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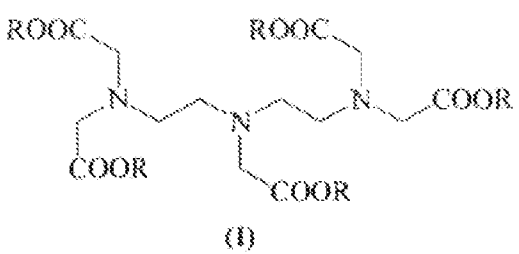
(54) **Title**: LARGE-SCALE HIGH YIELD MANUFACTURING PROCESS FOR HIGH PURITY PENTAALKYL ESTERS OF DTPA

(57) **Abstract**: A process is provided for the preparation of pentaalkyl esters of diethylenetriaminepentaacetic acid and pentaethyl ester of diethylenetriaminepentaacetic acid.

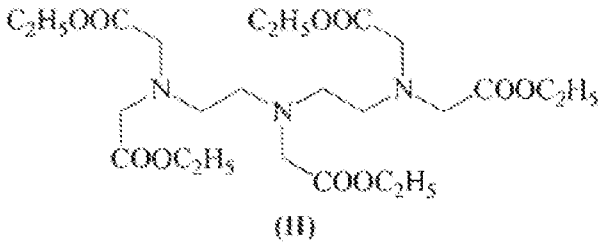
LARGE-SCALE, HIGH YIELD MANUFACTURING PROCESS FOR HIGH PURITY PENTAALKYL ESTERS OF DTPA

FIELD OF THE INVENTION

[0001] The present invention relates to the development of a large-scale manufacturing process applicable to the preparation of pentaalkyl esters of diethylenetriaminepentaacetic acid (hereinafter referred to as DTPA) of formula (I), and more particularly the pentaethyl ester of diethylenetriaminepentaacetic acid (hereinafter referred to as C2E5) of formula (II).



(I)



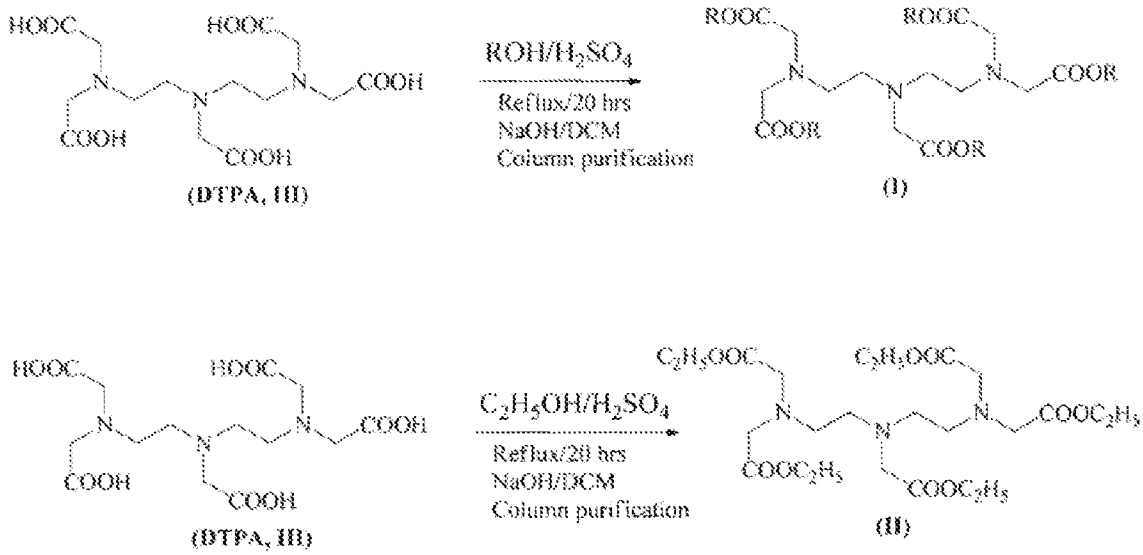
(II)

