the methylene bridge $-(CH_2)_n$. Moreover, according to the peculiar features of the oxime group, which is part of the compounds of the present invention, an additional isomerism of geometric type can be present. Compounds possessing E or Z configuration originate from the oxime group isomerism. Compounds possessing this type of isomerism can be obtained in a single form or as a mixture; in particular cases one isomer may be converted to the other. It is to be understood that the invention covers all such isomers both of optical and geometric type and mixture thereof.

A preferred group of compounds, according to the present invention, is the one formed by the compounds of general formula (I) wherein A is the residue of an azabicycloalkane, n is o, R_1 is hydrogen, lower C_{1-2} alkyl group or halogens and R_2 is hydrogen or lower

C_{1-3} alkyl group optionally substituted by alkoxyl or halogen, C_{2-6} alkynyl or halogen.

Particularly preferred compounds, according to the present invention, are the following:

R(-)-O-(1-Azabicyclo[2.2.2]oct-3-yl)-N-ethylidenhydroxylamine, hydrochloride (Compound 2)

(±)-Exo-O-(1-Azabicyclo[3.2.1]oct-6-yl)-N-ethylidenhydroxylamine, hydrochloride (Compound 22)

(±)-Exo-O-(1-Azabicyclo[2.2.1]hept-3-yl)-N-ethylidenhydroxylamine, fumarate (Compound 20)

(±)-Exo-O-(1-azabicyclo[3.2.1]oct-3-yl)-N-ethylidenhydroxylamine fumarate

(Compound 24)

S(+)-O-(1-azabicyclo[2.2.2]oct-3-yl)-N-(2.2.2-trifluoroethyliden)-hydroxylamine, fumarate

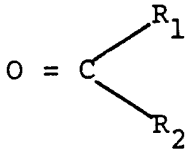
(Compound 7)

The compounds of general formula (I) may, for example, be prepared by the following process which constitute a further feature of the present invention.

Compounds of formula (I) are obtained by reacting azacyclo or azabicyclo O-substituted hydroxylamine of formula (II)

$$A-(CH_2)_n-O-NH_2 \qquad (II)$$

with a carbonyl derivative of formula (III)

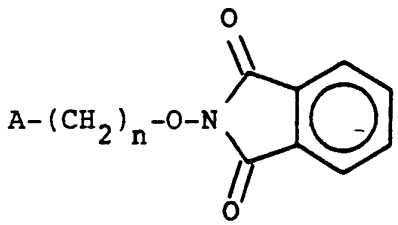


(III)

in which A, n, R_1 and R_2 are as hereinbefore defined. The reaction can be conveniently carried out in an hydroxylic solvent selected from methanol, ethanol, isopropanol, or in tetrahydrofuran or in toluene prefera-

bly in methanol. The reaction temperature is generally kept between 0°C and the boiling point of the solvent of choice, preferably at room temperature. The intermediates of formula (II) used as starting material may be used as free bases or, if desired, as salt addition derivatives.

The intermediates of formula (II) of the previously described process, can be prepared, in turn, by reducing O-substituted hydroxy-phthaloyl derivatives of general formula (IV)

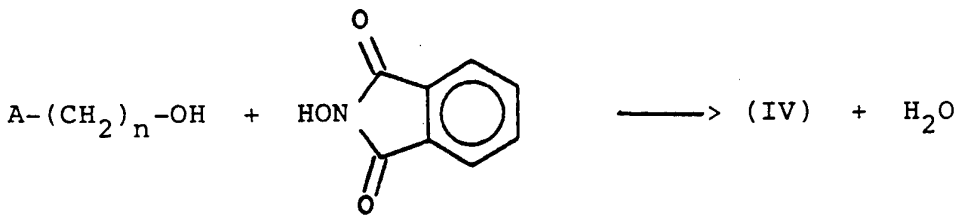


(IV)

wherein A and n are as hereinbefore defined.

The process is carried out by means of a suitable reducing agent such as hydrazine hydrate or ethanolamine, preferably hydrazine hydrate in an alcoholic solvent such as methanol, ethanol and isopropanol, preferably methanol. The temperature of the reaction process is kept between 10°C and 80°C preferably at room temperature.

The phthaloyl derivatives of general formula (IV) are conveniently obtained from the suitable azacyclic or azabicyclic hydroxy derivative of formula (V) and hydroxyphthalimide (VI), according to a procedure known as the Mitsunobu reaction [Mitsunobu O., Synthesis 1 (1981)]



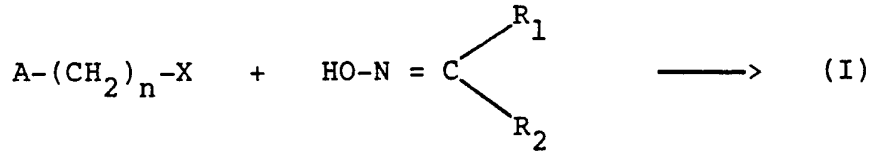
(V) (VI)

wherein A and n are as hereinbefore defined.

The condensation-dehydratation process is carried out in an anhydrous aprotic solvent such as diethyl ether or tetrahydrofuran at room temperature or below in the presence of triphenyl phosphine as dehydrating agent and utilizing DEAD (diethylazodicarboxylate) as activating agent.

The key intermediates of formula (III) and (V) (hydroxyl derivatives) used in the steps of the described process are commercially available or obtained according to already known proceedings described in the literature.

According to a different option, the compounds of general formula (I) can be prepared by reacting a compound of formula (VII) with an oxime of formula (VIII)



(VII) (VIII)

wherein R_1, R_2, A and n are as hereinbefore defined, and X is a suitable leaving groups such as mesyl or tosyl or halogen, preferably chlorine.

The reaction is carried out in a protic or aprotic solvent such as methanol, ethanol or dimethylformamide, preferably methanol, in the presence of sodium or NaH to activate the oxime function. The temperature is kept

between 30°C and 100°C preferably at 60°C. Oximes of formula (VIII) are obtained by reacting carbonyl compound of formula (III) previously described with hydroxylamine hydrochloride in methanol at room temperature, according to a well known procedure (Organic Functional Groups Preparation, Vol. III Sec. Edition by Sadler and Karo, Academic Press S. Diego, 1989).

The compounds of general formula (I) may be, if desired, converted into the corresponding salts of physiologically acceptable inorganic or organic acid by conventional methods, for example by reacting the compounds as bases with a solution of the corresponding acid in a suitable solvent.

Examples of salts of physiologically acceptable acids are those formed with hydrochloric, fumaric, maleic, succinic, citric, tartaric, phosphoric, sulphuric, salicylic, lactic, gluconic, aspartic or methanesulphonic acid [see for example Berg S.M. et al. "Pharmaceutical "Salts" in J. Pharm. Sci. 66, 1 (1977)].

Particularly preferred acids include for example hydrochloric, tartaric and fumaric acid.

As already mentioned hereinbefore, the new compounds of formula (I) have interesting pharmacological properties owing to their capacity to stimulate the different muscarinic receptor subtypes M_1, M_2 and M_3 with an intrinsic efficacy which is peculiar to each subtype. Therefore the new compounds are therapeutically useful in the treatment or in the prevention of disorders related to a central cholinergic deficit. In particular their use may be beneficial in the treatment

of cognitive disorders, age associated memory impairment, in different forms of dementia, in Alzheimer's disease, in Huntington's chorea, in tardive dyskinesia, in hyperkinesia, in Tourette syndrome. Moreover, as centrally acting muscarinic agents, the compounds included in the present invention can be also of use as analgesics in the treatment of pain.

The compounds of the present invention can be administered orally, parenterally or rectally at a daily dose of 0.01 to 100 mg/kg of body weight, preferably about 0.5 to 10 mg/kg, and may be administered on a regimen of 1 to 4 times a day.

The pharmaceutical formulations which constitute a further feature of the present invention comprise tablets, pills, capsules, powders, granules, sterile parenteral solutions or suppositories.

In the solid pharmaceutical compositions together with the active principle is used a suitable pharmaceutic carrier such as corn starch, lactose, sorbitol, magnesium stearate, etc. The liquid forms in which the novel compounds may be incorporated for orally administration or injection, include aqueous solutions, flavoured syrup and emulsions with oils or other vehicles. Also dispersing or suspending agents are of use.

It may be advantageous, in order to prevent peripheral side effects, to include in the pharmaceutical composition a peripherally acting cholinergic antagonist such as N-methylscopolamine, or glycopyrrolate or propantheline.

Pharmacology

The affinity of the compounds (I) for the M_1, M_2

and M_3 muscarinic receptor subtypes was assessed "in vitro" by receptor binding studies in three tissues endowed with M_1, M_2 and M_3 receptor subtypes (rat cerebral cortex, heart and submandibular glands, respectively). The potency and the intrinsic activity of the compounds of formula (I) at M_1, M_2 and M_3 receptor subtypes was checked in three functional models: the rat superior cervical ganglion (M_1), the guinea pig atrium (M_2) and the guinea pig ileum (M_3).

Receptor binding studies

Tissue Preparation. Rat tissues were removed, cleaned, homogenized (w/v: cerebral cortex, 1:100; whole heart, 1:200; submandibular salivary glands, 1:200) with an Ultra-Turrax at maximal speed for 30 s, followed by use of a Potter-Elvehjem homogenizer (30 strokes), in Na^+-Mg^{2+}-HEPES buffer, pH 7.4 (nM: NaCl, 100; $MgCl_2$, 10; HEPES, 20), and filtered through two layers of cheesecloth.

