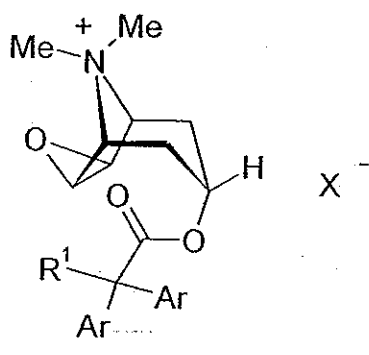


79863pri.210

Process for preparing scopine esters

The invention relates to a new process for preparing scopine esters of general formula 1



wherein X^- and the groups R^1 and Ar may have the meanings given in the claims and in the specification.

Background to the invention

Anticholinergics may appropriately be used to treat a number of diseases. Particular mention should be made, for example, of the treatment of asthma or COPD (chronic obstructive pulmonary disease). For treating these diseases WO 92/16528 proposes, for example, anticholinergics which have a scopine, tropenol or tropine basic structure.

The problem on which WO 92/16528 is based is the preparation of anticholinergically active compounds which are characterised by their long-lasting activity. To solve this problem WO 92/16528 discloses *inter alia* benzoic acid esters of scopine, tropenol or tropine.

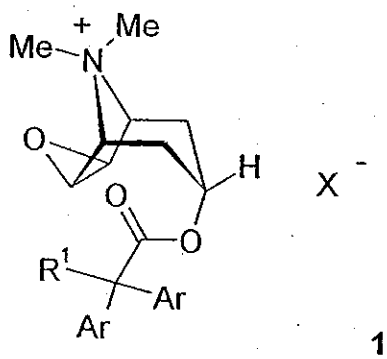
For treating chronic diseases it is often desirable to prepare pharmaceutical compositions with a longer-lasting effect. This will generally ensure that the concentration of the active substance needed to achieve the therapeutic effect is present in the body for a longer period of time without the need for the pharmaceutical composition to be administered repeatedly and all too frequently. Moreover, if an active substance is administered at longer intervals of time, this contributes to the feeling of well-being of the patient to a considerable degree. It is particularly desirable to provide a pharmaceutical composition which can be used to therapeutically good effect by administering it once a day (single dose). A single application per day has the advantage

that the patient can become accustomed relatively quickly to the regular taking of the medicament at a particular time of the day.

If it is to be used as a medicament for administration once a day, the active substance which is to be given must meet particular requirements. First of all, the desired onset of the activity after the administration of the pharmaceutical composition should occur relatively quickly and ideally the activity should remain as constant as possible over a fairly lengthy ensuing period. On the other hand the duration of activity of the pharmaceutical composition should not greatly exceed a period of about one day. Ideally, an active substance should have an activity profile such that the preparation of a pharmaceutical composition which is intended to be administered once a day and contains the active substance in therapeutically appropriate doses can be properly controlled.

It has been found that the esters of scopolamine, tropenol or tropine disclosed in WO 92/16528 do not meet these more stringent requirements. Because of their extremely long duration of activity, significantly exceeding the period of about one day specified above, they cannot be used therapeutically in a single once-a-day dose.

In contrast to the compounds disclosed in WO 92/16528, for example, it is possible to prepare anticholinergically active pharmaceutical compositions which can be administered once a day if scopolamine esters of formula 1



wherein X^- and the groups R^1 and Ar may have the meanings specified hereinafter are used.

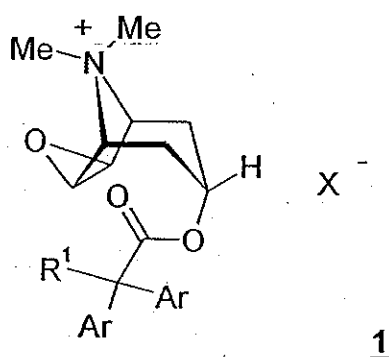
In addition to the methods of synthesis disclosed in WO 92/16528 for preparing scopolamine esters, processes for preparing esters of scopolamine are also disclosed in EP 418 716 A1, for example. These processes known in the art

may also be used to prepare the compounds of formula 1. However, these methods of synthesis are in some cases more complex procedures involving a number of synthesis steps.

