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TRIS-TRIIODOISOPHTHALAMIC ACIDS AND DERIVATIVES

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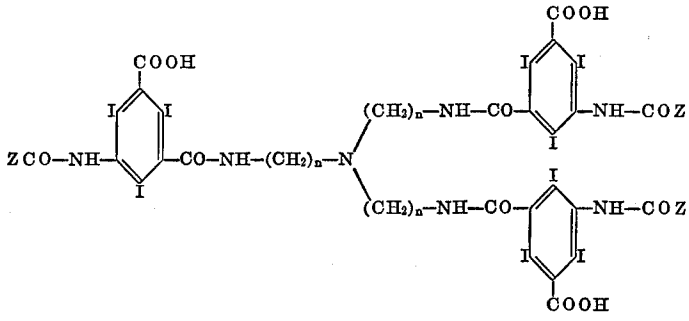
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ABSTRACT OF THE DISCLOSURE

This invention relates to new tris-triiodoisophthalamic acid compounds having the formula



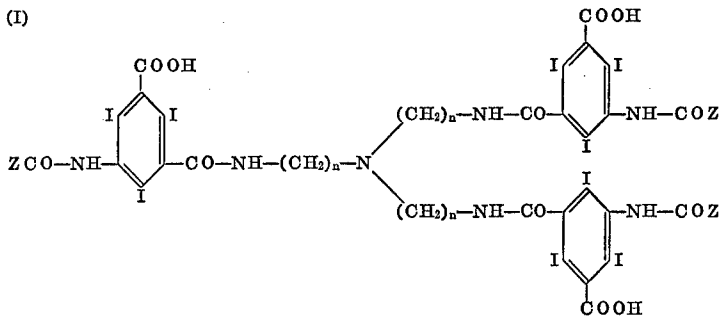
wherein Z is an alkyl chain of up to 6 carbon atoms, or a radical of the formula



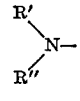
wherein R′ is an alkyl chain of up to 6 carbon atoms, and R″ is hydrogen or an alkyl chain of up to 6 carbon atoms, *n* is an integer from 2 to 4, and to salts and lower alkyl esters of these compounds. These compounds are useful as radiopaque agents.

This invention relates to new compounds of Formula I

(I)



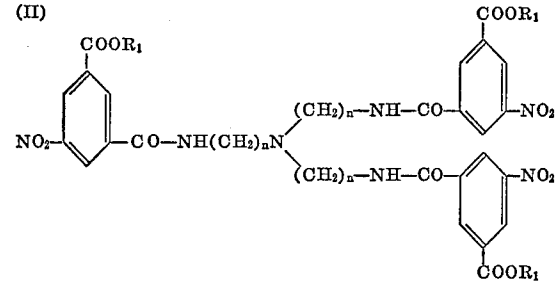
wherein Z is an alkyl chain of up to 6 carbon atoms or a radical of the formula



wherein R′ is an alkyl chain of up to 6 carbon atoms and R″ is hydrogen or an alkyl chain of up to 6 carbon atoms, and *n* is an integer from 2 to 4 and to basic salts of these compounds, e.g. alkali metal salts such as, for example, the sodium or potassium salts, alkaline earth salts such as, for example, calcium, ammonium salts and amine salts such as, for example, the N-methylglucamine salt, as well as lower alkyl esters such as, for example, the methyl, ethyl, butyl and hexyl esters, of the new compounds of Formula I. As used in this specification, the term "lower alkyl" includes straight and branched chain saturated radicals of up to four carbon atoms.

The new compounds of Formula I are produced by reacting 1 mole of a tris (aminoalkylene) amine with 3 moles of a 3-carboalkoxy-5-nitrobenzoyl halide (preferably the chloride) to form compounds of Formula II

(II)

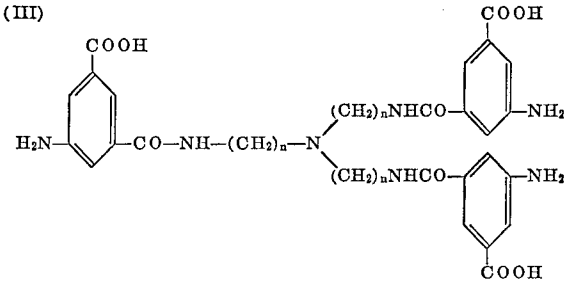


wherein *n* is as defined before and R_1 is lower alkyl. This reaction may be effected in an aqueous alkaline solution.

