United States Patent

Bernstein et al.

[15] **3,666,800**

[45] **May 30, 1972**

[54] SUBSTITUTED TRIIODOISOPHTHALAMIC ACIDS

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[22] Filed: **June 19, 1970**

[21] Appl. No.: **47,886**

[52] **U.S. Cl.**.....**260/518 A,** 260/471 R, 260/501.11, 424/5

[51] **Int. Cl.**.....**C07c 103/30**

[58] **Field of Search**.....424/5; 260/518 A, 471 R, 501.11

[56] **References Cited**

OTHER PUBLICATIONS

Fieser, L. F., et al. Organic Chemistry, 3rd Edit. (1956), pub. by Reinhold Pub. Corp. page. 608 cited.

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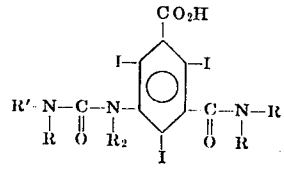
[57] **ABSTRACT**

Compounds having the formula



wherein R and R_2 are hydrogen or alkyl and R′ is alkyl, as well as salts and lower alkyl esters of these compounds are useful as radiopaque agents.

5 Claims, No Drawings

SUBSTITUTED TRIIODOISOPHTHALAMIC ACIDS

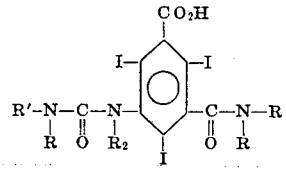
OBJECTS OF THE INVENTION

It is an object of the present invention to provide new compounds which are useful radiopaque agents. Another object is to provide methods for the preparation of these compounds. These and other objects of the present invention will be apparent from the following description.

DETAILED DESCRIPTION

The present invention relates to new compounds of the formula

I



and to basic salts of these compounds, e.g., alkali metal salts such as, for example, sodium and potassium; alkaline earth salts such as, for example, calcium; ammonium salts such as, for example, N-methylglucamine, as well as lower aliphatic esters of up to 6 carbon atoms such as methyl, ethyl, propyl, i-propyl, n-butyl, i-butyl, n-pentyl, 2-methylbutyl, neopentyl, n-hexyl, 2-methylpentyl, 3-methylpentyl, 2,2-dimethylbutyl and 2,3-dimethylbutyl esters. In the compounds of the present invention the R and R_2 are hydrogen or an alkyl radical of up to six carbon atoms and R' is an alkyl radical of up to six carbon atoms.

The new compounds of the present invention include the following compounds as well as the above-mentioned basic salts and aliphatic esters thereof:

5-(3-methylureido)-2,4,6-triiodo-N-methyl-isophthalamic acid

5-(3-n-butylureido)-2,4,6-triiodo-N-methyl-isophthalamic acid

5-(3-n-hexylureido)-2,4,6-triiodo-N-methyl-isophthalamic acid

5-(3-methylureido)-2,4,6-triiodo-N-ethyl-isophthalamic acid

5-(3-methylureido)-2,4,6-triiodo-N,N-dimethyl-isophthalamic acid

5-(3-ethylureido)-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid

5-(3,3-dimethylureido)-2,4,6-triiodo-N-methyl-isophthalamic acid

5-(3-methyl-1-n-propylureido)-2,4,6-triiodo-N-methylisophthalamic acid

5-(3,3-dimethyl-1-n-propylureido)-2,4,6-triiodo-N-methylisophthalamic acid

5-(3-methyl-1-n-propylureido)-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid

5-(3,3-dimethyl-1-n-propylureido)-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid

5-(3-n-butylureido)-2,4,6-triiodoisophthalamic acid

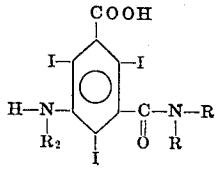
5-(3,3-dimethylureido)-2,4,6-triiodoisophthalamic acid

5-(3-methyl-1-ethylureido)-2,4,6-triiodoisophthalamic acid

5-(1,3,3-triethylureido)-2,4,6-triiodoisophthalamic acid

The compounds of the present invention may be prepared by the reaction of an appropriately substituted 5-amino-2,4,6-triiodoisophthalamic acid of the formula

II

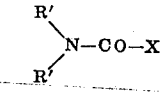


wherein R and R_2 are as previously defined with an alkyl isocyanate of the formula

R'—NCO III

or a dialkylcarbamoyl halide of the formula

IV



wherein X is a halogen, preferably chlorine and R' is as previously defined.

