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(54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLING AF BENDAMUSTIN-ALKYLESTERE, BENDAMUSTIN OG DERIVATER AF SAMME**

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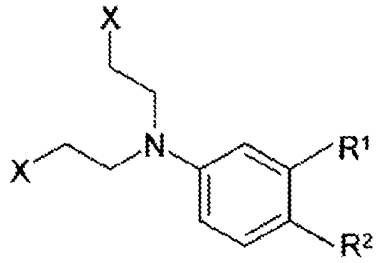
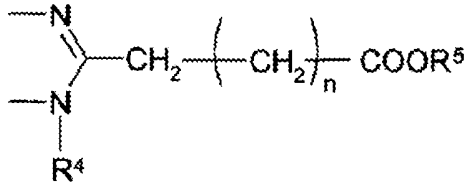
WERNER W ET AL: "Synthesis of a potential metabolite of the anticancer drug bendamustine (CytostasanR)", DIE PHARMAZIE, GOVI VERLAG PHARMAZEUTISCHER VERLAG GMBH, ESCHBORN, DE, Bd. 46, Nr. 2, 1. Februar 1991 (1991-02-01), Seiten 113-114, XP008149662, ISSN: 0031-7144
WERNER W ET AL: "Hydrolyseprodukte des Cancerostaticums Cytostasan (Bendamustin)", DIE PHARMAZIE, GOVI VERLAG PHARMAZEUTISCHER VERLAG GMBH, ESCHBORN, DE, Bd. 42, Nr. 4, 1. Januar 1987 (1987-01-01) , Seiten 272-273, XP008060249, ISSN: 0031-7144
R. GUST ET.AL.: "Investigations on the stability of bendamustin, a cytostatic agent of the nitrogen mustard type, I. Synthesis, Isolation, and characterization of reference substances", MONATSHEFTE FÜR CHEMIE, Bd. 128, 1997, Seiten 291-299, XP002672681,

Process for producing bendamustine alkyl esters, bendamustine and derivatives of same

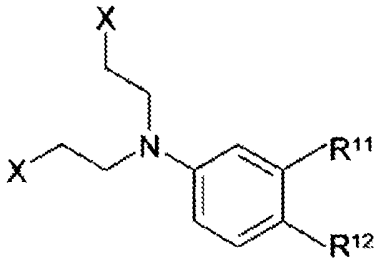
This invention concerns a method for producing ester compounds represented by Formula (I)



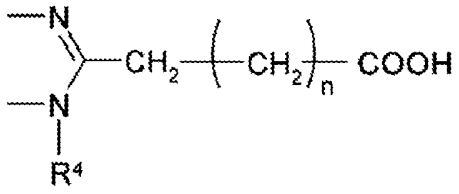
or salts thereof, wherein X is a halogen residue, R^1 and R^2 are selected such that (1) R^1 is H, and R^2 is $-CH_2(CH_2)mCOOR^3$, (2) R^1 is $-CH_2(CH_2)mCOOR^3$, and R^2 is H, or (3) R^1 and R^2 together represent a residue represented by Formula (II)



wherein R^3, R^4, and R^5 independently represent an alkyl residue, and wherein m and n independently are a number in the range of 0 - 12. This invention also concerns a method for producing the appropriately hydrolysed ester, i.e. a compound represented by Formula (VII)



or a salt thereof, wherein X is a halogen residue, R^{11} and R^{12} are selected such that (1) R^{11} is H, and R^{12} is $-CH_2(CH_2)mCOOH$, (2) R^{11} is $CH_2(CH_2)mCOOH$, and R^{12} is H, or (3) R^{11} and R^{12} together represent a residue represented by Formula (VIII)



wherein R^4 is an alkyl residue, and m and n are independently a number in the range of 0 - 12.

Compounds of the above structure according to Formel (VII) are used for chemotherapy in various cancers. Their effect is based on the alkylation of the cell's own DNA or RNA, which leads, in particular, to suppression of DNA replication and, as a result, to apoptosis of the cell in question. The applications of the aforementioned compounds particularly include therapy of various leukaemias and lymphomas, plasmocytoma, and bronchial carcinoma. Structurally, these compounds are derived from nitrogen mustard.

Bendamustine 4-[5-[Bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid, a representative of this group, was first described in 1963 by Ozegowski and Krebs (J. Prakt. Chem. 1963; 20: 178-86).

An advantageous method for producing bendamustine is known from DD 34727. The synthesis disclosed therein is carried out via the corresponding bendamustine ester, 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid ester, which is produced by chlorination of 4-[5- [bis(2-hydroxyethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid ester. Thionyl chloride is used to substitute the two terminal hydroxyl groups of this initial compound with chlorine. It is in fact possible to obtain bendamustine in significant quantities by themethod described in DD 34727. However, one disadvantage of this method is that bendamustine is obtained in widely fluctuating yields, which also significantly decrease as the amounts of the starting compounds are increased.

The documents WERNER W ET AL, DIE PHARMAZIE, Bd. 46, Nr. 2, 1991, pp. 113-114, and WERNER W ET AL: DIE PHARMAZIE, Bd. 42, Nr. 4, 1987, pp. 272-273, also teach the use of thionyl chloride as a chlorinating agent.

To solve this problem, DD 159877 proposes the addition of the reaction mixture of thionyl chloride and 4-[5-[bis(2-hydroxyethyl)amino]-1 -methylbenzimidazol-2-yl]butanoic acid ester directly into aqueous hydrochloric acid in order to stop the reaction, with the excess thionyl chloride being broken down. This measure allowed for a quantitative increases in the yields of bendamustine ester, and ultimately bendamustine.

