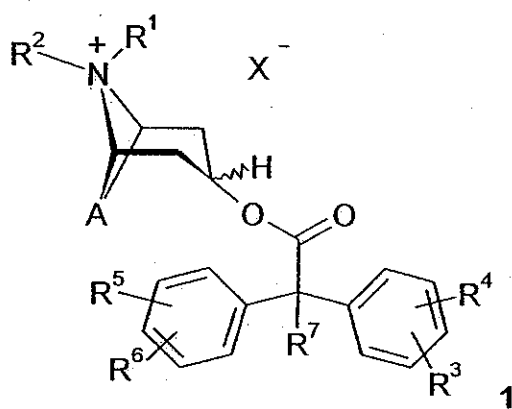


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**Novel anticholinergic agents that can be used as medicaments
and method for the production thereof**

5 The present invention relates to new anticholinergics of general formula 1



wherein A, X⁻ and the groups R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ may have the meanings given in the claims and specification, processes for preparing them as well

10 as their use as medicaments.

Background to the invention

Anticholinergics may be used to therapeutic effect in a wide range of illnesses.

Special mention should be made, for example, of the treatment of asthma or COPD

15 (chronic obstructive pulmonary disease). For treating these complaints, WO 92/16528 proposes anticholinergics which have a scopolamine, tropenol or tropine basic structure.

The underlying objective of WO 92/16528 is the preparation of anticholinergically effective compounds which are characterised by their long-lasting activity. To achieve this aim WO 92/16528 discloses, *inter alia*, benzoic acid esters of scopolamine, tropenol or tropine.

For treating chronic diseases it is often desirable to prepare medicaments with a longer duration of activity. As a rule, this ensures that the concentration of the active substance in the body needed to achieve the therapeutic effect is guaranteed for a longer period without the need to re-administer the drug at frequent intervals. Moreover, giving an active substance at longer time intervals contributes to the wellbeing of the patient to a high degree. It is particularly desirable to prepare a pharmaceutical composition which can be used therapeutically by administration once a day (single dose). The use of a drug once a day has the advantage that the

patient can become accustomed relatively quickly to regularly taking the drug at certain times of the day.

In order to be used as a medicament taken once a day, the active substance to be
5 given must meet particular requirements. First of all, the onset of the desired activity should take place relatively quickly after administration of the drug and ideally should have as constant an effect as possible over a subsequent fairly long period of time. On the other hand, the duration of activity of the drug should not substantially exceed a period of about one day. Ideally, an active substance has an activity profile such
10 that the preparation of a drug for administration once a day, which contains the active substance in therapeutically beneficial doses, can be deliberately controlled.

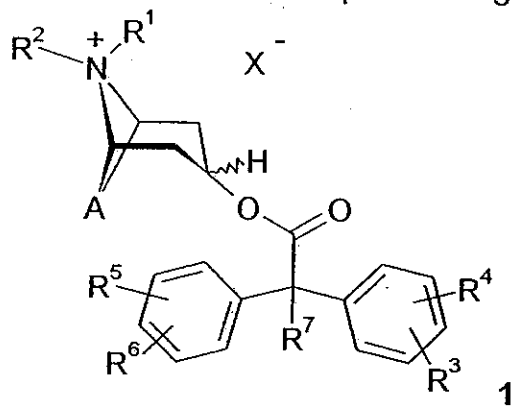
It has been found that the benzilic acid esters of scopine, tropenol and tropine disclosed in WO 92/16528 do not meet these stringent requirements. Because of
15 their extremely long period of activity, which significantly exceeds the above-mentioned period of about one day, they cannot be used therapeutically for administration in a single dose per day.

The aim of the present invention is therefore to provide new anticholinergics which,
20 by virtue of their activity profile, make it possible to prepare a drug for administration once a day. A further objective of the invention is to prepare compounds characterised by a relative rapid onset of activity. The invention further sets out to provide compounds which, after a rapid onset of activity, have as constant an activity as possible over a subsequent lengthy period of time. A further aim of the invention
25 is to provide compounds whose duration of activity does not substantially exceed a period of about one day in therapeutically beneficial doses. Finally, the invention sets out to provide compounds which have an activity profile which ensures good control of the therapeutic effect (i.e. total therapeutic effect without side effects caused by a build-up of the substance in the body).

Detailed Description of the Invention

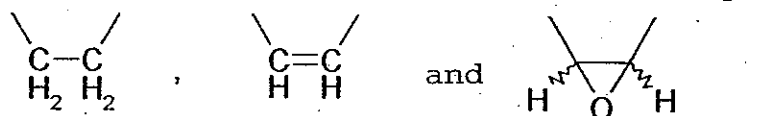
Surprisingly, it has been found that the above objectives are achieved by means of compounds of general formula 1 wherein the group R^7 does not denote hydroxy.

5 Accordingly the present invention relates to compounds of general formula 1



wherein

A denotes a double-bonded group selected from among

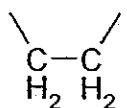


10 X^- denotes an anion with a single negative charge,
 R^1 and R^2 denote C_1 - C_4 -alkyl, which may optionally be substituted by hydroxy or halogen;

R^3 , R^4 , R^5 and R^6 , which may be identical or different, denote hydrogen,
 C_1 - C_4 -alkyl, C_1 - C_4 -alkyloxy, hydroxy, CF_3 , CN , NO_2 or halogen;

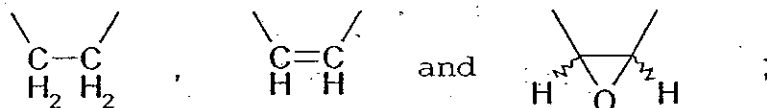
15 R^7 denotes hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkyloxy, C_1 - C_4 -alkylene-halogen, halogen- C_1 - C_4 -alkyloxy, C_1 - C_4 -alkylene-OH, CF_3 ,
 $-C_1$ - C_4 -alkylene- C_1 - C_4 -alkyloxy, $-O-COC_1$ - C_4 -alkyl,
 $-O-COC_1$ - C_4 -alkyl-halogen, $-O-COCF_3$ or halogen,

while

20 if A denotes ,
 R^1 and R^2 denote methyl and
 R^3 , R^4 , R^5 and R^6 denote hydrogen,
 R^7 cannot also be hydrogen.

Preferred compounds of general formula 1 are those wherein

A denotes a double-bonded group selected from among



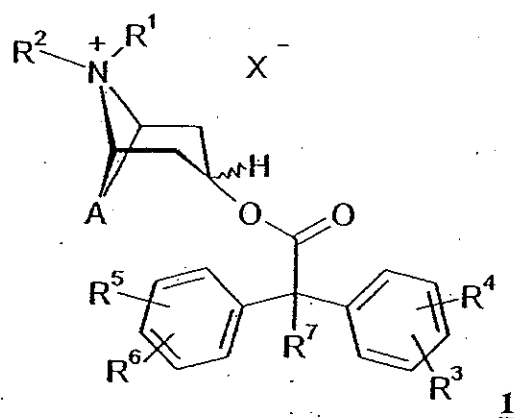
5 X - denotes an anion with a single negative charge selected from among chloride, bromide, methylsulphate, 4-toluenesulphonate and methanesulphonate, preferably bromide,

R¹ and R² which may be identical or different denote a group selected from among methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;

10 R³, R⁴, R⁵ and R⁶, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF₃ or NO₂;

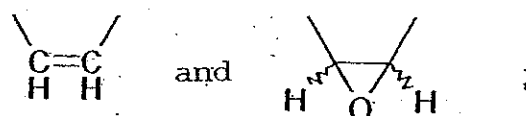
15 R⁷ denotes hydrogen, methyl, ethyl, methyloxy, ethyloxy, -CH₂-F, -CH₂-CH₂-F, -O-CH₂-F, -O-CH₂-CH₂-F, -CH₂-OH, -CH₂-CH₂-OH, CF₃, -CH₂-OMe, -CH₂-CH₂-OMe, -CH₂-OEt, -CH₂-CH₂-OEt, -O-COMe, -O-COEt, -O-COCF₃, -O-COCF₃, fluorine, chlorine or bromine.

In one aspect of the present invention, there is provided, compound of general formula 1



wherein

A denotes a double-bonded group selected from among



X - denotes an anion with a single negative charge preferably selected from among chloride, bromide, methylsulphate, 4-toluenesulphonate and methanesulphonate;

4a

R^1 and R^2 which may be identical or different denote a group selected from among methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine;

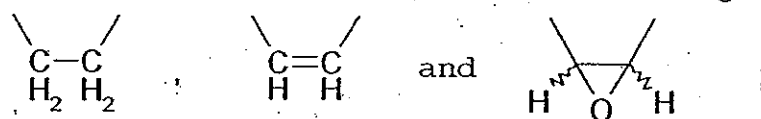
R^3 , R^4 , R^5 and R^6 , which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF_3 or NO_2 ;

R^7 denotes methyl, ethyl, methyloxy, ethyloxy, $-CH_2-F$, $-CH_2-CH_2-F$, $-O-CH_2-F$, $-O-CH_2-CH_2-F$, $-CH_2-OH$, $-CH_2-CH_2-OH$, CF_3 , $-CH_2-OMe$, $-CH_2-CH_2-OMe$, $-CH_2-OEt$, $-CH_2-CH_2-OEt$, $-O-COMe$, $-O-COEt$, $-O-COCF_3$, $-O-COCF_3$, fluorine, chlorine or bromine, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

Particularly preferred are compounds of general formula 1,

20 wherein

A denotes a double-bonded group selected from among



X - denotes an anion with a single negative charge selected from among chloride, bromide and methanesulphonate, preferably bromide;

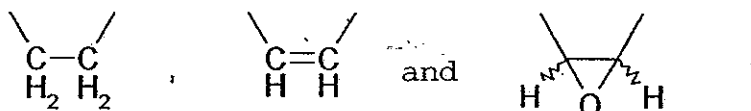
25 R^1 and R^2 which may be identical or different denote a group selected from methyl and ethyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;

R^3 , R^4 , R^5 and R^6 , which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine or bromine;

30 R^7 denotes hydrogen, methyl, ethyl, methyloxy, ethyloxy, CF_3 , or fluorine.

Preferred compounds of general formula 1 according to the invention are those wherein

A denotes a double-bonded group selected from among



5 X⁻ denotes bromide;

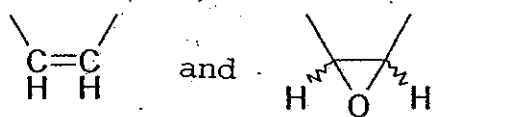
R¹ and R² which may be identical or different denote a group selected from methyl and ethyl, preferably methyl;

R³, R⁴, R⁵ and R⁶, which may be identical or different, denote hydrogen, methyl, methoxy, chlorine or fluorine;

10 R⁷ denotes hydrogen, methyl or fluorine.

Of particular importance according to the invention are compounds of general formula 1, wherein

A denotes a double-bonded group selected from among



15

X⁻ denotes bromide;

R¹ and R² which may be identical or different denote methyl or ethyl, preferably methyl;

R³, R⁴, R⁵ and R⁶, which may be identical or different, denote hydrogen or fluorine, preferably hydrogen;

20

R⁷ denotes hydrogen, methyl or fluorine, preferably methyl or fluorine, most preferably methyl.

