Title: PROCESS FOR THE PREPARATION OF 5-BROMOPHTHALIC ACID

Abstract: A process, which comprises reducing 4-bromophthalic anhydride in an organic solvent, to obtain a mixture of 5-bromophthalic acid and 6-bromophthalic acid, acidifying the reaction mixture, separating the same into aqueous and organic phases, and selectively crystallizing 5-bromophthalic acid from the organic phase.
PROCESS FOR THE PREPARATION OF 5-BROMOPHTHALIDE

Field of the Invention
The present invention relates to a process for the preparation of 5-bromophtalide. More specifically, the present invention discloses a novel, efficient process for the preparation of 5-bromophtalide by the reduction of 4-bromophthalic anhydride.

Background of the Invention
5-Bromophtalide is a useful starting material for the preparation of certain pharmacologically active substances, including the antidepressant drug citalopram. The preparation of this compound from 5-bromophtalide is described in US 4,136,193 (Kefalas A/S). This publication, however, is silent in relation to the preparation of 5-bromophtalide itself.

Several methods for the preparation of 5-halophthalides have been described in the prior art. For example, both J. Tirouflet [Bull. Soc. Sci. Bretagne Spec. No. 26, 7-122 (1951)] and L.P. Levy and H. Stephen [J. Chem. Soc. 867-871 (1931)] describe the preparation of 5-bromophtalide from 4-nitrophthalimid, using a four-stage process, that results in an overall yield of approximately 30%.

A completely different route for the preparation of 5-bromophtalide is described in an article by G. Uzulniec et al. [Latv. PSR Zinat. Akad. Vestis. Kim. Ser. 5: 617-620]
(1978)). In the method described therein, 5-bromophthalide is obtained by the liquid-phase catalytic oxidation of 4-bromo-o-xylene.

The art also describes methods for preparing 5-chlorophthalide. In the method described in one publication [Nikulin, V.I. & Pisarenko, L.M. Izv. Akad. Nauk SSSR Ser. Khim. (1) 151-5 (1985)], 4-chlorophthalic anhydride is reduced with Zn-HCl using AcOH as the solvent. The yield of the reaction is 62%. One problem associated with this reaction is the very large quantity of zinc-containing waste that is produced, in view of the fact that the process requires the use of a large molar excess of zinc (Zn : 4-chlorophthalic anhydride = 7:1).

A further method for producing 5-chlorophthalide from 4-chlorophthalic anhydride is described in a paper published by C. Donati et al. [Austr. J. Chem. 42: 787-795 (1989)]. In this method, 4-chlorophthalic anhydride is reduced with sodium borohydride, using dimethylformamide (DMF) as the reaction solvent. The crude product is crystallized from aqueous ethanol.

It is a purpose of the present invention to provide an efficient process for the preparation of 5-bromophthalide.

It is another purpose of the invention to provide such a process that enables all stages of said process (from initial reaction until final purification) to be carried out in the same solvent, if desired.
It is a further purpose of the invention to provide a process for the preparation of 5-bromophthalide that overcomes the problems and drawbacks associated with previously described methods.

Further objects and advantages of the present invention will become apparent as the description proceeds.

**Summary of the Invention**

It has now been found that it is possible to prepare 5-bromophthalide by the reduction of 4-bromophthalic anhydride, since, unexpectedly, although the product obtained following the reduction of the starting material is a mixture comprising approximately equal amounts of the 5-bromophthalide and 6-bromophthalide isomers, the reaction mixture may be treated in a simple and efficient manner to selectively isolate the desired 5-bromophthalide therefrom. The entire process from the initial reduction reaction to the final purification step may be performed using the same solvent, if desired.

The present invention is primarily directed to a process for the preparation of 5-bromophthalide, comprising reducing 4-bromophthalic anhydride in an organic solvent, to obtain a mixture of 5-bromophthalide and 6-bromophthalide, acidifying the reaction mixture, separating the same into aqueous and organic phases and selectively crystallizing 5-bromophthalide from the organic phase.
The term "selectively crystallizing 5-bromophthalide from the organic phase" indicates that the crude solid that is caused to precipitate from the organic phase is specifically enriched with respect to the 5-isomer. Preferably, the percentage of the 5-isomer in the crude product is above 55%, more preferably above 70%, and most preferably above 80%, as determined by HPLC and gas chromatography.

