(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
23 July 2009 (23.07.2009)  PCT

(10) International Publication Number
WO 2009/089677 A1

(51) International Patent Classification:
C07D 473/04 (2006.01)

(21) International Application Number:
PCT/CN2008/001998

(22) International Filing Date:

(25) Filing Language:
English

(26) Publication Language:
English

(30) Priority Data:
200710116000.8
14 December 2007 (14.12.2007) CN
200710116201.8
14 December 2007 (14.12.2007) CN

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(54) Title: THEOBROMINE PRODUCTION PROCESS

(57) Abstract: A process for preparing theobromine by methylating 3-methyl xanthine disodium salt comprises reacting 3-methyl xanthine disodium salt with dimethyl sulfate by using aceton as solvent in the presence of sodium carbonate and acidifying. The present application also provides a process for refining theobromine which comprises dissolving coarse theobromine in liquid alkaline solution, decolorizing, filtering, adding reducing agent in filtrate, and acidifying at 60-80 °C until pH is 5-6, filtering, and drying to obtain theobromine.
THEOBROMINE PRODUCTION PROCESS

FIELD OF THE INVENTION

[0001] The present invention relates to the field of synthetic chemistry and more particularly to a novel process for preparing and purifying theobromine.

BACKGROUND OF THE INVENTION

[0002] Theobromine, also known by the name 3,7-dihydro-3,7-dimethyl-1H-purine-2,6-dione, is represented by the following structural formula:

![Structural formula of theobromine](image)

[0003] Theobromine is the principal alkaloid of the cacao bean which contains 1.5-3% of the base and hence it is found in chocolate. It is also found in cola nuts and in tea. Theobromine belongs to the class of xanthine compounds, which also includes caffeine and theophylline. Although the name of the compound is "theobromine" it contains no bromine because the name is actually derived from Theobroma, the name of the genus of the cacao tree.

[0004] Theobromine is a crystalline substance having the formula C_{7}H_{8}N_{4}O_{2}. It is sparingly soluble in water (0.5 g/liter), partly soluble in boiling water (1g/150 ml), and it is almost insoluble in ether and chloroform. However, theobromine is soluble in concentrated acids and moderately soluble in ammonia.

[0005] As a methylated xanthine, theobromine is a potent cyclic adenosine monophosphate phosphodiesterase inhibitor (cAMP), inhibiting the enzyme phosphodiesterase from converting the active cAMP into an inactive form. cAMP is a second messenger in various metabolic systems. Theobromine can serve as starting material for
preparing pentoxifylline, which is a methylxanthine derivative. Pentoxifylline improves blood flow and it is used to treat intermittent claudication and vascular dementia.

![Pentoxifylline structure]

According to Czech Patent 279270, theobromine is prepared from 1-methyl-5-formylmethylamino-6-aminouracil, as depicted in Scheme 1 below:

Scheme 1

![Scheme 1 diagram]

1-methyl-5-formylmethylamino-6-aminouracil

The reaction comprises refluxing the compound 1-methyl-5-formylmethylamino-6-aminouracil in aqueous ethanol containing KOH, isolating the theobromine potassium salt, dissolving it in water and acidifying to pH 6, neutralizing with acetic acid and obtaining the product. However, the above-mentioned process is not practical because the starting material 1-methyl-5-formylmethylamino-6-aminouracil is not a commercial material.

European Patent 0319854 discloses a process for preparing theobromine starting from 3-methylxanthine by reacting it with dimethyl carbonate for 2 1/2 hours under pressure of 100 bar in 1N HCl at 170°C. European Patent 0319854 discloses also a process for preparing theobromine starting from xanthine by reacting it with dimethyl carbonate for 2 1/2 hours under pressure of 160 bar in 1N HCl at 200°C.
The process is depicted in Scheme 2 below:

Scheme 2

3-methylxanthine

$\xrightarrow{(\text{CH}_3\text{O})_2\text{CO}}$ $\xrightarrow{\text{HCl, pressure, } \triangle}$

theobromine

xanthine

$\xrightarrow{(\text{CH}_3\text{O})_2\text{CO}}$ $\xrightarrow{\text{HCl, pressure, } \triangle}$

theobromine

[0008] Czech Patent 281006 discloses a process for preparing theobromine starting from 3-methyl-2,6-dioxo-1,2,3,6-tetrahydro-1H-purine (3-methylxanthine), by reacting the starting material with dimethyl carbonate in N,N-dimethylformamide (DMF) in the presence of triethylbenzene ammonium chloride (TEBAC). The process is depicted in Scheme 3 below:

Scheme 3

3-methylxanthine

$\xrightarrow{(\text{CH}_3\text{O})_2\text{CO}}$ $\xrightarrow{\text{TEBAC, DMF}}$

theobromine
[0009] Other processes for preparing theobromine starting from 3-methylxanthine are described, e.g., in Romanian Patent RO 101894, wherein 3-methylxanthine is methylated with PhSO$_3$Me in the presence of NaOH; in, e.g., Czech Patent 267100, wherein 3-methylxanthine is methylated with chloromethane (MeCl) in methanol and in the presence of NaOH; in, e.g., Korean Application KR 2008076146, wherein 3-methylxanthine is suspended in sulfolane and methylated in the presence of a base. However, the use of reagents such as, e.g., chloromethane is disadvantageous because it is highly flammable and toxic. Sulfolane, for example, has a very high boiling point of 284°C, so it is difficult to eliminate residual traces of this solvent from the final product.

[0010] Niegel et al. describe in Patent DD 222026 (East Germany) a synthesis of theobromine by reacting 3-methylxanthine with dimethyl sulfate in, e.g., a mixture of water and methanol in the presence of potassium carbonate (example 1) to obtain theobromine in 73% yield, but the patent is silent with respect to the purity of the obtained theobromine. While searching for an improved process for preparing theobromine, the inventors of the present invention have reproduced example 1 of Patent DD 222026 and obtained theobromine having very low purity (by HPLC), as described in Reference Example 1.

[0011] It is apparent to those skilled in the art that obtaining highly pure theobromine by the processes described hereinabove may not be an easy task to achieve, and that the purified theobromine is liable to be obtained in a relatively low yield. Therefore, there is a need in the art for an improved process for producing theobromine using readily available starting materials and solvents. Furthermore, the process should enable isolating the product in high purity and yield, wherein the content of the impurities is minimal.

**BRIEF SUMMARY OF THE INVENTION**

[0012] The present invention provides a novel process for preparing theobromine by methylating 3-methylxanthine or a salt thereof (e.g., the disodium salt) in a solvent, which can be an organic solvent or a mixture of an organic solvent and water in the presence of a base to afford high yields of theobromine.

[0013] In one embodiment, the present invention provides a process for preparing theobromine in high yield, comprising:

(a) heating a mixture of crude 3-methylxanthine or a salt thereof, a solvent and
a base;
(b) adding a methylating agent and heating; and
(c) acidifying the reaction mixture to produce theobromine.

[0014] According to the present invention, after acidifying the reaction mixture it is further cooled to afford a solid, which is obtained by filtration and dried.

[0015] Preferably, the theobromine which is obtained as is by the process provided herein without any further purification, has a purity of at least 99% by weight, or at least 99.5% by weight.

[0016] Preferably, the solvent used in step (a) is an organic solvent such as acetone or a mixture of an organic solvent, e.g., acetone, and water.

[0017] According to a preferred embodiment of the present invention, as demonstrated e.g., in Examples 2 and 3 respectively, the reaction is preferably carried out either using 3-methylxanthine in a solvent mixture of acetone and water or using 3-methylxanthine disodium salt in acetone without the addition of water.

[0018] In a preferred embodiment of the present invention, the process for producing theobromine can be carried out by reacting 3-methylxanthine disodium salt with dimethyl sulfate in the presence of sodium carbonate, with acetone as a solvent and then acidifying to afford the product.

[0019] According to another preferred embodiment, the process for producing theobromine can be carried out by reacting 3-methylxanthine with dimethyl sulfate in the presence of sodium bicarbonate, with a mixture of acetone and water as a solvent and then acidifying to afford the product.

