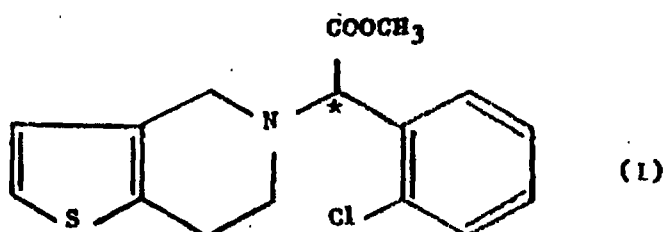


The present invention relates to a salt of the dextrorotatory enantiomer of α -(4,5,6,7-tetrahydrothieno[3,2-c]pyrid-5-yl)(2-chlorophenyl) methyl acetate, its preparation process and the pharmaceutical compositions in which it is contained..

This enantiomer corresponds to the following formula (I):



in which the carbon C* is an asymmetrical carbon. In fact this formula represents not only the dextrorotatory molecule but also its laevorotatory enantiomer. The racemic mixture corresponding to this formula was described in the French patent application published under number 2 530 247. The dextrorotatory enantiomer will be designated hereinafter as I_d and the laevorotatory enantiomer as I_l.

It is known that the rotatory power of a compound depends on the solvent in which it is measured and on its concentration in this solvent. The dextrorotatory isomer according to the invention has a positive rotatory power in solution in methanol.

Unexpectedly, only the dextrorotatory enantiomer I_d has an anti-aggregant platelet activity, while the laevorotatory enantiomer I_l is inactive. Furthermore, the inactive laevorotatory enantiomer I_l is the least well tolerated of the two enantiomers.

The compound (I_d) is an oil,, whereas its hydrochloride presents as a white powder. Oily products are usually difficult to purify and for the preparation of pharmaceutical compositions it is preferable to use crystalline products which can usually be purified by re-crystallisation.

In this case, however, it was found that certain salts of the compound (I_d) usually precipitate in amorphous form and/or are hygroscopic, which makes them tricky to handle at the industrial stage. Traditional pharmaceutical carboxylic and sulphonic acid salts were therefore prepared, such as acetic, benzoic, fumaric, maleic, citric, tartaric, gentisic, methanesulphonic, ethanesulphonic, benzenesulphonic and laurylsulphonic acids, together with the salt of dobesilic acid ($F = 70^\circ\text{C}$), and that of para-toluenesulphonic acid ($F = 51^\circ\text{C}$), which proved difficult to purify.

Amongst the salts of the organic and mineral acids of the dextrorotatory isomer of the I_d formula compound, salts were found which crystallise easily, are not hygroscopic and are sufficiently hydrosoluble for their use as active ingredients in medicines to be particularly advantageous.

Thus the present invention concerns more particularly the hydrogen sulphate of the dextrorotatory enantiomer of α -(4,5,6,7-tetrahydrotheino[3,2-c]pyrid-5-yl)(2-chlorophenyl) methyl acetate.

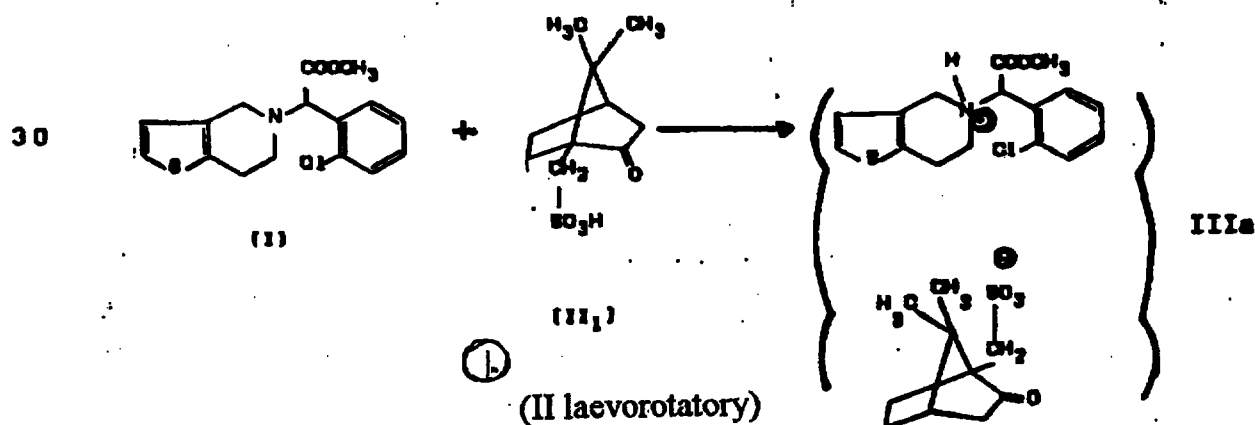
This salt is prepared in the traditional way by the action of the corresponding acid on the base in solution in a solvent in which it precipitates spontaneously or after the addition of a non-solvent of the salt.

