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Process for preparing enantiomerically pure  
tropic acid esters

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The invention relates to a process by which esters of (+)- and (-)-tropic acid can be prepared with a high degree of purity and in good yields.

10 The problem of synthetically producing enantiomerically pure esters of (+)- and (-)-tropic acid has not hitherto been solved with any degree of satisfaction. The enantiomeric separation of racemic tropic acid esters also frequently comes up against surprising experimental  
15 problems and cannot generally be carried out. This applies particularly to the higher substituted homologues and analogues of atropine, such as N-isopropylnoratropine, the precursor of the commercial product ipratropium bromide.

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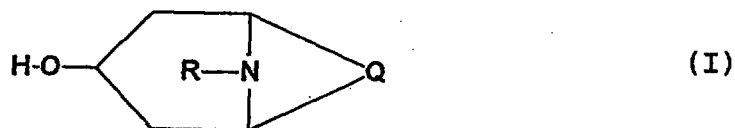
The conventional synthesis of tropic acid esters according to I. Mamlock and R. Wolffenstein (Ber. dtsh. Chem. Ges. 41, 731 (1908)), in which O-acetyltropic acid chloride is reacted with tropine hydrochloride does not  
25 produce satisfactory results, possibly on account of the poor solubility of tropine hydrochloride. The method has not been used for optically active tropic acid.

30

The process is problematic because side reactions can easily occur. This is true of basic conditions, with which there is a danger that water is eliminated, whilst on the other hand the use of salts of the amino alcohols, which are usually poorly soluble, requires elevated temperatures which can lead to the formation of  
35 highly disruptive by-products; mention should be made particularly of dehydrated compounds (apocompounds) and dimerisation products.

It has now been found that enantiomerically pure (+)- and (-)-tropic acid esters of amino alcohols of the formula

5



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wherein

Q denotes  $\text{CH}_2\text{-CH}_2$ ,  $\text{CH}_2\text{-CH}_2\text{-CH}_2$ ,  $\text{CH=CH}$  or

$\begin{array}{c} \text{CH} - \text{CH} \\ \diagdown \quad \diagup \\ \text{O} \end{array}$

15

R denotes a straight-chained or branched  $\text{C}_{1-4}$ -alkyl group,

can surprisingly be prepared by

20

(a) acetylating the corresponding optically active tropic acid,

(b) converting the resulting O-acetyl tropic acid with thionyl chloride into the acid chloride,

25

(c) reacting the latter at ambient temperature in an inert solvent, optionally with the addition of excess aluminium oxide, with the methanesulphonate of an amino alcohol of formula I,

30

(d) deacetylating the resulting compound by the action of a strong acid and

35

(e) isolating the optically active tropic acid ester obtained.

The (+)- and (-)-tropic acid required as starting material can be obtained from D,L-tropic acid by first



preparing a salt with an optically active base in a manner known *per se* and recrystallising this salt several times. A suitable base might be, for example, (-)-quinine whilst the solvent for crystallisation might be ethanol. The (+)-tropic acid thus prepared has a  
5     purity of 99.8% ( $[\alpha]_D^{20} = +73.1$ ;  $c = 1$  in ethanol).

The reaction according to (a) is preferably carried out at ambient temperature and the reaction according to (b)  
10     which is carried out immediately afterwards is preferably performed without intermediate isolation of the acetylated acid at ambient temperature or slightly elevated temperature.

15     Step (c) takes place within a few days, when the methanesulphonate of a compound of formula (I) is reacted in an inert solvent, such as methylene chloride, at temperatures between 0°C and about 30°C, preferably at ambient temperature, with stirring, whilst excess  
20     aluminium oxide may be used to bind the acid. Once the solvent has been eliminated under reduced pressure, the residue can be further processed directly.

In step (d), favourable results are obtained if the  
25     deacetylation is carried out with a dilute aqueous inorganic acid, such as 2 - 20% hydrochloric acid, preferably 3 - 10% hydrochloric acid, at ambient temperature. Thus, for example, total reaction is obtained with 5% hydrochloric acid within about 2 days.

30     The reaction product can be isolated as a base (step (e)) by stirring the acidic reaction solution into excess dilute (e.g. 20%) sodium hydroxide solution or into aqueous alkali metal carbonate solution and  
35     filtering off the crystalline product precipitated. Temperatures of between -15 and +50°C may be used; it is preferable to use sodium carbonate solution at about



20°C. The salts, e.g. the corresponding hydrochloride, can easily be prepared from the base by adding a stoichometric quantity of ethereal hydrochloric acid to the solution of the base, e.g. in methylene chloride.