However, further trials showed that not even the method of DD 159877 is able to achieve an increase of the bendamustine ester/bendamustine yields by more than 80 %. Additionally, it was found that this method gives rise to by-products that are difficult to separate from bendamustine ester/bendamustine, thus adversely affecting product quality. Additionally, the resultant bendamustine ester/bendamustine yields were not reproducible, fluctuating substantially despite although the same experimental conditions were maintained. This was shown in particular by the attempt to carry out the method of DD 159877 on an industrial scale.

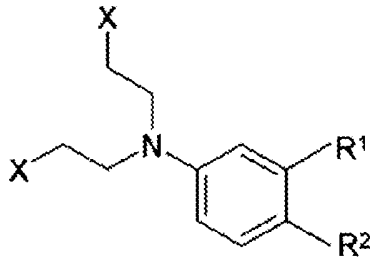
Reaction control in this context was difficult due to the large thionyl chloride excess required. Another problem arises from issues of process economy raised by the fact that the use of thionyl

chloride gives rise to large amounts of acidic process exhaust, with attendant high demands on exhaust purification. Similar problems arise when the method of DD 159877 is transferred to the production of other compounds that can be represented by the formulae (I) and/or (VII).

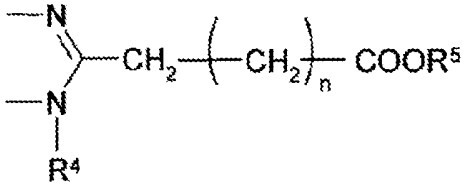
Given the prior art, the objective of this invention was to provide a method allowing for the production of compounds having the structures shown above in reproducibly high yields. The method should also be easily applied on an industrial scale. Additionally, the method should not give rise to large amounts of acidic process exhaust.

This objective is met by the method set forth in the independent claims.

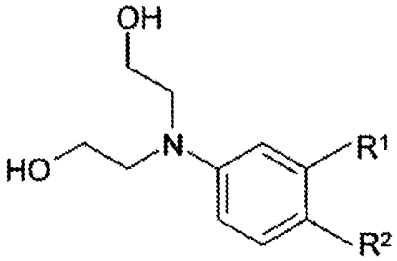
The invention thus provides a method for producing a compound represented by Formula (I)



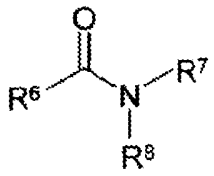
or a salt thereof, wherein X is a halogen residue, R^1 and R^2 are selected such that (1) R1 is H, and R^2 is $-CH_2(CH_2)mCOOR_3$, (2) R^1 is $-CH_2(CH_2)mCOOR_3$, and R^2 is H, or (3) R^1 and R^2 together represent a residue represented by Formula (II),



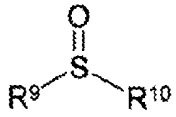
wherein R^3, R^4, and R^5 are independently an alkyl residue, and wherein m and n independently are a number in the range of 0 - 12, wherein a compound represented by Formula (III)



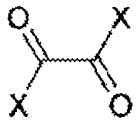
is reacted with a mixture selected from the group including a compound represented by Formula (IV)



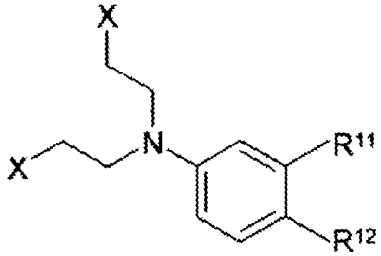
wherein R^6 is H or an alkyl residue, and R^7 and R^8 independently are an alkyl residue, and a compound represented by Formula (V),



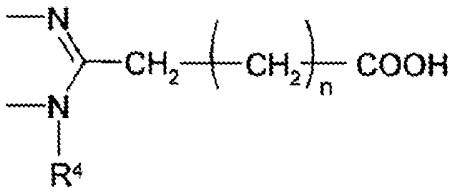
wherein R^9 and R^{10} are independently an alkyl residue, and a compound (ii), represented by Formula (VI)



This invention also provides a method for producing a compound represented by Formula (VII)



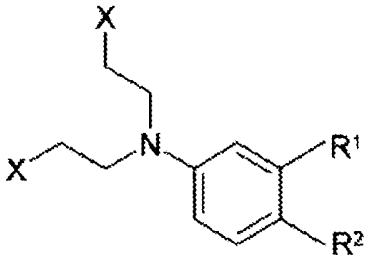
or a salt thereof, wherein X is a halogen residue, R^{11} and R^{12} are selected such that (1) R^{11} is H, and R^{12} is $-CH_2(CH_2)_mCOOH$, (2) R^{11} is $CH_2(CH_2)_mCOOH$, and R^{12} is H, or (3) R^{11} and R^{12} together represent a residue represented by Formula (VIII),



wherein R^4 is an alkyl residue, and m and n are independently a number in the range of 0 – 12, wherein the aforementioned method is carried out, and the resultant ester compound represented by Formula (I) is subjected to ester hydrolysis.

It was surprisingly found that the use of a mixture comprising at least one of the compounds according to Formulae (IV) and (V) as well as compounds according to Formula (VI) allows for the selection substitution of the terminal hydroxyl groups in the compound of Formula (I) with halide groups under mild conditions and moderate reaction times, with the desired product being obtained in reproducibly high yields. Without intending to be bound by theory, this reaction likely occurs by means of an activated imminium ion that is formed in the interim from the compound of Formula (VI) or (V) and the compound of Formula (VI).

On the one hand, the method according to the invention comprises the production of a compound represented by Formula (I) or a salt thereof.



In Formula (I), residue X is a halogen residue. The halogen residue may be, e.g., a chlorine or bromine residue. According to the invention, both residues X represent the same substituent in Formula (I). According to a particularly preferred embodiment, these halogen residues are chlorine residues.