[0020] According to the present invention, as shown in Table 1, different combinations of solvents and bases do not produce equally good results with respect to the yield and the purity of the isolated theobromine. Many of these combinations of solvents and bases are unsuitable for obtaining theobromine having the required purity.

[0021] According to the present invention, theobromine can be purified by a process comprising the steps of:
(a) mixing theobromine with water adding a base and heating the mixture;
(b) adding activated carbon, stirring and filtering the activated carbon;
(c) heating and acidifying the mixture; and
(f) cooling, filtering the solid, washing and drying.
Preferably, the process for purifying theobromine further comprises adding a reducing agent prior to acidifying the mixture and filtering.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel process for preparing theobromine by methylating 3-methylxanthine or a salt thereof (e.g., the disodium salt) in a solvent, which can be an organic solvent or a mixture of an organic solvent and water in a presence of a base.

It is apparent to those skilled in the art that obtaining highly pure theobromine may not be an easy task to achieve, and that the purified theobromine is liable to be obtained in a relatively low yield. Therefore, there is a need in the art for an improved process for producing theobromine in high purity and yield, wherein the content of the impurities is minimal. Thus, in one embodiment, the present invention provides a process for preparing theobromine in high yield, comprising:

(a) heating a mixture of crude 3-methylxanthine or a salt thereof, a solvent and a base;

(b) adding a methylating agent and heating; and

(c) acidifying the reaction mixture to produce theobromine. The term "methylating", as defined herein, refers to a reaction of methylation, that is, adding a methyl group to a molecule using a methylating agent.

As used herein, the term “crude 3-methylxanthine” refers to 3-methylxanthine having a purity up to 98.9% by weight, preferably up to about 98.5% by weight of 3-methylxanthine.

As used herein, the term “highly pure theobromine” or “purified theobromine” refers to theobromine, having a purity of at least 99.0% by weight, preferably at least 99.5% or at least 99.8% by weight of theobromine.

According to the present invention, after acidifying the reaction mixture it is further cooled to afford a solid, which is obtained by filtration and dried.

Preferably, theobromine can be obtained as is by the process provided herein without any further purification, having a purity of at least 99% by weight, or at least 99.5% by weight.
[0031] According to some embodiments of the present invention, the methylating agent is selected from diazomethane, dimethyl carbonate, dimethoxypropane, dimethyl sulfate, dimethylzinc, iodomethane, methyl fluorosulfonate and methyl triflate. Preferably, the methylating agent is dimethyl sulfate.

[0032] According to some other embodiments, the mixture of crude 3-methylxanthine, a solvent and a base can be heated to a temperature of at least about 55°C. The temperature can be at least about 60°C, at least about 65°C, at least about 70°C, at least about 75°C, at least about 80°C, at least about 85°C, or at least about 90°C. The temperature to which the solution is heated depends upon the solvent used to prepare the solution and the solvent’s physical properties (e.g., boiling point), a determination of which is within the skill of a person of the relevant art.

[0033] According to some embodiments, the solvent used in the reaction can be an organic solvent selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, tert-butanol, 1-methoxy-2-propanol, toluene, acetone, methyl ethyl ketone, methyl isobutyl ketone and the like, and mixtures thereof. For example, the organic solvent can be acetone or a mixture of the organic solvent and water, e.g., a mixture of acetone and water.

[0034] According to a preferred embodiment of the present invention, as demonstrated in, e.g., Examples 2 and 3 respectively, the reaction is preferably carried out either using 3-methylxanthine in a solvent mixture of acetone and water or using 3-methyl-xanthine disodium salt in acetone without the addition of water.

[0035] According to the present invention, as shown in Table 1, different combinations of solvents and bases do not produce equally good results with respect to the yield and the purity of the isolated theobromine. Many of these combinations of solvents and bases are unsuitable for obtaining theobromine having the required purity.

[0036] According to some other embodiments, the base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, lithium bicarbonate, cesium bicarbonate, and combinations thereof. Preferably, the base is sodium carbonate or sodium bicarbonate.

