PATENT SPECIFICATION

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COMPLETE SPECIFICATION

Improvements in and relating to Quaternary Ammonium Compounds and the preparation thereof

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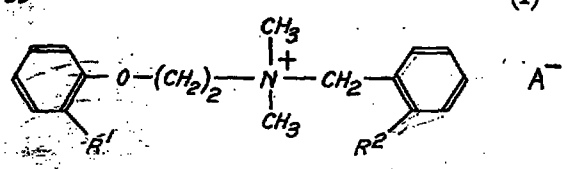
We, THE ~~WELCOME~~ FOUNDATION LIMITED, a British Company of 183—193 Euston Road, London, N.W.1, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed to be particularly described in and by the following statement:—

The present invention relates to quaternary ammonium compounds and the preparation thereof.

It has previously been discovered by the applicants (though not published before the priority date of this application) that compounds of the general formula (I) are active against nematodes closely associated with the mucosa of the lumen, examples of which are the trichostrongyles in sheep and cattle, parasites of considerable economic importance. The activity of the compounds of formula (I) has been established by screening tests carried out against *Nippostrongylus muris* in the rat. The compounds also exhibit activity against the intestinal parasites *Aspiculuris tetraptera* and *Nematospiroides dubius* in mice.

When administered to sheep, activity of various members of the series has been found against the parasitic organisms *Nematodirus* sp., *Ostertagia circumcinota*, *O. trifurcata*, *Cooperia curticei*, *Haemonchus contortus* and *Trichostrongylus axei*. The activity against the first four parasites is important as against these certain preparations of phenothiazine frequently used in veterinary medicine have a low efficiency.

(I)



In this formula, R^1 is a hydrogen, chlorine or bromine atom or a methyl or nitro group, R^2 is a hydrogen, chlorine or bromine atom, or a methyl group, and A^- is an anion.

It has now been found that the toxic effects of these compounds upon the host are much reduced when they are administered as salts of organic anions which are sparingly soluble in water, though such derivatives still retain their anthelmintic properties, particularly in larger animals such as sheep.

The present invention in one aspect therefore comprises a salt of the general formula (I) (wherein A^- is an anion equivalent of an organic acid) whose solubility in water is less than 1.00% w/v at 20° C.

Particularly useful in this respect have been the salts of the above general formula in which two cations falling within the cationic structure shown in formula (I) are combined with one divalent anion of embonic acid, namely 2:2¹ - dihydroxy - 1:1¹ - dinaphthylmethane-3:3¹-dicarboxylic acid. Other useful water-insoluble salts include the naphthalene-1- and -2- sulphonates and the 2-hydroxy-3-naphthoates.

The following table compares the solubilities of some of the compounds of the invention with that of the corresponding chloride.

N-Benzyl-*N*: *N*-dimethyl-*N*-2-phenoxyethyl-ammonium salts
Solubility in water at 20°C.

Chloride	50	% w/v
Naphthalene-2-sulphonate	0.6	% w/v
Naphthalene-1-sulphonate	0.3	% w/v
Naphthalene-1: 5-disulphonate	0.2	% w/v
1-Naphthoate	0.06	% w/v
2-Hydroxy-3-naphthoate	0.05	% w/v
Embonate	0.03	% w/v

Such salts are conveniently prepared, according to a feature of the present invention, by reacting in aqueous solution a soluble salt of formula (I) with a water soluble salt of the

appropriate acid (for example disodium embonate). The reagents are preferably used in equivalent proportions. The desired insoluble salt is thereby precipitated from solution and collected in the usual way.

The compounds of the present invention may be presented in various pharmaceutical compositions, such as tablets, suppositories, capsules, a suspension in syrup, or an aqueous suspension containing if desired suitable suspending agents. Pharmaceutical compositions containing the above defined quaternary ammonium salts also form part of the present invention.

It has also been found that mixtures of the compounds of the present invention with other more soluble salts (such as the chlorides) of the cation formula (I) are useful in treating certain nematode infestations. Such mixtures and pharmaceutical compositions containing them also form part of the present invention.

