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DIVISION DE NUEVAS CREACIONES

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EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

PCT FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **534**

DE FECHA **28 DE NOVIEMBRE DE 2003** EL TERMINO HABIL SEÑALADO POR

LA LEY EXPIRA EL **25 DE FEBRERO DEL 2004**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI _____ NO **X**

Bogotá D.C, SEPTIEMBRE DE 2007

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US005770738A

United States Patent [19]

Banholzer et al.

[11] Patent Number: 5,770,738

[45] Date of Patent: Jun. 23, 1998

[54] ESTERS OF BI- AND TRICYCLIC AMINO ALCOHOLS, THEIR PREPARATION AND THEIR USE IN PHARMACEUTICAL COMPOSITIONS

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[73] Assignee: Boehringer Ingelheim KG, Ingelheim am Rhein, Germany

[21] Appl. No.: 412,408

[22] Filed: Mar. 28, 1995

Related U.S. Application Data

[63] Continuation of Ser. No. 117,199, Dec. 2, 1993, abandoned.

[30] Foreign Application Priority Data

Mar. 5, 1992 [WO] WIPO PCT/EP92/00489

[51] Int. Cl.⁶ A01N 43/42

[52] U.S. Cl. 514/304; 546/129; 546/130; 546/131

[58] Field of Search 546/125, 126, 546/128, 129, 130, 131; 514/304

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[57] ABSTRACT

The new compounds of formula



(wherein A and Z are defined as explained in the specification) can be prepared by conventional methods; they are suitable as active substances for pharmaceutical compositions.

14 Claims, No Drawings

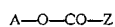
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ESTERS OF BI- AND TRICYCLIC AMINO ALCOHOLS, THEIR PREPARATION AND THEIR USE IN PHARMACEUTICAL COMPOSITIONS

This is a continuation of application Ser. No. 08/117,199, filed Dec. 2, 1993, abandoned.

The invention relates to new esters of bi- and tricyclic amino alcohols, the preparation of these compounds and their use in pharmaceutical compositions.

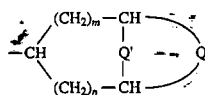
The new compounds correspond to the formula



(I)

wherein

A represents the group

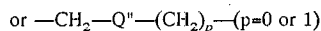
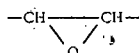
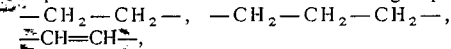


wherein

m represents 0, 1 or 2,

n represents 1 or 2 and m+n<3,

Q' represents one of the double-bonded groups



and

Q' represents the group $=NR$, the group $=NRR'$ or the group CH_2 , wherein R represents an optionally halo- or hydroxy-substituted C_{1-4} -alkyl group, R' represents a C_{1-4} -alkyl group and R and R' together may also form a C_{4-6} -alkylene group, and, in the case of quaternary compounds, an equivalent of an anion ($X^{\ominus}$), is associated with the positive charge of the N-atom, and

Q'' has the same meanings as Q', with the exception of CH_2 , and with the proviso that Q represents $-CH_2-Q''-(CH_2)_p$ when Q' represents CH_2 ,

Z represents the group



(III)

wherein

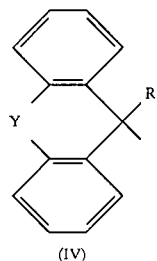
R₁ represents H, OH, CH_2OH , C_{1-4} -alkyl or C_{1-4} -alkoxy, R₂ and R₃, which may be identical or different and one of which may also be H, represent

(a) phenyl, furyl, an aromatic group which is isoelectronic with thienyl, C_{5-7} -cycloalkyl, pyridyl, C_{5-7} -cycloalkenyl or, in particular if m is equal to 0 and/or Q is equal to $-CH_2-Q''-(CH_2)_p$, R₂ may also represent thienyl,

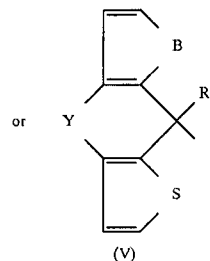
(b) an aliphatic group having up to 20 carbon atoms optionally interrupted by oxygen, or a C_{1-6} -alkyl group substituted by phenyl, phenoxy, thienyl, furyl, C_{5-7} -cycloalkyl or fluorine,

