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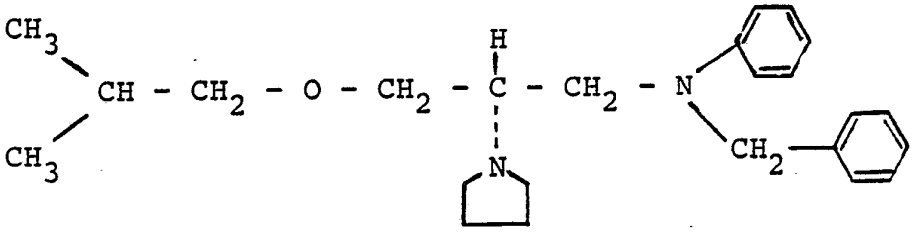
(54) Title: ETHER OF N-PROPANOLAMINE DERIVATIVE

(I)



(57) Abstract

S-(levo-rotatory) isomer of a compound of the formula (I), a process for its preparation and pharmaceutical preparations containing same.

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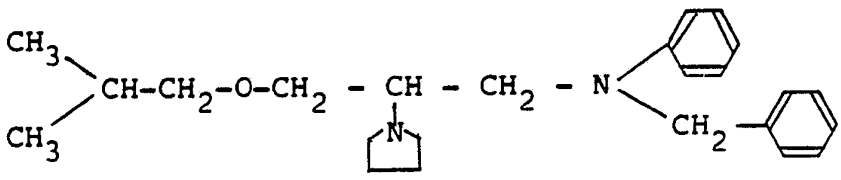
Ether of n-propanolamine derivative.

The present invention relates to a novel ether of a n-propylamine derivative and acid addition salts thereof, to a method for their preparation and to a pharmaceutical composition containing these compounds as the active principle.

Ethers of n-propanolamine derivatives are known from the U.S. patent specification RE 30.577, where a derivative has been described of the formula:



IA

This compound of formula IA, presently known as bepridil, is effective as a medicament in the treatment of cardiovascular disorders.

Its clinical use has, however, in rare cases been attended by a self limiting rhythm disturbance of the so called ventricular tachycardia type.

It has been noticed that this rhythm disturbance predominantly occurs in elderly patients and often is associated with hypokalaemic conditions of the patient, mainly caused by the use of (non K^+-sparing) diuretics as co-medication.

This rare arrhythmogenic potential of the compound may nevertheless cause serious adverse effects in certain patients and may limit the general use of this compound.

The finding of a drug with a better anti-arrhythmic activity but without said arrhythmogenic potential would be a definite step forward in the safe treatment of certain high risk patient groups suffering from rhythm disturbances.

Surprisingly it has now been found in relevant animal tests, that both separate optical isomers of the compound of formula I do not possess arrhythmogenic activity under specific hypokalaemic conditions in the rat where the racemate exacerbates arrhythmias.

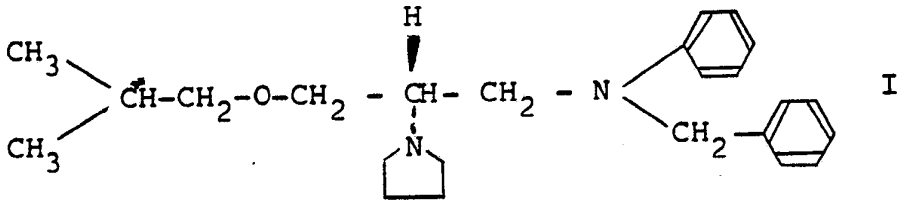
This finding is the more surprising because it suggests that the adverse arrhythmogenic potential of the racemate is merely caused by the combined presence of the dextro- and levo-rotatory isomers in the racemate.

It has, moreover, been found that the further pharmacological profile of either of the two optical isomers does not differ essentially from that of the racemate. Nevertheless the levo-rotatory isomer does show an increase

of anti-arrhythmic activity, as compared with either the racemate or the R-isomer. Its anti-anginal potency is less than that of the racemate and the R-isomer, so that the S-isomer represents a more specific anti-arrhythmic compound. Moreover the S-isomer is much better soluble in water than the racemate.

These findings all together render the S-(levo-rotatory) isomer extremely suitable in the treatment of rhythm disturbances especially under circumstances specified above where the racemate is less suitable in view of its arrhythmogenic potential.