The reaction is carried out in an inert solvent such as ethylene glycol dimethyl ether, diethylene glycol dimethyl ether, dimethylformamide, dimethylacetamide, tetrahydrofuran, dimethylsulfoxide and the like. In those cases where a dialkylcarbamoyl chloride is a reactant, it is advantageous to use a hydrogen chloride acceptor, such as pyridine, N-methylmorpholine, triethyl-amine, etc., in which case the hydrogen chloride acceptor may also be used as the solvent, if desired.

The starting materials of formula II in which R_2 is hydrogen are readily obtained by the procedure described by Hoey et al. [J. Med. Chem. 6, 24 (1963)]. The starting materials of formula II in which R_2 is alkyl are obtained by condensing 5-amino-N-substituted-isophthalamic acids with an aldehyde, followed by reduction of the Schiff base thus obtained to the 5-alkylamino-N-substituted-isophthalamic acid.

To prepare salts of the compound of formula I, the acids are reacted with an inorganic or organic base, e.g., alkali metal hydroxide such as sodium hydroxide, or amines, such as n-methylglucamine. The esters may be formed by treating an alkaline solution of a compound of formula I with a di(lower alkyl) sulfate such as dimethyl sulfate or by treatment with a diazoalkane such as diazomethane. The salts, especially insoluble salts, frequently provide a convenient means of 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 percent bound iodine, preferably about 37 percent, 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 illustrate the present invention without, however, limiting the same thereto. All temperatures are given on the Centigrade scale.

EXAMPLE 1

5-(3-Methylureido)-2,4,6-Triiodo-N-Methylisophthalamic Acid

To a solution of 1 gram of 5-amino-2,4,6-triiodo-N-methylisophthalamic acid in 100 ml of ethylene glycol dimethyl ether there is added 1 ml of methyl isocyanate and the reaction mixture heated under reflux for 20 hours. The solvent is removed by distillation under reduced pressure and the residue dissolved in dilute sodium hydroxide solution. The solution is treated with decolorizing carbon, filtered and made strongly acid with 10 percent hydrochloric acid. The precipitated solid is filtered, washed with dilute hydrochloric acid and dried under reduced pressure at about 100°. The 5-(3-methylureido)-2,4,6-triiodo-N-methylisophthalamic acid thus obtained is a white solid melting at about 180°–185° with decomposition.

EXAMPLE 2

5-(3-n-Butylureido)-2,4,6-Triiodo-N-Methylisophthalamic Acid

Following the procedure of Example 1 but substituting an equivalent amount of n-butyl isocyanate for the methyl iso-

cyanate, there is obtained the desired 5-(3-n-butyl-ureido)-2,4,6-triiodo-N-methylisophthalamic acid.

EXAMPLE 3

5-(3-N-Hexylureido)-2,4,6-Triiodo-N-Methylisophthalamic Acid

Following the procedure of Example 1 but substituting an equivalent amount of n-hexyl isocyanate for the methyl isocyanate, there is obtained the desired 5-(3-n-hexyl-ureido)-2,4,6-triiodo-N-methylisophthalamic acid.

EXAMPLE 4

5-(3-Methylureido)-2,4,6-Triiodo-N-Ethylisophthalamic Acid

Following the procedure of Example 1 but substituting an equivalent amount of 5-amino-2,4,6-triiodo-N-ethylisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methylisophthalamic acid, there is obtained the desired 5-(3-methylureido)-2,4,6-triiodo-N-ethylisophthalamic acid.