(c) the entire group III may also represent the tricyclic group of the formula

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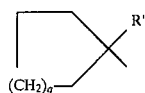


(IV)



(V)

or a group of formula

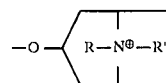
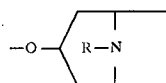
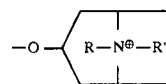
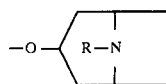
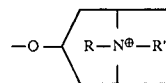
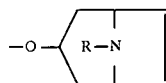
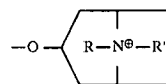
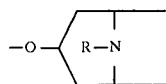
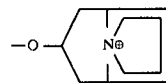
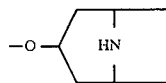
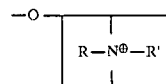
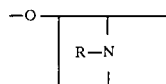
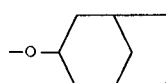


(VI)

wherein B may represent S or $CH=CH$, R₁ has the same meaning as R₁ and may additionally represent phenyl, thienyl, furyl, thiazolyl, thiadiazolyl or methoxyphenyl, Y represents a single bond, an O- or S-atom or one of the groups $-CH_2-$, $-CH_2-CH_2-$, $-CH=CH-$, $-OCH_2-$ or $-S-CH_2-$ and q represents 1, 2 or 3.

In the compounds of formula I R₂ preferably represents OH. The group $-OA$ preferably has an α -configuration and is derived for example from scopine, tropine, granatoline or 6,7-dehydrotropine or the corresponding nor-compounds; $-OA$ may, however, also have the β -configuration as in pseudotropine or pseudoscopine.

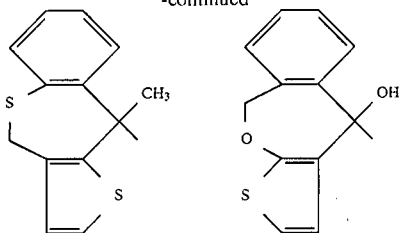
Examples of corresponding groups include:

 $X^{\ominus}$  $O^{\ominus}$  $X^{\ominus}$  $X^{\ominus}$  $X^{\ominus}$  $X^{\ominus}$  $X^{\ominus}$

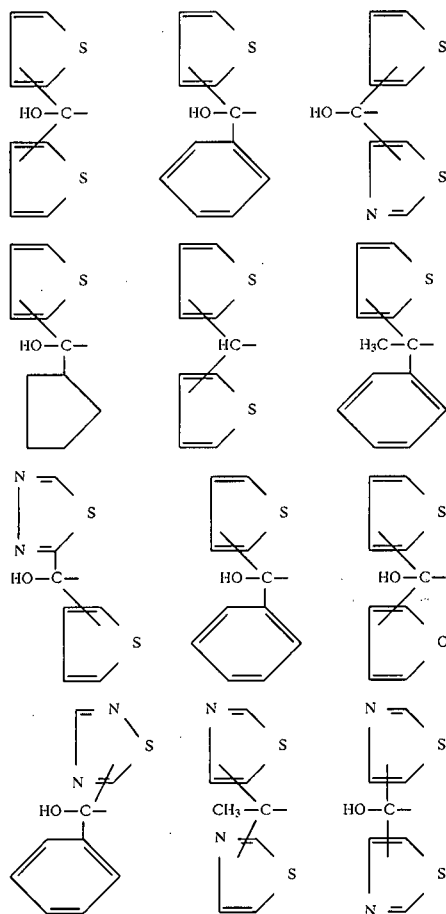
N-R

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-continued



If in the group II m represents O and/or Q represents $-\text{CH}_2-\text{Q}-(\text{CH}_2)_p-$, the group III may have the following additional meanings, in particular:



The quaternary compounds of formula I are particularly suitable for therapeutic use, while the tertiary compounds are important not only as active substances but also as intermediate products.

The compounds according to the invention are anticholinergics with a potent and long-lasting effect. At dosages in the microgram range, periods of effect of more than 24 hours are achieved after inhalation. Moreover, the toxicity is in the same range as that of the standard commercial product ipratropium bromide, whilst at the same time the therapeutic effect is in some cases significantly greater.

