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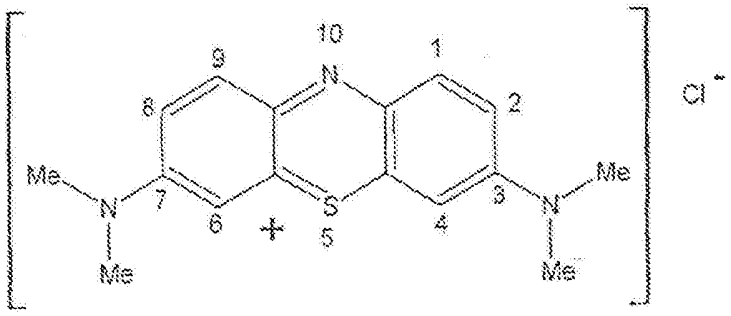
(54) **Eljárás diamino-fenotiazinium vegyületek előállítására**

PROCESS FOR PREPARING DIAMINOPHENOTHIAZINIUM COMPOUNDS

The subject of the present invention is a novel process for preparing compounds of the diaminophenothiazinium type, in particular a process for purifying these compounds. It relates in particular to methylene blue, and also describes products resulting from this process, for which the degree of purity is greater than those known from the prior art. It also discloses the use of these compounds in the preparation of medication.

Methylthioninium chloride, also known as methylene blue or 3,7-bis(dimethylamino)phenothiazin-5-ylium chloride, is an organic compound represented by the following formula:



The compound has long been used as a redox indicator and dye, an optical discloser in biophysical systems, in nanoporous materials as a separating material, and in photoelectrochromic imaging. It is also known for its uses as an antiseptic, anti-infective, as an antidote and diagnostic agent. It finds uses in particular in gynecology, neonatology, cancerology, oncology, urology, ophthalmology and gastroenterology. New uses in the therapeutic field are in the process of being developed, such as the reduction of pathogenic contaminants in the blood (GB2373787), or the prevention or inhibition of an exaggerated haemodynamic reaction (WO03/082296).

Many methods of synthesis have been described for this compound, the first being in 1877 (German patent No. 1886). All these methods have in common the use of metal compounds in at least one synthetic step:

Patent DE-1886 describes a process in which oxidative coupling of N,N-dimethyl-1,4-diaminobenzene is performed using H_2S and $FeCl_3$.

Fiez David *et al.*, "Fundamental Processes of Dye Chemistry", 1949, Interscience, 308-314 describes a process in which the thiazine ring is formed through treatment with manganese dioxide or copper sulfate. This process also involves treatment with zinc chloride, sodium dichromate and aluminum thiosulfate.

Document WO 2005/054217 describes methylene blue derivatives and a process for their preparation. The preparation method for these compounds employs phenothiazine as the starting product. All known methods for preparing phenothiazine require metal reagents in which the metal atoms chelate the phenothiazine at the end of the

synthesis. The products obtained via this process are therefore naturally contaminated with metal residues, in addition to the usual organic contaminants such as azure B.

Document WO 2006/032879 describes a process for preparing methylene blue consisting of a reduction step using iron, an oxidation step using sodium dichromate and an oxidation step using copper sulfate.

These processes require tedious and expensive purification to be performed in order to reduce the impurities, in particular metal impurities in methylene blue. Despite the subsequent purification steps, these various processes inevitably produce a methylene blue containing many metal impurities and organic impurities, in particular azure B, azure C and azure A.

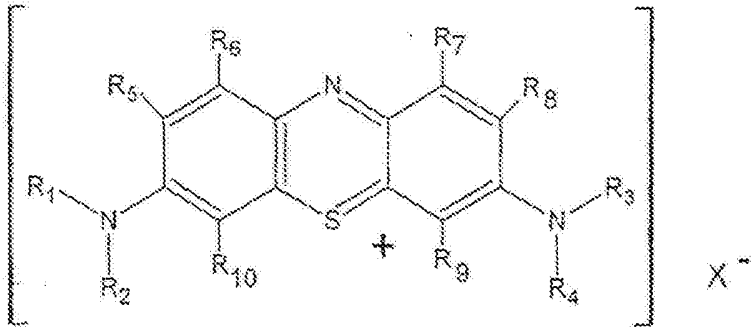
Document WO 2006/032879 claims that it is possible to achieve a level of metal impurity representing 10% of the maximum threshold fixed by the European Pharmacopœia, butit has been established from the examples that this level is not obtained simultaneously for all metals, and that the results of the purification steps are not always reproducible. A detailed analysis of the metal content of various commercially available methylene blues is provided in this document.

The European Pharmacopœia was recently amended (April 2006) so as to increase the tolerance thresholds for metal impurities since no producer of methylene blue was able to produce, and even less so to produce in industrial quantities, a methylene blue of a quality compliant with the previous requirements.

A first subject of the invention was therefore the development of a process for preparing methylene blue offering access to a methylene blue with a high degree of purity, in particular one that contains a very low level of metal and organic impurities, that can be extrapolated to an industrial scale under satisfactory economic conditions and that is not subject to variations in quality. According to one variation, the process of the invention is a process for purifying methylene blue.