EXAMPLE 5

5-(3-Methylureido)-2,4,6-Triiodo-N,N-Dimethylisophthalamic Acid

Following the procedure of Example 1 but substituting an equivalent amount of 5-amino-2,4,6-triiodo-N,N-dimethylisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methylisophthalamic acid, there is obtained the desired 5-(3-methylureido)-2,4,6-triiodo-N,N-dimethylisophthalamic acid.

EXAMPLE 6

5-(3-Ethylureido)-2,4,6-Triiodo-N-Ethyl-N-Methylisophthalamic Acid

a. Methyl N-Ethyl-N-Methyl-5-Nitroisophthalamate

A solution of 55.6 grams of 3-carbomethoxy-5-nitrobenzoyl chloride in 200 ml of carbon tetrachloride is added slowly to a well-stirred mixture of 13.5 grams of ethylmethylamine, 200 ml of water, 50 ml of acetone and 9.3 grams of sodium hydroxide. The carbon tetrachloride and acetone are removed by concentration under reduced pressure. The residue is cooled and the precipitated methyl N-ethyl-N-methyl-5-nitroisophthalamate separated from the aqueous layer.

b. N-Ethyl-N-Methyl-5-Nitroisophthalamic Acid

The crude methyl N-ethyl-N-methyl-5-nitroisophthalamate obtained in (a) is dissolved in a minimum amount of alcohol and an equal volume of water is added. Sodium carbonate is added until the pH of the mixture is 8 and the reaction mixture is then heated to reflux with stirring for 1 hour. The mixture is diluted with water, filtered and the filtrate poured into excess hydrochloric acid. The precipitated solid is filtered, washed with water and redissolved in dilute aqueous ammonia. The solution is treated with decolorizing carbon, filtered and acidified with dilute hydrochloric acid. The precipitate is collected by filtration, washed with water and then recrystallized from aqueous alcohol to yield the desired N-ethyl-N-methyl-5-nitroisophthalamic acid.

c. 5-Amino-N-Ethyl-N-Methylisophthalamic Acid

A mixture of 12 grams of N-ethyl-N-methyl-5-nitroisophthalamic acid, 1 gram of 5 percent palladium on carbon and 150 ml of methanol is shaken in a Parr hydrogenator under a pressure of 50 lbs/sq.in. of hydrogen. After the theoretical quantity of hydrogen has been absorbed, the mixture is filtered and the catalyst washed thoroughly with methanol. The filtrate and washings are combined and concentrated under reduced pressure to yield the desired 5-amino-N-ethyl-N-methylisophthalamic acid.

d. 5-Amino-2,4,6-Triiodo-N-Ethyl-N-Methylisophthalamic Acid

To a stirred suspension of 20 grams of 5-amino-N-ethyl-N-methylisophthalamic acid in 250 ml of water there is added over the course of 1 hour a solution of 16 grams of iodine monochloride and 19 grams of potassium chloride in 150 ml of water. The reaction mixture is stirred for 5 hours after the addition is complete and a solution of 10 grams of sodium hydroxide in 25 ml of water added. To this stirred mixture there is then added a solution of 8 grams of iodine monochloride and 9.5 grams of potassium chloride in 75 ml of water over the course of 1 hour. The reaction mixture is stirred for 24 hours and the 5-amino-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid filtered and washed thoroughly with water. The product may be purified by crystallization of the ammonium salt and conversion of the ammonium salt to the free acid by treatment with hydrochloric acid.

e. 5-(3-Ethylureido)-2,4,6Triiodo-N-Ethyl-N-Methyl-Isophthalamic Acid

Following the procedure of Example 1 but substituting an equivalent amount of ethyl isocyanate for the methyl isocyanate and an equivalent amount of 5-amino-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methylisophthalamic acid, there is obtained the desired 5-(3-ethylureido)-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid.

