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Process for producing dithiobis-alkanesulfonates and phosphonates

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(71) Applicant(s)
BioNumerik Pharmaceuticals, Inc.

(72) Inventor(s)
Kochat Haridas

(74) Agent/Attorney
CARTER SMITH and BEADLE, Qantas House, 2 Railway Parade, CAMBERWELL VIC 3124

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(71) Applicants (for all designated States except US): BION-UMERIK PHARMACEUTICALS, INC. [US/US]; Suite 1250, 8122 Datapoint Drive, San Antonio, TX 78229 (US); LUCAS, Brian, Ronald [GB/GB]; Lucas & Co., 135 Westhall Road, Warrington, Surrey CR6 9HJ (GB).			
(72) Inventor; and (75) Inventor/Applicant (for US only): HARIDAS, Kochat [IN/US]; 2507 Steepleway, San Antonio, TX 78248 (US).			
(74) Agent: LUCAS & CO., 135 Westhall Road, Warrington, Surrey CR6 9HJ (GB).			
(54) Title: PROCESS FOR PRODUCING MERCAPTOALKANESULFONATES AND PHOSPHONATES AND DERIVATIVES THEREOF DIETHIOBISALKANESULFONATES AND PHOSPHONATES			
(57) Abstract A two step single-pot process for producing dimesna ($\text{NaSO}_3-(\text{CH}_2)_2-\text{S}-\text{S}-(\text{CH}_2)_2-\text{SO}_3\text{Na}$) begins by reacting an ω-alkenesulfonate with a sulfide such as NaSH to yield mesna ($\text{HS}-(\text{CH}_2)_2-\text{SO}_3\text{Na}$). (This can be isolated or converted to a C_{1-4} thioalkyl ether thereof by reaction with sodium alkoxide and an alkyl halide). In the second step, mesna is oxidised <i>in situ</i> with oxygen gas to yield dimesna. Higher alkane homologues and analogous phosphonates are prepared similarly. When preparing a phosphonate analogue a haloalkane phosphonate is an alternative starting compound. The C_{1-4}-alkylene chain analogues of these compounds can be prepared similarly.			



PROCESS FOR PRODUCING DIETHIOBIS-ALKANESULFONATES
AND PHOSPHONATES

FIELD OF THE INVENTION

This invention relates to a process for producing
5 dithiobis-alkanesulfonates and phosphonates especially
disodium 2,2'-(dithiobis)ethane sulfonate (dimesna;
 $\text{NaSO}_3\text{CH}_2\text{CH}_2\text{-S-S-CH}_2\text{CH}_2\text{SO}_3\text{Na}$).

BACKGROUND OF THE INVENTION

Compounds of the general formula:

10 (I): $\text{R}_2\text{-(CH}_2\text{)}_m\text{-S-S-(CH}_2\text{)}_m\text{-R}_2$

wherein R_2 is SO_3M or PO_3M_2 wherein M or each M
independently is sodium, potassium or hydrogen and m is
2, 3 or 4, are useful *inter alia* as chemotherapeutic
protective agents used to mitigate the toxicity of
15 platinum complex antitumor drugs which are given to
patients with certain types of cancer. Thus, dimesna can
be co-administered with cisplatin (cis-
diamminedichloroplatinum) to protect the body against
nephrotoxicity, and with carboplatin (cisdiammine-1,1-
20 cyclobutanedicarboxylatoplatinum) to protect the body
against myelosuppression.

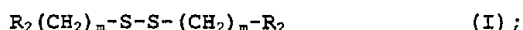
The chief prior processes for synthesizing dimesna
(and like disulfides) include the conversion of various
alkanesulfonic acids into their respective mercaptan
25 derivatives (such as mesna) and the subsequent oxidation
of the mercaptans into their respective disulfides (such
as dimesna) by use of iodine-containing reagents, such as
iodate. These processes, while efficient, required
isolation procedures to be performed to isolate and
30 purify the end products from the reagents used. These
processes generated environmental pollutants, which
required disposal and could not be carried out in a
single reaction vessel.



SUMMARY OF THE INVENTION

The present invention limits these disadvantages in the production of dimesna and provides a more convenient method of making dithiobis-alkanesulfonates and phosphonates.

The invention provides a process of producing compounds of the general formula:



wherein R_2 is SO_3M or PO_3M_2 wherein M is sodium,

potassium or hydrogen;

and m is 2, 3 or 4,

which comprises heating a mercaptan of formula:



wherein M is as defined above,

with oxygen gas under pressure.

