Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2401588 A1 2001/11/22

(21) 2 401 588

(12) DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION

(13) A1

(86) Date de dépôt PCT/PCT Filing Date: 2001/05/03
(87) Date publication PCT/PCT Publication Date: 2001/11/22
(85) Entrée phase nationale/National Entry: 2002/08/27
(86) N° demande PCT/PCT Application No.: EP 2001/004963
(87) N° publication PCT/PCT Publication No.: 2001/087818
(30) Priorité/Priority: 2000/05/16 (100 23 955.2) DE

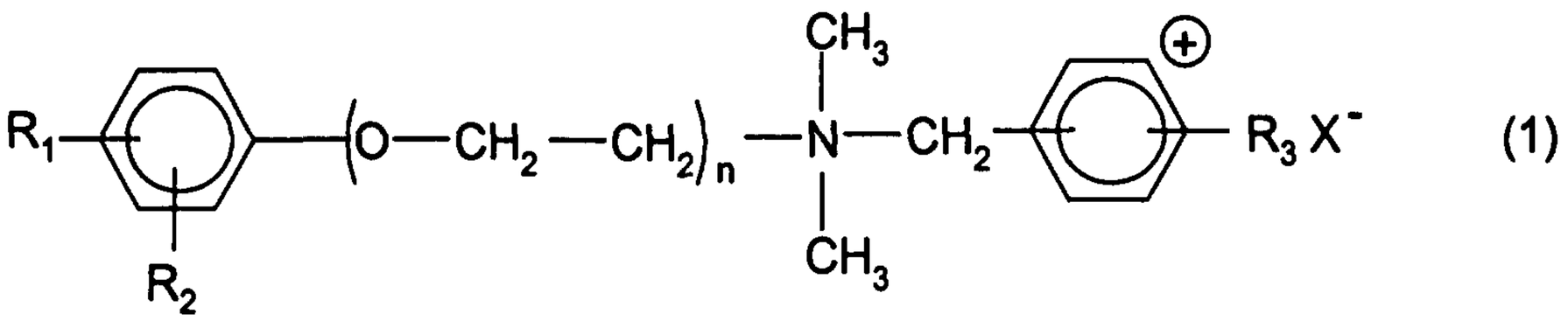
(51) Cl.Int.^{7}/Int.Cl.^{7} C07C 213/00, C07C 217/64

(71) Demandeur/Applicant:
CLARIANT GMBH, DE

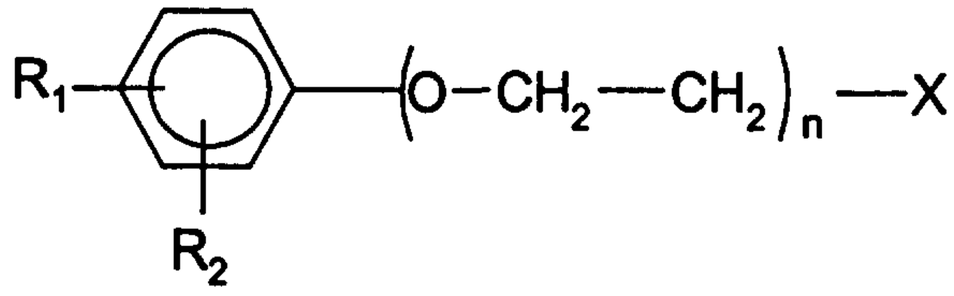
(72) Inventeurs/Inventors:
RAAB, KLAUS, DE;
CRASS, GERHARD, DE;
AIGNER, RUDOLF, DE

(74) Agent: FETHERSTONHAUGH & CO.

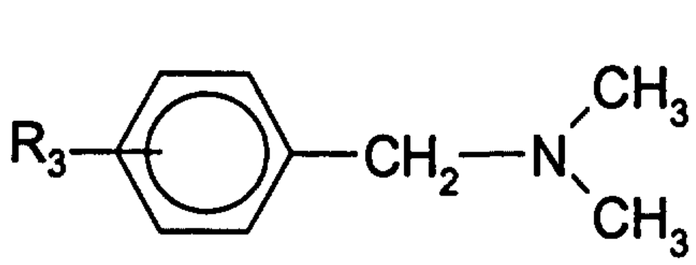
(54) Titre : PROCEDE DE FABRICATION DE DERIVES D'ARYLPOLY(OXALKYLE)-BENZYLDIMETHYLAMMONIUM
(54) Title: METHOD FOR PRODUCING ARYLPOLY(OXALKYL)-BENZYLDIMETHYL-AMMONIUM DERIVATIVES



(1)



(2)



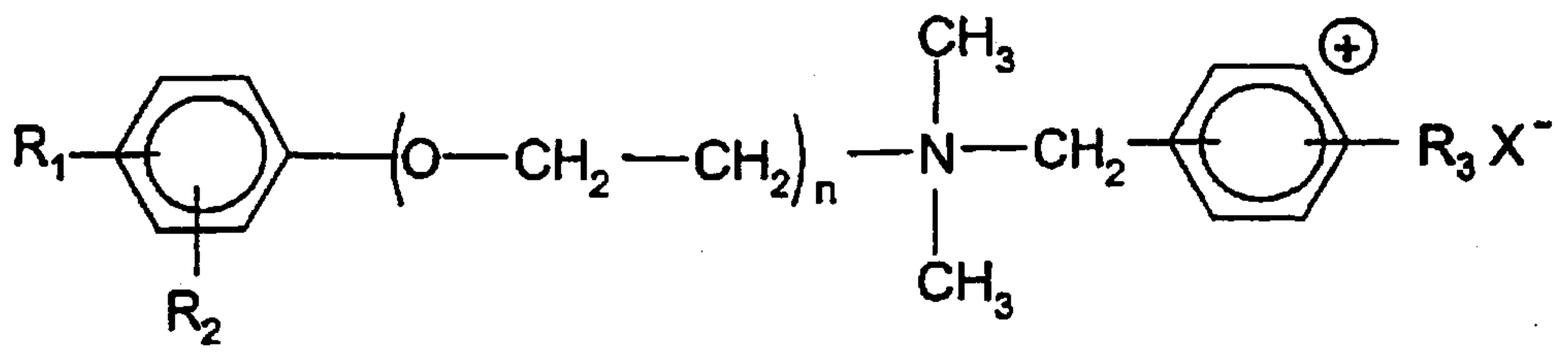
(3)