The dextrorotatory isomer of α -(4,5,6,7-tetrahydro-thieno(3,2-c)pyrid-5-yl)2-chlorophenyl) methyl acetate may be prepared by producing the salt of the racemic compound by an acid optically active in a solvent, successive recrystallisations of the salt until a product with constant rotatory power is obtained, and then liberation of the dextrorotatory isomer of its salt by a base; if necessary the salt of the dextrorotatory isomer is produced with a pharmaceutically acceptable acid.

The optically active acid may preferably be laevorotatory 10-camphosulphonic acid.

A single solvent may be used for producing the salt and for recrystallisation; in this case acetone is perfectly suitable.

Laevorotatory chiral 10-camphosulphonic acid of the formula (II₁) is placed to react in an inert solvent with the racemic mixture of the formula (I) according to the following reaction diagram:

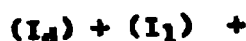


The salt may be produced in solvents such as alcohols, ketones, and dimethylformamide. The salt precipitates spontaneously or is isolated by salting-out or evaporating the solvent. A mixture of the two diastereoisomers of formula (IIIa) is formed. By successive re-crystallisations in a solvent such as acetone, the precipitate is enriched in salt of the dextrorotatory isomer of the compound (I). After each re-crystallisation the rotatory power $[\alpha]_{D20}$ of the precipitate is measured at 20°C in methanol, at a concentration between 1.5 and 2 g/100 ml. When $[\alpha]_{D20}$ no longer changes, the base of formula (I_d) is liberated from the salt (IIIa), by the action of a base such as sodium or potassium hydrogen carbonate in aqueous medium at temperatures of between 5°C and 20°C.

Evaporation of the filtrate of the first re-crystallisation IV after filtration of the crystals of the precipitated salt (IIIa) gives a mixture enriched in salt of the enantiomer (I_l). Alkanisation of this mixture of diastereoisomeric salts, with a weak base such as sodium or potassium hydrogen carbonate, in aqueous solution, at temperatures of between 5°C and 20°C, produces a mixture of the two enantiomers (I_d) + (I_l), enriched with laevorotatory enantiomer (I_l).

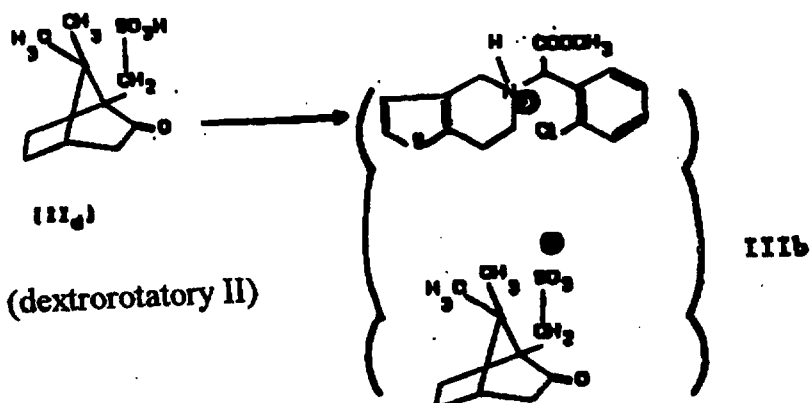
This mixture (I_d) + (I_l) enriched in enantiomer (I_l) is reacted with dextrorotatory 10-camphosulphonic acid, which we shall call (II_d), in a solvent, according to the following reaction diagram:

25



30

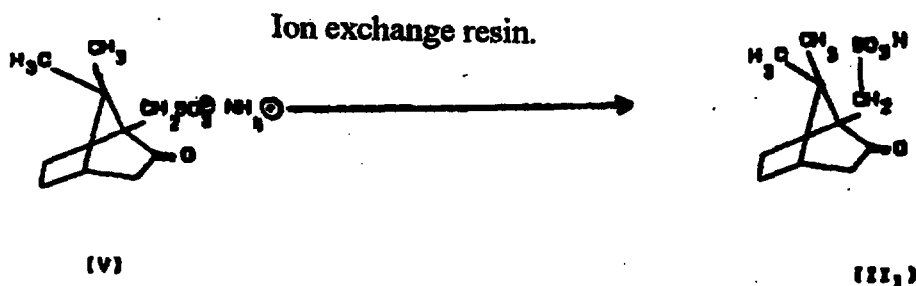
With (I_l) in majority



The mixture of crystalline diastereoisomeric salts (IIIb) obtained is re-crystallised in acetone until the rotatory power $[\alpha]_{D20}$ of the precipitate is constant. As before, the rotatory power $[\alpha]_{D20}$ of the diastereoisomeric salt (IIIb) is determined after each re-crystallisation.

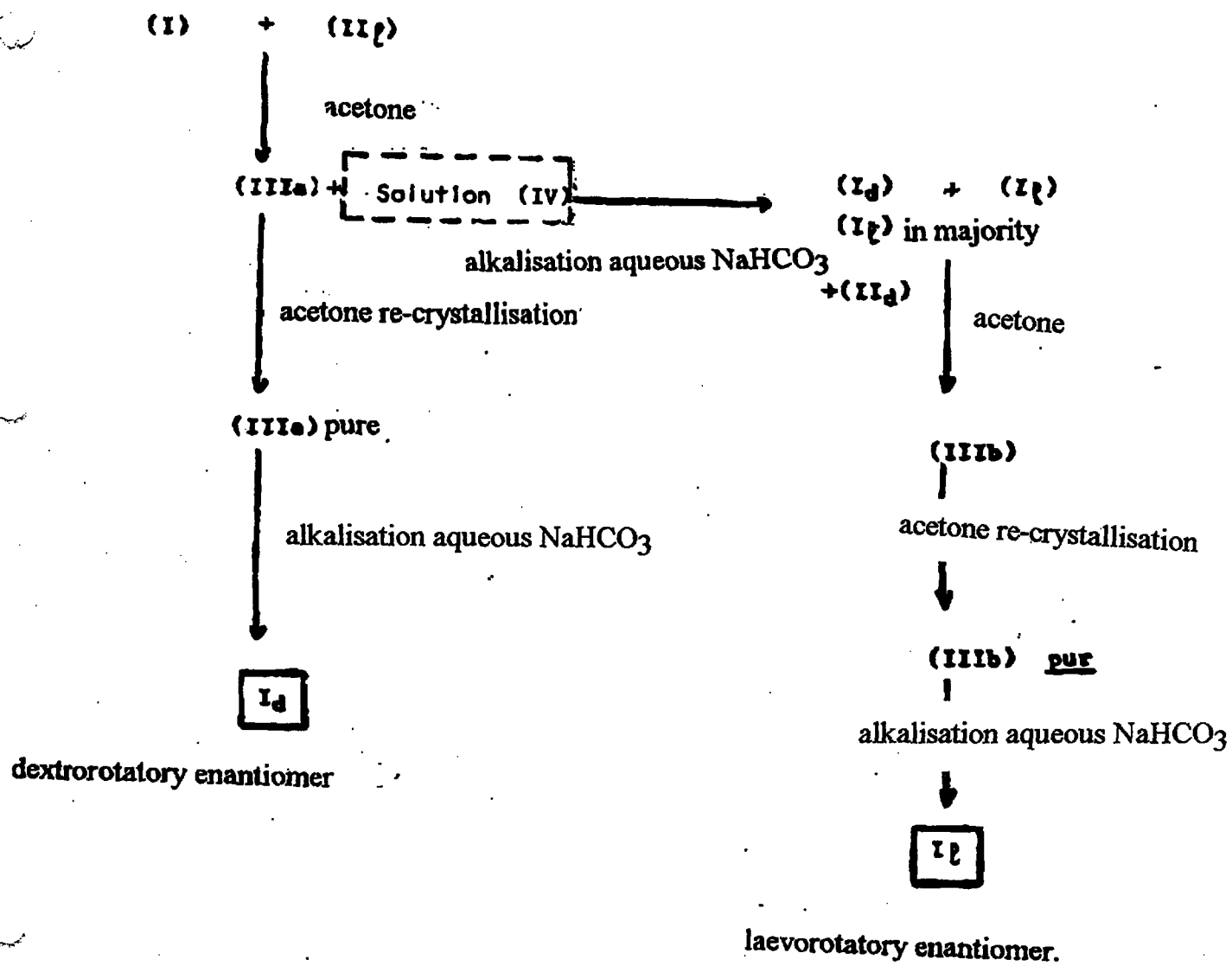
Liberation of the stereoisomer (I_1) of its salt is performed in the traditional manner, as is that of the compound (I_d).