The process that has been developed applies not only to methylene blue, but also to other derivatives of the diaminophenothiazinium type.

The process of the invention is a process for preparing compounds corresponding to the following formula (I):



(I)

in which each of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 and R_{10} may be chosen, independently of the others, from the group consisting of:

- a hydrogen atom,
- saturated or unsaturated, linear, branched or cyclic C_1-C_6 alkyl groups, that may be substituted by one or more functions chosen from among a halogen atom or a C_1-C_6 alkoxy function in C_1-C_6 alkyloxycarbonyl or -$CONH_2$ function,
- aryl groups optionally substituted by one or more functions chosen from: a C_1-C_4 alkyl, a halogen atom, and a C_1-C_6 alkoxy, C_1-C_6 alkyloxycarbonyl or -$CONH_2$ function,

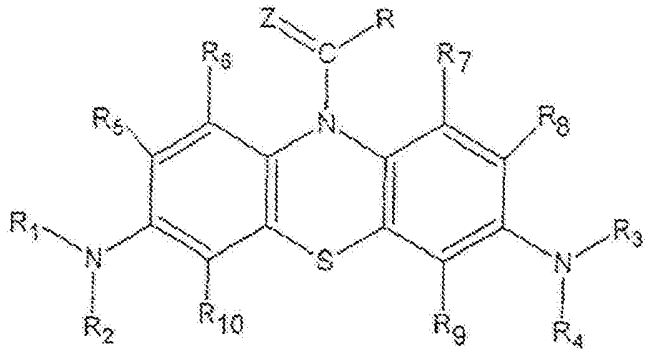
it being understood that two Ri groups (i=1,2...10) placed successively in figure (I) may be joined to form a ring. For example, R_1 with R_5, or R_5 with R_6, R_7 with R_8, R_8 with R_3, R_3 with R_4, R_4 with R_9, R_{10} with R_2, or R_2 with R_1 may consist of a single alkyl chain wthat could be substituted so as to form a fourth ring.

Furthermore, each of R_5, R_6, R_7, R_8, R_9 and R_{10} may be chosen, independently of the others, from the halogen atoms: F, Cl, Br and I,

X^- represents an organic or inorganic anion.

The anions that can be used include, for example, anions of inorganic acids such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid or nitric acid; the anions of organic acids such as, for example, acetic acid, trifluoroacetic acid, oxalic acid, tartaric acid, succinic acid, maleic acid, fumaric acid, gluconic acid, citric acid, malic acid, ascorbic acid or benzoic acid; they also include OH^-

This process is characterized by the fact that it includes at least one step during which a compound of the formula (II):



(II)

is subjected to a purification step under conditions that make it possible to separate the metal compounds from the formula compounds (II), the R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 and R_{10} groups having the same definition as in formula (I), and R representing a group chosen from:

- a phenyl or benzyl group, optionally substituted by one or more functions chosen from: a C_1-C_4 alkyl, a halogen atom, a C_1-C_4 haloalkyl and a nitro group,

- a linear, branched or cyclic C_1-C_8 alkyl group,

- a C_1-C_8 alkylamino group,

- a C_1-C_8 alkoxy group,

- a phenyloxy or benzyloxy group optionally substituted on the aromatic nucleus by one or more functions chosen from: a C_1-C_4 alkyl, a halogen atom, a C_1-C_4 haloalkyl and a nitro group,

Z representing an atom chosen from O and S.

The purification of the compounds of formula (II) is performed under conditions that make it possible to separate the metal compounds from the compounds of formula (II): filtration through a medium capable of retaining the metal compounds, crystallization in an appropriate solvent, or any other method known to those skilled in the art.

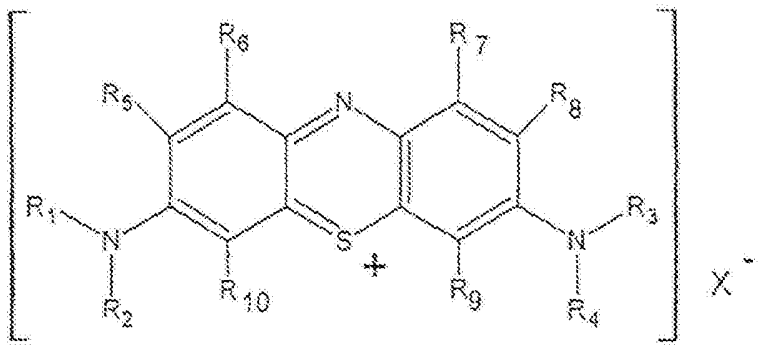
When purification is performed by means of filtration through a medium capable of retaining the metal compounds, such a medium may be chosen from among: a silica gel, an alumina gel (neutral, basic or acidic), an optionally modified diatomite, celite, a microporous membrane, resins grafted with metal-capturing groups and fibers grafted with metal-capturing groups, such as thiol, carboxylic acid or tertiary amine functions, or any other medium having the property of retaining metals. Among the grafted fibres, mention should be made, in particular, of the products sold by the Johnson Matthey company under the Smopex® trademark. Of the the diatomites, mention should be made of the products sold by the CECA company under the Clarcel® trademark.

