

QUATERNARY AMINE COMPOUNDS WITH ISOPROPYLMETHYLPHENOL
ESTER MOIETIES AS ANTIVIRALS, ANTIBACTERIALS AND ANTIMYCOTICS

The present invention relates to compounds that may be used to treat viral infections, bacterial infections and fungal infections.

Background

5 The Herpesviridae is a large family of DNA viruses that are responsible for a number of diseases in both humans and animals. The most common Herpesviridae that cause diseases amongst humans are Varicella Zoster virus, Epstein-Barr virus, Cytomegalovirus, Herpes Simplex virus 1 and Herpes Simplex virus 2.

10 Varicella zoster virus is a common virus that causes chickenpox in children and herpes zoster (shingles) in adults.

Epstein-Barr virus is the virus that commonly causes infectious mononucleosis (glandular fever), while also being associated with cancers such as Hodgkin's lymphoma, Burkitt's Lymphoma and gastric cancer.

15 Cytomegalovirus, is further member of the Herpesviridae viral family. Human cytomegalovirus (HCMV, or CMV or human herpesvirus-5 (HHV-5)) is a virus associated with the salivary glands and is typically unnoticed by healthy individuals, but can be life threatening for immunocompromised, such as patients having HIV, recipients of organ transplants and new born infants.

20 Herpes Simplex Virus 1 and Herpes Simplex Virus 2 are both viruses responsible for the viral disease Herpes Simplex. Both viruses can cause oral infections and genital infections, although HSV-1 is more commonly associated with oral infections (e.g. oral herpes), while HSV-2 is more commonly associated with genital infections (e.g. genital herpes). The Herpes Simplex viruses cause infections that affect between approximately 60% and 95% of adults world wide (Chayavichitsilp P, Buckwalter JV, Krakowski AC, Friedlander SF (April 2009). "Herpes
25 simplex". *Pediatr Rev.* 30 (4)).

Oral herpes is typically associated with the face and/or the mouth and may result in small blisters that form Herpes labialis (cold sores). Oral Herpes can also include other symptoms such as sore throat, fever, muscle pains, swollen lymph nodes, head ache and malaise, particularly in the first episode after the patient becomes infected.

Genital herpes is typically associated with the genitals and may result in small lesions in the genital regions, inner thigh, buttocks and/or anus. Other typical symptoms associated with this virus include pain, itching, burning, discharge, fever, headache, muscle pain, swollen lymph nodes and malaise.

- 5 Oral Herpes may be treated with antiviral drugs, which can reduce the duration of the symptoms, but not completely kill the responsible virus. After the symptoms of an oral herpes infection resolve, the herpes virus (e.g. HSV-1 or HSV-2) generally remains dormant in the facial nerve branches, and the virus may periodically reactivate to create Herpes labialis in the same area of the mouth or face as the site of the original infection. In some humans, the virus
10 remains asymptomatic, although transmission may be possible even when symptoms are not present.

Genital herpes can also be treated with antiviral drugs, which may reduce the duration of the symptoms. However, as for oral herpes, there is no licensed medication that completely eradicates the responsible virus from the human body.

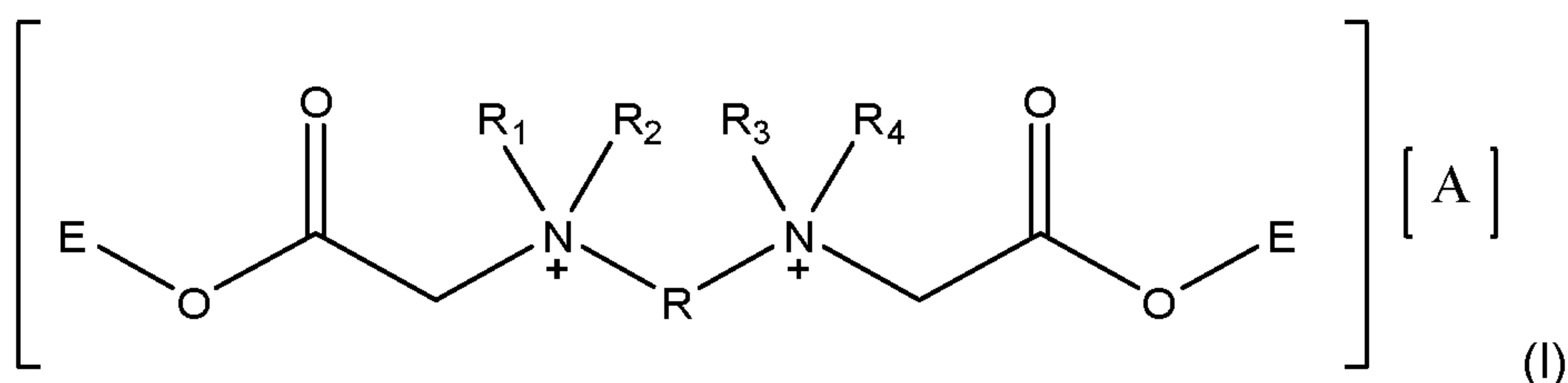
- 15 Human Papilloma virus (HPV) is responsible for Human papillomavirus infection which generally cause no symptoms and resolve spontaneously. However, in some cases infections persist and result in warts or precancerous lesions. The precancerous lesions may increase the risk of a number of cancer types, and these include cancer of the cervix, vagina, penis, anus, mouth and throat (Ljubojevic, Suzana; Skerlev, Mihael (2014). "HPV-associated diseases".
20 Clinics in Dermatology. 32 (2): 227–234.). HPV is the most common sexually transmitted infection globally and most people are infected at some point during their lives (Milner, Danny A. (2015). Diagnostic Pathology: Infectious Diseases. Elsevier Health Sciences. p. 40).

- Bacterial and fungal infections are common throughout the world. Various drugs have been developed to treat such infections and these may target specific or broad types of bacterial and
25 fungal species and strains. Antibiotic resistance, and more recently antifungal resistance, is becoming more prevalent and an ever increasing problem worldwide. With this in mind, there is a global need for new drugs that are able to treat bacterial and fungal infections.

- Bearing in mind the prevalence of the Herpes virus (particularly Herpes Simplex virus) and Human papilloma virus, as well as the range of diseases associated with these viruses, there is
30 a need for a treatment that targets these viruses and can treat the diseases associated with these viruses.

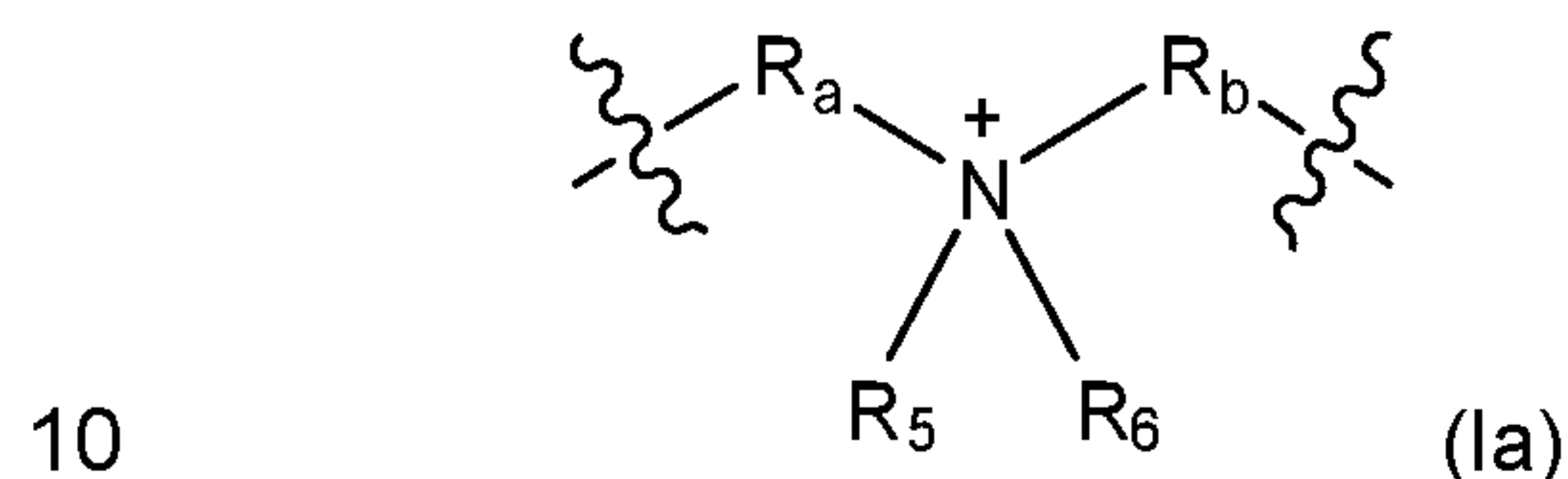
Compounds have been disclosed which have shown anti-bacterial, antifungal and anti-viral effects, examples of such compounds are disclosed in WO2018132066. There is an ongoing need for compounds that have an anti-bacterial, anti-viral and anti-fungal effect.

In a first aspect of the present invention there is provided a compound having the following
5 formula:



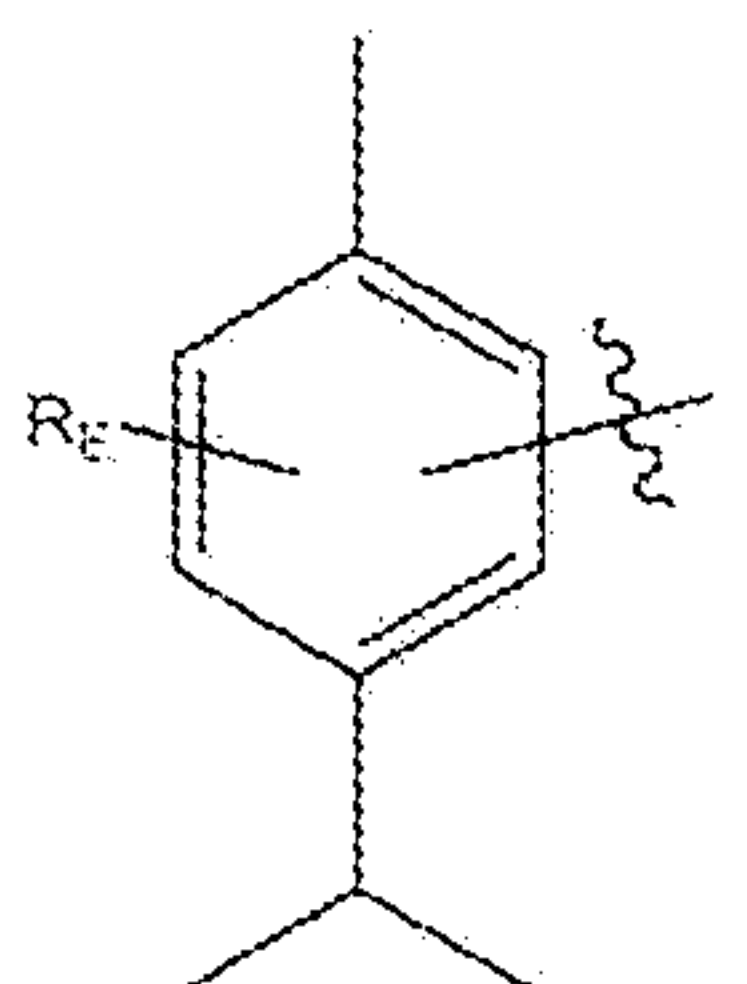
wherein R is an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -2;

or R is a quaternary amine having the following formula:



wherein R_a and R_b are each an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -3;

R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are each independently selected from C_{1-10} alkyl and H; and



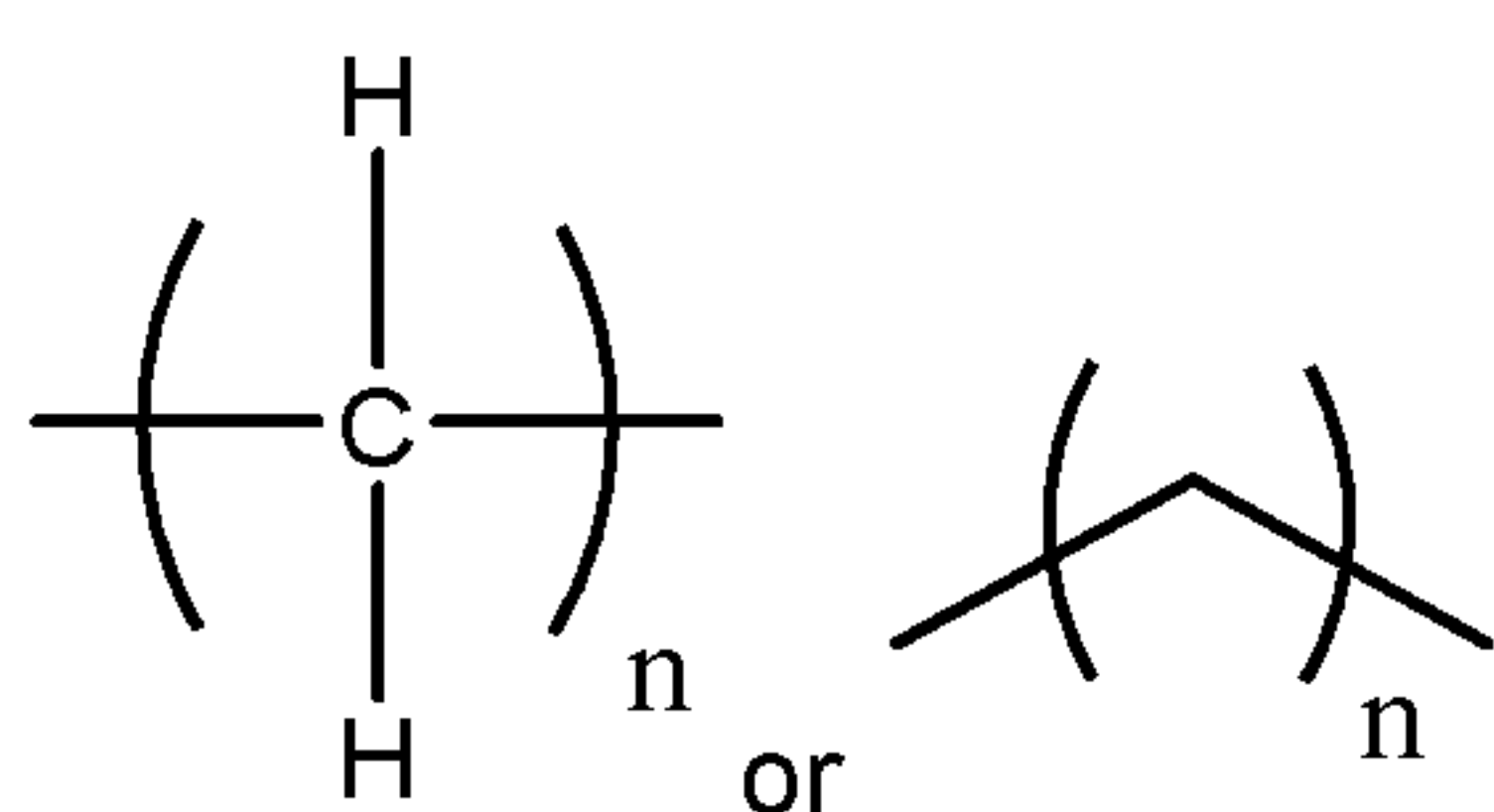
E has the following formula
15 (Ib), wherein the ester oxygen is bonded to the aromatic ring of each E at the same position, the position being position 2 or 3; and wherein R_E is H or a halide.

R may be, for example, a linear or branched saturated or unsaturated alkylene chain having between 8 and 18 carbon atoms, for example 8 and 16 carbon atoms, for example 8 and 14 carbon atoms, for example 9 and 15 carbon atoms, for example 10 carbon atoms. Preferably, R

is a linear saturated alkylene chain having between 8 and 16 carbons, for example 10 carbon atoms. Herein alkylene means an alkane based di-radical, so has two points of attachment to the rest of the molecule.

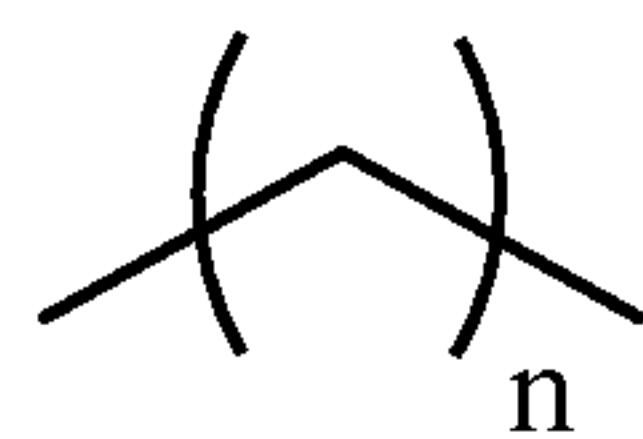
- R may be, for example, a quaternary amine according to formula (Ia), in which R_a and R_b are each a linear or branched saturated or unsaturated alkylene chain having between 8 and 18 carbon atoms, for example 8 and 16 carbon atoms, for example 8 and 14 carbon atoms, for example 9 and 15 carbon atoms, for example 10 carbon atoms. R_a and R_b may each be a linear or branched saturated alkylene chain having a different number of carbon atoms or the same number of carbon atoms.
- Preferably, R_a and R_b are each a linear saturated alkylene chain having between 8 and 16 carbon atoms, for example 10 carbon atoms.

A saturated linear alkylene chain may be represented by the following formula:



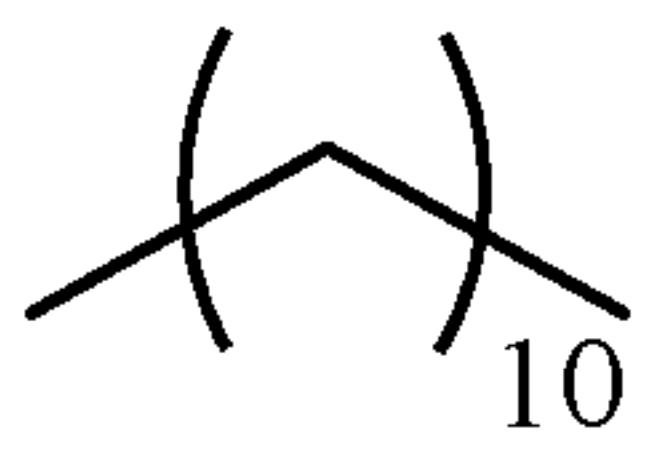
wherein n is the number of repeat units, that is the number of carbon atoms in the linear alkylene chain. Thus, in the case of R being an alkylene chain having

- between 8 and 20 carbon atoms, it is preferred that R is $\left(\text{---} \text{CH}_2 \text{---} \right)_n$ wherein n is between 8 and 16, for example 10. In the case of R being a quaternary amine having the formula (Ia) as



set out above, it is preferred that R_a and R_b is $\left(\text{---} \text{CH}_2 \text{---} \right)_n$ wherein n is between 8 and 16, for example 10.

In the case of, for example, R being an alkylene chain having 10 carbons, R may be



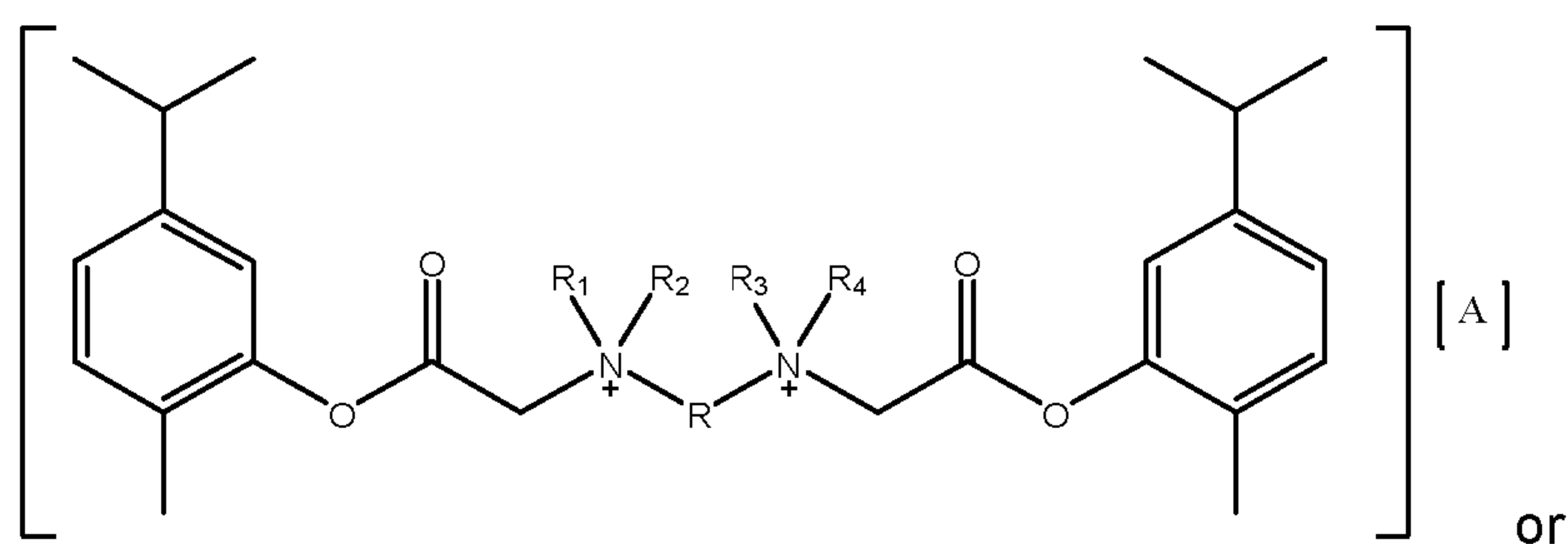
- represented by the following formula

A may, for example, comprise halide ions, such as chloride (Cl^-) ions, bromide (Br^-) ions, iodide ions (I^-) and/or fluoride ions (F^-). A may, for example, comprise ions of other organic and non-organic acids, such as sulphate (SO_4^{2-}), carbonate (CO_3^{2-}), hydrogen carbonate (HCO_3^-), hydrogen sulphate (HSO_4^-), acetate ions (CH_3COO^-), and/or formate ions (HCOO^-). In the case

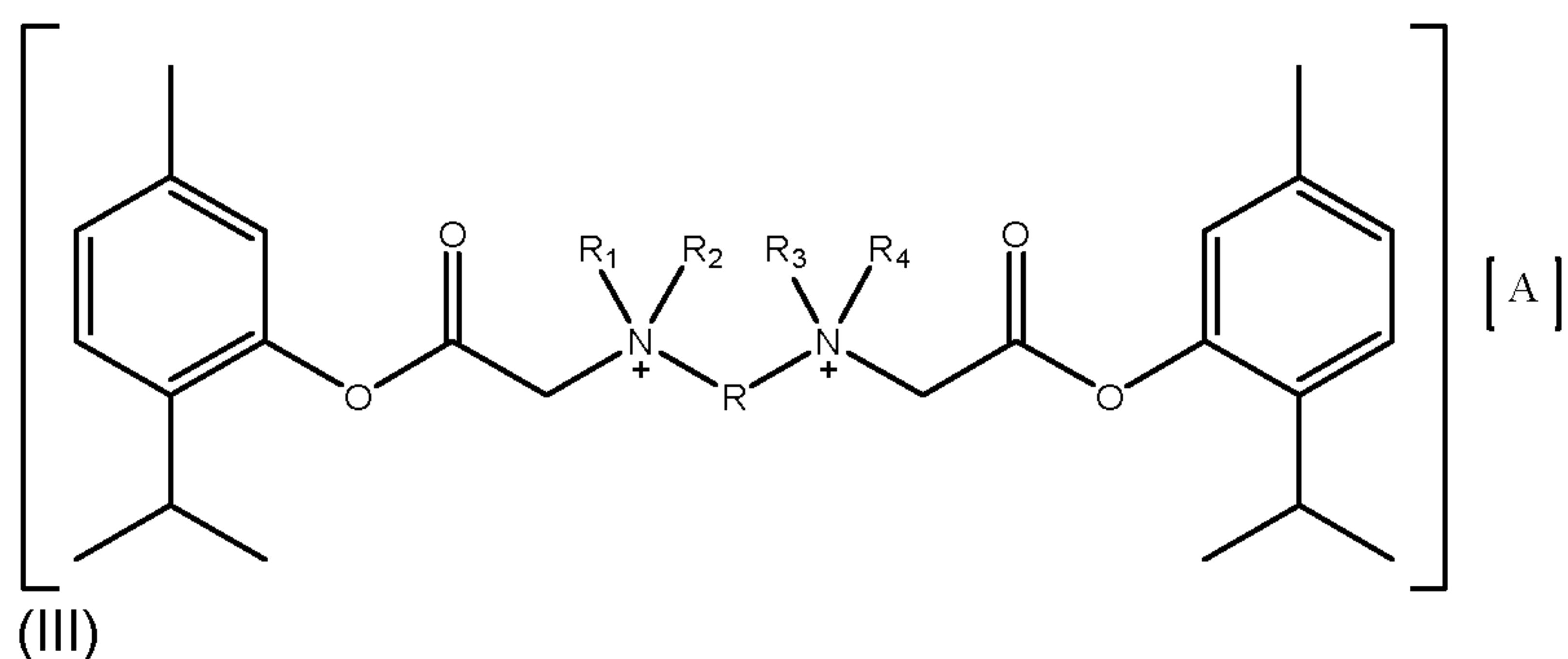
of R being an alkylene chain having between 8 and 20 carbon atoms, preferably A comprises two halide ions, for example two chloride ions, thus having a total charge of -2. In the case of R being a quaternary amine having formula (Ia) as set out above, preferably A comprises two chloride ions and a bromide ion, thus having a total charge of -3.

- 5 R_1, R_2, R_3, R_4, R_5 and R_6 may each independently be selected from C_{1-4} alkyl and H, for example R_1, R_2, R_3, R_4, R_5 and R_6 may each be methyl. R_E may be chloride, bromide, iodide, or fluoride. In the case of the ester oxygen being bonded to the aromatic ring of E at position 2 with respect to the methyl group, R_E may be bonded to the aromatic ring at position 3, 5 or 6 with respect to the methyl group. In the case of the ester oxygen being bonded to the aromatic group of E at position 3 with respect to the methyl group, R_E may be bonded to the aromatic ring at position 2, 5 or 6 with respect to the methyl group.
- 10

Preferably, the compound of formula (I) above has the following formula:



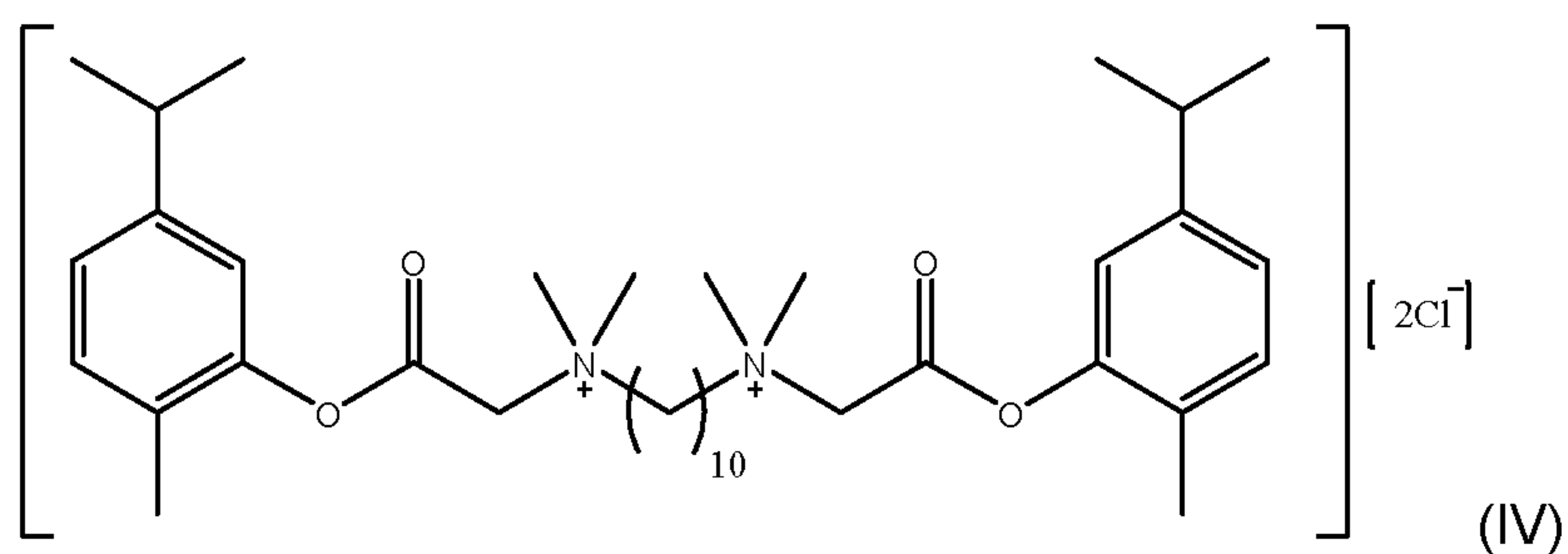
(II)



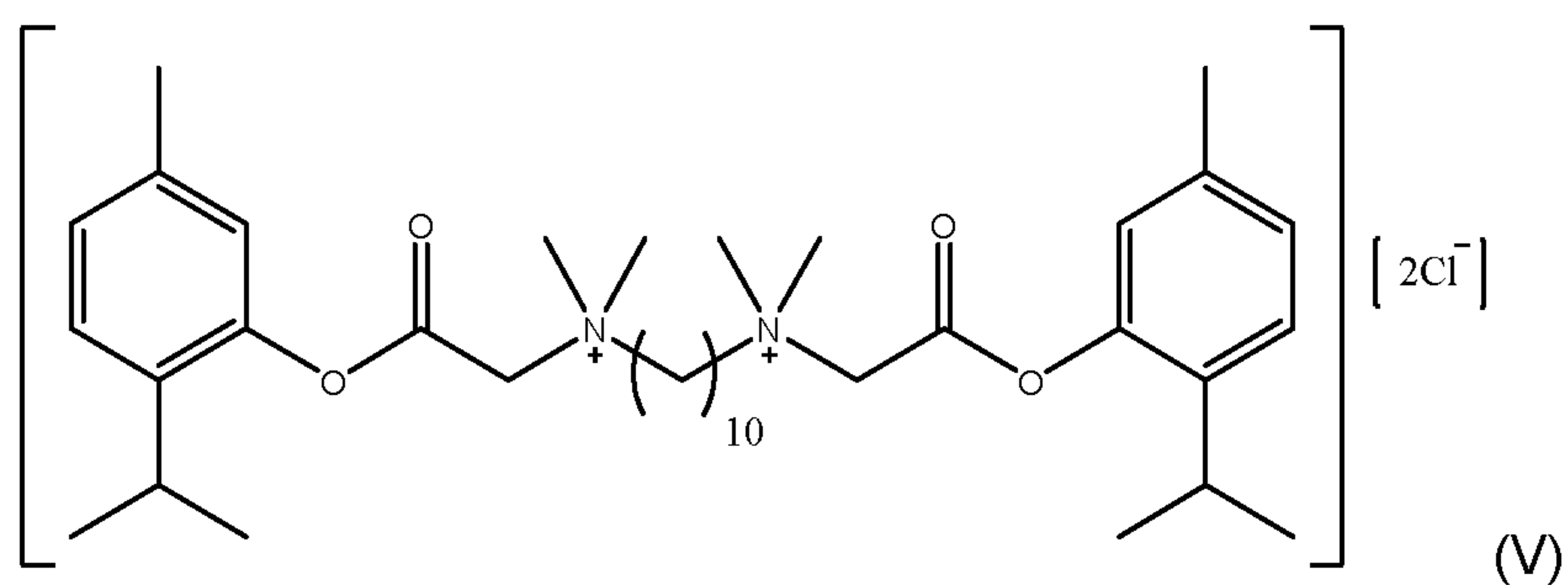
in which R, R_1, R_2, R_3, R_4 and A are as defined above for formula (I).