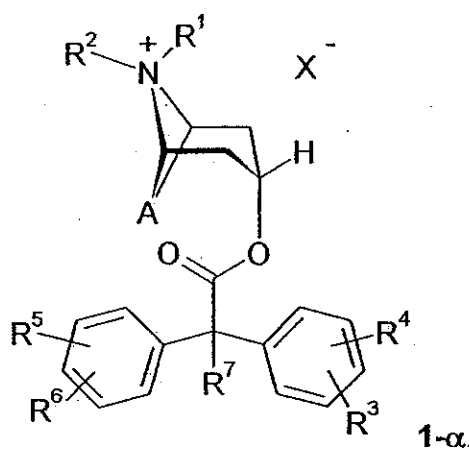
The invention relates to the compounds of formula 1, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

In the compounds of general formula 1 the groups R³, R⁴, R⁵ and R⁶, provided that they do not denote hydrogen, may each be in the ortho, meta or para position relative to the bond to the "-C-R⁷" group. Provided that none of the groups R³, R⁴, R⁵ and R⁶ denotes hydrogen, R³ and R⁵ are preferably linked in the para-position and R⁴ and R⁶ are preferably linked in the ortho- or meta-position, most preferably in the meta-position. If one of the groups R³ and R⁴ and one of the groups R⁵ and R⁶ denotes hydrogen, the other group in each case is preferably linked in the meta- or para-position, most preferably in the para-position. If none of the groups R³, R⁴,

35

R^5 and R^6 denotes hydrogen, according to the invention the compounds of general formula 1 wherein the groups R^3 , R^4 , R^5 and R^6 have the same meaning are particularly preferred.

- 5 Of particular importance according to the invention are the compounds of general formula 1 wherein the ester-substituent on the nitrogen-bicyclic group is in the α -configuration. These compounds correspond to general formula 1- α



10

According to the invention, the following compounds are of particular importance:

- tropenol 2,2-diphenylpropionate-methobromide;
- scopine 2,2-diphenylpropionate-methobromide;
- scopine 2-fluoro-2,2-diphenylacetate-methobromide;
- tropenol 2-fluoro-2,2-diphenylacetate-methobromide;

15

Unless otherwise stated, the alkyl groups are straight-chained or branched alkyl groups having 1 to 4 carbon atoms. The following are mentioned by way of example: methyl, ethyl, propyl or butyl. In some cases the abbreviations Me, Et,

20

Prop or Bu are used to denote the groups methyl, ethyl, propyl or butyl. Unless otherwise stated, the definitions propyl and butyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes n-propyl and isopropyl, butyl includes iso-butyl, sec-butyl and tert.-butyl, etc.

25

Unless otherwise stated, the alkylene groups are branched and unbranched double-bonded alkyl bridges having 1 to 4 carbon atoms. The following are mentioned by way of example: methylene, ethylene, propylene or butylene.

30

Unless otherwise stated, the alkylene-halogen groups are branched and unbranched double-bonded alkyl bridges having 1 to 4 carbon atoms which are mono-, di- or

trisubstituted, preferably monosubstituted, by a halogen. Accordingly, unless otherwise stated, the alkylene-OH groups are branched and unbranched double-bonded alkyl bridges having 1 to 4 carbon atoms which are mono-, di- or trisubstituted, preferably monosubstituted, by a hydroxy.

5

Unless otherwise stated, the term alkyloxy groups denotes branched and unbranched alkyl groups having 1 to 4 carbon atoms which are linked via an oxygen atom. Examples of these include: methyloxy, ethyloxy, propyloxy or butyloxy. The abbreviations MeO-, EtO-, PropO- or BuO- are used in some cases to denote the groups methyloxy, ethyloxy, propyloxy or butyloxy. Unless otherwise stated, the definitions propyloxy and butyloxy include all possible isomeric forms of the groups in question. Thus, for example, propyloxy includes n-propyloxy and iso-propyloxy, butyloxy includes iso-butyloxy, sec.butyloxy and tert.-butyloxy, etc. In some cases, within the scope of the present invention, the term alkoxy is used instead of the term alkyloxy. Accordingly, the terms methoxy, ethoxy, propoxy or butoxy may also be used to denote the groups methyloxy, ethyloxy, propyloxy or butyloxy

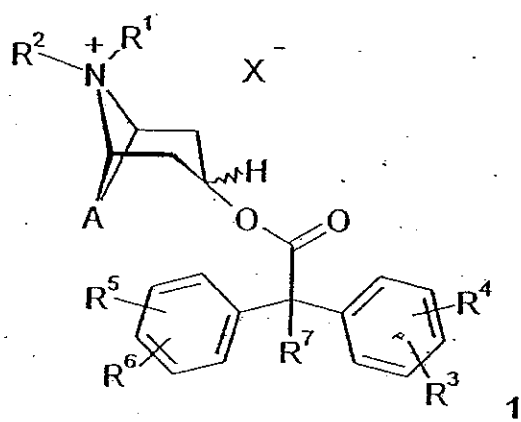
Unless otherwise stated, the term alkylene-alkyloxy groups denotes branched and unbranched double-bonded alkyl bridges having 1 to 4 carbon atoms which are mono-, di- or trisubstituted, preferably monosubstituted, by an alkyloxy group.

Unless otherwise stated, the term -O-CO-alkyl groups denotes branched and unbranched alkyl groups having 1 to 4 carbon atoms which are linked via an ester group. The alkyl groups are linked directly to the carbonyl carbon of the ester group. The term -O-CO-alkyl-halogen group should be understood in the same way. The group -O-CO-CF₃ denotes trifluoroacetate.

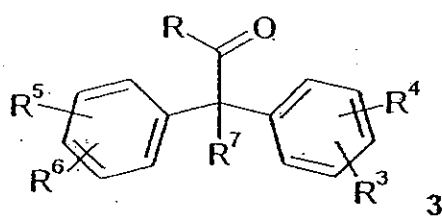
Halogen within the scope of the present invention denotes fluorine, chlorine, bromine or iodine. Unless stated otherwise, fluorine and bromine are the preferred halogens. The group CO denotes a carbonyl group.

In another aspect of the present invention, there is provided a process for preparing a compound of general formula 1

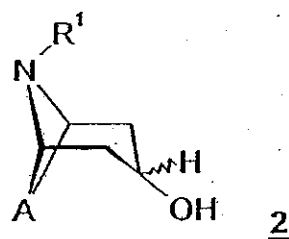
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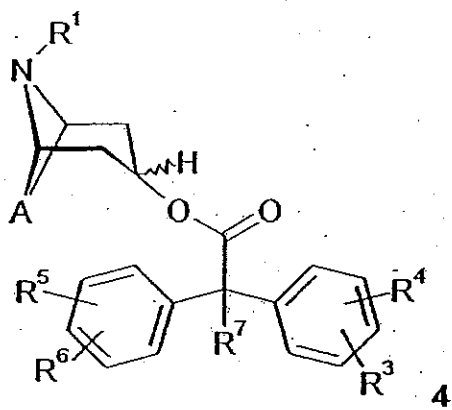
wherein A, X^- and the groups R^1 , R^2 , R^3 , R^4 , R^5 , R^6 and R^7 may have the meanings as defined above, characterised in that in a first step a compound of general formula 3



wherein the groups R^3 , R^4 , R^5 , R^6 and R^7 may have the meanings given in claims 1 to 4 and R denotes chlorine or a C_1 - C_4 -alkyloxy, is reacted with a compound of formula 2



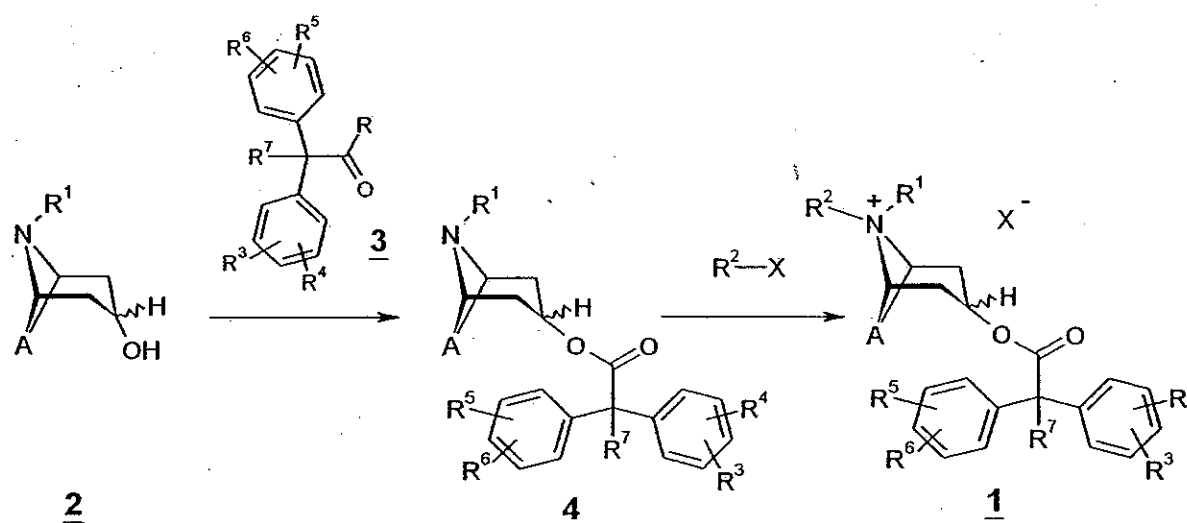
wherein A and R^1 may have the meanings as defined above, to obtain a compound of formula 4



7b

wherein A and the groups R^1 , R^3 , R^4 , R^5 , R^6 and R^7 may have the meanings given in claims 1 to 4, and this is then quaternised by reacting with a compound R^2-X , wherein R^2 and X may have the meanings as defined above to obtain a compound of formula 1.