In a preferred embodiment of the present invention, the solvent used in the reduction reaction comprises an ether, wherein said ether is preferably selected from the group consisting of cyclic ethers, such as tetrahydrofuran (THF) and 1,4-dioxan, or ethers containing linear or branched alkyl groups, such as ethylene glycol dimethyl ether (EGDME) and methyl tert-butyl ether. Particularly preferred ethers are tetrahydrofuran and ethylene glycol dimethyl ether. One of the unexpected advantages of this embodiment of the invention is that the ether solvent is suitable both for the reduction reaction and for the subsequent crystallization, allowing the preferential crystallization of the 5-bromophthalide isomer from the reaction mixture, with significantly lower amounts of crystalline 6-bromophthalide being crystallized. Thus, according to one preferred embodiment of the invention, the reduction reaction and the subsequent selective crystallization may be accomplished using the same ether solvent.

Preferably, the reducing agent used in the reduction reaction of 4-bromophthalic anhydride is sodium borohydride.
It has also been found that it is particularly preferable to carry out the reduction reaction in tetrahydrofuran or EGDME, using sodium borohydride, at relatively low temperatures, preferably in the range of 3-15 °C, since at this temperature range the selectivity of the reduction reaction is shifted towards the formation of the 5-bromophthalide.

According to an alternative embodiment of the invention, following the phase separation, most of the solvent is removed from the organic phase. A second solvent, which is preferably an alcohol, or a mixture of alcohol and water, is then added to said organic phase residue, and, subsequently, said 5-bromophthalide is caused to crystallize selectively from the organic phase containing said second solvent.

In one preferred embodiment of the invention, the crude 5-bromophthalide obtained following the selective crystallization is further purified by re-crystallization or reslurry, preferably from the same solvent used for the first crystallization or from an aqueous mixture thereof.

Another aspect of the present invention relates to the preparation of the therapeutically active compound citalopram.
and pharmaceutically acceptable salt thereof, comprising reducing 4-bromophthalic anhydride in an organic solvent, to obtain a mixture of 5-bromophthalide and 6-bromophthalide, acidifying the reaction mixture and separating the same into aqueous and organic phases, selectively isolating 5-bromophthalide from the organic phase, and converting said 5-bromophthalide into citalopram or a pharmaceutically acceptable salt thereof.

All the above and other characteristics and advantages of the present invention will be further understood from the following illustrative and non-limitative examples of preferred embodiments thereof.

**Detailed Description of Preferred Embodiments**

The present invention relates to a process for the production of 5-bromophthalide that is based on the reduction of 4-bromophthalic anhydride in an organic solvent according to the following reaction scheme:
following which the reaction mixture is treated to selectively isolate the 5-bromophthalide therefrom.

The starting material, 4-bromophthalic anhydride is commercially available (Dead Sea Bromine Group, Be’er Sheva, Israel). The preparation of 4-bromophthalic anhydride is described in IL 115814. Briefly, the 4-bromophthalic anhydride starting material may be prepared by the bromination of disodium phthalate with bromine in water. At the end of the reaction, the excess bromine is removed from the crude reaction mixture, the mixture is acidified, the organic compounds are extracted using an inert organic solvent, the solvent is distilled, thereby transforming the phthalic acid moieties into anhydrides, and the crude product is distilled, to yield substantially pure 4-bromophthalic anhydride.

Preferably, the reduction is carried out in an ether solvent, which is most preferably selected from the group consisting of tetrahydrofuran (THF), 1,4-dioxan, ethylene glycol dimethyl ether (EGDME) and methyl tert-butyl ether. Other suitable ether solvents include diethyl ether, diisopropyl ether, dibutyl ether and tetrahydropyran.
Alternatively, the reduction may be carried out in a mixture of solvents comprising ether and one or more additional solvents that are inert with respect to the reduction reaction, wherein said one or more additional solvents are preferably selected from the group of hydrocarbons or halogenated hydrocarbons, such as toluene and 1,2-ethylene dichloride (EDC).