5

The esters obtained in this way consist of more than 99% of the pure optically active compound, assuming that the starting acid is correspondingly pure.

10 The optically active esters which may be obtained according to the invention are valuable intermediate products for producing the corresponding anticholinergic quaternary compounds, such as the corresponding methobromides or methomethanesulphonates, which may be  
15 used, for example, as agents for treating asthmatic diseases or obstructive diseases of the respiratory tract.

The quaternary compounds may be prepared by conventional  
20 methods without racemisation.

The reaction according to the invention is explained more fully in the Examples which follow, but the reaction conditions according to the invention are not  
25 limited to the specific data provided.

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Example 1

(-)-Tropic acid-N-isopropyl-nortropine ester  
hydrochloride

5 (a) 13.3 g of (-)-Tropic acid are added to 31.4 g of  
acetyl chloride with stirring and at ambient temperature  
and within one hour a clear solution is formed. After  
another hour, the reaction is virtually complete,  
according to thin layer chromatography (TLC). 47.5 g of  
10 thionyl chloride are added dropwise to the (-)-O-acetyl  
tropic acid solution over 30 minutes. The solution is  
stirred overnight at ambient temperature, then for a  
further hour at 50°C. After evaporation at 35°C under  
reduced pressure, 18.9 g of a brownish liquid remain,  
15  $[\alpha]_D^{20} = -87.8$  (c = 0.5 in chloroform). The presence of  
the desired compound can be confirmed by spectroscopy.

(b) 7.26 g (0.0275 mol) of N-isopropyl-nortropine  
methanesulphonate and 6.20 g (0.0275 mol) of the product  
20 obtained in (a) are stirred in 45 ml of methylene  
chloride at ambient temperature. After seven days the  
reaction solution is evaporated down under reduced  
pressure at 30°C. The residue (16.9 g) is used for the  
next step without being further worked up.

25 (c) 11.1 g of the product according to (b) are  
dissolved in 60 ml of 5% hydrochloric acid and stirred  
for 2 days at ambient temperature. TLC indicates  
quantitative deacetylation.

30 The reaction solution is extracted twice with a little  
diethylether, then any residual ether is eliminated  
under reduced pressure. Excess 20% aqueous sodium  
carbonate solution is then stirred into the solution,  
and a crystalline product is precipitated. It is  
35 filtered off and washed with cold water until the  
filtrate running away shows only a slightly alkaline  
reaction, and is then dissolved in methylene chloride.

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After drying over sodium sulphate, the solvent is distilled off under reduced pressure and the residue is recrystallised from acetonitrile. White crystals are obtained, m.p. 131°C,  $[\alpha]_D^{20} = -19.1$  (c=1 in ethanol).

5 In order to prepare the hydrochloride, the solution of the base in methylene chloride is combined with the stoichiometric amount of ethereal hydrochloric acid. After the product has been recrystallised from ethanol and acetonitrile, the (-)-tropic acid-N-isopropyl-nortropine ester hydrochloride is obtained in the form of white crystals, m.p. 214-8°C.

10  $[\alpha]_D^{20} = -27.8$  (c=1 in water); optical purity >99.8%. The presence of the compound was confirmed by elemental analysis and spectroscopy.

15 Quaternisation to obtain the methobromide is carried out, for example, by reacting with methyl bromide in methylene chloride/acetonitrile at ambient temperature. White crystals are obtained (yield 75.2% of theory, m.p. 238-42°C with decomposition).

20  $[\alpha]_D^{20} = -24.5$  (c = 1 in water); optical purity >99.5%. The presence of the compound was confirmed by elemental analysis and spectroscopy.

## 25 Example 2

### (+)-Tropic acid-N-isopropyl-nortropine ester-hydrochloride

Starting from (+)-tropic acid, which may be obtained by racemate cleaving from D,L-tropic acid with (-)-quinine, 30  $[\alpha] = +73.1$  (c = 1 in ethanol; optical purity 99.8%), the title compound is obtained analogously to Example 1 in the form of white crystals, m.p. 214-7°C, with decomposition,  $[\alpha]_D^{20} = +27.8$  (c = 1 in water). Yield 35 55.7% of theory. Once again, the presence of the compound is confirmed by elemental analysis and spectroscopy.

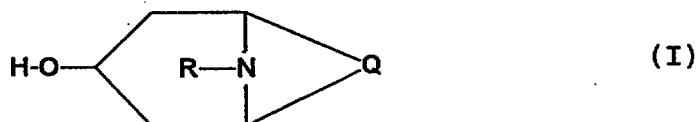
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As described in Example 1, the compound obtained is reacted to form the methobromide; m.p. 238-41°C (decomp.),  $[\alpha]_D^{20} = +25.3$  (c = 1 in water).