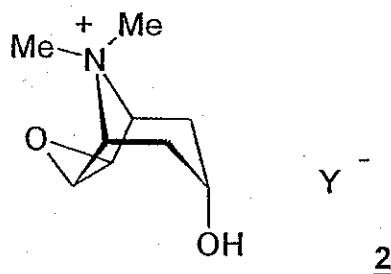
The aim of the present invention is to provide a method of synthesis which allows the compounds of general formula 1 to be synthesised more easily.

Detailed description of the invention

Surprisingly it has been found that compounds of formula 1

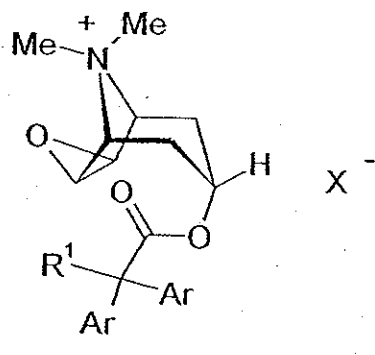


wherein X^- and the groups R^1 and Ar may have the meanings specified hereinafter, may be obtained in a single reaction step if compounds of formula 2



are used as starting material.

Accordingly, the present invention relates to a process for preparing compounds of formula 1



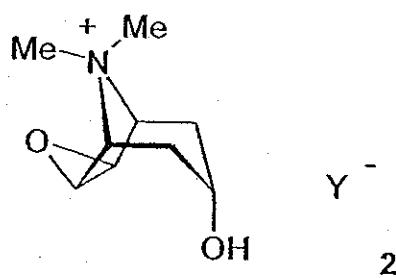
wherein

X^- may represent chlorine, bromine, iodine, methanesulphonate or trifluoromethanesulphonate;

R^1 may represent hydroxy, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, CF_3 or fluorine;

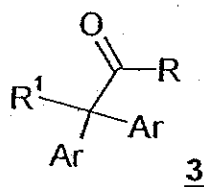
Ar may represent a group selected from among phenyl, naphthyl, thienyl and furyl, which may optionally be mono- or disubstituted by one or two groups selected from among C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, hydroxy, fluorine, chlorine, bromine or CF_3 .

characterised in that a compound of formula 2



wherein

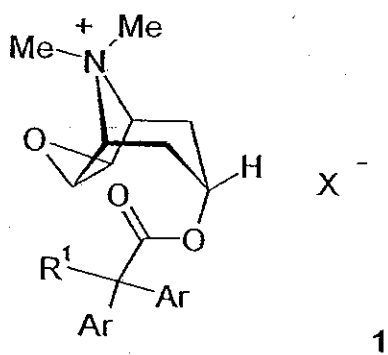
Y^- may denote chlorine, bromine, iodine, methanesulphonate or trifluoromethanesulphonate is reacted in one step with a compound of formula 3



wherein

R denotes a group selected from among hydroxy, methoxy, ethoxy, O-N-succinimide, O-N-phthalimide, phenyloxy, nitrophenyloxy, fluorophenyloxy, pentafluorophenyloxy, vinyloxy, 2-allyloxy, -S-methyl, -S-ethyl and -S-phenyl and
the groups R^1 and Ar may have one of the above meanings.

Preferably, the present invention relates to a process for preparing compounds of formula 1



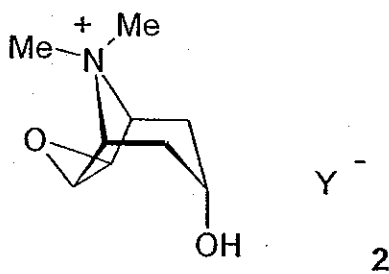
wherein

X^- may represent bromine, methanesulphonate or trifluoromethanesulphonate;

R^1 may represent hydroxy, methyl, CF_3 or fluorine;