BACKGROUND OF THE INVENTION

[0002] DTPA of formula (III) is a ligand widely used for the clathration of metal ions (Wenzel, T. J., Bogyo, M.S. and Lebeau, E. L.; J. Am. Chern. Soc.; 1994; 116; 4858). The calcium and zinc salts of DTPA are both approved by the Food and Drug Administration for the removal (decorporation) of transuranic radionuclides such as Plutonium, Americium and Curium from the body of humans following contamination by these highly toxic elements. However, DTPA is a highly polar compound and therefore must be administered intravenously in order to enter the bloodstream and remove the contaminating radionuclides, which are eliminated in the urine and feces following chelation by DTPA. Given the increasing possibility of a mass contamination event (such as the terroristic detonation of a "dirty bomb" or the contamination of a municipal water supply with these radioactive elements), the United States government has been seeking a means to treat large numbers of poisoned individuals with this decorporation agent. Such a scenario would require a form of the drug that could easily be distributed to large numbers of individuals and could be taken orally and facilitate efficient absorption of the compound into the blood stream from the gastrointestinal tract. The compound, pentaethyl ester of diethylenetriaminepentaacetic acid

(C2E5) of formula (II) was reported as a useful ligand for the decorporation of radioactive compounds following oral administration to mammals (US Patent No. 8,030,358).

[0003] Several methods for the synthetic preparation of pentaalkyl esters of diethylenetriaminepentaacetic acid of formula (I), or the pentaethyl ester of diethylenetriaminepentaacetic acid (C2E5) of formula (II) have already been described and/or patented (US Patent No. 8,030,358 to Jay et al.; US Patent No. 5,780,670 to Yamamato, et al.; Nemoto, et al.; 1995 International Chemical Congress of Pacific Basin Societies; December 17-22, 1995), but all of these methods have been applied to very small (mg to gm) quantities and all incorporate the use of silica gel chromatography to obtain the final product in a pure form. They also are performed in dichloromethane, which is a hazardous chlorinated solvent and they further teach the final wash with sodium hydroxide which partially hydrolyzes the fully esterified product, hence reducing the yield and the purity of the product. An example of the currently used process is given below as detailed in US Patent No. 5,780,670 referenced above.



Scheme 1

[0004] Though this process is satisfactory for the preparation of very small quantities of the various esters, it cannot be scaled up to any significant quantities and also presents the following additional disadvantages.

[0005] 1) The use and handling of a highly volatile halogenated solvent i.e., dichloromethane (DCM) to extract the final product. Dichloromethane vapors are toxic and possibly carcinogenic. It should also be noted that DCM is denser than the aqueous layer and therefore comprises the bottom layer in a reaction vessel. To obtain the product from a bottom layer on a large-scale process is extremely cumbersome and labor-intensive.

[0006] 2) The use of aq. NaOH solution to remove acidic impurities is likely to hydrolyze the ester product resulting in a decrease in the yield and final purity of the product.

[0007] 3) Finally, the purification of the product by column chromatography cannot possibly be performed on a large scale.

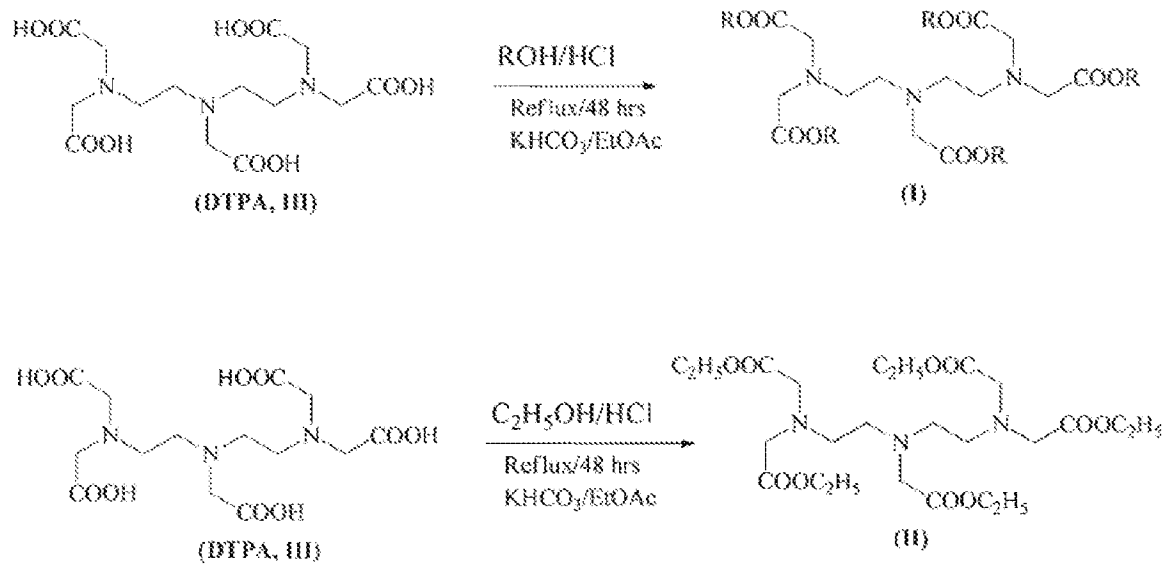
[0008] To overcome the above problems, there exists a need to develop a commercially viable, scalable, operationally simple, safe and eco-friendly process for the synthesis of pentaalkyl esters of diethylenetriaminepentaacetic acid of formula (I), and particularly the pentaethyl ester of diethylenetriaminepentaacetic acid of formula (II).