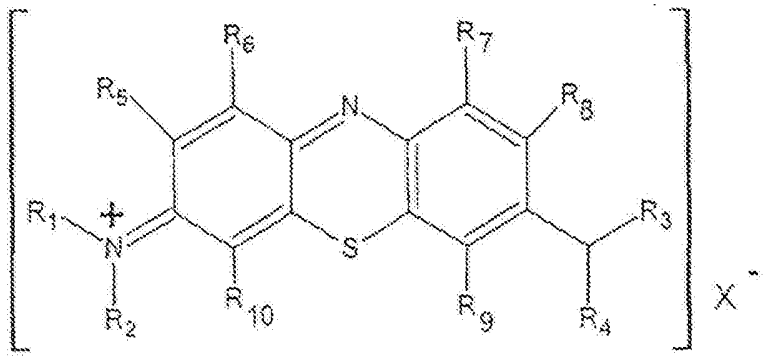
The formula (II) compound may be obtained starting from the formula (I) compound, through reduction of the formula (I) compound, then by reaction of the amine function of the phenothiazinium ring with a suitable protective group R-CZ-Y in which R and Z have the same definition as above and Y represents a starting group chosen from: a halogen atom such as F, Cl, I or Br, a C_1-C_6 alkoxy group, a -OCOR (anhydride) group, and a hydroxyl group, possibly in the presence of an activator of the dicyclohexylcarbodiimide (DCC) type. Advantageously, R is chosen from a phenyl group and a toluyl group.

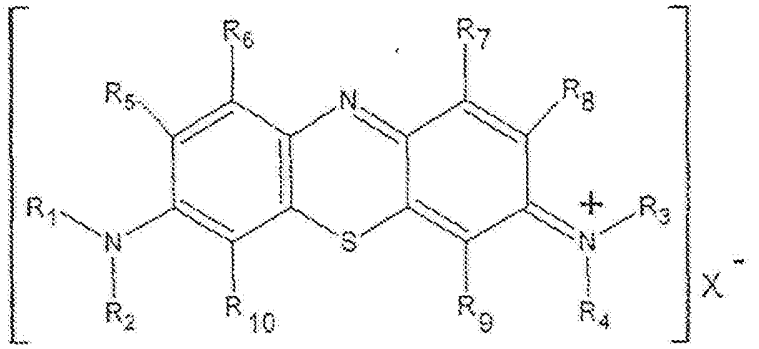
When the compound of formula (II) is obtained from a compound of formula (I), the overall process is one of purification of the formula compound (I). However, the formula compound (II) may be obtained through other processes that do not use the product (I) as starter product.

Some compounds of formula (II), such as benzoyl leuco methylene blue, are available commercially.

The compound represented by formula (I) may be represented by several equivalent resonant structures. By way of non-restrictive illustration, other structures are represented below that are equivalent to the structure of formula (I):







In formula (I) and in formula (II), R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 and R_{10}, which may be identical or different, are chosen from a hydrogen atom and a C_1-C_4 alkyl. Advantageously, R_5, R_8, R_9 and R_{10} represent H.

Again advantageously, one or more of the following requirements have been verified:

- X represents Cl or OH,
- R_1, R_2, R_3 and R_4, which may be identical or different, are chosen from a hydrogen atom and methyl,
- R_6 represents a hydrogen atom,
- R_7 represents a hydrogen atom,
- Z represents O.

Advantageously, the compound of formula (I) is tetramethylthionine chloride or methylene blue.

According to another variant, the compound of formula (I) is dimethylthionine chloride or Azure A, or trimethylthionine chloride or Azure B, or monomethylthionine chloride or Azure C.

According to the invention, the process for preparing the compound of formula (I) consists of at least one step for purification of a compound of formula (II); in particular, this purification consists of at least one step for filtration of a compound of formula (II) through a medium capable of retaining metal compounds, such as a silica gel, an alumina gel (neutral, basic or acidic), an optionally modified diatomite, a resin functionalized with metal-detecting agents, fibres functionalized with metal-detecting agents, celite, a microporous membrane or any other medium capable of retaining metal compounds.

In greater detail, according to this variant, the compound of formula (II) is solubilized in an appropriate solvent, and a filter is prepared with the filtration medium introduced into an appropriate vessel, such as a glass column, a sintered glass filter or an industrial spin-dryer. The vessel packed with the chosen filtration medium is moistened, preferably with the same solvent as that in which the compound of formula (II) was dissolved.

The solution containing the compound of formula (II) is deposited on the filter, the solution passing through the filter is recovered, and the filter is rinsed several times with a solvent which may be identical to or different from that which served to solubilize the compound of formula (II). The eluted fractions are recovered and optionally concentrated.

Among the solvents that can be used to solubilize the compounds of formula (II), mention may preferably be made of: chlorinated solvents, for instance dichloromethane or chloroform, alcohols such as isopropanol, ethanol or methanol, or acetonitrile, ethyl acetate or tetrahydrofuran, or a mixture othereof.