Ar may represent a group selected from among phenyl, thienyl and furyl,

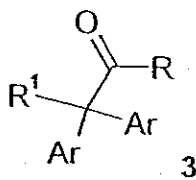
characterised in that a compound of formula 2



wherein

Y^- may denote bromine, methanesulphonate or trifluoromethanesulphonate

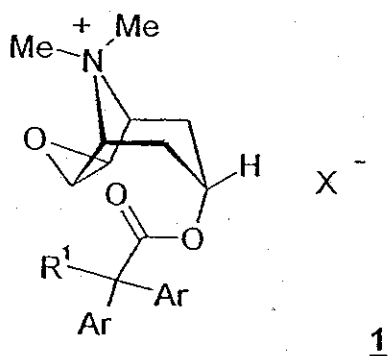
is reacted in one step with a compound of formula 3



wherein

R denotes a group selected from among hydroxy, O-N-succinimide, O-N-phthalimide, vinyloxy and 2-allyloxy and the groups R¹ and Ar may have one of the above meanings.

More preferably, the present invention relates to a process for preparing compounds of formula 1

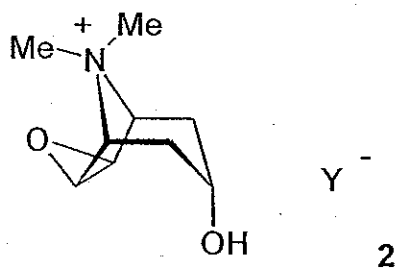


wherein

X⁻ may represent bromine, methanesulphonate or trifluoromethanesulphonate;

R¹ may represent hydroxy or methyl;

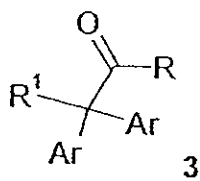
Ar may represent phenyl or thienyl,
characterised in that a compound of formula 2



wherein

Y⁻ may represent bromine, methanesulphonate or trifluoromethanesulphonate

is reacted in one step with a compound of formula 3



wherein

R denotes a group selected from among hydroxy, O-N-succinimide, O-N-phthalimide, vinyloxy and 2-allyloxy, preferably vinyloxy and 2-allyloxy, and

the groups R¹ and Ar may have one of the above meanings.

To perform the process according to the invention the following procedure may be used.

In a first step the compound of formula 3 is taken up in a suitable organic solvent, preferably in a polar organic solvent, most preferably in a solvent selected from among acetonitrile, nitromethane, formamide, dimethylformamide, N-methylpyrrolidinone, dimethylsulphoxide and dimethylacetamide, while of the abovementioned solvents dimethylformamide, N-methylpyrrolidinone and dimethylacetamide are particularly preferred. Of particular importance according to the invention are dimethylformamide and N-methylpyrrolidinone, the latter being particularly preferred.

Preferably, between 0.5 and 2 L, most preferably between 0.75 and 1.5 L of the abovementioned solvent are used per mol of the compound of formula 3 used.

Depending on the choice of the compound of formula 3 it may be useful in some cases to activate it before the reaction with the compound of formula 2. If derivatives wherein R = OH are used as the compound of formula 3, it is preferable according to the invention to use, for example, corresponding activating reagents such as carbonyldiimidazole, carbonyldi-1,2,4-triazole, dicyclohexylcarbodiimide or ethyl-dimethylaminopropylcarbodiimide, while in this context the use of carbonyldiimidazole is particularly preferred. Between 1 and 2 mol of the coupling reagent are used per mol of the compound 3 used wherein R=hydroxy. Preferably, 1 - 1.5 mol of the coupling reagent are used.

If the abovementioned coupling reagents are used, as is preferred when R = hydroxy, the reaction mixture then obtained is preferably stirred for a period of 1-8 hours, preferably 3-7 hours, at a temperature in the range from 15-35°C, preferably at 20-25°C, before further reaction as described hereinafter.

The reaction mixture of 3 in the abovementioned solvent, optionally after the addition of one of the abovementioned coupling reagents in the case of R = hydroxy, is then adjusted to a temperature below 30°C, preferably to a temperature between -20°C and 20°C, most preferably to a temperature between -10°C and 5°C, and the compound of formula 2 is added thereto. Based on the compound 3 originally used, stoichiometric amounts of the compound of formula 2 may be added. However, it is preferable according to the invention for 3 to be present in excess in relation to 2. According to the invention, between 0.5 and 1 mol, preferably between 0.7 and 0.95 mol, most preferably between 0.75 and 0.9 mol of 2 are used per mol of the compound 3 used.

