



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(54) Title: PROCESS FOR THE MANUFACTURE OF 2-BROMO-6-METHOXYNAPHTHALENE</p>		
<p>(57) Abstract</p> <p>Process for the preparation of 6-bromo-2-methoxynaphthalene, which comprises the steps of: (a) brominating 2-naphthol to 1,6-dibromo-2-naphthol, (b) reducing 1,6-dibromo-2-naphthol to 6-bromo-2-naphthol, and (c) methylating 6-bromo-2-naphthol to 6-bromo-2-methoxynaphthalene.</p>		

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**PROCESS FOR THE MANUFACTURE OF 2-BROMO-6-METHOXYNAPHTHALENE**

**Field of the Invention**

This invention relates to a process for the manufacture of 2-bromo-6-methoxynaphthalene, which is an intermediate in the synthesis of the antiinflammatory drug Naproxen.

**Background of the Invention**

Naproxen, (S)-6-Methoxy-2-naphthaleneacetic acid, is an important antiinflammatory drug, which was described and claimed in USP 3,904,682. It can be manufactured by different processes, as for instance described in USP 3,651,149. The most widely accepted process calls for the preparation of 2-bromo-6-methoxynaphthalene as an intermediate.

2-bromo-6-methoxynaphthalene, which will be designated hereinafter sometimes by "BMN", is also an intermediate for the preparation of other valuable pharmaceuticals, in particular, nabumetone and methallenestril. The art teaches to prepare BMN starting from  $\beta$ -naphthol by: a) brominating  $\beta$ -naphthol to 1,6-dibromo- $\beta$ -naphthol; b) reducing 1,6-dibromo- $\beta$ -naphthol to 6-bromo- $\beta$ -naphthol; and c) methylating 6-bromo- $\beta$ -naphthol to yield BMN. This sequence of reactions is mentioned in Organic Process Research & Development (1997) 1, 72-76.

For the preparation of 6-bromo-2-naphthol, see Organic Synthesis, Collective Volume III, 132(1955).

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The bromination of organic compounds, particularly aromatic compounds, with bromine in a halogenated organic solvent and in the presence of a catalyst is a known process. For instance, it is described in USP 5,426,243, wherein the catalyst is a quaternary ammonium salt.

USP 5,426,243 mentions the preparation of 1,6-dibromo-2-alkoxynaphthalenes by bromination of the corresponding 2-alkoxynaphthalenes.

The reduction of dibrominated naphthalenes to monobrominated naphthalenes is described, for instance, in EP-A 179 447, in which the reducing agent is a metal such as iron or tin. USP 5,243,088 teaches the said reduction by means of nascent hydrogen and a catalyst.

BP 380563 describes the reduction of 1,6-dibromo-2-hydroxynaphthalene to the corresponding monobrominated compound by means of an alkali sulfite in methyl or ethyl alcohol and is isolated after distillation of the solvent.

The methylation of 2-naphthol to yield 2-methoxy naphthalene under controlled pH is described in EP 0 353 755 (1990).

### **Summary of the Invention**

The process for the preparation of 6-bromo-2-methoxynaphthalene, according to the invention, comprises the steps of:

brominating 2-naphthol to 1,6-dibromo-2-naphthol,

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reducing 6-dibromo-2-naphthol to 6-bromo-2-naphthol, and methylating 6-bromo-2-naphthol to 6-bromo-2-methoxynaphthalene.

More specifically, the invention comprises:

- I. The bromination of  $\beta$ -naphthol to the 1,6-dibromo derivative in a chlorinated solvent in the absence of a catalyst.
- II. The reduction of the above by sulfite in a two-phase system consisting of aqueous  $\text{Na}_2\text{SO}_3$  and organic alcohol (immiscible or partially immiscible with water) solution of the naphthol derivative.
- III. The methylation of the second product (6-bromo-2-naphthol) with MeBr in the same solvent in the presence of an aqueous solution of NaOH, without any special control of the pH.
- IV. The crystallization of BMN from the above-mentioned solution in a very pure form (GC >99.5%), without the need of any additional purification step.