[0037] In a preferred embodiment of the present invention, the process for producing theobromine can be carried out by reacting 3-methylxanthine disodium salt with dimethyl sulfate in the presence of sodium carbonate, with acetone as a solvent and then acidifying to afford the product.
According to another embodiment, the temperature for carrying out the reaction of 3-methylxanthine disodium salt with dimethyl sulfate is 55-60°C; dimethyl sulfate is added dropwise in 3 to 5 hours and the reaction period is 0.5 to 1.5 hours.

According to another embodiment, the ratio of 3-methylxanthine disodium salt: sodium carbonate: dimethyl sulfate is 1:0.3-0.5:0.95 by weight and the ratio of 3-methylxanthine disodium salt: solvent is 1g: 4-6 ml.

According to another embodiment, the temperature is reduced after the completion of reaction; the reactant is acidified until pH being 4-6 and is then filtered, washed and dried to afford theobromine.

According to another preferred embodiment, the process for producing theobromine can be carried out by reacting 3-methylxanthine dimethyl sulfate in the presence of sodium bicarbonate, with a mixture of acetone and water as a solvent and then acidifying to afford the product.

Preferably, the ratio of the crude 3-methylxanthine to the solvent, i.e., 3-methylxanthine: solvent ratio, is about 1 gram (g) 3-methylxanthine per at least 2 milliliter (ml) of solvent, preferably the ratio is about 1 g 3-methylxanthine per about 5 to about 10 ml of solvent.

In cases where the solvent is a mixture of an organic solvent and water, e.g., a mixture of acetone and water, the acetone: water ratio is about 2-12 ml of acetone per at least 1 milliliter (ml) of water; preferably the ratio is about 6 ml of acetone per at least 1 milliliter (ml) of water.

According to the present invention, theobromine can be purified by a process comprising the steps of:

(a) mixing theobromine with water, adding a base and heating the mixture;
(b) adding activated carbon, stirring and filtering the activated carbon;
(c) heating and acidifying the mixture; and
(d) cooling, filtering the solid, washing and drying.

Preferably, the process for purifying theobromine further comprises adding a reducing agent prior to acidifying the mixture and filtering.

According to some embodiments of the present invention, the base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate, potassium
bicarbonate, sodium bicarbonate, lithium bicarbonate, cesium bicarbonate, and combinations thereof. Preferably, the base is sodium hydroxide.

[0047] According to a preferred embodiment, the theobromine solution is dissolved by adding aqueous 30% sodium hydroxide, decolourized, and filtered; a reducing agent is added into the filtrate; the filtrate is then acidified at 60-80°C until pH=5-6, filtered and dried to obtain a theobromine final product.

[0048] According to the present invention, adding a 30% sodium hydroxide to the crude theobromine dissolves it as a sodium salt forming dark brown color because part of the theobromine is oxidized, which makes the color darker. Preferably, a small amount of reducing agent can be optionally added. At a certain temperature, while the acidification proceeds, part of oxidized theobromine is reduced back to theobromine, which makes the color become lighter.

[0049] According to another embodiment, the reducing agent is sodium sulfite, sodium bisulfite, sodium metabisulfite, sodium sulfide, sodium thiosulfate or hydrogen sulfide.

[0050] According to another embodiment, the weight ratio of crude theobromine to reducing agent is 1:0.01 to 0.03.

[0051] According to another embodiment, the ratio of theobromine: 30% aqueous NaOH: reducing agent is 1:0.75:0.01-0.03 by weight.

[0052] According to other embodiments of the present invention, the acid is selected from hydrochloric acid, perchloric acid, periodic acid, phosphoric acid, sulfurous acid, sodium hydrogen sulfate and sulfuric acid, preferably hydrochloric acid.

[0053] In order to facilitate precipitation, the mixture containing the theobromine can be cooled. Preferably, the mixture is cooled to a temperature of about -10°C to about 25°C. The solution can be cooled for a sufficient time to effect maximum precipitation of theobromine.

EXAMPLES

REFERENCE EXAMPLE 1

[0054] This example demonstrates the preparation of theobromine according to Example 1 of Patent DD 222026.