The reaction mixture mentioned above is then combined with a suitable base dissolved in one of the abovementioned solvents. Organic or inorganic bases may be used. Preferably, alkali metal imidazolides are used as the organic bases, which may be generated *in situ* from the alkali metals and imidazole or the alkali metal hydrides and imidazole, for example. Preferred alkali metal imidazolides include imidazolides of lithium, sodium or potassium, while sodium or lithium imidazolidate are preferred according to the invention. Most preferably, lithium imidazolidate is used. Preferred inorganic bases are hydrides of lithium, sodium or potassium. Most preferably, sodium hydride is used as the inorganic base. Of all the abovementioned bases, lithium imidazolidate is most preferably used.

If the intention is to prepare compounds of formula 1 wherein R¹ denotes hydroxy, instead of the abovementioned base-catalysed reaction, transesterification under milder reaction conditions may also appear advantageous. Zeolites may advantageously be used as catalysts.

If the reaction is carried out with one of the abovementioned bases, at least stoichiometric quantities of base are used per mol of compound 2 used. Preferably, 1 to 1.5 mol, preferably 1.1 to 1.3 mol of base are used per mol of compound 2 used. If the base is added in the form of a solution, as is the case

particularly with the base lithium imidazolid preferred according to the invention which is generated *in situ* beforehand, it is preferable to use for this purpose the solvent which is already being used to carry out the steps mentioned above. Preferably between 0.3 and 1.3 L, most preferably between 0.5 and 1 L of the abovementioned solvent are used per mol of the base used. Once all the base has been added the mixture is stirred for a period of 4-48 hours, preferably 8-36 hours, in a temperature range from 15-35°C, preferably at 20-25°C.

An acid H-X is added to the resulting suspension at constant temperature. The choice of acid depends on the anion X^- in the desired end product of general formula 1. Insofar as compounds of general formula 1 wherein X^- denotes bromide are preferably synthesised within the scope of the present invention, the following procedure is described for the preparation of the bromide-containing end products of formula 1 which are preferred according to the invention. It will be apparent to the skilled man that by a suitable choice of the reagent H-X a corresponding procedure can also be used analogously to prepare compounds wherein X^- does not denote bromide.

In order to prepare compounds of formula 1 wherein X^- = bromide, preferably 2 to 4 mol, more preferably 2 to 3 mol, most preferably 2.2 to 2.6 mol of hydrogen bromide, based on the compound of formula 3 used, are added at constant temperature. The hydrogen bromide used may be added either in gaseous form or in the form of preferably saturated solutions. Preferably, according to the invention, the hydrogen bromide is added after being dissolved in glacial acetic acid. Most preferably, a 33% hydrogen bromide solution in glacial acetic acid is used. After the addition has ended the mixture is stirred at constant temperature, possibly also while cooling with ice (between 0.5 and 6 hours).

Finally, the solution obtained is combined with a non-polar organic solvent, preferably with a solvent selected from among acetone, toluene, n-butyl acetate, dichloromethane, diethyl ether, tetrahydrofuran and dioxane, most preferably toluene or acetone.

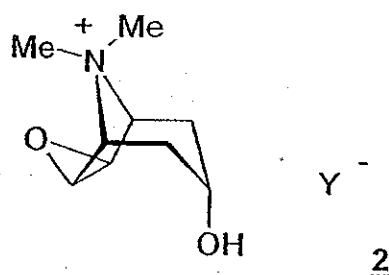
After thorough mixing the product that crystallises out is separated off and washed with the non-polar solvent mentioned above. In order to remove any

water-soluble impurities, the crude product may be treated with aqueous bromide solutions, e.g. sodium or potassium bromide solution.

Further purification of the compounds of formula 1 thus obtained may, if necessary, be carried out by chromatography over silica gel or by recrystallisation from suitable solvents such as e.g. lower alcohols, for example isopropanol.