The reduction of 6-dibromo-2-naphthol and the methylation of 6-bromo-2-naphthol are carried out in the same solvent, which is preferably butanol. The chlorinated solvent used for the bromination of 2-naphthol is preferably methylene chloride. The solvent is changed after the bromination and preferably before the reduction.

The methylation is preferably carried out with methyl bromide at a nearly atmospheric pressure, from  $^+0.1$  to  $^+1.5$  atma. The 6-bromo-2-methoxynaphthalene is recovered from the methylation product by allowing the same to separate into an aqueous and an organic phase, preferably at a temperature from 50 to 85°C, and causing the 6-bromo-2-

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methoxynaphthalene to crystallize from said organic phase, preferably at a temperature from 90° to 15°C.

Preferably, the bromination is carried out with bromine at a molar excess of about 5-10% and the reduction is carried out with sodium bisulfite.

### **Detailed Description of Preferred Embodiments**

As stated hereinbefore, the process for the preparation of BMN according to the invention, comprises the stages of brominating  $\beta$ -naphthol to 1,6-dibromo-2-naphthol, changing the solvent, reducing the 1,6-dibromo-2-naphthol to 6-bromo-2-naphthol and methylating this latter to 6-bromo-2-methoxynaphthalene. In a preferred manner of carrying out the process of invention, the aforesaid process stages are carried out as follows.

#### **Bromination**

The bromination of  $\beta$ -naphthol is carried out with bromine in an organic solvent, which is preferably a halogenated solvent (viz.  $\text{ClCH}_2\text{CH}_2\text{Cl}$ ,  $\text{CH}_2\text{ClBr}$ ,  $\text{CH}_2\text{Br}_2$ ,  $\text{CH}_3\text{-CCl}_3$ ) and more preferably methylene chloride, but may be an alcohol. The molar ratio of bromine to  $\beta$ -naphthol is from 2.0 to 2.20, and preferably about 2.10. The weight ratio between methylene chloride and  $\beta$ -naphthol is from 9 to 4 and preferably about 4.6. The reaction temperature is from  $-5^\circ$  to  $38^\circ\text{C}$ . In a preferred manner of carrying out the reaction, the  $\beta$ -naphthol is added to the methylene chloride, which may be pure or recycled from previous preparations.  $\beta$ -naphthol is not soluble in methylene chloride and remains in the solid state. The addition of bromine is carried at a temperature of from  $0^\circ$  to  $15^\circ\text{C}$  and preferably about  $10^\circ\text{C}$  in a period of time of 0.5 to 4 hours.

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During said addition, the  $\beta$ -naphthol dissolves in the methylene chloride. After the addition of the bromine has been completed, the temperature is gradually raised to 25° to 40°C and preferably to about 35°C, in a period of time of 0.5 to 2 hours and is maintained at said temperature for a period of 3 to 6 hours, and preferably about 4 hours from the moment that the temperature has reached 25°C. The unreacted bromine is reduced, by means of a reducing agent, e.g. sodium bisulfite preferably as an aqueous solution e.g. at 38% concentration, in an amount of 0.06 to 0.02 moles to a mole of the starting  $\beta$ -naphthol. Some 2-3% reduction of organic bromine may also occur, with the generation of minor amounts of 6-bromo-2-naphthol. Thereafter, the reaction mass, which comprises residues of HBr produced in the bromination and in the reduction, is neutralized, preferably by means of a 20% NaOH solution, until a pH of 5-6 is obtained.

