

632411

FORM 1

CULLEN & CO.

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

CONVENTION APPLICATION FOR A STANDARD PATENT

I/We, FOURNIER INDUSTRIE ET SANTE, a French body corporation of 38, avenue Hoche, 75008, Paris, France, hereby apply for the grant of a standard patent for an invention entitled:

NOVEL SULFONYLPHENYL- β -D-THIOXYLOSIDES, THEIR METHOD OF PREPARATION AND THEIR USE IN THERAPEUTICS

which is described in the accompanying complete specification.

DETAILS OF BASIC APPLICATION(S):-

Number of basic application(s):-

90 04 173

Name(s) of Convention Country(ies) in which Basic Application(s) was/were filed:-

France

Date(s) of Basic applications(s):-

2.4.90

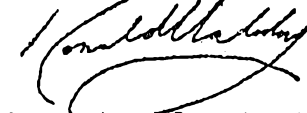
The address for service is:-

Cullen & Co.,
240 Queen Street,
Brisbane, Queensland, 4000,
Australia.

DATED this 27th day of March 1991

FOURNIER INDUSTRIE ET SANTE

By:



Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
AUSTRALIA.

COMMONWEALTH OF AUSTRALIA
The Patents Act 1952

G.R. CULLEN & CO.

DECLARATION IN SUPPORT OF AN
APPLICATION FOR A PATENT

In support of the Application made for a patent for an invention

Insert
Title of Invention

entitled: Novel sulfonylphenyl- -D-thioxylosides, their
method of preparation and their use in therapeutics.

Insert
Full Name and
Address of
declarant

I, Francois Picart of

~~XXX~~ FOURNIER INDUSTRIE ET SANTE

of 38, avenue Hoche 75008 Paris, France

do solemnly and sincerely declare as follows:-

~~XX~~

(or, in the case of an application by a body corporate)

Insert Full Name(s)
of applicant(s)

1. I am/We are authorised by FOURNIER INDUSTRIE ET SANTE

the applicant(s) for the patent to make this declaration on its/their behalf.

~~XX~~

~~XXXXXXXXXXXXXXXXXXXX~~

(or, where a person other than the inventor is the applicant)

Insert Full Name
and Address of each
Inventor

2. 1) Soth SAMRETH, 2, rue de la deuxième Escadre 21600 Longvic, France

2) Patrice RENAUT, 3, ruelle de Plombières, Hauteville Lès Dijon
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3) Jerzy BAJGROWICZ, 2, promenade du Rhône, 21000 Dijon, France

4) Jean MILLET, 15, rue du Tremblois, Corcelles Les Citeaux, 21910 Saulon La Rue,
is/are the actual inventor(s) of the invention and the facts upon which the France

applicant(s) is/are entitled to make the application are as follows:-

The application was made for the applicant by the inventors
in the course of their employment with the applicant.

State how Applicant(s)
derive title from inventor(s)
e.g. The Applicant(s)
is/are the assignee(s) of the
invention from the
inventor(s), or The invention
was made for the Applicant(s)
by the inventor(s) in the course
of his/their employment with
the Applicant(s).

*Note: Paragraphs
3 and 4 need only be
completed for a
Convention Application

Basic Country(ies)
Priority Date(s)
Basic Applicant(s)

3. The basic application(s) as defined by Section 141 of the Act was/were made
in FRANCE on 2 April 1990
by FOURNIER INDUSTRIE ET SANTE
in on
by

4. The basic application(s) referred to in paragraph 3 of this Declaration was/
were the first application(s) made in a Convention country in respect of the
invention(s) the subject of the application.

Declared at Paris this 28 day of February 1991

FOURNIER INDUSTRIE ET SANTE

To: The Commissioner of Patents

 Francois Picart
Signature of Declarant(s)

François PICART, administrator.

(12) PATENT ABRIDGMENT (11) Document No. AU-B-73835/91
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 632411

(54) Title
NOVEL SULFONYLPHENYL-BETA-D-THIOXYLOSIDES, THEIR METHOD OF PREPARATION AND THEIR USE IN THERAPEUTICS

(51)⁵ International Patent Classification(s)
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C07C 323/65

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(71) Applicant(s)
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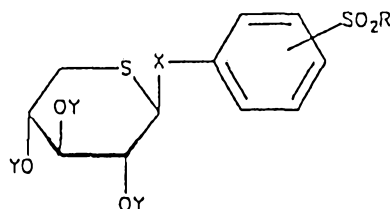
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(56) Prior Art Documents
AU 43560/89 C07H A61K
AU 602210 15219/88 C07H C07C
US 4877808

(57) Claim

1. An oside compound selected from the group consisting of the sulfonylphenyl- β -D-thioxylosides of the formula



in which:

- X is a sulfur atom or an oxygen atom;
- R is a C₁-C₄ alkyl group, a substituted amino group NR₁R₂ (where R₁ and R₂, which are identical or different, are each a C₁-C₄ alkyl group, it being possible for R₁ and R₂, taken together, to form a piperidinyl or morpholinyl group with the nitrogen atom to which they are bonded) or a phenyl group which is unsubstituted or substituted in the para position by a cyano group or by a halogen atom; and
- Y is a hydrogen atom or a C₂-C₅ aliphatic acyl group.

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4. A therapeutic composition containing, in association with a physiologically acceptable excipient, at least one oside compound according to any one of claims 1 to 3.

5. Use of a substance according to any one of claims 1 to 3 in order to obtain an antithrombotic drug for use in therapeutics to combat disorders of the venous circulation.

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COMMONWEALTH OF AUSTRALIA

Patents Act 1952

Name of Applicant(s): FOURNIER INDUSTRIE ET SANTE

Address of Applicant(s): 38, avenue Hoche, 75008
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COMPLETE SPECIFICATION FOR THE INVENTION ENTITLED:

NOVEL SULFONYLPHENYL- β -D-THIOXYLOSIDES, THEIR METHOD OF
PREPARATION AND THEIR USE IN THERAPEUTICS

The following statement is a full description of the invention
including the best method of performing it known to us:

Novel sulfonylphenyl- β -D-thioxylosides, their method of preparation and their use in therapeutics

05 The present invention relates, by way of novel industrial products, to the sulfonylphenyl- β -D-thioxyloside compounds of formula I below. It further relates to their method of preparation and to their use in therapeutics as antithrombotics, especially venous antithrombotics.