The solution of the formula (II) compound is advantageously in a concentration ranging from 1 g/l to 10^3 g/l. Lower concentrations result in the use of solvent volumes that are too great, that could impact on the safety and the size of the material. Higher concentrations are difficult to envisage owing to the solubility of the products.

It is planned to use approximately 0.1 to 10 kg of filtration medium per kg of product to be filtered. It is advantageously planned to rinse the filter with 0.1 to 50 l of solvent per kg of formula (II) product until complete elution of the formula (II) product. The process of the invention has the advantage of freeing the product of formula (II) from its metal impurities.

When a solvent is chosen to purify the compound of formula (II) through crystallization, it may be advantageously chosen from: an alcohol such as ethanol and a chlorinated solvent such as methylene chloride.

Advantageously, the compound of formula (II) is produced starting from the compound of formula (I) which is made to react with a protective group R-CZ-Y in which Y is advantageously chosen from: F, Cl, Br, I, a C_1-C_6 alkoxy group, an -OCOR (anhydride)

group, and an hydroxyl group, optionally in the presence of an activator of the dicyclohexylcarbodiimide (DCC) type.

The reaction is performed conventionally in a basic or neutral medium in water or in a mixture of water and another solvent such as, for example, acetonitrile, tetrahydrofuran, dichloromethane or any other appropriate organic solvent.

The reaction is exothermic, means of cooling are preferably used in order to make it possible to maintain the temperature of the mixture at about ambient temperature.

The starting product (I) is either commercially available or is prepared by known methods, such as those described in WO 2006/032879.

In general, the products of formula (I) are prepared by means of synthetic processes that call for the use of the metal derivatives that are found as impurities in the products (I). That is the case as far as methylene blue is concerned, but also for azure A, azure B and azure C.

The compounds of formula (I) cannot have their metal and organic impurities removed directly, simply and efficiently. The prior art methods call for successive recrystallizations but this does not produce satisfactory yields and products are produced whose level of residual impurities is difficult to check.

In addition, the products of formula (I) have the property of chelating the metals, whereas the products (II) are non-chelating. They are thus much more efficiently purified than through direct purification of the formula (I) compounds.

In the various steps of the process of the invention, care has been taken to use non-metal materials and reagents and solvents free of metal residues so as not to introduce any external contamination.

After the product of formula (II) has been purified, and in particular subjected to filtration, according to the process of the invention, a step for deprotection of the amine of the phenothiazine ring of the compound of formula (II) is advantageously performed. This deprotection may be performed by any means known to those skilled in the art, while avoiding the introduction of metal contaminants and under conditions that prevent degradation of the formula (I) compound. Among the means that can be used for deprotection of the R-CZ- group, mention may be made of: quinones, for instance 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), HNO_3, $HClO_4$, I_2, HCl, H_2SO_4, H_2O_2, and treatment with ultraviolet radiation. A quinone is preferably used for this step, and very preferably 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. Advantageously, this deprotection reaction is performed using a solvent chosen from: ethyl acetate, acetonitrile, tetrahydrofuran and acetone. The solvent preferred for this step is acetonitrile.

Advantageous deprotection conditions plan for the use of between 0.80 and 1.1 molar equivalents of DDQ relative to compound (II), even more advantageously from 0.85 to 1.05 molar equivalents of DDQ relative to compound (II), advantageously from 0.90 to 1 molar equivalent. This deprotection should preferably be performed at a temperature of between -40°C and -5°C. Although not completely excluded, a lower temperature would

have the drawback of lengthening the reaction times, and a higher temperature could lead to the formation of by-products.

Depending on the means of deprotection used, it may be necessary to perform an ion exchange in order to obtain the formula (I) compound containing the desired X^- anion. Preferably, this ion exchange is carried out by treatment with HCl, advantageously in ethyl acetate. Other solvents could be used, but some are capable of causing the formation of by-products.

The conditions for deprotection of the compounds of formula (II) disclosed above are particularly advantageous in that they make it possible to achieve a compound of formula (I) without introducing metal impurities during this step or the formation of organic impurities. According to one variant of the invention, the compound of formula (II) could be purified by means other than filtration in a medium capable of retaining metals, for instance by crystallization from an appropriate solvent. According to this variant, the compound of formula (II) is subsequently deprotected, using any means of deprotection not involving the use of metal compounds, in particular using a quinone, in particular DDQ, preferably under the conditions disclosed above.

Another subject of the invention is therefore a process for preparing compounds corresponding to formula (I) described above, characterized in that it comprises at least one step for deprotection of the R-CZ- group of the amine of the phenothiazine ring of the compound of formula (II) using deprotection means not involving the use of metal compounds.

The "means of deprotection not involving the use of metal compounds" is taken to mean the use of non-metal reactants, and solvents not containing metal residues (preferably <0.01 ppm), in reactors not containing any metal parts, for instance enamelled reactors.