### **Solvent Change**

After the bromination has been completed, the methylene chloride is removed and substituted with butanol

Operating in the preferred way, butanol is added to the reaction mass (after the aforesaid reduction with bisulfite and addition of soda to pH 5-6). The amount of butanol added is 1.4 to 2.4 parts, referred to the weight of the starting  $\beta$ -naphthol. The methylene chloride is then distilled in a distillation column from the resulting mixture. The distilled methylene chloride contains only a small amount, e.g., a few tenths of a unit percent, of butanol.

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Alternatively, the methylene chloride could be vaporized from the reaction mass before adding the butanol.

An alternative is to perform the whole sequence in one solvent, i.e., butanol. In this case, the bromination is carried out with bromine and an oxidizing agent, preferably  $H_2O_2$ . This last reagent oxidizes  $HBr$  to  $Br_2$ , thus preventing the formation of butyl bromide (from the solvent), which can be detrimental to the last step.

### Reduction

The reduction of 1,6-dibromo-2-naphthol to 6-bromo-2-naphthol is carried out with a reducing agent chosen from among Li, Na and K sulfites, preferably a bisulfite and more preferably, sodium bisulfite, in the presence of butanol as a solvent and under stirring. The reduction is carried out in a pH range of 7-9, preferably 8, which is obtained by adding gradually a base, preferably NaOH as a 20% aqueous solution, to the reaction mass. The sodium bisulfite is preferably added as 37% of the aqueous solution. The reaction temperature is from 75° to 94°C and preferably about 94°C. The completion of the reaction mass occurs within 2 to 6 hours, preferably about 3 hours, and is carried out under stirring. At the end of the reaction time, the mass is cooled to 40° to 80°C, preferably to about 50°C. The stirring is stopped. The reaction mass separates into an upper organic layer and a lower aqueous layer. The two phases are then separated, and the organic phase undergoes the methylation. The aqueous phase contains only 0.2 - 0.5% of butanol.

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### Methylation

The methylation is carried out by means of a methyl halide, preferably methyl bromide. The molar ratio of methyl bromide to 6-bromo-2-naphthol is from 1.0 to 1.3, and preferably about 1.1. The reaction temperature is from 35° to 70°C and preferably about 50°C. The reaction is carried out approximately at atmospheric pressure. Preferably, the reactor is subjected to moderate vacuum, e.g., from 0.3 to 0.7 atma, and then introduction of methyl bromide is carried out under vigorous stirring. During the methylation the product separates in part as a solid. The duration of the reaction is from 3 to 6 hours, and preferably about 4 hours. The reaction mass is kept at reaction temperature for a period of time after the introduction of methyl bromide has stopped, e.g., for about 0.5 to 1 hour. The reactor is then opened and the reaction mass is then preferably heated to 70° to 100°C, e.g. about 90°C, whereupon all the solids dissolve and the reaction mass separates into an upper organic phase and a lower aqueous phase. The aqueous phase is discharged. The organic phase is cooled gradually, after adding more butanol and water, e.g. at a rythm of 10°C/hr. The final product begins to crystallize at 60-70°C, but the cooling is continued, e.g. to 15°C. The precipitated product is filtered and washed with butanol and with water. The product has a purity in excess of 99.5%. The butanol can be recovered by distillation and recycled. The yield of the entire process is about 76-80%, based on the starting 2-naphthol.

Product of purity <99.5% may be further purified by reslurrying it in 3 volumes/weight unit of aqueous butanol.

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The following examples illustrate the inventive process without involving any limitations.

### Example 1

#### Bromination of $\beta$ -naphthol

Methylene chloride (700 ml, 924 g) and  $\beta$ -naphthol (144 g; 1 mole) are fed to a stirred reactor. The suspension is cooled to 10°C and bromine (336 g, 2.1 moles) is added gradually during two hours, maintaining the temperature. During the addition, HBr gas starts to be released and it is trapped in a water scrubber. After the bromine addition is ended, the temperature is raised to 25°C and is kept at this temperature for 3-4 hours until the reaction is completed and most of the HBr has escaped. A gas chromatographic analysis gives the following results: 1,6-dibromo- $\beta$ -naphthol: 95.4%; 6-bromo- $\beta$ -naphthol: 1.8%; 1-bromo- $\beta$ -naphthol: 0.7%; only ca. 2% of other by-products were formed.