(57) Abrégé/Abstract:
The invention relates to a method for producing arylpoly(oxalkyl)-benzyldimethyl-ammonium derivatives of formula (1) by conversion of compounds of formulas (2) and (3), wherein X= Br, Cl, S-SO_3 with R = alkyl, alkylaryl; R_1 = H, C_1-to C_{16}-alkyl or O-C_1 to O-C_{16}-alkyl in ortho-, meta- or para-position; R_2 = H, C_1- to C_4-alkyl or O-C_1- to O-C_4-alkyl; R_3 = H, C_1- to C_{16}-alkyl or O-C_1- to O-C_{16}-alkyl in ortho-, meta- or para-position, and n = 1, 2, 3 or 4, at temperatures between 60 and 160 °C, in a solvent under the pressure produced in a closed reaction container.

Abstract

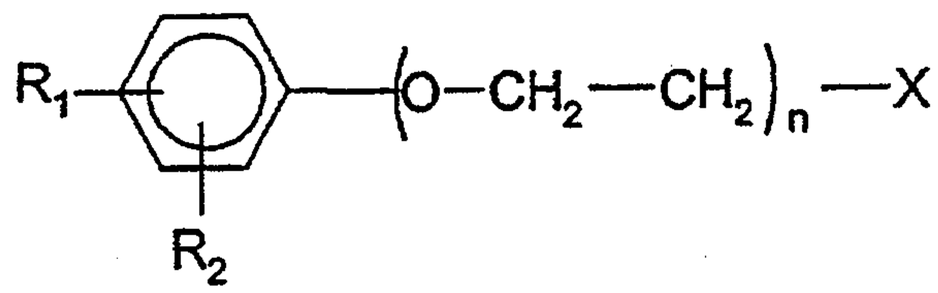
Preparation of arylpoly(oxalkyl)benzyldimethylammonium derivatives

The invention provides a process for preparing arylpoly(oxalkyl)benzyldimethylammonium derivatives of the formula (1)

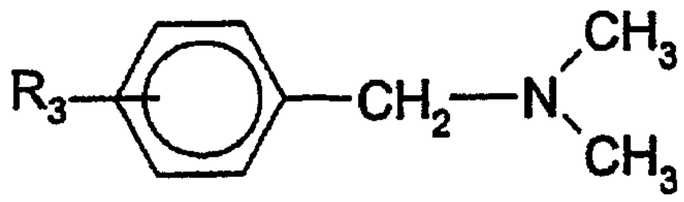


(1)

which comprises reacting compounds of the formulae (2) and (3)



(2)



(3)

where

X = Br, Cl, R-SO_3 with R = alkyl, alkylaryl

R_1 = H, C_1- to C_{16}-alkyl or O-C_1- to O-C_{16}-alkyl in the ortho, meta or para position,

R_2 = H, C_1- to C_4-alkyl or O-C_1- to O-C_4-alkyl,

R_3 = H, C_1- to C_{16}-alkyl or O-C_1- to O-C_{16}-alkyl in the ortho, meta or para position, and

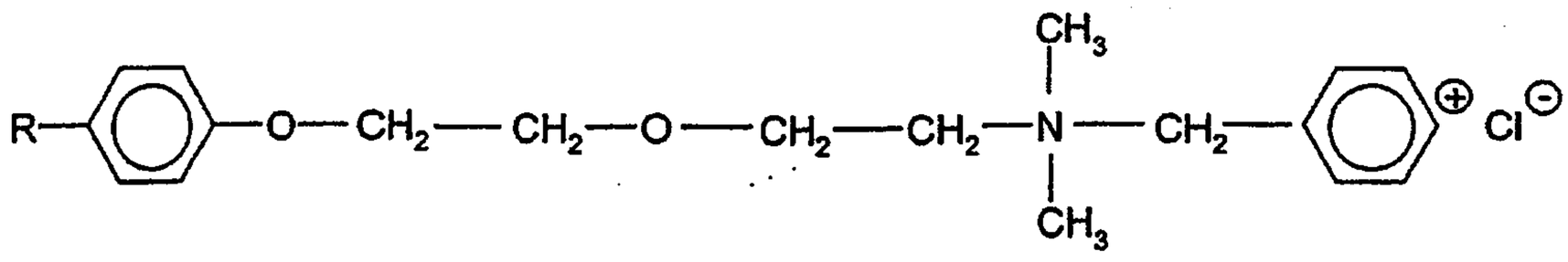
n = 1, 2, 3 or 4,

at temperatures of from 60 to 160°C in a solvent under the autogenous pressure in the closed reaction vessel.

