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3,660,464  
**TRI-IODINATED DIAMINOBENZOIC ACID  
DERIVATIVES**

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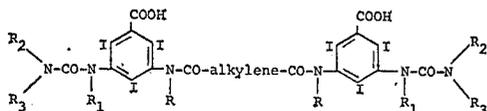
Int. Cl. C07c 127/16

U.S. Cl. 260-470

6 Claims

**ABSTRACT OF THE DISCLOSURE**

This invention relates to new iodinated diaminobenzoic acid derivatives of the general formula

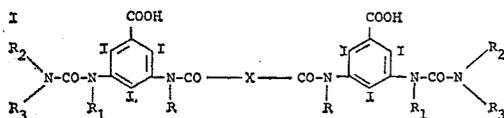


and to salts and lower alkyl esters of these compounds, which are useful as radiopaque agents.

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.

**SUMMARY OF THE INVENTION**

This invention relates to new radiopaque compounds of the formula



wherein R, R<sub>1</sub> and R<sub>2</sub> are hydrogen or lower alkyl, R<sub>3</sub> is lower alkyl, X is an alkylene chain containing up to 10 carbon atoms, which may be interrupted by heterocyclic atoms such as oxygen, sulfur or



and to the basic salts of these compounds, e.g., alkali metal salts such as sodium and potassium, alkaline earth salts such as calcium, ammonium salts and amine salts, such as N-methylglucamine, as well as lower aliphatic esters such as the methyl, ethyl and butyl esters.

The new compounds of the present invention include the following types of compounds as well as the above-mentioned basic salts and aliphatic esters thereof: N,N'-bis[5-(alkylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamides, such as

- N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide,
- N,N'-bis[5-(3-ethylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide and
- N,N'-bis[5-(3-n-butylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide;
- N,N'-bis[5-(dialkylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamides, such as
- N,N'-bis[5-(3,3-dimethylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide,
- N,N'-bis[5-(1,3-dimethylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide,
- N,N'-bis[5-(1-methyl-3-ethylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide and
- N,N'-bis[5-(1-ethyl-3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide;

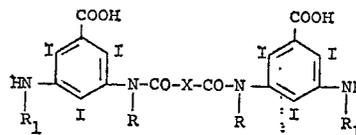
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- N,N'-bis[5-(trialkylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamides, such as
- N,N'-bis[5-(1,3,3-trimethylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide;
- 5 N,N'-dialkyl-N,N'-bis[5-(alkylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamides, such as
- N,N'-diethyl-N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide;
- 10 N,N'-dialkyl-N,N'-bis[5-(dialkylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamides, such as
- N,N'-diethyl-N,N'-bis[5-(3,3-dimethylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide and
- N,N'-diethyl-N,N'-bis[5-(1,3-dimethylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide; and
- 15 N,N'-dialkyl-N,N'-bis[5-(trialkylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamides, such as
- N,N'-diethyl-N,N'-bis[5-(1,3,3-trimethylureido)-3-carboxy-2,4,6-tri-iodophenyl] adipamide,

20 as well as the corresponding derivatives of succinamide, glutaramide, suberamide, pimelamide, sebacamide, 3-oxoglutaramide and 3-methyl-3-azaglutaramide.

The compounds of this invention may be prepared by the reaction of a compound of formula

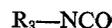
25 II



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with an alkyl isocyanate of the formula

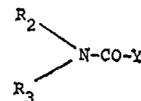
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or a dialkylcarbonyl halide of the formula

IV



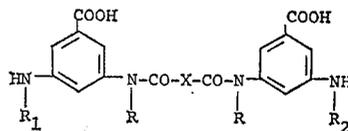
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wherein Y is halogen, preferably chlorine and R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and X are as previously defined. The reaction is carried out in an inert solvent such as ethylene glycol dimethyl ether, diethylene glycol dimethyl ether or dimethyl formamide. When a compound of Formula IV is one of the reactants, the reaction is preferably carried out in the presence of a hydrogen halide acceptor such as pyridine, N-methylmorpholine, triethylamine and the like. In such cases, the hydrogen halide acceptor may also be used as a solvent for the reaction.

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The compounds of the Formula II may be prepared by the iodination of a compound of the formula

50 (V)



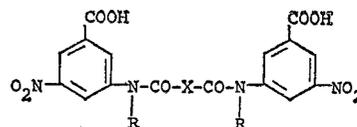
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with iodine chloride in aqueous medium or with sodium or potassium iododichloride in aqueous medium.

The compounds of Formula V in which R<sub>1</sub> is hydrogen may be prepared by the reduction of a nitro compound of the formula

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(VI)



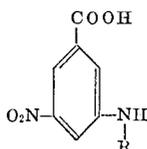
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The compounds of Formula V in which R<sub>1</sub> is lower alkyl may be prepared by the reduction of the Schiff base of a compound of Formula V in which R<sub>1</sub> is hydrogen.