By using the compounds of formula 2, which are known in the prior art, as starting materials for synthesising the structures of formula 1, these anticholinergically active structures may be obtained in only one reaction step.

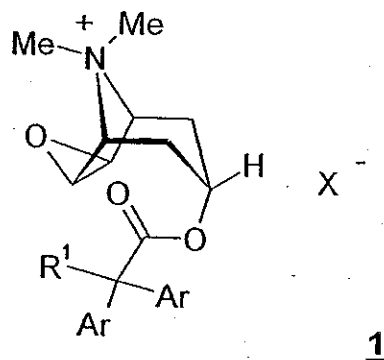
Accordingly, in another aspect, the present invention relates to the use of compounds of formula 2



wherein

Y^- denotes chlorine, bromine, iodine, methanesulphonate or trifluoromethanesulphonate,

as starting materials for preparing compounds of formula 1



wherein

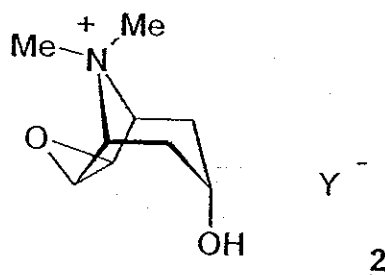
X^- may represent chlorine, bromine, iodine, methanesulphonate or trifluoromethanesulphonate;

R^1 may represent hydroxy, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, CF_3 or fluorine;

Ar may represent a group selected from among phenyl, naphthyl, thienyl and furyl, which may optionally be mono- or disubstituted by one or two groups selected from among C₁-C₄-alkyl, C₁-C₄-alkoxy, hydroxy, fluorine, chlorine, bromine or CF₃.

Preferably, the present invention relates to the use of compounds of formula

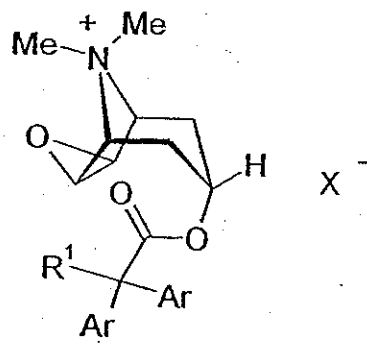
2



wherein

Y⁻ denotes bromine, methanesulphonate or trifluoromethanesulphonate,

as starting materials for preparing compounds of formula 1



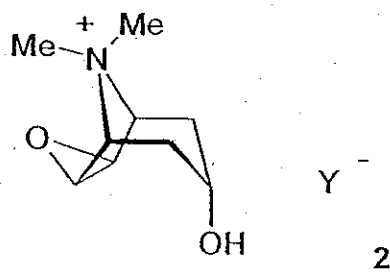
wherein

X⁻ may represent bromine, methanesulphonate or trifluoromethanesulphonate;

R¹ may represent hydroxy, methyl, CF₃ or fluorine;

Ar may represent a group selected from among phenyl, thienyl and furyl.

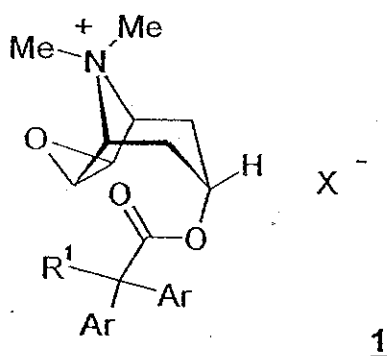
Most preferably, the present invention relates to the use of compounds of formula 2



wherein

Y^- denotes bromine, methanesulphonate or trifluoromethanesulphonate

as starting materials for preparing compounds of formula 1



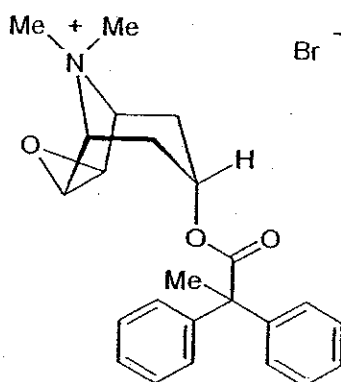
wherein

X^- may represent bromine, methanesulphonate or trifluoromethanesulphonate;

R^1 may represent hydroxy or methyl;

Ar may represent phenyl or thienyl.