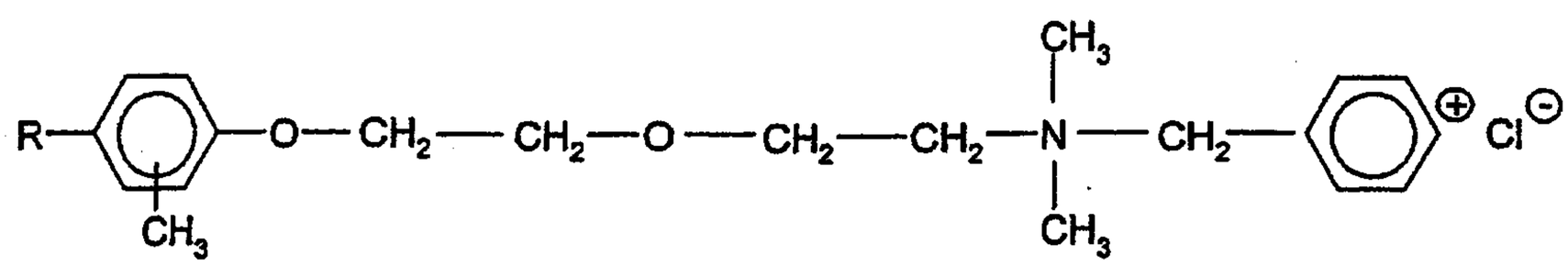
Preparation of arylpoly(oxalkyl)benzyldimethylammonium derivatives

The present invention relates to a novel process for preparing arylpoly-(oxalkyl)benzyldimethylammonium derivatives by reaction of arylpoly-(oxalkyl) compounds with benzyldimethylamine or substituted benzyl-dimethylamines in a suitable solvent.

Some representatives of the compound class of arylpoly(oxalkyl)benzyl-dimethylammonium halides such as benzethonium chloride



or methylbenzethonium chloride



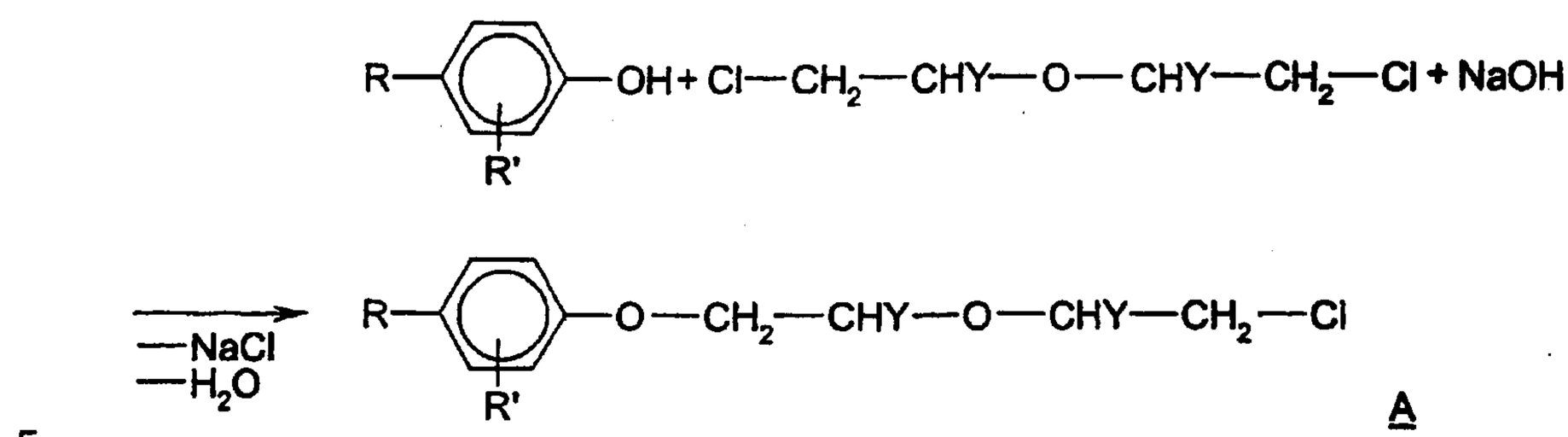
where
R = $(CH_3)_3C\text{-}CH_2\text{-}C(CH_3)_2$-

have long been used commercially as biocides. These are crystalline powders whose purity requirements are described in various pharmacopeias. Solutions of these crystalline powders are also used. These compounds have bactericidal and fungicidal activity. Their areas of application as active components of formulations are, for example, disinfection in the hospitals sector, in the pharmaceutical sector or in the veterinary and foods sector. They are also used as preservatives for cosmetics such as hair conditioners, cleansing lotions or shampoos, in particular in rinse-off products, and also as odor control agents.

According to Workbook for Organic Synthesis: The Disconnection Approach, Stuart Warren, John Wiley & Sons, 1982, on pages 49 to 51 the preparation of such compounds where Y = H and R' = H according to the

