Esters of thiényl carboxylic acids and amino alcohols and their quaternization products

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Field of Classification Search ......................... 546/77,
546/18, 91, 125; 514/291, 304

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Compounds of the formula

of which, in exemplary compounds, the thiényl group is attached via the 2-position and;
(a) A is 3α-(6β, 7β-epoxy)-tropanyl methobromide and R1 is 2-thienyl;
(b) A is 3α-(6β, 7-dehydro)-tropanyl methobromide and R1
is 2-thienyl;
(c) A is 3β-tropanyl methobromide and R1 is 2-thienyl;
and,
(d) A is 3α-(N-isopropyl)-nortropanyl methobromide and R1 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
OTHER PUBLICATIONS


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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 speci-
cation; 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 continu-
ation 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 aban-
don.

The invention relates to novel thiencarboxylic acids 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

\[
\text{R}_1\text{CO-OA,}
\]

in which
\[
A = \text{group (II)}
\]

\[
\text{R} \begin{array}{c}
  \text{CH} \\
  \text{CH}_2
\end{array}
\]

wherein
\[
m \text{ and } n \text{ independently of one another denote } 1 \text{ or } 2,
\]

\[
\text{Q represents one of the double-bonding groups}
\]

\[
\text{CH}_2-\text{CH}_2, \quad \text{CH}_2-\text{CH}_2-\text{CH}_2, \quad \text{CH}==\text{CH}, \quad \text{CH}-\text{CH}
\]

and
\[
\text{Q represents the group } \equiv \text{NR or the group } \equiv \text{NRR'},
\]

wherein
\[
R \text{ denotes H or an optionally halogen-substituted or}
\]

hydroxy-substituted C_1-C_2-alkyl radical, R' denotes a
C_1-C_2-alkyl radical and R and R' together may also
form a C_1-C_2-alkylene radical, and wherein, in the case of
quaternary compounds, one equivalent of an anion (X^-)opposes the positive charge of the N atom,

\[
R_1 \text{ represents thiencarbonyl, phenyl, furyl, cyclopentyl}
\]

or cyclohexyl radical, wherein these radicals may also be
methyl-substituted, thiencarbonyl and phenyl may also be
fluoro-substituted or chloro-substituted,

\[
R_2 \text{ represents hydrogen, OH, C_1-C_2-alkoxy or C_1-C_2-}
\]

alkyl,

\[
R_3 \text{ represents H, F, Cl or CH}_3
\]

and, if \( \equiv \text{NR} \) denotes a secondary or tertiary amino group, also the acid addi-
tion salts.

In the compounds of formula (I), R_1 preferably represents
thiencarbonyl, R_2 preferably represents OH. The group —OA preferably has the \( \alpha \)-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 \( \beta \)-configuration, as in pseudotropine, pseudo-
scopine.

Corresponding radicals are, for example

\[
\text{R}_1\text{CO-OA,}
\]

The substituent R is preferably a lower alkyl radical, such
as CH_3, C_2H_5, n-C_3H_7, i-C_4H_9. R' is preferably CH_3, R and
R' together are, for example \((\text{CH}_2)_5\) and.

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 \(-\text{CH}_2-\text{CH}_2\text{F} \) or \(-\text{CH}_2-
\]

CH_3OH. Accordingly, the group A represents, for example
the radicals of scopine, N-ethylscopine, N-isopropylscopine,

N-propylscopine, tropine, N-propylnortropine, 6,7-
dehydrotropine, N-\( \beta \)-fluoroethylnortropine, N-isopropyl-6,

7-dehydrotropoline, N-methylgranatoline or the corre-
sponding quaternary compounds, wherein the anion is
preferably Br^- or CH_3SO_3^-.

As the acid radical

\[
\text{R}_1\text{CO-OA,}
\]

the following are particularly suitable:
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 liquefied 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

<table>
<thead>
<tr>
<th>Component</th>
<th>1.00%</th>
<th>0.95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorbitan trioleate</td>
<td>0.1</td>
<td>0.05</td>
</tr>
<tr>
<td>monothiouretrichloromethane and</td>
<td>to 100</td>
<td>to 100</td>
</tr>
<tr>
<td>Dithiouretrichloromethane 2:3</td>
<td>95</td>
<td>95</td>
</tr>
</tbody>
</table>

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 0.20 wt. %).

