US00RE39820E

(19) **United States**

(12) **Reissued Patent**

Banholzer et al.

(10) **Patent Number: US RE39,820 E**

(45) **Date of Reissued Patent: Sep. 4, 2007**

(54) **ESTERS OF THIENYL CARBOXYLIC ACIDS AND AMINO ALCOHOLS AND THEIR QUATERNIZATION PRODUCTS**

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(21) Appl. No.: **11/254,213**

(22) Filed: **Oct. 18, 2005**

Related U.S. Patent Documents

Reissue of:

(64) Patent No.: **5,610,163**
Issued: **Mar. 11, 1997**
Appl. No.: **08/405,111**
Filed: **Mar. 16, 1995**

U.S. Applications:

(63) Continuation of application No. 08/254,324, filed on Jun. 6, 1994, now abandoned, which is a continuation of application No. 08/100,822, filed on Aug. 2, 1993, now abandoned, which is a continuation of application No. 07/838,724, filed on Mar. 13, 1992, now abandoned.

(30) **Foreign Application Priority Data**

Sep. 16, 1989 (DE) 39 31 041.8
Sep. 8, 1990 (EP) PCT/EP90/01517

(51) **Int. Cl.**
A61K 31/435 (2006.01)
C07D 451/12 (2006.01)

(52) **U.S. Cl.** **514/291**; 514/304; 546/18; 546/91; 546/125

(58) **Field of Classification Search** 546/77, 546/18, 91, 125; 514/291, 304
See application file for complete search history.

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(Continued)

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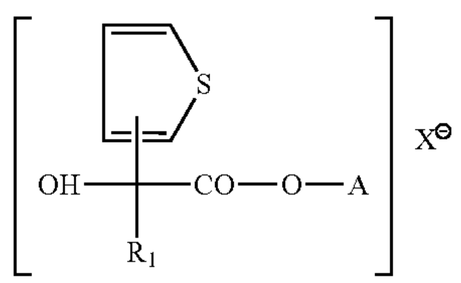
(57) **ABSTRACT**

Compounds of the formula



of which, in exemplary compounds, the thienyl group is attached via the 2-position and;

(a) A is 3α-(6β, 7β-epoxy)-tropanyl methobromide and R_1 is 2-thienyl;

(b) A is 3α-(6, 7dehydro)-tropanyl methobromide and R_1 is 2-thienyl;

(c) A is 3β-tropanyl methobromide and R_1 is 2-thienyl; and,

(d) A is 3α-(N-isopropyl)-nortropanyl methobromide and R_1 is cyclopentyl.

There are anticholinergics. Administered by inhalation, they are useful for the treatment of chronic obstructive bronchitis or slight to moderately severe asthma. Administered by the intravenous or oral routes, they are useful for the treatment of vagally induced sinus bradycardia.

16 Claims, No Drawings

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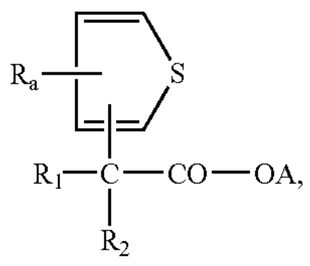
ESTERS OF THIENYL CARBOXYLIC ACIDS AND AMINO ALCOHOLS AND THEIR QUATERNIZATION PRODUCTS

Matter enclosed in heavy brackets [ ] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

This is a continuation of application Ser. No. 08/254,324, filed on Jun. 6, 1994, now abandoned which is a continuation of application Ser. No. 08/100,822, filed on Aug. 2, 1993, now abandoned, which is a continuation of application Ser. No. 07/838,724, filed on Mar. 13, 1992, now abandoned.

The invention relates to novel thienylcarboxylates of amino alcohols and their quaternary products and to the preparation of the novel compounds and their use as active ingredients in medicaments.

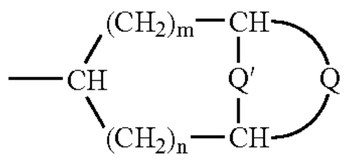
The novel compounds correspond to the formula



(I)

in which

A represents the group

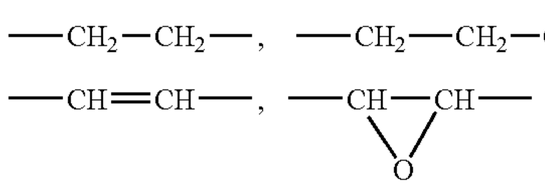


(II)

wherein

m and n independently of one another denote 1 or 2,

Q represents one of the double-bonding groups



and

Q' represents the group =NR or the group =NRR', wherein

R denotes H or an optionally halogen-substituted or hydroxy-substituted C_1-C_4-alkyl radical, R' denotes a C_1-C_4-alkyl radical and R and R' together may also form a C_4-C_6-alkylene radical, and wherein, in the case of quaternary compounds, one equivalent of an anion (X^-)opposes the positive charge of the N atom,

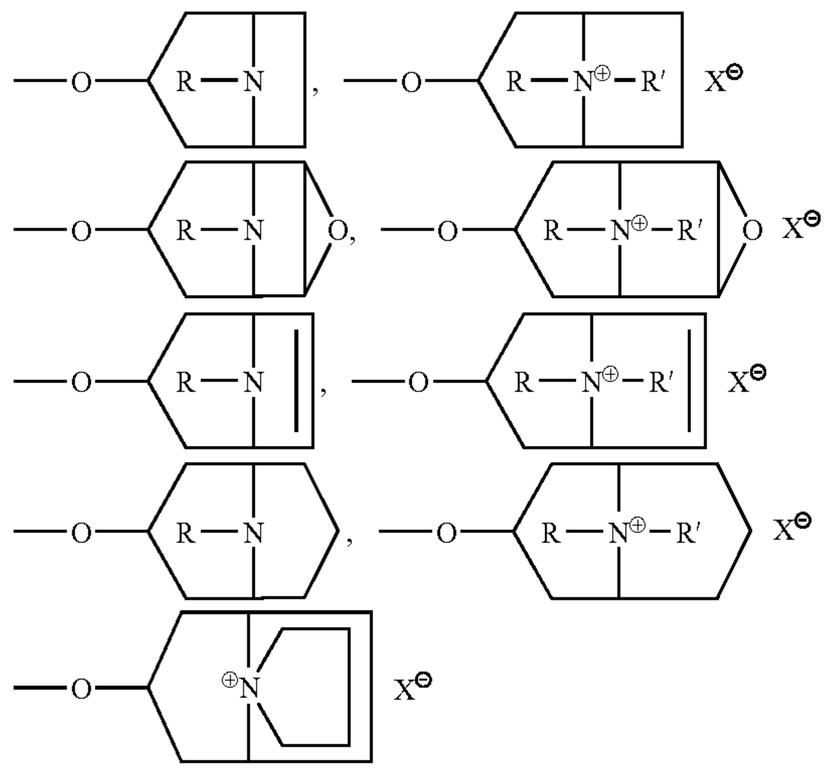
R_1 represents a thienyl, phenyl, furyl, cyclopentyl or cyclohexyl radical, wherein these radicals may also be methyl-substituted, thienyl and phenyl may also be fluoro-substituted or chloro-substituted,

R_2 represents hydrogen, OH, C_1-C_4-alkoxy or C_1-C_4-alkyl,

R_a represents H, F, Cl or CH_3 and, if =NR denotes a secondary or tertiary amino group, also the acid addition salts.