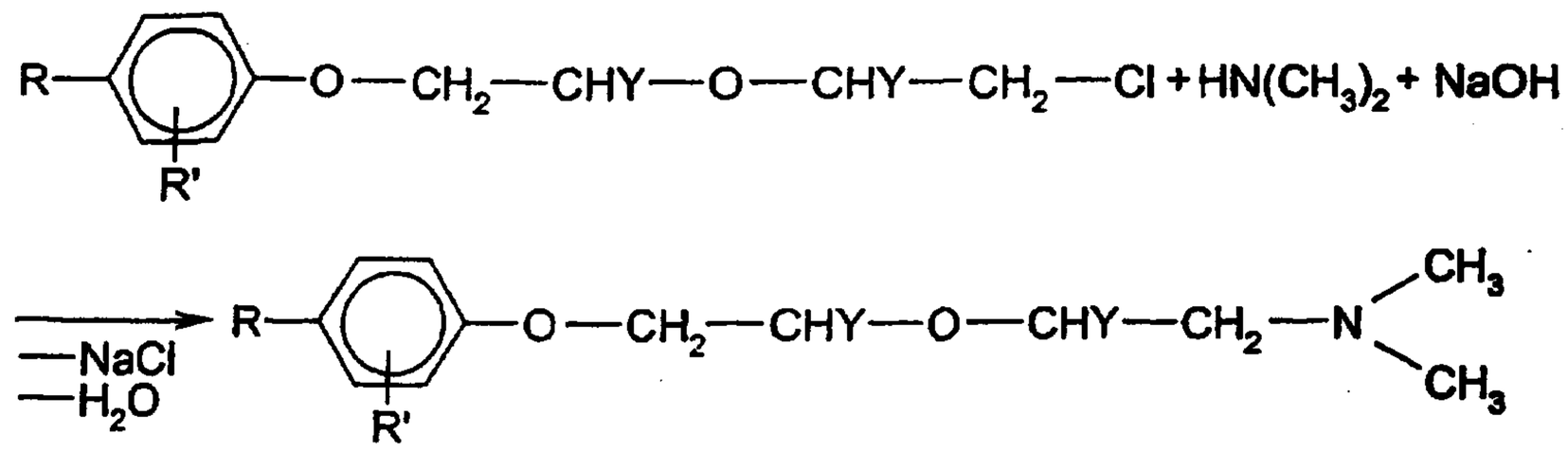
prior art is as shown in the equations 1 to 3.

Equation 1:



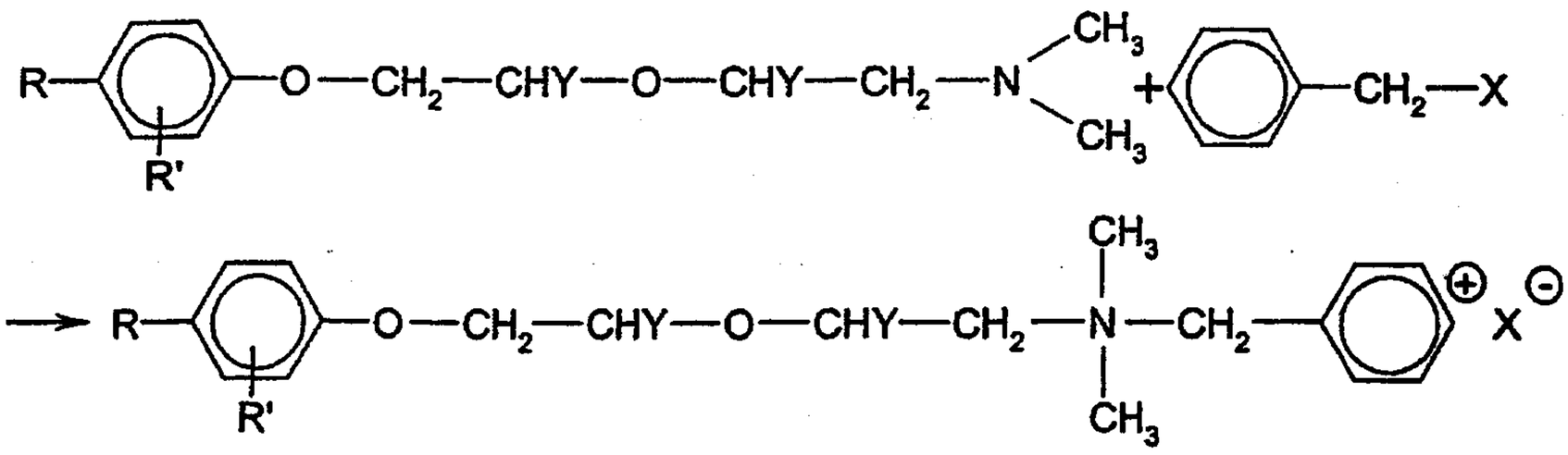
A

Equation 2:



B

Equation 3:



C

where

R is alkyl

R' is H, alkyl

Y is H, CH_3 or alkyl

X is Cl, Br.

US-2 098 203 discloses arylpoly(oxalkyl) chlorides of the formula A where Y = H or C_1- to C_5-alkyl, R = C_8- to C_{18}-alkyl and R' = H, alkyl or alkoxy. Compounds of this type are the starting materials of the process of the invention.

US-2 170 111 discloses tertiary amines of the formula B and further tertiary amines of similar structure to B. Their preparation takes place in a similar fashion to equation 2 by reaction of arylpoly(oxalkyl) chlorides of the formula A with amines such as dimethylamine, diethylamine, diethanolamine or morpholine, basic workup, washing and subsequent vacuum distillation.

