

Patent No. 1410506
Foreign Applications
5 October 1971
25 May 1972

Date of Patent... 2 October 1972
Date of Sealing... 11 February 1976



Elizabeth the Second by the Grace of God of the United Kingdom of Great Britain and Northern Ireland and of Her other Realms and Territories, Queen, Head of the Commonwealth, Defender of the Faith: To all to whom these presents shall come greeting:

WHEREAS a request for the grant of a patent has been made by

Sandoz Ltd., 35 Lichtstrasse, 4002 Basle/Switzerland; a Swiss Body Corporate,

for the sole use and advantage of an invention for

A novel pleuromutilin derivative:

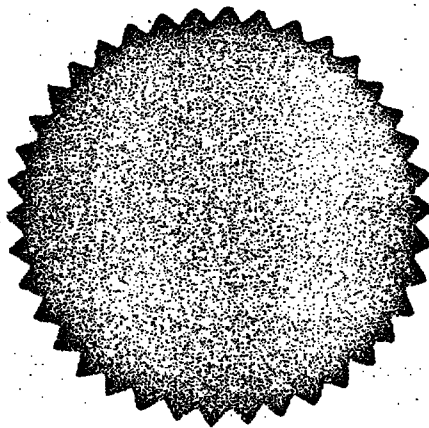
AND WHEREAS We, being willing to encourage all inventions which may be for the public good, are graciously pleased to condescend to the request:

KNOW YE, THEREFORE, that We, of our especial grace, certain knowledge, and mere motion do by these presents, for Us, our heirs and successors, give and grant unto the person(s) above named and any successor(s), executor(s), administrator(s) and assign(s) (each and any of whom are hereinafter referred to as the patentee) our especial licence, full power, sole privilege, and authority, that the patentee or any agent or licensee of the patentees and no others, may subject to the conditions and provisions prescribed by any statute or order for the time being in force at all times hereafter during the term of years herein mentioned, make, use, exercise and vend the said invention within our United Kingdom of Great Britain and Northern Ireland, and the Isle of Man, and that the patentee shall have and enjoy the whole profit and advantage from time to time accruing by reason of the said invention during the term of sixteen years from the date hereunder written of these presents: AND to the end that the patentee may have and enjoy the sole use and exercise and the full benefit of the said invention, We do by these presents for Us, our heirs and successors, strictly command all our subjects whatsoever within our United Kingdom of Great Britain and Northern Ireland, and the Isle of Man, that they do not at any time during the continuance of the said term either directly or indirectly make use of or put in practice the said invention, nor in anywise imitate the same, without the written consent, licence or agreement of the patentee, on pain of incurring such penalties as may be justly inflicted on such offenders for their contempt of this our Royal Command, and of being answerable to this patentee according to law for damages thereby occasioned:

PROVIDED ALWAYS that these letters patent shall be revocable on any of the grounds from time to time by law prescribed as grounds for revoking letters patent granted by Us, and the same may be revoked and made void accordingly:

PROVIDED ALSO that nothing herein contained shall prevent the granting of licences in such manner and for such considerations as they may by law be granted: AND lastly, We do by these presents for Us, our heirs and successors, grant unto the patentee that these our letters patent shall be construed in the most beneficial sense for the advantage of the patentee.

IN WITNESS whereof We have caused these our letters to be made patent
as of the second day of October
one thousand nine hundred and seventy-two and to be sealed.



Edward Amis

Comptroller-General of Patents
Designs, and Trade Marks

PATENT SPECIFICATION

(11) 1410500

1410506

- (21) Application No. 16338/75 (22) Filed 2 Oct. 1972
 (62) Divided out of No. 1410505
 (31) Convention Application No. 14450/71 (32) Filed 5 Oct. 1971
 (31) Convention Application No. 7738/72 (32) Filed 25 May 1972 in
 (33) Switzerland (CH)
 (44) Complete Specification published 15 Oct. 1975
 (51) INT CL² C07C 149/26 A61K 31/13 31/14//A61K 31/13 31/045
 31/10 31/12)

(19)



(52) Index at acceptance

C2C 123X 200 225 227 22Y 290 29X 29Y 30Y 323 32Y 351
 353 360 362 366 368 36Y 373 37Y 612 620 650 790
 79Y RL

(72) Inventors HELMUT EGGER and
 HELLMUTH REINSHAGEN

(54) A NOVEL PLEUROMUTILIN DERIVATIVE

(71) We, SANDOZ LTD., of 35
 Lichtstrasse, 4002 Basle, Switzerland, a Swiss
 Body Corporate, do hereby declare the inven-
 tion, for which we pray that a patent may be
 granted to us, and the method by which it
 is to be performed, to be particularly des-
 cribed in and by the following statement:—

This invention relates to a 14 - desoxy
 mutilin derivative.

The present invention provides 14 -
 desoxy - 14 - [(2 - diethylaminoethyl)mer-
 captoacetoxy]mutilin in free base form or in
 the form of an acid addition or quaternary
 salt.

The compound 14 - desoxy - 14 - [(2 -
 diethylaminoethyl) - mercaptoacetoxy]mutilin
 has pharmacological activity. In particular,
 the compound is indicated for use as an
 antimicrobial agent as indicated, for example,
 in tests *in vitro* with the agar plate test, in
 tests in which an inhibiting effect towards
 mycoplasmas was observed, and *in vivo* by
 tests infected with different strains of bacteria.

An indicated suitable daily dosage is from
 about 50 to 1000 mg, preferably from 100
 to 500 mg, conveniently administered in
 divided dosages of from about 10 mg to 500
 mg or in sustained release form.

