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CONTRAST AGENT

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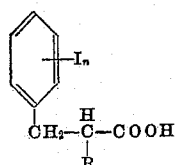
10 Claims. (Cl. 167—95)

This invention relates to a new group of compounds having contrast properties. More particularly, the invention relates to polyiodinated phenyl fatty acids and their non-toxic metal and amine salts having a definite selectivity for visualization of the gall bladder.

It is known that all X-ray diagnostic agents for gall bladder visualization which have gone into clinical use contain an amino or hydroxyl group attached to a halogen-carrying aromatic ring. These groups are, however, in many cases undesirable, as they are responsible for certain side reactions, but their presence has been considered necessary to aid in solubilizing the compounds.

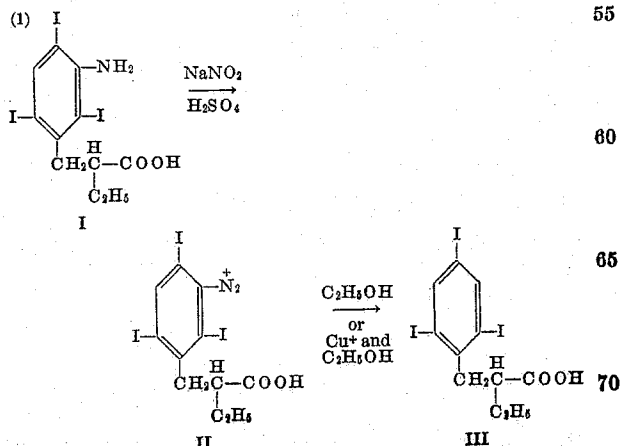
We have found that polyiodinated phenyl fatty acids having only one phenyl ring, with such ring devoid of the hydrophilic amino and hydroxyl groups, represent highly satisfactory contrast agents, particularly for the gall bladder. These compounds have only iodine on the phenyl nucleus and form adequately soluble non-toxic metal and amine salts.

The compounds of the present invention include the free acids of the general formula:



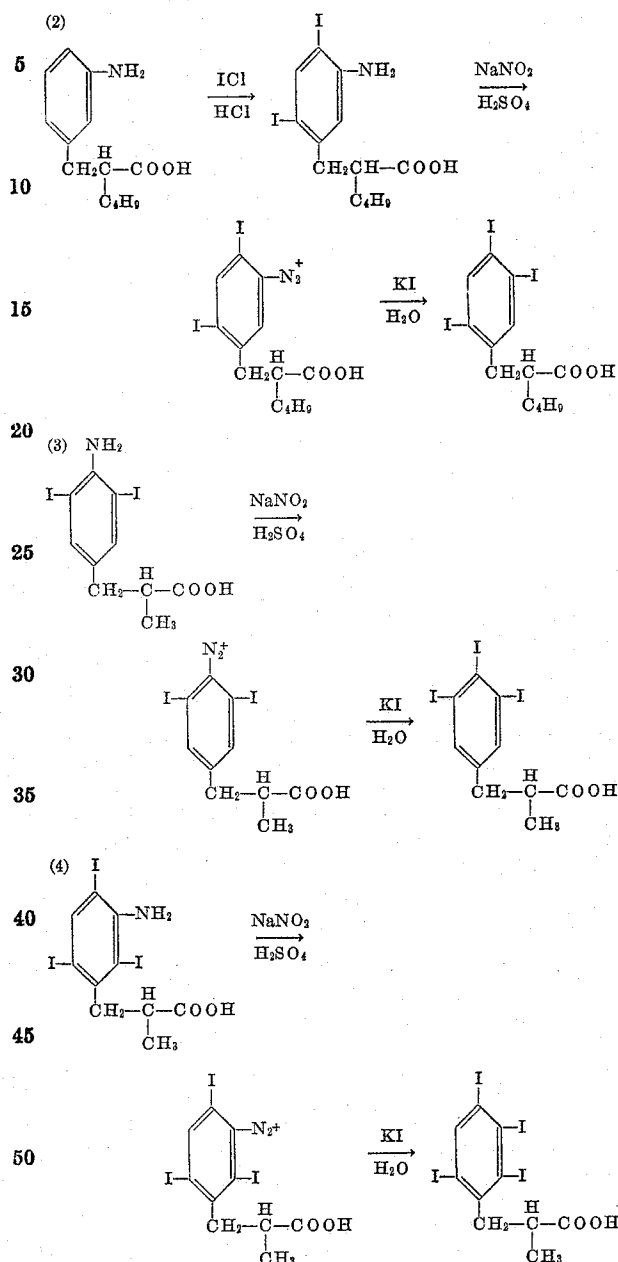
wherein R is an alkyl group having from 1 to 5 carbon atoms, and n is 3 or 4, and their non-toxic alkali and alkaline earth metal salts, preferably the sodium salts, and their non-toxic amine salts, like the alkylolamine, e. g. diethanolamine salts, and the dialkylamine, e. g. diethylamine salts.