6

In accordance with their nature as anticholinergics, the new compounds are suitable, for example, for treating chronically obstructive bronchitis and (slight to moderate) asthma and also for treating vagally induced sinus bradycardia. Whereas in diseases of the respiratory tract it is chiefly recommended to administer the new active substances by inhalation (especially the quaternary compounds), thereby largely eliminating any side effects, the compounds are preferably administered by intravenous or oral route in the case of sinus bradycardia. It has been found to be advantageous that the new compounds have virtually no effect on gastrointestinal motility.

For use, the compounds according to the invention are processed with known excipients and/or carriers to form conventional galenic preparations, e.g. solutions for inhalation, suspensions in liquefied propellant gases, preparations containing liposomes or proliposomes, injectable solutions, plain or coated tablets, capsules, powders for inhalation for use in conventional inhalers.

Examples of formulations (amounts given in percent by weight):

1. Metering aerosol

Active substance according to the invention	0.005
Sorbitantriolate	0.1
Monofluorotrichloromethane and difluorodichloromethane 2:3	to 100

The suspension is poured into a conventional aerosol container with a metering valve.

Preferably, 50 μl of suspension are dispensed on each actuation. The active substance may also be dispensed in a higher dosage if desired (e.g. 0.02% by weight).

2. Tablets

Active substance according to the invention	0.05
Colloidal silica	0.95
Lactose	65.00
Potato starch	28.00
Polyvinylpyrrolidone	3.00
Na-cellulose glycolate	2.00
Magnesium stearate	1.00

The ingredients are processed in the usual way to form tablets weighing 200 mg.

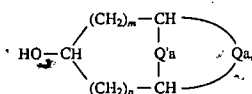
The advantageous properties of the new compounds are found for example in their inhibition of bronchospasm in rabbits (acetylcholine spasm i.v.). After intravenous administration of the new active substances (dosage 3 $\mu\text{g}/\text{kg}$ i.v.) the maximum effect was obtained after 10 to 40 minutes. Even on isolated organs, e.g. on the guinea-pig ileum or rectum, numerous compounds according to the invention were found to have a long duration of activity.

The new compounds may be prepared by methods known per se.

1. Preferably an ester of formula



wherein Z is as hereinbefore defined and R^1 represents a C_{1-4} -alkyl group, preferably methyl or ethyl, is transesterified, in the presence of a conventional transesterification catalyst, with an aminoalcohol of formula



wherein m and n are as hereinbefore defined, Q'' represents NR' or NH ; Q' has the same meaning as Q'' with the proviso that if Q' represents $CH_2-Q''-(CH_2)_p$, Q'' can only represent NR' , and wherein the OH -group is in the α - or β -position, or

2. a reactive derivative (R''' represents a readily cleavable group)



of the acid $Z-CO-OH$, particularly an acid chloride or imidazolid thereof, is reacted with an alcohol of formula VIII, optionally in excess or in the presence of a tertiary amine such as triethylamine, and optionally the resulting compound

- if Q' represents NR' , is quaternised with a reactive monoderivative $X-R'$ of R' corresponding alkane- β (X =leaving group) or
- if Q' represents NH , is quaternised with a terminally disubstituted alkane $X-(C_{4-6}\text{alkylene})-X$ without intermediate isolation or
- if Q' equals $CH_2-NR'-(CH_2)_p$, is quaternised with a reactive monoderivative $X-R$.

Alternatively, starting compounds may be quaternised, in which the starting compound VIII contains R representing a "halo- or hydroxy-substituted alkyl group" instead of R' at the nitrogen atom.

The transesterification according to process 1 is carried out with heating in an organic solvent, e.g. toluene, xylene or heptane, or in a melt, using strong bases such as sodium methoxide, sodium ethoxide, sodium hydride or metallic sodium as catalyst. In order to eliminate the lower alcohol released from the equilibrium, reduced pressure is used, and possibly the alcohol is distilled off azeotropically. The transesterification is carried out at temperatures generally not exceeding 95°C . Frequently, trans-esterification proceeds more easily in a melt. The reaction according to process 2 is carried out in an organic solvent or mixture of solvents which is sufficiently inert under the reaction conditions, e.g. acetone or acetonitrile, at temperatures between about 0°C . and the boiling temperature of the reaction mixture.