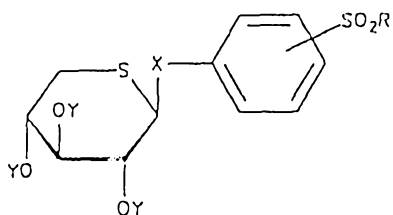
10 EP-B-0 051 023 has already disclosed benzoylphenyloside and α -hydroxybenzylphenyloside derivatives as anti-ulcer agents, platelet aggregation inhibitors, antithrombotics and cerebral oxygenators.

15 Also, EP-A-0 133 103 has disclosed benzylphenylosides which are useful as hypocholesterolemics and hypolipidemics, some of these compounds, in particular the product of Example 1, having antithrombotic effects as well.

20 Finally, EP-A-0 290 321 has disclosed benzoylphenylthioxylose, α -hydroxybenzylphenylthioxylose and benzylphenylthioxylose derivatives as antithrombotics.

25 It has now just been found that the sulfonylphenyl- β -D-thioxyloside compounds according to the invention, which are structurally different from the known products of the prior art, are useful in the treatment and prevention of diseases associated with circulatory disorders, and especially as venous antithrombotics.

30 The novel products according to the invention are selected from the group consisting of the sulfonylphenyl- β -D-thioxylosides of the formula



(I)

in which:

- X is a sulfur atom or an oxygen atom;
- R is a C_1 - C_4 alkyl group, a substituted amino group NR_1R_2 (where R_1 and R_2 , which are identical or different, are each a C_1 - C_4 alkyl group, it being possible for R_1 and R_2 , taken together, to form a piperidinyl or morpholinyl group with the nitrogen atom to which they are bonded) or a phenyl group which is unsubstituted or substituted in the para position by a cyano group or by a halogen atom; and
- Y is a hydrogen atom or a C_2 - C_5 aliphatic acyl group. The preferred aliphatic acyl group is CH_3CO .

C_1 - C_4 alkyl group is understood here as meaning a linear or branched hydrocarbon radical containing 1 to 4 carbon atoms, the preferred alkyl group being the methyl group.

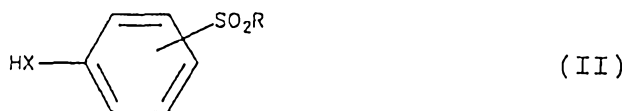
Halogen atom is understood here as meaning a chlorine, fluorine or bromine atom, the preferred halogen atom being the fluorine atom.

According to the invention, the preferred compounds of formula I are those in which X is the sulfur atom.

The compounds of formula I and the corresponding acylated compounds can be prepared by a glycosylation reaction which comprises

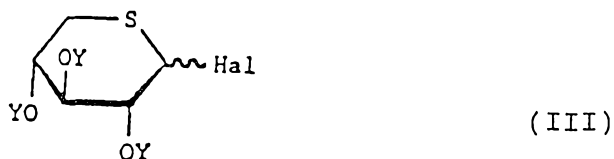


(i) reacting a compound of the formula

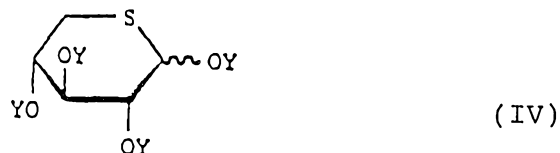


in which X and R are as defined above,
with a thioxyclose derivative selected from the group
consisting of

10 (i) the acylthioxyclosyl halides of the formula

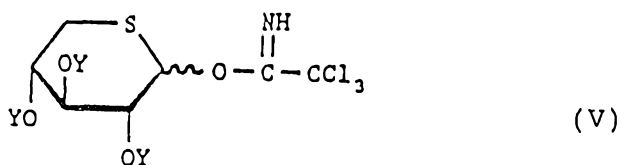


(ii) the peracylated thioxycloses of the formula



and

25 (iii) the acylthioxyclosyl trichloroacetimidates of
the formula



35 in which Hal is a halogen atom such as Cl or Br (the
bromine atom being the preferred halogen atom here)
and Y is ~~an acyl group, especially~~ an aliphatic acyl



group containing a total of 2 to 5 carbon atoms and preferably the acetyl group, in an inert solvent, at a rate of 1 mol of II to about 0.6 to 1.2 mol of compound III, IV or V, especially in the presence of an acid acceptor and/or a Lewis acid, and

(ii) if necessary, subjecting the resulting compound of formula I in which Y is a C_2-C_5 acyl group to a deacylation reaction at a temperature of between $0^\circ C$ and the reflux temperature of the reaction medium, in a C_1-C_4 lower alcohol (preferably methanol), in the presence of a metal alcoholate (preferably magnesium methylate or sodium methylate), to give a compound of formula I in which Y is H.

Compounds III, IV and V can be in the α or β configuration or in the form of an anomeric mixture of both configurations.

The glycosylation reactions of the compounds of formula II were carried out either starting from compound III in the presence of a catalyst such as salts or oxides of silver, mercury or zinc, or starting from compound V in the presence of a Lewis acid, especially boron trifluoride etherate or zinc chloride, or starting from compound IV in the presence of a Lewis acid.

According to one preferred mode of carrying out the invention, it is recommended to condense 1 mol of the compound of formula II with about 1.1 to 1.2 mol of acylthioxylosyl halide III in an inert solvent selected from polar or apolar solvents (such as, for example, dimethylformamide, tetrahydrofuran, dioxane, acetonitrile, nitromethane, benzene, toluene, xylenes and mixtures thereof), in the presence of mercuric cyanide.