The compounds of the present invention are prepared by diazotizing the appropriate amino derivative and replacing the diazonium group either with hydrogen or with iodine. The following equations are illustrative of these transformations:



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For the replacement of the amino group by iodine, the following equations illustrate the procedures:



The compounds of the invention may be used in the form of the free acids or in the form of their salts. They may be dispensed either in tablet form using inert carriers like the usual starch, gums, sugars and the like, or may be combined with edible emulsifiers for use in fluid form. The dosage is $\frac{1}{4}$ to $\frac{1}{2}$ that for known gall bladder contrast agents, such as "Priodax" (α -phenyl- β -(3,5-diiodo-4-hydroxy-phenyl)-propionic acid).

The following examples illustrate in greater detail satisfactory methods for the preparation of the compounds of the invention, but are not intended to indicate the scope of the invention.

EXAMPLE I

α -Ethyl- β -(2,4,6-triiodophenyl) propionic acid

To a refluxing solution of 5.0 g. of α -ethyl- β -(2,4,6-triiodo-3-aminophenyl) propionic acid (J. Amer. Chem.

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Soc. 71, 3753 (1949)) in 60 ml. of benzene, 13 ml. of ethanol and 2.5 ml. of concentrated sulfuric acid, are added, portionwise, 2.5 g. of powdered sodium nitrite. When the ensuing evolution of nitrogen diminishes, most of the solvents are removed by distillation and the residue allowed to stand overnight at room temperature. The solid is filtered off and, after washing with warm water, is recrystallized from benzene-petroleum ether to yield α -ethyl- β -(2,4,6-triiodophenyl) propionic acid.

An alternative synthesis of this compound is carried out by diazotizing a chilled solution of 5.0 g. of α -ethyl- β -(2,4,6-triiodo-3-aminophenyl) propionic acid in 45 ml. of concentrated sulfuric acid with 2.5 g. of solid sodium nitrite. After standing for two hours at 0° C., the solution is poured over 200 g. ice and the aqueous solution slowly added to a suspension of 2 g. of cuprous oxide in 150 ml. of cold alcohol. After the initial evolution of nitrogen diminishes, the mixture is refluxed until the nitrogen evolution ceases. The mixture is then cooled, poured into water and the resulting precipitate filtered. After extracting the solid with ether, the ether layer is washed with sodium thiosulfate solution and dried over sodium sulfate. Evaporation of the solvent followed by recrystallization of the residue from chloroform-petroleum ether yields α -ethyl- β -(2,4,6-triiodophenyl) propionic acid.

EXAMPLE II

α -Ethyl- β -(3,4,5-triiodophenyl) propionic acid

To a chilled solution of 3.5 g. of α -ethyl- β -(3,5-diiodo-4-aminophenyl) propionic acid (J. Amer. Chem. Soc., 71, 3753 (1949)) in concentrated sulfuric acid are added, portionwise, 2.0 g. of powdered sodium nitrite. After standing for two hours at 0°, the solution is poured on ice and then a solution of 9.0 g. of potassium iodide in 20 ml. of water is added slowly. The mixture is heated on a steam bath until the evolution of nitrogen ceases, and then poured into a saturated sodium bisulfite solution. The precipitate is filtered off, washed with water and recrystallized from acetone to give the triiodo acid of this example.

