JOSE LLOREDA CAMACHO & CO.
Calle 72 No. 5-83 Piso 5, Bogotá, D.C. Tel: 6069700 Fax 6069701

~~127~~ 132

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: P1.-**ASTRAZENECA AB y RENOVIS, INC.**-Solicitud de patente de Invención para **"PROCESO NOVEDOSO PARA LA PREPARACION DE α-(2,4 DISULFOFENIL)-N-TER-BUTILNITRONA"**.-Clase **A.61.**- Expediente número **01-000.729.-**

1. Me refiero a mi memorial de 24 de Enero de 2005.

2. Por medio del presente atentamente ruego a usted, se sirva pronunciarse en relación con la solicitud arriba nombrada, ya que desde el 30 de Mayo de 2003, esto hace mas de **(2) años**, que fue publicado el extracto de la presente solicitud en la Gaceta de la Propiedad Industrial No. 528, de 30 de Mayo de 2003, y el examen de patentabilidad correspondiente fue solicitado en su debido momento mediante memorial de 23 de Octubre de 2003, sin que haya sido adelantado ningún otro trámite.

3. Cabe anotar que esta demora en el trámite acarrea grave perjuicio para mi representado.

Señor Superintendente,

ALICIA LLOREDA RICAURTE
T.P. 53.215

AMCW/fegv

Industria y Comercio
SUPERINTENDENCIA

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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **01-729**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **528**, DE

FECHA **30** DE **MAYO** DE **2003**, EL TERMINO HABIL SEÑALADO POR LA LEY

EXPIRA EL **29** DE **AGOSTO** DE **2003**.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ____ _____ NO ____ **X** _____

Carrera 13 No. 27-00 Piso 5 y 10
Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@sic.gov.co
Santa Fe de Bogotá D.C. - Colombia

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K	A2	(11) International Publication Number: WO 95/17876
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(60) Parent Application or Grant
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US 08/173,579 (CIP)
Filed on 23 December 1993 (23.12.93)

(71) Applicants *(for all designated States except US)*: OKLAHOMA MEDICAL RESEARCH FOUNDATION [US/US]; 825 Northeast 13 Street, Oklahoma City, OK 73104 (US). UNIVERSITY OF KENTUCKY RESEARCH FOUNDATION [US/US]; Bowman Hall, Lexington, KY 40506 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: CARNEY, John, M. [US/US]; 4033 Palomor, Lexington, KY 40503 (US).

(74) Agents: HELLWEGE, James, W.; Jones, Tullar & Cooper, P.C., P.O. Box 2266 Eads Station, Arlington, VA 22202 (US) et al.

(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: 2,4-DISULFONYL PHENYL BUTYL NITRONE, ITS SALTS, AND THEIR USE AS PHARMACEUTICALS

(57) Abstract

2,4-disulfonyl α-phenyl-tert-butyl nitrone and its pharmaceutically acceptable salts are disclosed. These materials are useful as pharmaceutical agents for oral or parenteral, e.g. intravenous administration to patients suffering from acute central nervous system oxidation as occurs in a stroke or from gradual central nervous system oxidation which can exhibit itself as progressive central nervous system function loss. The materials are also used to ameliorate the side effects of oxidative-damage causing antineoplastic disease treatments.

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Compound Preparation

As detailed in Figure 1 and demonstrated in Example 1, the compound of this invention can be prepared by a two step reaction sequence. In the first step, commercially available tertiary butyl nitrate (2-methyl-2-nitropropane) is converted to the corresponding n-hydroxyl amine using a suitable catalyst such as an activated zinc/acetic acid catalyst or an aluminum/mercury amalgam catalyst. This reaction can be carried out in 0.5 to 12 hours and especially about 2 to 6 hours or so at a temperature of about 15 to 100°C in a liquid reaction medium such as alcohol/water mixture in the case of the zinc catalyst or an ether/water mixture in the case of the aluminum amalgam catalyst.

In the second step, the freshly formed hydroxylamine is reacted with 4-formyl-1,3-benzenedisulfonic acid, typically with a slight excess of the amine being used. This reaction can be carried out at similar temperature conditions. This reaction is generally complete in 10 to 24 hours.

The product so formed is the free acid and is characterized by a molecular weight of 89 g/mole. It is a white powdery material which decomposes upon heating. It is characterized by a solubility in water of greater than 1 gram/ml and a ^1H NMR spectrum in D_2O of 8.048 ppm (dd, 8.4, 1.7 Hz); 8.836 ppm (d, 8.4 Hz); 8.839 ppm (d, 1.7 Hz); 8.774 ppm (s).