- 20 Preferably, the compound of formula (I) has the following formula:

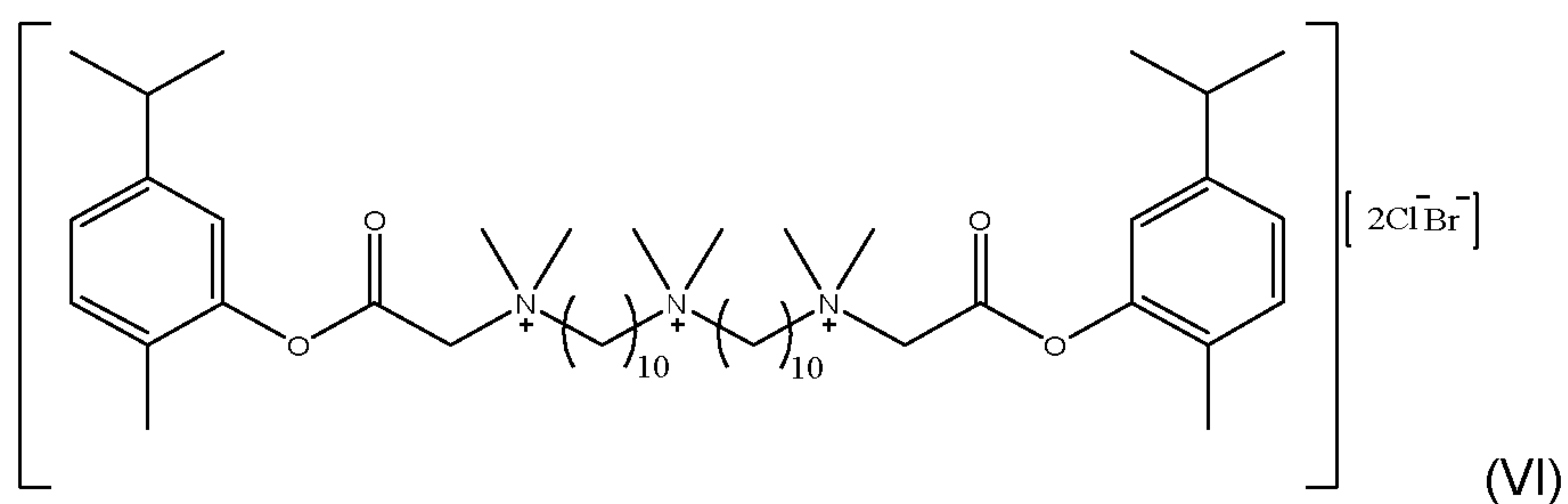
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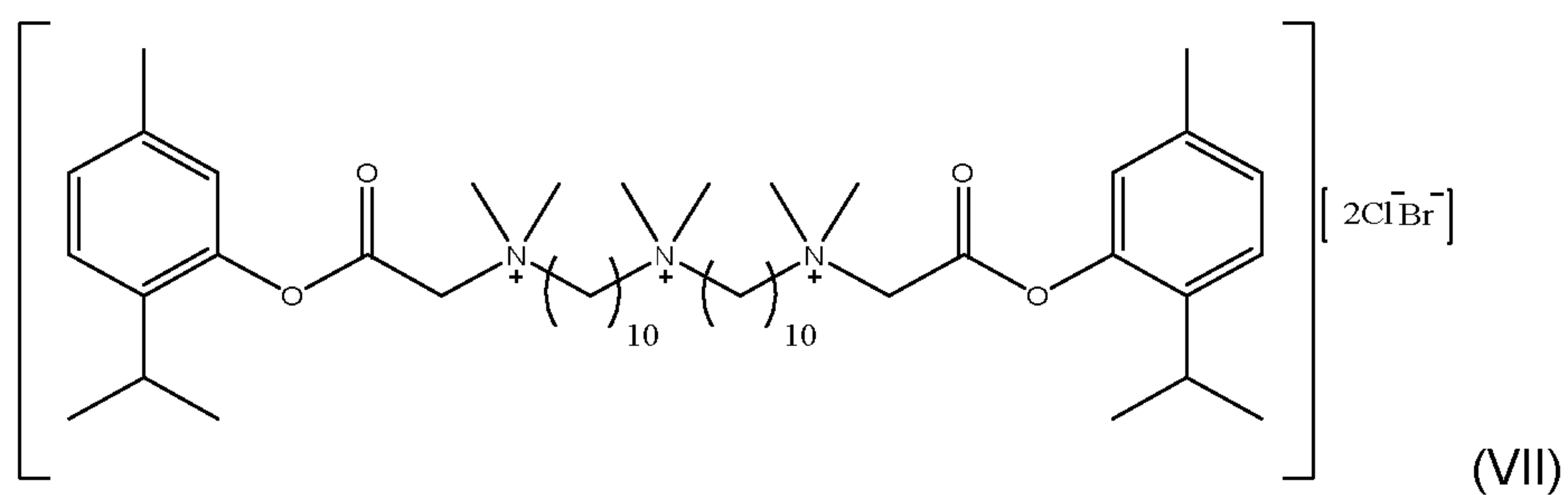
or



or



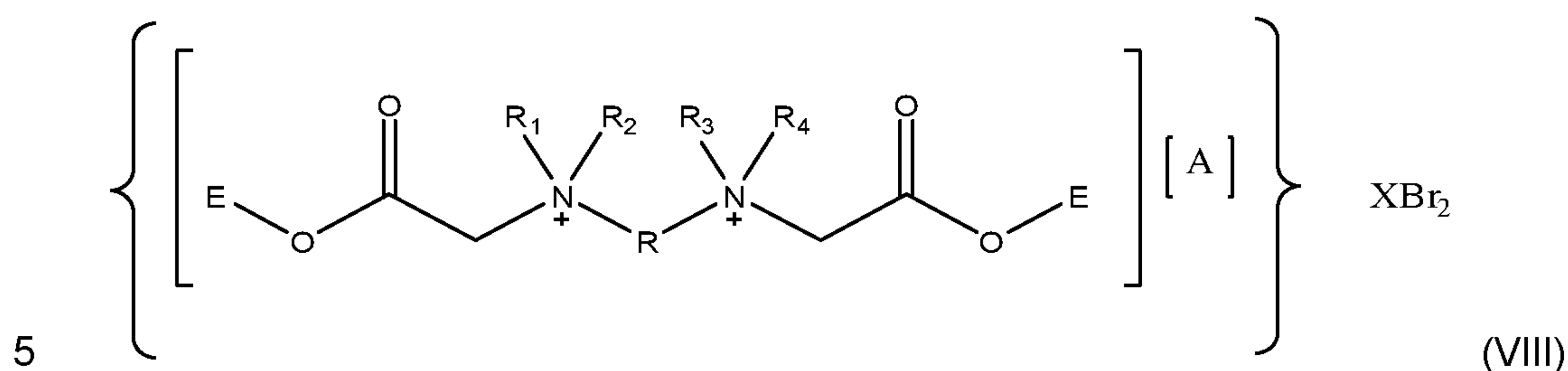
or



In formula IV and V, it will be appreciated that R is a linear saturated alkylene chain having 10 carbon atoms, and A is two chloride ions. In formula VI and VII, it will be appreciated that R is a quaternary amine, in which R_a and R_b are each saturated linear alkylene chains having 10 carbon atoms, and A is two chloride ions and one bromide ion. It will be appreciated that in

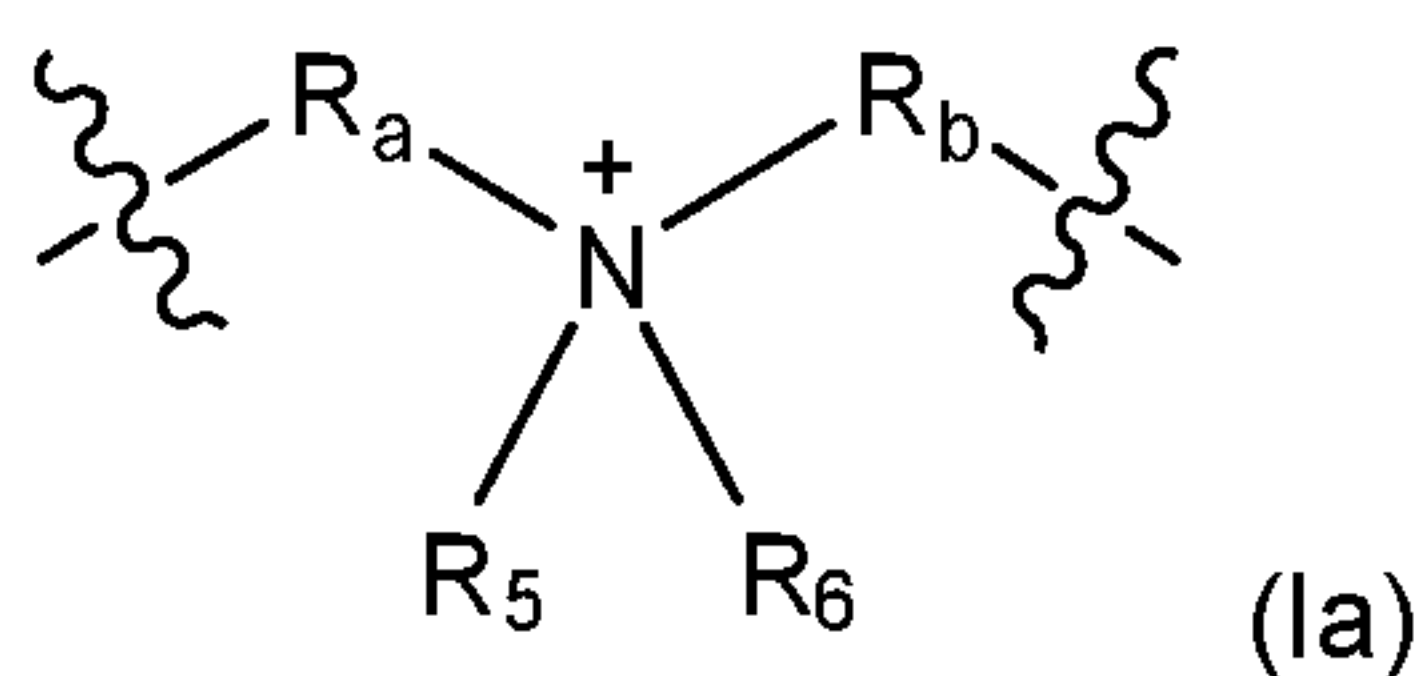
formula IV and V, R_1 , R_2 , R_3 and R_4 are each methyl. It will be appreciated that in formula VI and VII, R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are each methyl.

In another embodiment of the invention, there is provided a compound having the following formula:



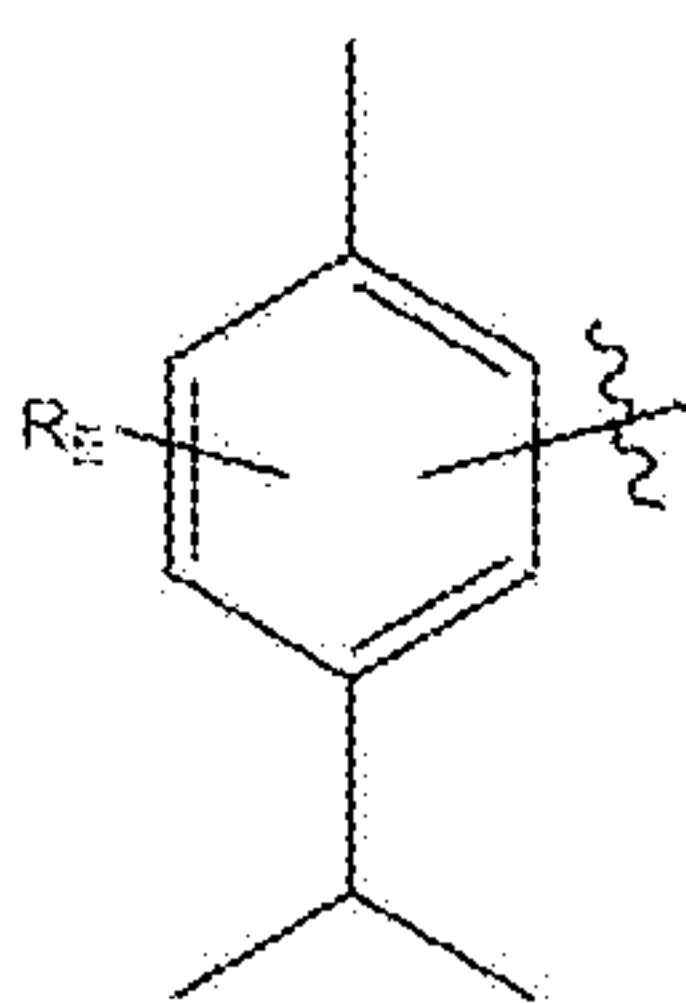
wherein R is an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -2;

or R is a quaternary amine having the following formula:



10 wherein R_a and R_b are each an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -3;

R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are each independently selected from C_{1-10} alkyl and H;



E has the following formula (Ib), wherein the ester oxygen is bonded to the aromatic ring of each E at the same position, the position being 2 or 3; wherein R_E is H or a halide and wherein X is 2, 3, 4 or 6.

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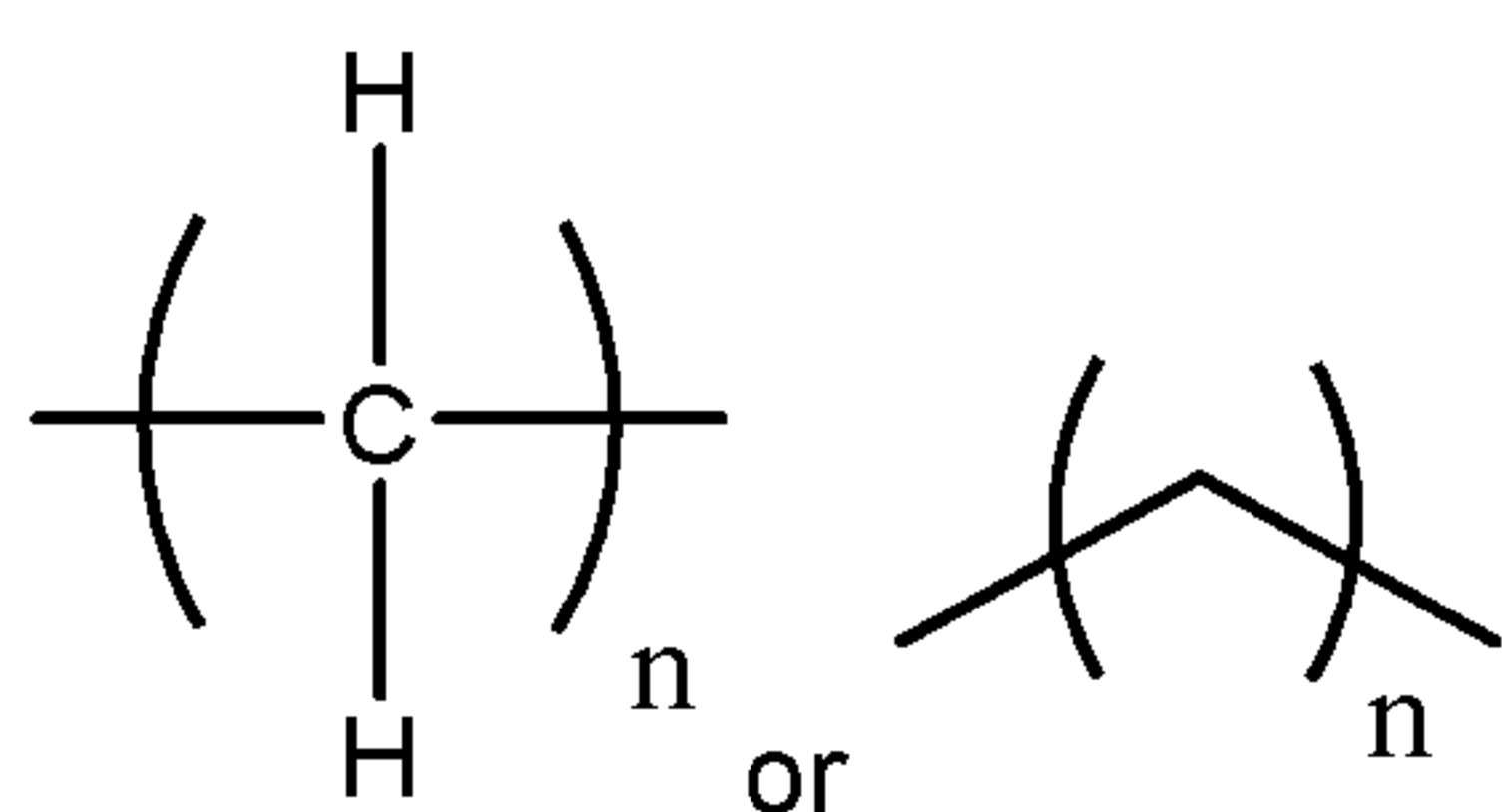
R may be, for example, a linear or branched saturated or unsaturated alkylene chain having between 8 and 18 carbon atoms, for example 8 and 16 carbon atoms, for example 8 and 14 carbon atoms, for example 9 and 15 carbon atoms, for example 10 carbon atoms. Preferably, R

is a linear saturated alkylene chain having between 8 and 16 carbons, for examples 10 carbon atoms.

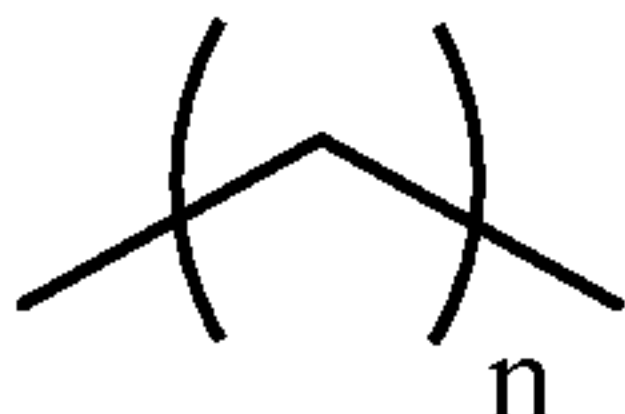
R may be, for example, a quaternary amine according to formula (Ia), in which R_a and R_b are each linear or branched saturated or unsaturated alkylene chains having between 8 and 18 carbon atoms, for example 8 and 16 carbon atoms, for example 8 and 14 carbon atoms, for example 9 and 15 carbon atoms, for example 10 carbon atoms. R_a and R_b may each be linear or branched saturated alkylene chains having a different number of carbon atoms or the same number of carbon atoms.

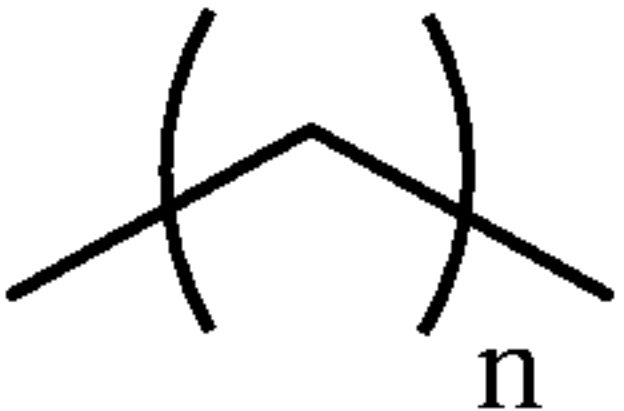
Preferably, R_a and R_b are each a linear saturated alkylene chain having between 8 and 16 carbon atoms, for example 10 carbon atoms.

A saturated linear alkylene chain may be represented by the following formula:

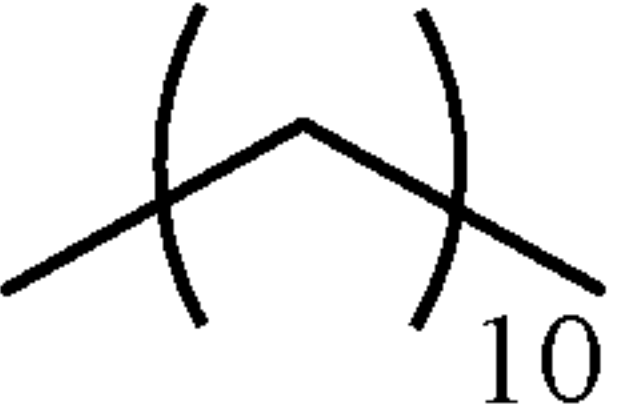


wherein n is the number of repeat units, that is the number of carbon atoms in the linear alkylene chain. Thus, in the case of R being an alkylene chain having

between 8 and 20 carbon atoms, it is preferred that R is  wherein n is between 8 and 16, for example 10. In the case of R being a quaternary amine having the formula (Ia) as

set out above, it is preferred that R_a and R_b is  wherein n is between 8 and 16, for example 10.

In the case of, for example, R being an alkylene having 10 carbons, R may be represented by

the following formula .

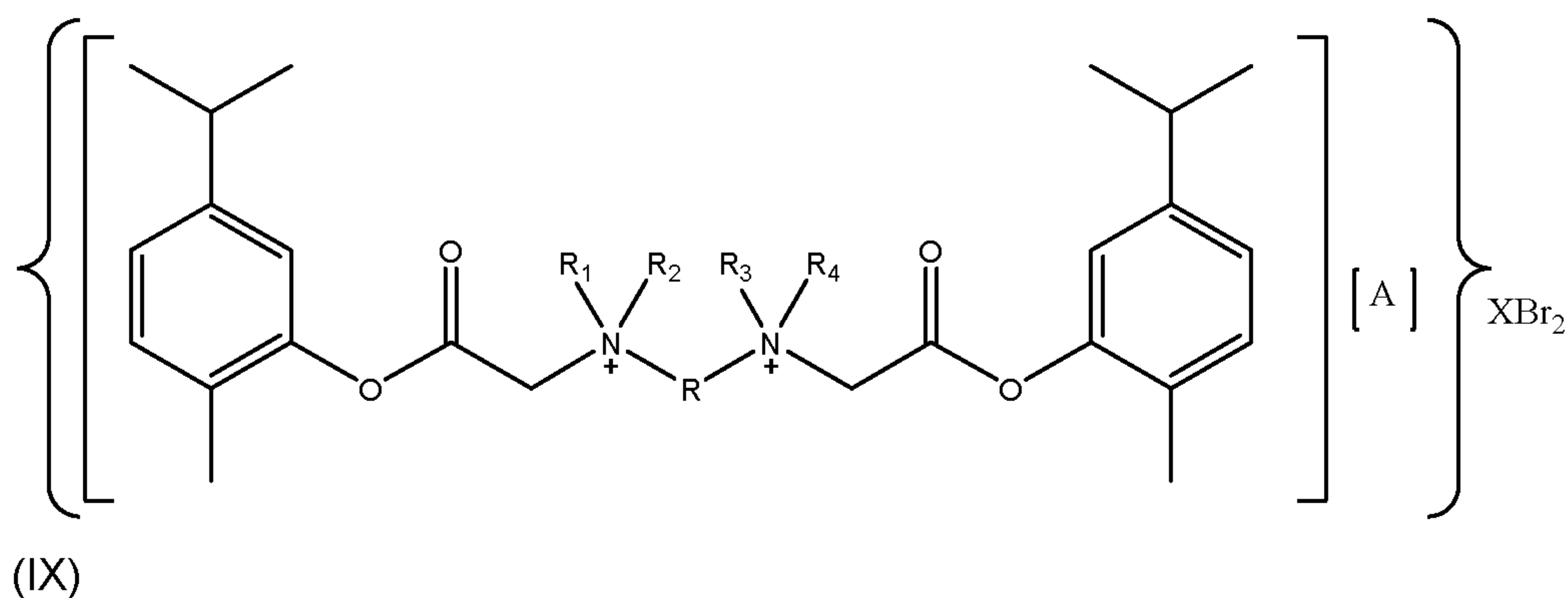
A may, for example, comprise halide ions, such as chloride (Cl⁻) ions, bromide (Br⁻) ions iodide ions (I⁻) and/or fluoride ions (F⁻). A may, for example comprise ions of other organic and non-organic acids, such as sulphate (SO₄²⁻), carbonate (CO₃²⁻), hydrogen carbonate (HCO₃⁻), hydrogen sulphate (HSO₄⁻), acetate (CH₃COO⁻), and/or formate ions (HCOO⁻). In the case of R being an alkylene chain having between 8 and 20 carbon atoms, preferably A comprises two

halide ions, for example two chloride ions, thus having a total charge of -2. In the case of R being a quaternary amine having formula (Ia) as set out above, preferably A comprises two chloride ions and a bromide ion, thus having a total charge of -3.

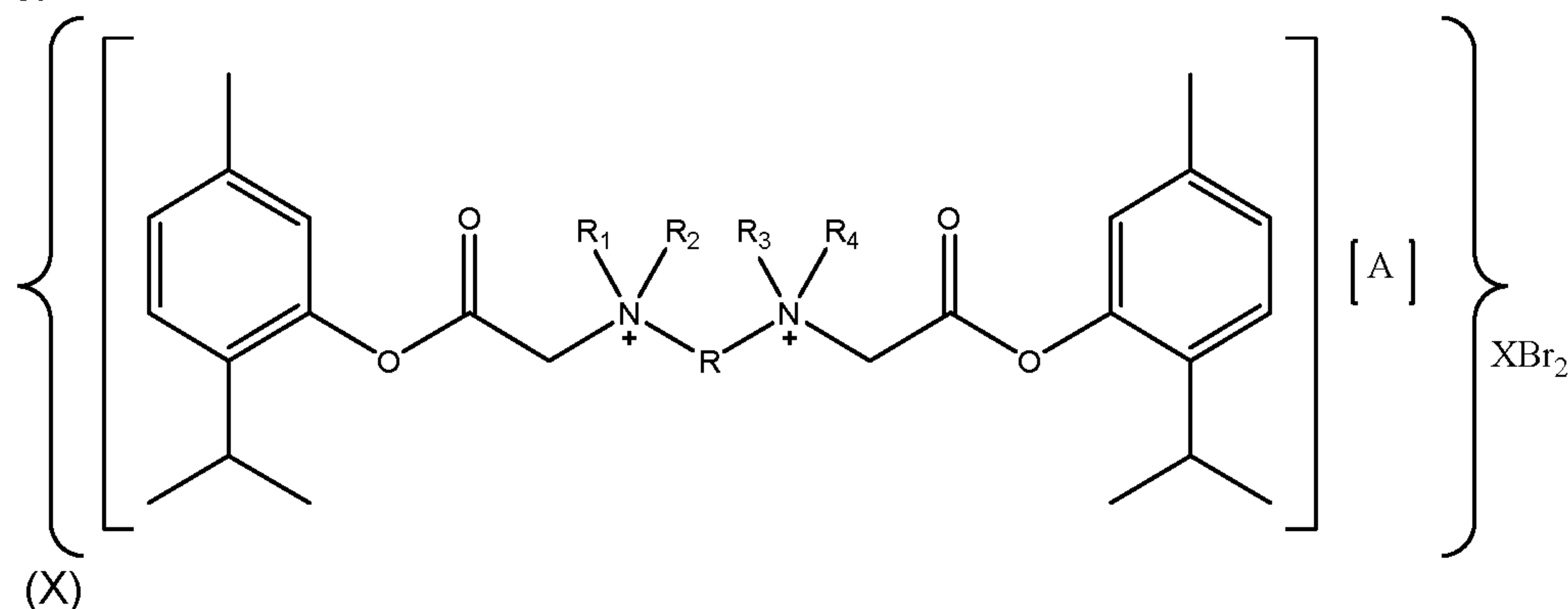
5 R_1, R_2, R_3, R_4, R_5 and R_6 may each independently be selected from C_{1-4} alkyl and H, for example R_1, R_2, R_3, R_4, R_5 and R_6 may each be methyl.

R_E may be chloride, bromide, iodide, or fluoride. In the case of the ester oxygen being bonded to the aromatic ring of E at position 2 with respect to the methyl group, R_E may be bonded to the aromatic ring at position 3, 5 or 6 with respect to the methyl group. In the case of the ester oxygen being bonded to the aromatic group of E at position 3 with respect to the methyl group,
 10 R_E may be bonded to the aromatic ring at position 2, 5 or 6 with respect to the methyl group.

Preferably, the compound of formula (VIII) above has the following formula:



15 or

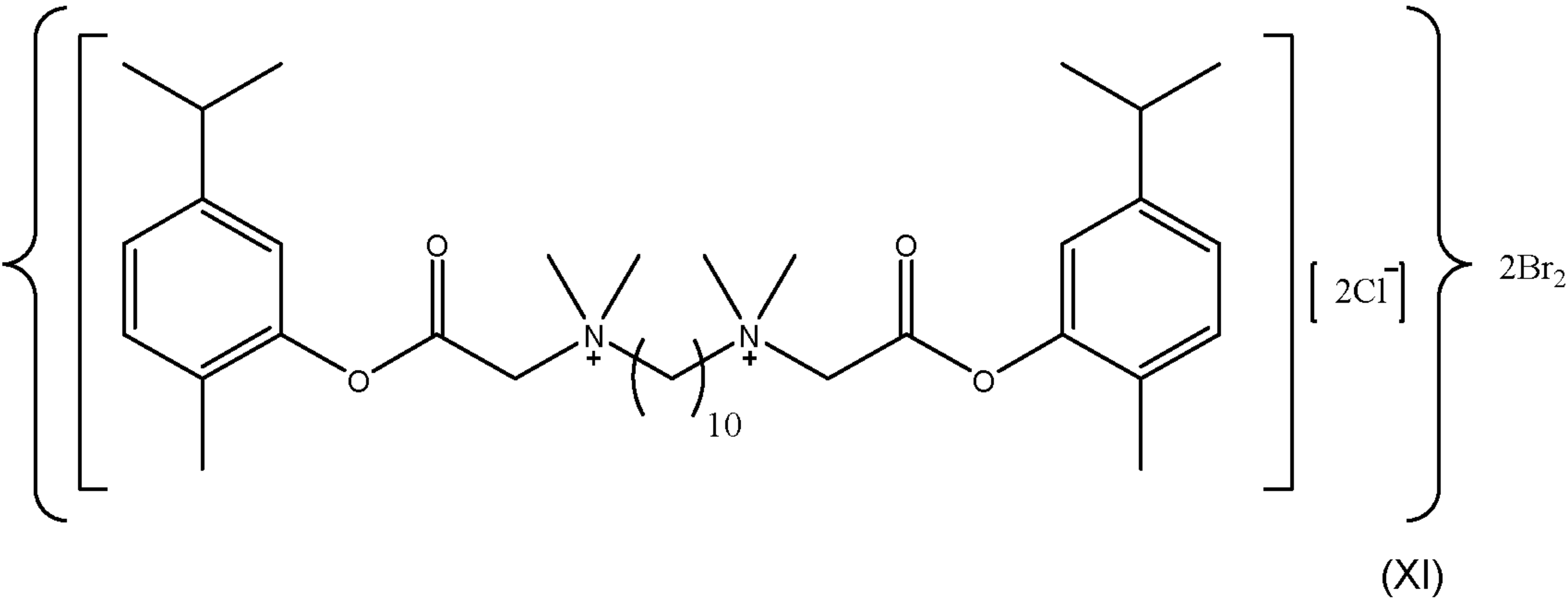


wherein R, R_1, R_2, R_3, R_4, X and A are as defined above for formula (IX).