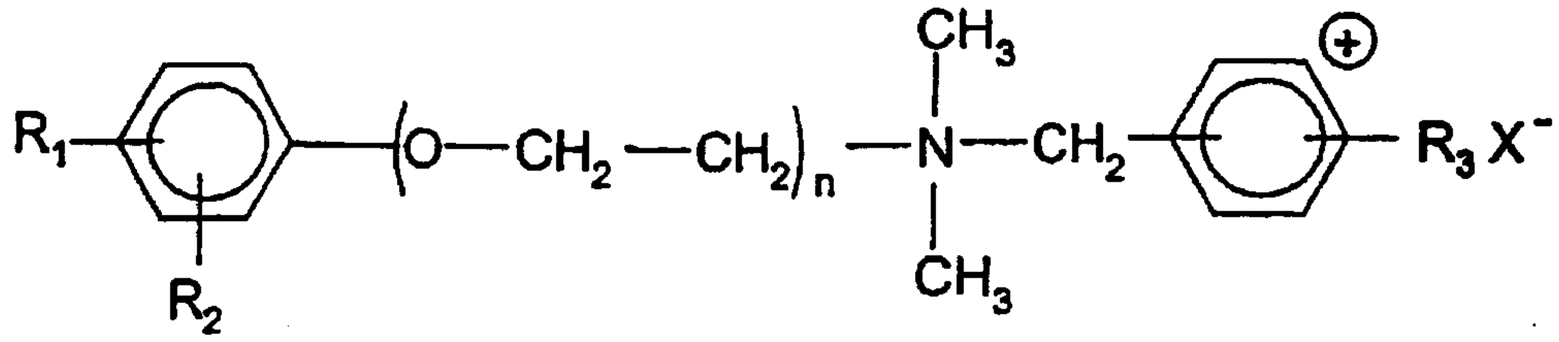
Arylpoly(oxalkyl)benzyldimethylammonium chlorides of the formula C and also similarly substituted quaternary ammonium cations with further anions are disclosed in US-2 115 250. They are obtained by reaction of the tertiary amines of the formula B or tertiary amines with a similar structure to B with alkylating agents such as benzyl chloride, dimethyl sulfate, diethyl sulfate, dimethyl oxalate, methyl iodide or ethyl bromide in a similar fashion to equation 3.

In Journal of the American College of Toxicology, Volume 4, Number 5, 1985 on page 66, the reaction of the required tertiary amines with benzyl chloride at 60 to 80°C is likewise given as a route to benzethonium chloride and methylbenzethonium chloride.

In view of the complexity of this multistep reaction sequence including the necessary workup steps, and in view of the undesirable stoichiometric precipitation of sodium chloride or similar salts, it is an object of the present invention is to provide a simplified preparative process for arylpoly(oxalkyl)benzyldimethylammonium derivatives, in particular for benzethonium chloride or methylbenzethonium chloride.

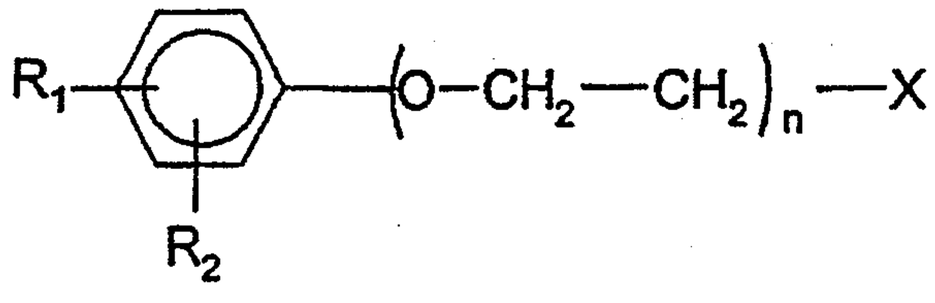
This object is surprisingly achieved by a process involving the reaction of arylpoly(oxalkyl) compounds of the formula (2) with benzyldimethylamine or substituted benzyldimethylamines of the formula (3) in a suitable solvent to give the arylpoly(oxalkyl)benzyldimethylammonium derivatives of the formula (1).

The invention therefore provides a process for preparing arylpoly-(oxalkyl)benzyldimethylammonium derivatives of the formula (1)

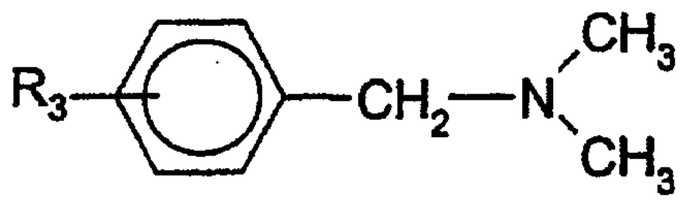


(1)

which comprises reacting compounds of the formulae (2) and (3)



(2)



(3)

where

X = Br, Cl, R-SO_3 with R = alkyl, alkylaryl

R_1 = H, C_1- to C_{16}-alkyl or O-C_1- to O-C_{16}-alkyl in the ortho, meta or para position,

R_2 = H, C_1- to C_4-alkyl or O-C_1- to O-C_4-alkyl,

R_3 = H, C_1- to C_{16}-alkyl or O-C_1- to O-C_{16}-alkyl in the ortho, meta or para position, and

n = 1, 2, 3 or 4,

at temperatures of from 60 to 160°C in a solvent under the autogenous pressure in the closed reaction vessel.

R_1 is preferably C_4- to C_{12}-alkyl, in particular octyl or isooctyl in the para position. R_2 is preferably H or CH_3. n is preferably 2. R_3 is preferably H. X is preferably Cl.

When $R_1 = (CH_3)_3C\text{-}CH_2\text{-}C(CH_3)_2$ in the para position, $R_2 = H$, $n = 2$, $R_3 = H$, $X = Cl$, benzethonium chloride is obtained, and when $R_1 = (CH_3)_3C\text{-}CH_2\text{-}C(CH_3)_2$ in the para position, $R_2 = CH_3$, $n = 2$, $R_3 = H$, $X = Cl$, methylbenzethonium chloride is obtained. The processes for preparing these compounds constitute preferred embodiments of the invention.

Useful solvents for the process of the invention are preferably polar solvents, such as short-chain alcohols having from 1 to 6, preferably from 1 to 4 carbon atoms, which may be mono- or polyhydric, for example methanol, ethanol, isopropanol or monoethylene glycol, their mixtures with water and in particular water itself.