The laevorotatory 10-camphosulphonic acid (II_1) may be obtained from commercial ammonium 10-camphosulphonate of the formula (V) in accordance with the reaction diagram:



An aqueous solution of ammonium salt (V) is chromatographed on an Amberlite resin IRN-77. After lyophilisation of the eluate, 10-camphosulphonic acid of formula (II_1) is recovered.

The whole process is shown in the following diagram:



Each of the enantiomers (I_d) and pure (I_l) may have the salt produced according to traditional methods: for example the hydrochlorides are prepared by adding a solution of hydrochloric gas in diethylic ether to a solution of (I_d) or (I_l) in diethylic ether.

Determining the enantiomeric purity of dextrorotatory (I_d) and laevorotatory (I_l) enantiomers.

Two methods were used:

- RMN spectroscopy of the proton with the addition of chiral rare earth
- high pressure liquid chromatography using a chiral stationary phase.

a) RMN spectroscopy of the proton with the addition of chiral rare earth.

Enantiomeric purity (optical purity) was determined by 60MHz RMN¹H spectroscopy, in the presence of chiral complex of rare earth, according to the method described by G.M. WHITESIDES et al. (J. Am. Chem. Soc. 1974, 96, 1038).

On the racemic product (I), the hydrogen fixed to the centre of asymmetry, as α of the ester function, appears as a singlet (chemical displacement $\delta = 4.87$ ppm, in $CDCl_3$ as the solvent). Addition of the complex of the rare earth $Eu(tfc)_3$ [europium tris (trifluoromethyl 3-hydroxymethylene)-d-camphorate (III)] in the probe, containing the solution of the racemic (I) in $CDCl_3$, leads to the splitting of the initial singlet into two clearly separate singlets, corresponding to the proton of each of the two enantiomers (I_d) and I_l . For a molar ratio complex rare earth/compound (I) = 0.4, the separation between the two singlets is 6Hz.

With each of the two enantiomers prepared (I_d) and (I_l), the same procedure was used as for the racemic (I). The smallest chemical displacement corresponds to the proton of the dextrorotatory enantiomer (I_d) and the greatest chemical displacement corresponds to the laevorotatory enantiomer (I_l).

The precision of the method was determined by comparing the RMN¹H (60Hz) spectra obtained with or without the addition of the rare earth complex, for each of the two enantiomers (I_D) and (I_L), pure or in mixture with increasing quantities of the other enantiomer. It was found possible to easily detect more than 5% by weight of one of the enantiomers in mixture with the other.

b) High pressure liquid chromatography using a chiral stationary phase.

The study was conducted with an HP-1084 liquid chromatograph using a 215nm UV detector. The chiral stationary phase was DEAE (10 microns) silica, grafted with an alpha-1 acidic alphaprotein (0.4 x 100 mm) (ENANTIOPAC R-LKB). The mobile phase consisted of an aqueous buffer phosphate mixture (NaH₂PO₄/Na₂HPO₄)-8mM, containing 0.1 M of NaCl, adjusted to pH = 7.4 and containing 15% isopropanol (V/V). The flow rate was set at 0.3 ml/minute and the column temperature was maintained at around 18-20°C.

Under these conditions the dextrorotatory enantiomer (I_D) has a retention time of 45 minutes and the laevorotatory enantiomer (I_L) has a retention time of 35 minutes.