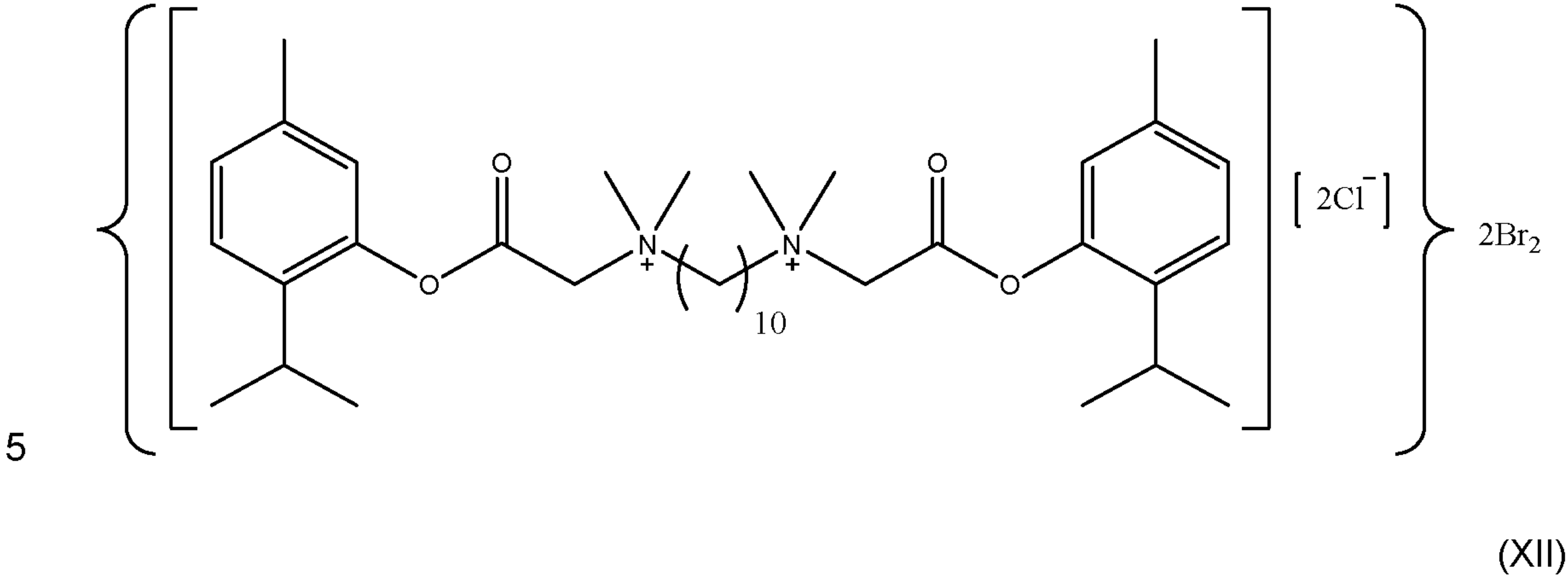
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Preferably, the compound of formula (VIII) has the following formula:

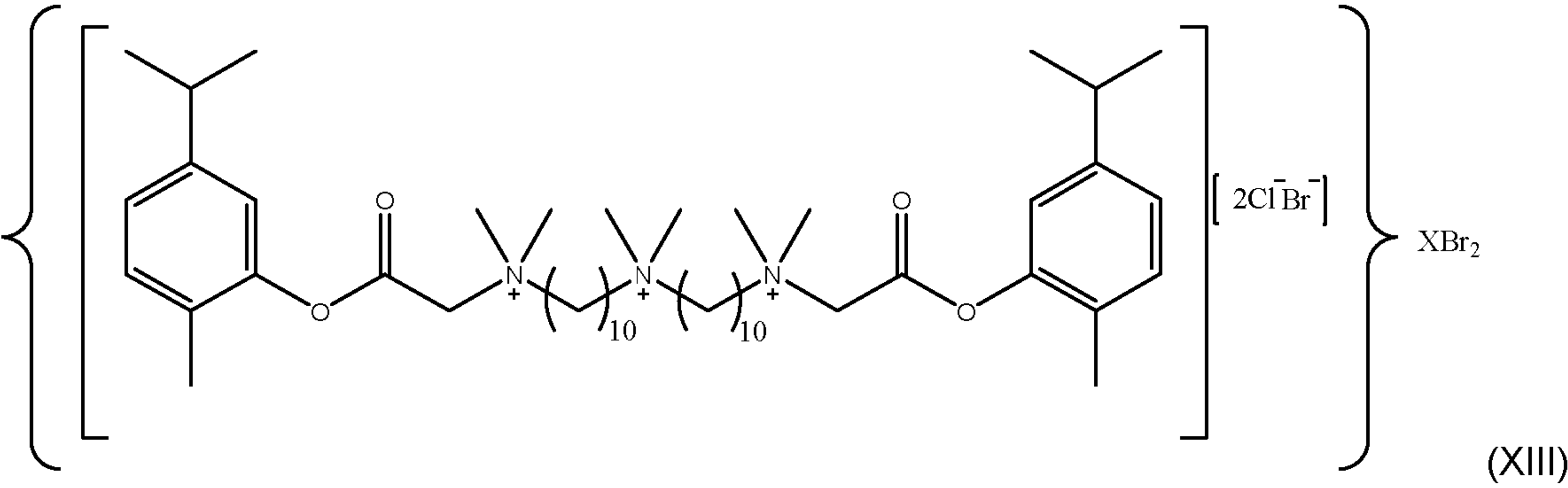
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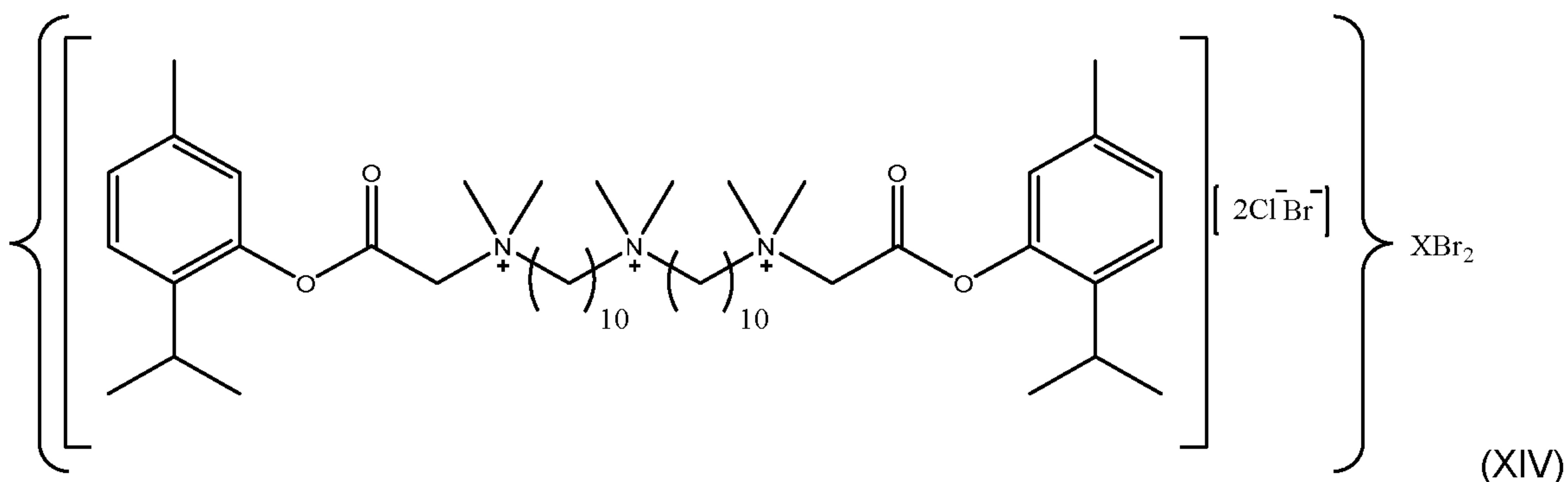
or



or



or



wherein X is 3 or 6.

In formula (XI) and (XII), it will be appreciated that R is a linear saturated alkylene chain having 10 carbon atoms; and A is two chloride ions.

In formula (XIII) and (XIV), it will be appreciated that R is a quaternary amine, in which R_a and R_b are each saturated linear alkylene chains having 10 carbon atoms, and A is two chloride ions and one bromide ion. It will be appreciated that in formula (XI) and (XII), R_1 , R_2 , R_3 and R_4 are each methyl. It will be appreciated that in formula (XIII) and (XIV), R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are each methyl.

The applicant has found that the above compounds represented by formula I to XIV demonstrate surprising anti bacterial, antifungal and antiviral activity. Without being bound by any particular theory, it is hypothesised that this antibacterial and antifungal activity may stem from the combination of the aromatic thymol and carvacrol groups, quaternary ammonia groups and long chain alkyl groups. Additionally, complexing compounds according to formulae I-IV with bromine may further increase their antibacterial and antifungal properties.

The applicant has found that the compounds represented by formulas I to XIV demonstrate enhanced antibacterial, antifungal and antiviral activity over similar compounds in which the ester oxygen is bonded to the aromatic ring of each group E at different positions.

In another aspect of the invention, there is provided a pharmaceutical composition (for example a human pharmaceutical composition and/or a veterinary pharmaceutical composition), comprising a compound according to formulae (I) to (XIV) above.

The pharmaceutical composition may be in a form suitable for one or more of oral, rectal, parenteral, transdermal, intravenous, intra-arterial, intraosseous infusion, intracerebral, intracerebroventricular, intrathecal, intramuscular, subcutaneous, intravaginal, intraperitoneal,

epidural, intracerebral, intraosseous infusion, intravitreal, transmucosal, buccal, or nasal administration.

5 The pharmaceutical composition may comprise a compound according to formulae (I) to (XIV), a pharmaceutically acceptable carrier, such as aqueous solution, non-toxic excipients, including salts and preservatives, buffers and the like.

10 Examples of suitable aqueous and non-aqueous pharmaceutical carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate.

15 Examples of pharmaceutically acceptable excipients include antiadherents, binders, coatings, colourings, disintegrant, flavourings, glidants, lubricants, preservatives, sorbents and sweeteners.

20 The pharmaceutical compositions of the present invention may also contain additives such as but not limited to preservatives, wetting agents, emulsifying agents, surfactants and dispersing agents. Antibacterial and antifungal agents can be included to prevent growth of microbes and includes, for example, m-cresol, benzyl alcohol, paraben, chlorobutanol, phenol, sorbic acid, and the like. If a preservative is included, benzyl alcohol, phenol and/or m-cresol are preferred; however, the preservative is by no means limited to these examples. Furthermore, it may be desirable to include isotonic agents such as sugars, sodium chloride, and the like.

25 A pharmaceutical composition suitable for oral administration may be in the form of, for example, a tablet, a pill, a sugar coated agent, a powder, a capsule, a liquid, a gel, a syrup, a slurry, a suspension, a cachet and the like. The composition may comprise a pharmaceutically acceptable carrier, for example liposomes, lactose, trehalose, sucrose, mannitol, xylitol, crystalline cellulose, chitosan, calcium carbonate, talc, titanium oxide, silica and the like.

30 The pharmaceutical composition may be obtained, for example, by combining the compounds of the invention with a solid excipient, pulverizing the mixture (if necessary) and inserting into a capsule, for example, a soft sealed capsule consisting of a gelatin capsule, gelatin and coating (e.g., glycerol or sorbitol) or a capsule composition suitable for vegetarians. In the soft capsule, 35 the composition may be dissolved or suspended in an appropriate liquid, such as a fatty oil, liquid paraffin or liquid polyethylene glycol, with or without a stabilizer.

In a further aspect of the present invention there is provided a compound or a pharmaceutical composition as set out above for use as a medicament.

5 In a further aspect of the present invention there is provided a compound or a pharmaceutical composition as set out above for use in the treatment of Herpes virus, Human Papilloma Virus, bacterial infections and/or fungal infections.

10 The Herpes virus may be one or more of a Herpes Simplex virus, Herpes Simplex virus 1 (HSV-1), Herpes Simplex virus 2 (HSV-2), Varicella zoster virus (VZV), Epstein-Barr virus, Cytomegalovirus, Human Cytomegalovirus, Roseolovirus, Kaposi's Sarcoma-associated herpesvirus, animal Herpesviruses, such as Pseudorabies virus, and Bovine herpesvirus 1.

15 Preferably, the Herpes virus is a Herpes Simplex virus (for example Herpes Simplex virus 1 or Herpes Simplex virus 2) or Cytomegalovirus.

The bacterial infections may include those caused by gram positive and/or gram negative bacteria.

20 The bacterial infections may be caused by, for example, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and/or *Salmonella enterica* bacteria.

The fungal infections may be superficial mycoses, cutaneous mycoses, subcutaneous mycoses, and/or systemic mycoses.

25 The fungal infections may be caused by, for example, *Candida albicans*.

In a further aspect of the invention, there is provided the use of a compound or pharmaceutical composition as set out above in the manufacture of a medicament for treating Herpes virus, Human Papilloma Virus, bacterial infections and/or fungal infections.

30 The herpes virus may be one or more of a Herpes Simplex virus, Herpes Simplex virus 1 (HSV-1), Herpes Simplex virus 2 (HSV-2), Varicella zoster virus (VZV), Epstein-Barr virus, Cytomegalovirus, Human Cytomegalovirus, Roseolovirus, Kaposi's Sarcoma-associated herpesvirus, animal Herpesviruses, such as Pseudorabies virus, and Bovine Herpesvirus 1.

35 Preferably, the Herpes virus is a Herpes Simplex virus (for example Herpes Simplex virus 1 or Herpes Simplex virus 2) or Cytomegalovirus.

The bacterial infections may include those caused by gram positive and/or gram negative bacteria.

5 The bacterial infections may be caused by, for example, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and/or *Salmonella enterica* bacteria.

The fungal infections may be superficial mycoses, cutaneous mycoses, subcutaneous mycoses, and/or systemic mycoses.

10 The fungal infections may be caused by, for example, *Candida albicans*.

In a further aspect of the invention, there is provided a method of treatment of Herpes virus, Human Papilloma Virus, bacterial infections and/or fungal infections, comprising a step of administering to a subject a compound or pharmaceutical composition as set out above.

15

The herpes virus may be one or more of a Herpes Simplex virus, Herpes Simplex virus 1 (HSV-1), Herpes Simplex virus 2 (HSV-2), Varicella zoster virus (VZV), Epstein-Barr virus, Cytomegalovirus, Human Cytomegalovirus, Roseolovirus, Kaposi's Sarcoma-associated Herpesvirus, animal Herpesviruses, such as Pseudorabies virus, and Bovine Herpesvirus 1.

20

Preferably, the herpes virus is a Herpes Simplex virus (for example Herpes Simplex virus 1 or Herpes Simplex virus 2) or Cytomegalovirus.

25 The bacterial infections may include those caused by gram positive and/or gram negative bacteria.

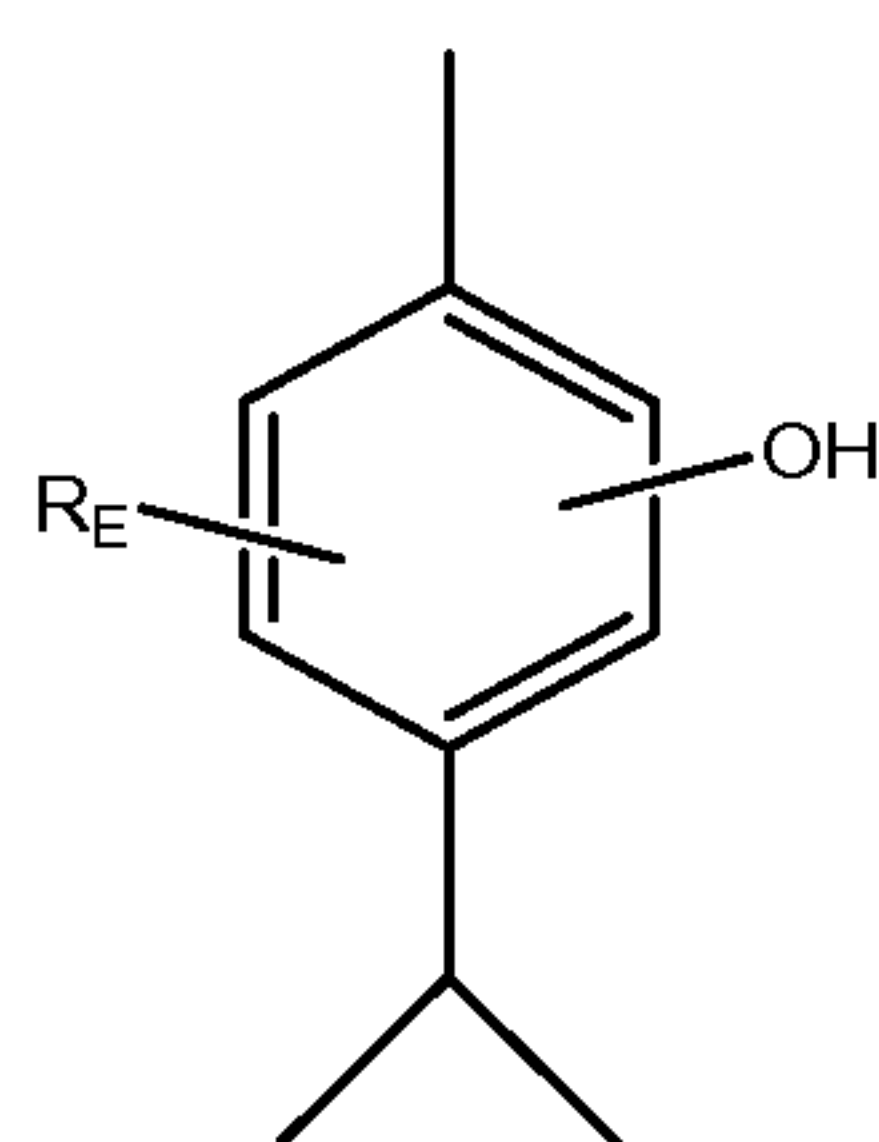
The bacterial infections may be caused by, for example, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa* and/or *Salmonella enterica* bacteria.

30 The fungal infections may be superficial mycoses, cutaneous mycoses, subcutaneous mycoses, and/or systemic mycoses.

The fungal infections may be caused by, for example, *Candida albicans*.

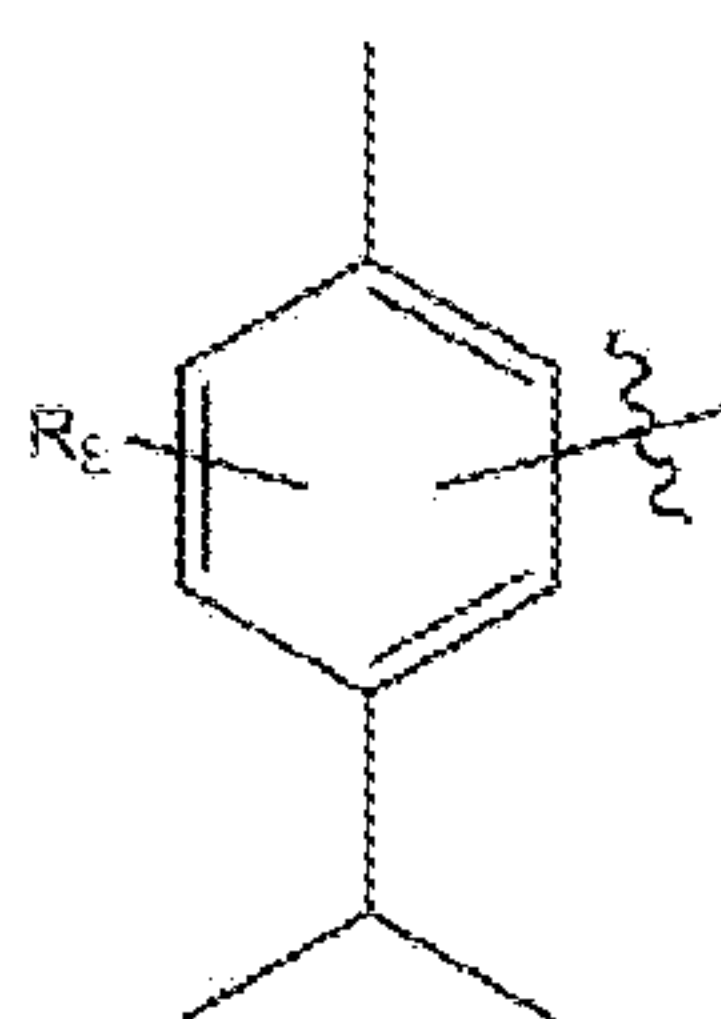
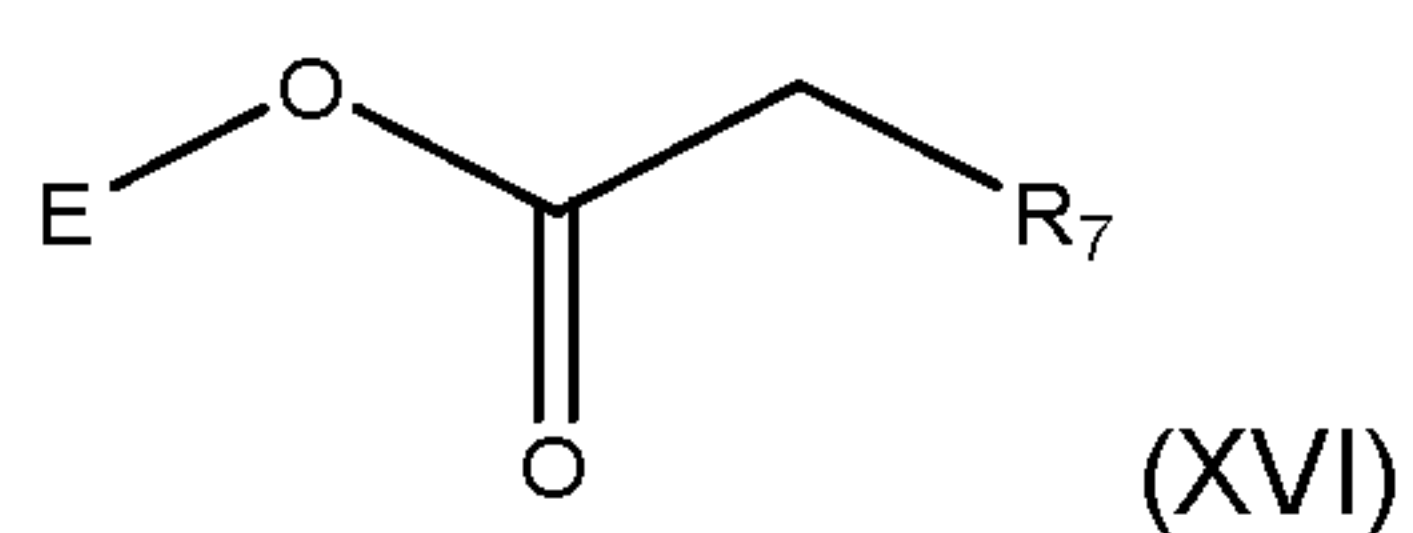
35 In a further aspect of the present invention, there is provided a process for producing the compound according to formula (I) comprising the following steps:

i) reacting a compound having the formula (XV)



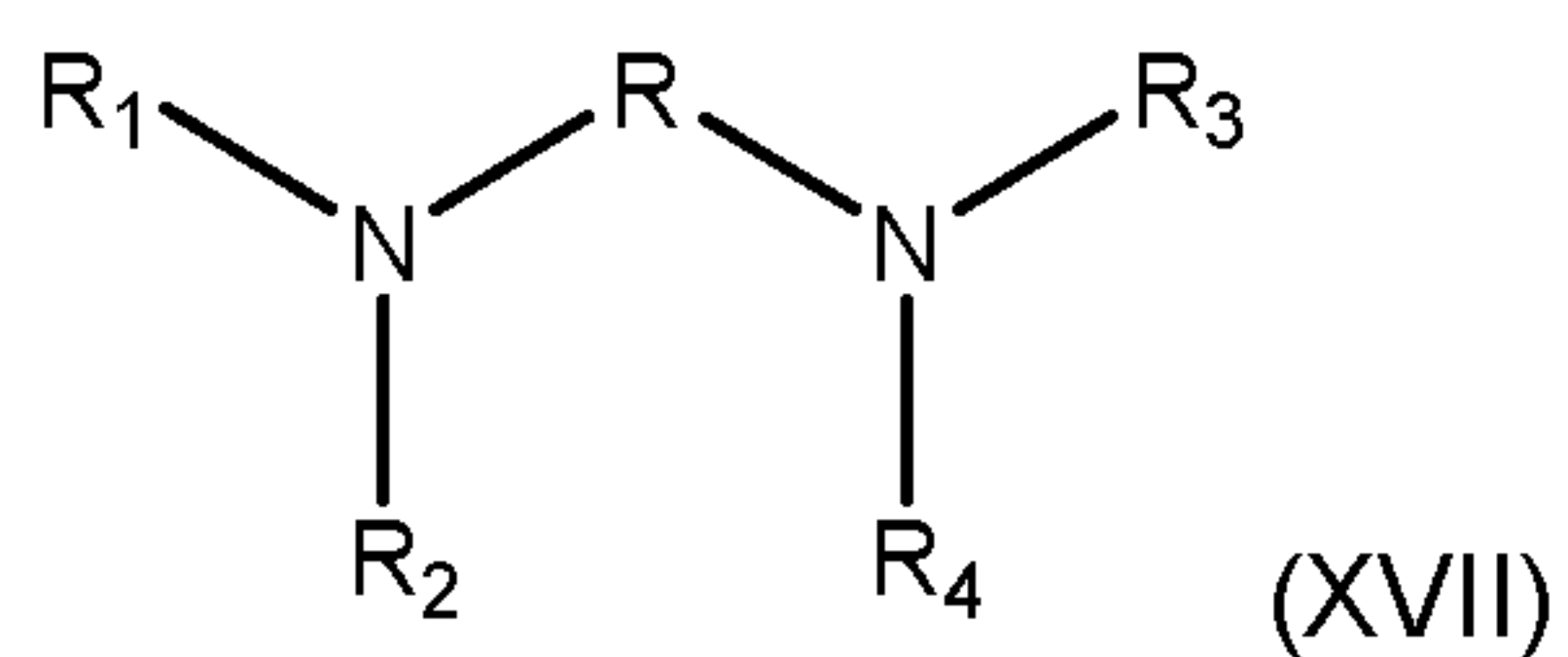
(XV), wherein the alcohol group is bonded to the benzene ring in position 2 or 3 and wherein R_E is H or halide,

with R_7CH_2COCl to form a compound having the formula (XVI):

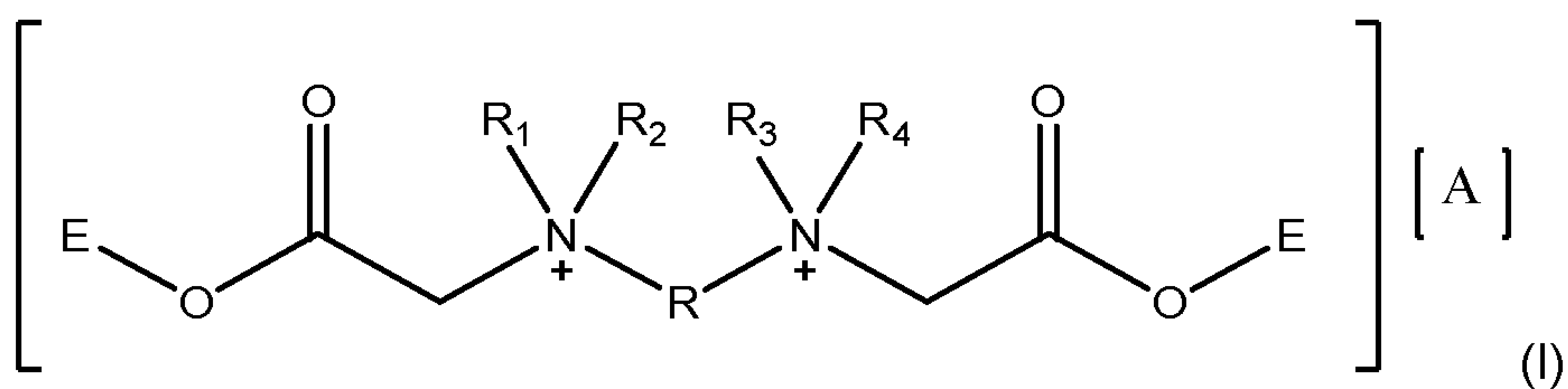


- 5 wherein R_7 is chloride or bromide, E is (Ib), wherein the ester oxygen is bonded to the aromatic ring of E at position 2 or 3, and R_E is H or halide; and

ii) reacting 1 molar equivalents of the compound having the formula (XVII)

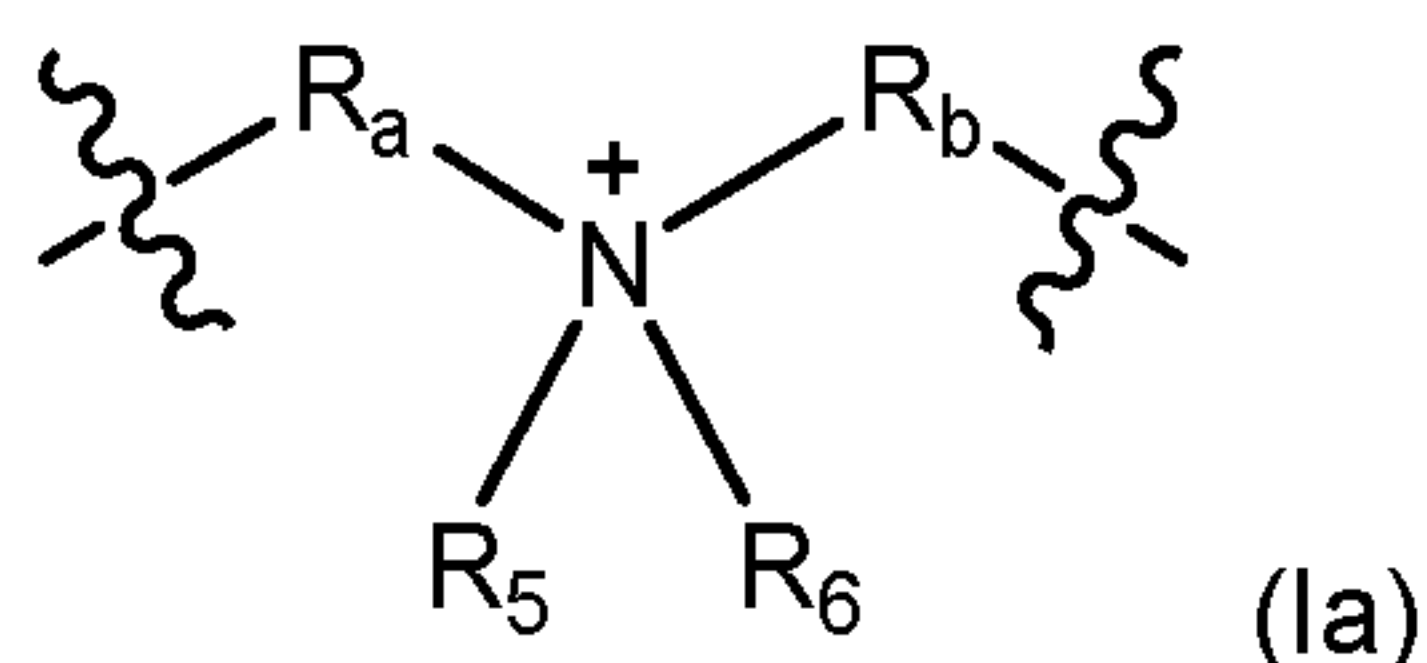


- 10 with 2 molar equivalent of the compound having formula (XVI) to form a compound having the formula

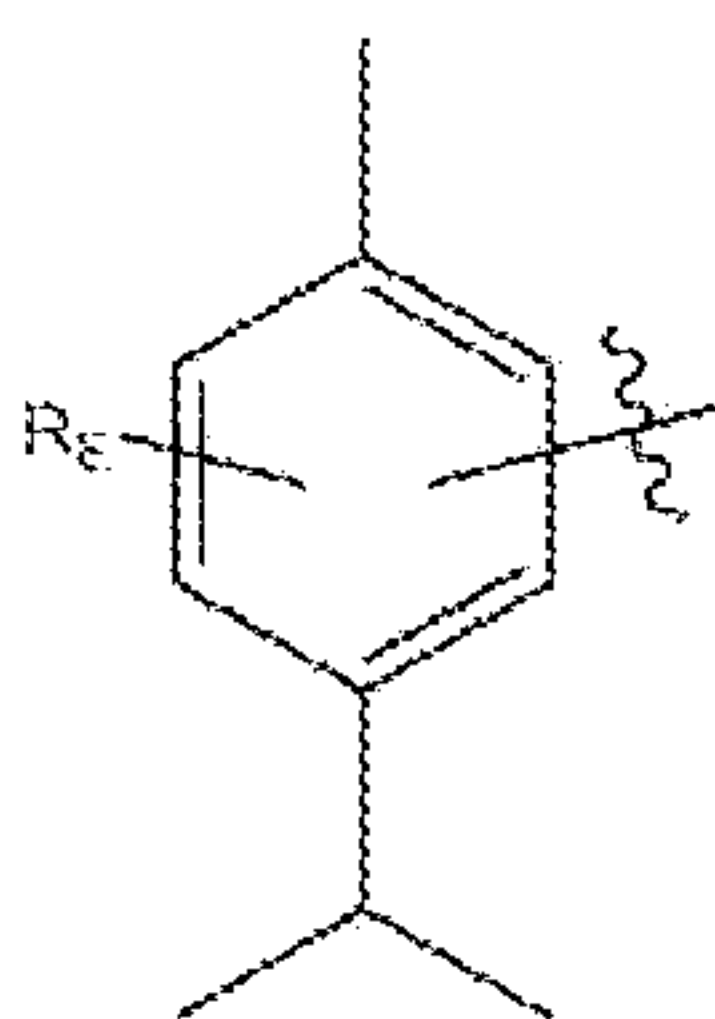


wherein R is an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -2;

or R is a quaternary amine having the following formula:



- 5 wherein R_a and R_b are each an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -3;



E has the following formula (Ib), wherein the ester oxygen is bonded to the aromatic ring of each E at the same position, the position being position 2 or 3, and R_E is H or halide;

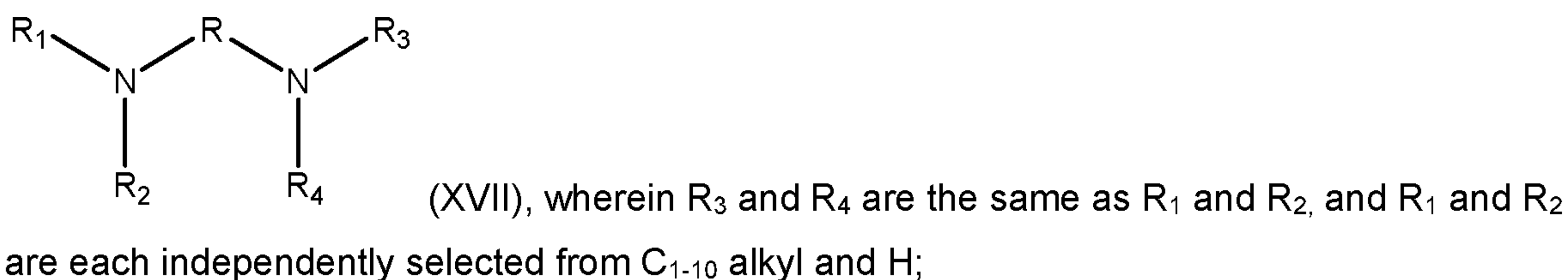
- 10 R₁, R₂, R₃, R₄, R₅ and R₆ are each independently selected from C₁₋₁₀ alkyl and H.