EXAMPLE III

α -Ethyl- β -(2,3,4,6-tetraiodophenyl) propionic acid

The amino group in α -ethyl- β -(2,4,6-triiodo-3-aminophenyl) propionic acid is diazotized and replaced by iodine according to the method of Example II to give this tetraiodo acid, recrystallizable from benzene.

EXAMPLE IV

α -Ethyl- β -(2,4,5-triiodophenyl) propionic acid

The requisite intermediate, α -ethyl- β -(2,4-diiodo-5-aminophenyl) propionic acid, is prepared as follows:

To a stirred solution of 19.3 g. of α -ethyl- β -(5-aminophenyl) propionic acid (J. Amer. Chem. Soc., 71, 3753 (1949)) in 70 ml. of 6 N hydrochloric acid at 70° were slowly added a solution of 34 g. of iodine monochloride in 200 ml. of 6 N hydrochloric acid. After heating the mixture at 70° for an additional hour, 500 ml. of water were added dropwise over a half hour period. The mixture was then cooled, saturated with sulfur dioxide, and the resultant precipitate filtered off and recrystallized from aqueous methanol to yield the above-named intermediate. The amino acid is converted to the triiodo compound by the procedure of Example II.

EXAMPLE V

α -Methyl- β -(2,4,6-triiodophenyl) propionic acid

Diazotization of α -methyl- β -(3-amino-2,4,6-triiodophenyl) propionic acid (J. Amer. Pharm. Assoc., 40, 618 (1951)) and replacement of the diazonium group by hydrogen according to the procedure of Example I yields the triiodo acid as a white crystalline compound after recrystallization from benzene-hexane.

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EXAMPLE VI

α -Methyl- β -(2,4,5-triiodophenyl) propionic acid

The intermediate α -methyl- β -(2,4-diiodo-5-aminophenyl) propionic acid is prepared from α -methyl- β -(3-aminophenyl) propionic acid and iodine monochloride by the method described in Example IV. Diazotization of a chilled solution of 5.0 g. of the amino acid in concentrated sulfuric acid with 4.0 g. of sodium nitrite followed by treatment with a solution of 15 g. of KI in 30 ml. of water, as described in Example II, yields the crude triiodo acid. Purification is effected by recrystallization from acetone.

EXAMPLE VII

α -Methyl- β -(2,3,4,6-tetraiodophenyl) propionic acid

This acid is obtained from α -methyl- β -(2,4,6-triiodo-3-aminophenyl) propionic acid according to the procedure of Example II, as a white crystalline compound after recrystallization from benzene-petroleum ether.

EXAMPLE VIII

α -Propyl- β -(3,4,5-triiodophenyl) propionic acid

Treatment of a solution of 4.0 g. of α -propyl- β -(3,5-diiodo-4-aminophenyl) propionic acid in 35 ml. of concentrated sulfuric acid with 3.0 g. of powdered sodium nitrite, followed by decomposition with ice and water yields an intermediate which is treated with 12 g. of potassium iodide in 25 ml. of water to give, according to the procedure of Example II, the above-named triiodo acid. The product is recrystallizable from benzene-hexane.

EXAMPLE IX

α -Propyl- β -(2,4,6-triiodophenyl) propionic acid

A solution of 6 g. of α -propyl- β -(2,4,6-triiodo-3-aminophenyl) propionic acid in 65 ml. of benzene, 15 ml. of ethanol and 3 ml. of concentrated sulfuric acid was diazotized with 3 g. of powdered sodium nitrite. After treating the resultant solution according to the procedure of Example I, the crude triiodo acid of this example was obtained and purified by recrystallization from benzene-petroleum ether.

