Title: AN IMPROVED PROCESS FOR THE MANUFACTURE OF TOPIRAMATE

Abstract: An improved process for the manufacture of 2,3,4,5-bis-O-(1-methylthiylene)-α-D-fructopyranose sulfamate, viz. Topiramate is reported. It consists of subjecting an intermediate of the formula 2,3,4,5-bis-O-(1-methylthiylene)-β-D-fructopyranose to a sulfamoylation reaction with sulfamoyl halide in a suitable solvent of high dielectric constant and in presence of a suitable organic base at a temperature from -50 to 100°C followed by extraction and crystallization to afford a crude product which is finally crystallized from a solvent to afford the title derivative in vastly improved yields and quality. Further the process affords the title compound possessing a good stability.
'AN IMPROVED PROCESS FOR THE MANUFACTURE OF TOPIRAMATE'

FIELD OF THE INVENTION

The present invention relates to an improved process for the manufacture of 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate, (I) which is a potent anticonvulsant.

The compound of the formula I is a well-known anticonvulsant drug used for the treatment of epileptic disorders. Topiramate blocks the action potentials elicited repetitively by a sustained depolarization of the neurons in a time-dependent manner. Also, Topiramate increases the frequency at which gamma-aminobutyric acid (GABA) activates GABA_A receptors, thereby enhancing GABA-induced influx of chloride ions into neurons.

BACKGROUND AND PRIOR ART

EP 138441 relates to sulfamates II (wherein X is O or CH2, R1 is H, alkyl, R2, R3, R4 & R5 are H, lower alkyl; ) and when X is oxygen R2, R3 and R4, R5 may form a methylenedioxy group and were prepared by reacting 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose of the formula III
with sulfamoyl chloride or N-substituted sulfamoyl chloride in the presence of a base such as sodium hydride or potassium t-butoxide at a temperature of about -20°C to ambient and in a solvent such as toluene, THF or DMF. This process utilizes hazardous chemicals especially a combination of sodium hydride with DMF, which can have an uncontrollable exotherm and is hence potentially dangerous. Further the procedures for isolation and purification are difficult and inconvenient to carry out. Besides this process gives the compound in low yields and purities and is hence not economical and commercially viable.

Maryanoff and coworkers also reported (J. Med. Chem. 1987, 30(5), 880) the synthesis of the compound of the formula (I) by the following three processes wherein the compound of the formula (III) was reacted with:

i. sulfamoyl chloride in the presence of sodium hydride
ii. sulfuryl chloride in the presence of pyridine and reacting the resultant chlorosulfonate with amines
iii. sodium azide and reacting the resultant azide with Cu in methanol or catalytic hydrogenation

Also reported was the reaction of the compound of the formula (III) with sulfamoyl chloride affording Topiramate at an yield of 46%. These yields are not economically viable on a commercial scale.

EP 533483 (eidem US 5387700) relates to the preparation of sulfamates comprising of converting an alcohol of the formula III to the chlorosulfonate derivative of the formula IV using sulfuryl chloride as the reagent at -78°C to 40°C in presence of a base such as pyridine, pyridine derivatives or triethylamine and solvents such as toluene. In the 2nd stage the chlorosulfonate (IV) is condensed with ammonia or amines at -50°C to 50°C in presence of a base such as pyridine using solvents such as THF affording the sulfamate
ester of 2,3:4,5-bis-O-(\(\text{\text{\text{\text{\text{-methylethylidene}}\text{-D-fructopyranose. These are further recrystallized using a medium such as alcohol and water or ethyl acetate/hexane. The process is further characterized by the fact that the amination is carried out between ambient to moderate pressures. This process isolates the thermally labile and not so stable intermediate, namely the chlorosulfonate, IV. Also this process requires handling of several solvents, which would necessitate better recoveries for recycling and is hence not economically practical.

US patent application No. 2004/02-15004 reports a one step process for preparing sulfamates comprising of converting an alcohol with sulfuryl diamide at elevated temperature, in the presence of 0-10% of water, to yield the title sulfamate, I. This process apart from requiring elevated temperatures of the order of 120-130\(\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{\text{°C, necessitating the use of a pressure autoclave, does not clearly specify the yields and purities obtained and is hence not clear.

SUMMARY
An important aspect of any synthetic process is to afford a bulk active which possesses acceptable stability characteristics for dosage form preparation. The processes described in the prior art afford the compound of the formula I in a form with unproven stability and hence the need to develop a process which affords the compound of the formula I in high yields while meeting the stringent requirements of quality and stability.

An object of the present invention is to provide a process for the transformation of a compound of the formula III to a compound of the formula I in high yields and purities.

Another object of the present invention is to provide a process for the manufacture of the compound of the formula I that is simple, easy and convenient to carry out.

Another object of the invention is to provide a process for the manufacture of the compound of the formula I that is economical and commercially viable.

An important object of the invention is to provide a process which affords the compound of the formula I which is stable to storage at ambient temperatures.
According to the invention there is provided a process for the manufacture of the compound of the formula I consisting of reacting a compound of the formula III with a compound of the formula V in a solvent selected from the group comprising of polar aprotic solvents and a base selected from the group comprising of organic bases at ambient temperatures followed by extraction and isolation (Scheme). The product is finally crystallized from a solvent. The present invention affords the compound of the formula I in high yields. Further the product is of good quality and stability.

As a polar aprotic solvent one can utilize the solvents selected from dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide etc, preferably dimethyl acetamide.