The reactions of step ii may be carried out in acetonitrile as solvent.

In the case of R being an alkylene chain having between 8 and 20 carbon atoms, the process may include an additional step of reacting a compound having the formula

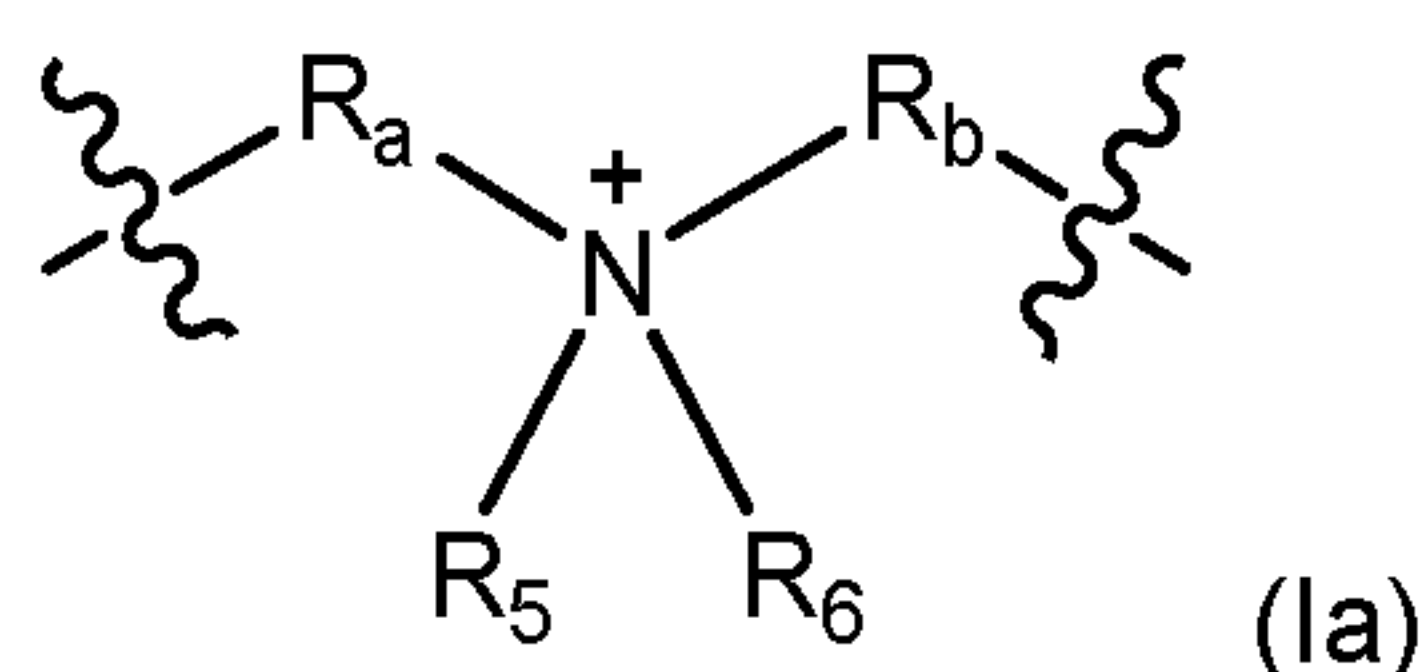


- 15 (XIX) to form a di tertiary amine having the following formula



wherein R_8 is a halide, for example bromide or chloride; and R is an alkylene chain having between 8 and 20 carbon atoms.

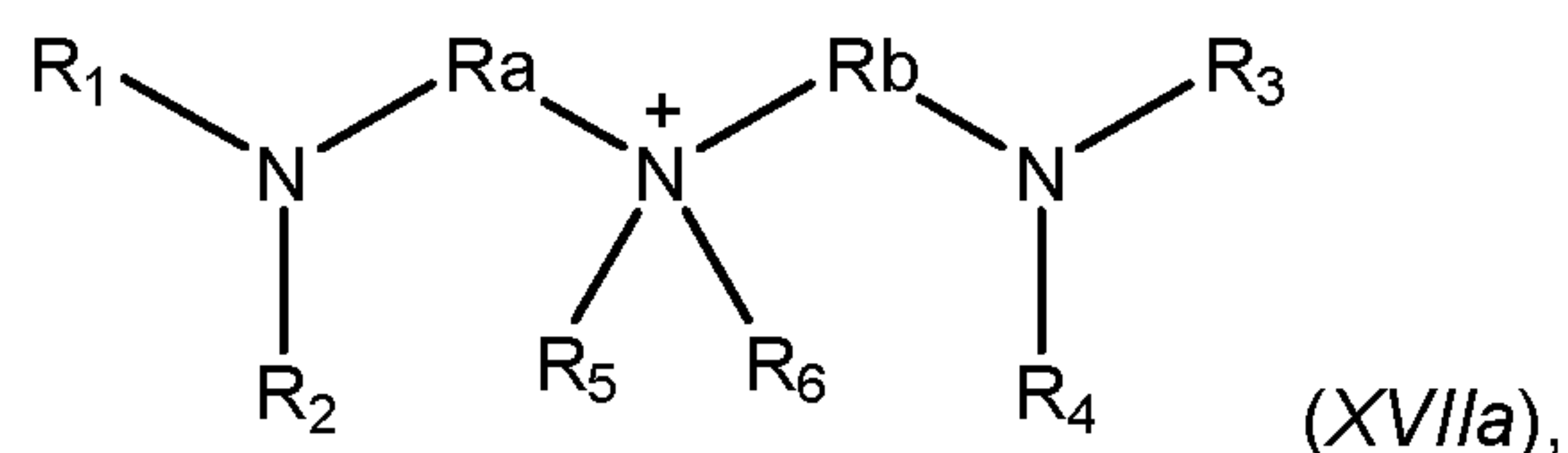
In the case of R being a quaternary amine having the following formula:



- 5 wherein R_a and R_b are each an alkylene chain having between 8 and 20 carbon atoms, and R_5 and R_6 are each independently selected from C_{1-10} alkyl and H, the process may include an additional step of reacting a 2 molar equivalents of a compound having the formula



with three molar equivalents of R_1-NH-R_2 (XIX) to form a



quaternary amine having the following formula

- 10 wherein R_a is an alkylene chain having between 8 and 20 carbon atoms, R_8 is a halide, for example bromine or chlorine, R_a and R_b are the same and are each an alkylene chain having between 8 and 20 carbon atoms, R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are the same and are selected from C_{1-10} alkyl and H.

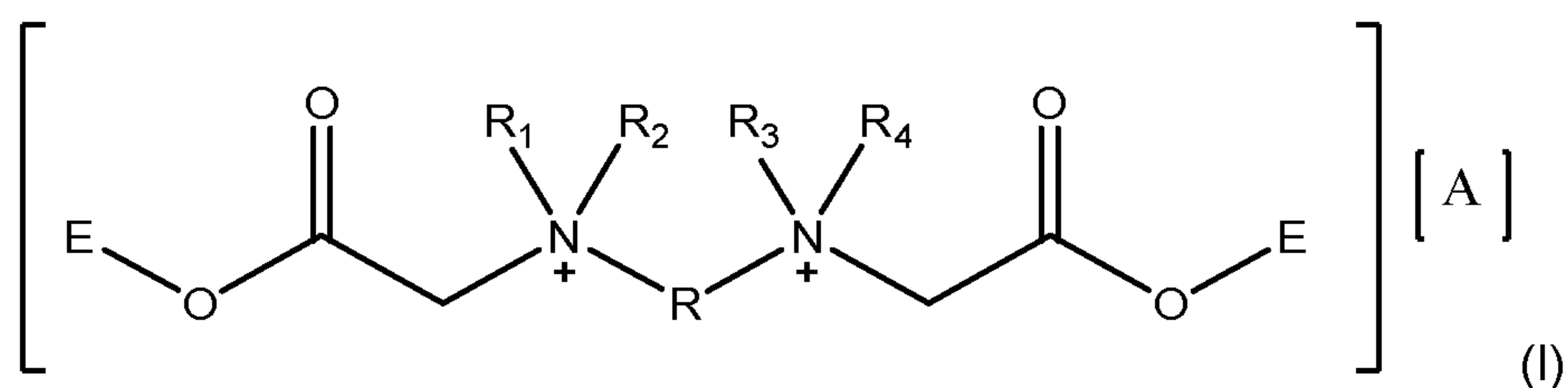
The reactions in step i may both take place at a temperature of -10°C .

15

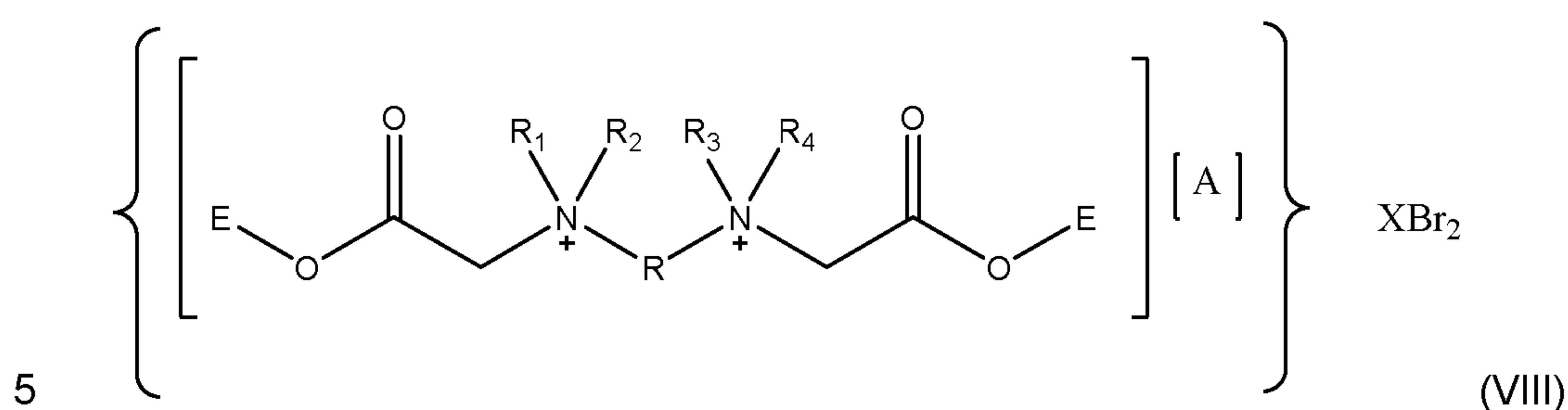
The process may further comprise one or more steps of separation and or extraction, for example a separation step may include column chromatography, low pressure liquid chromatography, high performance liquid chromatography and the like. Purification steps may include standard purification processes known in the art, for example, filtration, evaporation, liquid-liquid extraction, crystallisation, adsorption, recrystallization, chromatography, distillation and the like.

20

In a further aspect of the present invention there is provided a process for the production of a compound according formula (VIII) comprising reacting the compound having formula (I)

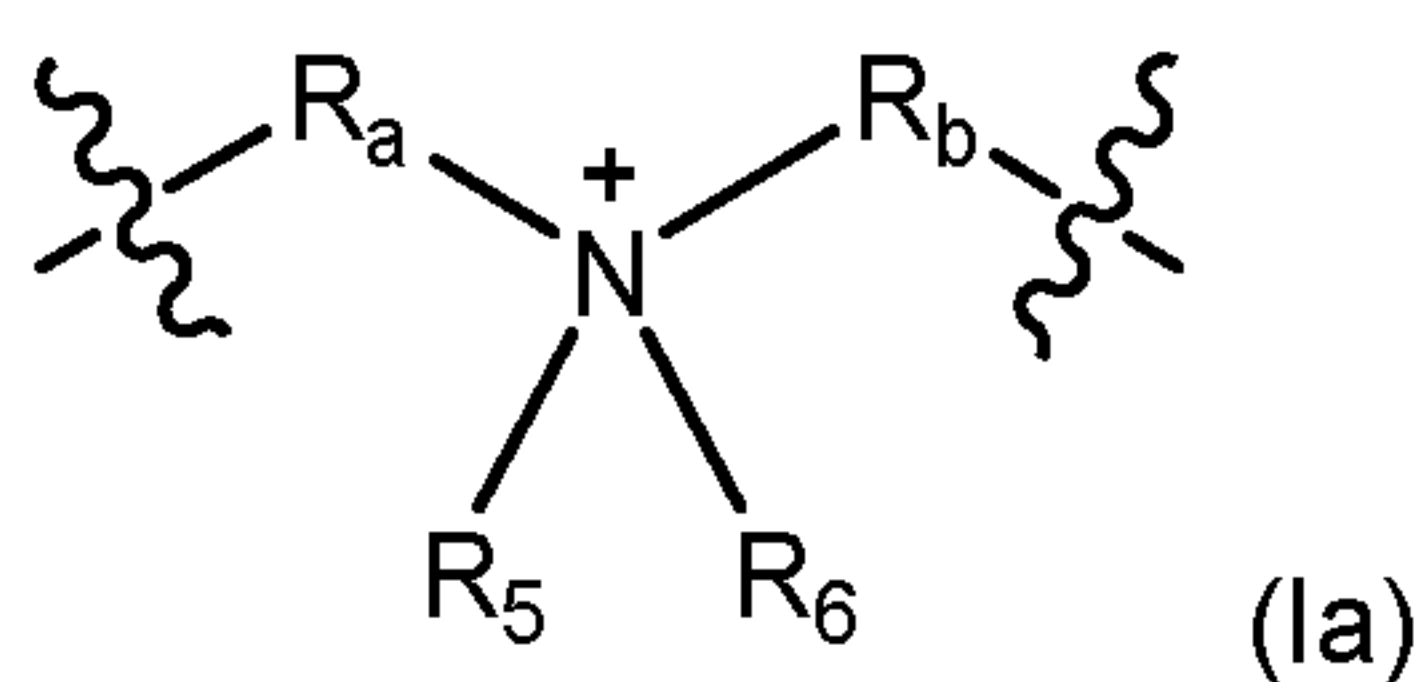


with bromine to form a compound having formula (VIII)



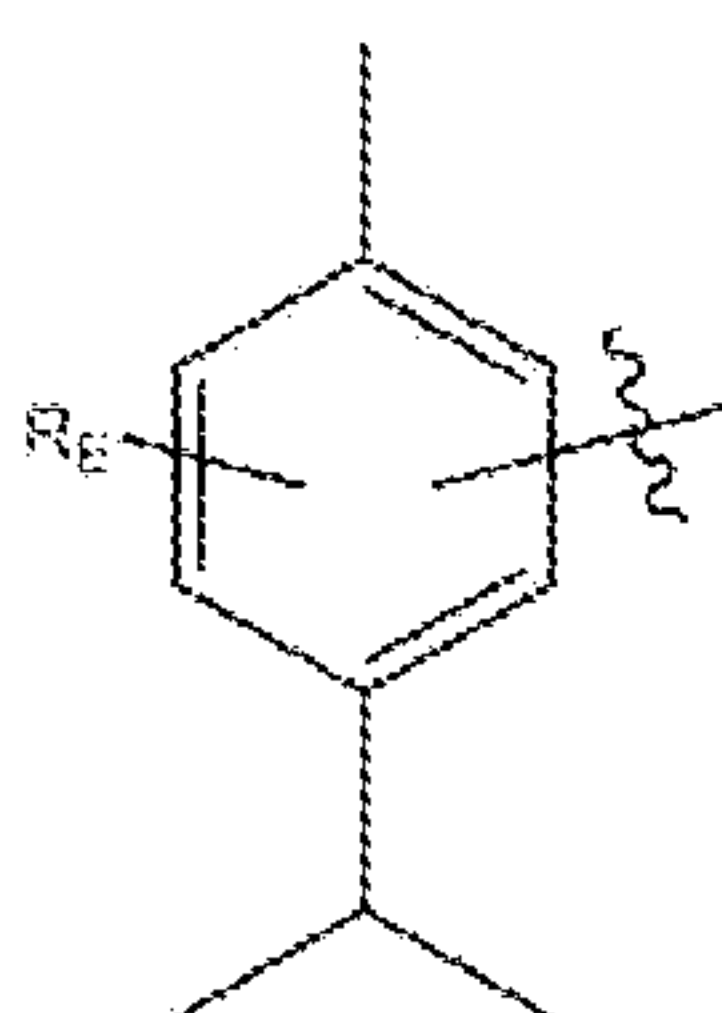
wherein R is an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -2,

or R is a quaternary amine having the following formula:



10 wherein R_a and R_b are each an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -3;

R₁, R₂, R₃, R₄, R₅ and R₆ are each independently selected from C₁₋₁₀alkyl and H;



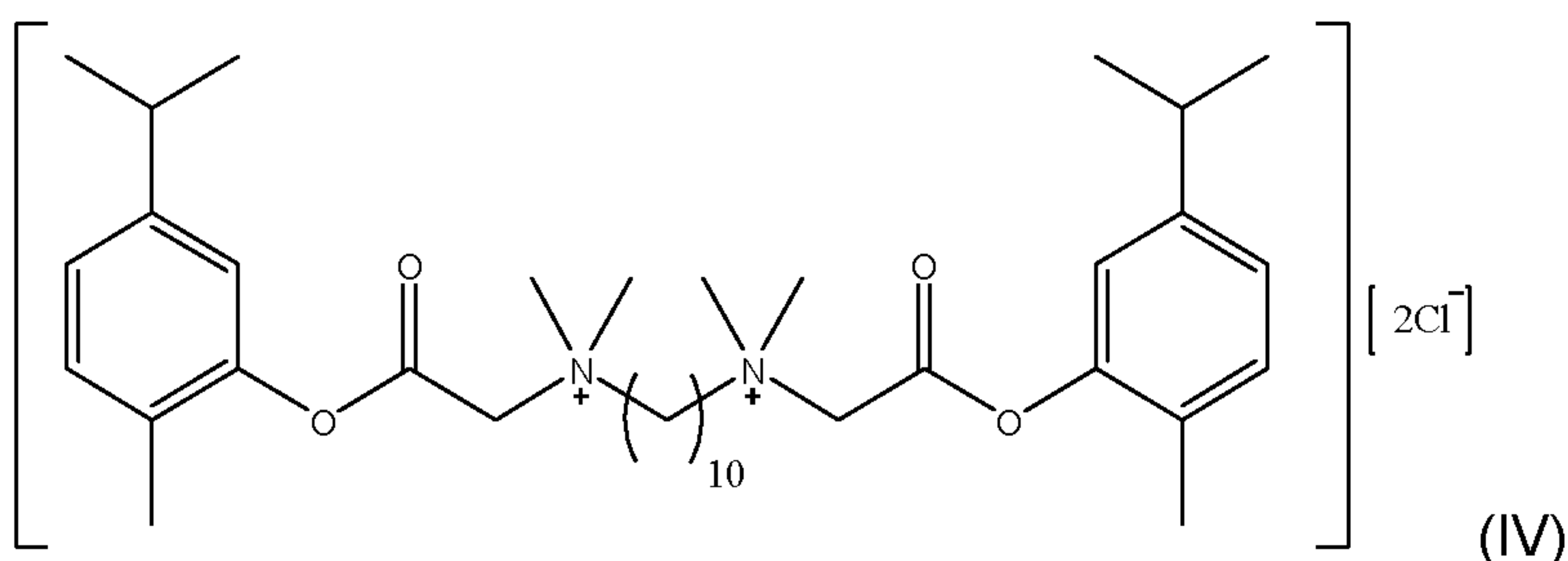
E and has the following formula (Ib), wherein the ester oxygen is bonded to the aromatic ring of each E at the same position, the position being 2 or 3; R_E is H or halide;

and wherein X is 2, 4, 3 or 6.

The present invention will now be described with reference to the following examples.

Example 1

5 Synthesis of the compound of formula (IV).



In a first step, 1,10-dibromodecane is reacted with 2 molar equivalents of dimethylamine to form 1,10-Bis(dimethylamino)decane. The reaction takes place at 4-5° C in a suitable solvent such as benzene, diethyl ether or dimethylamine and is followed by a step of acid extraction followed by alkaline treatment and extraction with diethyl ether. The extracted fractions are dried over magnesium sulphate and then purified by vacuum distillation.

In a second step, Carvacrol (2-Methyl-5-(1-methylethyl)-phenol) is reacted with chloroacetyl chloride. The reaction is carried out at -10° C for 1 hour and then stirred at room temperature for 12 hours. The reaction mixture is then washed with acid, followed by treatment with sodium bicarbonate and then water. The organic layer is dried over sodium sulphate, filtered and the solvent is removed under vacuum.

In a third step, 2 molar equivalents of the compound formed in the second step is reacted with one molar equivalent of 1,10-Bis(dimethylamino)decane to form the compound of formula (IV). The reaction in the third step is carried out using an appropriate solvent such as acetonitrile and the reaction mixture is stirred for 24 hours.

It will be appreciated that further purification and separation steps may also be included in the process, for example between each of the above steps and also after the process is complete to purify the final compound having formula (IV).

Separation steps may include steps of performing column chromatography, low pressure liquid chromatography, high performance liquid chromatography and the like. Purification steps may include standard purification processes known in the art, for example, filtration, evaporation,

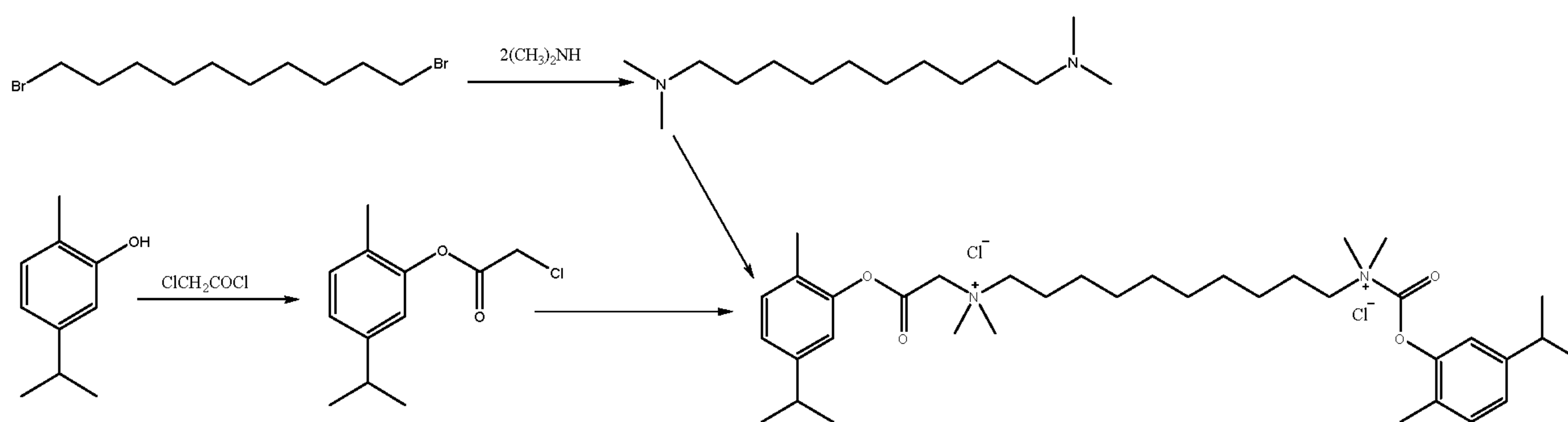
liquid-liquid extraction, crystallisation, adsorption, recrystallization, chromatography, distillation and the like.

The compound of formula (IV) has the following systematic name, formula and molecular weight:

- 5 Systematic name: N1,N10-bis(2-(5-isopropyl-2-methylphenoxy)-2-oxoethyl)-
N1,N1,N10,N10-tetramethyldecane-1,10-diaminium dichloride

Formula: $C_{38}H_{62}N_2O_4^{+2} 2Cl^-$

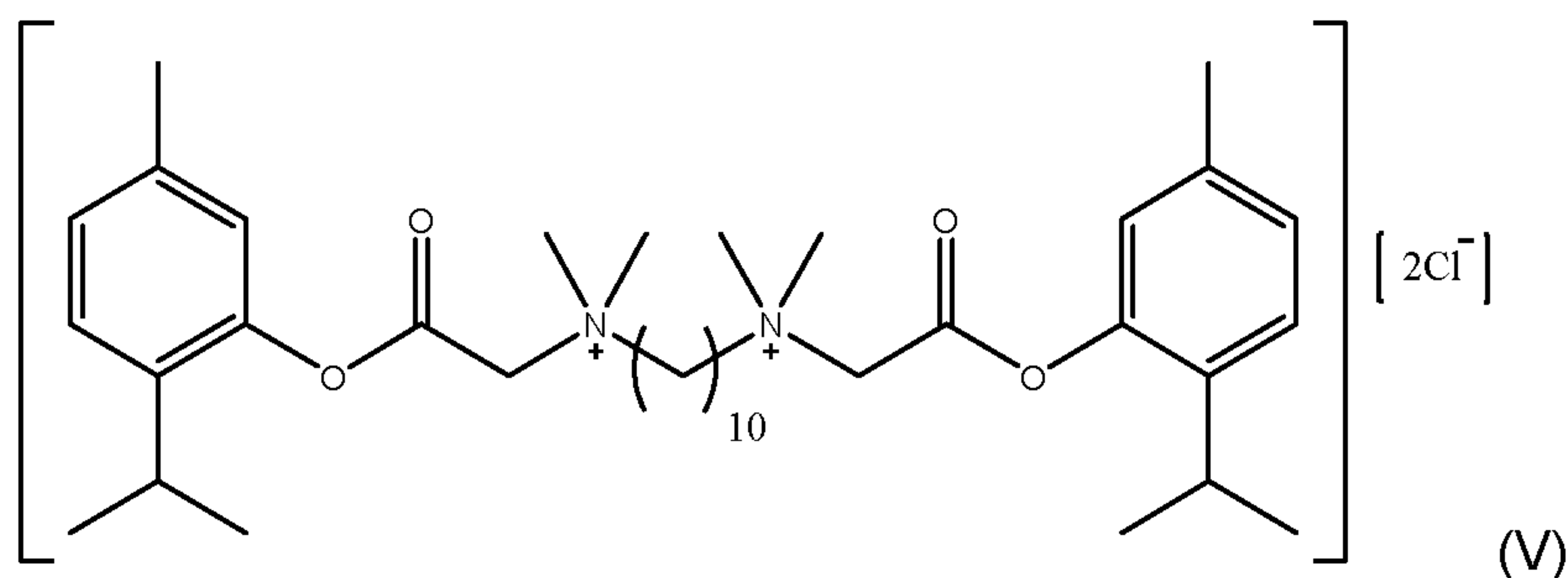
Molecular weight: 681.81



10 Scheme 1

Example 2

Synthesis of the compound of formula (V)



- 15 In a first step, 1,10-dibromodecane is reacted with 2 molar equivalents of dimethylamine to form 1,10-Bis(dimethylamino)decane. The reaction takes place at 4-5° C in benzene in a suitable solvent such as benzene, diethyl ether or dimethylamine and is followed by a step of acid extraction followed by alkaline treatment and extraction with diethyl ether. The extracted fractions are dried over magnesium sulphate and then purified by vacuum distillation.