The invention will now be described with reference to the accompanying examples in which all temperatures are given in degrees centigrade.

EXAMPLE 1

A solution of disodium embonate (187 g.) in hot water (2 litres) was slowly added to a stirred solution of *N*-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium chloride (253 g.) in cold water (800 ml.). At first a clear mixture was formed which rapidly deposited fine crystals as the addition proceeded. After the addition was completed, the mixture was stirred for a further 2 hours, the solid was filtered off, washed with fresh water (200 ml.) and dried in vacuo. The product, di-(*N*-benzyl - *N*:*N* - dimethyl-*N*-2-phenoxyethylammonium) embonate monohydrate, was a pale yellow solid, melting point 144—146°.

EXAMPLE 2

1-Dimethylamino-2-*o*-methylphenoxyethane (358 g.) was dissolved in acetone (1 litre) and benzyl chloride (278 g.) was slowly added with stirring. The mixture became warm and *N*-benzyl-*N*:*N*-dimethyl-*N*-2-(*o*-methylphenoxyethyl) ammonium chloride crystallised out. After 72 hours this salt was filtered off, washed with fresh acetone (200 ml.) and dried immediately *in vacuo*. It melted at 135—138°.

A solution of this chloride (300 g.) in cold water (1 litre) was stirred during the gradual addition of a solution of disodium embonate (212 g.) in hot water (2 litres). As described in Example 1, a solid separated as the addition proceeded. After standing for 2 hours, the solid was filtered off, washed with fresh water (400 ml.) and dried *in vacuo*. The product was di-[*N*-benzyl-*N*:*N*-dimethyl-*N*-(2-*o*-methylphenoxyethyl) ammonium] embonate, melting point 68—69°.

EXAMPLE 3

A solution of sodium naphthalene-2-sulphonate (7.1 g.) in hot water (50 ml.) was slowly added to a solution of *N*-benzyl-*N*:*N*-dimethyl - *N* - 2-phenoxyethylammonium chloride (9 g.) in water (50 ml.) with stirring. An oil separated and then crystallised. After the addition was complete, the mixture was stirred for 2 hours. The insoluble salt was then filtered off, washed with water and dried *in vacuo*. The resulting *N*-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium naphthalene-2-sulphonate was a colourless solid. It was recrystallised from a mixture of ethanol and ether and melted at 137—139°.

EXAMPLE 4

N - Benzyl - *N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium naphthalene-1-sulphonate was prepared by the method described in Example 3 using sodium naphthalene-1-sulphonate. It was recrystallised from *iso*-propanol and melted at 128—130°.

EXAMPLE 5

2-Hydroxy-3-naphthoic acid (1.88 g.) was dissolved in hot aqueous sodium hydroxide (0.5*N*; 20 ml.) and the resulting solution was slowly added to a solution of *N*-benzyl-*N*:*N*-dimethyl - *N* - 2 - phenoxyethylammonium chloride (2.9 g.) in water (5 ml.). A gum separated at first but it solidified on scratching. After the addition was complete, the mixture was allowed to stand at room temperature for 2 hours and then filtered. The residue was washed with water and dried *in vacuo* to give *N*-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium 2 - hydroxy - 3 - naphthoate, melting point 170—171°.

EXAMPLE 6

N - Benzyl - *N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium 1-naphthoate was prepared by the method described in Example 5, using 1-naphthoic acid. It was recrystallised from ethanol and melted at 170.5—171.5°.

EXAMPLE 7

N - Benzyl - *N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium 2-naphthoate was prepared by the method described in Example 5 using 2-naphthoic acid. It was a gum sparingly soluble in water.

EXAMPLE 8

Di - (*N* - Benzyl - *N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium) 4:4¹-dihydroxydiphenylmethane-3:3¹-dicarboxylate was prepared by the method described in Example 5 using 4-4¹-dihydroxydiphenylmethane-3:3¹-dicarboxylic acid. It was a gum sparingly soluble in water.