The invention further provides a preferred process of making compounds of the general formula I, said process comprising

(1) reacting a compound of formula



wherein

X and Y together complete an olefinic carbon-carbon double bond or, where R_2 is PO_3M_2 , X can be halo and Y is then hydrogen;

n is 0, 1 or 2; and

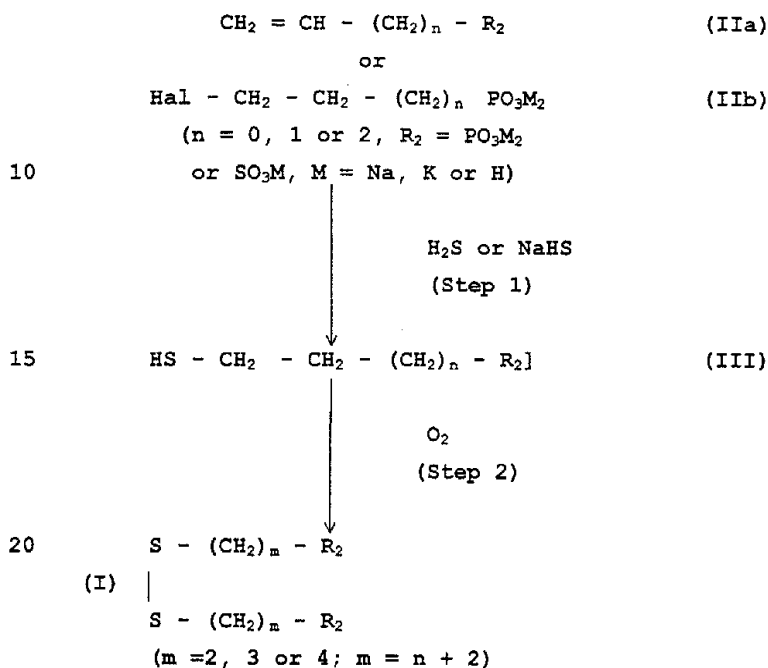
R_2 is as defined above, with a sulfide of the general formula $Z-SH$, wherein Z is hydrogen, sodium or potassium, provided that where R_2 is PO_3M_2 , the reaction is carried out in the presence of a free radical initiator when X and Y together represent a said double bond or with the aid of heat when X represents halo and Y is hydrogen;

to form a mercaptan of formula $HS-(CH_2)_m-R_2$; wherein R_2 and m are as defined above, and



(2) heating the mercaptan produced in Step (1) with oxygen gas, under pressure, to produce the compound of formula (I).

The preferred process is summarised by the following chart:



DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred process of this invention for preparing the compounds of formula I involves two steps in a single-pot, which results in the conversion of an alkenyl sulfonate salt or acid (^ω-alkenesulfonate or -sulfonic acid) to the desired formula I compound, especially dimesna which can be produced thereby in a highly pure form, on a large scale.

Step 1 involves the addition of a sulfhydryl moiety in an anti-Markovnikov fashion to the unsaturated terminal double bond by generating an sp³ center. The



addition to the double bond is effected by reacting the starting alkenyl sulfonate salt with a hydrosulfide salt or with hydrogen sulfide, preferably in a slightly basic solution (pH from 8 to 9.5). The sulfide is preferably present in at least a stoichiometric proportion and usually in a molar excess of at least 2:1, preferably from 3:1 to 5:1. This step forms a mercapto- (alternatively termed a sulfhydryl-) alkanesulfonate.

Step 2 of this process involves the oxidization of the mercaptoalkanesulfonate to a disulfide and is performed in an aqueous medium and in the same reaction vessel as step 1, without the need to purify or isolate the product of step 1. Step 2 includes the introduction of oxygen gas, preferably by bubbling, into the reaction vessel, along with an increase in pressure and temperature above ambient values, preferably at a slightly basic pH. The preferred pH is from 8 to 9.5. It can remain unadjusted from step 1 which is a big advantage. The preferred temperature is at least 40°, most preferably at least 60°C. A range of 40 to 100°C is contemplated for most purposes. The preferred gauge (superatmospheric) pressure is at least 20psi (138 kPa), more preferably at least 30psi (207 kPa) and most desirably at least 50psi (345kPa). A range of 20 to 60psi (138 to 414kPa) is contemplated for most purposes. Dimesna or a homologue or analogue thereof can be formed in substantially quantitative yield. The desired final product can be easily crystallized from the aqueous reaction medium itself.

When a phosphonate of formula I is desired, the starting compound can be a haloalkanephosphonate, preferably a bromoalkane- or chloroalkanephosphonate. Preferably n is 0 or 1, the starting material then being a haloethane- or halopropanephosphonate. The two step,



single pot process involves first the treatment of this starting compound with sodium hydrosulfide or hydrogen sulfide at elevated temperature, especially from 40 to 120°. The sulfide is preferably used in molar excess, as described above. Alternatively, step 1 may be achieved by converting the alkenephosphonic acid to the mercaptan by addition of a sulfur source, conditions and reagents being as described above, in the presence of a free radical initiator. Step 2, the oxidation to the disulfide, is the same as described above.

The following non-limiting examples illustrate the invention.

EXAMPLE 1

Disodium 2,2'-(dithiobis)ethanesulfonate

100mL of a 25% aqueous stock solution (25 grams VSA, 0.192 mole) of vinylsulfonic acid (VSA) sodium salt (Aldrich Chemical Company) was taken up in a Parr vessel, and argon gas bubbled in for one hour to deoxygenate the aqueous solution. To this solution was added 33.5 grams (0.598 mole, reckoned as NaSH) of sodium hydrosulfide monohydrate (Aldrich Chemical Company) and 10mL of sodium hydroxide. The pH of the solution was approximately 9.0. The reaction mixture was agitated in a Parr apparatus for two hours, during which time NMR monitoring was conducted at 30 minute intervals.