### 2. Tablets

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. %).

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, i.e. in some cases considerably more, than 5 hours, as made clear by the residual effects after 5 hours listed below:

<table>
<thead>
<tr>
<th>Compound A</th>
<th>Residual effect in %</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>76</td>
</tr>
<tr>
<td>B</td>
<td>76</td>
</tr>
<tr>
<td>C</td>
<td>81</td>
</tr>
<tr>
<td>D</td>
<td>61</td>
</tr>
<tr>
<td>E</td>
<td>68</td>
</tr>
<tr>
<td>F</td>
<td>73</td>
</tr>
<tr>
<td>G</td>
<td>69</td>
</tr>
</tbody>
</table>

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, i.e. in some cases considerably more, than 5 hours, as made clear by the residual effects after 5 hours listed below:
Notes:
1. The compounds in which R<sub>1</sub> is not 2-thienyl are racemates.
2. The compounds are 3C-compounds in each case.

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

An ester of the formula

\[
\text{HO-C-CO-O} \left( \text{CH}_2\text{m} \right) \left( \text{CH}_2\text{n} \right) \left( \text{CH}_2\text{k} \right) \]

wherein \( \text{m} \), \( \text{n} \) and \( \text{Q} \) have the above meanings. \( \text{Q}\) represents =\(\text{NH}\) or =\(\text{NR}\) and the \(\text{OH}\) group is in the \(\alpha\)- or \(\beta\)-position, in the presence of a conventional transesterification catalyst, and the compound obtained is optionally quaternised.

a) if \(\text{Q}\) represents =\(\text{NR}\) \((\text{R}\neq \text{H})\), using a reactive monofunctionalised derivative \(Z-(\text{C}_1-\text{C}_2\text{-alkyl})\) of a corresponding alkane \((\text{Z}=\text{leaving group})\) or is optionally quaternised

b) if \(\text{Q}\) represents =\(\text{NH}\), using a terminally dissubstituted alkane \((\text{C}_4-\text{C}_6\text{-alkylene})\)-\(\text{Z}\) 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 \(\text{Q}\) represents \(\text{NH}\) are used as starting materials for those compounds in which \(\text{R}\) and \(\text{R}'\) together represent a \(\text{C}_4\text{-C}_6\text{-alkylene}\) 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 phenylglyoxyxylate and 2-thienyl magnesium bromide or from methyl (2-thienyl)glyoxyxylate and phenyl magnesium bromide.

Methyl 2-thienylglyoxyxylate 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.

Pseudopseudone may be obtained in accordance with M. Polonovski et al., Bull. soc. chim. 43, 79 (1928). Pseudopseudone may be removed from the mixture, (fractional crystallisation or distillation) which is obtained, for example in accordance with V. Hayakawa et al., Amer. Chem. Soc. 1978, 100(6), 1786 or R. Noyori et al., Amer. Chem. Soc. 1974, 96(10), 3336.

The corresponding methyl esters may be prepared in a conventional manner starting from 2-furyl glyoxyxylitrile or 3-furyl glyoxyxylitrile via the 2-furyl glyoxylic acid or 3-furyl glyoxylic 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-thienylglyoxyxylate or methyl 3-thienylglyoxyxylate to give the corresponding glycolates.

Thienylglycolates, in which the thiophene ring contains fluorene 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 (1898) 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 benzoic acid rearrangement. The following examples illustrate the invention without limiting it.