EXAMPLE 9

Di - (*N* - benzyl - *N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium) naphthalene-1:5-disulphonate was prepared by the method described in Example 3, using disodium naphthalene-1:5-disulphonate. It was recrystallised from ethanol and melted at 209—209.5°.

EXAMPLE 10

Di - (*N* - benzyl - *N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium) naphthalene-2:7-di-

sulphonate was prepared by the method described in Example 2, using disodium naphthalene-2:7-disulphonate. It was a gum sparingly soluble in water.

EXAMPLE 11

Di - (*N* - benzyl - *N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium) 1-naphthol-3:6-disulphonate was prepared by the method described in Example 3, using disodium 1-naphthol-3:6-disulphonate. It was a gum sparingly soluble in water.

EXAMPLE 12

Di - (*N* - benzyl - *N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium) 2-naphthol-3:6-disulphonate was prepared by the method described in Example 3, using disodium 2-naphthol-3:6-disulphonate. It was a gum sparingly soluble in water.

EXAMPLE 13

N - Benzyl - *N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium diphenyl-4-sulphonate was prepared by the method described in Example 3, using sodium diphenyl-4-sulphonate. It was a gum sparingly soluble in water.

EXAMPLE 14

N - Benzyl - *N*:*N* - dimethyl - *N* - 2-(*o* - methylphenoxy)ethylammonium 2-hydroxy-3-naphthoate was prepared by the method described in Example 5, using *N*-benzyl-*N*:*N*-dimethyl - *N* - 2 - (o-methylphenoxy)-ethylammonium chloride. It was a gum sparingly soluble in water.

EXAMPLE 15

Tablets were prepared as follows:—

	g./tablet	batch quantity
N-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium embonate in very fine powder	2.500	5000 g.
lactose	1.250	2500 g.
starch	0.250	500 g.
polyoxyethylene sorbitan monolaurate	0.005	10 g.
magnesium stearate	0.050	100 g.
	4.055	8110 g.

Mix the *N*-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium embonate with the lactose and part of the starch and granulate the mixture with a 10% solution of gelatin or a 5% starch mucilage containing the polyoxyethylene sorbitan monolaurate. Sift through a sieve having 6.4 meshes/cm. Dry at 43—55°. Sift as before and incorporate the remainder of the starch and all the magnesium stearate. Compress into tablets.

EXAMPLE 16

Tablets were prepared as follows:—

	mg./tablet	batch quantity
N-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium embonate in very fine powder	250.0	5000 g.
lactose	200.0	4000 g.
starch	50.0	1000 g.
polyoxyethylene sorbitan monolaurate	0.5	10 g.
magnesium stearate	5.0	100 g.
	505.5	10110 g.

Mix the *N*-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium embonate and the lactose with part of the starch and granulate with a 5% starch mucilage containing the polyoxyethylene sorbitan monolaurate. Sift through a sieve having 7.9 meshes/cm. and dry at 43—55°. Sift as before and incorporate the remainder of the starch and the magnesium stearate. Compress into tablets.

EXAMPLE 17

A dispersible powder was prepared by milling together in a ball-mill:—

N-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium embonate	90.0 parts
calcium silicate	9.8 parts
cetrimide	0.2 parts

EXAMPLE 18

A draft was prepared by stirring 1.5 g. of the dispersible powder of Example 17 in 100 ml. of water.

EXAMPLE 19

A drench for animals was prepared by stirring 7.5 g. of the dispersible powder of Example 17 in 60 ml. of water.

EXAMPLE 20

Hard gelatin capsules were each packed with 500 mg. of the dispersible powder of Example 17.

EXAMPLE 21

Soft gelatin capsules were each packed with 500 mg. of the dispersible powder of Example 17.

EXAMPLE 22

A pleasantly flavoured syrup suspension was made as follows:—

N-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium embonate in very fine powder	253.0 g.
sucrose	500.0 g.
polyoxyethylene sorbitan mono-oleate	1.0. g.
oil of lemon	0.5 ml.
ethanol	10.0 ml.
water	to make one litre.