In a second step, thymol (2-isopropyl-5-methylphenol) is reacted with chloroacetyl chloride. The reaction is carried out at -10°C for 1 hour and then stirred at room temperature for 12 hours. The reaction mixture is then washed with acid, followed by treatment with sodium bicarbonate and then water. The organic layer is dried over sodium sulphate, filtered and the solvent is removed under vacuum.

In a third step, 2 molar equivalents of the compound formed in the second step is reacted with one molar equivalent of 1,10-Bis(dimethylamino)decane to form the compound of formula (V). The reaction in the third step is carried out using an appropriate solvent such as acetonitrile and the reaction mixture is stirred for 24 hours.

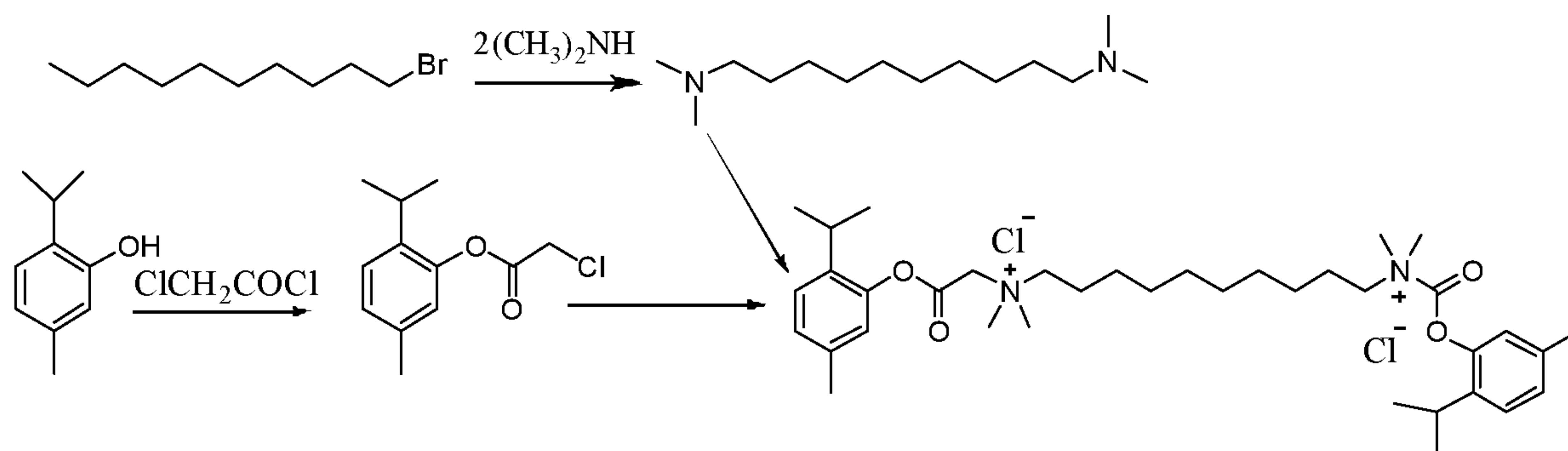
It will be appreciated that further purification and separation steps may also be included in the process, for example between each of the above steps and also after the process is complete to purify the final compound having formula (V).

Separation steps may include steps of performing column chromatography, low pressure liquid chromatography, high performance liquid chromatography and the like. Purification steps may include standard purification processes known in the art, for example, filtration, evaporation, liquid-liquid extraction, crystallisation, adsorption, recrystallization, chromatography, distillation and the like.

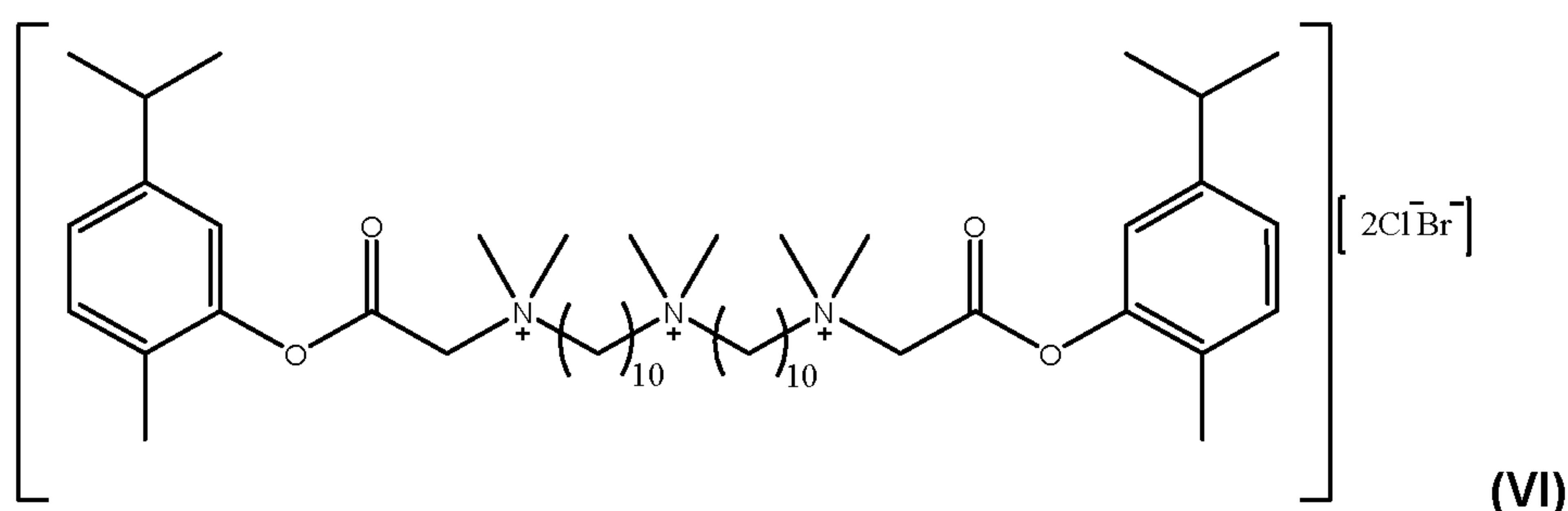
Systematic Name: N1,N10-bis(2-(2-isopropyl-5-methylphenoxy)-2-oxoethyl)-N1,N1,N10,N10-tetramethyldecane-1,10-diaminium dichloride

Formula: $\text{C}_{38}\text{H}_{62}\text{N}_2\text{O}_4^{+2} 2\text{Cl}^-$

Molecular Weight: 681.81



Scheme 2

Example 3**Synthesis of the compound of formula (VI)**

In a first step, 2 molar equivalents of 1,10-Dibromodecane are reacted with 3 molar equivalents
 5 of dimethylamine. The reaction takes place at 4-5° C in a suitable solvent such as benzene or diethyl ether and is followed by a step of acid extraction followed by alkaline treatment and extraction with diethyl ether. The extracted fractions are dried over magnesium sulphate and then purified by vacuum distillation.

In a second step, carvacrol (2-Methyl-5-(1-methylethyl)-phenol) is reacted with chloroacetyl
 10 chloride. The reaction is carried out at -10 C for 1 hour and then stirred at room temperature for 12 hours. The reaction mixture is then washed with acid, followed by treatment with sodium bicarbonate and then water. The organic layer is dried over sodium sulphate, filtered and the solvent is removed under vacuum.

In a third step, one molar equivalent of the compound formed in step 1 is reacted with the 2
 15 molar equivalents of the compound formed in step 2 to form the compound having formula (VI). The reaction in the third step is carried out using an appropriate solvent such as acetonitrile and the reaction mixture is stirred for 24 hours.

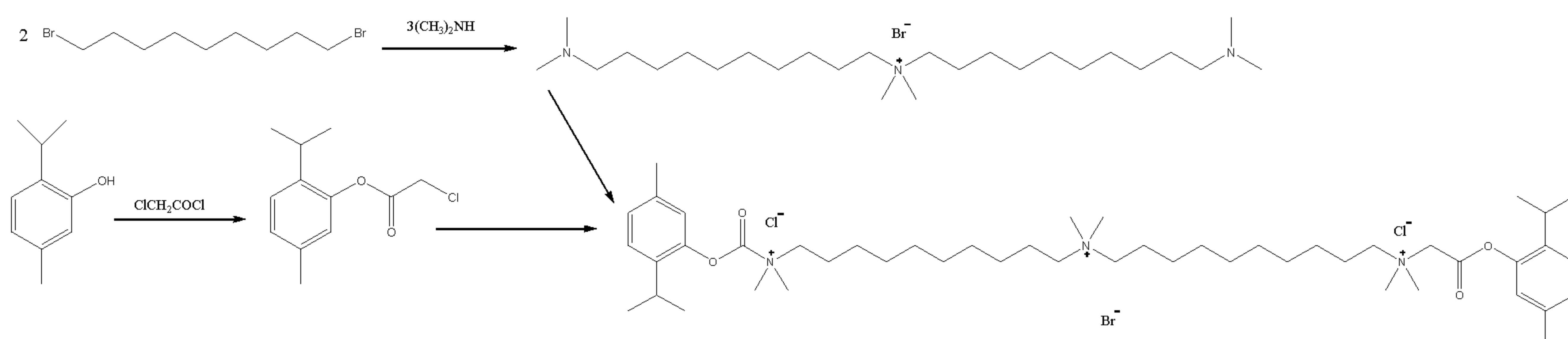
It will be appreciated that further purification and separation steps may also be included in the process, for example between each of the above steps and also after the process is complete
 20 to purify the final compound having formula (VI).

Separation steps may include steps of performing column chromatography, low pressure liquid chromatography, high performance liquid chromatography and the like. Purification steps may include standard purification processes known in the art, for example, filtration, evaporation, liquid-liquid extraction, crystallisation, adsorption, recrystallization, chromatography, distillation
 25 and the like.

Systematic Name: N1-(2-(5-isopropyl-2-methylphenoxy)-2-oxoethyl)-N10-(10-((2-(5-isopropyl-2-methylphenoxy)-2-oxoethyl)dimethylammonio)decyl)-N1,N1,N10,N10-tetramethyldecane-1,10-diaminium bromide dichloride

Formula: $C_{50}H_{88}N_3O_4^{+3} Br^-2 Cl^-$

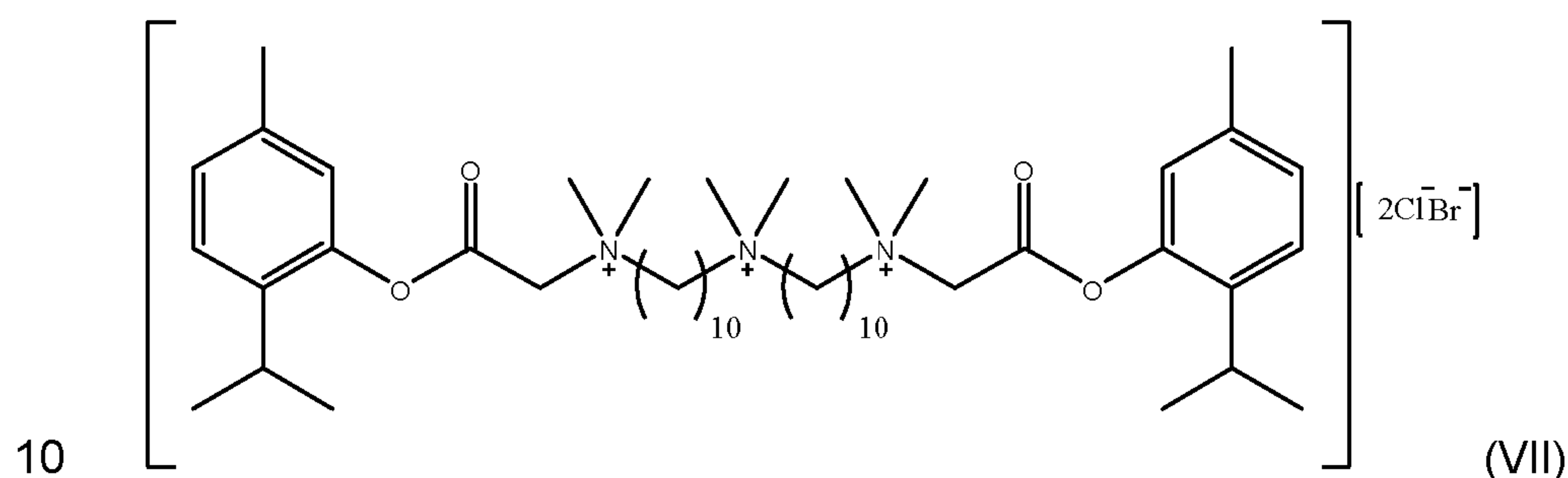
5 Molecular Weight: 946.06



Scheme 3

Example 4

Synthesis of the compound of formula (VII)



In a first step, 2 molar equivalents of 1,10-Dibromodecane are reacted with 3 molar equivalents of dimethylamine. The reaction takes place at 4-5° C in a suitable solvent such as benzene or diethyl ether and is followed by a step of acid extraction followed by alkaline treatment and extraction with diethyl ether. The extracted fractions are dried over magnesium sulphate and then purified by vacuum distillation.

In a second step, thymol (2-isopropyl-5-methylphenol) is reacted with chloroacetyl chloride. The reaction is carried out at -10 C for 1 hour and then stirred at room temperature for 12 hours. The reaction mixture is then washed with acid, followed by treatment with sodium bicarbonate and then water. The organic layer is dried over sodium sulphate, filtered and the solvent is removed under vacuum.

In a third step, one molar equivalent of the compound formed in step 1 is reacted with the 2 molar equivalents of the compound formed in step 2 to form the compound having formula (VII). The reaction in the third step is carried out using an appropriate solvent such as acetonitrile and the reaction mixture is stirred for 24 hours.

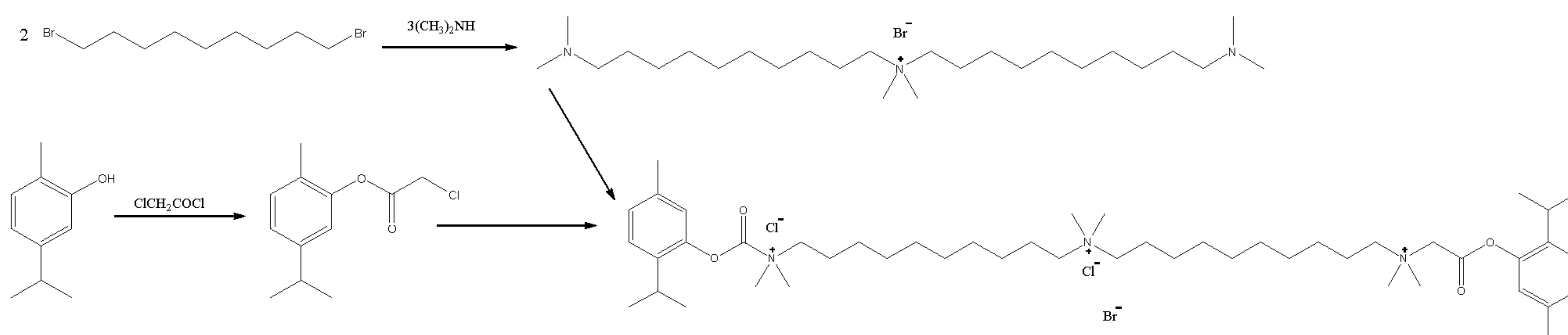
- 5 It will be appreciated that further purification and separation steps may also be included in the process, for example between each of the above steps and also after the process is complete to purify the final compound having formula (VII).

Separation steps may include steps of performing column chromatography, low pressure liquid chromatography, high performance liquid chromatography and the like. Purification steps may
10 include standard purification processes known in the art, for example, filtration, evaporation, liquid-liquid extraction, crystallisation, adsorption, recrystallization, chromatography, distillation and the like.

Systematic Name: N1-(2-(2-isopropyl-5-methylphenoxy)-2-oxoethyl)-N10-(10-((2-(2-isopropyl-5-methylphenoxy)-2-oxoethyl)dimethylammonio)decyl)-
15 N1,N1,N10,N10-tetramethyldecane-1,10-diaminium bromide dichloride

Formula: $C_{50}H_{88}N_3O_4^{+3} Br^-2Cl^-$

Molecular Weight: 946.06



Scheme 4

- 20 It will be appreciated that to synthesis the Bromine complexes defined by formula XI to XIV, the compounds of formula IV to VII are treated with bromine to form the complexes of formulas XI to XIV. It will be appreciated that further purification and separation steps may also be included in this process.

Example 5

- 25 **Minimum inhibitory concentration (MIC) determination by broth micro dilution**

Equipment

- McFarland standard 0.5
- Falcon round-bottom 5 ml tubes
- Disposable loops (1 µl and 10 µl)
- Pipettes tips (0.5 µl - 1000 µl)
- Tissue Culture plate, 96well
- Multichannel micropipettes (5-50 µl),(30-300 µl)
- Disposable Petri dishes
- Disposable reagent reservoirs

Media

- Sterile normal saline
- TSB (Tryptic Soy Broth)
- TSA (Tryptic Soy Agar)
- 0,02% resazurin sterile solution

Bacterial strains

- *Staphylococcus aureus* ATCC -6538
- *Escherichia coli* ATCC-8739

Procedure**Standardisation of inoculum**

From a pure o/n culture, material from at least 3-4 colonies was chosen and suspended totally in 2 ml saline in tubes. The suspensions were mixed.

The inoculums were standardized according to the scale of 0.5 MacFarland (dilution factor 1:10, sterile saline solution) to obtain the final concentration of 1.5×10^4 cfu/ml. The inoculums were mixed. The suspension was used for inoculation within 15 minutes.

Inoculation and incubation

Each sample was dissolved in an appropriate solvent (water / 96% ethanol) to a concentration of 5000 µg / ml. Using the method of serial dilutions, the concentration of the initial solution was adjusted to 625 µg / ml for gram negative bacteria and 78 µg / ml for gram positive bacteria. For fungi, the working concentration was 1250 µg / ml.

The tests were performed in 96 well plates, in which each well received 100 µl of sterile TSB.

100 µl of the initial concentration of the sample was added to the first well. Serial dilutions were made by transferring 100 µl from each previous well to the subsequent one (dilution factor 1: 1). In each well, 20 µl of the inoculum is added. Each well had a final volume of 120 µl.

The microbial growth, sterility of the medium and the solvent were controlled simultaneously.

The plates were incubated at 37 ± 1 °C, for 24 h for bacteria and at 34 ± 1 °C, for 48 h for

yeasts . The inhibition of growth of bacteria was revealed by the addition of resazurin sterile solution (20 µl, 0.02 %, w/v) and re-incubation for 3 hours. Minimum inhibitory concentration (MIC), which is defined as the lowest concentration of sample capable of inhibiting the growth of microorganisms, was determined by the permanence of blue coloration in the wells. A change of color from blue to red (due to the reduction of dye) indicated bacterial growth. The wells that showed no apparent growth were selected to evaluate the MIC, which was determined by the absence of microbial growth on plates containing TSB.

The results of these experiments are set out below in the following tables.

***Staphylococcus aureus* ATCC 6538 4.5x10³ Cfu/ml**

Compound	MIC / µg/mL
Comparative compound 1	1.95
Formula VII	0.98

Table 1

***Escherichia coli* ATCC-8739 6.5x10³ Cfu/ml**

Compound	MIC / µg/mL
Comparative compound 1	7.8
Formula VII	3.9

Table 2

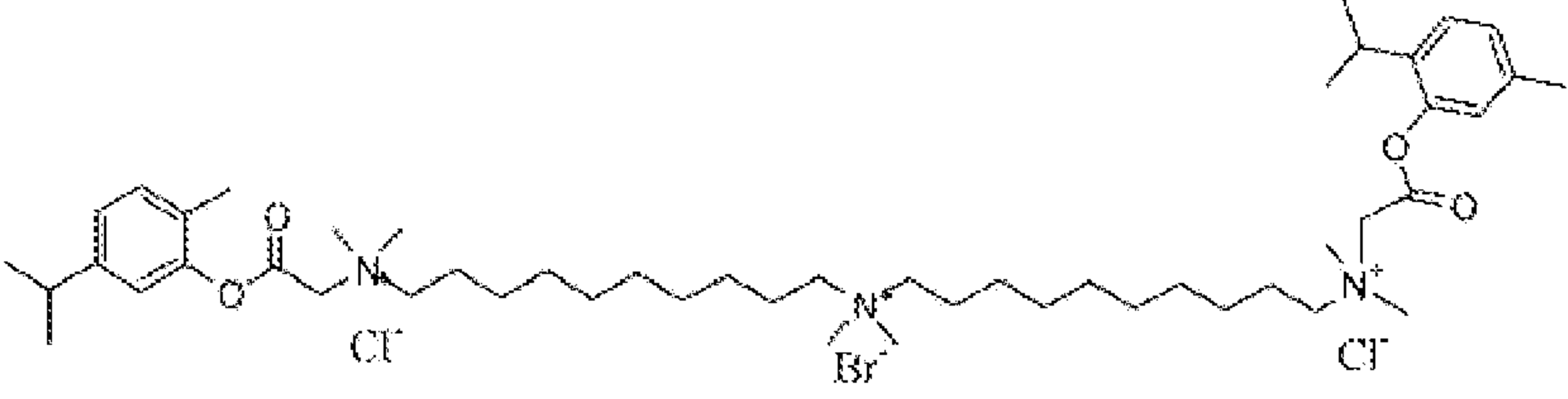
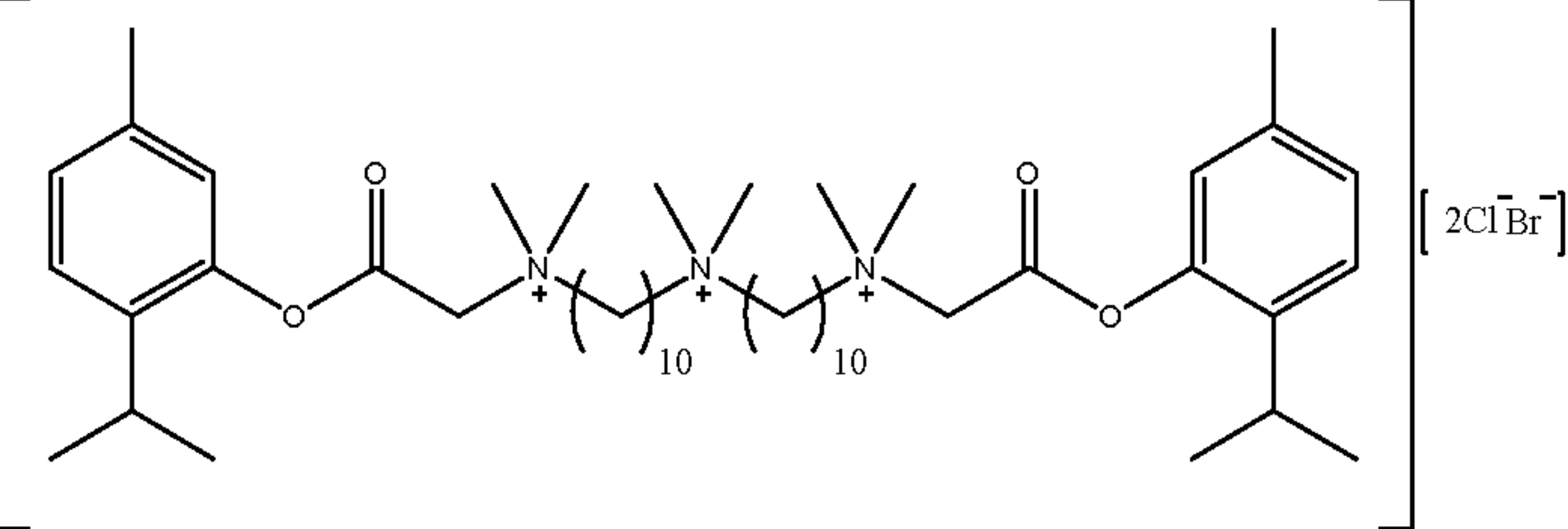
Compound	Structure
Comparative Compound 1	
Formula VII	

Table 3

Example 6**MIC determination by broth micro dilution****Equipment**

- 5
- McFarland standard 0.5
 - Falcon round-bottom 5 ml tubes
 - Disposable loops (1 µl and 10 µl)
 - Pipettes tips (0.5 µl - 1000 µl)
 - Tissue Culture plate, 96well
- 10
- Multichannel micropipettes (5-50 µl),(30-300 µl)
 - Disposable Petri dishes
 - Disposable reagent reservoirs

Media

- 15
- Sterile normal saline
 - TSB (Tryptic Soy Broth)
 - TSA (Tryptic Soy Agar)
 - 0,02% resazurin sterile solution

Bacterial strains

- 20
- *Staphylococcus aureus* ATCC -6538
 - *Escherichia coli* ATCC-8739
 - *Pseudomonas aeruginosa* ATCC-9027
 - *Candida albicans* ATCC -10231
- 25
- *Candida albicans* NCTC-885-653
 - *Saccharomyces cerevisiae* ATCC-9763
 - *Salmonella enterica* serovar Typhimurium ATCC 14028
 - *Saccharomyces cerevisiae* ATCC-2601

Procedure**Standardisation of inoculum**

- 35
- From a pure o/n culture, material from at least 3-4 colonies was chosen. The material was suspended totally in 2 ml saline in tubes and mixed.

The inoculums were standardized according to the scale of 0.5 MacFarland (dilution factor 1:10, sterile saline solution) to obtain the final concentration of 1.5×10^4 cfu/ml. The inoculums were mixed. The suspension was used for inoculation within 15 minutes.

40

Inoculation and incubation

- Each sample was dissolved in an appropriate solvent (water/96% ethanol) to a concentration of 5000 µg / ml. Using the method of serial dilutions, the concentration of the initial solution was
- 45
- adjusted to 625 µg / ml for gram negative bacteria and 78 µg / ml for gram positive bacteria. For fungi the working concentration was 1250 µg / ml.

The tests were performed in 96 well plates, in which each well received 100 µl of sterile TSB. 100 µl of the initial concentration was added to the first well. Serial dilutions were made by transferring 100 µl from each previous well to the subsequent one (dilution factor 1: 1). In each well 20 µl of the inoculum was added. Each well had a final volume of 120 µl. The microbial growth, sterility of the medium and the solvent were controlled simultaneously. The plates were incubated at 37 ± 1 °C, for 24 hours for bacteria and at 34 ± 1 °C, for 48 hours for yeasts. The inhibition of growth of bacteria was revealed by the addition of resazurin sterile solution (20 µl, 0.02 %, w/v) and re-incubation for 3 h.

MIC, which is defined as the lowest concentration of sample capable of inhibiting the growth of microorganisms, was determined by the permanence of blue coloration in the wells. A change of color from blue to red (due to the reduction of dye) indicated the bacterial growth. The wells that showed no apparent growth were selected to evaluate the MIC, which was determined by the absence of microbial growth on plates containing TSB.

The results of these experiments are set out in the following tables.

***Escherichia coli* ATCC-8739 1.7x10⁴ Cfu/ml**

Compound	MIC / µg/mL
Comparative compound 2	7.8
Formula V	3.9
Formula IV	3.9
Vancomycin	78

Table 4

***Salmonella enterica* serovar *Typhimurium* ATCC 14028 1.3x10⁴ Cfu/ml**

Compound	MIC / µg/mL
Comparative compound 2	7.8
Formula IV	3.9
Vancomycin	78

Table 5

***Escherichia coli* ATCC-8739 6.6x10³ Cfu/ml**

Compound	MIC / µg/mL
Comparative compound 2	7.8
Formula V	3.9

Table 6

Pseudomonas aeruginosa ATCC-9027 1.9x10⁴ Cfu/ml

Compound	MIC / µg/mL
Comparative compound 2	7.8
Formula V	3.9

Table 7

5 *Escherichia coli* ATCC-8739 4.1x10³ Cfu/ml

Compound	MIC / µg/mL
Comparative compound 2	3.9
Formula V	1.95
Formula IV	1.95

Table 8

Pseudomonas aeruginosa ATCC-9027 4.7x10³ Cfu/ml

10

Compound	MIC / µg/mL
Comparative compound 2	1.95
Formula IV	0.98

Table 9

	MIC / µg/mL		
	Comparative compound 2	Formula V	Formula IV
Candida albicans ATCC 10231	15.6	3.9-7.8	3.9-7.8

Table 10

15

	Comparative compound 2	Formula V
Candida albicans NCTC 885-653	15.6	3.9-7.8

Table 11

Staphylococcus aureus ATCC 6538 4.5x10³ Cfu/ml

20

Compound	MIC / µg/mL
Comparative compound 2	1.95
Formula V	0.98

Table 12

25

Escherichia coli ATCC-8739 6.5x10³ Cfu/ml

Compound	MIC / µg/mL
Comparative compound 2	7.8
Formula V	3.9
Comparative compound 3	7.8
Formula XI	3.9

Table 13

5

Salmonella enterica serovar Typhimurium ATCC 14028 (log 4 conditions)

Compound	MIC / mKg/mL
Comparative compound 2	7.8
Formula IV	3.9

Table 14

10

Escherichia coli ATCC-8739 (log 4 conditions)

Compound	MIC / µg/mL
Comparative compound 2	7.8
Formula V	3.9
Formula IV	3.9

Table 15

15

Pseudomonas aeruginosa ATCC-9027 (Log 4 conditions)

Compound	MIC / µg/mL
Comparative compound 3	7.8
Formula XI	3.9

Table 16

20

The means of MIC for different isomers (µg/ml) were tested against various fungal strains that were clinical isolate resistant or sensitive to Fluconazole and Voriconazole (resistance indicated for more than 20 fungal generations, cultivated in the presence of Fluconazole or Voriconazole).

MIC values for Voriconazole and Fluconazole for all tested strains were 255 µg/ml and 511 µg/ml respectively.

25

Candida albicans ATCC-10231 Voriconazole resistant (20 G)

Compound	MIC / µg/mL
Comparative compound 2	7.8
Formula V	3.9

Table 17

30

Candida albicans ATCC-10231 Fluconazole resistant (20 G)

Compound	MIC / µg/mL
Comparative compound 2	15.6
Formula V	7.8

5 **Candida albicans NTCT- 885-653 Voriconazole resistant (20 G)**

Compound	MIC / µg/mL
Comparative compound 2	1.95
Formula V	0.98

Table 18

Saccharomyces cerevisiae ATCC-9763 Fluconazole resistant (20 G)

10

Compound	MIC / µg/mL
Comparative compound 2	3.9
Formula IV	0.98

Table 19

Saccharomyces cerevisiae ATCC-2601 Fluconazole resistant (20 G)

Compound	MIC / µg/mL
Comparative compound 2	1.95
Formula IV	0.98
Formula V	0.98

15

Table 20

Example 7

Antiviral activity

20 MRC5 cells were seeded in 96 well plates at a density of 20,000 cells/well and cultured at 37 °C under 5% CO₂ overnight. The next day, a medium containing serially diluted compounds and the virus were added to the wells. The resulting cultures were incubated at 37 °C and under 5% CO₂. Four days post infection, the medium was replenished. Seven days post infection, fluorescence intensity was determined using Acumen Cellista. Antiviral activity of the
25 compounds was calculated based on the inhibition of expression of GFP at each concentration normalized by the cell control. Cytotoxicity of the compounds was assessed under the same conditions, but without virus infection, in parallel. Cell viability was measured with CCK8 following the manufacturer’s manual.

Antiviral activity and cytotoxicity of the compounds was expressed as % Inhibition and % Viability, respectively, and calculated with the formulas below:

$$\text{Inhibition (\%)} = 100 - (\text{Raw data CPD} - \text{Average CC}) / (\text{Average VC} - \text{Average CC}) * 100$$

$$\text{Viability (\%)} = (\text{Raw data CPD} - \text{Average MC}) / (\text{Average CC} - \text{Average MC}) * 100$$

- 5 Raw data CPD indicates the values of the compound-treated wells; Average VC, Average CC and Average MC indicate the average values of the virus control, cell control and medium control wells, respectively.