In the compounds of formula I, R_1 preferably represents thienyl, R_2 preferably represents OH. The group —OA preferably has the α-configuration and is derived from, for example scopine, tropine, granatoline or 6,7-dehydrotropine or the corresponding nor-compounds; however, —OA may also have the β-configuration, as in pseudotropine, pseudoscopine.

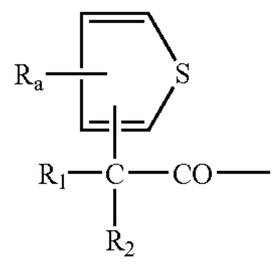
Corresponding radicals are, for example



The substituent R is preferably a lower alkyl radical, such as CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, R' is preferably CH_3. R and R' together are, for example —$(CH_2)_5$—. As halogen substituents for R, F or, as second choice, Cl are suitable.

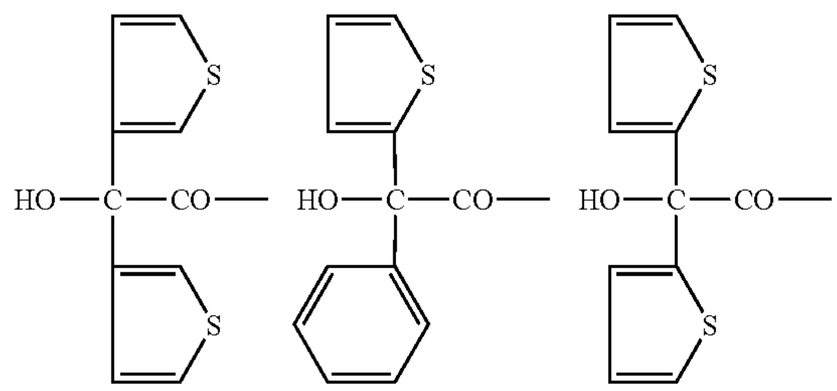
If R denotes a halogen-substituted or hydroxy-substituted alkyl radical, it is preferably —CH_2—CH_2F or —CH_2—CH_2OH. Accordingly, the group A represents, for example the radicals of scopine, N-ethylnorscopine, N-isopropylnorscopine, tropine, N-isopropylnortropine, 6,7-dehydrotropine, N-β-fluoroethylnortropine, N-isopropyl-6,7-dehydronortropine, N-methylgranatoline or the corresponding quaternary compounds, wherein the anion is preferably Br^- or $CH_3SO_3^-$.

As the acid radical



(III)

the following are particularly suitable:



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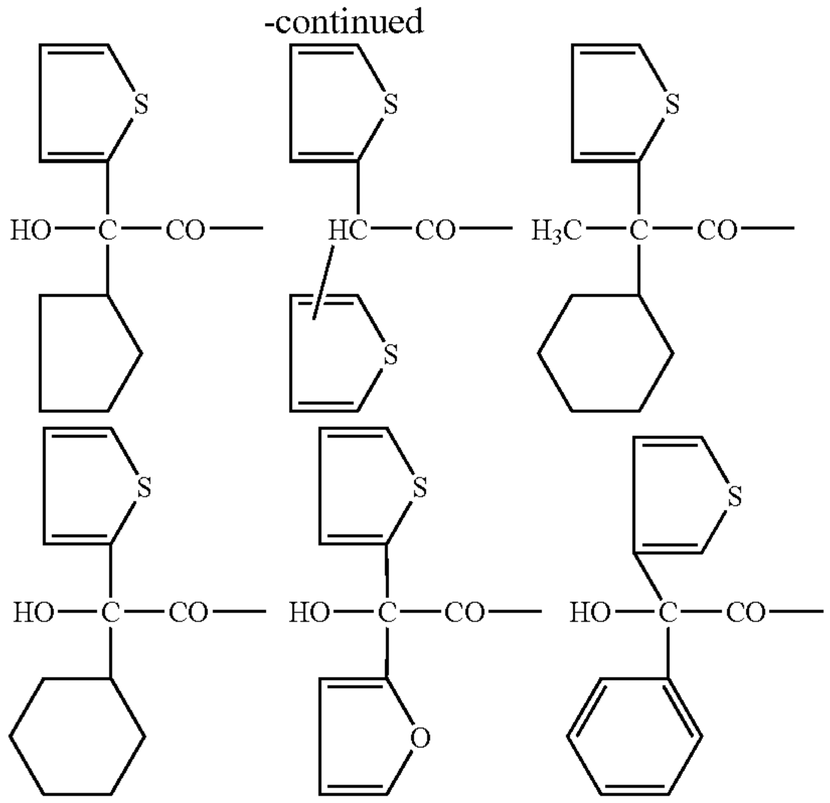


The quaternary compounds are particularly suitable for therapeutic application, whereas the tertiary compounds are important not only as active ingredients but also as intermediate products.

The compounds of the invention are strong anti-cholinergic agents and have prolonged action. Action lasting at least 24 hours is achieved at inhaled dosages in the μg range. In addition, the toxicity is in the same range as the commercial product Ipratropium bromide, while at the same time the therapeutic effect is stronger.

The novel compounds are suitable, in accordance with their anti-cholinergic nature, for example for the treatment of chronic obstructive bronchitis and (slight to moderately severe) asthma, also for the treatment of vagally induced sinus bradycardia.

Whereas application of the novel active ingredients (in particular the quaternary compounds) by inhalation is mainly recommended for respiratory tract diseases, as a result of which side-effects are largely eliminated, the application for sinus bradycardia is preferably carried out intravenously or orally. It has thus proved to be advantageous that the novel compounds leave the gastro/intestinal motility largely unaffected.

For administration the compounds of the invention are processed using known auxiliaries and/or excipients to give conventional galenic preparations, for example inhalation solutions, suspensions in liquified propellants, preparations containing liposomes or proliposomes, injection solutions, tablets, coated tablets, capsules, inhalation powders for use in conventional inhalation apparatus.

Formulation examples (measures in weight per cent):

1. Controlled dosage aerosol	
Active ingredient according to the invention	0.005
Sorbitan trioleate	0.1
monofluorotrichloromethane and Difluorodichloromethane 2:3	to 100

The suspension is poured into a conventional aerosol container with a dosage valve. 50 μl of suspension are preferably dispensed per actuation. The active ingredient may also be metered in a higher amount if required (for example 0.02 wt. %).