EXAMPLE 7

5-(3,3-Dimethylureido)-2,4,6-Triiodo-N-Methylisophthalamic Acid

To 3 grams of 5-amino-2,4,6-triiodo-N-methylisophthalamic acid in 25 ml of anhydrous pyridine there is added dropwise, with vigorous stirring, a solution of 1 gram of dimethylcarbamoyl chloride in 10 ml of anhydrous benzene. The reaction mixture is warmed gently to complete the reaction and then concentrated under reduced pressure to remove the benzene. The residue is poured onto a mixture of ice and 20 percent hydrochloric acid. The precipitated solid is filtered, washed with dilute acid, and dried at 100° under reduced pressure to yield the desired 5-(3,3-dimethyl-ureido)-2,4,6-triiodo-N-methylisophthalamic acid. The product may be purified by solution in dilute alkali and reprecipitation with hydrochloric acid.

EXAMPLE 8

5-(3-Methyl-1-n-Propylureido)-2,4,6-Triiodo-N-Methylisophthalamic Acid

a) 5-n-Propylamino-N-Methylisophthalamic Acid

To a solution of 9.7 grams of 5-amino-N-methylisophthalamic acid in 150 ml of methanol, there is added 4 ml of propionaldehyde and the mixture hydrogenated at room temperature and atmospheric pressure using 4 grams of Raney nickel as catalyst. The catalyst is filtered off, and the filtrate concentrated under reduced pressure to yield the desired 5-n-propylamino-N-methylisophthalamic acid.

b. 5-n-Propylamino-2,4,6-Triiodo-N-Methylisophthalamic Acid

Following the procedure of Example 6*d* but substituting an equivalent amount of 5-n-propylamino-N-methylisophthalamic acid for the 5-amino-N-ethyl-N-methylisophthalamic acid, there is obtained the desired 5-n-propylamino-2,4,6-Triiodo-N-methylisophthalamic acid.

c. 5-(3-Methyl-1-n-Propylureido)-2,4,6-Triiodo-N-Methylisophthalamic Acid

Following the procedure of Example 1, but substituting an equivalent amount of 5-n-propylamino-2,4,6-triiodo-N-methylisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methylisophthalamic acid, there is obtained the desired 5-(3-methyl-1-n-propylureido)-2,4,6-triiodo-N-methylisophthalamic acid.

EXAMPLE 9

5-(3,3-Dimethyl-1-n-Propylureido)-2,4,6-Triiodo-N-Methyl-Isophthalamic Acid

Following the procedure of Example 7 but substituting an equivalent amount of 5-n-propylamino-2,4,6-triiodo-N-methylisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methylisophthalamic acid, there is obtained the desired 5-

(3,3-dimethyl-1-n-propylureido)-2,4,6-triiodo-N-methyl-isophthalamic acid.

EXAMPLE 10

5-(3-Methyl-1-n-Propylureido)-2,4,6-Triiodo-N-Ethyl-N-Methylisophthalamic Acid

a) 5-n-Propylamino-2,4,6-Triiodo-N-Ethyl-N-Methylisophthalamic Acid

Following the procedure of Example 8 *a,b*, but substituting an equivalent amount of 5-amino-N-ethyl-N-methylisophthalamic acid for the 5-amino-N-methylisophthalamic acid, there is obtained the desired 5-n-propylamino-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid.

b. 5-(3-Methyl-1-n-Propylureido)-2,4,6-Triiodo-N-Ethyl-N-Methylisophthalamic Acid

Following the procedure of Example 1 but substituting an equivalent amount of 5-n-propylamino-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methylisophthalamic acid, there is obtained the desired 5-(3-methyl-1-n-propylureido)-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid.

EXAMPLE 11

5-(3,3-Dimethyl-1-n-Propylureido)-2,4,6-Triiodo-N-Ethyl-N-Methylisophthalamic Acid

Following the procedure of Example 7 but substituting an equivalent amount of 5-n-propylureido-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methylisophthalamic acid, there is obtained the desired 5-(3,3-dimethyl-1-n-propylureido)-2,4,6-triiodo-N-ethyl-N-methylisophthalamic acid.