Reduce the particle size of the *N*-benzyl-*N*:*N* - dimethyl - *N* - 2 - phenoxyethylammonium embonate still further milling it with polyoxyethylene sorbitan mono-oleate in sufficient water. Add the sucrose and dissolve with the aid of gentle heat if necessary. Dissolve the oil of lemon in the alcohol and add it to the suspension.

EXAMPLE 23

Tablets were prepared as follows:—

	g./tablet	batch quantity
N-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium hydroxynaphthoate in very fine powder	2.500	5000 g.
lactose	1.250	2500 g.
starch	0.250	500 g.
polyoxyethylene sorbitan monolaurate	0.005	10 g.
magnesium stearate	0.075	150 g.
	4.080	8160 g.

Mix together the *N* - benzyl - *N*:*N* - dimethyl - *N* - 2 - phenoxyethylammonium hydroxynaphthoate, the lactose and part of the starch. Granulate the mixture with 5% mucilage of starch containing the polyoxyethylene sorbitan monolaurate. Sift through a sieve having 6.4 meshes/cm. and dry at 43—45°. Sift as before and incorporate the remainder of the starch and the whole of the magnesium stearate. Mix and compress into tablets.

EXAMPLE 24

Tablets were prepared as follows:—

	mg./tablet	batch quantity
N-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium hydroxynaphthoate in very fine powder	433.0	4330 g.
lactose	200.0	2000 g.
starch	50.0	500 g.
polyoxyethylene sorbitan monolaurate	0.5	5 g.
magnesium stearate	10.0	100 g.
	693.5	6935 g.

Mix the *N*-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium hydroxynaphthoate with the lactose and part of the starch. Granulate the mixture with 5% starch mucilage containing the polyoxyethylene sorbitan monolaurate. Sift through a sieve having 7.9 meshes/cm. and dry at 43—55°. Sift as before and incorporate the remainder of the starch and the magnesium stearate. Compress into tablets.

EXAMPLE 25

A dispersible powder was prepared by incorporating in finely powdered *N*-benzyl-*N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium hydroxynaphthoate a suitable proportion of a surface active agent, for example 0.2% of cetrimide.

EXAMPLE 26

Hard gelatin capsules were each packed with 434 mg. of the dispersible powder of Example 25.

EXAMPLE 27

Soft gelatin capsules were each packed with 434 mg. of the dispersible powder of Example 25.

EXAMPLE 28

N - Benzyl - *N*:*N* - dimethyl - *N* - 2-(*o*-methylphenoxy)ethylammonium embonate was finely ground with a suitable quantity of an inert substance, such as 10% of calcium silicate, until a very fine powder was obtained. This mixture was incorporated with a suitable surface active agent, such as 0.2% of polyoxyethylene sorbitan mono-oleate, to give a dispersible powder.

EXAMPLE 29

A draft was prepared by stirring 1.5 g. of the dispersible powder of Example 28 in 100 ml. of water.

EXAMPLE 30

Hard gelatin capsules were each packed with 500 mg. of the dispersible powder of Example 28.

EXAMPLE 31

Soft gelatin capsules were each packed with 500 mg. of the dispersible powder of Example 28.

EXAMPLE 32

A flavoured sweetened syrup suspension was prepared from *N*-benzyl-*N*:*N*-dimethyl-*N*-2-(*o*-methylphenoxy)ethylammonium embonate by the method of Example 22, using oil of aniseed in place of oil of lemon.

EXAMPLE 33

Equivalent quantities of 1-dimethylamino-2-phenoxyethane and *o*-chlorobenzyl chloride were reacted in acetone by the method of Example 2 to give *N*-*o*-chlorobenzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium chloride monohydrate, melting point 65—66°.

This chloride was converted by the method of Example 1 into di-(*N*-*o*-chlorobenzyl-*N*:*N*-dimethyl - *N* - 2 - phenoxyethylammonium) embonate dihydrate, melting point 103—104°, solubility in water 0.07% w/v at 20°.