### Example 2

#### Bromination of $\beta$ -naphthol

A bromination is carried out as in Example 1, however, only 500 ml methylene chloride is used. 326 g of bromine (2.04 moles) are added during one hour at 5°C and the reaction mixture is stirred after allowing it to warm up to 25°C for 21 hours. Gas chromatographic results show: 1,6-dibromo- $\beta$ -naphthol: 95.6%; 6-bromo- $\beta$ -naphthol: 0.8%; 1-bromo- $\beta$ -naphthol: 0.8%; only ca. 2.8% of other by-products were formed.

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### Example 3

#### Bromination of $\beta$ -naphthol

A solution of  $\beta$ -naphthol (144 g, 1 mole) in butanol (400 ml) is stirred at 35°C. Bromine (218 g; 1.36 mole) is added gradually. After 40% of the bromine has been added, hydrogen peroxide (52% solution, 51.0 g; 0.75 mole) is added simultaneously and in parallel to the remaining bromine. The addition of both reagents is terminated after 2.5 hours.

The mixture is stirred for another 0.5 hours. GC analysis of the mixture showed: 1,6-dibromo- $\beta$ -naphthol: 90.5%; 6-bromo- $\beta$ -naphthol: 1.9%; 1-bromo- $\beta$ -naphthol: 1.9%; others: 5.7%. This solution may be used for the next step, the reduction to 6-bromo- $\beta$ -naphthol.

### Example 4

#### Reduction of 1,6-dibromo- $\beta$ -naphthol to 6-bromo- $\beta$ -naphthol

A solution of 37% sodium bisulphite (328 g; 1.2 moles), which has been brought to pH 9-10 with a 20% NaOH solution (220 g; 1.1 moles), is added to the 1,6-dibromo- $\beta$ -naphthol solution obtained in Example 1, with stirring. The methylene chloride is recovered by evaporation by heating the mixture up to 70°C. The recovered  $\text{CH}_2\text{Cl}_2$  may be reused in subsequent brominations without any further treatment. n-Butanol (300 ml) is added to the aqueous slurry and the mixture is heated to reflux at 94°C. The pH of the reaction medium is kept constant in the range of 8 by the continuous addition of a 20% NaOH solution (ca. 100 g) monitored by an immersed electrode which controls the metering pump feeding the NaOH solution. After 1.5-2 hours the pH stabilizes at 8-8.5. The stirring is stopped and the mixture separates into two layers. Separation of the

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phases is effected at 70°C. The lower aqueous layer contains mainly : Br<sup>-</sup>: 6-10%; SO<sub>3</sub><sup>=</sup> : 3-5%; SO<sub>4</sub><sup>=</sup>: 7-10%; Na<sup>+</sup> 8-10% and only 0.2-0.5% .. The upper organic layer was analyzed by GC: 6-Bromo-β-naphthol: 96.4%; 1,6-dibromo-β-naphthol: 0.15%. Other impurities: total 3.15%.

This solution was used for the next step, methylation.

### Example 5

#### Reduction of 1,6-dibromo-β-naphthol to 6-bromo-β-naphthol

The final reaction mixture obtained in Example 1 is treated with a 37% sodium bisulphite solution (20 ml) to reduce any free bromine present, then the mixture is neutralized to pH 6-7 with a 20% sodium hydroxide solution (ca. 50-70 ml). n-Butanol (300 ml) is added to the vessel and methylene chloride is recovered by distillation using an appropriate column. The recovered CH<sub>2</sub>Cl<sub>2</sub> may be used in subsequent brominations without any further treatment. A solution of 37% sodium bisulphite (328 g; 1.2 moles) is added to the residue and the reduction is carried out at 94°C and at pH 8 as described in Example 4, by the controlled addition of 20% NaOH (ca. 320 g; 1.6 moles). After phase separation, the organic layer is analyzed by GC: 6-Bromo-β-naphthol: 96.2%; β-naphthol: 0.8%; 1,6-dibromo-β-naphthol: 1.7%. Other impurities: 1.3%.