[0009] The document describes a new commercially viable, safe and industrially suitable process for the preparation of pentaalkyl esters of diethylenetriaminepentaacetic acid of formula (I), and the pentaethyl ester of diethylenetriaminepentaacetic acid of formula (II) by using concentrated hydrochloric acid (Conc. HCl) instead of concentrated sulfuric acid (Conc. H_2SO_4) as an acid for the esterifaction of DTPA of the formula (III). The pentaalkyl or pentaethyl ester product is extracted with ethyl acetate (EtOAc) instead of dichloromethane (DCM), and then washed with aq. Potassium bicarbonate (aq. $KHCO_3$) solution instead of aq. Sodium hydroxide (aq. NaOH) solution to remove acidic impurities. Finally, the organic layer (which forms as the top layer of the reaction mixture is subjected to vacuum distillation at 65-70°C under 20 torr pressure to remove EtOAc and other volatiles to yield the pure product as a pale yellow oil. This process is devoid of the above described disadvantages and avoids the use of column purification to produce the pure product.

DETAILED DESCRIPTION OF THE INVENTION

[0010] The syntheses of pentaalkyl esters of diethylenetriaminepentaacetic acid of formula (I), and the pentaethyl ester of diethylenetriaminepentaacetic acid of formula (II) are

shown in Scheme 2:



Scheme 2

[0011] In one embodiment, an acid used for the esterification of DTPA is selected from both Bronstead acids, but more particularly, Concentrated Hydrochloric acid (Conc. HCl). For purposes of this document, concentrated hydrochloric acid has a molar concentration of greater than about 12M. The alcohol used is not particularly restricted. A lower molecular weight alcohol is preferably used, more particularly methanol, ethanol, propanol, iso-propanol and the like, and most preferably ethanol. The alcohol must be used in excess and there is no need to use other solvents in the esterification reaction.

[0012] In another embodiment, the esterification reaction temperature may preferably be at reflux temperature of the alcohol employed. A preferred reaction time may be from 1 to 48 hours depending on the volume of the reaction being performed.

[0013] In yet another embodiment, after completion of the esterification reaction, the crude product is extracted with a suitable solvent selected from methylacetate, ethyl acetate, propylacetate, benzene, toluene, xylene, diethyl ether, diisopropyl ether, t-butyl methyl ether and other non-halogenated organic solvents, and the like mixtures thereof, but more particularly ethyl acetate (EtOAc).

[0014] In still another embodiment, after completion of the esterification reaction and extraction of the crude product, the resulting organic layer is washed with aq. Alkaline solution selected from aq. Potassium bicarbonate (aq. $KHCO_3$), aq. Potassium carbonate (aq. K_2CO_3), aq. Sodium bicarbonate (aq. $NaHCO_3$), aq. Sodium Carbonate (aq. Na_2CO_3), and other mild inorganic bases, but more particularly aq. Potassium bicarbonate (aq. $KHCO_3$) solution.

[0015] The present embodiments are illustrated with the following examples, which should not be construed as limiting in scope.

Example-1

[0016] Preparation of pentaalkyl esters of diethylenetriaminepentaacetic acid (I): DTPA (20 kg) was added to a mixture of alcohol (500 L) and concentrated hydrochloric acid (32% w/v, 6.8 kg) at 20-25°C. The reaction mixture was slowly heated to reflux temperature of the alcohol and maintained for 48 hours at reflux temperature. The progress of the reaction was monitored on thin layer chromatography (TLC). After completion of the reaction, the reaction mixture is concentrated under vacuum distillation at 60-65 °C to remove ethanol, water, hydrochloric acid, and other volatiles to give a thick glassy oil. The obtained residue was dissolved in ethyl acetate (80 L). The resultant solution was washed 4 times with saturated aq. Potassium bicarbonate solution (saturated aq. $KHCO_3$, 10 lit x 4) to remove un-reacted DTPA and other process related acidic substances. The organic layer was concentrated by distillation at 20 torr pressure at 65-70°C to remove ethyl acetate and other volatile compounds to afford pentaalkyl esters of diethylenetriaminepentaacetic acid. The products are cooled to 40-60°C and filtered to give pure pentaalkyl esters of diethylenetriaminepentaacetic acid (20-25 Kg).