The ester of Formula II is then converted to the free acid by treatment with alkali, such as sodium carbonate, to give compounds of Formula II in which R_1 is hydrogen. The nitro groups are then reduced to amino groups, e.g. catalytically in the presence of a noble metal catalyst

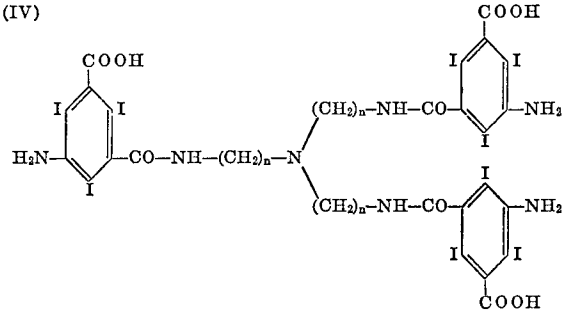
such as palladium, to obtain a compound of the Formula III

(III)



The compounds of Formula III are then iodinated. This may be effected by treating the compounds of Formula III with an iodinating agent, e.g. an iodine halide dissolved in an aqueous potassium chloride (which forms $KICl_2$) to give compounds of the Formula IV

(IV)



The compounds of Formula IV are then treated with an acylating agent to give products of the Formula I. The acylating agents may be acid anhydrides, such as acetic anhydride or butyric anhydride; acyl halides, such as acetyl chloride or propionyl chloride; substituted carbamoyl halide, such as dimethyl carbamoyl chloride or dibutyl carbamoyl chloride; and isocyanates, such as methyl isocyanate, ethyl isocyanate, hexyl isocyanate, phenyl isocyanate, p-chlorophenyl isocyanate or benzyl isocyanate.

These products form salts with inorganic or organic bases, e.g. alkali or alkaline earth metal hydroxides such as sodium hydroxide or amines such as ammonia or N-methylglucamine or may be converted to esters of lower alkanols, e.g. by treatment of an alkaline solution with a di(lower alkyl) sulfate, or by treatment of the acid with a diazoalkane, such as diazomethane. The salts, especially insoluble salts, frequently provide a convenient means for isolating and purifying the product.

The new products of Formula I are useful as radiopaque agents for visualization of animal systems or organs, preferably in the form of physiologically acceptable salts such as sodium or methylglucamine salts for the preparation of solutions for intravascular injection for urography and for vasographic techniques such as angiocardiography, arteriography, nephrography and venography. The water-insoluble esters are useful in visualizing hollow organs and cavities having external orifices through which the contrast preparation can be introduced in preparation for the examination and removal after the examination is completed. Solutions having about 20 to 50% bound iodine, preferably about 37%, may be used, or on a weight basis from about 20 g. to about 75 g. of a compound of Formula I per 100 ml. of water.

The following examples are illustrative of the invention. All temperatures are on the centigrade scale.

EXAMPLE 1

(a) Preparation of N,N',N''-(nitrilotrisethylene)tris-(5)-nitroisophthalamic acid)trimethyl ester

To a solution of 1.46 grams of tris(2-aminoethyl)amine in 50 ml. of acetone there is added a solution of 2.52 grams sodium bicarbonate in 50 ml. of water. The suspension is cooled to from about −5 to +5° and 7.29 grams of 3-carbomethoxy-5-nitrobenzoyl chloride are added, in small portions, with vigorous stirring during thirty minutes. The reaction mixture is allowed to warm to room temperature and is then stirred for an additional four hours. The solid is filtered by suction and washed with water and alcohol to yield N,N',N''-(nitrilotrisethylene)tris(5-nitroisophthalamic acid)trimethyl ester.

(b) N,N',N''-(nitrilotrisethylene)tris(5-nitroisophthalamic acid)

To a suspension of 3.84 grams of N,N',N''-(nitrilotrisethylene)tris(5-nitroisophthalamic acid)trimethyl ester in a mixture of 60 ml. of acetone and 60 ml. of water there are added 1.59 grams of sodium carbonate. The mixture is stirred at room temperature for one hour and then heated on a steam bath for 2½ hours. The clear solution is concentrated under reduced pressure to remove the acetone and the aqueous solution is treated with decolorizing carbon. The solution is filtered and the filtrate is made strongly acid with 20% hydrochloric acid. The precipitated solid is filtered and washed with water to yield the desired N,N',N''-(nitrilotrisethylene)tris(5-nitroisophthalamic acid).