EXAMPLE 34

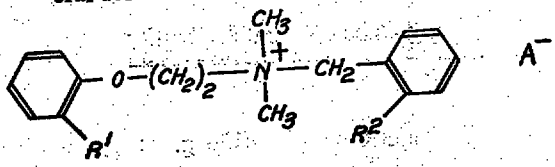
Di - (*N* - *o* - bromobenzyl - *N*:*N* - dimethyl-*N*-2-phenoxyethylammonium) embonate was prepared from *N*-*o*-bromobenzyl-*N*:*N* - dimethyl - *N* - 2 - phenoxyethylammonium bromide by the method of Example 1. It melted at 102—103°.

EXAMPLE 35

Di - (*N* - benzyl - *N*:*N* - dimethyl - *N* - 2-(*o*-nitrophenoxy)ethylammonium) embonate was prepared from *N*-benzyl-*N*:*N*-dimethyl-*N*-2-(*o*-nitrophenoxy)ethylammonium chloride by the method of Example 1. It was a gum sparingly soluble in water.

WHAT WE CLAIM IS:—

1. Quaternary ammonium salts of the general formula



(wherein R^1 is a hydrogen, chlorine or bromine atom or a methyl or nitro group, R^2 is a hydrogen, chlorine or bromine atom, or a methyl group, and A^- is an anion equivalent of an organic acid) whose solubility in water is less than 1.00% w/v at 20°C.

2. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion equivalent of $2:2^1$ - dihydroxy - $1:1^1$ - dinaphthylmethane-$3:3^1$-dicarboxylic (embonic) acid.

3. Quaternary ammonium salts as claimed in Claim 1 where A^- is an anion of naphthalene-1-sulphonic acid.

4. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion of naphthalene-2-sulphonic acid.

5. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion of 2-hydroxy-3-naphthoic acid.

6. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion of 1-naphthoic acid.

7. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion of 2-naphthoic acid.

8. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion equivalent of $4:4^1$-dihydroxydiphenylmethane-$3:3^1$-dicarboxylic acid.

9. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion equivalent of naphthalene-1:5-disulphonic acid.

10. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion equivalent of naphthalene-2:7-disulphonic acid.

11. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion equivalent of 1-naphthol-3:6-disulphonic acid.

12. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion equivalent of 2-naphthol-3:6-disulphonic acid.

13. Quaternary ammonium salts as claimed in Claim 1 wherein A^- is an anion of diphenyl-4-sulphonic acid.

14. A process for preparing quaternary ammonium salts as claimed in Claim 1 which comprises reacting in aqueous solution a water-soluble salt of the cation with a water-soluble metallic salt (for example the sodium salt) of the desired organic acid.

15. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is $2:2^1$-dihydroxy-$1:1^1$-dinaphthylmethane - $3:3^1$ - dicarboxylic (embonic) acid.

16. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is naphthalene-1-sulphonic acid.

17. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is naphthalene-2-sulphonic acid.

18. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is 2-hydroxy-3-naphthoic acid.

19. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is 1-naphthoic acid.

20. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is 2-naphthoic acid.

21. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is $4:4^1$-dihydroxydiphenylmethane-$3:3^1$-dicarboxylic acid.

22. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is naphthalene-1:5-disulphonic acid.

23. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is naphthalene-2:7-disulphonic acid.

24. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is 1-naphthol-3:6-disulphonic acid.

25. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is 2-naphthol-3:6-disulphonic acid.

26. A process for preparing quaternary ammonium salts as claimed in Claim 14 wherein the organic acid is diphenyl-4-sulphonic acid.

27. Anthelmintic pharmaceutical compositions comprising a quaternary ammonium salt as claimed in Claim 1 mixed with a pharmaceutically inert excipient.