The various salts can be easily formed by admixing the free acid in aqueous medium with two equivalents of the appropriate base, for example, KOH for the potassium salt, and the like.

adriamycin per square meter of surface area with adriamycin dosing occurring every seven or twenty-one days. Compound I may be administered before the adriamycin, for example, up to 60 minutes before, at the same time or after, such as hours after and on subsequent days. The pediatric dose is typically lower for both drugs. Higher doses may be used for treatment of multidose resistant tumors.

EXAMPLES

Example 1

Synthesis of 2,4-disulfonylphenyl-N-t-butylnitrone (Compound "I" in subsequent Examples). This preferred synthesis is based on the work by R.H. Hinton and E.G. Janzen (J. Org. Chem. 57:2646-2651, 1992). As shown in Fig. 1 it involves the condensation of an aldehyde with a hydroxylamine. The hydroxylamine is unstable and is prepared fresh on the day of use using an activated zinc catalyst. The synthesis is as follows:

Prerequisite Chemicals

1. 95% Ethanol
2. 2-Methyl-2-nitropropane
3. Zinc dust
4. Glacial acetic acid
5. Diethyl ether
6. Saturated sodium chloride
7. Magnesium Sulfate, Anhydrous solid
8. 4-Formyl-1,3-benzenesulfonic acid (MW 310.21 g/mole), disodium salt, hydrate
9. Methanol
10. Dichloromethane

10. The solid melts just above room temperature, but could be dried further in a vacuum oven (no more than a few minutes), leaving 38 to 45 g of solid.
11. The solid can be used as is or was purified by recrystallization from pentane.
12. Molecular weight = 89 g/mole.

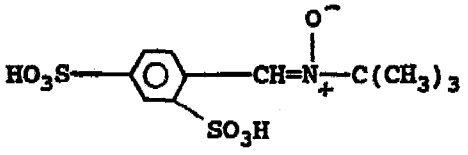
B. Preparation of 2,4-disulfonylphenyl-N-t-butylnitrone

1. A 250 ml flask was equipped with a stir bar and a Friedrichs condenser cooled with recirculated ice water.
2. The flask was charged with 71.8 ml of methanol, 14.5 g of 4-formyl-1,3-benzenedisulfonic acid (46.7 mmoles, 1 eq.), and 5.0 g of N-t-butylhydroxylamine (56.2 mmoles, 1.2 eq.).
3. The mixture was refluxed overnight.
4. The reaction product was transferred to round-bottom flask and rotovaped to dry.
5. The solid residue was mashed with ether, the ether was decanted off (yellow).
6. Step 5 was repeated.
7. Product ("Compound I") was crystallized from methanol following a hot methanol filtration to remove insoluble precipitates and recrystallized twice from methanol.

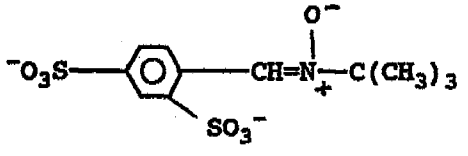
What is claimed is:

1. 2,4-disulfonyl α-phenyl tertiary butyl nitrone.

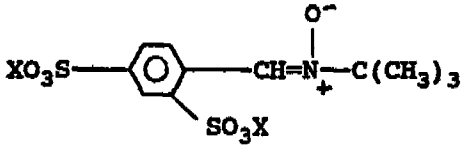
2. A compound of the formula of



3. A pharmaceutically acceptable salt of



4. The salt of claim 3 having the formula:



wherein X is selected from the group consisting of Na, K, NH_4, Ca, Mg, CaY and MgY, wherein
Y is a pharmaceutically acceptable monovalent anion.

5. A pharmaceutical composition comprising the compound of claim 1 in a pharmaceutically acceptable parenterally injectable carrier.

6. A pharmaceutical composition comprising the compound of claim 2 in a pharmaceutically acceptable parenterally injectable carrier.

1D2

United States Patent Office 3,397,234 Patented Aug. 13, 1968

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3,397,234

PROCESS FOR THE PREPARATION OF α-PHENYL-N-METHYL NITRONE

Earl W. Cummins, Wilmington, Del., assignor to E. I. du Pont de Nemours and Company, Wilmington, Del., a corporation of Delaware

No Drawing. Continuation-in-part of application Ser. No. 375,946, June 17, 1964. This application Mar. 2, 1967, Ser. No. 619,965

11 Claims. (Cl. 260—566)

ABSTRACT OF THE DISCLOSURE

α-Phenyl-N-methyl nitrone is prepared by mixing an aqueous solution of N-methylhydroxylamine sulfate, bisulfate or chloride with benzaldehyde and then adding sodium or potassium hydroxide in amounts sufficient to maintain the pH of the aqueous phase between 1 and 6 and to attain a final stable pH between 4 and 6. Salting-out of the nitrone can be achieved by utilizing reactants at concentrations which will result in the final aqueous phase being approximately saturated with the by-product inorganic salt.

Related applications

This application is a continuation-in-part of my copending application, Ser. No. 375,946 filed June 17, 1964, now abandoned.