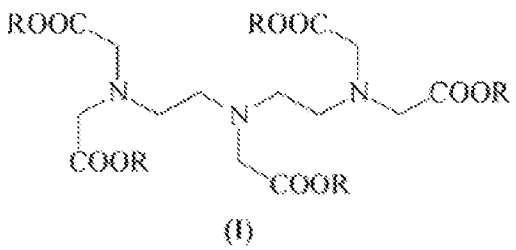
Example-2

[0017] Preparation of pentaethyl ester of diethylenetriaminepentaacetic acid (II): DTPA (20 Kg) was added to a mixture of ethanol (500 L) and concentrated hydrochloric acid (32% w/v, 6.8 kg) at 20-25°C. The reaction mixture was slowly heated to 76°C and maintained for 48 hours at 76-78°C. The progress of the reaction was monitored using thin layer chromatography (TLC). After completion of the reaction, the reaction mixture was

concentrated under vacuum distillation at 60-65°C to remove ethanol, water, hydrochloric acid, and other volatile components to give a thick glassy oil. The residue was dissolved in ethyl acetate (80 L). The resulting solution was washed 4 times with saturated aq. Potassium bicarbonate solution (saturated aq. $KHCO_3$, 10 lit x 4) to remove unreacted DTPA and other process related acidic substances. The organic layer was concentrated by distillation at 20 torr pressure and 65-70°C to remove ethyl acetate and other volatiles to yield the pentaethyl ester of diethylenetriaminepentaacetic acid (C2E5) as a pale yellow oil. The product was cooled to 40-60°C and filtered to give highly pure pentaethyl ester of diethylenetriaminepentaacetic acid (C2E5) as a pale yellow oil at a high yield (20 Kg).

WHAT IS CLAIMED:

1. A process of preparation of pentaalkyl ester of diethylenetriaminepentaacetic acid of formula (1), and pentaethyl ester of diethylenetriaminepentaacetic acid of formula (II)



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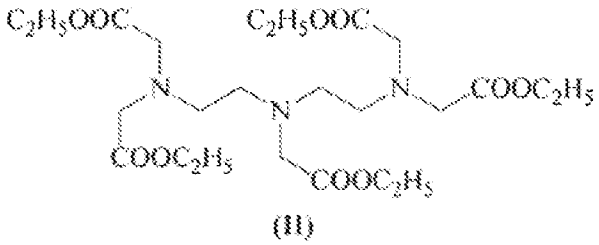
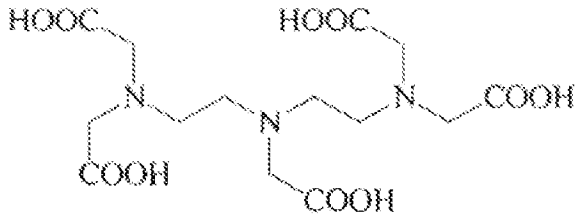


(II)

comprising steps of:

(i) esterifying diethylenetriaminepentaacetic acid (DTPA, III):



(DTPA, III)

with a an alcohol in the presence of a Bronstead acid, at a reflux temperature of said alcohol to give crude pentaalkyl esters of DTPA;

(ii) extracting said crude pentaalkylesters of DTPA with a solvent selected from a group consisting of methyl acetate, ethyl acetate, propyl acetate, benzene, toluene, xylene, diethyl ether, diisopropyl ether, t-butyl methyl ether, other non-halogenated organic solvents, and mixtures thereof and recovering a resulting organic layer;

(iii) washing said resulting organic layer with aq. alkaline solution to remove un-reacted DTPA and other process related acidic substances;

(iv) concentrating and filtering the resulting organic layer to obtain said pentaalkyl ester of diethylenetriaminepentaacetic acid of formula (I), or pentaethyl ester of diethylenetriaminepentaacetic acid of formula (II).

2. The process of claim 1 wherein said Bronstead acid is concentrated hydrochloric acid having a molar concentration of greater than about 12M.

3. The process of claim 1, wherein said alcohol is a low molecular weight alcohol selected from a group consisting of methanol, ethanol, propanol, isopropanol and mixtures thereof.