- 5 For reacting the O-acetyltropic acid chlorides with the compounds (I), yields of between 60 and 70% are obtained if the reactions continue at room temperature for several days, and in addition to methylene chloride, for example, dimethylformamide or acetonitrile as reaction
- 10 medium will give similar results.

Claims

1. Process for preparing enantiomerically pure (+)-  
and (-)-tropic acid esters of amino alcohols of the  
5 formula



wherein

Q denotes  $\text{CH}_2\text{-CH}_2$ ,  $\text{CH}_2\text{-CH}_2\text{-CH}_2$ ,  $\text{CH=CH}$  or  
15  $\begin{array}{c} \text{CH} - \text{CH} \\ \diagdown \quad \diagup \\ \text{O} \end{array}$

R denotes a straight-chained or branched  $\text{C}_{1-4}$ -alkyl  
group,

20 characterised in that

- (a) the corresponding optically active tropic acid is acetylated,
- (b) the resulting O-acetyltropic acid is converted with  
25 thionyl chloride into the acid chloride,
- (c) the latter is reacted at ambient temperature in an inert solvent with the methanesulphonate of an amino alcohol of formula (I),
- (d) the resulting compound is deacetylated by the  
30 action of a strong acid and
- (e) the resulting optically active tropic acid ester is isolated.

2. Process according to claim 1 (c), characterised in  
35 that the reaction is carried out in the presence of excess aluminium oxide.

3. Process according to claim 1 (e), characterised in



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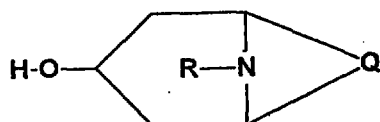
that the optically active tropic acid ester is precipitated from the acid solution using aqueous sodium carbonate solution.

- 5      4.    Process according to claims 1 to 3, characterised in that N-isopropyl nortropine methanesulphonate is used as the compound of formula (I).

Abstract

Precursors of anticholinergically active quaternary  
compounds can be synthesised from optically active  
5 tropic acid by acetylation, conversion into the acid  
chloride, reaction with amino alcohols of formula (I)

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(I)

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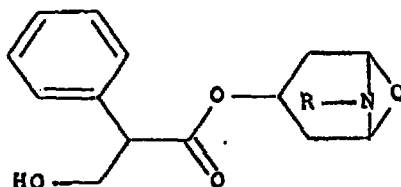
(as the methanesulphonate; Q and R are explained in the  
specification), deacetylation and isolation of the  
reaction product.

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It has now been found that enantiomerically pure (+)- and (-)-tropic acid esters of amino alcohols of formula II,



(II)

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5  
10 wherein

Q denotes  $\text{CH}_2\text{-CH}_2$ ,  $\text{CH}_2\text{-CH}_2\text{-CH}_2$ ,  $\text{CH=CH}$  or  $\text{CH}-\text{CH}$ ,  
O

15 R denotes a straight-chained or branched  $\text{C}_{1-4}$ -alkyl group,

can surprisingly be prepared by

- 20 (a) acetylating the corresponding optically active tropic acid ( $\text{HOCH}_2\text{-C}_h^*\text{-COOH}$ ),
- (b) converting the resulting O-acetyl tropic acid with thionyl chloride into the acid chloride,
- 25 (c) reacting the latter at ambient temperature in an inert solvent, optionally with the addition of excess aluminium oxide, with the methanesulphonate of an amino alcohol of formula I,



(I),

30  
35 wherein R and Q are as defined above

- (d) deacetylating the resulting compound by the action of a strong acid and

(e) isolating the optically active tropic acid ester obtained.

5 The (+)- and (-)-tropic acid required as starting material can be obtained from D,L-tropic acid by first preparing a salt with an optically active base in a manner known *per se* and recrystallising this salt several times. A suitable base might be, for example, (-)-quinine whilst the solvent for crystallisation might  
10 be ethanol. The (+)-tropic acid thus prepared has a purity of 99.8% ( $[\alpha]_D^{20} = +73.1$ ;  $c = 1$  in ethanol).

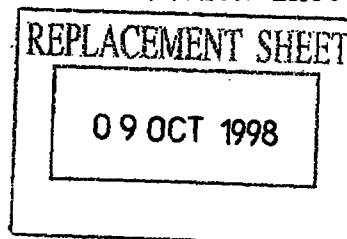
The reaction according to (a) is preferably carried out at ambient temperature and the reaction according to (b)  
15 which is carried out immediately afterwards is preferably performed without intermediate isolation of the acetylated acid at ambient temperature or slightly elevated temperature.