Binding Experiments. Binding curves for the different compounds were derived indirectly from competition experiments against 0.5 nM [^{3}H]pirenzepine labelling the cerebral cortex muscarinic receptors, and 0.3 nM [^{3}H]NMS for the muscarinic receptors of the heart and submandibular glands. A 1 ml portion of homogenate was incubated for 45 min at 30°C in the presence of the marked ligand and different concentrations of the cold ligand. The incubation was terminated by centrifugation (12000 rpm for 3 min) at room temperature with an Eppendorf microcentrifuge. The resultant pellet was washed twice with 1.5 ml of saline to remove the free radioactivity and the final pellet was allowed to drain.

The tips of the tubes containing the pellet were cut off and 200 µl of tissue solubilizer (Lumasolve, Lumac) was added and left to stand overnight. Radioactivity was then counted after addition of 4 ml of liquid scintillation solution (Lipoluma, Lumac). Assays were carried out in triplicate and the nonspecific binding was defined as the radioactivity bound or entrapped in the pellet when the incubation medium contained 1 µM 3-quinuclidinyl benzylate racemic mixture (QNB). Nonspecific binding averaged less than 30% and 10%, respectively. The inhibition constants (Ki) were calculated after correction for the radioligand occupancy shift with the equation of Cheng and Prusoff (see Cheng Y. et al., Biochem. Pharmacol. 22, 3099, 1973).

The results are reported in Table I.

TABLE I

"In vitro" Receptor Binding Studies (Ki x 10^{-6} M)

Compound	Cerebral rat cortex (M_1)	Rat heart (M_2)	Submandibular rat gland (M_3)
2	5.0	7.4	19.4
4	1.0	4.4	4.3
6	0.43	3.2	1.9
7	1.7	5.2	11.8
8	0.50	2.4	3.3
11	3.3	7.4	11.9
13	2.0	6.6	11.8
15	0.51	6.7	18.2
17	0.90	4.4	5.9
20	9.0	2.2	31.0
22	3.0	2.2	6.2
24	2.2	2.2	8.8
25	3.1	3.1	21.3
26	0.51	0.50	2.5
28	1.0	1.5	5.0
42	0.29	2.1	1.3
46	6.0	14.8	17.6

Functional studies

Rat superior cervical ganglion

Superior cervical ganglia were excised from male Sprague-Dawley rats, weighing 150-200 g, which had been anaesthetized with urethan (1.2 g/kg i.p.). Each ganglion was desheathed under a microscope and then submerged in a three compartments bath. The ganglion body was situated in the central compartment and the preganglionic (cervical sympathetic) and postganglionic (internal carotid) trunks protruded through greased slots into two outer chambers. The central compartment (volume approx. 0.5 ml) was continually perfused (2-2.5 ml min^{-1}) with Krebs-Henseleit solution at 25°C, pre-equilibrated with 5% carbon dioxide in oxygen; the same solution in the outer compartments was static. The medium was an aqueous solution containing (mM): NaCl 124.1, KCl 4.8, $NaHCO_3$ 24.8, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, glucose 10.

Ganglionic potential changes, induced by drug perfusion, were recorded using Ag/AgCl electrodes between the chambers containing the ganglion body (earthed) and the postganglionic trunk. The potentials were amplified and plotted on a potentiometric chart recorder. After a 30' stabilization period, 1 μM muscarine was superfused for 75 sec periods at 15 min intervals, until two consecutive equally sized depolarizing responses were observed (usually 3-4 applications). The last of these responses, measured in every experiment, was considered as standard maximum response. Following the return to a stable base-line, one agonist was superfused for 75 sec periods in increasing semi-logarithmic molar concentra-

tion units (e.g. 1, 3, 10 μM) until the maximum response was evoked. These applications were usually made at 10-15 min intervals, but longer intervals were used in case of a slower return to the base-line. After obtaining the maximum response, pirenzepine was superfused at 0.1 μM for 60 min, followed by re-determination of the agonist concentration-response curve in the presence of pirenzepine in the superfusion medium. The concentration of agonist producing 50% of its maximal response (EC_{50}) was calculated by the least squares linear regression analysis applied to the first concentration-response curve. The relative maximum (RM) was obtained by comparing the agonist maximum response to the standard maximum response to 1 μM muscarine taken as 1. To verify the muscarinic nature of the response to the agonist, the dose-ratio was calculated at the EC_{50} level from the rightward displacement by pirenzepine of the concentration-response curve to the agonist, after checking for parallelism of the curves. The affinity value for pirenzepine (pA_2) was calculated as described by Furchgott (Handbook of Experimental Pharmacology, vol. 33, H. Blaschko & E. Muschall (Eds.), 283-335, Springer-Verlag, Berlin, 1972): pA_2 = -log ([antagonist]/dose-ratio-1).

The results are reported in Table II.

TABLE II

"In vitro" functional studies

	RAT SUPERIOR CERVICAL GANGLION	
Compound	**EC_{50} (μM)**	**RM***
2	14.4	1
7	0.4	1.1
20	0.8	1
22	2	1
24	1.1	0.8

*RM = Relative maximum, in comparison with the effect of 1 μM muscarine taken as 1

The following examples illustrate some of the compounds according to the present invention, but they are not considered in any way limitative of the scope of the invention itself:

Example 1

R (-)N-[(1-azabicyclo[2.2.2]-oct-3-yl)-oxy]-phthalimide

A mixture of S(+) 1 azabicyclo[2.2.2]-octan-3-ol (37.5 g) [Eur. J. Med. Chem. 14, 111 (1979)], triphenylphosphine (77.3 g), N-hydroxy-phthalimide (48.1 g) and Molecular Sieve (70 g) in dry THF (750 ml) was stirred for 2 hours at room temperature and then cooled with ice-bath. Diethylazodicarboxylate (DEAD) (51.4 g) was added dropwise and the resulting solution was stirred overnight. Water was added (300 ml) and the Molecular Sieve filtered off; the THF was removed in vacuo and the residue, acidified with 10% aqueous HCl solution, was washed 2-times with ethyl acetate. The

aqueous layer was basified with K_2CO_3 and extracted exhaustively with ethyl acetate. The combined organic layers were dried and evaporated to dryness to obtain the desired product as a white solid (33.5 g).

M.p. > 280°C (ethanol, as hydrochloride salt)

MS (C.I.) = 273 m/e [M + H]

$[\alpha]_D$ = - 36.34° (c = 1% in 1N HCl)

According to the above described procedure the following compounds have been prepared:

S(+)N-[(1-azabicyclo[2.2.2]-oct-3-yl)-oxy]-phthalimide, starting from R(-)1-azabicyclo[2.2.2]-octan-3-ol [Eur. J. Med. Chem. 14, 111 (1979)]

M.p. > 280°C (ethanol, as hydrochloride salt)

MS (C.I.) = 273 m/e [M + H]

$[\alpha]_D$ = +36.15° (c = 1% in 1N HCl)

(±)-endo-N-[(1-azabicyclo[2.2.1]-hept-3-yl)-oxy]-phthalimide, starting from (±)-exo-1-azabicyclo[2.2.1]-heptan-3-ol [J. Org. Chem. 34, 3674 (1969)]

M.p. = 220-225°C dec. (as hydrochloride salt).

MS (C.I.) = 259 m/e [M+H]

(±)-exo-N-[(1-azabicyclo[2.2.1]-hept-3-yl)-oxy]-phthalimide, starting from (±)-endo-1-azabicyclo[2.2.1]-heptan-3-ol [EP 427390]

M.p. 145-150°C

MS (C.I.) = 259 m/e [M + H]

(±)-endo-N-[1-azabicyclo[3.2.1]-oct-6-yl)-oxy]-phthalimide, starting from (±)-exo-1-azabicyclo[3.2.1]-octan-6-ol [J. Org. Chem. 33, 4376 (1968)]

M.p. > 250°C (as hydrochloride salt)

MS (C.I.) = 273 m/e [M + H]

(±)-exo-N-[1-azabicyclo[3.2.1]-oct-6-yl)-oxy]-phthali-

mide, starting from (±)-endo-1-azabicyclo[3.2.1]-octan-6-ol [J. Org. Chem. 33, 4376 (1968)]

M.p. 148-152°C

MS (C.I.) = 273 m/e [M + H]

(±)-endo-N-[1-azabicyclo[3.2.1]-oct-3-yl)-oxy]-phthalimide, starting from (±)-exo-N-[(1-azabicyclo[3.2.1]-octan-3-ol [J. Org. Chem. 33, 4376 (1968), EP 257741]

M.p. = 110-118°C dec.