Background of invention

This invention relates to the reaction of N-methylhydroxylamine with benzaldehyde to form α-phenyl-N-methyl nitrone which is a valuable intermediate in the production of the halosubstituted phenylmethylmethoxyureas of U.S. Patent 2,960,534, issued Nov. 15, 1960, to Otto Scherer and Paul Heller.

In the prior art method of preparing α-phenyl-N-methyl nitrone, for example, U.S. Patent 3,178,467, column 5, lines 1 through 16, N-methylhydroxylamine as a dilute aqueous solution and benzaldehyde are reacted under strongly basic conditions. In the practice of this prior art method, caustic is added to the amine solution followed by addition of the benzaldehyde. Efficient cooling during the entire process is required because of the evolution of heat during the caustic addition and the reaction of the amine and benzaldehyde and because of the heat-sensitivity of N-methylhydroxylamine. The nitrone is isolated from the dilute, aqueous reaction mass by repeated solvent extractions.

In the process of my invention, the yield and cooling efficiency are greater than in the prior art process whereas the time and the reaction mass volume required to produce a given amount of nitrone are both significantly less. Furthermore, the isolation of the nitrone can be greatly simplified.

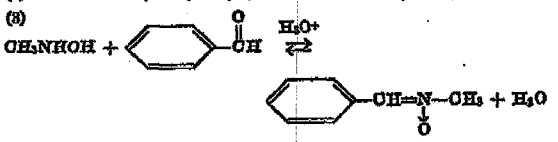
Process of this invention

This invention is directed to a process for the preparation of α-phenyl-N-methyl nitrone comprising maintaining the pH of the aqueous phase of a two phase system comprising benzaldehyde and an aqueous solution of N-methylhydroxylamine sulfate, bisulfate or chloride within the range of from 1 to 6 until reaction of the benzaldehyde and N-methylhydroxylamine substantially ceases, the pH being maintained between 1 and 6 by admixing sodium or potassium hydroxide with the mixture. This invention is also directed to a method of isolating α-phenyl-N-methyl nitrone from an aqueous solution thereof.

The mechanism by which this process is believed to proceed can best be understood by reference to the following:

(1)
$$[CH_3NH_2OH]^+{}_nX^{n-} + nH_2O \rightleftarrows nCH_3NH_2OH + nH_3O^+ + X^{n-}$$

(2)
$$nMOH + nH_3O^+ + X^{n-} \longrightarrow M_nX + 2nH_2O$$

(3)


where X is $SO_4^{=}$, HSO_4^- or Cl^- and M is sodium or potassium.

The aqueous solution of a salt of N-methylhydroxylamine employed as a starting material in my process will usually have a pH of less than 1. Thus in equilibrium (1), the salt is originally predominant. When benzaldehyde is added to this solution essentially no reaction occurs. However, upon addition of an amount of base sufficient to raise the pH of the aqueous phase to within the range of from 1 to 6, Equation (2), a portion of the N-methylhydroxylamine is liberated from the salt and free N-methylhydroxylamine is available for the acid-catalyzed reaction with the benzaldehyde, (3). This reaction takes place rapidly under the acidic conditions which prevail. As the free N-methylhydroxylamine is consumed the pH of the aqueous phase decreases and additional base is added to maintain the pH between 1 and 6. To obtain maximum yields, addition of base is continued until the pH remains stable at a value within the range of from 4 to 6, preferably about 6.

The proper total amount of base added during the reaction is that stoichiometrically equivalent to the anion in the N-methylhydroxylamine salt. In practice, the N-methylhydroxylamine salt solution can contain free acid as other amine salts. In such cases, additional base is needed to release all of the N-methylhydroxylamine. The proper amount of base in all cases can be computed from analysis. Alternatively, the required amount of base can readily be determined by titrating a sample of the N-methylhydroxylamine salt solution starting material to pH 8.5 with standard base.

The appropriate rate for bsae addition is simply "as fast as one can add the base while keeping the pH in the range of 1 to 6, preferably 4 to 6." This rate will be quite fast at the beginning of the reaction and will slow down toward the end. If base is added so rapidly that the pH rises above 6, the acid-catalyzed reaction ceases because of the absence of sufficient acid. If the pH becomes too high, the pH is adjusted to the range of about 5 to 6 by the addition of a mineral acid such as sulfuric or hydrochloric.

The amount of benzaldehyde used is not critical. One to two moles of benzaldehyde per mole of the N-methylhydroxylamine salt is the preferred range. Amounts in excess of one mole per mole of the amine can be beneficial not only to accelerate the reaction by the well-known principle of mass action but also to aid the drying of the nitrone by distillation.