It is advantageous to use 2,3,4-tri-O-acetyl-5-thio- α -D-xylopyranosyl bromide in a benzene/nitromethane mixture (1/1 v/v), in the presence of 1.1 to

1.3 mol of mercuric cyanide, at a temperature of between 0°C and the reflux temperature of the reaction medium, preferably at about 40-50°C, for 1 to 4 hours, preferably for about 2 hours.

05 According to a second preferred mode of carrying out the invention, it is recommended to condense 1 mol of the compound of formula II with about 1.1 to 1.2 mol of acylthioxylosyl halide III in an inert solvent (such as, for example, methylene chloride or acetonitrile), in the presence of silver imidazolate and
10 zinc chloride.

 It will be advantageous to use 2,3,4-tri-O-acetyl-5-thio-D-xylopyranosyl bromide in methylene chloride or a methylene chloride/acetonitrile mixture,
15 in the presence of 1.5 to 1.7 mol of silver imidazolate and 2 to 2.2 mol of zinc chloride, at a temperature of between 0°C and the reflux temperature of the reaction medium, preferably at about 40-60°C, for 24 to 48 hours.

20 According to a third preferred mode of carrying out the invention, it is recommended to condense 1 mol of the compound of formula II with about 0.6 to 1 mol of acylthioxylosyl halide III in an inert solvent (such as, for example, toluene and/or acetonitrile), in the
25 presence of zinc oxide.

 It will be advantageous to use 2,3,4-tri-O-acetyl-5-thio-D-xylopyranosyl bromide in a toluene/acetonitrile mixture, in the presence of 0.5 to 1.2 mol of zinc oxide, at a temperature between room temperature and the reflux temperature of the reaction medium,
30 preferably at about 40-60°C, for 18 to 48 hours.

 According to a fourth preferred mode of carrying out the invention, it is recommended to condense 1 mol of the compound of formula II with about 1.1 to 1.3
35 mol of acylthioxylosyl trichloroacetimidate in an inert

solvent (such as, for example, methylene chloride or acetonitrile), in the presence of boron trifluoride etherate or zinc chloride.

05 It will be advantageous to use 2,3,4-tri-O-acetyl-5-thio- α -D-xylopyranosyl trichloroacetimidate in methylene chloride, in the presence of a solution of 0.1 to 0.4 mol of boron trifluoride etherate in methylene chloride or acetonitrile, or in the presence of zinc chloride, at a temperature of between -40°C and
10 room temperature ($15-25^{\circ}\text{C}$), preferably at about -20°C to 0°C , for 1 to 5 hours.

In all cases, the glycosylation reaction yields a mixture of the isomers of α and β configuration in variable proportions.

15 The isomer of β configuration is isolated by the methods known to those skilled in the art, such as, for example, fractional crystallization or chromatography, especially flash chromatography [i.e. chromatography on a silica column, under pressure, according
20 to the technique described by W.C. STILL et al. in J. Org. Chem. (1978) 42 (n $^{\circ}$ 14) 2923].

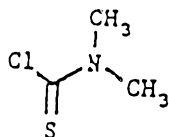
Where appropriate, the derivatives obtained are subjected to deacylation, and more particularly to deacetylation, which is carried out at a temperature of
25 between 0°C and the reflux temperature of the reaction medium, in a $\text{C}_1\text{-C}_4$ lower alcohol, in the presence of the corresponding metal alcoholate. Preferably, methanol will be chosen as the lower alcohol and sodium or magnesium methylate as the metal alcoholate.

30 If desired, the deacylation reaction can be carried out after glycosylation without isolation of the acylated intermediate formed.

It is also possible to carry out the deacylation reaction enzymatically, for example using pork
35 liver esterase.

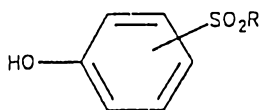
To obtain the intermediates of formula II in which X = S, it is recommended to

(i) condense dimethylaminothiocarbonyl chloride of the formula



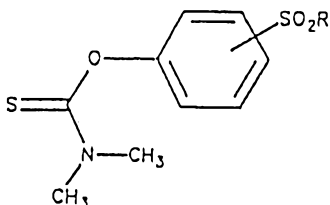
(VI)

in a strong basic medium with a compound of the formula



(IIa)

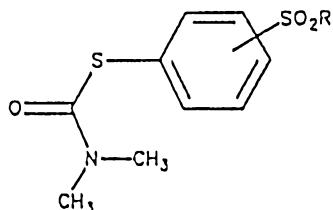
in which R is as defined above, to give a compound of the formula



(VII)

in which R is as defined above,

(ii) subject the resulting compound of formula VII to a Newmann rearrangement (J. Org. Chem. (1966) 31, p. 3980), by heating, to give a compound of the formula



(VIII)

in which R is as defined above, and

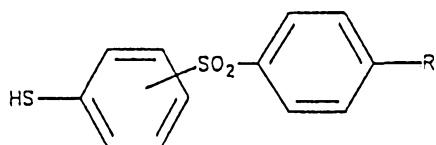
(iii) treat the resulting compound of formula VIII with a metal alcoholate, preferably sodium or magnesium methyllate, in a C₁-C₄ lower alcohol, preferably methanol, dimethylformamide or dioxane, to give a compound of formula II in which X = S.

The intermediates of formula II in which X = S can also be obtained by the nucleophilic substitution of an appropriate halogenobenzene compound using the method described by L. TESTAFERRI in Tetrahedron Letters, vol. 21, p. 3099-3100 (1980).

Some of the intermediates of formula II in which X = S are novel compounds.

The compounds of the formula

15



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in which R' is a fluorine atom, a bromine atom or a cyano group therefore form one of the subjects of the invention.

25

According to the invention, a therapeutic composition is proposed which contains, in association with a physiologically acceptable excipient, at least one compound selected from the group consisting of the products of formula I. Of course, in such a composition, the active ingredient is present in a therapeutically effective amount.