28. Tablets containing a quaternary ammonium salt as claimed in Claim 1.

29. A dispersible powder containing a quaternary ammonium salt as claimed in Claim 1.

30. An aqueous suspension containing a quaternary ammonium salt as claimed in Claim 1.

31. Hard gelatin capsules containing a quarternary ammonium salt as claimed in Claim 1.

32. Soft gelatin capsules containing a quaternary ammonium salt as claimed in Claim 1.

33. A syrup containing in suspension a quaternary ammonium salt as claimed in Claim 1.

34. Anthelmintic pharmaceutical compositions substantially as herein described with

reference to any one of the foregoing examples.

35. A method for the manufacture of anthelmintic pharmaceutical compositions comprising the admixture of a quaternary ammonium salt as claimed in Claim 1 with a pharmaceutically inert excipient.

36. A method as claimed in Claim 35 wherein the mixture is compressed into tablets.

37. A method for the manufacture of dispersible powders as claimed in Claim 35 wherein the excipient is or includes a surface-active agent.

38. A method for the manufacture of an aqueous suspension wherein a dispersible powder as claimed in Claim 37 is stirred into water.

39. A method as claimed in Claim 35 wherein the active ingredient, with or without other excipient, is filled into ~~soft~~ gelatine capsules.

40. A method wherein a dispersible powder as claimed in Claim 37 is filled into hard gelatin capsules.

41. A method as claimed in Claim 35 wherein the active ingredient, with or without other excipient, is filled into soft gelatin capsules.

42. A method wherein a dispersible powder as claimed in Claim 37 is filled into soft gelatin capsules.

43. A method as claimed in Claim 35 wherein the excipient is or includes a syrup.

44. Methods for the manufacture of anthelmintic pharmaceutical compositions substantially as herein described with reference to any one of the foregoing examples.

R. F. HASLAM,
Agent for the Applicants.

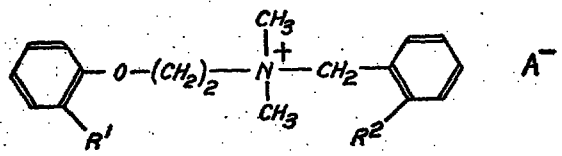
PROVISIONAL SPECIFICATION

Improvements in and relating to Quaternary Ammonium Compounds and the preparation thereof

We, THE ~~WELCOME~~ FOUNDATION LIMITED, a British Company of 183—193 Euston Road, London, N.W.1, do hereby declare this invention to be described in the following statement:—

The present invention relates to quaternary ammonium compounds and the preparation thereof.

It has previously been discovered by the applicants (though not published before the priority date of this application) that quaternary ammonium compounds of the general formula (I) are active against nematodes.



(I)

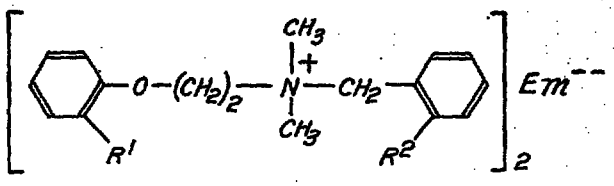
In this formula R^1 is a hydrogen, chlorine or bromine atom or a methyl group, R^2 is a hydrogen, chlorine, bromine atom or a methyl group and A^- is the anion of a pharmaceutically acceptable acid such as chloride, bromide, iodide, methosulphate or any other anion which is not toxic at the dose level at which the compound is administered.

It has now been found that the toxic effects of these compounds upon the host are much reduced when they are administered as salts which are sparingly soluble in water, though such derivatives still retain their anthelmintic properties, particularly in larger animals such as sheep.

The present invention in one aspect therefore comprises a salt of the general formula (I) which is sparingly soluble in water.

Particularly useful in this respect have been the salts of the above general formula in which two cateions falling within the cationic structure shown in formula (I) are combined with one divalent anion of embonic acid, namely 2:2¹-dihydroxy - 1:1¹ - dinaphthylmethane-3:3¹-dicarboxylic acid (see Barber & Gaimster, Journal of Applied Chemistry, 1952 vol. 2, page 565).