[0055] 8.3 g of 3-methylxanthine (0.05 mol), 50 ml water and 21 g potassium carbonate were mixed at 85-90°C to obtain a solution in a 500 ml four-neck reaction vessel
equipped with a mechanical stirrer. The solution was cooled to 70°C and 50 ml of methanol was added, forming a gel, which was not easily stir-able, followed by drop-wise addition of 9.45 g of dimethyl sulfate for half an hour, during which time the temperature rose to 80°C. The reaction was continued for an hour at 70-80°C. A sample was withdrawn, filtered, diluted and injected to the HPLC. The purity of theobromine at the end of the reaction was 26.8%.

EXAMPLE 2
[0056] This example demonstrates the preparation of theobromine in a mixture of acetone and water in the presence of sodium bicarbonate.
[0057] 16.6 g of 3-methylxanthine (0.1 mol) was mixed with 100 ml acetone in a 500 ml four-neck reaction vessel equipped with a mechanical stirrer and 20 ml water was added. 36 g of sodium bicarbonate was added under stirring and heating to a temperature of 55-60°C was applied. 20 g of dimethyl sulfate was added drop-wise during 3.5 hours and stirring was maintained for half an hour at 55-60°C. Then, the acetone was distilled off and recovered. 50 ml water was added and the reaction vessel was heated to 80°C. Then, 32% HCl was added slowly to the mixture and a pH in the range of 5-6 was measured. The mixture was cooled to 25°C and the thus formed solid was obtained by precipitation, washed with water and dried at 70°C; 15.7 g of theobromine was obtained in 87% yield, having purity of 99.9% by HPLC.

EXAMPLE 3
[0058] This example demonstrates the preparation of theobromine in acetone and in the presence of sodium carbonate.
[0059] In a 500 ml four-neck reaction vessel equipped with a stirrer, 3-methylxanthine disodium salt (63 g), acetone (304 ml) and sodium carbonate (19.1 g) were added under constant stirring. The mixture was heated slowly to a temperature of about 55°C. Dimethyl sulfate (60 g) was added dropwise over a period of 4 hours. Then, the reaction was kept at 55°C for another half an hour. Acetone was distilled under normal pressure and water (50 ml) was added. The resultant solution was neutralized by using 32% hydrochloric acid at 30°C until the pH value was about 5. Then, the solution was filtered, washed with warm water at 40°C (15 ml), filtered under reduced pressure to remove the water, and dried at 70 °C to afford crude theobromine in 86.7% yield.
EXAMPLE 4

[0060] This example demonstrates the preparation of theobromine in acetone and in the presence of sodium carbonate.

[0061] In a 500 ml four-neck reaction vessel equipped with a stirrer, 3-methylxanthine disodium salt (63 g), acetone (304 ml) and sodium carbonate (19.1 g) were added under stirring. The mixture was heated to 55°C and dimethyl sulfate (60 g) was added dropwise over a period of 3.5 hours. Then, the reaction was kept at 55°C for another half an hour. Acetone was distilled under normal pressure. Water (50 ml) was added. The resultant solution was neutralized by using 32% industrial hydrochloric acid at 30°C until the pH value was about 6. The solution was then filtered, washed with warm water at 40°C (10 ml), filtered under reduced pressure to remove the water, and dried at 70°C to afford theobromine in 84.3% yield.

EXAMPLE 5

[0062] This example demonstrates the preparation of theobromine in acetone and in the presence of sodium carbonate.

[0063] In a 1000 ml four-neck reaction vessel equipped with a stirrer, 3-methylxanthine disodium salt (126 g), acetone (610 ml) and sodium carbonate (38.5 g) were added under stirring. The mixture was heated slowly to a temperature of 55°C and dimethyl sulfate (120 g) was added dropwise over a period of 3.5 hours. Then, the reaction was kept at 57°C for another half an hour. Acetone was distilled under normal pressure. Water (100 ml) was added and the resultant solution was neutralized by using 32% hydrochloric acid at 30°C until the pH value was about 6. Then, the solution was filtered, washed with warm water at 40°C (20 ml), filtered under reduced pressure to remove the water, and dried at 70°C to afford theobromine in 84.9% yield.