The present invention is therefore dealing with the S-(levo-rotatory) isomer of the formula:

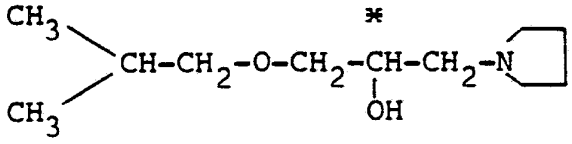


I

and acid addition salts thereof, being substantially free from the corresponding R-isomer, with a process for the preparation of this S-(levo-rotatory) isomer and with pharmaceutical preparations containing this S-(levo-rotatory) isomer as the active constituent and which is substantially free from the corresponding R-isomer.

The S-(levo-rotatory) isomer according to this invention may be prepared by resolution of the racemate using well known methods for resolving racemates. It was found, however, that - by using these conventional methods - the yields were extremely low, so that these methods are not suitable for large scale production.

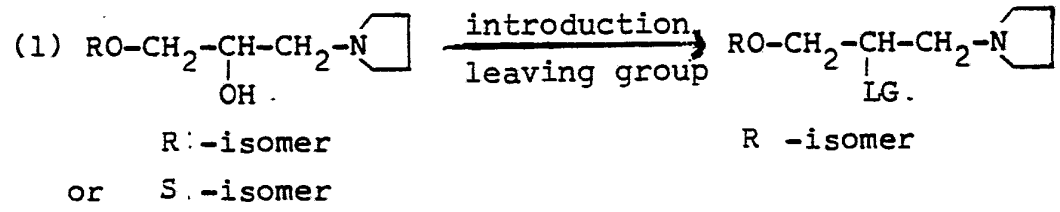
A very suitable method for preparing the S-(levo-rotatory)isomer according to the invention is starting with the resolution of a racemic compound of the formula II

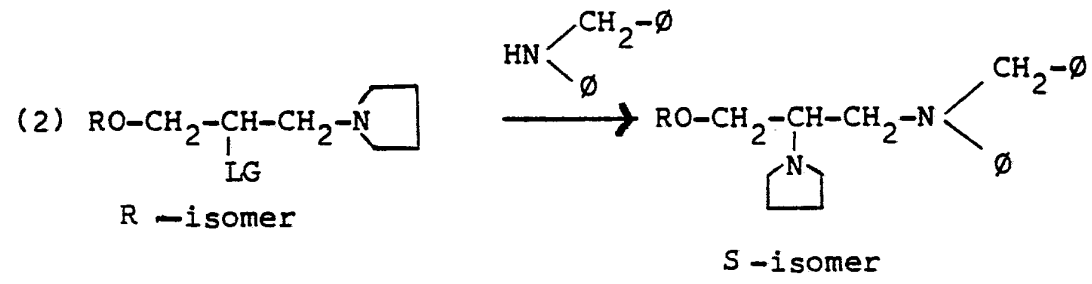


II

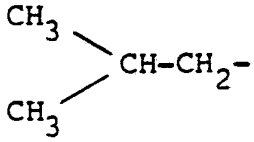
(the asterisk indicates the chiral carbon atom). This resolution can be carried out in a conventional manner using well known optically active carboxylic acids. The use of L-(-)dibenzoyl tartaric acid is preferred.

One of the optically active isomers of formula II thus obtained is subsequently converted into the S-(levo-rotatory) isomer of formula I using the following reaction steps:





LG = leaving group such as halogen.

R = isobutyl 

Ø = phenyl

The leaving group can be introduced with retention of configuration or through a SN_2 type reaction mechanism causing inversion, depending on the method selected.
Using, for example, $SOCl_2$ in toluene as LG-introducing agent the levo-rotatory alcohol of formula II is converted into its dextro-rotatory halogen derivative (R-isomer).

Pharmaceutically acceptable acid addition salts of the S-(levo-rotatory) isomer according to this invention are for example derived from hydrochloric acid, hydrobromic acid, sulphuric acid, methane-sulphonic acid, acetic acid, maleic acid, fumaric acid, tartaric acid, ascorbic acid and citric acid. Depending upon the water content of the final reaction mixture, the S-(levo-rotatory) isomer or its acid addition salt, isolated therefrom, may further be obtained in a hydrated form.

As already said the use of the S-(levo-rotatory) isomer according to this invention (and acid addition salts thereof) being substantially free from the corresponding R-isomer is extremely advantageous in the treatment of rhythm disturbances but especially in those circumstances where rhythm disturbances are accompanied with abnormally low plasma potassium levels (hypokalemic conditions), which for example may be caused by the use of diuretics as co-medication.