The free bases may be obtained from acid addition salts of the tertiary amines, if desired, using suitable basic compounds in a manner known per se. The quaternisation is carried out in suitable solvents, e.g. acetonitrile or acetonitrile/methylene chloride, preferably at ambient temperature; the preferred quaternising reagent is a corresponding alkyl halide, e.g. alkyl bromide, or a corresponding sulphonic acid derivative, e.g. a methane- or toluenesulphonic acid derivative. Transesterification products wherein Q' represents NH are used as starting materials for those compounds in which R and R' together represent a C_{4-6} alkylene group. Conversion into the tertiary and then quaternary compound is carried out using suitable 1,4-, 1,5- or 1,6-dihaloalkanes without intermediate isolation.

The starting compounds, where they have not already been described, may be obtained analogously to known compounds.

EXAMPLES

Methyl di-(2-thienyl)glycolate from dimethyloxalate and 2-thienylmagnesium bromide;

Ethyl di-(2-thienyl)glycolate from (2-thienyl)glyoxylic acid and 2-thienyllithium;

Ethyl hydroxyphenyl-(2-thienyl)acetate from methylphenylglyoxylate and 2-thienylmagnesium bromide or from methyl (2-thienyl)glyoxylate and phenylmagnesium bromide.

Similarly, methyl 2-thienylglyoxylate and cyclohexyl- or cyclopentylmagnesium bromide may be reacted.

There are also several possible methods of preparing the aminoalcohols.

Pseudoscopine can be obtained according to M. Polonovski et al., Bull. soc. chim. 43, 79 (1928).

Pseudotropenol can be isolated from the mixture (by fractional crystallisation or distillation) which is obtained, for example, according to V. Hayakawa et al., J. Amer.Chem.Soc. 1978, 100(6), 1786 or R. Noyori et al., J.Amer.Chem.Soc. 1974, 96(10), 3336.

N-ethylnorscopine and N-isopropylnorscopine may be prepared by hydrogenolysis from the corresponding N-alkylnorscopolamines analogously to Banholzer DE-A P 3215933. 6-methyl-6-azabicyclo[3.2.1]octan-3- α -ol can be prepared according to F. I. Carroff et al., J. Med.Chem. 30, 805 (1987), and 7-methyl-7-azabicyclo-[2.2.1]heptan-2- α -ol may be obtained according to J. R. Pfister et al., J. Pharmac. Sciences 74, 208 (1985).

Starting from 2- or 3-furylglyoxynitrile the corresponding methylesters may be prepared in conventional manner via the 2- or 3-furylglyoxylic acid obtainable from the starting material. From these methylesters, the corresponding glycolic acid esters may be obtained as described with the organometallic derivatives of 2- or 3-bromothiophene. The organometallic compounds obtainable from 2-, 3- or 4-halopyridine can be reacted with methyl 2- or 3-thienylglyoxylate to obtain the corresponding glycolic acid esters.

Thienylglycolic acid esters in which the thiophene ring in the 2- or 3-position contains fluorine may be obtained, for example, starting from 2-fluorothiophene or 3-fluorothiophene (bromination to obtain 2-bromo-3- fluoro- or 2-bromo-5-fluorothiophene and, after conversion into corresponding organometallic compounds, reaction with suitable glyoxylic acid esters to obtain the glycolic acid esters.

2-fluorothiophene and 3-fluorothiophene may be reacted analogously to Unterhalt, Arch.Pharm. 322, 839 (1989) to obtain the corresponding glyoxylic acid esters which may then in turn be reacted with 2- or 3-thienyl derivatives, for example, to obtain glycolic acid esters, as described above. By a suitable choice of components, symmetrically substituted dithienylglycolic acid esters may be prepared analogously.

A method analogous to benzoin condensation and benzylic acid rearrangement is also possible.

The acid chlorides required may be obtained from the acids and thionyl chloride whilst the imidazoles may be obtained from the acids and carbonyldiimidazole.

The following Examples illustrate the invention without restricting it.

EXAMPLE 1

Benzylic acid scopine ester-methobromide

- Benzylic acid scopine ester from α -chlorodiphenylacetic acid chloride and scopine
26.5 g (0.1 mol) α -chlorodiphenylacetic acid chloride are added to a solution of 31.0 g (0.2 mol) of scopine in 60 ml of anhydrous pyridine at 0°C . within 50 minutes with stirring. After it has all been added the

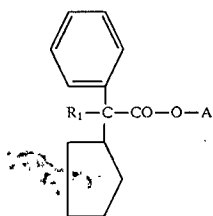
carboxylic acid scopine ester is obtained in the conventional manner; white crystals from acetonitrile/ether, m.p. 223° C. (decomp.); yield 21.8 g.