(c) N,N',N''-(nitrilotrisethylene)tris(5-aminoisophthalamic acid)

To a solution of 7.25 grams of N,N',N''-(nitriolotrisethylene)tris(5-nitroisophthalamic acid) in 30 ml. of N—NaOH solution there are added 75 ml. of water and 750 mg. of 5% palladium on charcoal catalyst. The mixture is shaken at room temperature at 50 p.s.i. of hydrogen until the absorption of hydrogen is complete. The catalyst is removed by filtration and the aqueous filtrate is acidified with acetic acid. The precipitated solid is filtered and washed with water to yield the desired N,N',N''-(nitrilotrisethylene)tris(5-aminoisophthalamic acid).

(d) N,N',N''-(nitrilotrisethylene)tris(5-amino-2,4,6-triiodoisophthalamic acid)

To a mixture of 75 ml. of water and 90 ml. of acetic acid there are added 11.2 grams of N,N',N''-(nitrilotrisethylene)tris(5-aminoisophthalamic acid) and the mixture is heated to 50°. To this mixture there are then added 66 ml. of a 2.68 M $KICl_2$ solution and the reaction mixture heated at 50–55° for 24 hours. An additional 33 ml. of 2.68 M $KICl_2$ solution are then added and the reaction mixtures heated for an additional 65 hours. The cooled reaction mixture is poured onto cracked ice and the precipitated solid is filtered and washed with water. The product is dissolved in alcohol, treated with decolorizing carbon and recovered by concentration of the solvent. For further purification the product is adsorbed on an alumina column and eluted with aqueous alcoholic ammonia. The elutes are acidified and concentrated under reduced pressure to yield the desired product.

(e) N,N',N''-(nitrilotrisethylene)tris(5-acetamido-2,4,6-triiodoisophthalamic acid)

A mixture of 12 grams of N,N',N''-(nitriolotrisethylene)tris(5-amino-2,4,6-triiodoisophthalamic acid), 300 ml. of acetic acid and 30 ml. of acetic anhydride, to which has been added 1 ml. of concentrated H_2SO_4, is heated with stirring to reflux. The mixture is refluxed for four hours and then concentrated under reduced pressure to remove most of the solvent. The residue is suspended in water and, after two hours, made strongly acid with 20% hydrochloric acid. The solid is filtered and washed with dilute hydrochloric acid. After air drying it is then washed with ether and finally dried at 110° under reduced pressure for 24 hours to yield the desired N,N',N''-(trinitrilotrisethylene)tris(5-acetamido - 2,4,6 - triiodoisophthalamic acid).

EXAMPLE 2

Following the procedure of Example 1, but substituting an equivalent amount of tris(3-aminopropyl)amine for

the tris(2-aminoethyl)amine, there is obtained the desired N,N',N'' - [nitrilotris(trimethylene)]tris(5 - acetamido-2,4,6-triiodoisophthalamic acid).

EXAMPLE 3

Following the procedure of Example 1 but substituting an equivalent amount of tris(4-aminobutyl)amine for the tris(2-aminoethyl)amine, there is obtained the desired N,N,N''-]nitrilotris(tetramethylene)]tris(5 - acetamido-2,4,6-triiodoisophthalamic acid).

EXAMPLE 4

Following the procedure of Example 1 but substituting an equivalent amount of butyric anhydride for the acetic anhydride and butyric acid for the acetic acid, there is obtained the desired N,N',N''-(nitrilotrisethylene)tris(5-butyramido-2,4,6-triiodoisophthalamic acid).

EXAMPLE 5

To a solution of 3 grams of N,N',N''-(nitrilotrisethylene)-tris(5-acetamido-2,4,6-triiodoisophthalamic acid) in 50 ml. of dimethylformamide there is added slowly, with vigorous stirring, an excess of a solution of diazomethane in ether. The mixture is stirred for two hours, a few drops of acetic acid are added to destroy the excess diazomethane and the solvents removed by concentration under reduced pressure. The residue is suspended in dilute sodium hydroxide and the insoluble trimethyl ester of N,N',N''-(nitrilotrisethylene)tris - (5 - acetamido-2,4,6-triiodoisophthalamic acid) recovered by filtration.

EXAMPLE 6

To a suspension of 189.5 grams of N,N',N''-(nitrilotrisethylene)tris(5 - acetamido-2,4,6-triiodoisophthalamic acid in 1.5 liters of water there is added 300 ml. of N-NaOH solution and the resulting solution lyophilized to yield the desired trisodium salt of N,N',N''-(nitrilotrisethylene)tris(5 - acetamido-2,4,6-triiodoisophthalamic acid).

Similarly, by using an equivalent amount of N-methylglucamine there is obtained the desired N-methylglucamine salt of N,N',N''-(nitrilotrisethylene)tris(5-acetamido-2,4,6-triiodoisophthalamic acid).