The reduction of the 4-bromophthalic anhydride starting material is accomplished by means of a reducing agent, which is most preferably sodium borohydride.

Preferably, the reducing agent is provided as a slurry in the solvent intended for use. The optimal molar ratio of sodium borohydride to 4-bromophthalic anhydride is in the range of 0.5:1 to 0.65:1. More preferably, this ratio should have a value in the range of 0.55:1 to 0.60:1. Most preferably, this molar ratio has the value 0.57:1.

In the case that the ether solvent is THF or EGDME, the weight ratio of the solvent and the 4-bromophthalic anhydride is preferably in the range of 2:1 to 5:1. More preferably, this ratio should have a value in the range of 2:1 to 3:1. Most preferably the amounts of the solvent and 4-bromophthalic anhydride should be adjusted such that the aforementioned ratio has a value of about 2.2:1.

In one preferred embodiment of the invention, the reduction is performed by adding the solution of 4-bromophthalic anhydride in the ether solvent to the slurry of sodium borohydride in the same solvent, in a gradual manner. The reduction reaction is immediate and is practically complete.
by the end of the addition of the 4-bromophthalic anhydride. The total time taken for the addition of the 4-bromophthalic anhydride solution to the reducing agent is in the range of 1 - 4 hours. The reaction temperature over this time period is preferably maintained within the range of 0 - 50° C, and more preferably between 10 to 30° C. It has been found that at relatively low temperatures, preferably in the range of 3-15 °C, the selectivity of the reduction reaction is shifted towards the formation of the 5-bromophthalide.

In another preferred embodiment, following the completion of the addition of the 4-bromophthalic anhydride solution to the reducing agent, the reaction is allowed to continue for a further period of time with stirring at about 20° C.

At the end of the reduction period, the excess reducing agent is neutralised, preferably by means of the addition of water and an acid, until a pH of less than 4 is obtained. More preferably the pH following the addition of the acid should be approximately 2. In a preferred embodiment of the invention, the acid is selected from the group consisting of 50% sulphuric acid and concentrated hydrochloric acid, although other inorganic or organic acids may be used.

In the case that the acid is hydrochloric acid, the weight ratio of water to concentrated hydrochloric acid is preferably in the range of 1-6:1. Most preferably this ratio has the value 3:1.
Following the addition of the water and acid, the reaction mixture is heated to a temperature of preferably between 50 and 65°C, most preferably between 55 and 60°C, at which temperature the reaction mixture separates into a lower aqueous phase and an upper, clear, organic phase containing the mixture of 5-bromophthalide and 6-bromophthalide in the organic solvent. Following phase separation, the organic phase is preferably washed with aqueous NaCl solution (10% w:w), to remove the residues of H₃BO₃ formed during the work-up.

According to a preferred embodiment of the invention, the desired product, that is, 5-bromophthalide, is selectively crystallized from the organic phase, which consists of the ether solvent used for the reduction reaction. The crystallization may be induced by decreasing the volume of the solution, or by cooling said solution, or by adding an antisolvent thereto, or, most preferably, by a combination of said operations. According to one embodiment, a portion of the ether solvent is removed by distillation. Preferably, the amount of the ether removed by distillation is 40 - 70% of the starting amount. The crude 5-bromophthalide is then selectively crystallized from the organic phase residue by gradual cooling to a final temperature of 30°C, and then holding the residue at that temperature for a period of one hour. Thus, the reduction reaction and the subsequent selective crystallization may be accomplished using the same ether solvent.

In the case that the organic solvent used for the reduction of the 4-bromophthalide anhydride starting material does
not comprise ether, the isolation of the desired 5-bromophthalalide may be accomplished according to the following route. Following the phase separation and the washing with NaCl solution, the organic phase may be treated to remove most (e.g., between 70 and 95%) of the solvent by distillation, following which an alcohol, or an aqueous solution of said alcohol, is added to the residual organic solvent containing the mixture of isomers. The desired 5-bromophthalalide is then selectively crystallized from said alcohol solution. Preferably, the alcohol is ethanol.