It is preferred for the benzaldehyde to be present in the reaction vessel before any N-methylhydroxylamine is freed from its salt and thus before addition of base is begun. It is preferred to make additions to the reaction vessel in the following order:

(a) benzaldehyde,
(b) aqueous solution of N-methylhydroxylamine salt,

(c) water (if needed), and
(d) base with pH control.

The reaction of the base with the amine salt and the reaction of the free amine with the benzaldehyde are exothermic. It will ordinarily be preferred to carry out the process of this invention at a temperature somewhat above that of available cooling water to permit the most economic heat transfer. However, temperatures should be held below the boiling point of the reaction mixture. Temperatures higher than those used in the prior art process discussed above can be used because the N-methylhydroxylamine reacts with the benzaldehyde almost as rapidly as it is liberated from its salt and therefore, is exposed to high temperatures for a much shorter time than in the prior art process. I prefer a reaction temperature between 20 and 70° C. and find temperatures between 60 and 70° C. to be most preferable. In normal commercial operation, it is most convenient to initiate the reaction at ambient temperatures and allow the heats of reaction to raise the temperature to about 65° C. before applying external cooling to maintain the temperature between 60 and 70° C.

At the completion of the reaction the nitrone can easily be separated from the reaction mixture if the aqueous phase is saturated with a sulfate or chloride salt of sodium or potassium. If the aqueous phase is so saturated, the nitrone is "salted-out" into a separate organic layer which can be isolated from the remainder of the reaction mixture by decantation or other suitable methods. Solvents for the nitrone can, of course, be used at this stage but are unnecessary in the practice of this invention.

Saturation of the final aqueous phase with sodium or potassium sulfate or chloride can be accomplished either by utilizing aqueous N-methylhydroxylamine salt and base at concentrations which will yield a saturated aqueous phase when the reaction is complete or by adding sodium or potassium sulfate or chloride to the final reaction mixture. The salting-out effect can be observed at less than the saturation point of salt but yield losses occur and economy of the operation suffers. If the aqueous phase is beyond the saturation point, salt crystals can form. If this does occur the crystals can be allowed to settle prior to decantation of the nitrone or can be redissolved by adding water to the reaction mixture.

For best utilization of equipment, it is desirable that the aqueous phase contain a maximum quantity of the by-product salt. The temperature of maximum solubility for sodium sulfate is about 33° C. Accordingly, I prefer to cool the reaction mass to about 30 to 40° C. for phase separation. If sodium chloride is involved, the phase separation temperature is less critical and any convenient temperature in the range of 20 to 50° C. can be used.

The use of the sulfate salt of N-methylhydroxylamine and sodium hydroxide is preferred. Ordinarily, it is preferred to use 50% aqueous sodium hydroxide, this being a commercial article of convenience. In this case, the preferred concentration of the aqueous N-methylhydroxylamine sulfate starting material is about 45% by weight. With these concentrations and materials, no additional water or salt is required to achieve saturation of the final aqueous phase with the by-product salt, sodium sulfate. Of course, if the N-methylhydroxylamine sulfate contains excess acid or other amine salts, slight adjustments in the amounts of sodium hydroxide and water can sometimes be necessary to give a final aqueous phase which is approximately saturated.

Concentrations of N-methylhydroxylamine sulfate above 45% can be used by simply adding sufficient water to the reactor to dilute to about 45%. By employing solid (100%) sodium hydroxide, N-methylhydroxylamine sulfate concentrations as low as 37.7% can be used with equivalent results, or, as described above, sodium sulfate can be added after completion of the reaction.

I prefer to use concentrations of N-methylhydroxylamine sulfate ranging from 38 to 75% and particularly prefer from 45 to 55% for ease of handling. Sodium hydroxide should not be more dilute than about 40% and as stated above, I greatly prefer 50%.

If the chloride or bisulfate salt of N-methylhydroxylamine is used, the reactant concentrations which will yield a saturated aqueous phase can be determined by simple calculations.

N-methylhydroxylamine sulfate solutions of preferred concentrations can be prepared by the method of U.S. Patent 3,173,953. Preferred amine bisulfate and chloride solutions can readily be prepared by simple modifications of this method or others described in the literature.

In a preferred process one admixes 45 to 46% aqueous N-methylhydroxylamine sulfate with one to two moles of benzaldehyde per mole of amine sulfate in an agitated reactor. One then adds 50% aqueous sodium hydroxide at a controlled rate which will adjust the pH of the aqueous phase to between 4 and 6 and maintain the pH within that range. The temperature increases as the addition of sodium hydroxide proceeds and when it reaches about 65° C. external cooling is applied. While maintaining the temperature between 60 and 70° C., the sodium hydroxide addition is continued until the pH remains stable at 6. The reaction mixture is then cooled to about 33° C., at which temperature the aqueous phase is saturated with respect to sodium sulfate. The α-phenyl-N-methyl nitrone exists primarily in a separate organic phase which is isolated from the aqueous phase by decantation. Although the nitrone is relatively soluble in pure water, the amount dissolved in the aqueous phase is only about 0.2%. The organic phase is comprised of 75% nitrone and 25% water. If an excess of benzaldehyde is employed the percentages of nitrone and water are correspondingly reduced.