MS (C.I.) = 273 m/e [M + H]

(±)-exo-N-[1-azabicyclo[3.2.1]-oct-3-yl)-oxy]-phthalimide, starting from (±)-endo-1-azabicyclo[3.2.1]-octan-3-ol [J. Org. Chem. 33, 4376 (1968)]

M.p. = 108-111°C

MS (C.I.) = 273 m/e [M +H]

(±)-endo-N-[1-azabicyclo[3.3.1]non-3-yl)-oxy]-phthalimide, starting from (±)-exo-1-azabicyclo[3.3.1]nonan-3-ol [J. Amer. Chem. Soc. 89, 1431 (1967), EP 257741]

M.p. = 135-140°C

MS (C.I.) = 287 m/e [M + H]

(±)-exo-N-[1-azabicyclo[3.3.1]non-3-yl)-oxy]-phthalimide, starting from (±)-endo-1-azabicyclo[3.3.1]nonan-3-ol [J. Amer. Chem. Soc. 89, 1431 (1967)

M.p. = 160°C dec.

MS (C.I.) = 287 m/e [M + H]

R(-)-N-[(1-azabicyclo[2.2.2]oct-3-yl)-methoxy]-phthalimide, starting from R(-)-1-aza-3-hydroxy-methyl-bicyclo[2.2.2] octane [EP 458214]

M.p. 85-95°C (isopropyl ether)

MS (C.I.) = 287 m/e [M + H]

$[\alpha]_D$ = - 27.49° (c = 1% in 1N HCl)

S(+)-N-[(1-azabicyclo[2.2.2]oct-3-yl)-methoxy]-phthali-

mide, starting from S(+)-1-aza-3-hydroxy-methyl-bicyclo[2.2.2]-octane [EP 458214]

M.p. 90-95°C (Isopropyl ether)

MS (C.I.) = 287 m/e [M + H]

$[\alpha]_D$ = + 25.93° (c = 1% in 1N HCl)

N-[(1-ethyl-1-azacyclobut-3-yl)-oxy]-phthalimide, starting from 1-ethyl-1-azacyclobutan-3-ol [see example 2]

N-[(1-azacyclobut-3-yl)-oxy]-phthalimide, starting from 1-azacyclobutan-3-ol [Synth. Comm. 20, 407 (1990)]

N-[(1-methyl-1-azacyclohex-4-yl)-oxy]-phthalimide

M.p. 95°C

MS (C.I.) = 261 m/e [M + H]

(±)-N-[(1-Methyl-1-azacyclohept-3-yl)-oxy]-phthalimide, starting from 1-methyl-1-azacycloheptan-3-ol [see example 3]

M.p. = 70-72°C

MS (C.I.) = 275 m/e [M+ + H]

Exo-N-[(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-oxy]-phthalimide

M.p. 255°C (dec.) (Isopropanol, as hydrochloride salt)

MS (C.I.) = 287 m/e [M + H]

(±)N-[(1-methyl-1-azacyclopent-3-yl)-oxy]-phthalimide

M.p. 87-91°C

MS (C.I.) = 247 m/e [M + H]

Example 2

1-Ethyl-1-azacyclobutan-3-ol

Example 3

a) **N-methyl-N-(ethoxy carbonylmethyl)-5-aminopentanoic acid, ethyl ester**

5-bromopentanoic acid ethyl ester (30 g) was added portionwise to a well stirred suspension of sarcosine

hydrochloride (22 g) and triethylamine (29 g) in toluene (220 ml). The reaction mixture was refluxed 20 hours, then cooled at 5°C. A solution of 5% aqueous hydrochloric acid (200 ml) was added, the organic layer separated and discharged. The aqueous solution was made alkaline with 17% Na_2CO_3 solution and the oil which separated was taken up with diethyl ether. The organic solution was washed with water, dried and evaporated to dryness to give the crude title compound. This was purified by distillation, g 17.5, b.p. 120°-125°C (0.5 mm Hg).

b) **1-Methyl-1-aza-2-ethoxycarbonyl-cycloeptan-3-one**

A solution of the previously described intermediate (8 g) in toluene (65 ml) was dropped into a refluxing solution of potassium tert-butylate (11 g) in anhydrous toluene (400 ml) under stirring.

The reaction mixture was refluxed for additionally 10 minutes and cooled at room temperature. A 5% hydrochloric acid solution was continuously introduced (50 ml) and the resulting organic solution was separated and discharged. The aqueous layer was made alkaline with a 17% sodium carbonate solution and the oily product which separated was extracted into ethyl acetate. From this solution after evaporation to dryness (5.78 g) of the crude intermediate was obtained sufficiently pure to be used in the next step. I.R. (nujol) = carbonyl absorption bands 1710 and 1740 cm^{-1}.

c) **1-Methyl-1-azacycloheptan-3-one**

A solution of the ethoxy carbonyl intermediate (5.68 g) in concentrated aqueous hydrochloric acid (56 ml) was refluxed for seven hours, then cooled at room

temperature. 15% Aqueous sodium hydroxide solution was added until a pH 9 was obtained. The separated oil was extracted into ethyl acetate, and from the dried and evaporated solution the decarboxylated keto derivative was obtained as a yellow oil (2.8 g).

The ^{1}H-NMR and M.S. were consistent with the proposed structure;

d) **1-Methyl-1-azacycloheptan-3-ol**

Li Al H_4 (1.04 g) was added portionwise to a cooled solution (5°C) of the above intermediate (3.5 g) in anhydrous tetrahydrofuran. The reaction mixture was further stirred for 1 hour, then a solution of tetrahydrofuran (30 ml) containing water (0.5 ml) was dropped in.

The separated salts were filtered and from the evaporated organic solution the title compound was obtained as a yellowish oil (3.5 g). The ^{1}H-NMR and M.S. were consistent with the proposed structure.

Example 4

R(-)-O-(1-azabicyclo[2.2.2]oct-3-yl)-hydroxylamine dihydrochloride

In absolute ethanol (300 ml) were dissolved R(-)-N-[(1-azabicyclo[2.2.2]-oct-3-yl)-oxy]-phthalimide (31.5 g) and hydrazine hydrate 85% (13.3 ml). The mixture was stirred overnight at room temperature, the solid was filtered and the filtrate evaporated to dryness. The residue was dissolved in water and, after cooling with ice-bath, acidified with 10% HCl solution; after stirring for 4-hours the solid was filtered off. The solution was evaporated to dryness and the title compound was obtained by crystallization from ethanol

as a white solid.

M.p. 195-200°C

MS (C.I.) = 143 m/e [M + H]

$[\alpha]_D$ = - 39.53° (c = 1% in 1N HCl)

Following the above described procedure and starting from suitable intermediates the following compounds have been prepared:

S(+)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-hydroxylamine dihydrochloride

M.p. 200-205°C (dec.)

MS (C.I.) = 143 m/e [M + H]

$[\alpha]_D$ = + 40° (c = 1% in 1N HCl)

(±)-Endo-O-(1-azabicyclo[2.2.1]-hept-3-yl)-hydroxylamine dihydrochloride

M.p. = 210-215°C dec.

MS (C.I.) = 129 m/e [M + H]

(±)-Exo-O-(1-azabicyclo[2.2.1]-hept-3-yl)-hydroxylamine dihydrochloride

M.p. 165-170°C

MS (C.I.) = 129 m/e [M + H]

(±)-Endo-O-(1-azabicyclo[3.2.1]-oct-6-yl)-hydroxylamine dihydrochloride

M.p. = 210-215°C dec.

MS (C.I.) = 142 m/e [M + H]

(±)-Exo-O-(1-azabicyclo[3.2.1]-oct-6-yl)-hydroxylamine

Thick oil

MS (C.I.) = 143 m/e [M + H]

(±)-Endo-O-(1-azabicyclo[3.2.1]-oct-3-yl)-hydroxylamine dihydrochloride

M.p. = 205-210°C dec.

MS (C.I.) =143 m/e [M + H]

(±)-Exo-O-(1-azabicyclo[3.2.1]-oct-3-yl)-hydroxylamine dihydrochloride

M.p. = 183-185°C dec.

MS (C.I.) = 143 m/e [M + H]

(±)-Endo-O-(1-azabicyclo[3.3.1]-non-3-yl)-hydroxylamine dihydrochloride

M.p. = 185-189°C dec.

MS (C.I.) = 157 m/e [M + H]

(±)-Exo-O-(1-azabicyclo[3.3.1]-non-3-yl)-hydroxylamine dihydrochloride

M.p. = 200-205°C dec.

MS (C.I.) = 157 m/e [M +H]

R(-)-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-methyl]-hydroxylamine dihydrochloride

M.p. 110-120°C (dec.)

MS (C.I.) = 157 m/e [M + H]

$[\alpha]_D$ = - 21.59° (c = 1% in 1N HCl)

S(+)-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-methyl]-hydroxylamine dihydrochloride

Hygroscopic solid

MS (C.I.) = 157 m/e [M + H]

$[\alpha]_D$ = + 21.22° (c = 1% in 1N HCl)

O-(1-ethyl-1-azacyclobut-3-yl)-hydroxylamine dihydrochloride

O-(1-azacyclobut-3-yl)-hydroxylamine dihydrochloride

O-(1-methyl-1-azacyclohex-4-yl)-hydroxylamine dihydrochloride

M.p. 195°C (dec.)

MS (C.I.) = 131 m/e [M + H]

(±)-O-(1-methyl-1-azacyclohept-3-yl)-hydroxylamine dihydrochloride

Thick oil

MS (C.I.) = 145 m/e [M + H]

(±)-O-(1-methyl-1-azacyclohex-3-yl)-hydroxylamine dihydrochloride

M.p. = 205-210°C dec.