The compounds according to the invention may partly be prepared, as illustrated below, analogously to procedures which are already known from the prior art (Diagram 1). The carboxylic acid derivatives of formula 3 are known in the art or may
35 be obtained using methods of synthesis known in the art. If only suitably substituted carboxylic acids are known in the art, the compounds of formula 3 may also be obtained directly from them by acid- or base-catalysed esterification with the corresponding alcohols or by halogenation with the corresponding halogenation reagents.

**Diagram 1:**

Starting from the compounds of formula 2 the esters of general formula 4 may be
 5 obtained by reacting the carboxylic acid derivatives of formula 3, wherein R may
 denote chlorine or a C₁-C₄-alkyloxy group, for example. When R denotes C₁-C₄-
 alkyloxy this reaction may be carried out, for example, in a sodium melt at elevated
 temperature, preferably at about 50-150°C, most preferably at about 90-100°C at low
 pressure, preferably below 500mbar, most preferably below 75mbar. Alternatively,
 10 instead of the derivatives 3 wherein R denotes C₁-C₄-alkyloxy, the corresponding
 acid chlorides (R equals Cl) may be used.

The compounds of formula 4 thus obtained may be converted into the target
 compounds of formula 1 by reacting the compounds R²-X, wherein R² and X may
 15 be as hereinbefore defined. This synthesis step may also be carried out analogously
 to the examples of synthesis disclosed in WO 92/16528.

Alternatively to the procedure illustrated in Diagram 1 for synthesising the
 compounds of formula 4, the derivatives 4 in which the nitrogen bicyclic group is a
 20 scopine derivative may be obtained by oxidation (epoxidation) of compounds of
 formula 4 wherein the nitrogen-bicyclic group is a tropanyl group. This may be done
 as follows, according to the invention.

Compound 4, wherein A denotes -CH=CH-, is suspended in a polar organic solvent,
 preferably in a solvent selected from among N-methyl-2-pyrrolidone (NMP),
 25 dimethylacetamide and dimethylformamide, preferably dimethylformamide, and then
 heated to a temperature of about 30-90°C, preferably 40-70°C. Then a suitable
 oxidising agent is added and the mixture is stirred at constant temperature for 2 to 8
 hours, preferably 3 to 6 hours. The preferred oxidising agent is vanadium pentoxide
 mixed with H₂O₂, most preferably H₂O₂-urea complex combined with vanadium

pentoxide. The mixture is worked up in the usual way. The products may be purified by crystallisation or chromatography, depending on their crystallisation tendencies.

Alternatively, the compounds of formula 4 wherein R^7 denotes halogen may also be obtained by the method shown in Diagram 2.

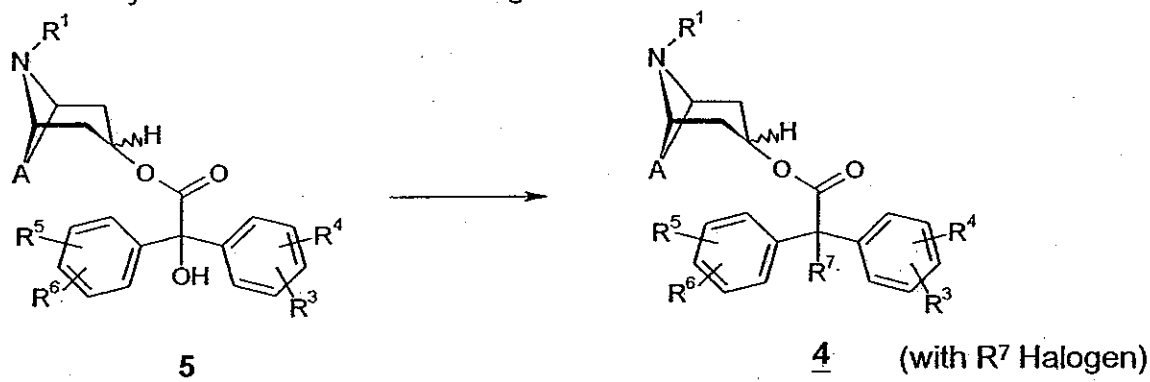
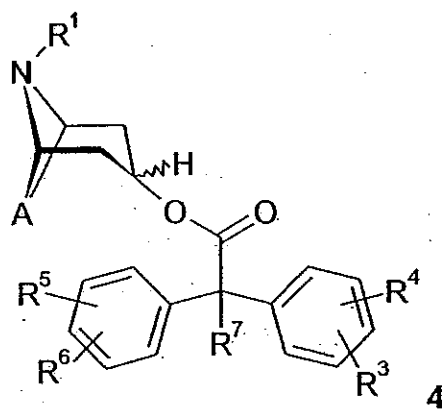


Diagram 2:

For this, the benzilic acid esters of formula 5 [verb missing (are converted?)], using suitable halogenating reagents, into the compounds 4 wherein R^7 denotes halogen. The reaction of halogenation to be carried out according to Diagram 2 is already sufficiently well known in the art.

The benzilic acid esters of formula 5 may be obtained in accordance with or analogously to methods known in the art (see e.g. WO 92/16528).

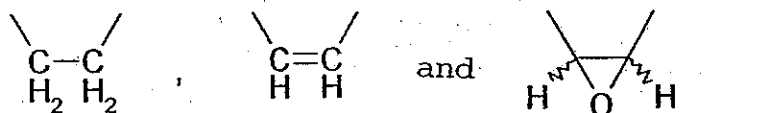
As shown in Diagram 1, the intermediate products of general formula 4 are of crucial importance. Accordingly, in another aspect, the present invention relates to the intermediates of formula 4



wherein

A

denotes a double-bonded group selected from among

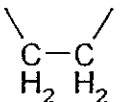


R^1 denotes C_1 - C_4 -alkyl, which may optionally be substituted by hydroxy or halogen;

R^3 , R^4 , R^5 and R^6 , which may be identical or different, denote hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkyloxy, hydroxy, CF_3 , CN , NO_2 or halogen;

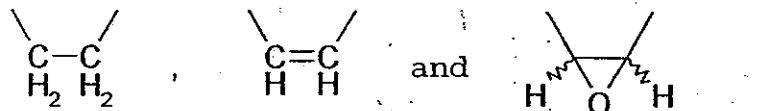
5 R^7 denotes hydrogen, C_1 - C_4 -alkyl, C_1 - C_4 -alkyloxy, C_1 - C_4 -alkylene-halogen, halogen- C_1 - C_4 -alkyloxy, C_1 - C_4 -alkylene-OH, CF_3 , - C_1 - C_4 -alkylene- C_1 - C_4 -alkyloxy, -O-COC $_1$ - C_4 -alkyl, -O-COC $_1$ - C_4 -alkyl-halogen, -O-COCF $_3$ or halogen,

while

10 if A denotes ,
 R^1 denotes methyl and
 R^3 , R^4 , R^5 and R^6 denote hydrogen,
 R^7 cannot be n-propyl.

15 Preferred are compounds of general formula 1,
 wherein

A denotes a double-bonded group selected from among



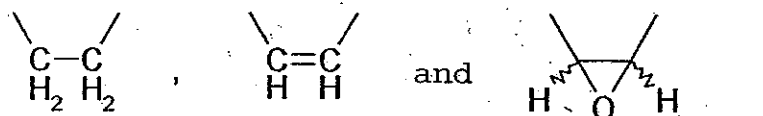
20 R^1 which may be identical or different denotes a group selected from among methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;

R^3 , R^4 , R^5 and R^6 , which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN , CF_3 or NO_2 ;

25 R^7 denotes hydrogen, methyl, ethyl, methyloxy, ethyloxy, - CH_2 -F, - CH_2 - CH_2 -F, -O- CH_2 -F, -O- CH_2 - CH_2 -F, - CH_2 -OH, - CH_2 - CH_2 -OH, CF_3 , - CH_2 -OMe, - CH_2 - CH_2 -OMe, - CH_2 -OEt, - CH_2 - CH_2 -OEt, -O-COMe, -O-COEt, -O-COCF $_3$, -O-COCF $_3$, fluorine, chlorine or bromine.

30 Particularly preferred are compounds of general formula 1,
 wherein

A denotes a double-bonded group selected from among



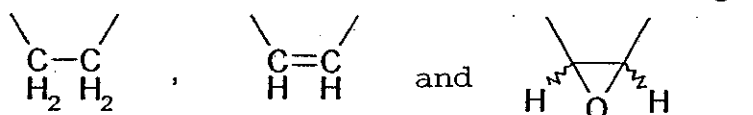
R¹ which may be identical or different denote a group selected from methyl and ethyl, which may optionally be substituted by hydroxy or fluorine, preferably unsubstituted methyl;

R³, R⁴, R⁵ and R⁶, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine or bromine;

R⁷ denotes hydrogen, methyl, ethyl, methyloxy, ethyloxy, CF₃, or fluorine.