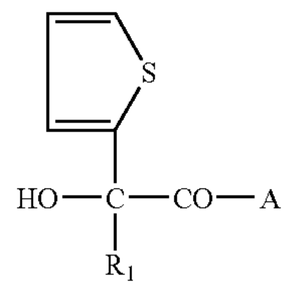
2. Tablets	
Active ingredient according to the invention	0.05
Colloidal silicic acid	0.95
Lactose	65.00
Potato starch	28.00
Polyvinylpyrrolidone	3.00
Na cellulose glycolate	2.00
Magnesium stearate	1.00

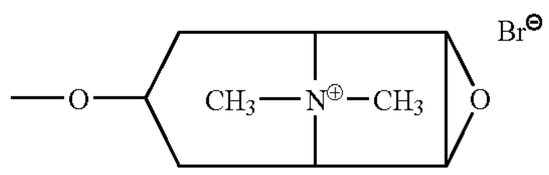
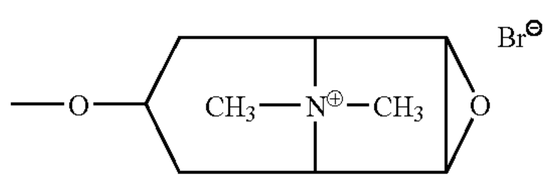
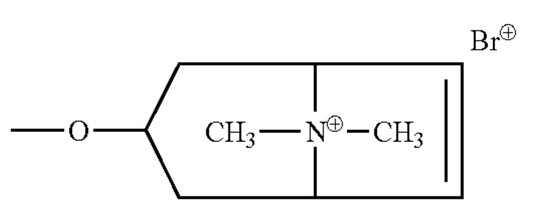
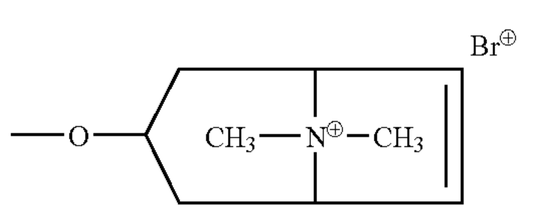
The constituents are processed in conventional manner to give tablets of 200 mg.

The advantageous properties of the novel compounds are shown, for example, in the inhibition of broncholysis in the rabbit (acetylcholine spasms intravenously). After intravenous administration of the novel active ingredients (dosage 3 μg/kg intravenously), the maximum effect occurred after 10 to 40 minutes. After 5 hours the inhibiting effect had still not been reduced to half, that is to say the half effect time is more, in some cases considerably more, than 5 hours, as made clear by the residual effects after 5 hours listed below:

Compound	Residual effect in %
A	76
B	76
C	81
D	61
E	68
F	73
G	69

Compounds of the formula



Compound	A		R_1
A		$Br^{\ominus}$	2-thienyl
B		$Br^{\ominus}$	3-thienyl
D		$Br^{\oplus}$	2-thienyl
E		$Br^{\oplus}$	3-thienyl

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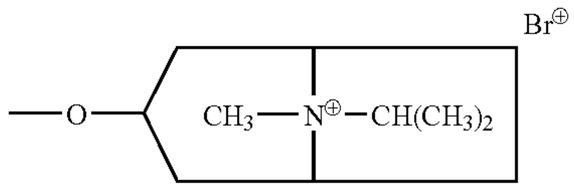
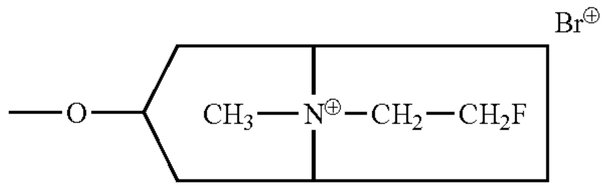
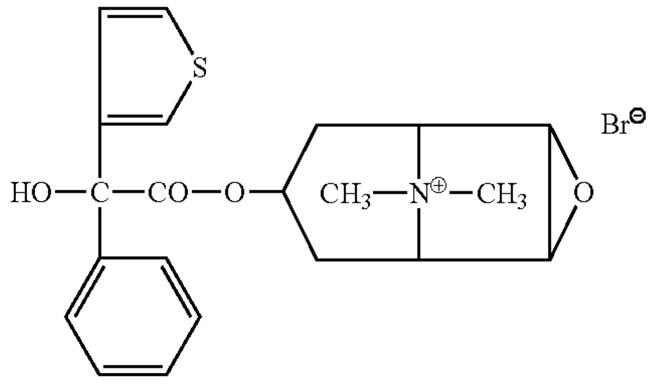
F		cyclo-pentyl
G		cyclo-pentyl

Compound C

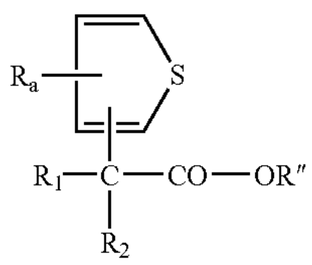


Notes:
1. The compounds in which R_1 is not 2-thienyl are racemates.
2. The compounds are 3α-compounds in each case.

Processes known per se are used to prepare the novel compounds.

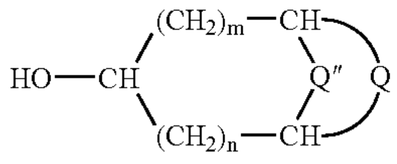
An ester of the formula

(IV)



wherein R" represents a C_1-C_4-alkyl radical, preferably a methyl or ethyl radical (R_1, R_2 and R_a have the above meanings), is preferably transesterified using an amino alcohol of the formula

(V)



wherein m, n and Q have the above meanings, Q" represents =NR or =NH and the OH group is in the α- or β-position, in the presence of a conventional transesterification catalyst, and the compound obtained is optionally quaternised

a) if Q" denotes =NR (R≠H), using a reactive monofunctionalised derivative Z-(C_1-C_4-alkyl) of a corresponding alkane (Z=leaving group)

or is optionally quaternised

b) if Q" denotes =NH, using a terminally disubstituted alkane Z-(C_4-C_6-alkylene)-Z without isolation of intermediates.

The transesterification is carried out with heat in an organic solvent, for example toluene, xylene, heptane, or in a melt, strong bases such as sodium methylate, sodium ethylate, sodium hydride, metallic sodium, being used as catalyst. Reduced pressure is used to remove the released lower alcohol from the equilibrium, the alcohol is optionally distilled off azeotropically. The transesterification takes place at temperatures which in general do not exceed 95° C. Transesterification often proceeds more favourably in a melt. If required, the free bases may be obtained in a manner known per se from acid addition salts of the tertiary amines using suitable basic compounds. Quaternisation is carried out in suitable solvents, for example acetonitrile or acetonitrile/methylene chloride, preferably at room temperature; a corresponding alkyl halide, for example alkyl bromide, is preferably used in the process as quaternising agent. Transesterification products wherein Q' represents NH are used as starting materials for those compounds in which R and R' together represent a C_4-C_6-alkylene group. Conversion into the tertiary and then quaternary compound then takes place with the aid of suitable 1,4-dihaloalkanes, 1,5-dihaloalkanes or 1,6-dihaloalkanes without isolation of intermediates.

The starting materials may be obtained analogously to known compounds—in as much as they have not already been described.

EXAMPLES

methyl di-(2-thienyl)glycolate from dimethyl oxalate and 2-thienyl magnesium bromide;

ethyl di-(2-thienyl)glycolate from (2-thienyl)glyoxylic acid and 2-thienyl lithium;

ethyl hydroxy-phenyl-(2-thienyl)acetate from methyl phenylglyoxylate and 2-thienyl magnesium bromide or from methyl (2-thienyl)glyoxylate and phenyl magnesium bromide.

Methyl 2-thienylglyoxylate and cyclohexyl or cyclopentyl magnesium bromide may be reacted in a similar manner.

Several processes are also available for the preparation of the amino alcohols.

Pseudoscopine may be obtained in accordance with M. Polonovski et al., Bull. soc. chim. 43, 79 (1928). Pseudotropenol may be removed from the mixture, (fractional crystallisation or distillation) which is obtained, for example in accordance with 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.