MS (C.I.) = 131 m/e [M + H]

Exo-O-(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-hydroxylamine dihydrochloride

M.p. 185°C (dec.)

MS (C.I.) = 157 m/e [M + H]

(±)-O-(1-methyl-1-azacyclopent-3-yl)-hydroxylamine dihydrochloride

M.p. 162-6°C

MS (C.I.) = 117 m/e [M + H]

Example 5

S(+)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-ethylidenhydroxylamine hydrochloride

(Compound 1)

A suspension of S(+)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-hydroxylamine dihydrochloride (0.6 g), methanol (10 cc) and sodium (64 mg) was stirred at room temperature until sodium has disappeared. Acetaldehyde (0.16 ml) was added dropwise to the cooled solution. The reaction was stirred overnight at 0-5°C. The methanol was evaporated, the residue dissolved in water and washed with ethyl acetate. The aqueous phase was basified with Na_2CO_3 and extracted into $CHCl_3$. The organic layers were combined, dried and evaporated to dryness. The residue was dissolved in ethyl acetate and the title compound was obtained as hydrochloride salt by adding an anhydrous HCl solution in diethyl ether. The solid was

filtered and dried in vacuo.

The pure title compound was obtained as a white solid (0.31 g).

M.p. 165-170°C

MS (C.I.) = 169 m/e [M + H]

$[\alpha]_D$ = + 38.70° (c = 1% in 1N HCl)

^{1}H-NMR ($CDCl_3$): 1.7÷2.3 (4H, m); 1.85 (3H, d); 2.52 (1H, m); 3.1÷3.7 (6H, m); 4.51 (1H, m); 6.84 and 7.46 (1H, 2q); 12.27 (1H, b)

Analysis: $C_9H_{17}ClN_2O$

	C	H	N	Cl
Found%	52.54	8.40	13.65	17.24
Calc.%	52.81	8.37	13.69	17.32

According to the above described procedure the following compounds have been prepared

R(-)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-ethylidenhydroxylamine hydrochloride

(Compound 2)

M.p. 158-161°C

MS (C.I.) = 169 m/e [M + H]

$[\alpha]_D$ = + 40.128° (c = 1% in 1N HCl)

^{1}H-NMR ($CDCl_3$): 1.7÷2.3 (4H, m); 1.85 (3H, d); 2.51 (1H, m); 3.1÷3.7 (6H, m); 4.54 (1H, m); 6.84 and 7.46 (1H, 2q); 12.20 (1H, b)

Analysis: $C_9H_{17}ClN_2O$

	C	H	N	Cl
Found%	52.31	8.42	13.57	17.27
Calc.%	52.81	8.37	13.69	17.32

S(+)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-propylidenhydroxylamine hydrochloride

(Compound 3)

M.p. 147°C

MS (C.I.) = 183 m/e [M + H]

$[\alpha]_D$ = +40.9 (c = 1% in 1N HCl)

^{1}H-NMR ($CDCl_3$): 1.08 (3H, t); 1.7÷2.6 (7H, m); 3.1÷3.5 (6H, m); 4.53 (1H, m); 6.72 and 7.45 (1H, 2t); 12.18 (1H, b)

Analysis: $C_{10}H_{19}ClN_2O$

	C	H	N	Cl
Found%	54.39	8.81	12.70	16.12
Calc.%	54.91	8.76	12.81	16.21

R(-)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-propylidenhydroxylamine hydrochloride

(Compound 4)

M.p. 150°C

MS (C.I.) = 183 m/e [M + H]

$[\alpha]_D$ = -42.33 (c = 1% in 1N HCl)

^{1}H-NMR ($CDCl_3$): 1.08 (3H, t); 1.7÷2.6 (7H, m); 3.1÷3.7 (6H, m); 4.53 (1H, m); 6.72 and 7.45 (1H, 2t); 12.31 (1H, b)

Analysis: $C_{10}H_{19}ClN_2O$

	C	H	N	Cl
Found%	54.40	8.76	12.77	16.15
Calc.%	54.91	8.76	12.81	16.21

S-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-isobutylidenhydroxylamine hydrochloride

(Compound 5)

M.p. = 160-162°C dec.

MS (C.I.) = 197 m/e [M + H]

$[\alpha]_D$ = +35.1 (c = 1% in Et OH]

^{1}H-NMR [DMSO + $CDCl_3$] 10.86 (b, 1H); 7.41 (d, 1H); 4.48 (m, 1H); 2.9 ÷ 3.7 (6H); 2.3 ÷ 2.6 (2H); 1.89 (m, 4H);

1.05 (d, 6H).

Analysis: $C_{11}H_{21}ClN_2O$

	C	H	N	Cl
Found%	55.18	8.35	11.91	15.12
Calc.%	56.76	9.09	12.04	15.23

R(-)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-isobutylidenhydroxylamine hydrochloride

(Compound 6)

M.p. = 165°C dec.

MS (C.I.) = 197 m/e [M + H]

$[\alpha]_D$ = -33.4 (c = 1% in Et OH]

^{1}H-NMR [DMSO] 10.92 (b, 1H); 7.47 (d, 1H); 4.45 (m, 1H); 3.0 ÷ 3.8 (6H); 2.50 (m, 1H); 2.29 (m, 1H); 1.6 ÷ 2.2 (4H); 1.03 (d, 6H).

Analysis: $C_{11}H_{21}ClN_2O$

	C	H	N	Cl
Found%	55.21	9.07	11.71	15.17
Calc.%	56.76	9.09	12.04	15.23

S(+)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-(2,2,2-trifluoroethyliden)-hydroxylamine fumarate

(Compound 7)

M.p. = 128-132°C dec.

MS (C.I.) = 223 m/e [M + H]

$[\alpha]_D$ = +31.3 (c = 1% in Et OH]

^{1}H-NMR [DMSO] 8.25 (q, 1H); ~ 7.3 (b, 2H); 6.51 (s, 2H); 4.60 (m, 1H); 3.40 (m, 1H); 2.8 ÷ 3.1 (5H); 2.23 (m, 1H); 1.5 ÷ 1.9 (4H).

Analysis: $C_{13}H_{17}F_3N_2O_5$

	C	H	N
Found%	46.01	5.12	8.10
Calc.%	46.16	5.07	8.28

R(-)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-(2,2,2-trifluoroethyliden)-hydroxylamine fumarate

(Compound 8)

M.p. = 138-140°C dec.

MS (C.I.) = 223 m/e [M + H]

$[\alpha]_D$ = -31.5 (c = 1% in Et OH]

^{1}H-NMR [DMSO] ~ 8.8 (b, 2H); 8.26 (q, 1H); 6.51 (s, 2H); 4.63 (m, 1H); 3.41 (m, 1H); 2.8 ÷ 3.2 (5H); 2.25 (m, 1H); 1.5 ÷ 2.0 (4H).

Analysis: $C_{13}H_{17}F_3N_2O_5$

	C	H	N
Found%	46.22	5.11	8.19
Calc.%	46.16	5.07	8.28

(±)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-(benzyliden)-hydroxylamine hydrochloride

(Compound 9)

M.p. 207-209°C

MS (C.I.) = 231 m/e [M + H]

^{1}H-NMR [$CDCl_3$] 12.42 (b, 1H); 8.12 (s, 1H); 7.2 ÷ 7.6 (5H); 4.68 (m, 1H); 3.0 ÷ 3.7 (6H); 2.62 (m, 1H); 1.6 ÷ 2.4 (4H).

Analysis $C_{14}H_{19}ClN_2O$

	C	H	N	Cl
Found%	62.81	7.27	10.43	13.23
Calc.%	63.02	7.19	10.50	13.29

(±)-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-methyl]-N-(benzyliden)-hydroxylamine hydrochloride

(Compound 10)

M.p. 200°C

MS (C.I.) = 245 m/e [M + H]

^{1}H-NMR [$CDCl_3$] 12.12 (b, 1H); 8.03 (s, 1H); 7.2 ÷ 7.7

(5H); 4.20 (d, 2H); 1.8 ÷ 3.7 (12H).

Analysis: $C_{15}H_{21}ClN_2O$

	C	H	N	Cl
Found%	63.98	7.61	9.88	12.58
Calc.%	64.16	7.54	9.98	12.63

Example 6

R(-)-O-(1-azabicyclo[2.2.2]oct-3-yl)-N-isopropylidenhydroxylamine dihydrochloride

(Compound 11)

Acetone (0.24 cc) was dropped into a cooled (10°C) solution of R(-)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-hydroxylamine dihydrochloride (0.7 g) in methanol (15 cc). The solution was stirred for 2 hours at 10°C and then stirring was maintained for 36 hours at room temperature. The methanol was evaporated, the residue dissolved in ethyl acetate and then evaporated to dryness. The residue was crystallized from ethyl acetate to obtain the title compound as a white solid (0.58 g).

M.p. 130-132°C

MS (C.I.) = 183 m/e [M + H]

$[\alpha]_D$ = - 41.65° (c = 1% in 1N HCl)

^{1}H-NMR (DMSO + $CDCl_3$;): 1.6÷2.1 (4H, m); 1.84 (3H, s); 1.85 (3H, s); 2.35 (1H, m); 2.9÷3.7 (6H, m); 4.47 (1H, m); 6.40 (1H + HDO, b); 10.82 (1H, b).