Preferred compounds of general formula 1 according to the invention are those wherein

A denotes a double-bonded group selected from among



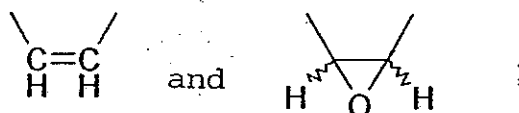
R¹ which may be identical or different denote a group selected from methyl and ethyl, preferably methyl;

R³, R⁴, R⁵ and R⁶, which may be identical or different, denote hydrogen, methyl, methyloxy, chlorine or fluorine;

R⁷ denotes hydrogen, methyl or fluorine.

Of particular importance according to the invention are compounds of general formula 1 wherein

A denotes a double-bonded group selected from among



R¹ which may be identical or different denote methyl or ethyl, preferably methyl;

R³, R⁴, R⁵ and R⁶, which may be identical or different, denote hydrogen or fluorine, preferably hydrogen;

R⁷ denotes hydrogen, methyl or fluorine, preferably methyl or fluorine, most preferably methyl.

As in the compounds of general formula 1, in the intermediates of formula 4, the groups R³, R⁴, R⁵ and R⁶, provided that they do not denote hydrogen, may each be in the ortho, meta or para position relative to the bond to the "-C-R⁷" group.

Provided that none of the groups R³, R⁴, R⁵ and R⁶ denotes hydrogen, R³ and R⁵ are preferably linked in the para-position and R⁴ and R⁶ are preferably linked in the ortho- or meta-position, most preferably in the meta-position. If one of the groups R³ and R⁴ and one of the groups R⁵ and R⁶ denotes hydrogen, the other group in each

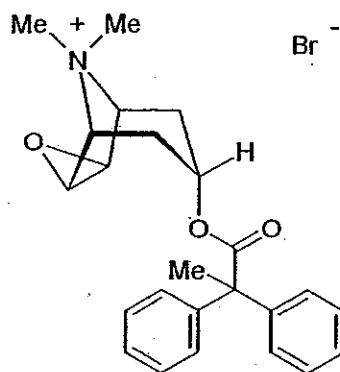
case is preferably linked in the meta- or para-position, most preferably in the para-position. If none of the groups R^3 , R^4 , R^5 and R^6 denotes hydrogen, according to the invention the intermediates of general formula 1 wherein the groups R^3 , R^4 , R^5 and R^6 have the same meaning are particularly preferred.

5

The examples of synthesis described hereinafter serve to illustrate the present invention still further. However, they are intended only as examples of procedures as an illustration of the invention without restricting the invention to the subject-matter described by way of example.

10

Example 1: scopine 2,2-diphenylpropionate-methobromide :



15 **1.1.: 2,2-diphenylpropionic acid chloride 3a:**

52.08 g (0.33 mol) of oxalyl chloride are slowly added dropwise to a suspension of 25.0 g (0.11 mol) of 2,2-diphenylpropionic acid, 100 ml of dichloromethane and 4 drops of dimethylformamide at 20° C. The mixture is stirred for 1 h at 20°C and 0.5 h at 50° C. The solvent is distilled off and the residue remaining is used in the next

20 step without any further purification.

1.2.: scopine 2,2-diphenylpropionate 4a:

The residue obtained in step 1.1. is dissolved in 100 ml dichloromethane and at 40°C a solution of 51.45 g (0.33 mol) of scopine in 200 ml dichloromethane is added

25 dropwise. The resulting suspension is stirred for 24 h at 40° C, then the precipitate formed is suction filtered and the filtrate is acidically extracted first with water, then with aqueous hydrochloric acid. The combined aqueous phases are made alkaline with aqueous sodium carbonate solution, extracted with dichloromethane, the organic phase is dried over Na_2SO_4 , evaporated to dryness and the hydrochloride is

30 precipitated from the residue. The product is purified by recrystallisation from acetonitrile.

Yield: 20.85 g (= 47 % of theory)

TLC: R_f value: 0.24 (eluant: sec. butanol/formic acid/water 75:15:10);
Melting point: 203-204°C.

1.3: scopine 2,2-diphenylpropionate-methobromide :

- 5 11.98 g (0.033 mol) of **4a**, 210 ml of acetonitrile, 70 ml of dichloromethane and 20.16g (0.1 mol) of 46.92 % bromomethane in acetonitrile are combined at 20°C and left to stand for 3 days. The solution is evaporated to dryness and the residue recrystallised from isopropanol.

Yield: 11.34 g (= 75 % of theory); Melting point: 208-209°C.

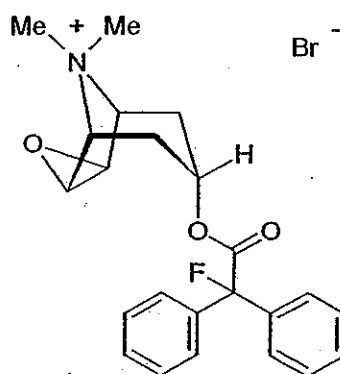
- 10 C₂₄H₂₈NO₃xBr (458.4);

Elemental analysis: calculated: C (62.89) H (6.16) N (3.06)

found: C (62.85) H (6.12) N (3.07).

Example 2: scopine 2-fluoro-2,2-diphenylacetate-methobromide :

15



2.1: Scopine benzilate **5a:**

- 20 The preparation of scopine benzilate is known in the art. It is described in WO 92/16528.

2.2: scopine 2-fluoro-2,2-diphenylacetate **4b:**

- 25 2.66 g (0.02 mol) of dimethylaminosulphur trifluoride are cooled to 0°C in 10 ml of dichloromethane and a solution of 5.48 g (0.015 mol) of scopine benzilate **5a** in 100 ml of dichloromethane is added dropwise. Then the mixture is stirred for a further 30 min at 0°C and 30 min at 20°C. While cooling the solution is combined with water, NaHCO₃ is added (to pH 7-8) and the organic phase is separated off. The aqueous phase is extracted with dichloromethane, the combined organic phases are washed with water, dried over Na₂SO₄ and evaporated to dryness.

- 30 The hydrochloride is precipitated from the residue and recrystallised from acetonitrile.

Yield: 6.90 g (= 85 % of theory)

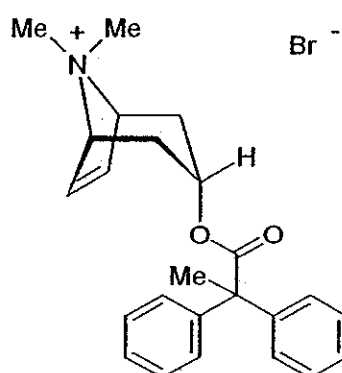
Melting point: 227°-230° C.

2.3: scopine 2-fluoro-2,2-diphenylacetate-methobromide :

2.88 g (0.0078 mol) of the free base of scopine benzilate are reacted analogously to
 5 the procedure in step 1.3. The product is purified by recrystallisation from
 isopropanol. Yield: 2.62 g (= 73 % of theory)
 TLC: R_f value: 0.31 (eluant as in step 1.2); Melting point: 130-134°C.

Example 3: tropenol 2,2-diphenylpropionate-methobromide :

10



3.1.: methyl 2,2-diphenylpropionate 3b:

37.60 g (0.247 mol) of DBU are added dropwise to a suspension of 50.8 g (0.225
 mol) of 2,2-diphenylpropionic acid and 200 ml of acetonitrile at 20°C. 70.10 g (0.494
 15 mol) of methyl iodide are added dropwise to the resulting solution within 30 min. Then
 the mixture is stirred overnight at 20° C. The solvent is evaporated down, the residue
 is extracted with diethylether/water, the organic phase is washed with water, dried
 over Na₂SO₄ and evaporated to dryness. Yield: 48.29 g of viscous residue 3b (= 89
 % of theory).

20

3.2: tropenol 2,2-diphenylpropionate 4c:

4.80 g (0.02 mol) of methyl 2,2-diphenylpropionate **3b**, 2.78 g (0.02 mol) of tropenol
 and 0.046 g of sodium are heated as a melt at 75 mbar for 4 h over a bath of boiling
 water, shaking from time to time. After cooling the sodium residues are dissolved
 25 with acetonitrile, the solution is evaporated to dryness and the residue extracted with
 dichloromethane/water. The organic phase is washed with water, dried over MgSO₄
 and evaporated to dryness.

From the residue, **4c** is precipitated as the hydrochloride and this is recrystallised
 from acetone.

30 Yield: 5.13 g (= 67 % of theory);

TLC: R_f value: 0.28 (eluant: sec. butanol/formic acid/water 75:15:10);

Melting point: 134-135°C.

3.3: tropenol 2,2-diphenylpropionate-methobromide :

2.20 g (0.006 mol) of **4c** are reacted analogously to Example 1, step 1.3. The crystals formed are suction filtered, washed with dichloromethane, dried and then
 5 recrystallised from methanol/diethylether.

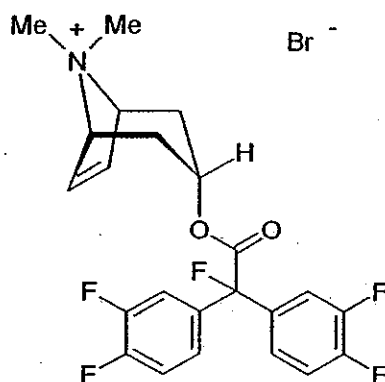
Yield: 1.84 g (=66 % of theory)

TLC: R_f value: 0.11 (eluant as in step 1.2); Melting point: 222-223°C.

C₂₄H₂₈NO₂xBr (442.4);

Elemental analysis: calculated: C (65,16) H (6.38) N (3.17)

10 found.: C (65,45) H (6.29) N (3.16).

Example 4: tropenol 2-fluoro-2,2-bis(3,4-difluorophenyl)acetate-methobromide :**15 4.1.: ethyl 3,3',4,4'-tetrafluorobenzilate 3c:**

The Grignard reagent is prepared from 2.24 g (0.092 mol) of magnesium chips, a few granules of iodine and 17.80 g (0.092 mol) of 1-bromo-3,4-difluoro-benzene in 100 ml of THF at 50° C. After the halide has all been added, the mixture is stirred for another hour. The Grignard reagent thus obtained is added dropwise to 18.81 g
 20 (0.088 mol) of ethyl 3,4-difluorophenylglyoxylate in 80 ml of THF at 10°-15° C and the mixture obtained is stirred for 2 hours at 5°C.