If desired, the organic phase can be dried by distillation under reduced pressure to yield essentially anhydrous α-phenyl-N-methyl nitrone. The nitrone can be methylated and then cleaved by the addition of water to form N,O-dimethylhydroxylamine as described in U.S. Patent 3,178,467. This N,O-dimethylhydroxylamine can be reacted with a substituted phenyl isocyanate to obtain the compounds of the aforementioned Scherer and Heller patent.

In order to further explain this invention, the following additional examples are provided. All parts and percentages are by weight unless otherwise indicated.

EXAMPLE 1

Mix together 105 parts of a 45.7% aqueous N-methylhydroxylamine sulfate and 53 parts benzaldehyde in an agitated reactor. Add 50% aqueous sodium hydroxide gradually to the acidic mixture. Do not allow the pH of the aqueous phase to exceed 6. When the temperature reaches 65° C. apply external cooling to maintain the temperature at 60 to 70° C. The reaction is complete when the pH remains stable at 6 with no further addition of sodium hydroxide. If the pH should rise above 6 before the reaction is complete adjust it back to 5 with sulfuric acid and resume caustic feed.

Cool the mixture to 40° C. and separate the phases. Discard the aqueous (lower) phase. Dry the α-phenyl-N-methyl nitrone (upper) phase by distilling out the water at a pressure of 5 to 10 mm. mercury. Do not heat the nitrone over 100° C. The residue contains 97.6% nitrone and 0.08% water, corresponding to a yield of 98.1%.

EXAMPLE 2

Mix together 105 parts of acidic 45.7% aqueous N-methylhydroxylamine sulfate and 106 parts benzaldehyde in an agitated vessel. Warm the mixture to 65° C. Add 50% aqueous sodium hydroxide to the mixture as described in Example 1 until a stable pH of 6 is reached. Keep the temperature at 65° C. during the caustic addition. Cooling will be required.

Cool the mixture to 40° C. and draw off the aqueous (lower) phase. Dry the nitrone (upper) phase by distilling off the water at a pot temperature of 90° C. under

partial vacuum. The residue contains less than 0.05% water. Analysis by ultraviolet absorption shows a nitrone yield of greater than 98%.

EXAMPLE 3

Repeat Example 2 but substitute 125 parts of 38.4% aqueous N-methylhydroxylamine sulfate for the 105 parts of 45.7% aqueous N-methylhydroxylamine sulfate and when the pH is stable at 6, add 10 parts of solid sodium sulfate (salt cake) to the reaction mixture. Essentially identical results are obtained.

EXAMPLE 4

Mix together 92.8 parts of 45% aqueous N-methylhydroxylamine chloride and 106 parts benzaldehyde in an agitated vessel. Warm the mixture to 65° C. Add 50% aqueous sodium hydroxide to the mixture as described in Example 1 until a stable pH of 6 is reached. Keep the temperature at 65° C. during the caustic addition. Cooling will be required.

Cool the mixture to 40° C. Solid sodium chloride will be present in the reaction mixture. Add water until solid sodium chloride is no longer present. Approximately 30 parts of water will be required. Separate the phases and dry the nitrone as described in Example 1. A good yield of the nitrone will result.

EXAMPLE 5

A batch of α-phenyl-N-methyl nitrone is prepared as described below, methylated with dimethylsulfate and the resulting product cleaved by the addition of water to form N,O-dimethylhydroxylamine, benzaldehyde and methyl hydrogen sulfate. These products are separated and the benzaldehyde, along with that removed during the nitrone drying operation, are used in the following example.

A stirred reactor is charged with 9 pounds of fresh benzaldehyde and 360 pounds of benzaldehyde obtained as described above, 85 pounds of water and 304 pounds of a 54.9% aqueous solution of N-methylhydroxylamine sulfate which also contains 4 pounds of sulfuric acid and 3 pounds of methylamine sulfate. Aqueous 50% sodium hydroxide is added to the resulting slurry. When the temperature reaches 65° C., external cooling is applied to maintain this temperature. The addition of sodium hydroxide is continued until a stable pH of 6 is obtained. This requires 146 pounds of the aqueous sodium hydroxide. The reaction mass is cooled to 35° C. and the lower aqueous layer is discarded. This phase contains essentially all the methylamine sulfate originally present. The upper nitrone-benzaldehyde phase is dried at a pot temperature of 90° C. under partial vacuum until a total of 76 pounds of distillate is obtained. The resulting residue contains less than 0.05% water. The yield of nitrone is 98.7% of theoretical as determined by ultraviolet analysis.