The arylpoly(oxalkyl) compounds of the formula (2) and the benzyldimethylamine or the substituted benzyldimethylamines of the formula (3) are preferably used in a molar ratio (2):(3) = 1:0.95 to 1:1.05. The reaction is carried out at temperatures in the range from preferably 100 to 140°C, in particular from 115 to 130°C, under the autogenous pressure of the reaction mixture. The reaction times are preferably chosen so that the concentrations of the starting compounds of the formulae (2) and (3) determined by HPLC analysis of samples taken are as low as possible.

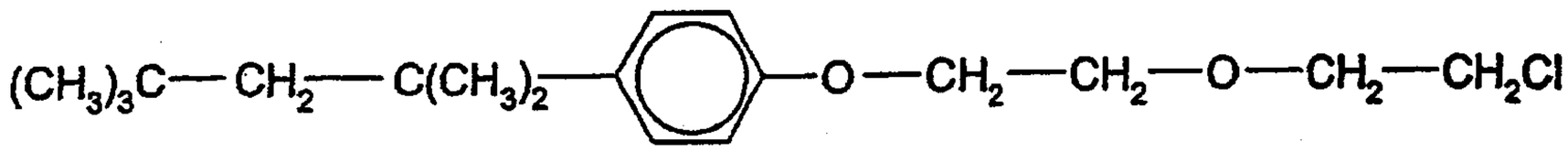
The arylpoly(oxalkyl)benzyldimethylammonium derivative of the formula (1) obtained from the reaction can be purified by recrystallization, for example from chloroform, ether, toluene or xylene. The solvent is preferably removed before recrystallization.

When water is used as the particularly preferred solvent in the reaction, the water can be removed for the purposes of workup after the end of the reaction, for example, by azeotropic distillation, vacuum drying, spray drying or fluidized-bed drying. The crude, water-free arylpoly(oxalkyl)-benzyldimethylammonium derivative of the formula (1) can be purified by recrystallization, for example from chloroform, ether, toluene or xylene.

The examples which follow illustrate the invention.

Example 1

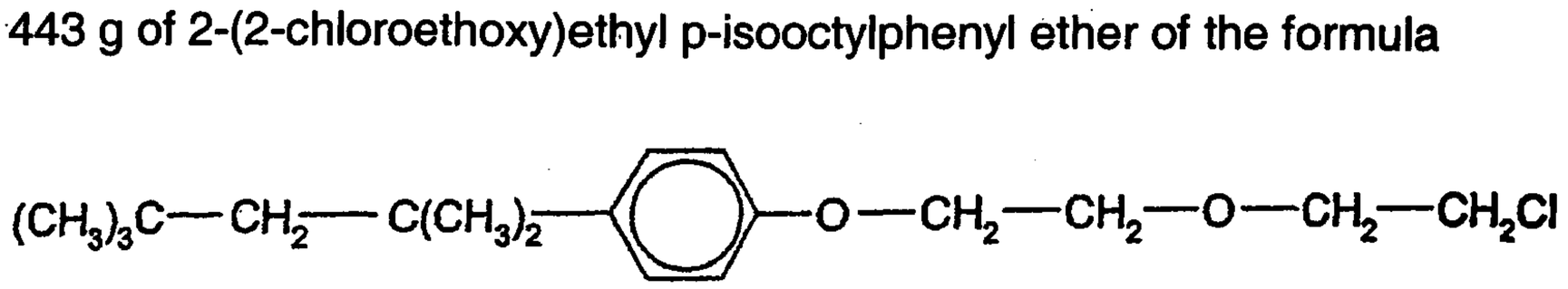
1 396 g of 2-(2-chloroethoxy)ethyl p-isooctylphenyl ether of the formula



603 g of benzyldimethylamine and 1 000 g of demineralized water are stirred in a 5 liter autoclave under a nitrogen atmosphere for 20 hours at 120°C and a pressure of 1.5 to 2.0 bar. The initially biphasic reaction mixture becomes monophasic in the course of the reaction. After depressurizing and cooling to about 80°C, the reaction mixture is transferred to a 10 liter stirred glass flask and admixed with 3 000 g of toluene. The water together with toluene is azeotropically distilled off with stirring. The colorless distillate separates into a toluene-containing upper phase, which is returned to the 10 liter stirred glass flask, and an aqueous lower phase, which is separated off. The yellow, clear water-free toluene solution is hot-filtered at about 110°C through a heated pressure filter. The hot filtrate is slowly cooled to 30°C under a nitrogen atmosphere and with slow stirring and addition of seed crystals. The resulting crystal slurry is filtered with suction and the crystals filtered off are washed repeatedly with toluene. The fine white crystals after they have been filtered off are dried at 80°C under reduced pressure. The yield after drying is 70%. The product has a melting point of 162°C and the purity determined by alkaline biphasic titration is above 99%.

Example 2

443 g of 2-(2-chloroethoxy)ethyl p-isooctylphenyl ether of the formula



192 g of benzyldimethylamine and 320 g of distilled water are stirred in an autoclave under a nitrogen atmosphere for 15 hours at 120 to 125°C and a pressure of 1.5 to 2.0 bar. The initially biphasic reaction mixture becomes monophasic in the course of the reaction. The autoclave is depressurized

and the warm reaction mixture freed of water by feeding into a dryer at about 80°C under reduced pressure. The now solid, water-free crude product is recrystallized from 950 g of toluene, washed repeatedly with toluene and dried at 80°C under reduced pressure. The yield of fine white crystals is 72% and the purity determined by HPLC is ≥ 98%.