30

The compounds of formula I are useful in therapeutics as antithrombotics. They are particularly useful in the prevention and treatment of disorders of the venous circulation.

35

According to the invention, it is recommended to use a substance belonging to the group consisting of the compounds of formula I in order to obtain an anti-

thrombotic drug for use in therapeutics to combat disorders of the venous circulation.

Further characteristics and advantages of the invention will be understood more clearly from the following description of Preparatory Examples, which in no way imply a limitation but are given by way of illustration, and results of pharmacological tests.

In the Preparatory Examples which follow, the α or β configuration has been specified in the compound names in cases where said configuration was determined. Where the configuration is not indicated, this means that the corresponding product is an anomeric mixture of the α and β configurations in proportions which were not determined.

PREPARATION I

I a) Preparation of 4-(phenylsulfonyl)benzenethiol

1.25 g of sodium thiomethylate are added under a nitrogen atmosphere to a solution of 15 g (0.0593 mol) of 1-chloro-4-(phenylsulfonyl)benzene in 150 ml of hexamethylphosphoramide. The mixture obtained is heated for 4 hours at 100°C and then cooled and hydrolyzed in an ice/water mixture. The reaction medium obtained is extracted with ethyl acetate and the aqueous phase obtained is then poured into a 4 N solution of hydrochloric acid at 0°C. The product formed precipitates. After filtration, washing with water until the pH of the washings is neutral, and drying, 13.44 g (yield: 90.5%) of the expected product are obtained.

M.p. = 117°C

I b) Preparation of 4-(phenylsulfonyl)phenyl 2,3,4-tri-O-acetyl-1,5-dithio- β -D-xylopyranoside (Example 1)

10.6 g of mercuric cyanide ($\text{Hg}(\text{CN})_2$) are added
05 under nitrogen to a solution of 10 g (0.0399 mol) of 1-
mercapto-4-(phenylsulfonyl)benzene in 300 ml of a
toluene/nitromethane mixture (1/1 v/v) and the mix-
ture obtained is then stirred for 1 hour at 40-45°C.
Precipitation is observed. 17.7 g (0.0498 mol) of
10 2,3,4-tri-O-acetyl-1-bromo-5-thio- β -D-xylopyranoside
are then added to the mixture. After stirring for
3.5 h at 40-45°C, the reaction medium becomes clear.
The organic phase obtained after cooling is washed
successively with a 1 N solution of hydrochloric acid
15 at 0°C, a 1 N solution of sodium hydroxide at 0°C,
water and then a saturated solution of sodium chloride.
After evaporation of the solvents, 24 g of a yellow
foam are obtained which crystallizes on the addition of
ether. 8.6 g of the expected product (yield: 41%) are
20 finally obtained.

M.p. = 159°C

$[\alpha]_D^{25} = +58.2^\circ$ (c = 0.5; CHCl_3)

25 I c) Preparation of 4-(phenylsulfonyl)phenyl 1,5-di-
thio- β -D-xylopyranoside (Example 2)

A solution of 0.35 cm³ of sodium methylate in
methanol (3.5 molar) is added to a suspension of 6.5 g
30 of 4-(phenylsulfonyl)phenyl 2,3,4-tri-O-acetyl-1,5-
dithio- β -D-xylopyranoside in 150 ml of methanol. The
mixture obtained is stirred at room temperature for
1.5 h under nitrogen and 250 cm³ of tetrahydrofuran are
then added. A clear solution is obtained, after which
35 Amberlite® IR 120 H⁺ resin is added to pH 6. The

mixture is filtered and the solvents are evaporated off under reduced pressure. After recrystallization from a methanol/water mixture (50/50 v/v), followed by dissolution in an ethanol/water mixture (50/50 v/v) and lyophilization, 3.3 g of the expected product (yield: 67%) are obtained.

M.p. = melting range from 85°C to 97°C

$[\alpha]_D^{23} = +44.8^\circ$ (c = 0.42; dimethyl sulfoxide)

PREPARATION II

II a) Preparation of 1-bromo-2-(methylsulfonyl)benzene

A solution of 5 g (0.0246 mol) of 1-bromo-2-(methylthio)benzene in 10 ml of methanol is cooled to 0°C under a nitrogen atmosphere and 1.27 g of 50% 3-chloroperoxybenzoic acid (MCPBA) are then added. Stirring at 0°C is maintained for 45 minutes, 6 g of potassium fluoride are then added and hydrolysis is continued for 12 hours. The medium obtained is filtered on Célite® and the product obtained after evaporation of the solvents is then purified by flash chromatography using a toluene/ethyl acetate mixture (95/5 v/v) as the eluent. 5.63 g (yield: 97%) of the expected product are obtained.

M.p. = 98°C

II b) Preparation of 2-(methylsulfonyl)benzenethiol

The expected product is obtained by following a procedure analogous to Preparation I a).

M.p. = 57°C

II c) Preparation of 2-(methylsulfonyl)phenyl 2,3,4-tri-O-acetyl-1,5-dithio-β-D-xylopyranoside (Example 3)

8.43 g (0.0251 mol) of 1-bromo-2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranoside are added to a mixture of 4.3 g (0.0228 mol) of 1-mercapto-2-(methylsulfonyl)-benzene and 1.95 g of zinc oxide in 90 ml of toluene/acetonitrile (1/1 v/v) and the mixture obtained is heated at 45°C for 2 hours. The medium obtained is filtered on Célite® and the organic phase is then washed with a 1 N solution of HCl, a 1 N solution of sodium hydroxide and then water until the pH of the washings is neutral. After evaporation of the solvents under reduced pressure, an oil is obtained which crystallizes on the addition of ether. The 5.33 g of crystalline product obtained are then purified by flash chromatography using a toluene/ethyl acetate mixture (8/2 v/v) as the eluent. 4.35 g (yield: 41%) of the expected product are obtained.