EXAMPLES 6-23

[0064] These examples detail the preparation of theobromine using different combinations of solvents and bases.

[0065] 3-methylxanthine was placed in a 500 ml four-neck reaction vessel equipped with a mechanical stirrer along with the solvent and base as detailed in Table 1. The mixed solution was stirred under reflux conditions as temperature was gradually raised to a temperature as detailed in Table 1, followed by drop-wise addition of dimethyl sulfate. Then,
the reaction was continued and worked-up essentially as described in Example 2. The results are summarized in Table 1.

<table>
<thead>
<tr>
<th>Example</th>
<th>Solvent</th>
<th>Base</th>
<th>Reaction temp, °C</th>
<th>% Purity (HPLC)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Water/MeOH</td>
<td>KOH/K₂CO₃</td>
<td>75-80</td>
<td>69.5</td>
<td>The yield was only 48%</td>
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<tr>
<td>7</td>
<td>MeOH</td>
<td>K₂CO₃/TMAOH</td>
<td>65-70</td>
<td>---</td>
<td>92.5% caffeine was produced</td>
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<tr>
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<td>Water/MeOH</td>
<td>K₂CO₃</td>
<td>85-90</td>
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<td></td>
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<tr>
<td>9</td>
<td>MeOH</td>
<td>KOH</td>
<td>reflux</td>
<td>26.9</td>
<td>Base was dripped in</td>
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<tr>
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<td>Water/toluene</td>
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<tr>
<td>11</td>
<td>Isopropanol</td>
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<td>38.3</td>
<td></td>
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<td>reflux</td>
<td>76.5</td>
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<tr>
<td>15</td>
<td>Isopropanol</td>
<td>Solid NaOH</td>
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<td>---</td>
<td>No reaction</td>
</tr>
<tr>
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<td>tert-BuOH</td>
<td>NaHCO₃/NaOH</td>
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<td>59.5</td>
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<td>Isopropanol/ Water</td>
<td>NaHCO₃/NaOH</td>
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<td>75-82</td>
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</tr>
</tbody>
</table>

TMAOH= tetramethylammonium hydroxide pentahydrate

**EXAMPLE 24**

[0066] This example details the purification of theobromine using activated carbon.

[0067] 50 g of theobromine was mixed with 500 ml water and 47% NaOH was slowly added until complete dissolution of theobromine. The mixture was heated to a temperature of at least 40°C and stirred for 30 minutes while 2-5 g of activated carbon (Norrit CA1 or SX ultra) was added. The activated carbon was filtered through a pressure filter and the mixture
was heated to 80°C. 32% HCl was added slowly and a pH of 5-6 was measured. The mixture was cooled to 25°C and the thus formed solid was filtered off, washed with water and dried at 70°C.

EXAMPLE 25

[0068] This example details the purification of theobromine using activated carbon and sodium metabisulfite as reducing agent.

[0069] In a 250 ml four-neck reaction vessel, equipped with a stirrer, crude theobromine (20 g), water (120 ml) and 30% NaOH solution (12 ml) were added under stirring. The reaction vessel was heated to a temperature of 70-80°C. Activated carbon (1 g) was added and the solution was decolorized for half an hour. The solution was filtered off, and sodium metabisulfite (0.2 g) was added into the filtrate, which was stirred at a temperature of about 65-70°C. Then, the filtrate was acidified with concentrated hydrochloric acid until the pH value was in the range of 5-6. Then, the temperature was reduced to about 25°C. The treated filtrate was filtered and washed with deionized water, then dried to obtain 18.5 g of theobromine. The thus obtained product passed each assay of CP 2005, EP 4 and USP 27.

EXAMPLE 26

[0070] This example details the purification of theobromine using activated carbon and sodium bisulfite as reducing agent.