Examples 3 to 11

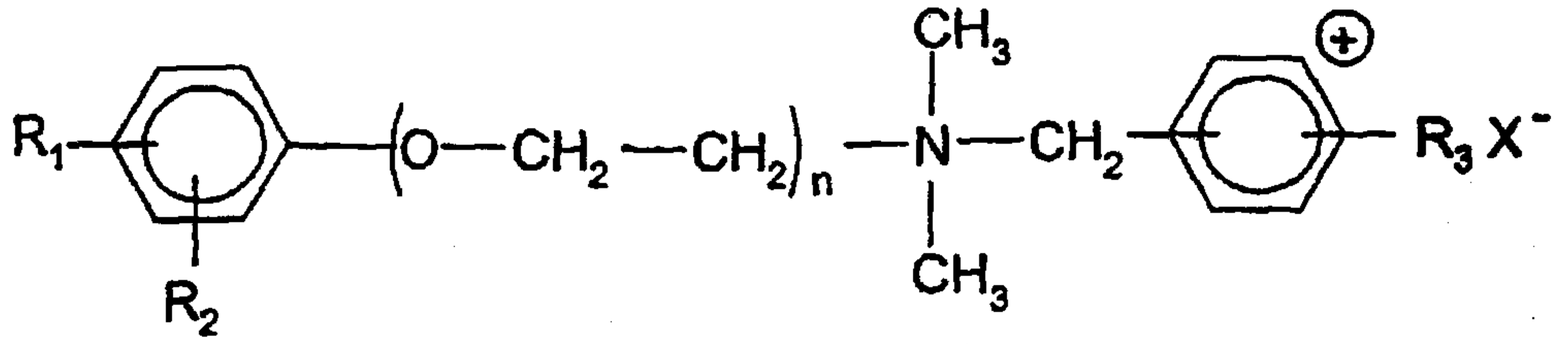
87.3 g of 2-(2-chloroethoxy)ethyl p-isooctylphenyl ether (a), 37.7 g of benzyldimethylamine and solvent (see table for quantity and type) are stirred in an autoclave under a nitrogen atmosphere at the autogenous pressure. The reaction conditions are listed in the table. Samples are taken of each crude product and analyzed by HPLC.

Example	Quantity and solvent	Reaction tempera-ture [°C]	Reaction time [h]	Yield of unisolated product by HPLC [%]	Yield of (a) by HPLC [%]
3	125 g water	135	4	70	89
4	125 g water	135	7	72	95
5	125 g water	115	7	56	63
6	125 g water	115	23	80	95
7	250 g water	120	7	66	75
8	250 g water	120	20	75	97
9	375 g water	120	20	76	97
10	125 g methanol	120	8	52	72
11	125 g mono-ethylene glycol	120	8	65	86

The workup and purification take place in a similar fashion to example 2 by stripping off the solvent under reduced pressure, subsequent recrystallization from toluene or xylene and vacuum drying of the white crystals filtered off by suction.

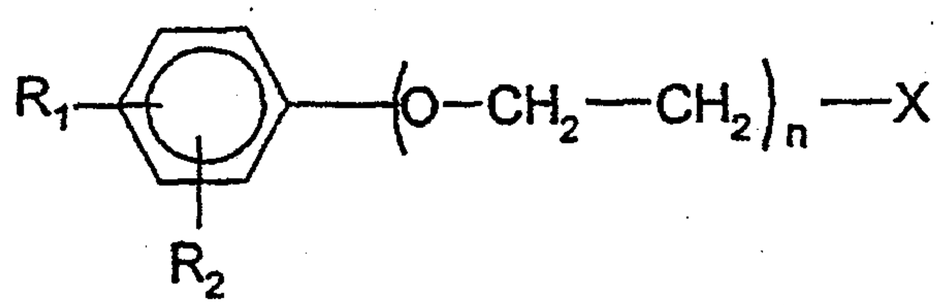
What is claimed is:

1. A process for preparing arylpoly(oxalkyl)benzyldimethylammonium derivatives of the formula (1)

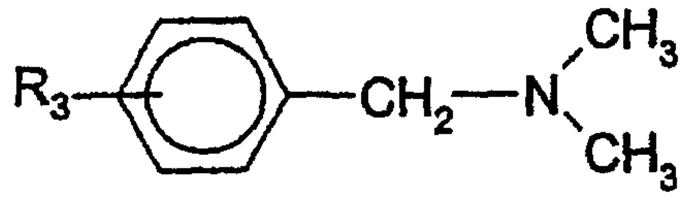


(1)

which comprises reacting compounds of the formulae (2) and (3)



(2)



(3)

where

X = Br, Cl, R-SO_3 with R = alkyl, alkylaryl

R_1 = H, C_1- to C_{16}-alkyl or O-C_1- to O-C_{16}-alkyl in the ortho, meta or para position,

R_2 = H, C_1- to C_4-alkyl or O-C_1- to O-C_4-alkyl,

R_3 = H, C_1- to C_{16}-alkyl or O-C_1- to O-C_{16}-alkyl in the ortho, meta or para position, and

n = 1, 2, 3 or 4,

at temperatures of from 60 to 160°C in a solvent under the autogenous pressure in the closed reaction vessel.

2. The process as claimed in claim 1, wherein the reaction of (2) and (3) is carried out in a polar solvent.

3. The process as claimed in claim 1 and/or 2, wherein the solvent is selected from the group consisting of short-chain alcohols having from 1 to 6 carbon atoms, water and mixtures thereof.