Analysis: $C_{10}H_{20}Cl_2N_2O$

	C	H	N	Cl
Found%	46.53	7.97	10.81	27.55
Calc.%	47.07	7.90	10.98	27.79

Following the above described procedure and starting from suitable intermediates the following compounds may be prepared

S(+)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-isopropyliden-hydroxylamine dihydrochloride

(Compound 12)

M.p. = 135-140°C

MS (C.I.) = 183 m/e [M + H]

$[\alpha]_D$ = + 41.4° (c = 1% in 1N HCl)

^{1}H-NMR (DMSO + $CDCl_3$;): 1.6÷2.1 (4H, m); 1.84 (3H, s); 1.85 (3H, s); 2.35 (1H, m); 2.9÷3.7 (6H, m); 4.47 (1H, m); 6.26 (1H + HDO, b); 10.73 (1H, b).

Analysis: $C_{10}H_{20}Cl_2N_2O$

	C	H	N	Cl
Found%	47.11	7.95	11.17	27.49
Calc.%	47.07	7.90	10.98	27.79

R(-)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-(2,2-difluoro-ethyliden)-hydroxylamine fumarate

(Compound 13)

M.p. 130-135°C dec.

MS (C.I.) = 205 m/e [M + H]

^{1}H-NMR [DMSO] 9.20 (b, 2H); 7.91 (m, 1H); 6.53 (s, 2H); 6.56 (m, 1H); 4.59 (m, 1H); 3.47 (m, 1H); 2.9 ÷ 3.3 (5H); 2.27 (m, 1H); 1.5 ÷ 2.0 (4H).

Analysis: $C_{13}H_{18}F_2N_2O_5$

	C	H	N
Found%	48.60	5.70	8.68
Calc.%	48.75	5.66	8.75

S(+)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-(2,2-difluoro-ethyliden)-hydroxylamine_hydrochloride

(Compound 14)

M.p. 110°C dec.

MS (C.I.) = 205 m/e [M + H]

^{1}H-NMR [$CDCl_3$] 7.51 (m, 1H); 6.11 (m, 1H); 4.65 (m,

1H); 3.58 (m, 1H); 3.2 ÷ 3.5 (5H); 2.56 (m, 1H); 1.7 ÷ 2.3 (4H).

Analysis: $C_9H_{15}ClF_2N_2O$

	C	H	N	Cl
Found%	44.80	6.35	11.55	14.62
Calc.%	44.91	6.28	11.64	14.73

R(-)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-(2-fluoro-ethyliden)-hydroxylamine fumarate

(Compound 15)

M.p. 118°C dec.

MS (C.I.) = 187 m/e [M + H]

^{1}H-NMR [DMSO] 7.75 and 7.26 (2m, 1H); 6.50 (s, 2H); ~6.4 (b, 2H); 5.30 and 4.99 (2m, 2H); 4.50 (m, 1H); 3.41 (m, 1H); 2.9 ÷ 3.2 (5H); 2.25 (b, 1H); 1.5 ÷ 2.0 (4H).

Analysis: $C_{13}H_{19}FN_2O_5$

	C	H	N
Found%	51.83	6.25	9.31
Calc.%	51.65	6.34	9.27

S(+)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-(2-fluoro-ethyliden)-hydroxylamine fumarate

(Compound 16)

M.p. 118°C dec.

MS (C.I.) = 187 m/e [M + H]

^{1}H-NMR [DMSO] 8.56 (b, 2H); 7.69 and 7.15 (2m, 1H); 6.54 (s, 2H); 5.25 and 4.95 (2m, 2H); 4.41 (m, 1H); 3.36 (m, 1H); 2.7 ÷ 3.2 (5H); 2.23 (m, 1H); 1.4 ÷ 2.1 (4H).

Analysis: $C_{13}H_{19}FN_2O_5$

	C	H	N
Found%	51.40	6.40	9.17
Calc.%	51.65	6.34	9.27

R(-)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-cyclobutyliden-hydroxylamine hydrochloride

(Compound 17)

M.p. = 185-190°C

MS (C.I.) = 195 m/e [M + H]

$[\alpha]_D$ = - 36.35 (c = 1% in EtOH)

^{1}H-NMR [DMS + $CDCl_3$]: 10.62 (b, 1H); 4.69 (m, 1H); 3.1 ÷ 3.9 (6H): 0.7 ÷ 2.7 (11H)

Analysis: $C_{11}H_{19}ClN_2O$

	C	H	N	Cl
Found%	57.11	8.32	12.17	15.01
Calc.%	57.26	8.30	12.14	15.36

S(+)-O-(1-azabicyclo[2.2.2]-oct-3-yl)-N-cyclobutyliden-hydroxylamine hydrochloride

(Compound 18)

M.p. = 190-195°C

MS (C.I.) = 195 m/e [M + H]

$[\alpha]_D$ = - 34.79 (c = 1% in EtOH)

^{1}H-NMR [DMSO + $CDCl_3$] 10.79 (b, 1H); 4.44 (m, 1H); 2.7 ÷ 3.7 (10H); 2.32 (m, 1H); 1.6 ÷ 2.2 (6H).

Analysis: $C_{11}H_{19}ClN_2O$

	C	H	N	Cl
Found%	55.60	8.32	12.08	15.23
Calc.%	57.26	8.30	12.14	15.36

(±)-endo-O-(1-azabicyclo[2.2.1]-hept-3-yl)-N-ethyliden-hydroxylamine fumarate

(Compound 19)

M.p. = 160°C

MS (C.I.) = 155 m/e [M + H]

^{1}H-NMR [DMSO]: ~ 8.8 (broad, 2H); 6.99 (s, 2H); 7.51 and 6.94 (2q, 1H); 4.79 (m, 1H); 3.43 (m, 1H); 3.17 (m, 1H); 2.8 ÷ 3.1 (4H); 2.60 (m, 1H); 1.6 ÷ 2.0 (2H); 1.79 and 1.80 (2d, 3H.)

Analysis: $C_{12}H_{18}N_2O_5$

	C	H	N
Found%	53.47	6.80	10.35
Calc.%	53.32	6.71	10.37

(±)-exo-O-(1-azabicyclo[2.2.1]-hept-3-yl)-N-ethyliden-hydroxylamine fumarate

(Compound 20)

M.p. 175°C

MS (C.I.) = 155 m/e [M + H]

^{1}H-NMR [DMSO + $CDCl_3$] 9.40 (b, 2H); 6.57 (s, 2H); 6.84 and 7.41 (2q, 1H); 4.25 (m, 1H); 2.4 ÷ 3.3 (7H); 1.81 (m, 1H); 1.78 (d 3H); 1.24 (m, 1H).

Analysis: $C_{12}H_{18}N_2O_5$

	C	H	N
Found%	52.98	6.71	10.18
Calc.%	53.32	6.71	10.37

(±)-Endo-O-(1-azabicyclo[3.2.1]-oct-6-yl)-N-ethyliden-hydroxylamine fumarate

(Compound 21)

M.p. 135-140°C dec.

MS (C.I.) = 169 m/e [M + H]

^{1}H-NMR [$CDCl_3$] 10.6 (b, 2H); 7.48 and 6.85 (2q, 1H); 6.81 (s, 2H); 5.09 (m, 1H); 4.04, (m, 1H); 3.3 ÷ 3.6 (3H); 3.0 ÷ 3.3 (2H); 2.73 (b, 1H); 2.21 (m, 1H); 1.7 ÷ 2.1, (3H); 1.86 and 1.88 (2d, 3H).

Analysis: $C_{13}H_{20}N_2O_5$

	C	H	N
Found%	54.84	7.25	9.74
Calc.%	54.92	7.09	9.85

(±)-Exo-O-(1-azabicyclo[3.2.1]-oct-6-yl)-N-ethyliden-hydroxylamine hydrochloride

(Compound 22)

M.p. 170-173°C

MS (C.I.) = 169 m/e [M + H]

^{1}H-NMR [$CDCl_3$] 12.84 (b, 1H); 8.03 (s, 1H); 7.2 ÷ 7.7 (5H); 4.20 (d, 2H); 1.8 ÷ 3.7 (12H).

Analysis: $C_9H_{17}ClN_2O$

	C	H	N	Cl
Found%	52.15	8.40	13.59	17.9
Calc.%	52.80	8.37	13.69	17.2

(±)-Endo-O-(1-azabicyclo[3.2.1]-oct-3-yl)-N-ethyliden-hydroxylamine fumarate

(Compound 23)

M.p. = 125-127°C dec.

MS (C.I.) = 169 m/e [M+H]

^{1}H-NMR [DMSO] 9.2 (b, 2H); 6.94 (q, 1H); 6.47 (s, 2H); 4.31 (b, 1H); 3.41 and 3.50 (d, m, 2H); 3.23 (m, 2H); 3.01 and 3.12 (m, d, 2H); 2.50 (m, 1H); 1.9 ÷ 2.2 (4H); 1.81 (d, 3H).

Analysis: $C_{13}H_{20}N_2O_5$

	C	H	N
Found%	54.43	7.11	9.75
Calc.%	54.92	7.09	9.85

(±)-Exo-O-(1-azabicyclo[3.2.1]-oct-3-yl)-N-ethyliden-hydroxylamine fumarate

(Compound 24)

M.p. 119-121°C dec.