The corresponding methyl esters may be prepared in a conventional manner starting from 2-furylglyoxylnitrile or 3-furylglyoxylnitrile via the 2-furylglyoxylic acid or 3-furylglyoxylic acid which can be obtained therefrom. The corresponding glycolates are obtained from these as described using the organometallic derivatives of 2-bromothiophene or 3-bromothiophene. The organometallic compounds which can be obtained from 2-, 3- or 4-halopyridine can be reacted with methyl 2-thienylglyoxylate or methyl 3-thienylglyoxylate to give the corresponding glycolates.

Thienylglycolates, in which the thiophene ring contains fluorine in the 2- or 3-position, are prepared, for example starting from 2-fluorothiophene or 3-fluorothiophene (bromination to give 2-bromo-3-fluorothiophene or 2-bromo-5-fluorothiophene), and after conversion to the corresponding organometallic compounds, reaction with suitable glyoxylates to give the glycolates.

2-Fluorothiophene and 3-fluorothiophene can be reacted analogously to give the corresponding glyoxylates Unterhalt, Arch. Pharm. 322, 839 (1989) which in turn, as already described, may be reacted with, for example 2-thienyl or 3-thienyl derivatives, to give glycolates. Symmetrically substituted di-thienylglycolates can be prepared analogously by selecting suitable components.

A further route is available via a process analogous to the benzoin condensation and benzilic acid rearrangement.

The following examples illustrate the invention without limiting it.

EXAMPLE 1

EXAMPLE 1

Scopine di-(2-thienyl)glycolate

50.87 g (0.2 mole) of methyl di-(2-thienyl)glycolate and 31.04 g (0.2 mole) of scopine are dissolved in 100 ml of absolute toluene and reacted at a bath temperature of 90° C. with addition of 1.65 g (0.071 gram atom) of sodium in several portions. The resulting methanol is distilled off at a reaction mixture temperature of 78°-90° C. under a pressure of 500 mbar. After a reaction time of about 5 hours, the reaction mixture is stirred into a mixture of ice and hydrochloric acid. The acid phase is separated off, rendered alkaline using sodium carbonate and the free base is extracted using methylene chloride. After drying over sodium sulphate, the methylene chloride is distilled off under reduced pressure and the residue is recrystallised from acetonitrile; beige-coloured crystals (from acetonitrile).

m.p. 149°-50° C.

Yield: 33.79 g (44.7% of theoretical).

EXAMPLE 2

Scopine di-(2-thienyl)glycolate

12.72 g (0.05 mole) of methyl di-(2-thienyl)glycolate and 7.76 g (0.05 mole) of scopine are melted in a heating bath at 70° C. under a water jet vacuum. 2.70 g (0.05 mole) of sodium methylate are introduced into this melt and heated for 1 hour in a heating bath at 70° C. under a water jet vacuum and subsequently for a further hour in a heating bath at 90° C. The solidified melt is taken up in a mixture of 100 ml of water and 100 ml of methylene chloride while monitoring the temperature, and the methylene chloride phase is extracted several times using water. The methylene chloride phase is extracted using the corresponding amount of dilute hydrochloric acid. The scopine di-(2-thienyl)glycolate is extracted from the combined aqueous phases using methylene chloride after adding the corresponding amount of sodium carbonate and dried over sodium sulphate. The hydrochloride is prepared from the dried methylene chloride solution in a conventional manner. The crystals are filtered off under suction, washed using acetone and dried under reduced pressure at 35° C. Pale yellow crystals (from methanol), m.p. 238°-41° C. (decomposition);

Yield: 10.99 g (53.1% of theoretical).

The hydrochloride may be converted to the base in a conventional manner.

EXAMPLE 3

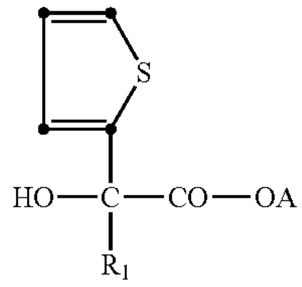
Scopine di-(2-thienyl)glycolate

38.15 g (0.15 mole) of methyl di-(2-thienyl)glycolate and 23.28 g (0.15 mole) of scopine are mixed, 0.34 g (0.015 gram atom) of sodium is added and the mixture is melted in a heating bath at 90° C. under a water jet vacuum. The reaction lasts 2.5 hours. 100 ml of absolute toluene are then added and the mixture is stirred at a heating bath temperature of 90° C. until a solution is produced. The reaction solution is cooled to room temperature and stirred into a mixture of ice and hydrochloric acid cooled using ice. The hydrochloride of the basic ester crystallising out is filtered off under suction and washed using a small amount of water and a large amount of diethyl ether. The filtrate phases are separated off and the aqueous phase is extracted using diethyl ether. The hydrochloride filtered off under suction is suspended in the (acid) aqueous phase and converted to the base while monitoring the temperature and adding the corresponding amount of sodium carbonate; the base is extracted using methylene chloride. The combined methylene chloride phases are dried over sodium sulphate. After distilling off the methylene chloride, crystals remain which are purified over active charcoal and recrystallised from acetonitrile. Pale yellow crystals (from acetonitrile), m.p. 148°-49° C.;

Yield: 39.71 g (70.1% of theoretical).

TABLE I

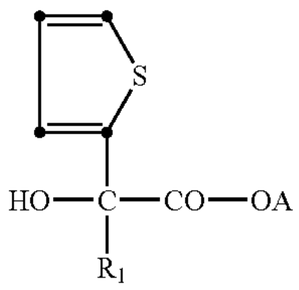
Compounds of the formula



No.	A	R_1	Base	M.p. [° C.] Hydrochloride
1	3α-(6β,7β-epoxy)-tropanyl	2-thienyl	149-50	238-41
2	3α-tropanyl	2-thienyl	167-8	253
3	3α-(6,7-dehydro)-tropanyl	2-thienyl	164-5	
4	3α-(N-β-fluoroethyl)-nortropanyl	2-thienyl		236
5	3α-(N-isopropyl)-granatanyl	2-thienyl		232
6	3α-(N-isopropyl)-nortropanyl	2-thienyl		256
7	3α-(6β,7β-epoxy)-N-isopropyl-nortropanyl	2-thienyl		206
8	3α-(6β,7β-epoxy)-N-ethyl nortropanyl	2-thienyl		212-3
9	3α-(N-ethyl)-nortropanyl	2-thienyl		256-7
10	3α-(N-N-methyl)-granatanyl	2-thienyl		241
11	3α-(6β,7β-epoxy)-N-β fluoroethylnortropanyl	2-thienyl		188-90
12	3α-(6β,7β-epoxy)-N-n propylnortropanyl	2-thienyl		104-6
13	3α-(6β,7β-epoxy)-N-n butylnortropanyl	2-thienyl		225-7
14	3α-(6β,7β-epoxy)-tropanyl	phenyl		246-7
15	3α-tropanyl	phenyl		243-4
16	3α-(N-β-fluoroethyl)-nortropanyl	phenyl		219-20
17	3α-(6,7-dehydro)-tropanyl	phenyl		181-3
18	3α-(N-ethyl)-nortropanyl	phenyl		231-2
19	3α-(N-isopropyl)-nortropanyl	phenyl		246-7
20	3α-tropanyl	cyclo-hexyl		260
21	3α-(N-β-fluoroethyl)-nortropanyl	cyclo-hexyl		203-4
22	3α-(6β,7β-epoxy)-tropanyl	cyclo-pentyl		237
23	3α-tropanyl	cyclo-pentyl		260
24	3α-(N-β-fluoroethyl)-nortropanyl	cyclo-pentyl		182-3
25	3α-(N-ethyl)-nortropanyl	cyclo-pentyl		227-8
26	3α-(N-isopropyl)-nortropanyl	cyclo-pentyl		174-5
27	3α-(6β,7β-epoxy)-tropanyl	2-thienyl		240-2