The present invention in another aspect comprises the embonate of the general formula (II)



(II)

in which Em^{--} is the divalent anion of embonic acid.

Other useful water-insoluble salts comprises the naphthalene-1-and -2-sulphonates and the 2-hydroxy-3-naphthoates.

Such salts are conveniently prepared, according to a feature of the present invention, by reacting in aqueous solution a soluble salt of formula (I) with a water soluble salt of the appropriate acid (for example disodium embonate). The reagents are preferably used in equivalent proportions. The desired insoluble salt is thereby precipitated from solution and collected in the usual way.

The invention will now be described with reference to the accompanying examples in which all temperatures are given in degrees Centigrade.

EXAMPLE 1

A solution of disodium embonate (187 g.) in hot water (2 litres) was slowly added to a stirred solution of *N*-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium chloride (253 g.) in cold water (800 ml). At first a clear mixture was formed which rapidly deposited fine crystals as the addition proceeded. After the addition was completed, the mixture was stirred for a further 2 hours, the solid was filtered off, washed with fresh water (200 ml.) and dried *in vacuo*. The product, di-(*N*-benzyl - *N*:*N* - dimethyl-*N*-2-phenoxyethylammonium) embonate monohydrate, was a pale yellow solid, melting point 144—146°.

EXAMPLE 2

1 - Dimethylamino - 2 - *o* - methylphenoxyethane (358 g.) was dissolved in acetone (1 litre) and benzyl chloride (278 g.) was slowly added with stirring. The mixture became warm and *N*-benzyl-*N*:*N*-dimethyl-*N*-2-(*o*-methylphenoxyethyl) ammonium chloride crystallised out. After 72 hours this salt was filtered off, washed with fresh acetone (200 ml.) and dried immediately *in vacuo*. It melted at 135—138°.

A solution of this chloride (300 g.) in cold water (1 litre) was stirred during the gradual addition of a solution of disodium embonate (212 g.) in hot water (2 litres). As described in Example 1, a solid separated as the addition proceeded. After standing for 2 hours, the solid was filtered off, washed with fresh water (400 ml.) and dried *in vacuo*. The product was di-[*N*-benzyl-*N*:*N*-dimethyl-*N*-(2-*o*-methylphenoxyethyl)ammonium] embonate dihydrate, melting point 68—69°.

EXAMPLE 3.

A solution of sodium naphthalene-2-sulphonate (7.1 g.) in hot water (50 ml.) was slowly added to a solution of *N*-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium chloride (9 g.) in water (50 ml.) with stirring. An oil separated and then crystallised. After the addition was complete, the mixture was stirred for 2 hours. The insoluble salt was then filtered off, washed with water and dried *in vacuo*. The resulting *N*-benzyl-*N*:*N*-dimethyl-*N*-2-phenoxyethylammonium, naphthalene-2-sulphonate was a colourless solid. It was recrystallised from a mixture of ethanol and ether and melted at 137—139°.

EXAMPLE 4

N - Benzyl - *N*:*N* - dimethyl - *N* - 2-phenoxyethylammonium naphthalene-1-sulphonate was prepared by the method described in Example 3 using sodium naphthalene-1-sulphonate. It was recrystallised from *iso*-propanol and melted at 128—130°.

EXAMPLE 5

2-Hydroxy-3-naphthoic acid (1.88 g.) was dissolved in hot aqueous sodium hydroxide (0.5*N*; 20 ml.) and the resulting solution was slowly aded to a solution of *N*-benzyl-*N*:*N*-dimethyl-N-2-phenoxyethylammonium chloride (2.9 g.) in water (5 ml.). A gum separated at first but it solidified on scratching. After the addition was complete, the mixture was allowed to stand at room temperature for 2 hours and then filtered. The residue was washed with water and dried *in vacuo* to give N-benzyl - *N*:*N* - dimethyl - *N* - 2 - phenoxyethylammonium 2-hydroxy-3-naphthoate, melting point 170—171°.

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