MS (C.I.) = 169 m/e [M + H]

^{1}H-NMR [DMSO + $CDCl_3$] 9.46 (b, 2H); 7.39 and 6.82 (2q, 1H); 6.53 (s, 2H); 4.46 (m, 1H); 2.5 ÷ 3.6 (7H); 1.4 ÷ 2.3 (4H); 1.75 and 1.77 (2d, 3H).

Analysis: $C_{13}H_{20}N_2O_5$

	C	H	N
Found%	53.60	6.93	9.42
Calc.%	53.73	6.87	9.53

(±)-Endo-O-(1-azabicyclo[3.3.1]-non-3-yl)-N-ethyliden-hydroxylamine fumarate

(Compound 25)

M.p. = hygroscopic solid

MS (C.I.) = 183 m/e [M+H]

^{1}H-NMR [DMSO] 8.3 (b, 2H); 7.51 and 6.93 (2q, 1H); 6.50 (s, 2H); 4.37 (m, 1H); 3.60 (m, 1H); 3.0÷3.3 (5H); 2.51 (m, 1H); 2.23 (m, 1H); 2.04 (b, 1H); 1.4÷1.9 (4H); 1.81 and 1.82 (2d, 3H).

Analysis: $C_{14}H_{22}N_2O_5$

	C	H	N
Found%	56.04	7.34	9.19
Calc.%	56.36	7.43	9.39

(±)-Exo-O-(1-azabicyclo[3.3.1]-non-3-yl)-N-ethyliden-hydroxylamine hydrochloride

(Compound 26)

M.p. 155-160°C dec.

MS (C.I.) = 183 m/e [M + H]

^{1}H-NMR [$CDCl_3$] 12.68 (b, 1H); 7.41 and 6.80 (2q, 1H); 4.98 (m 1H); 3.60 (m, 1H); 3.2 ÷ 3.5 (5H); 1.8÷2.5 (7H); 1.82 and 1.83, (2d, 3H).

Analysis: $C_{10}H_{19}ClN_2O$

	C	H	N	Cl
Found%	54.00	8.61	12.57	16.10
Calc.%	54.91	8.76	12.81	16.21

Exo-O-(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-N-ethyliden-hydroxylamine fumarate

(Compound 27)

M.p. = 145°C dec.

MS (C.I.) = 183 m/e [M+H]

^{1}H-NMR [$CDCl_3$] 11.40 (b, 2H); 6.82 (s, 2H); 7.40 and 6.75 (2q, 1H); 4.44 (m, 1H); 3.98 (b, 2H); 2.78 (s, 3H): 2.1÷2.4 (6H); 1.95 (d, 2H); 1.81 and 1.82 (2d, 3H).

Analysis: $C_{14}H_{22}N_2O_5$

	C	H	N
Found%	56.28	7.49	9.36
Calc.%	56.36	7.43	9.39

R(-)-O-[1-azabicyclo[2.2.2]-oct-3-yl]-methyl-N-methyliden-hydroxylamine

(Compound 50)

S(+)-O-[1-azabicyclo[2.2.2]-oct-3-yl]-methyl-N-methyliden-hydroxylamine

(Compound 51)

Example 7

R(-)-O-[(1-azabicyclo[2.2.2]-oct-3-yl)]-methyl-N-ethyliden-hydroxylamine hydrochloride

(Compound 28)

A mixture of R(-)-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-methyl]-hydroxylamine dihydrochloride (1.5 g), methanol (25 cc) and sodium (300 mg) was stirred at room temperature until sodium has disappeared, then was

cooled with ice-bath and acetaldehyde (0.37 cc) was added dropwise. The solution was stirred at room temperature for 2 hours and then the reaction mixture was evaporated to dryness. The residue was dissolved in water and washed with ethyl acetate. The aqueous layer was then basified with Na_2CO_3 and extracted into $CHCl_3$. The organic layers were combined, dried and evaporated to dryness. The crude residue was dissolved in ethyl acetate and the desired compound was obtained as hydrochloride salt by adding an anhydrous HCl solution in diethyl-ether. The solid was filtered and dried in vacuo. The pure title compound was obtained as a white solid (0.34 g).

M.p. 135-140°C

MS (C.I.) = 183 m/e [M + H]

$[\alpha]_D$ = - 39.46° (c = 1% in 1N HCl)

^{1}H-NMR ($CDCl_3$) 1.7÷2.8 (6H, m), 1.81 and 1.84 (3H, 2d), 2.9÷3.7 (6H, m), 4.03 and 4.13 (2H, 2d), 6.76 and 7.39 (1H, 2q), 12.05 (1H, b)

Analysis: $C_{10}H_{19}ClN_2O$

	C	H	N	Cl
Found%	54.18	8.82	12.63	16.15
Calc.%	54.91	8.76	12.81	16.24

According to the above described procedure and starting from suitable intermediates, the following compounds have been prepared

S(+)-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-methyl]-N-ethyliden-hydroxylamine hydrochloride

(Compound 29)

M.p. 145-150°C

MS (C.I.) = 183 m/e [M + H]

$[\alpha]_D$ = + 41.63° (c = 1% in 1N HCl)

^{1}H-NMR ($CDCl_3$) 1.7÷2.7 (6H, m), 1.80 and 1.84 (3H, 2d), 2.9÷3.7 (6H, m), 4.04 and 4.12 (2H, 2d), 6.76 and 7.39 (1H, 2q), 12.08 (1H, b)

Analysis: $C_{10}H_{19}ClN_2O$

	C	H	N	Cl
Found%	54.42	8.79	12.66	16.18
Calc.%	54.91	8.76	12.81	16.24

O-(1-ethyl-1-azacyclobut-3-yl)-N-ethyliden-hydroxylamine

(Compound 31)

(±)-O-(1-methyl-1-azacyclopent-3-yl)-N-ethylidenhydroxylamine oxalate

(Compound 33)

M.p. = 105-109°C dec.

MS (C.I.) = 143 m/e [M+H]

^{1}H-NMR [DMSO] 10.24 (b, 2H); 7.47 and 6.95 (2q, 1H); 4.81 (m, 1H); 3.2 ÷ 3.6 (4H); 2.80 (s, 3H); 2.30 (m, 1H); 2.07 (m, 1H); 1.78 and 1.80 (2d, 3H).

Analysis: $C_9H_{16}N_2O_5$

	C	H	N
Found%	46.39	7.04	11.80
Calc.%	46.55	6.94	12.06

(±)-O-(1-methyl-1-azacyclohept-3-yl)-N-ethylidenhydroxylamine maleate

(Compound 35)

M.p. 95-100°C dec.

MS (C.I.) = 171 m/e [M + H]

^{1}H-NMR [$CDCl_3$] 7.48 and 6.85 (2q, 1H); 6.29 (s, 2H); 4.53 (b, 1H); 3.1 ÷ 3.7 (b, 4H); 2.92 (s, 3H); 1.6 ÷ 2.2 (6H); 1.87 (d, 3H).

Analysis: $C_{13}H_{22}N_2O_5$

	C	H	N
Found%	54.12	7.75	9.59
Calc.%	54.53	7.74	9.78

O-(1-methyl-1-azacyclohex-4-yl)-N-ethylidenhydroxylamine fumarate

(Compound 37)

M.p. 90-95°C dec.

MS (C.I.) = 157 m/e [M + H]

^{1}H-NMR [DMSO + $CDCl_3$] 10.64 (b, 2H); 6.80 and 7.42 (2q, 1H); 6.57 (s, 2H); 4.12 (m, 1H); 2.4 ÷ 3.1 (4H); 2.46 (s, 3H); 1.79 (d, 3H); 1.7 ÷ 2.2 (4H).

Analysis: $C_{12}H_{20}N_2O_5$

	C	H	N
Found%	52.67	7.59	10.22
Calc.%	53.93	7.40	10.29

(±)-O-(1-methyl-1-azacyclohex-3-yl)-N-ethylidenhydroxylamine hydrochloride

(Compound 39)

M.p. 150-157°C dec.

MS (C.I.) = 157 m/e [M + H]

^{1}H-NMR [$CDCl_3$] 12.7 and 11.7 (2b, 1H); 7.80, 7.36 and 6.83 (3m, 1H); 4.48 (m, 1H); 3.58 (m, 2H); 2.84 (s, 3H); 2.6 ÷ 3.2 (2H); 1.5 ÷ 2.4 (4H); 1.82 and 1.83 (2d, 3H).

Analysis: $C_8H_{17}ClN_2O$

	C	H	N	Cl
Found%	49.56	8.99	14.44	18.32
Calc.%	49.87	8.89	14.54	18.40

R-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-N-(2,2,2-trichloroethyliden)-hydroxylamine hydrochloride

(Compound 40)

M.p. 225°C dec.

MS (C.I.) = 272 m/e [M + H]

$[\alpha]_D$ = - 30.0 (c= 1% in EtOH)

^{1}H-NMR [$CDCl_3$] 12.24 (b, 1H); 7.90 (s, 1H); 4.73 (m, 1H); 3.70 (m 1H); 3.2 ÷ 3.6 (5H); 2.61 (b, 1H); 1.8 ÷ 2.3 (4H).