M.p. = 209°C
[α]_D²⁰ = +38.4° (c = 0.5; CHCl₃)

II d) Preparation of 2-(methylsulfonyl)phenyl 1,5-dithio-β-D-xylopyranoside (Example 4)

The expected product is obtained by following a procedure analogous to Preparation I c).

M.p. = 139°C
[α]_D²⁰ = +38.8° (c = 0.5; CH₃OH)

PREPARATION III

III a) Preparation of 4-(methylsulfonyl)phenyl 2,3,4-tri-O-acetyl-1,5-dithio-β-D-xylopyranoside (Example 5)

05

By following a procedure analogous to Preparation II c), a colorless oil is obtained which crystallizes from ether.

10

M.p. = 105-110°C

$[\alpha]_D^{20} = +71^\circ$ (c = 0.5; CHCl₃)

III b) Preparation of 4-(methylsulfonyl)phenyl 1,5-dithio-β-D-xylopyranoside (Example 6)

15

By following a procedure analogous to Preparation I c), the expected product is obtained after recrystallization from a methanol/ethanol mixture.

20

M.p. > 250°C

$[\alpha]_D^{20} = +19.2^\circ$ (c = 0.5; CH₂Cl₂/CH₃OH (1/1 v/v))

PREPARATION IV

25

IV a) Preparation of 4-(methylsulfonyl)phenyl 2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranoside (Example 7)

30

A mixture of 2 g (0.012 mol) of 1-hydroxy-4-(methylsulfonyl)benzene, 3.17 g of zinc chloride (ZnCl₂), 4.5 g (0.013 mol) of 1-bromo-2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranoside and 3.1 g (0.0177 mol) of silver imidazolate (C₃H₃AgN₂) in 70 ml of methylene chloride is heated for 20 hours at 50°C. After cooling, the reaction medium is filtered, the organic phase obtained is then washed successively with a 1 N

35

solution of hydrochloric acid, water and a 1 N solution of sodium hydroxide and the solvent is then evaporated off under reduced pressure. 1.1 g of the expected product (yield: 21.2%) are obtained after purification
05 by flash chromatography using a toluene/ethyl acetate mixture (3/1 v/v) as the eluent, followed by precipitation in ethyl ether.

M.p. = 168°C
10 $[\alpha]_D^{22} = -75^\circ$ (c = 0.6; CHCl₃)

IV b) Preparation of 4-(methylsulfonyl)phenyl 5-thio-β-D-xylopyranoside (Example 8)

15 The expected product is obtained, after lyophilization, by following a procedure analogous to Preparation I c).

M.p. = 180°C
20 $[\alpha]_D^{22} = -77.2^\circ$ (c = 0.5; CH₃OH)

PREPARATION V

25 V a) Preparation of 4-(ethylsulfonyl)benzenethiol

The expected product is obtained in the form of an oil by following a procedure analogous to Preparation I a).

30 $n_D^{24} = 1.5891$

V b) Preparation of 4-(ethylsulfonyl)phenyl 2,3,4-tri-O-acetyl-1,5-dithio-β-D-xylopyranoside (Example 9)

35 The expected product is obtained by following a

procedure analogous to Preparation I b).

M.p. = 136-137°C

$[\alpha]_D^{23} = +36.7^\circ$ (c = 0.45; CHCl₃)

05

V c) Preparation of 4-(ethylsulfonyl)phenyl 1,5-dithio-
β-D-xylopyranoside (Example 10)

10 The expected product is obtained by following a
procedure analogous to Preparation I c).

M.p. = 130-135°C

$[\alpha]_D^{23} = +26.8^\circ$ (c = 0.485; methanol)

15

PREPARATION VI

VI a) Preparation of 4-(methylsulfonyl)phenyl 2,3,4-
tri-O-acetyl-1,5-dithio-β-D-xylopyranoside (Example 11)

20 The expected product is obtained by following a
procedure analogous to Preparation II c).

M.p. = 147-150°C

$[\alpha]_D^{21} = -10.5^\circ$ (c = 0.3; CHCl₃)

25

VI b) Preparation of 4-(methylsulfonyl)phenyl 1,5-di-
thio-β-D-xylopyranoside (Example 12)

30 The expected product is obtained by following a
procedure analogous to Preparation I c).

M.p. = 169-172°C

$[\alpha]_D^{22} = -12.2^\circ$ (c = 0.45; dimethyl sulfoxide)

35

PREPARATION VII

VII a) Preparation of 4-[(4-fluorophenyl)sulfonyl]-benzenethiol

05

A solution of sodium nitrite (302 mg in 1 ml of water) is added to a suspension of 1 g (0.00398 mol) of 4-[(4-fluorophenyl)sulfonyl]benzeneamine in a solution of hydrochloric acid (1.68 ml of concentrated hydrochloric acid in 5 ml of water) at -5°C. After stirring for 5 minutes, this solution is added dropwise to a solution of 2.47 g of potassium ethylxanthate in 5 ml of water at 70°C. The reaction mixture is diluted with ethyl acetate. The organic phase is washed with a 1 N solution of sodium hydroxide and a saturated solution of sodium chloride and then dried over magnesium sulfate. After evaporation of the solvents, the residue is taken up in 15 ml of ethanol. 1.47 g of potassium hydroxide are added and the reaction mixture is heated at 45°C for 10 minutes. It is then poured into iced water and partially purified by extraction with ethyl acetate. The aqueous phase, cooled with ice, is rendered acidic by the addition of concentrated hydrochloric acid and is then extracted with ethyl acetate. The organic phase is dried over magnesium sulfate and the solvents are evaporated off to dryness. 640 mg (yield: 60%) of the expected product are thus obtained.

30

M.p. = 116°C

VII b) Preparation of 4-[(4-fluorophenyl)sulfonyl]-phenyl 2,3,4-tri-O-acetyl-1,5-dithio-β-D-xylopyranoside (Example 13)

35

The expected product is obtained by following a

procedure analogous to Preparation II c).