The Examples that follow serve to illustrate some methods of synthesis carried out by way of example. They are intended solely as examples of possible procedures without restricting the invention to their content.

Example 1: 2,2-Diphenylpropionic acid scopine ester-methobromide:

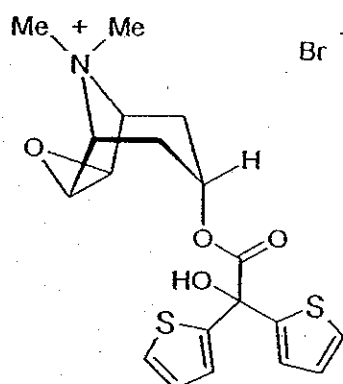
Carbonyldiimidazole (1206 g, 7.44 mol) is added batchwise to a solution of 2,2-diphenylpropionic acid (1629 g, 7.2 mol) in N-methylpyrrolidinone (9 L) and then stirred for 5 hours at ambient temperature (about 23°C). The reaction mixture is cooled to -3°C. Scopine methobromide (1501g, 6.0 mol) is added to the reaction mixture. Then a solution of lithium imidazolidine (prepared from lithium hydride (59.6g; 7.12 mol) as well as imidazole (490.2 g, 7.2 mol) in 5 L of N-methylpyrrolidinone is added dropwise. It is stirred for 17 hours at ambient temperature. Hydrogen bromide solution (33% in glacial acetic acid; 2460 ml, 14.25 mol) is added to the resulting suspension at 18-28°C with cooling. The suspension is stirred in the ice bath and then combined with toluene (14 L). It is filtered and the filter cake obtained is suspended twice with 5500 ml of 30% potassium bromide solution and suction filtered. The substance thus obtained is dried in the drying cupboard at 40°C. Yield: 2359.3 g = 85.8 % of theory.

To purify it, the crude product (2100 g) is recrystallised from 35.7 L of isopropanol.

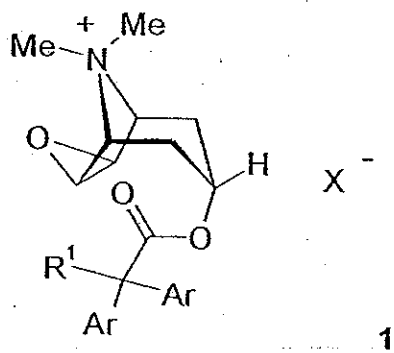
Yield: 1562.2 g; colourless flakes.

The following may be obtained analogously in a single synthesis step:

Example 2: (1 α ,2 β ,4 β ,5 α ,7 β)-7-[(hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.0^{2,4}]nonane-bromide

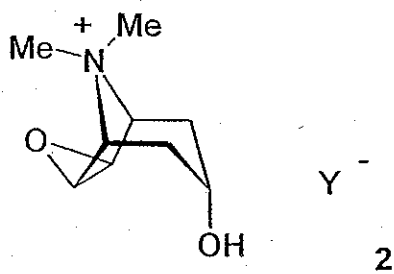


Patent Claims

1) Process for preparing compounds of formula 1

wherein

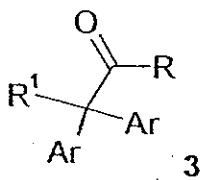
- X^- may represent chlorine, bromine, iodine, methanesulphonate or trifluoromethanesulphonate;
- R^1 may represent hydroxy, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, CF_3 or fluorine;
- Ar may represent a group selected from among phenyl, naphthyl, thienyl and furyl, which may optionally be mono- or disubstituted by one or two groups selected from among C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, hydroxy, fluorine, chlorine, bromine or CF_3 ,

characterised in that a compound of formula 2

wherein

- Y^- may represent chlorine, bromine, iodine, methanesulphonate or trifluoromethanesulphonate,

is reacted in one step with a compound of formula 3



wherein

R denotes a group selected from among hydroxy, methoxy, ethoxy, O-N-succinimide, O-N-phthalimide, phenyloxy, nitrophenyloxy, fluorophenyloxy, pentafluorophenyloxy, vinyloxy, 2-allyloxy, -S-methyl, -S-ethyl and -S-phenyl and

the groups R¹ and Ar may have one of the above meanings.