The precision with which the optical purity of the two enantiomers was determined was estimated by chromatographing each of the two enantiomers (I_D) and (I_L) prepared, either alone or in mixture with increasing quantities of the other enantiomer. It was found possible to easily detect:

- 2% (weight/weight) of enantiomer (I_D) in enantiomer (I_L)
- 4% (weight/weight) of enantiomer (I_L) in enantiomer (I_D).

Under these conditions it may be concluded that the optical purity of the two enantiomers (I_D) and (I_L) obtained in accordance with the examples is at least 96% for the dextrorotatory enantiomer (I_D) and at least 98% for the laevorotatory enantiomer (I_L).

The following non-restricting examples are given by way of illustration of the present invention.

EXAMPLE 1 - Salts of dextrorotatory α -(4,5,6,7-tetrahydrotheino[3,2-c]pyrid-5-yl)(2-chlorophenyl) methyl acetate.

a) Laevorotatory 10-camphosulphonic acid.

A column of IRN-77 Amberlite resin is prepared, and treated by passing through 1N hydrochloric acid; the column of acidified resin is then washed thoroughly with water. The laevorotatory 10-camphosulphonate ammonium is dissolved in the minimum amount of water and deposited on the prepared resin column. It is eluted with water. The elution fractions containing acid are lyophilised.

White crystals, $F = 198^{\circ}\text{C}$; $[\alpha]_{\text{D}20} = -20.53$ ($C : 2.075$ g/100 ml, water).

b) salt of 10-camphosulphonic acid of α -(4,5,6,7-tetrahydrotheino[3,2-c]pyrid-5-yl)(2-chlorophenyl) methyl acetate (SR 25990 B).

32 g (0.0994 mole) of racemic α -(4,5,6,7-tetrahydrotheino[3,2-c]pyrid-5-yl)(2-chlorophenyl) methyl acetate are dissolved in 150 ml of acetone. 9.95 g (0.0397 mole) of monohydric laevorotatory 10-camphosulphonic acid are added. The homogenous mixture is left at room temperature. After 48 hours, a few crystals appear. The reaction mixture is concentrated to 50 ml and left for 24 hours at room temperature. The crystals obtained are filtered, washed with acetone and dried (Yield : 55% as compared with starting racemic).

White crystals, $F = 165^{\circ}\text{C}$, $[\alpha]_{\text{D}20} = +24.67$ ($C = 1.58$ g/100 ml; methanol).

The crystals obtained previously are re dissolved in the minimum amount of boiling acetone (50 ml). The crystals obtained after cooling are filtered, washed with acetone and dried (yield: 80%).

White crystals, $F = 165^{\circ}\text{C}$, $[\alpha]_{\text{D}20} = + 24.75$ ($C = 1.68$ g/100 ml; methanol).

c) Dextrorotatory α -(4,5,6,7-tetrahydrotheino[3,2-c]pyrid-5-yl)(2-chlorophenyl) methyl acetate.

12 g (0.022 mole) of the pure product obtained in b) are dissolved in the minimum amount of water. By cooling to 5°C , the aqueous solution obtained is alkalinised with a saturated aqueous solution of sodium hydrogen carbonate. The aqueous alkaline phase is extracted with dichloromethane. The organic extracts are dried on anhydrous sodium sulphate. Evaporation of the solvent leaves a colourless oil (quantitative yield). Oil $[\alpha]_{\text{D}20} = + 51.52$ ($C = 1.61$ g/100 ml; methanol).

d) Hydrogen sulphate of dextrorotatory α -(4,5,6,7-tetrahydrotheino[3,2-c]pyrid-5-yl)(2-chlorophenyl)methyl acetate (SR 25990 C).

800 ml of a saturated aqueous solution of sodium bicarbonate are added to a suspension of 200 g of SR 25990 B in 800 ml of dichloromethane. After stirring, the organic phase is decanted, dried on sodium sulphate and the solvent eliminated at low pressure. The residue is dissolved in 500 ml of acetone cooled in ice and 20.7 ml of concentrated sulphuric acid (93.64 % $-d=1.83$) is added drop by drop. The resulting precipitate is isolated by filtration and washed with 1000 ml of acetone and then dried in a vacuum oven at 50°C .