M.p. = 80°C

$[\alpha]_D^{21} = +48.4^\circ$ (c = 0.5; CHCl₃)

05

VII c) Preparation of 4-[(4-fluorophenyl)sulfonyl]-phenyl 1,5-dithio-β-D-xylopyranoside (Example 14)

10 The expected product is obtained by following a procedure analogous to Preparation I c).

M.p. = 136-138°C

$[\alpha]_D^{21} = +40^\circ$ (c = 0.5; dimethyl sulfoxide)

15

PREPARATION VIII

VIII a) Preparation of 4-[(4-methoxyphenyl)sulfonyl]-benzonitrile

20

6 g (0.0248 mol) of 4-[(4-methoxyphenyl)thio]-benzonitrile and then 18.45 g of magnesium monoperoxyphthalate hexahydrate are added to a mixture of 120 ml of ethanol and 12 ml of water. The reaction medium is kept at 40°C for 20 minutes. After hydrolysis in iced water, the solution is filtered and the white solid is washed with water. 5.2 g (yield: 77%) of the expected product are thus obtained.

25

M.p. = 135°C

30

VIII b) Preparation of 4-[(4-hydroxyphenyl)sulfonyl]-benzonitrile

35 A mixture of 5.12 g (0.0187 mol) of 4-[(4-methoxyphenyl)sulfonyl]benzonitrile and 21.6 g of pyri-

dinium hydrochloride is kept at 200°C for 2 hours. After cooling, the reaction medium is hydrolyzed in a 1 N solution of hydrochloric acid. The precipitate formed is filtered off and rinsed with a 1 N solution
05 of hydrochloric acid and then with water until the pH of the washings is neutral. 4.5 g (yield: 99%) of the expected product are thus obtained in the form of a gray solid.

10 M.p. = 177°C

VIII c) Preparation of O-[4-((4-cyanophenyl)sulfonyl)-phenyl] dimethylthiocarbamate

15 2.36 g (0.0097 mol) of 4-[(4-hydroxyphenyl)-sulfonyl]benzonitrile are added to a solution of 570 mg of potassium hydroxide in 35 ml of water. The solution is kept at room temperature for 15 minutes. After cooling to 0°C, a solution of 1.38 g of N,N-dimethyl-
20 thiocarbamoyl chloride in 35 ml of acetone is added dropwise. After 4 hours, the reaction mixture is hydrolyzed in a 1 N solution of hydrochloric acid. The solution is extracted with ethyl acetate. The organic phase is washed with water until the pH of the washings
25 is neutral, dried over magnesium sulfate and concentrated to dryness. 3 g (yield: 100%) of the expected product are thus obtained.

M.p. = 158-167°C

30

VIII d) Preparation of S-[4-((4-cyanophenyl)sulfonyl)-phenyl] dimethylthiocarbamate

35 3 g (0.0096 mol) of O-[4-((4-cyanophenyl)sulfonyl)phenyl] dimethylthiocarbamate are kept at 200°C

for 30 minutes. After chromatography on silica gel using a toluene/ethyl acetate mixture (8/2 v/v) as the eluent, 2.29 g (yield: 76%) of the expected product are obtained.

05

M.p. = 140°C

VIII e) Preparation of 4-[(4-mercaptophenyl)sulfonyl]-benzonitrile

10

4.1 ml of sodium methylate (8% of Na (w/v) in methanol) are added to a solution of 2.25 g (0.0075 mol) of S-[4-((4-cyanophenyl)sulfonyl)phenyl] dimethylthiocarbamate in 45 ml of N,N-dimethylformamide at 0°C.

15

The reaction mixture is then hydrolyzed in an iced 1 N solution of hydrochloric acid. After filtration, the precipitate formed is washed with water and then dried. 1.54 g (yield: 78%) of the expected product are thus obtained.

20

M.p. = 166°C

VIII f) Preparation of 4-((4-cyanophenyl)sulfonyl)-phenyl 2,3,4-tri-O-acetyl-1,5-dithio-β-D-xylopyranoside

25

(Example 15)

The expected product is obtained by following a procedure analogous to Preparation I b).

30

M.p. = 194-195°C

$[\alpha]_D^{20} = +51^\circ$ (c = 0.5; CHCl₃)

35

VIII g) Preparation of 4-((4-cyanophenyl)sulfonyl)-phenyl 1,5-dithio-β-D-xylopyranoside (Example 16)

05 The expected product is obtained by following a procedure analogous to Preparation I c).

M.p. = 175-183°C

$[\alpha]_D^{20} = +58.6^\circ$ (c = 0.5; dimethyl sulfoxide)

10 PREPARATION IX

IX a) Preparation of 4-(N,N-dimethylsulfonamidyl)phenyl 2,3,4-tri-O-acetyl-1,5-dithio-β-D-xylopyranoside (Example 17)

15

The expected product is obtained by following a procedure analogous to Preparation I b).

M.p. = 120°C

20 $[\alpha]_D^{20} = +35.4^\circ$ (c = 0.56; CHCl₃)

IX b) Preparation of 4-(N,N-dimethylsulfonamidyl)phenyl 1,5-dithio-β-D-xylopyranoside (Example 18)

25

The expected product is obtained by following a procedure analogous to Preparation I c).

M.p. = 208-213°C

$[\alpha]_D^{24} = +21.4^\circ$ (c = 0.42; dimethyl sulfoxide)

30

35

PREPARATION X

X a) Preparation of 4-(N,N-dimethylsulfonamidyl)phenyl
2,3,4-tri-O-acetyl-5-thio-β-D-xylopyranoside

05 (Example 19)

The expected product is obtained by following a procedure analogous to Preparation IV a).

10 M.p. = 85°C then 164-167°C (double melting point)
[α]_D²⁵ = -57.6° (c = 0.33; CHCl₃)

X b) Preparation of 4-(N,N-dimethylsulfonamidyl)phenyl
5-thio-β-D-xylopyranoside (Example 20)

15

The expected product is obtained by following a procedure analogous to Preparation I c).