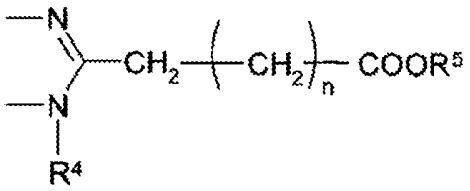
The residues R^1 and R^2 may have different meanings.

In a first alternative (1), the residue R^1 is hydrogen. In this case, residue R^2 represents residue -$CH_2(CH_2)mCOOR_3$. In this residue, R^3 is an alkyl residue. The alkyl residue may be a branched or unbranched alkyl residue. In a particularly preferred embodiment, this alkyl residue is an unbranched residue. The chain length of this alkyl residue is not subject to any further limitations. For example, this alkyl residue may have 1 – 20 carbon atoms, e.g., 1 – 12 carbon atoms, 1 – 8 carbon atoms, 1 – 4 carbon atoms, or 1 or 2 carbon atoms. The alkyl residue may, without limitation, be a methyl, ethyl, propyl, or butyl residue. In the residue R2, the index m may be an integer in the range of 0 – 12, preferably in the range of 0 – 10, more preferably in the range of 0 – 8, even more preferably in the range of 0 – 6, and most preferably in the range of 0 – 3. For example, the index m may be the number 2.

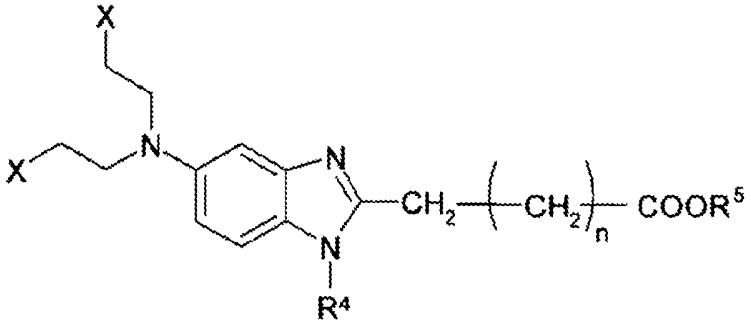
In a second alternative (2), the residue R^2 is hydrogen. In this case, residue R^1 represents residue -$CH_2(CH_2)_mCOOR_3$. In this residue, R^3 is an alkyl residue. The alkyl residue may be a branched or unbranched alkyl residue. In a particularly preferred embodiment, this alkyl residue is an unbranched residue. The chain length of this alkyl residue is not subject to any further

limitations. For example, this alkyl residue may have 1 – 20 carbon atoms, e.g., 1 – 12 carbon atoms, 1 – 8 carbon atoms, 1 – 4 carbon atoms, or 1 or 2 carbon atoms. The alkyl residue may, without limitation, be a methyl, ethyl, propyl, or butyl residue. In the residue R2, the index m may be an integer in the range of 0 – 12, preferably in the range of 0 – 10, more preferably in the range of 0 – 8, even more preferably in the range of 0 – 6, and most preferably in the range of 0 – 3. For example, the index m may be the number 2.

In a third alternative (3), the residue R^1 and the residue R^2 form a residue represented by Formula (II).



Accordingly, this alternative represents a heterocyclic ring system with a benzimidazole structure. It can be represented by Formula (IX) below

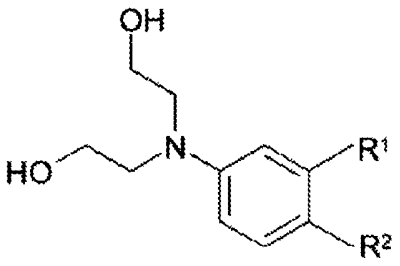


The residue R^4 is an alkyl residue. The alkyl residue R^4 may be a branched alkyl residue, or preferably an unbranched alkyl residue. The chain length of this alkyl residue is not subject to any further limitations. For example, this alkyl residue may have 1 – 20 carbon atoms, e.g., 1 – 12 carbon atoms, 1 – 8 carbon atoms, 1 – 4 carbon atoms, or 1 or 2 carbon atoms. The alkyl residue may, without limitation, be a methyl, ethyl, propyl, or butyl residue. The residue R^5 is also an alkyl residue. The alkyl residue R^5 may also be a branched alkyl residue, but is preferably an unbranched alkyl residue. The chain length of this alkyl residue is not subject to any further limitations. For example, this alkyl residue may have 1 – 20 carbon atoms, e.g., 1 – 12 carbon atoms, 1 – 8 carbon atoms, 1 – 4 carbon atoms, or 1 or 2 carbon atoms. The alkyl residue may, without limitation, be a methyl, ethyl, propyl, or butyl residue. The index n may be an integer in the range of 0 – 10. Preferably, n is an integer in the range of 0 – 10, more preferably an integer in the range of 0 – 6, even more preferably an integer in the range of 0 – 4, and most preferably an integer in the range of 0 – 3. For example, the index n may be the number 2.

In a preferred embodiment, the compound of Formula (I) is 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid alkyl ester or 4- [bis(2-chloroethyl)amino]benzenbutanoic acid alkyl ester. In an especially preferred embodiment, the compound of Formula (I) is 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid ethyl ester or 4- [bis(2-chloroethyl)amino]benzenebutanoic acid ethyl ester.

According to the invention, it is possible to produce not only the aforementioned ester, but also a salt thereof. In this salt, preferably at least one of the nitrogen atoms of the compound of Formula (I), in particular the nitrogen atom that is not part of the ring structure, is protonated. The protonated ester is then associated with a corresponding anion. This anion is preferably a halide ion. In a particularly preferred embodiment, the ester is a hydrochloride. In a particularly preferred embodiment, it is the hydrochloride of 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid alkyl ester or 4-[bis(2-chloroethyl)amino]benzenebutanoic acid alkyl ester, e.g., 4-[5-[bis(2- chloroethyl)amino]-1 -methylbenzimidazol-2-yl]butanoic acid ethyl ester or 4-[bis(2-chloroethyl)amino]benzenebutanoic acid ethyl ester.