Analysis: $C_9H_{14}Cl_4N_2O$

	C	H	N	Cl
Found%	34.80	4.65	8.99	46.18
Calc.%	35.09	4.58	9.09	46.05

S-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-N-(2,2,2-trichloro-ethyliden)-hydroxylamine hydrochloride

(Compound 41)

M.p. 225°C dec.

MS (C.I.) = 272 m/e [M + H]

$[\alpha]_D$ = + 31.3 (c= 1% in EtOH)

^{1}H-NMR [$CDCl_3$] 12.55 (b, 1H); 7.84 (s, 1H); 4.70 (m, 1H); 3.62 (m, 1H); 3.2 ÷ 3.5 (5H); 2.62 (b, 1H); 1.7 ÷ 2.3 (4H).

Analysis: $C_9H_{14}Cl_4N_2O$

	C	H	N	Cl
Found%	34.47	4.50	8.84	46.11
Calc.%	35.09	4.58	9.09	46.05

R-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-N-(2,2-dichloro-ethyliden)-hydroxylamine fumarate

(Compound 42)

M.p. 170-172°C dec.

MS (C.I.) = 238 m/e [M + H]

$[\alpha]_D$ = - 30.73 (c= 1% in EtOH)

^{1}H-NMR [DMSO + $CDCl_3$] 8.18 (b, 2H); 7.81 and 7.32,

(2d, 1H); 7.16 and 6.79 (2d, 1H); 6.56 (s, 2H); 4.49 (m, 1H); 3.42 (m, 1H); 2.8 ÷ 3.2 (5H); 2.26 (m, 1H); 1.5 ÷ 2.0 (4H).

Analysis: $C_{13}H_{18}Cl_2N_2O_5$

	C	H	N	Cl
Found%	44.04	5.20	8.01	19.95
Calc.%	44.21	5.14	7.93	20.08

S-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-N-(2,2-dichloro-ethyliden)-hydroxylamine fumarate

(Compound 43)

M.p. 172-174°C dec.

MS (C.I.) = 238 m/e [M + H]

$[\alpha]_D$ = - 31.61 (c= 1% in EtOH)

^{1}H-NMR [DMSO + $CDCl_3$] 9.75 (b, 2H); 7.81 and 7.34 (2d, 1H); 7.16 and 6.80 (2d, 1H); 6.56 (s, 2H); 4.47 (m, 1H); 3.44 (m, 1H); 2.8 ÷ 3.2 (5H); 2.24 (m, 1H); 1.5 ÷ 2.0 (4H).

Analysis: $C_{13}H_{18}Cl_2N_2O_5$

	C	H	N	Cl
Found%	44.00	5.22	7.85	20.19
Calc.%	44.21	5.14	7.93	20.08

R-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-N-(1-fluoroethyli-den)-hydroxylamine fumarate

(Compound 46)

M.p. 118-121°C dec.

MS (C.I.) = 187 m/e [M + H]

$[\alpha]_D$ = - 29.7 (c= 1% in EtOH)

^{1}H-NMR [DMSO] 6.52 (s, 2H); 4.34 (m, 1H); 3.42 (m, 1H); 2.9 ÷ 3.2 (5H); 2.27 (m, 1H); 2.19 and 2.04 (2d, 3H); 1.5 ÷ 2.0 (4H).

Analysis: $C_{13}H_{19}FN_2O_5$

	C	H	N
Found%	51.35	6.40	9.18
Calc.%	51.65	6.34	9.27

S-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-N-(1-fluoroethyliden)-hydroxylamine fumarate

(Compound 47)

M.p. 140°C dec.

MS (C.I.) = 187 m/e [M + H]

$[\alpha]_D$ = + 28.87 (c= 1% in EtOH)

^{1}H-NMR [DMSO] 8.2 (b, 2H); 6.53 (s, 2H); 4.35 (m, 1H); 3.42 (m, 1H); 2.9 ÷ 3.2 (5H); 2.18 and 2.04 (2d, 3H); 1.5 ÷ 2.0, (4H); 2.28 (m, 1H).

Analysis: $C_{13}H_{19}FN_2O_5$

	C	H	N
Found%	51.13	6.45	9.12
Calc.%	51.65	6.34	9.27

S-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-N-methylenhydroxylamine hydrochloride

(Compound 48)

M.p. 80-90°C dec. (hygroscopic solid)

MS (C.I.) = 155 m/e [M + H]

$[\alpha]_D$ = + 25.78 (c= 1% in MetOH)

^{1}H-NMR [DMSO] 10.86 (b, 1H); 7.16 (d, 1H); 6.75 (d, 1H); 4.56 (m, 1H); 3.0 ÷ 3.6 (6H); 1.5 ÷ 2.4 (5H).

Analysis: $C_8H_{16}Cl_2N_2O$

	C	H	N	Cl
Found%	41.94	7.19	12.20	31.32
Calc.%	42.30	7.10	12.33	31.22

R-O-[(1-azabicyclo[2.2.2]-oct-3-yl)-N-methylen-hydroxylamine hydrochloride

(Compound 49)

M.p. 145-150°C dec.

MS (C.I.) = 155 m/e [M + H]

$[\alpha]_D$ = - 26.32 (c= 1% in MetOH)

^{1}H-NMR [DMSO] 7.16 (d, 1H); 6.74 (d, 1H); 4.56 (m, 1H); 3.56 (m, 1H); ~3.6 (b, 1H); 3.0 ÷ 3.3 (5H); 2.30 (m, 1H); 1.6 ÷ 2.0, (4H).

Analysis: $C_8H_{16}Cl_2N_2O$

	C	H	N	Cl
Found%	41.96	7.21	12.30	31.04
Calc.%	42.30	7.10	12.33	31.22

Example 8

Endo-O-(8-methyl-8-azabicyclo[3.2.1]-oct-3-yl)-N-ethyliden-hydroxylamine hydrochloride

(Compound 44)

To a solution of sodium (0.237 g) in ethanol (10 cc) acetaldehyde oxime (1.97 cc) was added portionwise. The solution was stirred for 15' and then endo-8-methyl-3-chloro-8-azabicyclo[3.2.1]-octane (5.16 g) [J. Am. Chem. Soc. 80, 4677 (1958)] was added.

The solution was refluxed for 15 hours then cooled with ice-bath and the pH adjusted at 9 with an HCl solution in ethanol. The inorganic salts were filtered off and the solution evaporated to dryness. The crude residue was purified by flash column chromatography on Silica gel (eluent: 95:5:0.5: CH_2Cl_2:CH_3OH:NH_4OH 30%). The crude product obtained was dissolved in ethyl acetate, an anhydrous solution of HCl in diethyl ether was added and the solution evaporated to dryness. The title compound was obtained as a solid (0.13 g) after crystallization from diethyl ether.

M.p. 160°C

MS (C.I.) = 183 m/e [M + H]

^{1}H-NMR (DMSO + $CDCl_3$) 1.81 (3H, d), 2.0÷3.4 (8H, m), 2.68 (3H, d), 3.82 (2H, b), 4.26 (1H, m), 6.86 and 7.44 (1H, 2q), 11.36 (1H, b)

Analysis: $C_{10}H_{19}ClN_2O$

	C	H	N	Cl
Found%	53.55	8.83	12.49	15.98
Calc.%	54.91	8.76	12.81	16.21

According to the above described procedure the following compound was prepared

O-(1-methyl-1-azacyclohex-4-yl)-N-isopropylidenhydroxylamine hydrochloride

(Compound 45)

M.p. 140°C

MS (C.I.) = 171 m/e [M + H]

^{1}H-NMR (DMSO + $CDCl_3$) 1.8÷2.4 (10H, m), 2.73 (3H, d), 2.7÷3.6 (4H, m), 4.26 (1H, m), 10.92 (1H, b)

Analysis: $C_9H_{19}ClN_2O$

	C	H	N	Cl
Found%	51.54	9.30	13.25	16.88
Calc.%	52.29	9.26	13.53	17.15

Example 9

a) **(±)N-[(1-azacyclohex-3-yl)-oxy]-phthalimide**

A solution of N-[(1-methyl-1-azacyclohex-3-yl)oxy] phthalimide (1.1 g) and 1.8 bis dimethylamino naphthalene (proton sponge) (0.9 g) in 1,2 dichloroethane (50 ml) was cooled at 5°C and 1-chloro-ethyldichloroformate (0.6 ml) was dropped. The reaction mixture was stirred overnight at room temperature, then was washed first with diluted aqueous Na_2CO_3 solution; then with diluted aqueous HCl solution. The organic layer was dried and

evaporated to dryness. The crude residue was dissolved in methanol (50 ml) and the resulting solution was refluxed 2 hours and then evaporated to dryness. The crude intermediate obtained (0.9 g, after crystallization from a mixture of ethyl acetate and diethyl ether, m.p. 233-236) was sufficiently pure to be used in the next step;

b) **(±)O-(1-azacyclohex-3-yl)-hydroxylamine dihydrochloride**

The previously described intermediate (0.87 g) was dissolved into absolute ethanol (35 ml) and aqueous 85% hydrazine was dropped in under stirring. The reaction mixture was stirred further to 3 hours at room temperature and filtered. The clear solution was made acidic with aqueous 10% HCl solution and then evaporated to dryness. The title compound was obtained as a white solid after crystallization from ethanol 0.45 g, m.p. 158-161°C.