M.p. = 205°C
20 [α]_D²¹ = -70.4° (c = 0.27; methanol)

PREPARATION XI

XI a) Preparation of 4-mercapto-N-(piperidin-1-yl)-
25 benzenesulfonamide

The expected product is obtained by following a procedure analogous to Preparation I a).

30 M.p. = 93°C

35

XI b) Preparation of 4-(N-(piperidin-1-yl)sulfonamidyl)phenyl 2,3,4-tri-O-acetyl-1,5-dithio-β-D-xylopyranoside (Example 21)

05 The expected product is obtained by following a procedure analogous to Preparation I b).

M.p. = 175-180°C

$[\alpha]_D^{22} = +39.8^\circ$ (c = 0.425; CHCl₃)

10

XI c) Preparation of 4-(N-(piperidin-1-yl)sulfonamidyl)phenyl 1,5-dithio-β-D-xylopyranoside (Example 22)

15 The expected product is obtained by following a procedure analogous to Preparation I c).

M.p. = 145-149°C

$[\alpha]_D^{22} = +23.8^\circ$ (c = 0.21; methanol)

20

PREPARATION XII

XII a) Preparation of 4-mercapto-N-(morpholin-1-yl)-benzenesulfonamide

25

 The expected product is obtained by following a procedure analogous to Preparation I a).

M.p. = 128°C

30

XII b) Preparation of 4-(N-(morpholin-1-yl)sulfonamidyl)phenyl 2,3,4-tri-O-acetyl-1,5-dithio-β-D-xylopyranoside (Example 23)

35 The expected product is obtained by following a

procedure analogous to Preparation I b).

M.p. = 120-123°C

$[\alpha]_D^{22} = +39^\circ$ (c = 0.39; CHCl₃)

05

XII c) Preparation of 4-(N-(morpholin-1-yl)sulfonamidyl)phenyl 1,5-dithio-β-D-xylopyranoside
(Example 24)

10

The expected product is obtained by following a procedure analogous to Preparation I c).

M.p. = 90-105°C

$[\alpha]_D^{22} = +20.4^\circ$ (c = 0.56; dimethyl sulfoxide)

15

The compounds according to the invention have been collated in Table I below, without implying a limitation.

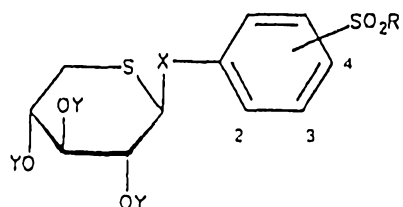
20 The antithrombotic activity of the products according to the invention was demonstrated using the following operating protocol for venous thrombosis:

A venous stasis under hypercoagulation is produced according to the technique described by WESSLER et al. (J. Applied Physiol. 1959, p. 943-946).
25 As in the technique described by J. HAUPMAN et al. (Thrombosis and Haemostasis 43(2), 1980, p. 118), the hypercoagulant used is a solution of activated factor X (Xa) supplied by Flow Laboratories (71 Knat per 12.5 ml of isotonic solution).

30 The study is performed on unfasted male Wistar rats weighing 250 to 280 g, divided into groups of 10 animals each. The test products are administered orally as a suspension in PEG 400. A thrombosis is induced 4 hours after this treatment and the thrombus
35 formed is removed and weighed.

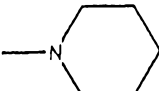
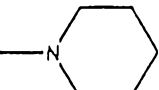
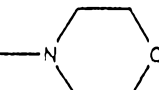
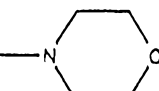
The results obtained at a dose of 3 mg/kg, administered orally, have been collated in Table I. The results obtained with the known products of the afore-mentioned prior art have also been collated in this Table.

TABLE I



Example	X	Position of SO ₂ R	R	Y	% inhibition at 3 mg/kg
1	S	4	-C ₆ H ₅	-COCH ₃	20
2	S	4	-C ₆ H ₅	-H	49
3	S	2	-CH ₃	-COCH ₃	29
4	S	2	-CH ₃	-H	26
5	S	4	-CH ₃	-COCH ₃	-
6	S	4	-CH ₃	-H	61
7	O	4	-CH ₃	-COCH ₃	-
8	O	4	-CH ₃	-H	30
9	S	4	-CH ₂ -CH ₃	-COCH ₃	31
10	S	4	-CH ₂ -CH ₃	-H	31
11	S	3	-CH ₃	-COCH ₃	-
12	S	3	-CH ₃	-H	43
13	S	4	4-F-C ₆ H ₅	-COCH ₃	58
14	S	4	4-F-C ₆ H ₅	-H	61
15	S	4	4-CN-C ₆ H ₅	-COCH ₃	-
16	S	4	4-CN-C ₆ H ₅	-H	66
17	S	4	-N(CH ₃) ₂	-COCH ₃	56
18	S	4	-N(CH ₃) ₂	-H	46
19	O	4	-N(CH ₃) ₂	-COCH ₃	23
20	O	4	-N(CH ₃) ₂	-H	58

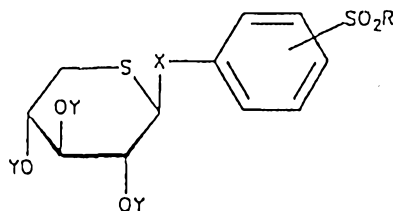
TABLE I (end)

Example	X	Position of SO ₂ R	R	Y	% inhibition at 3 mg/kg
21	S	4		-COCH ₃	-
22	S	4		-H	47
23	S	4		-COCH ₃	-
24	S	4		-H	-
A	Comparative product described in Example 1 of EP-A-0 133 103				14(1)
B	Comparative product described in Example 97 of EP-B-0 051 023				5.5(1)
C	Comparative product described in Example 3 of EP-A-0 290 321				20(2)

Notes: (1) product tested at 12.5 mg/kg, administered orally.
(2) product tested at 3 mg/kg, administered orally

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. An oside compound selected from the group consisting of the sulfonylphenyl- β -D-thioxylosides of the formula



(I)

in which:

- X is a sulfur atom or an oxygen atom;
- R is a C_1 - C_4 alkyl group, a substituted amino group NR_1R_2 (where R_1 and R_2 , which are identical or different, are each a C_1 - C_4 alkyl group, it being possible for R_1 and R_2 , taken together, to form a piperidinyl or morpholinyl group with the nitrogen atom to which they are bonded) or a phenyl group which is unsubstituted or substituted in the para position by a cyano group or by a halogen atom; and
- Y is a hydrogen atom or a C_2 - C_5 aliphatic acyl group.