- b) The base is liberated in the usual way from a sufficient quantity of the hydrochloride obtained in a). 36.3 g (0.1 mol) thereof are reacted in a solution of 47.5 g (0.5 mol) of methylbromide in 49 g of acetonitrile for 24 hours under slight overpressure. The crystals obtained are suction filtered, washed with acetone/ether and recrystallised from ethanol. Yield 44.0 g (95.8% of theory), white crystals, m.p. 139° C. The crystals contain 0.5 mol of ethanol. Elementary analysis and spectra confirm the presence of the title compound.

The other compounds according to the invention may also be obtained in accordance with the Examples given above. The compounds melt with decomposition.

TABLE I

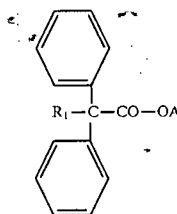
Compounds of formula



No.	R ₁	A	M.p. [°C.]
1	OH	3α-Tropanyl-methobromide	275-6
2	OH	3α-Tropanyl-β-fluorethobromide	205-6
3	H	3α-N-Ethyl-(6β,7β-Epoxy)-nortropanyl-methobromide	228
4	H	3α-N-Propyl-(6β,7β-Epoxy)-nortropanyl-methobromide	206-7
5	H	3α-N-Isopropyl-(6β,7β-Epoxy)-nortropanyl-methobromide	218
6	H	3α-(6β,7β-Epoxy)-tropanyl-methobromide	207
7	H	3α-(6,7-Dehydro)tropanyl-methobromide	226-8
8	H	3α-Tropanyl-methobromide	275-6
9	H	3α-N-Ethyl-nortropanyl-methobromide	256-7
10	H	(-)-3α-N-Isopropyl-nortropanyl-methobromide	256
11	H	(+)-3α-N-Isopropyl-nortropanyl-methobromide	256
12	H	3α-Nortropanyl-8,1'-pyrrolidinium-bromide	267-70
13	H	(+)-3α-Tropanyl-methobromide	278-81
14	H	(-)-3α-Tropanyl-methobromide	278-81

TABLE II

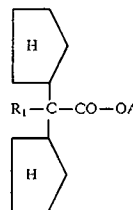
*Compounds of formula



No.	R ₁	A	M.p. [°C.]
1	OH	3α-N-Isopropyl-nortropanyl-methobromide	258
2	OH	3α-N-β-Chlorethyl-nortropanyl-methobromide	203
3	OH	3α-N-Ethyl-nortropanyl-methobromide	269
4	OH	3α-Tropanyl-ethobromide	258
5	OH	3α-(6β,7β-Epoxy)tropanyl-methobromide	200
6	OH	3α-N-Ethyl-(6β,7β-Epoxy)-nortropanyl-methobromide	220-1
7	OH	3α-(6β,7β-Epoxy)-N-isopropyl-nortropanyl-methobromide	234-5
8	OH	3α-N-Methylgranatanyl-methobromide	249
9	OH	3α-N-Isopropylgranatanyl-methobromide	219-20
10	OH	3α-(6,7-Dehydro)tropanyl-methobromide	207-8
11	H	3α-(6,7-Dehydro)tropanyl-methobromide	214-5
12	OH	3α-(6,7-Dehydro)-N-isopropyl-nortropanyl-methobromide	223
13	H	3α-Nortropanyl-8,1'-pyrrolidinium-bromide	231-2

TABLE III

Compounds of formula



No.	R ₁	A	M.p. [°C.]
1	H	3α-(6β,7β-Epoxy)-tropanyl-methobromide	213-4
2	H	3α-(6β,7β-Epoxy)-tropanyl-propargochloride	204-5
3	H	3α-N-Ethyl-(6β,7β-Epoxy)-nortropanyl-methobromide	201
4	H	3α-(6,7-Dehydro)tropanyl-methobromide	238-9
5	H	3α-Tropanyl-methobromide	203-5
6	OH	3α-(6β,7β-Epoxy)tropanyl-metho-methanesulphonate	