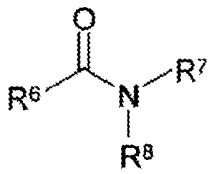
A compound represented by Formula (III) serves as a reactant for the production of the compound of Formula (I).



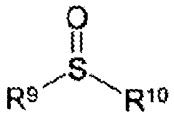
In this context, the residues R^1, R^2, R^3, R^4, and R^5, as well as indices m and n have the meanings assigned to them above. In an even more preferred embodiment, this reactant is 4-[5-[bis(2-hydroxyethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid alkyl ester or 4-[bis(2-hydroxyethyl)amino]benzenebutanoic acid alkyl ester, in particular 4-[5-[bis(2-hydroxyethyl)amino]-1 -methylbenzimidazol-2-yl]butanoic acid ethyl ester or 4-[bis(2-hydroxyethyl)amino]benzenebutanoic acid ethyl ester.

This reactant is reacted with a mixture containing at least one compound (i) and one compound (ii).

Compound (i) is selected from the group consisting of a compound of Formula (IV)



and a compound of Formula (V)



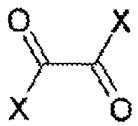
In the compound of Formula (IV), the residue R^6 is hydrogen or an alkyl residue. The alkyl residue may be branched, or preferably unbranched. These alkyl residues may preferably comprise 1 – 12 carbon atoms, more preferably 1 – 10 carbon atoms, even more preferably 1 – 6 carbon atoms, more preferably 1 – 4 carbon atoms, even more preferably 1 – 2 carbon atoms, and most preferably 1 carbon atom.

The residues R7 and R^8 are independently alkyl residues. Here, too, the alkyl residue may be branched, or preferably unbranched. These alkyl residues may preferably comprise 1 – 12 carbon atoms, more preferably 1 – 10 carbon atoms, even more preferably 1 – 6 carbon atoms, even more preferably 1 – 4 carbon atoms, and most preferably 1 – 2 carbon atoms.

Particularly preferred compounds of Formula (V) are dimethylformamide (DMF) and dimethylacetamide (DMAc).

The residues R^9 and R^{10} in Formula (V) are independently alkyl residues. The alkyl residue may be branched, or preferably unbranched. These alkyl residues may preferably comprise 1 – 12 carbon atoms, more preferably 1 – 10 carbon atoms, even more preferably 1 – 6 carbon atoms, more preferably 1 – 4 carbon atoms, even more preferably 1 – 2 carbon atoms, and most preferably 1 carbon atom. One preferred compound of Formula (V) is dimethylsulphoxide (DMSO).

Compound (ii) is a compound represented by Formula (VI),



with X being a halogen residue, preferably chlorine. Accordingly, oxalyl chloride is preferred as a compound of Formula (VI).

In a preferred embodiment, a 4-[5-[bis(2- chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid alkyl ester, or a salt thereof, is produced by reacting 4-[5- [bis(2-

hydroxyethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid alkyl ester with oxalyl chloride and dimethylformamide. In an especially preferred embodiment, a 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid ethyl ester, or a salt thereof, is produced by reacting 4-[5- [bis(2-hydroxyethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid ethyl ester with oxalyl chloride and dimethylformamide.

Compound (ii), which is represented by Formula (VI), is used in at least an equimolar quantity, but preferably in a molar excess with regard to the compound of Formula (III). In an especially preferred embodiment, the molar ratio of the compound of Formula (VI) to the compound of Formula (III) is at least 1.3, more preferably at least 1.5.

In a preferred embodiment of the invention, first, compounds (i) (i.e. the compounds of Formula (IV) and/or (VI)) and (ii) (i.e. the compound of Formula (VI)) are combined and then contacted with the compound of Formula (III). To this end, the compounds (i) and (ii), as well as the compound of Formula (III) are preferably dissolved both individually and in combination in a suitable solvent. Solvents that may be used include halogenated hydrocarbons such as dichloromethane or chloroform, or other aprotic solvents such as tetrahydrofuran or dioxane.

Preferably, in the method according to the invention, the compound of Formula (VI), dissolved in a suitable solvent, is provided in a reaction vessel and, if appropriate, cooled; in this regard, temperatures in the range of 0 – 10 °C, e.g., 1 – 5 °C or 1 – 3 °C have been found particularly advantageous.

Preferably, the compound of Formula (IV) or (V) is also dissolved in a suitable solvent and then cooled if appropriate. Here, too, temperatures in the range of 0 – 10 °C, e.g., 1 – 5 °C or 1 – 3 °C have been found particularly advantageous.

In one possible embodiment of the invention, in a subsequent step, the compound of Formula (VI) and the compound of Formula (IV) or (V) are combined. This may be achieved, e.g., by dosing the solution containing the compound of Formula (VI) into the solution containing the compound of Formula (IV) or (V), e.g., by dropping. However, the solution containing the compound of Formula (IV) or (V) may, of course, also be dosed, e.g., dropped, into the solution containing the compound of Formula (VI). Accordingly, in this step, a solution is preferably obtained that contains compounds (i) and (ii).

This solution is now preferably mixed with a solution containing the compound of Formula (III). To this end, for example, the solution containing the compound according to Formula (III) may be dripped into the solution containing the compounds (i) and (ii).

The reaction of the compounds contained in the reaction mixture thus obtained may then be controlled in a manner known to persons skilled in the art.

For example, the reaction mixture may be stirred at reflux.