The white suspension is poured onto ice/sulphuric acid for working up, extracted with ethyl acetate, the organic phase is washed with water, dried over MgSO₄ and evaporated to dryness. The crude product is purified by column chromatography
 25 (eluant: toluene).

Yield: 10.80 g of oil 1 (= 38 % of theory)

4.2.: tropenol 3,3',4,4'-tetrafluorobenzilate 5b:

4.27 g (0.013 mol) of ethyl 3,3',4,4'-tetrafluorobenzilate **3c**, 1.81 g (0.013 mol) of
 30 tropenol and 0.03 g sodium are heated as a melt at 75 mbar for 4 h over a bath of boiling water, shaking from time to time. After cooling the sodium residues are dissolved with acetonitrile, the solution is evaporated to dryness and the residue

extracted with dichloromethane/water. The organic phase is washed with water, dried over MgSO_4 and evaporated to dryness.

The residue remaining is mixed with diethylether/petroleum ether 1:9, suction filtered and washed. Yield: 2.50 g (= 46 % of theory);

5 TLC: Rf value: 0.29 (eluant: sec. butanol/formic acid/water 75:15:10);

Melting point: 147°-148°C.

4.3: tropenol 2-fluoro-2,2-bis(3,4-difluorophenyl)acetate 4d:

2.66 g (0.012 mol) of bis-(2-methoxyethyl)-aminosulphur trifluoride were placed in 10
10 ml of dichloromethane and within 20 minutes a solution of 0.01 mol of **5b** in 65 ml of dichloromethane was added dropwise at 15°-20°C.

The mixture is stirred for 20 h at ambient temperature, cooled to 0° C and carefully mixed with 80 ml of water with thorough stirring. The mixture is then carefully adjusted to pH 8 with aqueous NaHCO_3 solution, the organic phase is separated off,
15 the aqueous phase is extracted again with dichloromethane, the combined organic phases are washed with water, dried over MgSO_4 and evaporated to dryness. The hydrochloride is precipitated and recrystallised from acetonitrile/diethylether.

Yield: 2.60 g of white crystals (= 57 % of theory)

Melting point: 233° C

20

4.4: tropenol 2-fluoro-2,2-bis(3,4-difluorophenyl)acetate-methobromide :

2,20 g (0.0052 mol) of **4d** are reacted analogously to Example 1, step 1.3. The crystals formed are suction filtered, washed with dichloromethane, dried and then recrystallised from methanol/diethylether.

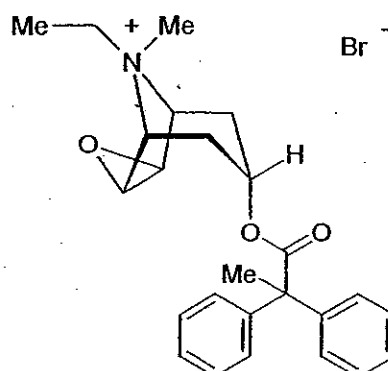
25 Yield: 1.95 g (=72 % of theory)

TLC: Rf value: 0.17 (eluant: n-butanol/water/formic acid(conc.)/acetone/dichloromethane 36:15:15:15:5); Melting point: 247°C.

$\text{C}_{23}\text{H}_{21}\text{F}_5\text{NO}_2\text{xBr}$ (518.3);

Elemental analysis: calculated: C (53.30) H (4.08) N (2.70)

30 found.: C (53.22) H (4.19) N (2.69).

Example 5: scopine 2,2-diphenylpropionate-ethylbromide

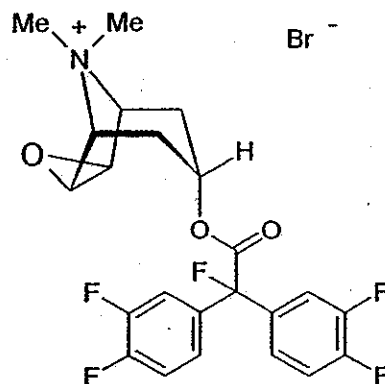
1.81 g (0.005 mol) of **4a**, 35 ml of acetonitrile and 1.64 g (0.015 mol) of ethylbromide
 5 are combined at 20°C and left to stand for 3 days. The solution is evaporated to dryness and the residue recrystallised from ethanol.

Yield: 1.38 g (= 58 % of theory); Melting point: 208-209°C.

TLC: R_f value: 0.33 (eluant as in step 1.2); Melting point: 210-211°C.

C₂₅H₃₀NO₃·Br (472.42);

10 Elemental analysis: calculated: C (63.56) H (6.40) N (2.96)
 found.: C (63.49) H (6.24) N (2.88).

Example 6: scopine 2-fluoro-2,2-bis(3,4-difluorophenyl)acetate-methobromide :**6.1.: scopine 3,3',4,4'-tetrafluorobenzilate 5c:**

3.61 g (0.011 mol) of ethyl 3,3',4,4'-tetrafluorobenzilate **3c**, 1.71 g (0.011 mol) of scopine and 0.03 g sodium are heated as a melt at 75 mbar over a bath of boiling water for 4 h, shaking from time to time. After cooling the sodium residues are
 20 dissolved with acetonitrile, the solution is evaporated to dryness and the residue extracted with dichloromethane/water. The organic phase is washed with water, dried over MgSO₄ and evaporated to dryness.

The residue remaining is combined with diethylether/petroleum ether 1:9, suction filtered and washed. Yield: 1.75 g (= 36 % of theory);

Melting point: 178-179°C.

6.2: scopine 2-fluoro-2,2-bis(3,4-difluorophenyl)acetate 4e:

0.6 ml (0.0033 mol) of bis-(2-methoxyethyl)-aminosulphur trifluoride are reacted with

5 1.2 g (0.0028 mol) of 5c analogously to Example 4, step 4.3.

Yield: 1.15 g of colourless oil (= 95 % of theory)

6.3: scopine 2-fluoro-2,2-bis(3,4-difluorophenyl)acetate-methobromide :

1.15 g (0.0026 mol) of 4e and 1.5 g (0.0079 mol) of 50% methyl bromide solution are

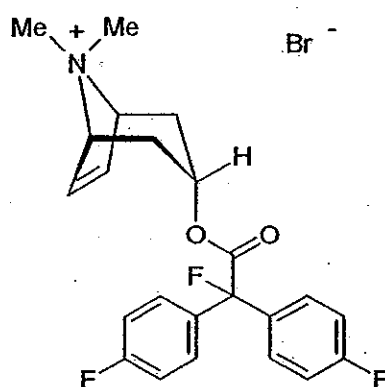
10 reacted analogously to Example 1, step 1.3. The crystals formed are suction filtered, washed with dichloromethane, dried and then recrystallised from acetone.

Yield: 0.88 g (=63 % of theory)

TLC: R_f value: 0.27 (eluant: n-butanol/water/formic acid(conc.)/acetone/
dichloromethane 36:15:15:15:5); Melting point: 212°C.

15 C₂₃H₂₁F₅NO₃·Br (535.33);

Example 7: tropenol 2-fluoro-2,2-bis(4-fluorophenyl)acetate-methobromide :



20 **7.1.: methyl 4,4'-difluorobenzilate 3d:**

7.1.1.: 4,4'-difluorobenzilic acid:

At about 100°C a solution of 24.62 g (0.1 mol) of 4,4'-difluorobenzil in 250 ml of dioxane is added dropwise to a solution of 49.99 g (1.25 mol) of NaOH flakes in 300 ml of water and stirred for 2 h. The dioxane is largely distilled off and the aqueous

25 solution remaining is extracted with dichloromethane. When the aqueous solution is acidified with sulphuric acid, a precipitate is formed which is suction filtered, washed and dried. The filtrate is extracted with dichloromethane, the organic phase is dried over Na₂SO₄ and evaporated to dryness.

Yield: 25.01 g (= 95 % of theory); melting point: 133°-136° C

30

7.1.2.: methyl 4,4'-difluorobenzilate:

25.0 g (0.095 mol) of 4,4'-difluorobenzilic acid are added to freshly prepared sodium ethoxide solution containing 2.17 g (0.095 mol) of sodium and 200 ml of ethanol at 20° C and stirred for 3 h. The solution is evaporated to dryness, the residue is dissolved in DMF, 22.57 g (0.16 mol) of methyl iodide are added dropwise at 20° C and the mixture is stirred for 24 h. It is worked up and purified analogously to compound **3b**. Yield: 21.06 g of **11** (= 80 % of theory)

7.2.: tropenol 4,4'-difluorobenzilate **5d:**

11.13 g (0.04 mol) of methyl 4,4'-difluorobenzilate **3d** and 5.57 g (0.04 mol) of tropenol are reacted with 0.09 g sodium analogously to Example 3, step 3.2. The product is recrystallised from acetonitrile.

Yield: 10.43 g (= 62 % of theory);

Melting point: 233-235°C.

7.3: tropenol 2-fluoro-2,2-bis(4-fluorophenyl)-acetate **4f:**

2.94 g (0.013 mol) of bis-(2-methoxyethyl)-aminosulphur trifluoride are reacted with 3.85 g (0.01 mol) of **5d** analogously to Example 4, step 4.3 in 100 ml of dichloromethane. The product is recrystallised from acetonitrile in the form of its hydrochloride.

Yield: 2.93 g (= 69 % of theory)

7.4: tropenol 2-fluoro-2,2-bis(4-fluorophenyl)-acetate-methobromide :

2.6 g (0.0067 mol) of **4f** and 1.9 g (0.0079 mol) of 50% methylbromide solution are reacted analogously to Example 1, step 1.3. The crystals formed are suction filtered, washed with dichloromethane, dried and then recrystallised from methanol/diethylether.