TABLE I-continued

Compounds of the formula



No.	A	R_1	Base	M.p. [° C.] Hydrochloride
28	3β-tropanyl	2-thienyl		217-9
29	3β-(6,7-dehydro)-tropanyl	2-thienyl		233-5
30	3α-(6,7-dehydro)-trapanyl	3-thienyl		247-8
31	3α-(6β,7β-epoxy)-tropanyl	3-thienyl		242-3
32	3α-(6β,7β-epoxy)-tropanyl	2-furyl		
33	3α-(6,7-dehydro)-tropanyl	2-furyl		
34	3α-tropanyl	2-furyl		
35	3α-tropanyl	2-pyridyl		
36	3α-(6β,7β-epoxy)-tropanyl	2-pyridyl		
37	3α-(6,7-dehydro)-tropanyl	2-pyridyl		
38	3α-tropanyl	3-thienyl		
39	3α-(6,7-dehydro)-tropanyl	cyclopentyl		
40	3α-(6β,7β-epoxy)-tropanyl	cyclohexyl		
41	3α-(6,7-dehydro)-tropanyl	cyclohexyl		

Note:
All hydrochlorides melt with decomposition.

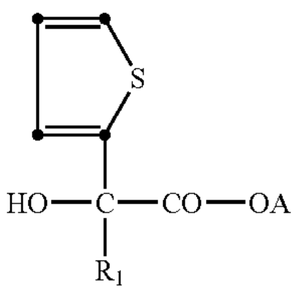
EXAMPLE 4

Scopine di-(2-thienyl)glycolate methobromide

10.0 g (0.0265 mole) of scopine di-(2-thienyl)glycolate are dissolved in a mixture comprising 20 ml of anhydrous methylene chloride and 30 ml of anhydrous acetonitrile and treated with 12.8 g (0.1325 mole) of methyl bromide (as 50% strength solution in anhydrous acetonitrile), and the reaction mixture is allowed to stand for 24 hours at room temperature in a tightly sealed reaction vessel. Crystals are precipitated during this time. They are filtered off under suction, washed using methylene chloride and dried at 35° C. under reduced pressure. White crystals (from methanol/acetone), m.p. 217°-8° C. (decomposition) after drying at 111° C. under reduced pressure.

TABLE II

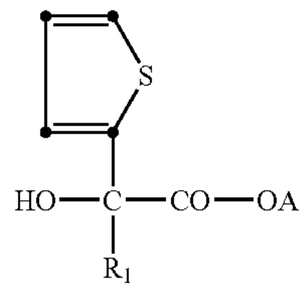
Quaternary compounds of the formula



No.	A	R_1	M.p. [° C.]
1	3α-(6β,7β-epoxy)-tropanyl methobromide	2-thienyl	217-18
2	3α-tropanyl methobromide	2-thienyl	263-64

TABLE II-continued

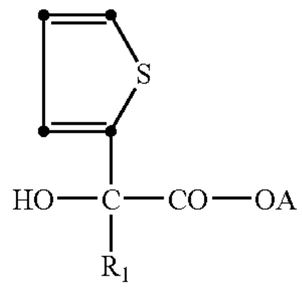
Quaternary compounds of the formula



No.	A	R_1	M.p. [° C.]
3	3α-(6,7-dehydro)-tropanyl methobromide	2-thienyl	191-92
4	3α-(N-β-fluoroethyl)-nortropanylmethobromide	2-thienyl	242-43
5	3α-tropanyl-β-fluoroethobromide	2-thienyl	214-15
6	3α-(N-isopropyl)-granatanyl methobromide	2-thienyl	229-30
7	3α-(N-isopropyl)-nortropanylmethobromide	2-thienyl	245-46
8	3α-(6β,7β-epoxy)-N-isopropyl-nortropanyl methobromide	2-thienyl	223-24
9	3α-(6β,7β-epoxy)-N-ethylnortropanyl methobromide	2-thienyl	215-16
10	3α-(N-ethyl)-nortropanyl methobromide	2-thienyl	260-61
11	3α-(N-methyl)-granatanyl methobromide	2-thienyl	246-47
12	3α-(6β,7β-epoxy)-N-fluoroethyl-nortropanyl methobromide	2-thienyl	182-83
13	3α-(6β,7β-epoxy)-N-n-propylnortropanyl methobromide	2-thienyl	209-10
14	3α-tropanyl-β-hydroxyethobromide	2-thienyl	231-32
15	3α-(6β,7β-epoxy)-tropanyl ethobromide	phenyl	217-18
16	3α-tropanyl methobromide	phenyl	273-74
17	3α-(N-β-fluoroethyl)-nortrapanylmethobromide	phenyl	
18	3α-(6,7-dehydro)-tropanyl methobromide	phenyl	110-71
19	3α-(N-ethyl)-nortropanyl methobromide	phenyl	249-50
20	3α-(N-isopropyl)-nortropanyl methobromide	phenyl	259-60
21	3α-tropanyl ethobromide	phenyl	248-49
22	3α-(N-ethyl)-nortropanyl ethobromide	phenyl	244-45
23	3α-(6β,7β-epoxy)-tropanyl ethobromide	phenyl	226
24	3α-tropanyl-β-fluoroethobromide	phenyl	241
25	3α-tropanyl methobromide	cyclohexyl	278
26	3α-(N-β-fluoroethyl)-nortropanyl methobromide	cyclohexyl	198
27	3α-tropanyl-β-fluoroethobromide	cyclohexyl	233-34
28	3α-tropanyl methobromide	cyclopentyl	260
29	3α-tropanyl ethobromide	cyclopentyl	235-36
30	3α-(N-ethyl)-nortropanyl methobromide	cyclopentyl	251-52
31	3α-(N-isopropyl)-nortropanyl-methobromide	cyclopentyl	244-45
32	3α-tropanyl-β-fluoroethobromide	cyclopentyl	189-90
33	3α-(N-β-fluoroethyl)-nortropanyl-methobromide	cyclopentyl	226-27
34	3α-(6,7-dehydro)-tropanyl metho-methanesulphonate	2-thienyl	225-6
35	3α-(6β,7β-epoxy)-tropanyl methobromide	2-thienyl	218-20

TABLE II-continued

Quaternary compounds of the formula



No.	A	R_1	M.p. [° C.]
36	3α-tropanyl methobromide	2-thienyl	243-4
37	3α-(6,7-dehydro)-tropanyl methobromide	2-thienyl	211-4
38	3α-(6,7-dehydro)-tropanyl methobromide	3-thienyl	182-3*
39	3α-(6β,7β-epoxy)-tropanyl methobromide	3-thienyl	217-8
40	(+) enantiomer of No. 1		
41	(−) enantiomer of No. 1		
42	3α-(6β,7β-epoxy)-tropanyl methobromide	2-furyl	
43	3α-(6,7-dehydro)-tropanyl methobromide	2-furyl	
44	3α-tropanyl methobromide	2-furyl	
45	3α-(6β,7β-epoxy)-tropanyl methobromide	2-pyridyl	
46	3α-(6,7-dehydro)-tropanyl methobromide	2-pyridyl	
47	3α-tropanyl methobromide	2-pyridyl	
48	3α-tropanyl methobromide	3-thienyl	
49	3α-(6,7-dehydro)-tropanyl methobromide	cyclopentyl	
50	3α-(6β,7β-epoxy)-tropanyl methobromide	cyclohexyl	
51	3α-(6,7-dehydro)-tropanyl methobromide	cyclohexyl	
52	3α-(6β,7β-epoxy)-tropanyl methobromide	cyclohexyl	

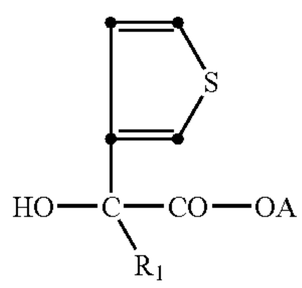
*contains crystalline methanol

Note:

All compounds in the table melt with decomposition.