Following the crystallization of the 5-bromophthalalide product, either from the ether solvent or from the alcohol, and subsequent solid-liquid phase separation, which is preferably accomplished by filtration, wet crude 5-bromophthalalide having an isomeric purity of between 80 and 90 wt% is obtained.

In a preferred embodiment, it is possible to further purify the 5-bromophthalalide to greater than 98% purity, by means of re-crystallization from, or reslurry in, the solvent used for the crystallization, either dry or in an aqueous mixture containing between 5-20% (wt) water. In the case that THF is used for the reduction and the subsequent selective crystallization, the amount of THF used for the re-crystallization is such that the weight ratio of THF to the crude 5-bromophthalalide is between 3.5:1 and 1.5:1, and preferably 2.0:1.
5-bromophthalide obtained according to the present invention is a useful intermediate in the preparation of the therapeutic agent citalopram (chemical name: 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile). Methods for converting 5-bromophthalide into the final therapeutic compound are well known in the art. According to one approach (US 4,136,193), citalopram may be obtained from 5-bromophthalide by reacting said 5-bromophthalide with a Gringard reagent of the formula \( \text{Hal Mg} \), wherein Hal is a halogen atom, to give the following intermediate

\[
\begin{array}{c}
\text{Br} \\
\text{H} \\
\text{H} \\
\text{O} \\
\text{O} \\
\text{F}
\end{array}
\]

(I), which is subsequently reacted with \( \text{N,N-dimethylaminopropyl magnesium halide} \) to produce a second intermediate

\[
\begin{array}{c}
\text{Br} \\
\text{H} \\
\text{H} \\
\text{O} \\
\text{O} \\
\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{N(CH}_3)\text{)} \\
\text{F}
\end{array}
\]

(II), following which said second intermediate is dehydrated to give the corresponding phthalane. The phthalane derivative is treated with a suitable cyano source (cuprous cyanide), to yield citalopram. Alternatively, 5-bromophthalide obtained according to the process of the present invention may be converted into 5-cyanophthalide, using the procedures described, inter alia, in WO 01/49672, according to which 5-bromophthalide is reacted with a cyano source, such as
cuprous cyanide. The intermediate obtained, 5-cyanophthalide, may be converted into citalopram according to the methods described, inter alia, in EP 171943 and WO 02/60886. For example, 5-cyanophthalide may successively react with suitable Grignard reagents (4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide), to give the following compound, (III), which is dehydrated, preferably by means of sulfuric acid, to form citalopram. Another procedure (see WO 02/60886) involves halogenating 5-cyanophthalide to produce (IV), reacting the same with 4-fluorophenyl magnesium halogenide, to obtain (V), and contacting said intermediate of formula V with N,N-dimethylaminopropyl magnesium halide.

The following non-limiting working examples illustrate various aspects of the present invention.

**Examples**

All the reactions described hereinbelow were performed in a reactor equipped with a cooling/heating jacket in order to regulate the temperature.
**Example 1**

Preparation and crystallization of 5-bromophthalide from tetrahydrofuran (THF)

The feed solution for the reaction was prepared by dissolving 197 g of 4-bromophthalic anhydride in 250 g of THF at 25° C. This solution (density = 1.15 g/ml) was then added to the reducing agent, which was prepared as a slurry of 18.5 g of sodium borohydride in 150 g THF pre-cooled to 5° C prior to the addition of said solution. As the starting material was added to the reducing agent slurry, an increase in temperature from 5°C to 15°C was noted. After approximately 2.5 hours, all of the 4-bromophthalic anhydride had been added to the sodium borohydride slurry, and the reaction was allowed to continue, with stirring, for a further one hour at 25° C.

Neutralisation of the excess sodium borohydride was performed by the careful addition of 120 g water and 60g hydrochloric acid (as a 32% aqueous solution). The pH of the neutralized reaction mixture dropped to pH 1-2, and the temperature rose from 25° C to 30° C.