The reaction mixture may, for example, be stirred at reflux for a period of at least 1 h, preferably a period of at least 2 h, even more preferably at least 4 h, and most preferably for a period of at least 6 h. In a preferred embodiment, the reaction mixture is stirred at reflux for a period of 1 – 24 h, more preferably for a period of 2 – 20 h, even more preferably 4 – 16 h, and most preferably for 6 – 12 h.

If necessary, the reaction may be carried out in an inert gas atmosphere, e.g., a nitrogen or noble gas atmosphere.

Following the reaction, the reaction product is present either as a free base or a salt depending on the pH of the reaction mixture. If the reaction product of Formula (I) is bendamustine methyl ester, for example, it is present at pH values of ≥ 7.5 as a free base, and at lower pH as a salt, e.g., hydrochloride. In this regard, it is possible to obtain the reaction product of Formula (I) as a free base or a salt by adjusting the pH to a suitable value.

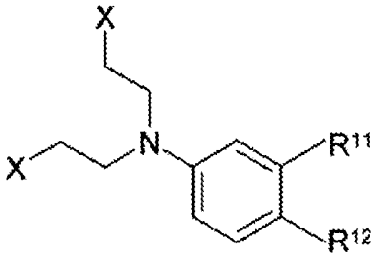
After the reaction, the reaction product represented by Formula (I) may be isolated from the reaction mixture in a first embodiment. Alternatively, to this end, in a second embodiment, the reaction mixture may also be directly used to conduct an ester hydrolisis in order to produce the product according to Formula (VII).

If the isolation of the reaction product of Formula (I) is desired, this may be done conventionally. For example, the reaction mixture may be mixed with water in order to generate an organic and an aqueous phase. Whilst the organic phase contains the reaction product of Formula (I), the purpose of the aqueous phase is to remove water-soluble components, such as salts, from the organic phase.

In a subsequent step, if desired or necessary, the pH may be adjusted in order to convert the reaction product of Formula (I) to the free base or a corresponding salt. If, for example, the reaction product is present in the reaction mixture as a salt, the pH of the reaction mixture may be increased by adding a base in order to convert the salt to the free base. This may be done, e.g., by adding basic solutions such as potassium carbonate to the reaction mixture that has been mixed with water.

Then, the mixture of reaction mixture and water is preferably intensively mixed in order to allow the water-soluble components to pass from the organic phase into the aqueous phase. Thereafter, the organic phase is preferably removed from the mixture and saved, whilst the aqueous phase is mixed with an organic solvent, e.g., (one of) the solution(s) used to dissolve the compounds of Formula (III) or the compounds (i)/(ii) before the reaction. The organic phase/the combined organic phases may then be dried to a constant weight, e.g., in vacuo, in order to obtain the reaction product of Formula (I).

The reaction product of Formula (I) usually serves as an intermediate for the production of a compound represented by Formula (VII) or a salt thereof.



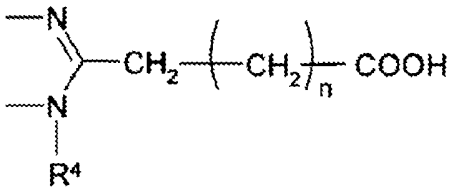
In Formula (VII), in turn, X is a halogen atom, preferably a chlorine or bromine atom, more preferably a chlorine atom.

The residues R^{11} and R^{12} may have different meanings.

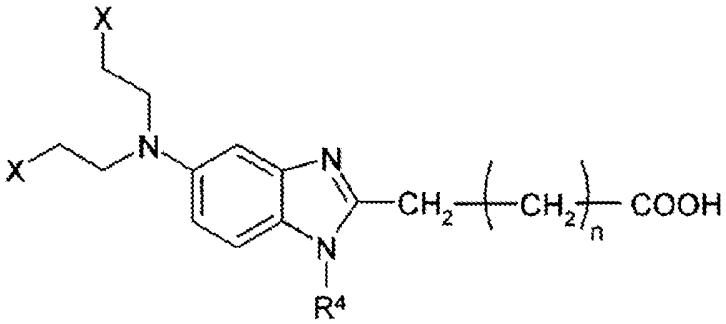
In a first alternative (1), the residue R^{11} is hydrogen. In this case, residue R^{12} represents residue -$CH_2(CH_2)_mCOOH$. In the residue R^{12}, the index m may be an integer in the range of 0 – 12, preferably in the range of 0 – 10, more preferably in the range of 0 – 8, even more preferably in the range of 0 – 6, and most preferably in the range of 0 – 3. For example, the index m may be the number 2.

In a second alternative (2), the residue R^{12} is hydrogen. In this case, residue R^{11} represents residue -CH2(CH2)mCOOH. In the residue R^{12}, the index m may be an integer in the range of 0 – 12, preferably in the range of 0 – 10, more preferably in the range of 0 – 8, even more preferably in the range of 0 – 6, and most preferably in the range of 0 – 3. For example, the index m may be the number 2.

In a third alternative (3), the residue R^{11} and the residue R^{12} form a residue represented by Formula (VIII).



Accordingly, this alternative represents a heterocyclic ring system with a benzimidazole structure. It can be represented by Formula (X) below



The residue R^4 is an alkyl residue. The alkyl residue R^4 may be a branched alkyl residue, or preferably an unbranched alkyl residue. The chain length of this alkyl residue is not subject to any further limitations. For example, this alkyl residue may have 1 – -20 carbon atoms, e.g., 1 – 12 carbon atoms, 1 – 8 carbon atoms, 1 – 4 carbon atoms, or 1 or 2 carbon atoms. The alkyl residue may, without limitation, be a methyl, ethyl, propyl, or butyl residue. The index n may be an integer in the range of 0 – 10. Preferably, n is an integer in the range of 0 – 10, more preferably an integer in the range of 0 – 6, even more preferably an integer in the range of 0 – 4, and most preferably an integer in the range of 0 – 3. For example, the index n may be the number 2.