20 Step (c) takes place within a few days, when the methanesulphonate of a compound of formula (I) is reacted in an inert solvent, such as methylene chloride, at temperatures between 0°C and about 30°C, preferably at ambient temperature, with stirring, whilst excess  
25 aluminium oxide may be used to bind the acid. Once the solvent has been eliminated under reduced pressure, the residue can be further processed directly.

In step (d), favourable results are obtained if the  
30 deacetylation is carried out with a dilute aqueous inorganic acid, such as 2 - 20% hydrochloric acid, preferably 3 - 10% hydrochloric acid, at ambient temperature. Thus, for example, total reaction is obtained with 5% hydrochloric acid within about 2 days.

35

The reaction product can be isolated as a base (step (e)) by stirring the acidic reaction solution into



excess dilute (e.g. 20%) sodium hydroxide solution or into aqueous alkali metal carbonate solution and filtering off the crystalline product precipitated. Temperatures of between -15 and +50°C may be used; it is  
5 preferable to use sodium carbonate solution at about 20°C. The salts, e.g. the corresponding hydrochloride, can easily be prepared from the base by adding a stoichiometric quantity of ethereal hydrochloric acid to the solution of the base, e.g. in methylene chloride.

10

The esters obtained in this way consist of more than 99% of the pure optically active compound, assuming that the starting acid is correspondingly pure.

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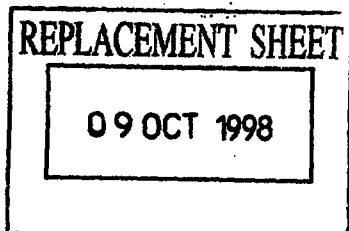
The optically active esters which may be obtained according to the invention are valuable intermediate products for producing the corresponding anticholinergic quaternary compounds, such as the corresponding methobromides or methomethanesulphonates, which may be  
20 used, for example, as agents for treating asthmatic diseases or obstructive diseases of the respiratory tract.

25

The quaternary compounds may be prepared by conventional methods without racemisation.

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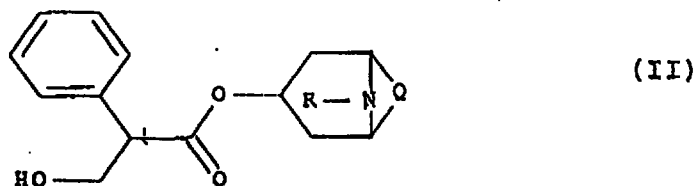
The reaction according to the invention is explained more fully in the Examples which follow, but the reaction conditions according to the invention are not limited to the specific data provided.





Claims

1. Process for preparing enantiomerically pure (+)-  
and (-)-tropic acid esters of amino alcohols of formula  
II,



wherein

Q denotes  $\text{CH}_2\text{-CH}_2$ ,  $\text{CH}_2\text{-CH}_2\text{-CH}_2$ ,  $\text{CH=CH}$  or  
 $\text{CH - CH}$ ,  
O

R denotes a straight-chained or branched  $\text{C}_{1-4}$ -alkyl  
group,

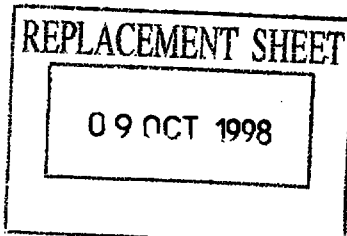
characterised in that

- (a) the corresponding optically active tropic acid is acetylated,
- (b) the resulting O-acetyltropic acid is converted with  
thionyl chloride into the acid chloride,
- (c) the latter is reacted at ambient temperature in an  
inert solvent with the methanesulphonate of an  
amino alcohol of formula (I),



wherein R and Q are as defined above

- (d) the resulting compound is deacetylated by the  
action of a strong acid and





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(e) the resulting optically active tropic acid ester is isolated.

5 2. Process according to claim 1 (c), characterised in that the reaction is carried out in the presence of excess aluminium oxide.

10 3. Process according to claim 1 (e), characterised in that the optically active tropic acid ester is precipitated from the acid solution using aqueous sodium carbonate solution.

15 4. Process according to claims 1 to 3, characterised in that N-isopropyl nortropine methanesulphonate is used as the compound of formula (I).

5. Process according to any one of claims 1 to 4 substantially as hereinbefore described.