Compounds of the Formula VI are prepared by treatment of a compound of the Formula VII

VII



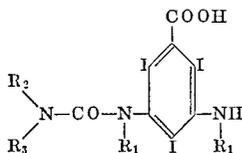
with an acyl halide, preferentially the chloride of the formula



wherein X and Y are as previously defined. The reaction is catalyzed by a trace of strong acid such as sulfuric or perchloric acid.

An alternate synthesis for the compounds of Formula I is the reaction of a compound of the formula

IX



with a compound of the Formula VIII. Compounds of the Formula IX are described in our copending application Ser. No. 47,902, filed concurrently herewith.

The lower alkyl groups R, R<sub>1</sub> and R<sub>2</sub> include straight or branched alkyl chains 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.

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 angiocardiology, 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 illustrate the present invention without, however, limiting the same thereto. All temperatures are on the centigrade scale.

## EXAMPLE 1

N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide

(a) N,N'-bis[5-nitro-3-carboxyphenyl]adipamide.—To a solution of 10 grams of 3-amino-5-nitrobenzoic acid in 75 ml. of toluene there is slowly added 4.5 grams of adipoyl chloride and the reaction mixture heated on a steam bath for six hours. The reaction mixture is cooled, and the solid filtered, washed with toluene and air-dried. It is then suspended in dilute hydrochloric acid, filtered and washed with water to yield the desired N,N'-bis[5-nitro-3-carboxyphenyl]adipamide. The product may be purified by crystallization of the ammonium salt and conversion to the free acid, which melts at about 300°.

(b) N,N'-bis[5-amino-3-carboxyphenyl]adipamide.—To a solution of 10 grams of N,N'-bis[5-nitro-3-carboxyphenyl]adipamide in an equivalent amount of dilute aqueous sodium hydroxide there is added one gram of Raney nickel catalyst and the reaction mixture shaken in a Parr hydrogenation apparatus at 50 p.s.i. of hydrogen until

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the theoretical amount of hydrogen is absorbed. The mixture is filtered and the filtrate neutralized with acetic acid. The precipitated solid is filtered, washed with water and dried to yield the desired N,N'-bis[5-amino-3-carboxyphenyl]adipamide, which melts at about 310° with decomposition.

(c) N,N'-bis[5-amino-3-carboxy-2,4,6-tri-iodophenyl]adipamide.—To a mixture of 13.3 grams of N,N'-bis[5-amino-3-carboxyphenyl]adipamide and 400 ml. of water there is added slowly, with vigorous stirring, 100 ml. of 2 N aqueous potassium iodochloride solution. The reaction mixture is stirred for twenty-four hours at room temperature and is then filtered. The solid thus obtained is dissolved in dilute aqueous sodium hydroxide, treated with aqueous sodium bisulfite and filtered. The filtrate is neutralized with dilute hydrochloric acid and the precipitate collected by filtration. The solid is washed with water and dried at 50° under reduced pressure to yield the desired N,N'-bis[5-amino-3-carboxy-2,4,6-tri-iodophenyl]adipamide. The product, which does not melt below 300°, may be purified by crystallization of its ammonium salt.

(d) N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.—A mixture of 2 grams of N,N'-bis[5-amino-3-carboxy-2,4,6-tri-iodophenyl]adipamide, 2 ml. of methyl isocyanate and 100 ml. of ethylene glycol dimethyl ether is heated to reflux for twenty-four hours. The solvent is removed by distillation under reduced pressure and the residue treated with dilute hydrochloric acid. The precipitated solid is filtered, dissolved in dilute alkali and treated with decolorizing carbon. The solution is filtered and made strongly acid with 20% hydrochloric acid. The precipitated solid is filtered, washed with water and dried under reduced pressure at 100° to yield the desired N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

Following this general procedure but substituting in part (a) equivalent amounts of the acyl chlorides derived from succinic acid, glutamic acid, suberic acid, pimelic acid, sebacic acid, 3-oxoglutaric acid and 3-methyl-3-azaglutamic acid, there is obtained

N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]succinamide,

N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]glutaramide,

N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]suberamide,

N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]pimelamide,

N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]sebacamide,

N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]-3-oxaglutaramide and

N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]-3-methyl-3-azaglutaramide,

respectively.