The S-(levo-rotatory) isomer according to formula I and acid addition salts thereof may be administered enterally or parenterally, whereby the administration per os and through a continuous

infusion into the vein is to be preferred.

Mixed with suitable carriers the compounds of the invention can be processed into a form which is suitable for enteral administration such as pills, tablets, capsules and suppositories. For injection or infusion purposes, the compounds of the present invention are dissolved, emulsified or suspended in a suitable liquid.

The S-(levo-rotatory) isomer according to this invention is preferably administered in a daily dosage of 0.5 - 20 mg per kg bodyweight. For oral administration to human beings the preferred daily dosage varies from 50 - 500 mg and for parenteral administration from 25 - 1000 mg.

Examples

1. S-α[(2-methylpropoxy) methyl]-1-pyrrolidine ethanol

250,0 g Of racemic α-[(2-methylpropoxy)-methyl]-1-pyrrolidine-ethanol were dissolved in 1 liter anhydrous ethanol after which 467 g (-) dibenzoyl tartaric acid monohydrate was added to the solution.

The precipitated salt crystals, obtained by filtration were then dried and recrystallised 4 times from anhydrous ethanol.
Melting point of the S - salt = 143.2 - 146.7 °C and $[\alpha]_D^{20} = -92.9^\circ$ (c = 0.5 CH_3OH).

This levo-rotatory salt was added to 758 ml of 1 n NaOH, after which the suspension was extracted with ether (3x) and the combined ether extracts washed with 120 ml water (5x). The ether extracts were then dried over magnesium sulphate whereupon the ether solvent was evaporated. The residue was distilled in vacuo.
Yield of the free base: 45.6 g (36%);

boiling point (0.3 mm): 83-90 °C;
$[\alpha]_D^{20}$: -13.06° (c = 0.55 CH_3OH).

2. R -1-[2-chloro-3-(2-methylpropoxy)-propyl]-pyrrolidine

45.6 g Of the levo-rotatory isomer obtained in 1. were dissolved in 135 ml anhydrous toluene and the solution was heated up to 40 - 45 °C.

Subsequently a solution of 35 ml thionyl-chloride in 45 ml toluene was slowly added to the previous solution in about 4 hours while stirring. The reaction mixture was heated to 70 - 75 °C and stirred for 2 hours. The mixture was then cooled down to 0 °C whereupon water (about 45 ml) was added very slowly (the temperature was not allowed to rise above 20 °C.

The mixture was then poured into ice-water, after which the toluene layer was separated and extracted with water again. To the combined water layers 135 ml toluene were added whereupon the two-layers system was adjusted to pH 9 by adding concentrated ammonia.

The two layers were separated. The toluene layer thus obtained was washed with water dried over magnesium sulphate and evaporated.
Yield: 44.4 g oily substance (89%);
$[\alpha]_D^{20}$ = +24.66° (c = 2; CH_3OH);
R_f = 0.42 in methylene chloride:methanol (5:1) on SiO_2.

3. S -β-[(2-methylpropoxy) methyl]-N-phenyl-N-(phenylmethyl)-1-pyrrolidine-ethanamine.HCl H_2O

A solution of 40.85 g N-benzylaniline in toluene was heated to about 80 °C and then slowly added (in about 30 minutes) to 10.0 g sodiumamide, suspended

in 100 ml anhydrous toluene, while stirring and under nitrogen atmosphere. The mixture was refluxed for two hours and cooled down to about 70 °C. Subsequently a solution of 44.4 g of the R-(dextrorotatory isomer (obtained in 2.) in 45 ml toluene was slowly added to the reaction mixture in about ½ hour.

The mixture was refluxed for 2 hours; then it was cooled down to about 10 °C, whereupon 45 ml water was slowly added.

The mixture obtained was poured into 180 ml ice-water after which it was stirred for 15 minutes.

The toluene layer was separated from the water layer, after which the toluene layer was washed, dried and evaporated, yielding about 82 grams oily substance.

The oil was purified by chromatography over a SiO_2 column and subsequently over a Al_2O_3 column.

Yielding about 54 g of an oily substance.

The purified oil was then dissolved in about 2000 ml ether. To this solution 75 ml 3.7 n HCl in ethanol was slowly added, after which the solvents were evaporated. The oily residue was subsequently dissolved in 500 ml moist ethylacetate. After cooling down this solution to about -15 °C crystals of the hydrochloride salt were obtained.