The compound is also indicated for use
 as a prophylactic additive for animal feeding
 stuffs and for animal drinking water. For
 such use, the indicated dosage is in the
 range from 0.05 to 5 p.p.m.

The compound may be admixed with con-
 ventional pharmaceutically acceptable diluents
 or carriers and may be administered in such
 forms as capsules or sterile injectable or in-
 stillation solutions, containing the compound.

The compound may be used in free base
 form or in the form of pharmaceutically
 acceptable acid addition or quaternary salt
 form. Such salt forms possess the same order

of activity as the free bases and are readily
 prepared in conventional manner. Suitable
 compounds for producing such salt forms in-
 clude organic acids such as maleic, fumaric
 or tartaric acid, mineral acids such as hydro-
 chloric, hydrobromic or sulphuric acid and
 quaternizing agents such as methyl chloride
 or iodide.

The invention also provides a pharmaceu-
 tical composition comprising the compound
 in free base or in pharmaceutically acceptable
 acid addition salt or quaternary salt form, in
 association with a pharmaceutically accept-
 able carrier or diluent.

The following Examples illustrate the in-
 vention, all temperatures being indicated in
 degrees Centigrade.

EXAMPLE 1

14 - Desoxy - 14 - [(2 - diethylamino-
 ethyl)mercaptoacetoxy]mutilin

1.30 g of sodium are dissolved in 50 cc of
 absolute ethanol. 3.40 g of finely pulverized
 2 - diethylaminoethanethiol hydrochloride,
 dried over phosphorus pentoxide, are added
 portionwise to the resulting solution in an
 atmosphere of nitrogen. A solution of 10.60 g
 of 14 - desoxy - 14 - tosyloxyacetoxymutilin
 in 30 cc of ethylmethyl ketone is subsequently
 added dropwise while stirring. The reaction
 solution is stirred at room temperature for a
 further 4 hours, is subsequently kept at
 50—55° for 30 minutes and is then con-
 centrated almost to dryness. The residue is
 taken up in ethyl acetate and the base is ex-
 tracted therefrom with 3 portions of 2N
 hydrochloric acid. The base is again taken up
 in ethyl acetate from the aqueous phase which
 has been rendered alkaline (pH 11) with
 sodium hydroxide. The ethyl acetate layer is
 finally washed twice with water, dried over

[Price 33p]

sodium sulphate and concentrated by evaporation in a vacuum.

The hydrochloride salt may be obtained by concentrating by evaporation with methanolic hydrochloric acid *in vacuo* or by taking up in methylene chloride, adding an equivalent amount of ethereal hydrochloric acid and concentrating by evaporation *in vacuo*. After drying over potassium hydroxide, the hydrochloride salt having a softening point of about 100° is obtained.

The diethylmethyl ammonium iodide salt may be produced by boiling at reflux 926 mg of the heading compound in 15 cc of methanol with 3.2 cc of methyl iodide for 1 hour. The solution is strongly concentrated, ether is added until the solution becomes turbid and the solution strongly cooled. Precipitation is completed by further addition of ether, the precipitate being filtered with suction, thoroughly washed with ether and dried over phosphorus pentoxide to yield the diethylmethyl ammonium iodide salt having a softening point of 110—115°.

EXAMPLE 2

14 - Desoxy - 14 - [(2 - diethylaminoethyl)mercaptoacetoxy]mutilin

10.0 g of sodium are first dissolved in 350 cc of well dried 2 - diethylaminoethanethiol hydrochloride are added portionwise to the solution in an atmosphere of nitrogen. A solution of 79.5 g of 14 - desoxy - 14 - tosyloxyacetoxy mutilin in 250 cc of ethylmethyl ketone is subsequently added dropwise while stirring. After stirring at room temperature for 4 hours, the reaction solution is concentrated almost to dryness in a vacuum, is taken up in ethyl acetate and carefully washed with ice water. The ethyl acetate solution is then dried over magnesium sulphate and concentrated by evaporation in a vacuum. The residue of the crude base is dissolved in 80 cc of methylene chloride, and 40 cc of 5.8 N hydrochloric acid in ether are added. The solvent is evaporated, the evaporation residue is taken up in 120 cc

of methanol, the solution is poured into 700 cc of distilled water and is extracted 5 times with a total of 700 cc of ether. The aqueous solution of the hydrochloride, which is homogeneous in accordance with thin layer chromatography, is filtered and then concentrated in a vacuum at a bath temperature of approximately 30°, whereby a foamy product is obtained, which is dried in a vacuum at 60° over potassium hydroxide.

Processes for the production of 14 - desoxy - 14 - [(2 - diethylaminoethyl)mercaptoacetoxy]mutilin are described and claimed in our co-pending application number 45259/72 [specification number 1,410,505].

WHAT WE CLAIM IS:—

1. 14 - Desoxy - 14 - [(2 - diethylaminoethyl)mercaptoacetoxy]mutilin.

2. The compound of claim 1, in free base form.

3. The compound of Claim 1, in the form of an acid addition salt.

4. The compound of Claim 1, in the form of a quaternary salt.

5. The compound of Claim 1, in the form of the hydrochloride salt.

6. The compound of Claim 1, in a fumaric acid addition salt form.

7. The compound of Claim 1, in the form of the diethylmethyl ammonium iodide salt.

8. A pharmaceutical composition comprising 14 - desoxy - 14 - [(2 - diethylaminoethyl)mercaptoacetoxy]mutilin, in free base or in pharmaceutically acceptable acid addition salt or quaternary salt form, in association with a pharmaceutically acceptable carrier or diluent.

9. A pharmaceutical composition according to Claim 8, substantially as herein described.

B. A. YORKE & CO.,
Chartered Patent Agents,
98, The Centre,
Feltham,
Middlesex TW 13 4 EP.