EXAMPLE 12

5-(3-n-Butylureido)-2,4,6-Triiodoisophthalamic Acid

Following the procedure of Example 1 but substituting an equivalent amount of 5-amino-2,4,6-triiodoisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methylisophthalamic acid and an equivalent amount of n-butyl isocyanate for the methyl isocyanate, there is obtained the desired 5-(3-n-butylureido)-2,4,6-triiodoisophthalamic acid.

EXAMPLE 13

5-(3,3-Dimethylureido)-2,4,6-Triiodoisophthalamic Acid

Following the procedure of Example 7 but substituting an equivalent amount of 5-amino-2,4,6-triiodoisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methylisophthalamic acid there is obtained the desired 5-(3,3-dimethylureido)-2,4,6-triiodoisophthalamic acid.

EXAMPLE 14

a. 5-Ethylamino-2,4,6-Triiodoisophthalamic Acid

Following the procedure of Example 8 *a,b*, but substituting an equivalent amount of 5-aminoisophthalamic acid for the 5-amino-N-methylisophthalamic acid and an equivalent amount of acetaldehyde for the propionaldehyde, there is obtained the desired 5-ethylamino-2,4,6-triiodo-isophthalamic acid.

b. 5-(3-Methyl-1-Ethylureido)-2,4,6-Triiodoisophthalamic Acid

Following the procedure of Example 1 but substituting an equivalent amount of 5-ethylamino-2,4,6-triiodoisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methylisophthalamic acid, there is obtained the desired 5-(3-methyl-1-ethylureido)-2,4,6-triiodoisophthalamic acid.

EXAMPLE 15

5-(1,3,3-Triethylureido)-2,4,6-Triiodoisophthalamic Acid

Following the procedure of Example 7 but substituting an equivalent amount of 5-ethylamino-2,4,6-triiodoisophthalamic acid for the 5-amino-2,4,6-triiodo-N-methyl-isophthalamic acid and an equivalent amount of diethyl-carbamoyl chloride for the dimethylcarbamoyl chloride, there is obtained the desired 5-(1,3,3-triethylureido)-2,4,6-triiodoisophthalamic acid.

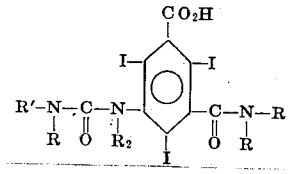
EXAMPLE 16

Ethyl 5-(3-methylureido)-2,4,6-Triiodo-N-Methylisophthalamate

To a stirred slurry of 21 grams of 5-(3-methyl-ureido)-2,4,6-triiodo-N-methylisophthalamic acid in 100 ml of absolute ethanol, there is added a solution of 2.2 grams of potassium hydroxide in 50 ml of absolute ethanol. To this mixture there is added 4.5 ml of diethyl sulfate. The mixture is allowed to stir overnight and 100 ml of water added. The reaction mixture is concentrated to dryness and suspended in dilute alkali. The solution is filtered and the crude ester thus obtained is the desired ethyl 5-(3-methylureido)-2,4,6-triiodo-N-methylisophthalamate. The product may be purified by solution in warm dimethylformamide, treating with decolorizing carbon and dilution of the filtrate with water to precipitate the desired ester.

What is claimed is:

1. A compound of the formula



wherein R and R_2 are hydrogen or alkyl of up to six carbon atoms and R′ is alkyl of up to six carbon atoms, as well as lower alkyl esters and physiologically acceptable salts thereof wherein the alkyl ester has up to six carbon atoms.

2. A compound of claim 1 wherein R and R_2 are hydrogen.

3. A compound of claim 1 wherein R and R_2 are alkyl.

4. A compound of claim 1 wherein R_2 is hydrogen and R is alkyl.

5. A compound of claim 1 wherein R_2 is alkyl and R is hydrogen.

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