EC50 and CC50 values were calculated using the GraphPad Prism software.

Virus	Cell line	Compound treatment duration	Detection reagent
US3-6-EGFP-HCMV-AD169	MRC5	7/Fluorometry	GFP, CCK8

10 Table 21

The results of the experiments are set out below in table 22.

Compound	EC ₅₀ (µg/ml)	CC ₅₀ (µg/ml)	SI (CC ₅₀ /EC ₅₀)
Comparative compound 2	41.47	>120.00	>2.89
Formula IV	32.75	>120.00	>3.66
Comparative compound 3	18.94	23.45	1.24
Formula XI	15.76	32.92	2.09

Table 22

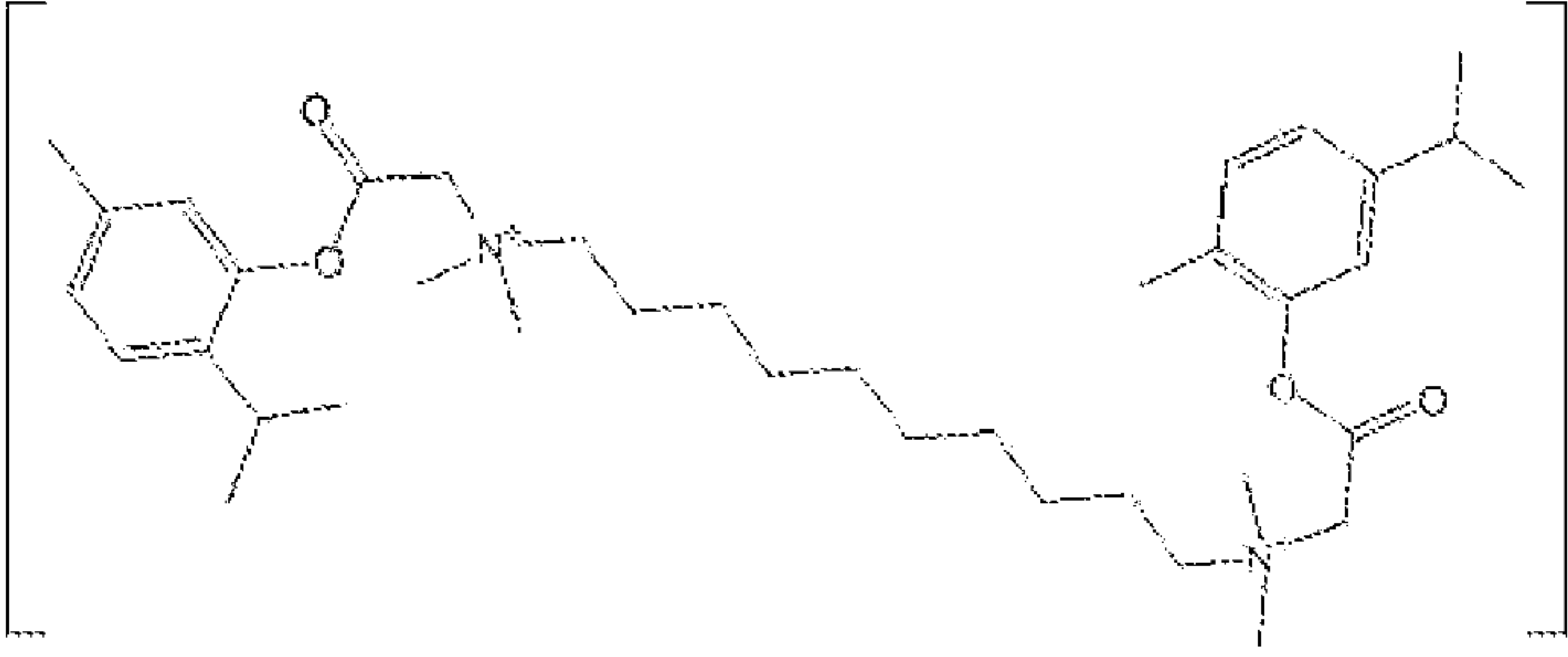
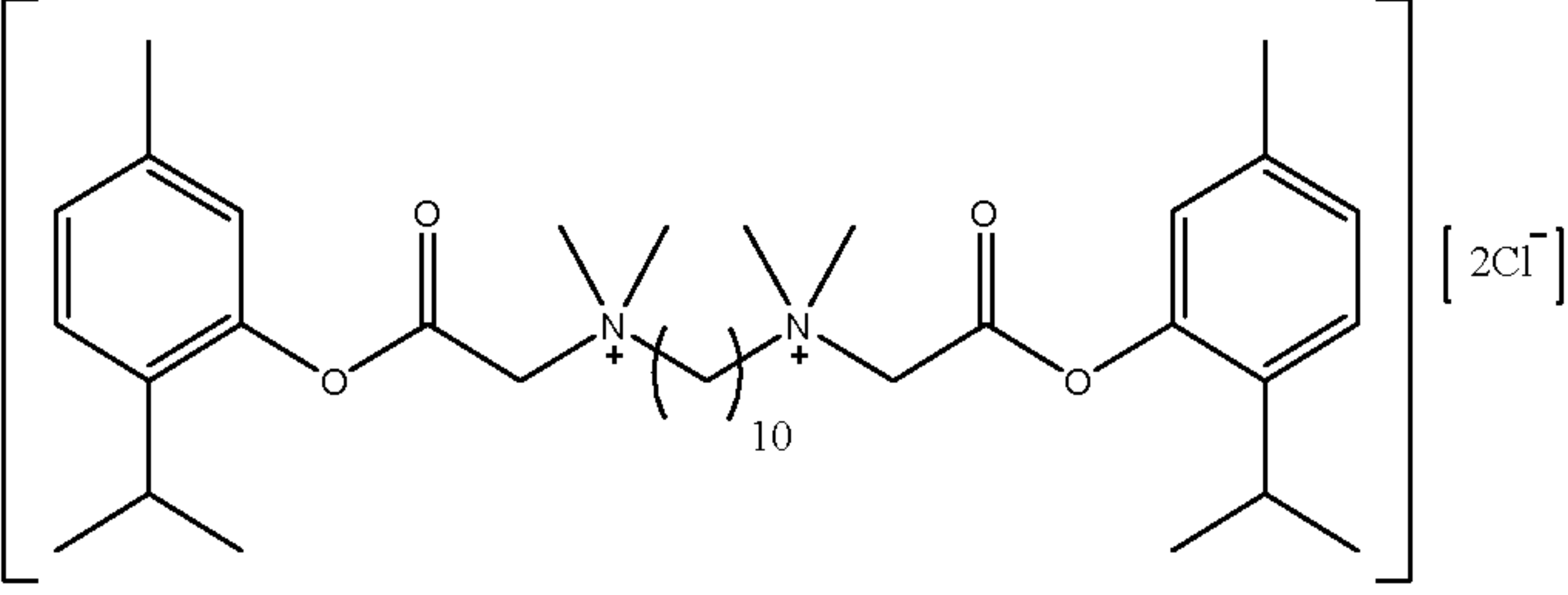
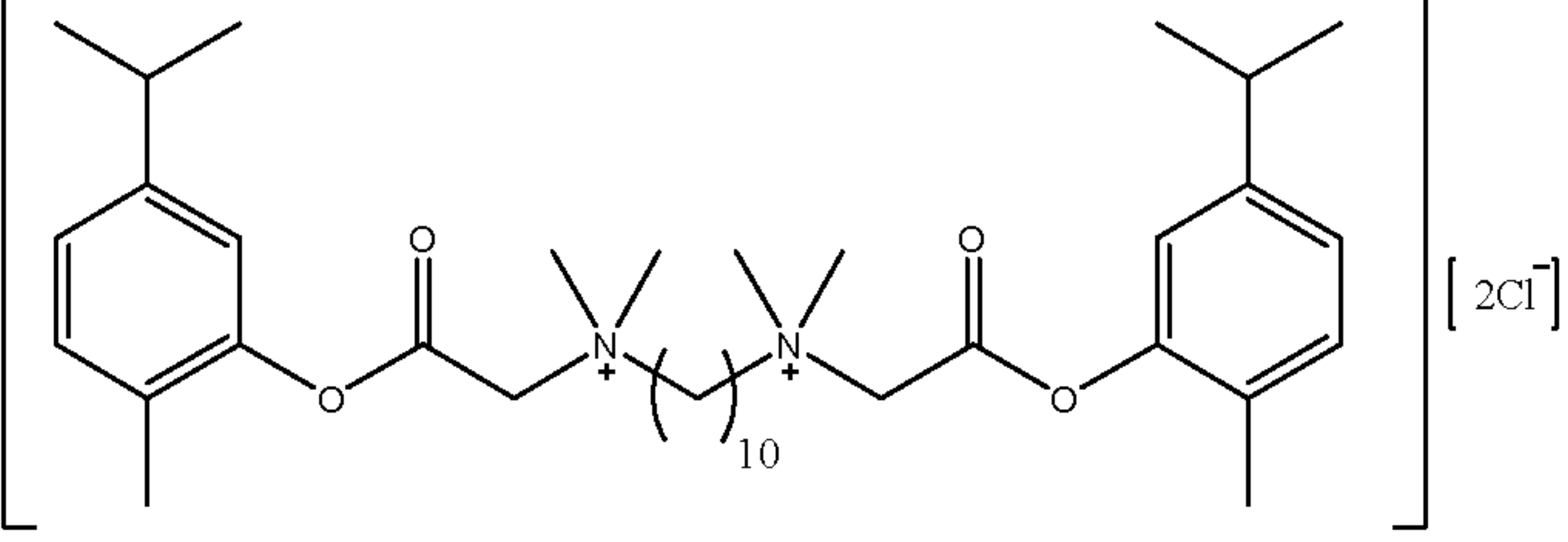
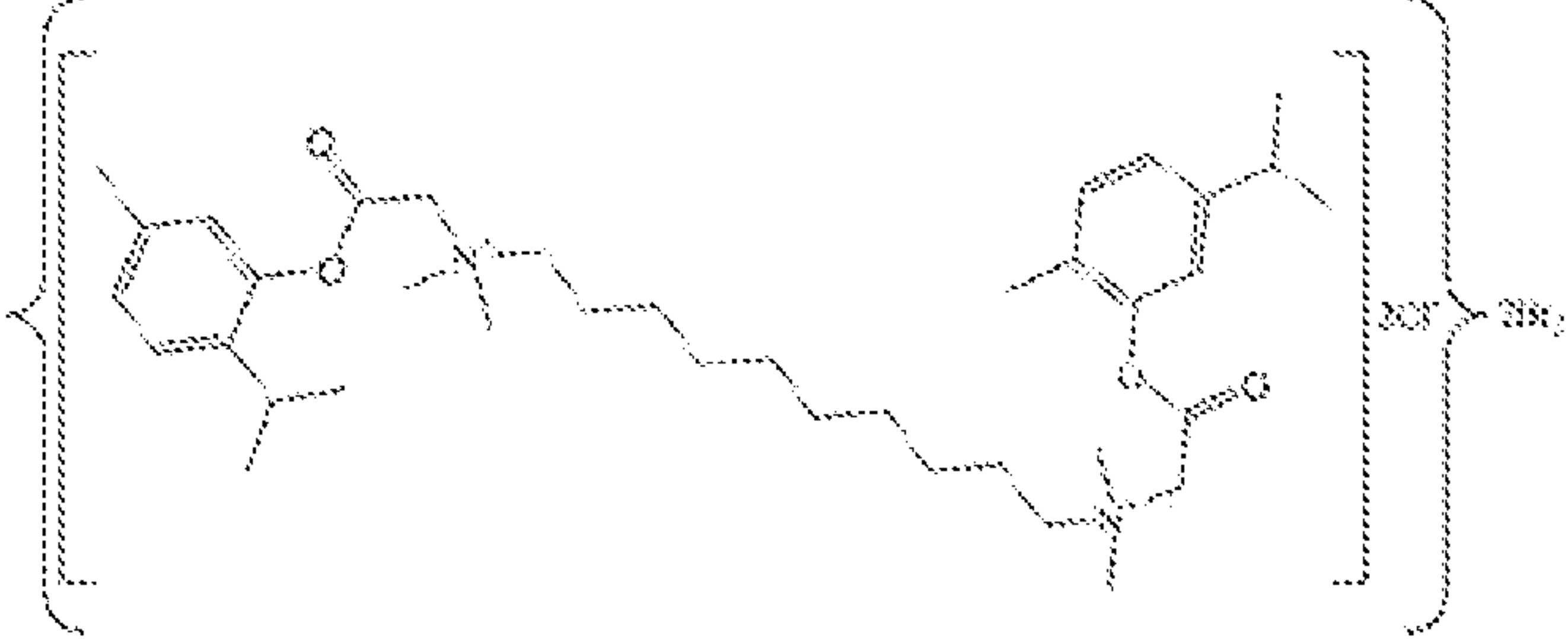
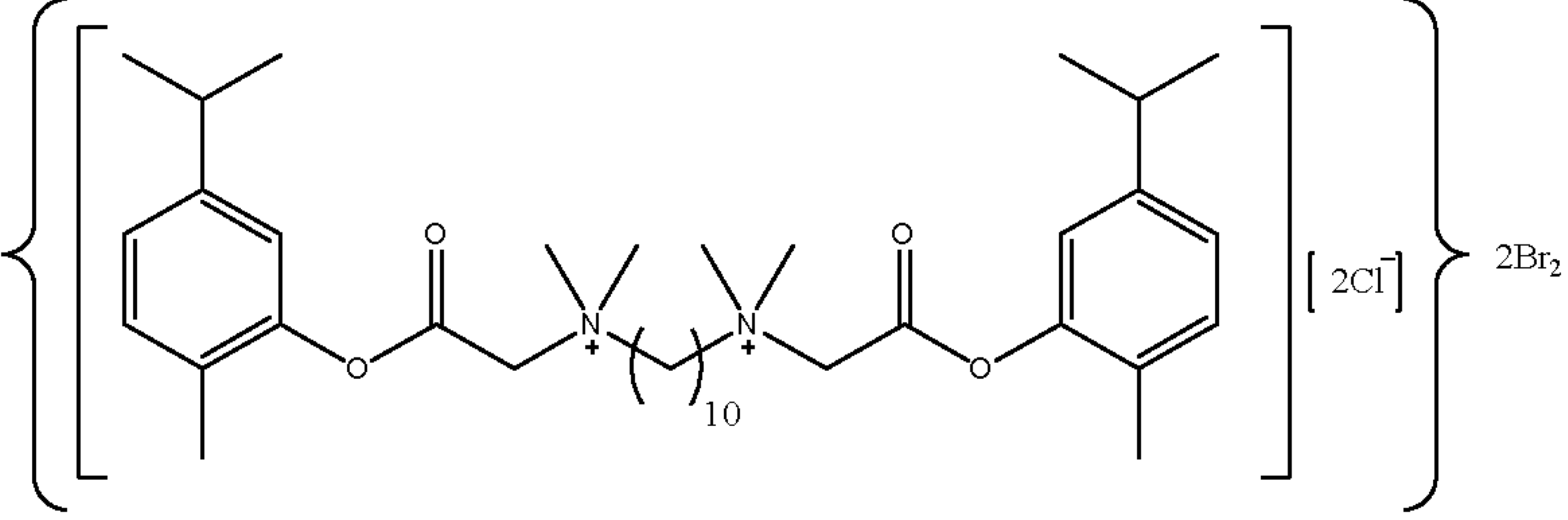
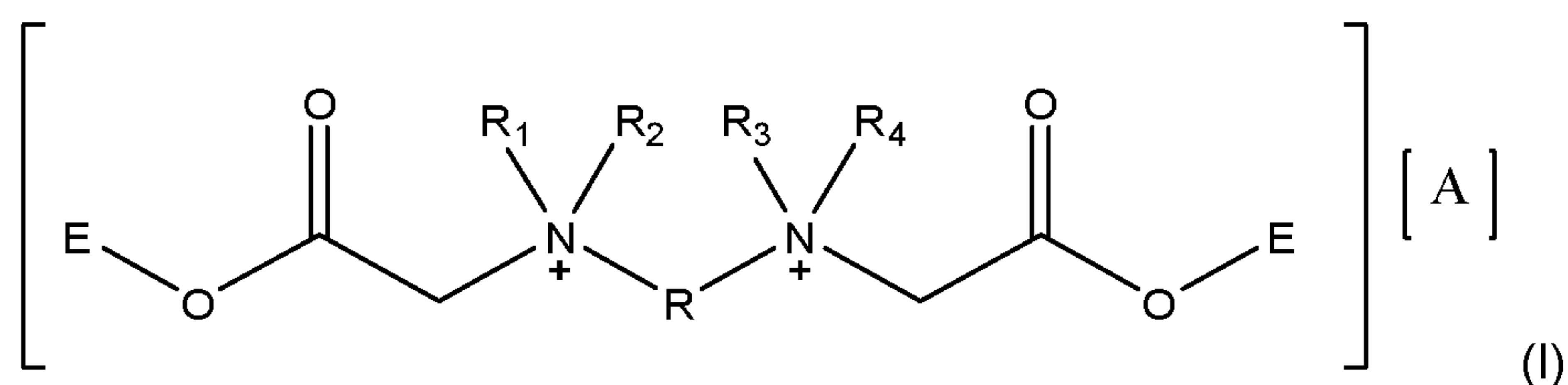
Compound	Structure
Comparative compound 2	
Formula V	
Formula IV	
Comparative compound 3	
Formula XI	

Table 23

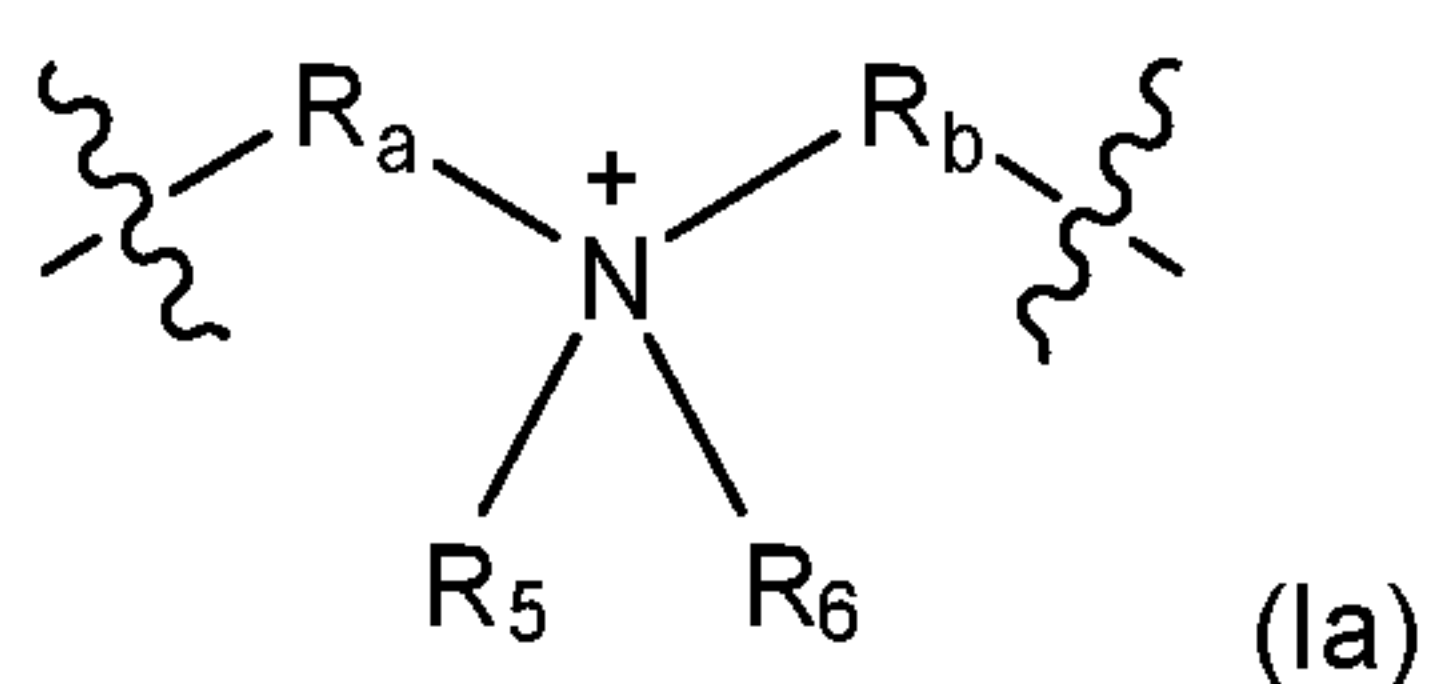
Claims

1. A compound having the following formula:



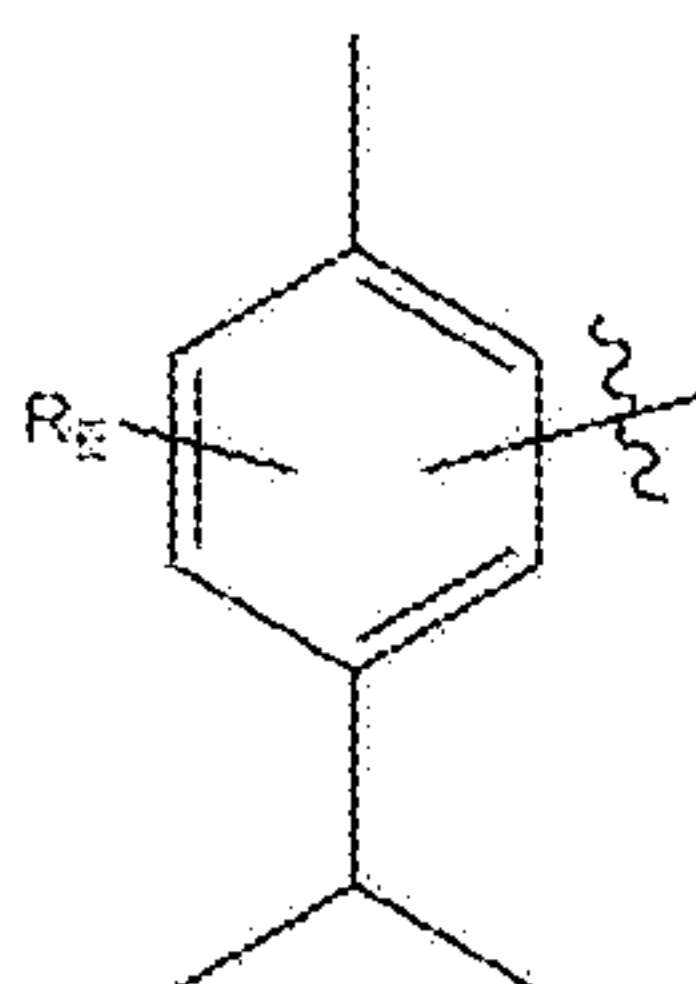
wherein R is an alkylene chain having between 8 and 20 carbon atoms, and A is one or more
5 anions having a total charge of -2,

or R is a quaternary amine having the following formula:



wherein R_a and R_b are each an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -3;

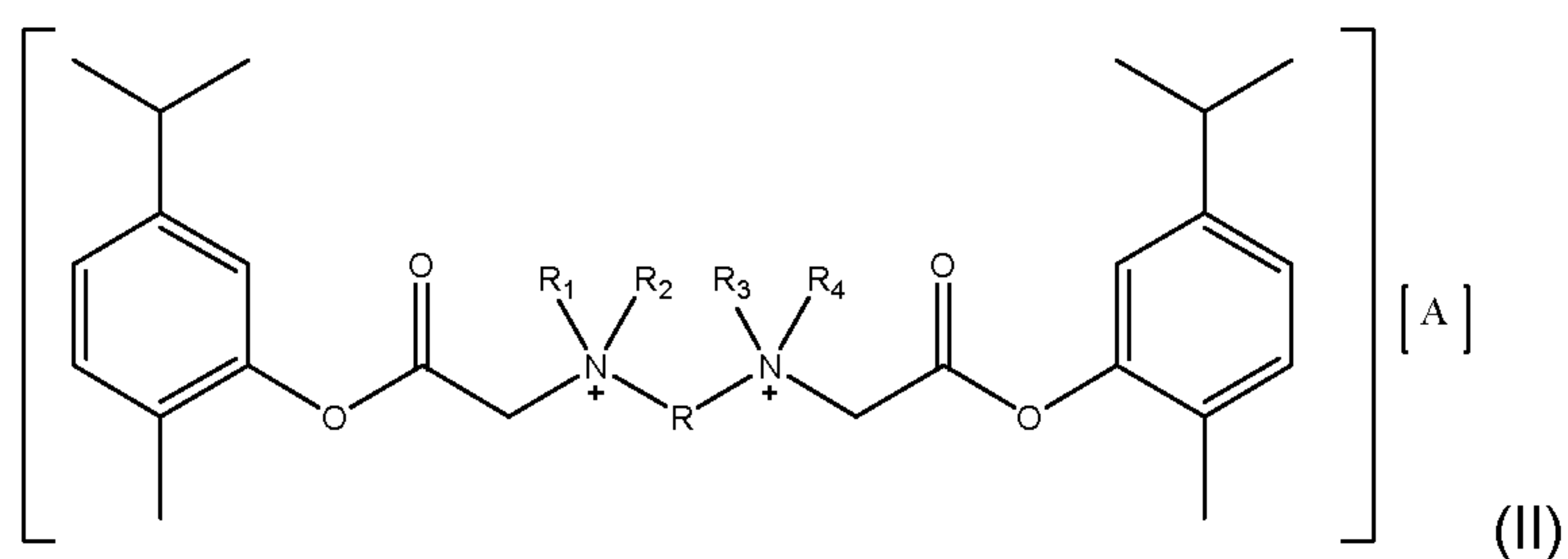
- 10 $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5$ and R_6 are each independently selected from C_{1-10} alkyl and H;



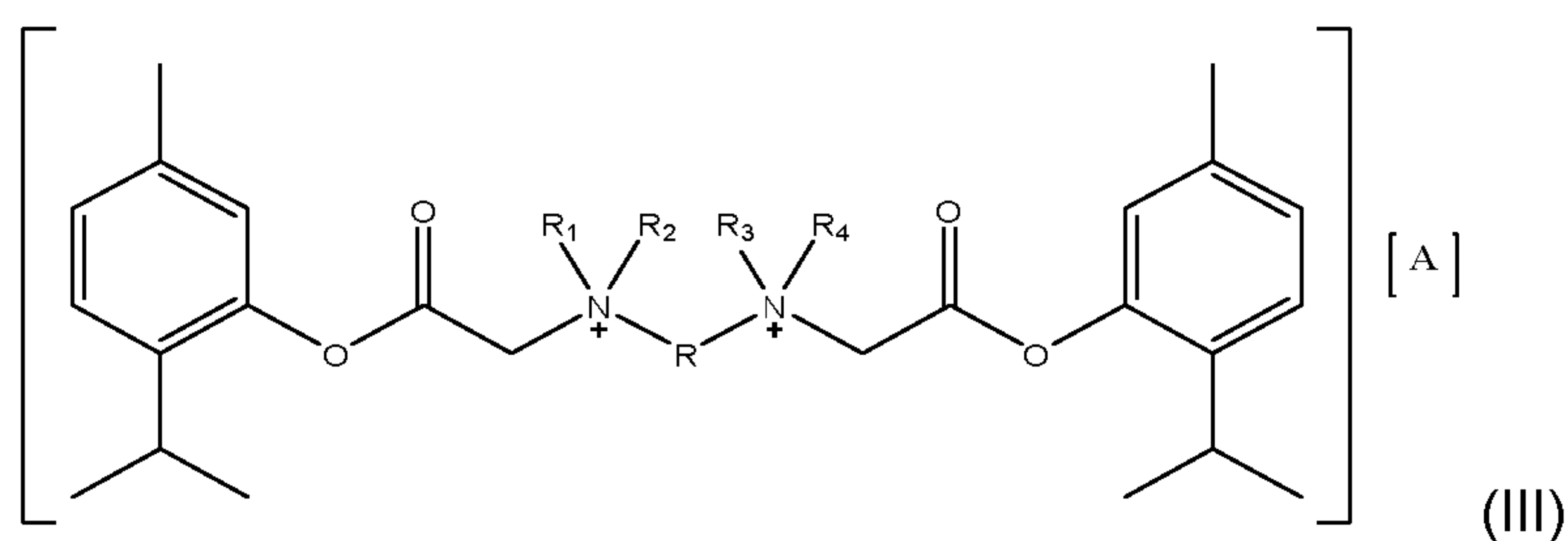
E has the following formula (Ib), wherein the ester oxygen is bonded to the aromatic ring of each E at the same position, the position being position 2 or 3; and wherein R_E is H or a halide.