The products prepared in the preceding examples are admirably suited for conversion to N,O-dimethylhydroxylamine.

What is claimed is:

1. A process for preparing α-phenyl-N-methyl nitrone comprising maintaining the pH of the aqueous phase of a two phase mixture comprising benzaldehyde and an aqueous solution of the sulfate, bisulfate or chloride salt of N-methylhydroxylamine within the range of 1 to 6 until reaction of said benzaldehyde and N-methylhydroxylamine is substantially complete, the pH being maintained within said range by admixing sodium hydroxide or potassium hydroxide with said mixture.

2. The process of claim 1 wherein said mixture is maintained at a temperature of from 20 to 70° C.

3. The process of claim 1 wherein said mixture is maintained at a temperature of from 60 to 70° C.

4. The process of claim 1 wherein the benzaldhyde: N-methylhydroxylamine salt mole ratio is from 1:1 to 2:1.

5. The process of claim 1 wherein said pH is maintained within the range of from 4 to 6.

6. The process of claim 1 wherein the final pH is within the range of from 4 to 6.

7. The process of claim 6 wherein the reactant concentrations are such that upon completion of said reaction, said aqueous phase is substantially saturated with the sulfate or chloride salt of sodium or potassium.

8. A process for preparing α-phenyl-N-methyl nitrone comprising adding sodium hydroxide to a two phase mixture comprising an aqueous solution of the sulfate, bisulfate or chloride salt of N-methylhydroxylamine and from 1 to 2 moles of benzaldehyde per mole of said salt in amounts sufficient to maintain the pH of the aqueous phase of said two phase mixture within the range of from 1 to 6 and to adjust said aqueous phase to a stable pH within the range of from 4 to 6.

9. The process of claim 8 wherein the concentration of said sodium hydroxide and said salt are such that the final aqueous phase is saturated with sodium sulfate or sodium chloride.

10. The process of claim 9 wherein the temperature of said mixture is maintained within the range of from 60 to 70° C.

11. A method of isolating α-phenyl-N-methyl nitrone from an aqueous solution thereof comprising saturating said solution with a sulfate or chloride salt of sodium or potassium.

References Cited

UNITED STATES PATENTS

3,178,467 4/1965 Gerjovich et al. ..... 260—566

CHARLES B. PARKER, *Primary Examiner.*

R. V. HINES, *Assistant Examiner.*

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020/
Bogotá, D.C.,

Doctor(a)
Alicia Lloreda Ricaurte **Oficio Nº** 5870
Apoderado(a)
ASTRAZENECA AB Y
RENOVIS, INC.

REFERENCIA	**Radicación**	**01 729**
	Trámite	**002**
	Evento	**001**
	Actuación	**430**
	Folios	**006**

Como resultado del examen de patentabilidad de la solicitud de patente de invención Nº 01 729, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

1. DOCUMENTOS ESTUDIADOS:

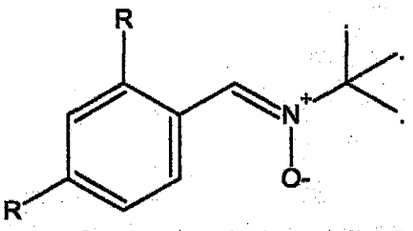
- El resumen y el capítulo descriptivo de la solicitud que se encuentran en los folios 4 y 5 a 10 respectivamente.
- Los ejemplos que ilustran la invención en los folios 11 a 16.
- Las cláusulas 1 a 10 relacionadas en el capítulo reivindicatorio de la solicitud y que se encuentran en los folios 17 y 18.
- La copia de la solicitud original mediante la cual se reivindica prioridad de Suecia SE0000055-4 de 10/01/2000 en los folios 29 a 43, junto con su traducción correspondiente en los folios 22 a 28.
- El primer examen de forma efectuado a la solicitud de oficio No. 1028, que se encuentra en el folio 45.
- La respuesta al primer examen de forma No, 1028, allegada mediante memorial de fecha 30/05/2001, que se encuentra en los folios 48 a 74 y que contiene las modificaciones correspondientes al título de la invención, entre otras.
- El memorial de fecha 23/10/2003, mediante el cual se modifica nuevamente el título y se solicita el examen de patentabilidad en los folios 78 a 84.
- El memorial de fecha 24/01/2005 mediante el cual se informa del traspaso de los derechos sobre la solicitud de la patente de la sociedad CENTAUR PHARMACEUTICALS, INC. a la sociedad RENOVIS INC, en los folios 93 a 136.