4. The process as claimed in one or more of claims 1 to 3, wherein R_1 is C_4- to C_{12}-alkyl.

5. The process as claimed in one or more of claims 1 to 4, wherein R_1 is octyl or isooctyl in the para position.

6. The process as claimed in one or more of claims 1 to 5, wherein R_2 is H or CH_3.

7. The process as claimed in one or more of claims 1 to 6, wherein n is 2.

8. The process as claimed in one or more of claims 1 to 7, wherein R_3 is H and X is Cl.

9. The process as claimed in one or more of claims 1 to 8, wherein the arylpoly(oxalkyl) compounds of the formula (2) and the benzyldimethylamines of the formula (3) are used in a molar ratio of from 1:0.95 to 1:1.05.

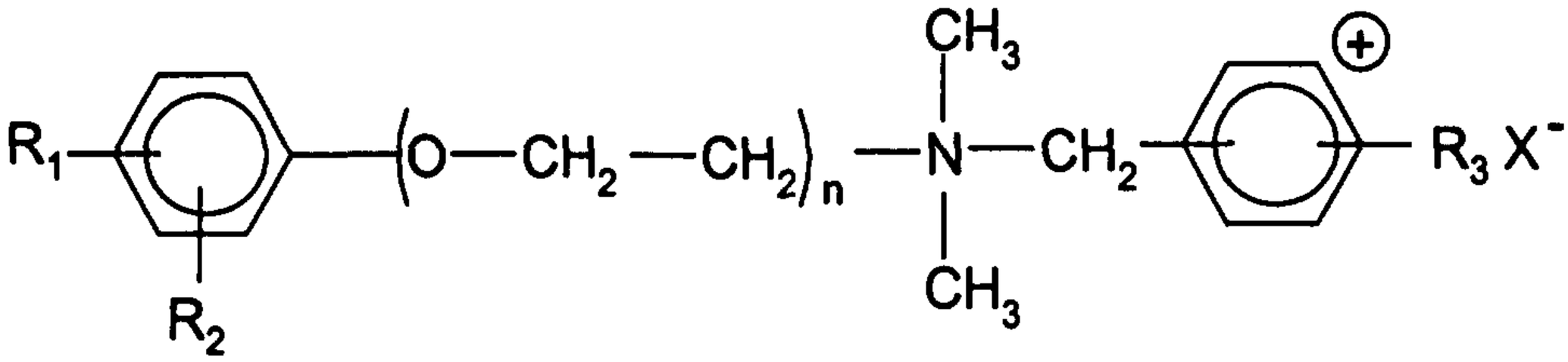
10. The process as claimed in one or more of claims 1 to 9, wherein the reaction of (2) and (3) is carried out at temperatures of from 100 to 140°C, in particular from 115 to 130°C, under the autogenous pressure of the reaction mixture.

11. The process as claimed in one or more of claims 1 to 10, wherein the solvent used in the reaction of (2) and (3) is removed after the reaction and the arylpoly(oxalkyl)benzyldimethylammonium derivative of the formula (1) is purified by recrystallization.

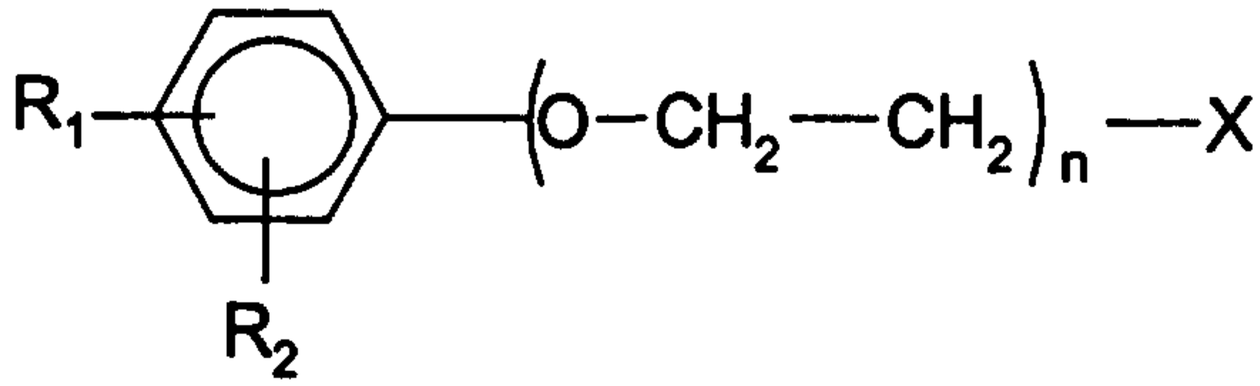
12. The process as claimed in claim 11, wherein water is used as the solvent in the reaction of (2) and (3) and is removed after the reaction, for example, by azeotropic distillation using toluene or xylene, vacuum drying, spray drying or fluidized-bed drying, and the

arylpoly(oxalkyl)benzyldimethylammonium derivative of the formula (1) is purified by recrystallization.

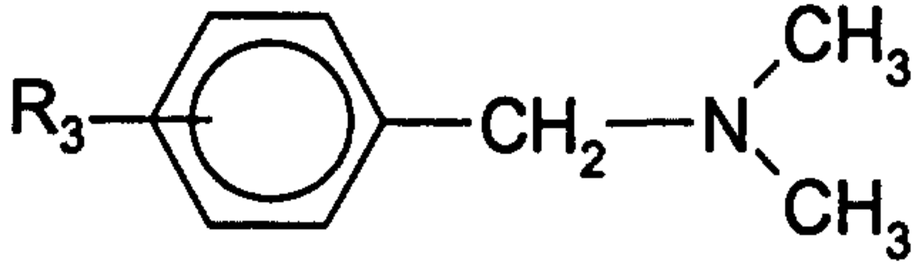
Fetherstonhaugh & Co.
Ottawa, Canada
Patent Agents



(1)



(2)



(3)