Among the means that can be used for the deprotection of the R-CZ- group, mention may be made of: quinones, for instance 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), HNO_3, $HClO_4$, I_2, HCl, H_2SO_4, H_2O_2, and treatment with ultraviolet radiation. A quinone is preferably used for this step, and very preferably 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. Advantageously, the conditions for using DDQ which were described above should be employed.

The method for deprotection of the compound (II) so as to result in compound (I) makes it possible to achieve a compound (I) that does not contain any additional metal impurities compared with the product (II). In addition, these deprotection conditions prevent the formation of organic degradation products. In fact, the compounds of formula (I) have limited stability and the use of certain treatment conditions results in degradation, for example of methylene blue to Azure A, B and C which are then difficult to separate out.

The process of the invention makes it possible to access a compound of formula (I) devoid of metal contaminants and having a high chemical purity, in a manner that is

reliable, reproducible and applicable on an industrial scale. These properties are essential for the ability to provide a product of formula (I) of pharmaceutical quality.

In particular, the preparation or purification process of the invention makes it possible to obtain, in industrial amounts and reproducibly, a methylene blue or tetramethylthionine chloride containing 0.02 µg/g or less of cadmium per g of methylene blue. The process of the invention gives access to a methylene blue or tetramethylthionine chloride with a degree of purity greater than 97%, preferably greater than 98%, or even better, greater than 99%, measured by HPLC (high performance liquid chromatography) under the conditions of European Pharmacopœia 5.4 (April 2006 edition) and containing less than 4.5 µg/g of aluminum, advantageously less than 3 µg/g of aluminum, even more advantageously less than 2.5 µg/g of aluminum per g of methylene blue.

The process of the invention gives access to a methylene blue or tetramethylthionine chloride with a degree of purity greater than 97%, preferably greater than 98%, even better, greater than 99%, measured by HPLC under the conditions of European Pharmacopœia 5.4 (April 2006 edition) and containing less than 0.5 µg/g of tin per g of methylene blue. The process of the invention gives access to a methylene blue or tetramethylthionine chloride wwith a degree of purity greater than 97%, preferably greater than 98%, even better, greater than 99%, measured by HPLC under the conditions of the European Pharmacopœia 5.4 (edition of April 2006) and containing less than 0.95 µg/g of chromium, advantageously less than 0.90 µg/g, even better, less than 0.80 µg/g per g of methylene blue.

The process of the invention is the only one to give access, in an industrial quantity, to a methylene blue or a tetramethylthionine chloride containing less than 3% of impurities, preferably less than 2%, even better, less than 1%, measured by HPLC under the conditions of the European Pharmacopœia 5.4 (April 2006 edition=) and a level of metal impurities of less than 20 µg/g, advantageously less than 15 µg/g, even more advantageously less than 10 µg/g.

The application discloses a compound of formula (I), with the exclusion of methylene blue or tetramethylthionine chloride and containing an overall level of metal impurities of less than 100 µg/g, advantageously less than 50 µg/g, in particular less than 30 µg/g. The application discloses that this compound is able to satisfy one or more of the following requirements:

- purity greater than 97%, preferably greater than 98%, even better, greater than 99%, measured by HPLC under the conditions of the European Pharmacopœia 5.4 (edition of April 2006),
- aluminium level of less than 5 µg/g, advantageously less than 4 µg/g, even more advantageously less than 3 µg/g,
- cadmium level of less than 0.1 µg/g, advantageously less than 0.05 µg/g, even better less than 0.02 µg/g,

- tin level of less than 0.5 µg/g, advantageously less than 0.4 µg/g and even more advantageously less than 0.3 µg/g.

Methylene blue has been used for decades in the treatment of various infections. It is used as an antiseptic, anti-infective, an antidote and a diagnostic agent. Its antiviral activity has recently been demonstrated, and it could be used in the preparation of medicines for combatting such pathological conditions as infections, in particular a septic shock, the presence of pathogenic contaminants in blood or plasma, an exaggerated haemodynamic reaction, HIV infection, West Nile virus or the hepatitis C virus, Alzheimer's disease, malaria, breast cancer or bipolar disorder.

Finally, it can also be used in cosmetics or for products destined for ophthalmic application.

For all these therapeutic uses, and in particular in the context of the prevention and treatment of Alzheimer's disease, it is necessary to have a methylene blue with a high degree of purity and in particular one that contains very few metal impurities.

The application discloses a medication consisting of a methylene blue of the invention, in a pharmaceutically acceptable carrier.

The carrier and the amounts of methylene blue to be administered are well known to those skilled in the art.

Another subject of the invention is a process for preparing a medicine containing a compound of formula (I), characterized in that this process comprises at least one process step as described above, in particular a step for purification of the compound of formula (I) and/or a step for deprotection of the compound (II) to produce (I).

EXPERIMENTAL SECTION

A commercially available methylene blue is purified in accordance with the process of figure 1.

1 - Synthesis of benzoyl leuco methylene blue (step A)

The following are introduced into a 120 l jacketed reactor equipped with a stirrer, and under nitrogen:

- 80 l of distilled water,
- 4.2 kg (10.7 mol) of methylene blue sold by the Leancare Ltd company under reference CI 52015, containing large amounts of metal impurities (Al, Fe, Cu, Cr).