Example 10

O-(1-azacyclohex-4-yl)-N-ethyliden-hydroxylamine hydrochloride

(Compound 36)

A solution of O-(1-methyl-1-azacyclohex-4-yl)-N-ethyliden hydroxylamine (0.4 g) and 1.8 bis dimethylamino naphthalene (proton sponge) (0.55 g) in 1,2 dichloroethane was cooled at 5°C. 1-chloroethyl-chloroformate (0.34 ml) was dropped into the stirred reaction mixture and the stirring was maintained overnight at room temperature. An aqueous Na_2Co_3 solution was added, the organic layer was separated, washed with 5% aqueous hydrochloric solution and evaporated to dry-

ness. The residue was dissolved in methanol and the resulting solution was refluxed for 1 hour. From the solution after evaporation to dryness, the crude hydrochloride of the title compound was obtained. 0.180 g after crystallization from ethyl acetate

M.p. 130-140°C dec.

MS (C.I.) = 143 m/e [M + H]

^{1}H-NMR [DMSO + $CDCl_3$] 9.16 (b, 2H); 7.45 and 6.85 (2q, 1H); 4.25 (m, 1H); 3.07 (m, 4H); 1.97 (m, 4H); 1.80 (d, 3H).

Analysis: $C_7H_{15}ClN_2O$

	C	H	N	Cl
Found%	46.81	8.56	15.48	19.70
Calc.%	47.06	8.46	15.60	19.84

According to the above described procedure and starting from suitable intermediates the following compounds may be prepared.

O-(1-azacyclobut-3-yl)-N-ethyliden-hydroxylanine

(Compound 30)

(±)O-(1-azacyclopent-3-yl)-N-ethyliden-hydroxylamine, oxalate

(Compound 32)

M.p. 150°C dec.

MS (C.I.) = 129 m/e [M + H]

^{1}H-NMR [DMSO] 9.27 (b, 3H); 7.46 and 6.96 (2q, 1H); 4.78 (m, 1H); 3.1. ÷ 3.4 (4H); 2.08 (m, 2H); 1.77 and 1.80 (2d, 3H).

Analysis: $C_8H_{14}N_2O_5$

	C	H	N
Found%	42.98	6.31	12.62
Calc.%	44.03	6.47	12.84

(±)O-(1-azacyclohept-3-yl)-N-ethyliden hydroxylamine, hydrochloride

(Compound 34)

M.p. 110°C dec.

MS (C.I.) = 157 m/e [M + H]

^{1}H-NMR [$CDCl_3$] 9.89 (b, 1H); 9.36 (b, 1H); 7.57 and 6.83 (2q, 1H); 4.58 (m, 1H); 3.2 ÷ 3.6 (4H); 1.6 ÷ 2.3 (6H); 1.86 and 1.91 (2d, 3H).

Analysis: $C_8H_{17}ClN_2O$

	C	H	N	Cl
Found%	50.10	8.99	14.27	18.25
Calc.%	49.87	8.89	14.54	18.40

(±)-O-(1-azacyclohex-3-yl)-N-ethyliden-hydroxylamine hydrochloride

(Compound 38)

M.p. 98-100°C dec.

MS (C.I.) = 143 m/e [M + H]

^{1}H-NMR [$CDCl_3$] 9.84 (b, 1H); 9.22 (b, 1H); 7.60 and 6.84 (2q, 1H); 4.45 (m, 1H); 3.0 ÷ 3.4 (4H); 1.7 ÷ 2.2 (4H); 1.85 and 1.96 (2d, 3H).

Analysis: $C_7H_{15}ClN_2O$

	C	H	N	Cl
Found%	46.45	8.52	15.58	19.78
Calc.%	47.06	8.46	15.60	19.84

Example 11

Tablets

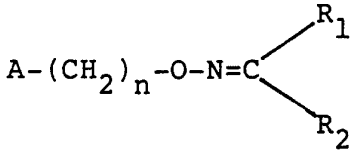
- Active ingredient	50	mg	100	mg
- Lactose	100	mg	200	mg
- Corn starch	4	mg	8	mg
- Magnesium stearate	0.95	mg	1.80	mg

Method of preparation: the active ingredient, lac-

tose and a portion of corn starch were mixed and granulated to a 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and magnesium stearate. The resulting granulation was then compressed into tablets containing 50 mg and 100 mg of the active ingredient per tablet.

CLAIMS

1. Compounds of general formula (I)



(I)

wherein:

A represents the residue of a 4-8 membered azacycloalkane, or of a 7-9 membered azabicycloalkane, optionally N- substituted by a C_{1-3} alkyl;

n represents 0 or 1;

R_1 and R_2 represent independently hydrogen; linear or branched C_{1-6} alkyl optionally substituted by alkoxy groups, alkylmercapto, CN or by halogen; C_{2-6} alkenyl; C_{2-6} alkynyl; halogen; aryl optionally substituted by halogen, C_{1-3} alkyl, C_{1-3} alkoxy; C_{6-12} aralkyl; heteroaryl; or together with the carbon atom to which they are linked, represent a 4-7 membered ring; the chain $-(CH_2)_n-O-N=CR_1R_2$ being linked to carbon atoms not close to the nitrogen atom of azacycloalkane or azabicycloalkane.

and acid addition salts thereof, optical and geometric isomers, diastereoisomers and mixtures thereof.

2. Compounds according to claim 1 in which the azacycloalkane residues A are 1-azacyclobutyl-3-yl, 1-azacyclopent-3-yl, 1-azacyclohex-3-yl, 1-azacyclohex-4-yl and 1-azacyclopent-3-yl group, optionally N-substituted by C_{1-3} alkyl.

3. Compounds according to claim 1, in which the azabicycloalkane residues A are 1-azabicyclo[2.2.1]-hept-

3-yl, 1-azabicyclo[2.2.2]-oct-3-yl, 1-azabicyclo[3.2.1]-oct-3-yl, 1-azabicyclo[3.2.1]-oct-6-yl, 1-azabicyclo[3.3.1]-non-3-yl and 8-azabicyclo[3.2.1]-oct-3-yl, optionally N-substituted by C_{1-3} alkyl.

4. Compounds of general formula (I) according to any previous claims characterized in that A is an azabicycloalkane residue, n is o, R_1 is hydrogen, lower C_{1-2} alkyl or halogen and R_2 is hydrogen or lower C_{1-3} alkyl group optionally containing an alkoxy group or halogen, C_{2-6} alkynyl or halogen.

5. A compound according to any previous claims selected from

R(-)-O-(1-Azabicyclo[2.2.2]oct-3-yl)-N-ethyliden-hydroxylamine, hydrochloride

(±)-Exo-O-(1-Azabicyclo[3.2.1]oct-3-yl)-N-ethyliden-hydroxylamine, hydrochloride

(±)-Exo-O-(1-Azabicyclo[3.2.1]oct-3-yl)-N-ethylidenhydroxylamine, fumarate

(±)-Exo-O-(1-azabicyclo[3.2.1]oct-3-yl)-N-ethylidenhydroxylamine, fumarate

S(+)-O-(1-azabicyclo[2.2.2]oct-3-yl)-N-(2.2.2-trifluoroethyliden)-hydroxylamine, fumarate.

6. Physiologically acceptable acid addition salts of compounds of general formula (I) according to claims 1-5.

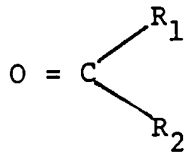
7. Salts according to claim 6, characterized in that the physiologically acceptable acids are hydrochloric, tartaric or fumaric acid.

8. Process for the preparation of compounds of general formula (I) according to claim 1, characterized in that an azacyclo or azabicyclo O-substituted hydroxyla-

mine of formula II

$$A\text{-}(CH_2)_n\text{-}O\text{-}NH_2 \qquad (II)$$

is reacted with a carbonyl derivative of formula III



(III)

in which A, n, R_1 and R_2 are as defined in claim 1 in an hydroxylic solvent at a temperature ranging from 0°C to the boiling point of the solvent of choice.

9. Process according to claim 8, characterized in that the hydroxylic solvent is selected from methanol, ethanol, isopropanol.

10. Pharmaceutical compositions comprising as active ingredient an effective amount of a compound of general formula (I) as defined in claim 1, or physiologically acceptable acid addition salts thereof, in association with pharmacologically acceptable carriers, diluents or excipients.

11. Pharmaceutical compositions according to claim 10 for the use in the treatment of patients suffering from neurological and mental disorders, in particular in cognitive disorders, age associated memory impairment, in different forms of dementia, in Alzheimer's disease, in Huntington's chorea, in tardive dyskinesia, in hyperkinesia, in Tourette syndrome.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 93/01493

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

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

Int.Cl. 5 C07D453/02; A61K31/395; C07D487/08; C07D471/08
C07D451/06; C07D205/04; C07D207/12; C07D223/08

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
A	EP,A,0 338 723 (BEECHAM GROUP PLC) 25 October 1989 see claims ---	1,11
A	EP,A,0 458 214 (BOEHRINGER INGELHEIM KG) 27 November 1991 see claims -----	1,11

° Special categories of cited documents :[10]

"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.

"&" document member of the same patent family

IV. CERTIFICATION

1

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
03 SEPTEMBER 1993	14. 09. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	VAN BIJLEN H.

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

EP 9301493
SA 76088

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 03/09/93

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