2. An oside compound according to claim 1, wherein X is the sulfur atom.

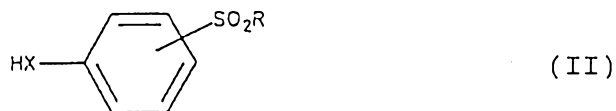
3. An oside compound according to claim 1 wherein Y is CH_3CO .

4. A therapeutic composition containing, in association with a physiologically acceptable excipient, at least one oside compound according to any one of claims 1 to 3.

5. Use of a substance according to any one of claims 1 to 3 in order to obtain an antithrombotic drug for use in therapeutics to combat disorders of the venous circulation.

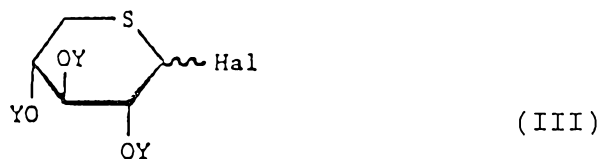


6. A method of preparing a sulfonylphenyl- β -D-thioxylo-
side of formula I according to claim 1, which comprises
(i) reacting a compound of the formula

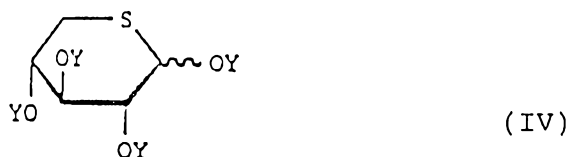


in which X and R are as defined above,
with a thioxylose derivative selected from the group
consisting of

(i) the acylthioxylosyl halides of the formula

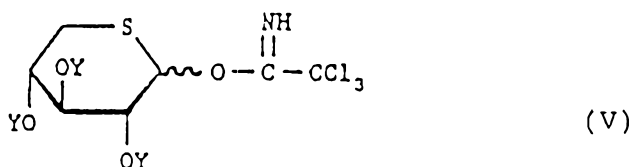


(ii) the peracylated thioxyloses of the formula



and

(iii) the acylthioxylosyl trichloroacetimidates of
the formula



in which Hal is a halogen atom such as Cl or Br ~~(the~~



and Y is a C₂-C₅ aliphatic acyl group, in an inert solvent, at a rate of 1 mol of II to about 0.6 to 1.2 mol of compound III, IV or V, in the presence of an acid acceptor and/or a Lewis acid, and

- 5 (ii) if necessary, subjecting the resulting compound of formula I in which Y is a C₂-C₅ aliphatic acyl group to a deacylation reaction at a temperature of the reaction medium, in a C₁-C₄ lower alcohol (preferably methanol), in the presence of a metal alcoholate (preferably magnesium methylate or sodium methylate), to give a compound of formula I in which Y is H.
- 10

7. A method according to claim 6, wherein, in addition, the compound of formula II in which X is the sulfur atom, involved in stage (i), is prepared according to the following steps:

- 15 a) condensation of dimethylaminothiocarbamoyl chloride of the formula

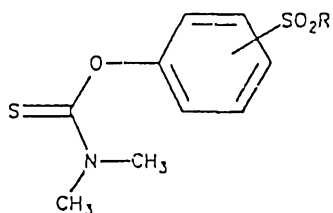


25 in a strong basic medium with a compound of the formula



30 in which R₁ and R₂ are as defined above, to give a compound of the formula

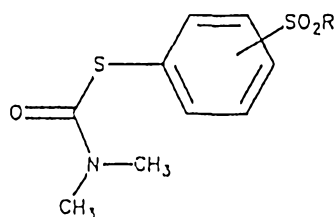




(VII)

in which R_1 and R_2 are as defined above,

b) rearrangement of the resulting compound of formula VII, by heating, to give a compound of the formula

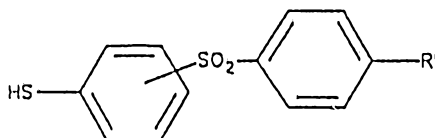


(VIII)

in which R_1 and R_2 are as defined above, and

c) treatment of the resulting compound of formula VIII with a metal alcoholate, preferably sodium or magnesium methylate, in a C_1 - C_4 lower alcohol, dimethylformamide or dioxane, to give a compound of formula II in which $X = S$.

8. ~~A novel~~^{An} intermediate involved in the synthesis of the sulfonylphenyl- β -D-thioxylosides of formula I in which X is the sulfur atom, according to claim 2, selected from the group consisting of the compounds of the formula



in which:

- R' is a fluorine atom, a bromine atom or a cyano group.



9. An oside compound substantially as herein described in the non-comparative examples.

10. A method according to claim 6, wherein Hal in formula (V' is bromine.

5 11. A method according to claim 6, wherein Y is an acetyl group.

12. An oside compound according to claim 2, wherein the group $-SO_2R$ is in the 4-position of the benzene ring, R is methyl and Y is hydrogen.

10 13. An oside compound according to claim 2, wherein the group $-SO_2R$ is in the 4-position of the benzene ring, R is 4-fluorophenyl and Y is hydrogen.

15 14. An oside compound according to claim 2, wherein the group $-SC_2R$ is in the 4-position of the benzene ring, R is 4-cyanophenyl and Y is hydrogen.

DATED this 27th day of October 1992

FOURNIER INDUSTRIE ET SANTE

By their Patent Attorneys

CULLEN & CO.