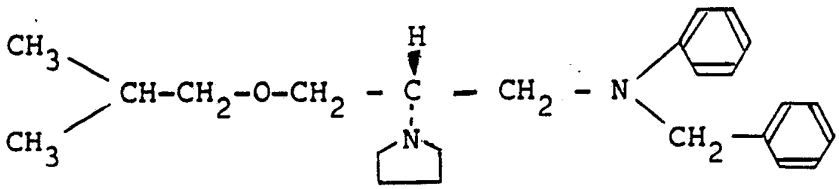
Yield: 27.5 g of the HCl salt (containing 1 mol. H_2O), melting point: 73-75.5 °C;

$[\alpha]_D^{20} = -14.90^\circ$ (c = 1; CH_2Cl_2).

Rf in n-butanol:acetic acid:water (4:1:5) = 0.65 on SiO_2.

CLAIMS

1. The S-(levo-rotatory) isomer of the formula:



I

and pharmaceutically acceptable acid addition salts thereof, being substantially free from the corresponding R-(dextro-rotatory) isomer.

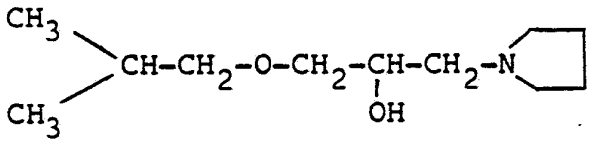
2. A pharmaceutical preparation containing as the active principle the levo-rotatory isomer described in claim 1 or a pharmaceutically acceptable acid addition salt thereof, which preparation is substantially free from the corresponding R-(dextro-rotatory) isomer.

3. An anti-arrhythmic pharmaceutical preparation according to claim 2 especially intended for administration to elderly patients with low plasma potassium levels.

4. A method of treating patients suffering from rhythm disturbances characterised by administering to said patient the S-(levo-rotatory) isomer described in claim 1 or an acid addition salt thereof in an anti-arrhythmically effective amount in admixture with one or more conventional pharmaceutical carriers and/or diluents, said levo-rotatory isomer being substantially free from the corresponding R-(dextro-rotatory) isomer.

5. Method according to claim 4 for the treatment of patients having low plasma potassium levels.

6. Process for the preparation of the S-levo-rotatory isomer according to claim 1 and acid addition salts thereof, characterised in that a racemic compound of the formula



is resolved into its separate (optical) enantiomers, after which a leaving group is introduced in one of these enantiomers resulting in the R-(dextro-rotatory) leaving group containing derivative and the R-derivative thus obtained is reacted with N-benzyl aniline or an alkali metal derivative thereof and optionally followed by conversion into an acid addition salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 84/00357

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC[4]: C 07 D 295/12; A 61 K 31/40

II. FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
IPC[4]	C 07 D 295/00; A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
A	GB, B, 1377327 (CENTRE EUROPEEN DE RECHERCHES MAUVERNAY) 5 November 1979, see claims; page 7, lines 23-28 --	1-3,6
A	GB, A, 2087233 (AKZO) 26 May 1982, see page 1	1-3

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* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
12th February 1985	02 AVR. 1985
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	G.L.M. Kruydenberg

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [x] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [x] Claim numbers 4,5, because they relate to subject matter not required to be searched by this Authority, namely:

- see PCT Rule 39.1(iv) Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods

2. [ ] Claim numbers....., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [2]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. [ ] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- [ ] The additional search fees were accompanied by applicant's protest.
- [ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON

INTERNATIONAL APPLICATION NO. PCT/EP 84/00357 (SA 8327)

This Annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 26/03/85

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Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-B- 1377327	11/12/74	NL-A-	7303117	10/09/73
		FR-A,B	2174655	19/10/73
		DE-A,B,C	2310918	20/09/73
		BE-A-	795735	18/06/73
		CH-A-	556815	13/12/74
		US-A-	3962238	08/06/76
		CA-A-	1015360	09/08/77
		CA-A-	1048027	06/02/79
		JP-A-	48099127	15/12/73
		US-E-	30577	14/04/81
GB-A- 2087233	26/05/82	BE-A-	890544	29/03/82
		JP-A-	57091919	08/06/82
		DE-A-	3138932	27/05/82
		US-A-	4430338	07/02/84