139 grammes of white, analytically pure crystals, with a melting point of 184°C are obtained in this way. Total formula: $\text{C}_{16}\text{H}_{16}\text{ClNO}_2\text{S}\cdot\text{H}_2\text{SO}_4$
 $[\alpha]_{\text{D}20^{\circ}\text{C}} = + 55.10$ ($C = 1.891$ g/100 ml, methanol),

EXAMPLE 2 - Salts of laevorotatory alpha-(4,5,6,7-tetrahydrotheino[3,2-c]pyrid-5-yl)(2-chlorophenyl) methyl acetate.

a) Salt of 10-d-camphosulphonic acid (SR 25989 B).

The acetonic solution obtained in example 1-b is evaporated, after separating the SR 25990 B.

The residue is recovered by water and diethylic ether. The etheric phase is decanted. The aqueous phase is cooled to 5°C and alkalinised with a saturated aqueous solution of sodium bicarbonate. The alkaline aqueous phase is extracted with diethylic ether. The ethered extracts are combined and dried on anhydrous sodium sulphate.

Evaporation leaves an oil that is purified by filtration on a silica bed (eluant: diethylic ether).

A colourless oil is recovered, consisting of a mixture of around 65% laevorotatory enantiomer and 35% dextrorotatory enantiomer, the proportions being determined by RMN¹H (60 MHz) spectroscopy with the addition of a complex of chiral rare earth.

16.66 g (0.0517 mole) of the mixture thus obtained are dissolved in 70 ml of acetone. To this are added 7.77 g (0.0310 mole) of dextrorotatory monohydrated 10-camphosulphonic acid. The homogenous mixture is left overnight at room temperature. The crystals obtained are filtered, washed with acetone and dried (Yield: 44% compared with the mixture).

The crystals obtained are dissolved in the minimum amount of acetone at reflux (60 ml). The precipitate obtained in this way is cooled to room temperature and then filtered, washed with acetone and dried. White crystals, $F = 167^{\circ}\text{C}$, $[\alpha]_{\text{D}20} = -24.85$ ($C = 1.79$ g/100 ml, methanol).

b) Laevorotatory α -(4,5,6,7-tetrahydrotheino[3,2-c]pyrid-5-yl)(2-chlorophenyl) methyl acetate.

11.3 g (0.0204 mole) of the 10-camphosulphonate obtained in a) are dissolved in the minimum amount of water. The aqueous solution obtained is alkalinised by cooling to 5°C with a saturated aqueous solution of sodium hydrogen carbonate. The alkaline aqueous phase is extracted with dichloromethane. The organic solution is dried and the solvent evaporated. A colourless oil is isolated (quantitative yield).

Oil $[\alpha]_{\text{D}20} = -50.74$ ($C = 1.58$ g/100 ml, methanol).

c) Hydrochloride of laevorotatory α -(4,5,6,7-tetrahydrotheino[3,2-c]pyrid-5-yl)(2-chlorophenyl) methyl acetate (SR 25989 A).

Prepared according to the method described in example 1d). Yield : 94%.

White crystals, $F = 117^{\circ}\text{C}$, $[\alpha]_{\text{D}20} = - 62.56$ ($C = 1.80$ g/100 ml, methanol).

d) Hydrogen sulphate of laevorotatory alpha-(4,5,6,7-tetrahydrotheino[3,2-c]pyrid-5-yl)(2-chlorophenyl) methyl acetate (SR 25989 C).

70 g (0.126 mole) of the camphosulphonate SR 25989 B obtained according to a) above are basified with a saturated aqueous solution of sodium bicarbonate in the presence of dichloromethane. The organic phase is decanted, dried on sulphate and evaporated dry.

7.2 ml (0.126 mole) of concentrated sulphuric acid are added drop by drop to the residue recovered with 300 ml of acetone. After stirring, the crystals formed are filtered and washed with acetone. 47.8 g of white crystals are obtained.

$F = 182^{\circ}\text{C}$ $[\alpha]_{\text{D}20} = - 51.61$ ($C = 2.044$ g/100 ml, methanol).

Analysis (C, H, N) correct.

PHARMACOLOGICAL STUDY

The antiaggregant activity and toxicity of the new compounds were compared with those of the racemic mixture described in French patent no. 82.12599 (publication no. 2 530 247).

There follows a description of the results of this study, which shows another advantage of the invention, i.e. that the salts of the dextrorotatory isomer have a better therapeutic index than the salt of the racemic mixture; in fact the laevorotatory isomer has almost no platelet antiaggregant activity and its toxicity is substantially greater than that of its dextrorotatory counterpart.