Phase separation was achieved by heating the mixture to 58° C, at which point two clearly distinguishable phases were observed: a heavy aqueous phase having a density of 1.15 g/ml, and a clear organic phase having a density of 1.03 g/ml. The lower, aqueous, phase (159 g) was carefully removed, following which the organic phase was washed with aqueous NaCl solution (140 g, 10% w/w) to remove the
residues of H$_2$BO$_3$ formed during the work-up, then the THF (267 g) was partially distilled off from the organic phase over a temperature range of 70 to 75° C in a reboiler. Crude 5-bromophthalide was then crystallized from the organic phase residue (317 g) by adding 30 g water and controlled cooling of said residue from 75° C to 30° C over a period of one hour, following which the temperature was held constant at 30° C for a further one hour. The crystallized material was filtered and washed with 100 g THF. The filtration residue thus formed (113 g, LOD ~25%) was found to contain approximately 90% 5-bromophthalide and 10% 6-bromophthalide.

In order to further purify the desired product, a slurry of 100 g of the wet, crude 5-bromophthalide was prepared in 140 g of THF containing 6% water at 25° C. This slurry was then heated to 60° C, and held at that temperature for one hour. Re-crystallization of the 5-bromophthalide was achieved by lowering the temperature from 60° C to 25°C over a period of one hour, and then holding at the lower temperature for a further one hour. The crystallized product was then filtered and washed with 40 g of THF, following which 65 g of wet residue was dried at 80° C for a period of 2 hours. The dried product thus formed (53 g) was subjected to HPLC and NMR analysis, and was found to contain >98% 5-bromophthalide. The direct yield was approximately 33%. The filtrate contained approximately 21 g of a recoverable mixture of 5-bromophthalide (70%) and 6-bromophthalide (30%). The overall yield of this process (after recycling the mother liquor) was between 37 and 40%.
Example 2

Preparation and crystallization of 5-bromophthalide from ethylene glycol dimethyl ether

The feed solution for the reaction was prepared by dissolving 227 g of 4-bromophthalic anhydride in 300 g of ethylene glycol dimethyl ether at 20° C. This solution was then added to the reducing agent, which was prepared as a slurry of 22.7 g of sodium borohydride in 200 g ethylene glycol dimethyl ether at 20°C. As the starting material was added to the reducing agent slurry, an increase in temperature from 20°C to 30°C was noted. After approximately 3.0 hours, all of the 4-bromophthalic anhydride had been added to the sodium borohydride slurry, and the reaction was allowed to continue, with stirring, for a further one hour at 26° C.

Neutralisation of the excess sodium borohydride was performed by the careful addition of 200 g water and 70 g hydrochloric acid (as a 32% aqueous solution). The pH of the neutralized reaction mixture dropped to pH 1-2, and the temperature rose from 26° C to 31° C.

Phase separation was achieved by heating the mixture to 50° C, at which point two clearly distinguishable phases were observed: a heavy aqueous phase and a clear organic phase. The lower, aqueous, phase (223 g) was carefully removed, following which the organic phase was washed with aqueous NaCl solution (200 g, 15% w/w) to remove the residues of \( \text{H}_3\text{BO}_3 \) formed during the work-up, then the aqueous ethylene glycol dimethyl ether (262 g) was partially distilled off.
from the organic phase over a temperature range of 74 to 91°C in a reboiler. Crude 5-bromophthalide was then crystallized from the organic phase residue by controlled cooling of said residue from 91°C to 25°C over a period of one hour, following which the temperature was held constant at 25°C for a further one hour. The crystallized material was filtered and washed with aqueous 50% ethylene glycol dimethyl ether. The filtration residue thus formed was found to contain approximately 80% 5-bromophthalide and 20% 6-bromophthalide.

In order to further purify the desired product, a slurry of 240 g of the wet, crude 5-bromophthalide was prepared in 240 g of aqueous 90% ethylene glycol dimethyl ether at 25°C. This slurry was then heated to 85°C to obtain a solution, and re-crystallisation of the 5-bromophthalide was achieved by lowering the temperature from 85°C to 25°C over a period of one hour, and then holding at the lower temperature for a further one hour. The crystallized product was then filtered and washed with 90 g of aqueous 90% ethylene glycol dimethyl ether, following which 97 g of wet residue was dried at 80°C for a period of 2 hours. The dried product thus formed (83 g) was subjected to HPLC analysis, and was found to contain >99% 5-bromophthalide. The direct yield was approximately 38%.