The product obtained from this step was taken to the next step without isolation, heated to 60°C, and oxygen bubbled into the vessel for thirty minutes. The vessel was then pressurized to 50psi (345kPa) gauge and agitated for six more hours at 60°C.

The completed reaction mixture was then worked up by concentrating the aqueous fraction at 80°C using an industrial vacuum, followed by diffused recrystallization from water. The crystallized product was then



lyophilized after adjusting the pH to 7.2 by adding 1N HCl and filtering through a 0.2 micrometre pore membrane filter. NMR and elemental analysis confirmed the presence of pure (99%) disodium 2,2'-(dithiobis)ethanesulfonate.

EXAMPLE 2

Tetrasodium 2,2'-(dithiobis)ethanephosphonate
2-Chloroethanephosphonic acid (1 gram; 6.9 mmoles) was taken up in anhydrous ethanol (10ml) and degassed with a continuous stream of argon for at least 30 minutes. This was then added to a boiling solution of sodium hydrosulfide hydrate (1.4 g, 25 mmol, reckoned as NaSH) in ethanol to obtain a reaction mixture with a final pH of approximately 9. The resultant reaction mixture was then refluxed for 10 hours. The reaction mixture was then cooled and the pH adjusted to 8 using 1N HCl. The solvent was removed and the product was purified by diffused crystallization. The white solid was then taken into a Parr bottle and 50 ml water added. The aqueous solution was then bubbled with a stream of oxygen for a period of at least one hour. Then the bottle was pressurized with 50psi (345kPa) gauge oxygen and shaken at 60°C for 4 hours. The product was isolated by concentrating the aqueous portion to half at 80°C under industrial vacuum, followed by crystallization. The product thus obtained was then characterized by high field NMR and elemental analysis and by comparing with an authentic sample.

EXAMPLE 3

Tetrasodium 2,2'-(dithiobis)ethanephosphonate
Example 2 was repeated except that the same molar amount of 2-bromoethanephosphonic acid was used as the starting material and the ethanol solvent replaced by water. The title compound thus obtained was then



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characterized by high field NMR and elemental analysis
and by comparing with an authentic sample.

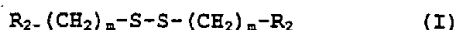
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THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process of producing compounds of the general formula:



5 wherein R_2 is SO_3M or PO_3M_2 wherein M is sodium, potassium or hydrogen;
and m is 2, 3 or 4,

which comprises heating a mercaptan of formula:



10 wherein m is as defined above,

with oxygen gas under pressure.

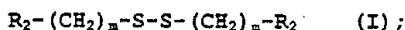
2. A process according to Claim 1, wherein the pressure is at least 20 psi (138 kPa) gauge and the reaction is carried out at a temperature of at least 60°C.

15 3. A process according to Claim 2, wherein the pressure is at least 30 psi (207 kPa) gauge.

4. A process according to Claim 1, 2 or 3 wherein R_2 is SO_3M and m is 2.

20 5. A process according to Claim 4, wherein M is sodium and the product is dimesna.

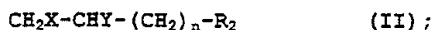
6. A process for producing compounds of the general formula:



25 wherein R_2 is SO_3M or PO_3M_2 wherein M is sodium, potassium or hydrogen and m is 2, 3 or 4,

which comprises:

(1) reacting a compound of formula



30 wherein X and Y together complete an olefinic carbon-carbon double bond, or, where R_2 is PO_3M_2 , X can be halo and Y is then hydrogen;

n is 0, 1 or 2; and

R_2 is as defined as above,



with a sulfide of the general formula Z-SH, wherein Z is hydrogen, sodium or potassium; provided that where R_2 is PO_3M_2 , the reaction is carried out in the presence of a free radical initiator when X and Y together complete a said double bond or with the aid of heat when X represents halo and Y is hydrogen;

to form a mercaptan of formula $HS-(CH_2)_m-R_2$;

wherein R_2 and m are as defined above; and

(2) heating the mercaptan produced in step (1) with oxygen gas under pressure to produce the compound of formula (I).

7. A process according to Claim 6, wherein in step (2), the pressure is at least 20 psi (138 kPa) gauge and the reaction is carried out at a temperature of at least 60°C.

8. A process according Claim 6 or 7, wherein R_2 is SO_3M and m is 2.

9. A process according to Claim 8, wherein the starting compound is a vinyl sulfonate of formula II wherein X and Y together form a double bond, n is 0 and R_2 is SO_3M , the mercaptan reaction product of step (1) is not isolated and step (2) is carried out in the same reaction vessel as for step (1).

10. A process according to Claim 8 or 9, wherein M is sodium and the product is dimesna.

11. A process according to any one of claims 1 to 10 substantially as hereinbefore described with reference to the examples.

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CARTER SMITH & BEADLE
Patent Attorneys for the Applicant:

BIONUMERIK PHARMACEUTICALS, INC.