The platelet antiaggregant and antithrombotic activities of the compounds were studied in the rat using traditional methods.

Activity on platelet aggregation induced by ADP or collagen was determined ex-vivo.

The products in solution in ethanol (200 mg/ml) diluted in water containing gum Arabic (5% p/v) were administered orally to batches of 5 female CD-COBS strain rats, weighing 250-300 g, with 10 ml of suspension per gramme, two hours prior to blood sampling.

Sampling was performed on sodium citrate in 3.8% aqueous solution (1 vol/9 volumes of blood) on the animals anaesthetised with diethyl ether, by puncturing the abdominal aorta. The platelet-rich plasma was then isolated by centrifuging at 200 g for 10 minutes.

Aggregation was induced by the addition of 2 μ l of aggregant for 400 μ l of platelet-rich plasma. The aggregant solutions used were: an aqueous solution of ADP sold by Boehringer Mannheim with concentration 500 μ M (final concentration 2.5 μ M), and a collagen solution sold by Sigma (type 1) at 0.25 g/100 ml in 3% acetic acid (v/v) (final concentration 12.5 μ g/ml).

Aggregation of the platelets was followed, using the method described by G.V.R. Born in Nature 194 p. 927 (1967), with a Coultronics^R aggregometer at a temperature of 37°C, stirring at 900 rpm.

For ADP aggregation, the aggregometer gave a curve showing platelet aggregation measured by a change in optical density.

The level of this curve is defined as the aggregation level. Percentage aggregation is the ratio between the measured aggregation level and the level corresponding to 100% aggregation x 100. Percentage inhibition is determined by the ratio:

$$\frac{\text{Reference aggregation level} - \text{product aggregation level}}{\text{Reference aggregation level}} \times 100$$

Table I shows the results obtained on ADP aggregation, for the hydrochloride of the racemic mixture (PCR 4099) and the hydrogen sulphates of the dextrorotatory (SR 25990 C) and laevorotatory (SR 25989 C) isomers on the one hand, and PCR 4099 and the hydrochlorides of the dextrorotatory (SR 25990 A) and laevorotatory (SSR 25989 A) isomers on the other; the results demonstrate that the laevorotatory isomer is inactive, and that the dextrorotatory isomer is at least as active as the racemic.

TABLE I

PRODUCT	DOSAGE mg/kg P.O.	QUANTITY of base adminis- tered	% AGGRE- GATION	% INHI- BITION	p**
Reference			42.4 +/- 1.5		
PCR 4099 (racemic)	4.48	3.84	29.8 +/- 2.4	30	0.01
	8.97	7.69	17.2 +/- 2.2	59	0.001
	17.9	15.38	11.1 +/- 2.3	74	0.001
SR 25989C	20	15.38	41.0 +/- 1.5	3	n.s.
	40	30.76	37.1 +/- 1.7	13	n.s.
SR 25990C	1.25	0.96	39.4 +/- 1.3	7	n.s..
	2.5	1.92	28.4 +/- 2.3	33	0.01
	5	3.84	14.0 +/- 1.6	67	0.01
	10	7.69	8.5 +/- 1.6	80	0.001

* average of results +/- average standard deviation (ASD)

** Student test

For collagen aggregation, percentage inhibition is the difference between the slopes of the curves representing variation in optical density as a function of the time for the reference and the product to be tested, divided by the slope for the reference, multiplied by 100. The results in table II again demonstrate that only the dextrorotatory isomer is active, while the salts have comparable activities.

TABLE II

PRODUCT	DOSAGE mg/kg P.O.	QUANTITY of base administered	SLOPE	% INHI- BITION	P**
Reference			4.8 +/- 0.3		
PCR 4099 (racemic)	4.48	3.84	3.6 +/- 0.2	25	0.05
	8.97	7.69	2.7 +/- 0.3	44	0.01
	17.9	15.38	1.5 +/- 0.3	69	0.001
SR 25989C	20	15.38	4.3 +/- 0.2	10	n.s.
	40	30.76	4.0 +/- 0.2	17	n.s.
SR 25990C	1.25	0.96	4.5 +/- 0.3	6	n.s.
	2.5	1.92	4.1 +/- 0.2	15	n.s.
	5	3.84	2.3 +/- 0.1	52	0.001
	10	7.69	1.7 +/- 0.3	65	0.001

* Student test

** n.s. not significant

The antithrombotic activity of the compounds was also studied in the venous thrombosis test on the gimlet described by Kumada T. et al. in *Thromb. Res.* 18 p. 189 (1980).