### Examples 6-10

#### Reduction of 1,6-dibromo-β-naphthol to 6-bromo-β-naphthol

Reductions were performed as described in Example 4, however using different solvents, as given in Table 1 below; the table reports the results

of the GC analysis. All reactions were carried out under similar conditions, as in Example 4:

**Table 1**

Example No.	Solvent	Gas Chromatographic Analysis**			
		$\beta$ N	1,6-DiBrN	6-BrN	Others
6	Isoamyl alcohol	1.3	0.5	95.6	2.6
7	Isobutyl alcohol	1.6	1.4	94.3	2.7
8	Ethylene glycol monomethyl ether*	1.6	0.7	95.3	2.4
9	n-pentanol	1.4	1.8	96.7	0.1
10	2-butanol	1.6	1.4	94.2	2.8

\*this is an example using a high boiling water miscible alcohol.

\*\*  $\beta$ N =  $\beta$ -naphthol; 1,6-DiBrN = 1,6-dibromo- $\beta$ -naphthol; 6-BrN = 6-Bromo- $\beta$ -naphthol

### **Example 11**

#### **Methylation of 6-bromo- $\beta$ -naphthol.**

To the organic phase obtained in Example 4, consisting mainly of a solution of 6-bromo- $\beta$ -naphthol in aqueous butanol, is added a 40% NaOH solution (110 g; 1.1 mole) and n-butanol (330 ml). The mixture is kept at 50°C and methyl bromide is fed during 4 hours (the total weight of MeBr is 119 g; 1.25 moles). During the reaction, the product 2-bromo-6-methoxynaphthalene (BMN) starts to precipitate and forms a stirrable suspension. A typical GC result at this stage shows 90±2% of BMN in the organic phase (excluding solvent). More butanol (300 ml) is added to the mixture, which is then warmed up to 80-90°C until a full dissolution of organic material occurs. The stirring is stopped and after 15 minutes, the lower aqueous phase is separated at 80°C. This phase contains: Br: 26-32%; Na<sup>+</sup>: 8-11%; butanol: 0.5-1.5%. Water (200 ml) is added to the organic phase, and the mixture is slowly cooled to 15°C while stirring.

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Crystallization occurs between 70° and 60°C. The solid is filtered, washed with cold (20°C) butanol (50 ml) and water (2 x 100 ml), then dried under reduced pressure (40 mmHg) at 70°C until dry (KF <0,05%). The resulting BMN weighs 190 g (80% yield based on the  $\beta$ -naphthol used in the bromination stage) and has a GC analysis of >99.5%.

### Examples 12-16

#### Methylation of 6-bromo- $\beta$ -naphthol.

The methylation described in Example 11 was repeated on solutions obtained from Examples 6-10 in a similar way, except that in each example, the appropriate solvent was used. Table 2 reports the final GC results of the isolated products.

Table 2

Example No.	Solvent	BMN - GC purity %
12	Isoamyl alcohol	99.0
13	Isobutyl alcohol	95.2
14	Ethylene glycol monomethyl ether	94.8
15	n-Pentanol	99.3
16	2-Butanol	96.3

### Example 17

#### Methylation of 6-bromo- $\beta$ -naphthol

The methylation described in Example 11 is repeated; however, prior to the MeBr addition, the pressure in the vessel is reduced to ca. 0.2 atma. Methyl bromide (113 g; 1.25 moles) is fed via a dip pipe into the stirred solution at 50°C without remarkable increase of the pressure.

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Work-up of the product, as described in Example 11, yields 185 g of BMN (78% yield) of >99.5% purity, as determined by GC.