[0071] In a 250 ml four-neck reaction vessel equipped with a stirrer, crude theobromine (20 g), water (120 ml) and 30% NaOH (12 ml) were added under stirring. The reaction vessel was heated to a temperature of 70-80°C and activated carbon (1 g) was added. The solution was decolorized for half an hour at a temperature of 70-80°C. The solution was filtered off, and sodium bisulfite (0.3 g) was added into the filtrate, which was stirred at a temperature of 65-70°C. Then, the filtrate was acidified with a concentrated hydrochloric acid until the pH range was in the range of 5-6. Then, the temperature was reduced to 25°C. The treated filtrate was filtered off and washed with deionized water, then dried to obtain 18.6 g of theobromine. The thus obtained product passed each assay of CP 2005, EP 4 and USP 27.

EXAMPLE 27

[0072] This example details the purification of theobromine using activated carbon and sodium thiosulfate as reducing agent.
In a 250 ml four-neck reaction vessel equipped with a stirrer, crude theobromine (20 g), water (120 ml) and 30% NaOH (12 ml) were added under stirring. The reaction vessel was heated to a temperature of 70-80°C and activated carbon was added (1 g). The solution was decolorized for half an hour at a temperature of 70-80°C. The solution was filtered off, and sodium thiosulfate (0.4 g) was added into the filtrate, which was stirred at a temperature of 65-70°C. Then, the filtrate was acidified with concentrated hydrochloric acid until the pH value was in the range of 5-6. Then, the temperature was reduced to 25°C and the treated filtrate was filtered off, washed with deionized water and dried to obtain 18.2 g of theobromine. The thus obtained product passed each assay of CP 2005, EP 4 and USP 27.
CLAIMS:

1. A process for producing theobromine in high yield, comprising:
   (a) heating a mixture of crude 3-methylxanthine or a salt thereof, a solvent and a base;
   (b) adding a methylating agent and heating; and
   (c) acidifying the reaction mixture to produce theobromine.

2. The process of claim 1, wherein the methylating agent is selected from the group consisting of diazomethane, dimethyl carbonate, dimethoxypropane, dimethyl sulfate, dimethylzinc, iodomethane, methyl fluorosulfonate and methyl triflate,

3. The process of claim 1, wherein the solvent used in the reaction is an organic solvent selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, 1-methoxy-2-propanol, toluene, acetone, methyl ethyl ketone, methyl isobutyl ketone and mixtures thereof, or a mixture of the organic solvent and water.

4. The process of claim 1, wherein the base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, lithium bicarbonate, cesium bicarbonate, and combinations thereof.

5. The process for producing theobromine of claims 1-4, wherein said process is carried out by reacting 3-methylxanthine disodium salt with dimethyl sulfate in the presence of sodium carbonate, with acetone as a solvent and then acidifying to afford the product.

6. The process for producing theobromine of claim 5, wherein after acidifying the reaction mixture it is further cooled to afford a solid, which is obtained by filtration and dried.

7. The process of claims 5, wherein the temperature for carrying out the reaction of 3-methylxanthine disodium salt with dimethyl sulfate is 55-60°C; dimethyl sulfate is added dropwise in 3 to 5 hours and the reaction period is 0.5 to 1.5 hours.
8. The process of claim 5, wherein the ratio of 3-methylxanthine disodium salt: sodium carbonate: dimethyl sulfate is 1:0.3-0.5:0.95 by weight and the ratio of 3-methylxanthine disodium salt: solvent is 1g: 4-6 ml.

9. The process of claim 6, wherein the temperature is reduced after the completion of reaction; the reactant is acidified until pH being 4-6 and is then filtered, washed and dried to afford theobromine.

10. The process for producing theobromine of claims 1-4, wherein said process is carried out by reacting 3-methylxanthine and dimethyl sulfate in the presence of sodium bicarbonate, with a mixture of acetone and water as a solvent and then acidifying to afford the product.

11. The process for producing theobromine of claim 10, wherein after acidifying the reaction mixture it is further cooled to afford a solid, which is obtained by filtration and dried.

12. The process of claim 11, wherein the ratio of the crude 3-methylxanthine to the solvent is about 1 g 3-methylxanthine per 5 to 10 ml of solvent and the acetone: water ratio is about 2-12 ml of acetone per at least 1 milliliter of water.