In a preferred embodiment, the compound of Formula (I) is 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid or 4- [bis(2-chloroethyl)amino]benzenebutanoic acid.

According to the invention, it is possible to produce not only the aforementioned acid, but also a salt thereof. In this salt, preferably at least one of the nitrogen atoms of the compound of Formula (I), in particular the nitrogen atom that is not part of the ring structure, is protonated. The protonated ester is then associated with a corresponding anion. This anion is preferably a halide ion. In a particularly preferred embodiment, the ester is a hydrochloride. In a preferred embodiment, it is a hydrochloride of 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid or 4- [bis(2-chloroethyl)amino]benzenebutanoic acid.

To produce the compound of Formula (VII), first, the aforementioned method for producing the compound of Formula (I) is carried out, and the resultant reaction product is subjected to ester hydrolysis. To this end, the resultant reaction product may either – as described above – first be isolated and then hydrolysed, or it may be immediately (i.e. without prior isolation) converted to the acid.

In a particularly preferred embodiment, in the context of the invention, 4-[5- [bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid or a salt thereof is produced by reacting 4-[5-[bis(2-hydroxyethyl)amino]-1- methylbenzimidazol-2-yl]butanoic acid alkyl ester or a salt thereof with oxalyl chloride and dimethylformamide in a first step, forming a 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2- yl]butanoic acid alkyl ester or a salt thereof,

and hydrolysing the resultant 4-[5-[bis(2-chloroethyl)amino]-1-methylbenzimidazol-2-yl]butanoic acid alkyl ester or a salt thereof in a second step.

To hydrolyse the ester, the reaction product of Formula (I) is preferably mixed with an acid. Preferably, an inorganic acid is used here as the acid, in particular hydrochloric acid. Normally, the acid is used as a concentrated acid, e.g., concentrated hydrochloric acid (32 %). As a result of the reduction in pH caused by the addition of the acid, the reaction product of Formula (I), which is unstable at more basic pH values, is stabilised.

The reaction product of Formula (I) may be mixed with the acid by combining the acid with the isolated reaction product of Formula (I), with a solution of the isolated reaction product of Formula (I) in a suitable solvent, or with the aforementioned reaction mixture containing the isolated reaction product of Formula (I).

Thereafter, the resultant mixture is preferably stirred at a temperature in the range of 10 – 80 °C, more preferably 15 – 70 °C, and even more preferably at a temperature in the range of 20 – 60 °C.

The reaction time is preferably 30 min – 6 h, more preferably 1 – 4 h, and even more preferably 1 – 3 h.

After the reaction, any organics in the mixture, e.g., solvents or solvent residues, may be removed. This may be achieved preferably by distilling these organic components.

In a further optional step, the mixture, which contains the acid as well as the (now hydrolysed) ester of Formula (VII), is mixed with activated charcoal and mixed. The activated charcoal may be used to absorptively bind any impurities contained in the mixture. The activated charcoal may then be separated from the rest of the mixture, e.g., by filtration.

The acid contained in the mixture is then removed in the conventional fashion from the hydrolysed ester of Formula (VII). To this end, the acid is preferably separated from the hydrolysed ester of Formula (VII) by distillation. The compound of Formula (VII) is left as a residue, which may be present, e.g., as a solid or an oily liquid.

The residue may be further purified if necessary. If the residue is present, e.g., as an oily liquid, the compound of Formula (VII) may first be precipitated with a suitable solution. Possible precipitation solutions include those containing water in addition to a ketone or alcohol. Acetone has been found to be a suitable ketone, and ethanol to be a suitable alcohol. After the precipitation, the resultant residue may be separated from the precipitation solution.

Then, the remaining residue may, if necessary, be washed with a suitable washing solution and then dried. Preferably, water and ethyl acetate may be used as the washing solution.

The invention is described by reference to the following examples, which are not to be construed as limiting.

Exemplary Embodiment 1a: Production of Bendamustine Methyl Ester

26.7 g oxalyl chloride (1,6 Eq) was dissolved in 279 ml Dichlormethan and cooled down to 1 °C. At 1 °C, a mixture of 18 ml dimethylformamide (DMF) and 50 ml dry dichloromethane was slowly added. To the reaction mixture thus obtained was added a solution of 23 g ethyl-4-(5-(bis-(2-hydroxyethyl)-amino)-1-methyl-1H-benzo[d]imidazol-2- yl)butanoate in 115 ml DCM. The reaction mixture was stirred for 8 h at reflux (45 °C shell temperature), cooled down, and then mixed with 50 ml ultrapure water. By adding a 25 % K_2CO_3 solution, the pH was adjusted to 8 – 9.5. After intensive mixing, the organic phase was separated, and the aqueous phase was extracted with another 83 ml dichloromethane. The combined organic phases were dried to constant weight in vacuo.

This trial was carried out six times. The following bendamustine ethyl ester yields were obtained:

V1a-1	V1a-2	V1a-3	V1a-4	V1a-5	V1a-6	Mean yield	Maximum deviation from mean yield
93.2%	92.7%	92.5%	90.4%	93.4%	93.0%	93.0%	+0.4% / -2.6%

Exemplary Embodiment 1b: Production of Bendamustine

The raw product bendamustine ethyl ester obtained in exemplary embodiment 1a was dissolved in 210 ml 32 % HCl and stirred for 2 h at a shell temperature of 40 °C. The solution was cooled to room temperature, mixed with 8 g activated charcoal, stirred for 30 min, and filtered over a sterile filter. The hydrochloric acid was removed by distillation, and the residue was mixed with 400 ml water/acetone. The precipitate was filtered off, washed with water and ethyl acetate, and dried.