**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 methylium 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

<table>
<thead>
<tr>
<th>No.</th>
<th>A</th>
<th>R</th>
<th>Base</th>
<th>M.p. [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-(6,7-epoxy)-tropanyl</td>
<td>2-thienyl</td>
<td>Hydrochloride</td>
<td>149-50</td>
</tr>
<tr>
<td>2</td>
<td>3o-tropanyl</td>
<td>2-thienyl</td>
<td></td>
<td>167-8</td>
</tr>
<tr>
<td>3</td>
<td>3o-(6,7-dehydro)-tropanyl</td>
<td>2-thienyl</td>
<td></td>
<td>164-5</td>
</tr>
<tr>
<td>4</td>
<td>3o-(N-B-fluoroethyl)- norTropanyl</td>
<td>2-thienyl</td>
<td></td>
<td>236</td>
</tr>
<tr>
<td>5</td>
<td>3o-(N-isopropyl)- granatanyl</td>
<td>2-thiayl</td>
<td></td>
<td>232</td>
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<td>6</td>
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<td>2-thiayl</td>
<td></td>
<td>256</td>
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<tr>
<td>15</td>
<td>3o-tropanyl</td>
<td>phenyl</td>
<td></td>
<td>243-4</td>
</tr>
<tr>
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<td></td>
<td>219-20</td>
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<td></td>
<td>260</td>
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<td></td>
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<td></td>
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<td></td>
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<td>27</td>
<td>3o-(6,7-epoxy)-tropanyl</td>
<td>2-thiayl</td>
<td></td>
<td>249-2</td>
</tr>
</tbody>
</table>
### TABLE I-continued

<table>
<thead>
<tr>
<th>No.</th>
<th>A</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M.p. [°C]</th>
<th>Hydrochloride</th>
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<tr>
<td>28</td>
<td>3β-tropanyl</td>
<td>2-thienyl</td>
<td>217-9</td>
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<tr>
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<tr>
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<tr>
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<td>3α-(6β,7β-epoxy)-tropanyl</td>
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<td>242-3</td>
<td></td>
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<td>2-furyl</td>
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</tr>
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<td>33</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>2-furyl</td>
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</tr>
<tr>
<td>35</td>
<td>3α-tropanyl</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>3α-(6β,7β-epoxy)-tropanyl</td>
<td>2-pyridyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>2-pyridyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>3α-tropanyl</td>
<td>3-thianyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>cyclo-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pentyld</td>
<td>cyclo-</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>3α-(6β,7β-epoxy)-tropanyl</td>
<td>cyclo-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pentyld</td>
<td>hexyl</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>cyclo-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pentyld</td>
<td>hexyl</td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>No.</th>
<th>A</th>
<th>R&lt;sub&gt;1&lt;/sub&gt;</th>
<th>M.p. [°C]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3α-(6β,7β-epoxy)-tropanyl methobromide</td>
<td>2-thienyl</td>
<td>217-18</td>
</tr>
<tr>
<td>2</td>
<td>3α-tropanyl methobromide</td>
<td>2-thienyl</td>
<td>263-64</td>
</tr>
</tbody>
</table>
### TABLE II-continued

<table>
<thead>
<tr>
<th>No.</th>
<th>A</th>
<th>R₁</th>
<th>M.p. [° C.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>36</td>
<td>3α-tropanyl methobromide</td>
<td>2-thienyl</td>
<td>243-4</td>
</tr>
<tr>
<td>37</td>
<td>3α-(6,7-dehydro)-tropanyl methobromide</td>
<td>2-thienyl</td>
<td>211-4</td>
</tr>
<tr>
<td>38</td>
<td>3α-(6,7-dehydro)-tropanyl methobromide</td>
<td>3-thienyl</td>
<td>182-3*</td>
</tr>
<tr>
<td>39</td>
<td>3α-(6,7,7β-epoxy)-tropanyl methobromide</td>
<td>3-thienyl</td>
<td>217-8</td>
</tr>
<tr>
<td>40</td>
<td>(+) enantiomer of No. 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>(-) enantiomer of No. 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>3α-(6,7,7β-epoxy)-tropanyl methobromide</td>
<td>2-furyl</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>3α-(6,7-dehydro)-tropanyl methobromide</td>
<td>2-furyl</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>3α-tropanyl methobromide</td>
<td>2-furyl</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>3α-(6,7,7β-epoxy)-tropanyl methobromide</td>
<td>2-pyridyl</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>3α-(6,7-dehydro)-tropanyl methobromide</td>
<td>2-pyridyl</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>3α-tropanyl methobromide</td>
<td>2-pyridyl</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>3α-tropanyl methobromide</td>
<td>3-thiencyl</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>3α-(6,7-dehydro)-tropanyl methobromide</td>
<td>cyclopentyl</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>3α-(6,7,7β-epoxy)-tropanyl methobromide</td>
<td>ciclohexyl</td>
<td></td>
</tr>
<tr>
<td>51</td>
<td>3α-(6,7-dehydro)-tropanyl methobromide</td>
<td>ciclohexyl</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>3α-(6,7,7β-epoxy)-tropanyl methobromide</td>
<td>ciclohexyl</td>
<td></td>
</tr>
</tbody>
</table>