Yield: 2.82 g of white crystals (=87 % of theory)

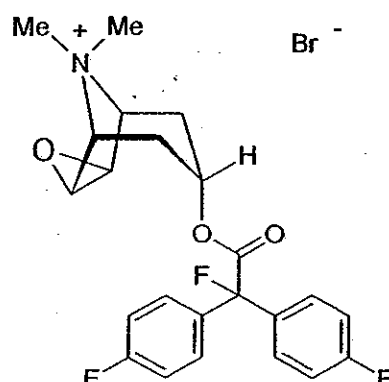
TLC: R_f value: 0.55 (eluant: according to Example 1, step 1.2);

Melting point: 230-231°C.

30 C₂₃H₂₃F₃NO₂xBr (482,34);

Elemental analysis: calculated: C (57.27) H (4.81) N (2.90)

found: C (57.15) H (4.84) N (2.96).

Example 8: scopine 2-fluoro-2,2-bis(4-fluorophenyl)acetate-methobromide :**8.1: scopine 4,4'-difluorobenzilate 5e:**

- 5 4.22 g (0.01 mol) of tropenol 4,4'-difluorobenzilate **5d** are suspended in 80 ml of DMF. At an internal temperature of about 40°C a solution of 2.57 g (0.0273 mol) of H₂O₂-urea in 20 ml of water, together with 0.2 g (0.0011 mol) of vanadium-(V)-oxide is added and the resulting mixture is stirred for 4.5 h at 60°C. After cooling to 20°C the precipitate formed is suction filtered, the filtrate is adjusted to pH3 with 4 N
- 10 hydrochloric acid and combined with Na₂S₂O₅ dissolved in water. The resulting green solution is evaporated to dryness, the residue is extracted with dichloromethane/water. The acidic aqueous phase is made basic with Na₂CO₃, extracted with dichloromethane and the organic phase is dried over Na₂SO₄ and concentrated.
- 15 Then 0.5 ml of acetylchloride is added at about 15°C and stirred for 1.5 h. After extraction with 0.1 N hydrochloric acid, the aqueous phase is made basic, extracted with dichloromethane, the organic phase is dried over Na₂SO₄ and evaporated to dryness. The hydrochloride is precipitated from the residue and recrystallised from methanol/diethylether.
- 20 Yield: 3.61 g of white crystals (= 78 % of theory);
Melting point: 243-244°C.

8.2: scopine 2-fluoro-2,2-bis(4-fluorophenyl)-acetate 4g:

- 25 1.48 g (0.0067 mol) of bis-(2-methoxyethyl)-aminosulphur trifluoride are reacted with 2.0 g (0.005 mol) of **5e** analogously to Example 4, step 4.3 in 80 ml of dichloromethane. The product is recrystallised from ethanol in the form of its hydrochloride.
- Yield: 2.07 g (= 94 % of theory); Melting point: 238-239°C.

8.3: scopine 2-fluoro-2,2-bis(4-fluorophenyl)-acetate-methobromide :

1.6 g (0.004 mol) of **4g** and 1.14 g (0.0079 mol) of 50% methylbromide solution are reacted analogously to Example 1, step 1.3. The crystals formed are suction filtered, washed with dichloromethane, dried and then recrystallised from acetonitrile.

5 Yield: 1.65 g of white crystals (=61 % of theory)

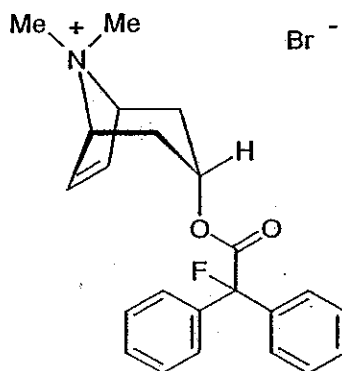
TLC: R_f value: 0.25 (eluant: according to Example 1, step 1.2);

Melting point: 213-214°C.

C₂₃H₂₃F₃NO₃xBr (498.34);

Elemental analysis: calculated: C (55.43) H (4.65) N (2.81)

10 found.: C (54.46) H (4.67) N (2.80).

Example 9: tropenol 2-fluoro-2,2-diphenylacetate-methobromide :**15 9.1.: Tropenol benzilate **5f**:**

Tropenol benzilate and processes for preparing it are known from WO 92/16528.

9.2: tropenol 2-fluoro-2,2-diphenylacetate **4h:**

15.86 ml (0.086 mol) of bis-(2-methoxyethyl)-aminosulphur trifluoride are reacted
 20 with 25 g (0.072 mol) of **5f** analogously to Example 4, step 4.3 in 480 ml of chloroform. The product is recrystallised from acetone in the form of its hydrochloride. Yield: 18.6 g of white crystals (= 67 % of theory);
 Melting point: 181-182°C;

25 9.3: tropenol 2-fluoro-2,2-diphenyl-acetate-methobromide :

11.12 g (0.032 mol) of **4h** and 18.23 g (0.096 mol) of 50% methylbromide solution are reacted analogously to Example 1, step 1.3. The crystals formed are recrystallised from acetonitrile.

Yield: 11.91 g of white crystals (=83 % of theory)

30 TLC: R_f value: 0.4 (eluant: according to Example 4, step 4.4);

Melting point: 238-239°C.

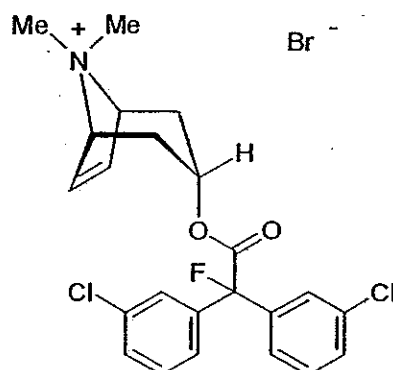
C₂₃H₂₅FNO₂xBr (446.36);

Elemental analysis: calculated: C (61.89) H (5.65) N (3.14)

found.: C (62.04) H (5.62) N (3.17).

Example 10: tropenol 2-fluoro-2,2-(3-chlorophenyl)acetate-methobromide :

5



10.1.: methyl 3,3'-dichlorobenzilate 3e:.

10.1.1.: 3,3'-dichlorobenzil:

100 ml of ethanol are used at ambient temperature and 50.0 g (0.356 mol) of
 10 3-chlorobenzaldehyde and 4.54 g (0.018 mol) of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide are added. Then 10.7 g (0.11 mol) of triethylamine are added dropwise. The mixture is refluxed for 3 hours and evaporated to dryness. The residue is taken up in ethyl acetate and extracted with water, sodium pyrosulphite in water and Na₂CO₃ solution. After drying over MgSO₄ it is evaporated to dryness. The
 15 product obtained is recrystallised from isopropanol and petroleum ether.

Yield: 13.2 g of white crystals (= 13% of theory); melting point: 69-70°C.

13.0 g of the acyloin thus obtained are dissolved in 460 ml acetonitrile at RT, 0.0867 g of vanadium-(V)-oxytrichloride are added and oxygen is piped in. After 1.5 h the
 20 solution is evaporated to dryness, extracted with ethyl acetate and water, as well as Na₂CO₃ solution, dried over MgSO₄ and evaporated to dryness. The residue remaining is stirred with petroleum ether/ethyl acetate 95:5.

Yield: 12.59 g of yellow crystals (= 97% of theory); melting point: 116-117°C.

25 10.1.2.: 3,3'-dichlorobenzilic acid:

51.45 g (1.286 mol) of sodium hydroxide in 1000 ml water are placed in a bath of boiling water with thorough stirring and a solution of 28.5 g (0.102 mol) of 3,3'-dichlorobenzil in 700 ml dioxane is added dropwise and then stirred for another 1 h. After cooling the dioxane is evaporated down, the residue is diluted with water and
 30 extracted with diethylether. The organic phase is acidified, extracted with dichloromethane, dried over MgSO₄, evaporated to dryness.

Yield: 32.7 g (= 71% of theory).

10.1.3.: methyl 3,3'-dichlorobenzilate:

From 100 ml of ethanol and 1.97 g (0.0855 mol) of sodium, a sodium ethoxide solution is prepared to which 26.6 g (0.0855 mol) of 3,3'-dichlorobenzilic acid in 50 ml of ethanol are added dropwise. The mixture is then stirred for 4 h at ambient temperature. After the solvent has been distilled off the residue is dissolved in 150 ml DMF and 24.27 g (0.171 mol) of methyl iodide are added dropwise, then stirred for another 24 h. While cooling with ice, 300 ml of water and 200 ml of diethylether are added dropwise, the phases are separated, the aqueous phase is extracted with diethylether, then the organic phases are washed with Na_2CO_3 solution and shaken with water till neutral. After drying over Na_2SO_4 the mixture is evaporated to dryness. Yield: 22.91 g of yellow oil (= 82% of theory).

10.2.: tropenol 3,3'-dichlorobenzilate 5g:

22.9 g (0.074 mol) of methyl 3,3'-dichlorobenzilate **3e**, 15.37 g (0.11 mol) of tropenol and 0.17 g of sodium are heated for 4 h as a melt over a bath of boiling water at 75 mbar with occasional shaking. After cooling the sodium residues are dissolved with acetonitrile, the solution is evaporated to dryness and the residue is extracted with dichloromethane/water. The organic phase is washed with water, dried over MgSO_4 and evaporated to dryness.

The product is recrystallised from acetonitrile in the form of its hydrochloride. Yield: 16.83 g of white crystals (= 50 % of theory);
melting point: 184-185°C.

10.3: tropenol 2-fluoro-2,2-bis(3-chlorophenyl)acetate 4i:

1.48 g (0.0067 mol) of bis-(2-methoxyethyl)-aminosulphur trifluoride are used in 10 ml of dichloromethane and within 20 minutes at 15°–20° C a solution of 2.09 g of **5g** in 65 ml of dichloromethane is added dropwise.

The mixture is stirred for 20 h at ambient temperature, cooled to 0° C and carefully combined with 80 ml of water with thorough stirring. The mixture is then carefully adjusted to pH 8 with aqueous NaHCO_3 solution, the organic phase is separated off, the aqueous phase is again extracted with dichloromethane, the combined organic phases are washed with water, dried over MgSO_4 and evaporated to dryness. The hydrochloride is precipitated and recrystallised from acetonitrile/diethylether.