While specific embodiments of the invention have been described for the purpose of illustration, it will be understood that the invention may be carried into practice by skilled persons with many modifications, variations and adaptations, without departing from its spirit or exceeding the scope of the claims.

## CLAIMS

1. Process for the preparation of 6-bromo-2-methoxynaphthalene, which comprises the steps of:

brominating 2-naphthol to 1,6-dibromo-2-naphthol,

reducing 1,6-dibromo-2-naphthol to 6-bromo-2-naphthol, and

methyating 6-bromo-2-naphthol to 6-bromo-2-methoxynaphthalene.

2. Process according to claim 1, wherein the reduction of 6-dibromo-2-naphthol and the methylation of 6-bromo-2-naphthol are carried out in the same solvent.

3. Process according to claim 2, wherein the solvent is an alcohol immiscible or partially immiscible with water.

4. Process according to claim 2, wherein the solvent is butanol.

5. Process according to claim 1, wherein the bromination of 2-naphthol is carried out in a chlorinated solvent or in an alcohol.

6. Process according to claim 5, wherein the chlorinated solvent is methylene chloride.

7. Process according to claim 3, comprising recovering the 6-bromo-2-methoxynaphthalene from the methylation product by allowing the same

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to separate into an aqueous and an organic phase and causing the 6-bromo-2-methoxynaphthalene to crystallize from said organic phase.

8. Process according to claim 7, wherein the separation into an aqueous and an organic phase occurs at a temperature from 70° to 100°C and the crystallization begins at a temperature from 60° to 70°C.

9. Process according to claim 1, wherein the methylation is carried out with methyl bromide at a pressure from 0.1 to 1.5 atma.

10. Process according to claim 1, wherein the bromination is carried out with bromine at a molar excess of about 5-10%.

11. Process according to claim 1, wherein the reduction is carried out with sodium bisulfite.

12. Process according to claim 1, which comprises:

I. The bromination of  $\beta$ -naphthol to the 1,6-dibromo derivative in a chlorinated solvent or in an alcohol, in the absence of a catalyst.

II. The reduction of the above by sulfite in a two-phase system consisting of aqueous  $\text{Na}_2\text{SO}_3$  and organic 1-butanol solution of the naphthol derivative.

III. The methylation of the second product (6-bromo-2-naphthol) with MeBr in the same solvent in the presence of an aqueous solution of NaOH, without any special control of the pH.

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IV. The crystallization of BMN from the above-mentioned solution in a very pure form (GC >99.5%), without the need of any additional purification step.

13. Process according to claim 12, wherein the reduction of 6-dibromo-2-naphthol and the methylation of 6-bromo-2-naphthol are carried out in the same solvent.

14. Process according to claim 12, wherein the solvent is butanol.

15. Process according to claim 12, wherein the solvent of the bromination of 2-naphthol is methylene chloride or butanol.

16. Process according to claim 15, wherein the solvent is changed after the bromination and before the reduction.

17. Process for the preparation of 6-bromo-2-methoxynaphthalene, substantially as described and exemplified.

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL 98/00115

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC 6 C07C39/38 C07C37/62 C07C37/00 C07C41/01 C07C43/225

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

**B. FIELDS SEARCHED**

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

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**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PETER J. HARRINGTON AND E. LODEWIJK: "Twenty years of Naproxen Technology" ORGANIC PROCESS RESEARCH & DEVELOPMENT, vol. 1, no. 1, 15 January 1997, pages 72-76, XP002068989 cited in the application * page 73, left column *	1-17
A	GB 380 563 A (I.G. FARBENINDUSTRIE AKTINGESELLSCHAFT) 22 September 1932 cited in the application see the whole document	1-4, 11-14, 16
A	EP 0 353 755 A (DONEGANI GUIDO IST) 7 February 1990 cited in the application * pages 1,4 and examples 1-4 *	1,9, 12-14

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

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