**Example 3 (comparative)**

Use of DMF as the reaction solvent

The feed solution for the reaction was prepared by dissolving 57 g of 4-bromophthalic anhydride in 53 g of DMF
at 25° C. This solution was then added to the reducing agent, which was prepared as a slurry of 9.5 g of sodium borohydride in 100 g DMF, pre-cooled to 5° C prior to addition of said solution. After approximately 3 hours, all of the 4-bromophthalic anhydride had been added to the sodium borohydride slurry, and the reaction was allowed to continue, with stirring, for a further one hour.

Neutralisation of the excess sodium borohydride was performed by careful addition of the reaction mixture to a solution of 200 g water and 62 g concentrated HCl. The precipitate, in the form of a paste, was filtered on a Buchner filter, and washed with 200 g water. 85 g of a wet mixture of isomers was obtained.

It was impossible to crystallize 5-bromophthalide from DMF. However, the crystallization of the mixture was carried out in 140 g ethanol to give 30.9 g of the wet, crude product containing 70% 5-bromophthalide.

In order to further purify the desired product, a slurry of 30.3 g of the wet, crude 5-bromophthalide was prepared in 50 g of ethanol at 25° C. This slurry was then heated to 75° C and held at that temperature for one hour. Recrystallization of the 5-bromophthalide was achieved by lowering the temperature from 75 to 25° C over a period of one hour, and then holding at the lower temperature for a further one hour. The crystallized product was then filtered and washed with ethanol, prior to being dried at 80° C for a period of two hours. The dried product thus formed (8.1 g) was subjected to HPLC and NMR analysis, and
was found to contain approximately 90% 5-bromophthalide. The overall yield of 5-bromophthalide was approximately 15%.

**Examples 4 - 7**

Effect of reaction temperature on selectivity for 5-bromophthalide

Four reactions were carried out essentially as described in Example 1 at four different temperature ranges: 3-7° C, 10-15° C, 10-25° C and 23-37° C. The selectivity of the reaction for 5-bromophthalide was determined following the phase separation, by gas chromatography (GC) or by HPLC. The results of this determination are presented in Table I.

**Table I**

<table>
<thead>
<tr>
<th>EXAMPLE</th>
<th>TEMPERATURE °C</th>
<th>SELECTIVITY BY HPLC, AREA %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3-7</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>10-25</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>10-15</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>23-37</td>
<td>56</td>
</tr>
</tbody>
</table>

**Examples 8 - 11**

Effect of the sodium borohydride: 4-bromophthalic anhydride ratio on 4-bromophthalic anhydride conversion

Operating essentially as described in Example 1, the effect of changing the molar ratio of sodium borohydride:4-
bromophthallic anhydride (NaBH₄:4-BPAn) on the conversion of 4-bromophthallic anhydride to 5-bromophthalide (5-BP) and 6-
bromophthalide (6-BP) was investigated. HPLC was used in
order to determine the relative amounts of the starting
material and products. The results are presented in Table
II.

Table II

<table>
<thead>
<tr>
<th>EXAMPLE</th>
<th>MOLAR RATIO</th>
<th>COMPOSITION BY HPLC, AREA %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NaBH₄:4-BPAn</td>
<td>4-BPAn</td>
</tr>
<tr>
<td>8</td>
<td>0.60</td>
<td>2.9</td>
</tr>
<tr>
<td>9</td>
<td>0.56</td>
<td>3.5</td>
</tr>
<tr>
<td>10</td>
<td>0.53</td>
<td>5.1</td>
</tr>
<tr>
<td>11</td>
<td>0.50</td>
<td>8.4</td>
</tr>
</tbody>
</table>

From the results shown in Table II, it follows that the optimal NaBH₄:4-BPAn molar ratio is approximately 0.56 - 0.58, which corresponds to a weight ratio of approximately 96±2 g NaBH₄ to 1 kg 4-BPAn.