Yield: 1.20 g of white crystals (= 53 % of theory)

Melting point: 136-137° C

10.4: tropenol 2-fluoro-2,2-bis(3-chlorophenyl)acetate-methobromide :

1.0 g (0.002 mol) of **4h** are reacted analogously to Example 1, step 1.3. The crystals formed are suction filtered, washed with dichloromethane, dried and then recrystallised from methanol/diethylether.

5 Yield: 0.82 g of white crystals (=80 % of theory)

TLC: R_f value: 0.14 (eluant: n-butanol/water/formic acid(conc.)/acetone/
dichloromethane 36:15:15:15:5); Melting point: 180-181°C.

C₂₃H₂₃Cl₂FO₂xBr (515.25).

10 As has been found, the compounds of general formula **1** are characterised by their versatility in therapeutic use. Particular mention should be made of those applications for which the compounds of formula **1** according to the invention are preferably used on the basis of their pharmaceutical activity as anticholinergic agents. These include, for example, the treatment of asthma or COPD (chronic
15 obstructive pulmonary disease). The compounds of general formula **1** may also be used to treat vagally induced sinus bradycardia and to treat heart rhythm disorders. In general, the compounds according to the invention may also be used to treat spasms, e.g. in the gastrointestinal tract, with therapeutic benefit. They may also be used in the treatment of spasms in the urinary tract and in menstrual disorders, for
20 example. Of the ranges of indications mentioned above, the treatment of asthma and COPD using the compounds of formula **1** according to the invention is of particular importance.

The compounds of general formula **1** may be used on their own or combined with
25 other active substances of formula **1** according to the invention.

The compounds of general formula **1** may optionally also be combined with other pharmacologically active substances. These include, in particular, betamimetics, antiallergic agents, PAF-antagonists, leukotriene-antagonists and corticosteroids and
30 combinations of these active substances.

Examples of betamimetics which may be used in conjunction with the compounds of formula **1** according to the invention include compounds selected from among bambuterol, bitolterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline,
35 ibuterol, pirbuterol, procaterol, reproterol, salmeterol, sulphonterol, terbutaline, tulobuterol, 4-hydroxy-7-[2-[[2-[[3-(2-phenylethoxy)propyl]sulphonyl]ethyl]-amino]ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-

hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino]ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluoromethylphenyl)-2-*tert.*-butylamino]ethanol and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(*tert.*-butylamino]ethanol, optionally in the form of their racemates, their enantiomers, their diastereomers, as well as optionally their pharmacologically acceptable acid addition salts and hydrates. It is particularly preferable to use, as betamimetics, active substances of this kind, combined with the compounds of formula 1 according to the invention, selected from among fenoterol, formoterol, salmeterol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino]ethanol, optionally in the form of their racemates, their enantiomers, their diastereomers, as well as optionally their pharmacologically acceptable acid addition salts and hydrates. Of the betamimetics mentioned above, the compounds formoterol and salmeterol, optionally in the form of their racemates, their enantiomers, their diastereomers, as well as optionally their pharmacologically acceptable acid addition salts and hydrates, are particularly important.

The acid addition salts of the betamimetics selected from among the hydrochloride, hydrobromide, sulphate, phosphate, fumarate, methanesulphonate and xinafoate are preferred according to the invention. In the case of salmeterol, the salts selected from among the hydrochloride, sulphate and xinafoate are particularly preferred, especially the sulphates and xinafoates. Of outstanding importance according to the invention are salmeterol $\times \frac{1}{2} \text{H}_2\text{SO}_4$ and salmeterol xinafoate. In the case of formoterol, the salts selected from among the hydrochloride, sulphate and fumarate are particularly preferred, especially the hydrochloride and fumarate. Of outstanding importance according to the invention is formoterol fumarate.

Within the scope of the present invention, the term corticosteroids, which may optionally be used in conjunction with the compounds of formula 1, denotes

compounds selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, GW 215864, KSR 592, ST-126 and dexamethasone. The preferred corticosteroids within the scope of the present invention are those selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide and dexamethasone, while budesonide, fluticasone, mometasone and ciclesonide, especially budesonide and fluticasone, are of particular importance. The term steroids may be used on its own, within the scope of the present patent application, instead of the term corticosteroids. Any reference to steroids within the scope of the present invention also includes a reference to salts or derivatives which may be formed from the steroids. Examples of possible salts or derivatives include: sodium salts, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates. The corticosteroids may optionally also be in the form of their hydrates.

15

Within the scope of the present invention, the term dopamine agonists, which may optionally be used in conjunction with the compounds of formula 1, denotes compounds selected from among bromocriptine, cabergolin, alpha-dihydroergocryptine, lisuride, pergolide, pramipexol, roxindol, ropinirol, talipexol, tergurid and viozan. It is preferable within the scope of the present invention to use, as combination partners with the compounds of formula 1, dopamine agonists selected from among pramipexol, talipexol and viozan, pramipexol being of particular importance. Any reference to the abovementioned dopamine agonists also includes, within the scope of the present invention, a reference to any pharmacologically acceptable acid addition salts and hydrates thereof which may exist. By the physiologically acceptable acid addition salts thereof which may be formed by the abovementioned dopamine agonists are meant, for example, pharmaceutically acceptable salts selected from among the salts of hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid.

30

Examples of antiallergic agents which may be used according to the invention as a combination with the compounds of formula 1 include epinastin, cetirizin, azelastin, fexofenadin, levocabastin, loratadine, mizolastin, ketotifen, emedastin, dimetinden, clemastine, bamipin, cexchloropheniramine, pheniramine, doxylamine, chlorphenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastin, desloratidine and meclizine. Preferred antiallergic agents which may be used within the scope of the present invention in combination with the compounds of formula 1 according to the invention are selected from among epinastin, cetirizin, azelastin,

35

fexofenadin, levocabastin, loratadine, ebastin, desloratidine and mizolastin, epinastin and desloratidine being particularly preferred. Any reference to the abovementioned antiallergic agents also includes, within the scope of the present invention, a reference to any pharmacologically acceptable acid addition salts thereof which may
5 exist.

The following are examples of PAF antagonists which may be used in conjunction with the compounds of formula 1 according to the invention:

4-(2-chlorophenyl)-9-methyl-2-[3(4-morpholinyl)-3-propanon-1-yl]-6H-

10 thieno-[3,2-f] [1,2,4]triazolo[4,3-a][1,4]diazepine,

6-(2-chlorophenyl)-8,9-dihydro-1-methyl-8-[(4-morpholinyl)carbonyl]-4H,7H-cyclopenta-[4,5]thieno-[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine.

If the compounds of formula 1 are used in conjunction with other active substances,
15 the combination with steroids or betamimetics is particularly preferred of all the categories of compounds mentioned above. Combinations with betamimetics, particularly betamimetics having a long-lasting activity, is of particular importance. The combination of the compounds of formula 1 according to the invention with salmeterol or formoterol is particularly preferred, whilst the combination with
20 formoterol is most preferred.

Suitable preparations for administering the compounds of formula 1 include tablets, capsules, suppositories, solutions, etc.

Of particular importance according to the invention (particularly when treating
25 asthma or COPD) is the administration of the compounds according to the invention by inhalation. The proportion of pharmaceutically active compound or compounds should be in the range from 0.05 to 90 % by weight; preferably 0.1 to 50 % by weight of the total composition. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as
30 calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

35

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers.

Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine,

- 5 cyclamate, glycerol or sugar and a flavour enhancer, e.g. a flavouring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

10

Solutions are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, optionally using emulsifiers and/or dispersants, whilst if water is used as the diluent, for example, optionally organic solvents may

- 15 optionally be used as solvating agents or dissolving aids, and transferred into injection vials or ampoules or infusion bottles.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert

- 20 carriers such as lactose or sorbitol and packing them into gelatine capsules.

Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

Excipients which may be used include, for example, water, pharmaceutically

acceptable organic solvents such as paraffins (e.g. petroleum fractions), vegetable

- 25 oils (e.g. groundnut or sesame oil), mono- or polyfunctional alcohols (e.g. ethanol or glycerol), carriers such as e.g. natural mineral powders (e.g. kaolins, clays, talc, chalk), synthetic mineral powders (e.g. highly dispersed silicic acid and silicates),

sugars (e.g. cane sugar, lactose and glucose), emulsifiers (e.g. lignin, spent sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g.

- 30 magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

In yet another aspect of the present invention, there is provided a use of a compound of general formula 1 as defined above as a medicament.

In still another aspect of the present invention, pharmaceutical preparations containing as active substance one or more compounds of general formula 1 as defined above or the physiologically acceptable salts thereof, optionally combined with conventional excipients and/or carriers.

28a

The preparations are administered by the usual methods, preferably by inhalation in the treatment of asthma or COPD. For oral administration the tablets may, of course, contain, apart from the abovementioned carriers, additives such as sodium
35 citrate, calcium carbonate and dicalcium phosphate together with various additives such as starch, preferably potato starch, gelatine and the like. Moreover, lubricants such as magnesium stearate, sodium lauryl sulphate and talc may be used at the same time for the tableting process. In the case of aqueous suspensions the active

substances may be combined with various flavour enhancers or colourings in addition to the excipients mentioned above.

The dosage of the compounds according to the invention is naturally greatly
 5 dependent on the route of administration and the complaint to be treated. When administered by inhalation the compounds of formula 1 are characterised by high efficacy even at doses in the μg range. The compounds of formula 1 can also be used effectively above the μg range. The dosage may then be in the gram range, for example. Particularly when administered by a method other than inhalation, the
 10 compounds according to the invention may be given in higher doses (in the range from 1 to 1000 mg, for example, although this does not imply any limitation).