2) Process according to claim 1, for preparing compounds of formula 1 wherein

X - may represent bromine, methanesulphonate or trifluoromethanesulphonate;

R¹ may represent hydroxy, methyl, CF₃ or fluorine;

Ar may represent a group selected from among phenyl, thienyl and furyl,

characterised in that a compound of formula 2, wherein

Y - may represent bromine, methanesulphonate or trifluoromethanesulphonate,

is reacted in one step with a compound of formula 3, wherein

R denotes a group selected from among hydroxy, O-N-succinimide, O-N-phthalimide, vinyloxy and 2-allyloxy and

the groups R¹ and Ar may have one of the above meanings.

3) Process according to claim 1 or 2 for preparing a compound of formula 1, wherein

X - may represent bromine, methanesulphonate or trifluoromethanesulphonate;

R¹ may represent hydroxy or methyl;

Ar may represent phenyl or thienyl,

characterised in that a compound of formula 2, wherein

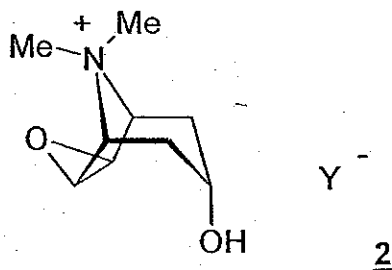
Y - may represent bromine, methanesulphonate or trifluoromethanesulphonate,

is reacted in one step with a compound of formula 3, wherein

R denotes a group selected from among hydroxy, O-N-succinimide, O-N-phthalimide, vinyloxy and 2-allyloxy, preferably vinyloxy and 2-allyloxy, and

the groups R¹ and Ar may have one of the above meanings.

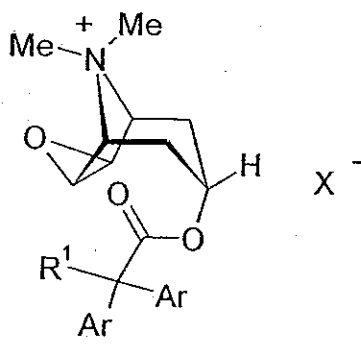
- 4) Process according to one of claims 1 to 3, characterised in that the reaction is carried out in an organic solvent selected from among acetonitrile, nitromethane, formamide, dimethylformamide, N-methylpyrrolidinone, dimethylsulphoxide and dimethylacetamide.
- 5) Process according to one of claims 1 to 4, characterised in that when a compound of formula 3 is used in which R denotes =OH, activating reagents selected from among carbonyldiimidazole, carbonyldi-1,2,4-triazole, dicyclohexyl carbodiimide and ethyldimethylaminopropyl carbodiimide are used.
- 6) Process according to one of claims 1 to 5, characterised in that the reaction is carried out at a temperature below 30°C, preferably at a temperature between -20°C and 20°C.
- 7) Process according to one of claims 1 to 6, characterised in that the reaction is carried out in the presence of an organic or inorganic base.
- 8) Process according to one of claims 1 to 6, characterised in that if R¹ denotes hydroxy in the compounds of formula 1, the reaction is carried out in the presence of zeolites as catalyst.
- 9) Use of a compound of formula 2



wherein

Y^- denotes chlorine, bromine, iodine, methanesulphonate or trifluoromethanesulphonate,

as a starting material for preparing compounds of formula 1



wherein

X^- may represent chlorine, bromine, iodine, methanesulphonate or trifluoromethanesulphonate;

R^1 may represent hydroxy, C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, CF_3 or fluorine;

Ar may represent a group selected from among phenyl, naphthyl, thienyl and furyl, which may optionally be mono- or disubstituted by one or two groups selected from among C_1 - C_4 -alkyl, C_1 - C_4 -alkoxy, hydroxy, fluorine, chlorine, bromine or CF_3 .