The mixture is agitated for 15 min and then 6.9 kg of sodium hydrosulfite $Na_2S_2O_4$ in an aqueous solution at 85% is added. The colour changes from blue to beige. The mixture is agitated for a further 45 min, and then 2.69 kg of sodium hydroxide in the form of pellets is added. The reaction temperature is maintained at between 18 and 20°C. The addition time is 30 min and the resulting mixture is agitated for a further 30 min. 7.90 l of benzoyl chloride is subsequently added drop-by-drop. The reaction mixture turns a greenish-beige color. The time of the addition is 2 h and the resulting mixture is then agitated for 20 h.

Processing:

After agitation has stopped, the mixture is left to decant for 15 min and the supernatant is drawn off. 80 l of water (25 volumes) are added and, after stirring and separation by settling out, the supernatant is again drawn off. 24 l of EtOH is added and, after stirring for approximately 5 min, 16 l of water is added. After agitating for 15 min, the mixture is filtered into a recipient. This operation is repeated 3 times. After drying, 2.9 kg (yield: 66%) of benzoyl leuco methylene blue is obtained.

2 - Purification

4.25 kg of benzoyl leuco methylene blue derived from the first step, solubilized in 30 l of CH_2Cl_2, is used. The solution is filtered through 3 parts of silica (Merck Gerudan Si60) (11.5 kg) and 0.5 kg of Fontainebleau sand, rinsing being performed using 30 litres of CH_2Cl_2. The CH_2Cl_2 is eliminated through evaporation in a vacuum. 6 l ethanol is added. The mixture is cold-agitated then filtered into a recipient. The resulting product is dried in a vacuum. 3.4 kg of purified benzoyl leuco methylene blue is obtained (yield: 80%).

Purity: +99% HPLC

Metals: the metal content (in µg/g) is shown for 3 tests in table 1.

Table 1

Test	Test 1	Test 2	Test 3
Al	0.5	0.5	0.1
Cu	0	0	0.4
Fe	0	0	0.1
Zn	0.9	0.7	0.5
Ni	0.1	0.1	0.1
Cr	0.3	0.3	0.03
Mo	0.1	0.1	0.1
Mn	0.02	0	0
Sn	0.5	0.4	0.5
Pb	5	3.2	2.4
Cd	0.2	0.2	0.07

3 - Debenzoylation

The following are introduced into a 100 l jacketed enameled reactor at ambient temperature:

- 45 l of acetonitrile (ACN),

- 1.6 kg of benzoyl leuco methylene blue derived from the second step, and agitated. The mixture is agitated for 30 min at ambient temperature and the temperature is then reduced to -18°C. One 950 g portion of DDQ solubilized in 4 l of ACN is added. The mixture is agitated for 2 h at -18°C then filtered. A complex of the

3,7-bis(dimethylamino)phenothiazine with the DDQ is obtained and is used directly in the subsequent step.

4 - Salification

The cake derived from the third step is reintroduced, in several pieces, into the jacketed enameled reactor. 4 l of EtOAc are added. The mixture is stirred for 30 min at ambient temperature. The temperature is decreased to -18°C. 2.5 kg of HCl in 16 l of EtOAc (4N solution) is added. The mixture is stirred for 2 h at -18°C. The mixture is filtered and the cake is then returned to the reactor. 30 l of EtOAc is added at -18°C and the mixture is again filtered.

5 - Neutralization

30 l of acetone is added, followed by a solution of 200 g of NaOH dissolved in 500 ml of water. The mixture is filtered. The product derived from the fourth step is introduced into the reactor with 30 l of acetone. The medium is agitated for 1 h at ambient temperature. The pH is 4.0. The medium is filtered. It is left in a vacuum in the recipient.

6 - Purification and hydration

1.9 kg of product from the fifth step and 30 l of a 50/50 mixture of CH_2Cl_2/EtOH are introduced into a 40 l enamelled reactor under N_2, at ambient temperature. The resulting mixture is refluxed (43°C). It is filtered under hot conditions using a microfibre filter (Whatman GF/D). This operation is performed twice. The reactor is cleaned with demineralized water. The filtrate is reintroduced into the reactor. 24 litres of solvent are distilled in a vacuum at 28°C (3 h). The medium is returned to the reactor. 1 l of microfiltered water is added. The mixture is cooled to -18°C. 40 l of EtOAc are added and the resulting mixture is left overnight in cold agitation. It is then filtered. It is turned into a paste with 10 l of EtOAc. 1.4 kg of purified methylene blue in trihydrate form is obtained.

The metal impurities have been analyzed and are reported in table 2.