Female rats of the same type as before, with 10 animals per batch, were anaesthetised with diethyl ether and their vena cava isolated following abdominal incision.

A metal gimlet consisting of a dental paste tamper 21 mm long, sold by Dyna (France) size no. 30, was introduced into this vein, just below the renal bifurcation descending towards the iliac veins, without causing lesion to the wall; the gimlet was inserted through a length of 19 to 20 mm and extended 1 mm beyond the outside and the re-closed abdomen.

Thrombi formed rapidly and, five hours later, under pentobarbital anaesthesia, the abdomen was re-opened and ligatures were made upstream and downstream of the gimlet which was withdrawn following longitudinal incision of the vein and the isolated thrombus was weighed.

The results in table III show that the laevorotatory isomer is inactive in this test, unlike the dextrorotatory isomer and the racemic.

TABLE III

PRODUCT	DOSAGE mg/kg P.O. Administered	QUANTITY of base	WEIGHT of thrombi *	VARI- ATION %	p**
Reference			3.9 +/- 0.3		
PCR 40099 (racemic)	4.48	3.84	2.17 +/- 0.24	44	0.001
	8.97	7.69	1.39 +/- 0.15	64	0.001
	17.9	15.38	1.00 +/- 0.19	74	0.001
SR 25989C	40	30.76	4.17 +/- 0.42	-7	n.s.
SR 25990c	1.25	0.96	3.11 +/- 0.32	20	n.s.
	2.5	1.92	2.29 +/- 0.22	41	0.01
	5	3.84	1.71 +/- 0.24	56	0.01
	10	7.69	1.26 +/- 0.19	67	0.01
	20	15.38	1.20 +/- 0.13	69	0.01

* = weight of thrombi in mg +/- standard average deviation

P = Kruskal-Wallis U test

For the toxicological study, the compounds were administered orally as a suspension in the same volume of water with the addition of 10% (p/v) gum Arabic to batches of 10 female Sprague Dawley strain rats, weighing 120 to 135 grammes, on an empty stomach.

The mortality rate was determined 14 days after administration of the product to be studied. The lethal dosages determined in this way, expressed as weight of salt administered, are shown in table IV; these results show firstly that

the toxicity of the racemic mixture is close to that of the laevorotatory isomer, whereas the dextrorotatory isomer is substantially less toxic, and secondly that toxicity depends on the type of acid used for producing the salt.

TABLE IV

PRODUCTS	D 10	D 50 ()	D 90	ABSOLUTE LETHAL DOSE
PCR 4099 (racemic)	1318	1615 (1448-1747)	1979	2000
SR 25989 A	1259	1702 (1443-1797)	2299	2000
SR 25990 A	3055	4316 (3569-5705)	6137	5000
SR25990 C	2257	2591 (2372-2805)	2974	4000

() = confidence interval



CLAIMS

(Contracting states: DE, AT, BE, FR, GR, IT, NL, GB, LU,
5 SE, CH, LI)

1. Hydrogen sulphate of the dextrorotatory isomer of
alpha-(4,5,6,7-tetrahydrothieno[3,2-c]pyrid-5-yl)(2-
chlorophenyl)methyl acetate.

10 2. Process for preparing the compound according to
claim 1, characterised in that racemic alpha-(4,5,6,7-
tetrahydrothieno[3,2-c]pyrid-5-yl)(2-chlorophenyl)methyl
acetate is converted into a salt in acetone with
15 laevorotatory 10-camphosulphonic acid, successive
recrystallisations of the salt are carried out in
acetone until a product having a constant rotatory power
is obtained, then the dextrorotatory isomer is liberated
from its salt by a base and converted into a salt with
sulphuric acid.

20 3. Pharmaceutical composition, characterised in that
it contains, as active principle, a compound according
to claim 1.

25 4. Composition according to claim 3, characterised in
that each dosage unit contains from 0.001 g to 0.100 g
of active principle.