*contains crystalline methanol

Note:
All compounds in the table melt with decomposition.

### TABLE III

<table>
<thead>
<tr>
<th>No.</th>
<th>A</th>
<th>R₁</th>
<th>M.p. [° C.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3α-(6,7,7β-epoxy)-tropanyl</td>
<td>phenyl</td>
<td>246-7</td>
</tr>
<tr>
<td>2</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>phenyl</td>
<td>251-2</td>
</tr>
<tr>
<td>3</td>
<td>3α-(6,7,7β-epoxy)-tropanyl</td>
<td>3-thiencyl</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>3-thiencyl</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3α-tropanyl</td>
<td>3-thiencyl</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3α-(N-methyl)-granatanyl</td>
<td>3-thiencyl</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE IV

<table>
<thead>
<tr>
<th>No.</th>
<th>A</th>
<th>R₂</th>
<th>M.p. [° C.]</th>
<th>Hydrochloride</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3α-(6,7,7β-epoxy)-tropanyl</td>
<td></td>
<td></td>
<td>H</td>
</tr>
<tr>
<td>2</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td></td>
<td></td>
<td>H</td>
</tr>
<tr>
<td>3</td>
<td>3α-(6,7,7β-epoxy)-tropanyl</td>
<td>methy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>methy</td>
<td></td>
<td>210-2.5</td>
</tr>
<tr>
<td>5</td>
<td>3α-(6,7,7β-epoxy)-tropanyl</td>
<td>methoxy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>methoxy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### TABLE V

<table>
<thead>
<tr>
<th>No.</th>
<th>A</th>
<th>R₂</th>
<th>R₃</th>
<th>M.p. [° C.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3α-(6,7,7β-epoxy)-tropanyl</td>
<td>2-thiencyl</td>
<td></td>
<td>5-methyl</td>
</tr>
<tr>
<td>2</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>2-thiencyl</td>
<td></td>
<td>5-methyl</td>
</tr>
<tr>
<td>3</td>
<td>3α-tropanyl</td>
<td>2-thiencyl</td>
<td></td>
<td>5-methyl</td>
</tr>
<tr>
<td>4</td>
<td>3α-(6,7,7β-epoxy)-tropanyl</td>
<td>2-(5-methyl) thiencyl</td>
<td></td>
<td>5-methyl</td>
</tr>
<tr>
<td>5</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>2-(5-methyl) thiencyl</td>
<td></td>
<td>5-methyl</td>
</tr>
<tr>
<td>6</td>
<td>3α-tropanyl</td>
<td>2-(5-methyl) thiencyl</td>
<td></td>
<td>5-methyl</td>
</tr>
<tr>
<td>7</td>
<td>3α-(6,7,7β-epoxy)-tropanyl</td>
<td>2-thiencyl</td>
<td></td>
<td>5-fluoro</td>
</tr>
<tr>
<td>8</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>2-thiencyl</td>
<td></td>
<td>5-fluoro</td>
</tr>
<tr>
<td>9</td>
<td>3α-tropanyl</td>
<td>2-thiencyl</td>
<td></td>
<td>5-fluoro</td>
</tr>
<tr>
<td>10</td>
<td>3α-(6,7,7β-epoxy)-tropanyl</td>
<td>2-(5-fluoro) thiencyl</td>
<td></td>
<td>5-fluoro</td>
</tr>
<tr>
<td>11</td>
<td>3α-(6,7-dehydro)-tropanyl</td>
<td>2-(5-fluoro) thiencyl</td>
<td></td>
<td>5-fluoro</td>
</tr>
<tr>
<td>12</td>
<td>3α-tropanyl</td>
<td>2-(5-fluoro) thiencyl</td>
<td></td>
<td>5-fluoro</td>
</tr>
</tbody>
</table>
TABLE VI