2. A compound according to claim 1, having the following formula:

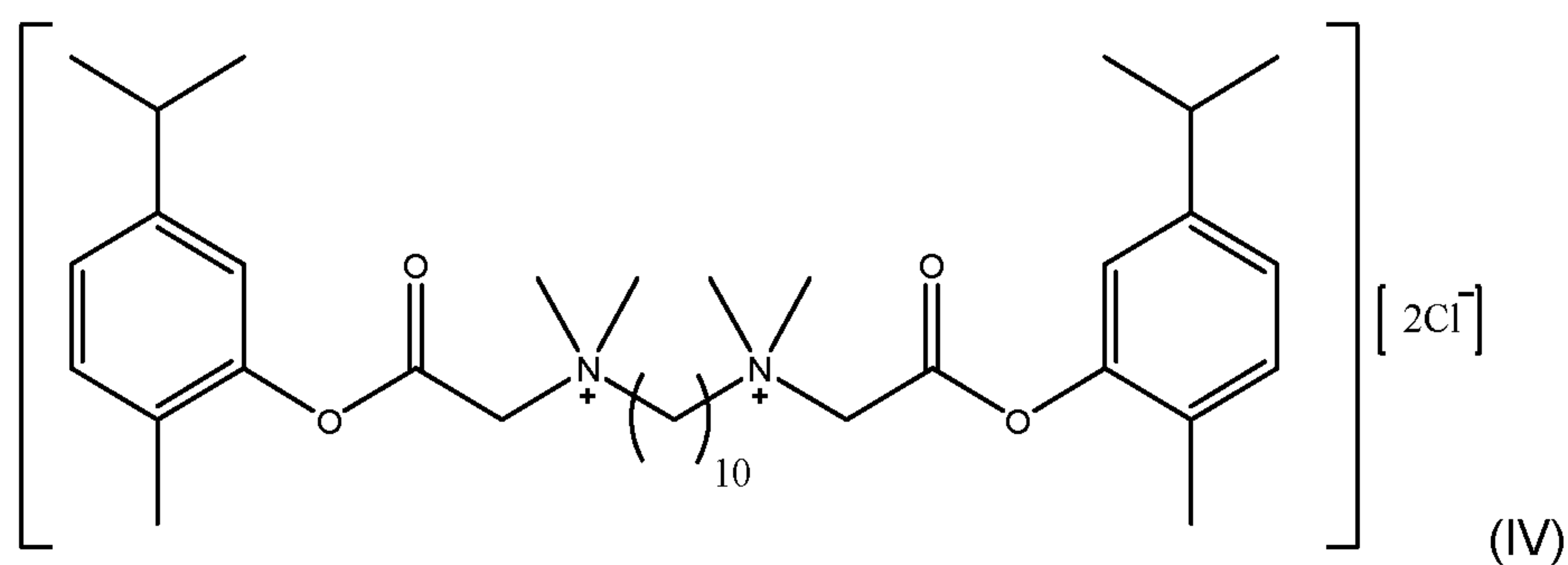
35



or

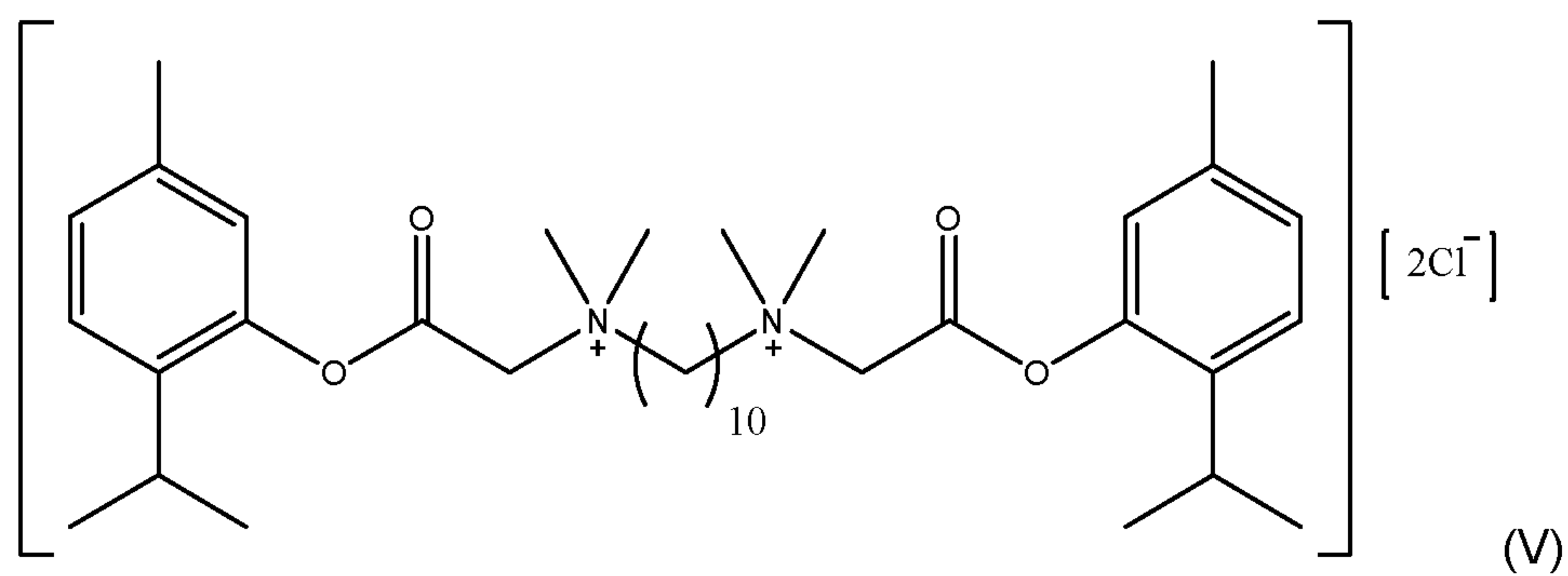


3. A compound according to claim 1, wherein R is a saturated linear alkylene chain having
5 between 8 and 16 carbon atoms, for example 10 carbon atoms.
4. A compound according to claim 1, wherein R_a and R_b are each a saturated linear alkylene chain having between 8 and 16 carbon atoms, for example 10 carbon atoms.
5. A compound according to any preceding claim, wherein the one or more anions are selected from chloride anions and bromide anions.
- 10 6. A compound according to any preceding claim, wherein R₁, R₂, R₃, R₄, R₅ and R₆ are each methyl.
7. A compound according to claim 1, having the following formulae:

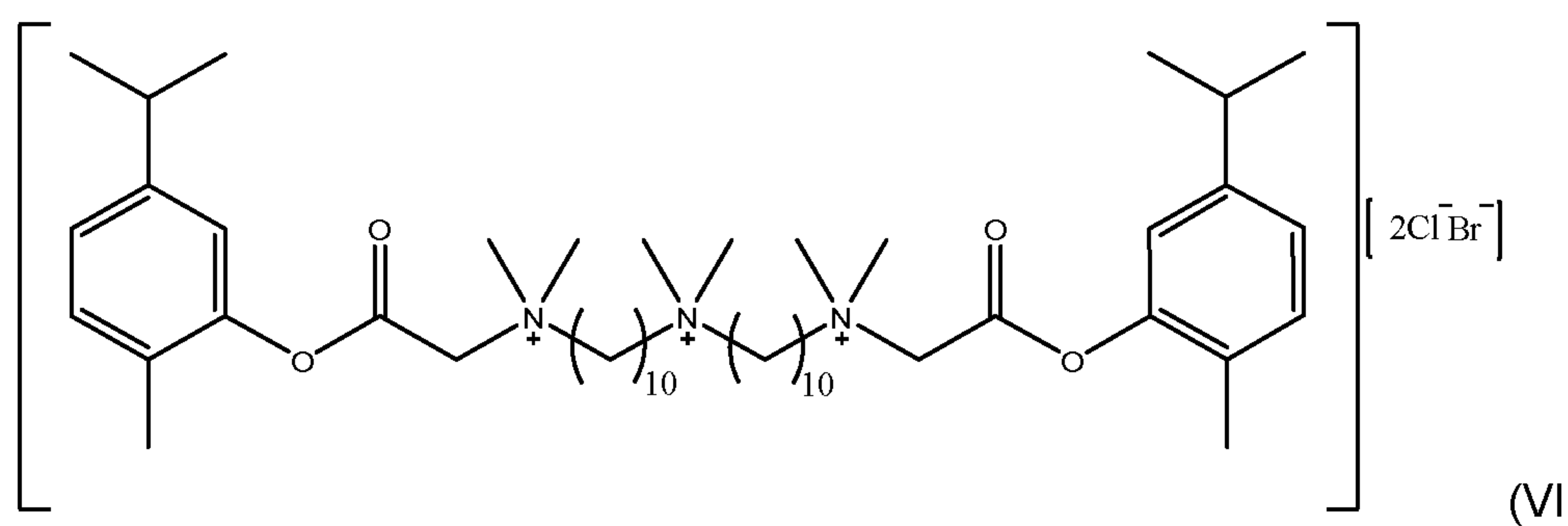


or

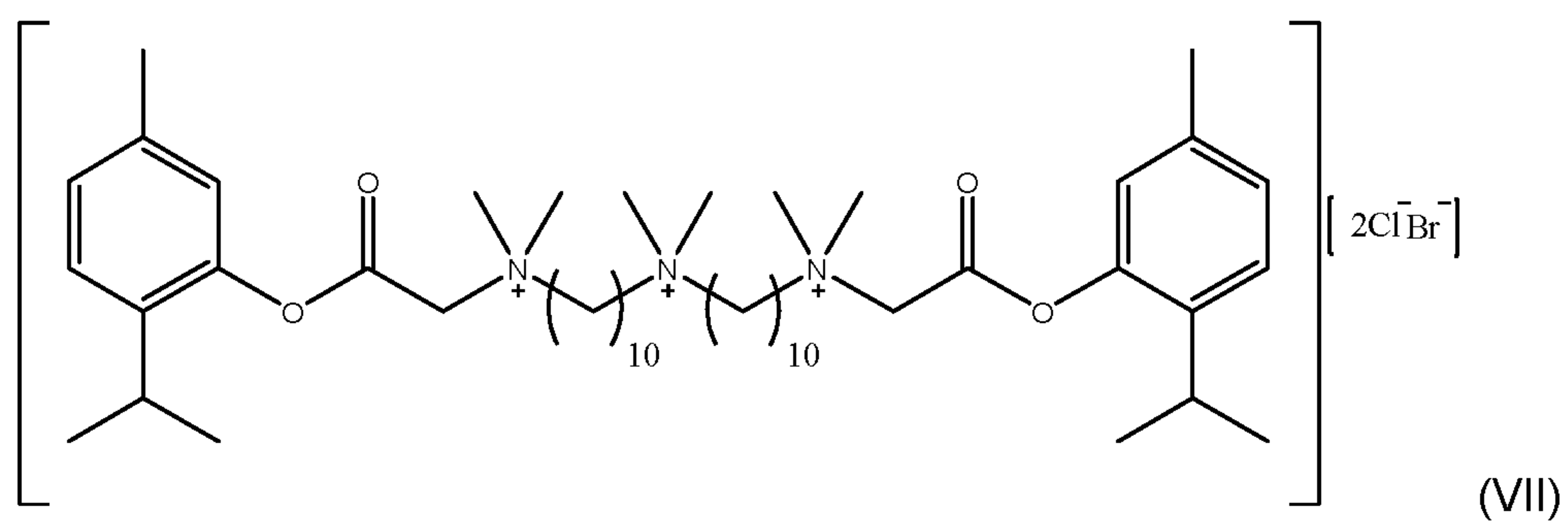
36



or

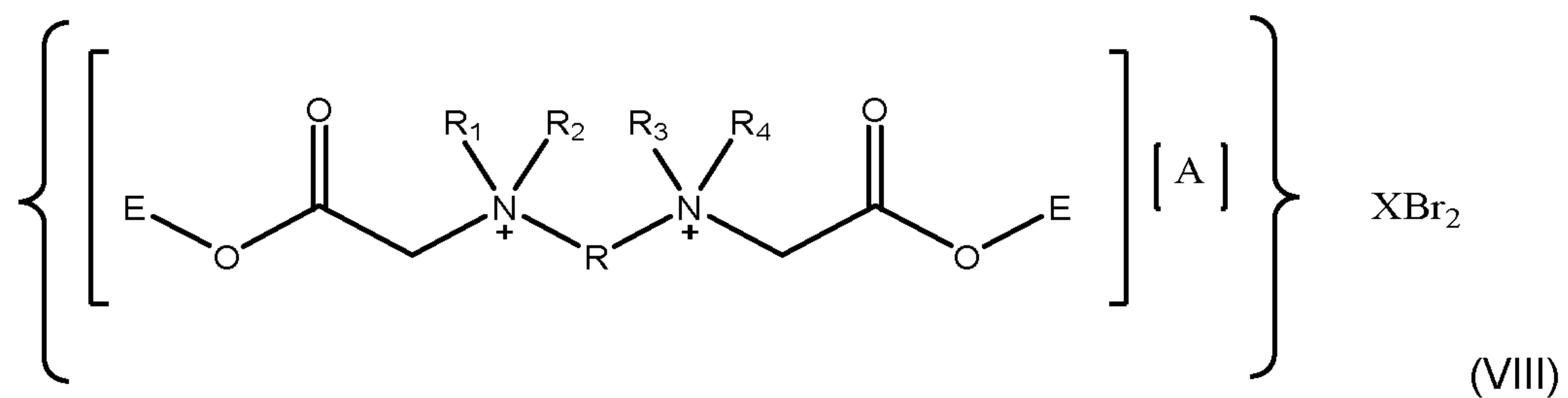


or



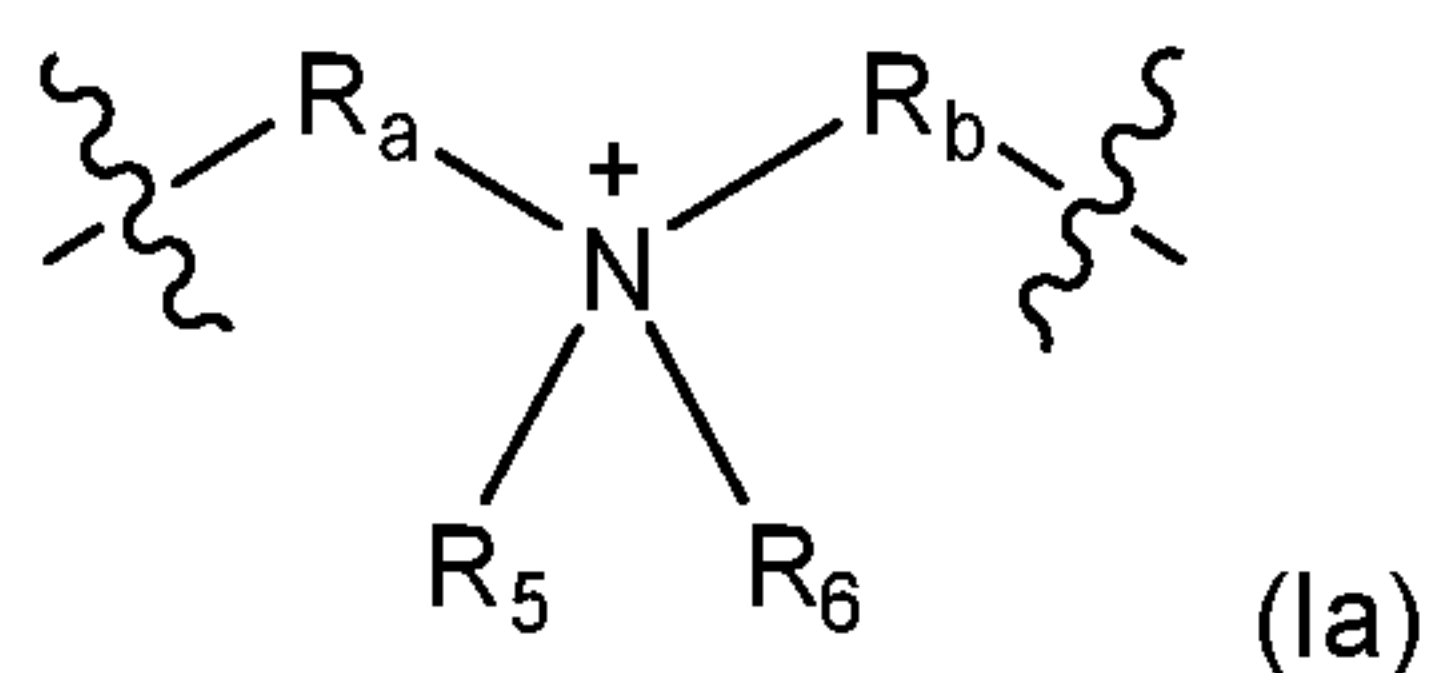
5

8. A compound having the following formula:



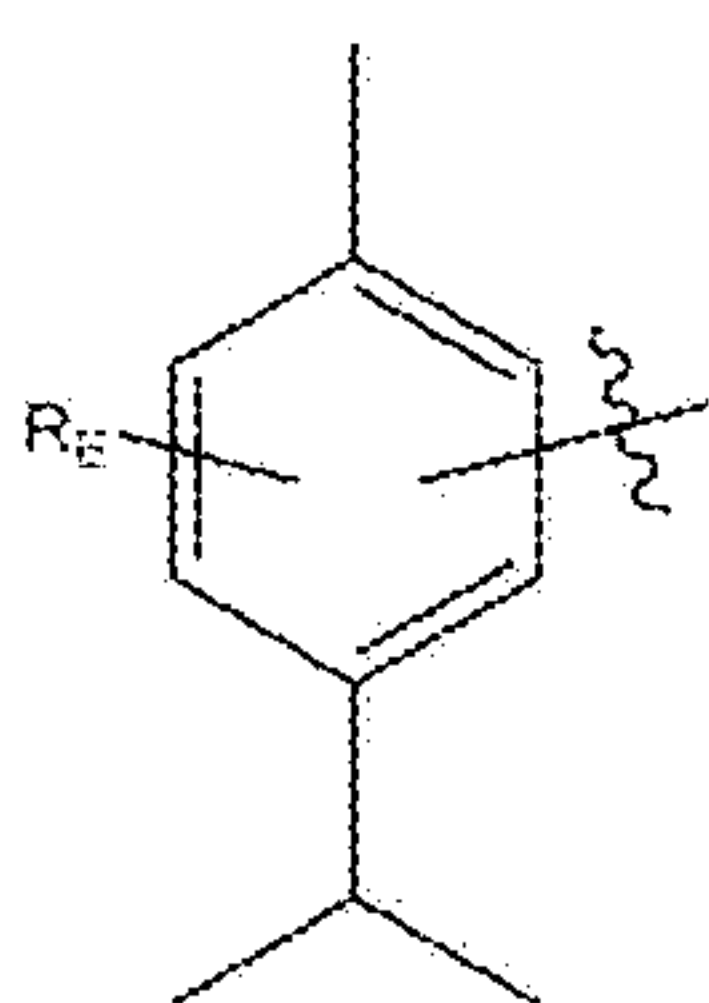
wherein R is an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -2,

or R is a quaternary amine having the following formula:



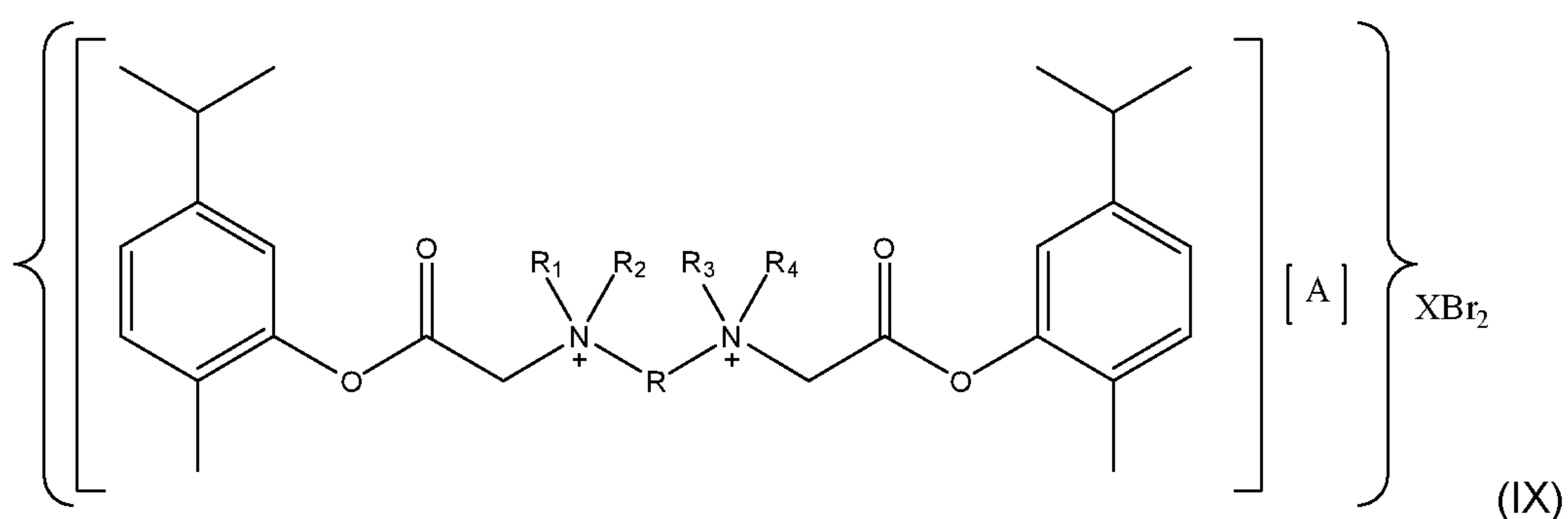
wherein R_a and R_b are each an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -3;

- 5 R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are each independently selected from C_{1-10} alkyl and H;



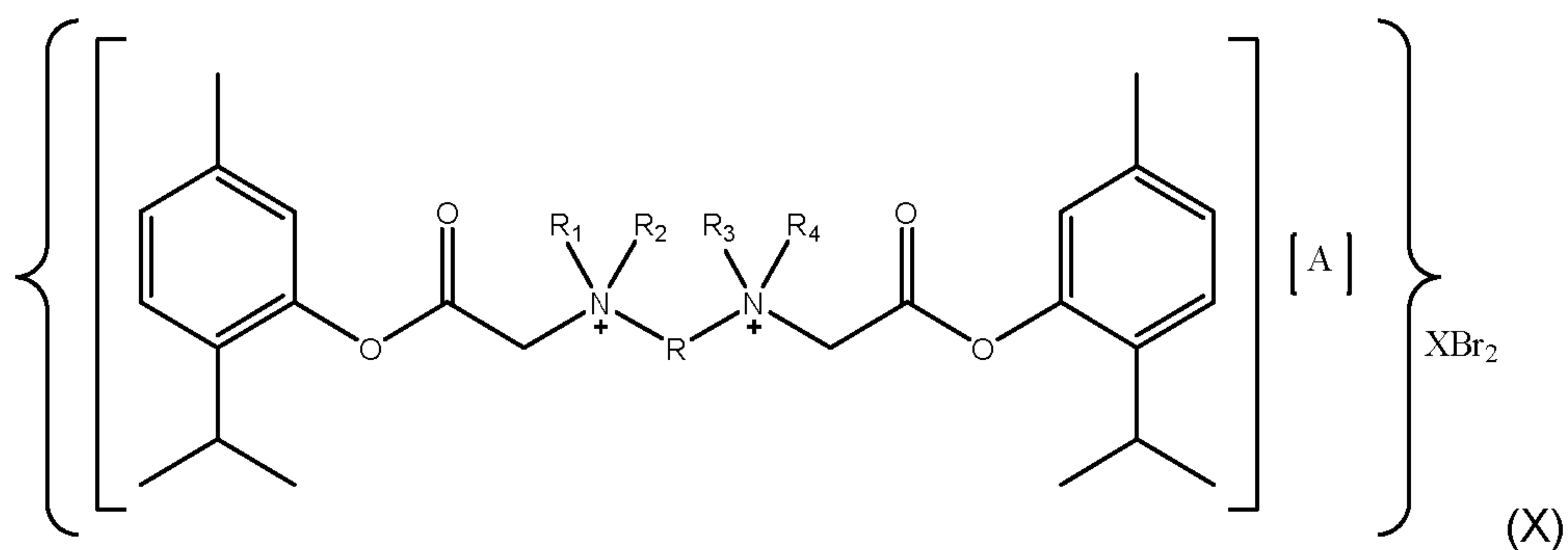
E has the following formula (Ib), wherein the ester oxygen is bonded to the aromatic ring of each E at the same position, the position being 2 or 3; wherein R_E is H or a halide and wherein X is 2, 3, 4 or 6.

9. A compound according to claim 8 having the following formula:



or

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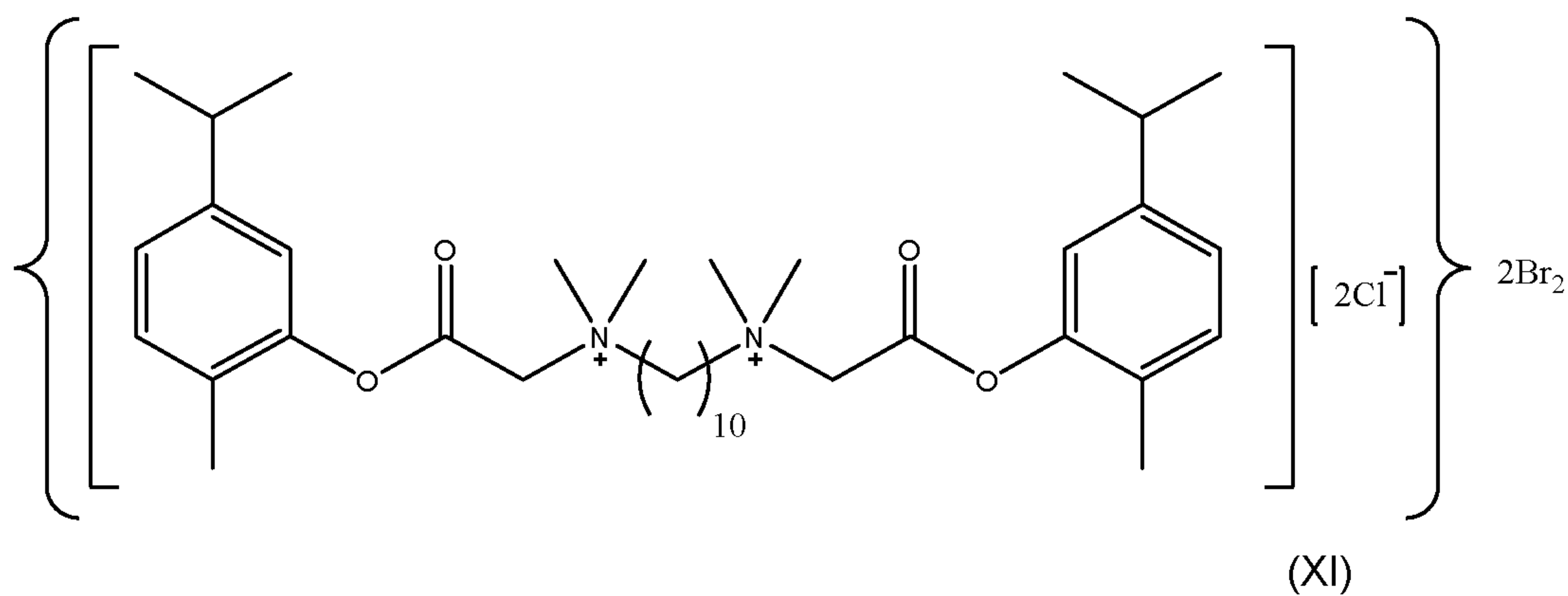


10. A compound according to claim 8 or 9, wherein R is a saturated linear alkylene chain having between 8 and 16 carbon atoms, for example 10 carbon atoms.

11. A compound according to claim 8 or 9, wherein R_a and R_b are each a saturated linear alkylene chain having between 8 and 16 carbon atoms, for example 10 carbon atoms.

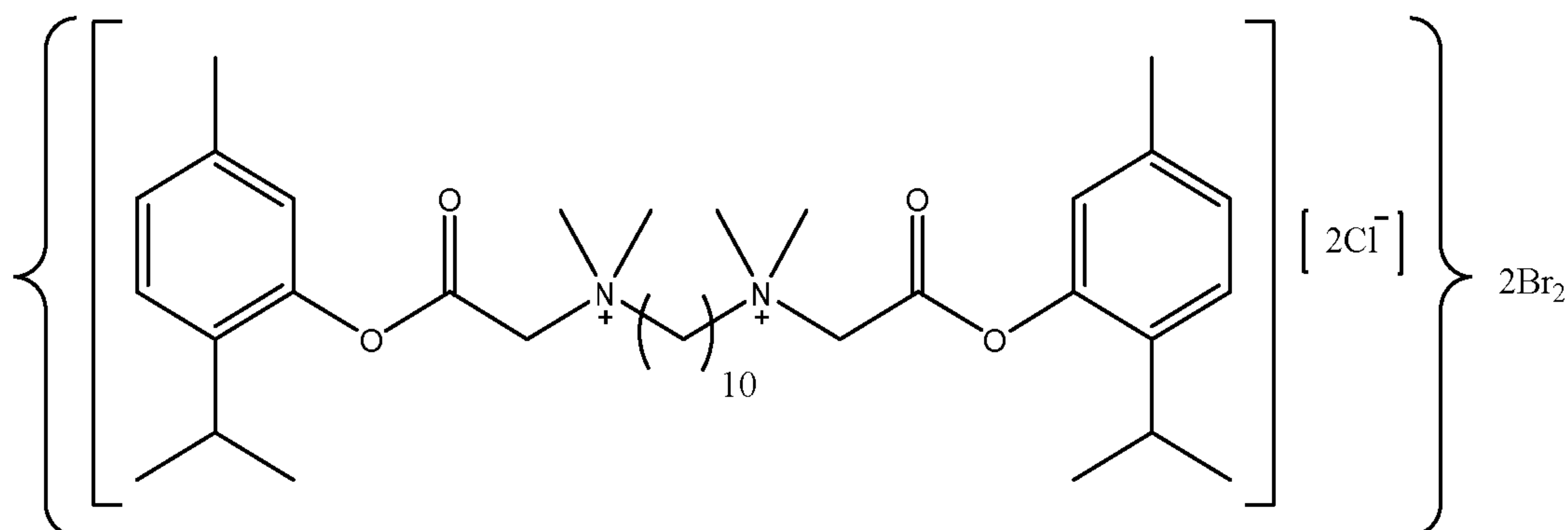
12. A compound according to any one of claims 8 to 11, wherein the one or more anions are selected from chloride anions and bromide anions.