As a base one can also utilize the trialkylamines such as triethylamine, trimethylamine, tri n- and iso- propylamines, tributylamine, N-methylmorpholine, pyridine, lutidines, picolines etc, preferably N-methylmorpholine. These bases can be
employed in the ratio from 1.0-1.2 equivalents with respect to the substrate, preferably 1.05%.

Typically the condensation reaction of the fructose diacetonide with sulfamoyl chloride is conducted from -50 to 100°C, preferably about 50°C.

The following examples are illustrative of the invention but not limitative to the scope thereof.

Sulfamoyl chloride is manufactured according to the procedures well described in literature [{(Reference: Ger. 937,645 (assigned to Farbwerke Hoechst A.-G; inventor Roderich Graf)]}

EXAMPLE 1

Topiramate crude

2,3:4,5-bis-O-(l-methylethylidene)-β-D-fructopyranose (50 gm) (III) and N-methylmorpholine (26 gm) were suspended in 100 ml dimethyl acetamide. The mass was cooled to 5°C followed by addition of 29.8 gm of sulfamoyl chloride (V). The reaction mass was stirred at that temperature for 1 hr and extracted with 250 ml ethyl acetate followed by further extraction with 2 x 100 ml ethyl acetate. The organic layer was washed with 400 ml water and 200 ml 20% sodium chloride solution and concentrated in vacuum to a mass. This was then crystallized with a mixture of 75 ml ethyl acetate and 150 ml cyclohexane. The crystalline product was filtered and dried at 55°C under vacuum to get 50 gm of Topiramate crude.

Topiramate pure

50 gm of the above crude was dissolved in 2200 ml diisopropyl ether at reflux temperature till a clear solution was obtained. Activated carbon (2.5 gm) was added and the contents were refluxed for another 30 min followed by filtration under hot conditions. The filtrate was concentrated till a residual volume of 250 ml was achieved. The crystallized product was cooled to 10°C and filtered. The product was dried at 50°C under vacuum to get 45 gm of Topiramate pure.

Water content (by Karl Fisher) = 0.15%; Chemical assay (by HPLC) = 99.2%; Yield = 77% (by theory)

EXAMPLE 2

The procedure of example 1 was followed with 26 gm of triethylamine instead of N-methylmorpholine.
Water content (by Karl Fisher) = 0.17%; Chemical assay (by HPLC) = 99.1%; Yield = 75% (by theory)

EXAMPLE 3
The procedure of example 1 was followed with 100 ml dimethylformamide instead of dimethyl acetamide.
Water content (by Karl Fisher) = 0.13%; Chemical assay (by HPLC) = 99.0%; Yield = 76% (by theory)

EXAMPLE 4
The procedure of example 1 was followed with the change that the reaction temperature was maintained at 10°C instead of 5°C.
Water content (by Karl Fisher) = 0.17%; Chemical assay (by HPLC) = 99.3%; Yield = 72% (by theory)
We Claim:

1. A process for the manufacture of a compound of the formula I by reaction of 2,3:4,5-bis-O-(l-methylethylidene)-β-D-fructopyranose (III) and sulfamoyl chloride (V)

![Diagram of compounds III and V]

in a solvent of high dielectric constant in the presence of a suitable base at a temperature in the range from -50°C to 100°C and subsequently subjecting the reaction to hydrolytic workup and extraction followed by distillation of the solvent and crystallization to afford a compound of the formula I in a crude form which is finally crystallized from a solvent to obtain a compound of the formula I in a pure form.

2. A process as claimed in claim 1, wherein the solvent of high dielectric constant is selected from the group comprising of dimethyl formamide, dimethyl acetamide, dimethyl sulfoxide etc, preferably dimethyl acetamide.

3. A process as claimed in claim 1, wherein the base is selected from a group comprising of the trialkylamines such as triethylamine, trimethylamine, tri n- and iso- propylamines, tributylamine, N-methylmorpholine, pyridine, lutidines, picolines etc, preferably N-methylmorpholine.

4. A process as claimed in claim 1, wherein the reaction is carried out at a temperature from -50°C to 100°C, preferably 50°C.
5. A process as claimed in claim 1, wherein the solvent for crystallizing Topiramate in the crude form is selected from a group comprising of hydrocarbons such as hexane, n-heptane, cyclohexane, ethers such as diethyl ether, diisopropyl ether, methyl tertbutyl ether, ketones such as acetone, methyl ethyl ketone or methyl isobutyl ketone or esters such as methyl acetate, ethyl acetate or n-butyl acetate.

6. A process as claimed in claim 5, wherein the preferred solvent for crystallization of crude Topiramate is diisopropyl ether.
**INTERNATIONAL SEARCH REPORT**

A. **CLASSIFICATION OF SUBJECT MATTER**

Int. Cl.

**C07H9/04 (2006.01) C07H 1/00 (2006.01)**

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)

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)

Database: STN; Files CA, WPIIDS; Keywords: topiramate, fructopyranose, sulfamate, chlorosulfamic acid, sulfamoyl chloride, chlorimidosulfuric acid, amidosulfonyl chloride, aminosulfonyl chloride

C. **DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>1-2, 4-6</td>
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<tr>
<td>X</td>
<td>EP 0533483 B1 (McNEILAB, Inc.) 11 March 1998 See in particular page 3 lines 5-39</td>
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[X] Further documents are listed in the continuation of Box C  
[X] See patent family annex

* Special categories of cited documents:
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Date of the actual completion of the international search
05 September 2006

Date of mailing of the international search report 13 SEP

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<td>MARYANOFF, B. et al &quot;Anticonvulsant O-Alkyl Sulfamates. 2,3:4,5-Bis-O-(1-</td>
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END OF ANNEX