EXAMPLE 7

A mixture of 5 grams of N,N',N''-(nitrilotrisethylene)-tris(5-amino-2,4,6-triiodoisophthalamic acid), 50 ml. of dimehylformamide and 2 grams of methyl isocyanate is heated on a steam bath for six hours. The dimethylformamide is removed by distillation under reduced pressure and the residue triturated with water to which dilute hydrochloric acid has been added. The precipitated solid is filtered, washed with dilute hydrochloric acid and allowed to air dry to yield the desired N,N',N''-(nitrilotrisethylene)tris[5-(3-methylureido) - 2,4,6 - triiodoisophthalamic acid]. The product may be purified by solution in dilute sodium hydroxide, treatment with decolorizing carbon, filtration and precipitation with dilute hydrochloric acid.

EXAMPLE 8

To a mixture of 3.5 grams of N,N',N''-(nitrilotrisethylene)tris(5-amino-2,4,6-triiodoisophthalamic acid), 5 ml. of N-methylmorpholine and 50 ml. of dimethylformamide, there is added, dropwise, with vigorous stirring 1.6 grams of diethylcarbamoyl chloride. The reaction mixture is stirred for one hour at room temperature and is then warmed on a steam bath for eight hours. The dimethylformamide is removed by distillation under reduced pressure and the residue added to 100 ml. of 10% hydrochloric acid. The precipitated solid is filtered, dissolved in 10% sodium hydroxide, filtered and reprecipitated with dilute hydrochloric acid to yield the desired N,N',N''-(nitrilotrisethylene)tris[5 - (3,3 - diethylureido) - 2,4,6 - triiodoisophthalamic acid].

EXAMPLE 9

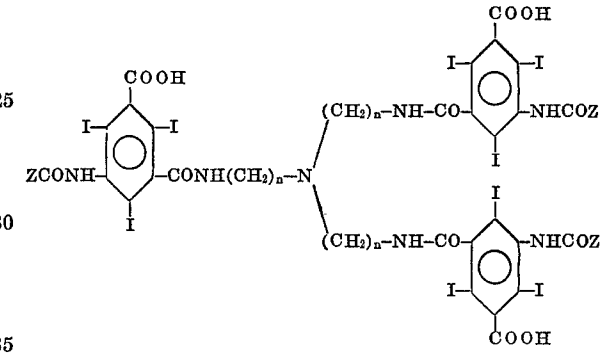
A solution suitable for use in intravenous urography has the following composition (per 100 ml.):

N,N',N''-(nitrilotrisethylene)tris - (5 - acetamido-2, 4,6-triiodoisophthalamic acid), sodium salt	grams__ 67
Sodium citrate (as buffer)	mg__ 320
Disodium ethylenediaminetetracetic acid dihydrate acid dihyrate (sequestering agent)	mg__ 40
Methylparaben (as preservative)	mg__ 100
Propylparaben (as preservative)	mg__ 30

The solution is prepared by dissolving the sodium salt in a limited amount of sterile water, adjusting the pH to about 7, adding the rest of the components and adjusting the final volume to 100 ml.

What is claimed is:

1. Tris-triiodoisophthalamic acid compounds having the formula



wherein Z is an alkyl chain of up to 6 carbon atoms or a radical of the formula



wherein R' is an alkyl chain of up to 6 carbon atoms and R'' is hydrogen or an alkyl chain of up to 6 carbon atoms, and *n* is an integer from 2 to 4, and to pharmaceutically acceptable basic salts and lower alkyl esters of the compounds.

2. A sodium salt of a compound of claim 1.

3. An N-methylglucamine salt of a compound of claim 1.

4. A compound of claim 1 having the name N,N',N''-(nitrilotrisethylene)tris(5 - acetamido - 2,4,6 - triiodoisophthalamic acid).

5. A compound of claim 1 having the name N,N',N''-[nitrilo-tris(tetramethylene)]tris(5-acetamido - 2,4,6 - triiodoisophthalamic acid).

6. A compound of claim 1 having the name N,N',N''-(nitrilotrisethylene)tris(5 - butyramido - 2,4,6 - triiodoisophthalamic acid).

7. A compound of claim 1 having the name N,N',N''-(nitrilotrisethylene)tris[5-(3-methylureido) - 2,4,6 - triiodoisophthalamic acid].

8. A compound of claim 1 having the name N,N,'N''-(nitrilotrisethylene)tris[5-(3,3-diethyluredio) - 2,4,6 - triiodoisophthalamic acid].

References Cited

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HENRY R. JILES, Primary Examiner

L. A. THAXTON, Assistant Examiner

U.S. Cl. X.R.

260—471 R, 518 A; 424—5