## EXAMPLE 2

N,N'-bis[5-(3-ethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide

Following the procedure of Example 1d, but substituting an equivalent amount of ethyl isocyanate for the methyl isocyanate, there is obtained the desired N,N'-bis[5-(3-ethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

## EXAMPLE 3

N,N'-bis[5-(3-n-butylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide

Following the procedure of Example 1d but substituting an equivalent amount of n-butyl isocyanate for the methyl isocyanate, there is obtained the desired N,N'-bis[5-(3-n-butylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

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**EXAMPLE 4**

N,N'-dimethyl-N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide

Following the procedure of Example 1, but substituting an equivalent amount of 3-methylamino-5-nitrobenzoic acid for the 3-amino-5-nitrobenzoic acid in part (a), there is obtained the desired N,N'-dimethyl-N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

Similarly by substituting equivalent amounts of 3-ethylamino-5-nitrobenzoic acid and 3-n-butylamino-5-nitrobenzoic acid for the 3-amino-5-nitrobenzoic acid, there is obtained N,N'-diethyl-N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide and N,N'-di-n-butyl-N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

**EXAMPLE 5**

N,N'-bis[5-(3,3-dimethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide

To a stirred mixture of 2 grams of N,N'-bis[5-amino-3-carboxy-2,4,6-tri-iodophenyl]adipamide in 20 ml. of anhydrous pyridine there is added dropwise, with cooling, a solution of 1 gram of dimethylcarbonyl chloride in 10 ml. of anhydrous benzene. The reaction mixture is stirred for two hours and is then concentrated under reduced pressure to remove the benzene. The residue is mixed with ice and dilute hydrochloric acid. The precipitated solid is filtered, dissolved in dilute aqueous sodium hydroxide and treated with decolorizing carbon. The solution is filtered and made strongly acid with 20% hydrochloric acid. The solid is filtered, washed with water and dried at 60° under reduced pressure to yield the desired N,N'-bis[5-(3,3-dimethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

Similarly by employing an equivalent amount of diethylcarbonyl chloride for the dimethylcarbonyl chloride there is obtained the desired N,N'-bis[5-(3,3-diethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

**EXAMPLE 6**

N,N'-bis[5-(1-ethyl-3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide

(a) N,N'-bis[5-ethylamino-3-carboxyphenyl]adipamide.—A mixture of 10 grams of N,N'-bis[5-amino-3-carboxyphenyl]adipamide and 5 ml. of acetaldehyde in 200 ml. of absolute ethanol is allowed to stand for 12 hours and is then hydrogenated at room temperature and pressure using 5 grams of Raney nickel as the catalyst. The catalyst is filtered and the filtrate concentrated under reduced pressure to yield the desired N,N'-bis[5-ethylamino-3-carboxyphenyl]adipamide. The product may be purified by crystallization from aqueous alcohol.

(b) N,N'-bis[5-ethylamino-3-carboxy-2,4,6-tri-iodophenyl]adipamide.—Following the procedure of Example 1(c), but substituting an equivalent amount of N,N'-bis[5-ethylamino-3-carboxyphenyl]adipamide for the N,N'-bis[5-amino-3-carboxyphenyl]adipamide, there is obtained the desired N,N'-bis[5-ethylamino-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

(c) N,N'-bis[5-(1-ethyl-3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.—Following the procedure of Example 1(d), but substituting an equivalent amount of N,N'-bis[5-ethylamino-3-carboxy-2,4,6-tri-iodophenyl]adipamide for the N,N'-bis[5-amino-3-carboxy-2,4,6-tri-iodophenyl]adipamide, there is obtained the desired N,N'-bis[5-(1-ethyl-3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

**EXAMPLE 7**

N,N'-bis[5-(1-ethyl-3,3-dimethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide

Following the procedure of Example 5, but substituting an equivalent amount of N,N'-bis[5-ethylamino-3-carboxy-2,4,6-tri-iodophenyl]adipamide for the N,N'-bis[5-amino-3-carboxy-2,4,6-tri-iodophenyl]adipamide, there is

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obtained the desired N,N'-bis[5-(1-ethyl-3,3-dimethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

**EXAMPLE 8**

N,N'-dimethyl-N,N'-bis[5-(1-ethyl-3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide

(a) N,N'-dimethyl-N,N'-bis[5-amino-3-carboxyphenyl]adipamide.—Following the procedure of Example 1(a), (b), but substituting an equivalent amount of 3-methylamino-5-nitrobenzoic acid for the 3-amino-5-nitrobenzoic acid in part (a), there is obtained the desired N,N'-dimethyl-N,N'-bis[5-amino-3-carboxyphenyl]adipamide.