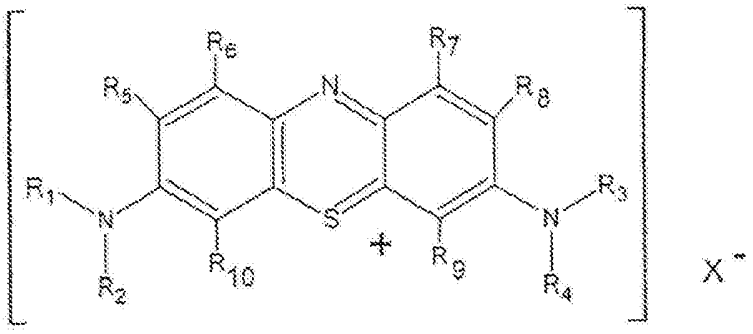
Element	Amount (µg/g)
Al	1.3
Cu	0.5
Fe	1.9
Zn	1.7
Ni	0.5
Cr	0.8
Mo	0.2
Mn	0.08
Sn	0.4
Pb	0.1
Cd	0.04

Table 2

ELJÁRÁS DIAMINO-FENOTIAZINIUM VEGYÜLETEK ELŐÁLLÍTÁSÁRA

Szabadalmi igénypontok

1. Eljárás egy vegyület előállítására, amely az alábbi (I) képletű:



(I)

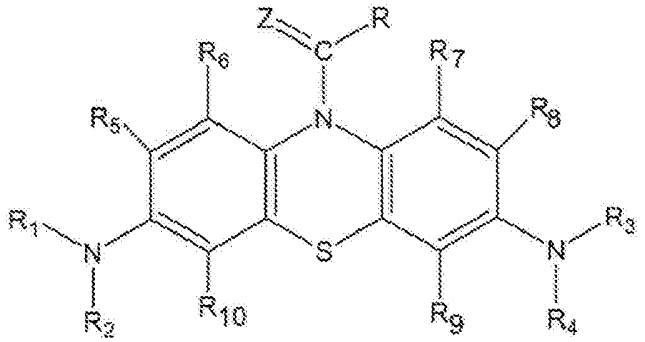
ahol mindegyik R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9 és R_{10} közül, egymástól függetlenül, a következőkből álló csoportból választható:

- egy hidrogén atom,
- telített vagy telítetlen, egyenes láncú, elágazó láncú vagy ciklusos C_1-C_6-alkil-csoportok, amelyek adott esetben szubsztituáltak egy vagy több funkciós csoporttal a következők közül választva: egy halogénatom és egy C_1-C_6-alkoxi-, C_1-C_6-alkil-oxi-karbonil- vagy -$CONH_2$-funkciós csoport,
- aril-csoportok, amelyek adott esetben szubsztituáltak egy vagy több funkciós csoporttal a következők közül választva: egy C_1-C_4-alkil, egy halogénatom és egy C_1-C_6-alkoxi-, C_1-C_6-alkil-oxi-karbonil- vagy -$CONH_2$-funkciós csoport,

továbbá mindegyik R_5, R_6, R_7, R_8, R_9 és R_{10} közül, egymástól függetlenül, a következő halogénatomok közül választható: F, Cl, Br és I,

X^- jelentése egy szerves vagy szervetlen anion,

azzal jellemezve, hogy az magában foglal legalább egy lépést, amely során a következő (II) képletű vegyület:



(II)

ahol R jelentése egy csoport, amely a következők közül van választva:

- egy fenil- vagy benzil-csoport, amely adott esetben szubsztituált egy vagy több funkciós csoporttal a következők közül választva: egy C_1-C_8-alkil, egy halogénatom, egy C_1-C_4-halogén-alkil és egy nitro-csoport,
- egy egyenes láncú, elágazó láncú vagy ciklusos C_1-C_8-alkil-csoport,
- egy C_1-C_8-alkil-amino-csoport,
- egy C_1-C_8-alkoxi-csoport,
- egy fenil-oxi- vagy benzil-oxi-csoport, amely adott esetben szubsztituált az aromás magon egy vagy több funkciós csoporttal a következők közül választva: egy C_1-C_4-alkil, egy halogénatom, egy C_1-C_4-halogén-alkil és egy nitro-csoport,

Z jelentése egy atom, amely O és S közül van választva,

alá van vetve egy tisztítási lépésnek olyan körülmények között, amelyek lehetővé teszik, hogy fémvegyületek legyenek elválasztva a (II) képletű vegyületekből, ahol ez a lépés magában foglal legalább egy szűrést egy szűrési hordozóanyagon keresztül, amely a következők közül van választva: egy szilikagél, egy semleges, bázikus vagy savas alumínium-oxid-gél, egy mikroporózus membrán, egy fémmegkötő-csoportokkal oltott gyanta és fémmegkötő-csoportokkal oltott rostok.

2. Eljárás az 1. igénypont szerint, ahol R_1, R_2, R_3, R_4, R_5 és R_6, amelyek lehetnek azonosak vagy különbözőek, egy hidrogénatom és egy C_1-C_4-alkil közül vannak választva.

3. Eljárás az előző igénypontok bármelyike szerint, ahol a következő követelmények közül egy vagy több van teljesítve:
   - R_5, R_8, R_9 és R_{10} jelentése H,
   - X jelentése Cl vagy OH,
   - R_1, R_2, R_3 és R_4, amelyek lehetnek azonosak vagy különbözőek, egy hidrogénatom és a metil közül vannak választva,
   - R_6 jelentése egy hidrogénatom,
   - R_7 jelentése egy hidrogénatom,
   - Z jelentése O.