2. OBJETO DE LA INVENCIÓN

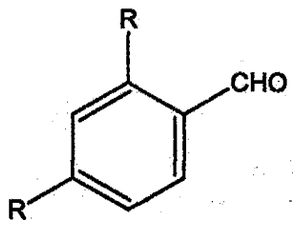
La solicitud hace referencia a ***"Proceso novedoso para la preparación de α-(2,4-disulfofenil)-N-ter-butilnitrona"***

- **Reivindicaciones 1 a 3 y 10:**

Se reivindica un proceso para la preparación de un compuesto de fórmula general (I)



En donde cada R representa de manera independiente SO_3H o una sal del mismo como $SO3^-Na^+$, en donde el proceso comprende la reacción de un aldehído de fórmula (II), en donde R es como se definió antes, con acetato de N-ter-butilhidroxilamonio en un solvente líquido de reacción.



Se reivindica el proceso en el cual 1,25 a 2,5 equivalentes de acetato de N-ter-butilhidroxilamonio (III) se utilizan por equivalente de aldehído (II).

En particular se reclama el proceso en el cual 1,6 a 2,0 equivalentes de acetato de N-ter-butilhidroxilamonio (III) son utilizados por equivalente de aldehído (II).

- **Reivindicaciones 4 a 6:**

Se reclama el proceso en el cual el solvente de reacción incluye un alcohol (metanol) o una mezcla de alcoholes.

- **Reivindicaciones 7 y 8:**

Se reclama un proceso en el cual el solvente de reacción contiene hasta un 10% en volumen de agua y preferiblemente 5% en volumen de agua.

- **Reivindicación 9:**

Se reivindica un proceso en el cual el producto es aislado mediante cristalización y se caracteriza porque la cristalización se logra mediante adición de isopropanol a la mezcla de reacción.

Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K $^{31}/_{12}$** de la **Clasificación Internacional de Patentes**.

4. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la solicitud en estudio - 10.01.2000-, relacionados con la materia técnica reivindicada:

Nº	Documento	Título	Fecha de Publicación
D1	WO9517876	"2,4-disulfonyl phenyl butyl nitrote, its salts, and their use as pharmaceuticals"	06/07/1995
D2	US3397234	"Process for the preparation of α-phenyl-N-methyl nitrone"	13/08/1968

Anterioridades **D1** y **D2** en los folios 139 a 146.

5. EVALUACIÓN DE LOS REQUISITOS DE PATENTABILIDAD:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: "*Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial*"

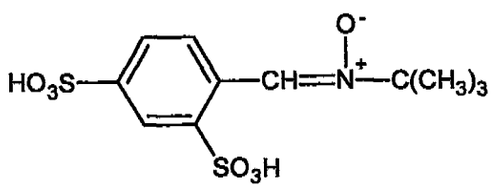
En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

5.1 Evaluación de NOVEDAD:

El artículo 14 de la Decisión 486 contempla que: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica.*

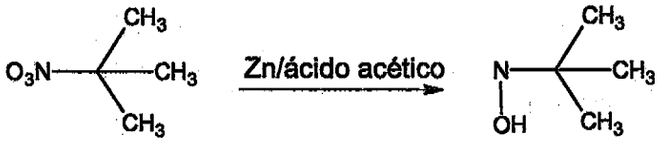
El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida".

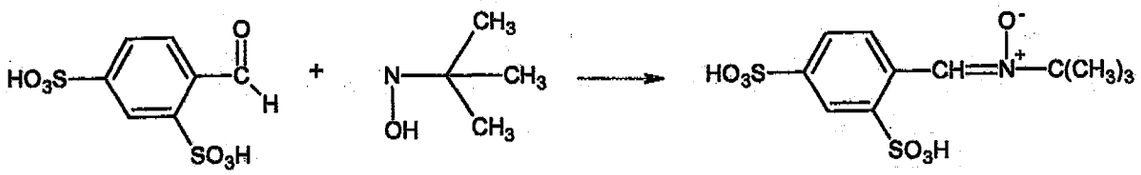
La anterioridad **D1** comprende en su aparte descriptivo un proceso para la preparación de un compuesto 2,4-disulfonil α-fenil-butil-nitrona terciaria de fórmula:



El proceso, en su primera etapa convierte el compuesto ter-butil nitrato (2-metil-2-nitropropano) en su correspondiente N-hidroxil-amina, usando como catalizadores Zinc/ácido acético o aluminio/amalgama de mercurio.

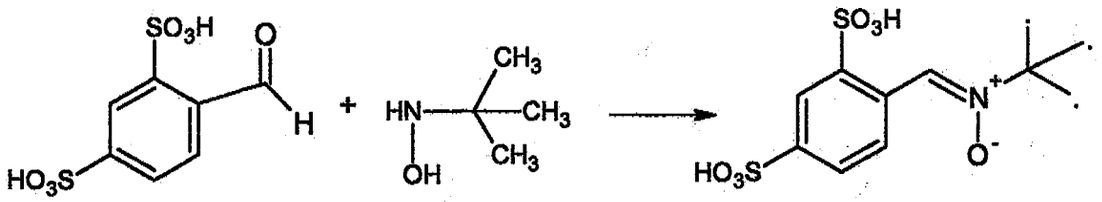
En la segunda etapa de reacción la hidroxilamina formada se somete a la acción del ácido 4-formil-1,3-bencenodisulfónico.