13. A process for purification of theobromine comprising the steps of:
   (a) mixing theobromine with water, adding a base and heating the mixture;
   (b) adding activated carbon, stirring and filtering the activated carbon;
   (c) heating and acidifying the mixture; and
   (d) cooling, filtering the solid, washing and drying.

14. The process of claim 13, wherein the base is selected from sodium hydroxide, potassium hydroxide, lithium hydroxide, cesium hydroxide, potassium carbonate, sodium carbonate, lithium carbonate, cesium carbonate, potassium bicarbonate, sodium bicarbonate, lithium bicarbonate, cesium bicarbonate, and combinations thereof.

15. The process of claim 14, wherein the base is sodium hydroxide.
16. The process of claim 13 further comprises adding a reducing agent prior to acidifying
the mixture and filtering.

17. The process of claim 13-16, wherein the theobromine solution is dissolved by adding
aqueous 30% sodium hydroxide, decolourized, and filtered; a reducing agent is added into the
filtrate; the filtrate is then acidified at 60-80°C until pH=5-6, and filtered and dried to obtain
the theobromine final product.

18. The process of claim 17, wherein said reducing agent is sodium sulfite, sodium bisulfite,
sodium metabisulfite, sodium sulfide, sodium thiosulfate or hydrogen sulfide.

19. The process of claim 17, wherein the weight ratio of crude theobromine to reducing
agent is 1:0.01 to 0.03.

20. The process of claim 17, wherein the ratio of theobromine: 30% aqueous NaOH:
reducing agent is 1:0.75:0.01-0.03 by weight.

21. The process of claim 13, wherein said acidifying is carried out by using an acid selected
from hydrochloric acid, perchloric acid, periodic acid, phosphoric acid, sulfurous acid,
sodium hydrogen sulfate and sulfuric acid.

22. The process of claim 21, wherein the acid is hydrochloric acid.

23. The process of claim 1, wherein theobromine is obtained having a purity of at least 99%
by weight.

24. The process of claim 23, wherein theobromine is obtained having a purity of at least
99.5% by weight.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

According to International Patent Classification (IPC) or to both national classification and IPC

C07D473/04(2006.01)i

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: C07D473/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPDOC, PAJ, CPRS, CNKI, CA, REG Nos [83-67-0] and [1076-22-8], theobromine, methylat+, prepar+, produc+, purify+, xanthine, salt

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<td>CN 1090578A (HOECHST AG) 10 Aug. 1994 (10.08.1994), full text, especially examples 1-3 and description pages 7-10.</td>
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<td>DD 222026 A1 (VEB ARZNEIMITTELWERK DRESDEN) 08 May 1985 (08.05.1985) Abstract from WPI</td>
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☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

“A” document defining the general state of the art which is not considered to be of particular relevance

“E” earlier application or patent but published on or after the international filing date

“L” document which may throw doubts on priority claim (S) or which is cited to establish the publication date of another citation or other special reason (as specified)

“O” document referring to an oral disclosure, use, exhibition or other means

“P” document published prior to the international filing date but later than the priority date claimed

“T” later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

“X” document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

“Y” document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

“&” document member of the same patent family

Date of the actual completion of the international search

06 Mar. 2009 (06.03.2009)

Date of mailing of the international search report

26 Mar. 2009 (26.03.2009)

Name and mailing address of the ISA/CN

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Form PCT/ISA/210 (second sheet) (April 2007)
INTERNATIONAL SEARCH REPORT

**Box No. II  Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. □ Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. □ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. □ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III  Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1.

- If: Claims 1-12, 23 and 24 are drawn to a process for preparing theobromine by methylating 3-methyl xanthine and its salt; and
- If: Claims 13-22 are drawn to a process for refining theobromine.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

- Groups I and II, although drawn to same technical features of compound theobromine, but it is not new. Thus, there is no special technical feature among the groups I and II. Therefore, groups I and II lack unity of invention.

1. □ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. □ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fee.

3. □ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. □ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on protest** □ The additional search fees were accompanied by the applicant’s protest and, where applicable, the payment of a protest fee.

- □ The additional search fees were accompanied by the applicant’s protest but the applicable protest fee was not paid within the time limit specified in the invitation.

- □ No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (2)) (April 2007)
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