It is apparent from the results, that the ratio NaBH₄:4-BPAn in THF is lower than the ratio NaBH₄:4-BPAn in DMF, according to example 3. This is a further unexpected advantage of the use of ether solvents: when an ether solvent such as THF is used in the reduction reaction, lesser quantities of the reducing agent (e.g., sodium borohydride) are required to accomplish the reaction in comparison to a corresponding reaction in DMF.
Example 12

Preparation of 5-bromophthalide in THF and crystallization from aqueous ethanol

The feed solution for the reaction was prepared by dissolving 455 g of 4-bromophthalic anhydride in 545 g of THF at 25°C. This solution was then added to the reducing agent, which was prepared as a slurry of 48 g of sodium borohydride in 450 g THF pre-cooled to 5°C prior to the addition of said solution. As the starting material was added to the reducing agent slurry, an increase in temperature from 5°C to 15°C was noted. After approximately 3 hours, all of the 4-bromophthalic anhydride had been added to the sodium borohydride slurry, and the reaction was allowed to continue, with stirring, for a further one hour at 25°C.

Neutralisation of the excess sodium borohydride was performed by the careful addition of 300 g water and 150 g hydrochloric acid (as a 32% aqueous solution). The pH of the neutralized reaction mixture dropped to pH 1-2, and the temperature rose from 25°C to 32°C.

Phase separation was achieved by heating the mixture to 55°C, at which point two clearly distinguishable phases were observed: a heavy aqueous phase and a clear organic phase. The lower, aqueous, phase (600 g) was removed, following which the organic phase was washed with aqueous NaCl solution (400 g, 10% w/w) to remove the residues of H₃BO₃ formed during the work-up, then the aqueous THF (750 g) was distilled off from the organic phase over a temperature
range of 70 to 77°C in a reboiler. Aqueous ethanol (700 g, 95%) and water (150 g) were added to the organic phase residue, which was heated to reflux. Crude 5-bromophthalide was then crystallized by controlled cooling of the solution from 75°C to 30°C over a period of one hour, following which the temperature was held constant at 30°C for a further one hour. The crystallized material was filtered and washed with 250 g aqueous ethanol (95%). The filtration residue thus formed (272 g, LOD ~23%) was found to contain approximately 80% 5-bromophthalide and 20% 6-bromophthalide.

In order to further purify the desired product, a slurry of 260 g of the wet, crude 5-bromophthalide was prepared in 540 g of ethanol containing 5% water at 25°C. This slurry was then heated to 70-80°C, and held at that temperature for one hour. Recrystallization of the 5-bromophthalide was achieved by lowering the temperature from 80°C to 25°C over a period of one hour, and then holding at the lower temperature for a further one hour. The crystallized product was then filtered and washed with 150 g of aqueous 95% ethanol, following which 180 g of wet residue was dried at 80°C for a period of 2 hours. The dried product thus formed (145 g) was subjected to HPLC and NMR analysis, and was found to contain >98% 5-bromophthalide. The yield was approximately 35%.
Examples 13 to 15
Preparation of 5-bromophthalide in various solvents

Three reactions were carried out essentially as described in Example 1 using different solvent systems. The conversion of the starting material was determined after the completion of the addition of the 4-BPAn solution, by gas chromatography (GC). The results of this determination are presented in Table III.

<table>
<thead>
<tr>
<th>EXAMPLE</th>
<th>Solvent</th>
<th>Conversion of 4-BPAn BY GC, AREA %</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Toluene/THF (1:1)</td>
<td>85</td>
</tr>
<tr>
<td>14</td>
<td>1,4-dioxane</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>Methyl tertbutyl ether</td>
<td>50</td>
</tr>
</tbody>
</table>

While specific embodiments of the invention have been described for the purpose of illustration, it will be understood that the invention may be carried out in practice by skilled persons with many modifications, variations and adaptations, without departing from its spirit or exceeding the scope of the claims.
1. A process, which comprises reducing 4-bromophthalic anhydride in an organic solvent, to obtain a mixture of 5-bromophthalide and 6-bromophthalide, acidifying the reaction mixture, separating the same into aqueous and organic phases, and selectively crystallizing 5-bromophthalide from the organic phase.

2. Process according to claim 1, wherein the solvent used in the reduction stage comprises an ether.

3. Process according to claim 2, wherein the ether is selected from the group consisting of cyclic ethers and ethers containing linear or branched alkyl groups.