This trial was carried out twice. The following bendamustine yields, each relating to the method based on ethyl-4-(5-(bis-(2-hydroxyethyl)-amino)-1-methyl-1H-benzo[d]imidazol-2-yl)butanoate, were obtained.

V1b-1	V1b-2	Mean yield	Maximum deviation from mean yield
82.0%	77.6%	79.8%	+2.2% / -2.2%

Comparative Example 2a: Production of Bendamustine Methyl Ester

An alternative method for producing bendamustine alkyl ester is also based on an ethyl-4-(5-(bis-(2-hydroxyethyl)amino)-1-methyl-1 H-benzo[d]imidazol-2-yl)alkyl ester as a reactant. The tendency of the hydroxyl groups in this reactant to leave is increased by adding an activating roup (e.g., a p-tosyl, mesyl, or triflate group). This activating group is then exchanged with a halide under mild conditions, e.g., by treatment with lithium chloride in dimethylformamide or ethanol.

In a corresponding trial, 42.2 g ethyl-4-(5-(bis-(2-hydroxyethyl)amino)-1- methyl-1H-benzo[d]imidazol-2-yl)butanoate) was dissolved in 500 ml dry dichloromethane and mixed with 41.6 ml triethylamine (TEA). This solution was slowly mixed with 52.2 g methanesulphonic anhydride in 150 ml dry dichloromethan, and stirred for 3 h at 25 °C. The reaction solution was freed of solvents at 30 °C in vacuo. The resultant residue was dissolved in 400 ml dry ethanol, mixed with 30.5 g lithium chloride, and stirred for 18 h at 70 °C. Then, ethanol was removed by distillation at 40 °C, and the residue was taken up into 400 ml DCM, and mixed with 16.6 ml TEA. After adding 200 ml water, the pH was adjusted to 7.5 – 9 with a concentrated K_2CO_3 solution. The resultant phases were separated, the aqueous phase was extracted with another 250 ml DCM, the combined organic phases were washed with 100 ml semiconcentrated sodium chloride solution, dried over $MgSO_4$, and solvents were removed in vacuo.

This trial was carried out four times. The following bendamustine ethyl ester yields were obtained:

V2a-1	V2a-2	V2a-3	V2a-4	Mean yield	Maximum deviation from mean yield
82.9%	85.2%	81.9%	80.1%	82.5%	+2.7% / -2.4%

Comparative Example 2b: Production of Bendamustine

The raw product bendamustine ethyl ester obtained in comparative example 2a was dissolved in 210 ml 32 % HCl and stirred for 2 h at a shell temperature of 40 °C. The solution was cooled to room temperature, mixed with 8 g activated charcoal, stirred for 30 min, and filtered over a sterile filter. The hydrochloric acid was removed by distillation, and the residue was mixed with 400 ml water/acetone. The precipitate was filtered off, washed with water and ethyl acetate, and dried.

This trial was carried out twice. The following bendamustine yields, each relating to the method based on ethyl-4-(5-(bis-(2-hydroxyethyl)-amino)-1-methyl-1H-benzo[d]imidazol-2-yl)butanoate, were obtained.

V2b-1	V2b-2	Mean yield	Maximum deviation from mean yield
69.8%	71.3%	70.6%	+0.5% / -0.8%

Comparative Example 3a: Production of Bendamustine Methyl Ester

Bendamustine methyl ester was produced following the exemplary embodiment of DD 159877. Thus, 18.3 mol thionyl chloride (2.175 kg) was used to substitute 22.3 mol hydroxyl groups (in

4.305 kg 4-[5-[bis(2-hydroxyethyl)amino]-1-methylbenzimidazol-2- yljbutanoic acid ethyl ester). However, this resulted in incomplete conversion, with approximately 47 % by area of the desired product present.

For this reason, the amount of thionyl chloride was increased in subsequent trials. Trebling the amount of thionyl chloride relative to 4-[5-[bis(2-hydroxyethyl)amino]-1- methylbenzimidazol-2-yl]butanoic acid ethyl ester (from 0.82 Eq according to DD 159877 to 2.46 Eq) resulted in 87 % by area of the desired product and was the optimum result amongst the variants studied.

The following bendamustine ethyl ester yields were obtained:

V3a-1	V3a-2	Mean yield	Maximum deviation from mean yield
75.0%	59.0%	67.0%	+8.0% / -8.0%

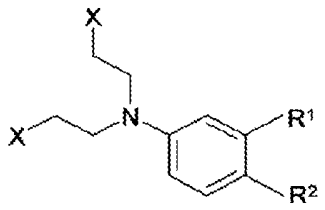
The material obtained by means of the above procedure failed to meet the specification requirements of the ICH Guidelines despite two recrystallisations.

These trials show that the method according to the invention surprisingly provides a significantly increased, reproducible yield compared to the known methods.