TABLE III

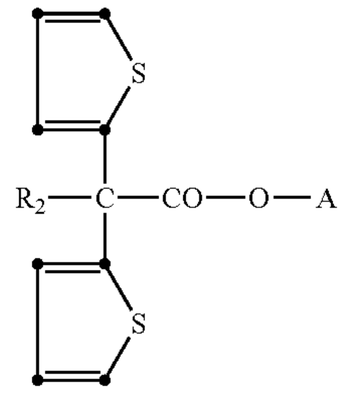
Compounds of the formula



No.	A	R_1	M.p. [° C.] Hydrochloride
1	3α-(6β,7β-epoxy)-tropanyl	phenyl	246-7
2	3α-(6,7-dehydro)-tropanyl	phenyl	261-2
3	3α-(6β,7β-epoxy)-tropanyl	3-thienyl	
4	3α-(6,7-dehydro)-tropanyl	3-thienyl	
5	3α-tropanyl	3-thienyl	
6	3α-(N-methyl)-granatanyl	3-thienyl	

TABLE IV

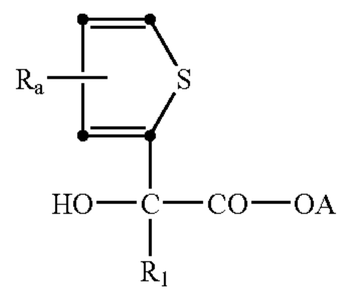
Compounds of the formula



No.	A	R_2	M.p. [° C.] Hydrochloride
1	3α-(6β,7β-epoxy)-tropanyl	H	
2	3α-(6,7-dehydro)-tropanyl	H	
3	3α-(6β,7β-epoxy)-tropanyl	methyl	
4	3α-(6,7-dehydro)-tropanyl	methyl	210-2.5
5	3α-(6β,7β-epoxy)-tropanyl	methoxy	
6	3α-(6,7-dehydro)-tropanyl	methoxy	

TABLE V

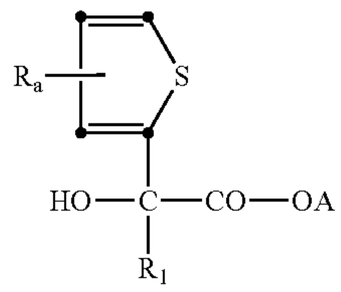
Compounds of the formula



No.	A	R_2	R_a	M.p. [° C.]
1	3α-(6β,7β-epoxy)-tropanyl	2-thienyl	5-methyl	
2	3α-(6,7-dehydro)-tropanyl	2-thienyl	5-methyl	
3	3α-tropanyl	2-thienyl	5-methyl	
4	3α-(6β,7β-epoxy)-tropanyl	2-(5-methyl)-thienyl	5-methyl	
5	3α-(6,7-dehydro)-tropanyl	2-(5-methyl)-thienyl	5-methyl	
6	3α-tropanyl	2-(5-methyl)-thienyl	5-methyl	
7	3α-(6β,7β-epoxy)-tropanyl	2-thienyl	5-fluoro	
8	3α-(6,7-dehydro)-tropanyl	2-thienyl	5-fluoro	
9	3α-tropanyl	2-thienyl	5-fluoro	
10	3α-(6β,7β-epoxy)-tropanyl	2-(5-fluoro)-thienyl	5-fluoro	
11	3α-(6,7-dehydro)-tropanyl	2-(5-fluoro)-thienyl	5-fluoro	
12	3α-tropanyl	2-(5-fluoro)-thienyl	5-fluoro	

TABLE VI

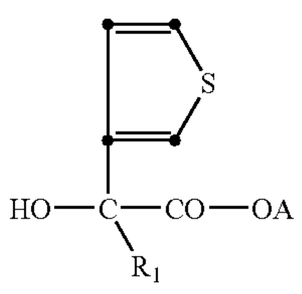
Compounds of the formula



No.	A	R_1	R_a	M.p. [° C.]
1	3α-(6β,7β-epoxy)-tropanyl methobromide	2-thienyl	5-methyl	
2	3α-(6,7-dehydro)-tropanyl methobromide	2-thienyl	5-methyl	
3	3α-tropanyl-methobromide	2-thienyl	5-methyl	
4	3α-(6β,7β-epoxy)-tropanyl methobromide	2-(5-methyl)-thienyl	5-methyl	
5	3α-(6,7-dehydro)-tropanyl methobromide	2-(5-methyl)-thienyl	5-methyl	
6	3α-tropanyl methobromide	2-(5-methyl)-thienyl	5-methyl	
7	3α-(6β,7β-epoxy)-tropanyl methobromide	2-thienyl	5-fluoro	
8	a-(6,7-dehydro)-tropanyl methobromide	2-thienyl	5-fluoro	
9	3α-tropanyl methobromide	2-thienyl	5-fluoro	
10	3α-(6β,7β-epoxy)-tropanyl methobromide	2-(5-fluoro)-thienyl	5-fluoro	
11	3α-(6,7-dehydro)-tropanyl methobromide	2-(5-fluoro)-thienyl	5-fluoro	
12	3α-tropanyl methobromide	2-(5-fluoro)-thienyl	5-fluoro	

TABLE VII

Compounds of the formula

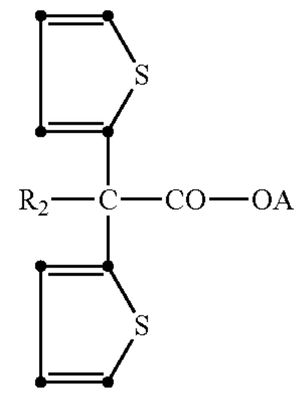


No.	A	R_1	M.p. [° C.]
1	3α-(6β,7β-epoxy)-tropanyl methobromide	phenyl	211-2
2	3α-(6,7-dehydro)-tropanyl methobromide	phenyl	158-60*
3	3α-(6β,7β-epoxy)-tropanyl methobromide	3-thienyl	
4	3α-(6,7-dehydro)-tropanyl methobromide	3-thienyl	
5	3α-tropanyl methobromide	3-thienyl	
6	3α-(N-methyl)-granatanyl methobromide	3-thienyl	

*(with crystalline methanol)