The examples of formulations which follow illustrate the present invention without restricting its scope:

15

Examples of pharmaceutical formulations

A)	<u>Tablets</u>	<u>per tablet</u>
20	active substance	100 mg
	lactose	140 mg
	corn starch	240 mg
	polyvinylpyrrolidone	15 mg
	magnesium stearate	5 mg
25		500 mg

The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the
 30 remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B)	<u>Tablets</u>	<u>per tablet</u>
35	active substance	80 mg
	lactose	55 mg
	corn starch	190 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	15 mg
	sodium-carboxymethyl starch	23 mg

magnesium stearate

2 mg

 400 mg

The finely ground active substance, some of the corn starch, lactose,

5 microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

10

C) Ampoule solution

active substance 50 mg

sodium chloride 50 mg

15

water for inj. 5 ml

The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into
20 ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

D) Metering aerosol

25

Active substance 0.005

Sorbitan trioleate 0.1

Monofluorotrichloromethane and
difluorodichloromethane 2 : 3 ad 100

30 The suspension is transferred into a conventional aerosol container with a metering valve. Preferably, 50 µl of suspension are delivered per spray. The active substance may also be metered in higher doses if desired (e.g. 0.02 % by weight).

E) Solutions (in mg/100ml)

35

Active substance 333.3 mg

Formoterol fumarate 333.3 mg

Benzalkonium chloride 10.0 mg

EDTA 50.0 mg

HCl (1n)

ad pH 3.4

This solution may be prepared in the usual manner.

5 F)

Powder for inhalation

Active substance	6 µg
Formoterol fumarate	6 µg
Lactose monohydrate	ad 25 mg

10 The powder for inhalation is produced in the usual way by mixing the individual ingredients together.

G)

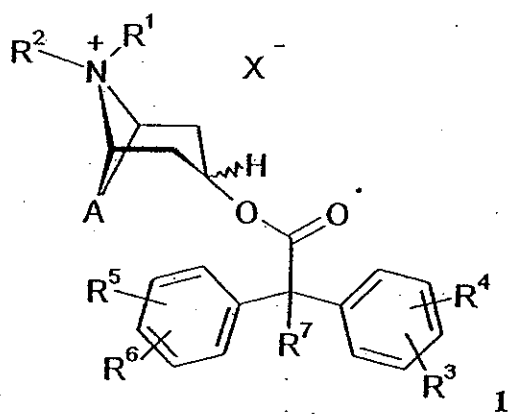
Powder for inhalation

Active substance	10 µg
Lactose monohydrate	ad 5 mg

The powder for inhalation is produced in the usual way by mixing the individual ingredients together.

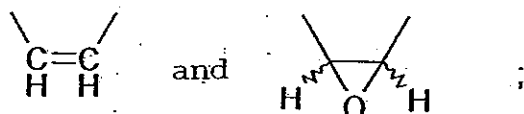
Patent Claims

1) Compounds of general formula 1



wherein

A denotes a double-bonded group selected from among



X⁻ denotes an anion with a single negative charge preferably selected from among chloride, bromide, methylsulphate, 4-toluenesulphonate and methanesulphonate;

R¹ and R² which may be identical or different denote a group selected from among methyl, ethyl, n-propyl and iso-propyl, which may optionally be substituted by hydroxy or fluorine;

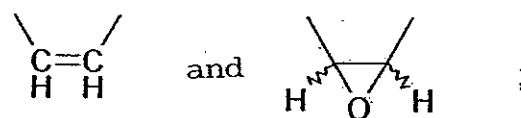
R³, R⁴, R⁵ and R⁶, which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine, bromine, CN, CF₃ or NO₂;

R⁷ denotes methyl, ethyl, methyloxy, ethyloxy, -CH₂-F, -CH₂-CH₂-F, -O-CH₂-F, -O-CH₂-CH₂-F, -CH₂-OH, -CH₂-CH₂-OH, CF₃, -CH₂-OMe, -CH₂-CH₂-OMe, -CH₂-OEt, -CH₂-CH₂-OEt, -O-COMe, -O-COEt, -O-COCF₃, -O-COCF₃, fluorine, chlorine or bromine, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

2) Compounds of general formula 1, according to claim 1,

wherein

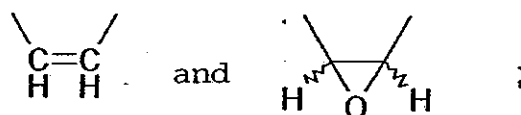
A denotes a double-bonded group selected from among



- X^- denotes an anion with a single negative charge selected from among chloride, bromide and methanesulphonate;
- R^1 and R^2 which may be identical or different denote a group selected from methyl and ethyl, which may optionally be substituted by hydroxy or fluorine;
- R^3 , R^4 , R^5 and R^6 , which may be identical or different, denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, hydroxy, fluorine, chlorine or bromine;
- R^7 denotes methyl, ethyl, methyloxy, ethyloxy, CF_3 or fluorine, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

3) Compounds of general formula 1, according to one of claims 1 or 2, wherein

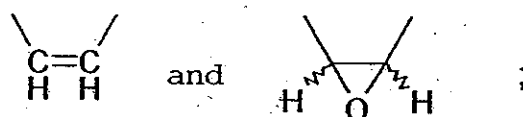
A denotes a double-bonded group selected from among



- X^- denotes bromide;
- R^1 and R^2 which may be identical or different denote a group selected from methyl and ethyl;
- R^3 , R^4 , R^5 and R^6 , which may be identical or different, denote hydrogen, methyl, methyloxy, chlorine or fluorine;
- R^7 denotes methyl or fluorine, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

4) Compounds of general formula 1, according to one of claims 1 to 3, wherein

A denotes a double-bonded group selected from among



- X^- denotes bromide;
- R^1 and R^2 which may be identical or different denote methyl or ethyl;

R^3 , R^4 , R^5 and R^6 , which may be identical or different, denote hydrogen or fluorine;

R^7 denotes methyl or fluorine, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates thereof.

5) Use of a compound of general formula 1 according to one of claims 1 to 4 as a medicament.

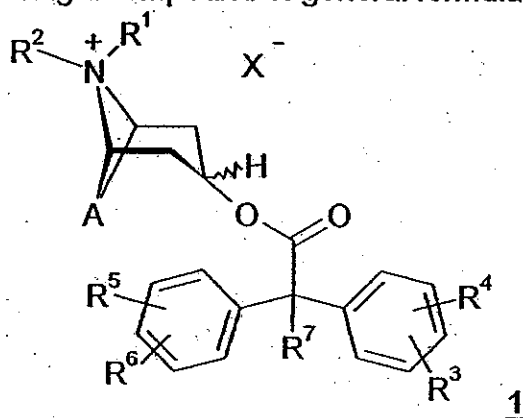
6) Use of a compound of general formula 1 according to one of claims 1 to 4 for preparing a medicament for the treatment of asthma, COPD, vagally induced sinus bradycardia, heart rhythm disorders, spasms in the gastrointestinal tract, spasms in the urinary tract and menstrual disorders.

7) Use of a compound of general formula 1 according to claim 6 for preparing a medicament for the treatment of asthma or COPD.

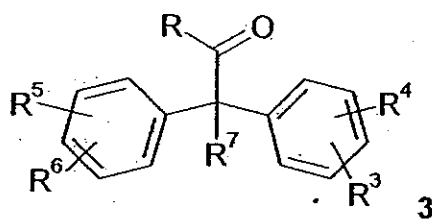
8) Pharmaceutical preparations containing as active substance one or more compounds of general formula 1 according to one of claims 1 to 4 or the physiologically acceptable salts thereof, optionally combined with conventional excipients and/or carriers.

9) Pharmaceutical preparations according to claim 8, characterised in that they contain, in addition to one or more of the compounds of formula 1, at least one further active substance which is selected from among the β -mimetics, antiallergic agents, PAF-antagonists, leukotriene-antagonists and steroids.

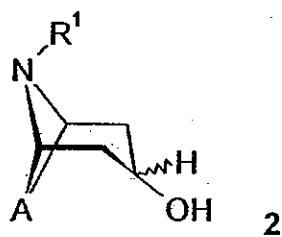
10) Process for preparing a compound of general formula 1



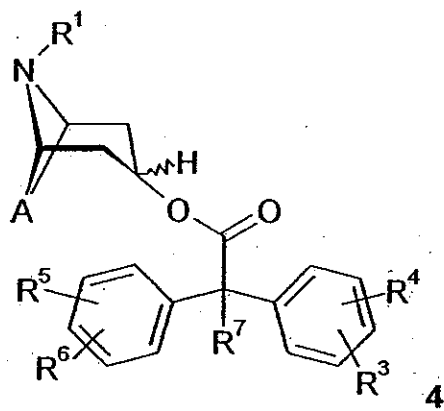
wherein A, X⁻ and the groups R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ may have the meanings given in claims 1 to 4, characterised in that in a first step a compound of general formula 3



wherein the groups R³, R⁴, R⁵, R⁶ and R⁷ may have the meanings given in claims 1 to 4 and R denotes chlorine or a C₁-C₄-alkyloxy, is reacted with a compound of formula 2



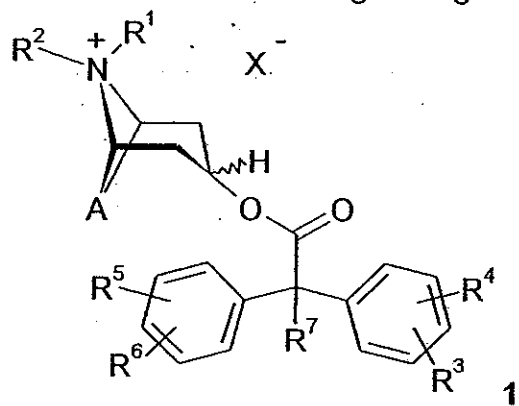
wherein A and R¹ may have the meanings given in claims 1 to 4, to obtain a compound of formula 4



wherein A and the groups R¹, R³, R⁴, R⁵, R⁶ and R⁷ may have the meanings given in claims 1 to 4, and this is then quaternised by reacting with a compound R²-X, wherein R² and X may have the meanings given in claims 1 to 4 to obtain a compound of formula 1.

Abstract

The present invention relates to new anticholinergics of general formula 1



- 5 wherein A, X⁻ and the groups R¹, R², R³, R⁴, R⁵, R⁶ and R⁷ may have the meanings given in the claims and in the specification, processes for preparing them and their use as pharmaceutical compositions.