Compounds of the formula

<table>
<thead>
<tr>
<th>No.</th>
<th>A</th>
<th>R₁</th>
<th>R₂</th>
<th>M.p. [° C.]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3α-(6β,7β-epoxy)-tropanyl methobromide</td>
<td>2-thienyl</td>
<td>5-methyl</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3α-(6,7-dehydro)-tropanyl methobromide</td>
<td>2-thienyl</td>
<td>5-methyl</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3α-tropanyl methobromide</td>
<td>2-thienyl</td>
<td>5-methyl</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3α-(6β,7β-epoxy)-tropanyl methobromide</td>
<td>2-(5-methyl)-thienyl</td>
<td>5-methyl</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>3α-(6,7-dehydro)-tropanyl methobromide</td>
<td>2-(5-methyl)-thienyl</td>
<td>5-methyl</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>3α-tropanyl methobromide</td>
<td>2-(5-methyl)-thienyl</td>
<td>5-methyl</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3α-(6β,7β-epoxy)-tropanyl methobromide</td>
<td>2-thienyl</td>
<td>5-fluoro</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>α-(6,7-dehydro)-tropanyl methobromide</td>
<td>2-thienyl</td>
<td>5-fluoro</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>3α-tropanyl methobromide</td>
<td>2-thienyl</td>
<td>5-fluoro</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>3α-(6β,7β-epoxy)-tropanyl methobromide</td>
<td>2-(5-fluoro)-thienyl</td>
<td>5-fluoro</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>3α-(6,7-dehydro)-tropanyl methobromide</td>
<td>2-(5-fluoro)-thienyl</td>
<td>5-fluoro</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>3α-tropanyl methobromide</td>
<td>2-(5-fluoro)-thienyl</td>
<td>5-fluoro</td>
<td></td>
</tr>
</tbody>
</table>

We claim:

1. A compound of the formula

\[
\begin{align*}
S & \quad CO \quad O \quad R^2
\end{align*}
\]

wherein

Q is a group of the formula \([-\text{CH}_2-\text{CH}_2-\])

\(-\text{CH}=\text{CH}-\) or

R and R' are each independently C₁-C₄-alkyl;
R₁ 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 \( \text{CH}_3, \text{C}_2\text{H}_5, n-\text{C}_3\text{H}_7, \) or \( i-\text{C}_3\text{H}_7; \)
- \( R' \) is \( \text{CH}_3; \) 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 \( \text{Br}^- \) or \( \text{CH}_3\text{SO}_3^- \).

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 anion.

7. A compound of the formula

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

8. A compound of the formula

wherein \( R_1 \) is 2-thienyl and \( A \) is 3\( \beta \)-tropanyl methobromide.

9. A compound of the formula

10. A compound of the formula

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, or 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, or 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, or 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.

* * * * *
Michael P. Morris  
Boehringer 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  

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

Attention: Beverly Friedman
UNITED STATES PATENT AND TRADEMARK OFFICE

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

PATENT NO. : RE 39820
REISSUED : September 4, 2007
INVENTOR : Rolf Banholzer et al.
PATENT OWNER : Boehringer Ingelheim Pharma GMBH & Co. KG
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

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
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 “[CH₃SO₃]CH₃SO₃⁻” to --[CH₃SO₃] CH₃SO₃⁻ --

Column 15, line 67, change “onion.” to --anion.--

Column 16, line 10, after the figure, insert --wherein R₁ 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

[Signature]

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