TABLE VIII

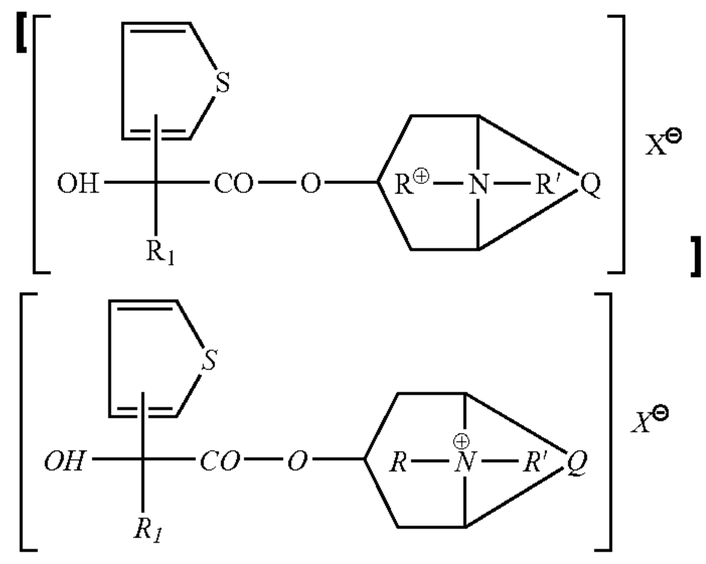
Quaternary compounds of the formula



No.	A	R_2	M.p. [° C.]
1	3α-(6β,7β-epoxy)-tropanyl methobromide	H	
2	3α-(6,7-dehydro)-tropanyl methobromide	H	
3	3α-(6β,7β-epoxy)-tropanyl methobromide	methyl	
4	3α-(6,7-dehydro)-tropanyl methobromide	methyl	206-8
5	3α-tropanyl methobromide	methoxy	
6	3α-(N-methyl)-tropanyl methobromide	methoxy	

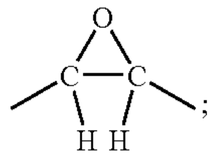
We claim:

1. A compound of the formula



wherein

Q is a group of the formula [—CH_2—CH_2—,] —CH═CH— or



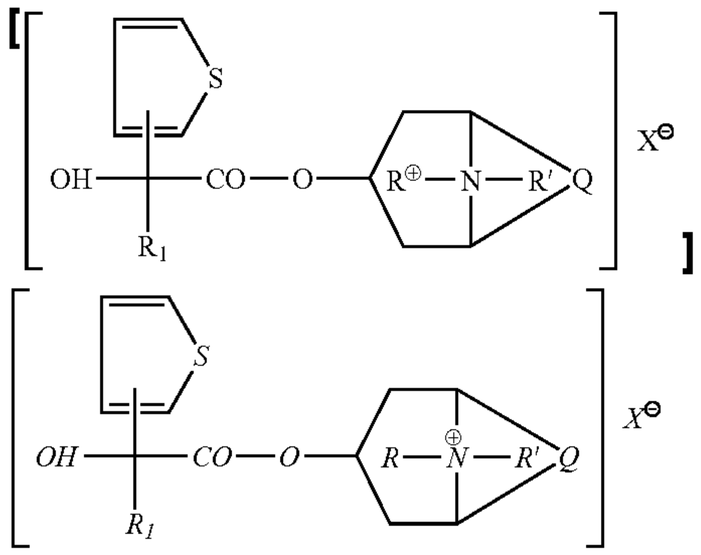
;

R and R' are each independently C_1-C_4-alkyl;

R_1 is thienyl, phenyl, cyclopentyl or cyclohexyl; and,

X^- is a physiologically acceptable anion.

2. A compound in accordance with claim 1, of the formula



wherein

R is CH_3, C_2H_5, n-C_3H_7, or i-C_3H_7;

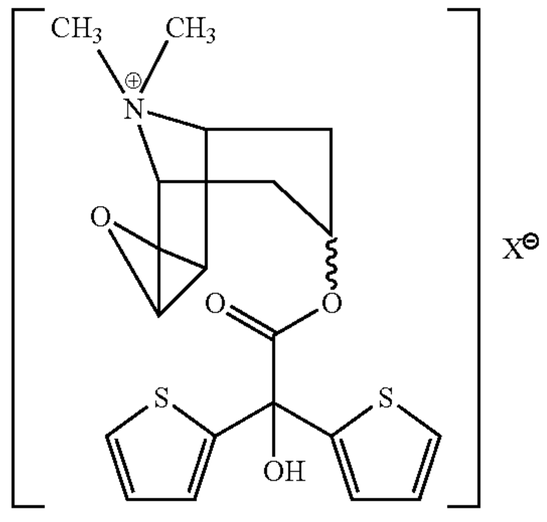
R' is CH_3; and

R_1, Q and X^- are as defined in claim 1.

3. A compound in accordance with claim 2 wherein R_1 is thienyl.

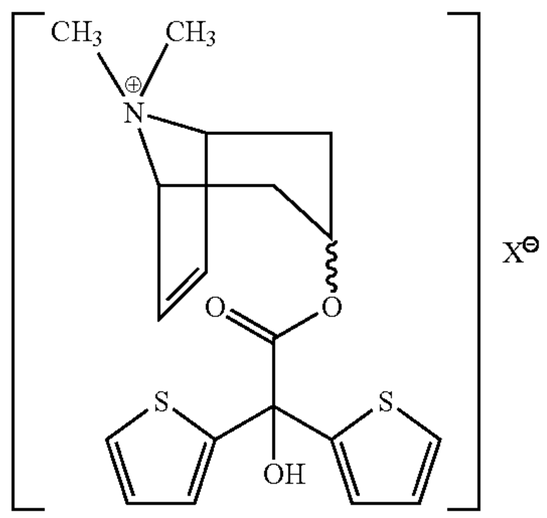
4. A compound in accordance with claim 2 wherein X^- is Br^- or [CH_3SO_3] $CH_3SO_3^-$.

5. A compound of the formula



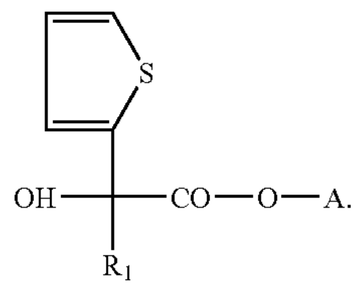
wherein X^- is a physiologically acceptable anion.

6. A compound of the formula

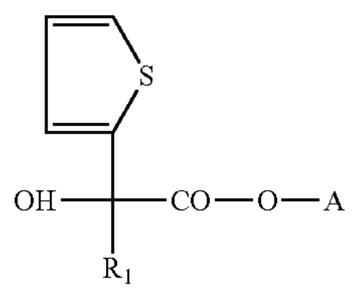


wherein X^- is a physiologically acceptable onion.

7. A compound of the formula

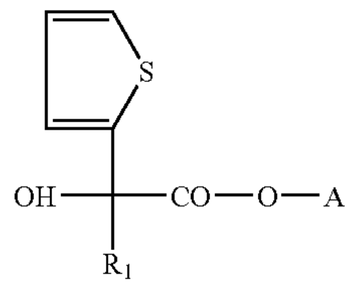


8. A compound of the formula



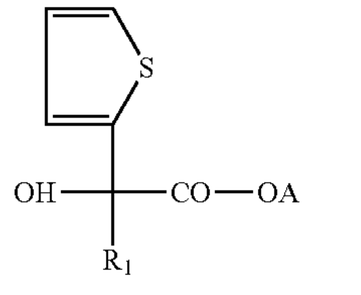
wherein R_1 is 2-thienyl and A is 3α-(6,7-dehydro)-tropanyl methobromide.

