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SEÑORES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. _____ S. _____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 07-058647-00003-0000

Fecha: 2008-02-22 11:56:34 Dep: 2020 NULCREACIONE
Tra: 11 PATENTACIONE Eya: 379 FASLNACIONALII
Act: 538 PLTACION Folios: 2

Ref.: Expediente No. 07-058.647

Solicitud de Patente de Invención titulada: "PROCESO DE FABRICACION DE SALICILAMIDAS N-SUSTITUIDAS."

Solicitante: NOVARTIS A.G.

SOLICITUD DE EXAMEN DE PATENTABILIDAD SEGÚN
EL ARTÍCULO 44 DE LA DECISION 486, GACETA No. 587

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, D.C., identificado tal como aparece al pie de mi firma, en mi condición de apoderado de la sociedad de la referencia, respetuosamente me permito solicitar que se examine si la invención reúne los requisitos de patentabilidad previstos en la misma, dando cumplimiento a lo establecido en el artículo 44 de la Decisión 486 de la comisión de la Comunidad Andina. Adjunto recibo por el monto de \$420.000 pesos para cubrir la tasa correspondiente, según la Resolución 44372 de 26 de diciembre 2007.

Atentamente,

CARLOS R. OLARTE
C.C. 79.782.747 de Bogotá
T.P. 74.295

Anexo: Recibo por \$420.000 pesos

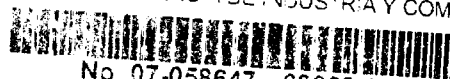
LMB/P2007/000005 000218 Sol Exam

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 15,390
FECHA : FEBRERO 21 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No 07-058647-00003-0000

EXAMEN DE PATENTABILIDAD DE INVEN
17-01-2008 Y 17-02-2008
ASIGNACIONALII

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
OLARTE RAISBECK	CONSIGNACION	BANCO DE BOGOTA	062754387	1493221	21/02/2008	22,239,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
		85 EXAMEN DE PATENTABILIDAD DE INVEN	420,000.00
		TOTAL :	\$ 420,000.00

SON: CUATROCIENTOS VEINTE MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 07-58647

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

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **587** DE

FECHA **18 DE ENERO DE 2008** EL TÉRMINO HÁBIL SEÑALADO POR LA LEY

EXPIRA EL **16 DE ABRIL DE 2008**

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



US 20030216593A1

155

(D1)

(19) **United States**(12) **Patent Application Publication** (10) **Pub. No.: US 2003/0216593 A1**
Bay et al. (43) **Pub. Date: Nov. 20, 2003**(54) **METHOD OF PREPARING SALICYLAMIDES**(52) **U.S. Cl. 560/143; 564/134**(76) **Inventors: William E. Bay, Ridgefield, CT (US);**
JoAnne P. Corvino, Harrison, NY (US)(57) **ABSTRACT****Correspondence Address:**
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NEW YORK, NY 10150-5257 (US)

The present invention provides a fast, high yield method for preparing salicylamide intermediates. The method comprises reacting a C_4 or higher alkyl ester of salicylic acid or derivative thereof with at least one amine selected from the group consisting of monoalkylamines, dialkylamines, ammonia, and any combination of any of the foregoing in alcohol to yield the sali-cylamide. The C_4 or higher alkyl ester of salicylic acid or a derivative thereof is preferably prepared by reacting salicylic acid or a derivative thereof with a C_4 or higher alcohol in presence of at least one of sulfuric acid, a sulfonic acid, and a mineral acid. This process for preparing salicylamide intermediates from salicylic acid or derivative thereof generally has a cycle time of about 2 days, and yields about 95% of a 99% pure material. In comparison, when a C_3 or lower alkyl ester is used in lieu of the C_4 or higher alkyl ester, the process generally has a cycle time of 7-9 days and yields about 60% of a 95% pure material. Methods of preparing an alkylated salicylamide are also provided.

(21) **Appl. No.: 10/297,156**(22) **PCT Filed: Jun. 4, 2001**(86) **PCT No.: PCT/US01/18118****Related U.S. Application Data**(60) **Provisional application No. 60/209,039, filed on Jun. 2, 2000.****Publication Classification**(51) **Int. Cl.⁷ C07C 231/02**

some off-gassing and a slight exothermic reaction. 77.5 kg of dry 6-chloro-2H-1,3-benzoxazine-2,4(3H)-dione is charged to the reactor. Quickly, 88 kg of dry ethyl-8-bromooctanoate is charged to the reactor. The reaction is evacuated to 22-24 inches of vacuum and the reactor temperature is raised to 65-75° C. The reactor temperature is maintained and the contents are watched for foaming. The reactor mixture is sampled and monitored for conversion by monitoring for the disappearance of the bromo ester in the reaction mixture by gas chromatography. The reaction is complete after 7 hours. The vacuum is broken and the reactor contents are cooled to 45-50° C. The contents are centrifuged and the filtrate sent into a second 200 gallon glass-lined reactor. 119 L of ethanol (200 proof denatured with 0.5% toluene) is charged to the first 200 gallon reactor, warmed to about 45° C. and the filter cake washed with warm ethanol and this wash is charged to the reaction mixture in the second 200 gallon reactor.