(b) N,N'-dimethyl-N,N'-bis[5-ethylamino-3-carboxy-2,4,6-tri-iodophenyl]adipamide.—Following the procedure of Example 6(a), (b), but substituting an equivalent amount of N,N'-dimethyl-N,N'-bis[5-ethylamino-3-carboxyphenyl]adipamide for the N,N'-bis[5-amino-3-carboxyphenyl]adipamide in part (a), there is obtained the desired N,N'-dimethyl-N,N'-bis[5-ethylamino-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

(c) N,N'-dimethyl-N,N'-bis[5-(1-ethyl-3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.—Following the procedure of Example 1(d), but substituting an equivalent amount of N,N'-dimethyl-N,N'-bis[5-ethylamino-3-carboxy-2,4,6-tri-iodophenyl]adipamide for the N,N'-bis[5-amino-3-carboxy-2,4,6-tri-iodophenyl]adipamide, there is obtained the desired N,N'-dimethyl-N,N'-bis[5-(1-ethyl-3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

Similarly, but substituting an equivalent amount of 5-ethylamino-3-nitrobenzoic acid for the 5-methylamino-3-nitrobenzoic acid in part (a), there is obtained N,N'-diethyl-N,N'-bis[5-(1-ethyl-3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

**EXAMPLE 9**

N,N'-dimethyl-N,N'-bis[5-(1-ethyl-3,3-dimethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide

Following the procedure of Example 5, but substituting an equivalent amount of N,N'-dimethyl-N,N'-bis[5-ethylamino-3-carboxy-2,4,6-tri-iodophenyl]adipamide for the N,N'-bis[5-amino-3-carboxy-2,4,6-tri-iodophenyl]adipamide, there is obtained the desired N,N'-dimethyl-N,N'-bis[5-(1-ethyl-3,3-dimethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

**EXAMPLE 10**

N,N'-bis[5-(1,3,3-trimethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide

Following the procedure of Example 1(a), but substituting 3 grams of 3-amino-5-(1,3,3-trimethylureido)-2,4,6-tri-iodobenzoic acid for the 3-amino-5-nitrobenzoic acid, there is obtained the desired N,N'-bis[5-(1,3,3-trimethylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide.

**EXAMPLE 11**

N,N'-bis[5-(3-methylureido)-3-carbomethoxy-2,4,6-tri-iodophenyl]adipamide

Following the general procedure of Example 1, but substituting an equivalent amount of methyl 3-amino-5-nitrobenzoate for the 3-amino-5-nitrobenzoic acid, there is obtained the desired N,N'-bis[5-(3-methylureido)-3-carbomethoxy-2,4,6-tri-iodophenyl]adipamide.

**EXAMPLE 12**

N,N'-dimethyl-N,N'-bis[5-(3-methylureido)-3-carbomethoxy-2,4,6-tri-iodophenyl]adipamide

To a mixture of 20 grams of N,N'-dimethyl-N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide and 100 ml. of absolute ethanol there is added a solution of 2 grams of potassium hydroxide in 50 ml. of absolute ethanol. There is then added 4.5 ml. of diethyl sulfate and the reaction mixture is stirred for twenty-four

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hours. To this mixture there is then added 150 ml. of water and the mixture concentrated to dryness. The residue is suspended in dilute aqueous sodium hydroxide, filtered and washed thoroughly with water. The product is dried at 50° under reduced pressure to yield the desired N,N' - dimethyl - N,N' - bis[5 - (3 - methylureido)-3-carboxy-2,4,6-tri-iodophenyl]adipamide. The product may be purified by solution in hot dimethyl formamide, treatment with decolorizing carbon and dilution of the filtrate with water.

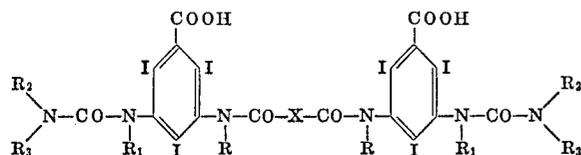
## EXAMPLE 13

## N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]-3-thiaglutaramide

Following the procedure of Example 1, but substituting in part (a) an equivalent amount of the acyl chloride derived from 3-thiaglutaric acid, there is obtained N,N'-bis[5-(3-methylureido)-3-carboxy-2,4,6-tri-iodophenyl]-3-thiaglutaramide.

What is claimed is:

1. A compound of the formula



wherein R, R<sub>1</sub> and R<sub>2</sub> are hydrogen or lower alkyl of up to 6 carbon atoms, R<sub>3</sub> is lower alkyl of up to 6 carbon

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atoms, X is an alkylene chain of up to 10 carbon atoms which may be interrupted by heterocyclic atoms selected from the group consisting of oxygen, sulfur or



as well as lower alkyl esters and physiologically acceptable salts thereof wherein the alkyl ester has up to 6 carbon atoms.

2. A compound of claim 1 wherein R, R<sub>1</sub> and R<sub>2</sub> are hydrogen.

3. A compound of claim 1 wherein R, R<sub>1</sub> and R<sub>2</sub> are lower alkyl.

4. A compound of claim 1 wherein one R is hydrogen and the other R is lower alkyl.

5. A compound of claim 1 wherein one R<sub>1</sub> is hydrogen and the other R<sub>1</sub> is lower alkyl.

6. A compound of claim 1 wherein one R<sub>2</sub> is hydrogen and the other R<sub>2</sub> is lower alkyl.

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