EXAMPLE X

α -Butyl- β -(2,4,6-triiodophenyl) propionic acid

A chilled solution of 5 g. of α -butyl- β -(2,4,6-triiodo-3-aminophenyl) propionic acid in 40 ml. of concentrated sulfuric acid was diazotized with 2.5 g. of solid sodium nitrite. After working up according to the alternative procedure of Example I, and recrystallizing from chloroform-petroleum ether, the above-named acid was obtained.

EXAMPLE XI

α -Butyl- β -(3,4,5-triiodophenyl) propionic acid

Treating a chilled solution of 4 g. of α -butyl- β -(3,5-diiodo-4-aminophenyl) propionic acid in 40 ml. of concentrated sulfuric acid with 2.5 g. of powdered sodium nitrite, followed by iodination with a solution of 10 g. of potassium iodide in 25 ml. of water yields, according to the procedure of Example II, the triiodo acid of this example.

EXAMPLE XII

α -Butyl- β -(2,3,4,6-tetraiodophenyl) propionic acid

A chilled solution of 4 g. of α -butyl- β -(2,4,6-triiodo-3-aminophenyl) propionic acid in 40 ml. of concentrated sulfuric acid is diazotized with 2.5 g. of powdered sodium nitrite, followed by iodination with a solution of 10 g. of potassium iodide in 20 ml. of water, to yield, according to the procedure of Example II, the tetraiodo acid as a crystalline powder recrystallizable from benzene.

Each of the above acids can readily be converted into its non-toxic alkali, and alkaline earth metal and amine salts, in known manner, to yield more or less neutral

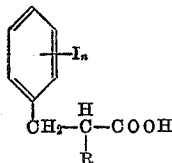
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products. The preferred salts are those of sodium and of diethanolamine and diethyl amine, with each of the polyiodophenyl aliphatic acids.

From the foregoing, it will be seen that we have provided polyiodo-phenyl aliphatic acids which in the phenyl nucleus are free from solubilizing substituents, and particularly from amino and hydroxy groups.

We claim:

1. An X-ray contrast agent suitable for visualization of the gall bladder by the oral route, and comprising a pharmaceutical carrier having distributed therein a member of the class consisting of propionic acids of the formula

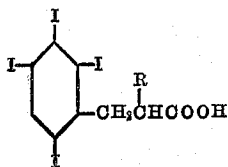


wherein R is an alkyl group having from 1 to 5 carbon atoms and n is an integer from 3 to 4, and their non-toxic alkali and alkaline earth metal and amine salts.

2. An X-ray contrast agent suitable for visualization of the gall bladder by the oral route, and comprising a tablet containing a binder and a member of the group consisting of α -alkyl- β -polyiodophenyl propionic acids and their non-toxic alkali and alkaline earth metal and amine salts, the number of iodine atoms being from 3 to 4 and the alkyl group containing from 1 to 5 carbon atoms.

3. An X-ray contrast agent suitable for visualization of the gall bladder by the oral route, said contrast agent being in the form of an aqueous preparation containing an edible emulsifier and a member of the group consisting of α -alkyl- β -polyiodophenyl propionic acids and their non-toxic alkali and alkaline earth metal and amine salts, the number of iodine atoms being from 3 to 4 and the alkyl group containing from 1 to 5 carbon atoms.

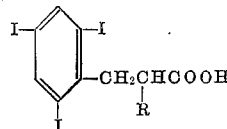
4. A compound having the formula



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wherein R is an alkyl group having from 1 to 4 carbon atoms.

5. A compound having the formula:



wherein R is an alkyl group having from 1 to 4 carbon atoms.

6. α -Ethyl- β -(2,4,6-triiodophenyl) propionic acid.

7. α -Ethyl- β -(2,3,4,6-tetraiodophenyl) propionic acid.

8. α -Methyl- β -(2,4,6-triiodophenyl) propionic acid.

9. An X-ray contrast agent comprising a pharmaceutical carrier having distributed therein α -methyl- β -(2,3,4,6-tetraiodophenyl) propionic acid.

10. α -Propyl- β -(2,4,6-triiodophenyl) propionic acid.

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