[0141] The agitator is started on the second 200 gallon reactor. The reactor contents are cooled to about 29° C. 120 L. distilled water is slowly charged to the second reactor, with the water falling directly into the batch. The reactor contents are cooled to about 8° C. The intermediate comes out of solution and is held for 9.5 hours. The resultant slurry is centrifuged. 70 L. ethanol is charged to the reactor, cooled to about 8° C., and the centrifuge cake is washed. The wet cake is unloaded into double polyethylene bags placed inside a paper lined drum. This yields ethyl 8-(6-chloro-2H-1,3-benzoxazine-2,4(3H)-dionyl)octanoate.

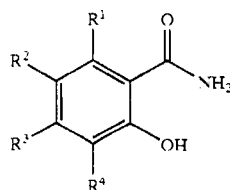
[0142] 400 L. purified water, USP and 45.4 kg sodium hydroxide pellets are charged to a 200 gallon glass-lined reactor and the agitator is set to 100-125 rpm. 123.5 kg of the ethyl 8-(6-chloro-2H-1,3-benzoxazine-2,4(3H)-dionyl)octanoate wet cake is charged to the reactor. The charging port is closed. Cooling water applied to the condenser and the valve reactor overheads are set for atmospheric distillation. The reactor contents are heated to about 98° C. and the conversion is monitored by HPLC. Initially (approximately 40 minutes) the reactor refluxes at about 68° C., however, as the ethanol is removed (over 3 hours) by distillation the reactor temperature rises to about 98° C. The starting material disappears, as determined by HPLC, at approximately 4 hours. The reactor contents are cooled to about 27° C. 150 L purified water, USP is charged to an adjacent 200 gallon glass-lined reactor and the agitator is set to 100-125 rpm. 104 L concentrated (12M) hydrochloric acid is charged to the reactor and cooled to about 24° C. The saponified reaction mixture is slowly charged (over 5 hours) to the 200 gallon glass-lined reactor. The material (45 L and 45 L) is split into 2 reactors (200 gallons each) because of carbon dioxide evolution. The product precipitated out of solution. The reaction mixture is adjusted to pH 2.0-4.0 with a 50% sodium hydroxide solution (2l. water, 2 kg sodium hydroxide). The reactor contents are cooled to about 9-15° C. The intermediate crystallizes out of solution over approximately 9 hours. The reactor slurry is centrifuged to isolate the intermediate. 50 L. purified water, USP is charged to a 200 gallon glass-lined reactor and this rinse is used to wash the centrifuge wet cake. The wet cake is unloaded into double polyethylene bags placed inside a plastic drum. The N-(5-chlorosalicyloyl)-8-aminocaprylic acid is dried under vacuum (27" Hg) at 68° C. for 38 hours. The dry cake is unloaded into double polyethylene bags placed inside a

55-gallon, steel unlined, open-head drums with a desiccant bag placed on top. This yields N-(5-chlorosalicyloyl)-8-aminocaprylic acid.

[0143] All patents, publications, applications, and test methods mentioned above are hereby incorporated by reference. Many variations of the present matter will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the patented scope of the appended claims.

What is claimed is:

1. A method for preparing a salicylamide comprising the step of reacting a C₄ or higher alkyl ester of salicylic acid or a derivative thereof with at least one amine selected from the group consisting of monoalkylamines, dialkylamines, ammonia, and any combination of any of the foregoing in alcohol to yield the salicylamide.
2. The method of claim 1, wherein the C₄ or higher alkyl ester of salicylic acid or a derivative thereof is a C₄-C₈ alkyl ester of salicylic acid or a derivative thereof.
3. The method of claim 2, wherein the C₄ or higher alkyl ester of salicylic acid or a derivative thereof is a butyl ester of salicylic acid or a derivative thereof.
4. The method of claim 1, wherein the alcohol is selected from the group consisting of C₁-C₄ alcohols, glycols, and any combination of any of the foregoing.
5. The method of claim 4, wherein the alcohol is methanol.
6. The method of claim 1, wherein the amine is selected from the group consisting of monomethylamine, monoethylamine, dimethylamine, diethylamine, ammonia, and any combination of any of the foregoing.
7. The method of claim 1, wherein the amine is ammonia.
8. The method of claim 7, wherein the ammonia is anhydrous ammonia.
9. The method of claim 1, wherein the monoalkylamine is 8-aminocaprylic acid.
10. The method of claim 1, wherein the C₄ or higher alkyl ester is reacted in an environment substantially free of water.
11. The method of claim 10, wherein the environment has less than about 1% by weight of water.
12. The method of claim 1, wherein the reaction is performed at a temperature of from about 25 to about 80° C.
13. The method of claim 1, wherein the reaction is performed at a pressure of from about 1 to about 10 atm.
14. The method of claim 1, wherein the salicylamide has the formula



wherein

R¹, R², R³, and R⁴ are independently hydrogen, —OH, —O—R⁵, substituted or unsubstituted alkyl, substituted or unsubstituted alkenyl, substituted or unsubstituted alkoxy, substituted or unsubstituted aryl, carboxy,