[9. A compound of the formula



wherein R_1 is 2-thienyl and A is 3β-tropanyl methobromide.]

[10. A compound of the formula



wherein R_1 is cyclopentyl and A is 3α-(N-isopropyl)-nortropanyl methobromide.]

11. A method for treating chronic obstructive bronchitis which comprises administering, by inhalation, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims **1**, **2**, **3**, **4**, **6**, **7**, *or* **8**[, **9**, **10**].

[12. A method for treating slight to moderately severe asthma which comprises administering, by inhalation, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims **1**, **2**, **3**, **4**, **6**, **7**, **8**, **9**, **10**.]

13. A method for treating vagally induced sinus bradycardia which comprises administering, by the intravenous or oral routes, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claims **1**, **2**, **3**, **4**, **6**, **7**, *or* **8**[, **9**, **10**].

14. A pharmaceutical composition, for administration by inhalation, suitable for the treatment of chronic obstructive bronchitis [or slight to moderately severe asthma], which comprises a compound in accordance with claims **1**, **2**, **3**, **4**, **6**, **7**, *or* **8**[, **9**, **10**].

15. A pharmaceutical composition for oral administration, suitable for the treatment of vagally induced sinus

bradycardia, which comprises a compound in accordance with claims **1**, **2**, **3**, **4**, **6**, **7**, *or* **8[**, **9**, **10]**.

16. A pharmaceutical composition, for intravenous administration, suitable for the treatment of vagally induced sinus bradycardia, which comprises a compound in accordance with claims **1**, **2**, **3**, **4**, **6**, **7**, *or* **8[**, **9**, **10]**.

17. A method for treating chronic obstructive bronchitis which comprises administering, by inhalation, to a subject suffering from the same, a therapeutic amount of a compound in accordance with claim 5.

18. A pharmaceutical composition, for administration by inhalation, suitable for the treatment of chronic obstructive bronchitis, which comprises a compound in accordance with claim 5.

19. A pharmaceutical composition, for administration by inhalation, suitable for the treatment of chronic obstructive bronchitis, comprising an inhalation powder comprising a compound in accordance with claim 5.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : RE 39,820 E
APPLICATION NO. : 11/254213
DATED : September 4, 2007
INVENTOR(S) : Banholzer et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Column 15, line 29, change "[CH_3SO_3]CH_3SO_3-" to --[CH_3SO_3] $CH_3SO_3^-$ --

Column 15, line 67, change "onion." to --anion.--

Column 16, line 10, after the figure, insert --wherein R_1 is 2-thienyl and A is 3α-(6β, 7β-epoxy)-tropanyl methobromide.--

Column 16, line 50, change "1, 2, 3, 4, 6, 7, or 8 [,9, 10]" to --1, 2, 3, 4, 6, 7, or 8 [, 9 or 10]--

Column 16, line 54, change "1, 2, 3, 4, 6, 7, 8, 9, 10" to --1, 2, 3, 4, 6, 7, 8, 9 or 10--

Column 16, line 59, change "1, 2, 3, 4, 6, 7, or 8[, 9, 10]" to --1, 2, 3, 4, 6, 7, or 8 [, 9 or 10]--

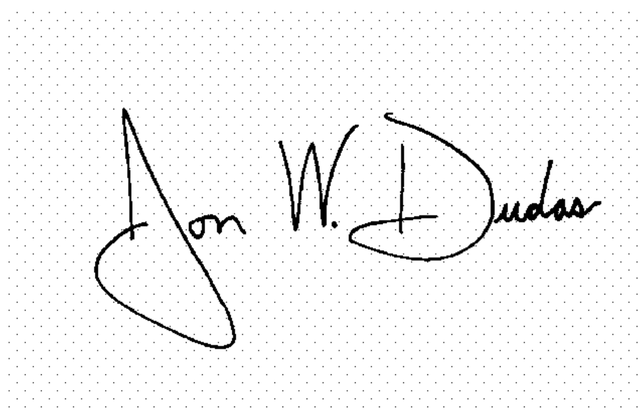
Column 16, line 64, change "1, 2, 3, 4, 6, 7, or 8[, 9, 10]" to --1, 2, 3, 4, 6, 7, or 8 [, 9 or 10]--

Column 17, line 2, change "1, 2, 3, 4, 6, 7, or 8[, 9, 10]" to --1, 2, 3, 4, 6, 7, or 8 [, 9 or 10]--

Column 17, line 6, change "1, 2, 3, 4, 6, 7, or 8[, 9, 10]" to --1, 2, 3, 4, 6, 7, or 8 [, 9 or 10]--

Signed and Sealed this

Eighth Day of January, 2008



JON W. DUDAS
Director of the United States Patent and Trademark Office

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SEP 13 2007

Michael P. Morris
Booehringer Ingelheim Corporation
PO Box 368
900 Ridgebury Road
Ridgefield CT 06877-0368

In Re: Patent Term Extension
Application for
U.S. Patent No. RE 39820

Dear Mr. Morris :

A certificate under 35 U.S.C. § 156 is enclosed extending the term of U.S. Patent No. RE 39820 for a period of 1,421 days. While a courtesy copy of this letter is being forwarded to the Food and Drug Administration (FDA), you should directly correspond with the FDA regarding any required changes to the patent expiration dates set forth in the Patent and Exclusivity Data Appendix of the Orange Book (Approved Drug Products with Therapeutic Equivalence Evaluations) or in the Patent Information set forth in the Green Book (FDA Approved Animal Drug Products). Effective August 18, 2003, patent submissions for publication in the Orange Book and Docket *95S-0117 need to be submitted on form FDA-3542 which may be downloaded from FDA's Electronic Forms Download Website: http://www.fda.gov/opacom/morechoices/fdaforms/default.html (http://www.fda.gov/opacom/morechoices/fdaforms/FDA-3542.pdf).

Inquiries regarding this communication should be directed to the undersigned by telephone at (571) 272-7755, or by e-mail at mary.till@uspto.gov.

Mary C. Till
Legal Advisor
Office of Patent Legal Administration
Office of the Deputy Commissioner
for Patent Examination Policy

cc: Office of Regulatory Policy
HFD-7
5600 Fishers Lane (Rockwall II Rm 1101)
Rockville, MD 20857

Attention: Beverly Friedman

RE: Spiriva® HandiHaler® (tiotropium bromide inhalation powder)
FDA Docket No.: 2004E-0304

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68)	PATENT NO.	:	RE 39820
(45)	REISSUED	:	September 4, 2007
(75)	INVENTOR	:	Rolf Banholzer et al.
(73)	PATENT OWNER	:	Boehringer Ingelheim Pharma GMBH & Co. KG
(95)	PRODUCT	:	Spiriva® HandiHaler® (tiotropium bromide inhalation powder)

This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. RE 39820 based upon the regulatory review of the product Spiriva® HandiHaler® (tiotropium bromide inhalation powder) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) 1,421 days

from March 11, 2014, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).

I have caused the seal of the United States Patent and Trademark Office to be affixed this 12th day of September 2007.

Jon W. Dudas
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office