4. Process according to claim 3, wherein the ether is selected from the group consisting of tetrahydrofuran and ethylene glycol dimethyl ether.

5. Process according to claim 1, wherein the reduction of 4-bromophthalic anhydride is accomplished using sodium borohydride.

6. Process according to claim 5, wherein the molar ratio of sodium borohydride to 4-bromophthalic anhydride is between 0.5:1 to 0.65:1.

7. Process according to claim 4, wherein the reduction reaction is performed at a temperature in the range of 0-50 °C.
8. Process according to any one of claims 2-7, wherein the 5-bromophthalide is selectively crystallized from the organic phase containing the ether solvent used in the reduction reaction.

9. Process according to claim 1, wherein, following the phase separation, the organic phase is washed with an aqueous solution of a suitable salt, to remove residues of boric acid (H₃BO₃), and 5-bromophthalide is selectively crystallized from said washed organic phase.

10. Process according to claim 1, wherein, following the phase separation, the organic phase is washed with an aqueous solution of a suitable salt, to remove residues of boric acid (H₃BO₃), most of the solvent is removed from the organic phase, and a second solvent is added to the organic phase residue, and, subsequently, said 5-bromophthalide is selectively crystallized from the organic phase containing said second solvent.

11. Process according to claim 10, wherein said second solvent is an alcohol or an aqueous alcohol.

12. Process according to claim 11, wherein the alcohol is ethanol.

13. Process according to claim 1, wherein the 5-bromophthalide is further purified by re-crystallization from, or reslurry in, the solvent used for the selective crystallization or an aqueous mixture thereof.
14. 5-Bromophthalide, whenever prepared by the process of claims 1-13.

15. Process according to any one of the preceding claims 1 to 13, which further comprises converting the 5-bromophthalide into citalopram

or into an acid addition salt thereof.

16. Process according to claim 15, wherein 5-bromophthalide is reacted with a Gringard reagent of the formula

\[
\text{HalMg} - \text{F} \quad (\text{II})
\]

wherein Hal indicates a halogen atom, to obtain a first intermediate of the formula (I)

\[
\begin{align*}
\text{Br} & \quad \text{H} & \quad \text{H} \\
\text{Bk} & \quad \text{H} & \quad \text{O} \\
\text{F} & \quad \text{O} & \quad \text{OH}
\end{align*}
\]

(I)

following which said first intermediate is converted into citalopram.

17. Process according to claim 16, comprising reacting the first intermediate of formula (I) with N,N-dimethylaminopropyl magnesium halide to produce a second intermediate of the formula (II)
dehydrating said second intermediate to give the corresponding phthalane, and treating said phthalane with a suitable cyano source to obtain citalopram, and isolating citalopram as the free base or as an acid addition salt thereof.

18. Process according to any one of claims 1 to 13, which further comprises reacting 5-bromophthalalde with a cyanide source, to give 5-cyanophthalalde, and optionally converting said 5-cyanophthalalde into citalopram.

19. Process according to claim 18, wherein 5-cyanophthalalde is successively reacted with 4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide to obtain

which is dehydrated to give citalopram.
20. Process according to claim 18, comprising halogenating 5-cyanophthalide to produce the intermediate of formula (IV),

$$\text{Hal}$$

(wherein Hal indicates halogen, reacting said intermediate of formula (IV) with 4-fluorophenyl magnesium halide, to obtain the following intermediate:

$$\text{Hal}$$

and contacting said intermediate of formula (V) with N,N-dimethylaminopropyl magnesium halide to form citalopram.

21. Process according to any of the preceding claims 15 to 20, which further comprises reacting citalopram with a pharmaceutically acceptable acid to form a pharmaceutically acceptable acid addition salt thereof.
A. CLASSIFICATION OF SUBJEC T MATTER
IPC 7 CO7D307/88

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

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
IPC 7 CO7D

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

Electronic database consulted during the international search (name of database and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 98 01437 A (BASF AG; NASSONNE KLEMENS (DE); BECKER RAINER (DE); REIF WOLFGANG) 15 January 1998 (1998-01-15) * Scheme 2, compound 18 *</td>
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