En síntesis, la anterioridad **D1** revela la condensación de un aldehído con una hidroxilamina. El producto (compuesto I) se cristaliza en metanol caliente para remover impurezas.

Por su parte la solicitud reclama el proceso:



Así las cosas, al existir identidad entre el proceso reivindicado por la solicitud y aquel que se describe en la anterioridad **D1**, es evidente que la materia objeto del presente estudio no cumple con el requisito de NOVEDAD.

5.2 Evaluación del NIVEL INVENTIVO:

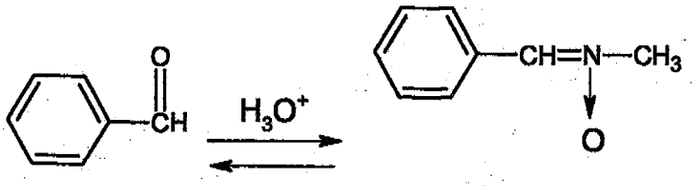
El artículo 18 de la decisión 486 dispone "*Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la Materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica*".

La anterioridad **D2** por su parte presenta un proceso para la preparación de α-fenil-N-metil-nitrona que requiere mantener el pH de la fase acuosa entre 4 y 6 mediante la adición de NaOH o KOH, la fase acuosa se encuentra en un sistema bifásico que comprende benzaldehído y una solución acuosa de N-metilhidroxil-amina-sulfato, bisulfato o clorhidrato.

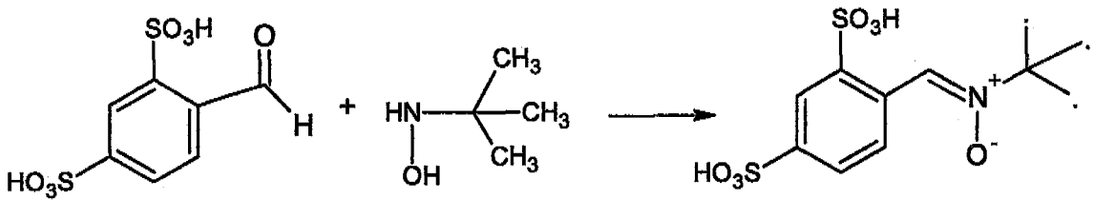
El proceso cursa con el siguiente mecanismo de reacción:

1 $[CH_3NH_2OH]^+_nX^{n-} + nH_2O \rightleftharpoons nCH_3NH_2OH + nH_3O^+ + X^{n-}$

2 $nMOH + nH3O^+ + X^{n-} \longrightarrow MnX + 2nH_2O$

3 $CH_3NHOH +$  $+ H_2O$

Así las cosas, resulta evidente para una persona versada en la materia, diseñar un proceso de reacción, como el que contempla el capítulo reivindicatorio en estudio, en el que un aldehído de fórmula (II) se condense con acetato de N-terbutilhidroxilamonio (fórmula III) en metanol, con posterior cristalización del producto de interés en isopropanol, tal como lo muestra el esquema:



Porque ya las anterioridades **D1** y **D2** enseñaban sobre la reacción de condensación que se produce entre un aldehído aromático e hidroxil-amina, tal y como se reivindica en la solicitud en estudio.

En este sentido, la solicitud carece de nivel inventivo, por cuanto se derivaba de manera evidente del estado de la técnica el hecho de hacer reaccionar un ácido 2-formil-disulfónico con la 2-hidroxilamina de 2-metil-propano, tal como lo demuestra el alcance del capítulo descriptivo y reivindicatorio de la anterioridad **D2**. Y tampoco se evidencia un salto cualitativo en la regla técnica, por cuanto la reacción tiene curso sobre estructuras análogas a las descritas en la publicación en cuestión, con la única diferencia que el benzaldehído que participa en la reacción reclamada, cuenta con dos grupos sufonilo en posición 1 y 5 del anillo, no obstante dichos grupos no interfieren en el mecanismo de reacción que sigue la condensación entre la hidroxil-amina y el grupo carbonilo de la posición 2, hecho que ratifica la falta de altura inventiva del proceso reivindicado.

En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

Nº	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO9517876	1 a 10	Novedad
			Nivel Inventivo
D2	US3397234	1 a 10	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única Nº 10 de 2001.

Alix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

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El anterior requerimiento fue notificado por fijación en lista, de fecha 01 JUN. 2006 ~~152~~

CONCEPTO TÉCNICO Número 0824	**EXAMINADOR TÉCNICO** Código 202044