13. A compound according to claim 8 or 9 having the following formula:



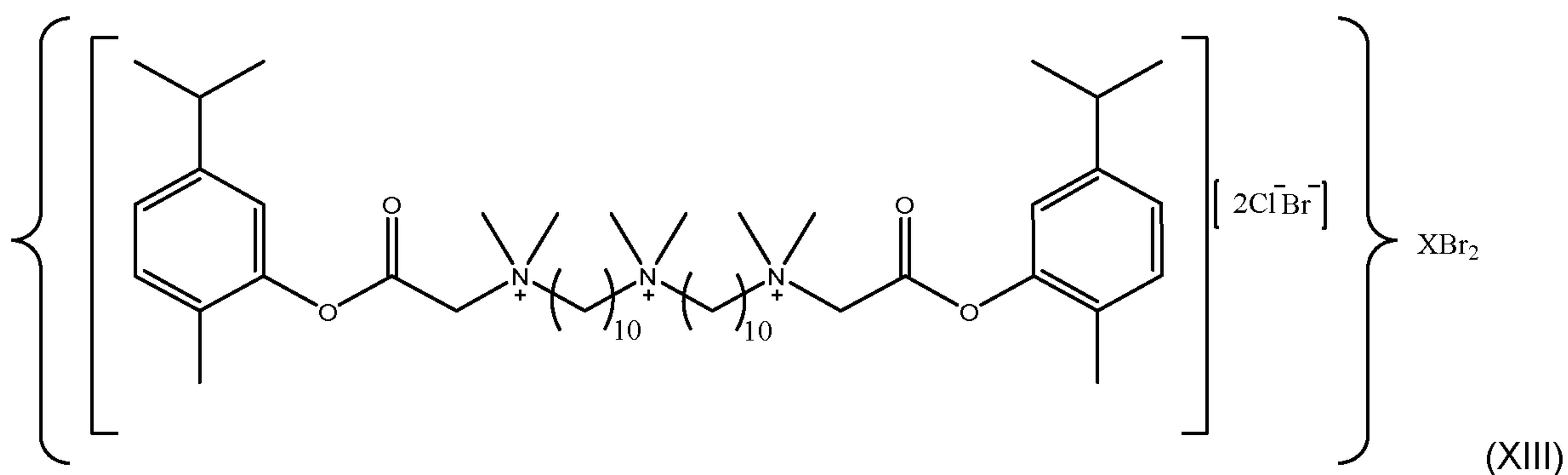
10

or

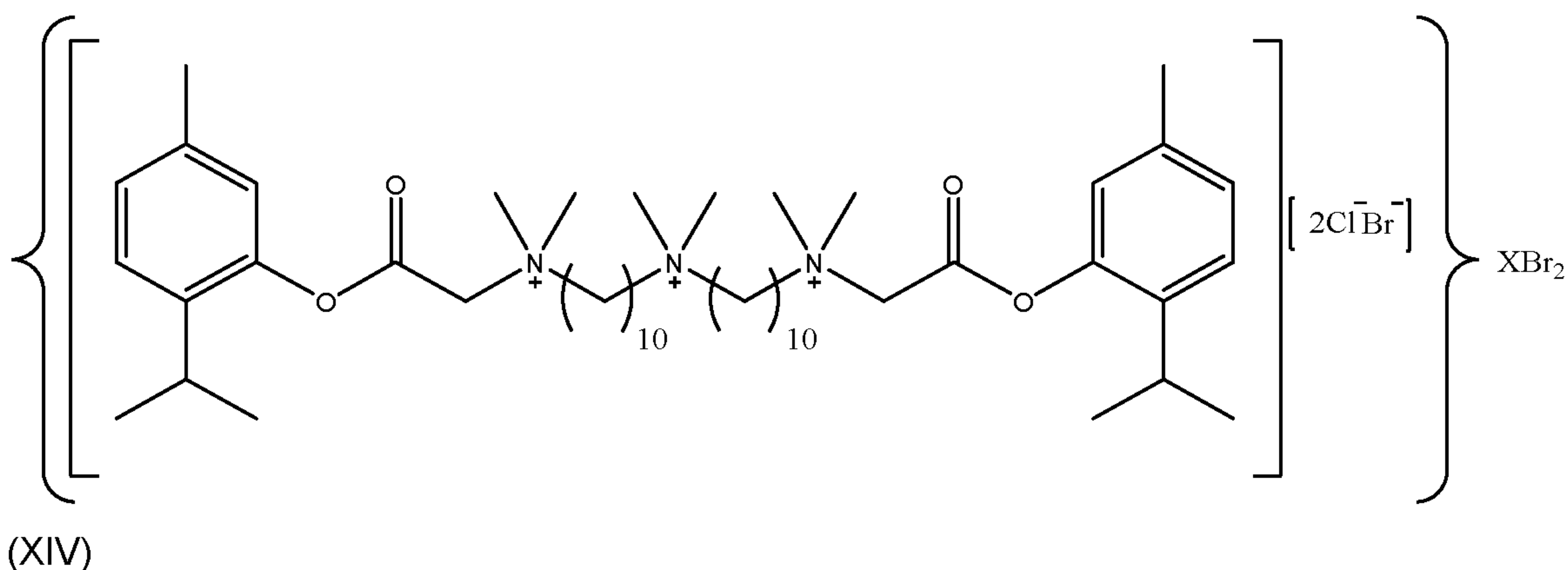


(XII)

or

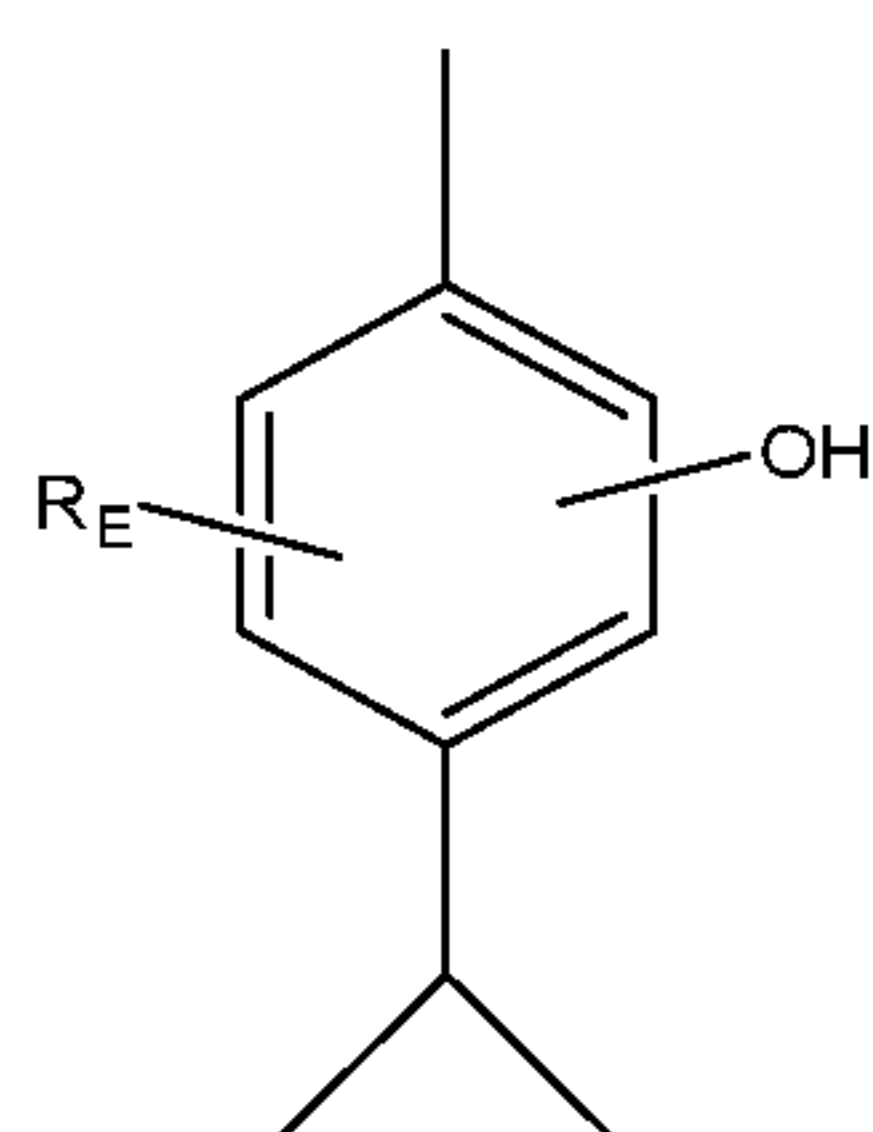


5 or



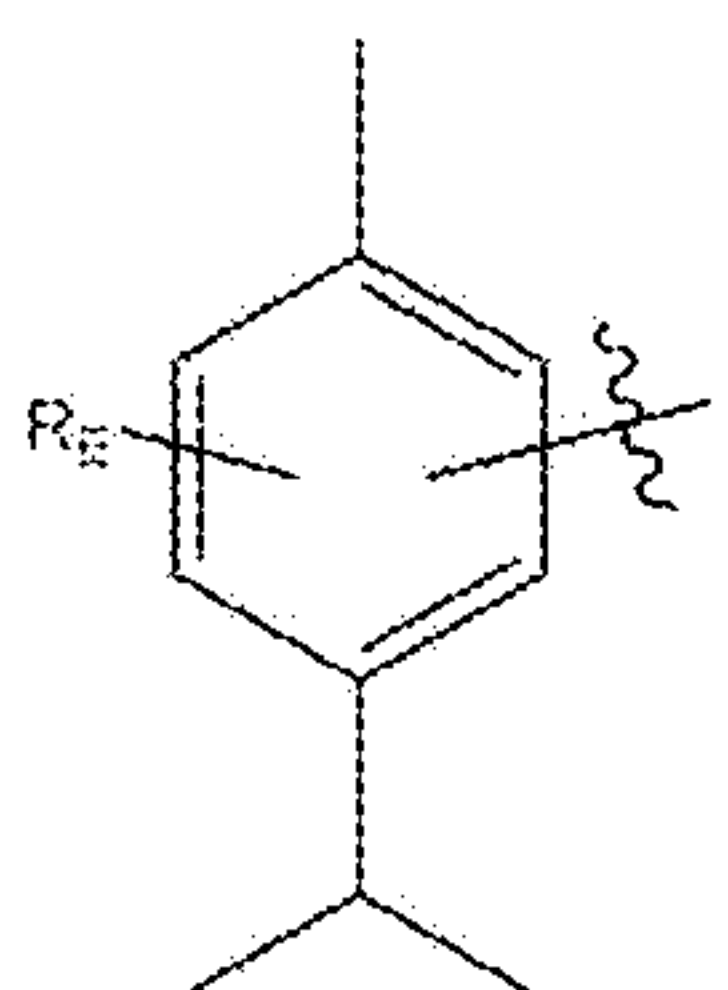
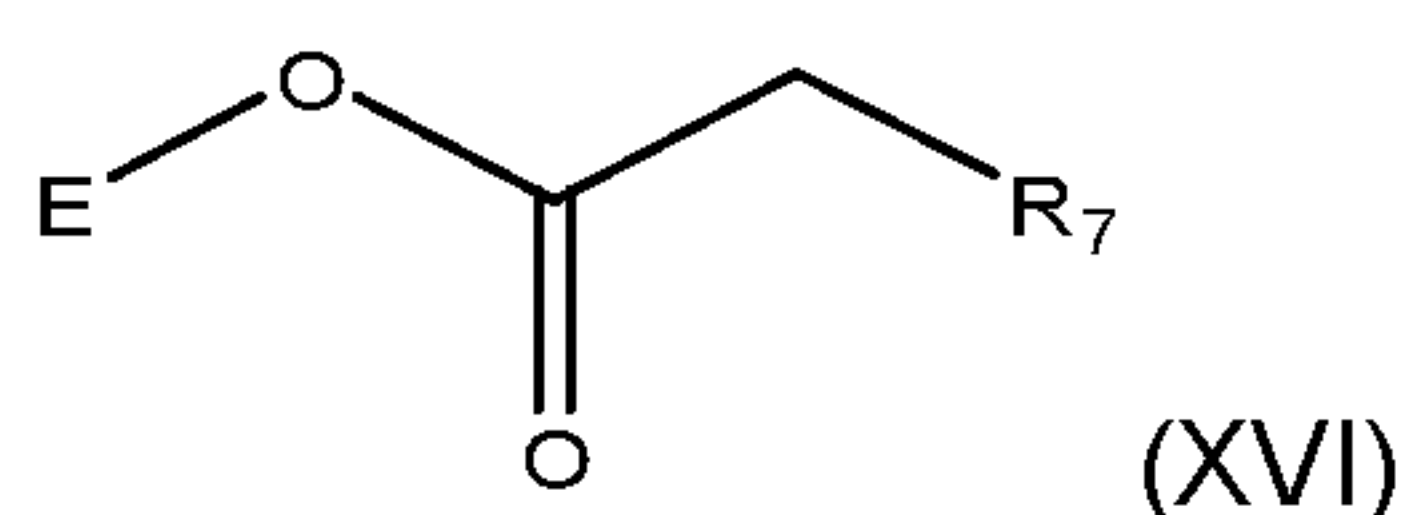
wherein X is 3 or 6.

- 10 14. A pharmaceutical composition comprising the compound of any preceding claim.
15. A compound according to any one of claims 1 to 13 for use as a medicament.
16. A compound according to any one of claims 1 to 13 for use in the treatment of fungal infections and/or bacterial infections.
17. A compound according to any one of claims 1 to 13 for use in the treatment of Herpes virus and/or Human Papilloma virus.
- 15 18. A process for producing the compound according to claim 1 comprising:
- i) reacting a compound having the formula (XV)



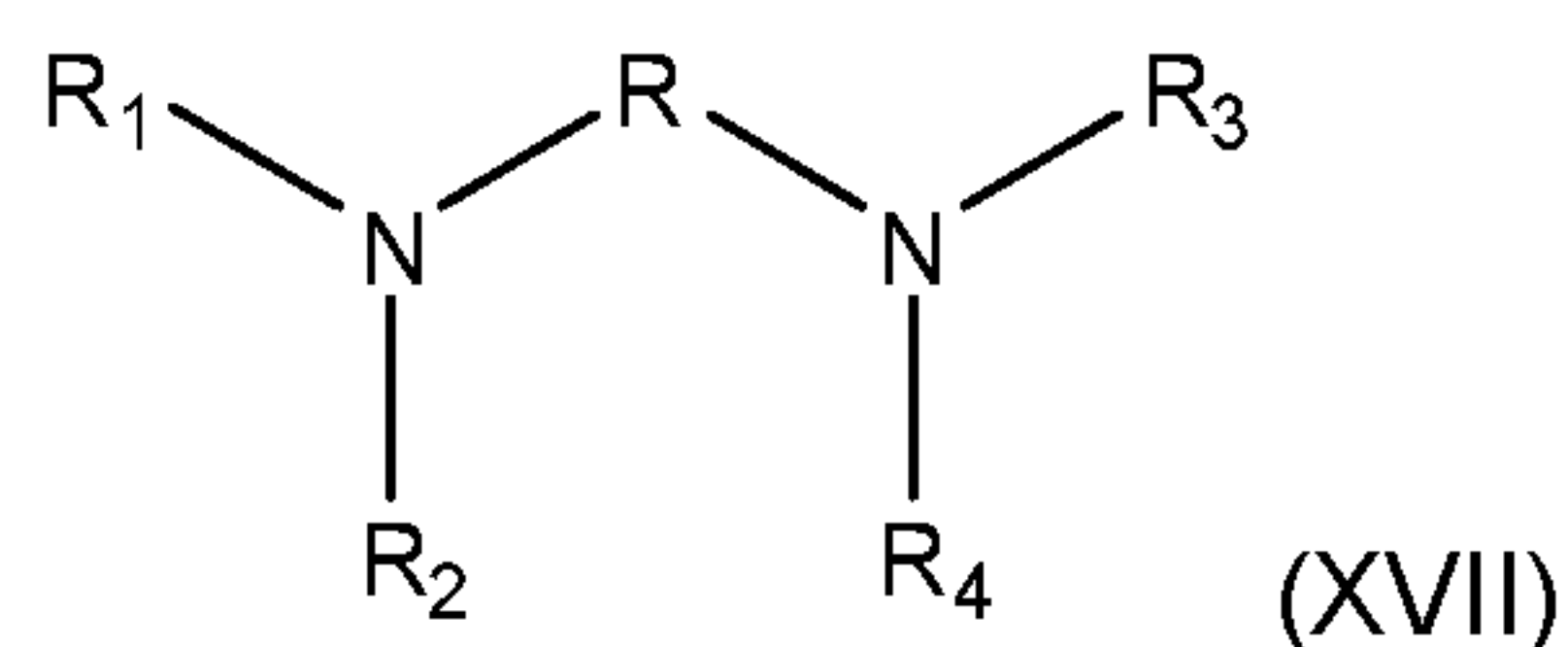
(XV), wherein the alcohol group is bonded to the benzene ring in position 2 or 3, and R_E is H or a halide,

with R_7CH_2COCl to form a compound having the formula (XVI):

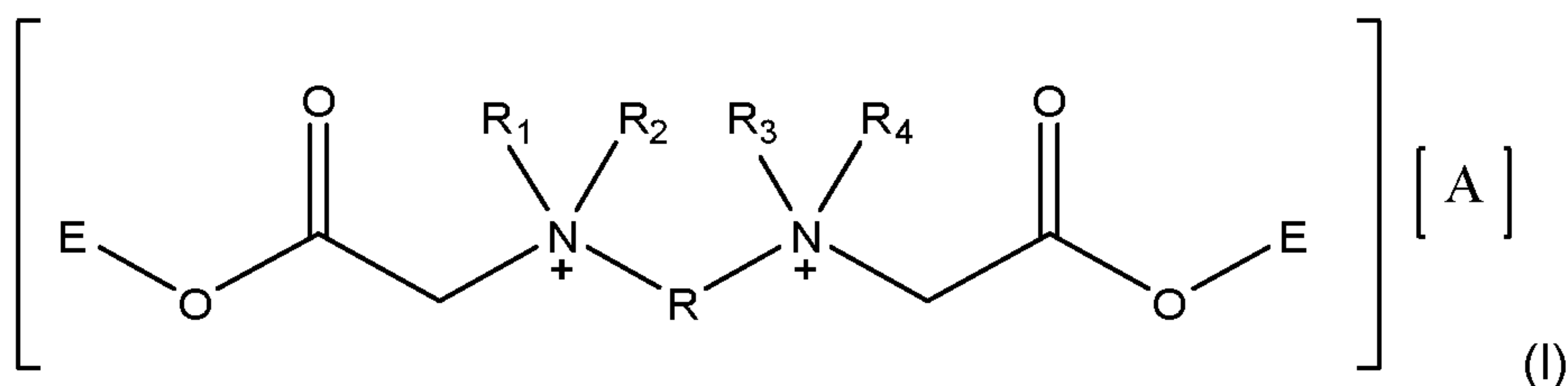


5 wherein R_7 is chlorine or bromine, E is (Ib) wherein the ester oxygen is bonded to the aromatic ring of E at position 2 or 3, and wherein R_E is H or a halide; and

ii) reacting 1 molar equivalents of the compound having the formula (XVII)

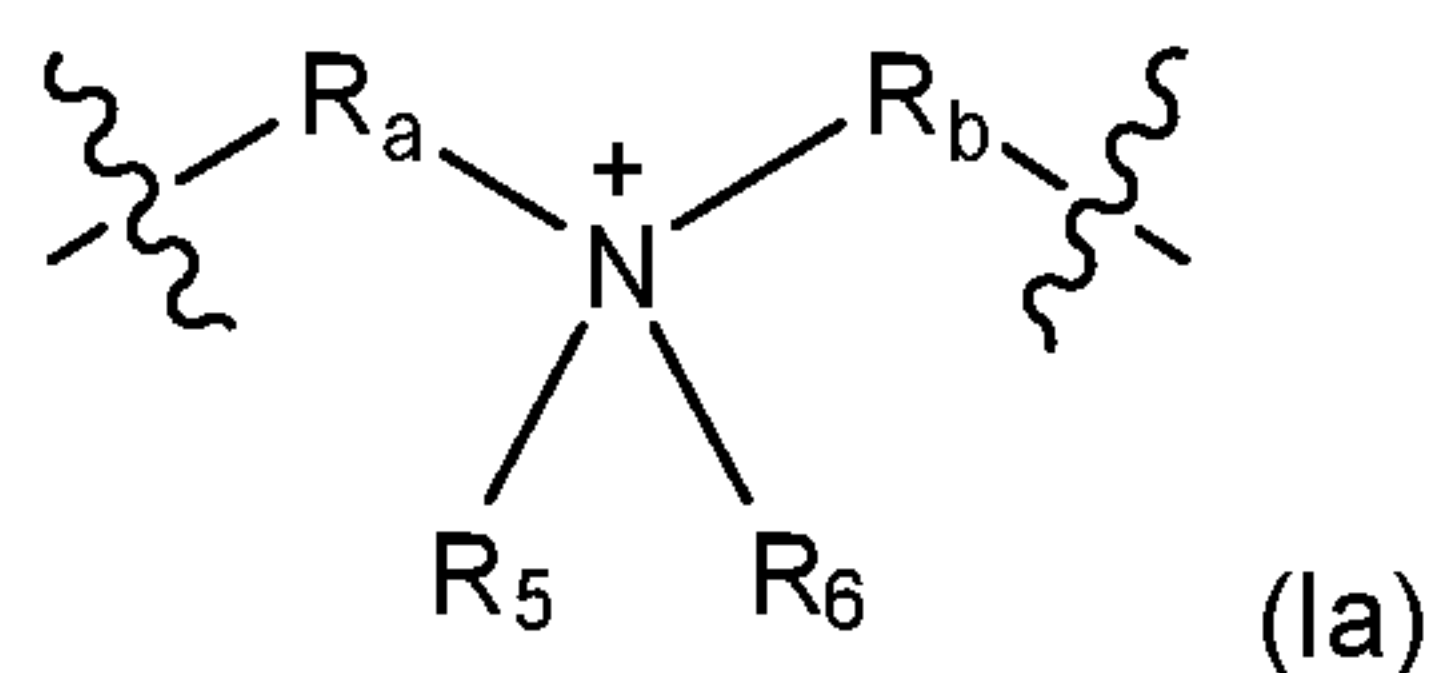


10 with 2 molar equivalent of the compound having formula (XVI) to form a compound having the formula

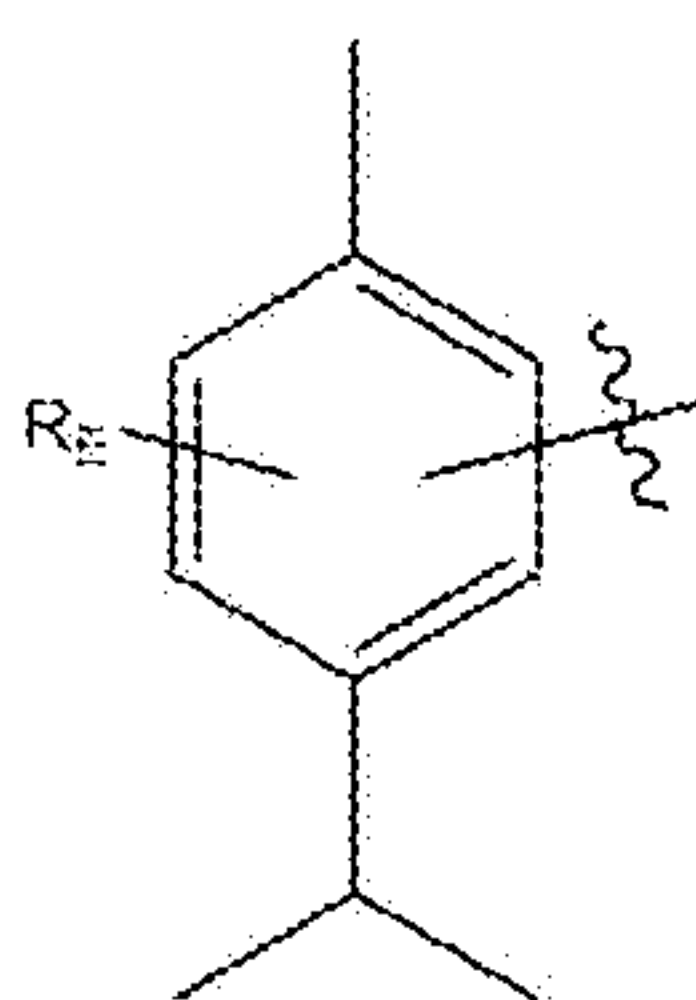


wherein R is an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -2;

or R is a quaternary amine having the following formula:



wherein R_a and R_b are each an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -3;

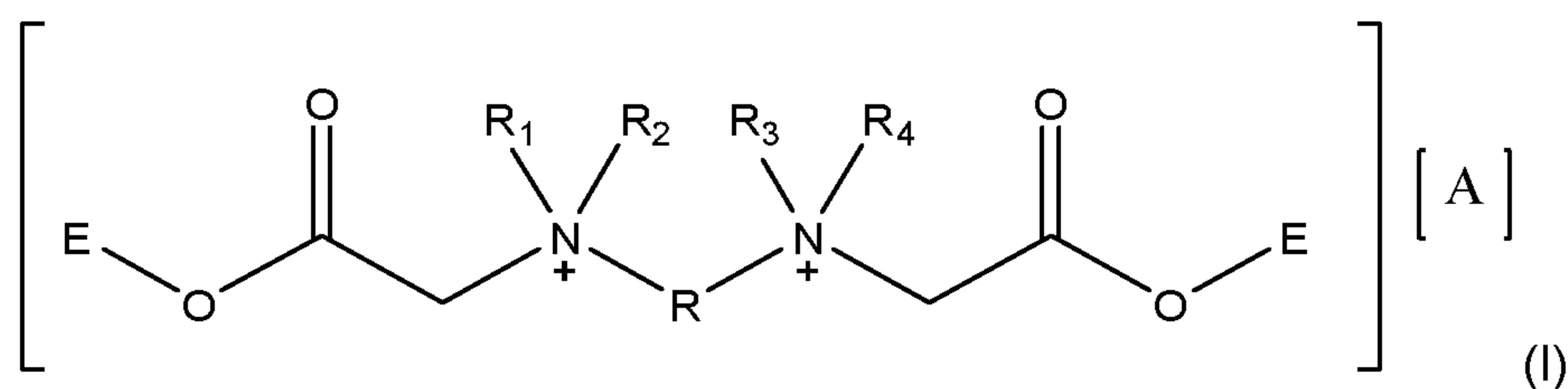


- 5 E has the following formula (Ib), wherein the ester oxygen is bonded to the aromatic ring of each E at the same position, the position being position 2 or 3 and wherein R_E is H or a halide;

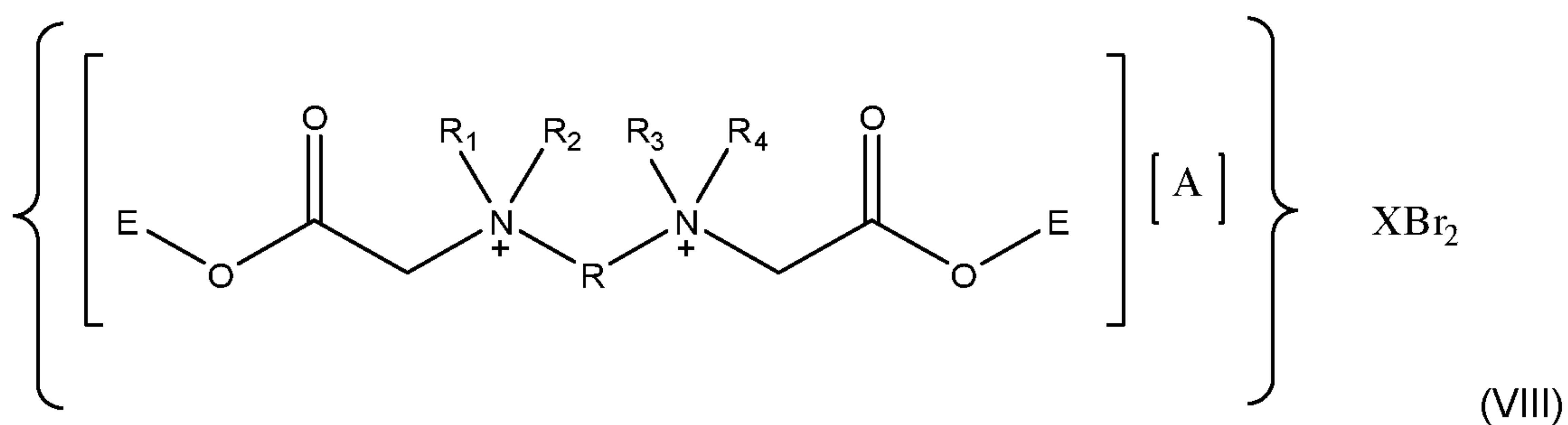
R_1 , R_2 , R_3 , R_4 , R_5 and R_6 are each independently selected from C_{1-10} alkyl and H.

- 10 19. The process according to claim 18, wherein the reactions of step II is carried out in acetonitrile as solvent.

20. A process for the production of a compound according to claim 8 comprising reacting the compound having formula (I)

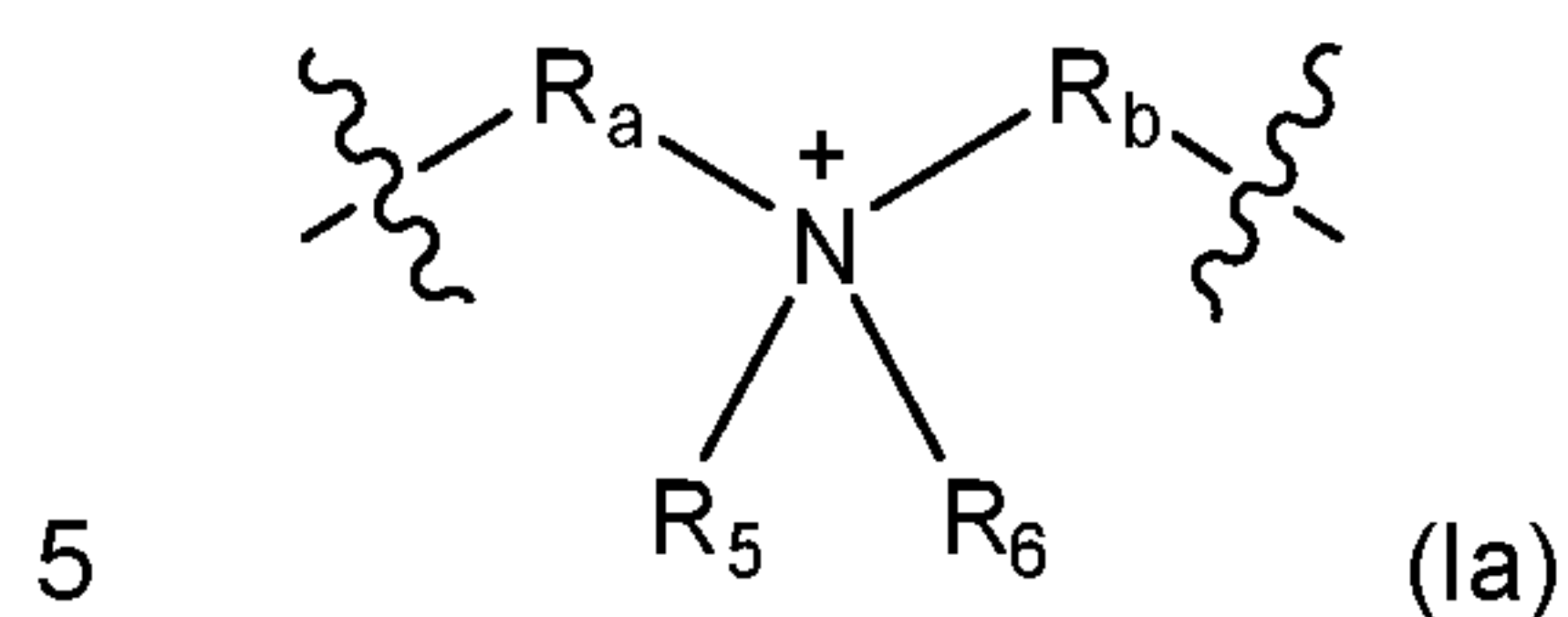


with bromine to form a compound having formula (VIII)



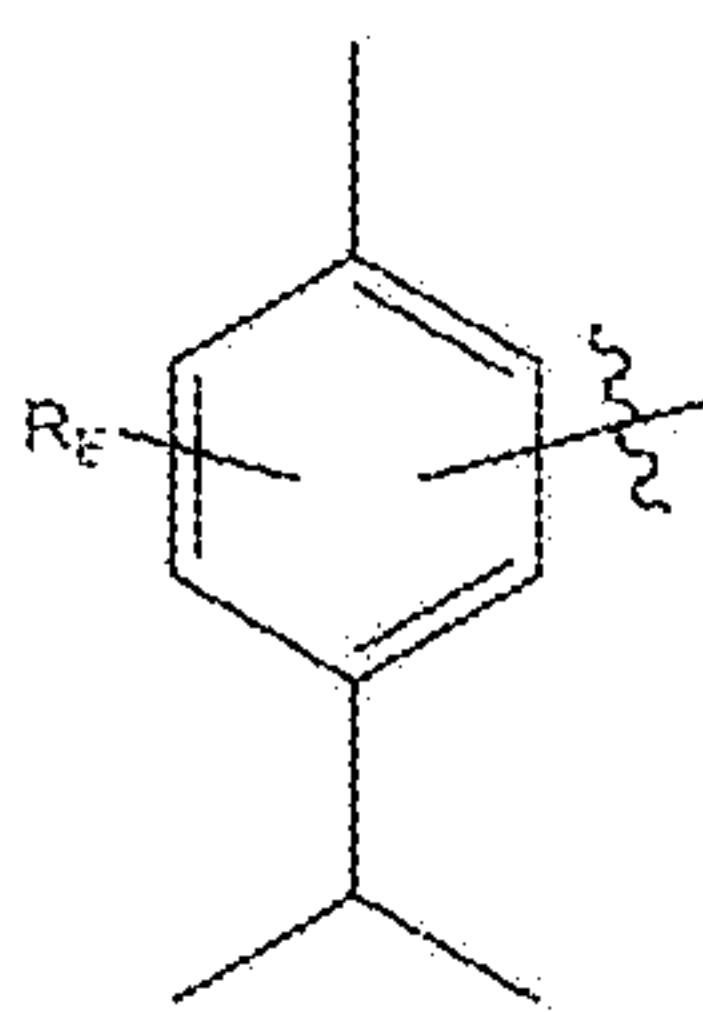
wherein R is an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -2,

or R is a quaternary amine having the following formula:



wherein R_a and R_b are each an alkylene chain having between 8 and 20 carbon atoms, and A is one or more anions having a total charge of -3;

R₁, R₂, R₃, R₄, R₅ and R₆ are each independently selected from C₁₋₁₀ alkyl and H;



10 E has the following formula (Ib), wherein the ester oxygen is bonded to the aromatic ring of each E at the same position, the position being 2 or 3; wherein R_E is H or a halide; and wherein X is 2, 3, 4 or 6.