4. Eljárás az előző igénypontok bármelyike szerint, ahol az (I) képletű vegyület a tetrametil-tionin-klorid vagy metilénkék.

5. Eljárás az 1.-től 4.-ig igénypontok bármelyike szerint, ahol az (I) képletű vegyület a következők közül van választva:

   dimetil-tionin-klorid vagy Azúr A,

   trimetil-tionin-klorid vagy Azúr B,

   monometil-tionin-klorid vagy Azúr C.

6. Eljárás az előző igénypontok bármelyike szerint, ahol a szűréshez a (II) képletű vegyület fel van oldva egy oldószerben, amely a következők közül van választva: klórozott oldószerek, mint amilyen a diklór-metán vagy kloroform, alkoholok, mint amilyen az etanol, izopropanol, metanol, acetonitril, etil-acetát, tetrahidrofurán, vagy ezek az oldószerek egy keveréke.

7. Eljárás az 1.-től 6.-ig igénypontok bármelyike szerint, ahol a szűrési hordozóanyag a következők közül van választva: egy szilikagél.

8. Eljárás az előző igénypontok bármelyike szerint, ahol az továbbá magában foglal egy lépést, amely a (II) képletű vegyület fenotiazin-gyűrűjének az amin-védőcsoportjának eltávolításából áll egy eszköz révén, amely a következők közül van választva: kinonok, mint amilyen a 2,3-diklór-5,6-diciano-1,4-benzokinon, HNO_3, $HClO_4$, I_2, HCl, H_2SO_4, H_2O_2, egy kezelés ultraibolya sugárzás által.

9. Eljárás a 8. igénypont szerint, **azzal jellemezve, hogy** a védőcsoport-eltávolítás a 2,3-diklór-5,6-diciano-1,4-benzokinon által van teljesítve.

10. Eljárás a 8. és 9. igénypontok bármelyike szerint, **azzal jellemezve, hogy** az továbbá magában foglal egy ioncserélő lépést, HCl-val történő kezelés által.

11. Eljárás az előző igénypontok bármelyike szerint, ahol egy metilénkék (3,7-bisz(dimetil-amino)fenotiazin-5-ilium-klorid) van kapva, amely 3%-nál kevesebb szennyeződést tartalmaz és egy 20 µg/g-nál kisebb fémszennyeződés-szinttel rendelkezik.

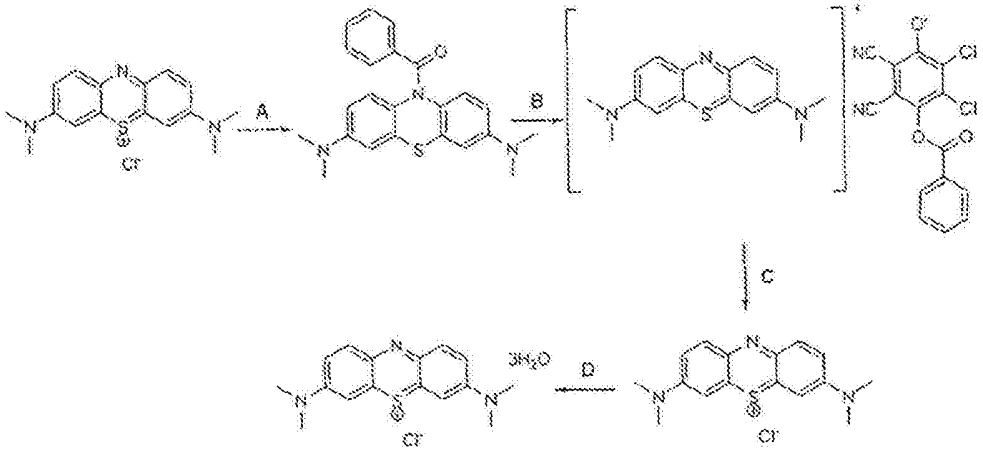
12. Eljárás a 11. igénypont szerint, ahol egy metilénkék van kapva, amely 3%-nál kevesebb szennyeződést tartalmaz és egy 15 µg/g-nál kisebb, előnyösen 10 µg/g-nál kisebb, fémszennyeződés-szinttel rendelkezik.

13. Eljárás egy gyógyszer előállítására, amely tartalmaz egy (I) képletű vegyületet az 1. igénypont szerint, **azzal jellemezve, hogy** az (I) képletű vegyület egy eljárás révén van előállítva, amely magában foglal legalább egy lépést az 1.-től 12.-ig igénypontok bármelyike szerint.

14. Eljárás a 13. igénypont szerint, ahol az (I) képletű vegyület a metilénkék.

Drawings

Summary diagram for Methylene Blue



A. H_2O/Na_2SO_4, NaOH, Benzoyl chloride
B. DDQ/CH_3CN
C. Ion exchange then $NaOH/H_2O$ pH 4
D. Hydration (H_2O)

Figure 1