4. The process of claim 1, wherein said alcohol is ethanol.

5. The process of claim 1, wherein said alkaline solution is selected from a group consisting of aqueous potassium bicarbonate ($KHCO_3$), aqueous potassium carbonate (K_2CO_3), aqueous sodium bicarbonate ($NaHCO_3$), aqueous sodium carbonate (Na_2CO_3) and mixtures thereof.

6. The process of claim 1, wherein said alkaline solution is aqueous potassium bicarbonate ($KHCO_3$).

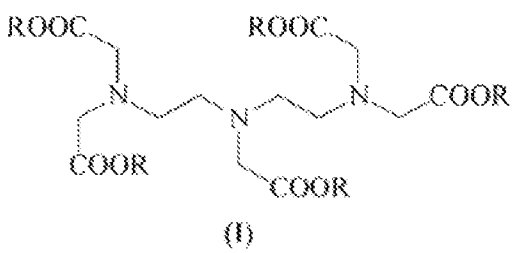
7. The process of claim 1, wherein said solvent is selected from a group consisting of methyl acetate, ethyl acetate, propyl acetate, benzene, toluene, xylene, diethyl ether, diisopropyl ether, t-butyl methyl ether, a non-hydrogenated organic solvent and mixtures thereof.

8. The process of claim 1, wherein said solvent is ethyl acetate.

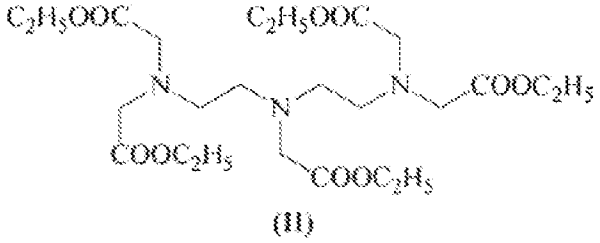
9. The process of claim 1, wherein said alcohol is ethanol, said Bronstead acid is hydrochloric acid, said solvent is ethyl acetate and said alkaline solution is aqueous potassium bicarbonate ($KHCO_3$).

10. The process of claim 1 wherein said concentrating is completed under vacuum distillation.

11. A process of preparation of pentaalkyl ester of diethylenetriaminepentaacetic acid of formula (I) and pentaethyl ester of diethylenetriaminepentaacetic acid of formula (II);



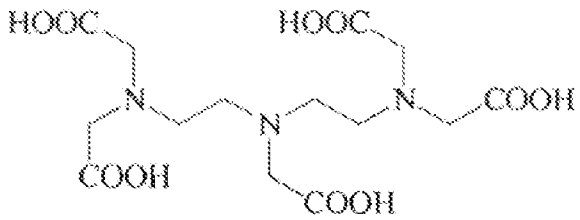
(I)



(II)

comprising steps of:

(i) esterifying diethylenetriaminepentaacetic acid (DTPA, III) to give crude pentaalkyl esters of DTPA;



(ii) extracting said crude pentaalkyl esters of DTPA with a non-halogenated organic solvent and recovering a resulting organic layer;

(iii) washing said resulting organic layer with an alkaline solution;

(iv) concentrating said resulting organic layer after washing followed by filtration to obtain said pentaalkyl ester of diethylenetriaminepentaacetic acid of formula (I) and pentaethyl ester of diethylenetriaminepentaacetic acid of formula (II).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 12/40347

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A01N 33/02 (2012.01)
USPC - 514/663
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)
USPC - 514/663

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 514/663,673,674 (text search - see terms below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PubWEST (USPT, PGPB, EPAB, JPAB, DWPI) and Google Patent/Scholar
Search terms: DTPA, C2E5, diethylenetriaminepentaacetic acid; pentaalkyl, pentaethyl, pentaester; ethyl acetate, etoac

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 8,030,358 B2 (Jay et al) 04 October 2011 (04.10.2011) col 8, ln 1-10; col 11, ln 1-25	1-11
Y	US 7,279,149 B2 (Poduslo et al) 09 October 2007 (09.10.2007) col 5, ln 30-67	1-11
Y	5,780,670 A (Yamamoto et al.) 14 July 1998 (14.07.1998) especially abstract; col 2-4	1-11
A	US 4,831,175 A (Gansow et al.) 16 May 1989 (16.05.1989) entire document especially	1-11

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 August 2012 (06.08.2012)	21 AUG 2012
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-3201	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774