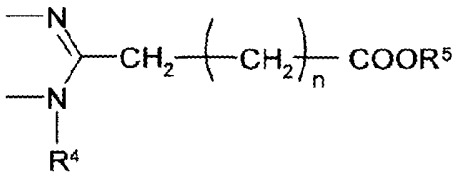
FREMGANGSMÅDE TIL FREMSTILLING AF BENDAMUSTIN-ALKYLESTERE, BENDAMUSTIN OG DERIVATER AF SAMME

PATENTKRAV

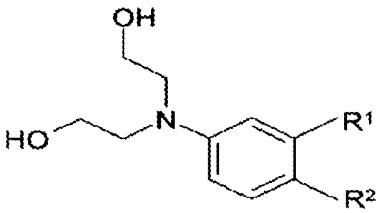
1. Fremgangsmåde til fremstilling af en forbindelse, der er repræsenteret ved formlen (I)



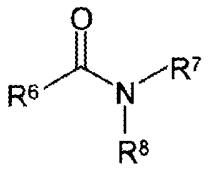
eller et salt deraf, hvor X står for en halogenrest, R^1 og R^2 er valgt således, at (1) R^1 er H og R^2 er $CH_2(CH_2)mCOOR^3$, (2) R^1 er $CH_2(CH_2)mCOOR^3$ og R^2 er H eller (3) R^1 og R^2 sammen står for en rest, som er repræsenteret ved formlen (II)



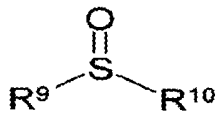
hvor R^3, R^4 og R^5 uafhængigt af hinanden står for en alkylrest, og hvor m og n uafhængigt af hinanden repræsenterer et tal i området 0 - 12, kendetegnet ved, at man bringer en forbindelse, der er præsenteret ved formlen (III),



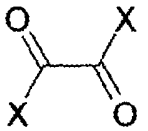
til reaktion med en blanding, der er repræsenteret af en forbindelse (i), som er valgt fra gruppen, der består af en forbindelse, som er repræsenteret ved formlen (IV),



hvor R^6 står for H eller en alkylrest, og R^7 og R^8 uafhængigt af hinanden står for en alkylrest, og en forbindelse, som er repræsenteret ved formlen (V),



hvor R^9 og R^{10} uafhængigt af hinanden står for en alkylrest, består og indeholder en forbindelse (ii), som er repræsenteret ved formlen (VI).



2. Fremgangsmåde ifølge krav 1, kendetegnet ved, at X repræsenterer en klorid.

3. Fremgangsmåde ifølge krav 1 eller 2, kendetegnet ved, at R^1 og R^2 sammen står for en rest, der er repræsenteret ved formlen (II).

4. Fremgangsmåde ifølge krav 3, kendetegnet ved, at n er et heltal i området 1 – 3.

5. Fremgangsmåde ifølge krav 4, kendetegnet ved, at R^4 står for en alkylrest, der er valgt fra gruppen, der består af en methylrest, en ethylrest og en propylrest.

6. Fremgangsmåde ifølge krav 5, kendetegnet ved, at R^4 står for en methylrest.

7. Fremgangsmåde ifølge et af kravene 1 - 6, kendetegnet ved, at R^5 står for en alkylrest, der er valgt fra gruppen, som består af en methylrest, en ethylrest, en propylrest og en butylrest.

8. Fremgangsmåde ifølge krav 1 eller 2, kendetegnet ved, at R^1 er H og R^2 er $CH_2(CH_2)_mCOOH$.

9. Fremgangsmåde ifølge krav 8, kendetegnet ved, at m er et heltal i området 1 – 3.

10. Fremgangsmåde ifølge krav 9, kendetegnet ved, at m er lig med 2.

11. Fremgangsmåde ifølge et af kravene 1 - 11, kendetegnet ved, at der ved forbindelsen, som er repræsenteret ved formlen (IV), er tale om en diakylformamid.

12. Fremgangsmåde ifølge krav 11, kendetegnet ved, at der ved diakylformamid er tale om dimethylformamid.

13. Fremgangsmåde ifølge et af kravene 1 - 12, kendetegnet ved, at der ved forbindelsen, som er repræsenteret ved formlen (IV), er tale om dimethylacetamid.

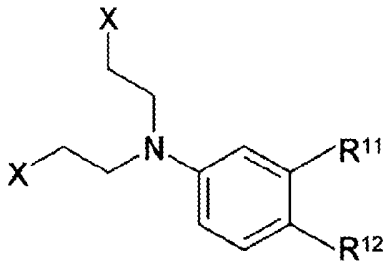
14. Fremgangsmåde ifølge et af kravene 1 - 12, kendetegnet ved, at der ved forbindelsen, som er repræsenteret ved formlen (V), er tale om dimethylsulfoxid.

15. Fremgangsmåde ifølge et af kravene 1 - 14, kendetegnet ved, at der ved forbindelsen, som er repræsenteret ved formlen (VI), er tale om oxalylklorid.

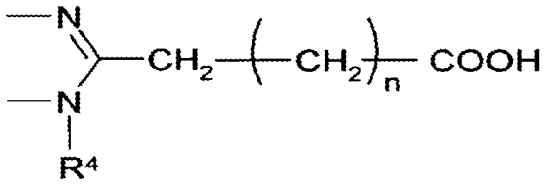
16. Fremgangsmåde ifølge et af kravene 1 - 15, kendetegnet ved, at molforholdet mellem forbindelsen ifølge formel (VI) og forbindelsen ifølge formel (III) andrager mindst 1,3.

17. Fremgangsmåde ifølge et af kravene 1 - 16, kendetegnet ved, at reaktionen gennemføres i et kloreret opløsningsmiddel eller i et aprotisk opløsningsmiddel.

18. Fremgangsmåde til fremstilling af en forbindelse, som er repræsenteret ved formlen (VII),



eller et salt deraf, hvor X står for en halogenrest, R^{11} og R^{12} er valgt således, at (1) R^{11} er H og R^{12} er $CH_2(CH_2)_mCOOH$, (2) R^{11} er $CH_2(CH_2)_mCOOH$ og R^{12} er H eller (3) R^{11} og R^{12} sammen står for en rest, som er repræsenteret ved formlen (VIII),



hvor R^4 står for en alkylrest, og hvor m og n uafhængigt af hinanden repræsenterer et tal i området 0 – 12,

kendetegnet ved, at man udfører fremgangsmåden ifølge krav 1 og udsætter den opnåede esterforbindelse, som er repræsenteret ved formlen (I), for en esterhydrolyse.